



REVIEW

Intestine-on-a-Chip: A New Frontier in Nutritional Research and Precision Nutrition

Jianhua Lu^{1,2}, Weijian Sun^{1,*} and Changyuan Hu^{1,2,*}

¹Wenzhou Medical University-Monash BDI Alliance in Clinical and Experimental Biomedicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

²Computational Systems Oncology Program, South Australian immunoGENomics Cancer Institute (SAiGENCI), The University of Adelaide, Adelaide, Australia

*Corresponding Authors: Weijian Sun. Email: weijiansun@wmu.edu.cn; Changyuan Hu. Email: changyuan.hu@monash.edu

Received: 10 September 2026; Accepted: 14 October 2026; Published: 27 October 2026

ABSTRACT: Nutrition is a dynamic exposure shaped by digestion, intestinal location, microbial metabolism and host state, where faithful recapitulation of these interconnected processes is essential for advancing precision nutrition. Conventional nutritional models rarely integrate such multifactorial control with a physiologically relevant intestinal interface, and remain limited in host-microbiome fidelity, individual predictability and clinical translatability. Recent developments in intestine-on-a-chip systems offer promising solutions to these challenges by enabling defined luminal exposures coupled with epithelial, barrier, transport, microbial and immune readouts under controlled flow. In this review, we systematically evaluate these systems as nutrition-responsive functional phenotyping platforms and examine their applications in modeling nutrition-microbiome-host interactions and in recapitulating disease phenotypes arising from nutritional perturbations. The potential of patient-derived chips for capturing interindividual variability and advancing precision nutrition is further explored, alongside the convergence of multi-omics, artificial intelligence, and multi-organ modules for mechanistic deconvolution and predictive phenotyping. Finally, we examine the critical challenges of clinical translation, proposing a staged framework from controlled nutritional exposure to donor-resolved phenotype, human concordance, and prospective utility testing. This review aims to facilitate the development of intestine-on-a-chip platforms for precision nutrition, while providing insightful guidance for researchers seeking to bridge nutritional science with microphysiological systems.

KEYWORDS: Intestine-on-a-chip; microbiome; patient-derived models; precision nutrition; artificial intelligence

1 Introduction

Nutrition is a time-varying exposure rather than a fixed property of food [1,2]. Digestion, intestinal location, transit and nutrient-sensing pathways determine what the mucosa encounters after a meal [3,4]. Large human cohorts have shown marked interindividual variation in postprandial glycemic and lipemic responses to identical foods [5,6]. The magnitude and direction of a response also depend on baseline metabolic and microbial state [7]. Diet-associated microbial and lipid-mediator responses also vary substantially between individuals [8,9]. Precision nutrition therefore seeks individual-level predictions rather than population-average dietary effects [6,10]. However, observational and intervention studies rarely resolve the intestinal mechanisms that connect a controlled exposure to a person-specific phenotype [10].

The intestinal mucosa integrates absorption, metabolism, barrier regulation, mucus, microbial products, immune signals and communication with the circulation [11,12]. Two-dimensional cultures and Transwells

provide useful exposure control but generally lack flow, tissue deformation and durable multicellular interfaces [13,14]. Intestinal organoids preserve epithelial provenance and regional programs more effectively than immortalized monolayers [15–17]. Their value is greatest when epithelial identity and regional composition are explicitly validated rather than inferred from morphology alone [16]. Their enclosed lumen and predominantly static culture nevertheless complicate repeated apical dosing, vectorial transport and long-term host–microbe experiments [18,19]. Animal models remain indispensable for systemic physiology, yet species-specific intestinal biology limits direct extrapolation to human nutrition [20,21]. These models are complementary, and their value depends on the biological question [11,14].

Intestine organ chips occupy an intermediate experimental scale between reductionist monolayers and whole organisms [13]. They combine controlled luminal and basal perfusion with selected epithelial, mechanical, vascular, immune or microbial modules [22,23]. The conceptual gain is experimental access to directional, time-resolved responses at a human intestinal interface [24]. Early intestine chips showed that flow and cyclic deformation could support villus-like differentiation and microbial coculture [25,26]. Flow-dependent gradients were subsequently shown to regulate human intestinal morphogenesis in micro-engineered culture [27]. Biopsy-derived chips demonstrated differentiated epithelial functions, including sucrose hydrolysis, while duodenum chips supported transporter and CYP3A4 assays [18,28]. Anaerobic platforms later enabled complex microbial communities to coexist with a polarized epithelial barrier [29,30].

A nutrition experiment must distinguish precise dosing from physiological realism [31]. Defined compounds isolate mechanisms but may not reproduce digestion, food structure or postprandial concentration profiles [2,20]. Digested food fractions add matrix realism but also introduce compositional and recovery uncertainties [32]. Transport claims require directional flux, barrier qualification and a credible human or established *in vitro* comparator [33–35]. Microbiome claims additionally require sterile, metabolite-only and live-microbe controls with documented oxygen conditions [36–38]. Disease-oriented claims require a reference phenotype that is demonstrably relevant to the human condition.

Accordingly, an intestine chip should be treated as a functional assay, not as a miniature intestine [39]. Its interpretability rests on a transparent relation among exposure, module, endpoint and comparator [12,40]. Chips cannot replace human cohorts, dietary trials or animal studies [1]. They can instead convert population associations into controlled mechanistic tests and generate phenotypes for subsequent human validation [18,41]. This review evaluates that evidence chain from defined nutritional exposure to donor-resolved phenotyping, prediction and clinical validation (Fig. 1).

2 Engineering a Nutritionally Responsive Intestine

A nutritionally responsive chip should be engineered around a defined causal question rather than maximal anatomical resemblance, because the required architecture differs for direct epithelial responses, vectorial transport, microbial transformation, and immune-mediated phenotypes [13]. Region-appropriate epithelium forms the core sensor for most nutritional studies, as transporter expression, metabolic activity, barrier properties, and enteroendocrine programs vary substantially along the intestinal axis [4,18,28]. The small intestine is the principal site of nutrient digestion and absorption; in the duodenum, nutrient sensing also links luminal exposure to local epithelial responses and systemic metabolic regulation [4,18]. Primary small-intestine chips derived from human organoids can generate villus-like epithelial structures and support functional assays such as sucrose hydrolysis, illustrating their utility for studying defined digestive processes (Fig. 2a) [18]. Duodenum Intestine-Chips have further reproduced selected transporter activities and CYP3A4-related responses to 1,25-dihydroxyvitamin D3, providing a platform for investigating region-specific intestinal metabolism (Fig. 2b) [28]. In contrast, the colon supports microbial fermentation

of unabsorbed dietary substrates and short-chain fatty acid uptake, while its mucus barrier limits direct microbial contact with the epithelium [42–44]. For distal-intestinal questions, bioengineered colon organoids with enhanced cellular complexity provide a complementary mucosal model, while continuous colon-chip culture enables direct monitoring of mucus-layer accumulation that is difficult to resolve in enclosed organoid systems (Fig. 2c) [16,44]. Induced pluripotent stem cell (iPSC)-derived and innervated intestinal platforms can additionally incorporate mesenchymal or neural lineages, although their functional maturity remains dependent on the differentiation protocol and model architecture [45–47]. These systems therefore reproduce selected regional intestinal functions but do not independently capture meal digestion, systemic nutrient handling, or organism-level absorption.

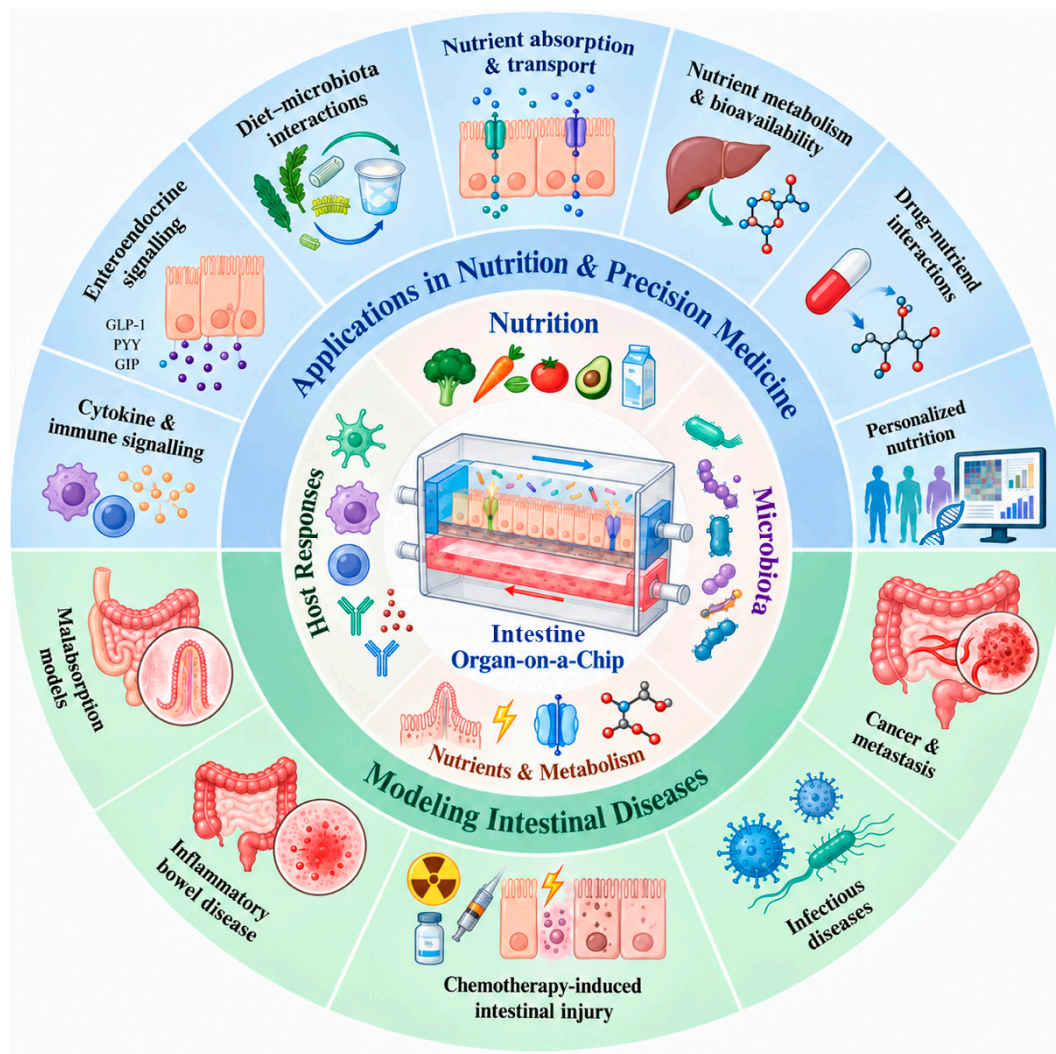


Figure 1: Overview of intestine organ-on-a-chip platforms for nutritional research, precision medicine, and modeling of intestinal diseases, highlighting their applications in nutrient absorption and metabolism, diet–microbiota interactions, host responses, personalized nutrition, and disease-related intestinal dysfunction.

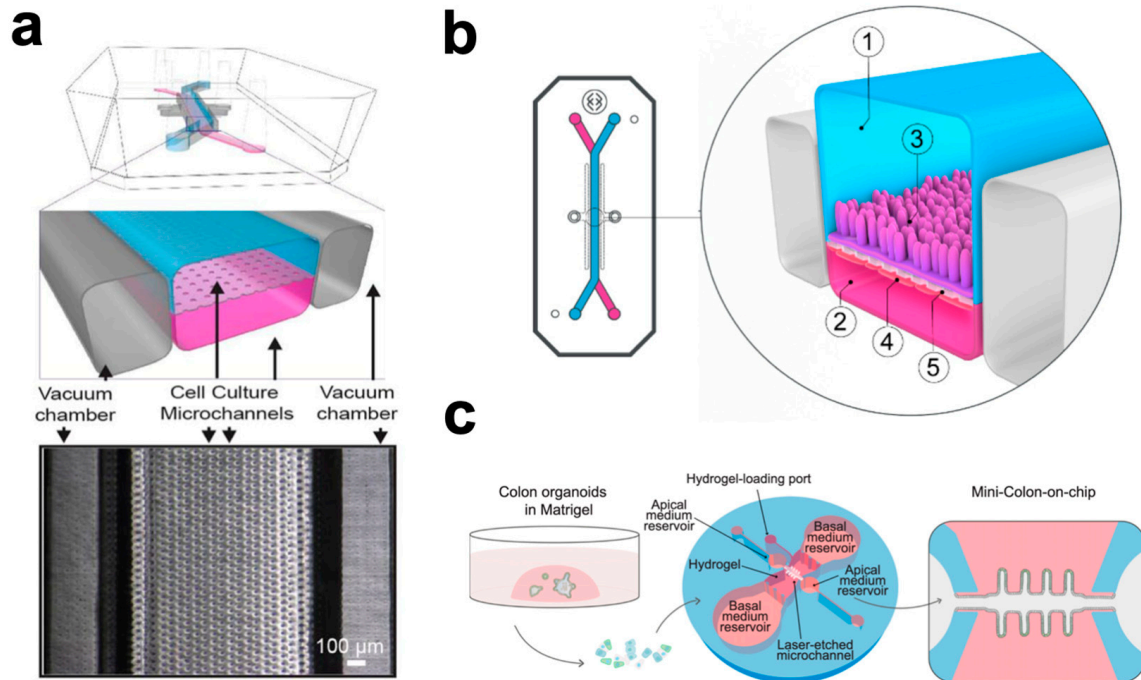


Figure 2: From regional epithelial architecture to Nutrition-Responsive intestinal function. (a) A primary human intestinal chip developed using organoids. Reproduced with permission [18]. Copyright 2018, Springer Nature. (b) A duodenum intestinal chip. Reproduced with permission [28]. Copyright 2020, eLife Sciences Publications, Ltd. (c) A bioengineered human colon organoid chip with similar complexity and functionality to *in vivo* cells. Reproduced with permission [16]. Copyright 2024, Elsevier.

Current intestinal-chip architectures range from relatively simple molded or tape-based devices to bioprinted tubular constructs and scaffold-supported systems [48–50]. Three-dimensional villus scaffolds and bioprinted matrices can improve epithelial organization and tissue geometry, but structural resemblance alone does not establish physiological function [51,52]. Microengineered platforms have also improved the handling and differentiation of iPSC-derived and adult-organoid epithelia, facilitating more reproducible access to human intestinal tissue sources [23,53]. *Ex vivo* and organoid-chip systems can retain aspects of native tissue organization or reproduce defined oxygen dynamics while supporting barrier and permeability measurements [54,55]. Two-compartment *ex vivo* platforms and higher-throughput chip formats provide complementary strategies for gastrointestinal screening, although increased throughput should not compromise exposure control or biological qualification [56–58]. Material selection is equally important because membranes, extracellular matrices, and elastomers can influence optical access, molecular recovery, cell–matrix signaling, and compound partitioning [59]. Quantifying device-associated adsorption and recovery is particularly important for lipophilic nutrients, microbial metabolites, and drugs delivered under continuous perfusion [60].

Flow and cyclic mechanical deformation provide experimentally controllable features that can reveal biological responses obscured in static culture [24,25,27]. Perfusion alters mass transport, boundary layers, and local exposure kinetics, meaning that static and dynamic assays cannot be compared solely on the basis of nominal compound concentration [22,34,61]. Mechanical deformation has been shown to influence bacterial overgrowth and inflammatory phenotypes in human intestine chips, demonstrating that physical forces can modify host–microbe interactions (Fig. 3a) [25]. Peristalsis-like motion can also alter enteric

pathogen invasion, further illustrating the importance of mechanical context in selected disease and microbiome studies [62,63]. Mechanical inputs should therefore be incorporated when epithelial adaptation, microbial ecology, pathogen interactions, or dynamic transport represents a predefined component of the hypothesis rather than as a universal requirement [63]. Similarly, a basal endothelial compartment can support measurements of directional transfer and vascular responses, but it does not reproduce systemic circulation, lymphatic uptake, or whole-body bioavailability [39,64–66].

Microbial co-culture introduces additional engineering requirements because intestinal epithelial cells and obligately anaerobic microorganisms occupy fundamentally different oxygen environments [36,67]. Oxygen gradients should therefore be measured and controlled as engineered boundary conditions rather than assumed to reproduce *in vivo* intestinal oxygen tension [30]. Anaerobic intestine-on-a-chip systems have maintained complex human microbial communities adjacent to an oxygenated epithelial compartment, providing an important basis for mechanistic studies of host–microbiota interactions (Fig. 3b) [68]. Primary colonic platforms have also supported continuous co-culture with the highly oxygen-sensitive commensal *Faecalibacterium prausnitzii*, allowing microbial and epithelial responses to be examined under controlled conditions (Fig. 3c) [69]. Related anaerobic interface systems have further enabled bacterial co-culture with primary human colonic epithelium and a functional mucus layer [29]. Immune modules can extend these models by distinguishing primary epithelial injury from secondary immune amplification in inflammatory settings [70]. Primary inflammatory intestine chips and more recent immunocompetent scaffold-supported systems illustrate the feasibility of incorporating defined immune components into intestinal microphysiological models (Fig. 3d) [70]. Stromal or patient-derived mesenchymal components may provide additional mechanistic information by revealing compartment-specific responses that epithelial or immune-only models cannot capture [66,71]. Nevertheless, most current platforms reproduce only a fraction of the intestinal immune repertoire and rarely integrate donor-matched epithelial, stromal, immune, and microbial components within the same system [12,72].

These observations support fit-for-purpose complexity as the most appropriate design principle for nutritional intestine-chip studies [13,40]. A direct nutrient or microbial-metabolite question may require only differentiated, region-appropriate epithelium and a validated functional endpoint, whereas excessive cellular or architectural complexity can introduce medium incompatibility, biological variability, and ambiguity in attributing observed effects [11,13,18,33]. By contrast, a nutrient-to-microbe-to-host hypothesis requires additional validation of microbial viability, oxygen conditions, metabolite generation, and host responses [29,38,73]. Immune-mediated questions may further require macrophages or circulating immune cells, but these modules are most informative when their contribution can be experimentally separated from epithelial and microbial effects [70,71,74]. Modules should therefore be added only when they test a prespecified causal step and provide information that cannot be obtained from a simpler configuration [12]. Accordingly, the minimum components, primary functional readouts, and current evidence boundaries for representative nutrition-related questions are summarized in Table 1.

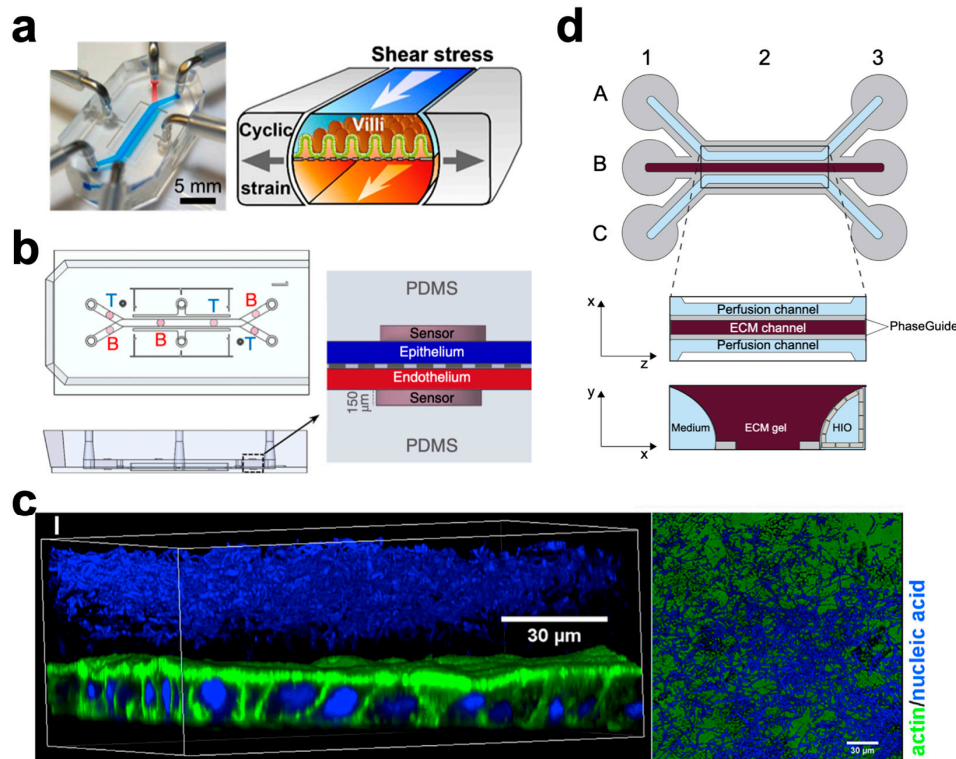


Figure 3: Conditional integration of mechanical, microbial, endothelial, and immune modules in intestinal chips. (a) An intestinal chip investigating the effects of mechanical deformation on bacterial growth and inflammatory phenotypes in intestinal chips. Reproduced with permission [25]. Copyright 2015, Proceedings of the National Academy of Sciences of the United States of America. (b) An intestine-on-a-chip that cultivates complex human gut microbiota under controlled luminal anaerobiosis. Reproduced with permission [68]. Copyright 2019, Springer Nature. (c) 3D And top-down views showing *F. prausnitzii* colonization above the colonic epithelium, with a distinct DAPI-negative gap corresponding to the inner mucus layer. Reproduced with permission [69]. Copyright 2021, Elsevier. (d) A human-derived intestinal chip for simulating intestinal inflammation. Reproduced with permission [70]. Copyright 2020, Springer Nature.

Table 1: Fit-for-Purpose design of intestine organ chips for nutritional research.

Question	Minimum Components	Primary Readout	Current Evidence Boundary
Direct epithelial nutrient effect	Region-appropriate epithelium	Barrier, transporter or metabolic endpoint	Established for selected compounds [28]
Vectorial transport	Epithelium plus separated basal compartment	Apical-to-basal transfer	Does not equal whole-body absorption [75]
Microbial transformation	Epithelium plus oxygen-managed microbiota	Metabolite and host response	Emerging; complete causal chains remain uncommon [76]
Immune-mediated response	Epithelium plus defined immune module	Cytokine, barrier or immune phenotype	Proof-of-concept; partial immune repertoires [77]
Individual response prediction	Patient tissue plus standardized exposure and validation cohort	Predefined individual target	Not established [78]

Functional qualification should precede nutritional interpretation because morphological resemblance and molecular marker expression alone do not establish the transport, metabolic, barrier, or microbial functions required for a specific nutritional claim [79,80]. Baseline acceptance criteria should therefore be defined for each cell source, intestinal region, chip configuration, and intended endpoint before nutritional perturbation is introduced [81]. For absorption and transport studies, directional transfer, barrier integrity, and recovery of the administered compound should be verified rather than inferred from changes in epithelial markers alone [34,35,75]. Microbiome experiments should similarly quantify microbial viability, community composition, and the local oxygen environment before host responses are interpreted [30,36,76]. Time-resolved sampling is particularly valuable because epithelial responses, microbial adaptation, metabolite production, and basolateral mediator release may occur over different temporal scales [19,22,82]. Sensor-integrated and real-time barrier-monitoring platforms can improve longitudinal phenotyping, although increased analytical resolution does not itself establish physiological or clinical validity [83]. Negative findings are also more informative when they arise from a functionally qualified system with a documented exposure than when they are obtained from a highly complex but insufficiently characterized model [11,81]. Standardized reporting of cell source, intestinal region, flow conditions, microbial strain or community, culture medium, matrix, compound recovery, oxygen conditions, and experimental controls will therefore be essential for reproducibility and cross-platform comparison [48,60].

3 Modeling Nutrition–Microbiome–Host Interactions

The exposure class defines the boundary of inference in nutrition-related intestine-chip studies because whole foods, digested food fractions, purified nutrients, microbial metabolites and live microorganisms represent biologically distinct inputs [20,31,32,40]. Nominal concentration alone is insufficient to characterize exposure when digestion, device adsorption, microbial consumption or chemical transformation alters the bioavailable fraction reaching the intestinal epithelium [2,32,60]. A sucrose-hydrolysis assay, for example, demonstrates brush-border-associated digestive function, whereas vitamin-D-induced CYP3A4 activity represents a component-specific metabolic response [18]. Neither assay reproduces dietary exposure in its complete physiological context, including food structure, digestion, repeated intake and systemic nutrient handling [32]. Studies should therefore report exposure composition, concentration, digestion state, duration, compartment and comparator before extending observations from a defined component to broader nutrition- or diet-level conclusions [31,84]. Early microscale three-dimensional gastrointestinal scaffolds provided a structural foundation for biomimetic intestinal experimentation by recreating selected features of the gastrointestinal microenvironment, although structural mimicry alone does not establish nutritional function (Fig. 4a) [85].

The strongest direct nutritional evidence from current intestine-chip studies comes from nutrient-deficiency models of environmental enteric dysfunction (EED) [86]. In donor-derived Intestine Chips, depletion of niacinamide and tryptophan altered villus morphology, epithelial permeability, fatty-acid uptake, amino-acid transport and inflammatory outputs. Transcriptomic analysis further linked these functional abnormalities to disease-associated molecular programs, strengthening the mechanistic interpretation of the deficiency phenotype [41]. A subsequent study extended this framework by evaluating mucus production, nutrient absorption and proteomic responses during sulfadoxine–pyrimethamine treatment [86]. Together, these studies establish experimentally controlled causal contrasts between defined nutrient availability and intestinal dysfunction within EED models. EED nevertheless represents a specific deficiency paradigm and should not be generalized to all forms of malnutrition or dietary exposure. These models also do not

reproduce complex food matrices, repeated meals, microbial substrate conversion or individualized dietary interventions [32].

Microbiome-enabled platforms extend this framework by making selected nutrient–microbe–host mechanisms experimentally accessible [12,38,87]. Anoxic–oxic interfaces permit obligate anaerobes to coexist with an oxygenated intestinal epithelial compartment, thereby enabling controlled investigation of host–microbiota interactions [29,30]. Continuous co-culture with *Faecalibacterium prausnitzii* has linked a butyrate-rich microbial environment with epithelial barrier and transcriptional responses [69]. An adult human intestine-chip model exposed to inulin further demonstrated measurable host–microbial metabolite interactions under controlled conditions (Fig. 4b) [73]. Such experiments should document microbial community stability because substrate-driven ecological shifts can change both metabolite production and the effective host exposure over time [30,37,73]. Direct administration of microbiota-derived metabolites is also mechanistically useful, as illustrated by studies linking 3-phenylpropionic acid to AhR-dependent enhancement of epithelial barrier function [88]. However, direct metabolite dosing cannot establish that a tested diet or microbial community generated the same metabolite within the chip [38].

Microbial provenance provides an additional dimension of biological context but does not by itself demonstrate nutritional causality [89,90]. Patient-derived microbiota have been introduced into microfluidic gut-chip systems to reproduce selected disease-associated microbial and physiological characteristics, including phenotypes associated with depression-related microbial communities (Fig. 4c) [90]. Such models can identify provenance-dependent host responses, but dietary mechanisms require additional evidence connecting a defined substrate to microbial transformation and downstream host effects [38]. Community-level studies must also resolve bacteria–bacteria interactions rather than treating the microbiota as a single experimental reagent [91]. Longitudinal measurements of microbial abundance and metabolite production are therefore required to distinguish transient exposure effects from stable ecological changes [30,37]. This distinction is particularly important because epithelial barrier dysfunction can itself reshape inflammatory host–microbiome interactions, making biological directionality an experimental question rather than an assumed causal sequence [92,93].

Defined microbial and food-related interventions provide tractable mechanisms-first approaches for testing individual links within these complex networks [84,94]. A simulated synbiotic regimen altered transcriptional and lactate-associated features in colorectal-cancer (CRC)-derived cells, demonstrating how defined microbial–nutritional interventions can be interrogated mechanistically without establishing diet-level clinical efficacy [95]. Live probiotics improved selected barrier, mucus and inflammatory endpoints in a pathomimetic leaky-gut chip [96]. Chitosan oligosaccharides have similarly been tested across epithelial, endothelial and immune configurations under experimentally induced intestinal injury [97]. A cellular chip–mass spectrometry platform further examined interactions between *Lactobacillus rhamnosus* GG and irinotecan in CRC-derived cells, illustrating the potential for simultaneous functional and metabolic analysis [98]. More recently, an artificial-intelligence (AI)-assisted intestine-chip platform was used to rapidly prioritize probiotic candidates with anti-enteritis activity in preclinical models (Fig. 4d) [99]. Such AI-assisted workflows can improve candidate ranking and screening efficiency, but they do not yet establish patient-specific nutritional prediction or comparative dietary efficacy [99,100].

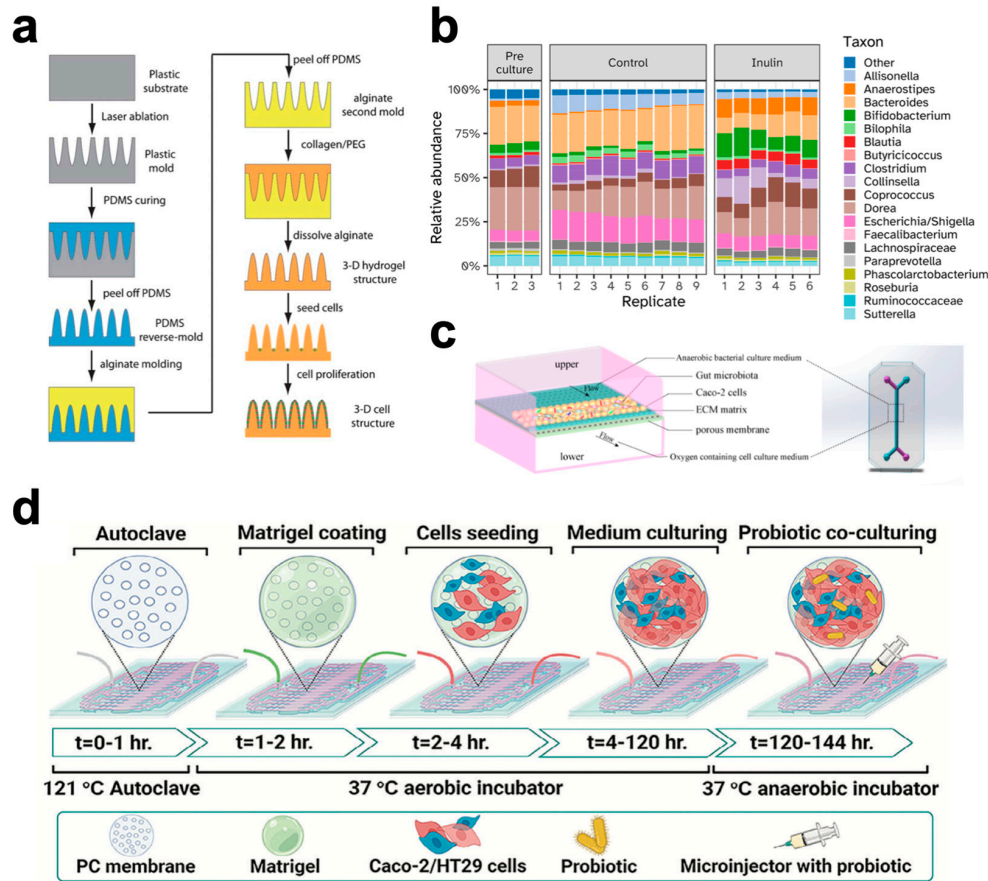


Figure 4: From biomimetic gastrointestinal models to intelligent Intestine-on-a-Chip platforms. (a) An organ-on-a-chip that mimics the villi of the gastrointestinal tract. Reproduced with permission [85]. Copyright 2011, Royal Society of Chemistry. (b) A chip model of host-microbe metabolite interactions in adult small intestine for microbial detection. Reproduced with permission [73]. Copyright 2024, OAE Publishing Inc. (c) Unveiling the gut microbiome of depressed patients with microfluidic intestine-on-a-chip technology. Reproduced with permission [90]. Copyright 2024, Royal Society of Chemistry. (d) Smart intestinal chip that can quickly screen probiotics that can relieve enteritis. Reproduced with permission [99]. Copyright 2024, Wiley.

Food structure and digestion should also be considered when moving from purified compounds toward more realistic nutritional exposures [2]. A small-intestine model incorporating a food matrix and a mock bacterial community demonstrated how digestion and microbial context can be experimentally integrated, although the system was not microfluidic [32]. This distinction is important because food structure and digestive processing determine substrate availability before microbial transformation or epithelial sensing occurs. Accordingly, studies using purified nutrients, digested fractions and intact food-related preparations should not be interpreted as equivalent forms of dietary exposure [31]. Chips are particularly useful for deconstructing individual steps in these pathways, but they currently model defined components more convincingly than habitual dietary patterns or long-term dietary behavior [101].

Nutritional classes should likewise not be collapsed into a single experimental category because carbohydrates, proteins and lipids engage distinct transport, sensing and microbial pathways [3,4,102]. Dietary fibers can alter luminal fermentation and microbial ecology, while specific modified fibers may additionally influence microbial resilience during environmental perturbations such as antibiotic exposure [42,103,104]. Short-chain fatty acids provide a prominent mechanistic link between microbial fermentation and host

metabolism, but their biological effects depend on concentration, compartment and underlying tissue state [42,105]. High-fat dietary patterns can profoundly alter microbial and metabolic signaling *in vivo*, whereas current intestine-chip platforms rarely reproduce the chronic systemic phenotype associated with long-term high-fat feeding [106,107]. Dietary context can also influence microbiota and immune phenotypes independently of overt disease, as demonstrated by changes associated with gluten-free diets in healthy individuals [108]. Prebiotic, probiotic and postbiotic effects are similarly dependent on substrate composition, strain identity, viability and host baseline state [94,96]. These considerations reinforce the need to name the actual tested exposure rather than use the broader term “diet” when only a defined component or microorganism has been applied [31,40].

Readout selection ultimately determines whether a nutrition-related response can be interpreted mechanistically [12,38]. Barrier permeability, nutrient transport, mucus production, cytokine secretion and molecular profiles reflect distinct biological processes and should not be treated as interchangeable indicators of intestinal health [81,83]. Concordant changes in functional and molecular endpoints strengthen inference when they are measured under the same exposure conditions and against an appropriate comparator [86]. Evidence for a causal nutrition–microbiome–host sequence becomes stronger when a candidate mediator is quantitatively measured and changes directionally between the nutritional exposure and downstream host phenotype [92]. Conversely, large multiparametric datasets cannot compensate for the absence of an *a priori* hypothesis, appropriate controls or clearly defined causal contrasts [10]. The next technical objective is therefore to establish a measured sequence from nutritional exposure and availability, through microbial transformation and metabolite production, to host sensing and functional phenotype, rather than merely linking these processes conceptually [38]. Until these elements are demonstrated within the same experimental framework, nutrition–microbiome–host pathways should be regarded as testable mechanistic models rather than completed causal networks.

4 From Nutritional Perturbation to Disease Phenotypes

Disease-oriented intestine chips are most informative when they reveal how a defined nutritional or environmental perturbation interacts with a susceptible intestinal background rather than merely reproducing a disease-like morphology [109]. Building on the EED experiments described in Section 3, these models enable mechanistic testing of how nutrient deficiency interacts with donor-associated epithelial vulnerability and whether injury can be pharmacologically reversed [41,86]. Their disease relevance, however, is strongest for the epithelial and transport phenotypes actually measured and should not be generalized to every clinical manifestation of EED or interpreted as evidence for an optimal diet in an individual patient.

Inflammatory bowel disease (IBD) models further illustrate how disease-background tissue, stromal components and immune modules can modify experimentally induced intestinal responses [71,110]. A versatile intestine-on-a-chip system reconstructed key epithelial–immune interactions associated with IBD, providing a controllable platform for investigating inflammatory signaling and therapeutic responses (Fig. 5a) [110].

More advanced patient-derived systems have incorporated epithelial and stromal compartments together with mechanical stimulation and circulating immune cells, revealing contributions of diseased stroma and host background to inflammatory and fibrotic phenotypes [71]. Pumpless and immunocompetent IBD platforms have likewise enabled assessment of barrier injury, macrophage polarization and responses to interventions such as 5-aminosalicylic acid or mesenchymal-stem-cell-derived exosomes [111]. These

developments improve mechanistic resolution of disease-context responses but do not yet establish IBD-subtype-specific dietary prediction or clinical nutritional responder stratification.

Defined nutrition-related interventions have nevertheless demonstrated that inflammatory phenotypes can be experimentally modified in controlled intestinal models [97]. Live probiotics improved selected barrier, mucus and inflammatory endpoints in a pathomimetic leaky-gut chip, whereas chitosan oligosaccharides altered barrier and cytokine-related responses across epithelial, endothelial and immune configurations [96]. Such findings concern specific products under induced injury conditions and should not be interpreted as evidence for comprehensive dietary treatment of IBD [109]. Human studies independently show that dietary exposures can influence IBD biology, but translating these observations into chip-based nutritional inference requires clearly defined exposures, disease provenance and appropriate clinical comparators [21]. Accordingly, disease-chip studies should distinguish whether the tissue is patient-derived, whether inflammation is intrinsic or experimentally induced, and which cellular compartment mediates the observed response [112].

Intestinal injury models outside classical IBD provide complementary evidence for the ability of chips to reproduce controlled tissue damage and treatment responses [113]. Human intestine-on-a-chip systems have recapitulated radiation-induced epithelial injury and cell death while enabling evaluation of countermeasure drug responses under defined microphysiological conditions (Fig. 5b) [113]. For nutritional research, the measured villus and barrier injury endpoints provide a potential basis for testing whether nutritional interventions preserve epithelial integrity or promote recovery; however, the cited study evaluated pharmacological countermeasures rather than dietary efficacy [113]. These models should therefore be viewed as mechanistic injury platforms rather than nutritional disease-prediction systems [60].

Infection models similarly show that epithelial polarity, flow and mechanical deformation can substantially influence pathogen entry and tissue injury [114]. Because these physical variables can alter invasion independently of nutrition, they should be controlled before protection is attributed to a nutrient or dietary intervention [62]. An immunocompetent human intestine chip has supported enteric coronavirus infection and therapeutic testing, enabling epithelial and immune responses to be examined under controlled exposure conditions [115]. Crypt-derived intestinal organoids have also modeled *Salmonella*–epithelial interactions and provide a complementary system for studying host–bacterial responses (Fig. 5c) [116]. Their relevance to nutrition lies in the opportunity to test nutrient-dependent barrier resilience and host–pathogen responses under controlled conditions, given the links among nutritional status, microbiota and enteric infection [21]. However, these models have not yet established how specific diets alter infection susceptibility or recovery in a patient-specific manner.

Colorectal cancer (CRC) chips serve as powerful platforms for investigating epithelial and microbial mechanisms. Furthermore, these models extend the application of disease-on-a-chip technology to the study of epithelial heterogeneity, tumor plasticity, microbe–host interactions, and treatment-associated metabolism [117,118]. Patient-derived organoid biobanks and single-cell-derived tumor-organoid arrays preserve aspects of interpatient and intratumoral heterogeneity, thereby providing an experimental basis for donor-resolved response studies [119]. Because culture conditions can themselves induce plastic phenotypic states, stability of the tumor phenotype remains an important qualification when such models are used for nutrition-related experiments [117]. Patient-derived CRC organoids have predicted selected chemotherapeutic responses, but this evidence concerns drug sensitivity rather than nutritional response [78,120]. Integrated *in vitro* and *in silico* modeling has further shown that a defined synbiotic regimen can alter transcriptional and lactate-associated features of CRC-derived cells, providing a mechanistic framework for studying microbiome-related interventions in CRC (Fig. 5d) [95]. Related chip–mass spectrometry

studies combining *Lactobacillus rhamnosus* GG with irinotecan further illustrate the feasibility of examining nutrition–microbe–drug interactions in cancer-related systems [98]. These studies provide useful mechanistic precedents, although CRC-associated host–microbiota maladaptation and diet-related carcinogenic mechanisms remain substantially broader than any single chip reconstruction [121,122].

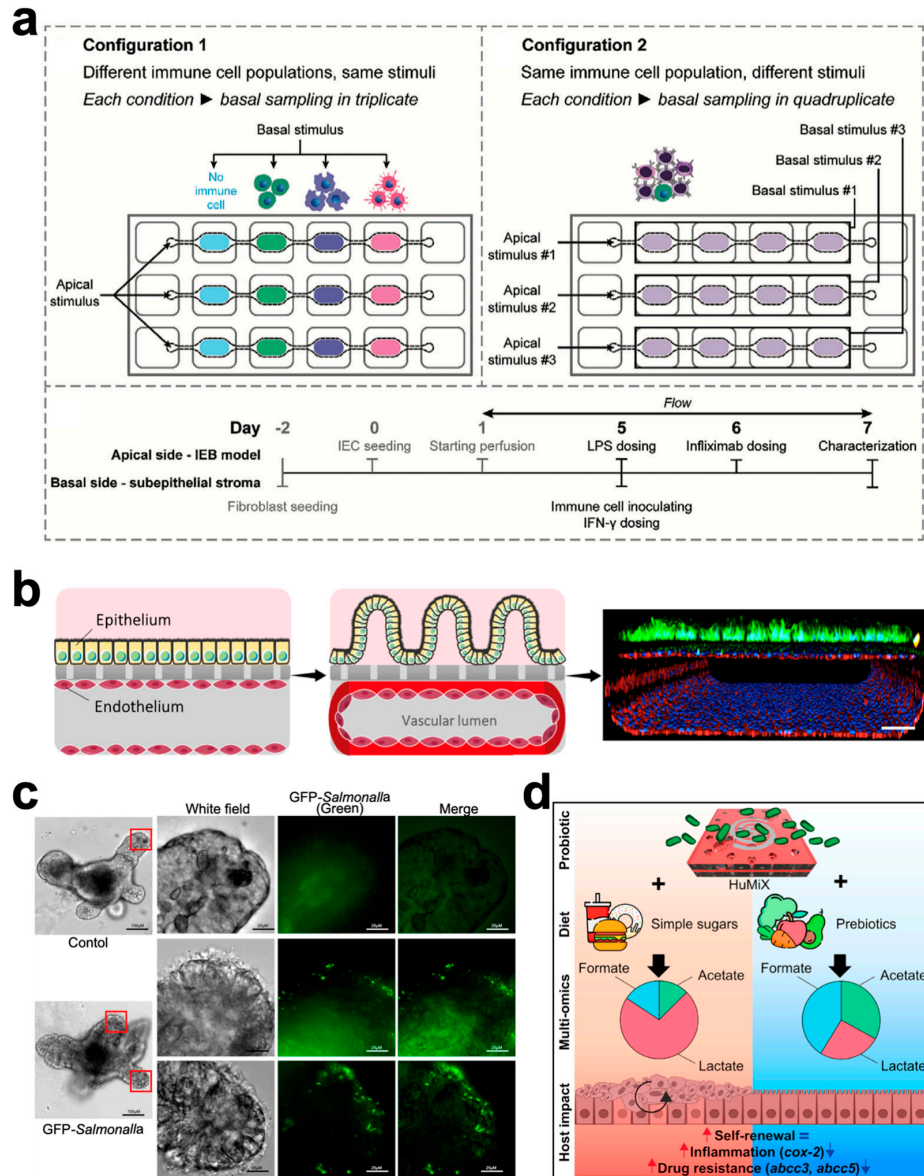


Figure 5: Disease-Relevant Intestine-on-a-Chip models for mechanistic and therapeutic studies. **(a)** A versatile intestine-on-a-chip platform for reconstructing epithelial–immune interactions and deciphering the immunopathogenesis of inflammatory bowel disease. Reproduced with permission [110]. Copyright 2024, Wiley. **(b)** A human intestine-on-a-chip model recapitulating radiation-induced intestinal injury and enabling evaluation of counter-measure drug responses (bar, 100 μ m). Reproduced with permission [113]. Copyright 2018, Springer Nature. **(c)** A *Salmonella*-infected crypt-derived intestinal organoid model for investigating host–bacterial interactions during enteric infection. Reproduced with permission [116]. Copyright 2024, Wiley. **(d)** Integrated *in vitro* and *in silico* modeling for delineating the molecular and metabolic effects of a synbiotic regimen on CRC-derived cells. Reproduced with permission [95]. Copyright 2024, Elsevier.

Metabolic disease represents a less mature application of intestine-chip technology despite strong evidence that intestinal nutrient sensing contributes to systemic glucose and metabolic regulation [123,124]. Human precision-nutrition studies have demonstrated marked interindividual variation in postprandial and cardiometabolic responses to diet, including microbiome-associated heterogeneity [8]. However, no verified intestine-chip platform has yet demonstrated reliable stratification of obesity- or metabolic-disease-related dietary responses at the individual level [6]. Disease transferability should therefore not be confused with nutritional translation, and the near-term objective should be to identify reproducible disease-context vulnerabilities under defined perturbations and test their concordance with independently measured human phenotypes.

More broadly, reproduction of a disease-associated phenotype is not equivalent to development of a clinically predictive model [125,126]. Barrier disruption, cytokine release, epithelial injury, altered nutrient transport or microbe-associated inflammation may represent valid mechanistic endpoints without reproducing the complete origin, heterogeneity or trajectory of a disease [71,110]. This distinction is particularly important for IBD and CRC, in which genetic susceptibility, immune history, medication exposure, microbiome composition and environmental factors vary substantially between individuals [127]. A disease chip can therefore test whether a defined nutritional perturbation amplifies or attenuates a selected phenotype, but it cannot establish that the same effect determines disease onset or clinical benefit without independent human evidence [109].

Nutritional response stratification should consequently be treated as an experimental endpoint rather than an assumed consequence of using patient-derived or disease-specific tissue. Robust stratification will require adequate donor numbers, predefined response criteria, standardized exposures and comparison with independently measured human nutritional or clinical outcomes. Until these requirements are satisfied, the most defensible interpretation is that intestine chips model disease-associated mechanisms and context-dependent nutritional vulnerability, rather than provide individualized dietary guidance [126].

5 Patient-Derived Chips and Precision Nutrition

Patient-derived material is essential for donor-resolved experimentation, but biological provenance alone is not equivalent to personalized medicine or precision nutrition [125]. Biopsy-derived organoids have been used to generate small-intestine chips with differentiated epithelium and measurable digestive functions, while adult donor-derived duodenum chips support transporter- and metabolism-related assays [128]. Patient-derived small-intestinal myofibroblasts have also been incorporated into microfluidic intestine-on-a-chip systems to support perfused and physiologically responsive capillary development, illustrating the potential to reconstruct donor-associated stromal–vascular interactions (Fig. 6a) [66]. Similarly, patient-derived intestinal organoid epithelium has been regenerated within a physiodynamic mucosal interface-on-a-chip, enabling three-dimensional epithelial organization under controlled fluidic and mechanical conditions (Fig. 6b) [128]. Incorporating donor-matched stromal components can improve biological relevance, although it also introduces additional variation associated with donor background, cell passage and culture history [66]. These models therefore preserve selected aspects of cellular and tissue provenance while not reproducing an individual's complete diet, microbiota, immune history or longitudinal clinical trajectory.

Donor-specific functional phenotypes are most convincing when tissue origin varies while device architecture, exposure conditions and readouts remain standardized [86]. EED models illustrate this principle by exposing healthy and disease-associated donor-derived intestinal tissues to nutrient-replete and nutrient-deficient conditions under otherwise controlled experimental settings. Such designs can distinguish selected

disease-associated epithelial vulnerabilities from variation caused by exposure conditions or platform configuration [41]. However, existing EED models involved limited donor numbers and were not primarily designed to predict interindividual nutritional responses. They also did not incorporate donor-matched microbiota, limiting conclusions about person-specific microbial mediation of nutritional effects. Human studies of inulin supplementation and personalized postprandial diets nevertheless demonstrate that microbiome composition can contribute to interindividual dietary responses, indicating that future chip models may require donor-linked rather than generic microbial communities [129]. Reconstructing this level of heterogeneity on-chip will require explicit qualification of microbial provenance, engraftment and functional stability [126].

A useful precision-readiness ladder can separate biological provenance from increasingly demanding levels of clinical utility, while serving as an evidentiary framework rather than a regulatory classification [125]. Level 1 represents the use of patient-derived biological material, whereas Level 2 requires a reproducible donor-resolved functional phenotype under standardized conditions [128]. Level 3 requires demonstration of a reproducible patient-specific response to a defined nutritional exposure [8]. Level 4 requires prediction of a prespecified individual nutritional or clinical outcome rather than retrospective description of donor differences. Levels 5–7 further require external validation, prospective decision utility and eventual implementation under standardized operating conditions [126]. Current intestine-chip evidence supports Level 1 and selected Level 2 applications, but does not yet establish Level 4–7 precision-nutrition capability [41,86].

Terminology should reflect these different levels of evidence [126]. “Patient-derived” describes the biological source of the cells or tissues used to construct the model [125]. “Patient-specific” requires a reproducible functional phenotype that differs meaningfully among individuals under controlled experimental conditions [14]. “Precision nutrition” further requires an individual-level target and evidence that the model improves prediction, intervention selection or decision-making beyond existing approaches [8]. Patient-derived colorectal organoids illustrate the distinction because donor-specific response testing has been achieved, but their strongest validation currently concerns anticancer drug sensitivity rather than nutritional interventions [78,120]. A chip assay may therefore be biologically personalized or precision-ready without being clinically actionable for dietary decision-making.

Donor heterogeneity should consequently be incorporated into study design rather than treated as a *post hoc* observation [1]. Tissue procurement, culture interval, passage number, intestinal region, device batch and exposure conditions should be harmonized or explicitly modeled as potential sources of variation [125,126]. Biological variables including age, sex, disease activity, medication history and microbiome provenance may explain true response heterogeneity but can also act as confounders when unevenly distributed across study groups [1]. The sex-associated responses observed in recent patient-derived IBD models illustrate why donor metadata should be considered part of experimental interpretation rather than optional descriptive information [71]. A strong patient-specific claim therefore requires a predefined chip endpoint to correlate with an independently measured phenotype from the same individual [6,126]. The relationship should then be evaluated using a locked protocol in an independent or held-out cohort to distinguish reproducible prediction from descriptive donor variation. Such designs represent the critical transition from donor-resolved experimentation to evidence for individualized predictive utility.

The field should also avoid an implicit one-donor-one-answer assumption because nutritional responses can vary within the same individual across time, physiological state and exposure history [1]. Repeated sampling and predefined stability criteria will therefore be required before a donor-derived chip phenotype can reliably inform a nutritional decision [126]. Future matched systems should ideally combine

donor-derived epithelium with donor-linked or experimentally defined microbial communities, standardized nutrient delivery and longitudinal patient-level metadata [130]. Microbial engraftment, compositional stability and metabolic function will need to be qualified for each matched host–microbiota configuration [30]. Such systems could better resolve interaction effects but will simultaneously increase biological variability, logistical burden and statistical complexity [10].

Beyond reconstruction of the intestinal compartment itself, multi-organ systems provide a technological route for examining how intestinal exposures propagate to downstream organs [131–135]. A microfluidic gut–brain platform incorporating a human neurovascular unit and functional blood–brain barrier has demonstrated the feasibility of modeling intestine-associated signals across organ interfaces (Fig. 6c) [135]. Gut–liver organ-on-chip platforms have likewise been developed to simulate intestinal–hepatic drug metabolism and first-pass processes, providing a foundation for studying how luminal exposures may influence downstream metabolic responses (Fig. 6d) [132]. These systems are relevant to future precision-nutrition research because many dietary effects emerge through inter-organ communication rather than the intestinal epithelium alone [136,137]. However, increasing the number of personalized modules does not itself generate a clinically meaningful individual model, and each component requires independent functional benchmarking before system-level conclusions are justified [126]. Modular validation is therefore more credible than assuming that a fully personalized reconstruction of an individual can be achieved simply by combining donor-derived cells, microbiota and multiple organ compartments.

6 Multi-Omics, AI and Multi-Organ Integration

Multimodal phenotyping can increase the mechanistic resolution of intestine-chip experiments when different measurements are obtained from the same experimental configuration, exposure window and comparator [138]. EED intestine-chip studies illustrate this principle by combining morphology, barrier function, nutrient transport, inflammatory mediators and transcriptomic profiling within the same disease-relevant framework [41]. A subsequent rescue study further integrated proteomic measurements with functional endpoints, enabling molecular changes to be interpreted alongside epithelial and absorptive responses. Such integration is most informative when shared sampling schemes and batch controls ensure that molecular and functional datasets describe the same biological event [86]. Integrated sensors and real-time monitoring can complement endpoint omics by providing continuous measurements of barrier integrity or metabolic activity [82,83]. However, increasing molecular depth is useful only when it explains or predicts a predefined functional phenotype, and multi-omics alone does not constitute a predictive model [100,139].

AI should likewise be defined by its specific task rather than by the mere presence of automated data processing [99]. Automated image segmentation and feature extraction can improve measurement consistency, whereas predictive AI requires a prespecified outcome, transparent input variables, appropriate model evaluation and independent validation [100]. The integration of organ-on-a-chip technologies with AI has been proposed across drug development workflows, including experimental design, platform control, image and signal extraction, response modeling and screening optimization. These approaches also highlight the trade-off among throughput, reproducibility, physiological relevance and biological complexity across conventional *in vitro* systems and advanced organ-on-a-chip models (Fig. 7a,b) [100]. In intestine-chip research, machine-learning-assisted platforms have already been used to prioritize probiotic candidates with anti-enteritis activity in preclinical screening workflows [99]. This represents a useful candidate-ranking application, but it does not demonstrate prediction of an individual patient's nutritional response [139]. Related interpretable microbiome–metabolome and nutrition-aware modeling approaches

show how heterogeneous human datasets may be computationally integrated, but they remain distinct from validated chip-based precision-nutrition prediction [10]. Internal cross-validation is insufficient when datasets are small or repeatedly reused, and predictive claims therefore require separated training and test sets, calibration, external validation and explicit uncertainty reporting.

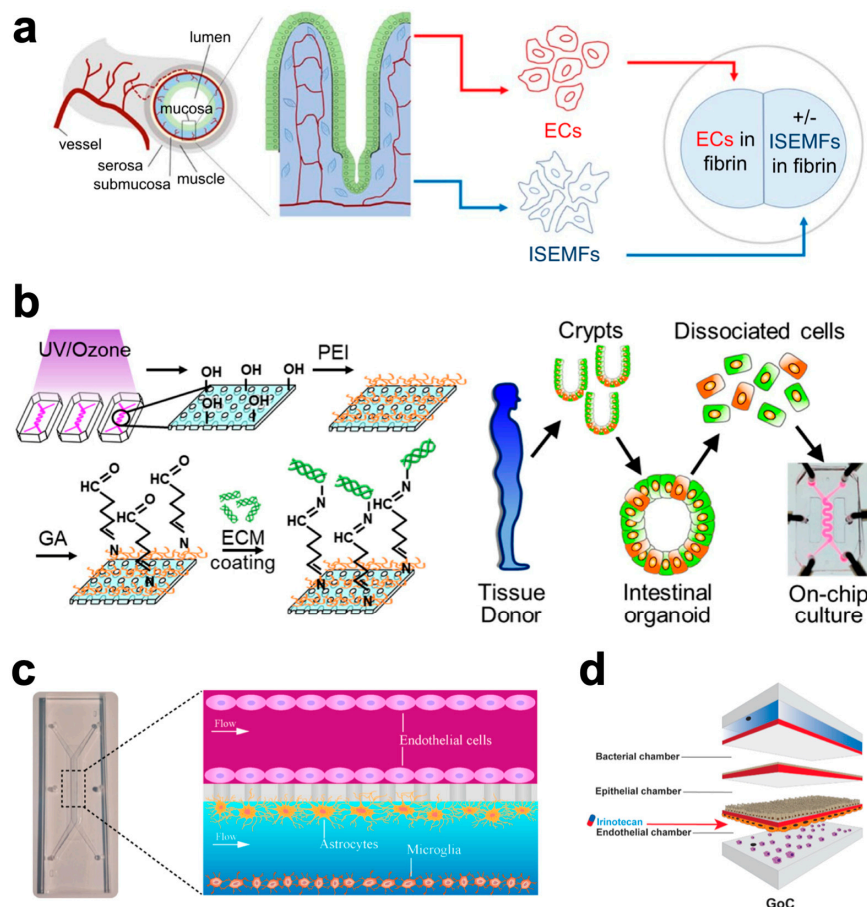


Figure 6: From Patient-Derived Intestine-on-a-Chip models to Multi-Organ microphysiological systems. (a) A patient-derived intestine-on-a-chip model in which small-intestinal myofibroblasts support the formation of perfused and physiologically responsive capillary networks. Reproduced with permission [66]. Copyright 2020, Springer Nature. (b) Three-dimensional regeneration of patient-derived intestinal organoid epithelium in a physiodynamic mucosal interface-on-a-chip. Reproduced with permission [128]. Copyright 2020, MDPI. (c) A microfluidic gut-brain axis platform integrating a human neurovascular unit and functional blood-brain barrier to model inter-organ communication. Reproduced with permission [135]. Copyright 2025, Royal Society of Chemistry. (d) A gut-liver organ-on-chip platform for simulating intestinal-hepatic drug metabolism and downstream metabolic interactions. Reproduced with permission [132]. Copyright 2024, Wiley.

Multi-organ coupling can extend a localized intestinal mechanism into a defined systemic hypothesis by linking intestinal exposure with downstream tissue responses [133,140]. Gut-liver platforms provide the most developed example, having modeled serial exposure, first-pass metabolism, oral bioavailability and pharmacokinetic behavior across coupled intestinal and hepatic compartments [132,137]. Earlier integrated systems similarly demonstrated the feasibility of quantitative gastrointestinal-hepatic pharmacokinetic analysis and first-pass concepts under controlled microfluidic conditions [64]. Inter-organ interpretation

nevertheless requires attention to mass balance, compartment scaling, flow ratios and residence times appropriate to the physiological question being modeled [18,140]. Three-tissue and gut–liver systems have also captured selected inflammatory interactions, illustrating that inter-organ coupling can extend beyond pharmacokinetics to mechanistic disease studies [105,141]. Short-chain fatty acids provide a relevant nutrition-related example because they participate in gut fermentation and systemic exchange, yet their downstream inflammatory effects were context dependent in gut–liver physiommimetic systems [142,143]. These studies establish the feasibility of modeling intestinal–systemic communication but do not yet demonstrate clinically validated nutrition-specific prediction [131,133].

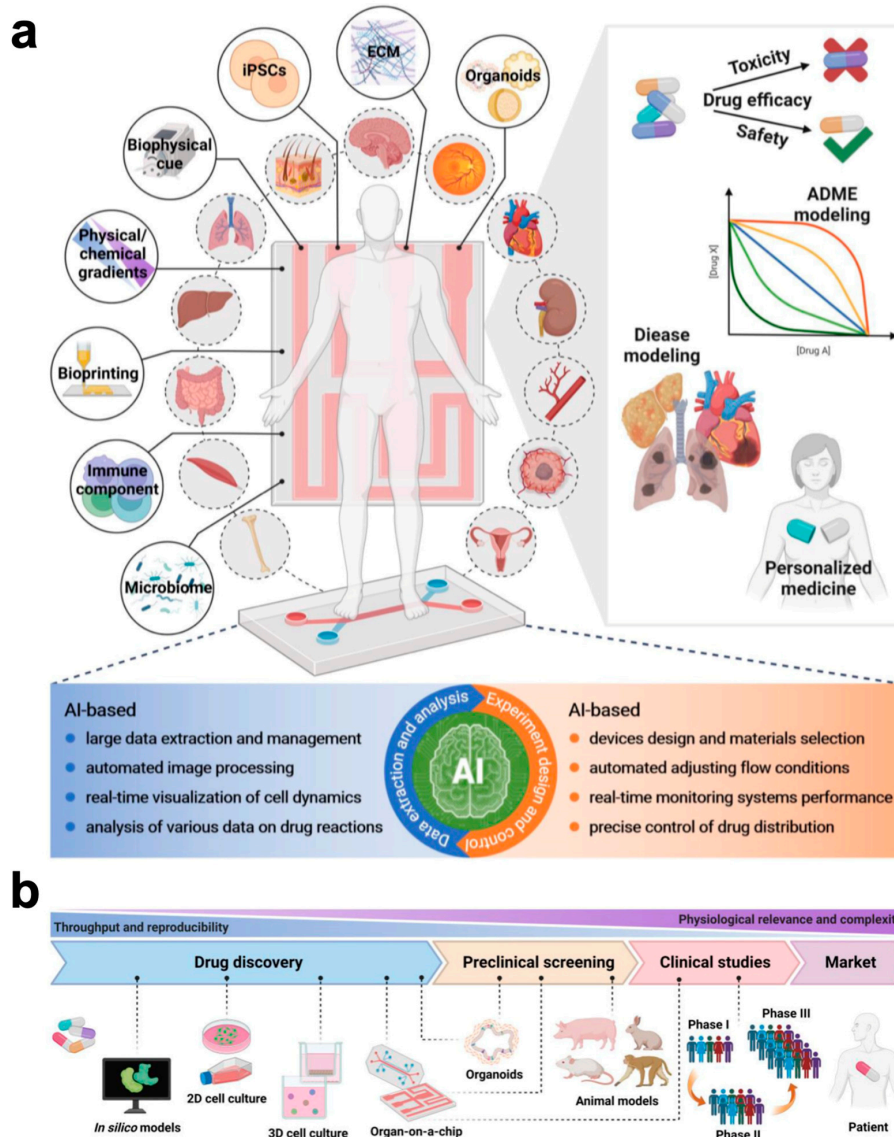


Figure 7: Integration of artificial intelligence with Organ-on-a-Chip platforms for drug evaluation. **(a)** Schematic illustration of the integration of artificial intelligence with organ-on-a-chip systems for drug evaluation, including experimental design, platform control, data extraction, analysis and response prediction. **(b)** Comparison of different *in vitro* drug evaluation models across stages of drug development in terms of throughput, reproducibility, physiological relevance and biological complexity. Reproduced with permission [100]. Copyright 2010, American Association for the Advancement of Science.

Gut–brain platforms represent another emerging direction for extending intestine-chip studies beyond the local mucosal compartment [134,135]. Existing systems have primarily examined drug transport, barrier function, neurovascular responses or extracellular-vesicle trafficking across linked gut and brain-related compartments [136]. Related organ-on-chip studies have proposed extracellular vesicles as potential mediators of microbiota–gut–brain communication, providing a mechanistic basis for future nutrition-oriented experiments [144–146]. Independent biological evidence supports neural, endocrine and metabolic communication following intestinal nutrient sensing, reinforcing the relevance of the gut–brain axis to nutritional physiology [4,147]. Nevertheless, most current gut–brain chip studies remain pharmacological or transport-oriented, and nutrition-specific human validation is still limited [134,136,145]. Gut–muscle and gut–adipose microphysiological systems are even less mature within the current intestine-chip evidence base [131,140]. Inter-organ modules should therefore be incorporated only when they close a prespecified mechanistic loop and provide a validated downstream endpoint that cannot be resolved in a single-organ system [131,133].

Data provenance and biological timing are critical when integrating multimodal and multi-organ measurements [100]. Barrier measurements, secreted mediators, imaging, transcriptomics, proteomics, metabolomics and microbiome profiles should be traceable to the same chip configuration and biologically relevant exposure interval [138]. Otherwise, high-dimensional datasets may increase analytical complexity without strengthening causal interpretation [10]. Predictive modeling must also define an outcome that matches the intended level of use, because a model that classifies chip images is fundamentally different from one that predicts nutrient absorption, clinical response or dietary benefit [100,139]. Small donor datasets are particularly vulnerable to data leakage, confounding and unstable performance estimates, making independent validation essential [139]. Interpretability is also important because apparently predictive features may reflect batch effects or technical artifacts rather than biologically meaningful nutritional mechanisms [10].

The same evidentiary caution applies to digital-twin terminology [100]. A digital representation of an intestine chip may integrate longitudinal measurements, simulate perturbations and generate mechanistic hypotheses, but it becomes a clinically meaningful digital twin only when it is continuously calibrated against individual-level observations and validated for a defined decision [126]. Using digital-twin terminology before these requirements are satisfied risks conflating sophisticated data integration with validated individual forecasting [100]. Current intestine-chip systems are therefore more appropriately described as multimodal microphysiological research platforms with emerging computational and predictive capabilities rather than established digital twins for precision nutrition.

7 Conclusions

The translational challenge is not simply to build more elaborate devices. A deployable platform must pass distinct stages of validation. Technical validation requires stable exposure delivery, material recovery, oxygen and flow control, and reproducible quality criteria. Biological validation requires appropriate cell identity, tissue function and module-specific controls. Human concordance requires a prespecified comparison with tissue, fluid, physiological or clinical data. External validation then tests whether the result survives a locked protocol in an independent cohort or laboratory.

Prospective utility is a separate threshold from technical and biological validity [126]. A precision-nutrition assay must improve a defined decision compared with an appropriate alternative [8]. Nutritional exposure, donor metadata, microbiome provenance and batch effects require standardized reporting. Throughput, cost, data governance and equitable access will also determine deployability [49,50]. Regula-

tory acceptance will additionally require a defined context of use and reproducible performance across sites [140]. No verified nutrition-relevant intestine chip has completed this full pathway.

The most mature evidence supports selected questions in human epithelial physiology, barrier function, microbial coculture and disease mechanisms. The strongest nutrition-specific examples remain controlled nutrient deficiency and defined component exposure [41,86]. Patient-derived systems and computational methods extend experimental resolution but do not substitute for external validation [100,126]. The field should therefore progress from exposure qualification to functional phenotype, donor comparison, human concordance and prospective utility [14]. This sequence protects mechanistic discovery from premature clinical claims.

A practical roadmap begins with technical validation of dosing, recovery, contamination control and assay stability [48,49,60]. Biological validation then tests baseline tissue functions and module-specific controls [11,81,83]. Human concordance assesses whether the chip endpoint matches an independently measured human phenotype [6,28]. External validation tests transportability across laboratories, donors and device lots [126,133]. Preanalytical procedures and metadata standards must be locked before that comparison is interpretable. Prospective utility determines whether the assay improves a nutritional decision, while implementation addresses quality systems and access. Success at one stage does not guarantee success at the next.

Intestine organ chips should not be presented as universal intestinal replicas or established personalized-diet tests [40]. Their present value is a controlled experimental route for testing why intestinal responses differ among exposures, disease contexts and donors [41,86]. Their future value will depend on reproducible patient-linked phenotypes, independent validation and demonstrated decision utility [126]. With these boundaries preserved, intestine chips can become reliable components of a broader precision-nutrition ecosystem [140].

Acknowledgement: None.

Funding Statement: This work was supported by the National Natural Science Foundation of China (81972261 and 82272172), the Summit Advancement Disciplines of Zhejiang Province (Wenzhou Medical University Pharmaceuticals) (2025A01430), the Medical Science and Technology Project of Zhejiang Province (WKJ-ZJ-2322), the Medical Science Technology Project of Zhejiang Province (KLZ25H300001), the Mindray Joint Fund of Zhejiang Provincial Natural Science Foundation of China under Grant (LMRD26H030001), the Independent deployment project of Hangzhou Institute of Medical Sciences (2024ZZBS16).

Author Contributions: Weijian Sun and Changyuan Hu conceived the idea and revised manuscripts. Jianhua Lu conducted the investigation and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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