

Selected Lectures of the Metabolomics Marathon

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LECT 1

HOW METABOLOMICS HAS CHANGED THE WAY I PRACTICE PEDIATRICS

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The ability to assess metabolic activity in real time – that is, to investigate the interactions among the genome, epigenetics, the environment, diet, and the microbiota – is changing the way several conditions commonly encountered in pediatric practice are interpreted. Metabolomics is the study of an organism's biochemical phenotype, encompassing the metabolic changes that arise from the continuous interaction between the genetic background and the exposome. It should not be regarded as a replacement for conventional laboratory medicine, but rather as an approach that complements and integrates different diagnostic methods. In this context, we examine two conditions that, although encountered with different frequencies, are both part of everyday pediatric practice: children with autism spectrum disorder (ASD) and children with attention-deficit/hyperactivity disorder (ADHD) or other neurodevelopmental vulnerability.

In children with ASD, the assessment of a range of physical and behavioral symptoms – from abdominal colic and food selectivity to aggression and behavioral disturbances – may be complemented by analysis of the urinary metabolomic profile. Several studies have reported correlations between metabolic alterations and the severity of clinical manifestations. Alterations in tryptophan metabolism, organic acids of gut bacterial origin, and markers of oxidative stress provide insight into the role of the gut-brain axis in the biological mechanisms associated with ASD [1]. Conventional clinical assessment can therefore be complemented by an analysis of the patient's functional characteristics, allowing targeted interventions involving nutrition, the microbiota, and nutraceutical supplementation, in close collaboration with the family.

ADHD and neurodevelopmental vulnerability are also frequently encountered in everyday pediatric practice. In these children and adolescents, metabolomics may help identify metabolic conditions that could potentially modulate clinical expression, including: deficiencies in nutrients and enzymatic cofactors such as vitamin B6, whose active derivative, pyridoxal 5'-phosphate, acts as a cofactor in the synthesis of neurotransmitters such as GABA, dopamine, and serotonin; alterations in mitochondrial function and energy production; and intestinal dysbiosis that may interfere with communication along the gut-brain axis [2].

One case from my pediatric practice involved a girl with 47,XXX syndrome, combined-type ADHD, emotional and anxiety-related vulnerability, and stabilized focal epilepsy. She underwent metabolomic assessment in conjunction with the diagnostic evaluation and therapeutic interventions provided by a child neuropsychiatrist. Specific metabolic alterations and potentially correctable micronutrient deficiencies were identified. These findings made it possible to develop a precision nutritional and nutraceutical intervention aimed at supporting bioenergetic function and neurotransmission, while monitoring potential interactions with long-term pharmacological treatments. This approach was implemented in close collaboration with the child neuropsychiatry team and the family [3].

The common thread – almost an Akai Ito – linking these two conditions points toward a change in the pediatrician's approach to both the patient and the disease. We are moving from a model of medicine focused on repairing a diseased organ toward one that seeks to interpret signals from the biological milieu before they develop into overt symptoms. Metabolomics complements clinical assessment and conventional laboratory testing; it does not replace them. The integrated interpretation of clinical findings, conventional laboratory tests, and metabolomic analyses can provide a functional snapshot of the child at a specific point in time, helping us understand how the child may respond to an acute or chronic health condition. Metabolomics describes the patient's current biological state and provides insight into how the biological milieu in which disease develops can potentially be modulated, representing a meaningful change in everyday pediatric practice.

REFERENCES

- [1] Mussap M, Siracusano M, Noto A, Fattuoni C, Riccioni A, Rajula HSR, Fanos V, Curatolo P, Barberini L, Mazzone L. The Urine Metabolome of

Young Autistic Children Correlates with Their Clinical Profile Severity. *Metabolites*. 2020;10(11):476.

[2] Predescu E, Vaidean T, Rapciuc AM, Sipos R. Metabolomic Markers in Attention-Deficit/Hyperactivity Disorder (ADHD) among Children and Adolescents-A Systematic Review. *Int J Mol Sci*. 2024;25(8):4385.

[3] Bardanzellu F, Fanos V. How could metabolomics change pediatric health? *Ital J Pediatr*. 2020;46(1):37.

LECT 2

METABOLOMICS AND PROBIOTICS

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The establishment of the gut microbiota during early life is a highly dynamic process with important implications for intestinal, metabolic, and immune maturation. This process is particularly vulnerable in preterm infants and in neonates exposed to factors such as Cesarean delivery, antibiotic treatment and formula feeding, which may interfere with physiological microbial colonization. Probiotic supplementation has therefore attracted considerable interest as a strategy to promote a more favorable intestinal ecosystem. However, changes in microbial composition alone provide only a partial view of probiotic activity and do not fully explain the mechanisms through which these microorganisms may influence neonatal physiology.

Metabolomics provides a functional readout of host-microbiota interactions by characterizing microbial metabolites and the metabolic response of the host. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS)-based approaches can therefore complement microbiome analysis, moving the investigation from microbial composition to microbial function.

Evidence from neonatal studies illustrates the potential of this approach. In preterm infants, *Bifidobacterium spp.* and *Lactobacillus spp.* supplementation has been associated with increased fecal acetate and lactate, enhanced utilization of human milk oligosaccharides and lower intestinal pH [1]. In breastfed term infants with colic, probiotic supplementation modified the fecal metabolome despite the absence of detectable changes in microbiota composition, suggesting that metabolic responses may occur without major taxonomic shifts [2].

More recently, an integrated longitudinal microbiome-metabolome study in healthy, formula-fed infants

delivered by elective Cesarean section showed, during supplementation with *Lactocaseibacillus rhamnosus LGG®* and *Bifidobacterium longum subsp. infantis*, an increase in *Bifidobacteriaceae*, a reduction in *Enterobacteriaceae* and changes in fecal fermentation metabolites, including acetate, lactate, and propionate [3]. Urinary ¹H NMR metabolomics revealed parallel temporal changes in energy and amino acid metabolism and microbial co-metabolism, together with marked interindividual variability [3]. Experimental evidence from a neonatal model of necrotizing enterocolitis further suggests that *B. infantis* may modulate systemic tryptophan metabolism and indole-related metabolites involved in intestinal barrier and immune regulation [4].

Together, these findings demonstrate how metabolomics can bridge the gap between microbial composition and biological function. Integration of microbiome and metabolome data may help identify metabolic signatures of probiotic response, clarify strain-specific mechanisms of action and characterize individual trajectories of host-microbiota co-maturation, providing a functional framework for the evaluation of probiotic interventions in neonatal care.

REFERENCES

- [1] Alcon-Giner C, Dalby MJ, Caim S, Ketskemety J, Shaw A, Sim K, Lawson MAE, Kiu R, Leclaire C, Chalklen L, Kujawska M, Mitra S, Fardus-Reid F, Belteki G, McColl K, Swann JR, Kroll JS, Clarke P, Hall LJ. Microbiota Supplementation with Bifidobacterium and Lactobacillus Modifies the Preterm Infant Gut Microbiota and Metabolome: An Observational Study. *Cell Rep Med*. 2020;1(5):100077.
- [2] Baldassarre ME, Di Mauro A, Tafuri S, Rizzo V, Gallone MS, Mastromarino P, Capobianco D, Laghi L, Zhu C, Capozza M, Laforgia N. Effectiveness and Safety of a Probiotic-Mixture for the Treatment of Infantile Colic: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial with Fecal Real-Time PCR and NMR-Based Metabolomics Analysis. *Nutrients*. 2018;10(2):195.
- [3] Cannas F, Zuddas N, Cesare Marincola F, Pisano MB, Al Jamal O, Moi M, Trapani G, Pintus R, Dessì A, Fanos V. Impact of early probiotic supplementation on the gut microbiota and urinary and fecal metabolome of formula-fed infants delivered via elective cesarean section. *J Pediatr Neonat Individual Med*. 2026;15(1):e150107.
- [4] Li J, Lan H, Liu Y, Wang X, Wu S, Zhao W, Hung WL, He J, Fang B, Zhang M. From microbiota to metabolomics: how Bifidobacterium infantis YLGB-1496 shields neonates from necrotizing enterocolitis. *Food Funct*. 2025;16(21):8391-403.

LECT 3

METABOLOMICS AND AUTISM

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The global prevalence of autism spectrum disorder (ASD) has been increasing over the past thirty years, with an estimated median of approximately 1 in 100 children worldwide, positioning it as a genuine global public health challenge. Diagnosis is currently based on clinical and behavioral assessment, often delayed to age 3-4 years or beyond, with characteristics that vary across the spectrum of cases, resulting in considerable heterogeneity of the disorder [1, 2]. The etiology of the condition is likely multifactorial, arising from the interaction between genetic and environmental factors, and the metabolome constitutes its ultimate expression, offering a single snapshot of the individual's physiological state [2]. Precisely because of this capacity to synthesize the combined effect of multiple determinants, the study of the metabolome represents a valuable tool for investigating the biological mechanisms underlying such a complex condition, although validated biomarkers for diagnosis, prognosis and personalized treatment are still lacking to date. Recent research has indeed reinforced the hypothesis that the metabolome, regardless of the biological matrix of origin, represents a key tool for understanding the biological complexity of ASD, while acknowledging the need for future studies on larger samples to achieve clinical validation of the identified biomarkers [1, 2]. This approach has made it possible to divide the ASD population into phenotypically homogeneous groups, each characterized by a specific metabolic signature, suggesting different biological mechanisms underlying the heterogeneity of autism [2], while also highlighting the central role of the microbiota-gut-brain axis [1]. A large-scale multi-omic analysis, integrating microbiome, metabolome, brain transcriptome, cytokine profile and dietary data, further revealed a notable overlap between metabolic pathways altered at the intestinal level and those expressed in the brain tissue of individuals with ASD, reinforcing the hypothesis of a shared functional architecture along the gut-brain axis and suggesting a possible causal role of the microbiota in modulating autistic symptoms [3]. Overall, metabolomics emerges as a central tool for understanding the biological complexity of ASD. However, further studies are still needed to identify and validate reliable biomarkers, not only for diagnostic and prognostic purposes, but also to guide targeted therapeutic interventions,

from correcting intestinal dysbiosis to personalized nutritional strategies, toward a precision medicine approach in autism.

REFERENCES

- [1] Suárez-Jaramillo A, Cifuentes SG, Baldeón M, Cárdenas P. Intestinal Metabolome for Diagnosing and Prognosing Autism Spectrum Disorder in Children: A Systematic Review. *Metabolites*. 2025;15(4):213.
- [2] Prince N, Chu SH, Chen Y, Mendez KM, Hanson E, Green-Snyder LA, Brooks E, Korrick S, Lasky-Su JA, Kelly RS. Phenotypically driven subgroups of ASD display distinct metabolomic profiles. *Brain Behav Immun*. 2023;111:21-9.
- [3] Morton JT, Jin DM, Mills RH, Shao Y, Rahman G, McDonald D, Zhu Q, Balaban M, Jiang Y, Cantrell K, Gonzalez A, Carmel J, Frankiensztajn LM, Martin-Brevet S, Berding K, Needham BD, Zurita MF, David M, Averina OV, Kovtun AS, Noto A, Mussap M, Wang M, Frank DN, Li E, Zhou W, Fanos V, Danilenko VN, Wall DP, Cárdenas P, Baldeón ME, Jacquemont S, Koren O, Elliott E, Xavier RJ, Mazmanian SK, Knight R, Gilbert JA, Donovan SM, Lawley TD, Carpenter B, Bonneau R, Taroncher-Oldenburg G. Multi-level analysis of the gut-brain axis shows autism spectrum disorder-associated molecular and microbial profiles. *Nat Neurosci*. 2023;26(7):1208-17

LECT 4

METABOLOMICS AND NUTRITION. FROM THE URINARY METABOLOME TO THE PLATE: HOW THE METABOLIC FINGERPRINT CAN GUIDE PRECISION NUTRITION IN CHILDREN

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Pediatric nutritional assessment traditionally relies on growth monitoring, dietary evaluation, clinical history, and conventional biochemical parameters. However, between dietary intake and the biological response of the organism lies a complex and dynamic network of metabolic transformations. In this context, urinary metabolomics may provide a complementary perspective, offering information on bioenergetic processes, amino acid metabolism, dietary exposure, and host-gut microbiota co-metabolism.

Studies conducted in pediatric populations have shown that urinary metabolomic profiles can reflect different dietary patterns and overall diet quality [1]. Nutritional interventions have also been associated with measurable changes in urinary metabolites related to protein, amino acid, and lipid metabolism within a relatively short period of time [2]. More recent evidence further supports the identification of urinary metabolites reproducibly associated with the intake of specific food groups, strengthening

the link between diet and the urinary metabolome during childhood and adolescence [3].

This lecture proposes a nutritional interpretation framework based on three “nutritional windows”: bioenergetics, redox balance, and substrate/cofactor availability. The gut-microbiota axis is considered a cross-cutting component, as it may contribute to the production and transformation of several metabolites detectable in urine.

The aim is not to assign diagnostic meaning to a single metabolite, nor to translate every biochemical abnormality directly into a dietary or supplementation prescription. The value of metabolomics emerges from the integration of the urinary metabolic profile with medical diagnosis, growth trajectory, dietary history, symptoms, and conventional laboratory findings

An anonymized pediatric clinical case will illustrate the pathway from urinary organic acid and amino acid profiling to the development of an individualized nutritional strategy.

Urinary metabolomics does not prescribe the diet. Rather, it may increase the resolution with which we observe the child and contribute to a more personalized and clinically contextualized approach to precision nutrition.

REFERENCES

- [1] Stratakis N, Siskos AP, Papadopoulou E, Nguyen AN, Zhao Y, Margetaki K, Lau CHE, Coen M, Maitre L, Fernández-Barrés S, Agier L, Andrusaityte S, Basagaña X, Brantsaeter AL, Casas M, Fossati S, Grazuleviciene R, Heude B, McEachan RRC, Meltzer HM, Millett C, Rauber F, Robinson O, Roumeliotaki T, Borrás E, Sabido E, Urquiza J, Vafeiadi M, Vineis P, Voortman T, Wright J, Conti DV, Vrijheid M, Keun HC, Chatzi L. Urinary metabolic biomarkers of diet quality in European children are associated with metabolic health. *Elife*. 2022;11:e71332.
- [2] Andueza N, Muñoz-Prieto D, Romo-Hualde A, Cuervo M, Navas-Carretero S. Changes in urinary metabolomic profile show the effectiveness of a nutritional intervention in children 6-12 years old: The ALINFA study. *Food Sci Nutr*. 2024;12(8):5663-76.
- [3] Yuan L, Muli S, Goerden J, Rattner J, Merdas M, Achaintre D, Foraita R, Wolters M, De Henaau S, Hunsberger M, Huybrechts I, Lissner L, Molnár D, Moreno LA, Russo P, Veidebaum T, Ahrens W, Nöthlings U, Keski-Rahkonen P, Oluwagbemigun K. Exploratory Screening and Replication of Urinary Biomarkers of Fruit and Vegetable Intake in Free-living European Children and Adolescents Using Untargeted Metabolomics. *J Nutr*. 2026;156(2):101302.

LECT 5

METABOLOMICS AND OBESITY

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Obesity is a chronic, multifactorial condition associated with an increased risk of cardiometabolic complications. Although body mass index (BMI) remains the most widely used tool for classifying obesity, it does not fully capture metabolic heterogeneity or individual differences in cardiometabolic risk. Metabolomic studies have identified specific molecular signatures associated with BMI, while also revealing substantial metabolic heterogeneity among individuals with similar levels of adiposity. In this context, metabolomics may contribute to a more accurate characterization of the metabolic phenotype of obesity.

Within the European BETTER4U consortium, which also includes the University of Cagliari, metabolomic data from 314,767 participants across nine cohorts from six countries were analyzed using three targeted platforms. Associations between metabolites and BMI were assessed using harmonized analyses, random-effects meta-analysis, and meta-regression to investigate geographic heterogeneity. Higher BMI was associated with a metabolic profile characterized by higher levels of triglyceride-rich lipoproteins, particularly large very-low-density lipoprotein particles, as well as glycerol, branched-chain and aromatic amino acids, and acetylated glycoproteins, together with lower levels of large high-density lipoprotein particles, glycine, glutamine, choline-related metabolites, and phosphatidylcholines. Meta-regression also revealed significant geographic heterogeneity, suggesting that individuals with similar BMI values may exhibit different metabolic profile and levels of cardiometabolic risk.

These findings confirm that obesity defined solely by BMI does not correspond to a single metabolic state. Integrating BMI with metabolomic profilin could improve risk stratification, facilitate the early identification of individuals with an unfavorable metabolic phenotype, and support more personalized prevention and intervention strategies.

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LECT 6

METABOLOMICS AND DENTAL HEALTH

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The oral cavity is a dynamic environment in which the microbiota, host tissues, diet, medications, and immune responses interact. Dental examination remains essential, but it primarily identifies lesions and damage that are already clinically evident. Metabolomics offers a complementary perspective by measuring end products and intermediates of metabolic pathways, with molecular weights below 1,500 daltons, generated by both human and microbial metabolism. This information may help identify biological alterations that precede clinically detectable damage.

Saliva is the most promising matrix because it can be collected easily, repeatedly, and noninvasively. Its metabolome encompasses signals derived from the oral microbiota, salivary glands, mucosal tissues, inflammatory cells, diet, and the systemic circulation [1]. However, this wealth of information requires careful interpretation. Blood and urine may also be useful when the focus is on systemic metabolism, nutrition, medications, or environmental exposures. In dentistry, metabolomics is being investigated for its potential to assess caries risk, periodontal disease activity, alterations associated with potentially malignant oral lesions, and responses to preventive or therapeutic interventions. Rather than necessarily seeking a single biomarker, metabolomic approaches may identify panels of metabolites capable of characterizing microbial fermentation, acidification, oxidative stress, tissue degradation, and inflammation

For general practitioners, the relevance of metabolomics stems from the close relationship between oral and systemic health. Conditions such as diabetes, chronic kidney disease, and cardiometabolic disorders, as well as smoking and pharmacological treatments, can affect salivary secretion and periodontal vulnerability. Oral dysbiosis and inflammation may also be associated with an increased systemic inflammatory burden. Metabolomic information could therefore contribute to personalized prevention strategies and to the monitoring of patients with multimorbidity.

It should be emphasized that, before metabolomics can be implemented in clinical practice, sample collection, storage, and analysis will need to be standardized, confounding factors carefully controlled, and findings validated in independent populations. At present, metabolomics should therefore be regarded as a complementary tool for research and biological stratification rather than as a replacement for clinical examination or

established diagnostic procedures. Its future value will depend on the availability of reproducible metabolite panels that are easy to measure and provide clinically meaningful information for patient care and decision-making.

REFERENCE

- [1] Montis N, Cotti E, Noto A, Fattuoni C, Barberini L. Salivary Metabolomics Fingerprint of Chronic Apical Abscess with Sinus Tract: A Pilot Study. *Sci World J.* 2019;2019:3162063.

LECT 7

SPORTOMICS: METABOLOMICS APPLIED TO SPORT

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Sportomics is the application of metabolomics to sports. Metabolomics analyzes the metabolites produced by the body – that is, low-molecular-weight substances found in all biofluids – providing a detailed map of the biochemical and metabolic processes taking place within the body. Metabolomics represents the body's secret language, one that we can now decipher: a language through which cells communicate with other cells, cells with microorganisms, and microorganisms with organs. Each person's metabolomic profile is like a unique fingerprint, forming the basis of personalized medicine and, in our case, personalized sports science. Metabolomics is regarded as the “Rosetta Stone” of microbiomics.

Microbiomics studies the microbiota – the community of microorganisms that inhabit the human body – with particular emphasis on those residing in the gut. This presentation aims to shed light on the intersection between “omics” disciplines, such as metabolomics and microbiomics, and sports. This rapidly evolving field has opened up new perspectives in recent years for studying human physiology and, in particular, improving athletic performance.

These two emerging scientific fields provide innovative tools for better understanding how the body functions, personalizing nutritional interventions, and optimizing training strategies. There is no single formula that works for every athlete. Metabolic requirements and microbiota characteristics vary considerably among individuals, and the ability to adapt strategies to these differ-

ences is crucial for maximizing performance and preventing injuries. For example, athletes whose gut microbiota is rich in species such as *Veillonella atypica* may be able to convert lactate into propionate, a compound that provides additional energy during prolonged exercise.

Athletes are frequently exposed to substantial – and sometimes extreme – physiological and psychological stress, which can negatively affect their gut microbiota and metabolic balance. A combination of targeted dietary interventions, prebiotic and probiotic supplementation, and personalized recovery strategies may help mitigate these effects and promote long-term well-being. For example, supplementation with specific probiotics during periods of intense training may reduce the risk of respiratory infections and improve sleep quality, both of which are critical to athletes' overall health and physical recovery.

Another key objective is to further investigate the role of metabolomics and microbiomics in injury prevention. Metabolomics, for example, can identify early markers of cellular “distress,” inflammation, or oxidative stress, which often precede muscle or tendon injuries.

Particular attention will be devoted to soccer, one of the world's most popular sports and the sport most extensively studied from a metabolomics perspective. However, many other sports will also be discussed, including rugby, basketball, volleyball, cycling, swimming, water polo, rowing, marathon running, and ultramarathon running.

How can we improve athletes' health? How can we prevent injuries? How can personalized nutritional strategies be implemented? Is it possible to optimize recovery from fatigue? These are all questions of extraordinary importance for athletes – not only elite athletes – who seek to achieve peak performance as safely as possible.

REFERENCES

- Bongiovanni T, Lacomme M, Fanos V, Martera G, Cione E, Cannataro R. Metabolomics in Team-Sport Athletes: Current Knowledge, Challenges, and Future Perspectives. *Proteomes*. 2022;10(3):27.
- Bongiovanni T, Pintus R, Dessì A, Noto A, Sardo S, Finco G, Corsello G, Fanos V. Sportomics: metabolomics applied to sports. The new revolution? *Eur Rev Med Pharmacol Sci*. 2019;23(24):11011-9.
- Fanos V. Footballomics: urinary metabolomics in adolescents and athletes playing football (soccer) – Review of the literature and practical approach. *J Pediatr Neonat Individual Med*. 2025;14(1):e140109.
- Fanos V. Sportomica. La scienza della metabolomica al servizio dello sport. Quartu Sant'Elena: Hygeia Press, 2025.
- Pintus R, Bongiovanni T, Corbu S, Francavilla VC, Dessì A, Noto A, Corsello G, Finco G, Fanos V, Cesare Marincola F. Sportomics in professional

soccer players: metabolomics results during preseason. *J Sports Med Phys Fitness*. 2021;61(2):324-30.

LECT 8

METABOLOMICS AND THE MICROBIOME: INTERCONNECTIONS

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The study of the gut microbiota has traditionally relied on sequencing techniques, including 16S rRNA sequencing and shotgun metagenomics, which provide a description of the taxonomic composition of the microbial populations present at a given time. Although fundamental, this approach provides an essentially static, descriptive snapshot: it tells us who is present, but not necessarily what they are doing from a functional perspective.

Metabolomics represents a qualitative leap forward in this investigative process. Through the quantitative and qualitative analysis of metabolites produced by the microbiota – including short-chain fatty acids, secondary bile acids, indoles, polyamines, and other bioactive compounds – it is possible to move beyond a snapshot of the microbial population toward a functional and dynamic assessment of its actual activity in the “here and now” [1].

In other words, metabolomics does not merely integrate compositional data; it complements these data by revealing the microbiota's actual biological output in its continuous dialogue with the host. Metabolites are, in fact, the key molecular mediators through which the microbiota communicates with systemic metabolism, the immune system, and developmental processes, with significant implications beginning as early as the neonatal and pediatric periods [2].

The integration of microbiomic and metabolomic data within a multi-omics approach therefore enables a more accurate, dynamic, and clinically relevant understanding of microbiota function [3]. The microbiota can no longer be viewed simply as a catalog of species, but rather as a continuously active metabolic network capable of modulating host health in real time. This paradigm shift has tangible implications for pediatric clinical practice, paving the way for new functional biomarkers and targeted therapeutic strategies aimed at modulating not only the composition of the microbiota but also its metabolic activity.

REFERENCES

- [1] Muller E, Algavi YM, Borenstein E. The gut microbiome-metabolome dataset collection: a curated resource for integrative meta-analysis. *NPJ Biofilms Microbiomes*. 2022;8(1):79
- [2] Duan D, Wang M, Han J, Li M, Wang Z, Zhou S, Xin W, Li X. Advances in multi-omics integrated analysis methods based on the gut microbiome and their applications. *Front Microbiol*. 2024;15:1509117.
- [3] Puig-Castellví F, Pacheco-Tapia R, Deslande M, Jia M, Andrikopoulos P, Chechi K, Bonnefond A, Froguel P, Dumas ME. Advances in the integration of metabolomics and metagenomics for human gut microbiome and their clinical applications. *TrAC Trends Anal Chem*. 2023;167:117248.

LECT 9

FOOD COMMUNICATES WITH THE MICROBIOTA

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Taste receptors distributed throughout the digestive tract show that their primary role is to protect the intestinal environment [1]. To do so, the digestive tract must try to obtain nutrients for its cells, the short chain fatty acids, from what enters: frugivores, from the fermentation of indigestible fibers in the cecum, while predatory carnivores, from the breakdown of saturated fats in the stomach. During the drastic climate changes of the Pleistocene, Neanderthals faced the risk of extinction. These led to modifications of the gastrointestinal tract, significantly reducing the length of the colon: from 60% of the total length (as observed in frugivores) to 20% – a figure just 5% higher than that of carnivores [2]. The energy saved by shortening the colon allowed the modification of the brain. Despite their considerable size, Neanderthal brains were not particularly high-performing. *Homo Sapiens* brains developed relatively larger frontal and parietal lobes, as well as a larger cerebellum – areas closely linked to social communication, the innovation of complex tools, and abstract thought.

While on the one hand the higher energy consumption of a more high-performing brain increased the risk of extinction, on the other, it made it possible to find effective solutions for survival, such as reducing the energy used for temperature regulation by inventing blankets and clothing, and by learning to manage fire. It reduced a large, highly energy-consuming

intestinal fermentation system by targeting saturated fats instead of indigestible fibers. It also developed the gallbladder to make bile salts quickly available. An unscientific war on saturated fats diminished the digestive system's protective strength, compounded by industrial processes that made food harder to digest. Food that has not been rendered safe reaches the colon and fuels an inflammatory response that risks becoming chronic and low-grade. In this type of inflammatory response, we produce unable anti-inflammatory cytokines instead of able ones. Through these cytokines, the microbiota repairs tissues and controls the functioning of all organs. We produce these functional cytokines only if the gut microbiota is characterized by high biodiversity. Microbiota biodiversity increases after birth – during weaning – in response to food. The digestive system is like a muscle; to keep it strong, I have to nourish it and take it to the gym. You need to fuel it with easily accessible fats – like those found in butter and cheese – and then use “difficult” foods, much like heavy barbells in weightlifting. If, by maintaining a robust digestive system, we provide the microbiota with a comfortable environment, it can increase its biodiversity and express up to 9 million gene units – compared to our own 20,000 (similar to those of insects) – thereby keeping us healthy for its own benefit, given that our cellular body serves merely as its living space [3]. Years ago, someone defined food as the best medicine; recent studies confirm this.

REFERENCES

- [1] Depoortere I. Taste receptors of the gut: emerging roles in health and disease. *Gut*. 2014;63(1):179-90.
- [2] Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, Yáñez-Sepúlveda R, Rubio-Zarapuz A, Martín-Rodríguez A, Navarro-Jimenez E, Tornero-Aguilera JF. Human Digestive Physiology and Evolutionary Diet: A Metabolomic Perspective on Carnivorous and Scavenger Adaptations. *Metabolites*. 2025;15(7):453.
- [3] Mainardi P, Carta P, Mainardi M, Striano P. How Knowledge on Microbiota may be Helpful to Establish an Optimal Diet for Health Maintenance. *Int J Nutr*. 2018;3(2):6-12.

LECT 10

CARDIOTWIN: A PATIENT-SPECIFIC CARDIOVASCULAR DIGITAL TWIN FOR THE PREDICTION AND PREVENTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY

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Anthracyclines, including doxorubicin, epirubicin, daunorubicin, and idarubicin, remain essential components of chemotherapy regimens across pediatric and adult oncology. Despite their therapeutic efficacy, their clinical use is limited by cumulative, potentially irreversible type I cardiotoxicity, which may lead to left ventricular dysfunction and heart failure [1]. Current cardio-oncology strategies rely predominantly on serial monitoring and the detection of cardiac injury after it has occurred, highlighting the need for predictive approaches capable of identifying patients at risk before clinically relevant myocardial damage develops.

CardioTwin proposes a patient-specific cardiovascular digital twin designed to predict individual susceptibility to anthracycline-induced cardiotoxicity and support personalized cardio-oncology management. The initial model will integrate clinically accessible longitudinal data, including electrocardiography, echocardiography, cardiac biomarkers such as troponin and NT-proBNP, clinical and hemodynamic parameters, and medical history. The framework is designed to potentially accommodate genomic and transcriptomic information as additional layers of personalization, enabling the identification of molecular determinants and genetic variants underlying patient-specific susceptibility to anthracycline-induced cardiac injury.

To train, calibrate, and validate the computational architecture of CardioTwin, the framework

will leverage the comprehensive, real-world clinical database MIMIC-IV [2]. By inferring patient-specific parameters from routine clinical measurements, CardioTwin overcomes the computational limitations of conventional mechanistic models to perform rapid *in silico* stress testing: AI and surrogate modelling approaches, such as physics-informed neural networks, variational autoencoders, and Bayesian emulators, will be employed to enable efficient model inversion and patient-specific parameter estimation [3]. This allows the platform to forecast dynamic cardiovascular responses to chemotherapy and predict critical endpoints, including QTc prolongation, arrhythmogenesis, and subclinical decline in ejection fraction and global longitudinal strain prior to the onset of overt cardiac damage. Ultimately, by identifying vulnerable patients early, CardioTwin supports proactive cardioprotective strategies and tailored monitoring, establishing a progressive precision-medicine framework for cardio-oncology.

REFERENCES

- [1] Neufeldt D, Cushman S, Bär C, Thum T. Circular RNAs at the intersection of cancer and heart disease: potential therapeutic targets in cardio-oncology. *Cardiovasc Res.* 2023;119(7):1495-508.
- [2] Johnson A, Bulgarelli L, Pollard T, Gow B, Moody B, Horng S, Celi LA, Mark R. MIMIC-IV (version 3.1). Available at: <https://physionet.org/content/mimiciv/3.1/>, date of publication: October 2024, last access: September 2026.
- [3] Passini E, Zhou X, Trovato C, Britton OJ, Bueno-Orovio A, Rodriguez B. The virtual assay software for human *in silico* drug trials to augment drug cardiac testing. *J Comput Sci.* 2021;52:101202.