

THE PRECISION IBD PROGRAM AT MOUNT SINAI

ACCELERATING BREAKTHROUGHS FOR PATIENTS AND FAMILIES

While research has made advances in inflammatory bowel disease (IBD)—some of which you may have experienced firsthand—we are still unable to answer questions about someone’s prognosis when diagnosed, how long they will need to remain on medication, or even what the right medication is for that individual. However, with the recent ascent of technology combined with new knowledge and insights, answers to all these questions and more are firmly in our sights, and will build on our efforts to unlock the mysteries of IBD. Driven by crucial philanthropic investments, this understanding will create new potential to bring precision medicine to people with IBD, harnessing the power of rapidly evolving technologies and creating radically improved outcomes.

*With your generous support, we seek to launch a new signature IBD program, the **Precision IBD Program**, focused on precision biology and translating that research to benefit the patient rapidly and precisely. The next cascade of breakthroughs associated with this research will transform how we diagnose, treat, and target the disease, bringing us closer to the end of IBD as we know it today.*

IBD AT MOUNT SINAI: WORLD-CLASS LEADERS IN RESEARCH, EDUCATION, AND PATIENT CARE

Mount Sinai is one of the world's undisputed leaders advancing IBD research globally combined with the largest footprint of IBD patients in the U.S., with over 10,000 patients cared for annually. Our goal at this moment is twofold: First to catch those with IBD as early as possible, to treat and target the disease with absolute precision, **personalizing therapies to an individual's genetic makeup**, quieting the disease throughout their life while optimizing health and wellness. Second, to prevent IBD from developing in the first place. These aims are within our grasp, and we are pursuing them while working to end IBD for all. Our work will catalyze stunning insights and knowledge, moving the entire field forward, towards this ultimate goal.

There is no entity better positioned to accomplish this than Mount Sinai. Nearly a century after Mount Sinai physician Burrill B. Crohn, MD, and his colleagues performed research and published a landmark 1932 article that first described regional ileitis—which would later be called Crohn's disease—Mount Sinai's research-driven treatment of IBD remains the global standard-bearer in the field. Mount Sinai physicians care for more patients with IBD at every stage of life than any other medical center in the country. Our internationally-renowned team of experts is privileged to care for one of the largest, most diverse patient populations in the country. Gastroenterologists from around the world send their most challenging cases to us and they look to Mount Sinai for the latest in IBD research and treatment strategies. In 2022, *Newsweek* ranked The Mount Sinai Hospital #3 in the world for GI care.

Our clinical team is only equaled by our scientists, who nimbly advance high-risk/high-reward research, rapidly and seamlessly bringing transformative breakthroughs from the labs to our patients.

We are advancing multiple interlocking IBD research initiatives, collaborating throughout Mount Sinai with our multidisciplinary teams in genomics, immunology, and multi-scale biology. To substantially accelerate this work and realize the power and promise of precision medicine for those we serve, we must deepen and expand our efforts with an emphasis on understanding the individual differences in the biology of IBD that can inform their care. Armed with this critical knowledge, we will be able transform our approach and, most importantly, the lives of people with IBD now and those at risk in the future.

A PATIENT-CENTRIC APPROACH: USING BOLD TECHNOLOGIES TO BENEFIT PATIENTS

We will take a patient-centered approach focused on precision biology, translating that research to rapidly and precisely benefit the patient. We will use every tool in our arsenal, analyzing tissue from the gut barrier to the skin barrier, combining computational data science with translational biology, with the goal of being able to tailor and personalize individual approaches for each patient. This will **ensure the right therapy for the right patient**, understanding the right dose at the right time, and creating targeted therapeutics to regulate the system, controlling and quieting active inflammation. At the same time, we will use precision medicine to intercept and reverse disease in its earliest stage—before symptoms have even begun—essentially reversing what would have become full blown IBD. We believe that this work, combined with multiple scientific efforts and global collaborations currently underway, will reveal staggering insights into

why and how the disease develops. This will help us and researchers around the globe identify new and novel approaches towards ending IBD as we know it for all.

Our multidisciplinary IBD team utilizes a comprehensive strategy to rapidly bring scientific breakthroughs to our patients. We are developing new tools and technologies at Mount Sinai, backed by our research, which are enabling us to practice precision medicine approaches now. Using these tools, we are creating personalized treatment plans that focus on early intervention, preventing serious bowel damage, helping patients keep debilitating symptoms or disability at bay. At the same time, we are actively engaged in next-generation research that seeks to determine how we can use it to catch IBD early, before symptoms develop, and unlock the mysteries of the disease.

EARLY DETECTION AND PREVENTING DISEASE PROGRESSION

Early detection and treatment can prevent progression of IBD. It often takes years of symptoms, suffering, and permanent bowel damage before a patient is diagnosed with Crohn's disease. At Mount Sinai, we are performing research in siblings from families at high genetic risk of developing Crohn's disease to identify pre-clinical signs and predictors before symptoms even occur. Drawing on our unique cohort of families with three or more first-degree relatives with IBD, we are following siblings, screening for early bowel changes every four to six months for a four-year period. And we are doing this with the use of non-invasive ultrasound technology to detect early signs of inflammation in the intestines. We are currently the first center in the U.S. to use ultrasound to detect and monitor inflammation at the point-of-care, in real-time, making treatment decisions based on findings at routine clinic visits within a context of thorough research.

The standard of care in the U.S. currently means being monitored with repeated blood tests, stool studies, MRI or CT scans, and colonoscopies. This is invasive, expensive, and often requires bowel preparation, sedation, anesthesia, intravenous contrast agents, and radiation. If ultrasound yields results in our research, it could be a game-changing tool for high-risk families to follow siblings, eliminating the need for repeated colonoscopies and diagnostic delays, allowing us to intervene early before complications or even symptoms develop. This could potentially prevent any chronic damage to the intestines and lead to healing that lasts a lifetime.

PRECISION IBD: PERSONALIZED TREATMENT OVER TIME

One of our main goals is to understand individual biology to match the right treatment, to the right person, with the right dose, at the right time. Our team is using automation made possible by computer programs to change how doctors treat IBD by creating a precision medicine approach to apply all the known genetic variants and associated 'omics 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 are produced by 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.

We are using this new clinical algorithm, developed by our team at Mount Sinai, based on the genetic variants that affect patient response to biologics and immune modulator therapy. As we use this algorithm with patients, we are diligently studying it to see if it will change physician practice and help patients stick with a treatment program. We are also investigating 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.

While there are a growing number of new treatments for IBD, including new classes of oral agents, we are identifying how to select the best treatments for individual patients. Using powerful new stem cell biologic approaches, we can develop ‘patient avatars’ whereby patient-specific therapies may be tested for their capacity to predict treatment responses. Treatment decisions based on an individual’s genetic and immunologic makeup taking into account their environment and various exposures which will significantly improve long-term outcomes, lengthening remission and reducing complications and surgeries for people with IBD.

For young adults, being diagnosed with a chronic disease inevitably brings anxiety and concern. At Mount Sinai, we are boldly leading the way in providing patients and families with the best information, coping strategies, and hope for the future. The Precision IBD Program will help us chart this course, creating highly accurate disease prediction tools and bringing us closer to our goal of knowing the exact treatment pathway for these individuals based on their genetic and biological makeup. The ultimate goal of reversing disease development and restoring the individual to health, completely free of disease, is also on the near horizon.

THE IMPORTANCE OF IBD PREDICTION

Beyond providing relief for patients with more advanced treatments, we are now focused on the next phase: prediction. This means targeting the pre-clinical phase of disease, or the window between disease initiation and actual diagnosis where risk factors converge into full-blown disease. We are advancing multiple research initiatives to uncover the genetic, biologic, and environmental factors that contribute to the development of IBD in this critical stage. These can help us to predict not only who will develop IBD, but when it will start, along with disease severity, triggers, and other information that will lead to more precise and effective care.

Accurate IBD prediction will allow us to not only design therapies that minimize risk or attenuate or delay the onset of disease, but also determine at which stage of development they are most impactful. Also, by following patients over time, we will identify markers that indicate the transition from no disease to active disease.

Mastering IBD prediction will be essential in the near future, as experts predict an exponential increase of patients with IBD across the world. Adding complexity is the aging of current IBD patients who may face additional health conditions later in life, along with the uniquely high mental health burden of the disease. With global issues of accessibility, affordability, and variation in health care resources, there is a pressing need for prevention to not only improve the lives of patients, but to lessen the burden on health care systems around the world.

A SIGNATURE IBD PROGRAM

The Precision IBD Program will serve as Mount Sinai's signature IBD program, focused on the most innovative and novel approaches that will change the lives of patients with IBD and those at risk in the future. The program will be led by **Drs. Marla Dubinsky, Bruce Sands, and Judy Cho**, all of whom are the foremost leaders in IBD, both at Mount Sinai and internationally. It will enable the growth of the team, including the recruitment of key expertise in computational and translational science, while fueling and accelerating powerful research platforms and providing the resources for big data and novel technology, equipment, and research infrastructure.

It will also include the work of our young scientists and our clinicians, who apply many of these groundbreaking innovations from the laboratory to the care of young adults newly diagnosed with IBD. This broader "whole patient" approach remains a hallmark of the IBD Center at Mount Sinai and has become a model for IBD care in the U.S. and around the world.

This work sits at the intersection of GI, multi-scale biology, personalized medicine, and immunology. Year 1 will integrate powerful existing and new datasets being newly built by the work of our clinicians and young scientists. This effort is particularly timely, given the imminent FDA approvals of new classes of IBD agents. This will require the collection of additional data to define protocols for new treatment paradigms for patients at Mount Sinai and worldwide. In addition to our high ranking for GI care internationally, the Mount Sinai IBD Center currently holds six National Institutes of Health (NIH) Career Development Awards, assuring that the future leaders in IBD research, education, and clinical care will be centered at Mount Sinai.

PHILANTHROPIC OPPORTUNITY

All too often, research with the power to transform a field of medicine—and people's lives—can languish due to lack of funding. This is why we are seeking philanthropic partners who are as visionary as our doctors and scientists, and who can recognize the opportunity and urgency at hand. Creating the **Precision IBD Program at Mount Sinai** at this moment will have a seismic impact that will reverberate throughout every level of GI care, both at Mount Sinai and throughout the world.

We are pleased to share that we have secured a lead gift for this work. With your generous investment in the range of \$500-\$1M over three to five years, the Program will become a beacon, attracting yet more philanthropy and crucial grants from the NIH. More importantly, this is a chance to definitively change the lives of those with IBD now and in the future, leading to the ultimate eradication of this disease. **Thank you for your consideration of this remarkable program.**

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