**Progress Report on ASIST: Algorithmic Support for IBD Thera-Diagnostics**
**Prepared for Stacy Dylan**

## Brief Summary of the Project

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." 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 clinical "algorithm" to target that first therapy to a patient's own genetic variants will lead to improved outcomes. We further have a clinical decision support tool aimed at explaining these variants to the patient in simple terms to include them in this decision-making process.

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 future arms to incorporate further data, like data collected from the patient's skin, which may serve as a non-invasive way to have a window into the aberrant biology of the patient in the gut, to help further optimize the selection of therapy. It will also allow a framework to nimbly incorporate these precision findings into practice as there is often a delay in implementing significant findings in real-time in the clinic.

## Recent Accomplishments

While rolling out the algorithm for ASIST, gastroenterologists noted that, for patients with inflammatory bowel disease (IBD), optimized monotherapy with infliximab (i.e. infliximab without thiopurine or methotrexate but with careful monitoring of infliximab levels) was very commonly used in the United States. This strategy differed from the original study that took place the United Kingdom, which identified one of the genetic variants that can affect patients'

responses to these IBD medications and influence side effects. It was unknown at the time the impact this variant may have on patients receiving optimized monotherapy. Physicians expressed that they would rather continue to use this than combination therapy, even if recommended by the algorithm.

To learn more about the impact of the genetic variant, we completed a post-hoc analysis of existing data from a prospective study on optimized monotherapy. In a recently published analysis,[1] we found that patients with this risk variant did well when managed with proactive optimized monotherapy. Based on this feedback, we have altered the original algorithm created for ASIST, allowing physicians to select between combination therapy or proactively optimized monotherapy, as either strategy is effective. To aid discussions with patients regarding genetic testing and the genetic variant, we also consulted with a shared decision-making expert, Corey Siegel, MD, MS, who recommended incorporating an option grid into the ASIST algorithm, which helps explain the information in lay terms.

We also initiated a pilot project that uses skin taping to assess if markers from the skin, such as gene expression and proteomics, could determine if a patient was at high risk of developing a paradoxical skin reaction to anti-TNF, warranting a different therapy (ustekinumab). Skin taping—which uses a circular piece of tape—is a minimally invasive way to collect skin samples, and has been used by a collaborator within Mount Sinai's dermatology department, Emma Guttman, MD, PhD, to determine what type of skin condition a patient has. We believe, given the ties between IBD and skin conditions like atopic dermatitis and psoriasis, that the skin could be a window into the aberrant biology occurring in the intestine, and could be helpful in selecting the best therapies. We hope that this method will help us—with as little invasive testing as possible—incorporate multi-omics (genomic, gene expression, and proteomic) data into the ASIST algorithm, ultimately enabling us to choose better therapies for patients with IBD.

**Future Plans**

We are currently recruiting patients using the edited algorithm, which—as described above—now includes a choice of combination or proactively optimized monotherapy and the option grid. Depending on the results of the pilot study that uses skin taping (which already has sufficient patient participation and is being sent to Dr. Guttman for analysis), we may incorporate this in future studies.

We are working to finish recruitment of the 93 patients required to power the ASIST study by the end of 2022 to both answer our original research question looking at the use of the clinical algorithm incorporating pharmacogenomics and to answer the benefit of using a shared decision-making tool.

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[1] Spencer EA, Stachelski J, Dervieux T, Dubinsky MC. Failure to Achieve Target Drug Concentrations During Induction and Not HLA-DQA1*05 Carriage is Associated with Anti-Drug Antibody Formation in Patients with Inflammatory Bowel Disease. *Gastroenterology*. 2022.