ANCA SAFTA: I thank you for being here. I thank you for inviting me to present to you what's become my passion and my mission, especially since moving to Baltimore, to North Carolina. Celiac-- oh, how do I use this? Sorry.

I was fortunate enough to train with Dr. Fasano, who is one of the fathers of celiac disease at Baltimore. And we had the opportunity to develop a celiac center in Baltimore. And that's what I'm actually trying to bring here to Winston-Salem and to our community.

I have no disclosures to make.

I would like to go over the definition of celiac disease, present to you the clinical manifestations, how to make a correct diagnosis, treatment, and future treatments.

Celiac disease is an autoimmune enteropathy. We know that you have to have the genetic predisposition. There are two genes that are most commonly involved in celiac disease. And those are HLA-DQ2 and HLA-DQ8. This causes a permanent sensitization to the gluten protein.

It is a unique autoimmune enteropathy because we know the trigger, and we also know the autoantigen. And we know that eliminating the trigger, it resolves the disease process.

Gluten is found in wheat, rye, and barley. These come from a grass family. You will probably hear a lot of times about oats and avoiding oats. However, oats do not have a protein that is antigenic. But due to the process of cross-contamination, it's commonly avoided initially.

Gluten is a protein formed of a lot of prolamins and glutamines. And each grain has a different prolamin. The wheat has gliadins, rye has secalin, barley has hordein, and oat has avenin. The avenin is not antigenic.

This is formed of a 33-amino-acid peptide, rich in glutamine and prolines. This peptide is poorly digested. And it also penetrates freely through the digestive, the epithelial tract. And presented to the tissue transglutaminase enzyme, it deaminates the glutamine into the glutamic acid. This increases the affinity of the protein, and now it binds freely to the HLA-DQ2 molecule and the antigen-presenting cells.

Once this happens-- whoops-- we have the tissue damage. Celiac disease is not an allergic

process. An allergic process is IgE-mediated. It's usually diagnosed by RAST testing, skin prick testing, patch testing, or elimination diets. Fructan sensitivities also confused a lot of times with manifestations and symptoms of celiac disease. And part of those being of the IBS syndrome.

Gluten sensitivity is also confused with celiac disease because they have similarities in presentation. However, there is no tissue damage.

So we know there is a genetic predisposition. We know that there's an environmental trigger. But we don't know that black box in between. What makes a two-year-old develop celiac disease and what makes a nine-year-old all of a sudden develop celiac disease? There is still great research going on. There are a lot of theories. Nothing is proven so far.

The HLA-DQ2 is the one gene that is found in 90% to 95% of these patients. About 10% is the HLA-DQ8. However, 30% of patients who do have the genetic component do not necessarily develop celiac disease. So testing for gene does not mean that you have a confirmatory test for the celiac disease.

Gender was thought to be a factor in developing celiac disease. Infant feeding, that has gone back and forth and now has been disproved. They always thought that early introduction or late introduction of gluten in the diet were predisposed to developing celiac disease. Recent studies have shown now that it really does not matter, the timing of gluten introduction.

Infectious processes, exposure to antibiotics, change in the gut flora, vaccinations. Many, many theories. However, nothing proven yet.

The clear situation is that it does cause intestinal damage. And causing intestinal damage, it will cause malabsorption and especially of vitamin D and causing an iron deficiency. This also increases the permeability of the gut. Hence, toxins and the possibility of developing other autoimmune disorders.

Celiac disease is known as the great iceberg. And the reason is that we're only diagnosing the surface. And the reason we're diagnosing from the surface is because it's what we see, the symptomatic cases. What we try to go beyond is pick up a lot of the silent celiac disease.

Silent celiac disease, they are basically patients who have the genetic predispositions. They have the positive serology testing, yet they do not have any symptoms. Versus those who are latent celiac disease, they have just the positive genetic testing, positive serology, but they do not have mucosal changes.

So the reason we are trying to catch the silent celiac disease is because we can make a difference there. They do have the disease. We can intervene early on, before they develop complications from celiac disease or other autoimmune disorders.

Our endocrinologists are wonderful. They refer a lot of patients to us, especially type 1 diabetics. They're at very high risk for developing celiac disease. There is no point even testing genetically for the HLA-DQ2 or DQ8 in patients with diabetes, as they share the same gene locus. The same goes for those with Down Syndrome.

However, we find a lot of celiac disease in those who have thyroid problems, arthritis, autoimmune liver disease, Sjogren's syndrome, IgA nephropathy. Pretty much if you have an autoimmune disorder and if you have any questions, any GI manifestations, you should think also of celiac disease.

Then great referrals come to us also from our geneticists and, as I mentioned, Down Syndrome. The same thing in Down Syndrome, not to test for the HLA-DQ2 or DQ8 as they will be positive. Turner, Williams, another great group. And IgA deficiencies. They have about 30% to have celiac disease.

They're also very-- the number is wrong, 7. They have also a great-- the labs are not easily interpreted because the labs that we test for celiac disease are IgA dependent.

The incidence in the healthy population is 1 in 133. In those who now have symptoms, it goes to 1 in 40. And we test all first-degree family members. And as you can see, second-degree family members highly recommended because they are even at higher risk than those who have actually symptoms in the general population.

The classic symptoms of celiac disease in less than two-- that's when we usually have the diagnosis-- is recurrent diarrhea, abdominal distension, the bloating that they will complain, anorexia, and the failure to thrive. However, in about 10% of patients with constipation, we do find celiac disease. I always test those who come for constipation, for thyroid disorders, and celiac disease.

This is what celiac disease used to look like. Very rare do we find such patients. Because of the knowledge now and the screening tools from families that we pick up a lot earlier through the family screening.

The reason I call it the great masquerader is because it can present with absolutely any type of symptom, from GI symptoms to outside of the GI tract. Some of the most common extra-intestinal manifestations are dermatitis herpetiformis, a very intense pruritic vesicular rash. I have some pictures to share with you. Dental enamel issues, bone density problems, short stature, delayed puberty are the most common.

In adults, though, iron deficiency, anemia, resistant to iron supplementation very common. Hepatitis, arthritis. Yes, seizure disorders that have a proven focus of calcification in the occipital area.

Infertility. Huge. About 10% of those who have infertility issues, you have to think of celiac disease also and do testing.

This is dermatitis herpetiformis. As I mentioned, it is a vesicular rash, intensely pruritic. We're not talking about just slightly. They scratch and scratch and scratch and cry. And the majority of the time, they do not have any intestinal manifestations.

So if you have such a patient, there is not even-- the first thing you should do, you should send to the dermatologist to get a biopsy from the skin. And if you find that indeed it is dermatitis herpetiformis, there is not even a need to send to the gastroenterologist to do an intestinal biopsy because you can confirm the diagnosis of celiac disease just with a skin biopsy.

And in the skin biopsies, yes, you will find the IgA deposits. It takes quite some time to resolve the symptoms of dermatitis herpetiformis on a gluten-free diet. If the patient has intense symptoms and needs quicker resolution, dapsone is an option.

Recurrent apthous stomatitis. It's always a red flag in the GI world. It is not just for celiac disease. Any autoimmune, any GI disorders, if we hear apthous ulcerations, immediately they raise a little bit of suspicion that there might be something going on. Of course, there is isolated apthous stomatitis, but this will be added on the list.

The dental enamel issues. Bone density caught through the DXA scans. Osteopenia is in children, osteoporosis in adults. And then the one thing that I really try to prevent. This is a disease that is treated just by diet alone, yet it can have huge complications of other autoimmune disorders. And also, it can predispose to this enteropathy-associated T cell lymphoma.

And if we can prevent it, patients who have been on a diet, on a gluten-free diet, five years out, their risk comes to zero. That is huge in my book.

In children, short stature. If you have someone with just short stature, please think celiac disease. About 10% of these children will have serology positive. Also, delayed menarche is another. Just delayed menarche, no other GI symptoms, to think of celiac disease.

As mentioned, in adults, iron-deficient anemia resistant to iron supplementation. In pediatrics, it's different. You will have anemia, but it's not the sole presentation. You can, but it's not as common as in adults.

How do we diagnose celiac disease? It's very important to make the right diagnosis, as this changes one's entire life. The diet is changing. Their family lifestyle is changing. Now they could have children who might have celiac disease. So huge quality of life implications.

First thing to think are serological tests. And if you cannot do the serological tests, you can always refer, if you have a suspicion, to the gastroenterologist so we can do them. The first ones were the antigliadin antibodies. Pretty much no one is using them anymore. And the only time that we use them as gastroenterologists, if someone comes to us with neurological manifestations and seizures. And there might be of value to obtain the antigliadin antibodies because they can be positive in those with neurological manifestations isolated.

The new kid on the block are the Deaminated Gliadin Peptide antibodies, DGPs. And all of these antibodies are either IgA or IgG antibodies. As first screen, please just obtain the IgA antibodies. Always, always obtain a total IgA as an initial screen. And remember, you want to make sure that the total IgA is robust and they're not deficient. Because if they're deficient, your serology can look falsely negative.

The antiendomysial antibodies are not antibodies to obtaining your screening process. They're expensive, and they're operator dependent. Please obtain them.

Though if you have a diabetic person, that is the only person that you should screen with an antiendomysial antibodies. Because the tissue transglutaminase antibodies will be positive in those who have diabetes just because of the diabetes. It's an autoimmune disorder, and they can be positive. So we want to get that EMA-positive before we put a child through an endoscopy.

The one antibody that we use for general testing and screening are that Tissue

Transglutaminase antibody, the TTG, TTG IgA. If you have a patient who has IgA deficiency and you want to have an antibody for later purpose for monitoring would be to get the TTG IgG.

The HLA typing I only obtain in families that have a lot of children or they want to know if they're at risk, basically, and they do not want to do the yearly screening. Because now, if you diagnose one family member, basically all of the other family members they should be tested yearly. So that adds up a lot. And for kids, it can be traumatic to get the testing yearly.

So then I will offer the HLA typing. And actually, I just found out that we have an HLA typing at Baptist, and it's very, very reasonable compared to the commercial ones. And if they're negative, high negative predictive value, they're eliminated out of the equation. They don't have to get the future screening. So that's a great thing for that child.

Then, once you have a positive antibody or any question and they come to us, about 10% can be still negative serology. And they can have the symptoms. Please, of course, then send to us for further evaluation. And because of the symptoms, not because of the antibody testing, will drive the next step. And the next step is a procedure, the endoscopy, so we can obtain biopsies.

And I always encourage the family to go through the procedure, through the endoscopy and obtain biopsies and not make a diagnosis on the serology alone. There are some newer criteria coming from the European Community suggesting that you can make a diagnosis of celiac disease based on serology alone. But you have to have the TTG IgA above 100. You have to have a family member with celiac disease. You have to have HLA-positive. You have to have the resolution of the symptoms on a gluten-free diet, reintroduction, and reappearance of symptoms.

So you can in such a group make a diagnosis of celiac disease. However, even in these patients, I do not encourage that process because I have been many times in the situation where that was the case and the gluten-free diet was commenced. That patient could have had also another autoimmune GI disorder going on at the same time, such as Crohn's disease or any eosinophilic disorder such as eosinophilic esophagitis, about 10% prevalence in celiac disease.

So if they're not doing well, then I'm pretty stuck now with a child who is not doing well, is

behind the eight ball, and I don't have a clear diagnosis of what's going on. So I want to be able to give the family a true this is it, that's all you have. If you're developing something else later, we'll deal with that. We know how to address it.

So the first picture shows you the duodenum. Usually it's the D2. The disease process starts proximal and works its way distal. So it's most of the time that we're finding the positive. It's in the duodenum and in the duodenal bulb and in D2.

The second picture shows you actually pretty severe celiac disease. Whenever you start getting the scalloping, you can see the little folds there, the little indentations. That's pretty pathognomonic. When I see that on the endoscopy, even without biopsies, I can tell with confidence that, well, we have celiac disease.

And third one. It's pretty much-- I know that probably it's going to be complete villous atrophy. And histologically, the first picture it's normal intestine or normal villi. Second one, you're starting to have the lymphocytic infiltrative changes in the epithelium. It makes about 10% of the diagnosis.

So you can have other things, allergic enteropathies, giardia, inflammatory bowel disease. So it really does not make the diagnosis in the Marsh 1, in the infiltrative through the process whenever you step into the Marsh 2, which is the third picture where the villi starts to get a little bit fatter. The creep starts getting wider. It makes about 90% of diagnosis. We're increasing from 10% to 90%.

So I can tell with pretty confidence that now I have the antibodies positive, the histology, that the child has celiac disease. Going into the Marsh 3a, b, and c, those are very obvious. You're starting to lose the villous tip in March 3a, about 2/3 of it in Marsh 3b, and total villous atrophy in Marsh 3c.

Once you go on a gluten-free diet, in about 70% of the patients very quickly you will see symptom resolution. And of course, that does not mean that the disease process has gone away. It just means that they're starting to feel better. It takes a long time for the tissue to start healing. It takes anywhere between six months to 12 months for the tissue to become normal.

For the serology, we do not even screen anytime or sooner than six months. So six months, 12 months. If it becomes normal at 12 months, then yearly.

There is something that is called non-responsive celiac disease. It is pretty rare. And, just as

the name says, it's not responding to a gluten-free diet. And you're still having the same symptoms.

Unfortunately, it takes about, yes. You want to give the time for the diet to work. Families get very frustrated. And that's because you might have something else going on. You probably did not make the right diagnosis. Most of the time they're not very compliant, so it's very important that they meet with a dietitian and the dietitian who basically lives and breathes gluten-free diets and is able to guide families.

Pancreatic insufficiency. The reason is because there is at villous damage. So the enterokinases that stimulate the pancreas can be deficient. So you can get pancreatic insufficiency from that process.

Also, as you lose the villous height, you are losing the lactase or disaccharidase enzymes on the tip of the villi, so you can get a lactase deficiency and lactose intolerance. So patients might be actually lactose intolerant in that phase and have the same bloating and diarrhea type of symptoms. And they would think that they're not improving. And eliminating dairy products, lactose, from the diet might be the answer.

And sometimes there are other associated disorders like lymphocytic colitis, collagenous colitis that can go along with celiac disease. Very, very rare refractory disease in celiac patients. Actually, there are only two described in the world. One is in Sweden and one was at Maryland. And it takes a very long process to make that diagnosis.

It is this non-responsive celiac disease, but now we go through a period of 12 months. And you want to make sure that you excluded the dietary factor. Now you're going to exclude absolutely all grains from the diet. The next step would be to go to an enteral nutrition with just formulum. And the next would be to just put the child on TPN. And if the tissue is still persistently damaged even on TPN, that would make the diagnosis of a refractory celiac disease.

So basically, what we have, we have the genetics, we have the histology, and antibodies present while we eliminated the trigger. There will be, obviously, more weight loss and more symptoms.

There are two types of refractory celiacs disease. Type I acts basically like an inflammatory bowel, disease like Crohn's disease. So the treatment will be with immunosuppressants, just

like you would for Crohn's disease. Type II is the one that will lead to the intestinal lymphoma. And the differentiation, basically it happens with the T cell population. The type I still has polyclonal T cells, where the type II, now it has oligoclonal T cells. And these patients will undergo chemotherapy.

Now to the brighter side, though, the majority of patients responds to a gluten-free diet. And the gluten free diet, you have to be very strict. You can't be, I'm doing it sometime. I'm almost doing it. It has to be all the time, and it has to be 100%.

And yes, you avoid wheat, rye, and barley. But how about oats? So what we do in our clinic, we ask the patient in the first year while we're working in this process of learning and normalizing the antibodies to please eliminate the oats. And as I've mentioned before, the oats are not eliminated because the avenues are immunogenic. It's because in the process, they can have cross-contamination. And usually it happens in the field or in the factory.

Good news, that Cheerios is changing their Cheerios, and they're all going to be gluten free. There are not going to be Cheerios that are gluten-containing anymore.

These are some of the grains to avoid that are wheat, rye, and barley components. Some of the obvious sources of gluten, of course, the pastas, the bakeries, breads. But the not so obvious sources. Candy, communion wafers. They made now gluten-free communion wafers. Cured meat products, drinks, gravies. So you can see that it can become quite cumbersome for the family. And then really they're not the obvious sources for the gluten contamination.

Some of the safe grains. There are quite a few, which is great. What I ask the families is not to buy them from the Whole Foods, where they're open and they can just self-serve because they're around other gluten-containing products and there could be cross-contaminating there. So always buy them in the pre-sealed packages.

Cosmetics. And this is a debatable area. Gluten does not cross the skin barrier. The glidin peptide does not cross the skin barrier. But applying it to the mucous membranes. Yes, you could. I mean, if you're going to put a lot of the lip glosses and products, you could theoretically be exposed. But majority of the time, we try to allow patients to have some normalcy unless they're not responding to the gluten-free products. And then we'll try to remove other not obvious sources.

The guidelines both for children and adults, they're pretty much the same. And it's very

important to be in an environment that supports you. Programs, that's what we're trying to develop. And we actually formed it's called GLADD Program at Brenner's, Gluten and Allergic Digestive Disorders. And we have a dietitian that we work with. And we're open now to pediatrics and adults, as this is a family thing.

And it's diet. It's going to happen in a family. And wherever we diagnose a child, we're going to diagnose another family member. And it serves a great purpose that they are going to hear the same information and be able to eat the same things.

So the patient is feeling better. It's a great motivator. But for those who did not have any symptoms, they're having a little bit harder time. So bringing those in and monitoring their blood work, those become the motivator piece for that type of patient.

Having a very positive outlook is very important for our patients. And we're not telling them that they need to be on a diet. They are just modifying the way they're eating. And gluten-free foods these days, luckily to the industry, they're a lot tastier. They've become a little bit more reasonably priced, more excessive. And we're now trying to go into restaurants and do a lot of education in the restaurants and how to try to cook gluten free so we can provide for our patients with a lot more variety and try to have some normalcy in their lives.

Weight management can become a concern because now that intestine is healing, the absorption is better. But the gluten-free products, in order to become tastier, guess what they're doing? They're fortifying them, so they're putting a lot more sugar. And if you're eating a lot of those products, you can gain a lot of weight. Whoops. I'm going backwards.

So what I would like the messages to take home. So whenever you have a think about celiac disease, yes, it is a great masquerader. It can present with GI issues, outside of the GI tract issues. If you have any concerns, please call us. Send the patients to us. Or do a quick screen, serological screen.

Please always remember, biopsies are very, very important. Try not to start a gluten-free diet. I know that sometimes a push is because you might not be able to get to the specialist in time and the child has symptoms. We're trying to work with the community with practitioners and trying to bring the patients in as quick as we can.

Gluten free is the only treatment. There is a lot-- 10 years ago when I started this, I thought that, yes, we're going to be in the era where we're going to talk about vaccinations. We're

going to have the enzymes that we can take, just like the lactase pill that we can take and be able to have some gluten in the diet. We are not there.

I didn't even put a slide with anything that is being worked on because there really are not any advances. There's a lot of work being done, but we're not anywhere close to it. So really, the gluten-free diet is the only thing. And the industry has helped us to bring a lot of products on so we can serve our patients. And please remember to screen the higher risk groups.