THERAPIES BASED ON SUBSTANCES OF HUMAN ORIGIN (SoHO)

Review

A "movement" worth making: why and how Transfusion Services can play a role in Fecal Microbiota Transplant programs

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Fecal Microbiota Transplantation (FMT) is an innovative therapy with growing applications, particularly for recurrent *Clostridioides difficile* infections (rCDI). However, the broader use of FMT is challenged by the complexities of donor recruitment, the necessity of stringent screening protocols, and the need for maintaining high-quality stool biobanks. This paper explores the integration of FMT programs within transfusion medicine departments, taking advantage of their expertise in donor management and biological material processing. Despite the complexities of donor screening, including a low eligibility rate, the collaboration between transfusion services and other hospital departments demonstrates a viable model for expanding FMT access. Additionally, the recent EU regulations on substances of human origin (SoHO) offer a framework for standardizing and scaling stool banking, enhancing the safety and efficacy of FMT procedures.

Keywords: *fecal microbiota transplantation (FMT); transfusion services; innovative therapies; substances of human origin.*

INTRODUCTION

Fecal Microbiota Transplantation (FMT) is an emerging therapy with great potential to improve patient care and advance biomedical research. The procedure involves transferring fecal bacteria and other microorganisms from a healthy donor to a recipient with a compromised gut microbiome and can be administered *via* various methods including colonoscopy, enema, oral capsules, or nasoenteric tube[1]. The first description of FMT was published by Eiseman *et al.* in 1958 for treating pseudomembranous colitis[2], but interest in this approach has been renewed in recent years as the technique proved effective in treating patients with recurrent infections caused by *Clostridioides difficile* infection (rCDI)[3-5]. Moreover, there is growing interest in FMT as an experimental therapy for various diseases and conditions, especially in gastroenterology, oncology, hepatology, hematology, and neuroscience[6-8]. Currently, there are 866 clinical trials registered on ClinicalTrials.gov using FMT as treatment[9].

However, the broader implementation of FMT in both standard care and clinical trials remains limited by several obstacles, including the lack of dedicated collection centers, difficulties in finding and motivating donors, regulatory complexities, production

costs, and the need for strict quality controls. The synergy of FMT centers with the infrastructure of transfusion centers might overcome many obstacles: blood establishments are already an integral part of modern healthcare systems with extensive experience in donor recruitment, management, and processing of human-derived substances for medical treatments for various clinical indications.

This article examines the important role that transfusion services could play in FMT programs, particularly in the recruitment and selection of donors, as well as in the preparation, storage and distribution of fecal suspensions. This role may become even more key in light of recent EU regulations, which set new standards for the quality and safety of substances of human origin (SoHO).

UNDERSTANDING THE HUMAN GUT MICROBIOTA

The human gut microbiota is a complex ecosystem, consisting of approximately 500 to 1,000 different microbial species[10], with a total biomass of nearly 0.5 kg[11]. This microbial community includes bacteria, Archaea, and Eukarya, with population density increasing significantly from the small intestine to the colon. Recent estimates indicate that the human body contains approximately 30 to 40 trillion microbial cells, which roughly equal the number of human cells, resulting in a ratio close to one to one[11]. The gut microbiota's genetic content, known as the "microbiome", may contain 100 times more genes than the human genome, reflecting its broad biological significance[12,13].

Functionally, the gut microbiota serves as a metabolic organ, providing capabilities that humans have not fully evolved independently. These include the degradation of complex plant polysaccharides, biotransformation of conjugated bile acids, degradation of dietary oxalates and the synthesis of essential vitamins[14,15]. Additionally, microbiota plays a role in educating the immune system, helping to maintain immune tolerance and reducing allergic responses[16,17]. The gut microbiota's dynamic nature is evident in its influence on postnatal gut development and overall host physiology. For example, certain bacteria can direct the synthesis of glycans in the gut epithelium, facilitating colonization and nutrient absorption[18,19]. Moreover, the gut microbiota maintains the intestinal mucosal barrier and modulates host immune responses, which are essential for homeostasis and protection against pathogens[20].

These host-microbe interactions provide a rationale FMT. By restoring a balanced microbiome, FMT can treat conditions linked to dysbiosis, such as rCDI, and potentially other gastrointestinal and systemic diseases.

EFFICACY AND SAFETY OF FMT

European and American guidelines for evidence-based use of FMT have been recently published[1,4,5]. Furthermore, both established and emerging therapeutic applications have been critically reviewed and comprehensively summarized by Yadegar and colleagues[21].

FMT has become a well-established treatment for rCDI. Clinical guidelines widely recommend FMT for patients who have experienced at least two episodes of recurrence of CDI after standard antibiotic treatment, with reported efficacy rates ranging from 80 to 90%[1,4,22,23]. Various delivery methods, such as colonoscopy, oral capsules, and enemas, have been shown to be effective, with endoscopic administration generally yielding the highest success rates[24,25].

Beyond rCDI, FMT is being explored as a therapeutic option for other gastrointestinal conditions. Preliminary evidence suggests that FMT may be beneficial in inducing remission in patients with ulcerative colitis, although larger randomized controlled trials are needed to confirm these data[26]. Similarly, while FMT has shown potential in treating irritable bowel syndrome (IBS), the evidence remains preliminary, and further studies are required to establish its role in clinical practice[27,28].

In addition to gastrointestinal applications, FMT is being investigated for its potential in managing systemic and immune-mediated conditions. Early studies suggest that FMT might be a valuable adjunctive therapy for fulminant CDI, particularly in critically ill patients, where standard antibiotic therapy alone may not be sufficient[29,30]. Moreover, ongoing research is exploring the role of FMT role in treating conditions such as graft-versus-host disease[31,32] and immune checkpoint inhibitor-induced colitis[33,34].

Emerging experimental applications of FMT include its potential in treating metabolic syndrome and neurodegenerative disorders, where early findings suggest that FMT may influence systemic immune responses and

gut-brain axis interactions[15,35,36]. Additionally, FMT is being investigated for its role in improving the efficacy of immunotherapy for the treatment of several neoplasia, including melanoma[37].

The safety profile FMT is generally favorable, particularly in the treatment of recurrent rCDI[25]. However certain risks necessitate careful management. Adverse events can range from mild gastrointestinal symptoms, such as diarrhea, cramping, and bloating, to more severe complications, including the transmission of infectious diseases through donor stool[24]. The risk of transmitting multidrug-resistant organisms (MDROs) is a significant concern, with documented cases of severe complications, including death[38].

The use of FMT in immunocompromised patients poses additional risks, as these individuals may be more susceptible to infections and other adverse outcomes. Serious infections following FMT in immunocompromized patients highlight the need for careful patient selection and monitoring[38]. Moreover, long-term safety data are still limited, and further research is needed to fully understand the potential risks associated with FMT, particularly in applications beyond rCDI[1].

To mitigate these risks, standardized protocols for donor screening, stool processing, and patient monitoring are essential. The development of standardized FMT products, such as those derived from a single donor and subjected to rigorous safety testing, may help reduce the variability in outcomes and improve the safety profile of FMT[22].

Given the diverse and evolving landscape of FMT applications, ongoing research is crucial to refine treatment protocols, ensure long-term safety, and explore new therapeutic strategies. The integration of advanced omics technologies and bioinformatics is expected to play a key role in personalizing FMT therapy and optimizing its outcomes[39,40].

ORGANIZING A STOOL BANK

A broader use of FMT, both for the treatment of rCDI and in experimental settings, is challenged by difficulties in recruiting donors and managing the production and storage of transplants. The establishment of stool banks, as suggested by Cammarota *et al.*[41] and Baunwall *et al.*[42], is crucial for ensuring a consistent and safe supply of donations. According to a recent international estimate, the current European FMT activity covers approximately 10% of the patients with indication[42]. Centralized stool banks could streamline logistics and distribution, enhancing FMT accessibility while adhering to rigorous safety and quality standards.

The organization involves several critical steps, beginning with the recruitment of potential donors, who must undergo a meticulous and often multi-tiered selection process. This process typically starts with an initial screening via detailed questionnaires to rule out individuals with any history of infectious diseases, gastrointestinal disorders, or lifestyle factors that could compromise the quality of the microbiota. Following this, candidates undergo extensive blood and stool testing to detect a wide range of pathogens and other health issues. Only candidates who pass these initial screenings are considered eligible donors. However, even with thorough pre-screening, the acceptance rate of donors remains low. A study from a large Italian stool bank highlighted the significant challenge of donor recruitment, revealing that out of 114 candidates, only 29 (25%) were deemed suitable after the comprehensive evaluation process[43]. This low yield is not uncommon; other studies have reported acceptance rates sometimes as low as 2-3%[44,45,46]. The high exclusion rates can be attributed to a variety of factors, ranging from logistical issues, such as the candidate's ability to consistently provide samples within the required time frame, to more complex medical exclusions following detailed laboratory tests. Even for initially accepted donors, repeated screenings are required to ensure the quality and safety of each donation, with every stool sample undergoing additional testing before being approved for use in FMT. Indeed, an Italian study found that 21% of stool samples were later excluded, after initial stool testing revealed the presence of pathogens, despite the donors being asymptomatic[43]. There is also an ongoing debate about the best practices for maintaining donor engagement and minimizing dropouts. In countries like the United States and Australia, compensation is allowed, which might help mitigate attrition rates. This is not feasible in Europe, where SoHO are usually collected only from voluntary, non-remunerated donors[45].

REGULATORY ASPECTS

The recent adoption of the EU Regulation on SoHO (Regulation [EU] 2024/1938)47 expands the scope of EU regulation to include substances like intestinal microbiota which were previously left unregulated at the EU level, acknowledging their critical role in medical applications. According to new directives, entities and establishments involved in the collection, processing, and storage of fecal microbiota must meet the same high standards required for other human-origin substances.

This new SoHO regulation could facilitate the integration of stool banking within transfusion medicine departments. Given their extensive experience in handling and issuing biological materials while ensuring compliance with rigorous safety standards, transfusion services are well-positioned to take on the additional functions related to stool banking. By doing so, they can support the broader application of FMT, ensuring that both the collection and processing of stool samples meet the highest quality standards.

Moreover, the regulation emphasizes the need for clear and coordinated oversight of all SoHO activities, which could further streamline the inclusion of stool banking within existing blood and tissue establishments. This novel and harmonized regulatory framework not only facilitates cross-border exchanges but also ensures consistent quality and safety measures across Europe.

While awaiting the full implementation of EU regulations, Italy has implemented the "*National Program on Human Fecal Microbiota Transplantation (FMT) - regulatory, clinical, and organizational aspects*"[48]. This program provides comprehensive guidelines for the use of both fresh and frozen fecal material, with a strong emphasis on safety, preparation, storage, and administration. It underscores the importance of rigorous donor selection, laboratory eligibility criteria, and standardized microbiota characterization methodologies. Donors undergo thorough screening through questionnaires, biohumoral tests, and rapid pathogen tests, including SARS-CoV-2, to ensure the safety and efficacy of the transplant. FMT can only be administered in hospitals where the fecal transplant program has been authorized by the Italian National Transplant Center (Centro Nazionale Trapianti [CNT]).

THE POSSIBLE ROLE OF TRANSFUSION MEDICINE DEPARTMENTS

Italian regulations currently do not specifically mandate the involvement of Transfusion Medicine departments in FMT processes, which mainly involve gastroenterology, infectious diseases, and microbiology departments[48]. Nonetheless, as already mentioned, the extensive experience of transfusion services in donation management, biological material handling, and safety standards positions them as valuable contributors to FMT's expansion. Their collaborative integration with the other departments could enhance stool donor recruitment, establish stool banks, and thus improve therapy accessibility and effectiveness. Success stories in Northern Europe[49] and Australia[50] highlight the potential of recruiting stool donors from the pool of blood donors, leveraging existing infrastructures and trust in the donation process. Costs are expected to be lower when donors are recruited, and stool is processed within blood and tissue establishments due to savings in donor screening, efficient lab processing, and shared use of existing facilities. For instance, a study conducted by Odense University in Denmark[51] found that the cost of producing one stool unit for transplantation among blood donors was approximately USD 590, substantially below (i.e., 50-60% lower) the costs reported by other nonprofit stool banks, such as the American OpenBiome facility (USD 1,595 per dose) and the Netherlands Donor Feces Bank (USD 1,155), which do not rely on blood donors. However, current literature also highlights significant challenges, including logistical barriers, stringent screening criteria that lead to high rejection rates, and ambivalence among potential donors due to concerns about the process and its impact on personal health. Solutions include better communication and support for ineligible donors[52,53].

THE EXPERIENCE OF THE POLICLINICO OF MILAN

Recently, the FMT Program at the Fondazione IRCCS Ca' Granda Policlinico di Milano -the main public research hospital in Italy- was accredited and officially authorized by the CNT to participate in the National Program for FMT, as detailed in the official authorization (Delibera CNT No. 0031380, 17/07/2024). The accreditation process took more than two years to complete. This accreditation

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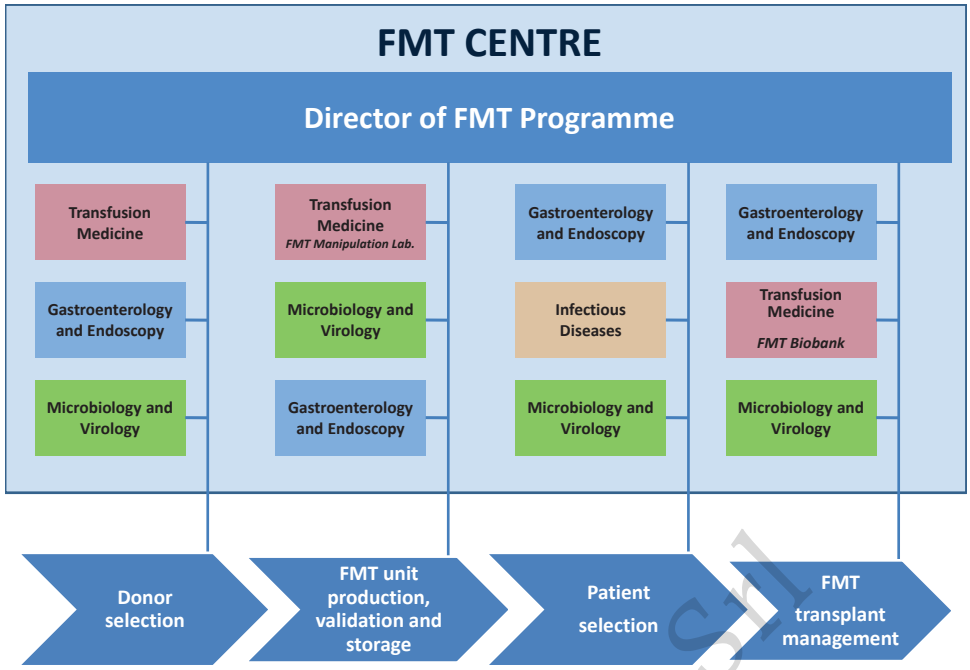

Figure 1 - The organizational structure of the FMT program at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

validates the hospital's capability to conduct FMT under stringent national guidelines, positioning the transfusion medicine department as a key player in the safe and effective implementation of FMT.

The organizational structure of the FMT program at Policlinico di Milano (**Figure 1**) is designed to ensure comprehensive and integrated care across multiple specialties. The program involves collaboration between several key departments, including the Transfusion Medicine Unit, Gastroenterology and Endoscopy, Microbiology and Virology, and Infectious Diseases. The Transfusion Medicine Unit is responsible for donor selection, production, and validation of FMT units, while the Gastroenterology and Endoscopy department manages patient selection and the transplant procedure. The Microbiology and Virology department plays a crucial role in screening and validating stool samples, ensuring that all procedures meet the highest safety and quality standards.

Inspired by the hematopoietic stem cell transplantation model, the interdisciplinary team integrates clinical units for therapy application, donation collection, and substance processing, preservation, and distribution, typically handled by transfusion services. The initiative encompasses three core processes: donor and donation suitability assessment, FMT unit production and cryopreservation, and transplantation with patient follow-up, ensuring safety and efficacy through multi-specialty collaboration. Donor selection involves a thorough three-tier suitability process, including stringent anamnestic requirements, diagnostic tests similar to those required for blood donations, and pathogen screenings in donated stool (**Table I**). Additionally, validation tests for FMT unit processing, freezing, thawing, release, and transport were conducted as required by the accreditation procedure.

The Department of Transfusion Medicine at IRCCS Ca' Granda Policlinico di Milano can rely on approximately 30,000 regular blood donors, who potentially represent an important resource in the hospital's stool banking program. Donor recruitment began in March 2024. Up to the time of writing, 19 regular blood donors were offered the opportunity to participate in the stool donation program during their pre-blood donation visit. All agreed

to take part (100%) and had no initial contraindications based on their medical history questionnaire; they subsequently signed the informed consent for stool donation. Of these, 14 donors were subjected to microbiological screening and 4 (28.5%) were ultimately deemed eligible for stool donation. Among those who were not eligible, we observed 3 bacterial reactivities (5 *E. coli*, 1 *H. pylori*, 1 carbapenem-resistant *Pseudomonas aeruginosa*) and 5 parasitic reactivities (1 *Giardia Lamblia*, 2 *Dientamoeba fragilis*, 2 *Blastocystis hominis*). Additionally, 4 donors were excluded due to positive fecal occult blood results (**Table II**).

Table I - *Comprehensive procedure for donor selection in Fecal Microbiota Transplantation (FMT)*

Enrollment of candidate donors
• Potential donors are identified among blood donors. • The transfusion medicine doctor explains the FMT program, its importance, and addresses any questions, providing informational materials. • If interested, the candidate signs an informed consent form and completes a dedicated anamnesis questionnaire.
Management of serological results, home collection, and delivery of stool samples
• In the absence of contraindications from blood tests or concerns arising from the medical history, further investigations are conducted*. • The candidate is instructed on how to collect fecal samples at home and deliver them for analysis.
Donor microbiological investigations and suitability evaluation
• Samples are delivered to the microbiology and virology laboratory for analysis**. • If results are within normal ranges, the candidate is contacted to schedule the stool donation.
Stool donation
• The donor undergoes a re-evaluation of the anamnesis before donation. • The procedure for stool collection is explained in detail, and samples are collected and assessed for suitability.
Stool preparation and transfer to the laboratory
• The collected stool is securely packaged and transferred to the FMT manipulation laboratory for processing. • Before processing, two stool samples are sent to the microbiology and virology laboratory for testing for major enteric pathogens and SARS-CoV-2. • The stool donation is processed, and the resulting microbiota units are packaged and stored in quarantine.
Final review and approval for clinical use
• The results of the laboratory investigations and the processing documentation are reviewed. • A final judgment, regarding both the donor and the microbiota units, is issued. If deemed suitable for clinical use, theunits can be released for transplantation.

(*): **Blood/serum tests.** Tri-NAT (HIV RNA, HBV DNA, HCV RNA), HBsAg, HCV Ab, HIV-1 and HIV-2 Ab/Ag, *Treponema pallidum* Ab, anti-HBcAg (total and IgM), HAV IgM, HEV IgM, CMV Ab IgM, EBV Ab IgM, *Entamoeba histolytica* Ab. Complete Blood Count, ESR (Erythrocyte Sedimentation Rate), CRP (C-Reactive Protein), Blood Glucose, Albumin, Creatinine, Electrolytes (Na, K), Transaminases, Bilirubin (Total, Conjugated), ɤGT (Gamma-Glutamyl Transferase), Alkaline Phosphatase; and, only in the presence of risk factors: Serology for HTLV I and II, Serology for *Strongyloidesstercoralis*, Serology for *Toxocaracanis*, Monkeypox MPXV (Real-Time PCR on vesicle swab, only when indicated). (**) **Fecal tests.** Immuno assays: *Clostridioides difficile* (toxigenic), *H. pylori* (fecal antigen). Molecular tests: *Yersinia enterocolitica*, *Escherichia coli* VT-producing, enteroaggregative, enteropathogenic, enterotoxigenic, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Clostridioides difficile* toxin A/B, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*, *Plesiomonas shigelloides*, Rotavirus, Adenovirus, Norovirus, Astrovirus, Sapovirus, *Giardia lamblia*, *Cryptosporidium* spp, *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Dientamoeba fragilis*, *Blastocystis hominis*. Search for Helminths: *Strongyloides* spp., *Necator americanus*, *Ancylostoma* spp., *Ascaris* spp., *Trichuris trichiura*, *Enterobius vermicularis*, *Hymenolepis* spp., *Taenia* spp., *Enterocytozoon* spp./*Encephalitozoon* spp.; Culture tests: *Listeria monocytogenes*, Vancomycin-resistant Enterococci, *Carbapenem-resistant Enterobacteria* or ESBL-producing, *Carbapenem-resistant Pseudomonas aeruginosa*, *Methicillin-resistant Staphylococcus aureus*, *Carbapenem-resistant Acinetobacter baumannii*; Other tests: Eggs, cysts, and life forms of intestinal parasites (coproparasitological examination, microscopic and macroscopic, including *Isospora*, *Microsporidia* and *Helminths*), Fecal occult blood; and, only in presence of risk factors: Fecal calprotectin.

Table II - *Microbiological screening results and exclusion criteria for stool donation program*

Donors	Pre-selected regular donors No. (%)	Withdrawing from the program No. (%)	Donor microbiological investigations No. (%)	Tested donors eligible No. (%)	Tested donors non eligible No. (%)	
Male	14 (74%)	1 (7%)	13 (93%)	3 (23%)	10* (77%)	
					*Microbiological abnormalities	
					One	6 (60%)
					Two	2 (20%)
					Three	2 (20%)
Female	5 (16%)	4 (80%)	1 (20%)	1 (100%)	0 (0%)	
Total	19 (100%)	5 (26%)	14 (74%)	4 (28.5%)	10 (71.5%)	

RESEARCH OPPORTUNITIES

In our opinion, the research pipeline in stool banking should prioritize donor recruitment and retention strategies, along with expedited screening for donor suitability. These efforts require a multifaceted approach that includes non-financial incentives, comprehensive educational outreach, and a streamlined donation process, with the aim of enhancing and maintaining the pool of available donors, ultimately ensuring a rich diversity in the microbiota available for transplantation purposes. Simultaneously, the refinement of rapid screening methods for assessing donor suitability is a critical component for the safe and effective implementation of FMT. The adoption of advanced technologies, such as metagenomic sequencing, coupled with the integration of machine learning approaches for predictive analyses, facilitates a more nuanced and effective evaluation of potential donors. Moreover, the development and application of point-of-care testing tools have the potential to further streamline the screening process, enabling real-time assessments that can significantly expedite donor selection.

CONCLUSIONS

The involvement of Transfusion Medicine departments in FMT programs represents a promising approach for overcoming the logistical and regulatory challenges currently limiting the broader application of FMT. By leveraging the existing infrastructure and expertise of transfusion services in donor recruitment, biological material handling, and adherence to strict safety standards, and by following the long-established model used in hematopoietic stem cell transplantation programs, it is possible to streamline the donor selection process and enhance the safety and efficacy of FMT. The establishment of stool banks within blood and tissue establishments may significantly improve the availability and accessibility of FMT, addressing the growing demand for this therapeutic intervention for rCDI while supporting clinical trials for experimental applications.

Moreover, the recent adoption of new regulations on SoHO provides a robust regulatory framework that ensures consistent safety and quality measures across Europe. These regulations, combined with the collaborative efforts of transfusion medicine departments, could help the standardization of FMT practices, ensuring that they are safe, effective, and widely available to patients in need.

Our initial experience suggests that such integration could be both feasible and beneficial. As research continues to explore new therapeutic applications of FMT, the involvement of transfusion medicine departments could be key to the successful expansion and optimization of this emerging treatment.

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AUTHORS' CONTRIBUTIONS

DP conceptualized, designed, and drafted the initial version of the manuscript. LV, FC, LS, VDA, and CA contributed to the writing and provided critical revisions. All Authors revised and approved the final version for submission.

CONFLICTS OF INTEREST

DP serves as Section Editor in BT and has received travel and research grants, speaking fees, and teaching fees from Diasorin, Diamed, Diatech Pharmacogenetics, Grifols, Immucor, Macopharma, Ortho Clinical Diagnostics, Terumo, Cerus. LS serves as Editorial Office Manager in BT. LV has received speaking fees, consulting fees, and unrestricted grant support from Viatris, Novo Nordisk, Pfizer, Boehringer Ingelheim, Resalis, and Gilead. VDA serves as Section Editor in BT. The other Authors declare no conflicts of interest.

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