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Review Article

Precision Microbiome Modulation in Type 2 Diabetes: Deciphering Metabolite-Signaling Cascades, PADI4-Mediated NETosis, and AI-Driven Therapeutic Paradigms

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ABSTRACT

Type 2 diabetes mellitus is increasingly understood as an immune-metabolic disorder in which diet, host factors, intestinal ecology, microbial metabolites, epithelial barrier function, and innate immune activation interact rather than operate as independent pathways. This review examines a precision framework that links gut microbial community structure to metabolite signaling, PADI4-dependent neutrophil extracellular trap formation, and artificial intelligence guided therapeutic stratification. Evidence from metagenomic, metabolomic, experimental, and clinical studies indicates that short-chain fatty acids, bile acids, tryptophan-derived metabolites, succinate, imidazole propionate, and microbial products such as lipopolysaccharide can influence incretin release, insulin signaling, barrier integrity, and inflammatory tone. Recent experimental evidence places PADI4-dependent NETosis at the microbiota intestinal interface, where excessive NET formation can increase gut permeability and facilitate systemic exposure to bacterial products. Precision interventions therefore need to target functions and signaling pathways rather than assume that a single bacterial taxon is universally beneficial. Dietary fiber, probiotics, synbiotics, next-generation microbes, Akkermansia-based approaches, fecal microbiota transplantation, and metabolite directed strategies show varying levels of evidence. AI and multi-omics can integrate microbial, metabolic, clinical, and continuous glucose monitoring data to identify responder phenotypes and predict treatment response, but external validation, causal inference, interpretability, and standardized microbiome measurement remain essential. The review proposes an integrated microbiome metabolite

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PADI4 NETosis AI framework and identifies priorities for mechanistic validation and clinical translation.

INTRODUCTION

Type 2 diabetes mellitus (T2D) is a chronic metabolic disease characterized by progressive insulin resistance, impaired beta-cell function, and persistent hyperglycaemia. Current diagnostic criteria include abnormal glycated haemoglobin or plasma glucose measurements, but these clinical measures capture the metabolic phenotype rather than the upstream ecological and inflammatory processes that may contribute to disease heterogeneity [1]. The global burden continues to expand, and the latest International Diabetes Federation estimates emphasize substantial regional variation and a continuing rise in diabetes prevalence [2]. This heterogeneity is important because individuals with apparently similar glycaemic indices can differ in diet, medication exposure, adiposity, intestinal ecology, inflammatory tone, and metabolic response.

The intestinal microbiome has emerged as one component of this heterogeneity. Early metagenomic studies identified disease associated microbial functions in T2D, including reduced representation of some butyrate producing organisms and enrichment of opportunistic or stress tolerant functions [3]. Subsequent work demonstrated that medication exposure, particularly metformin, can substantially modify microbial signatures and therefore complicate attempts to define a disease specific microbiome [4]. More recently, cross cohort strain resolved analyses have shown that microbial signatures can be reproducible at the functional or strain level while still displaying important geographic and cohort variation [5]. These observations argue against a simplistic model in which one universal “diabetic microbiome” exists.

Recent reviews have consolidated evidence linking T2D with altered microbial diversity, microbial function, intestinal barrier disturbance, and metabolite profiles, but they also emphasize inconsistent taxonomic findings across populations [6–9]. The more useful question is therefore not whether the microbiome is associated with T2D, but which microbial functions generate biologically active signals, which host receptors receive them, and whether these pathways can be modified in a patient specific manner.

This review develops that mechanistic perspective around three linked axes. The first is the metabolite signaling cascade, in which microbial products communicate with enteroendocrine, hepatic, adipose, immune, and epithelial systems. The second is PADI4 mediated NETosis, which provides a plausible immune bridge between diet modified microbiota, intestinal barrier dysfunction, endotoxin exposure, and metabolic inflammation. The third is AI driven precision medicine, in which multi-omics, continuous glucose monitoring, clinical phenotyping, and machine learning may help identify the patients and interventions most likely to respond. The aim is not to portray these components as a single established causal pathway, but to synthesize the evidence and define where causality is strong, where it remains experimental, and where precision intervention could be tested.

2. Review methodology

Figure 2: ***PRISMA 2020-informed literature selection schematic. The absence of fabricated record counts is intentional because this article is a structured narrative review rather than a registered systematic review [69–71].***

A structured narrative review approach was used to integrate evidence relevant to T2D, gut microbiome ecology, microbial metabolites, intestinal barrier signaling, PADI4 and NETosis, microbiome modifying interventions, and AI or machine learning. Targeted searches were performed across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar using combinations of terms including "type 2 diabetes", "gut microbiome", "metagenomics", "microbial metabolites", "short-chain fatty acids", "bile acids", "tryptophan", "succinate", "PADI4", "PAD4", "NETosis", "neutrophil extracellular traps", "probiotics", "synbiotics", "fecal microbiota transplantation", "Akkermansia", "machine learning", "artificial intelligence", and "multi-omics". Priority was given to human studies, randomized or controlled interventions, mechanistic animal studies with direct pathway evidence, high quality systematic reviews, and recent methodological literature. Reference lists of key papers were also screened to identify seminal mechanistic studies. PRISMA 2020 was used to inform transparent reporting, while STORMS principles were considered for microbiome specific methodological reporting [69–71].

Because the present manuscript is a structured narrative review rather than a prospectively registered systematic review with a pre-specified protocol, effect sizes were not pooled and a numerical PRISMA count was not manufactured. Figure 2 therefore presents a PRISMA 2020-informed flow schematic that transparently distinguishes identification, screening, eligibility, and synthesis without implying that an audited systematic-review database was created.

3. From dysbiosis to functional microbiome phenotypes

The first generation of T2D microbiome research focused heavily on relative abundance. This approach remains useful for ecological description but is insufficient for precision therapeutics. A bacterial species can contain strains with different metabolic capacities, and two communities with similar taxonomic profiles

can produce different metabolite outputs. The large cross cohort study of 8,117 metagenomes provides an important example: strain level signatures and microbial functions can improve resolution beyond genus level classifications [5].

Earlier observational synthesis also found that lower abundance of taxa such as Faecalibacterium prausnitzii, Roseburia, and Akkermansia muciniphila and higher abundance of several facultative or potentially pro-inflammatory taxa were reported in at least two studies, but the direction and magnitude of taxonomic differences were not uniform across all cohorts [7, 10]. This inconsistency is biologically plausible because diet, age, geography, obesity, glycaemic control, antibiotic exposure, renal function, and medication use all influence the microbiome.

Metformin illustrates why medication must be incorporated into any precision microbiome model. In treatment exposed cohorts, metformin can alter the abundance and function of microbial communities, including pathways related to short-chain fatty acid production and organisms associated with gastrointestinal adverse effects [4, 11]. A model that interprets a metformin associated microbial signature as a disease biomarker without medication adjustment can therefore produce misleading conclusions.

Functional profiling provides a more stable therapeutic target. Dietary fiber can enrich groups of short-chain fatty acid producing organisms, and a controlled clinical study showed that selected fiber responsive strains were associated with improved glycated haemoglobin and increased glucagon-like peptide 1 production [14]. More recent human work has extended this concept by connecting fiber intake, microbial features, and circulating metabolites to diabetes related phenotypes [11]. The emerging principle is therefore ecological engineering: rather than attempting to normalize every taxon, interventions can be designed to increase desired metabolic functions while suppressing harmful metabolite pathways.

4. Metabolite signaling cascades linking microbiota to glucose homeostasis

Microbial metabolites are attractive precision targets because they are closer to biological function than taxonomic abundance alone. They can act locally within the gut, enter the portal circulation, or reach systemic tissues. Their effects depend on concentration, receptor expression, substrate availability, microbial cross feeding, host metabolism, renal clearance, and medication exposure [9, 15]. Table 1 summarizes major metabolite pathways that are relevant to precision modulation.

Table 1: Major Microbiome Metabolite Signaling Axes Relevant to Precision Modulation in T2D

Metabolite/pathway	Representative products	Primary host signaling	Potential metabolic consequence	Evidence and limitation	Key references
Short-chain fatty acids	Acetate, propionate, butyrate	FFAR2/GPR43, FFAR3/GPR41; epithelial and immune signaling	Incretin secretion, barrier support, inflammatory regulation, insulin sensitivity	Human intervention evidence is encouraging but heterogeneous	[14–17]
Bile acids	Secondary bile acids and conjugated species	TGR5 and FXR	GLP-1 secretion, energy metabolism, glucose and lipid regulation	Strong mechanistic basis; microbial and host metabolism are interdependent	[18, 19]
Succinate	Microbial and host succinate	SUCNR1 and intestinal gluconeogenesis pathways	Can support glucose homeostasis in defined contexts; excess systemic succinate may be inflammatory	Context dependent and concentration dependent	[20, 21]

Metabolite/pathway	Representative products	Primary host signaling	Potential metabolic consequence	Evidence and limitation	Key references
Imidazole propionate	Histidine derived microbial metabolite	p38γ/p62/mTORC1	Impaired insulin receptor substrate signaling and glucose tolerance	Human association plus experimental causality; therapeutic targeting remains early	[26]
TMAO	Trimethylamine N-oxide	Systemic metabolic and vascular signaling	Associated with diabetes and cardiometabolic risk	Association is influenced by diet, kidney function and medications	[27–29]
Tryptophan metabolites	5-HIAA, indole, indole derivatives	AhR and related epithelial or hepatic pathways	Barrier integrity, GLP-1 secretion, hepatic insulin signaling	Growing mechanistic evidence; several findings remain preclinical	[30–33]
LPS and microbial products	Lipopolysaccharide and other bacterial products	TLR4/NF-κB and innate immune pathways	Metabolic endotoxemia, inflammatory signaling, insulin resistance	Causal evidence is strongest in experimental models	[36]

Table 1 sources: [14–21, 26–33, 36]. The table deliberately separates established receptor mechanisms from disease specific clinical evidence; the existence of a signaling pathway does not by itself prove that changing the pathway improves T2D outcomes.

4.1 Short-chain fatty acids and incretin signaling

Acetate, propionate, and butyrate are produced predominantly through microbial fermentation of nondigestible carbohydrates. Their biological effects include activation of free fatty acid receptors, modulation of epithelial function, and regulation of immune responses [15, 16]. Experimental work demonstrated that SCFAs can stimulate GLP 1 secretion through FFAR2, while other studies established the importance of GPR43 signaling in inflammatory regulation [17, 19]. These pathways provide a mechanistic link between dietary fiber, microbial fermentation, enteroendocrine signaling, and glucose homeostasis.

Clinical evidence is more nuanced than the mechanistic model. A 2024 systematic review and meta-analysis found that interventions associated with increased SCFAs were linked to lower fasting insulin and improved HOMA-IR, whereas fasting glucose did not show a consistent significant change [15]. This distinction matters for precision medicine because a biomarker can move in a favorable direction without producing a large immediate change in glycated haemoglobin.

The clinical intervention literature also suggests that fiber quality and microbial response are important. In a randomized study, a selected group of SCFA producing strains was promoted by a high fiber intervention, and the abundance of these responders was related to improved HbA1c and GLP 1 [14]. More recent studies of intrinsic chicory root fiber have linked changes in colonic butyrate producing pathways with improved insulin sensitivity [16]. A 2026 proof of concept trial of oral sodium butyrate further illustrates the transition from ecological modulation toward direct metabolite replacement, although the sample size was small and such interventions require larger trials before routine clinical use [17].

4.2 Bile acid signaling through FXR and TGR5

Bile acids are synthesized by the host but extensively transformed by intestinal microorganisms. These transformations alter the ligand pool available to host receptors such as the farnesoid X receptor and the G protein coupled bile acid receptor TGR5. Experimental activation of TGR5 increases energy expenditure and stimulates intestinal GLP 1 secretion, demonstrating

that bile acids can function as endocrine signals rather than merely digestive detergents [18].

The precision implication is that changing the abundance of a bacterial taxon is not necessarily the therapeutic objective. The relevant target may instead be a bile acid transformation capacity, such as deconjugation or secondary bile acid formation. This functional view also explains why responses to identical microbial interventions can vary between patients: substrate availability and host bile acid pools differ between individuals.

4.3 Succinate as a context dependent metabolic signal

Succinate illustrates why microbial metabolites should not be classified as simply beneficial or harmful. In a seminal experimental study, microbiota derived succinate generated during fiber rich feeding supported intestinal gluconeogenesis and improved glucose homeostasis in mice [20]. However, succinate can also participate in inflammatory signaling and systemic metabolic responses, with its effects dependent on tissue, receptor expression, concentration, and metabolic state [21]. Precision modulation should therefore aim at appropriate flux rather than maximal production of any single metabolite.

4.4 Imidazole propionate, TMAO, and other potentially adverse metabolites

Imidazole propionate provides one of the clearest examples of a disease associated microbial metabolite with a defined intracellular signaling cascade. Its levels are increased in people with T2D, and experimental exposure impairs insulin signaling through activation of p38γ, p62, and mTORC1 [26]. This pathway suggests that precision microbiome interventions could be designed around suppression of metabolite producing functions rather than simply increasing the abundance of presumed beneficial bacteria.

TMAO provides a more complex example. Observational studies have linked microbiota dependent TMAO to T2D and cardiometabolic outcomes [27, 28], while updated meta-analytic evidence supports an association between circulating TMAO and diabetes risk [29]. However, TMAO is influenced by dietary substrate, microbial composition, hepatic FMO3 activity, kidney function, and medication use. It should therefore be treated as a context dependent biomarker and potential target rather than an isolated causal driver.

Tryptophan metabolism provides another rapidly developing area. Integrative human analyses have linked host and microbial tryptophan metabolism with T2D [30]. Experimental work has shown that microbial 5-HIAA can improve insulin sensitivity through hepatic AhR/TSC2/mTORC1 signaling and that fecal 5-HIAA is lower in people with T2D [31]. Other experimental studies have linked indole derivatives with intestinal barrier repair and AhR signaling [32], while a 2026 mouse study reported that indole itself can improve glucose homeostasis through enhanced GLP 1 secretion and L cell differentiation [33]. These findings are promising but should not be translated directly into human treatment recommendations until controlled clinical studies establish dose, safety, and durability.

5. Intestinal barrier dysfunction and metabolic endotoxemia

The gut barrier is a critical checkpoint between the microbial ecosystem and systemic immunity. Diet induced dysbiosis can alter mucus, tight junction integrity, epithelial metabolism, and microbial product exposure. Experimental work demonstrated that metabolic endotoxemia can promote low grade inflammation and insulin resistance, providing an early mechanistic foundation for the gut barrier hypothesis [36].

A precision model should therefore distinguish three related but different events: microbial community alteration, increased intestinal permeability, and systemic exposure to microbial products. They do not necessarily occur together. A patient may have taxonomic dysbiosis without substantial endotoxemia, whereas another patient may have relatively modest taxonomic changes but a pronounced barrier defect. This distinction becomes especially important when considering NETosis, because recent work indicates that neutrophil derived extracellular traps can themselves damage the intestinal barrier.

6. PADI4 mediated NETosis as an immune metabolic bridge

PADI4, also known as PAD4, is a calcium dependent enzyme that citrullinates arginine residues in proteins, including histones. Histone citrullination promotes chromatin decondensation and is a major component of classical NET formation [55]. PAD4 deficient neutrophils show impaired NET formation in experimental settings, establishing its importance in NET biology [55]. NETs can be protective during infection, but excessive or persistent NET formation can damage tissue and amplify inflammation.

Diabetes provides a clinically relevant example of this imbalance. Neutrophils from people and mice with diabetes show increased susceptibility to NETosis, and increased PAD4 expression and citrullinated histone H3 have been associated with impaired wound healing [56]. Experimental PAD4 deficiency or NET disruption can improve diabetic wound healing, supporting a causal role for excessive NET formation in at least some diabetic complications [56–58].

The conceptual advance for the present review comes from the 2025 study by Albiero and colleagues. Their experiments connected diet modified microbiota, PADI4 dependent NETosis, intestinal hyperpermeability, metabolic endotoxemia, and dysmetabolism [59]. In high fat diet models, genetic or pharmacological suppression of PADI4 reduced gut barrier disruption and improved metabolic phenotypes. Importantly, Padi4 deletion did not simply prevent dysbiosis. Instead, it appeared to interrupt the host response to dysbiosis at the microbiota intestinal interface [59]. This distinction is central to precision therapy because it suggests that microbiome correction and host immune modulation could be complementary rather than competing strategies.

The same study also provides a cautionary message. PADI4 inhibition did not eliminate the metabolic effects of lipopolysaccharide in every experimental setting, indicating that NETosis is one component of a larger network of microbial and host signals [59]. Thus, PADI4 should not be regarded as a universal master switch for T2D. Its therapeutic value may be greatest in phenotypes characterized by excessive NET formation, barrier dysfunction, neutrophilia, and inflammatory metabolic impairment.

Other experimental work supports a broader role for NETs in diabetic complications. NETosis has been linked to delayed wound healing through endothelial to mesenchymal transition pathways [60], and reviews of obesity related inflammation describe interactions among adipose neutrophils, gut permeability, microbial products, and systemic inflammation []. PAD4 inhibition is pharmacologically attractive, but PAD4 has physiological roles in antimicrobial defense and chromatin biology. Any clinical program would therefore need to define dose, tissue selectivity, infection risk, and patient selection carefully [61].

7. The microbiome PADI4 NETosis cascade

The combined evidence supports a working model in which diet and medication exposure shape microbial community function; microbial metabolites and bacterial products modify epithelial and immune signaling; barrier dysfunction increases systemic exposure to microbial products; and activated neutrophils can generate PADI4 dependent NETs that further impair barrier integrity. This creates a potentially self reinforcing loop between dysbiosis, permeability, innate immune activation, and metabolic inflammation.

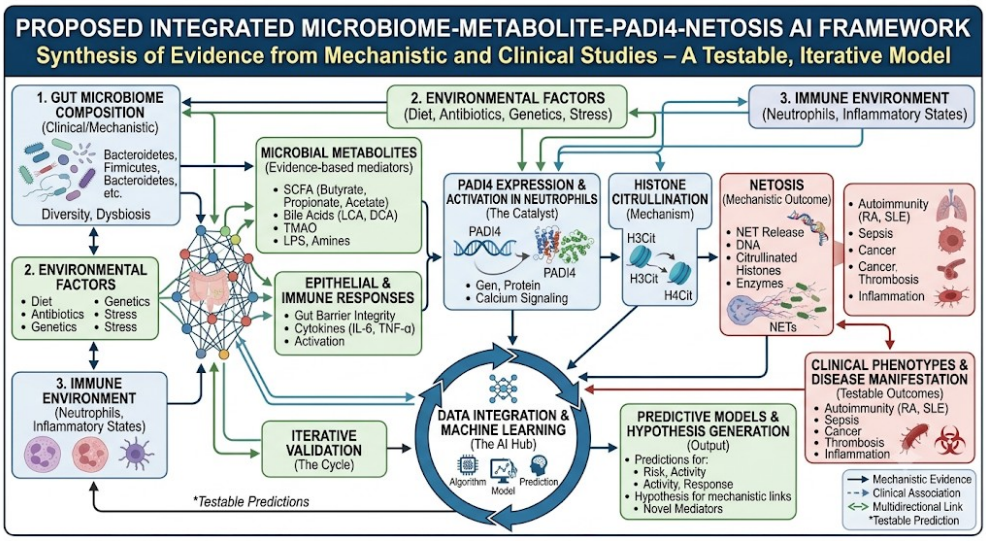


Figure 1: ***Proposed integrated microbiome metabolite PADI4 NETosis AI framework. The diagram is a synthesis of evidence from mechanistic and clinical studies and should be viewed as a testable model rather than a single proven linear pathway [3–5, 14–21, 26, 30–33, 36, 55–61].***

Table 2: Data Layers for a Precision Microbiome Program in T2D

Layer	Representative variables	Methods	Precision use	Major limitation	References
Microbial ecology	Taxa, strains, pathways, CAZymes	Shotgun metagenomics; strain profiling	Identify functional responder or risk signatures	Cross cohort variability; medication confounding	[4, 5, 10, 11]
Metabolome	SCFAs, bile acids, indoles, imidazole propionate, TMAO, succinate	Targeted/untargeted metabolomics	Quantify active signals and pathway flux	Diet, renal function, host metabolism affect concentrations	[15, 18, 21, 26–31]
Barrier phenotype	LPS, permeability markers, epithelial proteins	Serum biomarkers; permeability assays	Identify barrier dominant phenotype	Markers lack perfect specificity	[36, 59]
NETosis phenotype	PADI4, citrullinated histone H3, MPO DNA complexes, NET burden	Circulating and tissue assays	Identify inflammatory NET dominant phenotype	Assay standardization and tissue specificity remain issues	[56, 59–61]
Clinical phenotype	HbA1c, fasting glucose, HOMA IR, lipids, BMI, complications	Routine clinical measures	Define metabolic severity and endpoints	Do not capture mechanistic heterogeneity	[1, 2]
Continuous glucose response	Postprandial glucose patterns	CGM and meal logs	Personalized diet or treatment response	Sensor duration, adherence and confounding	[]
AI model	Multimodal microbiome, metabolome and clinical data	RF, gradient boosting, neural networks, causal ML	Prediction, stratification and treatment response	Overfitting, leakage, calibration, explainability	[62–64, 65]

8. Precision microbiome modulation: from broad probiotics to ecological engineering

The therapeutic landscape is moving from generic probiotic supplementation toward interventions selected according to microbial function, host phenotype, and expected response. Dietary interventions remain the most scalable approach. Meta analytic evidence suggests that dietary strategies can modify

microbial communities and metabolic outcomes, although heterogeneity in diet composition and microbiome response remains substantial [12, 13].

Probiotics, prebiotics, and synbiotics have produced modest improvements in some glycaemic endpoints in clinical trials, but effects are not uniform across formulations and populations [42–44]. Recent dose response and network meta analyses reinforce the importance of strain, dose, duration, and background therapy rather than treating all probiotics as interchangeable [42]. Combining microbiome interventions with standard therapies such as metformin is another important strategy, because drug microbiome interactions may contribute to both efficacy and tolerability [4, 46].

Akkermansia muciniphila is a useful example of a next generation microbial therapy. A randomized pilot study in overweight or obese insulin resistant adults found that daily supplementation was safe and that pasteurized A. muciniphila improved insulin sensitivity and several metabolic parameters [39]. More recent evidence continues to support the translational potential of pasteurized preparations, including a 2026 randomized trial focused on weight maintenance [40]. However, these findings should not be interpreted as proof that Akkermansia is universally beneficial in established T2D; strain differences, baseline abundance, host phenotype, and endpoint selection remain important.

Fecal microbiota transplantation represents a stronger ecological intervention because it transfers a community rather than a single strain. Earlier work showed that transfer from lean donors could transiently improve insulin sensitivity in people with metabolic syndrome [38]. More recent T2D studies and meta analyses suggest possible improvements in insulin resistance and metabolic measures, but donor selection, colonization durability, safety, standardization, and long term clinical outcomes remain unresolved [41, 45]. FMT should therefore be viewed as an experimental precision strategy rather than a routine treatment for T2D.

An emerging alternative is metabolite replacement or pathway selective inhibition. Examples include butyrate supplementation, suppression of imidazole propionate production, modulation of bile acid transformation, or restoration of specific tryptophan derived metabolites [17, 26, 31–33]. Such approaches may be more reproducible than whole community transplantation because the therapeutic target can be chemically defined. They may also be combined with PADI4 inhibition in patients in whom microbial restoration alone does not normalize inflammatory signaling.

Table 3: Precision Microbiome Intervention Classes and Translational Status

Intervention	Primary target	Evidence	Potential value	Key limitation	References
High fiber / resistant carbohydrate	Increase fermentation and SCFA production	Human RCT and meta analytic support	Scalable and physiologically aligned	Response depends on baseline microbiome and adherence	[14–16]
Probiotic / synbiotic	Add or support selected strains	Multiple RCT meta analyses	Potential modest glycaemic benefit	Strain and formulation heterogeneity	[42–44]
Akkermansia	Mucus associated next generation microbe or pasteurized preparation	Human pilot and later randomized evidence	Barrier and metabolic signaling	Small T2D specific evidence base; strain dependence	[39, 40, 47, 48]
FMT	Whole microbial community transfer	Human metabolic syndrome and T2D studies	Rapid ecological perturbation	Safety, durability, donor effects, standardization	[38, 41, 45]
Direct metabolite therapy	Butyrate or defined microbial metabolites	Early human or preclinical evidence	Mechanistically defined intervention	Dose, bioavailability and off target effects	[17, 31–33]

Intervention	Primary target	Evidence	Potential value	Key limitation	References
Pathway inhibition	Suppress harmful metabolite or immune pathway	Mechanistic/preclinical	High mechanistic specificity	Safety and compensatory pathways	[26, 29, 59, 61]
Combined microbiome plus PADI4 strategy	Restore function plus reduce excessive NETosis	Preclinical rationale	Potentially addresses both cause and host response	No established clinical protocol	[59–61]

9. AI driven therapeutic paradigms

AI becomes most useful when microbiome data are treated as one layer within a multimodal patient representation rather than as a standalone classifier. Modern microbiome studies can combine shotgun metagenomics, metabolomics, host transcriptomics, clinical laboratory data, medication exposure, diet, continuous glucose monitoring, and longitudinal outcomes. A 2025 review in Gastroenterology describes machine learning and AI as increasingly relevant for biomarker discovery, treatment response prediction, and fine tuning of microbiome modulating therapies [].

Personalized nutrition provides the clearest proof of principle. Zeevi and colleagues developed a machine learning model that integrated clinical, lifestyle, dietary, anthropometric, and microbiome features to predict postprandial glycaemic responses []. A randomized intervention based on these predictions demonstrated that personalized food selection could reduce postprandial glucose excursions. Follow up work in prediabetes and diabetes has continued to explore the interaction among diet, microbiome composition, and glucose responses [65]. These studies suggest that the microbiome may contribute useful predictive information even when the immediate therapeutic output is a diet rather than a microbial product.

For T2D precision microbiome medicine, several AI tasks are particularly attractive. First, supervised learning can classify phenotypes such as high NETosis, high endotoxemia, or high imidazole propionate production. Second, unsupervised learning can identify patient clusters with distinct microbiome metabolite profiles. Third, multimodal models can predict response to fiber, probiotics, metabolite therapy, or other interventions. Fourth, causal machine learning can help distinguish predictive biomarkers from variables that merely correlate with disease [62, 63].

Deep learning can capture nonlinear relationships among taxa, microbial genes, metabolites, and host variables, but increased model complexity does not automatically increase clinical value. The principal threats include data leakage, overfitting, batch effects, compositionality, unmeasured confounding, and poor external calibration. Explainable AI methods such as SHAP can help identify influential variables, but feature importance is not equivalent to biological causality [62–64].

A particularly important future direction is response adaptive intervention. Instead of predicting whether a patient has T2D, an AI system could estimate which intervention is most likely to alter the patient's metabolic phenotype. For example, a model could integrate baseline fiber intake, SCFA producing gene capacity, metabolite concentrations, CGM response patterns, medication exposure, and inflammatory biomarkers to estimate the probability of benefit from a fiber intervention. A separate model could incorporate PADI4 or NET biomarkers to identify patients who may require host immune pathway modulation in addition to microbiome restoration. Such a framework should be prospectively validated and compared with standard care rather than evaluated only by retrospective AUC.

Table 4: AI Opportunities Across the Precision Microbiome Workflow

AI approach	Typical models	Data inputs	Clinical/research use	Validation requirement	References
Supervised ML	RF, gradient boosting, SVM	Microbiome + clinical data	Phenotype classification; responder prediction	Cross validation plus external cohort	[64]
Deep learning	Neural networks, multimodal architectures	Microbiome + CGM + diet + clinical variables	Postprandial response and longitudinal prediction	Needs large harmonized datasets	[65]
Unsupervised learning	Clustering, latent representation	Microbiome + metabolome	Patient stratification and endotype discovery	Clusters may not be clinically reproducible	[]
Causal ML	Causal forests, longitudinal models, mediation frameworks	Multi-omics + interventions	Distinguish predictive from potentially causal variables	Requires strong design assumptions and validation	[62, 63]
Explainable AI	SHAP and related methods	Any model layer	Interpretability and feature auditing	Explanations do not establish causality	[64]
Digital twin / adaptive modeling	Dynamic multimodal model	CGM, diet, microbiome, metabolome, treatment history	Simulate and update individualized intervention plans	Currently conceptual for microbiome T2D	[62–65]

10. A proposed precision workflow for T2D

A clinically useful workflow should begin with phenotype definition rather than microbiome sequencing alone. Step one is clinical stratification using glycaemic control, adiposity, medication history, renal function, diabetes duration, complications, and dietary pattern. Step two is functional microbiome characterization using shotgun metagenomics or equivalent approaches, with explicit recording of antibiotics, metformin, GLP 1 receptor agonists, sodium glucose cotransporter 2 inhibitors, and other relevant medications. Step three is targeted metabolomics focused on SCFAs, bile acids, tryptophan derivatives, imidazole propionate, succinate, and TMAO. Step four is immune phenotyping, including validated NETosis measures where clinically justified.

Step five is computational integration. A model should first be evaluated for technical robustness and external reproducibility, then for clinical calibration, and only after that for treatment selection. Step six is intervention assignment, which could include dietary fiber optimization, a defined microbial preparation, metabolite supplementation, or an immune targeted strategy. Step seven is longitudinal monitoring. CGM, HbA1c, weight, symptoms, medication changes, microbiome composition, metabolite concentrations, and inflammatory markers should be collected at predefined intervals.

This workflow also creates an opportunity for adaptive learning. If a patient receives a fiber intervention but SCFA production fails to increase, the model should identify whether the limiting factor is substrate dose, microbial capacity, intestinal transit, medication exposure, or another host variable. If microbial metabolites improve but NETosis remains high, the patient may represent a phenotype in which host inflammatory signaling has become partly uncoupled from the original microbial disturbance. This is precisely the type of heterogeneity that a one size fits all probiotic strategy cannot capture.

11. Evidence hierarchy and major translational gaps

The current evidence base is strongest for association between T2D and altered microbiome composition or function, for receptor level effects of several microbial metabolites, and for the contribution of NETs to selected diabetic complications. Evidence is more limited for causal microbiome manipulation in established

human T2D and is particularly limited for the combined microbiome PADI4 NETosis pathway. The 2025 PADI4 study is therefore important because it supplies experimental evidence for a mechanistic bridge, but it should not be interpreted as proof that PADI4 inhibition will improve diabetes outcomes in humans [59].

A second gap is standardization. Microbiome results are affected by stool collection, storage, DNA extraction, sequencing platform, reference database, bioinformatic pipeline, and compositional normalization. The STORMS checklist provides a useful reporting framework for improving transparency [68]. AI adds another layer of complexity because models can learn laboratory batch effects or cohort specific dietary patterns rather than disease biology. External validation across countries, sequencing platforms, and medication backgrounds is therefore essential [62–64, 68].

A third gap is causal inference. A microbial feature can be a cause, consequence, mediator, marker, or medication associated passenger. Intervention studies that alter a defined microbial pathway and measure downstream metabolites and host phenotypes are needed. Mendelian randomization, longitudinal sampling, gnotobiotic transfer, isotope tracing, and carefully designed randomized trials can complement machine learning by testing directionality.

A fourth gap is safety. Broad manipulation of the microbiome can have effects outside glucose metabolism. FMT can transmit organisms or resistance genes, probiotics can cause adverse events in susceptible patients, and immune pathway inhibition can alter antimicrobial defense. Precision microbiome therapy should therefore be developed with the same attention to pharmacology, dose response, manufacturing quality, and adverse event surveillance as conventional therapeutics.

12. Future research priorities

- Define T2D microbiome endotypes using strain resolved metagenomics and metabolite measurements rather than genus abundance alone.
- Develop standardized PADI4 and NETosis phenotyping protocols suitable for longitudinal human studies.
- Test whether microbial metabolites predict NETosis independently of obesity, glycaemia, medication exposure, and renal function.
- Conduct intervention studies that simultaneously measure microbiome function, metabolites, intestinal permeability, NETosis, and glycaemic outcomes.
- Compare ecological interventions with defined metabolite therapies and determine which patients require combined host and microbial targeting.
- Build AI models on prospectively collected multimodal datasets with external validation and transparent calibration.
- Use causal machine learning to identify treatment effect heterogeneity rather than optimizing classification accuracy alone.
- Establish regulatory and manufacturing standards for next generation microbes, defined microbial consortia, and microbiome derived metabolites.
- Design clinical trials around mechanistic end points as well as HbA1c, so that a negative clinical result can still reveal where the proposed cascade failed.
- Create open, interoperable microbiome and metabolomics datasets with standardized metadata to improve reproducibility and reduce model bias.

CONCLUSION

Precision microbiome modulation in T2D is moving from a taxonomic concept toward a functional and mechanistic framework. The central opportunity is to connect microbial ecology with measurable metabolite signals, epithelial barrier status, innate immune activation, and individualized metabolic responses. SCFAs, bile acids, succinate, tryptophan metabolites, imidazole propionate, and microbial products such as LPS demonstrate that the microbiome can communicate with host tissues through defined signaling pathways. At the same time, the emerging PADI4 NETosis literature provides a plausible host immune mechanism linking dysbiosis and barrier dysfunction with systemic inflammation and dysmetabolism.

The most important translational lesson is that no single organism, metabolite, or immune pathway is likely to explain the full heterogeneity of T2D. Precision

treatment will probably require layered interventions selected according to microbial function and host phenotype. AI and multi-omics can provide the computational infrastructure for this approach, but only if models are externally validated, biologically interpretable, and embedded within well designed intervention studies. The next phase of research should therefore move beyond association toward mechanism guided, response adaptive clinical trials in which microbiome composition, microbial metabolites, PADI4 dependent NETosis, and metabolic outcomes are measured together.

Abbreviations

Abbreviation	Full form
AI	Artificial intelligence
AhR	Aryl hydrocarbon receptor
BA	Bile acid
CAZyme	Carbohydrate active enzyme
CGM	Continuous glucose monitoring
FFAR2	Free fatty acid receptor 2
FFAR3	Free fatty acid receptor 3
FMT	Fecal microbiota transplantation
FXR	Farnesoid X receptor
GLP 1	Glucagon like peptide 1
HOMA IR	Homeostatic model assessment of insulin resistance
LPS	Lipopolysaccharide
ML	Machine learning
NET	Neutrophil extracellular trap
NETosis	Neutrophil extracellular trap formation
PADI4/PAD4	Peptidyl arginine deiminase 4
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
SCFA	Short chain fatty acid
SUCNR1	Succinate receptor 1
T2D/T2DM	Type 2 diabetes mellitus
TMAO	Trimethylamine N oxide
TLR4	Toll like receptor 4

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