

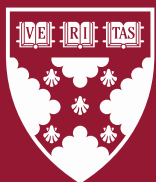
Working Paper 21-132

Case Histories of Transformational Advances

Fecal Microbiota Transplants –Too Simple to be Safe?

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CASE HISTORIES OF TRANSFORMATIONAL ADVANCES

Fecal Microbiota Transplants – Too Simple to be Safe?

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Abstract: This case history describes the development of Fecal Microbiota Transplants through 2013.

Fecal Microbiota Transplants – Too Simple to be Safe?

Transplanting the stool of healthy donors to treat gastrointestinal (GI) diseases¹ has ancient origins. Ge Hong, a fourth-century Chinese physician, used transplanted stool in the form of “yellow soup” he gave patients to treat diarrhea.² Veterinarians transplanted stool, orally and rectally, to treat animals in the 17th century, and in the Second World War, warm camel stool, recommended by the Bedouins, was used to treat German soldiers for dysentery.³

In the 1950s, physicians in US hospitals successfully performed stool transplants, but the procedure did not become routine. For the next half-century, just a small ‘underground network’ of physicians used it on patients with deadly or crippling diseases.

Some of these physicians also attempted to codify and systematically evaluate the safety and effectiveness of the transplants. Concurrently, scientific research suggested that transplants replaced damaged ‘microbiota’ – the ‘community’ of microbes living in the intestinal tract – that provide natural protection against disease-causing pathogens.

By 2013, stool transplants – now called Fecal Microbiota Transplants (FMT) – had attracted widespread attention. Case histories and the results of a just-published randomized trial suggested that FMTs were remarkably effective in treating debilitating colitis produced by antibiotic-resistant bacterial infections. However, only a few dozen medical centers in the US offered FMT while many physicians resisted the procedure. More transplants were, therefore, performed by desperate patients in their homes than in medical centers.

The US Food and Drug Administration (FDA) had expressed concerns about unregulated FMTs but had not issued any formal guidance or rules. Then, in May 2013, the FDA announced that it would regulate treatments using human stool in the same way that it regulated pharmaceutical drugs.⁴

The first section of this Note summarizes recent conjectures and findings about how intestinal microbes (‘microbiota’) affect health. The remaining sections describe 1) pioneering fecal transplants performed in the 20th century, 2) the development of the transplants after 2000, and 3) the situation in May 2013 when the FDA announced its new – and controversial policy.

1. Conjectures and Findings about ‘Microbiota’ (as of 2013)

Much of what had been learned about the role of microbiota by 2013 was based on research undertaken in the previous ten years.⁵ Researchers had found thousands of different kinds of bacteria, viruses, and other microbes living inside bodies and on skin. The microbes numbered in the trillions – more than ten

This case history does not present original research or a new thesis. Instead, it summarizes historical developments and includes questions to stimulate reflection and discussion.

times as many as ‘human’ cells.⁶ Most lived in the gastrointestinal tract and constituted about 40 percent of excreted stool.⁷

Researchers believed that although the microbiota did not contain human cells, it had such an important effect on health it could be considered a human ‘organ.’ Intestinal microbes were believed to help produce vitamins, build and strengthen the immune system, digest food, and even influence mood and behavior.⁸ Researchers further suggested that good health required a diverse or balanced microbiota rather than just the presence of ‘desirable’ microbes: lower diversity increased the risks of autoimmune disorders, allergies, obesity, and chronic GI diseases, such as Ulcerative Colitis, Crohn’s Disease, and Irritable Bowel Syndrome (See **Exhibit 1**).⁹

Diets apparently affected the composition of microbiota and their influence on health. For instance, low-fiber diets decreased the proportion of microbes that helped strengthen the immune system and prevented obesity.¹⁰ Conversely, some researchers attributed declining microbial diversity in advanced economies to the increased consumption of sugar, starch, and meat.

Antibiotic treatments were also thought to reduce microbial diversity. The ‘germ theory’ popularized by Louis Pasteur and Robert Koch in the 19th century had spurred the development of antibiotics that attacked pathogenic bacteria. The average American child was now estimated to receive between 10 and 20 courses of antibiotics by the age of 18.¹¹ These courses could kill a wide range of microbes along with disease-causing bacteria. Similarly, many farmers fed their livestock antibiotics to increase their weight quickly, and eating the meat of animals who had been fed antibiotics could kill off some of the eater’s intestinal bacteria.¹²

Another hypothesis attributed the reduced diversity of gut microbes to urbanization (which reduced contact with microbe-rich soil) and anti-microbial cleaning agents. Paradoxically, according to this ‘hygiene’ hypothesis, reduced exposure to germs might have increased the incidence of allergies and autoimmune diseases.

2. Pioneering Transplants (1958 through the 1990s)

The mainly 21st-century research described above supported the less detailed conjectures of a few physicians in the 1950s who had attempted fecal transplants, as we will now see.

In the 1940s and 1950s, physicians began using penicillin (developed to treat soldiers in the Second World War) and other antibiotics to treat infections, including those that caused diarrhea. Physicians also routinely gave antibiotics to patients undergoing surgery to prevent infections. However, some physicians noted diarrhea often followed antibiotic treatments and suspected this resulted from killing protective intestinal bacteria (then called the ‘microflora’). In 1958, a doctor in a New England hospital tried an unusual solution: he asked patients to give him stool samples before their operations. After their operations, he would give patients gelatin capsules containing their own “pre-operative” stool to replenish the intestinal bacteria that the antibiotics normally administered after surgeries might have killed. Although this seemed to reduce patients’ diarrhea, flatulence, and indigestion, the hospital’s chief administrator ended the practice when he heard of it, and the results were never officially published.¹³

That very year, Benjamin Eiseman, Chief of Surgery at a US Veteran's Administration Hospital in Colorado,¹⁴ and his colleagues first reported successful fecal transplants in a medical journal. Eiseman's transplants attempted to restore "the balance of nature" that antibiotic treatments had disturbed by killing "normal organisms" in patients' intestines.¹⁵ However, the stool was taken from healthy women in the hospital's maternity ward (rather than from the patients themselves), administered through rectal enemas^a (rather than capsules), and used to treat a form of colitis^b (rather than to counter the after-effects of antibiotics given to patients after their operations).

Eiseman successfully treated four patients (three in critical condition) who had not responded to traditional therapies and whose colitis then had a fatality rate of 75%.¹⁶ The symptoms of all four patients resolved just hours after fecal enemas were administered. Later research (the first of which was published in 1978) suggested that Eiseman's patients had been infected with *Clostridioides difficile* (*C. difficile*) bacteria.¹⁷ The bacteria can live harmlessly in the intestines of many people, possibly because other gut microbes help control the harmful effects.¹⁸ But, repeated antibiotic treatments can make *C. difficile* infections life-threatening, possibly by weakening protective microbial communities and making the bacteria resistant to antibiotics.

Eiseman and his colleagues had anticipated that fecal transplants would become standardized and simplified,¹⁹ possibly by administering stool capsules. Instead, before researchers had studied the risk of antibiotics entrenching *C. difficile* infections, a new treatment became the standard of care for colitis. Paradoxically, the new treatment was based on the antibiotic vancomycin (first marketed in the US in 1958.)²⁰

Some physicians nonetheless continued Eiseman's pioneering fecal transplants to treat the colitis of patients who had failed to respond to standard therapies. In 1981, Talmadge Bowden (a general surgeon who taught at the Medical College of Georgia in Augusta) and his colleagues were the first to report the results of their attempts: Over the previous 18 years, the Georgia physicians had given fecal enemas to sixteen patients. Thirteen patients had "responded dramatically, with decreases in diarrhea, temperature, white blood cell counts, and a rapid convalescence." Of the three patients who died, two did not have inflamed colons at death. And "no ill effects from the fecal enemas [had been] noted."²¹

Later research showed how the fecal treatments might have been effective. A 2008 genetic analysis of the gut microbes of patients with *C. difficile* infections showed a reduction in the diversity of the microbes. A 2010 study then showed a significant change in gut microbes after fecal transplants: Fourteen days after their transplants, patients had distributions of gut bacteria resembling that of healthy individuals.²²

Questions (for reflection and discussion):

Based just on what you have read so far, please write down (in less than ten words) what you think would be necessary to make FMTs an accepted treatment for *C. difficile* (and other diseases).

- _____

^a Enema: An injection of a fluid (including gases, liquids, and slurries) into the rectum through a small tube.

^b Colitis: Chronic inflammation of the colon that produces debilitating symptoms including diarrhea, abdominal bleeding, pain, and cramps.

3. Developments after 2000

Informal network and practices. For many years, Thomas Borody, an Australian gastroenterologist, was “virtually the only proponent” of fecal transplants. Borody had performed his first transplant in 1988 after reading Eiseman’s three-decade-old paper.²³ Then, gradually, “a small underground of gastroenterologists and infectious-disease specialists began experimenting with the procedure.”²⁴ Christina Surawicz, a gastroenterologist at the University of Washington’s medical school (and a long-time researcher on *C. difficile*), “took a leap of faith” with her first patient in 2004. She then became known as an FMT pioneer.²⁵

Patients sometimes prompted physicians to learn the procedure from pioneers since professional bodies had not standardized the techniques. Colleen Kelly, a gastroenterologist at Brown University’s Medical Center, in Providence, RI performed her first transplant in 2008 on a 26-year-old medical student. She had previously thought the procedure was “something at the far fringes of medicine.” At her patient’s insistence, Kelly contacted Lawrence Brandt, a professor of medicine and surgery at the Albert Einstein College of Medicine in New York, to learn about his process for performing transplants.²⁶ Brandt had been performing the procedure since 1999.²⁷

With members of the network “making up protocols as they went,”²⁸ criteria for screening stool donors and their stool could vary considerably. In 2011, an international working group suggested guidelines (see **Exhibit 3**) based on expert opinion rather than evidence. In practice, however, some physicians used more stringent criteria than others.²⁹ Similarly, while the working group guidelines proposed using saline or milk with 4% fat to dilute stool, some physicians used water.³⁰

The guidelines also suggested: homogenizing stool in a household blender to produce a slurry-like consistency; filtering out particulate matter from the slurry using gauze pads or urine stone strainers; and smaller volumes (25–50 mL) if instilled into the upper intestine and larger volumes (250–500 mL) for instillation in the lower intestine.³¹

Physicians usually gave patients bowel preparations (like the ones used for colonoscopies^c) to clear out *C. difficile* bacteria before fecal transplants. Some also administered oral vancomycin for this, although no evidence showed that one practice produced better outcomes than the other.³²

Until 1989, enemas had been the most used method to transplant stool. By 2013, physicians were adapting other procedures. In about 75% of reported procedures, physicians had used colonoscopes and enemas to insert stool rectally into the colon. In the remaining 25% of cases, nasogastric tubes (inserted through the nose) and gastroscopes (through mouths) had been adapted to insert stool into stomachs.^d The different procedures and instruments posed different risks. Tubes inserted through the nose could accidentally introduce feces into the windpipe, while colonoscopes could, as in any colonoscopy, perforate

^c Examinations of the colon using a flexible scope inserted through the rectum. Also used to remove tumors or polyps (polypectomy) from colons. (See accompanying Note on the Development of Endoscopy)

^d Nasogastric tubes were normally used to insert fluids (including nutritional liquids and medicinal slurries) into the stomach through the nose. Gastroscopes (as described in the Note on Endoscopy) were flexible tubes inserted through the mouth and normally used to view and extract tissue samples from the inside of stomachs.

the colon. Yet, analyses of outcomes did not suggest any differences in effectiveness, and there was no consensus about the appropriate procedure.³³

Most clinicians who performed fecal transplants asked patients to find donors, preferably their own children, parents, or intimate partners. According to the University of Washington's Christina Surawicz, there was "something very intimate about putting someone else's stool in your colon, and you are already intimate with a spouse."³⁴ Another argument for intimate partners was the presumption that they already shared infectious exposures. However, there was no evidence that stool from related donors produced better results, and research on the safety of blood donations suggested that blood from donors identified by patients was more likely to contain pathogens.³⁵

The stool was usually "fresh" – transplanted within 24 hours of collection.³⁶ In 2011, however, researchers at the University of Minnesota – a leading center for fecal transplants – published a study describing the advantages of a stool bank they had set up. The bank secured and stored stool from volunteers recruited by the researchers, which could be instilled into any patient (see **Exhibit 4**). Another leading transplant center in Sydney, Australia, was also using stool secured from donors recruited by the center rather than by patients.

Treatment Results. By 2008, about 100 cases of fecal transplant treatments for *C. difficile* infections had been reported with a success rate of 89%. A comprehensive review published in 2011 analyzed reports of 317 *C. difficile* infections treated with fecal transplants. Ninety-two percent of patients had been reported symptom-free after their treatments, symptoms had recurred in 4%, and 4% had died.³⁷

All the studies reported in the 2011 review were case reports and case series. None was a randomized clinical trial.³⁸ Researchers in the Netherlands had finished a randomized trial comparing fecal transplants to vancomycin treatments in 2010 (which they had started in 2008) but had not yet published their results. By the end of 2011, three clinical trials of fecal transplants had also begun in Canada.³⁹ In 2012, US researchers secured funding from the National Institutes of Health (NIH) to start a randomized trial. The researchers (led by Colleen Kelly, included Lawrence Brandt and another transplant pioneer, Alexander Khoruts, from the University of Minnesota) expected to complete their study by September 2015.⁴⁰

In January 2013, the *New England Journal of Medicine (NEJM)* published the results of the Netherlands trial conducted on 43 patients with recurrent *C. difficile* infections. Researchers ended the trial in 2010 after interim results made it unethical to continue: fecal transplants had stopped the diarrhea of 94 percent of patients compared to less than a third of patients given vancomycin treatments.⁴¹

A 'state of the art' review published in 2013 (and which cited the January *NEJM* article) concluded that stool transplants were "relatively simple" and "short duration procedures" with a "high clinical cure rate" for the treatment of *C. difficile* infections. Their cost was "also bound to be lower" compared to "repeated courses of antibiotic therapy, hospitalization" and the "loss of work productivity caused by the persistence of diarrhea."⁴²

Transplants for other Diseases. Although *C. difficile* cases accounted for most of the 300 stool transplants reported in the medical literature by 2012, the procedure had been tried for other diseases. According to the ‘state of the art’ review, fecal transplants had shown promise in many non-infectious diseases, including irritable bowel syndrome, obesity, anorexia nervosa, and multiple sclerosis. However, no randomized trials had been reported and cure rates for other diseases were not as high as in *C. difficile*.⁴³

For example, a pilot study published online in May 2013 found that fecal enemas reduced symptoms in seven of nine children with ulcerative colitis. However, according to the study’s lead researcher, the results also suggested that fecal transplants for ulcerative colitis might require more prolonged treatment than for *C. difficile*.⁴⁴

Needs and Barriers. Illnesses and deaths from *C. difficile* infections were multiplying. In the United States, infection rates had doubled from 1996 to 2003, and in 2010, incidence was estimated at 500,000 infections per year, with up to 20,000 annual deaths. Increased infections were also reported in Europe, Taiwan, Korea, and Canada.⁴⁵

Virulent strains of *C. difficile* had developed which resisted standard vancomycin antibiotic treatments. Infections recurred after a course of vancomycin in about a fifth of patients. Likewise, 40% of patients treated after a first recurrence had a second recurrence; after two or more recurrences, the chances of another recurrence rose to 60%.⁴⁶ As a “last resort,” surgeons could remove infected colons, but about 50% of patients did not survive the operations.

Yet, many physicians remained reluctant to attempt transplants to treat recurrent *C. difficile* – or any other disease. Infectious disease specialist Judy Stone wrote that physicians seemed to “find the idea particularly distasteful.”⁴⁷ Similarly, according to Albert Einstein’s Brandt, knowledgeable patients faced a “major stumbling block” in the “intransigent negativism of their physicians,” who called the procedure “quackery,” a “joke,” and “snake oil.”⁴⁸ “When I called around about the possibility of treating my [recurrent] *C. difficile* with a fecal microbial transplant,” one patient wrote, physicians “refused to even entertain the idea, seemingly out of disgust.”⁴⁹

Moreover, physicians sympathetic to fecal transplants faced logistical and administrative challenges. They lacked the resources for “harvesting and processing suitable donor material,” as one gastroenterologist put it.⁵⁰ Private and public insurers did not reimburse patients for this procedure (including the costs of screening stool and donors). And, because it was considered experimental, many academic medical centers and hospitals required Institutional Review Board (IRB)^e approvals. Some hospitals simply refused to allow the procedure.⁵¹

^e Committees mandated in the U.S. by National Research Act of 1974 (and now governed by Title 45 Code of Federal Regulations Part 46.[3]) to evaluate and monitor research involving human subjects, The rules require IRBs to review all research that receives direct or indirect support from the United States federal government. IRBs are themselves regulated by the Office for Human Research Protections (OHRP) within the Department of Health and Human Services (HHS).

Self-Treatments. With many physicians unwilling or unable to perform fecal transplants, patients with *C. difficile* infections and other Inflammatory Bowel Diseases (including Crohn's disease and ulcerative colitis) were attempting self-administered treatments. For example, an August 2012 story in the Wisconsin State Journal reported how Cindy Staley, a night-shift nurse in a local hospital, cured her *C. difficile* infection. Six months of diarrhea that antibiotics could not stop had made Staley "desperate." She had read about fecal transplants, but her health plan refused to cover the procedure. Then, improvising from what she had read in the medical literature, the nurse used a blender to homogenize her husband's stool with saline and a turkey baster as an enema. "It didn't sound like that elaborate of a procedure, so I figured I could do it myself," Staley told the Wisconsin State Journal reporter.⁵²

Some physicians whose hospitals did not allow transplants (or faced other obstacles) instructed their patients on home administration.⁵³ Other patients followed step-by-step instructions provided in books, websites, and YouTube videos. A *New Yorker* article⁵⁴, for example, told the story of Tom Gravel, a project manager for a non-profit, who had endured three years of Crohn's disease. A "shifting regimen of enemas, suppositories, shots, supplements, and, for several months, intravenous infusions of Remicade, a potent immunosuppressant, at a cost of more than twelve thousand dollars each" had provided no relief. After reading an article in the *New York Times* about a man who had largely recovered from ulcerative colitis after fecal transplants – and his doctor had declined to provide the treatment or even advice – Gravel found a how-to book on Amazon. Following the book's instructions, Gravel (a project manager with no medical training) purchased a blender, a rectal syringe, saline solution, surgical gloves, and Tupperware containers. A neighbor donated his stool.

Gravel had followed instructions in his book to test his neighbor's stool – and paid for the tests. But tests could cost several hundred dollars and according to the *New Yorker* article, many patients were "circumventing the medical system altogether." Although documented instances of self-treatments "going terribly wrong" were scarce, there were "anecdotal reports" of bacterial and viral infections.⁵⁵

Improvements and Alternatives. Self-treatments alarmed some pioneering physicians. The University of Minnesota's Alexander Khoruts described a phone call from a "do-it-yourselfer" who had mixed stool from a neighbor and her son's mother-in-law and administered it to herself without results. "She wanted to know if maybe the chlorine in the water killed off everything. Six months later, she called me back and said her *C. difficile* was gone, but now she had parasites."⁵⁶

Khoruts and his colleagues, who had organized the stool bank in Minneapolis, hoped that freezing stool secured from "universal donors" would reduce risky self-treatments by decreasing the cost of donor screening – which, as mentioned, was not reimbursed. Using frozen stool would also limit "aesthetic concerns" by making execution of the procedure a "simple matter" of "loading... syringes with thawed, nearly odorless, material and a colonoscopy."⁵⁷

Outside Minneapolis and (as mentioned) Sydney, Australia, however, few other centers banked stool: The pioneering randomized control trial in the Netherlands, for instance, had recruited a pool of screened donors (rather than rely on patient-identified sources) but had collected stool on the day of its infusion. The Minneapolis bank did not supply its frozen stool to physicians in other centers.

Although the University of Minnesota had licensed some of its stool processing technologies to an Australian company, CIPAC Ltd., its researchers noted, in a 2012 article, that "the pharmaceutical industry ha[d] shown little interest in technological development of FMT-based therapeutics, in large part due to

the wide availability of donor material and its complex composition. Instead, development ha[d] been driven mostly by individual clinicians faced with desperate need in their patients.”⁵⁸

One such clinician-researcher, Thomas Louie, a Canadian infectious disease specialist at the University of Calgary, had administered donated feces in capsules swallowed by a patient who could not tolerate a transplant through the nose or rectum. Louie then experimented on 31 more patients, giving them 24-34 capsules containing freshly donated (rather than frozen) stool. Louie’s team coated the capsules with gelatin so they would survive digestive juices in the stomach and reach the intestines. Louie was following his patients’ clinical progress and changes in their gut microbiomes, with results expected in late 2013.⁵⁹

Elizabeth Hohmann, an infectious disease specialist at Boston’s Massachusetts General Hospital, had submitted (in early 2013) a proposal to her hospital’s human research committee to study transplants of encapsulated frozen stool. Hohmann planned to administer 30 acid-resistant capsules over two days to *C. difficile* patients. The proposal anticipated completing the experiment in early 2014 and publication of the results at the end of that year.⁶⁰

Another Canadian infectious disease expert, Elaine Petrof, at Queen’s University in Kingston, Ontario, had completed a pilot study of synthetic stool that would not have to be screened for infectious diseases, could be made for many people, and provided off-the-shelf.⁶¹ Petrof’s team had developed a “Robogut” – a mechanical device that mimicked the conditions in colons – to produce “RePOOPulate” containing 33 types of lab-grown bacteria (isolated from the stool of a single human donor).⁶² The synthetic stool had cured the *C. difficile* of two patients, but the equipment was expensive, and the bacteria were “finicky.”⁶³ The complexity of synthetic stool with 33 kinds of bacteria also posed “formidable manufacturing challenges,” but removing even a few strains of bacteria could “greatly reduce its efficacy by reducing the diversity of bacteria” in the mixture.⁶⁴ As another Canadian infectious disease specialist noted, human stool contained “thousands of different bacterial species in different concentrations, and to try to sort out which ones are the important ones and the protective ones [was] not a trivial matter.”⁶⁵

Researchers developing alternatives – or conducting clinical trials of existing FMT procedures – in the US had to satisfy sometimes confusing administrative and regulatory requirements. These did not exist when Eiseman performed his pioneering transplants in 1958: “Those were days when if one had an idea, we simply tried,”⁶⁶ he recalled. Later, experimenters at medical centers had to secure IRB approvals, as mentioned.

Projects funded by the NIH required more reviews and approvals. When Kelly applied for an NIH grant to conduct a randomized trial in 2011, the NIH told her she would first need to submit an Investigational New Drug (IND)^f application to the FDA and secure the FDA’s approval. As a clinician rather than a full-time researcher, she found the process unclear. She went back and forth with various FDA people by phone and email and consulted regulatory experts. Ultimately, after spending “hundreds of hours” on paperwork, she secured FDA approval for the IND and the NIH grant.⁶⁷

^f The FDA required researchers who wanted to experiment with a new drug (i.e., one that had not secured FDA approval) to first submit INDs containing detailed descriptions of their proposed experiment for the agency’s review and prior approval.

Questions (for reflection and discussion):

Before reading further, please write down (in less than ten words) what you found most significant or surprising about the development of FMT after 2000.

- _____

The Situation in May 2013

The January 2013 *NEJM* issue reporting the results of the first randomized trial of fecal transplants included an editorial assessment that the procedure had reached a turning point. According to the editorial, the Netherlands trial provided “important confirmation” of fecal transplants. Although the study was “unblinded and imperfect,” the results would stimulate advances that could make transplant therapies “acceptable and accessible to most patients and their physicians.” Besides stool banks that would provide “quality-controlled treatment materials,” the editorial foresaw the development of mixtures of cultured bacteria that would resist *C. difficile* infections. Cultured mixtures would also assuage concerns about transplants of infected stools (that screening donors and donated stool might miss).⁶⁸

As mentioned, pilot studies in academic centers (and the University of Minnesota stool bank) had already indicated the possibilities for more “quality-controlled treatment materials.” And although fecal transplants were “neither glamorous nor capable of promising a blockbuster drug,” as one observer put it,⁶⁹ a few startups were developing offerings for broad clinical use. One startup, OpenBiome, had been established as a not-for-profit stool bank. Others (including Rebiotix, Seres, and Vedanta) had received funding from venture capitalists and had applied for (or secured) patents. (See **Exhibit 5**).

Formalizing IND Requirements. According to a *New Yorker* article, the FDA had “watched the surging demand for fecal transplants with concern. In the early nineteen-eighties, at least twenty thousand people became infected with HIV after receiving blood transfusions contaminated with the virus because doctors didn’t know to screen for it. Could a similar, unknown threat be lurking in a donor’s stool?”⁷⁰ Yet, the FDA did not want to regulate stool transplants as it did blood transfusions or organ or skin transplants. Rather, by January 2013, according to Lawrence Brandt, the FDA “had begun to regard stool used for transplants as a drug, and to require doctors administering it to apply for permission.”⁷¹

The FDA had not, however, “publicly set forth any message” on permissions. Agency officials told physicians who enquired that in principle – and as with any experimental drug – performing transplants required prior approval of an IND application. The FDA would not, however, prosecute physicians who performed transplants just to treat patients; it would tolerate these procedures like any other unregulated “practice of medicine.” The FDA would only require INDs for research, such as the randomized trial that Brown’s Colleen Kelly had organized. (In contrast, regulators in some European countries did not regard fecal transplants as drugs, and the Netherlands trial completed in 2010 did not require IND-style applications and regulatory approvals.)⁷²

On February 25, 2013, the FDA announced a public workshop “to provide a forum for the exchange of information, knowledge, and experience among the medical and scientific community about the regulatory and scientific issues associated with FMT.” Some participants at the workshop, held on May 2-3, questioned the FDA’s claim that the “use of FMT and clinical studies to evaluate its safety and effectiveness [we]re

subject to regulation by FDA,” and “some health care providers stated that applying IND requirements w[ould] make FMT unavailable” for many patients.⁷³

Nonetheless, the FDA announced at the end of the workshop that it had decided to formally designate stool for transplant as a biologic drug and to require all physicians to obtain IND approvals thirty days before performing a fecal transplant (except in emergencies). “We want to provide regulatory clarity,” an FDA spokesman told NBC News. “Our intention is not to interfere with life-saving treatment, but to assure that patients’ rights and safety are protected and to encourage scientifically valid studies to determine the proper applications and procedures for fecal microbiota transplants.”⁷⁴

Charles Posternack, the chief medical officer at a 394-bed hospital in Florida, supported the FDA decision: IND requirements, he said, weren’t an undue burden. The process required some effort, but it quickly became second nature. According to Posternack, the FDA’s expanded role would foster collaboration and evidence-sharing among sites performing the procedure.⁷⁵

Virginia Commonwealth University medical school professor Michael Edmond had a different reaction. The new rules meant “a mountain of paperwork, writing protocols, writing exclusion and inclusion criteria, and explaining what I’ll do if someone has a side effect. I just can’t do it.” After “canceling all his upcoming fecal transplant appointments, Edmond advised his patients that they could still use at-home enema kits.”⁷⁶

Brown University’s Kelly agreed that without some form of regulation, “stupid things” would happen, such as the spread of infectious diseases. And while well-conducted trials were necessary, it would “take years to accumulate the data necessary to fully understand FMT.” Meanwhile, INDs would repel practicing physicians: “You need to put hours and hours of work into it, and then you’re still under FDA’s oversight because this is not an approved therapy. So that means you have to submit adverse events reports, keep records, and report annually on your program. And at any time, without any warning, [the FDA] can come and inspect your facility.”⁷⁷

Kelly’s research collaborator, Brandt, concurred: INDs required “a huge amount of paperwork documentation, record-keeping, and follow-up that the average practitioner was simply not going to do.”⁷⁸ Standardized compounds, Brandt predicted, would eventually replace fecal transplants. But until then, said Kelly, “we cannot deny this effective therapy” that used a “free substance” with “unlimited supply” to patients who have “failed all other available treatments.”⁷⁹

Questions (for reflection and discussion):

Based on this case history and others you previously read, would you expect fecal transplants to become a commonly used treatment in the next ten years?

- Yes/No

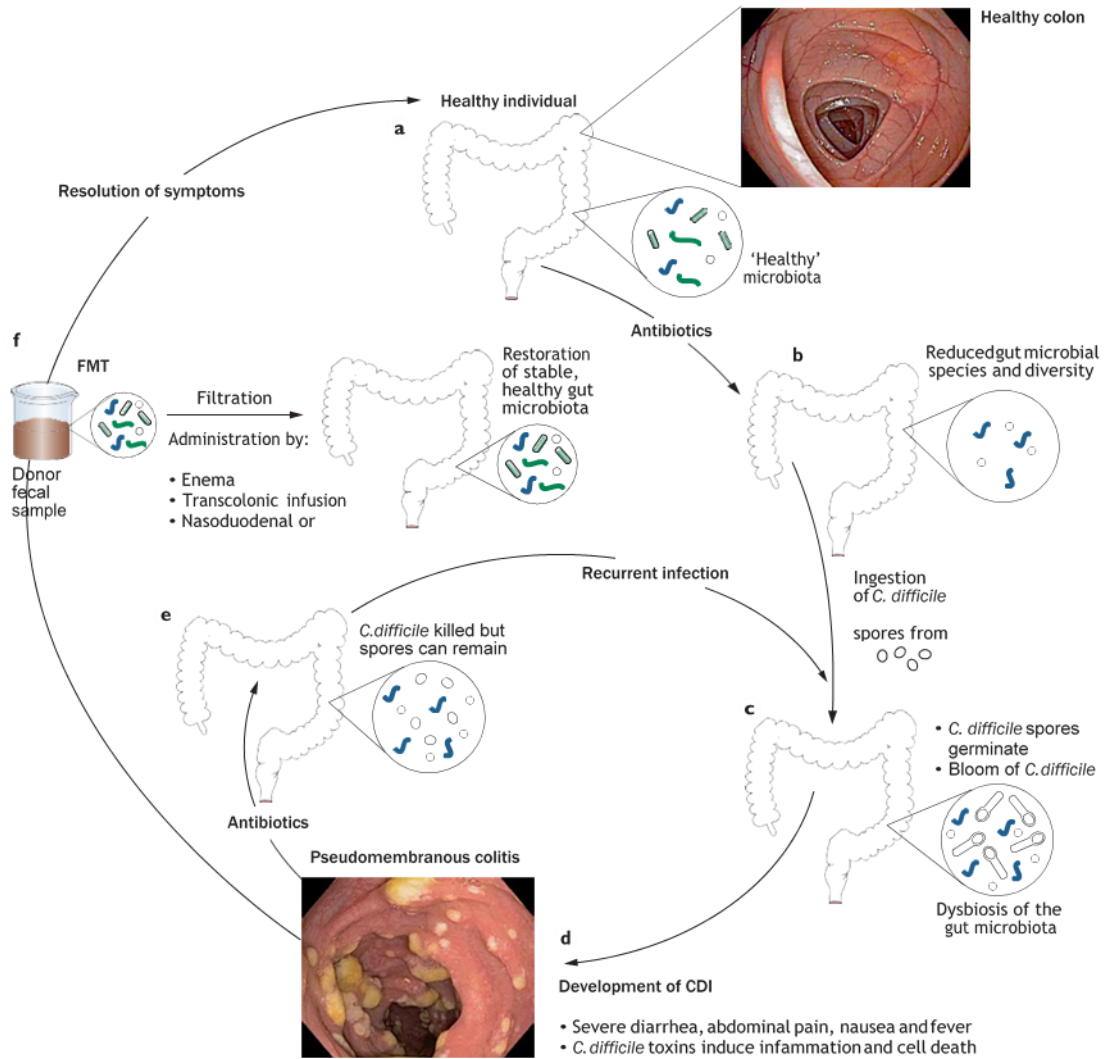
Explain why or why not (in less than ten words).

Exhibit 1 Examples of chronic, incurable gastrointestinal diseases

Name	Description	Symptoms	Treatments
Ulcerative Colitis	Inflammatory bowel disease (IBD) causing long-lasting inflammation and ulcers (sores) in digestive tracts. Affects the innermost linings large intestines (colon) and rectum.	Diarrhea, often with blood or pus Abdominal pain and cramping Rectal pain and bleeding – passing small amount of blood with stool. Urgency to defecate. Inability to defecate despite urgency. Weight loss Fatigue Fever	Drugs or surgery.
Crohn’s Disease	Inflammatory bowel disease (IBD), causing inflammation of different areas of the digestive tract in different people.	Diarrhea Fever Fatigue Abdominal pain and cramping Blood in stool Mouth sores Reduced appetite and weight loss Pain or drainage near or around the anus due to inflammation from a tunnel into the skin (fistula).	No cure. Treatments focused on reducing the inflammation that triggers symptoms.
Irritable Bowel Syndrome (IBS)	Disorder of the large intestine.	Abdominal pain, cramping, or bloating that is typically relieved or partially relieved by passing a bowel movement. Excess gas Diarrhea or constipation – sometimes alternating bouts of diarrhea and constipation Mucus in the stool	Treatments focused on relieving symptoms. Mild symptoms controlled by managing stress and by changes in diets and lifestyles.

Sources: Mayo Clinic posts on <https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/diagnosis-treatment/drc-20353331>; <https://www.mayoclinic.org/diseases-conditions/irritable-bowel-syndrome/symptoms-causes/syc-20360016>; and <https://www.mayoclinic.org/diseases-conditions/crohns-disease/symptoms-causes/syc-20353304#:~:text=Crohn’s%20disease%20is%20an%20inflammatory,digestive%20tract%20in%20different%20people>, accessed March 2021.

Exhibit 2 Development and Treatment of Recurrent *C. difficile* Infections (r. CDI)



Source: Borody, Thomas J. and Alexander Khoruts "Fecal microbiota transplantation and emerging applications," *Nature Reviews Gastroenterology & Hepatology* 9, 88 (2012). Page 90. <https://www.nature.com/articles/nrgastro.2011.244>

Exhibit 3 Working Group Guidelines for Screening Donors and Stool

Questionnaire

Use “American Association of Blood Banks Donor History Questionnaire” to exclude donors with known HIV or HCV or HBV infection, known exposure to HIV or viral hepatitis within the previous 12 months, high-risk sexual behaviors, use of illicit drugs, tattoo or body piercing within six months, incarceration, or history of incarceration, known current communicable disease, risk factors for variant Creutzfeldt-Jacob disease, travel (within the last six months) to areas of the world where enteric pathogens are endemic or the risk of traveler’s diarrhea is high, history of inflammatory bowel disease, history of inflammatory bowel syndrome, idiopathic chronic constipation, or chronic diarrhea, history of gastrointestinal malignancy or known polyposis, antibiotics within the preceding three months major immunosuppressive medications, systemic antineoplastic agents, recent ingestion of a potential allergen.

Baseline Stool Tests

Use FDA guidelines for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) to exclude donors whose stool tests positive for parasites and ova, *C. difficile*, *Helicobacter pylori*, and enteropathogenic bacteria, *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Isospora*.

Baseline Blood Tests

Use FDA guidelines for donors of HCT/Ps to exclude donors whose blood tests positive for HIV type 1 and 2, Hepatitis A, B, and C, and *Treponema pallidum*.

Source: Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA, Russell G, Surawicz C; Fecal Microbiota Transplantation Workgroup. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol*. 2011 Dec;9(12):1044-9. doi: 10.1016/j.cgh.2011.08.014. Epub 2011 August 24. PMID: 21871249; PMCID: PMC3223289.

Exhibit 4 Banking Stool

In 2009, researchers started a fecal transplant program at the University of Minnesota. The program evolved from using stool donors identified by patients to rigorously screened “universal” volunteer donors, and from crudely prepared, fresh stool to frozen extracts produced through a more standardized protocol.

Initially, patients had been asked to identify donors on their own. Donors had to submit medical records and have medical history interviews to assess risk factors for HIV, Hepatitis, and other communicable diseases. Recent travel to areas with a high prevalence of diarrheal illnesses and the use of antibiotics in the previous six months were “absolute criteria” for donor exclusion. Autoimmunity and allergic diseases were treated as “relative exclusion criteria.” Donors also had blood tests for HIV and Hepatitis B and C, and stool tests that included screening for microbes, ova, and parasites that caused intestinal diseases (such as *C. difficile*, Giardia, and Cryptosporidium).

The patient-identified donors arrived at the colonoscopy centers, where the transplants were performed a couple of hours before the scheduled transplantation procedure. Their stool was collected and processed in a dedicated bathroom.

Logistic difficulties, the unavailability of stool when it was needed, and the absence of evidence of any therapeutic benefit from related donors led the program to use two unpaid volunteer donors, one of whom provided most of the fecal material used. Stool from the two “universal donors” was not always used immediately. Instead, it could be stored frozen (after adding glycerol) at – 80 °C for up to 8 weeks until it was used (after thawing). Changes in equipment and processing also produced fecal material extract that was nearly odorless and less viscous.

The clinical efficacy of frozen preparations was “quickly evident” and became part of the standard protocol for stool transplants at the Minnesota center.

Source: Adapted from: Hamilton, Matthew J, Alexa R Weingarden, Michael J Sadowsky, and Alexander Khoruts. “Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium Difficile* Infection.” *American Journal of Gastroenterology* 107, no. 5 (May 2012): 761–67. <https://doi.org/10.1038/ajg.2011.482>.

Exhibit 5 Startups Developing FTM Products and Services

OpenBiome. Carolyn Edelstein, then a graduate student at Princeton’s Woodrow Wilson School, and Mark B. Smith, then completing his Ph.D. in microbiology at the Massachusetts Institute of Technology (MIT), conceived of a not-for-profit stool bank – “OpenBiome” -- in November 2012. Edelstein and Smith, who had been college classmates at Princeton, persuaded a third classmate, James Burgess, to join up. In the next six months, they secured a grant and office space at MIT, after which Burgess took a leave from MIT’s Sloan School, where Burgess was an MBA student, to serve as OpenBiome’s full-time executive director. OpenBiome expected to provide frozen stool “at cost” by the end of the year.⁸⁰

Rebiotix. Michael Berman and Lee Jones started the Minneapolis-based company, initially named “Mikrobex,” in 2011. Berman had previously started and invested in several medical device companies and served as the president of Boston Scientific’s cardiology business⁸¹, while Lee Jones had previously served as the CEO of Inlet Medical for nine years and as a general manager at Medtronic for fourteen years.⁸² Rebiotix was developing a “ready-to-use and physician friendly” suspension (to be administered by enema) produced by filtering and preserving screened stool obtained from healthy donors. By May 2013, the company had secured patents for some of its processes, applied for FDA Fast Track designation⁸ for the suspension (“RBX2660”) it was developing, and hoped to start phase 2 trials later in the year. Rebiotix raised more than \$5 million from individual investors. Co-founder Jones served as its CEO and a board member, as did co-founder Berman. Rebiotix had also added William McGuire, the former CEO of the United Health Group, and Erwin Kellen, a long-time venture capitalist, to its board.

Seres. Flagship Pioneering, a Cambridge, Massachusetts-based venture capital firm that creates and funds early-stage healthcare businesses, started Seres in “stealth mode” in 2010 “after a three-year exploration into the biology of the human microbiome” (according to a Flagship press release). David Berry, a Flagship partner, also served as Seres’s CEO. The company’s lead product, ‘SER-109,’ consisted of human stool that had (after cleaning and filtering) been treated with ethanol to remove all but a hundred or so bacterial strains. Seres researchers believed pills containing these strains would be sufficient to treat *C. difficile* infections. (The Seres removal process did not, however, involve culturing the chosen strains as the Canadian researchers had done with their synthetic ‘RePOOPulate’ described earlier.)⁸³

Vedanta. PureTech Ventures, a Boston-based incubator of life sciences businesses, and “a group of world-renowned experts in immunology and microbiology” (according to a company press release) had started the Cambridge, MA-based Vedanta in 2010.⁸⁴ The company was developing products consisting of a selected “consortium” of bacteria usually found in human stool, whose absence could lead to autoimmune diseases, such as Crohn’s disease. (Although the selected strains would originate in human stool, the company expected to culture therapeutic quantities of the bacteria in laboratories (rather than remove unwanted bacteria as in the Seres product).⁸⁵

⁸ The Fast Track designation was intended to facilitate and expedite the review of drugs and biologic products intended to treat serious or life-threatening and that demonstrate the potential for addressing unmet medical needs..

Endnotes

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⁶ In fact, for every human cell there are 10 microbes and 99 percent of a human's genetic information is microbial. Advancements in gene-sequencing technology allowed scientists to identify previously unknown microbes and explore the collective genetic makeup of the vast range of microbiota residing in the human body.

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