Stony Brook Medicine

August 30, 2019

Title: Fecal Microbial Transplantation in patients with Crohn's disease
ClinicalTrials.Gov NCT03267238

Please find enclosed the following documents:

1. IRB approved protocol	07/24/2019
2. Recipient permission-consent form	07/03/2019
3. Recipient assent form	07/03/2019
4. Donor permission consent form	07/03/2019
5. Donor assent form	07/03/2019

Sincerely,

Ellen Li, MD, PhD.
Professor of Medicine/ Division of Gastroenterology
Stony Brook Medicine

Stony Brook University Hospital
Department of Pediatrics, Division of Gastroenterology
Health Science Tower
101 Nicolls Road
Level 11 Room 080
Stony Brook, New York 11794-8111
P: 631-444-7269 F: 631-444-6045

Protocol

TITLE: Fecal microbial transplantation in patients with Crohn's disease.
ClinicalTrials.gov ID: NCT03267238, IND 16795

INVESTIGATORS:

Ellen Li M.D., PhD (Principal Investigator)	Professor of Medicine/Gastroenterology
Anupama Chawla M.D. (co-PI)	Professor of Pediatric Gastroenterology
Jeffrey Morganstern M.D.	Associate Professor of Pediatric Gastroenterology
Grace Gathungu M.D.	Assistant Professor of Pediatric Gastroenterology
Lesley Small-Harary M.D.	Assistant Professor of Pediatric Gastroenterology
Michelle Tobin M.D.	Assistant Professor of Pediatric Gastroenterology
Jonathan Buscaglia M.D.	Associate Professor of Medicine/Gastroenterology
Ramona Rajapakse M.D.	Associate Professor of Medicine/Gastroenterology
Juan Carlos Bucobo M.D.	Assistant Professor of Medicine/Gastroenterology
Tyson Collazo M.D.	Assistant Professor of Medicine/Gastroenterology
Lionel D'Souza M.D.	Assistant Professor of Medicine/Gastroenterology
Alexandra Guillaume M.D.	Assistant Professor of Medicine/Gastroenterology
Bradley Morganstern M.D.	Assistant Professor of Medicine/Gastroenterology
Farah Monzur M.D.	Assistant Professor of Medicine/Gastroenterology

A. SPECIFIC AIMS:

The following hypothesis will be tested in this study:

1. Fecal microbiota transplantation is a safe, tolerable procedure.

2. The fecal microbial diversity, composition and function in stool recipients after fecal transplantation will change to a similar microbial diversity, composition and functionality as found in donor stool.

Primary objectives:

1. To determine the short term safety and tolerability of fecal microbiota transplantation up to 12 weeks post-transplant in patients with Crohn's disease.

Secondary objectives:

1. To determine the long term safety and tolerability of fecal microbiota transplantation (FMT) up to one year post transplant in patients with Crohn's disease

2. To compare microbial diversity, composition and function in healthy donor stools compared to pre-FMT recipient stools collected from patients (recipients) with Crohn's disease

3. To compare microbial diversity, composition and function in healthy donor stools and pre-FMT recipient stools with 1 week post-transplant recipient stool samples collected from patients (recipients) with Crohn's disease

4. To compare microbial diversity, composition and function in healthy donor stools and pre-FMT recipient stools with 12 week post transplant recipient stool samples collected from patients (recipients) with Crohn's disease

5. Stool calprotectin levels will be measured in the recipient at baseline pre-FMT, 1 week and 12 weeks post FMT to determine if FMT causes a statistically significant change.

B. BACKGROUND AND SIGNIFICANCE

Clostridium difficile is the leading cause of antibiotic-associated diarrhea with increasing infection rates and economic burden in developed countries. [1-4] According to the United States Healthcare Cost and Utilization

Project Kids' Inpatient Database (HCUP-KID), there has been an increase in pediatric *Clostridium difficile* from a rate of 7.24/10000 hospitalizations in 1997 to 12.80/10000 hospitalizations in 2006.[5] As the *C. difficile* epidemic worsens, the numbers of failed treatments and patients who experience relapses or recurrences also continues to grow. Patients being treated with usual first-line treatments such as metronidazole and vancomycin are encountering "hypervirulent" and resistant strains of *C. difficile* such as North American Pulsed Field type 1 (NAP1), restriction-endonuclease analysis (REA) type BI, or polymerase-chain reaction ribotype 027 (referred to collectively as the NAP1/B1/027 strain).[6] The NAP1/B1/027 strain of *C. difficile* has been deemed "hypervirulent" for its ability to produce binary toxin *C. difficile* 126 adenosine diphosphate-ribosyltransferase not typically found in other strains of *C. difficile*. This, in combination with its ability to produce excessive quantities of enteroxins A and B, compared with other strains of *C. difficile*, makes it hypervirulent[7] Even the newer agent, fidaxomicin, which was approved by the FDA in 2011, has a similar effectiveness to vancomycin with respect to the clinical resolution of acute diarrheal disease due to *C. difficile*.[6] The problem is that after completing antibiotic treatment 20-35% of CDI patients experience a recurrence of CDI. Vancomycin tapers or fidaxomicin may be associated with a lower rate of recurrence. Once recurrent CDI occurs, 45-65% of patients will continue to experience recurrent infections over several years and have a higher mortality.[7-11]

Fecal microbial transplantation (FMT) of healthy donor stool into the patient's gut has emerged as one of the most effective treatments of recurrent CDI.[12-14] Patients with inflammatory bowel diseases (IBD), particularly ulcerative colitis (UC) and indeterminate colitis (IC) but also Crohn's disease (CD), are at increased risk of developing CDI.[15-20] FMT is also highly effective in treatment of recurrent CDI with IBD patients, although the effectiveness may be reduced compared to patients with recurrent CDI without IBD.[21-23] While some patients with recurrent CDI and IBD appear to benefit overall from the FMT, there have been reports of exacerbation of IBD after eradication of CDI, although it remains to be determined whether FMT contributed to the exacerbation.[24,25]

Thus far studies on the effectiveness of FMT in the treatment of IBD without CDI, have utilized different protocols and have yielded mixed results.[26-38] Performing FMT in patients with IBD without CDI appears to be safe. As noted above, a review of FMT trials conducted on IBD patients with and without CDI noted that post-FMT exacerbation of IBD patients without recurrent CDI appeared to occur less often than in IBD patients with recurrent CDI.[25]

Colonoscopic instillation into the right side of the colon of ~50 g stool is associated with the highest rates of preventing further CDI (~90%). The effectiveness of the oral capsule route, may be related to the total amount of stool ingested and ranges from 68 to greater than 90%.[39-41] In a very recent randomized trial of oral capsule vs. colonic instillation of 150g of stool, ingestion of oral capsules was noninferior to colonoscopic administration (96% in both arms).[41]

FMT is believed to restore the normal microbiological balance in the recipient primarily by transferring microbial components of the donor stool, although there is some evidence that non-microbial molecular components, such as short-chain fatty acids and bile acids may also play a role.[42,43] The normal microbiological balance may be perturbed in patients with C. difficile infection and or IBD.[44]

The overall goal of this study protocol registered as ClinicalTrials.gov ID: NCT03267238, 973349, is to better define the microbial and non-microbial components in donor stool that contribute to post-FMT changes in the microbiome in Crohn's disease:

D. RESEARCH DESIGN AND METHODS

1. Rationale/overview:

It is important to emphasize that this study is not designed to investigate clinical efficacy. FMT clinical efficacy for preventing further recurrence of CDI is now well established in the literature for recipients with recurrent or refractory CDI not responding to standard medical treatment, with and without IBD. However it remains to be determined what the key microbial or nonmicrobial components of the donor stool contribute to clinical efficacy. However, the efficacy of FMT in Crohn's disease remains to be determined. Before organizing a randomized clinical trial to test efficacy, it is critical to first define the baseline differences in microbial diversity, composition and function between Crohn's disease recipients and healthy donors. Consequently this study is designed to:

a. Measure baseline microbial imbalances in Crohn's disease. Measure whether FMT will alter recipient microbial imbalances one week and 12 weeks after the procedure.

b. Measure short (12 weeks) and long term (one year) safety and tolerability of FMT in Crohn's disease.

2. FDA statement on requirement for IND for FMT.

The March 2016 Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies Draft Guidance for Industry[45] states: "We, FDA or Agency, are informing members of the medical and scientific community and other interested persons that we intend to exercise enforcement discretion under limited conditions, regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat Clostridium difficile (C. difficile) infection not responding to standard therapies. FDA intends to exercise this discretion, provided that: 1) the licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. The consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and a discussion of its reasonably foreseeable risks; 2) the FMT product is not obtained from a stool bank; and 3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product for treatment of the patient. A stool bank is defined, for the purpose of this guidance, as an establishment that collects, prepares, and stores FMT product for distribution to other establishments, health care providers, or other entities for use in patient therapy or clinical research. An establishment that collects or prepares FMT products solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance. FDA does not intend to extend enforcement discretion for the IND requirements applicable to stool banks distributing FMT products. Such distributions are subject to the requirements that a sponsor, typically the stool bank, have an IND in effect before distributing the FMT product to investigators for administration to subjects in accordance with the investigational plan under the Public Health Service (PHS) Act (42 U.S.C. 262(a)(3)) and 21 CFR Part 312. However, as described in this guidance, an IND sponsor may request a waiver of certain IND regulations applicable to investigators for those licensed health care providers receiving FMT product to treat patients with C. difficile infection not responsive to standard therapies. (See 21 CFR 312.10). FDA has developed this policy to assure that patients with C. difficile infection not responding to standard therapies may have access to this treatment, while addressing and controlling the risks that centralized manufacturing in stool banks presents to subjects. FDA intends for this to be an interim policy, while the Agency develops a comprehensive approach for the study and use of FMT products under IND." At this time, since administration of FMT products from stool bank(s) has not been approved by SBUH regulatory committees in the Endoscopy suite in Stony Brook University Hospital, administration of FMT products from stool banks cannot be offered to recipients with recurrent CDI.

An IND (IND 16795) was obtained from the FDA for performing FMT on CD recipients without recurrent or refractory CDI not responsive to standard medical treatment.

3. Research Site(s):

The following research sites are all located within Stony Brook University Medical Center (SBUMC).

a. *Patient and donor recruitment and screening*. This will take place at Stony Brook University Medical Center (SBUMC) in both the hospital and outpatient Pediatric and Adult Gastroenterology Clinic setting. The Pediatric Gastroenterology Clinic is located at 4 Technology Drive, Suites 250 and 270, across the street from the Adult Gastroenterology Clinic, which is located at 3 Technology Drive, Suite 300.

b. *Preparation of donor stool for FMT.* The donor stool will be prepared for colonoscopic instillation following standard operating procedure, as described below, in a biosafety cabinet located within Dr. Li's laboratory within the Department of Medicine/Division of Gastroenterology research space located in in the Health Sciences Center Building (room HSC T17-080). The research laboratory in the HSC Building is connected by a bridge to Stony Brook University Hospital, allowing for rapid transport of the stool instillate to the Endoscopy unit on the 14th floor.

c. *Colonoscopic instillation of donor stool*. Colonoscopic administration of the FMT will be performed in the Stony Brook University Endoscopy Unit located

d. Processing of stool samples for microbiome analysis. The research stools samples obtained from the donor (at the time of transplant), and the recipient (pre-FMT, 1 week post-FMT, and 12 weeks post-FMT) will be processed in Dr. Li's laboratory within the Department of Medicine/Division of Gastroenterology research space

4. Participants

Each FMT will involve two participants, the **recipient** of the FMT, and a healthy known **donor** selected by the recipient or recipient's parents (pediatric recipient age <18).

a. Inclusion and exclusion criteria for recipients with Crohn's disease requiring step up therapy beyond 5-ASA or mesalamine therapy alone.

Inclusion: (see Appendix B)

i. Recipient age ≥ 7 years of age.
ii. Recipients diagnosed with CD by primary gastroenterologist as documented by colonoscopy, pathology and imaging findings based on review of medical records.
iii. Recipients who have undergone therapy beyond 5-ASA (mesalamine) treatment (e.g. treated with steroids, immunomodulators, biologics in the past).
iv. Recipient agrees to share medical records for FMT consultation at SBUMC

Exclusion: (see Appendix B)

i. Recipient age < 7 years of age.
ii. Scheduled for abdominal surgery within the next 12 weeks
iii. Pregnancy
iv. Grade 4 anemia (Hemoglobin < 6 g/dL)
v. Grade 1 neutropenia (Absolute Neutrophil Count <1500)
vi. Known diagnosis of Graft vs. host disease
vii. Major abdominal surgery within the past 3 months
viii. Administration of any investigational drug within the past 2 months
ix. Use of a TNF-α antagonist within 2 weeks of the proposed date of transplantation
x. Bacteremia within past 4 weeks (28 days)
xi. Any previous FMT

b. Inclusion and exclusion criteria for healthy donors.

Inclusion (see Appendix C):

i. Spouses, parents, family members, friends, or associates of the stool recipient who consent to completing donor screening questionnaire
ii. Age ≥ 7 years of age
iii. Agree to undergo laboratory testing for known pathogens within 4 weeks of FMT procedure (screening tests listed below).

Exclusion:

i. Potential donors who answer "yes" to and one of the following donor screening questionnaire questions (see Appendix C):

- Are you younger than 7 years of age?
- Do you have known HIV, tuberculosis, Hepatitis B or Hepatitis C infections?
- Have you been exposed to HIV, tuberculosis or viral hepatitis (within the past 12 months)
- Do you engage in any high-risk sexual behaviors (examples: sexual contact with anyone with HIV/AIDS, tuberculosis or hepatitis or engage in sex for money?
- Have you used illicit drugs within the past 3 months?
- Have you had a tattoo or body piercing within the past 6 months?
- Have you ever been incarcerated?
- Have you been to an area with Mad Cow disease (risk factor for Creutzfeld-Jakob disease?)
- Have you traveled within the past 3 months to developing countries?

- Do you have a history of inflammatory bowel disease or chronic diarrhea (i.e. > 3 loose stools daily for the past 3 months?
- Do you have a history of gastrointestinal malignancy or known polyposis?
- Have you needed to use systemic antibiotics within the preceding 3 months?
- Are you currently using any major immunosuppressive medications (e.g. calcineurin inhibitors, systemic anti-neoplastic, exogenous glucocorticoids, biologic agents?)
- Do you have eczema, allergies, or asthma requiring steroids or immunomodulating therapy?
- Do you have autoimmune disease, metabolic syndrome, chronic pain syndrome, neurologic or developmental disorder?
- Do you have contact with hospital patients?
- Have you been hospitalized or in a long term care facility in the past 6 months?
- Do you attend outpatient medical or surgical clinics more than once a month?
- Have you engaged in medical tourism in the past 6 months?

ii. Potential Donors who have positive laboratory testing for any one of the following tests :

- *C. difficile* toxin B
- Salmonella
- Shigella
- Campylobacter
- Shiga toxin (screen for Sorbitol negative E. coli or E. coli O157-H7)
- Vancomycin resistant enterococci (VRE)
- Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Giardia antigen
- Modified acid fast stain for Cryptosporidia, Cyclospora, Isospora
- Ova and parasite (including trichrome)
- HIV, type I and type II screen
- Hepatitis A IgM
- Hepatitis B (HepBs Ag, anti-HepB Core IgM)
- Hepatitis C Ab
- Syphilis RPR
- Syphilis Fluorescent treponemal antibody FTA-ABS
- Tuberculosis (QuantiFERON®-TB Gold)

iii. Donor reports having fever (T > 100.4 ^{o}F) within two weeks of FMT.

iv. Donor reports of having a runny nose and cough within two weeks of FMT

v. Donor reports ingesting foods that the recipient has an allergy to within one week of FMT

vi. Donor reports having diarrhea within two weeks of FMT.

vii. Donor stool appears grossly abnormal (e.g. presence of blood, etc) prior to processing for colonoscopic instillation.

5. Protocol for Recipient Involvement (CD without CDI). (see Appendix D for flow sheet)

Pre-FMT events for recipient.

a. Initial pre clinic visit screening of recipient eligibility. Recipients, families and referring physicians learn about the study through the ClinicalTrials.gov registry and have contacted by e-mail either the research coordinator, Dr. Chawla or Dr. Li for further information on **ClinicalTrials.gov ID: NCT03267238, IND 16795**. The research coordinator (or Drs. Li and Chawla) reply to the inquiry using a template e-mail that provides further information on the trial (see Appendix E). Pre-screening of recipients is carried out by Drs. Chawla (recipients age ≤18 y) and Li (recipients age ≥18 y) after they have reviewed the recipients' medical records to determine eligibility. **Dr. Chawla or Dr. Li will contact the primary gastroenterologist to discuss whether the patient's gastroenterologist feels that FMT is an appropriate intervention in this patient, discuss the possibility that the patient could flare post-FMT and to discuss whether the primary gastroenterologist agrees to clinically manage the patient's IBD after FMT**.

If the recipient is deemed eligible for the study based on pre-screening, he/she or the guardians of the patient will be given the donor screening criteria (Appendix C) and asked to identify a potential donor. The donor is deemed eligible if he/she answers **no** to each question on the checklist. .The

recipient and donor will then be scheduled to be seen for formal screening, including a physical exam in Adult or Pediatric GI clinic by either Dr. Li or Dr. Chawla, respectively.

b. Screening and recruitment of recipient in clinic. The recipient will be evaluated and recruited in a face to face encounter with either Dr. Chawla or Dr. Li. At this screening and recruitment clinic visit, additional baseline clinical data will be collected to confirm recipient eligibility (see Appendix F). The information will include past medical history in terms of previous episodes of *C. difficile* associated disease and/or inflammatory bowel diseases (age of diagnosis, duration, medications) and standard clinical information such as age, sex, race, disease phenotype, medications, and smoking history. The recipient and family members will be instructed on how to prepare for the colonoscopy procedure. If they consent to provide research samples and dietary information, they will be instructed on how to collect the research stool samples, complete the daily food diary one week prior to the FMT samples, reminded to stop antibiotics 48 h before the procedure. The colonoscopic FMT procedure will be scheduled with colonoscopists on the study team, so as to allow for donor screening results to be sent to the study team for review prior to the procedure.

c. 7 days before FMT- initiate recipient daily food diary: The recipients in all three groups will be asked to record their diet using a diary provided by the investigators, during the week that they provide stool samples (Appendix G). The purpose of this is to document the typical diet of the recipient. The ingested foods may also impact the microbial load of the recipient stool

d. 2-5 days before FMT-recipient instruction: The recipients will be contacted by phone to review study instructions. CDI recipients will be reminded again to stop antibiotics used to suppress CDI at least 48h before transplant (Appendix H).

e. 1 day before FMT - Collection of recipient pre-FMT research stool sample: The kits given to the recipient will include gloves, a commode specimen collection system, two specimen containers, biohazard bag and refrigerator packs to keep the stools cold during transport to the endoscopy suite. One of the specimen containers will be empty and the second will be filled with 10 ml RNAlater (Qiagen), an RNA stabilization solution, to better improve recovery of bacterial and human nucleic acids during the transport period.

f. 1 day before FMT- Recipient bowel prep for colonoscopy: The stool recipient will be reminded about instructions for a bowel prep based on the patient's weight. Participants and/or guardians will be told that in order to properly visualize their intestines, they must be "prepped" or flushed of their contents. These medications will cause diarrhea which is the desired effect. The recipient should be in an area with easy access to the bathroom when the medication is given. The goal is to be passing clear fluid without any formed stool. The recipients will be told to call the study coordinator if this does not occur, so that it can be determined whether any additional medications are necessary for preparation**. Once the prep has begun, the recipient will be told to be on a diet consisting of clear liquids only. Clear liquids are those that they can see through and they will be told to avoid red, orange or purple liquids.** Acceptable liquids include water, ginger ale, chicken broth (no chicken or noodles), apple juice, Pedialyte, or jello. **For the last 7 hours prior to the procedure, the recipient should have nothing to eat or drink.** Medications may be taken with a very small amount of water. The colon cleanout prep will be determined by the patient's gastroenterologist. The recipient should be passing clear stools by 5 PM day before FMT. If the recipient is not passing loose to watery clear stools by this time, they will be told to call the study coordinator or principal investigator.

Day of colonoscopic FMT for recipient.

g. Day of FMT, undergoing colonoscopic FMT and having research blood sample drawn in SBUMC Endoscopy unit.

Pre-procedure. The recipient is consented for colonoscopy by the colonoscopist performing the procedure in the pre-procedure area of the Endoscopy Suite. Female recipients of child bearing age will undergo poc urine pregnancy test, and if positive the procedure will be aborted. Research blood samples (total 20 ml) will be collected either during insertion of the IV in the pre-procedure area, or drawn separately shortly after the procedure, while the patient is still sedated.

Procedure. The colonoscopist will record the appearance of the colon to the terminal ileum. The colonoscopist will assign a Simple Endoscopic score for Crohn's disease (see Appendix I).[46] Upon reaching the ileum or the cecum, the donor stool (50-100 g in 250 to 300 ml of sterile saline, see below for standard operative procedure for preparing stool infusate), will be infused into the ileum and/or the cecum. No other colonoscopic intervention (e.g. biopsy or polypectomy) will performed during the procedure. If there is a colonoscopic finding that the colonoscopist feels needs to be

immediately addressed for clinical care by a therapeutic intervention including biopsy, then the FMT will be aborted and the stool infusate will not be administered.

h. *Post procedure*. The recipient will be placed in the right lateral decubitus position and monitored for at least an hour in the post procedure area of the Endoscopy suite, prior to discharge. The recipient will be instructed on collection of the 1 wk and 12 wk post-FMT research stool samples, and be given the stool collection kits to bring home after discharge from the Endoscopy suite. Each recipient will receive a diary card (Appendix J) where he/she or the recipient's guardian will note when the stool recipient experiences a new symptom or exacerbation of current symptoms. This diary card will be reviewed during the followed up phone calls.

Post-FMT events for recipient.

i. 1 day post-FMT. The recipient and/or guardian are contacted by phone by the study team in order to complete the Day after Transplant Case Report Form (see Appendix K).

j. 1st week post-FMT collection of recipient food diary and 1 wk post-FMT research stool sample. The recipient/family will complete a one week daily food diary during the week post-transplant and collect the 1 wk-post FMT research stool sample which will be shipped overnight in refrigerator packs to Dr. Li's research lab.

k. 1 week to 12 weeks post FMT. - weekly phone follow up of recipient. The recipient and/or recipient's (pediatric recipient) guardian are contacted by phone by the study team weekly during the first 12 weeks post-FMT to complete the Follow up Phone Call/Adverse Event Form, Appendix L). The forms contain a prompt to inform the Principal Investigator of any adverse events. Patients will be triaged to either the Emergency Department or to Adult or Pediatric Gastroenterology Clinic if any concerning adverse events occur. Any serious adverse events (Grades 3,4,5) will be documented (Appendix M), evaluated by the Principal Investigator and reported immediately to IRB as well as Safety Monitoring Committee.

l. 12 week post-FMT - collection of recipient food diary and 12 week post-FMT research stool sample. . The recipient/family will complete a one week daily food diary during the week post-transplant and collect the 12 wk-post FMT research stool sample which will be shipped overnight in refrigerator packs to Dr. Li's research lab. 3-4 mo post FMT flexible sigmoidoscopy. If the primary gastroenterologist caring for the patient, schedules the patient for a follow up flexible sigmoidoscopy, we will request that the colonoscopist obtain a Mayo endoscopic subscore during the procedure.

m. 4 mo to 12 mo post-FMT. – monthly phone call follow up of recipient. The recipient and/or recipient's (pediatric recipient) guardian are contacted by phone by the study team monthly between 4 and 12 months post-FMT to complete the Follow up Phone Call/Adverse Event Form (Appendix LI). Any serious adverse events (Grades 3,4,5) will be documented (Appendix M), evaluated by the Principal Investigator and reported immediately to IRB as well as Safety Monitoring Committee.

6. Protocol for Donor Involvement. (See Appendix D for flow sheet)

Pre-FMT events for donor.

a. Screening and recruitment of potential donor in clinic. Once the recipient has been entered into the study, the recipient will identify the donor. If the donor is age > 18 y will be screened and evaluated by Dr. Li in the Adult Gastroenterology Clinic (see Research Site, section D.3) with a complete history and physical to ascertain eligibility. If the donor is age ≥7 y and ≥ 18 y, the donor will be screened and evaluated by Dr. Chawla in the Pediatric Gastroenterology Clinic (see Research Site, section D.3) with a complete history and physical to ascertain eligibility.The donor will be consented to participate in the study, which requires undergoing stool and serological testing to assess for infectious pathogens that may theoretically be passed from the donor to the recipient. The donor (as well as the recipient) will sign an acknowledgement form that if medical insurance does not cover the costs of these tests, the costs of the donor screening tests will be borne by the recipient or donor. (The study team is in the process of applying for research grant funding that will cover the costs of donor screening for pathogens, but currently there are no research funds available to cover these costs). Once the donor has consented to the study, the donor will be instructed on collecting the stool to be used for the transplant, completing the one week food diary prior to providing the sample. Dr. Li OR Dr. Chawla will order the following laboratory tests for the donor to complete before the colonoscopic FMT is performed:

Stool tests:

- *C. difficile* toxin PCR (CPT 87493)
- Routine stool culture screen (CPT 87046) - includes Salmonella, Shigella, Campylobacter, Sorbitol negative E. coli or E. coli O157-H7 (Shiga toxin)
- Giardia Ag EIA (CPT 87328)
- Modified acid fast stain of stool (CPT 87015/87207) Cryptosporidia, Cyclospora,
- Ova and parasite with trichrome (CPT 87177) includes Isospora
- Vancomycin resistant enterococci (VRE), (CPT 87081)
- Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL), (CPT 87184)
- Carbapenem-resistant Enterobacteriaceae (CRE) , (CPT 87081)
- Methicillin-resistant Staphylococcus aureus (MRSA) , (CPT 87081)

Blood tests:

- HIV type 1 and type 2 screen (CPT 86701/86702)
- Acute Viral Hepatitis Panel: Hepatitis A IgM, Hepatitis Bs Ag, Hepatitis Bc IgM, Hepatitis C Ab (CPT 80074)
- Syphilis Rapid Plasma Reagin or RPR (CPT 86592)
- Fluorescence Treponemal Ab or FTA-Abs (CPT 86781)
- Tuberculosis (QuantiFERON®-TB Gold) (CPT 86480)

The laboratory test results must be dated <u>within 4 weeks</u> of the day the colonoscopic FMT is performed. The investigators are in the process of applying for grant support in order to cover the costs of donor screening, since this is not universally covered by medical insurance.

If the donor tests positive for a potential pathogen, Dr. Li or Dr. Chawla will inform the donor of the test results and will ask for the contact information for the donor's PCP to forward the test results to. The donor will be counseled to follow up with PCP to discuss the test results and the need for any further testing or treatment.

a. <u>7 days before FMT - initiate donor daily food diary</u>. The donor will initiate recording daily food diary and avoid ingesting any foods the recipient is allergic to. The ingested foods may also impact the microbial load of the donor stool..

b. <u>2-5 days before FMT – donor instructions</u>. The study team will contact the donor by phone to check that the donor has initiated the daily food diary, has not been febrile T > 100.4^{o} F within 2 weeks of the procedure, and has avoided ingesting any of the recipient's food allergens during the week prior to the transplant (see Appendix N).

c. <u>1-day before FMT – initiate collection of donor stool</u>. The donor will have been given two stool collection kits at the initial clinic visit. The donor is instructed to collect one stool within 24 h before the procedure and to keep the stool refrigerated with the refrigerator packs. If possible, the donor is instructed to collect a stool within 6 h before the procedure and kept the second stool refrigerated with the refrigerator packs. The donor will also have been instructed to aliquot research stool samples at both time points into specimen jars, one plain and the other filled with 10 ml of RNAlater as described for the recipient in section **D.5**.**e**. The donor is instructed to bring, or have the recipient bring both stool samples to the Endoscopy Suite for the research team to pick up 2 h before the FMT procedure is scheduled.

d. <u>Day of FMT. – Collection and evaluation of donor stool</u>
<u>*Preprocedure*</u>. The donor (or the recipient on behalf of the donor) will deliver the stools to the Endoscopy Suite for the research study team to pick up and process 2 h before the FMT procedure. The study team will complete Day of Transplant Donor Checklist Form (Appendix O) either face to face or by phone contact with the donor, to make sure no donor exclusions apply, prior to processing the stool to prepare the stool infusate, as described in the next section.

ii. **Protocol for preparation of donor stool infusate for colonoscopic infusion.**

The donor stool (refrigerated not frozen) is transported by the study team to Dr. Li's laboratory and processed for infusion via colonoscopy following standard operating procedures as previously described:[44]

- Stool preparation will occur in the biological safety hood
- Universal precautions will be adhered to. Those involved with mixing and/or handling the fecal transfusion material will wear a fluid-resistant gown, gloves, and mask with goggles, or eye shield

- Donor stool will be transferred to a single-use disposable container
- Preservative-free normal saline (250-500 mL) at room temperature will be used to dilute the stool sample until it reaches a liquid slurry consistency
- The stool slurry will then be filtered to remove as much particulate matter as possible. This will be accomplished using gauze pads lining the inside portion of a plastic disposable funnel
- The filtered stool slurry will be divided into aliquots of 50 mL and will be used within an hour of preparation

iii. **Protocol for Processing and Analysis of Recipient and Donor Samples:** As noted in sections 4 and 5, blood and stool samples may be collected from the recipient and from the donor for further analysis. Those recipients and donors who have agreed to provide clinical data, blood and stool samples are consented under a separate consent under a separate IRB ((IRB net ID: 163184-15) for collection and storage of samples within the Stony Brook GI satellite Biobank, which operates as a module under the Stony Brook Biobank New York State License for Biobanking. The clinical data, stripped of patient health identifiers, will be assigned a patient ID and a visit ID and will be stored in the Stony Brook University Digestive Diseases Research Tissue Procurement Facility clinical database. The patient samples will also be stripped of patient health identifiers and assigned a patient ID, visit ID and sample ID and will be archived within the Stony Brook University GI Biobank. The analysis of the samples and downstream products will including the following:

1. Genotyping for IBD risk alleles**.** DNA will be extracted from peripheral mononuclear blood cells (in blood) as previously described in Dr. Li's laboratory.[43] The DNA will be assigned the same patient ID, visit ID and sample ID from the original sample. We have used Taqman PCR assays, Sequenom, and array methods for analyzing genotypes thus far, but the technology is rapidly evolving.[22] We will seek the most cost effective means of obtaining accurate genotyping of established IBD risk alleles. If we submit the samples for genotyping at another facility, each of these samples will be assigned another sample ID, to further protect the privacy of the subjects, prior to shipping these samples to an outside facility.
2. 16S rRNA sequencing. 16S rRNA sequencing will provide a first tier of microbiome surveillance and will measure taxa based microbial diversity and composition.[43] This may involve shipping stool DNA to outside facilities for library construction and sequencing (University of Colorado). If we submit these DNA samples to outside institutions for analysis, each of these samples will be assigned another sample ID, to further protect the privacy of the subjects, prior to submission of these samples to an outside facility. For all rRNA sequence datasets, we routinely screen for and remove contaminating human DNA/RNA sequences by use of bowtie2 read-mapping software; thus, no human sequences will be analyzed beyond this step or will be included in public repositories. We propose to measure the alterations in microbial diversity and composition before and after fecal microbial transplantation.
3. Targeted qPCR sequencing**.** To detect targeted microbial taxa and functions we will utilize targeted qPCR and reverse transcriptase qPCR. These analyses will be carried out in Dr. Li's and Dr. Gathungu's laboratory.[46]
4. Fecal calprotectin. Fecal calprotectin is a marker of intestinal inflammation that will complement the colonoscopic scores and patient questionnaires. We propose to measure fecal calprotectin in each of the collected stools using the PhiCal commercial ELISA kit (CALPRO, Oslo, Norway) according to the manufacturer's instructions within Dr. Li's laboratory. Frozen stools archived at -80^{o}C will be batch extracted and analyzed along with the manufacturer's control to avoid interassay variability.
5. Shotgun metagenomics, bacterial metatranscriptomics, fecal metabolomics, fecal proteomic. We propose to conduct multiple omic studies on microbial function using the collected stool samples if we are successful in obtaining outside funding to support these studies. This may require sending aliquots of samples or their downstream products to other institutions for analysis. If so, the samples will be assigned another sample ID to further protect the privacy of the subjects before shipping these samples out to other institutions. For all meta-omic sequence datasets, we routinely screen for and remove contaminating human DNA/RNA sequences by use of bowtie2 read-mapping software; thus, no human sequences will be analyzed beyond this step or will be included in public repositories.

E. STATISTICS:

The number of patients enrolled will not be limited since a primary goal of this study is to establish safety and tolerability of FMT. It is anticipated that data from 80 FMTs with a balanced design of 20 FMTs performed on each of the following four groups of recipients (CDI without IBD, CDI with UC, CDI with CD, and UC without CDI) associated with a sister IRB protocol (ClinicalTrials.gov ID:NCT03268213, 479696, IND for UC only 15642), in combination with data from 20 FMTs performed on CD without CDI recipients recruited through this protocol (IRB 973349-5, ClinicalTrials.Gov ID NCT03267238, IND16795) will be needed to generate a power analysis on the multi-omic datasets. A linear mixed model will used to compare alpha-diversity (ShannonH) and beta-diversity (Bray-Curtis and Jaccard distance) between each time point (donor, pre-FMT, 1 week and 3 month post-FMT) and each disease group as previously described.[46] The two-way interaction term, Group*FMT, will be used to estimate the differences between any two time points within a specific disease group. Covariance structure to model correlation among measurements from the same patient and his/her corresponding donor will be selected based on Akaike Information Criteria (AIC). Possible covariance structures to model correlation among longitudinal measurement from the same patient and measurement in the corresponding donor included unstructured (UN), compound symmetry (CS), Toeplitz (TOEP), Heterogeneous CS (CSH) and Heterogeneous TOEP (HTOEP). Using the two-way interaction term between Group and FMT, generalized linear mixed models (GLMMIX) will be used to examine the possible change in individual OTU relative abundance after FMT in recipients and such difference between recipient and donor over time. The actual counts of each OTU will be assumed to follow a negative binomial distribution.[47] The log-transformed overall sequence count for each individual at each time point will be considered as an offset. In case that there is model converging issue GLMMIX, generalized estimating equation (GEE) will be used. In GEE, the dependence structure was chosen based on Quasi Information Criteria (QIC). The p-values from comparison analysis of all OTUs will adjusted for multiple comparisons by the Bonferroni correction or by the Benjamin-Hochberg method (FDR < 0.05). Principal coordinate analyses will be carried out using the R package *vegan*.

Similar models will be used to examine the difference in the expression level of a specific gene or protein based on metatranscriptomic data and metabolomic data between recipient and donor and the change in such difference over time. Beyond analysis of individual data-types integr-omic analyses that combine all data types (i.e. metabolomics, microbiome, and clinical) will rely on the use of Similarity Network Fusion,[47] which performs unsupervised clustering of patients based on each datatype and then fuses the obtained networks, strengthening links in complementary networks. These analyses will reveal the relationships among taxonomic composition, microbiome diversity and function and metabolomics which implies the mechanism how FMT works. All analysis will be performed in SAS 9.4 (SAS institute Inc., Cary, NC) and R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

F. FUNDING STATUS, DETAILS:

There is currently no funding for the procedure or evaluation of the recipient and donors in clinic, or the laboratory screening of the donor. The Simons Foundation Award is currently used to cover the costs of processing, sequencing and analysis of stool and blood samples.

G. HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK

1. **Risk to Subjects:**
   The risks to the recipient and the donor are described separately.
   a. Risk to recipient.
      i. *Risk of recipient undergoing colonoscopy*. The risks associated with the colonoscopy are infection, bleeding, and < 0.1% chance of perforation, which may require surgery. Additionally, there are risks associated with receiving anesthesia during colonoscopy including anaphylaxis, aspiration and respiratory distress.
      ii. *Risk of undergoing FMT in CD recipient.* Risks to FMT include bloating/flatulence, abdominal pain/cramping, diarrhea, blood in the stool, fatigue, and fever. In addition, there is a risk that there may be exacerbation of the underlying IBD.[25]
      iii. *Collection of stool and blood from recipient*. These are minimally invasive procedures. The risks of collecting blood are infection at the site of needle stick and bruising.

iv. *Risk of collecting recipient clinical data*. There is an extremely rare possibility that the patient data can be shared in a way that identifies the recipient. Great lengths will be made to restrict access to patient and sample codes.

b. Risk to donor

i. *Collection of stool from recipient*. This is minimally invasive procedure.

ii. *Risk of collecting recipient clinical data*. There is an extremely rare possibility that the clinical data can be shared in a way that identifies the donor. Great lengths will be made to restrict access to patient and sample codes.

2. Adequacy of Protection Against Risks:

The clinical data and stool samples will be stripped of patient health identifiers and assigned a patient code and sample code. The subject's participation will end after the collection of stool and clinical data is completed 1 year after enrollment in the study. We are only requesting that we be able to collect clinical metadata by prospective questionnaires and reviewing the medical records, and to collect recipient fecal and blood samples before FMT and after FMT. The consents will be obtained by the physicians or research staff, who have been trained in good clinical practices and are highly experienced in providing and obtaining informed consent in this patient population.

Additionally, all recipients will have adverse event monitoring as outlined below:

Day of fecal microbiota transplantation:

a. During the colonoscopy procedure: an anesthesiologist will be assigned to the recipient and the endoscopy unit will have full-code preparedness

b. Post colonoscopy procedure: the recipient will be monitored in the post-operative area of the endoscopy suite for one hour by continuous monitoring

*Post fecal microbial transplant*ation

The study team will closely monitor the recipient by phone call and an algorithm will be attached to the checklist to refer patients to either clinic or the Emergency Department if necessary.

a. 1 day post-transplant: The transplant recipient will receive a phone call the day after the procedure and questions will be asked from a standardized checklist containing the following items:
   i. General well being
   ii. Presence of abdominal pain
   iii. Presence of temperature greater than 100.4 degrees Fahrenheit
   iv. Presence of diarrhea (loose, watery stools) or blood in the stool
   v. Presence of new rash

b. Weekly monitoring 1-12 weeks post transplant: All recipients will have weekly monitoring via telephone call for 12 weeks. This will include the following additional questions:
   i. Has diarrhea stopped or improved?
   ii. If the diarrhea had stopped, is there a recurrence of diarrhea?
   iii. If the diarrhea has not improved, have you tried other treatments?
   iv. Has there been any need of antibiotics since the transplant?
   v. Did any medical condition you had before your fecal transplant go away after your fecal transplant? (for example, arthritis and chronic skin rash)
   vi. Has abdominal pain if present prior to fecal microbiota transplant resolved?
   vii. Have you developed any new medical conditions since the fecal transplant?

c. Monthly monitoring 4-12 months post transplant: All recipients will have monthly monitoring via telephone call between 4 and 12 months after the first twelve weeks.

d. Recipients and/or their guardians will be advised to call either the Pediatric Gastroenterology or Adult Gastroenterology offices for any questions or health related concerns for up to 1 year post-transplant.

e. The study team will meet with Drs. Chawla and Li on a monthly basis (last Wednesday of every month) to review follow up phone calls.

3. Potential Benefits of Proposed Research to the Subjects and Others:

The potential benefits of having the fecal transplantation for treatment of recurrent or refractory *CDI* not responsive to standard medical therapy is prevention of recurrent CDI.

The potential benefits of having the fecal transplantation for treatment of recurrent or refractory CDI not responsive to standard medical therapy, in addition to prevention of recurrent CDI is improvement in their IBD symptoms.

The potential benefits of having the fecal transplantation for treatment of UC or IC without CDI is improvement in their IBD symptoms.

Conducting research on these samples, including the research proposed in this application may create new tests, treatments, or cures. If it does the subjects (recipients or donors) who have donated samples will not receive any money from those products.

4. Importance of the Knowledge to be Gained:

This study will enable us to contribute to the literature regarding the safety, efficacy, and tolerability of fecal microbiota transplantation. Additionally, by collecting well phenotyped linked samples, future integrations of the microbiome data not only with phenotype but also with genetic data and metabolomics data will be possible. This will enable further studies investigating the mechanism(s) by which gut bacteria can affect susceptibility to medication refractory *Clostridium difficile* and/or ulcerative colitis or indeterminate colitis.

H. SAFETY MONITORING COMMITTEE (for more than minimal risk studies):

A safety monitoring committee (SMC) has been established and is composed of the three following experts:

a) Sharon Nachman, M.D., Chair of Safety Monitoring Committee, Professor of Pediatrics, Chief, Division of Infectious Diseases, Stony Brook University School of Medicine. Expertise in clinical trials.
b) Roy Steigbigel, M.D., Professor of Medicine, Pathology, Pharmacology and Microbiology, Division of Infectious Diseases, Stony Brook University School of Medicine. Expertise in infectious diseases.
c) Matthew Ciorba, M.D., Associate Professor of Medicine, Director of Research in the IBD Program Division of Gastroenterology and Hepatology, Washington University School of Medicine. Clinical and research expertise in the microbiome in inflammatory bowel diseases and colon cancer.

The committee will be asked to perform an interim assessment of safety 4 weeks after every ten subjects are enrolled in the study and undergo fecal transplant. This will help in determining whether or not this study protocol should continue to be implemented or requires modifications.

Adverse events (AE) will be recorded by follow up phone calls as per the following grading (Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events:[50]

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Grades 3, 4 and Grade 5 adverse events will trigger the team to request a safety monitoring committee review of the data and pause further enrollment.

Adverse events will be recorded when follow-up phone calls are made. Intensity and relationship of adverse events with FMT will be described using Common Terminology Criteria for Adverse Events (CTCAE version 4.0) and Toxicity Grading Guidance from Vaccine Clinical Trials (U.S. Food and Drug Administration, September 2008).

Four weeks after every 10th subject's enrollment and completion of fecal transplant a cumulative report will be submitted to SMC for formal review. SMC will have 1 week to respond. During this period there will be a safety hold. If no issues are identified, the study will be reopened and further enrollment will be allowed.
After the data on the next 10 subjects have been reviewed by SMC and no concerns are raised, the hold period will no longer be necessary.

Principal investigator may request an ad hoc SMC review if needed at any time point.

The committee may also require changes to the protocol to ameliorate the safety concerns that pose significant risk to stool recipients. In the absence of protocol changes, the SMC must follow the protocol-specified stopping rules.

I. LITERATURE CITED:

1. Hopkins MJ, MacFarlane GT. Changes in predominant bacterial populations in human faeces with age and with Clostridium difficile infection. *J Med Microbiol* 2001; 51:448-454.
2. Chang JY, Antonopoulos DA, Kalra A, et al. Decreased diversity of the fecal microbiome in recurrent Clostridium difficile-associated diarrhea. *J Infect Dis* 2008; 197:435-438.
3. Bouza E. Consequences of Clostridium difficile infection: understanding the healthcare burden. *Clin Microbiol Infect. Suppl* 2012; 6:5-12.
4. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; 108:500-508.
5. Pant C, Despande A, Altaf M, et al. Clostridium difficile infection in children: a comprehensive review. *Curr Med Res Opin*. 2013; 29:967-84.
6. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Eng J Med* 2011; 364:422-431.
7. Lancaster JW, Matthews SJ. Fidaxomicin: The newest addition to the armamentarium against Clostridium difficile infections. *Clin Ther* 2012; 34:1-13.
8. Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. *J Hosp Infect.* 2008;70:298-304.
9. Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. *The Journal of infection*. 2009;58:403-10.
10. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol*. 2002;97:1769-75.
11. Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent Clostridium difficile infection is associated with increased mortality. *Clin Microbiol Infect.* 2015;21:164-70.
12. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med. 2016;165:609-616.
13. Mattila E, Uusitalo-Seppala R, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology. 2012;14:490-6
14. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-80.
15. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5:339-44.
16. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5:345-51.
17. Ananthakrishnan AN, Binion DG. Impact of Clostridium difficile on inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2010;4:589-600.
18. Pascarella F, Martinelli M, Miele E, et al. Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. J Pediatr. 2009;154:854-8.
19. Martinelli M, Strisciuglio C, Veres G, et al. Clostridium difficile and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. Inflamm Bowel Dis. 2014;20:2219-25.
20. Saffouri G, Gupta A, Loftus EV, Jr., et al. The incidence and outcomes from Clostridium difficile infection in hospitalized adults with inflammatory bowel disease. Scand J Gastroenterol. 2017;52:1240-1247.
21. Hourigan SK, Chen LA, Grigoryan Z, et al. Microbiome changes associated with sustained eradication of Clostridium difficile after single faecal microbiota transplantation in children with and without inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42:741-52.
22. Fischer M, Kao D, Kelly C, et al. Fecal Microbiota Transplantation is Safe and Efficacious for Recurrent or Refractory Clostridium difficile Infection in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22:2402-9.

23. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2016;14:1433-8.
24. Newman KM, Rank KM, Vaughn BP, et al. Treatment of recurrent Clostridium difficile infection using fecal microbiota transplantation in patients with inflammatory bowel disease. Gut Microbes. 2017;8:303-309.
25. Qazi T, Amaratunga T, Barnes EL, et al. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis. Gut Microbes. 2017;8:574-588.
26. Jacob V, Crawford C, Cohen-Mekelburg S, et al. Single Delivery of High-Diversity Fecal Microbiota Preparation by Colonoscopy Is Safe and Effective in Increasing Microbial Diversity in Active Ulcerative Colitis. Inflamm Bowel Dis. 2017;23:903-11.
27. Kump PK, Grochenig HP, Lackner S, et al. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm Bowel Dis. 2013;19:2155-65.
28. Kump P, Wurm P, Grochenig HP, et al. The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis. Aliment Pharmacol Ther. 2018;47:67-77.
29. Kunde S, Pham A, Bonczyk S, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. J Pediatr Gastroenterol Nutr. 2013;56:597-601.
30. Michail S. Fecal Microbial Transplant In Children With Ulcerative Colitis: A Randomized, Double-Blinded, Placebo-Controlled Pilot Study. J Pediatr Gastroenterol Nutr. 2017.
31. Mizuno S, Nanki K, Matsuoka K, et al. Single fecal microbiota transplantation failed to change intestinal microbiota and had limited effectiveness against ulcerative colitis in Japanese patients. Intest Res. 2017;15:68-74.
32. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology. 2015;149:102-9
33. Nishida A, Imaeda H, Ohno M, et al. Efficacy and safety of single fecal microbiota transplantation for Japanese patients with mild to moderately active ulcerative colitis. J Gastroenterol. 2017;52(4):476-82.
34. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017;389:1218-28.
35. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology. 2015;149:110-8
36. Suskind DL, Singh N, Nielson H, Wahbeh G. Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr. 2015;60:27-9.
37. Uygun A, Ozturk K, Demirci H, et al. Fecal microbiota transplantation is a rescue treatment modality for refractory ulcerative colitis. Medicine (Baltimore). 2017;96:e6479.
38. Vermeire S, Joossens M, Verbeke K, et al. Donor Species Richness Determines Faecal Microbiota Transplantation Success in Inflammatory Bowel Disease. J Crohns Colitis. 2016;10:387-94.
39. Hirsch BE, Saraiya N, Poeth K, et al. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent Clostridium difficile infection. BMC Infect Dis. 2015;15:191.
40. Youngster I, Mahabamunuge J, Systrom HK, et al. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent Clostridium difficile infection. BMC Med. 2016;14:134.
41. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA. 2017;318:1985-1993.
42. Ott SJ, Waetzig GH, Rehman A, et al. Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With Clostridium difficile Infection. Gastroenterology. 2017;152:799-811
43. Li E, Hamm CM, Gulati AS, et al. Inflammatory bowel diseases phenotype, C. difficile and NOD2 genotype are associated with shifts in human ileum associated microbial composition. PLoS One. 2012;7:e26284.
44. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011;9:1044-9.
45. https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm488223.pdf
46. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60: 505-512.

47. Zhang Y, Rowehl L, Krumsiek JM, et al. Identification of Candidate Adherent-Invasive E. coli Signature Transcripts by Genomic/Transcriptomic Analysis. PLoS One. 2015;10:e0130902.
48. Mintz M, Khair S, Grewel S, et al. Longitudinal microbiome analysis of single donor fecal microbiota transplantation in patients with recurrent Clostridium difficile infection and/or ulcerative colitis. PLoS ONE, in press.
49. Son JS, Khair S, Pettet DW 3rd, et al. Altered Interactions between the Gut Microbiome and Colonic Mucosa Precede Polyposis in APCMin/+ Mice. PLoS One. 2015;10:e0127985.
50. Wang B, Mezlini AM, Demir F, et al. Similarity network fusion for aggregating data types on a genomic scale. Nat Methods. 2014; 11: 333-7.
51. https://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf

APPENDIX B

Stool Recipient Screening Questionnaire (Crohn's disease)

Recipient Name:_____ Date:_____

Inclusion: Recipient is deemed eligible if any one of the following criteria are met**.**

___ Patient is 7 years of age or greater and has been treated with steroid therapy for at least a month

___ Patient is 7 years of age or greater and has been treated with immunomodulatory therapy for at least one month

___ Patient is 7 years of age or greater and has been treated with biological therapy for at least a month.

_____ _____

Name of person completing this form Signature of person completing this form

Stool Recipient Screening Questionnaire (Crohn's disease)

Recipient Name:_____ Date:_____

Question	Yes*	No
1. Is the patient less than 7 years of age?		
2. Is he/she scheduled for abdominal surgery within the next 12 weeks?		
3. Has the patient had major abdominal surgery within the past 3 months?		
4. Is the patient pregnant (if applicable)?		
5. Does the patient have Hgb < 6 g/dL?		
6. Is the patient's absolute neutrophil count less than 1500/mm?		
7. Does the patient have a known diagnosis of graft vs. host disease?		
8. Presence of an intra-abdominal or perianal abscess		
9. Presence of intestinal cutaneous fistula		
10. Presence of severe intestinal stricture and/or intestinal obstruction		
11. Has the patient used an investigational drug within the past 2 months?		
12. Has the patient used a TNF-α antagonist within the past 2 weeks?		
13. Has the patient been diagnosed with Bacteremia within past 4 weeks?		
14. Severe Crohn's Disease determined by Pediatric Crohn's Disease Activity Index (PCDAI) value > 29		
15. Individuals with severe prior allergic reaction to food		
16. Individuals with intercurrent illness including but not necessarily limited to: febrile illness, decompensated liver cirrhosis, HIV/AIDS BMT within past 150 days, malignancy, or other severe immunodeficiency		
17. Individuals at increased risk for complications of endoscopy or procedural sedation (e.g., ASA classification IV and above).		
18. Has the patient had any previous FMT?		

***Answer of "yes" to any of the questions results in exclusion.**

_____ _____

Name of person completing this form Signature of person completing this form

APPENDIX C

Stool Donor Screening Questionnaire

Donor Name:_____ Date:_____

Question	Yes*	No
1. Are you younger than 7 years of age?		
2. Do you have known HIV, tuberculosis, Hepatitis B, or C infections?		
3. Have you been exposed to HIV, tuberculosis or viral hepatitis (within the previous 12 months)?		
4. Do you engage in any high-risk sexual behaviors (examples: sexual contact with anyone with HIV/AIDS, tuberculosis or hepatitis, sex for drugs or money)?		
5. Have you used illicit drugs within the past 3 months?		
6. Have you had a tattoo or body piercing within the past 6 months?		
7. Have you ever been incarcerated?		
8. Have you been to an area with Mad Cow Disease (risk factor for Creutzfeld-Jakob disease)?		
9. Have you traveled (within the last 3 months) to developing countries?		
10. Do you have a history of inflammatory bowel disease or chronic diarrhea (i.e. greater than 3 loose stools daily for the past 3 months)?		
11. Do you have a history of gastrointestinal malignancy or known polyposis?		
12. Have you used systemic antibiotics in the past 3 months?		
13. Are you currently using any major immunosuppressive medications (e.g., calcineurin inhibitors, systemic anti-neoplastic, exogenous glucocorticoids, biologic agents)?		
14. Do you have eczema, allergies or asthma requiring steroids or immune-modulating therapy?		
15. Do you have an autoimmune disease, metabolic syndrome, chronic pain syndrome, neurologic or developmental disorder?		
16. Do you have contact with hospital patients?		
17. Have you been hospitalized or in a long term care facility in the past 6 months ?		
18. Do you attend outpatient medical or surgical clinics more than once a month?		
19. Have you engaged in medical tourism in the past 6 months?		

***Answer of "yes" to any of the questions results in exclusion.**

_____ _____

Name of person completing this form Signature of person completing this form

Stool Donor Screening Questionnaire

Donor Name:_____ Date:_____

Did the Donor Test Positive For:	Yes	No
1. Clostridium difficile toxin A or B?		
2. Stool culture?		
3. Giardia antigen?		
4. Cryptosporidium antigen?		
5. Ova and parasites?		
6. Acid-fast stain for Cyclospora, Isospora?		
7. HIV, type 1 and 2		
8. Hepatitis A (HAV IgM)?		
9. Hepatitis B (HBsAg, anti-HBc, anti-HBs)?		
10. Hepatitis C (HCV Ab)?		
11. Syphilis (RPR and FTA-ABS)?		
12. Sorbitol negative E. Coli ?		
13. Tuberculosis		
14. Vancomycin resistant enterococci (VRE)		
15. Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL)		
16. Carbapenem-resistant Enterobacteriaceae (CRE**)**		
17. Methicillin-resistant Staphylococcus aureus (MRSA)		

***Answer of "yes" to any of the questions results in exclusion.**

_____ _____

Name of person completing this form Signature of person completing this form

APPENDIX D:

Study Flowsheet

Protocol	Day(s)		
Recruitment of stool recipient (Appendix F)	-28	Performed?	Yes
			No
Donor screening (Appendix C)	-28	Eligible?	Yes
			No
Donor Serum and Stool Screening	-28	Eligible?	Yes
			No
Diet Record completed by Recipient? (Appendix G)	-7 to 0	Yes	No
Diet Record completed by Donor? (Appendix G)		Yes	No
Pre-transplant stool collection?	-3 to -1	Yes	No
Recipient has stopped antibiotics	-3 to -2	Yes	No
Recipient undergoing bowel prep with resultant clear yellow stool?	-1	Yes	No
Donor stool processed? (Appendix P)	0	Yes	No
Day of transplant stool collection?	0	Yes	No
Recipient blood obtained?	0	Yes	No
Patient monitored?	0	Yes	No
Follow-up Phone Call? (Appendix L)	1	Yes	No
Protocol	**Week (s)**		
Follow-up Phone Call? (Appendix L)	1	Yes	No
Post-transplant stool collection?		Yes	No
Follow-up Phone Call? (Appendix L)	2	Yes	No
	3	Yes	No
	4	Yes	No
	5	Yes	No
	6	Yes	No
	7	Yes	No
	8	Yes	No
	9	Yes	No

	10	Yes	No
	11	Yes	No
Follow-up Phone Call? (Appendix L)	12	Yes	No
Post-transplant stool collection?		Yes	No
Protocol	**Month (s)**		
Follow-up Phone Call? (Appendix L)	4	Yes	No
	5	Yes	No
	6	Yes	No
	7	Yes	No
	8	Yes	No
	9	Yes	No
	10	Yes	No
	11	Yes	No
	12	Yes	No

APPENDIX E

TEMPLATE E-MAIL IN RESPONSE TO INQUIRY ABOUT, ClinicalTrials.gov ID: NCT03267238, IND 16795

Dear

Thank you for your interest. I am referring you to
(IF ADULT RECIPIENT) Dr. Ellen Li, Professor of Medicine/Gastroenterology,Stony Brook Medicine
(IF PEDIATRIC RECIPIENT) Dr. Anupama Chawla, Chief and Professor of Pediatrics/ Gastroenterology, Stony Brook Medicine.
We are currently open to enrollment and accept local and out-of-state candidates.

However, we need your gastroenterologist to be on board with this study, which is strictly observational and simply asking if we can change your microbiome. In addition, we need you to select a healthy donor who fulfills the attached screening criteria. The evaluation of both the patient (recipient of the transplant) and donor takes place at Stony Brook Medicine, NY. So, this requires two trips to Stony Brook. One for the initial recruitment and the second for the colonoscopic delivery of the transplant. We do not cover travel costs, donor screening costs or the cost of the colonoscopy (usually covered by your health insurance company). However, costs of analyzing the stools for all microbiome-related studies will be covered by us.

We prefer no change in your medications and no biologic therapy for at least 2 weeks prior to the transplant.

Please contact your gastroenterologist. If they are in agreement to proceed and you wish to move ahead, please send us the name, e-mail and fax of your primary gastroenterologist. The last office visit note should be sent to us via fax
(IF ADULT RECIPIENT) (631-444-5225) ATTN: DR. ELLEN LI or email: ellen.li@stonybrookmedicine.edu

(IF PEDIATRIC RECIPIENT) (631-444-6045) ATTN: DR. ANUPAMA CHAWLA or email: anupama.chawla@stonybrookmedicine.edu

It should also include the most recent colonoscopy, pathology and imaging reports.

Please see the attached detailed protocol, which you can share with your gastroenterologist.

Regards,
Katherine Markarian
Research Coordinator
631-444-3868

APPENDIX F (Crohn's disease with or without CDI):

STUDY PATIENT CHARACTERISTICS

Within 2 weeks prior to Fecal Transplantation

RECIPIENT CODED No.: _____ SEX: ☐M/☐F

DOB: ___ ___/___ ___/___ ___
WEIGHT: ____ KGS BMI: ____
HEIGHT: ____ CMS

1. Duration of symptoms related to Crohn's disease	____ Month(s)		
2. Date of IBD diagnosis	__ __/__ __/__ __		
3. Current medications	Name		
4. Medications for IBD the patient has been treated with:	Name		Duration (days)
5. Probiotics the patient has been treated with:	Name		Duration (days)
6. Diarrhea (BMs/day):	<3	3-6	>6
7. Blood in stool:	Yes		No
8. Mucous in stool:	Yes		No
9. Abdominal pain (Scale 0-10)	___/10		
10. Fatigue	Yes		No
11. Weight loss during illness	Yes ____KGs		No
12. Previous abdominal surgery	Yes Location_____		No
13. Smoker?	Yes Packs/day:_____ _		No

APPENDIX G

Stony Brook University Medical Center Food Diary

Coded Number: _____

Physician: _____

Record all food, fluid, supplement intake including Probiotics
Record all condiments, sauces, oils, etc.

Date:

MEAL	FOOD: Brand/Description (i.e. Whole milk, rye bread)	HOW WAS IT PREPARED (i.e. 3 ounces fried chicken)

****Record each day on separate sheet****

APPENDIX H

Checklist for instructing Recipient 2-5 days prior to Fecal Microbial Transplantation

RECIPIENT CODED No.: _____
DATE/TIME OF CALL: ___ ___/___ ___/___ ___:___AM/PM

RECIPIENT DATA:

1. Do you fully understand the colonoscopy prep procedure?	YES	NO
2. Have you completed tapering of any antibiotics (if applicable)? It is important that antibiotics must be stopped 48 h before the transplant because the antibiotics will kill the bacteria in the transplant*****	YES	NO
3. Do you fully understand the stool collection instructions & kit?	YES	NO
4. Will you arrive to Endoscopy 1.5-2 hrs before the scheduled procedure?	YES	NO
5. Have you been recording your diet in the food diary?	YES	NO

***FMT will not be performed if answered "no".**

RECIPIENT NOTES:

APPENDIX I:

Simple Endoscopic Score for Crohn's Disease

DAY OF TRANSPLANT___

RECIPIENT CODED No.: _____

SES-CD calculation table

	Ileum	Right colon	Transverse colon	Left colon and sigma	Rectum	Total
Ulcers? 0: no 1: aphthous (0.1-0.5 cm) 2: large (0.5-2 cm) 3: very large (>2 cm)	___+	___+	___+	___+	___=	___**+**
Surface involved by disease 0: 0% 1: <50% 2: 50-75% 3: >75%	___+	___+	___+	___+	___=	___**+**
Surface involved by ulcerations 0: 0% 1: <10% 2: 10-30% 3: >30%	___+	___+	___+	___+	___=	___**+**
Narrowings? 0: No 1: Single, can be passed 2: Multiple, can be passed 3: Cannot be passed	___+	___+	___+	___+	___=	___**+**
					Grand Total = SES-CD score	

Decoding table (2)

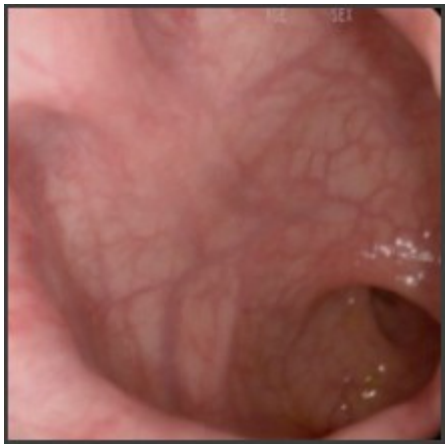
Score	Decoding

0 - 2	remission
3 - 6	mild endoscopic activity
7 - 15	moderate endoscopic activity
> 15	severe endoscopic activity

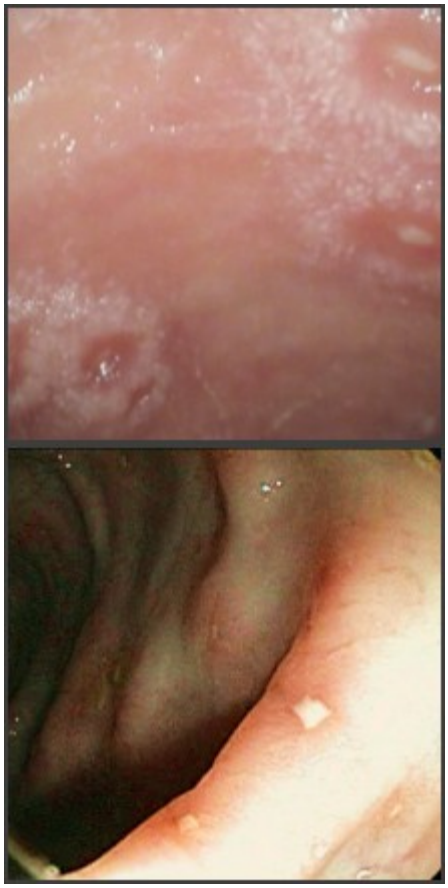
A decrease of 50% of the SES-CD score has recently been proposed as prognostically significant.

Below are some examples endoscopic images.

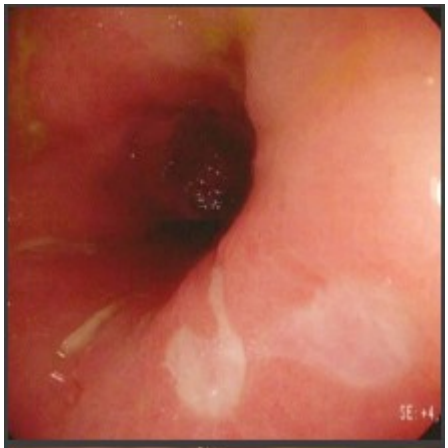
Ulcers: none

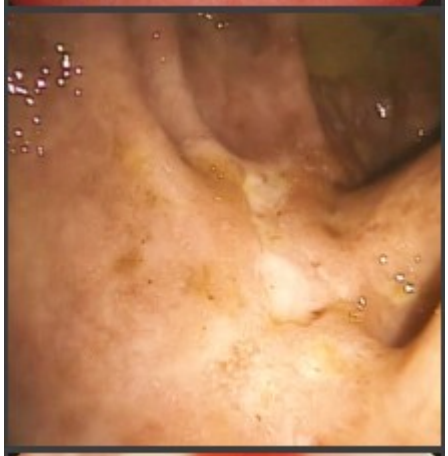


Aphtous ulcers (<0.5 cm)

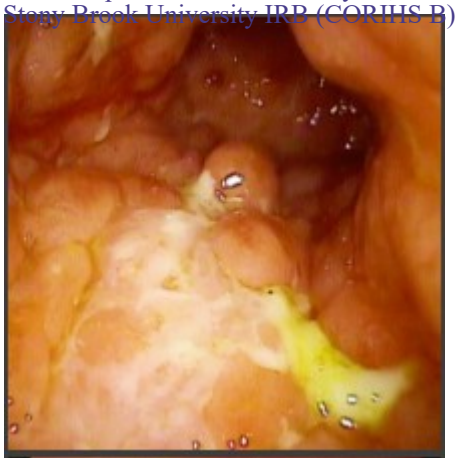


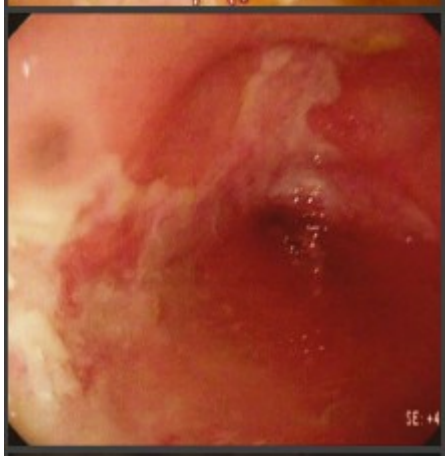
Large ulcers (from 0.5 to 2 cm)



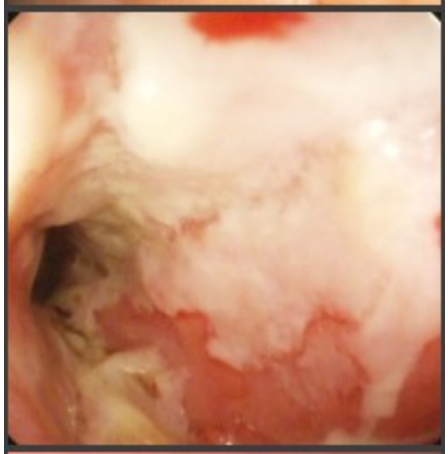


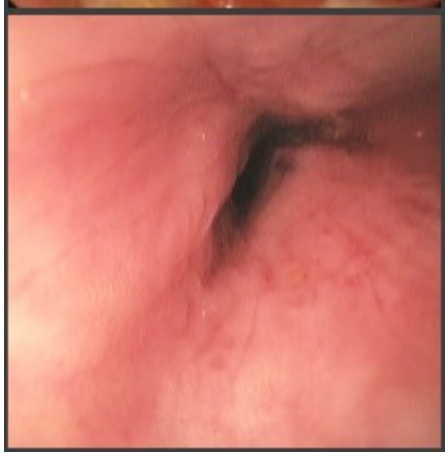
Very large ulcers (>2 cm)



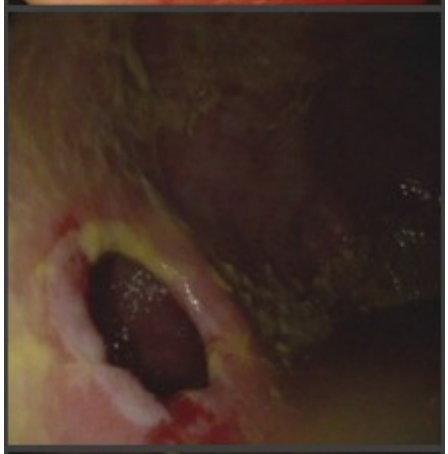


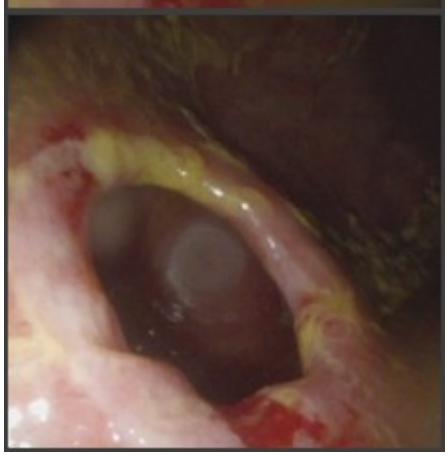
Impassable stenosis





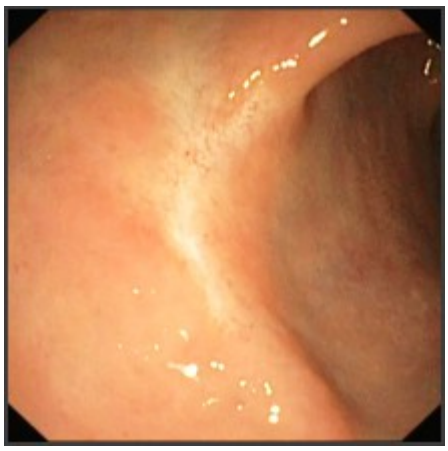
Single stenosis, can be passed



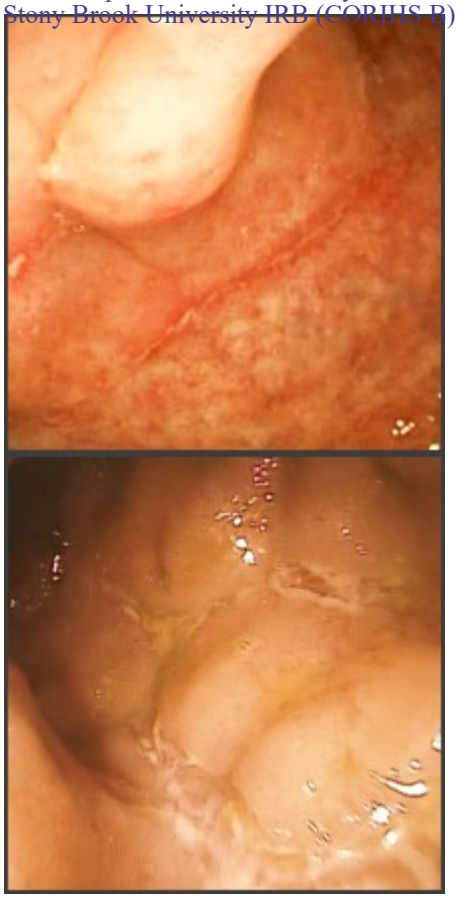


Surface involved by ulcerations

Surface involved by ulcerations 0% (none)

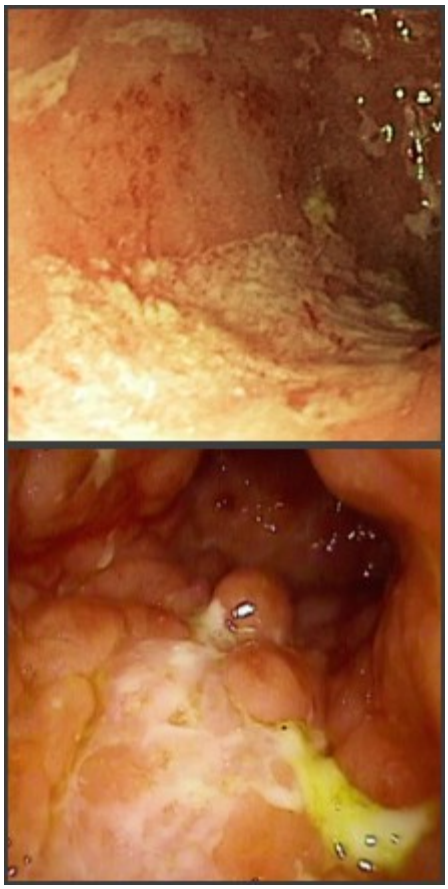


Surface involved by ulcerations <10%



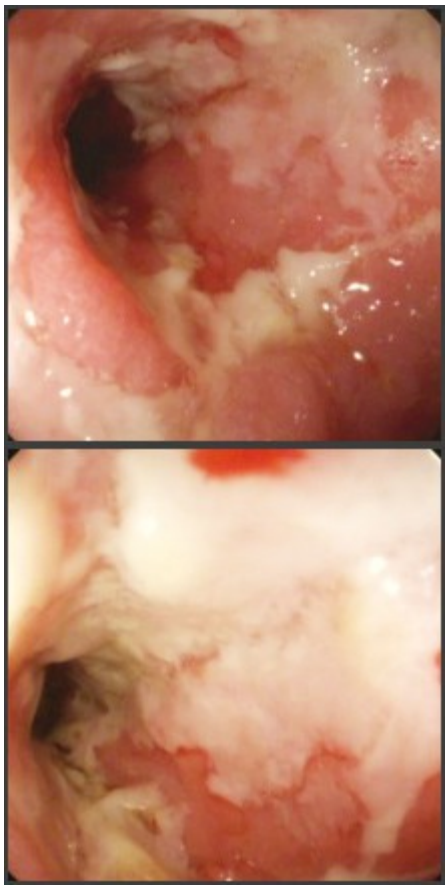
3% lesion9% lesion

Surface involved by ulcerations 10%-30%



22% lesion25% lesion

Surface involved by ulcerations >30%



52% lesion66% lesion

APPENDIX J:

DIARY CARD

DATE:_____

DESCRIPTION OF SYMPTOMS THAT ARE NEW OR WORSENED:

DATE:_____

DESCRIPTION OF SYMPTOMS THAT ARE NEW OR WORSENED:

DATE:_____

DESCRIPTION OF SYMPTOMS THAT ARE NEW OR WORSENED:

DATE:_____

DESCRIPTION OF SYMPTOMS THAT ARE NEW OR WORSENED:

Contact us (631-444-7225) immediately if you are seen in the emergency room or hospitalized <u>for any reason.</u>

APPENDIX K:

DAY AFTER TRANSPLANT: CASE REPORT FORM

RECIPIENT CODED No.: _____
DATE/TIME OF CALL: ___ ___/___ ___/___ ___ ___:___AM/PM

RECIPIENT DATA:

1. How do you feel today?	WELL		**UNWELL**
2. Have you had a fever > 100.4 degrees Fahrenheit in the past 2 weeks?	**YES**		NO
3. Is your abdominal pain:	BETTER	**WORSE**	SAME
4. Is your diarrhea:	BETTER	**WORSE**	SAME
5. Is the blood in your stool:	BETTER	**WORSE**	SAME
6. Is there a presence of a new rash on your body?	**YES**		NO

DESCRIPTION OF SYMPTOMS THAT HAVE WORSENED:

NAME OF PHYSICIAN INFORMED IF PATIENT RESPONSE CORRESPONDS TO ANY OF THE BOLDED ITEMS ABOVE:

_____MD/DO

PHYSICIAN DECISION OF FURTHER EVALUATION:

CLINIC	EMERGENCY ROOM	PHONE FOLLOW-UP

APPENDIX L (Crohn's disease):

FOLLOW UP PHONE CALL/ADVERSE EVENT: CASE REPORT FORM

WEEK(S)/MONTH(S) POST-TRANSPLANT ___

RECIPIENT CODED No.: _____

DATE/TIME OF CALL: ___ ___/___ ___/___ ___ ___:___AM/PM

1. How do you feel today?	WELL		**UNWELL**	
2. Have you had a fever > 100.4 degrees Fahrenheit since the last phone call?	**YES**		NO	
3. Has your abdominal pain:	RESOLVED	IMPROVED	**WORSENED**	N/A
4. Has your diarrhea:	RESOLVED	IMPROVED	**WORSENED**	N/A
5a. Frequency of stools/day:	<3	3-6	**>6**	
5b. Has the blood in your stool:	RESOLVED	IMPROVED	**WORSENED**	N/A
6. Have you been fatigued?	**YES**			NO
	Mild	**Moderate**	**Severe**	
7. Have you experienced weight changes since the last phone call?	NO	YES		± ____ LBS
8. Have you required antibiotics since the fecal transplant? If yes, what is the name of the antibiotic(s)?	YES Name of antibiotic(s): _____		NO	
9. Have you taken any new medication(s), including OTC or probiotics since the last phone call?	YES Name of medication(s): _____		NO	
10. Have you developed any NEW medical conditions since the last phone call?	**YES** **Please specify:** _____		NO	
11a. Did any medical condition(s) you had before your fecal transplant go away after your fecal transplant?	YES Please specify: _____		NO	
11b. Please list all medication(s) you take on a regular basis (dosage not necessary)	Name of medication(s): _____			

including chemotherapeutic agents, if applicable	

DESCRIPTION OF ADVERSE EVENT(S):

(An adverse event will be defined as any unfavorable or unintended sign, symptoms, disea1se, syndrome, abnormal laboratory finding, or concurrent illness that emerges or worsens relative to the recipient's pre-transplant baseline, whether or not it is considered to be related to the fecal transplantation)
All Grade 3 – 5 adverse events will be sent to the Safety Monitoring Committee.

NAME OF PHYSICIAN INFORMED IF PATIENT RESPONSE CORRESPONDS TO ANY OF THE BOLDED ITEMS ABOVE:

_____MD/DO

PHYSICIAN DECISION OF FURTHER EVALUATION:

CLINIC	EMERGENCY ROOM	PHONE FOLLOW-UP

DOCUMENTATION SENT TO SAFETY MONITORING COMMITTEE ON ___ ___/___ ___/___ ___:

YES	NO

APPENDIX M:

SERIOUS ADVERSE EVENT (SAE): CASE REPORT FORM

WEEK(S)/MONTH(S) POST-TRANSPLANT ___

☐ INITIAL REPORT/☐ FOLLOW-UP REPORT

RECIPIENT CODED No.: _____

ONSET OF EVENT: ___ ___/___ ___/___ ___

Severity of SAE	Grade 3	Grade 4	Grade 5

Outcome of SAE:	☐ RECOVERED WITH SEQUELAE	RECOVERY DATE ___ ___/___ ___/___ ___
	☐ RECOVERED WITHOUT SEQUELAE	
	☐ PERSISTING	☐ UNKNOWN/LOST TO FOLLOW-UP
	☐ DEATH	

SAE category:	☐ DEATH*	☐ LIFE THREATENING
	☐ HOSPITALIZATION REQUIRED#	☐ PROLONGED IN-PATIENT HOSPITALIZATION#
	☐ PERSISTENT/SIGNIFICANT DISABILITY OR INCAPACITY	☐ OTHER MEDICALLY IMPORTANT CONDITION

*IF DEATH HAS OCCURRED:

1. Date of death	___ ___/___ ___/___ ___
2. Primary cause of death (if known)	_____

#IF RECIPIENT HAS REQUIRED HOSPITALIZATION:

1. Hospital admission date	___ ___/___ ___/___ ___
2. Current duration of hospitalization	_____ (WEEKS/MONTHS)

DESCRIPTION OF SERIOUS ADVERSE EVENT(S):

NAME OF PHYSICIAN INFORMED OF SAE: _____MD/DO

DOCUMENTATION SENT TO SAFETY MONITORING COMMITTEE ON ___ ___/___ ___/___ ___:

YES	NO

APPENDIX N

Research Study: Fecal microbial transplantation in patients with Crohn's disease (IRBNet # 973349)
Principal Investigator: Dr. Ellen Li

FMT recipient _____
FMT donor _____

Dr. Ellen Li has discussed the screening test for the Donor with both recipient and donor as named above and explained that the costs involved in these tests might not be covered by the insurance. The research study does not provide any monetary support for these donor-screening tests.

Signature of Recipient _____
Signature of Donor _____

_____
Full name of person obtaining consent

_____
Signature of person obtaining consent Date

APPENDIX O

Checklist for instructing Donor 2-5 days prior to Fecal Microbial Transplantation

DONOR CODED No.: _____
DATE/TIME OF CALL: ___ ___/___ ___/___ ___:___AM/PM

DONOR DATA:

1. Do you fully understand the stool collection instructions & kit?	YES	NO
2. Have you been recording your diet in the food diary?	YES	NO
3. Have you ingested any known allergy/sensitivity of the recipient?* If so, see notes below	YES	NO
4. Will you be present with the recipient on day of transplant? (If no, complete TPF questionnaire over phone and schedule a time to complete "Day Of Transplant Case Report" form)	YES	NO

DONOR NOTES:

***Reschedule fecal microbial transplant.**

APPENDIX P:

DAY OF TRANSPLANT: DONOR CASE REPORT FORM

DATE OF STUDY: ___ ___/___ ___/___ ___ TIME OF STUDY: ___:___

DONOR CODED No.: _____

RECIPIENT CODED No.: _____

DONOR DATA:

1. Do you feel unwell today?	YES	NO
2. Have you had a fever > 100.4 degrees Fahrenheit in the past 2 weeks?	YES	NO
3. Have you had cough or runny nose within the last 2 weeks?	YES	NO
4. Have you ingested _____ (recipient allergen) in the past week?	YES	NO

If answer to any question is "yes", discuss with attending physician.

DONOR STOOL DATA:

1. What date and time was the stool produced?	__ __/__ __/__ __ AM/PM		
2. If produced > 6 hours before time of colonoscopy, was the stool kept at room temperature?	YES	NO	N/A
3. Was the stool collected with any contamination with the toilet bowl?	YES	NO	
4. Is there presence of blood in the stool?	YES	NO	
5. Is there presence of mucous in the stool?	YES	NO	
6. What is the consistency of stool?	Hard	Soft	Liquidy

If answer to any question from #2 to #5 is "yes", FMT will not be performed.

RECIPIENT RESEARCH PERMISSION/CONSENT FORM (CROHN'S)

Project Title: Fecal microbial transplantation in patients with Crohn's disease

Principal Investigator: Ellen Li, MD, PhD

Co-Investigator: Anupama Chawla, MD

Departments: Medicine/Gastroenterology and Pediatric Gastroenterology & Nutrition

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff. If you are a parent or legal guardian of a child who may take part in this study, permission from you is required and the assent (agreement) of your child may be required.

You are being asked to be a volunteer in a research study. You are encouraged to take your time in making your decision. You may want to discuss this study with your friends and family.

PURPOSE

The purpose of this study is:

- To determine the safety and tolerability of fecal (stool) transplantation to treat Crohn's Disease.
- Crohn's Disease (CD) is a chronic disease affecting the colon without a medical cure. The precise cause of having inflammatory bowel disease (IBD) such as Crohn's disease, Ulcerative colitis, or indeterminate colitis is unclear. However, genetics and the environment are thought to play a role. Studies have found that patients with Crohn's Disease have a decreased prevalence of protective bacteria and an increase in harmful bacteria in the colon. Inflammation in the colon in these patients is thought to be due to this imbalance between helpful and harmful bacteria. Currently, the treatment of IBD includes steroids, anti-inflammatory medications and biological therapy, each with its own side effects. Given the role of the gastrointestinal bacteria in driving inflammation in patients with IBD, treatments that manipulate these bacteria have been investigated, including the use of medications containing beneficial bacteria (probiotics), with some benefit. Fecal transplantation (FMT), the transfer of gastrointestinal bacteria (microbiota) from a healthy donor via infusion of a liquid stool suspension, is proving to be an effective alternative treatment for Crohn's Disease. The treatment appeared to improve clinical symptoms and lower inflammatory markers. The goal of this method is to remove the harmful bacteria in the colon and replace them with normal bacteria.

Since you have Crohn's Disease and your symptoms have not improved with the medications you are currently on, fecal transplantation is a treatment option for you. As mentioned before, several studies have found that this transplantation is helpful in improving the symptoms associated with IBD, such as abdominal pain and diarrhea. This study hopes to document fecal transplantation's safety and tolerability and improve or even eliminate your symptoms by performing the transplantation and then following-up routinely with you for one year. We will perform stool and genetic studies on you to see if the bacteria in your colon really did change after the transplantation and if any of your genes influence the composition of your colon bacteria.

We expect to enroll a minimum of 40 patients in this study at Stony Brook University Hospital.

PROCEDURES

If you decide to be in this study, your part will involve:

- You will first have to choose somebody who will donate the stool which will be transplanted. The donor can be anyone who we will consent separately and who meets eligibility criteria to donate stool. He/she will be asked questions and screened by performing bloodwork and stool studies to make sure he/she is a healthy candidate for stool transplantation. We will not share the lab results of your donor specimen with you even if they fail the inclusion criteria.
- After the donor is chosen and he/she meets criteria to donate stool, we will give you a date for the fecal transplantation which will be done during a colonoscopy.
- If you are of child-bearing age, a pregnancy test will be given to you as a clinic standard of care before the colonoscopy procedure. If the test result is positive for pregnancy we will not perform the fecal transplantation colonoscopy.
- During the week before fecal transplantation, we will ask you to record everything you have eaten on a diet record which we will provide to you. Stool for research will be collected 1-3 days before your day of fecal transplantation.
- On the day before your transplant, you will be given instructions for a bowel prep to clean out your colon completely so it can be visualized well when we perform the fecal transplantation and make the procedure more effective. For the last 7 hours before your scheduled fecal transplantation, you will have nothing to eat or drink.
- On the day of the transplantation, you will arrive at Stony Brook University Hospital and go to the Endoscopy Suite, located on the 14th Floor. There you will change into a hospital gown and an intravenous line (IV) will be placed to provide you with fluids and sedation during the colonoscopy. Four teaspoons of blood will be taken for research, to perform genetic studies.
- Your donor's stool will be prepared and while you are properly sedated, the stool will be instilled into your colon.

- At the time of scope and transplant, if the scope reveals anything clinically suspect that might require a biopsy, or the physician decides that the colon is not healthy enough, then the transplant will not be done.
- You will stay in the Endoscopy Suite, lying on your right side, for at least one hour. This is to maximize contact between the transplanted stool and your colon. If you are not cleared to depart after one hour, you will stay until the anesthesiologist (doctor who administered sedation during colonoscopy) does clear you to depart. You will be able to eat and drink right after you wake up and can resume normal activities as soon as the anesthesia wears off and you feel well.
- You will receive a phone call the day after the procedure, and be asked various questions to determine your general well-being.
- You will then receive weekly phone calls for 12 weeks at a convenient time for you, to ask you further general well-being questions.
- You will keep another diet record during the first week post-transplant. 1 week after your fecal transplantation you will collect stool for research, similar to how you collected stool prior to your stool transplantation.
- You will keep another diet record during the 12th week post-transplant. 12 weeks after your fecal transplantation you will collect stool for research, similar to how you collected stool prior to your stool transplantation.
- After your 12-week stool collection and testing, you will receive monthly phone calls until one year after the transplant to determine your general well-being.
- If you are diagnosed with bacteria in your blood within past 4 weeks (28 days) of intended FMT, you will be excluded from the study.

When you are first recruited for the study, you will be assigned a coded number. Stool and blood collected from you and follow-up questionnaires will all have your coded number so your information will not be directly linked to your samples and medical or diet diary information.

RISKS / DISCOMFORTS

The following risks/discomforts may occur as a result of you being in this study:

- Although donor stool is vigorously screened for infectious agents, there is a still a rare risk of an infection with harmful bacteria and multidrug resistant organisms (MDRO) being passed from the donor's stool to you. MDRO are common bacteria that have developed resistance to multiple types of antibiotics. These bacteria are present on the bodies of some people and they can co-exist with normal bacteria and cause no symptoms ("commensal") or lead to serious infection spreading to the blood and other organs ("invasive"). Invasive infection is more common in patients with compromised immunity. Infections caused by MDRO are correlated with increased illness, death and prolonged hospitalization. Measures

have been implemented for donor screening (exclude donors at higher risk of MDRO infection) and donor stool testing (exclude stool that tests positive for MDRO)

- Uncommon risks associated with fecal transplantation that have been documented in the literature include cramping, fullness, passing gas, bloating, diarrhea, fever, and blood in the stool. Since this is a research study, not all risks associated with fecal transplantation are known at this time; there may be unforeseen risks associated with study participation.
- There are risks associated with colonoscopy: infection, bleeding, and less than 1% chance of a perforation or hole being created (A separate consent form for colonoscopy will be given on the day of fecal transplantation).
- It's possible your Crohn's disease may progress or get worse after the transplantation.
- When your blood is drawn, temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection.
- There is a rare possibility that confidential information about you may be accidentally disclosed.
- Some of the research that will be done on your blood are genetic studies. The genetic studies are only for research, and will not be used in making decisions about your care. We will not contact you about any results of these genetic studies.

BENEFITS

The following benefits may occur as a result of being in this study:

The potential direct benefit of performing fecal microbiota transplantation for the treatment of Crohn's Disease is improvement or resolution of symptoms associated with having inflammatory bowel disease, such as diarrhea, abdominal pain, fatigue, poor appetite, and minimizing the need for stronger medications that have their own associated side effects.

The indirect benefits include contributions to our knowledge regarding the safety and tolerability of fecal microbiota transplantation. Additionally, by performing research studies examining the bacteria in your stool, as well as performing genetic studies, we hope to see if there is a link between genetics and colonic bacteria, as well as determine the relative abundance of each bacterium. This will also enable us to see if performing the stool transplant changed the composition of your stool and may one day lead to creating medications that increase healthy bacteria in the colon or target harmful bacteria.

PAYMENT TO YOU

You will not be paid for your participation in this study. This research might create new tests, treatment or cures. If it does, you will not get any money from those products.

CONFIDENTIALITY

We will take steps to help make sure that all the information we get about you is kept private. Your name will not be used wherever possible. We will use a code instead. All the study data that we get

from you will be kept locked up. The code will be locked up too. If any papers and talks are given about this research, your name will not be used.

We want to make sure that this study is being done correctly and that your rights and welfare are being protected. For this reason, we will share the data we get from you in this study with the study team, Stony Brook University's Committee on Research Involving Human Subjects, applicable Institutional officials, and certain federal offices. However, if you tell us you are going to hurt yourself, hurt someone else, or if we believe the safety of a child is at risk, we will have to report this.

This study requires that we collect very personal information about you. Therefore, we had the National Institutes of Health give us a Certificate of Confidentiality (COC). This piece of paper says that nobody can force the researchers to give out your information, even if a court of law asks for it. This will give you more protection. The only time information about you can be given out is:

If you are going to hurt yourself

If you are going to hurt someone else

If we believe the safety of a child is at risk.

If data about the fecal transplant needs to be reported to the Food and Drug Administration.

If the data are required by other federal, state or local laws, such as for reporting of communicable diseases.

You should know that the Certificate of Confidentiality does not apply to information about your participation in research, including a consent form that is placed in your medical record (though HIPAA protection does apply). This information may be disclosed to individuals requesting your medical record.

This Certificate doesn’t mean you can’t talk about this study. If you give written permission, your insurance company, your boss, or your medical doctor can be given the research information too.

While you are in this study we will get data about your health from your medical record. We will also get health data from the results of the tests you will have done in this study. You have a right to privacy but the data we get about your health in this study can be shared with the people referenced above (the study team, Stony Brook University's Committee on Research Involving Human Subjects, applicable institutional officials, and certain federal offices) as well as (as applicable):

- Your private doctor
- A board that reviews the safety of the study on an on-going basis

Your health data are shared to make sure the study is being done correctly, costs are charged correctly, and to make sure your rights and safety are protected. Not all of these people are

required by law to protect your health data. They might share it with others without your permission.

You have the right to stop allowing us to use or give out your health data. You can do this at any time by writing to Ellen Li, M.D. If you do this, we will stop collecting any new health data from you, except if we need to keep an eye on a bad side effect you were having in the study. We will use any data we collected before you wrote your letter. When you sign the consent form at the end, it means:

- That you have read this section.
- That you will allow the use and reporting of your health data as described above.
- You have received a form from the University Hospital. It is called the Notice of Privacy Practices form.

The Genetic Information Nondiscrimination Act (GINA):

You should know that a federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will generally protect you in the following ways:

§ Health insurance companies and group health plans may not request your genetic information from this research.

§ If health insurance companies and group health plans do somehow receive your genetic information from this research, they may not use it to make decisions about your eligibility or premiums.

§ Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you when setting the terms of your employment.

Be aware that this new law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

COSTS TO YOU

- If a colonoscopy is scheduled to perform the fecal transplant, we will obtain a prior authorization for colonoscopy to perform the transplant from your insurance company if needed. You may have to pay for a portion of the colonoscopy depending on your insurance plan. We encourage you to contact your insurance company to discuss this potential cost prior to consenting to be in the study.
- All stool tests and blood work for research purposes will be performed without any cost to you for participating in this study.

ALTERNATIVES

- An alternative to having the fecal microbiota transplantation is stepping up the medications you are currently on for your inflammatory bowel disease to immunomodulators and possibly biological agents such as Tumor Necrosis Factor - alpha antagonists, which carry their own risks.
- The other alternative to performing the fecal microbiota transplantation is living with symptoms of Crohn's Disease, such as bloody diarrhea, abdominal pain, fatigue, rashes, joint pains and other manifestations of inflammatory bowel disease.

IN CASE OF INJURY

If you are injured as a result of being in this study, please contact Dr. Ellen Li at telephone # 631-444-3460. The services of Stony Brook University Hospital will be open to you in case of such injury. However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

CONSEQUENCES OF WITHDRAWING

You may withdraw your consent at any time by contacting Dr. Ellen Li. If you do this, we will stop collecting any new health data from you for research purposes but will continue to use the data we collected prior to your withdrawal. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

YOUR RIGHTS AS A RESEARCH SUBJECT

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a signed and dated copy of this consent form to keep.
- You do not lose any of your legal rights by signing this consent form.

QUESTIONS ABOUT THE STUDY OR YOUR RIGHTS AS A RESEARCH SUBJECT

If you have any questions, concerns, or complaints about the study, you may contact Dr. Ellen Li, at telephone # (631-444-3460).

- If you have any questions about your rights as a research subject or if you would like to obtain information or offer input, you may contact the Stony Brook University Research Subject Advocate, Ms. Lu-Ann Kozlowski, BSN, RN, OR by e-mail, lu-ann.kozlowski@stonybrook.edu.

- Visit Stony Brook University's Community Outreach page, http://research.stonybrook.edu/orc/community.shtml#overview-of-volunteering-in-research for more information about participating in research, frequently asked questions, and an opportunity to provide feedback, comments, or ask questions related to your experience as a research subject.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you would like to be a volunteer in this study.

Please initial your response to each statement below.

1. I have been told about the risks, benefits, and alternatives to fecal microbiota transplantation, and I wish to undergo the procedure.

Yes_____ No _____

2. I agree to follow-up via telephone so that the study investigators can evaluate my general well-being for one year post-transplant.

Yes_____ No _____

3. I agree to give a stool specimen 1-3 days prior to the fecal microbiota transplantation, 1 week post-transplant, and 3 months post-transplant for research.

Yes_____ No _____

4. I agree to have my blood drawn on the day of fecal microbiota transplantation for research.

Yes_____ No _____

_____	_____	
Subject Name (Printed)	Subject Signature	Date
_____	_____	
Name of Person Obtaining Consent (Printed)	Signature of Person Obtaining Consent	Date

RECIPIENT RESEARCH ASSENT FORM (CROHN'S)

Project Title: Fecal microbial transplantation in patients with Crohn's disease

Principal Investigator: Ellen Li, MD, PhD

You are being asked to be in a research study.

Purpose: To determine the safety and tolerability of fecal (stool) transplantation to treat Crohn's Disease.

What Will Be Done: **If you decide to be in this study, your part will involve:**

- You will first have to choose somebody who will donate the stool which will be transplanted. The donor can be anyone who we will consent separately and meets eligibility criteria to donate stool. He/she will be asked questions and screened by performing bloodwork and stool studies to make sure he/she is a healthy candidate for stool transplantation.
- After the donor is chosen and he/she meets criteria to donate stool, we will give you a date for the fecal transplantation. During the week before fecal transplantation, we will ask you to write down everything you have eaten on a diet record which we will provide to you. Stool will be collected 1-3 days before your day of fecal transplantation for research.
- On the day before your transplant, you will be given instructions for a bowel prep to clean out your colon completely so it can be examined when we perform the fecal transplantation. For the last 7 hours before your scheduled fecal transplantation, you will have nothing to eat or drink.
- On the day of the transplantation, you will arrive at Stony Brook University Hospital and go to the Endoscopy Suite, located on the 14th Floor. There you will change into a hospital gown and an intravenous line (IV) will be placed to provide you with fluids and sedation during the colonoscopy. Four teaspoons of blood will be taken for research, to perform genetic studies.
- Your donor's stool will be prepared and while you are properly sedated, the stool will be instilled into your colon. You will stay in the Endoscopy Suite, lying on your right side, for at least one hour. This is to maximize contact between the transplanted stool and your colon.

If you are not cleared to depart after one hour, you will stay until the anesthesiologist (doctor who administered sedation during colonoscopy) does clear you to depart. You will be able to eat and drink right after you wake up and can resume normal activities as soon as the anesthesia wears off and you feel well.

- You will receive a phone call the day after the procedure and be asked various questions to determine your general well-being.
- You will then receive weekly phone calls for 12 weeks at a convenient time for you, to ask you further general well-being questions.
- You will keep another diet record during the first week after the transplant. 1 week after your fecal transplantation you will collect stool for research, similar to how you collected stool prior to your stool transplantation.
- You will keep another diet record during the 12th week after the transplant. 12 weeks after your fecal transplantation you will collect stool for research, similar to how you collected stool prior to your stool transplantation.
- After 12 weeks, you will receive monthly phone calls until one year after the transplant to determine your general well-being.

Costs to You:

- You may have to pay for a portion of the colonoscopy, depending on your insurance plan. We encourage you to contact your insurance company to discuss this potential cost prior to consenting to be in the study.
- Stool tests and bloodwork for research purposes will be performed without any cost to you for participating in this study.

Payments to you: You will not be paid for your participation in this study.

Risks/Discomforts:

- Although donor stool is checked for bad germs, there is a still a small chance of an infection being passed from the donor's stool to you.
- Uncommon risks associated with fecal transplantation include cramping, fullness, gas, bloating, diarrhea, fever, and blood in the stool. Since this is a research study, not all risks associated with fecal transplantation are known at this time; there may be unknown risks associated with being in this study.
- There are risks associated with colonoscopy: infection, bleeding, and less than a 1% chance of a perforation or hole being created (A separate consent form for colonoscopy will be given on day of fecal transplantation).
- It's possible your Crohn's disease could get worse after the transplantation.

- When your blood is drawn, temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection.
- There is a rare possibility that confidential information about you may be accidentally disclosed.

Benefits: The potential direct benefits to you of having the fecal transplantation for treatment of Crohn's Disease is improvement in your diarrhea, abdominal pain and symptoms associated with your Crohn's Disease.

The indirect benefits include increased knowledge regarding the safety and effectiveness of fecal transplantation. Additionally, by performing research studies examining the bacteria in your stool, as well as performing genetic studies, we hope to see if there is a link between genetics and colonic bacteria as well as determine the relative abundance of each bacteria. This will also help us see if performing the stool transplant changed the bacteria in your stool and may one day lead to creating medications that increase healthy bacteria in the colon or target harmful bacteria.

In Case of Injury: If you are injured as a result of being in this study, please contact Dr. Ellen Li at telephone # 631-444-3460. The services of Stony Brook University Hospital will be open to you in case of such injury. However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

Your Rights:

- You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a signed and dated copy of this assent form to keep.
- You do not lose any of your legal rights by signing this assent form.

Questions:

If you have any questions about this study, you can ask your parents, or talk to the study doctor, Dr. Ellen Li at 631-444-3460.

If you want to talk to someone about whether or not you have to be in this study, or about other things about this study that you don't want to talk over with your parents or the study doctor, you can call Ms. Lu-Ann Kozlowski, 631-632-9036, or e-mail her at lu-ann.kozlowski@stonybrook.edu.

You can visit this webpage,
http://research.stonybrook.edu/orc/community.shtml#overview-of-volunteering-in-research for

information about being in research studies. You can also ask questions or leave comments about how you feel about being a research subject in this study.

If you sign below, it means that you have read this form and you would like to be in this study.

Please initial your response to each statement below.

1. I have been told about the risks, benefits, and alternatives to fecal transplantation, and I wish to undergo the procedure.

Yes_____ No _____

2. I agree to follow-up telephone calls for one year after the transplant so that the study investigators can evaluate my health.

Yes_____ No _____

3. I agree to give a stool specimen 1-3 days before the fecal transplantation, 1 week after the transplant, and 3 months after the transplant for research.

Yes_____ No _____

4. I agree to have my blood drawn on the day of fecal transplantation for research.

Yes_____ No _____

_____	_____	_____
Subject Name (Printed)	Subject Signature	Date
_____	_____	_____
Name of Person Obtaining Assent (Printed)	Signature of Person Obtaining Assent	Date

DONOR RESEARCH PERMISSION/CONSENT FORM (CROHN'S)

Project Title: Fecal microbial transplantation in patients with Crohn's disease

Principal Investigator: Ellen Li, MD PhD

Co-Investigator: Anupama Chawla, MD

Departments: Medicine/Gastroenterology and Pediatric Gastroenterology & Nutrition

When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff. If you are a parent or legal guardian of a child who may take part in this study, permission from you is required and the assent (agreement) of your child may be required.

You are being asked to be a volunteer in a research study. You are encouraged to take your time in making your decision. You may want to discuss this study with your friends and family.

PURPOSE

The purpose of this study is:

- To determine the safety and tolerability of fecal (stool) transplantation to treat Crohn's Disease.
- Crohn's Disease (CD) is a chronic disease affecting the colon, without a medical cure. The precise cause of having inflammatory bowel disease (IBD) such as Crohn's disease, Ulcerative colitis, or indeterminate colitis is unclear. However, genetics and the environment are thought to play a role. Studies have found that patients with Crohn's Disease have a decreased prevalence of protective bacteria and an increase in harmful bacteria in the colon. Inflammation in the colon in these patients is thought to be due to this imbalance between helpful and harmful bacteria. Currently, the treatment of IBD includes steroids, anti-inflammatory medications and biological therapy, each with its own side effects. Given the role of the gastrointestinal bacteria in driving inflammation in patients with IBD, treatments that manipulate these bacteria have been investigated, including the use of medications containing beneficial bacteria (probiotics), with some benefit. Fecal transplantation (FMT), the transfer of gastrointestinal bacteria (microbiota) from a healthy donor via infusion of a liquid stool suspension, is proving to be an effective alternative treatment for Crohn's Disease. The treatment appeared to improve clinical

symptoms and lower inflammatory markers. The goal of this method is to remove the harmful bacteria in the colon and replace them with normal bacteria.

- _____(recipient's name) has this condition and has named you as a potential stool donor so that the fecal transplantation can be performed. This study hopes to document fecal transplant's safety and tolerability and improve or even eliminate _____'s symptoms by performing the transplantation and then follow-up routinely with him/her for one year.
- We will perform stool studies on you to see if the bacteria in your colon really did change the composition of _____'s colonic bacteria.

We expect to enroll a minimum of 40 patients in this study at Stony Brook University Hospital.

PROCEDURES

If you decide to be in this study, your part will involve:

- Answering a questionnaire to determine your eligibility to donate stool to the transplant recipient
- If you are eligible, you will be asked to have stool testing and blood work done in a laboratory to evaluate for infectious agents that may theoretically be transferred to the recipient by your stool.
- If all this testing is negative, then you and the stool recipient will be given a date for the stool transplant and you will be told to avoid _____ (recipient allergen) for up to one week before the transplant.
- During the week before fecal transplantation, we will ask you to record everything you have eaten on a diet record which we will provide to you.
- On the night before or morning of fecal transplantation, you will be told to collect the stool using Saran™ Wrap, plastic hat, or a collection container. The stool will need to be collected prior to any contamination with the toilet bowl. The stool should then be kept in an airtight container which will be provided to you.
- The stool may be kept at room temperature if used within 6 hours or kept in a refrigerator for up to 24 hours. Stool sample must not be frozen.
- Stool is to be transported from the home to the hospital on ice packs.
- On the day of transplant, you will come to Stony Brook University Hospital's Endoscopy Suite, located on the 14th Floor, and drop off the stool. You will be asked if you had a fever in the previous 2 weeks or accidentally ingested _____ (recipient allergen) in the past week.

When you are first recruited for the study, you will be assigned a coded number. Stool samples collected from you will have your coded number, so your information will not be directly linked to your samples, medical or diet diary information.

RISKS / DISCOMFORTS

The following risks/discomforts may occur as a result of you being in this study:

- When your blood is drawn, temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection.
- As part of the study, blood work to test for HIV (the virus that causes AIDS), Hepatitis B, Hepatitis C, and Syphilis will be performed. If these tests come back as positive, the results will be discussed with you in a confidential manner. If you do test positive for HIV infection, the importance of telling your sex or needle-sharing partners of possible exposure will be discussed.
- There is a rare possibility that confidential information about you may be accidentally disclosed.

BENEFITS

There is no direct benefit to you as a result of participating in this study.

The potential indirect benefits include helping the recipient feel better. Indirect benefits also include contributions to our knowledge regarding the safety and tolerability of fecal microbiota transplantation. Performing research studies on your stool may enable us to see if performing the stool transplant changed the composition of the recipient's stool and may one day lead to creating medications that increase healthy bacteria in the colon or target harmful bacteria.

PAYMENT TO YOU

You will not be paid for your participation in this study. This research might create new tests, treatment or cures. If it does, you will not get any money from those products.

PAYMENT TO THE INSTITUTION

This project has no outside funding.

CONFIDENTIALITY

Protecting Your Privacy in this Study

We will take steps to help make sure that all the information we get about you is kept private. Your name will not be used wherever possible. We will use a code instead. All the study data that we get from you will be kept locked up. The code will be locked up too. If any papers and talks are given about this research, your name will not be used.

We want to make sure that this study is being done correctly and that your rights and welfare are being protected. For this reason, we will share the data we get from you in this study with the study team, Stony Brook University's Committee on Research Involving Human Subjects, applicable Institutional officials, and certain federal offices. However, if you tell us you are going to hurt

yourself, hurt someone else, or if we believe the safety of a child is at risk, we will have to report this.

This study requires that we collect very private information about you. Therefore, we had the National Institutes of Health give us a Certificate of Confidentiality (COC). This piece of paper says that nobody can force the researchers to give out your information, even if a court of law asks for it. This will give you more protection. The only time information about you can be given out is:

If you are going to hurt yourself.

If you are going to hurt someone else.

If we believe the safety of a child is at risk.

If data about the fecal transplantation needs to be reported to the Food and Drug Administration.

If the data are required by other federal, state or local laws, such as for reporting of communicable diseases.

You should know that the Certificate of Confidentiality does not apply to information about your participation in research, including a consent form that is placed in your medical record (though HIPAA protection does apply). This information may be disclosed to individuals requesting your medical record.

This Certificate doesn't mean you can't talk about the study. If you give written permission, your insurance company, your boss, or your private doctor can be given the research information too.

While you are in this study we will get health data from the results of the tests you will have done in this study. You have a right to privacy but the data we get about your health in this study can be shared with the people referenced above (the study team, Stony Brook University's Committee on Research Involving Human Subjects, applicable institutional officials, and certain federal offices) as well as:

- Your private doctor
- A board that reviews the safety of the study on an on-going basis.

Your health data are shared to make sure the study is being done correctly, costs are charged correctly, and to make sure your rights and safety are protected. Not all of these people are required by law to protect your health data. They might share it with others without your permission.

You have the right to stop allowing us to use or give out your health data. You can do this at any time by writing to Ellen Li, MD. If you do this, we will stop collecting any new health data from you, except if we need to keep an eye on a bad side effect you were having in the study. We will use any data we collected before you wrote your letter. When you sign the consent form at the end, it means:

- That you have read this section.
- That you will allow the use and reporting of your health data as described above.
- You have received a form from the University Hospital. It is called the Notice of Privacy Practices form.

COSTS TO YOU

- You will be responsible for your stool and blood work for screening. Depending upon your insurance plan, the cost for this screening might not be covered and you may have to pay out of pocket for this process. We encourage you to contact your insurance company to discuss this potential cost prior to consenting to be in the study.
- When you are approved to be the donor for the research study from your screening results, all stool tests thereafter for research purposes will be performed without any costs to you for participating in this study.

ALTERNATIVES

Your alternative to being in this study is to simply not participate.

IN CASE OF INJURY

If you are injured as a result of being in this study, please contact Dr. Ellen Li at telephone # 631-444-3460. The services of Stony Brook University Hospital will be open to you in case of such injury. However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

CONSEQUENCES OF WITHDRAWING

You may withdraw your consent at any time by contacting Dr. Ellen Li. If you do this, we will stop collecting any new health data from you for research purposes but will continue to use the data we collected prior to your withdrawal. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled.

YOUR RIGHTS AS A RESEARCH SUBJECT

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.

- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a signed and dated copy of this consent form to keep.
- You do not lose any of your legal rights by signing this consent form.

QUESTIONS ABOUT THE STUDY OR YOUR RIGHTS AS A RESEARCH SUBJECT

- If you have any questions, concerns, or complaints about the study, you may contact Dr. Ellen Li at telephone # (631-444-3460).
- If you have any questions about your rights as a research subject or if you would like to obtain information or offer input, you may contact the Stony Brook University Research Subject Advocate, Ms. Lu-Ann Kozlowski, BSN, RN, (631) 632-9036, OR by e-mail, lu-ann.kozlowski@stonybrook.edu.
- Visit Stony Brook University's Community Outreach page, http://research.stonybrook.edu/orc/community.shtml#overview-of-volunteering-in-research for more information about participating in research, frequently asked questions, and an opportunity to provide feedback, comments, or ask questions related to your experience as a research subject.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you would like to be a volunteer in this study.

Please initial your response to each statement below.

1. I have been told about the risks, benefits and alternatives to being screened for fecal microbiota transplantation, and I wish to be a donor.

Yes_____ No _____

2. I agree to give a stool specimen on the day of the fecal microbiota transplantation for research.

Yes_____ No _____

_____	_____	
Subject Name (Printed)	Subject Signature	Date
_____	_____	
Name of Person Obtaining Consent (Printed)	Signature of Person Obtaining Consent	Date

DONOR RESEARCH ASSENT FORM (CROHN'S)

Project Title: Fecal microbial transplantation in patients with Crohn's disease

Principal Investigator: Ellen Li, MD PhD

You are being asked to be in a research study.

Purpose: To determine the safety and tolerability of fecal (stool) transplantation to treat Crohn's Disease

What Will Be Done: **If you decide to be in this study, your part will involve:**

- Answering a questionnaire to see if you are able to donate stool to the transplant recipient
- If you are eligible, you will be asked to have stool testing and blood tests done in a laboratory to see if you have harmful germs that might be transferred to the recipient by your stool. About 2-3 teaspoons of blood will be drawn from your arm vein for the blood tests.
- If all this testing is negative, then you and the stool recipient will be given a date for the stool transplant and you will be told to avoid _____ (recipient allergen) for up to one week before the transplant.
- During the week before fecal transplantation, we will ask you to record everything you have eaten on a diet record which we will provide to you.
- On the night before or morning of fecal transplantation, you will be told to collect the stool using Saran™ Wrap, plastic hat, or a collection container. The stool will need to be collected before any contamination with the toilet bowl. The stool should then be kept in an airtight container which we will give you.
- The stool may be kept at room temperature if used within 6 hours or kept in a refrigerator for up to 24 hours. Stool sample must not be frozen.
- Stool is to be transported from the home to the hospital on ice packs.
- On the day of transplant, you will come to Stony Brook University Hospital's Endoscopy Suite, located on the 14th Floor, where you will drop off the stool and be asked if you had a fever in the previous 2 weeks or accidentally ate _____ (recipient allergen) in the past week.

Costs to You:
You may have to pay for the screening stool and blood tests, depending on your insurance plan. We encourage you or your parent/guardian to contact your insurance company to discuss this before you agree to be in the study.

Payments to you: You will not be paid for being in this study.

Risks/Discomforts:

- When your blood is drawn, temporary pain and bruising where the needle enters the skin, and sometimes, fainting and/or infection.
- As part of the study, blood work to test for HIV (the virus that causes AIDS), Hepatitis B, Hepatitis C, and Syphilis will be performed. If these tests come back as positive, the results will be discussed with you. If you do test positive for HIV infection, the importance of telling your sex or needle-sharing partners of possible exposure will be discussed.
- There is a rare possibility that confidential information about you may be accidentally disclosed.

Benefits: There is no direct benefit to you as a result of participating in this study.

The potential indirect benefits include helping the recipient feel better. Indirect benefits also include helping us learn more about the safety and effectiveness of fecal transplantation. Performing research studies on your stool may help us find out if performing the stool transplant changed the bacteria in the recipient's stool and may one day lead to creating new medications that increase healthy bacteria in the colon or target harmful bacteria.

In Case of Injury: If you are injured as a result of being in this study, please contact Dr. Ellen Li at telephone # 631-444-3460. The services of Stony Brook University Hospital will be open to you in case of such injury. However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

Your Rights:

- The fact that you are in this study will be kept a secret.
- You do not have to be in this study if you do not want to be.
- You can change your mind at any time and leave the study without any problem and without telling us why.
- If we find out anything that may make you change your mind about being in this study, we will tell you.

Questions:
If you have any questions about this study, you can ask your parents, or talk to the study doctor, Dr. Ellen Li at 631-444-3460.

If you want to talk to someone about whether or not you have to be in this study or about other things about the study that you do not want to talk over with your parents or the study doctor, you can call Ms. Lu-Ann Kozlowski, 631-632-9036, or e-mail her at lu-ann.kozlowski@stonybrook.edu.

You can visit this webpage, http://research.stonybrook.edu/orc/community.shtml#overview-of-volunteering-in-research for information about being in research studies. You can also ask questions or leave comments about how you feel about being a research subject in this study.

If you sign below, it means that you have read this form and you would like to be in this study.

Please initial your response to each statement below.

1. I have been told about the risks, benefits, and alternatives to being screened for stool transplantation, and I wish to be a donor.

Yes_____ No _____

2. I agree to give a small part of my stool specimen on the day of the stool transplantation for research.

Yes_____ No _____

_____	_____	_____
Subject Name (Printed)	Subject Signature	Date
_____	_____	_____
Name of Person Obtaining Assent (Printed)	Signature of Person Obtaining Assent	Date