About IBD Podcast Episode 121 – IBD and Biomarkers: What You Need to Know With Andres Hurtado-Lorenzo, PhD

What if we knew which patients would have severe Crohn's disease or ulcerative colitis? And which wouldn't? How about if we could tell which drug would work best in which patient? Knowing these things would change how inflammatory bowel disease (IBD) is diagnosed and treated. Plus, more importantly: it would improve lives. Dr Andres Hurtado-Lorenzo, Vice President of Translational research and IBD Ventures at the Crohn's and Colitis Foundation explains biomarkers and how they may play into the future of how IBD is diagnosed, managed, and treated.

Resources:

- Crohn's & Colitis Foundation: https://www.crohnscolitisfoundation.org/
- IBD Plexus: https://www.crohnscolitisfoundation.org/research/current-research-initiatives/ibd-plexus/about
- RISK Study: https://www.crohnscolitisfoundation.org/research/current-research-initiatives/pediatric-risk-stratification
- IBD Ventures: https://www.crohnscolitisfoundation.org/research/grants-fellowships/entrepreneurial-investing/portfolio
- Olink: https://www.olink.com
- Foundation for the National Institutes of Health: https://www.fnih.org
- Genedata: https://www.genedata.com
- Glycominds: https://www.glycominds.com/blood-tests-1
- PredictImmune: https://www.predictimmune.com/

Research:

- Honig G, Heller C, Hurtado-Lorenzo A. Defining the Path Forward for Biomarkers to Address Unmet Needs in Inflammatory Bowel Diseases. *Inflamm Bowel Dis.* 2020;26(10):1451-1462. doi:10.1093/ibd/izaa210. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7500521/pdf/izaa210.pdf
- Honig G, Larkin PB, Heller C, Hurtado-Lorenzo A. Research-Based Product Innovation to Address Critical Unmet Needs of Patients with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2021;27(Suppl 2):S1-S16. doi:10.1093/ibd/izab230. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8922161/pdf/izab230.pdf
- Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389(10080):1710-1718. doi:10.1016/S0140-6736(17)30317-3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5719489/pdf/nihms923305.pdf
- Biasci D, Lee JC, Noor NM, et al. A blood-based prognostic biomarker in IBD. *Gut*. 2019;68(8):1386-1395. doi:10.1136/gutjnl-2019-318343. https://www.predictimmune.com/wp-content/uploads/2020/09/Biasci-et-al-A-blood-based-prognostic-biomarker-in-IBD-Gut-2019.pdf

- de Bruyn M, Ringold R, Martens E, et al. The Ulcerative Colitis Response Index for Detection of Mucosal Healing in Patients Treated With Anti-tumour Necrosis Factor. *J Crohns Colitis*. 2020;14(2):176-184. doi:10.1093/ecco-jcc/jjz125. https://doi.org/10.1093/ecco-jcc/jjz125

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[MUSIC: IBD Dance Party]

Amber Tresca (00:05):
I'm Amber Tresca and this is About IBD. It's my mission to educate people living with Crohn's disease or ulcerative colitis about their disease and to bring awareness to the patient journey.

Welcome to episode 121.

One of the most frustrating things about living with inflammatory bowel disease is how variable it is. Some people have mild disease or moderate, and others have severe disease. In some cases, a patient may have mild disease that never gets any worse, but then others have disease that starts out as severe from the very first flare up.

Amber Tresca (00:39):
Right now it might be difficult to know how any particular person's disease is going to behave over time. That's where biomarkers can come in. Researchers and scientists are studying biomarkers and the blood or stool of people with IBD to see what clues it can give about how a

patient's disease might change. If we know that someone is at risk for complications, for example, we might be able to give them a treatment that helps avoid that outcome.

On this episode, you'll hear from Dr. Andres Hurtado-Lorenzo, who is Vice President of Translational Research & IBD Ventures at the Crohn's & Colitis Foundation. He explains biomarkers and how they may play into the future of how IBD is diagnosed, managed, and treated.

Amber Tresca (01:25):
Dr. Hurtado-Lorenzo, thank you so much for coming on About IBD.

Andres Hurtado-Lorenzo, PhD (01:29):
Hello, Amber, and hello to the audience joining today podcast. And I also want to thank you, Amber, for inviting me to talk about the fascinating and impactful topic of biomarkers in your brilliant podcast series.

Amber Tresca (01:44):
Absolutely, thank you so much. This is something that I don't fully understand, so I'm really looking forward to you explaining it all to me.

Andres Hurtado-Lorenzo, PhD (01:51):
Absolutely. I will be delighted to do so.

Amber Tresca (01:54):
Okay. First though, I'm going to give you a minute to introduce yourself and let everyone know how you came to be involved in IBD research.

Andres Hurtado-Lorenzo, PhD (02:01):
All right. So, let me tell you a little bit about myself. I'm the Vice President of Translational Research & IBD Ventures at the Crohn's & Colitis Foundation. I'm responsible for the planning and oversight of the Foundation's translational research portfolio that aims to advance solutions for patients based on research in the fields of precision medicine, biomarkers, genetics, microbiome, stress, precision nutrition, pain, fibrosis, and biosensors. I also lead the Foundation's venture philanthropy program called IBD Ventures, which aims to advance new product development in IBD by making financial investments in for profit and non-profit organization. In this program, we are advancing novel therapies, biomarker based tests, and medical devices. Most of my professional career has been devoted to drug discovery and development in big pharma and biotech companies. And I have worked in all the stages of drug discovery from early discovery and lead optimization to I&D enabling research and clinical trials.

Andres Hurtado-Lorenzo, PhD (03:07):
I obtained my PhD in molecular medicine and gene therapy from the University of Manchester in England, where I pioneered work in gene therapy for Parkinson's disease. I completed my postdoctoral work at Harvard Medical School, Mass General Hospital and Columbia University,

where I conducted groundbreaking research focused on autophagy and other protein degradation pathways and enthralling neurological diseases. I became interested in IBD while working in drug discovery for Parkinson's disease in Pfizer, because one of the drug targets I was working on was a genetic risk factor for Parkinson's disease, but also for IBD.

Andres Hurtado-Lorenzo, PhD (03:44):
This led to my interest in IBD and the exploration of the fascinating brain gut axis circuitry, which actually we're studying in our translational research portfolio at the Foundation. Given my expertise in drug discovery and product development, the Crohn's & Colitis Foundation hired me to start our IBD Ventures program and to expand our translation of research portfolio. And I could not be more happy than to contribute to this reputable organization whose research and overall mission is focused on finding cures and bringing solutions to different and the needs of patients with IBD and to improve their quality of life.

Amber Tresca (04:24):
Thank you. And we are so grateful to have you working on IBD now. And so, I want to get a level set first and just understand on a basic level, what are biomarkers and why are they important in IBD?

Andres Hurtado-Lorenzo, PhD (04:39):
So, this is a fantastic question to start our conversation and to level set the audience. Biomarker is defined as a biological indicator of a disease state or biological process that can be measured. So for instance, cholesterol in blood is a biomarker that can be used to predict the risk of cardiovascular disease. Another biomarker widely used in the clinic is A1C, which is a biomarker of the risk of developing diabetes. In the case of IBD, fecal calprotectin, and CRP are biomarkers of inflammation that IBD patients are very familiar with. Okay now, there are different type of biomarkers and they are classified based on their different uses. And this is technically known as the context of use. I will mention some of the most common context of use that ideally should be used in IBD clinical practice.

Andres Hurtado-Lorenzo, PhD (05:40):
First, biomarkers can be used for initial diagnosis of disease, and they are known as diagnostic biomarkers. Second, biomarkers can be used to prognosticate disease scores, whether aggressive or quiescent, or with complications, which are known as prognostic biomarkers. Third, biomarkers can be used to predict response to different type of drug treatments, and they are known as predictive biomarkers. And fourth, biomarkers can be used for continuous evaluation or monitoring of the efficacy of treatments, and they are known as monitoring biomarkers. In addition to these, diagnostic, prognostic, predictive, and monitoring biomarkers that could be used by doctors for patient care, there are other context of use of biomarkers to support preclinical development of drugs and evaluation of novel investigational drugs in clinical trials. But I will not explain this context of use today. Biomarkers are important in IBD and medicine in general, because they can help make early and effective treatment decisions.

Andres Hurtado-Lorenzo, PhD (06:56):

However, while some biomarkers like fecal calprotectin and CRP have been used for decades by IBD doctors, the truth is that they are still far from ideal and do not cover all the main contexts of use I described. Currently, in fact, gastroenterologists lacked validated [inaudible 00:07:17] standard biomarkers to accurately diagnose inflammatory bowel diseases in a fast and minimal invasive way. And what is more important is that even after a correct diagnosis, current endoscopic, fecal, serologic, and biochemical biomarkers do not actually prognosticate whether a patient will have an aggressive or mild disease course. In addition, currently IBD doctors cannot predict whether a patient will respond or not to a treatment, and nor they can monitor the efficacy of a given treatment on the reduction of inflammation and/or induction of healing of the mucosa.

Andres Hurtado-Lorenzo, PhD (08:01):
So given these unmet needs, it becomes clear that identification and qualification of neural biomarkers and development of respective tests is a critical challenge that need to be addressed. Biomarkers with different contexts of use, have the potential to improve IBD patient care and outcomes. And it's in a strong area of focus of the Crohn's & Colitis Foundation and of several IBD research labs in the US and worldwide.

Amber Tresca (08:31):
Thank you for that. And we know that there are significant unmet needs in IBD. You mentioned a few of those at the top of the show, but another one is understanding which patients might be more at risk for complications. Could you let us know what kind of research is being done to try to find those patients soon after they're diagnosed?

Andres Hurtado-Lorenzo, PhD (08:50):
Absolutely. That is another great question. And let me start by saying that the accelerated development of high throughput technologies for the massive analysis of genes, proteins, microbes, and metabolites altogether known as multi-omics technologies, is opening the doors for the identification of this type of prognostic biomarkers. For instance, biomarkers based on gene expression patterns have demonstrated potential for prognosis of IBD. So regarding prognosis of adult patients at high risk of aggressive disease course, a clinical test based on gene expression signature in the blood has recently been validated in the UK to discriminate a diagnosis, IBD patients likely to experience a severe disease course in the subsequent 18 months. And it's been further evaluated in the United States in an observational validation trial called PRECious, and also in a biomarker stratified, interventional utility trial in the UK called Profile. However, this biomarker test called Predictor not necessarily will tell the doctor and patient if the high risk of aggressive disease course is due to unremitting inflammation or to particular complications like fistulas or fibrosis.

Andres Hurtado-Lorenzo, PhD (10:17):
However, in this regard, resource derived from the pediatric Crohn's disease study called RISK in which gene expression patterns of biopsies with a study. And this has demonstrated the potential to provide prognostic information regarding the risk of developing fibrotic and fistulizing complication in pediatric Crohn's disease. So I'm going to give a bit of more detail

about this study and what we're doing about that. So, the recent study supported by the Crohn's & Colitis Foundation for 13 years, and we're led by Dr. Subra Kugathasan and Dr. Ted Denson is the largest inception cohort of pediatric Crohn's disease patients, in which 1,000 patients with Crohn's disease were enrolled. This is an inception cohort, which means that patients were recruited at diagnosis and before treatment. And this make this cohort ideal for prognostic biomarker discovery. The aim of this study was to identify a diagnosis, clinical and biological predictors of complications.

Andres Hurtado-Lorenzo, PhD (11:25):
So a long story short, the researchers took intestinal biopsies from Crohn's disease patients at diagnosis, and found an mRNA biomarker signature of about 80 genes that could predict a diagnosis that a child diagnosed with Crohn's disease could develop intestinal fibrosis within the next three years. And they also found another mRNA biomarker signature of antigens to predict the livelihood of developing fistulas. This was a groundbreaking finding that was published in The Lancet five years ago, showing that by analyzing mRNA, basically genes of intestinal biopsies, prognosis of complications is possible.

However, as you can imagine, the development of a clinical test that is based on a multiplex gene expression panel with almost 80 genes for each complication is quite challenging. So at the Foundation, our research team, we roll up this leaps and embark in a new goal for the study, which is to translate these findings of the consortium into an optimized prognostic test that can predict complications in pediatric Crohn's disease.

Andres Hurtado-Lorenzo, PhD (12:39):
And to do that, we started by centralizing of the clinical data and bio samples of the RISK study into the Foundation's biobank called IBD Plexus. We used artificial intelligence methods to reanalyze the mRNA data from the patients and identify and optimize new biomarker panel of only 13 genes from the intestinal biopsies that can predict fibrotic and fistulizing complications. Now, we also ask the question of whether it will be possible to identify a less invasive prognostic biomarking blood, so no need for biopsies.

So for this, we used a novel technology called the proximity extension assay or PEA, that is developed by the Swedish company, Olink. This technology can detect proteins in blood, even if they are present at very low levels. So, we took the blood samples from the risk study, that were collected at diagnosis and run the samples in the Olink platform to measure the levels of about 1,000 proteins.

Andres Hurtado-Lorenzo, PhD (13:47):
We apply once again, artificial intelligence methods and in collaboration with a company called Genedata. And we identify out of these 1,000 proteins 14 proteins in blood that can predict a diagnosis, the likelihood of a child with Crohn's disease to develop complications within the next five years. And this is very exciting because these biomarkers are found in blood, which eliminates the need of invasive endoscopies and intestinal biopsies, as in the case of the mRNA

genetic signature. In contrast, a simple blood sample for a newly diagnosed child could be sufficient to predict disease course, if we can develop such protein test based on our research.

And now together with Olink, we have developed a prototype test that contains these 14 proteins and our proximal next step is to evaluate the stability of these biomarkers over time.

Andres Hurtado-Lorenzo, PhD (14:47):
In other words, can our protein biomarker stratify patients at risk of complications, irrespective of whether the test is done at diagnosis or several months after or years after the diagnosis of Crohn's disease. And while this is important, our most critical next step is to collaborate with other available pediatric cohorts to validate the performance of this prototype test in an independent cohort, different to the risk cohort than we used to discover these prognostic biomarkers.

[MUSIC: About IBD Transition]

Amber Tresca (15:41):
So patients are pretty familiar already with how IBD is diagnosed and treated because as you mentioned, it can be invasive to say the least, but I think what they want to know is how might biomarker testing change how IBD is diagnosed and treated in the future.

Andres Hurtado-Lorenzo, PhD (15:59):
Great question as well. So if we, as researchers and pro developers are successful in discovery and validate novel biomarkers and develop related tests, I believe there are three main reasons why biomarkers might change how IBD is diagnosed and treated. And the first reason is that novel, accurate, sensitive, and specific diagnostic biomarkers can be used for minimally invasive diagnosis of IBD, as well as for faster and more accurate distinction between Crohn's disease and ulcerative colitis, which is still up to this time a challenge.

The second reason is that prognostic biomarkers can be used as indicators early in the disease of how severe will be the course of the disease, with this information doctors can make early and effective treatment decisions, providing treatments that modify the course of the disease and leading in consequence to an improved patient outcome. The discovery and qualification of prognostic biomarkers is of critical importance in the context of IBD.

Andres Hurtado-Lorenzo, PhD (17:18):
And this is because IBD patients exhibit a highly valuable disease course with some patients experiencing more aggressive disease than others, which is characterized by unremitting disease, need for treatment escalation, development of fibrotic and fistulizing complications that require surgery. So in this context, prognostic biomarkers can help clinicians take informed decisions at the early clinical window of opportunity, that window that exists after initial diagnosis, but before the onset very severe intestinal inflammation in this way, doctors can provide early aggressive immunosuppressive treatment to high risk patients in order to modify the course of the disease, while at the same time, avoiding the unnecessary exposure to side

effects and the cost of immunosuppression in those patients at low risk of aggressive or complicated disease course.

Andres Hurtado-Lorenzo, PhD (18:20):
Okay now, the third reason of why biomarkers are important in IBD is because IBD patients not only exhibit a valuable disease course, but also a valuable response to treatment and estimated 30% to 40% of patients do not respond to biologics, which are the best treatment available. And for those who respond about 30% loss respond over time. So given this reality, the identification of predicted biomarkers that can stratify patients into responders and no responders to a specific therapy will be critical to enable the concept of precision medicine, so that the right medicine can be delivered to the right patient at the right time. In the absence of biomarkers, precision medicine will only be a dream.

Amber Tresca (19:15):
So, it's really clear to me that this research will change so much about IBD and right now monitoring IBD is done with those same invasive and sometimes expensive tests. Could biomarker testing also play a role in how the disease is monitored over the lifetime of a patient?

Andres Hurtado-Lorenzo, PhD (19:34):
Yes, monitoring biomarkers will be very important in IBD. And linking this question to the previous one... Actually, this is the fourth reason why biomarkers are important in IBD. And the reason is that monitoring biomarkers could help support the periodic monitoring of disease activity in response to treatment both in the clinical practice, as well as during clinical trials of new investigational drugs in a minimal invasive way.

And this is critical because in a lot of cases, significant discrepancy exist between how a patient feels and how the disease is progressing in the gastrointestinal tract. In fact, continuous intestinal mucosa inflammation can persist even if symptoms improve. And this is associated with proof long term outcomes, in contrast reduction in mucosa inflammation and healing of the intestinal mucosa is associated with improved clinical outcome in the long term. This process is known as mucosa healing and is becoming the preferred treatment target for the so-called treat to target approach.

Andres Hurtado-Lorenzo, PhD (20:52):
However, the challenge of this approach is that currently there is not a definitive consensus on the precise definition or the best method to assess mucosa healing clinicians rely on endoscopic methods, which are invasive, prone to pull up [inaudible 00:21:12] reliability and potential for significant bias. Therefore, the discovery of the so-called monitoring biomarkers that are able to identify and quality and quantify the mucosa healing and inflammation will be highly valuable. The biomarker research field is therefore searching for minimally invasive biomarkers for monitoring disease activity and treatment response, leading to mucosa healing. And they are based on blood, urine, or ultrasound imaging, all of which could be repeated more frequently than endoscopy. So in summary, monitoring biomarkers could have the potential to improve

the way in which therapies are used in support of the emerging concept of data target and will decrease the invasiveness of endoscopies.

Amber Tresca (22:04):
Okay. This all sounds really wonderful. I'm on board, but I'm going to ask what is a difficult question to get our hands around. What might the timeline look like for biomarkers and are biomarkers being used anywhere, or is it only in clinical trials right now?

Andres Hurtado-Lorenzo, PhD (22:22):
Yeah, so definitely a challenging answer, but I could predict that within the next five years, and before the end of this decade, we will start seeing novel biomarkers based test different to fecal calprotectin or CRP implemented in the clinic to support some or most of the biomarker context of use that I have discussed in this podcast. In fact, we are already starting to see some of new biomarkers reaching the clinic prognostic tests developed by the UK company PredictImmune called PredictSURE has gained market approval in the UK. And we at the Foundation are supporting under our venture philanthropy program, IBD Ventures, a clinical study called PRECious to validate the prognostic value of this blood test in the American population in support of its regulatory approval by FDA in the United States.

Andres Hurtado-Lorenzo, PhD (23:25):
We are also sponsoring a company called Glycomine, which is developing a biomarker test called UCRI that measures free proteins in blood that could be used to monitor the healing of the mucosa in response to biological treatment, which if this is successful, will help determine early the success or failure of therapies and minimize the use of invasive endoscopies while we were discussing in the previous question. We're also aiming to perform successful validation studies in new cohort of the blood based prognostic test that we are developing at the Foundation using the Olink technology for prediction of complicated disease course in pediatric Crohn's disease and in support of the development of this prognostic test and the use in the clinical practice.

Andres Hurtado-Lorenzo, PhD (24:23):
So in summary, I believe that the time is right in terms of technological advances and knowledge to build a path for success in the IBD biomarker field, and to discover biomarkers with different context of use and clinical utility whose implementation in clinical practice will improve patient management and outcomes. Now, these biomarkers will be also critical to improve the speed, the cost, and the outcome measures of clinical trials evaluating new IBD drugs.

Amber Tresca (24:57):
This is really exciting, but I have another really big question for you. In the IBD community in the United States, a huge problem is insurance coverage, do you have any thoughts on the costs of biomarker testing and if or when insurance companies might start to cover them?

Andres Hurtado-Lorenzo, PhD (25:15):

Great. So as I disclaimer, obviously I'm not an expert in health economics, but I will speculate that depending on the type of technology used and the complexity of the test, there will be biomarker test that have different cost. So more expensive or less, for example, a gene panel that measures the expression, let's say of 15 genes in blood will be more complicated and expensive than a panel that measures only one protein in a stool or blood. In regard to coverage by insurance companies, I will highlight the following concept. And this is that currently regulatory approval of novel tests is starting to require more often than not a utility clinical trial, which means that patients are biomarker stratified, and the trial evaluates whether such biomarker based patient certification used to decide the medical treatments, not only improve patient outcomes, but also achieve this in a cost effective manner.

Andres Hurtado-Lorenzo, PhD (26:24):
So, this information is not only critical for FDA test approval, but this evidence could provide the health economics data necessary to support the concept that a biomarker that helps improve treatment outcomes by preventing trial and error of several treatment paradigms and decreasing hospitalization due to effective treatment decisions guided by biomarkers, in the long run will save tremendous cost to insurance companies related to the prescription of unnecessary treatments. And this might support the adoption and coverage of novel biomarker test. This is my rational viewpoint about this topic. However, all the aspects differing to cost effective treatment outcomes guided by biomarkers might play a role in the insurance company decision to cover or not the cost of different biomarker tests.

[MUSIC: IBD Dance Party]

Amber Tresca (27:20):
That all sounds perfectly reasonable to me. So, I hope it does come to fruition. The outcome of this research is going to change people's lives. So Dr. Hurtado-Lorenzo, thank you for talking with me today, for explaining all of this, and for everything that you're doing on behalf of patients with IBD.

Andres Hurtado-Lorenzo, PhD (27:38):
Great. It is my pleasure. And finally, I also want to thank you Amber, once again for the opportunity to talk about these relevant topics of biomarkers, which is absolutely critical to build the future of precision medicine in IBD and to improve patient outcomes.

Amber Tresca (27:59):
Hey super listener, thanks to Dr. Hurtado-Lorenzo for taking the time to explain how the research he's doing is going to change the lives of those who are touched by IBD. People who live with IBD don't often hear directly from the scientific community about all the work that's being done behind the scenes. So, it is a real privilege to bring his voice and his work to you. Links to a written transcript, everyone's social media handles, and more information on the topics we discussed is in the show notes, and on my episode, 121 page on aboutibd.com. This episode was filled with a lot of information and the links and resources I provide there will help

you sort through it all. You can follow me, Amber Tresca across all social media as About IBD. Thanks for listening. And remember until next time, I want you to know more About IBD.

Amber Tresca:
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