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Systematic review

PERSONALIZED MICROBIOME BIOTHERAPEUTICS ACROSS RECURRENT CDI, CANCER IMMUNOTHERAPY, ULCERATIVE COLITIS AND MDRO DECOLONIZATION: A PRISMA 2020 SYSTEMATIC REVIEW WITH STRUCTURED NARRATIVE SYNTHESIS

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ABSTRACT

Background: Microbiome biotherapeutics range from standardized indication-specific products to donor-, recipient- and ecology-informed interventions. Personalization may involve donor selection, recipient stratification, disease-specific ecological conditioning, multi-omics prediction or response-guided adaptation, but these approaches have not been evaluated consistently across clinical indications.

Objective: To systematically evaluate the clinical efficacy, safety and reproducibility of microbiome biotherapeutics and to determine the extent to which donor, product, recipient and longitudinal multi-omics characteristics have been used to personalize treatment across recurrent CDI, cancer immunotherapy, ulcerative colitis and MDRO decolonization.

Materials and Methods: PubMed/MEDLINE, Cochrane CENTRAL and ClinicalTrials.gov were searched from inception to 8 July 2026, supplemented by FDA/CBER sources, targeted publisher searches and citation tracking. Two reviewers independently screened and extracted data. Personalization was classified as prospective treatment tailoring, personalization-enabling evidence or non-personalized indication-specific comparator evidence. A structured narrative synthesis was used because clinical and methodological heterogeneity precluded meta-analysis. Methodological limitations and confidence in the evidence were assessed descriptively using structured domains.

Results: The qualitative synthesis included 27 unique studies represented by 28 eligible reports: 7 studies represented by 8 reports in recurrent CDI, 8 studies in oncology and immunotherapy, 7 studies in ulcerative colitis and 5 studies in MDRO decolonization. Prospective personalization was uncommon. At the unique-study level, 4 studies were prospectively personalized, 14 were personalization-enabling, and 9 provided non-personalized indication-specific comparator evidence. Responder-donor selection was used in early melanoma studies, while donor effects, ecological conditioning and longitudinal engraftment or metabolomic analyses provided personalization-enabling evidence in ulcerative colitis and recurrent CDI. No study validated a universal donor-recipient matching algorithm. Evidence was most consistent for recurrent CDI, where standardized products reduced recurrence, but this represents disease-specific standardization rather than patient-level matching. Oncology and ulcerative colitis signals remained protocol-dependent, and MDRO decolonization remained uncertain.

Conclusions: Personalized microbiome biotherapeutics should be understood as a spectrum from disease-specific product selection to prospective donor-recipient matching and adaptive multi-omics-guided treatment. Current routine evidence is strongest for standardized microbiota-based prevention of recurrent CDI after antibacterial therapy, whereas validated patient-level personalization is not yet established. Future trials should prospectively define matching variables, compare tailored with non-tailored strategies and use standardized clinical, safety and multi-omics endpoints.

Keywords: personalized microbiome medicine; microbiome biotherapeutics; live biotherapeutic products; fecal microbiota transplantation; donor-recipient matching; metagenomics; metabolomics; immunotherapy; Clostridioides difficile; PRISMA 2020.

1. Introduction

Microbiome medicine has entered regulated clinical practice in a narrow setting. FDA product information identifies VOWST and REBYOTA for prevention of recurrent CDI in adults after antibacterial treatment for recurrent CDI, not for treatment of acute CDI [1, 2]. These products demonstrate that an ecological intervention can be standardized, but they do not by themselves establish patient-level personalization.

The main methodological challenge extends beyond the generic efficacy of FMT. The same label can conceal different donor-screening protocols, manufacturing processes, routes, doses, storage conditions, pretreatment regimens, sequencing platforms, bioinformatic pipelines and endpoints. Translational reviews and clinical-testing consensus documents therefore emphasize standardized product characterization and validated analytical interpretation [3, 4].

Clinically, the relevant question is not only whether a microbiome intervention works, but which donor or product, for which recipient, under which ecological conditions and with which monitoring strategy permits the effect to be predicted, reproduced and delivered safely. This distinction

is especially important in immuno-oncology, ulcerative colitis and MDRO decolonization, where mechanistic plausibility does not consistently translate into durable clinical benefit [3-5].

Safety is integral to personalized treatment because selection of a donor, product or recipient subgroup can alter both benefit and risk. Donor-derived interventions require validated donor screening, quarantine, traceability and surveillance for transmissible pathogens, while defined products require transparent manufacturing and postmarketing monitoring [6]. This systematic review examines whether current evidence supports genuine treatment personalization or only indication-specific standardization and exploratory biomarker stratification.

2. Objective and research questions

The objective of this systematic review was to evaluate the clinical efficacy, safety, reproducibility and translational requirements of personalized microbiome biotherapeutics in humans and to determine whether donor, product, recipient or longitudinal multi-omics characteristics have been used prospectively to tailor treatment or only retrospectively to explain response.

- Which personalization strategies were applied prospectively to donor selection, product choice, recipient selection, ecological conditioning, dosing or retreatment?
- Do baseline metagenomic, metabolomic, immune or resistome features predict clinical response, and are longitudinal post-intervention signatures more informative?
- Does personalized microbiome intervention improve recurrent CDI prevention, immune-checkpoint inhibitor response, steroid-free remission in ulcerative colitis or MDRO-related outcomes?
- Which personalization endpoints are clinically validated, and which remain exploratory, mechanistic or surrogate outcomes?

3. Materials and Methods

3.1. Reporting standard and protocol

Reporting followed PRISMA 2020 [7, 8]. PRISMA was used as a reporting guideline, not as a quality-assessment instrument. The protocol was not prospectively registered in PROSPERO. Core protocol elements, eligibility criteria, search strings, study-selection flow, extraction fields, methodological appraisal and evidence-confidence logic are reported in the manuscript and Supplementary material. During final eligibility reconciliation, six randomized clinical reports that met the stated eligibility criteria were reclassified from the background/excluded set to the included evidence set; this amendment is documented in the search and selection sections.

3.2. Operational definition and classification of personalization

For the final review framework, personalization was operationally defined as deliberate adaptation of donor, product or recipient selection, ecological conditioning, dose, route, retreatment or follow-up according to disease phenotype, previous treatment, baseline microbiome or metabolome, immune profile, colonization or resistome characteristics, or observed post-intervention response. This review-specific personalization framework was applied during final data extraction and synthesis and was not part of a prospectively registered protocol. Studies were classified as: (1) prospectively personalized interventions, in which donor, product, recipient or treatment characteristics influenced treatment assignment or delivery; (2) personalization-enabling studies, in which donor, recipient, microbiome, metabolome, immune or longitudinal response characteristics were analyzed but did not prospectively determine treatment allocation; or (3) non-personalized indication-specific comparator evidence retained to establish the clinical benchmark against which the added value of personalization could be assessed.

Because personalization terminology is inconsistently indexed, database eligibility was not restricted to records containing the words “personalized” or “precision”. Broad microbiome-intervention searches were used to avoid missing trials in which donor effects, recipient ecology, adaptive retreatment or multi-omics stratification were reported only in the full text. Personalization features were then classified during extraction and synthesis.

3.3. PICO and PECO framework and eligibility criteria

Eligibility criteria were defined to distinguish clinical interventional evidence from association-only microbiome research while retaining the indication-specific comparator trials needed to evaluate the added value of personalization. Regulatory documents, consensus statements and cross-cutting observational or mechanistic studies were used for contextual interpretation and were not treated as independent primary clinical effect estimates.

Table 1 separates clinical outcomes, mechanistic endpoints and personalization variables. Recurrence, remission, ORR/PFS and infection outcomes were interpreted as clinical endpoints. Engraftment, diversity, metabolome restoration and resistome reduction were treated as supportive biological evidence unless prospectively linked to treatment selection and clinical benefit.

Table 1. PICO and PECO framework

Element	Definition for this review
Population	Adults or mixed adult cohorts with recurrent CDI, solid tumors treated with immune checkpoint inhibitors, ulcerative colitis, or MDRO carriage/infection when a clinical endpoint was extractable.
Intervention/exposure	FMT, standardized fecal microbiota products, defined LBPs and personalization strategies based on donor phenotype, recipient ecology, disease subtype, microbiome or metabolome markers, ecological conditioning, dosing or response-guided adaptation.
Comparator	Placebo, standard of care, autologous/sham FMT, no microbiome intervention, alternative donor/product, or longitudinal baseline control.
Clinical outcomes	CDI recurrence, sustained clinical response, ORR/PFS/clinical benefit with ICI, steroid-free/endoscopic remission in UC, MDRO eradication/infection outcomes and adverse events.
Mechanistic outcomes	Engraftment, strain replacement, diversity, bile-acid or metabolome restoration, resistome change and immune or metabolic markers.
Personalization variables	Prospective donor or product selection; recipient selection or exclusion; disease- or organism-specific tailoring; baseline metagenomic, metabolomic, immune or resistome stratification; adaptive dosing or retreatment; longitudinal engraftment and response monitoring.
Study designs	RCTs, phase I/II/III clinical trials, prospective interventional cohorts, donor-recipient matching studies with clinical outcomes, and linked mechanistic analyses of eligible human interventions.

Abbreviations: CDI, Clostridioides difficile infection; FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; LBP, live biotherapeutic product; MDRO, multidrug-resistant organism; ORR, objective response rate; PECO, population-exposure-comparator-outcome; PFS, progression-free survival; PICO, population-intervention-comparator-outcome; RCT, randomized controlled trial.

Table 2 narrows the review to clinically interpretable evidence. This choice reduces the number of included reports, but prevents overinterpretation of biomarker-only or commercial testing literature.

Table 2. Eligibility criteria

Included	Excluded
Human interventional studies with a clinical endpoint and a microbiome-directed intervention or standardized product; linked human mechanistic analyses of eligible interventions evaluating engraftment, metabolome or resistome outcomes; RCTs, phase I/II/III trials, prospective interventional cohorts and donor-recipient studies. Studies were eligible when personalization was applied prospectively or when donor, product, recipient or longitudinal variables could inform personalization. Non-personalized trials were retained as indication-specific comparator evidence. Regulatory product information and safety communications were used for contextual interpretation and were not counted as included studies or reports.	Preclinical-only, animal-only or in vitro-only studies; single case reports without generalizable inference; narrative papers without systematic methods; consumer microbiome testing without clinical validation; association-only studies without a microbiome-directed intervention; reports without extractable clinical or linked mechanistic outcomes; personalization claims based only on unvalidated commercial profiling.

Abbreviations: CDI, Clostridioides difficile infection; FMT, fecal microbiota transplantation; LBP, live biotherapeutic product; MDRO, multidrug-resistant organism.

3.4. Information sources and search

PubMed/MEDLINE, Cochrane CENTRAL and ClinicalTrials.gov were searched from inception to 8 July 2026. Additional searches covered FDA/CBER product pages and safety communications, targeted publisher websites, backward reference checking and forward citation tracking. Embase and Web of Science were not searched and did not contribute records. The strategy deliberately used broad intervention and indication terms rather than requiring a personalization keyword, because donor effects, recipient ecology and multi-omics stratification were frequently reported only in full text. Source-specific export counts were not retained in the original search archive; therefore, the aggregate database/register yield is reported, and exact source-level reconstruction is identified as a review limitation rather than described as fully reproducible.

No date restriction was imposed. English-language biomedical sources were prioritized, while non-English records were considered when English title and abstract information permitted reliable eligibility assessment. Conference-only abstracts were used only when linked to a registry record or peer-reviewed report. During final eligibility reconciliation, six eligible randomized trials were identified within the screened corpus and moved from the excluded/background set into the clinical synthesis. The aggregate retrieval total was unchanged.

3.5. Study selection and data extraction

Two independent reviewers screened titles and abstracts and assessed full texts, regulatory records and registry-linked reports. The same reviewers extracted data using a structured form; disagreements were resolved by consensus and, when necessary, third-reviewer adjudication. Extracted items included indication, country and setting, design, sample size by group, intervention or product, comparator, route, pretreatment, dosing schedule, donor strategy, follow-up, primary endpoint, numerical effect estimate, adverse events, microbiome or metabolomic platform, funding and relevant conflicts of interest. Personalization-specific fields included prospective versus post hoc tailoring, donor-selection rule, recipient selection or stratification variables, ecological conditioning, adaptive dosing or retreatment, longitudinal monitoring and whether a donor-recipient or

biomarker algorithm was prospectively validated. Multiple reports from the same clinical study were linked and counted as one unique study. Effect measures were extracted as reported and were not recalculated.

3.6. Methodological appraisal and confidence in evidence

A structured study-level assessment of methodological limitations was undertaken using structured domains: randomization or confounding, deviations from intended intervention, missing data, outcome measurement and selective reporting. The assessment was informed by concepts used in RoB 2 and ROBINS-I but was not presented as a formal application of either algorithm. Overall judgments were therefore expressed as no major, some or major methodological limitations. Confidence in each evidence block and in personalization-specific conclusions was considered narratively across risk of bias, inconsistency, indirectness, imprecision and possible publication bias, without assigning formal GRADE certainty labels or producing a formal Summary of Findings table.

3.7. Synthesis methods

A structured narrative synthesis was performed across recurrent CDI, oncology and immunotherapy, ulcerative colitis and MDRO decolonization. Studies were grouped by indication, intervention class, comparator, route, regimen and endpoint, then compared according to personalization category: prospectively personalized, personalization-enabling or non-personalized comparator evidence. Clinical and linked mechanistic reports from the same study were presented together to prevent double counting. Cross-cutting diet, metagenomic, metabolomic, probiotic and strain-level studies were used only for contextual interpretation and were not counted in the clinical evidence set. A pooled estimate was not calculated because interventions, donor protocols, manufacturing processes, dosing schedules, analytical platforms and outcome definitions differed substantially. Statistical heterogeneity, subgroup meta-analysis and sensitivity analysis were therefore not undertaken.

4. Results

4.1. Study selection

The search identified 822 database or register records and 64 records through regulatory documents, publisher websites and citation searching. Of the database/register records, 215 duplicates were removed, leaving 607 records for title and abstract screening; 492 were excluded, 115 reports were sought, 7 were not retrieved and 108 were assessed for eligibility. Of 64 records identified through other methods, 22 were excluded before retrieval, 42 reports were sought, 2 were not retrieved and 40 were assessed. Across both routes, 148 reports were assessed. Final eligibility reconciliation reclassified six randomized reports from the background/excluded set to the included set. Consequently, 120 reports were excluded and 28 eligible reports corresponding to 27 unique studies were included in the qualitative synthesis. All included reports were subsequently classified according to the review-specific personalization framework applied during final data extraction and synthesis.

Most exclusions occurred because publications were preclinical, association-only without a microbiome-directed intervention, narrative without systematic methods, duplicate or non-extractable, or lacked sufficient intervention, product or outcome information. Grouped exclusion reasons sum to 120 reports after the six-report eligibility correction. The study-selection process is shown in Figure 1; exclusion categories and contextual reports are listed in Supplementary Tables S3A and S3B.

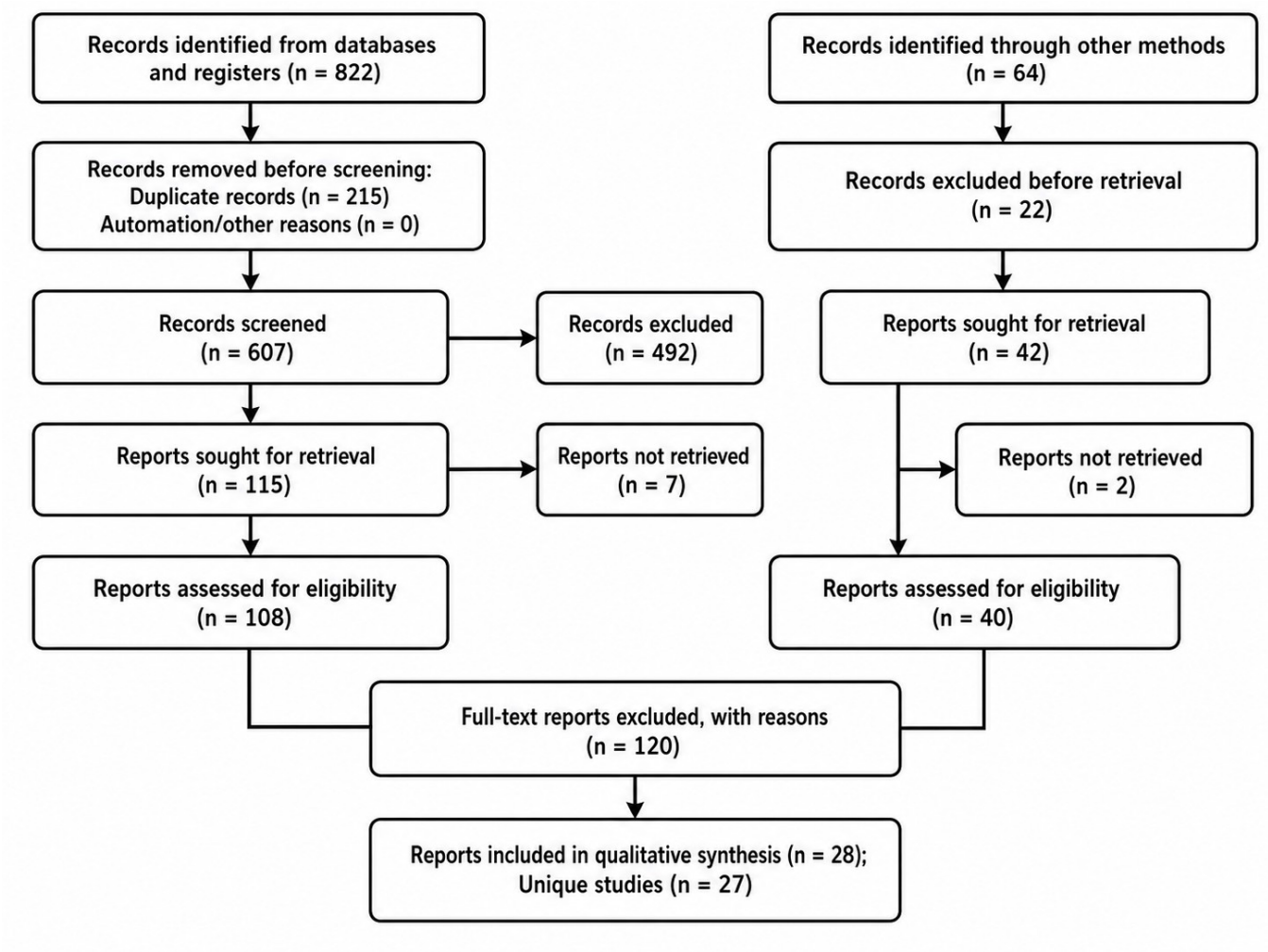

Figure 1. PRISMA 2020 flow diagram after final eligibility reconciliation

4.2. Evidence map and study characteristics

The 27 unique studies represented by 28 eligible reports were unevenly distributed across four clinical areas. Recurrent CDI was supported by seven unique studies reported in eight publications, including a linked multi-omics analysis of PUNCH CD3. Oncology evidence was mainly early phase or based on small randomized studies. Ulcerative colitis included seven randomized trials with inconsistent protocols, while MDRO evidence combined prospective studies, mechanistic trials and a recent negative sham-controlled RCT. Only a minority of studies prospectively used donor or treatment characteristics to tailor therapy; most generated personalization-enabling evidence or provided non-personalized comparator data. Full extraction details, including personalization classification, are provided in Supplementary Table S2. At the unique-study level, 4 of the 27 included studies were classified as prospectively personalized interventions, 14 as personalization-enabling studies, and 9 as non-personalized indication-specific comparator studies. The clinical and linked multi-omics reports from PUNCH CD3 [14, 16] were counted as one unique personalization-enabling study.

Table 3 summarizes the clinical evidence and its personalization context. Reproducibility is strongest where indication, product manufacturing, timing and endpoint are standardized. Personalization requires an additional step: prospective selection or adaptation based on donor, recipient or longitudinal features and evidence that this tailored strategy improves clinical outcomes over non-tailored care.

Table 3. Evidence map by clinical area and personalization context

Area	Evidence volume	Dominant design	Intervention focus	Interpretation
rCDI	7 unique studies / 8 reports	Randomized trials, standardized products and linked multi-omics analyses	Conventional donor FMT; SER-109/VOWST; RBX2660/REBYOTA; VE303	Most mature disease-specific evidence; standardization currently exceeds patient-level personalization.
Oncology/ immunotherapy	8 unique studies / 8 reports	Phase I/II trials, small randomized studies and responder-donor FMT	FMT plus anti-PD-1/ICI; CBM588 adjunctive strategies	Closest to prospective donor-based personalization, but matching algorithms are not clinically validated.

Area	Evidence volume	Dominant design	Intervention focus	Interpretation
Ulcerative colitis	7 unique studies / 7 reports	Randomized trials with heterogeneous donor selection, route, intensity and ecological support	Donor FMT, oral lyophilized FMT and fiber-supported strategies	Donor and protocol effects support personalization potential; no validated recipient-matching strategy.
MDRO decolonization	5 unique studies / 5 reports	Prospective studies, mechanistic trials and a sham-controlled RCT	FMT for MDRO carriage, resistome reduction and infection-related outcomes	Population- and resistome-directed concepts remain experimental.

Abbreviations: FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; LBP, live biotherapeutic product; MDRO, multidrug-resistant organism; rCDI, recurrent Clostridioides difficile infection.

4.3. Recurrent CDI

Early randomized trials established that donor FMT can be highly effective for recurrent CDI. Van Nood et al. reported resolution in 81% after one duodenal infusion and 94% after repeat infusion, compared with 31% with vancomycin alone and 23% with vancomycin plus bowel lavage [9]. Colonoscopic FMT achieved resolution in 90% versus 26% with vancomycin in the Cammarota trial [10], and donor FMT was superior to autologous FMT in the Kelly trial (90.9% vs 62.5% clinical cure) [11]. However, Hota et al. found no superiority of a single enema FMT after vancomycin over a six-week vancomycin taper; recurrence occurred in 56.2% and 41.7%, respectively [12].

Standardized products strengthened the evidence for secondary prevention after antibacterial treatment. SER-109 reduced recurrence by week 8 from 39.8% with placebo to 12.4% [13]. RBX2660/REBYOTA increased treatment success compared with placebo in PUNCH CD3, while VE303 demonstrated a dose-dependent signal, with recurrence in 13.8% of the high-dose group versus 45.5% with placebo [14, 15]. A linked PUNCH CD3 analysis showed restoration of microbial community structure and bile-acid composition after fecal microbiota, live-jslm [16].

The rCDI evidence is comparatively mature because the clinical endpoint is explicit and biological restoration of colonization resistance is plausible. Nevertheless, current clinical use is primarily indication-specific and product- or protocol-standardized rather than recipient-matched. Conventional FMT trials varied in donor source, delivery route, retreatment rules and antibiotic comparators, and none validated a prospective donor-recipient matching algorithm.

4.4. Oncology and immunotherapy modulation

Oncology evidence is biologically persuasive but clinically less mature. Davar et al. and Baruch et al. represent the clearest prospective donor-based personalization: fecal material was selected from patients who had responded to anti-PD-1 therapy and administered to refractory melanoma recipients. Both studies were small and non-randomized, and donor-response status was not combined with a validated recipient-selection algorithm [17, 18].

Newer trials strengthen the signal. Routy et al. reported a phase I safety and activity signal in advanced melanoma, while FMT-LUMINate, PERFORM and TACITO extended the concept to NSCLC, melanoma and metastatic renal cell carcinoma [19-22]. In TACITO, the prespecified 12-month progression-free survival endpoint was not met, although median progression-free survival, a secondary endpoint, favored donor FMT [22]. These data support microbiome modulation as an immunotherapy-adjacent strategy, but they do not establish broad routine use.

CBM588 trials show a second route, defined live bacterial supplementation rather than donor-derived FMT. The clinical signal is promising, yet the mechanism is not linear and the primary microbiome endpoints have not always aligned with response [23, 24].

4.5. Ulcerative colitis

Ulcerative colitis trials demonstrated heterogeneous effects from the outset. Moayyedi et al. reported remission in 24% with donor FMT versus 5% with placebo at week 7, with an apparent donor effect [25]. Rossen et al. found no statistically significant difference in the composite of clinical remission and endoscopic response at week 12 (30.4% vs 20.0%) [26]. Later trials by Paramsothy et al. and Costello et al. supported active donor FMT; Costello et al. reported steroid-free remission at 8 weeks in 32% versus 9% with autologous control [27, 28].

LOTUS suggested that antibiotic priming followed by oral lyophilized FMT can induce remission, whereas RESTORE-UC was halted for futility despite rigorous donor selection [29, 30]. MINDFUL-related data indicated that donor composition and fiber can shape strain engraftment, but fiber support did not guarantee additional clinical benefit [31].

The UC evidence shows that FMT is not a single interchangeable intervention. Donor composition, recipient inflammatory phenotype, pretreatment, route, dose intensity, endpoint definition and ecological support can materially alter both engraftment and clinical response. These findings support protocol-level and donor-informed personalization, but no trial prospectively validated a recipient-specific matching rule that outperformed non-tailored allocation.

4.6. MDRO decolonization

MDRO decolonization is mechanistically plausible because restoration of colonization resistance may reduce pathogenic niches and antimicrobial-resistance gene burden. Prospective and mechanistic human studies reported possible reductions in MDRO carriage, resistome burden or antibiotic-resistance genes [32-35].

The strongest current caution comes from randomized evidence. Narang et al. reported a double-blind sham-controlled trial in gastrointestinal disease patients and did not find significant superiority of single-session FMT for MDRO decolonization or AMR gene reduction, despite effects on microbiome composition [36].

For this area, personalization should be based on organism, resistome, host risk and intended clinical benefit rather than colonization status alone. Trials should prioritize infection incidence, antibiotic exposure, bacteremia, hospitalization and mortality in clearly defined populations such as hematology/HSCT, ICU, CRE/VRE carriers and pre-

transplant cohorts, and should test whether organism- or resistome-informed selection improves these outcomes.

4.7. Personalization domains across indications

Across the 27 included studies, prospective personalization was uncommon. The strongest example was responder-donor selection in refractory melanoma. In ulcerative colitis, donor effects, anaerobic processing, antibiotic priming, fiber support and repeat dosing represented protocol-level tailoring. In recurrent CDI, disease indication, recurrence history and standardized product selection determined treatment, but patient-level donor matching was not established. MDRO studies selected high-risk colonized populations and measured resistome changes without validating organism-specific allocation algorithms.

Most evidence was therefore personalization-enabling rather than prospectively personalized. Baseline metagenomics, metabolomics, immune profiling, donor-strain engraftment and resistome analysis helped explain heterogeneity, but these features rarely determined treatment assignment. Longitudinal signatures after intervention often appeared more informative than baseline diversity alone, particularly for bile-acid restoration in recurrent CDI and immunometabolic pathways in oncology [16, 37-40].

No included study validated a universal clinical algorithm that combined donor and recipient features to select a microbiome intervention prospectively and improve outcomes over non-tailored care. Consumer microbiome tests and empiric probiotics should therefore not be used as substitutes for validated personalization. Colonization resistance to probiotics differs across individuals and is not equivalent to a proven biotherapeutic effect [4, 41, 42].

Table 4 distinguishes clinically implemented personalization from exploratory or enabling evidence. The current field is dominated by indication- and protocol-level tailoring; validated patient-specific matching remains a research objective.

Table 4. Personalization domains and clinical readiness across indications

Clinical area	Prospective personalization	Personalization-enabling variables	Clinical interpretation
Recurrent CDI	Primarily indication- and recurrence-based product or protocol selection; repeat FMT permitted in some trials.	Donor source, route, pretreatment, engraftment, community restoration and bile-acid recovery.	Clinically mature standardization, but no validated patient-level donor matching.
Oncology / immunotherapy	Responder-donor selection in refractory melanoma; disease- and regimen-specific FMT or LBP combinations.	Baseline and longitudinal metagenomics, donor-strain engraftment, immune signatures and tumor context.	Closest to prospective donor-based personalization; still investigational and not algorithmically validated.
Ulcerative colitis	Selected donors, anaerobic preparation, antibiotic priming, oral delivery, fiber support and repeat dosing.	Donor effect, recipient inflammatory phenotype, strain engraftment and ecological support.	Protocol- and donor-informed tailoring; no validated recipient-specific matching rule.
MDRO decolonization	Selection of colonized or high-risk populations; no prospectively validated organism-specific allocation.	Baseline organism, resistome, strain replacement, antibiotic exposure and transplant or ICU context.	Experimental; clinical benefit and personalization strategy remain uncertain.
Cross-cutting evidence	No clinically validated treatment-allocation algorithm.	Baseline and longitudinal metagenomics/metabolomics, diet, probiotic colonization and host features.	Personalization-enabling only; unsuitable for routine decision-making without prospective validation.

Abbreviations: CDI, Clostridioides difficile infection; FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; LBP, live biotherapeutic product; MDRO, multidrug-resistant organism.

4.8. Safety and tolerability

Across the included studies, most commonly reported treatment-emergent events were transient gastrointestinal symptoms, including abdominal discomfort, bloating, diarrhea, constipation and nausea. Early rCDI trials did not identify consistent treatment-related serious adverse events, and standardized product trials generally reported similar overall adverse-event profiles between intervention and control groups [9-16]. In UC, serious events were uncommon but occurred in both donor and control groups, and sample sizes were insufficient to exclude rare harms [25-31]. Oncology and MDRO studies were too small or heterogeneous for precise comparative safety estimates [17-24, 32-36].

Donor-derived interventions carry risks not captured by short randomized follow-up, particularly transmission of bacterial, viral or other pathogenic agents. FDA safety communications therefore reinforce the need for donor screening, quarantine, traceability and active post-treatment surveillance [6]. Safety findings for each study are summarized in Supplementary Table S2.

4.9. Methodological appraisal

Methodological limitations differed mainly by design. Randomized rCDI and UC trials generally had no major or some methodological limitations, but several were open label, stopped early, used small samples or applied heterogeneous outcome definitions. Early oncology studies and most MDRO cohorts had major limitations because of confounding, small samples, surrogate endpoints and incomplete maturity of clinical outcomes. Study-level judgments and their basis are provided in Supplementary Table S4.

Table 5 summarizes the structured assessment by evidence block. These categories are author judgments of methodological limitations and should not be interpreted as formal RoB 2 or ROBINS-I outputs.

Table 5. Structured methodological limitations by evidence block

Evidence block	Dominant design	Overall methodological limitations	Main reasons
rCDI conventional FMT and standardized products	Randomized trials; one linked secondary analysis	Some limitations	Open-label designs in several early trials, early stopping, heterogeneous comparators and limited power for rare harms.
Oncology FMT/LBP	Early-phase and selected randomized studies	Major limitations	Small samples, open-label elements, heterogeneous tumors, confounding and immature hard endpoints.
Ulcerative colitis FMT	Randomized trials	Some limitations	Regimen and donor heterogeneity, short follow-up, inconsistent endpoints and imprecision.
MDRO decolonization	Prospective studies, mechanistic trials and sham-controlled RCT	Major limitations	Natural fluctuation of colonization, surrogate outcomes, mixed controlled evidence and imprecision.

Abbreviations: FMT, fecal microbiota transplantation; LBP, live biotherapeutic product; MDRO, multidrug-resistant organism; rCDI, recurrent Clostridioides difficile infection; RCT, randomized controlled trial.

4.10. Confidence in evidence

Confidence was greatest when randomized clinical endpoints, biological plausibility and regulatory assessment were aligned. Confidence was reduced when evidence depended on small early-phase studies, heterogeneous intervention protocols, inconsistent findings, surrogate outcomes or wide uncertainty. Formal publication-bias testing was not possible because too few sufficiently comparable studies were available within each outcome.

Table 6 presents the domain-by-domain evidence-confidence profile without assigning formal GRADE certainty categories. The most dependable clinical evidence concerns recurrent CDI, whereas oncology, ulcerative colitis and MDRO decolonization require further confirmatory trials.

Table 6. Evidence-confidence profile by clinical outcome

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Narrative confidence and interpretation
rCDI recurrence prevention	Generally limited in pivotal blinded product trials; greater concerns in open-label FMT trials	Some variation by route, product and comparator	Low for prevention after SOC antibiotics	Reduced for smaller conventional FMT trials; less for pivotal products	Higher confidence than other indications; supports indication-specific use after antibacterial treatment.
rCDI microbiome and metabolome restoration	Secondary-analysis limitations	Platform and time-point variation	Mechanistic outcomes are indirect for durable clinical benefit	Moderate sample limitations	Supportive mechanistic bridge, not a substitute for clinical recurrence outcomes.
Oncology FMT/LBP with ICI	Substantial concerns in small early-phase studies	Tumor type, donor, product and regimen heterogeneity	Hard clinical endpoints often secondary or immature	Marked imprecision	Limited confidence; investigational only.
Ulcerative colitis donor FMT	Generally some concerns	Direction and magnitude vary across trials	Protocol-specific effects limit generalizability	Small trials and wide uncertainty	Limited confidence; requires optimized, disease-specific protocols.
MDRO decolonization	Major concerns in non-randomized studies; fewer in sham-controlled trial	Controlled and uncontrolled findings conflict	Colonization and resistome outcomes may not predict infection benefit	Marked imprecision	Very limited confidence; clinical utility remains uncertain.

5. Discussion

The central finding of this systematic review is that personalized microbiome therapy remains a developmental spectrum rather than an established clinical model. Most included studies evaluated disease-specific products or protocols, not true recipient-specific matching. Recurrent CDI has reproducible clinical endpoints, multiple randomized comparisons and standardized products, but its clinical maturity reflects standardization more than personalization. Conventional donor FMT showed large effects in several early trials, although variation in route, donor source and comparator, together with the negative Hota trial, cautions against treating all protocols or donors as interchangeable [9-16].

This interpretation agrees with translational microbiome literature emphasizing standardization, product characterization, multi-omics and clinically meaningful endpoints [3-5]. It also aligns with the clinical microbiome testing consensus, which argues that microbiome profiles should not be used as routine clinical decision tools without validated analytical and interpretive standards [4].

The second finding concerns the level at which personalization occurs. Current evidence is strongest for protocol-level tailoring, including indication-specific products, responder-donor selection, anaerobic processing, antibiotic priming, fiber support and repeat dosing. Recipient-level matching based on baseline ecology, immune phenotype or resistome remains largely exploratory. Baseline diversity alone is insufficient for clinical decisions, and the evidence does not validate a universal donor-recipient matching algorithm [16, 37-43].

A clinically credible personalization strategy should be prespecified, reproducible and comparative. It should define

the variable used for treatment allocation, demonstrate analytical validity, and show that the tailored strategy improves a patient-important clinical outcome over a non-tailored alternative. Post hoc associations between microbiome features and response are valuable for hypothesis generation but should not be described as validated personalized treatment.

The third finding concerns safety and regulation. Donor-derived ecological efficacy must be converted into controlled manufacturing without losing biological activity. Donor screening, quarantine, traceability, pathogen surveillance and postmarketing monitoring are components of the therapeutic benefit-risk balance rather than administrative details [1, 2, 6].

The practical consequence is that success in recurrent CDI should not be generalized automatically to oncology, ulcerative colitis or MDRO decolonization. Each area requires its own trial architecture, disease-specific comparator, predefined clinical endpoint and prospectively specified microbiome and metabolomic analyses.

6. Limitations

The protocol was not prospectively registered in PROSPERO. Final eligibility reconciliation added six randomized reports that met the stated eligibility criteria. Although this amendment corrected the evidence set, post hoc changes reduce audit strength.

• Full RIS/CSV exports, source-specific retrieval counts and line-by-line screening decisions were not retained in an external repository. Aggregate PRISMA numbers are internally consistent, but exact source-level reconstruction is not possible; the manuscript therefore does not claim full PRISMA-S reproducibility.

• Embase and Web of Science were not searched and did not contribute to the evidence set. Subscription-indexed and conference-only records may therefore be underrepresented.

• Methodological limitations and evidence confidence were assessed descriptively rather than by complete outcome-level RoB 2, ROBINS-I and GRADE algorithms. The resulting judgments should be interpreted as structured author assessments.

• A quantitative meta-analysis was not performed because indications, interventions, routes, donor strategies, analytical platforms and endpoint definitions were too heterogeneous.

• Several oncology and MDRO studies were early phase, non-randomized or small randomized trials. Safety reporting was heterogeneous, follow-up was generally insufficient for rare transmissible events, and mechanistic outcomes were not treated as equivalent to clinical benefit.

• Personalization features were reported inconsistently and were frequently exploratory or post hoc. The absence of standard definitions limited comparison of donor selection, recipient stratification, adaptive treatment and longitudinal monitoring across studies.

• Non-personalized indication-specific trials were retained as comparator evidence because the added value of personalization cannot be judged without an untailored clinical benchmark. This broadens the scope beyond studies that explicitly used the term personalized, but the distinction is reported transparently.

7. Practice and research implications

• For recurrent CDI, current practice should use approved indication-specific products or established FMT protocols; available evidence does not justify commercial patient-level donor matching.

• Personalized trials should prospectively define the tailoring variable, analytical platform, decision rule and non-tailored comparator before recruitment.

• Oncology studies should compare responder-donor, healthy-donor and defined-product strategies within disease-specific randomized designs and validate recipient-selection signatures.

• Ulcerative colitis trials should distinguish donor selection, recipient inflammatory phenotype, ecological conditioning and adaptive retreatment rather than treating FMT as a generic intervention.

• MDRO trials should test organism- and resistome-informed allocation against clinical infection outcomes, antibiotic use, bacteremia, hospitalization and mortality.

• Consumer microbiome profiles should not guide treatment unless analytical validity, clinical validity and incremental clinical utility are demonstrated.

8. Conclusions

Personalized microbiome biotherapeutics should be treated as a spectrum of indication-specific standardization, donor- or protocol-informed tailoring and patient-level matching. Current evidence most strongly supports microbiota-based prevention of recurrent CDI after antibacterial treatment, but this evidence does not establish individualized donor-recipient allocation. Prospective personalization is most evident in responder-donor oncology studies and protocol-tailored ulcerative colitis trials, yet no validated algorithm has demonstrated superiority over non-tailored care. Routine adoption requires disease-specific randomized validation, explicit decision rules, standardized safety surveillance and prospectively specified clinical and multi-omics endpoints.

9. Other information

Registration and protocol. The review was not prospectively registered. Core protocol elements are described in the Materials and Methods section and Supplementary material; the final eligibility reconciliation amendment is reported explicitly.

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Competing interests. No competing interests are declared.

Data, code and materials. Search strategies, the revised extraction table with personalization classification, PRISMA flow diagram, full-text exclusion categories, selected contextual exclusions, study-level methodological appraisal and the completed PRISMA 2020 checklist are included as Supplementary material. Original source-specific exports and a complete screening log are not available and are explicitly reported as unavailable.

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Supplementary Table S1. Search strategy and source documentation

This table records the documented source-specific strategies and clarifies which sources contributed to the aggregate PRISMA counts. Exact source-level yields were not retained in the original search archive and are therefore reported as unavailable rather than reconstructed retrospectively.

Embase and Web of Science were not searched and did not contribute records. During final eligibility reconciliation, six randomized reports already present within the screened corpus were reclassified as eligible; the aggregate retrieval total did not change.

Source	Date/status	Search string	Notes	Source-specific yield
PubMed/ MEDLINE	8 Jul 2026	((microbiome[Title/Abstract] OR microbiota[Title/Abstract] OR "gut microbiome"[Title/Abstract] OR "fecal microbiota transplantation"[Title/Abstract] OR FMT[Title/Abstract] OR "live biotherapeutic"[Title/Abstract]) AND (randomized[Title/Abstract] OR trial[Title/Abstract] OR prospective[Title/Abstract] OR phase[Title/Abstract] OR intervention[Title/Abstract]) AND ("Clostridioides difficile"[Title/Abstract] OR CDI[Title/Abstract] OR immunotherapy[Title/Abstract] OR "immune checkpoint"[Title/Abstract] OR melanoma[Title/Abstract] OR "renal cell carcinoma"[Title/Abstract] OR "ulcerative colitis"[Title/Abstract] OR MDRO[Title/Abstract] OR "multidrug-resistant"[Title/Abstract] OR decolonization[Title/Abstract]))	Searched from inception; no date restriction; human clinical focus.	Not retained separately; included in aggregate database/register yield (n = 822)
Cochrane CENTRAL	8 Jul 2026	(microbiome OR microbiota OR FMT OR fecal microbiota transplantation OR live biotherapeutic) AND (Clostridioides difficile OR immunotherapy OR ulcerative colitis OR MDRO)	Searched from inception; trials and controlled clinical studies.	Not retained separately; included in aggregate database/register yield (n = 822)
ClinicalTrials.gov	8 Jul 2026	microbiome OR microbiota OR FMT OR fecal microbiota transplantation OR live biotherapeutic; filters - Interventional Studies; Clostridioides difficile OR immunotherapy OR ulcerative colitis OR multidrug-resistant organism	Searched from inception; interventional records and linked publications.	Not retained separately; included in aggregate database/register yield (n = 822)
FDA/CBER regulatory pages	8 Jul 2026	VOWST OR SER-109 OR fecal microbiota spores live-brpk; REBYOTA OR RBX2660 OR fecal microbiota live-jslm; FMT safety alert; donor screening	Regulatory product information and safety communications; part of the 64 additional-source records.	Not retained separately; included in aggregate additional-source yield (n = 64)

Source	Date/status	Search string	Notes	Source-specific yield
Publisher websites and citation searching	8 Jul 2026	Targeted searches for VOWST/SER-109, REBYOTA/RBX2660, VE303, FMT-LUMINate, PERFORM, TACITO, CBM588, LOTUS, RESTORE-UC and MDRO decolonization trials in Nature Portfolio, JAMA Network, The Lancet, Cell Press and Science/AAAS, followed by backward reference checking and forward citation tracking.	Additional-source search; included in the aggregate 64 records identified through other methods.	Not retained separately; included in aggregate additional-source yield (n = 64)
Embase replication strategy	Not searched	(microbiome OR microbiota OR gut microbiome OR gut microbiota OR fecal microbiota transplantation OR fecal microbiota transfer OR FMT OR live biotherapeutic*) searched in title, abstract and keywords AND (randomized OR trial OR prospective OR phase OR intervention*) searched in title, abstract and keywords AND (Clostridioides difficile OR recurrent CDI OR immunotherapy OR immune checkpoint OR melanoma OR renal cell carcinoma OR ulcerative colitis OR MDRO OR multidrug-resistant OR decolonization) searched in title, abstract and keywords	Replication strategy only; did not contribute records to the included evidence set.	Not applicable; source not searched
Web of Science replication strategy	Not searched	TS=((microbiome OR microbiota OR "gut microbiome" OR "gut microbiota" OR "fecal microbiota transplantation" OR "fecal microbiota transfer" OR FMT OR "live biotherapeutic*") AND (randomized OR trial OR prospective OR phase OR intervention*) AND ("Clostridioides difficile" OR "recurrent CDI" OR immunotherapy OR "immune checkpoint" OR melanoma OR "renal cell carcinoma" OR "ulcerative colitis" OR MDRO OR "multidrug-resistant" OR decolonization))	Replication strategy only; did not contribute records to the included evidence set.	Not applicable; source not searched

Abbreviations: CBER, Center for Biologics Evaluation and Research; CENTRAL, Cochrane Central Register of Controlled Trials; CDI, Clostridioides difficile infection; FDA, US Food and Drug Administration; FMT, fecal microbiota transplantation; MDRO, multidrug-resistant organism.

Supplementary Table S2. Study-level extraction of design, outcomes, safety, personalization category and translational characteristics

This table reports the complete study-level clinical and personalization data used in the synthesis. Numerical results are reproduced as reported in the primary publications, and linked mechanistic analyses are identified explicitly rather than counted as separate clinical studies.

Each report is assigned to one mutually exclusive category: prospectively personalized intervention, personalization-enabling study, or non-personalized comparator evidence. At the unique-study level, 4 studies were prospectively personalized, 14 were personalization-enabling, and 9 were non-personalized comparator studies. Khanna et al. [14] and Blount et al. [16] are linked reports from PUNCH CD3 and were counted as one personalization-enabling study.

Area	Study / design / sample	Intervention and comparator	Route, regimen and follow-up	Primary clinical endpoint	Main numerical result	Safety	Personalization category	Personalization features / analytical platform / funding and relevant COI
rCDI	van Nood et al., 2013 [9]; open-label RCT; 43 randomized	Donor FMT after short vancomycin and bowel lavage vs vancomycin alone or vancomycin plus lavage	Duodenal infusion; a second infusion was permitted after nonresponse; 10-week assessment	Resolution of diarrhea without relapse	Resolution occurred in 81% after one infusion and 94% after repeat FMT, compared with 31% with vancomycin and 23% with vancomycin plus lavage	Transient diarrhea and abdominal cramping were common; no consistent treatment-related serious adverse-event signal was identified	Non-personalized comparator evidence	Response-guided repeat dosing, but no donor-recipient matching. 16S rRNA community profiling; public/academic funding and no commercial product-manufacturer role reported.
rCDI	Cammarota et al., 2015 [10]; open-label RCT; n=39	Donor FMT vs standard vancomycin	Colonoscopic FMT; retreatment according to clinical and endoscopic findings; 10-week follow-up	Resolution of recurrent CDI	Resolution was achieved in 90% with FMT versus 26% with vancomycin	No significant treatment-related serious adverse events were reported in the small trial	Non-personalized comparator evidence	Protocol-level retreatment without donor-recipient matching. Microbiome profiling was not the primary analytic component; academic investigator-led study.
rCDI	Kelly et al., 2016 [11]; double-blind RCT; n=46	Donor FMT vs autologous FMT	Single colonoscopic administration; 8-week follow-up	Clinical cure without recurrence	Clinical cure occurred in 90.9% with donor FMT versus 62.5% with autologous FMT (P=0.042)	No FMT-related serious adverse event was identified	Personalization-enabling study	Donor engraftment and recipient community changes were analyzed, but did not determine allocation. 16S rRNA profiling; public/academic funding.
rCDI	Hota et al., 2017 [12]; open-label RCT; 30 randomized, 28 analyzed	Fourteen-day vancomycin followed by single donor FMT vs 6-week vancomycin taper	FMT by enema; 120-day follow-up	Recurrent CDI	Recurrence occurred in 56.2% after FMT versus 41.7% after vancomycin taper; FMT was not superior	No major differential safety signal was detected, although the sample was small	Non-personalized comparator evidence	Fixed donor-FMT strategy without prospective matching. 16S-based diversity analysis in available samples; public/academic funding.
rCDI	Feuerstadt et al., 2022; ECOSPOR III [13]; phase III RCT; n=182	SER-109 vs placebo after standard-of-care antibiotics	Oral purified Firmicutes spores once daily for 3 days; primary assessment at 8 weeks	CDI recurrence by week 8	Recurrence occurred in 12.4% with SER-109 versus 39.8% with placebo (risk ratio 0.32)	Adverse events were mainly mild or moderate gastrointestinal events; no treatment-related serious adverse events were identified	Non-personalized comparator evidence	Indication- and recurrence-based standardized product, not recipient-matched. Species-level engraftment analyses; Seres Therapeutics-sponsored with manufacturer involvement and disclosed author COI.
rCDI	Khanna et al., 2022; PUNCH CD3 [14]; phase III RCT; n=267	RBX2660/REBYOTA vs placebo after antibiotics	Single rectal dose; 8-week efficacy assessment and follow-up through 6 months	Treatment success without recurrent CDI	Model-estimated treatment success was 70.6% versus 57.5%, an absolute difference of 13.1 percentage points; posterior probability of superiority was 0.991	Abdominal pain and diarrhea were the most common events; no serious treatment-related adverse events were reported	Personalization-enabling study	The clinical trial used a standardized donor-derived product without recipient matching; however, the linked longitudinal microbiome and metabolome analysis [16] makes PUNCH CD3 personalization-enabling at the unique-study level. Rebiotix/Ferring-sponsored; developer employees and investigator relationships were disclosed.
rCDI	Louie et al., 2023 [15]; phase II RCT; n=79	High-dose or low-dose VE303 vs placebo	Oral defined bacterial consortium after antibiotics; 8-week primary follow-up	CDI recurrence	Recurrence occurred in 13.8% with high-dose VE303, 37.0% with low-dose VE303 and 45.5% with placebo	The high-dose regimen was generally well tolerated; gastrointestinal adverse events predominated	Non-personalized comparator evidence	Prospective dose comparison of a defined product, but no biomarker-based allocation. Defined-strain tracking; Vedanta-sponsored with developer involvement and disclosed COI.
rCDI	Blount et al., 2025 [16]; linked PUNCH CD3 multi-omics analysis	REBYOTA vs placebo samples from PUNCH CD3	Longitudinal stool sampling after a single rectal dose	Microbiome and bile-acid restoration linked to treatment response	REBYOTA recipients, particularly clinical responders, showed restoration of community structure and secondary bile-acid profiles toward a non-CDI state	No independent clinical safety estimate was generated because this was a linked mechanistic analysis	Personalization-enabling study	Longitudinal microbial and metabolic response signatures were evaluated but did not guide treatment. Sequencing plus LC-MS metabolomics; Ferring-supported with relevant company relationships disclosed.

Area	Study / design / sample	Intervention and comparator	Route, regimen and follow-up	Primary clinical endpoint	Main numerical result	Safety	Personalization category	Personalization features / analytical platform / funding and relevant COI
Oncology	Davar et al., 2021 [17]; phase I; n=15	FMT from anti-PD-1 responder donors plus pembrolizumab	Donor FMT followed by pembrolizumab re-challenge; longitudinal clinical and biospecimen follow-up	Clinical benefit in anti-PD-1-refractory melanoma	Clinical benefit was observed in 6 of 15 patients, including objective responses and prolonged disease stabilization	Feasibility was demonstrated, but the sample was too small for comparative safety estimates	Prospectively personalized intervention	Donors were prospectively selected for prior anti-PD-1 response; no validated recipient-matching algorithm. Shotgun metagenomics and immune profiling; academic/translational funding with relevant IP or consulting disclosures.
Oncology	Baruch et al., 2021 [18]; phase I; n=10	FMT from melanoma responders plus anti-PD-1 reinduction	Antibiotic conditioning followed by colonoscopic and oral FMT; longitudinal follow-up	Objective response or durable clinical benefit	Three of 10 patients achieved objective responses after FMT and anti-PD-1 reinduction	No dominant new safety signal was identified, but precision was limited by the very small sample	Prospectively personalized intervention	Donors were selected for previous response to anti-PD-1 therapy. Metagenomic and immune profiling; academic investigator-led funding.
Oncology	Routy et al., 2023 [19]; multicenter phase I; n=20	Healthy-donor FMT plus nivolumab or pembrolizumab	FMT before and during anti-PD-1 therapy; longitudinal follow-up	Safety, objective response and donor-strain engraftment	Objective response rate was 65% (13/20), including 4 complete responses (20%)	No grade 3 adverse events occurred from FMT alone; 5 patients (25%) developed grade 3 immune-related adverse events during combination therapy	Personalization-enabling study	Healthy-donor selection and longitudinal donor-strain engraftment were assessed, but did not determine recipient allocation. Shotgun metagenomics, metabolomics and immune profiling; academic/philanthropic support with relevant biotechnology disclosures.
Oncology	Duttagupta et al., 2026; FMT-LUMINate [20]; multicenter open-label phase II; NSCLC n=20, melanoma n=20	Single healthy-donor oral FMT before first-line ICI; anti-PD-1 in NSCLC and dual ICI in melanoma	Oral capsules after polyethylene-glycol bowel preparation; median follow-up 24 months	Primary: ORR in NSCLC; secondary: ORR in melanoma, safety and donor-host microbiome similarity	ORR was 80% (16/20; 95% CI 58.4-91.9) in NSCLC and 75% (15/20; 95% CI 53.1-88.8) in melanoma	No grade 3 or higher adverse events occurred in NSCLC; 13/20 melanoma patients had grade 3 or higher events during dual ICI, while FMT alone caused mainly grade 1 gastrointestinal events	Personalization-enabling study	Post-FMT loss of baseline taxa and longitudinal microbial shifts correlated with response, but did not assign treatment. Shotgun metagenomics and strain analysis; Canadian Cancer Society and Weston Family Foundation support, with LND Therapeutics/Curebiota affiliations and FMT-related IP disclosed.
Oncology	Fernandes et al., 2026; PERFORM [21]; open-label phase I; mRCC n=20	Encapsulated healthy-donor FMT (LND101) plus ipilimumab/nivolumab, pembrolizumab/axitinib or pembrolizumab/lenvatinib	Oral capsules with longitudinal sampling; median follow-up 21.9 months	Primary: safety; secondary: response, quality of life and microbiome/immune correlates	Among 18 evaluable patients, ORR was 50% (9/18), including 2 complete responses (11%)	Grade 3 immune-related adverse events occurred in 10/20; no serious FMT-related toxicities or grade 4-5 immune-related events were reported	Personalization-enabling study	Functional engraftment, metabolites and immune features correlated with response and toxicity but did not determine allocation. Shotgun metagenomics, metabolomics and immune phenotyping; philanthropic/academic support with LND Therapeutics affiliations and LND101-related IP disclosed.
Oncology	Porcari et al., 2026; TACITO [22]; randomized double-blind placebo-controlled phase IIa; n=45 treated	FMT from complete ICI responders vs placebo FMT, both with pembrolizumab and axitinib	First FMT by colonoscopy, then capsules at weeks 12 and 24; median follow-up 32 months	Proportion progression-free at 12 months	Twelve-month PFS was 70% versus 41% (P=0.053); median PFS was 24.0 versus 9.0 months (HR 0.50; P=0.035), and ORR was 52% versus 32%	The regimen was considered feasible; comparative safety did not identify a new dominant FMT-related signal in this limited sample	Prospectively personalized intervention	Donors were prospectively selected from complete ICI responders; recipient matching was not algorithmic. Shotgun metagenomics and strain-level engraftment; investigator-initiated public/European academic support with relevant advisory or speaker COI disclosed.

Area	Study / design / sample	Intervention and comparator	Route, regimen and follow-up	Primary clinical endpoint	Main numerical result	Safety	Personalization category	Personalization features / analytical platform / funding and relevant COI
Oncology	Dizman et al., 2022 [23]; randomized phase I; n=30	CBM588 plus nivolumab/ipilimumab vs nivolumab/ipilimumab alone	Oral live bacterial supplementation during systemic therapy; median follow-up about 12 months	Progression-free survival and response	Median PFS was 12.7 versus 2.5 months (HR 0.15; 95% CI 0.05-0.47; P=0.001); response rate was 58% versus 20% (P=0.06)	No significant difference in toxicity was observed between study arms	Non-personalized comparator evidence	Fixed defined-LBP supplementation without biomarker-based allocation. 16S/metagenomic endpoints; product-related support and author disclosures were reported.
Oncology	Ebrahimi et al., 2024 [24]; open-label randomized phase I; n=30	CBM588 plus cabozantinib/nivolumab vs cabozantinib/nivolumab alone	Oral CBM588 during systemic therapy; longitudinal follow-up	ORR, 6-month PFS and prespecified microbiome endpoint	ORR was 74% (14/19) versus 20% (2/10; P=0.01), and 6-month PFS was 84% versus 60%; the primary microbiome endpoint was not met	No significant between-group toxicity difference was identified in the small trial	Non-personalized comparator evidence	Fixed defined-LBP strategy without recipient matching. Longitudinal microbiome profiling; industry/product involvement and relevant author COI were disclosed.
UC	Moayyedi et al., 2015 [25]; randomized placebo-controlled trial; n=75	Donor FMT vs water placebo	Weekly retention enema for 6 weeks; primary endpoint at week 7	Clinical remission	Remission occurred in 24% with donor FMT versus 5% with placebo; response varied by donor	Overall adverse-event frequency did not differ materially between groups	Personalization-enabling study	A donor-dependent effect was identified, but donor-recipient matching did not determine allocation. Microbiome profiling; public/academic funding.
UC	Rossen et al., 2015 [26]; double-blind RCT; n=48	Healthy-donor FMT vs autologous FMT	Two nasoduodenal infusions 3 weeks apart; week-12 assessment	Clinical remission plus endoscopic response	The primary outcome occurred in 30.4% versus 20.0% (P=0.51)	Adverse events were mainly mild and self-limited	Non-personalized comparator evidence	Fixed donor-FMT comparator design without recipient matching. Microbiota profiling; academic investigator-led study.
UC	Paramsothy et al., 2017 [27]; randomized placebo-controlled trial; n=85	Intensive multidonor FMT vs placebo	Initial colonoscopic infusion followed by repeated enemas; 8-week primary follow-up	Steroid-free clinical remission with endoscopic remission or response	The primary endpoint occurred in 27% (11/41) versus 8% (3/40); risk ratio 3.6 (95% CI 1.1-11.9; P=0.021)	Adverse events occurred in 78% versus 83%, mainly transient gastrointestinal complaints, without a significant between-group difference	Personalization-enabling study	Multidonor pooling and donor/recipient microbial features were evaluated, but did not determine allocation. 16S-based microbiome analysis; public/academic funding.
UC	Costello et al., 2019 [28]; randomized clinical trial; n=73	Anaerobically prepared donor FMT vs autologous FMT	Initial colonoscopic infusion followed by two enemas; 8-week assessment	Steroid-free remission	Steroid-free remission occurred in 32% with donor FMT versus 9% with autologous FMT	Three serious adverse events occurred in the donor group and two in control; a causal FMT relationship was not established	Personalization-enabling study	Anaerobic processing and donor-related microbial features informed protocol development, but no recipient matching was used. Microbiome profiling; public/academic funding.
UC	Haifer et al., 2022; LOTUS [29]; double-blind placebo-controlled RCT; n=35	Antibiotic priming plus oral lyophilized donor FMT vs placebo	Two-week amoxicillin, metronidazole and doxycycline pretreatment, then oral FMT or placebo for 8 weeks; responders entered maintenance through week 56	Corticosteroid-free clinical remission with endoscopic remission or response at week 8	The primary endpoint occurred in 53% (8/15) versus 15% (3/20), a difference of 38.3 percentage points (95% CI 8.6-68.0; P=0.027)	Adverse events occurred in 67% versus 85% and were mostly mild gastrointestinal events; serious events included UC worsening in 2 FMT and 1 placebo patient and rectal bleeding in 1 placebo patient	Personalization-enabling study	Ecological antibiotic conditioning and response-dependent maintenance generated tailoring evidence, but allocation was not biomarker-based. Longitudinal microbiome profiling; academic/public support.
UC	Caenepeel et al., 2025; RESTORE-UC [30]; multicenter double-blind sham-controlled RCT; n=72 enrolled, 66 treated	Four anaerobically prepared, rigorously selected allogeneic FMTs vs autologous FMT	Repeated administrations; primary endpoint at week 8	Steroid-free clinical remission	Remission occurred in 3/30 allogeneic-FMT recipients and 5/36 autologous-FMT recipients (P=0.72); the trial stopped for futility	FMT was generally well tolerated and no new safety signal was reported	Prospectively personalized intervention	Allogeneic donors were prospectively selected by microbial cell count, enterotype and abundance of specific genera; no validated recipient-matching rule. Quantitative microbiome profiling; academic funding.
UC	Gogokhia et al., 2025; MINDFUL [31]; randomized double-blind placebo-controlled trial; n=27 analyzed	Single-donor FMT, FMT plus psyllium fiber, or placebo FMT with/without fiber	Single FMT at baseline with 8 weeks of psyllium or placebo; 17-week longitudinal sampling	Clinical response at week 8; secondary remission and endoscopic improvement	FMT improved clinical response, remission and endoscopic outcomes versus placebo (P<0.05), while fiber added no clinical benefit; the trial ended early after product discontinuation	The small sample was insufficient to assess rare harms; no new dominant safety signal was described	Personalization-enabling study	Donor-dependent durable engraftment and fiber-associated strains were identified, but did not allocate treatment by recipient profile. Longitudinal strain-resolved metagenomics; NIH/NIDDK funding (R01 DK128257).

Area	Study / design / sample	Intervention and comparator	Route, regimen and follow-up	Primary clinical endpoint	Main numerical result	Safety	Personalization category	Personalization features / analytical platform / funding and relevant COI
MDRO	Seong et al., 2020 [32]; prospective study; n=35	FMT for persistent MDRO colonization	Protocol-defined FMT with follow-up for up to 1 year	MDRO decolonization	Twenty-four of 35 patients (68.6%) were decolonized within 1 year; FMT was independently associated with decolonization (HR 5.343; 95% CI 1.877-15.212; P=0.002)	No precise controlled safety estimate was possible in the prospective cohort	Personalization-enabling study	MDRO type and baseline microbial characteristics were explored as response predictors, but no allocation algorithm was validated. Microbiome profiling; academic funding.
MDRO	Ghani et al., 2021 [33]; prospective clinical model/cohort; n=20 treated	FMT in patients colonized or infected with MDRO, compared with pre-FMT history and matched untreated controls	Clinical FMT pathway with longitudinal clinical follow-up	Antibiotic duration, bacteremia and hospital length of stay	FMT was associated with significant reductions in antibiotic duration, bacteremia and length of stay despite modest decolonization rates	Nonrandomized comparisons and clinical heterogeneity limited benefit-risk inference	Personalization-enabling study	High-risk clinical selection was used, but no validated microbiome or resistome decision rule guided allocation. Clinical microbiome/resistome context; academic funding.
MDRO	Woodworth et al., 2023; PREMIX [34]; randomized controlled mechanistic study	FMT vs control for MDRO decolonization in renal transplant recipients	Protocol-controlled FMT with longitudinal stool sampling	MDRO decolonization, resistome change and strain replacement	FMT accelerated decolonization in some participants and reduced antimicrobial resistance through replacement of resistant strains by susceptible strains	The study was underpowered for definitive clinical safety comparisons	Personalization-enabling study	Baseline strains, donor strain acquisition and resistome changes were evaluated as mechanistic determinants. Shotgun metagenomics and strain tracking; public/academic funding.
MDRO	Hyun et al., 2022 [35]; prospective mechanistic study	FMT in patients colonized or infected with MDROs	Clinical FMT with longitudinal stool and resistance-gene assessment	Antibiotic-resistance gene burden and microbiome change	FMT significantly reduced VanA abundance and produced smaller or nonsignificant changes in other resistance genes, supporting gene-specific rather than universal resistome effects	No controlled comparative safety estimate was available	Personalization-enabling study	Gene-specific response patterns, including VanA and carbapenemase genes, were characterized without a prospective allocation algorithm. Resistome/qPCR and microbiome analysis; academic funding.
MDRO	Narang et al., 2026 [36]; double-blind sham-controlled RCT; n=114	Single colonoscopic FMT vs sham sigmoidoscopy with saline	Single intervention; co-primary assessment at 4 weeks	MDRO decolonization and reduction in AMR-gene burden	Decolonization was 31.0% (18/58) versus 30.4% (17/56), absolute difference 0.6% (95% CI -16.2 to 17.6; P=0.94); AMR-gene burden also did not differ (P=0.68)	Adverse events were comparable between groups; no efficacy-justifying safety advantage was demonstrated	Non-personalized comparator evidence	Fixed single-session intervention without organism-specific matching. 16S rRNA microbiome, shotgun virome, ITS2 mycobiome and AMR-gene analyses; academic/public study with no commercial product role reported.

Abbreviations: AE, adverse event; AMR, antimicrobial resistance; ARG, antibiotic-resistance gene; CDI, Clostridioides difficile infection; COI, conflict of interest; FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; LC-MS, liquid chromatography-mass spectrometry; MDRO, multidrug-resistant organism; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; rCDI, recurrent CDI; RCT, randomized controlled trial; SOC, standard of care; UC, ulcerative colitis.

Supplementary Table S3A. Full-text and report exclusion categories

The categories below summarize full-text or regulatory reports excluded after eligibility assessment. They are grouped because many records were secondary reports or mechanistic papers rather than individual clinical trials.

Counts in this table sum to the 120 reports excluded after eligibility assessment. Six randomized reports previously treated as background or non-extractable were reclassified as eligible during final reconciliation and are not included in these exclusion counts.

Reason for exclusion	Reports, n
Association-only microbiome study without microbiome-directed intervention or extractable clinical endpoint	39
Preclinical, in vitro or animal-only report	27
Narrative, editorial or background paper without eligible primary interventional data	21
Duplicate, secondary or non-extractable report without additional eligible data	19
Insufficient intervention/product, donor or microbiome-platform detail	9
Consumer/commercial microbiome testing without clinical validation	5
Total excluded after eligibility assessment	120

Supplementary Table S3B. Contextual personalization studies excluded from the clinical evidence synthesis

These reports informed interpretation of predictive, ecological and analytical personalization but were excluded from the clinical evidence set because they did not meet the target indication, microbiome-directed intervention or clinical outcome criteria.

Report	Reason for exclusion from clinical evidence set	Use in this review
[37] Wastyk et al., 2021	Diet intervention outside the four target clinical indications and without a disease-specific therapeutic endpoint	Context for diet-microbiome-immune interactions
[38] Zeevi et al., 2015	Personalized nutrition study outside the target indications and intervention classes	Context for predictive personalization
[39] Gopalakrishnan et al., 2018	Association-only oncology microbiome study without a microbiome-directed intervention	Context for immunotherapy response biology
[40] Matson et al., 2018	Association-only oncology microbiome study without a microbiome-directed intervention	Context for immunotherapy response biology
[41] Zmora et al., 2018	Probiotic colonization study without a target-indication clinical endpoint	Context for host-specific colonization resistance
[42] Suez et al., 2019	Narrative review rather than eligible primary interventional evidence	Context for probiotic uncertainty
[43] Segata, 2018	Conceptual commentary without clinical intervention or extractable outcome	Context for strain-resolved methods

Abbreviations: FMT, fecal microbiota transplantation.

Supplementary Table S4. Study-level structured assessment of methodological limitations

Study/block	Design	Randomization/ confounding	Intervention deviations	Missing data	Outcome measurement	Selective reporting	Overall assessment
van Nood [9]	Open-label randomized trial	No major limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Cammarota [10]	Open-label randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Kelly [11]	Double-blind randomized trial	No major limitation	No major limitation	Some limitation	No major limitation	No major limitation	Some limitations
Hota [12]	Open-label randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Feuerstadt/SER-109 [13]	Randomized trial	No major limitation	No major limitation	Some limitation	No major limitation	No major limitation	Some limitations

Study/block	Design	Randomization/ confounding	Intervention deviations	Missing data	Outcome measurement	Selective reporting	Overall assessment
Khanna/RBX2660 [14]	Randomized trial	No major limitation	No major limitation	Some limitation	No major limitation	Some limitation	Some limitations
Louie/VE303 [15]	Randomized phase II trial	No major limitation	No major limitation	Some limitation	No major limitation	Some limitation	Some limitations
Blount multi-omics [16]	Secondary analysis	Some limitation	No major limitation	Some limitation	Some limitation	Some limitation	Some limitations
Davar melanoma FMT [17]	Phase I non-randomized study	Major limitation	Some limitation	Some limitation	No major limitation	Some limitation	Major limitations
Baruch melanoma FMT [18]	Phase I non-randomized study	Major limitation	Some limitation	Some limitation	No major limitation	Some limitation	Major limitations
Routy advanced melanoma [19]	Phase I non-randomized study	Major limitation	Some limitation	Some limitation	No major limitation	Some limitation	Major limitations
FMT-LUMINate [20]	Phase II non-randomized study	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
PERFORM [21]	Phase I non-randomized study	Major limitation	Some limitation	Some limitation	No major limitation	Some limitation	Major limitations
TACITO [22]	Randomized phase II trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Dizman CBM588 [23]	Randomized phase I trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Ebrahimi CBM588 [24]	Open-label randomized phase I	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Moayyedi UC [25]	Randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Rossen UC [26]	Double-blind randomized trial	No major limitation	No major limitation	Some limitation	No major limitation	Some limitation	Some limitations
Paramsothy UC [27]	Randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Costello UC [28]	Randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	No major limitation	Some limitations
LOTUS [29]	Randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
RESTORE-UC [30]	Randomized trial	Some limitation	Some limitation	Some limitation	No major limitation	Some limitation	Some limitations
Gogokhia UC/fiber [31]	Randomized trial	Some limitation	Some limitation	Some limitation	Some limitation	Some limitation	Some limitations
Seong MDRO [32]	Prospective non-randomized study	Major limitation	Major limitation	Some limitation	Some limitation	Some limitation	Major limitations
Ghani MDRO [33]	Prospective non-randomized study	Major limitation	Major limitation	Some limitation	Some limitation	Some limitation	Major limitations
Woodworth MDRO [34]	Randomized mechanistic study	Some limitation	Some limitation	Some limitation	Some limitation	Some limitation	Some limitations
Hyun MDRO [35]	Prospective mechanistic study	Major limitation	Some limitation	Some limitation	Some limitation	Some limitation	Major limitations
Narang MDRO [36]	Sham-controlled randomized trial	No major limitation	No major limitation	Some limitation	No major limitation	No major limitation	Some limitations

Note: These are descriptive author judgments based on structured domains. They are informed by risk-of-bias concepts but are not formal algorithm-generated RoB 2 or ROBINS-I ratings. Abbreviations: FMT, fecal microbiota transplantation; MDRO, multidrug-resistant organism; RCT, randomized controlled trial; UC, ulcerative colitis.

Supplementary Table S5. Completed PRISMA 2020 checklist

The checklist identifies where each PRISMA 2020 item is addressed. “Not applicable” is used where no meta-analysis, subgroup analysis or sensitivity analysis was performed.

Section/topic	Item	Reporting requirement	Location in manuscript
Title	1	Identify the report as a systematic review.	Title
Abstract	2	Provide a structured summary consistent with PRISMA abstract guidance.	Abstract
Introduction	3	Describe the rationale in the context of existing knowledge.	Section 1, Introduction
Introduction	4	State the review objective or research questions explicitly.	Section 2, Objective and research questions
Methods	5	Specify inclusion and exclusion criteria and grouping for synthesis.	Sections 3.2-3.3; Tables 1-2

Section/topic	Item	Reporting requirement	Location in manuscript
Methods	6	Specify all information sources and the last search date.	Section 3.4; Supplementary Table S1
Methods	7	Present complete search strategies, including filters and limits.	Supplementary Table S1; source-level yields reported as unavailable
Methods	8	Describe the study-selection process and number of reviewers.	Section 3.5, Study selection and data extraction
Methods	9	Describe data-collection methods and reviewer procedures.	Section 3.5, Study selection and data extraction
Methods	10a	List and define outcomes for which data were sought.	Sections 3.2-3.3; Table 1
Methods	10b	List other data items and assumptions.	Sections 3.2 and 3.5; Supplementary Table S2
Methods	11	Describe the method used to appraise methodological limitations or risk of bias.	Section 3.6; Supplementary Table S4
Methods	12	Specify effect measures used for each outcome.	Section 3.5, Study selection and data extraction
Methods	13a	Describe how studies were assigned to each synthesis.	Sections 3.2 and 3.7; personalization categories and indication groups
Methods	13b	Describe data preparation or conversion methods.	No effect estimates were recalculated
Methods	13c	Describe methods used to tabulate or visually display results.	Section 3.7; Tables 3-6; Supplementary Table S2
Methods	13d	Describe synthesis methods and justify the selected approach.	Section 3.7, Synthesis methods
Methods	13e	Describe methods used to explore heterogeneity.	Not applicable - no pooled statistical synthesis
Methods	13f	Describe sensitivity analyses.	Not applicable - no pooled statistical synthesis
Methods	14	Describe assessment of bias due to missing results.	Section 3.6, Methodological appraisal and confidence in evidence
Methods	15	Describe certainty or confidence assessment.	Section 3.6; Table 6
Results	16a	Report the search and selection results, ideally with a flow diagram.	Section 4.1; Figure 1
Results	16b	Cite potentially eligible excluded reports and explain exclusions.	Supplementary Tables S3A-S3B; amendment described in Methods and Results
Results	17	Cite included studies and present their characteristics.	Sections 4.2-4.8; Tables 3-4; Supplementary Table S2
Results	18	Present methodological appraisal or risk-of-bias results.	Section 4.9; Table 5; Supplementary Table S4
Results	19	Present results for individual studies, including estimates where available.	Sections 4.3-4.8; Supplementary Table S2
Results	20a	Summarize characteristics and methodological limitations for each synthesis.	Sections 4.2, 4.7 and 4.9; Tables 3-6
Results	20b	Present results of statistical syntheses.	Not applicable - no meta-analysis
Results	20c	Present investigations of heterogeneity.	Not applicable - no statistical synthesis
Results	20d	Present sensitivity analyses.	Not applicable - no statistical synthesis
Results	21	Present assessments of bias due to missing results.	Section 4.10; formal testing not possible
Results	22	Present certainty or confidence assessments for each outcome.	Section 4.10; Table 6
Discussion	23a	Interpret results in relation to other evidence.	Section 5, including interpretation of personalization readiness
Discussion	23b	Discuss limitations of the included evidence.	Sections 4.9-4.10 and 6
Discussion	23c	Discuss limitations of the review processes.	Section 6, Limitations
Discussion	23d	Discuss implications for practice, policy and future research.	Sections 5 and 7
Other information	24a	Provide registration information or state that the review was not registered.	Sections 3.1 and 9
Other information	24b	Indicate where the protocol can be accessed or state that none was prepared.	Sections 3.1 and 9
Other information	24c	Describe and explain amendments to the protocol or methods.	Sections 3.1, 3.4 and 4.1
Other information	25	Describe support and the role of funders.	Other information - Support
Other information	26	Declare competing interests.	Other information - Competing interests
Other information	27	Report availability of data, forms, extracted data, code and other materials.	Other information - Data, code and materials; Supplementary Tables S1-S5