Review Article

Fecal Microbiota Transfer

Reliable Indications, Donor Screening, and Modes of Application

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Summary

Background: Fecal microbiota transfer (FMT) is increasingly being used in Germany, as in other countries, for the treatment of recurrent *Clostridioides difficile* infection (rCDI). FMT is now being performed both for research and in individual patients outside of clinical trials. No compulsory standards have been established to date for donor screening or for the method of fecal transfer. Given the potential dangers of FMT, this would seem to be urgently necessary.

Methods: This review is based on pertinent literature retrieved by a selective search, including the reports of consensus conferences from Germany and abroad.

Results: Because of its high efficacy, FMT is the treatment of choice for rCDI. It is largely free of adverse side effects, even in immune-deficient patients, as long as comprehensive and repeated donor screening has been carried out, with extensive clinical and microbiological testing and with the use of structured questionnaires. The ingestion of frozen, encapsulated microbiota is just as effective as other modes of delivery for the treatment of rCDI.

Conclusion: Encapsulation of the fecal microbiome (FM) and storage at -20°C is the method of choice, because it can be standardized with the necessary quality controls and it is readily available. Patients with rCDI should undergo FMT by orally ingesting the capsules. There are ongoing research efforts to identify the active components of the FM. It is not yet clear when the ultimate goal of recombinant production can be achieved.

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In recent years, an increasing understanding of the importance of the gastrointestinal microbiome has led to the initiation of numerous research projects on fecal microbiota transfer (FMT). A current query on the clinical trials.gov website yields a total of 107 clinical trials, 22 of them in Europe, in which the efficacy of FMT for various indications is being, or has been, tested (query on 10 December 2019 with the search terms “fecal OR faecal,” “microbiota AND transplantation OR transfer”). The rationale for these trials is derived from pathogenetic considerations and from encouraging results with the use of FMT to treat recurrent *Clostridioides difficile* infection (rCDI). For instance, in one randomized, controlled trial, the cure rate was significantly higher after FMT (71%) than after the administration of either fidaxomicin (33%) or vancomycin (19%) ($p = 0.009$ and 0.001 , respectively) (1). It is problematic, however, that FMT is not only being used in clinical trials, but also in the treatment of an unknown (probably large) number of individual patients, with methods that are not publicly documented. The quality of the therapeutic agents being tested in clinical trials is regulated and controlled by the relevant government authorities; in contrast, the production and application of FMT materials for use in an individual patient are entirely up to the treating physician, and the quality standards to be applied are at his or her sole discretion. As a result, the necessary screening of FMT donors is not always performed in standardized fashion, leaving patients exposed to incalculable risks of side effects and complications. In the United States, the Food and Drug Administration (FDA) has issued a warning about the risk of severe bacterial infection after FMT (13 July 2019; e1). ESBL-forming *E. coli* were transferred to two patients via FMT who contracted invasive bacterial infections as a result; one of them died. Both had received a therapeutic agent prepared from the stool of a donor who had not been tested for multidrug-resistant pathogens.

As this very severe complication indicates, many questions remain unanswered despite the attractiveness of FMT on first sight and the many studies that have been carried out on FMT to date. In this review, we present the current state of knowledge on the subject, on the basis of a selective literature review (search terms: [“fecal or faecal”] and [“microbiota”] and [“transplantation or transfer”] and [“regulation”]), including the reports of consensus conferences from Germany and abroad.

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TABLE 1

Necessary stool tests as part of clinical FMT donor screening (from [e2])

Bacteria/Fungi	Viruses	Parasites
Salmonella	Norovirus GI, GII	Entamoeba histolytica
Shigella	Adenovirus	Giardia lamblia
Vibrio	Astrovirus	Cryptosporidium sp.
Campylobacter	Rotavirus	Dientamoeba fragilis
Yersinia	Enteroviruses (exc. rhinoviruses)	Blastocystis hominis
Clostridioides difficile (culture) C. difficile toxin B (PCR)	Aichivirus	Cyclospora, Isospora
Helicobacter pylori (stool PCR)	Sapovirus (I, II, IV, V)	Mikrosporidia
Listeria monocytogenes		Ova
Enterohemorrhagic E. coli (EHEC/STEC)		
Enteraggregative E. coli (EAEC)		
Enteropathogenic E. coli (EPEC)		
Enterotoxigenic E. coli (ETEC) lt/st		
Enteroinvasive E. coli (EIEC)		
Plesiomonas shigelloides		
Multi-drug-resistant organisms (MDRO): – carbapenem-resistant enterobacteriaceae (CRE) – Extended-spectrum-β-lactamase-resistant bacteria (ESBL) – methicillin-resistant S. aureus (MRSA) – vancomycin- and glycopeptide-resistant enterococci (VRE, GRE)		
Candida auris		

Necessary blood tests as part of clinical FMT donor screening (from [e2])

Bacteria	Viruses	Parasites
Treponema pallidum	Cytomegalovirus (CMV)	Strongyloides stercoralis
	Epstein-Barr virus (EBV)	Trichinella sp.
	Hepatitis virus (A, B, C, E)	Toxoplasma gondii
	HIV-1, -2	
	HTLV-1, -2	

HTLV, human T-lymphotropic virus; lt, heat-labile enterotoxin; MDRO, multi-drug resistant organism; PCR, polymerase chain reaction; st, heat-stable enterotoxin.

Clear evidence for the efficacy of FMT currently exists only for rCDI

There is better evidence for the efficacy of FMT against rCDI than against any other disease, derived both from randomized trials and from numerous non-randomized studies. It is important to understand that the positive findings in tests of FMT against rCDI cannot be assumed to apply to other conditions, e.g., chronic inflammatory bowel diseases (IBD). The essential difference in the latter case is that IBD are a group of chronic conditions, generally present for many years, that affect genetically susceptible persons. Twin studies in IBD patients have revealed to an impressive extent that the individual genetic repertoire controls the microbiome, including the pathological microbiome (2). A single FMT that is effective against rCDI alters the recipient's microbiome, but not necessarily over a

long period of time—which would be necessary for the treatment of a chronic disease (3). In about 40% of patients, the typical microbiome of the individual patient reconstitutes itself within one year, sometimes in the form of a “mixed microbiome” (4).

Unfortunately, it is also unclear which components or substances in FMT are responsible for its therapeutic effect against rCDI. Multiple working groups have postulated “therapeutic” bacteria (5); others consider the transfer of regulatory bile salts (6, 7) or of the virome (8) to be determinative. There are at least 1000 viral species in the microbiome; this is on the same order of magnitude as the number of bacterial species it contains. In addition to their direct effects on the host, viruses (particularly bacteriophages) also exert effects on the bacterial microbiota. Zuo et al. analyzed the virome, including bacteriophages, in

patients with rCDI (8): successful FMT led to normalization of the virome in the recipient, with increased diversity. Therapeutic success was associated with the transfer of bacteriophages from the taxon Caudovirales. An in vitro model for testing of the individual components of the donor microbiome would be desirable. At present, however, predictions of efficacy can only be made from findings made in actual patients who have been treated in clinical trials.

What type of donor screening is necessary?

To answer this question properly, it is important to know how the transfer of the microbiota from a donor to a patient is considered from the medicolegal viewpoint. In principle, fecal microbiotic transfer can be considered a “therapeutic procedure” (German, *Heilbehandlung*) in itself, as it is—for example—in Austria, where it is therefore not subject to regulation by laws relating to drugs, medical products, or organ transplantation (9, 10). In most European countries, including Germany, stool for transplantation is considered a “drug” or “pharmaceutical product” (as per the German Law on Pharmaceuticals [*Arzneimittelgesetz*, AMG] §2 Abs 1 Nr. 1 and Nr. 2a). If FMT is performed outside of a clinical trial, the preparation of the donor’s stool is considered an individual drug preparation under the AMG (§13 Abs. 2b). Consequently, the treating physician bears responsibility for the production and administration of the product and must be personally involved in it. Only his or her personal involvement exempts this individual treatment from the requirement for a production permit, as laid down in AMG §13. FMT is now being used to treat rCDI in this manner in at least 30 different facilities in Germany (11). The provision of microbiome to patients, in either liquid or encapsulated form, is now possible in Germany in one of only two ways: either in a clinical trial, or else directly by the treating physician who has made the preparation himself or herself.

The microorganisms transferred in FMT can include pathogens. Potentially communicable diseases must, therefore, be ruled out by donor screening, and a high safety standard must be required. The recommendations for the selection and examination of “stool donors” were initially modeled on the ones for blood donors, even though some of the pathogens tested generally cannot be transferred in stool (12). At present, the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) requires the screening shown in *Table 1* for the performance of clinical trials on immune-suppressed patients. No conclusion has yet been drawn on official recommendations for requirements in other patients, specifically those with no known immune compromise.

It is problematic that a diagnostic gap persists even after extensive screening: acute infections can arise even with pathogen concentrations below the technical threshold of detectability, and even in the absence of a serologic response. This gap can only be (nearly)

BOX

Diseases and risk constellations to be ruled out in FMT donor screening (according to [e2])

● Diseases

- gastrointestinal diseases (personal or family history), ulcerative colitis, Crohn’s disease, other inflammatory bowel diseases, irritable bowel syndrome, chronic constipation or diarrhea, celiac disease, status post bowel resection or gastric reduction procedure
- acute diarrhea (in the prospective donor or his/her contacts) in the past four weeks
- unformed stool in the past four weeks
- history of typhus or other salmonellosis
- tuberculosis (acute or past)
- systemic autoimmune diseases, e.g., multiple sclerosis
- atopic diseases
- neurological or psychiatric diseases (depression, chronic pain [fibromyalgia, chronic fatigue syndrome, etc.])
- cancer
- metabolic diseases (diabetes, obesity [BMI ≥ 30 kg/m²])
- risk factors for prion diseases, incl. Creutzfeldt-Jakob disease
- hospitalization in the past six months

● Medical treatment

- long-term drug treatment (e.g., with antibiotics, immune suppressants, proton-pump inhibitors, systemic antineoplastic drugs)
- antibiotic treatment in the past three months
- having been a participant in any clinical trial in the past six months

● Travel

- travel to any country with an increased risk of lower gastrointestinal tract infections in the past six months

● Social factors

- high-risk sexual behavior
- imprisonment
- illicit drug use
- body modifications such as tattooing, piercing, etc., in the past six months
- blood transfusions in the past five years
- occupational activity in a hospital or other health-care institution with patient contact; occupational activity in agriculture

closed with a second screening, performed 8–12 weeks later. Therefore, the stool sample obtained from the donor, once it has been processed into the therapeutic agent after a first screening, must be kept in “quarantine” thereafter, and can be used for FMT only after a second negative screening (personal communication from the BfArM in an advisory discussion on 9 July 2019). If this becomes the generally recommended procedure, it will double the costs of donor screening, which are currently 1530 Euro (internal calculation at Jena University Hospital).

The exclusion criteria for stool donors consist not only of certain positive findings on microbiological and other laboratory testing (*Box*), but also of a range

TABLE 2

Infectious complications of fecal microbiota transfer (FMT) in immune-deficient patients

First author	Patient collective (number of cases)	Indication	Infectious complications
Baxter 2016 (16)	unselected patients (n = 1555)	recurrent <i>Clostridioides difficile</i> infection (rCDI) (76.5%) ulcerative colitis (12%)	– Gram-negative bacteremia (n = 4) – fever (n = 11) – norovirus infection (n = 2) – influenza B infection (n = 1) – a total of 41 fatal cases that were not causally attributable to FMT
Webb 2016 (32)	markedly immune-deficient stem-cell-transplant recipients (n = 7)	rCDI	– no evidence of infections
Quraishi 2017 (33)	unselected patients (n = 1465)	rCDI (100%)	– 1 death due to aspiration pneumonia* – 2 deaths due to colon perforation (application via colonoscopy) – a total of 50 fatal cases that were not causally attributable to FMT – no infections in immune-deficient patients (n = 80)
Shogbesan 2018 (17)	immune-deficient patients (HIV, chemotherapy, status post organ transplantation) (n = 303)	rCDI	– 2 deaths (pneumonia after organ transplantation, aspiration pneumonia*) – bacteremia/fever (n = 10)
Cheng 2019 (34)	immune-deficient organ transplant recipients (n = 94)	rCDI	– reactivation of cytomegalovirus infection (n = 3) – high fever (n = 1) – no bacteremia

* This is the same case with a lethal complication that has been described in multiple reviews.

of diseases, medical treatments, travel history, and social factors. Aside from these exclusion criteria, the success rate of FMT, particularly for indications other than rCDI, might be improved by nutritional preconditioning of the donor (e.g., by a high-fiber diet or the ingestion of pre- or probiotic agents). This approach is also being tested in ongoing clinical trials.

Structured questionnaires are useful for the identification of risks arising from diseases, travel history, and social factors. Thus, it has been shown that risk factors for HIV infection among blood donors can be identified significantly more frequently through the use of structured questionnaires than by medical history taking alone. If one merely considers the frequency of tattooing in the general population—more than 25% in persons aged 25 to 34 (14)—one begins to appreciate the organizational and financial challenge of identifying suitable donors, including the necessary medical examinations and laboratory tests. At present, after all the necessary screening has been performed, only one in ten potential stool donors is actually allowed to donate stool (unpublished personal experience).

Reports to date of infectious complications after FMT have been limited to individual cases, even among patients with severe immune deficits, including organ transplant recipients and cancer patients actively undergoing chemotherapy (for an overview, see reference [15] and Table 2). Other side effects, such as diarrhea (10.6%), bloating (9.1%), and abdominal pain and a sensation of fullness (7.6%), have been reported to have a cumulative frequency of 25% (11,

16, 17). Serious adverse effects that are particularly associated with endoscopic application procedures arise in 6.1% of such applications via the upper gastrointestinal tract, and in 2.0% via the lower gastrointestinal tract. The infection rate has been reported to be 2.5%; it is not known whether the pathogens were derived from FMT (15). In one case, aspiration pneumonia occurred after endoscopically assisted FMT, and the patient died 48 hours later of *E. coli* sepsis (18). In another case, a patient who had an initially uncomplicated FMT via a percutaneously, endoscopically introduced gastric tube (PEG) went on to develop toxic megacolon, underwent emergency colectomy, and died four days later (19). Overall, however, infectious complications after FMT are rare, even among patients with severe immune deficiency.

Aside from potentially communicable infections, the question has repeatedly been raised whether FMT recipients might be at increased risk of contracting diseases that are thought to be causally linked to microbiome, but that have not (yet) arisen in the donor. Some research teams, for example, postulate that the microbiome can induce, or predispose to, colorectal carcinoma (20). Thus, one can ask whether this predisposition might be transferable to a recipient from a donor who is still healthy, but will go on to develop colorectal carcinoma some years later. Even if these considerations are theoretically well grounded, there is as yet no evidence of such an occurrence. For this mechanism to operate, the transferred microbiome must persist for years in the recipient, which does not occur as a rule. There is also clinical

TABLE 3

Comparison between endoscopic application and administration of encapsulated microbiome for recurrent *Clostridioides difficile* infection

Endoscopic application				Administration of encapsulated microbiome			
First author (ref. no.)	n	Material	Success (n/%)	First author (ref. no.)	n	Material	Success (n/%)
Youngster 2014 (35)	10	fresh	8 (80%)	Louie 2013 (36)	27	fresh	27 (100%)
Cammarota 2015 (37)	20	fresh	18 (90%)	Youngster 2014 (38)	20	frozen	14 (70%)
Kelly 2016 (39)	22	fresh	20 (91%)	Hirsch 2015 (40)	19	frozen	17 (89%)* ²
Jiang 2017 (26)	72	fresh, frozen, lyophilized	63 (87%)	Hecker 2016 (e3)	20	lyophilized	18 (90%)* ²
Kao 2017 (28)	59	frozen	57 (97%)	Youngster 2016 (25)	180	frozen	164 (91%)* ²
Peri 2019 (11)	73* ¹	fresh, frozen	63 (86%)	Staley 2017 (e4)	49	lyophilized	43 (88%)
				Kao 2017 (28)	53	frozen	51 (96%)
				Peri 2019 (11)	33	fresh, frozen	25 (76%)* ¹
Overall	256		229 (89%)	Overall	401		359 (90%)

*¹treatment response by day 90

*²after twofold treatment

evidence against the transfer of a genetic predisposition: In a case series, 31 patients with rCDI received the microbiome of a healthy 28-year-old donor. The donor developed bloody diarrhea two months later and was found to have Crohn's disease with ileocecal involvement. It is important to note that none of the FMT recipients developed any kind of IBD over the course of further follow-up, which was admittedly short, necessarily in the nature of such studies (median, 19.8 months) (21). On the basis of a single case report from the USA (22), it was long presumed that FMT could affect the body weight of the recipient, but this hypothesis was not substantiated in a recent randomized trial (23).

The performance of fecal microbiota transfer

The two basic approaches to FMT involve either the direct application of donor stool in liquid form, or some kind of processing of the stool. The mode of application is also important: the microbiome can be introduced directly into the patient by means of a regular or high enema, via endoscopy (jejunoscopy or colonoscopy), or through a nasojejunal tube. A further alternative is encapsulation of the microbiome in gastric-juice-resistant capsules that the patient can swallow.

Fresh versus frozen

The simplest way to process the donor's microbiome is to liquefy donor stool in normal saline and then filter it to eliminate the cellular component. This suspension can be used directly, or else frozen at -20 to -80°C for later use. The main advantage of the frozen microbiome

is its ready availability whenever needed, obviating the necessity of performing a time-consuming donor screen and preparing the stool sample for administration on short notice. Glycerol is added to the liquid preparation (final concentration, 10%) for storage, to increase the viability of the microbiota (24). Both the taxonomic composition of the microbiota and their viability will then remain unchanged, even after six months of storage at -20 to -80°C (25, 26). Successful treatment of rCDI with samples that have been stored for 9 to 12 months has been reported. Multiple retrospective analyses and randomized trials (24–27) have compared the efficacy of fresh and frozen microbiota without revealing any significant difference. Data from the German MicroTrans Registry (NCT02681068) showed no relevant difference in cure rates when using fresh or frozen preparations (cure rates by the 90th day after transfer: 113/146 [77.4%] vs. 40/50 [80%], $p = 0.844$) (11). In summary, the use of frozen microbiota is logistically less cumbersome, and it is also advisable from the point of view of patient safety.

Capsules versus colonoscopy

Encapsulated microbiota enable repeated administration or long-term treatment, as repeated endoscopy or tube placement would increase the risk of procedural complications and would be unlikely to meet with acceptance on the patients' part.

Unfortunately, data from randomized and controlled trials on the efficacy of different modes of application remain sparse to date (26, 28). The two relevant trials, along with relevant cohort studies,

Photographs: Jena University Hospital/Michael Szabó

Figure: a) Liquefied stool suspension for endoscopic application; b) high-pressure filtrate of a stool suspension; lyophilizate of the high-pressure filtrate; d) encapsulated microbiome from a).

show an overall efficacy of 89% for the endoscopic approach. The treatment of recurrent *Clostridioides difficile* infection with capsules, applied once or multiple times, led to a cure in approximately 90% of cases (Table 3). A further important, simplifying advance, the administration of lyophilized, encapsulated microbiome, was first reported in 2015 (29). In this method, the liquefied microbiome is freeze-dried, and the resulting powder (Figure) is put into gastric-acid-resistant capsules. An advantage of this method is the capsules can be stored in a refrigerator, enabling treatment for longer periods when necessary. A randomized, controlled trial showed the therapeutic equivalence of encapsulated, lyophilized microbiome and microbiome enemas, with rCDI cure rates of 84% and 88%, respectively (26). A remaining problem is that the lyophilizate cannot yet be well standardized; its therapeutic components are still unclear, making quality control a complex matter. Appropriate quality control is, however, a prerequisite for the approval of encapsulated and lyophilized microbiome as a drug.

Overview

In view of the available evidence, fecal microbiota transfer is now the treatment of first choice for recurrent *Clostridioides difficile* infection. The laborious screening of potential donors and the associated regulatory requirements still limit its broad application. To

limit the infectious complications that can arise despite intensive and repeated donor screening, and to minimize the theoretical risk of transmitting microbiome-associated susceptibility for diseases that can arise at a later time, a number of research groups have treated the microbiome suspension obtained from the donor with ethanol to remove vegetative bacteria, with ensuing encapsulation of the resulting spores. Such capsules, designated as therapeutic preparation SER-109, have now been tested in a pilot trial: 26 of 30 patients treated with these capsules for two days reached the clinical end point of the trial at eight weeks, namely, the absence of *Clostridioides difficile*-positive diarrhea (30). Unfortunately, these results were not confirmed in a phase II trial. Patients are now being recruited for a third trial with a modified design, which, it is hoped, will clarify the matter.

In another approach, the effect of a sterile, high-pressure filtrate of the donor microbiome, containing bacterial components, proteins, antimicrobial substances, metabolic products, and nucleic acids, was tested (31). In all five patients, the stool frequency normalized and the manifestations of rCDI resolved. An analyses of virus particles in the filtrate revealed that they were transferred. The role of bacteriophages as mediators of the efficacy of FMT is not yet clear.

These promising findings indicate that the entire microbiome of the donor need not be transferred to

achieve the therapeutic effect, at least not for rCDI. The molecular-genetic and biochemical characterization of the therapeutically active elements will surely lead, over the intermediate term, to the establishment of recombinant microbiome derivatives that can be pharmaceutically manufactured and that will be highly safe and effective.

Conflict of interest statement

Prof. Stallmach has served as a paid consultant for, and has received lecture honoraria from, the Astellas, Ferring, and MSD companies and the AllergoSan institute. He is the coordinator of a trial funded by the BMBF on fecal microbiome transfer in ulcerative colitis (German trial support number DLR 01KG1814; clinicaltrial.gov: NCT03843385).

Dr. Grunert has received reimbursement of scientific meeting participation fees and travel expenses from Janssen-Cilag and lecture honoraria from Pfizer.

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Prof. Vehreschild has served as a paid consultant for 3M, Alb-Fils Kliniken, Arderypharm, Astellas Pharma, DaVolterra, MaaT Pharma, Merck/MSD, and Ferring. She has overseen the use of third-party funding in research studies carried out on behalf of 3M, Astellas Pharma, DaVolterra, Gilead Sciences, MaaT Pharma, Merck/MSD, Morphochem, Organobalance, Seres Therapeutics, Evonik, and Glycom.

Arndt Steube and Prof. Hartmann state that they have no conflict of interest.

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Key messages

- Randomized trials have shown that fecal microbiota transfer (FMT) combined with antibiotic therapy is the treatment of first choice for recurrent Clostridioides difficile infection.
- In view of the dangers that may be associated with FMT, there is an urgent need for a compulsory standard for donor screening, including quarantine of the microbiome, to close any remaining diagnostic gap.
- The ingestion of encapsulated microbiota preparations has similar efficacy to endoscopic application, with the advantage of being better tolerated by patients as well as the potential of use over longer periods of time.
- Once the therapeutically active components of the fecal microbiota have been identified, it will be possible to manufacture recombinant preparations. These are not yet available.

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► Supplementary material

For eReferences please refer to:

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CLINICAL SNAPSHOT

Gas Gangrene of the Gallbladder

An 84-year-old man presented with right-sided upper abdominal pain and fulminant sepsis. The wall of the gallbladder could not be differentiated on sonography, and computed tomography revealed emphysematous cholecystitis with pneumatosis of the gallbladder wall (Figure, yellow arrows) and aerobilia of the bile ducts (not shown). Sepsis treatment by means of fluid replacement and antibiotics with piperacillin/tazobactam were accompanied by immediate laparoscopic cholecystectomy. A massive amount of *Clostridium perfringens* was demonstrated in the gallbladder aspirate. The toxic clinical picture with pneumatosis of the gallbladder corresponds to gas gangrene of the gallbladder. This life-threatening situation must be distinguished from the frequently encountered microbiological detection of *C. perfringens* in the gallbladder without related clinical symptoms. The treatment described above led to rapid recovery.

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Fecal Microbiota Transfer

Reliable Indications, Donor Screening, and Modes of Application

by Andreas Stallmach, Arndt Steube, Philip Grunert, Michael Hartmann,
Lena M. Biehl, and Maria J. G. T. Vehreschild

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