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Investigating the Latest Innovations in IBD

Dr. Nandi:
Welcome to *GI Insights* IBD Crosstalk on ReachMD. I'm your host, Dr. Neil Nandi. And joining me to discuss new innovations in IBD care and management is Dr. Peter Higgins. Dr. Higgins is a Professor of Medicine and Director of the IBD Center at the University of Michigan. He holds a master's in clinical research design and Statistical Analysis, and his focus is research efforts and molecular mechanisms of intestinal fibrosis, wielding biomarkers for IBD prognosis and management and more. Dr. Higgins is a distinguished educator and is a passionate, producer of educational videos online for both patients and clinicians alike. He is a member of the AGA IBD Quality Measures Committee and has participated in the development of national guidelines for high-quality IBD care for many, many years. In fact, Dr. Higgins has received many honors and awards, including the AGA IBD Clinical Research Excellence Award.

Dr. Higgins, welcome to our program.

Dr. Higgins:
Thank you, Dr. Nandi. Great to be here.

Dr. Nandi:
Absolutely. So, you know, it's 2022, and I've never been more excited to be in this field of inflammatory bowel disease. Things have rapidly changed in the last several years, and I know things are going to change going forth in terms of diagnosis, prognosis and management. So one of the prognostic assays that's been produced in the past have been serologic markers for IBD diagnosis on referencing antibacterial and antifungal antibody serologies. Where are we in terms of utilizing those for diagnosis? Or should we be avoiding them right now?

Dr. Higgins:
At this point, I think going back to the classics for diagnosis is essential, meaning endoscopy, biopsy, histology, adding in imaging. Biomarkers and serologies are helpful adjuncts, but they're not going to make a diagnosis for you. They are helpful in risk-stratifying patients, but I think it's important to take into account there are a lot of clinical data that help you risk-stratify patients. The age at diagnosis, younger are generally going to do worse. Small bowel or upper tract Crohn's disease are going to do worse. And in general, Crohn's disease is going to be a lot more difficult to treat than ulcerative colitis. And so most of the time I find that clinical history, the location of disease, much more helpful than adding serologies.

Dr. Nandi:
So I like what you said. You know, one of the newest innovations in the last few years has, or conclusions has come from the PANTS study, which is looking at a marker, HLA-DQA105, to predict the risk of anti-TNF drug antibody formation. Now, is this something that clinicians should be utilizing in clinical practice? Can you elaborate?

Dr. Higgins:
It is quite helpful. And this is present in about 40 percent of people of European ancestry, so it's pretty common for a genetic marker, and it dramatically increases the rate of developing antibodies to particularly the old-school biologics, adalimumab and infliximab. And, of course, there are higher rates for infliximab than adalimumab, but for both of those there are clear benefits to adding an immunomodulator. But the presence or absence of this HLA marker affects immunogenicity just as much as an immunomodulator, so adding an immunomodulator to someone with this HLA marker, DQA1*05, brings them up to the rate of immunogenicity of somebody who doesn't have that genetic marker at all. In somebody who doesn't have that genetic marker, it has a similar reduction in antibody formation. So you can help people in 2 ways. If they are lucky, they don't have this DQA1. If they do have it, you can add an

immunomodulator. Even if they don't have it, you get a similar benefit in terms of reducing antibodies to adding an immunomodulator to somebody who doesn't have this marker.

Dr. Nandi:
We know that there are some small patients that, that may have side effects from going on a thiopurine therapy. Now, if you've been trained well in how to use thiopurines, they can be prescribed quite safely. But one relatively recent mutation has been identified, NUDT15, Nudix Hydrolase 15, which, is present in certain ethnic populations that may increase the risk of neutropenia, leukopenia. Can you give us more insights as to how we should and what populations should we test NUDT15 in?

Dr. Higgins:
Most of the data on NUDT15, comes out of Japan, but a variety of locations in East Asia. And I think, broadly, if you see someone who is of East Asian origin or may have that intermixed in their background, it's worth checking for. It is a completely different pathway from the TPMT. But in terms of folks with East Asian descent, about 20% will be heterozygotes and will have trouble processing thiopurines, about 1% will be homozygotes. And the homozygotes, the people who have both copies of the mutation, will be very likely to get early leukopenia. Of the 20% who have heterozygotes, about 20% will get significant early leukopenia. And the interesting thing is you'll see really low white blood count and high MCV that persists for about 24 months or more even after you stop the drug, so this is a long-lasting effect on the bone marrow. And, honestly, while it's common in East Asians, I've seen this kind of effect in several of my patients who do not appear to be of East Asian descent. I had 1 patient who, despite having a looking-good TPMT, really dropped their white count very quickly, ended up with a viral meningitis. I was very concerned. We had persistently low blood counts, white cell counts and elevated MCV, but essentially put this patient after a week of therapy into a deep remission, which is both scary and really interesting that this, while toxic to her bone marrow, almost reset her immune system. , And I don't know that there's a way to do this safely, and I certainly wouldn't want to relive that week again, but it tells us something interesting about the bone marrow and what thiopurines are doing. I don't think we understand them well enough, at least with the pharmacogenomics.

Dr. Nandi:
I want to kind of talk about monitoring, and I want to talk about stool studies. I think in my mind the holy grail is a smart toilet so people can have true point of care stool submissions at home. We're not there yet. But, how do you use calprotectin in your practice? And are there other stool markers that may develop that are more sensitive for inflammation?

Dr. Higgins:
So I think both calprotectin and lactoferrin can be helpful and not exactly interchangeably but pretty darn close. They both are measuring neutrophil proteins, that are upregulated during inflammation. The noisy part of these—and they are noisy tests—is that they vary from bowel movement to bowel movement and how you sample the bowel movement, so it's helpful to instruct the patient to take a representative chunk of the stool that they send in—or at the very least, if there's a lot of mucus or pus in their stool, to mix it up a little bit. If a patient takes a sample just from the pus, either one of these markers are going to be sky high, and if they have a puddle of pus and they take it just from the stool part, it's going to be unrepresentatively lower. And so, you know, in a perfect world they would homogenize their stool, but they're not in the lab, and they're not putting their stool in a blender, so if you can instruct them to try to take an average or mixed sample, it really helps. But if you have a patient who's consistently had a very low calprotectin on therapy and then it's suddenly 500 or more, there's clearly something going on.

Dr. Nandi:
So, you know, we've talked a little bit about diagnosis and management, some monitoring. Now I want to think a little bit more fantastically. Looking at early prognosis, early prediction of a later IBD diagnosis, where is the science right now in 2022 in terms of early diagnosis, possibly intervention, in IBD?

Dr. Higgins:
So we know a lot going back to the RISK study in children on the date of diagnosis where they found that a lot of the kids, even at the date of diagnosis, were already progressing to ileal stenosis and that biopsies of the terminal ileum showed—if they showed a transcriptional program that was increased in fibrogenic molecules, those folks were much more likely to progress to stenosis in the next two years. This has been followed up with a couple of really interesting studies. First, the GEM project was similar in children, and they found that looking for lactulose and mannitol absorption in that excretion in the urine. Normally, you would expect lactulose not to be absorbed and to have a low lactulose in a urine and a relatively high mannitol, but if that ratio goes up, so suggesting they have a leaky gut, that they're absorbing lactulose inappropriately, those folks develop Crohn's disease more often within 2.7 years compared to the folks who didn't have it. And if you went out to 10 years, around 9 percent of those people with a high leaky gut score developed Crohn's disease within 10 years where only 2 percent in the people with a low leaky gut score, let's call it, a lactulose to mannitol ratio, and so it suggests that there's something going on before people are diagnosed for several years and that leaky gut is a part of that.

And you have to think about from the person's point of view—or if they are a minor, the parents' point of view—is this worth it to say, "Okay, your child has a 9 percent chance of developing Crohn's disease in the next 10 years. We could possibly, possibly reduce this to 2 percent if you take this therapy." I think it's a really interesting question because some of these therapies have significant risks, and giving them to a healthy person for a hypothetical benefit is pretty hard. And then there's the cost. Would any insurance company pay for a JAK inhibitor or infliximab to try to prevent Crohn's disease before it starts? It's a fascinating idea, and if we could identify relatively low-cost, relatively safe interventions, I think people would be really interested, especially in the kind of population in that GEM study where every one of those patients had a first-degree relative with Crohn's disease. So those are the folks who would probably be most motivated to try to prevent a new diagnosis of Crohn's.

Dr. Nandi:
I do think that this is absolutely fascinating. It's exciting, Dr. Higgins, to know how researchers like yourself are going to push the bounds and possibilities over the next decade.

Dr. Higgins, thank you so much for joining us on the program today. It was really great speaking with you.

Dr. Higgins:
Thank you.

Dr. Nandi:
For ReachMD's IBD Crosstalk, I'm Dr. Neil Nandi. To access this and other episodes in this series, please visit reachmd.com/giinsights, where you can Be Part of the Knowledge. Thanks for listening.