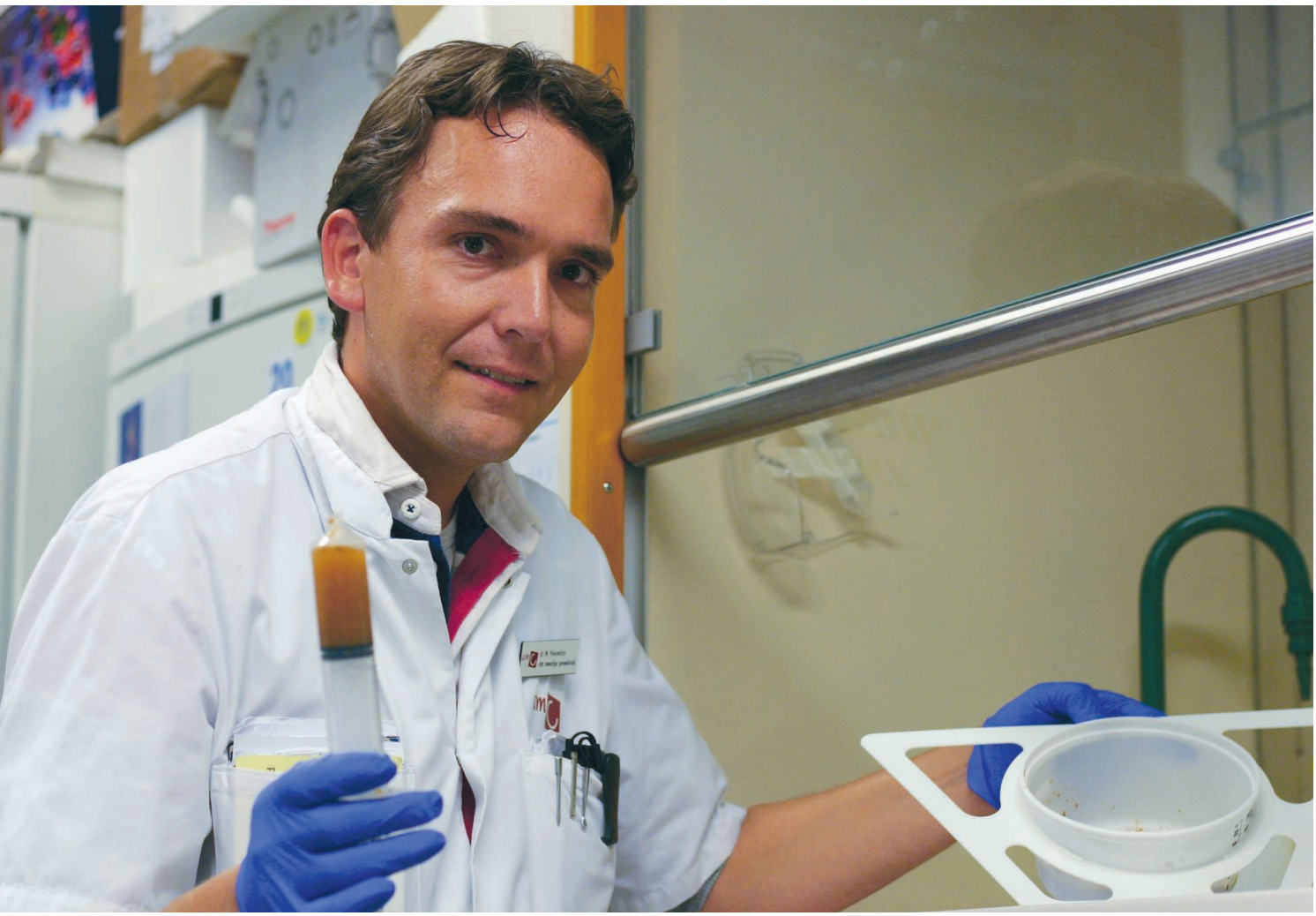

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MEDICAL RESEARCH

The Promise of Poop

Fecal transplants offer hope for treating many diseases. But they need to be studied more scientifically, says one of the treatment's pioneers

AMSTERDAM—Soon after Max Nieuwdorp started his residency at the internal medicine department of the Academic Medical Center (AMC) here in 2006, he was confronted with a sad case: an 81-year-old woman hospitalized for a complication after a urinary tract infection who seemed unlikely to survive. She had bed sores and high fevers and was unable to eat. After antibiotics had wiped out her colon's microbial population, an opportunistic bacterium called *Clostridium difficile* had taken over, causing terrible diarrhea and bowel inflammation.

C. difficile is a notorious pathogen that kills at least 14,000 patients a year in the United States alone; many patients suffer repeated bouts with the microbe. To treat it, the woman was given several courses of vancomycin, the standard antibiotic in such cases. But, as often happens, the bacteria had become resistant.

Nieuwdorp refused to accept the patient's fate—"I was young and naive," he says—and started searching PubMed for anything that could save her. When he found a 1958 paper by Ben Eiseman, a physician who was then at the University of Colorado, Denver, he knew what to do. "I want to try a fecal transplant," he told his supervisor, Joep Bartelsman.

Once he realized that Nieuwdorp wasn't joking, Bartelsman agreed. The plan was simple: The duo would flush the contents from the woman's colon, including, hopefully, the *C. difficile* population, and replace it with the healthy bacterial flora from a donor, in this case her son. To do so, they would mix the son's feces with saline in a blender and squirt it straight into the patient's duodenum, the upper part of her intestine, via a thin plastic tube inserted through her nose.

Three days after her treatment, the woman left the hospital—walking. Nieuwdorp and Bartelsman decided to treat another six *C. difficile* patients in the following months. Embarrassed about the unusual experiment, they waited for colleagues to break for lunch before infusing the stools. Four patients recovered immediately, the other two after another transplant from a second donor. The transplanted bacteria were apparently restoring the intestinal flora to health.

But when Nieuwdorp presented the results at a hospital meeting, an internist approached him with a condescending smile. "If you seriously want us to treat our *C. diff* patients with poop, why don't you infuse our cardiovascular patients as well?" the man asked, and left the room.

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Golden brown. Max Nieuwdorp prepares a human stool for transplantation.

That skepticism is gone. Many doctors now agree that intestinal *C. difficile* infections can be cured by transplanting stools from healthy people. Backed by a growing body of work linking the gut's microbial ecosystem to overall health, researchers also think that a wholesale replacement of the gut's microbial flora might help treat many other diseases, such as inflammatory bowel disease, diabetes, and the elusive chronic fatigue syndrome. More and more doctors perform fecal transplants, and online manuals for patients desperate enough to overcome the yuck factor show how to do it yourself.

What's still missing is a truly scientific approach to fecal transplants, says Nieuwdorp, who has become a leading advocate of more research. A paper that the AMC group published in *The New England Journal of Medicine* (*NEJM*) in January described a randomized controlled clinical trial of the transplants—the first such study ever reported. Nieuwdorp has also set up collaborations with lab scientists to better understand the underlying mechanisms. He hopes that these studies will eventually allow doctors to move from stool transplants to a more subtle approach: administering selected bacterial strains.

Becoming mainstream

The pioneering Eiseman paper, published in *Surgery*, described how the anal infusion of liquidized stool cured four patients from a disease called pseudomembranous enterocolitis, which had symptoms very similar to a severe *C. difficile* infection, although it was likely caused by a different microbe. It wasn't the first medical use of poop; fecal suspensions to treat food poisoning and severe diarrhea were first reported in the 4th century by a Chinese doctor and writer named Ge Hong, and as early as the 17th century, they were used to treat cows with intestinal problems.

Eiseman's paper was followed by occasional case reports, but for decades, the medical community paid little attention. Antibiotics had rendered the primitive, distasteful technique obsolete, it seemed.

Nieuwdorp didn't initially put his money on it either. After his first seven patients, he went to the University of California, San Diego, as a postdoc to study sugar molecules on the linings of blood vessels and intestines. After his return to Amsterdam in 2008, he resumed his work on the relation between gut microbiota and metabolism. He chose a Dutch medical journal to publish his fecal transplant results in that same year.

Gut Feeling

Researchers have reported positive effects with fecal transplants in more than 15 different diseases, but for most, the evidence is still weak.

Gastrointestinal Diseases

- Recurrent infection with *C. difficile* (photo above) 4
- Irritable bowel syndrome 3
- Chronic constipation 3
- Ulcerative colitis 3
- Crohn's disease 3

Nongastrointestinal Diseases

- Metabolic syndrome 4
- Chronic fatigue syndrome 2
- Multiple sclerosis 2
- Idiopathic thrombocytopenic purpura 2
- Autism 2
- Parkinson's disease 1
- Rheumatoid arthritis 1
- Sacroiliitis 1
- Halitosis 1
- Acne 1
- Insomnia 1
- Depression 1

KEY:
4 Randomized, controlled trial
3 Case series published
2 Isolated case(s) published
1 Unpublished clinical observations

But recurrent *C. difficile* infections were still on the rise, as was antibiotic resistance in the bacteria. Interest in fecal transplants grew in the United States after a 2010 article in *The New York Times* about the successful treatment of a very serious *C. difficile* case by Alexander Khoruts, a gastroenterologist at the University of Minnesota Medical Center in Minneapolis. "I realized that to let this therapy become accepted by the community of physicians, we would have to do a randomized clinical trial," Nieuwdorp says.

That study compared fecal transplants with vancomycin, the standard treatment for *C. difficile*, or vancomycin combined with bowel flushing. The researchers aimed to enroll 120 patients, but the study's data and safety monitoring board halted the study after just 43 patients, because continuing would be unethical: Ninety-four percent of the transplant patients were cured, versus 31% and 23%, respectively, in the control groups. The resulting *NEJM* paper "did bring the procedure closer to mainstream medicine," Khoruts says.

More evidence needed

Some doctors needed no convincing. One was gastroenterologist Thomas Borody of the Australian Centre for Digestive Diseases in Five Dock, who since 1988 has performed fecal transplants in more than 3000 patients, suffering not just from *C. difficile* but also from irritable bowel syndrome; inflammatory bowel syndrome; constipation; arthritis; and sacroiliitis, an inflammation of the sacroiliac joint. Borody has published some of his results; last year, for instance, he reported some improvement in 92% of 62 ulcerative colitis patients treated with fecal transplants and full recovery in 68%.

But although Borody is widely recognized as a pioneer, he has never carried out a randomized trial. Other researchers have reported encouraging results for nongastrointestinal disorders that appear to be associated with changes in the microbial flora, such as Parkinson's, autism, and multiple sclerosis. In most cases, however, the claims are based on a few cases, or a series of cases without a control group. (See table, left.)

More rigorous trials are now under way, including one in ulcerative colitis at McMaster University in Hamilton, Canada, and another in Crohn's disease at Nanjing Medical University in China. Nieuwdorp himself has just embarked on his second trial in patients with metabolic syndrome, the dysregulation of the body's metabolism as a result of overweight that is often a precursor to diabetes. Last year, his group reported that transferring the intestinal microbiota from lean donors increases insulin sensitivity in these patients—an encouraging sign.

Meanwhile, Lawrence Brandt of the Montefiore Medical Center in New York City, another fecal transplant pioneer, is doing a second trial with recurrent *C. difficile*. The study started before Nieuwdorp's *NEJM* paper, and unlike Nieuwdorp's, it is blinded and includes a placebo group. Both the patient and a donor donate their stool; the patient is infused with either the donor

CREDITS: (PHOTO) KARI LOUNATMAA/SCIENCESOURCE; (SOURCES) *CURR. OPIN. GASTROENTEROL.* **29** (2013); *GASTROINTESTINAL ENDOSCOPY* **78** (2013); *CURR. GASTROENTEROL. REP.* **15** (2013)

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Regulators Grapple With an Unorthodox Therapy

Taking one person's stool and putting it into the gut of another may be simple enough—but regulating it is not. The rapid rise of fecal transplantation, coupled with pressure from enthusiastic patients and doctors, has regulators wondering how to respond. The procedure occupies an odd place somewhere between tissue transplants and "probiotic" therapies—infusions of beneficial bacteria—and its risks are unknown. Coming up with sensible regulation is even harder because unlike, say, a blood transfusion, anyone can perform a stool transplant at home.

So far, the European Medicines Agency has not stepped in to regulate fecal transplants; the only thing that doctors need to do is get the patient's informed consent and comply with a donor screening protocol. Australia, where gastroenterologist Thomas Borody has carried out thousands of fecal transplants (see main story, p. 954), has similarly relaxed regulations.

Patient's voice. Catherine Duff spoke up at an FDA workshop in May.

In the United States, by contrast, the Food and Drug Administration (FDA) recently asserted its authority over the procedure. At a workshop on 2 and 3 May in Bethesda, Maryland, FDA's Jay Slater said that transplants are considered "an unapproved new drug." That meant any transplant can be done only as part of an official clinical trial, and doctors need to file an Investigational New Drug (IND) application—which can take months. (The agency said it might make exceptions for life-threatening conditions on a case-by-case basis.)

An FDA spokesperson says that Slater's comments didn't represent a policy change. But many researchers interpreted them as a clampdown. Lawrence Brandt of the Montefiore Medical Center in New York City says that he rejected 25 patients suffering from recurrent *Clostridium difficile* infection—where the evidence that fecal transplants work is strongest—after hospital lawyers told him to stop.

Patients and doctors have long urged the agency not to interfere with the treatment. At the Bethesda workshop, FDA officials heard testimony from Catherine Duff, a 57-year-old former medical case manager from Carmel, Indiana, who related how a fecal transplant had cured her recurrent *C. difficile* infection—and saved her life. "Please, do something not only for me, but for all those around the country and everywhere," she implored the FDA. "Please do something quickly."

Duff's appearance "definitely left an impression on the FDA officials," says Alexander Khoruts, a gastroenterologist at the University of Minnesota Medical Center in Minneapolis who attended the meeting. In new guidelines issued on 18 July, the agency announced it would "exercise enforcement discretion" in the case of *C. difficile*—meaning that, if they meet certain conditions, doctors can perform fecal transplants without prior approval. An IND is still needed for all other diseases and for *C. difficile* therapy in infants. The new guidance is widely regarded as a stopgap measure that gives the agency time to develop more comprehensive regulations.

FDA's task might get easier if scientists can replace fecal transplants with standardized mixes of microbial strains grown in the lab, which are simpler and presumably less risky. On 29 July, FDA approved a phase II trial with such a cocktail, developed by a company called Rebiotix. But Canada's federal regulatory agency clamped down on a similar product. After an academic collaboration named RePOOPulate treated two *C. difficile* patients with a mixture of 33 stool-derived microbial strains, Health Canada ordered a halt to the procedure in 2011; it said the mix is a "synthetic" product for which drug approval is needed and gave the scientists a long list of criteria to meet.

"Actually, they are not unreasonable," says RePOOPulate project leader Elaine Petrof. "Health Canada realizes this technique is not going away, and they want to sort this out with us." **–JDV**

stool or his own. That design is now standard, says Nieuwdorp, who uses it in the metabolic syndrome trial as well. "Some people claimed to smell that they had not received their own poop," he says. "They weren't always right, actually."

Borody says he is "very much for blinded trials"—he is involved in one with ulcerative colitis himself that is about to start at his university. But in the case of *C. difficile*, Nieuwdorp's study wasn't needed, he says—let alone Brandt's—because the evidence from case series was already overwhelming. "This trial should not have been approved by the ethics committee in the first place," Borody says, comparing Nieuwdorp's study to a randomized controlled trial to test whether parachutes can save lives.

Begging for a transplant

As word of mouth about fecal transplants has spread, many other doctors have gotten in on the game, and many private clinics see handsome profits from a relatively simple procedure. "The first generation of physicians involved in this technique were of the most idealistic type I can imagine," Khoruts says. "This changed, unfortunately." Patients are often desperate for the treatment; Nieuwdorp says he receives frequent phone calls, e-mails, and visits from people begging him for a transplant. He says that he rejects all such requests but refers some people to Borody.

Meanwhile, do-it-yourself transplants appear to be on the rise as well. Instructions on how to flush out your colon, prepare donor stool—at "chocolate milkshake thickness," as one website helpfully explains—and infuse it by enema or nasal tube have proliferated on the Internet. In one YouTube video, a patient describes how putting Vicks VapoRub under one's nose can help suppress the odor. There have even been reports about people drinking liquidized feces.

Such experiments are worrisome, scientists say, because fecal transplants aren't without risks. Earlier this month, for instance, two patients were reported to have developed norovirus gastroenteritis and diarrhea around the time of their fecal transplant. (The donors had tested negative for norovirus, and the doctors believe the patients may have picked up the virus somewhere else.) Also this month came a report of a 78-year-old man whose ulcerative colitis flared up instead of disappearing after a fecal transplant—although that may have been because his doctors stopped administering prednisone, a drug that reduces inflammation, prior to treatment.

To reduce the risks, most doctors screen donors for a battery of harmful viruses, bacteria, and parasites that might be transmitted through stool—including HIV, hepatitis B and C viruses, cytomegalovirus, Epstein-Barr virus, *Campylobacter jejuni,* and *Blastocystis*. But they can't be sure they're catching everything, and noninfectious dis-

Online
sciencemag.org
Podcast interview with author Jop de Vrieze (http://scim.ag/pod_6149).

CREDIT: COURTESY OF CATHERINE DUFF

eases are a concern as well. Diabetes, atherosclerosis, autism, and colorectal cancer have all been shown to be associated with certain gut microbiota compositions. Scientists are only beginning to tease out cause and effect, but Khoruts says that it's best to err on the side of caution and not use donors whose gut flora might cause trouble.

Khoruts is investigating the optimal donor characteristics and has set up a donor bank with frozen stool from healthy people who meet a long list of criteria. So far, most of his patients have brought in family members as donors, and few of them are in perfect health. "If the patient is 70 years old, you won't need a Greek god to cure her," Khoruts says. "But for a younger patient, you give bugs for the rest of his life—you want something better."

Underlying mechanisms

Knowing how fecal transplants work is key to making them safer. Do the donor populations take up residence in the gut after the transplant? Which strains make the difference, and how do the transplanted microbes interact with the resident ones? Nieuwdorp collaborates with Willem de Vos, a microbial ecologist at Wageningen University in the Netherlands, whose expertise is anaerobic bacteria, the group that dominates in the human gut. "We have shown that in *C. difficile* patients, some important species are absent, while others that you don't want are dominant," De Vos says. His research has also shown that the low microbial diversity in *C. difficile* patients is comparable to that of a 1-year-old child. But after a transplant, anaerobic bacteria from the donor settle in the recipient's gut and the diversity is restored.

Nieuwdorp also works with Fredrik Bäckhed of the University of Gothenburg in Sweden, who runs a facility housing mice that grow up without a single bacterium in their bodies. This allows the scientists to investigate the effects of specific microbial strains. "We are playing with different donors to find the superbacteria that make the difference between health and disease," Nieuwdorp says.

The hope is that in the end, doctors can abandon the poop and infuse just these bacteria. Such cultured cocktails might have downsides, however. They could be less powerful than the complete ecosystems found in stool, Borody says, and the bacteria might mutate in the lab, losing their healing power, as they are grown generation after generation.

Still, many others believe the cocktails are the way to go. A group led by Kenya Honda at the University of Tokyo recently reported curing mice of colitis and allergic diarrhea by treating them with 17 harmless *Clostridium* strains that had previously been shown to induce regulatory T cells of the immune system, quenching an overactive immune response.

In a project called RePOOPulate, a Canadian team led by Elaine Petrof of Queen's University in Kingston and Emma Allen-Vercoe from the University of Guelph has developed a stool-derived set of 33 microbial strains for the treatment of *C. difficile* and inflammatory bowel disease. They hope the strains will offer the benefits of a full fecal transplant but with less risk. Allen-Vercoe initially cultured 70 strains, from which Petrof made a selection based on each strain's pathogenicity and resistance to antibiotics. For the final selection, she says she used her judgment: "Would I put this bug into my mom? No? Then I would take it out."

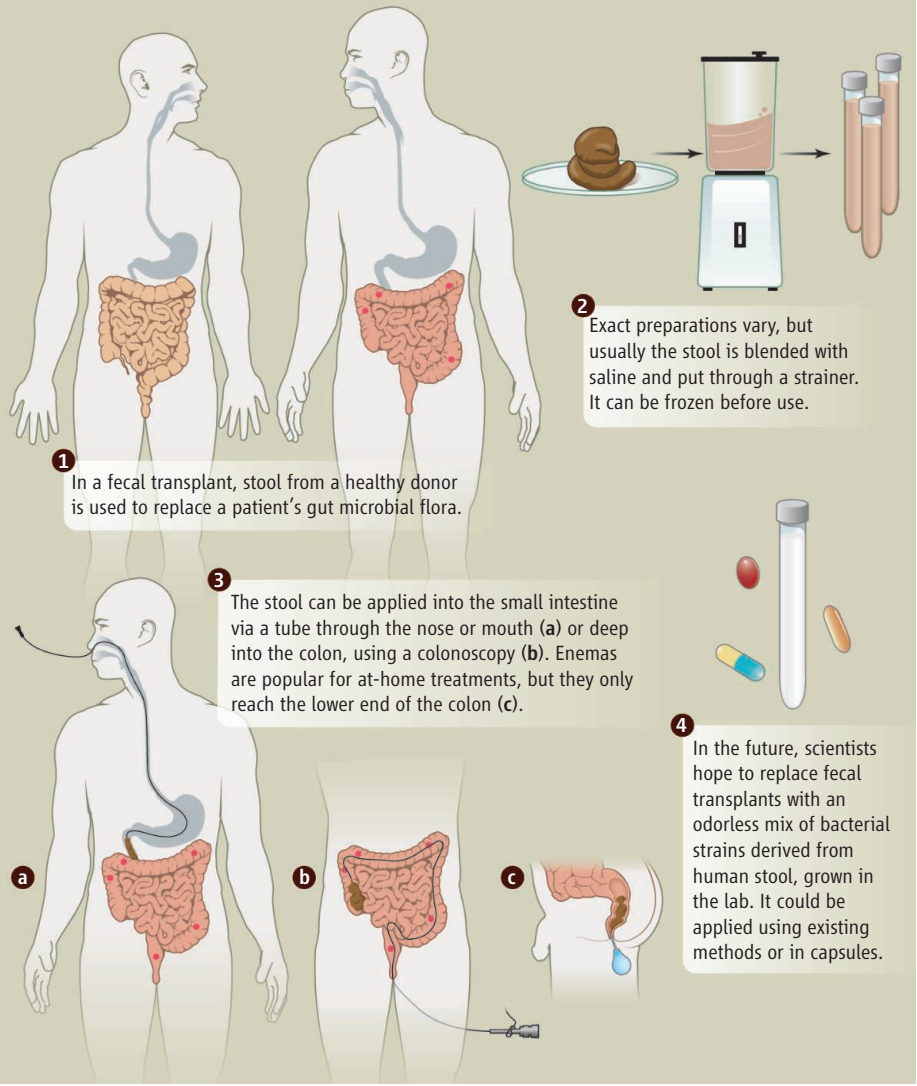
A U.S. company called Rebiotix is going the same route; the Food and Drug Administration recently greenlighted a phase II clinical trial of its mix of several hundred stool-derived strains to target *C. difficile* infection. "We don't consider our product a fecal transplant," Rebiotix founder and CEO Lee Jones writes in an e-mail. "Instead, we are developing a microbiota restoration therapy in the form of a biologic drug."

Nieuwdorp sees enormous possibilities for such therapies—but he says it will take time. "I'm 36 now. I'll be happy if by the time I'm 60, microbiota analysis will be standard procedure in hospital labs," he says. For now, he's happy that the taboo on fecal transplants is gone. At his own center, "specialists are lining up to test the impact of transplant on 'their' diseases," Nieuwdorp says. And yes, the list now includes cardiovascular diseases.

–JOP DE VRIEZE

Jop de Vrieze is a science writer in Amsterdam.

How Fecal Transplantation Works



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