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Precision Biomarkers for Gut Health: From Intestinal Histomorphology to Multi-Omics

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Abstract:

The gastrointestinal tract is no longer viewed as a digestive organ but its act as highly dynamic system which regulate nutrient utilization, immunity, metabolism and interaction with trillions of gut microbes. Traditional evaluation of gut health depends on gross pathology and intestinal morphology such as villus height and crypt depth. Recent advances in molecular biology have used various precision biomarkers which detect minute changes in intestinal structure, function, microbial ecology and metabolism. Modern technologies including microbiome sequencing, transcriptomics, proteomics, metabolomics and artificial intelligence (AI) which provide a comprehensive assessment of gut health by integrating multiple biological datasets. These biomarkers provide early disease detection, precision nutrition, personalized veterinary medicine and improved livestock productivity. This article discusses the evolution of gut health biomarkers from classical histological indicators to advanced multi-omics approaches and highlights their applications in animal and human health.

Keywords: Gut health, Intestinal morphology, Microbiome, Multi-omics, Precision nutrition

Introduction:

Recently, Gut health has become one of the most important concepts in modern nutrition, veterinary medicine and biomedical research. A healthy intestine not only digest and absorb nutrient efficiently but also act as a biological barrier against pathogens with hosting a complex microbial ecosystem that supports immunity and metabolism. Research has shown that disturbance in intestinal homeostasis leads to inflammatory bowel disease, obesity, diabetes, enteric infections and reduced animal productivity.

Historically, Researchers assessed gut health by using growth performance, feed efficiency, faecal quality and histological examination of intestinal tissues. While these indicators remain valuable, they identify disease only after considerable tissue damage has occurred. Advances in genomics, metabolomics and microbiome research now allow researchers to detect molecular alterations long before structural lesions become visible. This transition has led to the emergence of precision biomarkers, which provide highly sensitive and specific information about intestinal function.

Precision biomarkers integrating with structural, microbial, genetic and metabolic information provide a comprehensive assessment of intestinal health. They are not depending on a single measurement but they combine multiple biological signals to improve diagnosis, monitor treatment responses and design personalized nutritional interventions. Therefore, this comprehensive study was carried out for different biomarker for accessing gut health.

Evolution of Gut Health Biomarkers:

The assessment of gut health has evolved through various scientific stages as presented in Table 1. Initially, researchers depended almost mainly on intestinal morphology observed under light microscopy. Parameters such as villus height, crypt depth, epithelial thickness and inflammatory infiltration act as the primary indicators of intestinal function. Although these measurements remain important but they provide only structural information.

The development of immunological techniques such as cytokines and secretory immunoglobulin A (IgA) which improve understanding of mucosal immunity. Subsequently, next-generation sequencing revolutionized microbiome research by providing comprehensive characterization of intestinal microbial communities. Today, transcriptomics, proteomics, metabolomics and integrated multi-omics approaches allow simultaneous analysis of thousands of genes, proteins, metabolites and different microbial species.

Table 1. Evolution of Gut Health Biomarkers

Era	Major Biomarkers	Technology
Histology	Villus height, crypt depth	Light microscopy
Immunology	Cytokines, IgA	ELISA, Immunoassays
Microbiome	Bacterial diversity	16S rRNA sequencing
Omics Technology	Genes, proteins, metabolites	RNA-Seq, LC-MS/MS
Precision Medicine	Integrated multi-omics	AI and Machine Learning

Morphological Biomarkers:

Despite remarkable advances in molecular biology, intestinal morphology remains one of the most reliable indicators of gut health. Histological examination directly reflects epithelial integrity, nutrient absorptive capacity and tissue regeneration. In both veterinary and human medicine, morphological biomarkers serve as reference standard for evaluating intestinal health. Major morphological biomarker with its importance is presented in table 2.

- **Villus Height:**

Villi are finger-like projections which involving with increase the absorptive surface area of the small intestine. Increased villus height generally indicates enhanced nutrient absorption because a larger epithelial surface contains more mature enterocytes capable of transporting nutrients. In contrast, shortened villi are commonly associated with heat stress, enteric infections, inflammatory bowel disease, malnutrition and mycotoxicity.

- **Crypt Depth:**

Crypts contain intestinal stem cells responsible for the continuous generation of the intestinal epithelium. Moderate crypt depth is essential for maintaining of intestinal homeostasis. However, excessive crypt hyperplasia indicates increased epithelial turnover caused by acute inflammation or tissue injury. Researchers therefore interpret crypt depth together with villus height rather than as a single parameter.

- **Villus Height-to-Crypt Depth Ratio:**

The villus height-to-crypt depth ratio indicates absorptive function with epithelial regeneration. Higher ratios generally indicate improved digestive efficiency and lower epithelial stress, whereas reduced ratios frequently associated with intestinal disorders. This parameter is routinely reported in nutritional and pathological studies.

Table 2. Major Morphological Biomarkers

Biomarker	Biological Importance	Interpretation
Villus height	Nutrient absorption	Higher values indicate improved absorption
Crypt depth	Stem-cell proliferation	Excessive depth suggests inflammation
Villus: Crypt ratio	Overall intestinal function	Higher ratio indicates healthy mucosa
Goblet cell density	Mucus production	Higher number improve protection
Mucosal thickness	Tissue integrity	Indicate epithelial health

- **Goblet cell and mucosal thickness:**

Modern histology extends beyond simple measurements of villi and crypts to include specialized cellular biomarkers. Goblet cells synthesize mucins that form a protective mucus layer covering the intestinal epithelium. An increase in goblet cell density which enhanced mucosal defence and improved barrier protection. Similarly, Paneth cells produce antimicrobial peptides that regulate microbial homeostasis within intestinal crypts. Dysfunction of these cells has been linked to inflammatory bowel diseases and impaired host defence.

Researchers also quantify epithelial proliferation using immune-histochemical markers, while assessing programmed cell death with caspase-3 staining. Together, these histological biomarkers provide a detailed understanding of epithelial turnover, tissue repair, and intestinal adaptation to dietary interventions.

Intestinal Barrier Biomarkers:

A healthy intestine depends not only on its structure but also on the integrity of its epithelial barrier. This barrier acts as a selective filter, allowing nutrients, water and electrolytes to enter the body while

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preventing toxins, pathogens and harmful molecules from crossing into the bloodstream. Damaging to this barrier, often called "leaky gut," has been associated with inflammatory bowel disease, metabolic disorders, heat stress and enteric infections. Consequently, biomarkers that measure barrier function have become essential tools in precision gut health assessment and are presented in Table 3.

- **Tight Junction Proteins:**

  Tight junction proteins, including occludin, claudin and zonula occludens-1 (ZO-1), form the junction between neighbouring intestinal epithelial cells. Reduced expression or altered localization of these proteins increases intestinal permeability and enhances inflammation. Nutritional interventions such as probiotics, prebiotics, butyrate, glutamine and zinc have been shown to improve tight junction integrity in several experimental studies.

- **Functional Barrier Biomarkers:**

  Researchers also evaluate barrier function using physiological tests. The lactulose–mannitol permeability test measures the passage of two sugars across the intestinal wall, while fluorescein isothiocyanate dextran (FITC-dextran) assays are commonly used in animal studies to quantify leaky gut conditions. Elevated values indicate impaired barrier function and increased permeability.

Table 3. Major Intestinal Barrier Biomarkers

Biomarker	Biological Role	Significance
ZO-1	Tight junction	Indicates epithelial integrity
Occludin	Cell-to-cell adhesion	Reduced during barrier damage
Claudin	Regulates permeability	Altered in inflammation
Lactulose: Mannitol ratio	Functional permeability	Higher ratio indicates leaky gut
FITC-dextran	Intestinal leakage	Increased serum levels indicate barrier disruption

Immune Biomarkers:

Approximately 70% of the body's immune cells are associated with the gastrointestinal tract, the intestine being one of the largest immune organs. Immune biomarkers help evaluate mucosal defence mechanisms and inflammatory status. Major immune markers with its function is presented in Table 4.

- **Secretory Immunoglobulin A (IgA):**

  Secretory IgA is the predominant antibody found in the intestinal lumen. It neutralizes pathogens, prevents bacterial attachment to epithelial cells and maintains immune tolerance toward beneficial microorganisms. Increased faecal IgA is considered a marker of improved mucosal immunity.

- **Inflammatory Cytokines:**

  Cytokines are signalling molecules which coordinate immune responses. Increased concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6

(IL-6) indicate intestinal inflammation, while increased IL-10 reflects anti-inflammatory activity and tissue repair. Gene expression analysis and immunoassays are widely used to quantify these biomarkers.

- **Oxidative Stress Indicators:**

Oxidative stress damages epithelial cells and disrupts gut homeostasis. Biomarkers such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) are frequently measured to assess antioxidant defence and oxidative injury.

Table 4. Important Immune Biomarkers

Biomarker	Function	Interpretation
Secretory IgA	Mucosal immunity	Higher levels indicate stronger defence
TNF-α	Inflammation	Increased during disease
IL-1β	Pro-inflammatory cytokine	Tissue injury marker
IL-6	Acute inflammatory response	Increased in infection
IL-10	Anti-inflammatory cytokine	Increased healing
MDA	Lipid peroxidation	Indicates oxidative stress

Microbiome-Based Precision Biomarkers:

The gut microbiome contains trillions of microbes that collectively influence on digestion, nutrient metabolism, immune function and disease resistance in host. Recent technology not only focus on individual bacterial species but it evaluates the diversity, composition and functional capacity of the microbial community. Multi-omics methods, including metagenomics, metatranscriptomics, metaproteomics and metabolomics which provide more detailed in microbial activity.

Beneficial bacterial groups such as Bifidobacterium, Lactobacillus and Faecalibacterium are commonly associated with a healthy intestine because they produce short-chain fatty acids, strengthen epithelial barriers and regulate immune responses. Conversely, increasing of opportunistic pathogens may indicate dysbiosis and disease susceptibility.

- **Metabolomics:**

Metabolomics analyses small molecules produced by both the host and gut microbiota. These metabolites provide a functionality of intestinal physiology. Among them, short-chain fatty acids (SCFAs) mainly acetate, propionate, and butyrate are particularly important. Butyrate serves as the primary energy source for colonocytes which enhances tight junction protein expression, suppresses inflammation and supports epithelial regeneration. Other informative metabolites include bile acids, indole derivatives, amino acid metabolites and polyamines.

- **Transcriptomics and Proteomics:**

Transcriptomics measures RNA expression to identify genes activated during intestinal stress, immunity or nutrient absorption. Biomarkers such as OCLN, CLDN1, ZO-1 and MUC2 help to evaluate epithelial barrier integrity whereas inflammatory genes reveal immune activation. Proteomics complements transcriptomics by analysing proteins that regulate cellular functions. Modern mass spectrometry can identify thousands of proteins involved in epithelial maintenance, antioxidant defence, immune regulation and metabolism which provide a more direct assessment of gut physiology.

Multi-Omics and Artificial Intelligence:

None of the single biomarker can fully assess the gut health. Therefore, researchers increasingly integrate genomics, transcriptomics, proteomics, metabolomics, microbiomics and clinical data using multi-omics approaches. Artificial intelligence and machine learning algorithms analyse these complex datasets to identify disease-associated biomarker patterns, predict treatment responses and develop individual nutritional strategies for enhancing productivity. These technologies are being central to precision medicine and precision livestock production.

Conclusion:

The assessment of gut health has progressed from simple microscopic observations to multi-omics technologies capable of providing structural, microbial, molecular and metabolic changes. Classical biomarkers such as villus height and crypt depth remain fundamental because they directly reflect intestinal architecture. However, integrating barrier biomarkers, immune mediators, microbiome profiles, transcriptomics, proteomics and metabolomics provides a far more comprehensive understanding of intestinal function. The incorporation of artificial intelligence into multi-omics analysis, which revolutionizes precision nutrition, veterinary diagnostics and personalized medicine by enabling earlier disease detection and early targeted interventions.

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