The Susan and Leonard Feinstein IBD Clinical Center at Mount Sinai, Marla Dubinsky, MD

ASIsT: Algorithmic Support for IBD Thera-Diagnostics

While there are a growing number of new treatments for Inflammatory Bowel Disease (IBD), we are still trying to identify how to select the best treatments for individual patients. Recently, genetic variants were discovered that affect how patients respond to two of the most common medications in IBD, which are anti-TNF alpha therapy (e.g. infliximab and adalimumab) and thiopurines (e.g. 6-MP and azathioprine). The genetic variants can also predict which side effects a patient may experience from a particular drug. However the only variant being used by doctors today is the one which determines how patients respond to the class of drugs known as thiopurines.

We are supporting a more complete approach through our partnership with Mount Sinai scientists, using automation made possible by computer programs to change how doctors treat IBD by creating what is called a “precision medicine” approach. This will apply all the known genetic variants to tailor treatment to each person with IBD. We will also be able to add any variants we may discover in the future. The bulk of current IBD therapies are part of a class of medicine called “biologics,” because they contain living things. There is clear evidence that the first biologic therapy given to a patient is the most effective one. When second and third drugs need to be given, they are not as helpful. Thus, using a kind of software called an “algorithm” to target that first therapy to a patient’s own genetic variants will lead to improved outcomes.

This work we are funding examines the use of a new clinical algorithm based on the five known variants that affect patient response to anti-TNF alpha and thiopurine therapies. The study will see if using the algorithm will change physician practice and help patients stick with a treatment program and feel better about it. It also includes a future, exploratory arm to investigate the use of the variants in trying another biologic called, ustekinumab, with the intention of making the way we use algorithms to treat IBD even more successful.

The Mount Sinai IBD Road to Prevention Research

Dr. Dubinsky has been instrumental in bringing together a range of experts from across the Mount Sinai community and the country to work together on finding effective a long

lasting solutions to complex IBD problems. Her team comprises clinicians and researchers who excel in their chosen fields, which include medicine, genetics, genomics, microbiology, and immunology. With her colleagues across Mount Sinai,

including Jean-Frédéric Colombel, MD; Judy Cho, MD; Jeremiah Faith, PhD; and Bruce E. Sands, MD, MS; Dr. Dubinsky is able to draw on a wealth of knowledge and research insights as well as share her own—increasing the impact of your funding.

A pivotal study investigated whether healthy siblings are the key to prevention. The study sequenced and analyzed fecal samples from 21 pediatric IBD patients and their first-degree relatives which were then processed to paint a picture of the microbial composition and metabolites (the substance the microbes produce) of genetically similar individuals both affected and unaffected by IBD. Genetic data was also acquired, with a focus on immunity-related genes.

This project also represented the first IBD family study examining the microbiome ever done, leading to the most significant advances in IBD microbiome research in the world. In recognition of the relevance of this study, publication of this research, titled “A Disease-associated Microbial and Metabolomics State in Relatives of Pediatric Inflammatory Bowel Disease Patients” is forthcoming in Cellular and Molecular Gastroenterology and Hepatology.

Researchers at Mount Sinai then implanted human stool samples from both affected and unaffected members of the first family study in genetically-engineered humanized mice to observe the impact on the development of IBD. In short, researchers found that stool elicits the onset of disease. The Mount Sinai team is now working to identify which bacteria can protect patients from getting disease and which bacteria cause disease in order to develop targeted fecal transplant interventions.

Over the next two years, Mount Sinai will partner with communities where IBD is very common within families. Analysis of samples from both affected and unaffected family members will yield insights into the protective patterns that prevent certain family members from developing IBD. Dr. Dubinsky and her team will then follow family members to monitor which initially-unaffected members eventually develop the disease.

The ultimate goal is individualized intervention tailored to at risk patient's specific microbial fingerprint.

Imagine a day when someone at risk of IBD—say, an unaffected brother with a "pro-IBD" microbial profile whose sister is affected—may do something as simple as take a pill to restore his microbiome's homeostasis, thereby eliminating risk for the disease. A patient who today may develop IBD could tomorrow have the power of prevention in his own hands.