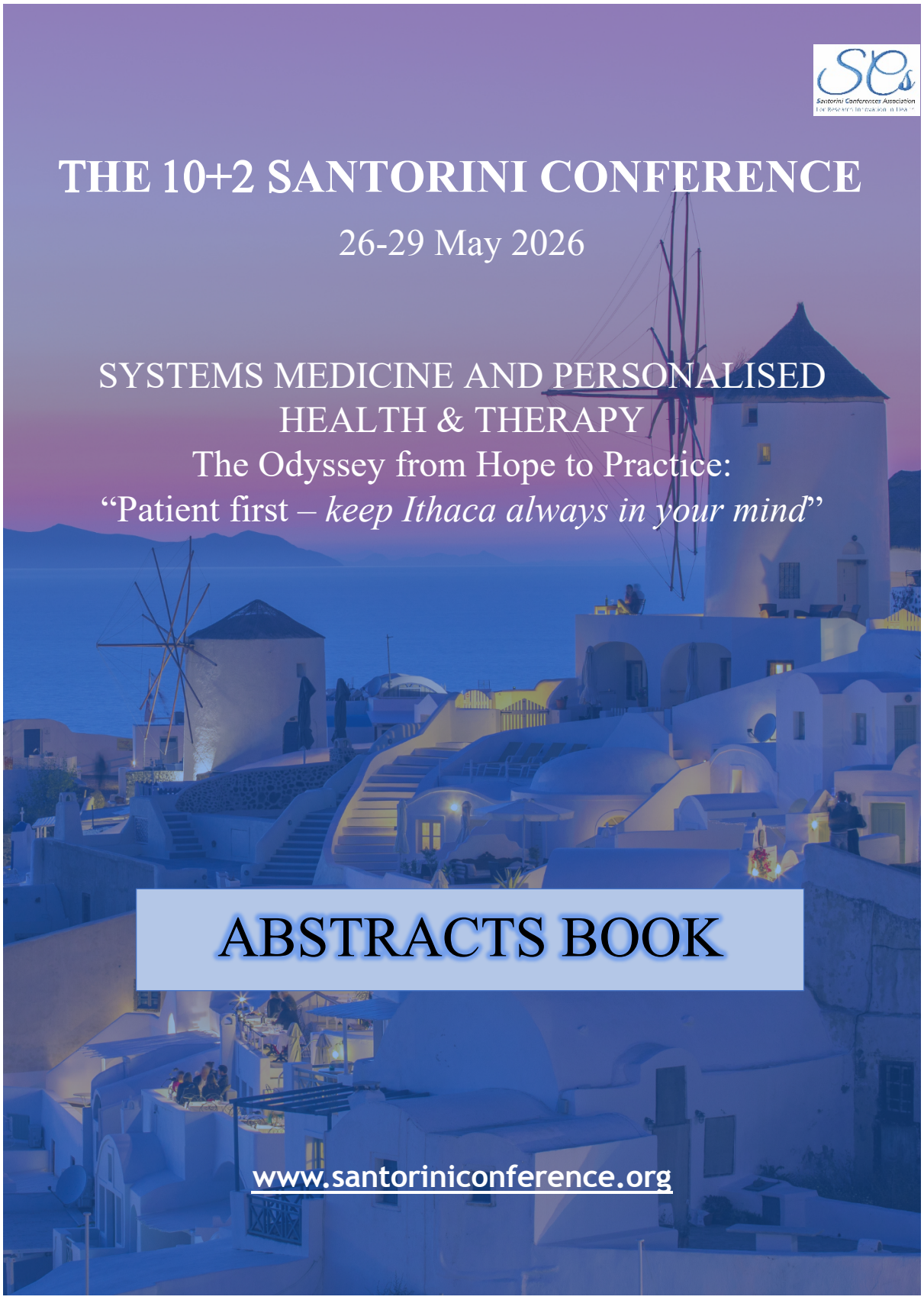

THE 10+2 SANTORINI CONFERENCE

26-29 May 2026

SYSTEMS MEDICINE AND PERSONALISED HEALTH & THERAPY

The Odyssey from Hope to Practice:

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ABSTRACTS BOOK

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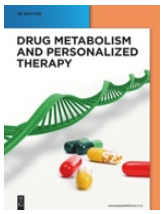

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TUESDAY 26 MAY 2026

WELCOME

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KEYNOTE LECTURE

Chair: Sofia Siest*, Bernécourt, France*

Unlocking Personalised Medicine in Obesity

Philippe Froguel, MD, PhD
Imperial College London, p.froguel@imperial.ac.uk.

More than 1 billion people worldwide have obesity, including 150 million children. Obesity is a complex, multifactorial condition with a strong genetic basis, encompassing both monogenic, oligogenic and polygenic contributions. Since the discovery of leptin, more than 85 forms of monogenic conditions have been identified, where early-onset obesity with impaired appetite regulation is the prominent phenotype, but usually associated with neuro developmental (and other) phenotypes which makes monogenic obesity mostly syndromic. Genome-wide association studies (GWAS) have identified over 1,000 loci associated with weight variation and with common forms of obesity. Most of these genes are expressed in the brain, and many are related to the reward and addiction circuities. While polygenic risk scores can predict risk (or protection) for incident obesity, lifestyle factors such as physical activity can partly mitigate this risk. A continuum exists between monogenic and polygenic obesity, likely including intermediate oligogenic forms. Innovative therapies, such as melanocortin 4 receptor (MC4R) agonists, and the incretins-receptors agonists that are anti-addictive drugs, are paving the way for precision medicine approaches. These advancements offer new opportunities to tailor prevention and treatments to the underlying genetic causes of obesity. Therefore, unlocking real-world personalized prevention and care of obesity and co-morbidities is both an opportunity and a challenge of these times.

PLENARY LECTURE

***Chair: Sofia Siest**, Bernécourt, France*

Green Labs for improving environmental sustainability. What are the Priorities of Medical Laboratories in switching to Green and Sustainable Labs?

Tomris Ozben
EuSpLM;
IFCC, President;
EFLM, Past-President;
Akdeniz University, Medical Faculty, Dept. of Medical Biochemistry, Antalya Turkiye**;**
University of Modena and Reggio Emilia, Medical Faculty, Clinical and Experimental Medicine, Ph.D. Program, Modena, Italy.

Laboratory medicine should contribute to a sustainable healthcare system ensuring that resources are used efficiently from ecological, social, and economical perspectives, while providing high-quality services to patients and physicians. It will be a challenge for clinical laboratories to achieve sustainable operations. Clinical laboratories use more energy and water than offices and generate huge amounts of hazardous and non-hazardous wastes every year. Clinical laboratories can limit their environmental impact and provide sustainable laboratory services making reductions in four key areas—energy consumption, water consumption, waste production, and use of hazardous chemicals. Establishing sustainable development goals and applying multiple means for reductions in these key areas, clinical laboratories can reduce their environmental impact. By being mindful of the environmental impact of everyday actions in a lab, and by taking steps to minimize energy, water, and hazardous chemical use, as well as waste generation, a clinical lab can be transformed into a safe, sustainable space. Sustainability measures should be a key feature in the rapidly changing healthcare environment to reduce their negative impacts on the environment and economy. Laboratory medicine community should lead the shift to carbon neutrality by decreasing their deleterious environmental impact and implementing efficient approaches to address the effects of climate change and pollution without compromising the quality of healthcare. To provide high-quality, effective, and safe healthcare services, sustainable healthcare systems need to overcome major economic and social challenges. Though there will be initial capital costs, there is a long-term cost-saving potential of a more efficient use of energy and other resources in healthcare systems. Despite this, there is a long way to go for environment-friendly hospitals, healthcare structures, and clinical laboratories to become the norm. Good collaboration among the healthcare systems and a common vision for future actions would help to achieve such goals.

INTRODUCTION TO THE CONFERENCE

Sofia Siest*, Bernécourt, France*

SESSION I – Hot topics in PGx

***Chairs: Mark Ruddock**, Antrim, United Kingdom / **Alexander Haushofer**, Salzburg, Austria*

Pharmacogenomics Implementation in Public Health Care: MedeA Initiative

Adrián Llerena
Pharmacogenetics and Personalized Medicine Unit, INUBE Extremadura Biosanitary Research Institute, Spain.

The Clinical Implementation of Personalized Medicine in Health Services Project (Applied Personalized Medicine-MedeA-) consists of a healthcare innovation program that has sought the involvement of private companies in its development through the use of Innovative Public Procurement (IPP). The innovation was to promote personalized drug prescription. The innovation is that, in addition to genetic analysis, other data must be integrated (personal and family history of response to drugs, information on environmental factors, other analytical data, etc.). This set of information should be used to generate ICT support tools that enable decision-making in individual drug prescription. The project has developed a Personalized Prescription System for the Extremadura Health System. In summary: MEDEA is a patient-centered Personalized or Precision Medicine project

that uses genetic information along with other relevant information to optimize prescribing in real-world conditions. In order to validate the implementation and determine genetically related adverse drug reactions, 8,100 patients have been clinically evaluated, and the results will be presented at the event.

Pharmacogenetics: Future Solution or Overstated Promise? A Critical View on the Current Situation

Alexander C. Haushofer
Medilab Dr. Mustafa, Dr. Richter Labor für medizinisch-chemische und mikrobiologische Diagnostik GmbH, 5020 Salzburg, Austria.

Pharmacotherapy is far more complex than can be adequately managed by pharmacogenetics (PGx) or pharmacogenomics alone. Factors such as absorption, protein binding, tissue distribution, and pharmacokinetics significantly influence therapeutic outcomes and may outweigh the impact of genetic variation. Currently, broadly applicable clinical decision-support tools to optimize individualized patient therapy are lacking for clinicians. PGx must still establish a stronger connection to clinical practice and, where possible, the expected effects should be confirmed individually with functional tests. At the same time, it is essential to clearly define the limitations of PGx. At present, PGx is often driven by commercial interests. After considerable expense, patients are sometimes given unrealistic expectations of avoiding adverse drug reactions and consistently achieving optimal therapeutic efficacy. This perspective ignores the fact that robust clinical evidence for PGx-guided therapy exists only for a limited number of drugs. Instead, research and debate frequently focus on individual polymorphisms for which clinical evidence is weak or absent. After decades a connection between specialists in PGx diagnostics and clinicians must be finally established! Some personal data are presented showing discrepancies between PGx results (standardized interpretation of metabolizer status) and functional assays.

Challenges and Considerations in Implementing Personalized Medicine

Ferrier Le
R&D, Genetic Sciences Group Thermo Fisher Scientific, Santa Clara, United States.

Personalized medicine continues to evolve rapidly, supported by advances in genomics, multi-omics, and emerging diagnostic technologies. While its potential impact on patient care is widely recognized, translating these advances into routine clinical and translational practice remains complex. This presentation will reflect on current challenges and emerging considerations in implementing personalized medicine. The talk will also consider how implementation approaches can support broader accessibility, with the goal of ensuring that personalized medicine delivers meaningful benefit more widely across healthcare systems.

WEDNESDAY 27 MAY 2026

SESSION II – New biomarkers/approaches in disease stratification and therapy to be taken into account in pharmacogenomics?
***Chairs: Helena Murray**, Antrim, United Kingdom / **Behrooz Alizadeh**, Gröningen, The Netherlands*

Trauma preconditioning of cytokine response: comparison of perioperative cytokine profiles in elective cardiac versus orthopaedic trauma surgery patients

William T. McBride[1], Allister Irvine[2], Mary Jo Kurth[2], Joanne Watt[2], Gavin McLean[1], John V. Lamont[2], Peter Fitzgerald[2], and **Mark W. Ruddock**[2]
[1]Department of Cardiac Anaesthesia, Belfast Health & Social Care Trust, 274 Grosvenor Road, Belfast BT12 6BA, Northern Ireland, UK;

[2]Randox Laboratories Ltd, Clinical Studies Group, 55 Diamond Road, Crumlin, County Antrim 11 BT29 4QY, Northern Ireland, UK.

Acute kidney injury (AKI) is a sudden decline in kidney function that poses a significant risk to patients undergoing surgery. Those who develop AKI face higher morbidity and mortality rates, extended hospital stays, and an increased risk of progressing to chronic kidney disease. Previously, we recruited two distinct patient cohorts, one undergoing elective cardiac surgery and one undergoing orthopaedic fracture surgery to investigate biomarkers involved in the pathophysiology of AKI. This study is a retrospective analysis of data from the two surgical cohorts to examine if there are any similarities between cytokine responses. Methods : Pre- and post-operative blood and urine biomarker data from elective cardiac surgery patients (n=401) and orthopaedic fracture surgery patients (n=237) were analysed to compare baseline, ratio, and delta change differences. Results: Pre-operatively, baseline levels of most biomarkers were significantly higher in orthopaedic fracture patients compared to elective cardiac surgery patients. Post-operatively, most biomarker levels remained significantly higher in orthopaedic fracture surgery patients with the exception of urinary anti-inflammatory biomarkers which were higher in cardiac patients. Preoperatively, renally favourable biomarker ratios were significantly higher in orthopaedic fracture surgery patients compared to elective cardiac surgery patients. In contrast, post operatively, renally favourable biomarker ratios were significantly higher in elective cardiac surgery patients. The delta differences between pre- and post-operative biomarker levels were generally higher in the elective cardiac surgery patients compared with orthopaedic fracture surgery patients. Discussion : In this study, in patients which have experienced a fracture, the trauma of the initial injury activated their pro- and anti-inflammatory cytokine responses such that renally favourable ratios prevailed pre-operatively. The further pro-inflammatory response from fracture repair (during surgery) was compensated by an already established anti-inflammatory perioperative response, suggesting that post-operative compensatory anti-inflammatory responses do not need to be of the same magnitude compared to a non-preconditioned (e.g. elective cardiac) response.

Pharmacogenomics of Sickle Cell Disease Therapeutics

Ioannis Papassotiriou
First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece.

Sickle cell disease (SCD) is the first disease whose genetic etiology was defined, and is one of the most common severe monogenic diseases in humans. SCD refers to a group of recessively inherited blood disorders characterized by the predominance of sickle hemoglobin (HbS), the result of a single nucleotide change in the structural gene for the beta unit of hemoglobin, causing sickling of red blood cells (RBCs) under hypoxic conditions, vaso-occlusion and adherence to other cells and endothelium, and downstream cellular and organ damage, ultimately resulting in higher morbidity and mortality relative to healthy people.
Data are emerging with pharmacogenomics (PGx) associations for therapeutics for patients with sickle cell disease, specifically with regard to hydroxyurea. Although early data suggest PGx associations with hydroxyurea, these have not yet resulted in clinical guidelines for use in guided therapy. Aside from disease-modifying therapy, patients with SCD receive many drugs for supportive care to manage symptoms such as pain, anticoagulation and iron chelation. Mental health issues are also very common, with the prevalence of depression estimated to be between 25% and 40%. The nature of SCD as a chronic disease results in high healthcare utilization and exposure to multiple drugs and drug classes over a patient's lifespan.
Furthermore, metabolic profiling differentiated SCD from healthy controls and patients with various genotypes. Associations with hemolysis, vaso-occlusive events, nephropathy, pulmonary hypertension, and mortality were identified, thus making metabolomics the most promising "omics" related to the SCD. Although several studies reported metabolic effects of hydroxyurea, transfusion therapy, and mitapivat, other therapies such as L-glutamine, crizanlizumab, and other curative treatments or drugs remain underexplored. Therapy adherence complicates the interpretation of treatment effects on the metabolome. This issue is specifically relevant for hydroxyurea, in which poor adherence is a well-known phenomenon. Metabolomics-based assessment of hydroxyurea exposure,

as already done for mitapivat, could reduce confounding factors, improve treatment predictions, and optimize disease management in SCD. While most studies compared metabolic profiles between treated and untreated patients, future research should also focus on understanding individual treatment responses to support personalizing treatment strategies. It seems that in SCD significant effort has gone into attempting to define a composite measure of sickle cell severity, which can be used to compare changes in either individual or panels of biomarkers.
As there has been no consensus in the field on a composite definition of sickle severity, it is likely that each clinical manifestation will have its own set of non-overlapping biomarkers, in addition to those that are in common. The former will be of greater interest for predicting severity and guiding appropriate therapeutic approaches or precision medicine.

Current approaches to multi-morbidity: A multidisciplinary task for Precision Medicine

Behrooz Alizadeh
Section of Clinical Epidemiology, Department of Epidemiology, University Medical Center Groningen; University of Groningen, Gröningen, The Netherlands.

Multi-morbidity—the coexistence of multiple chronic conditions—poses a major challenge for healthcare systems organized around single diseases. Traditional approaches fail to capture the complex interactions among diseases, resulting in fragmented care and polypharmacy. Evidence shows that multi-morbidity arises from intertwined biological, behavioral, and social mechanisms—including genetic susceptibility, shared inflammatory pathways, and lifestyle factors. Conditions as varied as mental health disorders, inflammatory diseases, and dermatological illnesses exhibit extensive comorbidity, reflecting the networked nature of disease processes. Modifiable factors like smoking, stress, and sedentary behavior contribute substantially to risk, while familial vulnerability highlights shared biological predispositions. Addressing this complexity requires a shift from disease-centered management to patient-centered, mechanism-informed care. My central argument is that precision medicine offers a transformative framework. By integrating multidimensional patient data—genomics, multi-omics, clinical phenotypes, lifestyle, and environment—with advances in artificial intelligence and systems biology, we can achieve three critical goals: First, identify shared disease pathways linking different conditions. Second, predict individual risk trajectories. Third, design individualized treatment strategies targeting the patient's unique disease network. This approach enables a shift from reactive, fragmented care to proactive, coordinated interventions—ultimately improving outcomes and quality of life for people struggling with multi-morbidity.

Contribution of Rare Variants in Identifying New Therapeutic Targets

Amélie Bonnefond
CNRS/INSERM UMR8199-1283, Univ Lille, CHU of Lille, Lille Pasteur Institute, France.

Diabetes ranks among the leading causes of mortality and disability worldwide, with a significant economic burden that affects healthcare systems globally. In this presentation, I will focus on type 2 diabetes (T2D), which accounts for approximately 90-95% of all diabetes cases. T2D is characterized by a progressive decline in insulin secretion often coupled with insulin resistance and metabolic syndrome. While lifestyle factors such as obesity and physical inactivity are well-known contributors, research over the past 25 years has demonstrated that T2D also develops on a genetically predisposed background, as indicated by substantial heritability estimates from family and twin studies (exceeding 40%).
Traditionally, T2D genetics has been viewed through a lens of either monogenic or polygenic causes. However, recent studies have highlighted a more nuanced continuum that includes monogenic, oligogenic, and polygenic factors, each playing a complementary role in T2D pathophysiology. Advances in rare variant research specific to oligogenic T2D are not only enhancing our understanding of disease mechanisms but are also opening avenues for precision medicine that could significantly improve T2D management. To identify these rare oligogenic variants, researchers have employed two main strategies: (i) targeted sequencing of specific candidate genes combined with functional genetic analysis and (ii) comprehensive whole-exome or whole-genome sequencing to uncover low-frequency variants associated with increased T2D risk.

In my presentation, I will explore several key genes implicated in oligogenic T2D, illustrating how these findings deepen our understanding of T2D mechanisms and reveal new potential targets for drug development.

SESSION III – Molecular advances in therapy using vaccines

***Chairs: Federica Marelli-Berg**, London, United Kingdom / **Tomas Zima**, Prague, Czech Republic*

Covid-19 mRNA vaccines and autoimmunity

Federica Marelli-Berg
William Harvey Research Institute, Barts and The London Faculty of Medicine and Dentistry, Queen Mary University of London, UK.

Infective endocarditis (IE) is a condition most often caused by bacterial infection of a native or prosthetic heart valve, but it can also involve infection of an implanted cardiac device or catheter. IE is more prevalent in lower socioeconomic groups and ethnic minorities, who also have higher rates of complication and lower overall survival. It is increasingly frequent and is associated with an extremely poor clinical outcome (with one-year mortality >30%) which exceeds that of than many common cancers. There are many risk factors described for the development of IE; nevertheless, up to 30–50% of patients with this diagnosis does not have any known risk factor. Therefore, it is likely that immunogenetic influences affect the risk of development and outcomes in IE. Our laboratory has discovered a subset of (cMet+) memory T-cells that are detectable in the peripheral blood of humans and mice and that specifically migrate to the heart during episodes of cardiac inflammation. Unexpectedly - we have detected very high levels of cMet+ memory T-cells in the peripheral blood of patients with IE (n=20), compared to healthy controls but also compared to inflammatory cardiomyopathies in which this subset is known to be significantly raised in the blood. Functionally, these T cells displayed a Th2-like phenotype. Crucially, cMet+ T cells were also found to infiltrate valves of IE patients undergoing surgery. We attempted to assess the specificity of these T cells, but found that, while all the patients examined responded to the recall antigen Tetanus Toxoid, only one patient responded to the cardiac autoantigens tested. The specificity of these T cells therefore remains to be established. In a novel model of periodontitis-induced IE, immunofluorescence microscopy and flow cytometric showed that cMet+ T cells infiltrate the valves of diseased animals, and they can be seen adhering to the endocardial endothelium and in the tissue. Echocardiography showed cardiac alteration consistent with valve damage and the cMet+ T cells produce Th2-type cytokines, like in human IE. Collectively, our data suggest that the host response plays an important role in the development of IE.

Integrating vaccinomics, precision vaccinology, and computational science into TPP-driven vaccine development

Eric Quéméneur
Inserm / Agence de Programmes de Recherche en Santé, Paris, France.

France Vaccins is a large R&D initiative aiming at boosting the vaccine development capacity of French public institutes and hospitals. By bridging the gap between preclinical research and clinical validation, it delivers decisive support to operational response capabilities in the perspective of emerging infectious disease outbreaks. This translation from TRL 4 to 7 is generally considered as a high-risk phase which might require major organizational, operational, and cultural changes, in addition to novel collaborative frames with Industry.
Vaccine development is undergoing a paradigm shift, driven by advances in vaccinomics, precision medicine, and computational sciences. These innovations offer unprecedented opportunities to tailor vaccines to specific populations, enhance immunogenicity, and accelerate the development pipeline. We will discuss how the Target Product Profile (TPP) approach, a strategic framework defining the desired characteristics of a vaccine candidate, can be significantly enriched by integrating these cutting-edge disciplines.
The next-generation of vaccines should not only be effective and safe but also tailored to the needs of global populations, including most vulnerable populations such as older adults or those affected by chronic and immune compromising medical conditions which have borne a disproportionate burden

of morbidity and mortality during outbreak. Characterizing vaccine responses in such populations presents unique challenges due to under-vaccination, sub-optimal vaccine responses, and distinct mechanisms of vaccine-induced protection. Multi-disciplinary strategies and international collaborations would be instrumental for innovative biomarkers, bioassays, and combination regimen in this field.

DIVIRNAM®: A novel sustained-release approach to respiratory viral infections

Nikolaos Drakoulis [1], Annia Tsolakou[1], Panagiotis Xintaropoulos[1], Constantine Chalkias[2], Aikaterini Petsimeri[2], Avgi Christodoulou[1], Garyfalia Poulakou[3], Athanasios Raptis[4], Nikolaos Tsirikos-Karapanos[5]
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[2]En Ygeia Clinic, Athens, Greece;
[3]3rd University Clinic of Internal Medicine, Sotiria Hospital for Respiratory and Thoracic Diseases, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece;
[4]Second Department of Internal Medicine, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece ;
[5]Metron Nutraceuticals, Cleveland, Ohio, USA.

Emerging challenges such as COVID-19 and influenza highlight the need for innovative, safe, and practical interventions that can support both patients and public health systems. The mechanism of action of DIVIRNAM®, a novel patent pending sustained-release formulation combining ammonium chloride with vitamin D, has recently been elucidated and was evaluated in two complementary clinical studies: A randomized double-blind placebo-controlled trial. Patients with mild COVID-19 or influenza who received DIVIRNAM® achieved significantly greater viral load reductions compared to placebo group. In a second 30-day supplementation trial in healthy volunteers, DIVIRNAM® was shown to be safe, well tolerated, and effective in restoring or maintaining vitamin D sufficiency in all participants. Together, these results demonstrate that DIVIRNAM® is not only pharmacologically active but also suitable for longer-term use, positioning it as a promising tool in the management of RNA-viral respiratory infections.

SESSION IV – Clinical Relevance of Liquid Biopsy Circulating Biomarkers: Who, What, Where, When, and Why?

***Chairs: Catherine Panabieres**, Montpellier, France / **Alexander Haushofer**, Wels, Austria*

The biology of metastasis-competent circulating tumor cells in colon and breast cancer

Catherine Alix-Panabières
Faculty of Medicine of Montpellier, France.

Circulating tumor cells (CTCs) represent the invasive fraction of malignant cells that escape the primary tumor and seed distant metastases. In colon and breast cancer, a minority of CTCs possess metastasis-competent traits, driven by dynamic phenotypic plasticity and microenvironmental cues. These cells frequently exhibit hybrid epithelial–mesenchymal states, stem-like features, altered metabolic programs, and immune-escaping capabilities that enable survival in the bloodstream and colonization of secondary niches. Interactions with platelets, neutrophils, and extracellular vesicles further enhance their invasive potential by shielding them from immune surveillance and promoting intravascular arrest and extravasation. Recent genomic and transcriptomic profiling reveals distinct mutational landscapes and signaling dependencies, suggesting tissue-specific molecular routes to dissemination. Understanding the biology of metastasis-competent CTCs and their adaptive traits provides a crucial foundation for the development of precision liquid biopsy strategies and anti-metastatic therapeutics across solid tumors.

Implementation of a Phenotype-Oriented Cardiogenetic Panel for Cardiomyopathies and Arrhythmias in Clinical Practice

Bernhard Strasser
Institute of Laboratory Medicine and Clinical Chemistry, Klinikum Wels-Grieskirchen, Wels, Austria.

Inherited cardiomyopathies and primary arrhythmia syndromes represent a major cause of heart failure and sudden cardiac death across all age groups. While next-generation sequencing enables the parallel analysis of large gene sets, broad testing strategies may generate findings beyond the primary clinical question and complicate interpretation. Therefore, the implementation of focused, phenotype-oriented cardiogenetic testing strategies is of increasing importance in routine care.
This presentation describes the introduction of a cardiogenetic panel based on a phenotype-driven and clinically curated gene selection for cardiomyopathies and arrhythmias in a tertiary care setting. The panel strategy emphasizes genes with well-established relevance for cardiac phenotypes, aiming to maximize clinical validity and diagnostic yield while minimizing incidental findings. Key aspects include panel design, analytical performance requirements, and integration into structured clinical workflows. Practical challenges encountered during implementation, such as variant interpretation, interdisciplinary communication, and embedding genetic results into existing care pathways, are discussed. The presentation demonstrates how a focused cardiogenetic panel can effectively support personalised cardiovascular medicine.

Salivary exosomes as carriers of novel biomarkers in pancreatic cancer

Silvia Rocchiccioli[1], Elisa Ceccherini[1], Antonio Morlando[1], Lucia Piazza[1,2], Rossella Mosca[2], Annalisa Comandatore[3], Luca Morelli[3], Giovanni Signore [1,2]
[1] Institute of Clinical Physiology, CNR, Pisa, Italy;
[2] Biochemistry Unit, Department of Biology, University of Pisa, Pisa, Italy;
[3] General Surgery Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy.

Pancreatic ductal adenocarcinoma cancer (PDAC) is an aggressive malignancy with a 3-year survival rate of 1%. Symptoms only manifest in advanced stages and tardive diagnosis significantly impact on the outcome. Discovery of biomarkers for early detection of PDAC remains a significant challenge. Liquid biopsies such as saliva offer further advantages including easy-collection and non-invasiveness. Exosomes carry a panel of factors that represent the molecular fingerprint of the source cells. This study aims at detecting biomarkers in the saliva of PDAC patients through a novel method for the high-quality collection and omics analyses.
Saliva of PDAC patients and healthy donors was collected and processed through an innovative, patented filtering device (Patent Number 102023000023502). Purified exosomes were characterized by transmission electron microscopy, dynamic light scattering and western blotting. Bottom-up proteomics analysis of exosomal constituents were performed to identify potential cancer biomarkers. Collected exosomes show a small variety in size and low grade of impurity. Proteins identified by proteomic analysis include classic exosomal biomarkers (CD9 tetraspanin), biomarkes primarily linked to salivary exosomes (DPP IV/CD26), and other 24 proteins already found in exosomes according to ExoCarta database. 12 proteins were found differentially expressed (5 upregulated, 7 downregulated, $p<0.05$) in PDAC vs. control samples. A functional analysis of identified Exocarta proteins performed with WikiPathways associates 6 proteins to PDAC-related pathways.
Proteomics analysis of ultra-purified saliva-derived exosomes provides a powerful strategy for the identification of potential PDAC biomarkers with intriguing translational potential.

Liquid biopsy-based detection and characterization of minimal residual disease in solid tumor patients: A new window of opportunity for post-adjuvant therapy

Klaus Pantel
Institute of Tumor Biology, University Cancer Center Hamburg, University Medical Center Hamburg Eppendorf, Hamburg, Germany, pantel@uke.de.

Liquid Biopsy has been defined as the analysis of tumor cells or products released from primary or metastatic tumor tissues into the blood or other body fluids. Over the past ten years, CTCs, ctDNA and

extracellular vesicles have received enormous attention as new biomarkers and subject of translational research (Alix-Panabieres & Pantel, Cancer Cell and Cancer Discovery 2025). In particular, CTC and ctDNA research has opened new avenues for a better understanding of tumor biology in cancer patients, including intra-patient heterogeneity and evolution towards resistance to therapy. Although both biomarkers are already used in numerous clinical trials, their clinical utility is still under investigation with first promising results. Clinical applications include early cancer detection, improved cancer staging, early detection of relapse and minimal residual disease (MRD), real-time monitoring of therapeutic efficacy and detection of therapeutic targets and resistance mechanisms. In particular, ultrasensitive ctDNA and CTC assays are now able to detect minute amounts of tumor signals in the blood of patients with completely resected solid tumors (Pantel & Alix-Panabieres, Nature Rev. Clin. Oncol. 2025), indicating the presence of MRD. This opens a new avenue for interventional clinical studies in the post-adjuvant setting which are aimed to demonstrate which therapy will be able to eradicate or control MRD and thereby prevent overt metastatic relapse. To achieve this important goal, assay harmonization and standardization as conducted by international consortia like the European Liquid Biopsy Society (ELBS; www.elbs.eu) and GUIDE-MRD (www.guidemrd-horizon.eu) are essential. Here, I will discuss the potential and current challenges of liquid biopsy for implementation of MRD diagnostics into precision medicine with emphasis on solid tumors.

SELECTED ABSTRACTS - ORAL COMMUNICATIONS SESSION

***Chairs: Stavroula Kanoni**, London, United Kingdom / **Enrico Iaccino**, Catanzaro, Italy*

Effects of the Mediterranean diet on the prevention and treatment of metabolic syndrome and associated disorders

Vesna Dimitrijevic Sreckovic
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Three decades ago, the Unit for Nutrition and Diabetes Prevention, Institute of Endocrinology, Diabetes and Metabolic Diseases assembled Mediterranean menus rich in complex carbohydrates, dietary fiber, monounsaturated fats and omega-3 polyunsaturated fats, and low in saturated fat. The menus have shown to be of great success in obese individuals and patients with metabolic syndrome, prediabetes, diabetes and other chronic complications.
The effects of the Mediterranean diet are manifested through the beneficial effects of monounsaturated fatty acids of olive oil, omega 3 fatty acids, increased intake of dietary fiber from fruits, vegetables and legumes and reduced intake of saturated fats of animal origin. Olive oil has beneficial effects on regulating blood pressure and lowering cholesterol levels. Omega-3-polyunsaturated fatty acids have anti-inflammatory and antithrombotic effects, lower triglycerides and increase insulin sensitivity. Reducing saturated fatty acids lowers serum lipids and reduces the risk of thrombosis. Fruits, vegetables and legumes are a source of antioxidants, potassium, which regulates blood pressure, folic acid, which has a beneficial effect on homocysteine, soluble fiber, which reduces reduced fat absorption, lowers cholesterol and increases HDL-cholesterol.
Our results show that the Mediterranean diet has a statistically significant effect on body mass index, reduction of obesity, insulin resistance, glycoregulation, lipid status, blood pressure, prevention and treatment of vascular complications, non-alcoholic fatty liver, sexual dysfunction, polycystic ovary syndrome, infertility, depression and cancer.

Integrated pharmacogenetic signature for the prediction of prostatic neoplasms in men with metabolic disorders

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Oncogenic processes are delineated by metabolic dysregulation. Drug likeness is pharmacokinetically tested through the cytochrome P450 (CYP450) enzymatic system, whose genetic aberrations under epigenetic stress could shift male organisms into prostate cancer (PCa) pathways. To predict susceptibility to prostatic neoplasia, focusing on benign prostatic hyperplasia (BPH) and prostate cancer (PCa), based on the pharmacoepigenetic and metabolic profile of Caucasian individuals. Two independent cohorts of 47,389 individuals in total were assessed to find risk associations between CYP450 gene variants and prostatic neoplasia risk. The metabolic profile of the first cohort was evaluated statistically, and frequencies of absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics were calculated. Additionally, pharmacoepigenetic targeting by microRNAs (miRNAs) was predicted. Patients with benign prostatic hyperplasia (BPH) and prostate cancer (PCa) in the first cohort exhibited common cardiometabolic patterns. Drug classes C08CA, C09AA, C09CA, C10AA, and C10AX (cardiovascular system), as well as G04CA and G04CB (genitourinary system), were associated with an increased risk of prostate cancer (PCa), while C03CA and N06AB of the cardiovascular and nervous systems were associated with a low prostate cancer (PCa) risk. The CYP3A4*1B polymorphism emerged as the most significant pharmacogenetic variant linked to PCa susceptibility. miR-200c-3p and miR-27b-3p appear to target CYP3A4, indicating possible epigenetic regulation of prostate cancer (PCa) risk. Metabolomic profiling revealed that 11β-OHT, 2β-OHT, 15β-OHT, 2α-OHT, and 6β-OHT were associated with high risk, while 16α-OHT and 16β-OHT indicated intermediate risk of the disease. Our results suggest a novel integrative molecular signature for prostate cancer susceptibility that combines pharmacogenetic, epigenetic, and metabolomic features. Further studies are warranted to validate its predictive utility.
Acknowledgements: The Authors are grateful to the healthcare personnel of the Panagia Voithia General University Hospital of Patras.

Genetic Variability in Vascular Endothelial Growth Factor A and Risk of Psoriasis

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Psoriasis is a chronic autoimmune disease characterized by epidermal hyperplasia, dermal inflammation and neoangiogenesis. Vascular endothelial growth factor A (*VEGFA*), a key regulator of angiogenesis, is overexpressed in psoriatic skin. Although certain *VEGFA* gene polymorphisms have been associated with autoimmune conditions, their role in psoriasis remains unclear, particularly among Caucasian populations. To investigate the association of three *VEGFA* promoter polymorphisms –rs699947 (−2578 C/A), rs2010963 (+405 G/C) and rs1570360 (-1154 G/A)– with psoriasis susceptibility, age at onset and the Koebner phenomenon in a Southeastern European Caucasian population. A total of 194 psoriasis patients and 476 ethnicity-matched general population controls were genotyped using qPCR and melting curve analysis. Genotypic and allelic distributions were evaluated under five genetic models. Associations were assessed using odds ratios (ORs) with 95% confidence intervals (CIs). The *rs699947* C allele was significantly associated with increased risk of psoriasis (OR = 1.52, p = 0.001), particularly under the additive model. *rs2010963* and *rs1570360* polymorphisms showed no association with disease susceptibility. Within the psoriasis cohort, the *rs699947* C allele and CC genotype, as well as the *rs2010963* CC genotype were more frequent in patients with late-onset disease. However, the A allele and AA genotype of *rs1570360* were more prevalent among patients with early psoriasis onset. Additionally, the *rs2010963* C allele and GC genotype were underrepresented in patients exhibiting the Koebner phenomenon (OR=0.61, $p < 0.05$), suggesting a protective effect. These findings suggest a role for *rs699947* in susceptibility to and age

at onset of psoriasis, and for *rs2010963* and *rs1570360* in age onset and modulating risk for trauma-induced lesion development. These *VEGFA* promoter gene variants may hold potential as molecular biomarkers for genetic risk stratification and personalized management in psoriasis.

Protective Effects of Hydrolyzed Clinoptilolite Zeolite Against Cadmium Toxicity in Human Intestinal Cells

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Heavy metal toxicity is one of the leading causes of carcinogenicity in humans. With the development of more research techniques and the advancement of medicinal sciences, an increasing amount of data proves that various metals are carcinogens or probable carcinogens. Among the metals, cadmium (Cd) is known to be responsible for DNA damage, resistance to apoptosis, degradation of proteins, and deregulation of cell growth that can all play a role in the cancer process. Cadmium is absorbed mainly via inhalation and secondarily via consumption in foods and digestion. Zeolites, are porous crystalline aluminosilicate compounds that have. Been showing great heavy metal attracting and retaining properties even since the age of the Roman Empire. In modern days, zeolite clinoptilolite (the most prominent form of zeolite) has been used pharmaceutically in humans as a detoxifying agent in suspensions or powders that are being consumed orally. Oral consumption of non-water-soluble zeolite suspensions poses the problem of low bioavailability as the largest portion of the suspensions cannot be absorbed by the gastrointestinal (GI) track. In this study, the effects of water-soluble hydrolyzed clinoptilolite zeolite (HCZ), a water solution of water-soluble zeolite clinoptilolite fragments with high bioavailability, were tested on human epithelial small intestinal cells in relationship to cadmium toxicity. In the experiments, HCZ and Cd were subsequently studied together in co-treatment, pre-treatment, or post-treatment protocols, with the viability of the treated cells quantified by using the trypan blue assay. For the co-treatment group the average cell viability difference was at 6% with statistical significance and in the post-treatment group the average cell viability difference was at 12% with statistical significance. The pre-treatment group showed an average cell viability difference that was only 1% with no statistical significance. Taken together, the results indicated that HCZ can positively impact human epithelial small intestinal cells and can yield higher viability under specific toxin exposure circumstances. Based on these results, HCZ could potentially be used to mitigate cadmium toxicity under the appropriate circumstances.

Precision Psychiatry Through Intermediate Phenotypes

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Precision psychiatry seeks to redefine mental disorders through mechanistic, biologically grounded constructs rather than descriptive categories. Guided by the Research Domain Criteria (RDoC) framework, my research behavioral genetics, neuroimaging, and causal inference to uncover pathways linking genomic variation to brain and behavior.

A central focus is on delay discounting (DD), a quantitative measure of intertemporal choice rooted in behavioural economics. Genome-wide and multivariate analyses show that DD has a polygenic architecture with estimated chip-based heritability between 10–20%, and shared genetic influences across executive function, reward sensitivity, and externalizing traits. Polygenic scores for DD predict both substance use and behavioral addiction phenotypes, supporting its role as a transdiagnostic intermediate phenotype that captures shared vulnerability to diverse forms of dysregulated reward behavior. Building on this foundation, we mapped the comorbidity structure of substance use disorders (SUDs) and other psychiatric conditions to the polygenic profiles of intermediate phenotypes such as DD. These analyses reveal that co-occurrence across psychiatric domains reflects

overlapping polygenic liabilities for core regulatory processes rather than disorder-specific mechanisms. Complementary efforts extend toward identifying neural correlates of addiction liability using integrative genetic–neuroimaging approaches, including reverse Mendelian randomization to explore potential causal pathways from genetic risk to brain structure and function.
These efforts collectively demonstrate the potential of intermediate phenotypes as a scaffold for linking genomic architecture, neural circuitry, and behavioral regulation. This research program operationalizes the RDoC vision, translating biologically grounded constructs into empirically testable models that trace how genetic variation shapes neural systems and behavior.

A Multimodal Precision Oncology Framework for Personalized Drug Suitability Scoring

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Background: AML is compromised by therapeutic heterogeneity, where standard chemotherapies often yield suboptimal responses and significant toxicity due to diverse patient genomics and tumor biology.
Objective: We show that a machine learning framework that integrates multi-omics data can accurately predict individual patient drug suitability and identify optimal therapeutic strategies.
Design: Curated a cohort of patients over 10 years with the integration of ex vivo drug sensitivity, clinical annotations, DNA and RNA sequencing. Our machine learning model was trained on this dataset to predict drug suitability using somatic mutations, gene expression, drug representation and clinical features as inputs. We propose a computational framework that leverages the AML cohort to devise and validate machine learning models for predicting drug response in cancer patients. Our approach integrates clinical, genomic, and transcriptomic profiles to engineer unified vector representations of drugs, patients, and their oncogenic pathways. By modeling patient-specific drug-pathway interactions, cellular states and, the framework accurately estimates individual drug response, advancing personalized therapy for AML. Specifically, using contrastive learning, we also model patients and drugs as two modalities and learn embeddings that pull responding pairs together and push non-responding pairs apart, based on their full feature representations.
Results: Our model achieved strong predictive performance for well-characterized drugs, like Venetoclax. Feature importance analysis revealed novel biomarkers and confirmed the significant impact of tumor cell differentiation state on drug susceptibility. The model also successfully stratified patients into distinct risk groups with significantly different clinical outcomes.
Conclusions: The path to personalized AML therapy is clear; the remaining challenge is implementation. Our model provides the clinical decision engine to make this a reality, transforming complex multi-omics data into simple, actionable directives to ensure the right drug is chosen the first time, for every patient.

Risk of malignancy in Thy3 thyroid nodules: a cohort study of 136 patients

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Background: Thy3 cytology represents an indeterminate category with variable reported malignancy rates, often leading to diagnostic hemithyroidectomy. Reported risks differ significantly between centres, making patient counselling challenging.
Objective: To determine the local risk of malignancy in Thy3a and Thy3f thyroid nodules following a change towards a more selective surgical approach.
Design: A retrospective review of all patients undergoing surgery for Thy3 cytology over a 5-year period in a single endocrine surgical unit. Final histology was correlated with pre-operative cytology.
Results: A total of 136 patients underwent surgery for Thy3 nodules. Of these, 109 were Thy3a and 27 Thy3f. Malignancy was confirmed in 19.3% of Thy3a nodules and 44.4% of Thy3f nodules. These rates were notably higher than those quoted in national guidance and varied from published series. The higher malignancy yield coincided with a more selective surgical strategy and careful MDT-based patient selection.

Conclusions: Almost every second patient with Thy3f cytology and one in five with Thy3a cytology were diagnosed with thyroid cancer. Given the marked variation between centres, endocrine units should evaluate their local malignancy rates to better inform patient discussions and surgical decision-making.

Single-Cell Analysis Reveals Regulatory T-Cell Dysfunction in Arrhythmogenic Right Ventricular Cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a severe inherited cardiac disorder characterized by fibrofatty myocardial replacement, ventricular arrhythmias, and a high risk of sudden cardiac death (SCD). It is a leading cause of premature mortality, accounting for up to 20% of SCDs in individuals under 35, 5–15% in young adults across Europe, and nearly one-quarter of exercise-related sudden deaths in athletes. Despite advances in genetics and clinical management, there is no curative therapy, and the mechanisms driving disease progression remain poorly understood. Although ARVC is frequently accompanied by inflammatory episodes resembling myocarditis, the contribution of adaptive immunity to disease onset and progression is unclear.
To address this, we investigated T-cell–mediated immune responses in ARVC patients (genotype-positive, phenotype-positive; G^+P^+), genotype-positive relatives without clinical disease (G^+P^-), and healthy controls. We have recently identified a subpopulation of circulating cardiotropic c-Met^+ memory T cells in ARVC patients, also present in the myocardium, with autoimmune specificities. c-Met^+ T cells were similarly observed in the circulation and hearts of mice carrying a pathogenic Desmoglein-2 mutation. Flow cytometry and functional assays revealed increased circulating c-Met^+ cardiotropic T cells mainly in G^+P^+ compare to G^+P^- individuals.
We discovered that regulatory T cells (Tregs), although present at similar frequencies across groups, exhibited reduced expression of key suppressive and activation markers in G^+P^+ patients, indicating functional impairment. Importantly, individuals with higher proportions of activated cardiotropic Tregs showed milder electrical abnormalities, suggesting a protective role. To define the mechanisms underlying Treg dysfunction, we isolated circulating Tregs and performed single-cell RNA sequencing, revealing distinct subpopulations in ARVC patients with altered metabolic programs and acquisition of pro-inflammatory features.
Together, these findings indicate that cardiac autoimmunity emerges in gene carriers before overt disease, while progression to clinical ARVC is associated with loss of effective immune regulation. Dysfunctional Tregs may therefore contribute to disease progression and represent a novel target for immunomodulatory therapy, highlighting the potential for precision immunological interventions in ARVC.

THURSDAY 28 MAY 2026

SESSION V – Functional tests, reference values, danger in popularisation, AI and pharmacogenomics

***Chairs: Khosrow Adeli**, Toronto, Ontario / **Alexander Haushofer**, Salzburg, Austria*

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PGx and functional markers in antiaggregating and anticoagulation therapies – Everything clear?

Alexander C. Haushofer
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Pharmacogenetics (PGx) and functional biomarkers are emerging as key tools to individualize antiplatelet and anticoagulant therapy, aiming to balance thrombotic risk against bleeding complications. In antiplatelet therapy, CYP2C19 variants are well established for clopidogrel. However, there are no robust PGx data for prasugrel, which is also a prodrug but provides more consistent platelet inhibition, or for ticagrelor, for which no evidence supporting PGx-guided therapy has been published or seems to be necessary until now because of very good antiaggregating effect. Platelet function testing (e.g., light transmission aggregometry, VerifyNow, Multiplate) helps to identify high on-treatment platelet reactivity and low responders, providing a functional correlate to PGx profiles, especially in clopidogrel therapy. In anticoagulation, VKORC1 and CYP2C9 polymorphisms significantly affect warfarin sensitivity and dose requirements, due to the high risk of bleeding complications at therapy initiation. For phenprocoumon (Marcoumar©, 4-hydroxycoumarin derivate), PGx analysis is not commonly established because of its delayed onset of anticoagulant effect. For direct oral anticoagulants (FIIa and FXa inhibitors), variants in genes related to drug transport and metabolism may modulate drug exposure. Global coagulation assays and specific activity measurements (e.g., anti-Xa levels, thrombin generation tests) offer complementary information on the achieved anticoagulant effect. In the future, integrating PGx data with functional markers may enable more precise patient stratification, optimized drug and dose selection, and dynamic therapy adjustment. However, implementation in routine care is still limited by heterogeneous evidence, variable assay standardization, cost, turnaround time, and uncertainty regarding which combinations of genetic and functional tests offer the greatest clinical utility. This review provides a brief overview of PGx variants and functional markers relevant to antiplatelet therapy, as well as a short summary of guidance for anticoagulant therapies.

Clinical Applications of Cardiac Markers in Pediatrics

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The clinical use of common cardiac biomarkers, such as brain natriuretic peptides and troponins, has traditionally been limited to adult populations in the assessment of heart failure and acute coronary syndrome, respectively. While many have discounted the value of these markers in pediatric populations, emerging evidence suggests they may be useful in the diagnosis and prognostication of many cardiac and noncardiac pathologies in neonates, children, and adolescents, and an increasing number of pediatric hospitals are routinely measuring cardiac markers in their clinical practice. In this presentation, I will summarize and critically evaluate the current literature regarding the application of cardiac biomarkers for clinical decision-making in the pediatric population. Main potential clinical indications to be discussed include primary cardiac disease, immune-related conditions, and

noncardiac disease. Important diagnostic and interpretative challenges will also be described in relation to each potential indication. Despite a general lack of clinical awareness regarding the value of cardiac biomarkers in pediatrics, there is increasing literature to support their application in various contexts. Cardiac biomarkers should be considered an undervalued resource in the pediatric population with potential value in the diagnosis and prognosis of myocarditis, congenital heart disease, and heart failure, as well as in the assessment of severity and cardiac involvement in immune-related and other systemic conditions. While interpretation remains challenging in pediatrics due to the age- and sex-specific dynamics occurring throughout growth and development, this should not prevent their application. Future research should focus on defining evidence-based cut-offs for specific indications using the most up-to-date assays.

Decoding lipoprotein (a): lessons of the past and prospects for the future

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Lipoprotein (a) (Lp(a)) is low-density lipoprotein-like particle contains an additional apolipoprotein(a) component, a highly polymorphic glycoprotein structurally homologous to plasminogen. Apo(a) exhibits significant sequence homology with plasminogen, particularly in its kringle IV, kringle V, and protease-like regions. Consequently, Lp(a) particles exhibit considerable heterogeneity in size and density, as copy-number variations in the kringle IV2 region of the LPA gene result in apo(a) proteins with varying numbers of kringle units, while maintaining an identical primary sequence. It is genetically inherited, with marked interindividual and ethnic variability and minimally influenced by lifestyle or environmental factors. It promotes atherosclerosis, triggers vascular inflammation, and increases the risk of thrombosis. Lp(a) is a key risk factor for atherosclerotic cardiovascular disease, aortic valve disease, but not for venous thrombosis. Lp(a) facilitates retention of apolipoprotein B particles, delivers pro-inflammatory oxidized phosholipids, drives endothelial cells, smooth muscle cells, and monocyte activation, contributes to microcalcifications, and is causally linked to MACE in both, primary and secondary prevention. About 20% of the general population has a high Lp(a) concentration, and for these individuals, it represents a very significant risk factor. Most relevant societies, including the ACC, AHA, ESC/EAS, Canadian Cardiovascular Society, Endocrine Society, etc. recommend that Lp(a) should be measured at least once in lifetime, preferably in nmol/L, for comprehensive cardiovascular risk assessment. For individuals with high Lp(a) concentrations, it is recommended to incorporate it into the overall risk assessment and accordingly manage other risk factors. With the emergence of new Lp(a)-lowering therapies (antisense oligonucleotides, small interfering ribonucleic acid agents) that significantly reduce circulating Lp(a) levels, and renewed optimism for targeted intervention and improved cardiovascular outcomes.

Cancer screening programmes

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The primary goal of a cancer screening program is early detection of cancer in people who do not have any symptoms of the disease, to improve treatment outcomes and survival rates, or even prevent cancer from developing by finding and treating precancerous lesions.
There are cancer screening programs organized in decades as colorectal cancer (CRC) screening options, including a high-sensitivity fecal immunochemical test (FIT) in Czech Republic with an accuracy of 95%, sensitivity of 79%, and specificity of 94%. Colonoscopy every 10 years or frequently due to findings or family history is the most precise screening method. Prostate cancer screening started a few years ago. This discussion of prostate cancer screening includes the life-expectancy of men and the uncertainties, benefits, and risks associated with serum PSA testing, with or without a digital rectal exam (DRE). Czech screening program scheme combines the levels of PSA and MRI. Widely accepted breast cancer screening modalities include mammography, breast magnetic resonance imaging (MRI), breast ultrasound, and breast self-examinations. Due to breast cancer screening, most cases are diagnosed at stage I, which has a 5-year survival rate of 100%. Cervical cancer screening tests include

the cervical smear, with or without HPV co-testing, and high-risk HPV (hrHPV) testing alone every 5 or 10 years. Lung cancer screening is a new one in risk population using the low-dose lung computed tomography (LDCT).
The CZECANCA panel (CZEch CAncer paNel for Clinical Application) is a diagnostic tool for cancer predisposition and improves germline genetic testing in families with cancer risk. Its main purpose is to provide a reliable and cost-effective NGS-based approach (a gene panel) for germline genetic testing, e.g pancreas, colon, ovary, breast, prostate.
Other screenings in risk populations exist (e.g. calcitonin - families with medullar cancer of the thyroid gland). Ovary cancer markers as CA 125 and HE4 are used in families with risk.
Screening programs lead to reduce mortality and incidence of cancers, mostly demonstrated in breast and colorectal cancers. The information of screening programs into public has a critical role for increasing the effectiveness of these preventive programs.
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Use of a BMI-independent biomarker-based prostate cancer risk score to identify and triage individuals at risk of prostate disease

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Prostate cancer (PCa) is the second most common cause of cancer related deaths in men in the UK. A national screening programme for PCa does not exist due to the unsuitability of the total prostate specific antigen (tPSA) test which is not specific for PCa and has a high false positive rate. Serum tPSA was measured in n = 25,356 male Randox Health clients. A biomarker-based (tPSA, EGF, MCP-1, IL-8) prostate cancer risk score (PCRS) was then applied to a retrospective cohort (n = 1,142/25,356) of individuals to assess PCa risk. A comparative analysis between tPSA and PCRS indicated that 90.5% of the cohort were assigned low risk of PCa. Of those with an elevated PCRS, 67.8% (78/115) had a normal tPSA value based on tPSA age-adjusted cut-offs. In addition, we observed a significant negative correlation between increasing body mass index (BMI) in men with high BMI (≥ 30) and tPSA levels. No correlation was observed between BMI and PCRS. The tPSA test is potentially unsuitable for use in males with BMI ≥ 30. Use of PCRS could provide more accurate PCa risk stratification for males with BMI ≥ 30. Future assessment of the clinical utility of PCRS is warranted.

Pharmacogenetics in Routine Clinical Diagnostics: Updated Experience from the Central Laboratory of the University Hospital of Innsbruck

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Introduction: Pharmacogenetic genotypes play a major role in interindividual variability in drug response, including differences in absorption, metabolism and pharmacodynamics. Consequently, pharmacogenetic testing enables the optimization of drug efficacy while minimizing drug-related toxicity. Although awareness of pharmacogenetics is increasing, its routine application in daily clinical practice has not yet been widely established.
Methods: Since 2012, several pharmacogenetic parameters have been analyzed in the Central Laboratory of the University Hospital of Innsbruck using PCR-based methods. These include *thiopurine methyltransferase* (TPMT), *dihydropyrimidine dehydrogenase* (DPD), *cytochrome P450* (CYP) enzymes

CYP2C19, CYP2C9, CYP3A4/5, and CYP2D6, *UDP-glucuronosyltransferase 1A1* (UGT1A1), and *solute carrier organic anion transporter family member 1B1* (SLCO1B1).
Results: In 2025, the most frequently requested pharmacogenetic parameters were DPD (417 tests, 52%) and TPMT (296 tests, 37%), followed by CYP enzymes (72 tests, 9%), UGT1A1 (14 tests, 2%), and SLCO1B1 (6 tests, 1%). While the number of requests for TPMT, CYP2C9, CYP3A4/5, and SLCO1B1 remained largely stable over the past seven years, marked increases were observed for several parameters. Requests for DPD testing increased substantially from 2019 onward, following guideline recommendations for DPD genotyping prior to fluoropyrimidine dosing. A significant rise in CYP2C19 testing was noted beginning in 2023, coinciding with the approval of mavacamten in the European Union. Similarly, UGT1A1 testing increased from 2022 onward due to growing scientific and clinical awareness of the importance of pharmacogenetic testing prior to treatment with sacituzumab, govitecan and irinotecan.
Conclusion: Pharmacogenetic testing has been successfully implemented in our laboratory. A marked increase in selected tests, particularly DPD, reflects the growing clinical relevance of pharmacogenetics driven by clinical guidelines, regulatory approvals, and therapeutic advances, underscoring its increasing importance in personalized medicine. Although awareness of pharmacogenetic testing is rising, there remains substantial potential for further improvement, and continued education of medical staff is essential.

Comprehensive Pharmacogenomics in Psychiatry: From Metabolic Genes to Pharmacodynamic Targets and HLA Typing

Nicolas Picard
Limoges University Hospital, France.

Pharmacogenomics is evolving toward more complete genomic profiling that encompasses both metabolic and pharmacodynamic pathways, and immune-related determinants of drug response. In this session, Nicolas Picard will share his team's experience with NGS-based PGx testing and new results obtained using the SOPHiA DDM™ Extended PGx Solution. The talk will focus on the extension of panel testing in psychiatric settings and the integration of high-resolution HLA typing into a single, comprehensive PGx workflow, moving beyond traditional marker-based approaches. Through examples from his research and laboratory practice, Prof. Picard will demonstrate how unified analysis and interpretation of a comprehensive set of variants can improve the identification of drug efficacy and hypersensitivity risks, supporting more informed clinical decisions.

SESSION VI – Key progression steps forward pharmacogenomics

Chairs: ***Ron Van Schaik****, Rotterdam, The Netherlands /* ***Jean Christophe Boyer****, Nîmes, France*

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Improving guidelines in pharmacogenomics

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Pharmacogenetics, the field of DNA analysis to improve drug therapy, has seen an exponential increase in the amount of publications in the last 20 years and an increase in clinical implementation in several countries. More markers are identified as potential factors for predicting drug response, starting from classics such as TPMT analysis for 6-mercaptopurine and azathioprine therapy, to reports on genetic polymorphisms in the Cytochrome P450 system, influencing 80% of commonly prescribed drugs. In total, the Dutch Pharmacogenetics Working group now has dosing advices for 60 drugs and 18 genes. With the increase in laboratories offering pharmacogenetic testing, the importance of quality standards and harmonization between laboratories (both on testing as in reporting) becomes important to maintain and enforce the power of pharmacogenetics in the clinical setting. Examples of the AMP, CPIC, DPWG and PharmVar guidelines to enforce this will be discussed.

Retrospective and Prospective Clinical Studies of *DPYD* Pharmacogenetics Within an Institutional Genetics Data Repository

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Background: Pre-treatment genetic testing for validated *DPYD* variants (i.e., *DPYD*2A, DPYD*13, DPYD p.Asp949Val, DPYD HapB3*) reduces severe fluoropyrimidine toxicity. Additional *DPYD* variants, including *DPYD p.Y186C*, have been identified but their association with toxicity has not been demonstrated. Additionally, *DPYD* testing only recently became standard of care in the United States, leaving many patients at risk for preventable toxicity. The objectives of this study were to use the Michigan Genomics Initiative institutional genetic data repository to investigate the association of uncommon *DPYD* polymorphisms with fluoropyrimidine toxicity and demonstrate the feasibility of using existing research-only data to identify *DPYD* variant carriers for confirmatory clinical testing prior to treatment.
Methods: Toxicity data was retrospectively collected from adult patients treated with standard doses of fluoropyrimidines for the retrospective association study. The primary toxicity endpoint was grade ≥3 toxicity or treatment modification due to toxicity in the first two cycles. Uncommon variants were analyzed in aggregate, excluding patients carrying any of the four validated variants. The prospective study used automated electronic medical record screening to identify Michigan Genomics Initiative participants who carried validated *DPYD* variants who were scheduled to receive fluoropyrimidines, to trigger confirmatory clinical testing.
Results: In the retrospective analysis of 799 patients who did not carry a validated variant, carriers of an uncommon variant (1.1% of patients) had significantly higher risk of toxicity than non-carriers (66.7% vs. 23.7%; adjusted odds ratio=7.36; 95% CI 1.75–38.2; p=0.009). The prospective study passively screened 2959 MGI participants who carried a validated *DPYD* variant. A rectal cancer patient planning to start fluoropyrimidine-containing chemotherapy underwent clinical testing that confirmed a *DPYD* c.1129-5923C>G (HapB3) variant and dosing was adjusted based on clinical guidelines.
Conclusions: This study demonstrated that an institutional genetic data repository can be used to identify uncommon *DPYD* variants that increase toxicity risk and identify *DPYD* carriers for clinical testing prior to fluoropyrimidine treatment.

Predicting life-threatening fluoropyrimidine toxicity beyond DPYD testing

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Pharmacodynamics of fluoropyrimidines (FP) potentially depends on polymorphisms of genes related to its catabolism, anabolism, folate pathways, its targets and transporters. Before starting FP-based chemotherapy, the European Medicines Agency (EMA) and the Clinical Pharmacogenetic Implementation Consortium (CPIC) recommend testing of 4 variants of the DPYD gene coding for the dihydropyrimidine dehydrogenase (DPD) enzyme, and subsequent FP dose reduction in variant carriers. However, the literature shows that these 4 DPYD variants are carried by only 7% of Caucasians explaining at best 20-30% of early FP-related severe toxicities. So, to improve current recommendations, FUSAFE2 international consortium aims at identifying a multigenic signature by sequencing the entire DPYD gene, 18 MIR genes, 185 additional pharmacogenes potentially relevant for FP, oxaliplatin, irinotecan and cetuximab pharmacodynamics. While expecting final results on the whole targeted pharmacogenes, we herein present a prediction model for G4-5 toxicities based on clinical covariates and expanded *DPYD* genotype. The online calculator ((https://fluoropyrimidine-toxicity-predictor.gustaveroussy.fr/) subsequently developed allows an estimation of the individual probability of developing severe toxicity. By using this new tool, clinicians could better manage the FP-related severe toxicities in clinical routine.

Democratizing Pharmacogenomics: Bridging NGS, AI, and Clinical Practice

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Pharmacogenomics (PGx) is a cornerstone of precision medicine, yet its clinical adoption is often hindered by the limitations of standard SNP arrays and the complexity of interpreting genetic data for drug response. In this presentation, we introduce the new SeqOne PGx Module, a transformative addition to our GermVar workset designed to unlock the full potential of Next-Generation Sequencing (NGS) data—from Capture panels to WES and WGS.
We will demonstrate how this module moves beyond the "known variant" limitations of SNP arrays by performing accurate Star Allele calling and identifying novel variants of interest. A key focus will be our integration of DiagAI, which allows for the identification of rare or novel deleterious variants (e.g., Loss of Function) in PGx genes that could significantly alter patient metabolism but are missed by traditional screening methods.
Finally, we will showcase our new AI Copilot, powered by an MCP (Model Context Protocol) grounded in ClinPGX guidelines. This feature bridges the gap between complex genomic data and clinical utility, allowing clinicians and pharmacists—regardless of their PGx expertise—to ask natural language questions regarding drug-gene interactions and posology adjustments.

SESSION VII – Personalised Lifestyle as part of Precision Medicine

***Chairs: Guillaume Paré**, Hamilton, Canada / **Nikolaos Drakoulis**, Athens, Greece*

Biobank-scale survey of gene-diet interactions informs precision nutrition polygenic scores

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Genome-guided dietary advice is a goal of precision nutrition. However, the contribution of gene-diet interactions (G×Ds) to disease risk remains unclear, hindering the identification of diet-outcome pairs more likely amenable to genetic-based recommendations. We thus implemented a two-step approach: first, we comprehensively assessed the contributions of genome-wide G×Ds to cardiometabolic outcomes across a broad array of dietary exposures in UK Biobank participants (N = 141,144 to 325,989). Second, we selected the 20 significant diet-outcome pairs from the 713 pairs tested ($p < 7.0\times10^{-5}$) and derived G×D polygenic scores. In an independent sample, all scores were

nominally associated with their corresponding outcomes, with 12 of 20 polygenic scores Bonferroni significant ($p < 0.0025$). Further analyses revealed G×D polygenic scores were associated with clinical outcomes such as incident gout, suggesting translational potential. For instance, each additional alcoholic drink per day was associated with increased odds of gout (OR=23.9% 95% CI 1.11-1.38) in individuals in the highest quintile of the corresponding G×D polygenic score, whereas no significant change was observed in the lowest quintile (OR=4.8% 95% CI 0.91-1.18). Altogether, these results showcase the promise of G×D scores to inform precision nutrition.

Operating today with the standards of tomorrow - the Metron Nutraceuticals state-of-the-art example

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Background: The global dietary supplements market has seen remarkable growth within the last 20 years. Valued approximately at USD 203 billion in 2025, further strong growth for it is projected to USD 400 billion by 2034. Despite its growth, the dietary supplements market suffers from over and under regulation in various segments, the presence of bad players, the dominance of marketing over science, and the resulting exposure of the public to dietary supplements of questionable quality and value. For these reasons the dietary supplements market is -to a certain degree- reasonably seen as the "wild west" by many health care professionals and various regulating organizations, and legislators. Entering into this market with the ambition to provide to the public innovative dietary supplements of excellent quality and value can be challenging, and financially risky.
Methods: Metron Nutraceuticals, a science-based R&D and manufacturing company entered the dietary supplements market with its own-developed and patented formulations in 2015. Since day one, the path followed by Metron was simple: R&D first, followed by extensive testing to confirm safety and efficacy, and finally marketing directed to the highest segment of the market – the licensed health care professionals. Metron's commitment to quality guided every Metron's decision related to production and testing. Just abiding to cGMP standards as set by the FDA for dietary supplements was never Metron's goal; it was only seen as a starting point. A plethora of non-FDA demanded tests were early adopted to ensure safety, including extensive testing for sixty-nine elements for Elemental Impurities testing (in contrast with the FDA-demanded testing for only four metals), additional microbiological testing in more production steps than the FDA-demanded, along with a long list of specific analytical chemistry tests tailored towards precision and accuracy in testing for Identity Composition, Purity, and Strength. After safety was sufficiently documented according to Metron's standards, efficacy was confirmed by the conduction -to the best of our knowledge for the first time in the dietary supplements industry- of complex, in-vitro pharmacokinetics studies, along with careful, detailed post-market follow up with licensed healthcare professionals and the with the conduction of the appropriate Clinical Studies in Academia.
Results: Six major inspections by the FDA and the Ohio Department of Agriculture (ODA) within the last eleven years have been completed with excellent outcomes. Successful completion of Academia-conducted bench and Clinical Studies has documented Metron's effort towards establishing its own, high-quality standards within the dietary supplements industry.
Conclusion: Operating above the FDA cGMP standards for dietary supplements, and for some aspects of production and testing above the FDA standards for pharmaceutical formulations is a path not frequently followed within the dietary supplements industry but provides the best security for longevity to the dietary supplements company that is committed to quality and understands the difference between spending and investing. With a portfolio of sixteen US and International patents, and the experience gained within the last eleven years Metron is looking forward to providing more high-quality, high-value dietary supplements to the global marker to substantially support wellness and healthy aging.

SESSION VIII – Predicting Disease risk – are integrated risk scores clinically useful?

***Chairs: Behrooz Alizadeh**, Gröningen, The Netherlands / **Stavroula Kanoni**, London, United Kingdom*

Development of a multimodal AI framework for precision cardiovascular risk prediction

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Cardiovascular disease (CVD) affects around 14% of adults and is a major global cause of death. It includes conditions such as coronary artery disease (CAD), myocardial infarction, heart failure and stroke, all of which place a substantial burden on healthcare systems. Managing modifiable risk factors (e.g. diet, exercise, smoking) together with early identification of genetic susceptibility (CAD heritability ~40–50%) is crucial, particularly for higher-risk groups such as South Asians.
Current CVD risk tools (QRISK3, SCORE2, PCE) rely on conventional factors and may not fully capture the broader atherogenic profile. Recent work shows that genetic predisposition, summarised through Polygenic Risk Scores (PRS), significantly influences CAD risk. Individuals in the top 10% of CAD-PRS have risk comparable to monogenic conditions like familial hypercholesterolaemia, but predictive power declines outside this group. There is therefore a clear need for AI-driven, multi-modal risk prediction tools that perform reliably across diverse populations.
We have developed an innovative AI-framework, that integrates multi-omics, lifestyle and clinical CVD risk for British South-Asians, with transferability to other ancestral populations. We have leveraged transcriptomic and proteomic data obtained from CVD-free British South Asians, selected from the lower (<10%), middle (45-55%) and upper (>90) deciles of the CAD multi-ancestry PRS distribution of a 52,000 participant-cohort. Employing state-of-the-art Machine Learning (ML) models and AI algorithms, we integrated the PRS with transcriptome signatures, proteomics data, clinical factors, and lifestyle information (diet, smoking, alcohol consumption, physical activity). This comprehensive approach aims to develop a high-precision prediction tool for CVD that outperforms existing models in performance and reliability. We will validate this tool externally in a subset of Middle East ancestry individuals (Qatari Biobank) and other multi-modal worldwide datasets.
This study represents an innovative effort to bridge the existing gap in cardiovascular risk prediction tools by combining clinical, biochemical, multi-omics and lifestyle information through AI implementations.

Proteomics and genomics as risk predictors of cardiometabolic diseases

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Cardiovascular disease (CVD) and type 2 diabetes (T2D) are interconnected chronic conditions, collectively considered cardiometabolic disease, which cause significant morbidity and mortality worldwide. To identify biomarkers for earlier detection and disease prevention, we are developing predictors of cardiometabolic disease endpoints using genomics and proteomics. We develop a Protein Risk Score (ProtRS) for incident disease prediction in the Trøndelag Health Study and FinnGen using targeted measurements from blood plasma. We evaluate the discrimination and calibration of these ProtRSs as novel predictors of disease in addition to polygenic scores and other conventional risk factors. We also characterize the gene ontology biological pathways indicated by the protein associations with CVD and T2D. Finally, we identify genome-wide protein quantitative trait loci (pQTL) for over 7,000 proteins measured on the SomaScan v4.1 assay. We use these to create pQTL-based polygenic scores and evaluate their predictive performance as well. These findings highlight the potential of the plasma proteome in disease risk stratification. Future validation in additional population biobanks will help determine the clinical utility of these protein-based risk predictors.

Predicting Outcomes in Mental Health Disorders: A Lifecourse-Informed, Multidimensional Framework

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Mental Health Disorders, such as Schizophrenia Spectrum Disorders (SSD) show profound heterogeneity in symptoms, cognition, and long-term outcomes, challenging traditional diagnostic frameworks and personalized care. Predicting who will recover, maintain social functioning, or develop chronic disability remains difficult. Drawing on large-scale cohort studies, including the Genetic Risk and Outcome of Psychosis (GROUP) study, this synthesis integrates genetic, developmental, cognitive, and psychosocial factors to map SSD trajectories. Lifecourse influences such as childhood trauma and premorbid adjustment have lasting effects on adult social functioning and quality of life. Psychosocial factors—including perceived stigma and self-esteem—interact dynamically with genetic liability and developmental experiences, shaping long-term outcomes. Polygenic risk scores reveal associations with symptom dimensions and behaviors, highlighting shared biological pathways that cut across traditionally distinct diagnostic categories. Data-driven analyses identify distinct cognitive and symptom subtypes, indicating multiple SSD sub-phenotypes with divergent trajectories. Importantly, early developmental functioning predicts later personal recovery, underscoring the value of early intervention. Together, these findings support a multidimensional, lifecourse-informed framework that enhances prognostic accuracy and guides targeted, mechanism-based interventions tailored to each individual's unique risk and strengths—laying the foundation for precision psychiatry from the earliest stages of illness. This approach reflects a broader shift from disease-centered management toward patient-centered, mechanism-informed care, recognizing that mental disorders do not occur in isolation but arise from intertwined biological, psychological, and social mechanism.

ML approaches for improved T2D risk stratification in the Qatar Biobank

Ammira Akil
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Type 2 diabetes (T2D) represents a significant health concern, particularly in Middle Eastern populations, where its prevalence is exceedingly high. Existing polygenic risk scores (PRS) based on European-derived cohorts show limited effectiveness within these diverse populations. This study aimed to enhance T2D risk stratification through multi-trait polygenic ensemble modeling using data from the Qatar Biobank, comprising over 14,000 participants. We conducted genome-wide association studies on T2D and 11 related metabolic traits, developing population-specific PRS that improved predictive performance, achieving an AUC of 0.85. Stratifying individuals by T2D-PRS revealed a sixfold increase in disease risk among the top decile. This optimization was validated externally in a diverse UK Biobank cohort, demonstrating an AUC of 0.82. Our findings underscore the importance of integrating correlated metabolic traits within ensemble machine-learning frameworks to improve risk prediction and transferability across ancestries. This research highlights the potential of tailored genetic models to enhance clinical strategies for managing T2D in underrepresented populations, paving the way for more effective precision medicine.

Use of "digital twin" simulations in healthcare, example(s) from autoimmune disease

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Type 1 diabetes (T1D) develops gradually before symptoms appear. When it is diagnosed late, people—especially children—may present with life-threatening diabetic ketoacidosis (DKA). With new therapies now able to delay progression, identifying individuals earlier has become increasingly important. Across three recent studies, we examined how best to predict, detect, and monitor early T1D.

We developed a risk prediction model combining genetic risk scores, age, family history, and diabetes-related antibodies. The model performs well across different screening settings but requires recalibration depending on who is screened. To support real-world use, we created an online tool to estimate individual risk and guide follow-up decisions. We also showed that genetic risk scores retain strong discrimination across diverse ancestries on all continents, although population-specific thresholds may improve risk stratification.

Finally, we integrated these findings into a simulation model to evaluate screening strategies that reduce DKA while balancing healthcare costs.

SESSION IX – **Functional genomics, understanding of disease pathophysiology**
***Chairs: Panos Deloukas**, London, United Kingdom / **Silvia Rocchiccioli**, Pisa, Italy*

Identification of regulatory variants in vascular genes causing coronary artery disease

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Genome-wide association studies have identified a plethora of coronary artery disease (CAD) susceptibility loci, the majority located in non-coding regions. Gene prioritisation and enrichment analyses have confirmed well-established pathways such as lipid metabolism and inflammation and added vascular-related pathways to those playing a major role in disease pathogenesis. We have examined the landscape of accessible chromatin in human coronary artery endothelial (HCAEC) and smooth muscle (HCASMC) cells, intersecting these potentially regulatory chromosomal regions with 21,461 CAD-associated variants at the 1% FDR level from 181,522 CAD cases (1,156,690 participants). These prioritised variants (n = 650) were examined using the STARR-seq massively parallel reporter assay (MPRA) to determine variants with allelic effects on reporter expression in vascular endothelial and smooth muscle cells. We also examined the effect of VEGF on allele-specific reporter expression in endothelial cells, due to its dual pro-atherogenic and protective roles in CAD progression. The MPRA assay identified 41 variants showing significant (logFC > 1, $p$adj < 0.05) allele-specific effects on gene expression (16 HUVEC, 17 HCASMC, 22 VEGF+ HUVEC), with many variants sharing functionality between cell types and ±VEGF stimulation. From the 41 significant variants, 16 were located proximal to genes with a known vascular involvement,
including *PODXL*, *FRS2*, *CXCR4*, *SMAD3*, *PDE5A* and *CD151*, regulating angiogenesis, vascular permeability, vascular remodelling and EC/SMC proliferation and migration. For the 25 variants proximal to genes not related to known vascular processes, ongoing work is involved to establish molecular mechanisms relating to CAD pathogenesis.

Integrating Multi-Omics and Biomarkers for Risk Prediction in Diabetes and Cognitive Health

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Type 2 diabetes (T2D) is a biologically heterogeneous disorder associated with variable risks for cognitive decline and cerebrovascular disease. We integrated multi-omics and biomarker data with clinical features to refine T2D subtyping and enhance prediction of neurovascular outcomes relevant to cognitive health. We analyzed 10,842 adults with T2D from two population-based cohorts with linked genomics, plasma proteomics, metabolomics, and neuroimaging data. Latent molecular factors were derived using a multi-omics factor analysis (MOFA+) framework capturing shared biological variation across omics layers. These factors, together with routinely measured clinical variables, were used to derive reproducible T2D subtypes via consensus clustering. Fine–Gray sub-distribution hazard models estimated risks of incident dementia and stroke accounting for death as a competing event, and Cox models assessed mortality. Linear models compared MRI phenotypes across subtypes, and predictive performance was evaluated using time-dependent C-index, calibration, and decision-curve analyses. Three distinct T2D subtypes emerged: mild metabolic diabetes (MMD), obesity–inflammation diabetes (OID), and vascular-aging diabetes (VAD). Compared with MMD, the VAD subtype showed higher risk of all-cause dementia (sub-distribution hazard ratio [SHR] = 1.79, p = 3.1×10^{-5}), vascular dementia (SHR = 2.04, p = 1.2×10^{-3}), and stroke (SHR = 1.55, p = 5.0×10^{-5}), independent of APOE genotype and T2D polygenic risk. Integrating omics data improved 5-year dementia prediction versus clinical-only models (ΔC-index = +0.08, p < 0.001). Multi-omics subtyping delineated biologically distinct T2D phenotypes with differential neurovascular and cognitive trajectories, highlighting vascular, inflammatory, and mitochondrial pathways as key mediators linking diabetes to cognitive health.

Future-Ready T1D Solutions: Bridging genetics and autoantibody testing

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Type 1 Diabetes (T1D) affects more than eight million people worldwide, with numbers projected to rise significantly to over 17 million by 2040. It is caused by an immune-associated destruction of insulin-producing pancreatic β cells in genetically predisposed individuals, leading to insulin deficiency and requirement for exogenous insulin supplement. Typically considered a disease of childhood and adolescence it can however occur at any age. Symptoms include polyuria, polydipsia, and weight loss. Acute complications involve diabetic ketoacidosis, which requires urgent management. Individuals with T1D are also at a higher risk for other autoimmune diseases and psychosocial issues. Correct diagnosis in young people (<20 years) is usually straightforward because it accounts for most cases (>85%) of diabetes in that population. Conversely, identification of T1D in adulthood (>30 years) is challenging due to a much higher prevalence of Type 2 Diabetes (T2D) and rising obesity rates. Clinical diagnosis is often based on poorly discriminatory clinical characteristics and as a result misdiagnosis is common. As such there is a clear unmet clinical need to improve the diagnostic accuracy of this life-threatening condition. As the genetic component of T1D is very pronounced, well characterized and remains unchanged throughout life it offers a means to identify individuals with higher genetic risk by combining analysis of both HLA and non-HLA-associated risk alleles thereby leading to disease prediction prior to symptom onset and aid disease classification. Furthermore, a clinical diagnosis of Stage 1 pre-T1D which can be asymptomatic and precede dysglycemia, can be substantiated by seroconversion of two or more islet autoantibodies (GAD, IA2, IAA, ZnT8) and may allow timely deployment of immune modulating therapies aimed at preserving islet function. Randox has the solution to provide both these testing options through proprietary biochip array technology (BAT) and state of the art instrumentation with the option of high throughput and near-patient testing. This combination of T1D genetics and AA testing has the potential to improve patient care, treatment plans and final outcomes and possibly aid in the introduction of pre-emptive therapies of lifestyle modification and pharmaceutical intervention to reduce T1D progression.

Role of the host response in Infective Endocarditis

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Infective endocarditis (IE) is a condition most often caused by bacterial infection of a native or prosthetic heart valve, but it can also involve infection of an implanted cardiac device or catheter. IE is more prevalent in lower socioeconomic groups and ethnic minorities, who also have higher rates of complication and lower overall survival. It is increasingly frequent and is associated with an extremely poor clinical outcome (with one-year mortality >30%) which exceeds that of than many common cancers. There are many risk factors described for the development of IE; nevertheless, up to 30–50% of patients with this diagnosis does not have any known risk factor. Therefore, it is likely that immunogenetic influences affect the risk of development and outcomes in IE. Our laboratory has discovered a subset of (cMet+) memory T-cells that are detectable in the peripheral blood of humans and mice and that specifically migrate to the heart during episodes of cardiac inflammation. Unexpectedly - we have detected very high levels of cMet+ memory T-cells in the peripheral blood of patients with IE (n=20), compared to healthy controls but also compared to inflammatory cardiomyopathies in which this subset is known to be significantly raised in the blood. Functionally, these T cells displayed a Th2-like phenotype. Crucially, cMet+ T cells were also found to infiltrate valves of IE patients undergoing surgery. We attempted to assess the specificity of these T cells, but found that, while all the patients examined responded to the recall antigen Tetanus Toxoid, only one patient responded to the cardiac autoantigens tested. The specificity of these T cells therefore remains to be established. In a novel model of periodontitis-induced IE, immunofluorescence microscopy and flow cytometric showed that cMet+ T cells infiltrate the valves of diseased animals,

and they can be seen adhering to the endocardial endothelium and in the tissue. Echocardiography showed cardiac alteration consistent with valve damage and the cMet+ T cells produce Th2-type cytokines, like in human IE. Collectively, our data suggest that the host response plays an important role in the development of IE.

NGS and AI in prenatal diagnosis: Issues and ethical implications

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The integration of Next-Generation Sequencing (NGS) into prenatal diagnostics offers unprecedented genomic insight, yet its marriage with automated AI interpretation of sequencing data from fetal DNA (either cell-free in the maternal circulation or extracted from fetal cells after amniocentesis or chorionic villi biopsy) introduces a fraught ethical landscape. A primary concern is the "black box" nature of these algorithms; when clinicians cannot parse the logic behind a variant's classification, the foundation of informed consent begins to crumble. This lack of transparency doesn't just hinder shared decision-making—it risks automating historical biases, potentially widening existing gaps in health equity.
Furthermore, the clinical stakes of misinterpretation are uniquely high in a prenatal context. As the International Society for Prenatal Diagnosis (ISPD) has noted, fetal sequencing is notoriously complex due to the ambiguity of genotype-phenotype correlations. Without a "human-in-the-loop" to provide expert context, automated systems may mislabel uncertain variants, leading to life-altering clinical decisions based on incomplete or misunderstood data. This risk extends to the accidental discovery of sensitive information, such as non-paternity or adult-onset conditions. Without robust, multidisciplinary oversight to filter these outputs, we risk violating parental privacy and undermining the very trust that underpins maternal-fetal medicine.

SESSION X – 4P (Prediction, Prevention, Precision and Participation) strategies for obesity and diabetes

***Chairs: Amelie Bonnefond**, Lille, France / **Sanja Stankovic**, Belgrade, Serbia*

4P's strategies in diabetes

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Efficient management of chronic diseases is often summarized by the concept of 4P medicine: Predictive, Preventive, Personalized and Participative. Applied to diabetes and related metabolic disorders, this approach rests on a simple but demanding principle: to prevent or delay largely non-curable diseases driven by age, lifestyle and environment, it is necessary to anticipate risk. This includes identifying individuals with a high intrinsic susceptibility, deleterious lifestyles or adverse environmental exposures, as well as those already presenting sub-clinical alterations preceding overt disease and co-morbidities.
The objectives span the full prevention spectrum: primary prevention in the general population, secondary prevention in high-risk individuals (for instance those with a family history of diabetes), tertiary prevention aimed at limiting complications in patients, and even quaternary prevention, with the goal of delaying disability and death. Often referred to as precision medicine, this strategy is even more accurately described as 5P medicine (adding Population studies), as it success critically depends on well-designed cohorts, longitudinal follow-up and advanced data analyses.
Such a paradigm can only be effective when supported by major therapeutic breakthroughs. While this remains a challenge in neurodegenerative diseases such as AD, it is now becoming a reality in cancer and diabetes and its cardiometabolic comorbidities. The emergence of a new generation of highly effective treatments targeting diabetes, obesity, dyslipidemia and hypertension — together with their renal, cardiovascular and cerebrovascular complications — offers an unprecedented opportunity to transform patient outcomes (Incretin receptors agonists, SGLT2 inhibitors, new medications against dyslipidemia including high lp(a) etc.... When administered at the right time to the right individuals, these therapies have the potential to dramatically reduce premature disability

and mortality associated with diabetes (up to 14 years of life expectancy reduction in patients with diabetes).
Growing evidence indicates that the integration of genetics, epigenetics, metabolomics and proteomics, combined with a holistic assessment of metabolic risk and early disturbances, can identify individuals at risk and guide optimal, individualized therapeutic strategies. It is particularly already true for genomic medicine where evidence shows that rare and frequent DNA variation as well as epigenetic marks can help to adapt the treatments to individual risks and needs. Personalized diabetes care is therefore no longer a theoretical concept, but a realistic and actionable roadmap for improving long-term outcomes in metabolic diseases.

4P's strategies in obesity

Anita Morandi
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Obesity decreases health and life expectancy and quality of life, mainly because of its metabolic, psychological, and oncological complications. The traditional care based on standard lifestyle goals, has proved limited long term efficacy to combat the disease. Thus, for long time, prevention has been considered the best tool to overcome the obesity epidemics. As early obesity tends to track into adulthood, prevention should be offered very early in life. Unfortunately, population-based programs targeting pregnant women or infants/toddlers have failed to show interesting results. These programs have generally focused on lifestyle and responsive feeding. Prevention could be more effective if it targets subgroups that are at increased risk to develop obesity because of socio-cultural and/or biological drivers, and if it uses precise and participative strategies taking into account the individual mechanisms leading to obesity. For example, the responsive feeding strategy, which is based on trusting the child's appetite regulation, cannot be effective if the child has a strong genetic predisposition to have a chronic positive energy balance until the achievement of a high body mass index. In this case, environmental protection and portion control may be more effective. Some targeted trials taking into account specific biological or socio-cultural etiologies of obesity, have been performed or are ongoing, bringing hope for upcoming evidence about effective preventive strategies. Of course, to guarantee a good impact in decreasing the overall prevalence of obesity, it is important that the targeted subgroups effectively capture the potential future patients. In other words, it is important to make good prediction. Only target trials based on predictive models whose accuracy is verified, will inform us on their population-level impact. Finally, 4-P strategies, including prediction, prevention, precision and participation, should be addressed also to treating obesity. In fact, the care should include all possible tools to predict the treatment response, to prevent the patient drop-out, and to make the treatment person-centered and precise. In this view, a large spectrum of tools, going from social support to precise drugs, should be adopted.

FLASH COMMUNICATIONS **from the Ibero American Network of Pharmacogenenetics and Pharmacogenomics (RIBEF)**

***Coordinator**: **Adrián LLerena**, Badajoz, Spain*

A Universal Implementation in Hispanics (MedeA Cohort)

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Pharmacogenetics has emerged as a critical pillar in precision therapeutics, offering mechanistic insights into interindividual variability in drug metabolism, response, and toxicity. Despite its demonstrated clinical utility, its systematic deployment within publicly funded healthcare systems remains inconsistent. In Extremadura, we undertook the ambitious goal of operationalizing a comprehensive, evidence-aligned pharmacogenetic framework embedded directly into routine clinical practice. This initiative centered on implementing a robust multi-gene panel encompassing highly

actionable pharmacogenes with substantial relevance for drug disposition, enzymatic activity modulation, and toxicity risk.
The program was progressively integrated across multiple medical specialties, accompanied by harmonized genotype-to-phenotype translation and standardized clinical decision support. Embedding pharmacogenomic outputs into the electronic health record enabled clinicians to access interpretative reports with immediate therapeutic implications. As the program expanded, variant frequencies observed within the population—particularly in CYP450 enzymes and fluoropyrimidine-related genes—underscored the relevance of pharmacogenetic stratification for Hispanic cohorts.
Oncology rapidly demonstrated measurable clinical benefit through systematic DPYD screening, substantially mitigating the incidence of severe fluoropyrimidine-related adverse reactions. In neuropsychopharmacology, CYP2C19 and CYP2D6-guided prescribing facilitated more rational selection and titration of psychotropics, reducing trial-and-error approaches. Complex, polymedicated patients represented a major area of impact, as pharmacogenomic data provided essential clarity in clinical contexts characterized by significant drug–drug interactions and comorbidities driven by underlying clinical factors. The experience gained demonstrates the feasibility, scalability, and clinical validity of integrating pharmacogenetic into a regional public health system. Clinical adoption has increased steadily, and the program has shown tangible contributions to safer, more individualized therapeutic strategies across disciplines. Collectively, these findings illustrate how pharmacogenomics can evolve from a specialized resource to an integral component of standard-of-care prescribing, advancing precision medicine at the population level.
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Pharmacogenetics in a Caribbean population in the Dominican Republic

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Interindividual variability in drug response represents a major clinical challenge, as it can compromise both therapeutic efficacy and safety, thereby increasing the risk of adverse drug reactions (ADRs). Genetic variants relevant to drug response show clear ethnogeographic distribution, highlighting the need for population-specific genotyping strategies. The Dominican Republic is a Caribbean population with a well-documented geographic and historical background that predicts a substantial African genetic ancestry component. This suggests a potential association between ancestry and the distribution of genetic variants in key drug-metabolizing enzymes used in clinical practice (*CYP2D6, CYP2C9*, and *CYP2C19*), as well as in genes involved in antineoplastic treatment (*DPYD*).
The study revealed a high proportion of African (AFR) ancestry in the Dominican population compared with other Latin American groups previously analyzed by the Ibero-American Network of Pharmacogenetics and Pharmacogenomics (RIBEF). This ancestry profile correlated with increased frequencies of variants typically enriched in African populations, resulting in the presence of metabolizer phenotypes that require adjusted dosing or alternative drug prescriptions according to current clinical guidelines. These findings highlight the urgency of expanding pharmacogenetic research in non-European populations to ensure equitable access to safe and effective pharmacotherapy. Moreover, they support the development of ancestry-informed genotyping panels tailored to the molecular characteristics of each population.
Acknowledgements: The authors acknowledge the 85% co-funding from the European Union (European Regional Development Fund) and the Regional Government of Extremadura. Managing Authority: Ministry of Finance. Project reference: GR24073. This study also received funding from the Instituto de Salud Carlos III and the European Union NextGeneration EU/Plan for Recovery,

Transformation and Resilience (PMP22/00099; BIOFRAM22 and PMP24/00026; SMARTomicS). In addition, this study received funding support partly from AEXCID-Junta de Extremadura 24IA001 and Fondo Nacional de Innovación y Desarrollo Científico y Tecnológico (FONDOCYT) República Dominicana.

Application of Antidepressant Pharmacogenomics

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Pharmacogenomics has emerged as a potential tool for providing mechanistic explanations for the wide interindividual variability observed in antidepressant pharmacokinetics, therapeutic effectiveness, and adverse drug reaction risk. Genetic polymorphisms in drug-metabolizing enzymes, particularly within the cytochrome P450 system, contribute substantially to this variability. Growing real-world evidence shows that integrating pharmacogenomic information with clinical factors and plasma concentration monitoring can support more precise antidepressant therapy, moving beyond traditional trial-and-error approaches. This talk will discuss current evidence supporting genotype-guided antidepressant therapy and outline challenges and future directions for implementing pharmacogenomic-based precision prescribing in routine mental health care.

CLOSING SESSION - ***Sofia Siest**, Bernécourt, France*

POSTERS

1. Cumulative effect of lipid-related SNPs on dyslipidemia risk and response to a plant-based LDL-lowering supplement

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Background & Objective: Dyslipidemia is a major cardiovascular risk factor influenced by both lifestyle and genetic predisposition. We investigated the cumulative impact of lipid-related single nucleotide polymorphisms (SNPs) on dyslipidemia risk and their potential role in modulating response to a plant-based LDL-lowering supplement.
Design: Blood samples from 84 patients with mild dyslipidemia and 503 healthy volunteers were genotyped for SNPs previously associated with HDL, LDL and triglyceride (TG) levels. Odds ratios were calculated for individual variants, and a total genotype score (TGS) was applied to estimate combined risk.
Results: Seven SNPs (rs328, rs4939883, rs17321515, rs693, rs646776, rs2228671, rs714052) showed significant associations with altered lipid profiles ($p<0.05$). According to the TGS, 51.2% of participants had increased risk for reduced HDL, 71.4% for elevated LDL and 59.5% for elevated TG. In a pilot study of 48 patients receiving the plant-based supplement, 23 did not achieve LDL reduction; 18 of these belonged to the high-risk LDL group according to the TGS.
Conclusion: These findings suggest that a cumulative genetic risk score may predict both dyslipidemia susceptibility and individual response to non-pharmacological interventions.

2. Multi-modal coronary artery disease prediction in diverse populations

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Background: Cardiovascular diseases (CVDs), responsible for approximately 18 million deaths annually, remain one of the leading causes of complications and death worldwide. A disproportionate burden of CVD exists across ancestral groups. South Asians show a higher prevalence, accounting for over 58% of reported CVD fatalities, alongside the increase in associated risk factors. Existing risk prediction tools, such as QRISK3, often underperform in these populations due to limited ancestral representation in genetic studies.
Aim: This study aims to evaluate how the integration of polygenic risk scores (PRS), transcriptomic markers, clinical risk factors and lifestyle factors can improve coronary artery disease (CAD) prediction in British South Asian populations, with the broader goal of enhancing prediction across diverse ancestries.
Methods: Using the Genes & Health cohort, we applied a published CAD PRS derived from large-scale genome-wide association studies (GWAS). 350 participants with no prior CVD events were classified into low, middle, and high PRS groups and recalled for clinical assessments, lifestyle surveys (diet, physical activity, smoking, alcohol), and blood sampling. Plasma was analysed for lipid profiles and lipoprotein(a) levels, RNA sequencing quantified transcriptomic markers of CVD risk. Statistical models will assess the predictive value of lifestyle, genetic, and transcriptomic data.
Results: Application of CAD PRS showed a clear association with cardiovascular risk among British South Asians. Among 350 participants (174 females, 176 males/ 258 Bangladeshi, 92 Pakistani) those in the high PRS group had elevated blood pressure and BMI. Lifestyle profiling revealed clustering of ex- and light smokers in high PRS categories. QRISK3 scores were higher in genetically high-risk individuals. Ten participants developed CAD events post recall; four were in the high PRS/high QRISK3 groups.
These findings suggest genetic risk interacts with modifiable factors, supporting a multi-modal risk assessment tool.
Keywords: Cardiovascular disease, transcriptomics, QRISK3, polygenic risk score, CAD

3. Ensuring Quality in External Quality Assurance through Structured Training of Laboratory Scientists

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Background: The retirement of older and experienced scientists highlights the urgent need for new staff members to maintain and expand the operation of EQA- CONFERENCEProficiency Testing (PT) providers. ESEAP addresses this by recruiting and training young laboratory scientists on all aspects of EQA schemes.
Objective: To describe the training process for new laboratory scientists in EQA schemes.
Design: Descriptive overview of the training program for new laboratory scientists in EQA operations.
Results: New colleagues first undergo training on the statistical analysis (consensus mean, CV%, SD, SDI, Δ%) used to evaluate the results and the graphs for displaying the statistics (histograms, Levey-Jennings diagrams, and Youden Plots). A lot of important information can be extracted from these. Additionally, new staff are introduced to the implementation and application of ISO 17043. The statistical evaluation of the results is crucial, as the possible causes of erroneous results should be detected at this step. Although control sample shipments are always accompanied by instructions for their handling, preparation, and reconstitution, sometimes these instructions may be lost or ignored, resulting in improper dilution of the lyophilized control samples and consequently wrong results (pre-analytical errors). Moreover, some of the most common errors are the incorrect entry of results due to typing errors, inappropriate reporting units of measurement, or exchanging the results of the first control sample with the second and vice versa (post-analytical errors). Another point of interest for someone new to EQA is the commutability of samples and the need for grouping specific methods or analytical systems. Some analyzers consistently measure higher or lower analyte concentrations than

others in the EQA samples, so a separate statistical analysis needs to be done and used within the group of these analyzers. Finally, the younger staff have to understand that EQA schemes are dynamic and continuously improved by developing existing schemes or designing new ones that cover new needs and enhance participants' performance, which positively impacts patients.
Conclusions: Effective recruitment and training of young laboratory scientists are essential for high-quality EQA operations, ensuring reliable results, continuous improvement, and better patient care.

4. Cybersecurity Challenges in Cloud-Based Laboratory External Quality Assessment Systems: Current Threats & Mitigation Strategies

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Background: Although IT continuity is assumed, EQA systems face frequent attacks. Data breaches due to weak authentication or misconfigured access are major risks, mitigated by multi-factor authentication, role-based access control, and encryption of data at rest (AES-256) and in transit (TLS/SSL).
Objective: Highlighting the importance of protecting our systems from hackers and how this can be achieved.
Design: We analyzed cybersecurity literature, expert input, and real EQA website breaches.
Results: Compliance with regulations such as HIPAA is essential and supported by cloud compliance tools, along with continuous monitoring and logging of data access.
Data sovereignty issues arise in multi-region data storage and can be addressed through geo-fencing and data residency controls to ensure compliance with local regulations
Shared infrastructure risks in multi-tenant cloud environments can lead to data leakage. Using virtual private clouds (VPCs) and network segmentation helps isolate sensitive workloads.
Insider threats from cloud provider employees can be mitigated with strict access controls, customer-managed encryption keys, and data encryption to keep information secure even if accessed.
Data loss and availability risks can be mitigated with automated backups, multi-region redundancy, regular disaster recovery testing, and high-availability solutions such as database geo-replication.
Evaluating cloud providers' security measures is essential. Reviewing certifications, compliance reports, and using advanced security services ensures robust security. Augmenting these with third-party solutions enhances protection.
Application vulnerabilities require secure development practices, regular code reviews, and using tools like SAST/DAST. Securing APIs with OAuth 2.0 and input validation prevents common attacks. Centralized logging, monitoring with SIEM solutions, and using Cloud Security Posture Management (CSPM) tools provide visibility and control.
Cloud security requires automated configuration management, continuous audits, and regular staff training on best practices.
Conclusions: We must consider these issues and act promptly because our continuity of operations and our reliability, which affects our laboratories' quality performance and accreditation status, depend on this.

5. Flow Cytometry as a Gatekeeper for Efficient and Targeted Testing: Implications for Laboratory Workflow and Precision Medicine

Serafeim Karathanos[1,2], Georgios Markatos[2], Nikos Georgakopoulos[2], Alexander Haliassos[1]
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Background: The diagnostic workup for suspected myelodysplastic syndromes (MDS) relies on bone marrow morphology, cytogenetics, and molecular testing, which have both diagnostic and therapeutic implications. However, bone marrow smear evaluation can be delayed, and cytogenetic and molecular analyses are often ordered early in the diagnostic pathway. This can lead to non-informative tests, increased costs, and suboptimal use of laboratory resources.

Objective: To evaluate the role of flow cytometry as a rapid diagnostic screening tool in samples referred for suspected MDS and its impact on downstream cytogenetic and molecular testing decisions.
Design: A retrospective analysis was performed on all bone marrow samples referred for suspected MDS over two years. Flow cytometry results were reviewed to identify cases with findings inconsistent with isolated MDS and suggestive of B-cell lymphoproliferative disorder (B-CLPD). The impact of flow cytometry findings on subsequent laboratory testing strategies was assessed using descriptive statistics.
Results: Of the 165 specimens referred for suspected MDS, 13 (7.9%) exhibited immunophenotypic features consistent with B-cell lymphoproliferative disorder. In these cases, flow cytometry findings prompted a reevaluation of the diagnostic approach, leading to modification or prioritization of cytogenetic and molecular analyses and avoidance of potentially non-informative tests focused on MDS. Rapid availability of flow cytometry results and immediate communication between laboratory scientists were essential for the timely adjustment of the diagnostic workflow.
Conclusions: Flow cytometry serves as an effective early tool in the diagnostic evaluation of suspected MDS, identifying alternative or additional hematological neoplasms in a clinically relevant subset of cases. Its rapid, automated nature enables more targeted use of cytogenetic and molecular tests, supporting cost-effective diagnostics and precision medicine. Future integration of artificial intelligence can further improve automated test selection and inter-laboratory communication, enhancing real-time decision-making.

6. Implementation of Pharmacogenetics in Routine Clinical Care in Spain: MedeA Cohort

Carmen Mata-Martín[1,2], Carla González de la Cruz[1], María Estévez-Paredes[1,2], Francisco Arias-Aragón[1], Alba Sánchez-Redondo[1], Adrián Llerena[1,2]
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Background: Pharmacogenetics is a key tool to understand interindividual variability in drug response, particularly regarding metabolism, efficacy and toxicity. Integrating genetic information into clinical decision making enables safer and more effective prescriptions. Although its routine use in public health systems remains uneven. Since 2019, the Extremadura Public Health System (SES) has progressively incorporated pharmacogenetic testing across multiple specialties.
Objective: To develop, consolidate and validate a comprehensive pharmacogenetic testing program for routine implementation, ensuring: (1) alignment with evidence-based and regulatory guidance (AEMPS and the National Health System Service Portfolio); (2) inclusion of actionable genes and population-relevant variants; and (3) effective integration of results into clinical workflows.
Design: A real-time PCR platform using TaqMan® allele-specific assays was applied to genotype a predefined pharmacogenes panel (*CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, SLCO1B1, DPYD, TPMT, NUDT15, VKORC1, CYP4F2*). Clinical cohorts from multiple specialties were incorporated, and results were integrated into electronic records with standardized phenotype translation and structured reporting.
Results: The panel showed high analytical reliability and adequate population representation of all variants. Oncology and mental health led implementation, with routine DPYD and CYP2C19/CYP2D6 testing improving therapy. Actionable findings were frequent in polymedicated patients, and integration into e-prescribing enabled individualized dosing. **Conclusion**: The SES successfully implemented a comprehensive, evidence-aligned pharmacogenetic program with broad clinical adoption. Its demonstrated impact across specialties confirms its feasibility and value for routine precision prescribing, contributing to safer and more effective medication use.
Acknowledgements: The authors acknowledge the 85% co-funding from the European Union (European Regional Development Fund) and the Regional Government of Extremadura. Managing Authority: Ministry of Finance. Project reference: GR24073.
This study also received funding from the Instituto de Salud Carlos III and the European Union

NextGeneration EU/Plan for Recovery, Transformation and Resilience (PMP22/00099; BIOFRAM22 and PMP24/00026; SMARTomicS).

7. Pharmacogenomic and Clinical Determinants of Fluoxetine and Venlafaxine Metabolism in Real-World Spanish Patients

Levin Thomas[1,2], Carla González de la Cruz[1,2], Carmen Mata-Martín[1,2], Idian González[1,3], Idilio González-Martínez[1,4], Eva M. Peñas-Lledó[1,2], Adrián Llerena[1,2]

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Background: Antidepressants such as fluoxetine and venlafaxine exhibit marked interindividual pharmacokinetic variability, which may contribute to suboptimal treatment response and adverse drug reactions. Cytochrome P450 (CYP) pharmacogenomics (PGx) and clinical factors have increasingly been recognized as key determinants of this variability, yet real-world evidence integrating these factors remains limited.

Objective: To assess the influence of *CYP2D6*, *CYP2C19*, and *CYP2C9* PGx and clinical factors on dose-normalized fluoxetine/norfluoxetine and venlafaxine/O-desmethylvenlafaxine (ODV) metabolic ratios (MRs) under routine clinical conditions.

Design: Prospective, real-world observational studies were conducted within the MedeA PGx implementation programme in Spain. Adult patients receiving fluoxetine (n = 47) and venlafaxine (n = 29) underwent genotyping for *CYP2D6*, *CYP2C19*, and *CYP2C9*. Steady-state trough plasma concentrations of parent drugs and their active metabolites were quantified using validated high-performance liquid chromatography methods. Dose-normalized MRs were compared across genotype-predicted metabolizer groups, and multivariable models were used to assess PGx and clinical determinants.

Results: *CYP2D6* genotype was identified as a significant determinant of the fluoxetine metabolism, with poor metabolizers showing significantly higher dose-normalized fluoxetine/norfluoxetine MRs than normal metabolizers. For venlafaxine, both *CYP2D6* and *CYP2C19* genotypes significantly influenced the venlafaxine/ODV MR. Sex was identified as a significant determinant of venlafaxine metabolism, whereas age, smoking status, and polypharmacy/hyperpolypharmacy showed no associations with the MRs of both drugs.

Conclusions: The study highlights drug-specific and enzyme-specific PGx effects on antidepressant metabolism, underscoring *CYP2D6* as a key determinant for both fluoxetine and venlafaxine, with an additional contributory role of *CYP2C19* for venlafaxine. Integration of PGx with plasma concentration monitoring may improve the interpretation of exposure variability and support individualized antidepressant prescribing.

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8. Influence of Genetic Ancestry on Key Pharmacogenetic Markers in the Dominican Republic

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Background: Pharmacogenetics has emerged as a translational discipline that studies how genetic variability influences drug efficacy or toxicity, enabling its clinical implementation in healthcare systems. However, most available data come from European populations, limiting its implementation in other populations.
Objective: To determinate the relationship between genetic variants involved in the metabolism of drugs widely used in clinical practice with the ancestral genetic background of a highly diverse Latin American population from the Dominican Republic, characterized by a significant African ancestry component.
Design: Genetic variants in *CYP2D6*, *CYP2C9*, *CYP2C19* and *DPYD* were analyzed in 196 healthy Dominican volunteers and ancestry was determined in 178 of them.
Results: A significant Afro-Latin American ancestral component was identified. The most frequent allelic variants of major drug-metabolizing enzymes matched those commonly reported in African populations, including *CYP2D6*17, CYP2D6*29 and CYP2C19*17.* The clinically relevant *DPYD* c.557A>G variant was found at a frequency comparable to certain African populations and higher than other populations. Notably, 5.1% of *DPYD* intermediate metabolizers would not be identified using variants currently recommended in clinical guidelines, leading to incorrect doce adjustment of fluoropyrimidines.
Conclusion: These findings support the need to consider the interethnic diversity and genetic ancestry of Afro-Latin American populations when designing strategies for the clinical implementation of the Persolanized Medicine in Latin America, contributing to improving equity in access to healthcare services and pharmacogenetic tools across these populations.
Acknowledgements: The authors acknowledge the 85% co-funding from the European Union (European Regional Development Fund) and the Regional Government of Extremadura. Managing Authority: Ministry of Finance. Project reference: GR24073.
This study also received funding from the Instituto de Salud Carlos III and the European Union NextGeneration EU/Plan for Recovery, Transformation and Resilience (PMP22/00099; BIOFRAM22 and PMP24/00026; SMARTomicS). In addition, this study received funding support partly from AEXCID-Junta de Extremadura 24IA001 and Fondo Nacional de Innovación y Desarrollo Científico y Tecnológico (FONDOCYT) República Dominicana.

9. Research relevance of legacy samples: utilization patterns in an academic biobank

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Background: Biobanks face strategic decisions regarding long-term storage of samples collected before implementation of standardized quality management (QM) systems. ISO 20387 defines legacy samples as those predating comprehensive QM documentation. The actual research utilization of such samples informs resource allocation between legacy sample curation and prospective collection efforts.
Objective: To assess the research relevance of samples from different storage periods by analyzing sample age at request and to determine whether utilization patterns are material-specific.
Design: Retrospective analysis of all sample requests at the Medical University of Vienna Biobank during 2025. For each requested sample, age at request was calculated. To simulate legacy sample status, samples were classified according to storage duration: less than 5 years (representing QM-compliant samples), 5-10 years, 10-15 years, and greater than 15 years (representing pre-QM implementation periods).
Results: Analysis of 20,185 sample requests revealed that 84.3% were from recent collections (less

than 5 years old), while 15.7% represented older storage periods (9.3% aged 5-10 years, 4.8% aged 10-15 years, 1.6% greater than 15 years). Material-specific patterns showed marked differences: punctate samples demonstrated highest utilization from older storage periods (40.2%), followed by DNA/whole blood (28.0%), serum (20.1%), EDTA plasma (17.7%), and citrate plasma (14.9%). Recently introduced sample types (plasma for isolation of circulating cell-free DNA, ccfDNA; faeces) showed no utilization from older periods. CSF samples were almost exclusively from recent collections (1.3% from older periods). Serum was the most frequently requested material (44.8% of total requests), followed by citrate plasma (19.2%), EDTA plasma (14.9%), and ccfDNA (13.4%).
Conclusions: Utilization patterns demonstrate continued research relevance of samples from extended storage periods, with material-specific differences. Stable sample types maintain research value after prolonged storage. These data provide evidence-based guidance for resource allocation decisions regarding legacy sample curation versus prospective collection under ISO 20387 compliance.

10. Implementation of a 12-Gene Pharmacogenetic Panel Test in 10,000 Patients Across Multiple Medical Specialties

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Background: Pharmacogenetic testing can be used to improve both the efficacy and safety of drug therapy. In January 2022, Helsinki University Hospital Diagnostic Center replaced single gene tests with an in-house developed 12-gene next-generation sequencing-based pharmacogenetic panel test aimed to be used pre-emptively across multiple medical specialties.
Objective: This study aimed to assess the clinical benefits of the pharmacogenetic panel and identify areas of underuse. In particular, the extent of its integration into routine practice and whether considering panel results reduces gene-drug interactions during initial and subsequent patient encounters were evaluated.
Design: This was a retrospective, registry-based study in which clinical data from electronic health records (EHRs) were combined with genomic information. The study cohort consisted of all patients at the Helsinki University Hospital who underwent pharmacogenetic panel testing from January 2022 onward. The study cohort was compared with two control cohorts: one with genomic data from the Helsinki Biobank and one without any genomic data (*n*=10,000 in each cohort).
Results: A total of 9,561 patients at the Helsinki University Hospital underwent pharmacogenetic panel testing between January 2022 and June 2025. Most tests were ordered in oncology (43.7%), followed by psychiatry (27.1%), cardiology (7.7%), and gastroenterology (7.2%). The vast majority (99.3.%) of the study cohort patients carried at least one pharmacogenetically actionable genotype in their genome. **Conclusions**: The 12-gene pharmacogenetic panel test has been integrated into clinical practice at the Helsinki University Hospital, particularly in specialties where its use can substantially improve medication safety and therapeutic outcomes.
Acknowledgements: This study was supported by funding from the Sigrid Jusélius Foundation (Helsinki, Finland) and State funding for university-level health research.

11. BETTER4ALL Pilot Study: Findings from a Seven-Country Pilot Integrating Digital Monitoring Tools for Personalized Obesity Prevention

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Background: Preventing and managing obesity increasingly relies on digital tools that capture real-time behavioural and environmental data to support personalized interventions. The BETTER4U project combines mobile technologies, wearables and artificial intelligence (AI)-driven analytics to improve weight-management strategies across European populations.
Objective: This pilot study assessed the usability, feasibility and acceptability of the BETTER4U mobile application (app), wearable use (smartwatches) and Intervention Platform. It also collected data from wearables to refine the project's causal AI model and optimize the delivery of personalized, AI-based obesity interventions.
Design: The BETTER4ALL Pilot Study was a longitudinal, correlational, observational study conducted in seven European countries. A total of 440 participants across seven European sites (Cyprus, France, Greece, Poland, Portugal, Spain and Sweden) tested the tools over 1-3 weeks, generating behavioural and environmental data for system evaluation.
Results: Baseline questionnaires were completed by 436 participants (median age 33 years; 64.2% women), with country samples ranging from 43 (Sweden) to 78 (Poland). The cohort included 353 end-users and 83 implementers. Most lived in urban areas (68%), nearly half were married or partnered (48%) and the majority held higher education degrees (74.5%). Most were never-smokers (78%) and free of chronic illness (75%). Across the Acceptability of Intervention Measure (AIM), 52% agreed or strongly agreed that the tools met their approval and 51% welcomed their use. Appropriateness ratings (IAM) were similarly favorable, with 57% agreeing the tools were applicable and 55% that they were suitable. Feasibility (FIM) received the strongest endorsement, with 74% agreeing the tools were doable and 71% finding them easy to use. Negative responses were consistently low across domains, supporting strong usability across diverse settings.
Conclusions: Findings indicate strong usability and feasibility of the BETTER4U digital tools across diverse European settings.
Acknowledgements: We gratefully acknowledge all participants across the seven study sites and the dedicated collaborators of the BETTER4U consortium for their invaluable contributions.

12. Concordance between point-of-care and central laboratory intra-operative parathyroid hormone measurement

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Introduction: Intra-operative parathyroid hormone (ioPTH) monitoring has transformed parathyroid surgery by providing real-time confirmation of successful excision of hyperfunctioning glands. Conventional central laboratory testing is accurate but time-consuming and resource-intensive. This study evaluated the concordance of the NBCL CONNECT point-of-care (POC) assay with a central laboratory standard, focusing on absolute PTH values, percentage drops, and clinical implications of discordant results.
Material & Methods: This prospective single-centre study (November 2023 – September 2025) included 90 patients undergoing parathyroidectomy. Paired venous samples were collected at pre-defined timepoints. Further sampling was omitted if a >50% PTH drop (Miami criterion) was achieved at the first post-excision measurement. Simultaneous analyses were performed on NBCL CONNECT and central laboratory platforms.
Results: A >50% PTH reduction on NBCL CONNECT between baseline and final samples was observed in 76 patients, with concordant >50% laboratory drops in 74 of these cases (97%). Two false-positive and six false-negative cases were identified. Correlation between pre-excision values was strong ($r=0.83$, $p<0.001$; mean bias -0.03pmol/L) but weakened post-excision (Table 1). Except at baseline, NBCL CONNECT consistently reported higher absolute values. Median % PTH drop was smaller on NBCL CONNECT at 5-minutes (53.2% vs 64.2%, $p<0.001$) and 10-minutes (67.5% vs 75.2%, $p<0.001$) post excision, but not at the final timepoint (67.5% vs 77.0%, $p=0.238$) when sampling extended beyond 10-minutes. Common causes of spurious results are discussed.
Conclusions: Point-of-care ioPTH measurement demonstrates strong concordance with central laboratory testing and provides clinically reliable real-time feedback during parathyroidectomy. Its use may streamline operative workflow without compromising decision-making.

13. Spatial Transcriptomics Uncovers Cardiotropic T Cells as a Therapeutic Target in Chronic Autoimmune Myocarditis

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Chronic myocarditis is a potentially life-threatening disorder that remains challenging to diagnose and treat. T cell–mediated autoimmunity is now recognised as a key mechanism in inflammatory cardiomyopathies leading to dilated cardiomyopathy (DCM) and heart failure. While acute immune activation may resolve, persistent adaptive immune responses can sustain myocardial inflammation and promote adverse ventricular remodelling.
Under physiologic conditions, regulatory mechanisms maintain peripheral tolerance and prevent spontaneous cardiac autoimmunity. However, tissue injury and innate immune activation promote expansion of autoreactive CD4+ effector T cells, facilitating progression from acute myocarditis to chronic inflammatory cardiomyopathy. Understanding how specific T cell populations contribute to disease persistence, and whether these mechanisms are reversible, is critical for the development of targeted therapies.
Our group previously identified a subset of memory T cells characterised by expression of cMet, the hepatocyte growth factor receptor, and selective localisation to inflamed myocardium. In our 2022 *Circulation* study, circulating cMet+ T cells were detected in patients with inflammatory cardiomyopathy and in murine models, supporting their translational relevance as markers of cardiac-specific immune activation.
In the present study, we investigated the role of memory cMet+ T cells during chronic experimental autoimmune myocarditis progressing to DCM. Using Xenium single-cell spatial transcriptomics, we defined the spatial gene expression architecture of established disease and examined the impact of pharmacologic cMet inhibition. Chronic myocarditis was characterised by organised inflammatory–fibrotic niches with coordinated activation of cytokine signalling, extracellular matrix remodelling, and stress-response transcriptional programs. Therapeutic cMet inhibition induced spatial

transcriptional reprogramming, attenuating inflammatory and fibrotic gene networks while restoring cardiomyocyte metabolic and contractile profiles.
These findings define cardiotropic T cell–driven pathogenic pathways as key regulators of chronic autoimmune cardiac remodelling and highlight them as a translationally actionable target in inflammatory cardiomyopathy.

14. Study of the use of mint (*Mentha piperita* L.) as a functional ingredient in wheat biscuits

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Introduction: In recent years, functional foods have become increasingly important in the nutrition of modern humans, due to their potential to contribute to maintaining good health and preventing a number of chronic diseases. In this context, the use of plant raw materials with a high content of biologically active substances is of significant scientific and practical interest. Peppermint (Mentha piperita L.) is an aromatic plant with proven antioxidant, antimicrobial, anti-inflammatory and digestive properties, which is a reason to use it as a functional ingredient in food products.
Materials and methods: The development investigates the possibility of including finely ground mint leaves as a functional additive in wheat biscuits. The biscuits were produced by partially replacing wheat flour with different amounts of finely ground mint leaves. The impact of this substitution on key physicochemical, geometric, color and spectral characteristics of flour mixtures, dough and finished biscuits was assessed. The sensory evaluation was conducted with the participation of trained tasters, assessing the indicators of taste, aroma, color, texture and overall acceptability.
Results: Experimental samples of wheat biscuits with the addition of dried and finely ground mint in different concentrations were developed. A control sample without the addition of mint was used for comparative analysis.
Analyses of basic physicochemical parameters were performed, including moisture content and textural characteristics, as well as determination of Active Acidity (pH), Electrical Conductivity (EC), Total Dissolved Solids (TDS) and Oxidation-Reduction Potential (ORP). No significant adverse changes in the texture and technological properties of the biscuits were found at optimal levels of the additive.
Sensory analysis showed good acceptability by consumers, who reported a feeling of freshness and an improvement in the taste profile of the biscuit. However, high concentrations of the additive can lead to a dominant aroma and a lower sensory evaluation.
Conclusion: In conclusion, the conducted study confirms the potential of mint as a functional ingredient in wheat biscuits and reveals opportunities for the development of innovative functional cereal products with a health focus, meeting the growing consumer demands for quality and functionality.
Key words: *Mentha piperita* L.; functional additives, physico-chemical characteristics, sensory characteristics, nutritional enhancement, healthy food.

15. Phytochemical profile and antioxidant activity of watercress in an aquaponics system with tilapia

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Background: Aquaponics is a sustainable integrated system that combines recirculating fish farming and plant production, whereby waste products from the fish are converted into nutrients for the plants. Through a closed water cycle, the system ensures efficient use of resources, independence from climate change, and is a good example of applying the principles of the circular economy.
Objective & Design: This study evaluated the antioxidant activity and content of bioactive compounds in stalk of watercress (*Nasturtium officinale*) grown in a recirculating aquaponics system integrated with tilapia (*Oreochromis niloticus*). The plants were cultivated under controlled conditions in an aquaponics system and analyzed for total phenolic compounds and alkaloids, with antioxidant capacity determined using the ABTS, DPPH, and FRAP methods.
Results: The studied watercress stem is characterized by pronounced antioxidant activity, proven by high values according to the ABTS (86.1 ± 4.5%), FRAP (0.78 ± 0.02 mmol Fe^{2+}/L), and DPPH (16.6 ± 0.9 mmol TE/L) methods. The observed antioxidant potential correlates with the significant content of bioactive compounds, represented by total phenolic compounds (64.6 ± 2.9 mmol GAE/L). The total content of alkaloids (27.6 ± 0.9 µmol AE/L) is significant low. This confirms the high functional value of the species. The high antioxidant activity found is consistent with data from the literature, which indicate a positive correlation between the phenolic profile and antioxidant capacity in *N. officinale*. The values obtained are comparable and, in some cases, higher than those reported for watercress grown under conventional and other soilless conditions, confirming the beneficial effect of the aquaponics system on the accumulation of bioactive compounds. Our data show that watercress grown in an aquaponics system with Nile tilapia is characterized by high antioxidant potential and significant content of bioactive compounds associated with proven health benefits.
Conclusions: Watercress (*Nasturtium officinale* L.), grown in an aquaponics system with Nile tilapia, is characterized by high antioxidant potential and significant content of bioactive compounds associated with proven health benefits. The accumulation of antioxidants suggests a potential role for watercress in the prevention of diseases associated with oxidative stress and justifies its use as a functional food with beneficial effects on human health.
Key words: Antioxidants; Aquaponics system; Tilapia; Watercress.
Acknowledgements: This research was funded by project Bulgarian National Recovery and Resilience Plan, Component "Innovative Bulgaria", through project BG-RRP-2.004-0006-C03 "Development of scientific research and innovation at Trakia University in the service of health and sustainable well-being", and by the BG16RFPR002-1.014-0012-C01 „Establishment and sustainable development of a Center of Competence „Agrifood Systems and Bioeconomy", financed by the European Regional Development Fund through the „Program for Research, Innovation and Digitalisation for Smart Transformation"(PRIDST).

16. Antioxidant and Antimicrobial Potential of Methanolic Extracts from Five Moss Species Naturally Distributed in Southern Bulgaria

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Background: Mosses are small, non-vascular flowerless plants belonging to the taxonomic division Bryophyta, along with Liverworts and Hornworts. Bryophytes generate a wide variety of secondary metabolites as an antioxidant defensive response, such as flavonoids, terpenes, polyphenols, cannabinoids, oxylipins, and even some alkaloids. In recent years, their biochemical content has attracted scientific interest and they have been the subject of extensive research.
Objective & Design: In this study, methanolic extracts of 5 species from different moss genera (*Plagiomnium undulatum* (Hedw.) T.J.Kop., *Dicranum scoparium* Hedw., *Anomodon viticulosus* (Hedw.) Hook. & Taylor, *Syntrichia ruralis* (Hedw.) F.Weber & D.Mohr, *Abietinella abietina* (Hedw.) M.Fleisch) were prepared. Their antioxidant, antibacterial (against *Bacillus cereus*, *Staphylococcus aureus*,

Escherichia coli, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*) and antifungal activities (against *Malassezia pachydermatis, Penicillium chrysogenum*, *Fusarium oxysporum*, *Aspergillus parasiticus*, *Aspergillus flavus*, *Aspergillus niger, Aspergillus carbonarius*, and *Aspergillus ochraceus*) were investigated and compared. The antioxidant potential of the extracts was evaluated through DPPH, ABTS, and FRAP assays, whereas antimicrobial activity was determined by the agar well diffusion method.

Results: The *P. undulatum* extracts are characterized with the highest levels of total phenols (18.8±1.9 mg GAE/g dm) and showed the greatest antioxidant activity across all three assays but contained the lowest amounts of total flavonoids (3.8±0.4 mg CE/g dm) and condensed tannins (7.7±0.8 mg CE/g dw). Generally, the antibacterial and antifungal potential of the extracts was low or absent at the tested concentration of 30 mg/ml. *D. scoparium* exhibited the highest activity against *M. pachydermatis and P. chrysogenum*.

Conclusions: The research reveals the promising potential of some moss species as antibiotic substitutes and food preservatives but further research is needed to meet the requirements of the pharmaceutical and food industries.

Key words: Antioxidants; Antimicrobial activity; Alkaloids; Bryophyta; Mosses.

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17. Visceral Adiposity Index performance in predicting pediatric obesity and related cardiometabolic risks

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Background: The increasing prevalence of childhood and adolescent obesity has become a critical global public health concern, linked directly to the early onset of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular diseases. Traditional anthropometric indices, such as Body Mass Index (BMI) and waist circumference (WC), while practical, are limited by their inability to differentiate between subcutaneous and visceral adipose tissue (VAT) or to account for adipose tissue dysfunction. The Visceral Adiposity Index (VAI), a gender-specific mathematical model incorporating both anthropometric (BMI and WC) and biochemical parameters (triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]), has emerged as a robust surrogate marker for visceral fat distribution and function.

Objective & Design: The aim of this systematic review was to examine the application of VAI in adolescents, evaluating its predictive capabilities for obesity and its related cardiometabolic changes and comparing its diagnostic accuracy against traditional indices.

The research covered all freely available and verified scientific studies published in the time interval from 2016 to 2025. The globally recognized databases used for search and selection were PubMed, Web of Science, Science Direct, Scopus, Research Gate, Google Scholar, DOAJ, EBSCO. All steps of search and selection of this survey were based on established guidelines on the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Results: Some research identifies VAI as a promising tool for identifying metabolic syndrome in children and adolescents with obesity. Higher VAI scores are associated with a significantly increased risk of abdominal obesity, low HDL-C, and impaired fasting blood glucose. Other studies have shown that VAI is a stronger correlate of insulin resistance and cardiometabolic dysfunction than either WC or WHtR in adolescents. However, another comparative survey suggests that the cardiometabolic Index (CMI) or WHtR may sometimes be more accurate for specific risks like arterial hypertension or metabolic syndrome in specific cohorts. Most evidence is derived from cross-sectional studies, which cannot establish causality between high VAI and pediatric obesity, as well as and related cardiometabolic alterations.

Conclusions: The VAI is a superior surrogate marker for detecting metabolic dysfunction and predicting obesity-related risks in adolescents compared to traditional indices like BMI and WC. By integrating biochemical data with anthropometry, VAI accurately reflects visceral fat dysfunction and serves as an effective tool for unmasking risks in metabolically unhealthy individuals across various weight categories. For clinical practice, the use of sex- and age-specific VAI cut-offs is recommended to enhance the early diagnosis and management of cardiometabolic risks in the pediatric population. Further longitudinal research is warranted to validate these predictors across diverse global populations and to establish universal diagnostic thresholds.

Keywords: Visceral Adiposity Index, pediatric obesity, cardiometabolic risks

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18. Antioxidant and Antimicrobial Potential of *Althaea officinalis* L. Extracts

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Background: *Althaea officinalis* L. belongs to the Malvaceae family and is known as "marshmallow". Due to its abundant content of mucilage (a mixture of hexoses, pentoses, and galacturonic acid), along with starch, pectin, and minerals, it has been extensively studied and been utilized in both the food and pharmaceutical industries.

Objective & Design: In this research, extracts from various parts (leaves, flowers and roots) of the plant were prepared using 70% ethanol and natural deep eutectic solvents based on choline chloride and acetic acid (NADES1) or choline chloride and glycerol (NADES2). Their antioxidant, antibacterial (against *S, aureus, E. coli, B. cereus,* and *P. aeruginosa*) and antifungal activities (against *P. chrysogenum, A. flavus, A. niger A. carbonarius*, *F. oxysporum, A. parasiticus,* and *A. ochraceus*) were compared. The antioxidant potential of the extracts was assessed through DPPH, ABTS, and FRAP tests, and did not differ significantly based on the solvent applied. Antimicrobial activity was determined via the agar well diffusion method.

Results: Ethanolic extracts showed the highest levels of total phenols (up to 176±4 mgGAE/L) and condensed tannins (up to 73±6 mgCE/L), whereas the highest content of total flavonoids was found in NADES1 extracts (up to 109±9 mgCE/L). The flower extracts were the richest in the antioxidants tested. Alkaloids were obtained in small amounts (ranging from 2.5±0.1 to 11.2±0.5 µgAE/L). Overall, the antibacterial activity of NADES1 extracts was higher than the activity of ethanolic extracts. NADES2 extracts displayed almost no antibacterial potential, with the sole exception of leaf and flower extracts against *S. aureus*.

Conclusions: The flower extracts were the richest in the antioxidants tested. Alkaloids were obtained in small amounts. The antibacterial activity of NADES1 extracts was higher than the activity of ethanolic extracts. NADES2 extracts displayed almost no antibacterial potential, Considering the negative control, *A. officinalis* extracts showed a lack of antifungal activity (NADES1 and NADES2 extracts) or only traces of it (some of the ethanolic extracts).

Key words: *Althaea officinalis* L. *;* Antioxidants; Antimicrobial activity; Marshmallow; NADES.

Funding: This work is financially supported by the EU and the Bulgarian Ministry of Education and Culture through project BG-RRP-2.004-0006-C03 "Development of scientific research and innovation at Trakia University in the service of health and sustainable well-being".

19. Personalized B-cell maturation antigen theranostics via cell-based peptide selection

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Plasmablastic lymphoma (PBL) patients—frequently immunocompromised with aggressive extramedullary disease—remain excluded from B-cell maturation antigen (BCMA)-directed therapies designed for multiple myeloma, as current biologics impose limiting constraints including dependence on Fc-effector functions, complex manufacturing, and poor tissue penetration. We developed differential cell-based phage display to select synthetic peptides recognizing native membrane-embedded BCMA, overcoming fundamental limitations of conventional recombinant protein screening. Phage display employs filamentous bacteriophages expressing randomized peptides as genotype-phenotype fusions, enabling evolutionary selection from libraries exceeding 10^9 independent clones without prior structural knowledge.
Standard protocols for membrane receptors typically use soluble ectodomains that fail to recapitulate native conformation, glycosylation, and lipid context—features particularly critical for TNF receptor superfamily members where they determine ligand recognition and therapeutic efficacy.
To address this, we utilized isogenic H929 wild-type and BCMA-knockout lines for stringent differential selection, first depleting non-specific binders on KO cells then enriching for genuine receptor-specific clones on WT cells expressing physiological BCMA levels. Screening employed CX7C-constrained and linear 12-mer libraries with progressively stringent washing and BAFF-competitive elution to specifically enrich for native ligand-site binders, thereby preserving physiological receptor context while achieving specificity comparable to purified protein screening. Lead candidates demonstrated in silico docking to BCMA functional residues, cellular specificity confirmed by KO abrogation and antibody competition, broad activity across molecularly distinct tumor B cell models including different PBL cell lines, and primary specimen validation.
Suitable for PET imaging and targeted radionuclide therapy, these modular theranostics enable rapid pharmacokinetic optimization independent of target binding. By translating evolutionary selection into personalized BCMA-directed care for aggressive lymphomas currently orphaned from clinical trials, we demonstrate that putting patient first begins with reimagining how we discover tomorrow's therapeutics.

20. Baseline omics features are associated with significant weight loss after an AI-powered precision nutrition intervention

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Background: Artificial intelligence (AI)-driven precision nutrition may support healthy, sustainable diets and obesity management, yet dietary programs neglect individual variability in response and the underlying biological factors.
Objective: To assess the impact of an AI-powered precision nutrition intervention on the gut microbiome and plasma metabolome of individuals with overweight/obesity and to identify baseline features associated with weight loss.
Design: Nineteen Greek individuals with overweight/obesity (body mass index; BMI≥25Kg/m^2, mean age 45.2yrs, 52.6% females) used for six weeks an AI-based mobile application. Clinical, gut microbiome and plasma metabolomics data were collected pre- and post-intervention. Differentially abundant genera or metabolites were identified, while baseline features were screened for association with changes in weight and with a clinically meaningful weight loss (≥5% reduction in initial weight) using mixOmics (DIABLO) package.

Results: We identified twelve genera changed over time, including *Eubacterium nodatum group* (linked to the oral-gut axis), *Akkermansia*, (promotes gut health) and *Adlercreutzia* (short chain fatty producer associated with lipid metabolism). Metabolites levels did not change over time. Participants lost on average ~3Kg (range -21.2 to 1.6kg), while seven baseline features (three genera and four metabolites) were associated with weight change. Clinically meaningful weight loss (≥5%) was achieved by five participants (26.3%), while DIABLO identified 77 baseline discriminative features. Participants achieving a substantial weight loss had higher baseline atheromatic index and levels of lipoprotein particles and greater abundance of *Oscillibacter* and *Ruminococcus* (genera linked to obesity and inflammation), forming a bacteria-metabolite-clinical cluster that may inform further causal studies. A significant reduction in body fat mass (~2Kg) and hip circumference (~4cm) was also found, with 43 and 15 baseline features associated with the respective changes.
Conclusions: Our findings may guide future precision nutrition interventions. However larger studies are needed to confirm our results.
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21. Identification of common phenotypes in metabolic syndrome over aging using cross-study metabolomics data integration

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Background: Due to the multifactorial character of metabolic diseases (system diseases), the understanding of the associated complex processes requires deep characterization of metabolic phenotypes in an integrated strategy. Today, metabolomics is a powerful mature tool, allowing access to a global exploration of metabolism, to stratify populations within the development of precision approaches. However, even though it generates insightful data, it often lacks a sizable population, limiting its impact.
Objectives: In this context, the present work aims to investigate the validity of links between metabolic profiles from individuals analyzed in different health status. It addressed the major challenge of identifying early common phenotypes in the aging trajectory, with a particular focus on metabolic syndrome (MetS) for a deeper understanding of pathophysiological processes and modulators involved.
Design: In this work, a novel cooperative learning framework for metabolomics data integration, designed to improve biomarker discovery by balancing integration across datasets while mitigating study-specific confounders, was applied to serum untargeted metabolomic datasets from 2 independent cohorts: one MetS case-control study (n=52 males, 22-38 y.o.) performed within the Haguenau community-based cohort, focusing on young adults; the second one conducted within the NuAGE cohort (121 males, 68-82 y.o.) in an elderly population.
Results: The results showed the ability of the present approach to identify the common part of the MetS phenotype independent of age, highlighting systemic alterations related to insulin resistance, b-oxidation, inflammation and obesity. Additionally, specific aspects of the MetS phenotype were also identified, with modulated signaling metabolites in young adults, whereas specific markers of hypertriglyceridemia and dysbiosis in elderly.
Conclusions: This work is a promising paradigm for multi-source data integration, enabling integrative studies in metabolic research, opening new avenues within the framework of personalized prevention strategies.
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22. Survival outcomes after *UGT1A1* genotype-guided dosing of irinotecan: Results of a multicentre survival analysis

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Background: *UGT1A1* genotype-guided dosing reduces the incidence of febrile neutropenia in UGT1A1 poor metabolisers (PM) treated with irinotecan and results in a therapeutically effective systemic drug exposure (Hulshof *et al*. Eur J Cancer 2022). However, the impact of *UGT1A1* genotype-guided reduced dosing on survival outcomes is unknown. In this study, progression-free (PFS) and overall survival (OS) were compared between PMs treated with an initial 30% dose-reduction with fully dosed intermediate/normal metabolisers (IM/NMs).
Methods: Survival analysis was done in patients treated irinotecan dosing for pancreatic (PC) or colorectal cancer (CRC) at 6 Dutch hospitals (2017-2024). Patients were eligible if irinotecan was dosed in cycle 1 according to genotype (i.e. 100% dose intensity for IM/NMs and 70% for PMs; ±10% deviation allowed). PFS events were defined as radiological progression (RECIST 1.1), clinical progression or death from any cause. Kaplan Meier and multivariable Cox regression analyses, stratified per tumour type, were performed.
Results: In total, 779 patients were included, of whom 76 (9.8%) were PM. The median follow-up was 27.8 months. All baseline characteristics were evenly distributed across genotype groups. No significant differences in median PFS or OS were found. In multivariable analysis, the hazard ratio (HR) for PFS in PMs *vs* IM/EMs was 1.015 (95%CI: 0.781-1.319; *p*=0.91). For OS, the HR in PMs *vs* IM/EMs was 1.109 (95%CI: 0.828-1.487; *p*=0.49).
Conclusion: An upfront 30% dose reduction of irinotecan in UGT1A1 PMs resulted in comparable survival as fully-dosed IM/NMs. Therefore, UGT1A1 genotype-guided dosing of irinotecan can be confidently performed to improve patient safety.

23. Personalized pharmacometabolomic optimization of treatment for hypertension: The Hypermarker trial

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Background: Hypertension is a leading modifiable cause of cardiovascular, cerebrovascular, and renal disease worldwide, yet blood pressure control remains inadequate for many treated patients. Current treatment selection is largely based on guideline recommendations and clinician judgement, despite substantial interindividual variation in response, side effects, and adherence.
Objective: Hypermarker aims to develop and evaluate a pharmacometabolomic-guided clinical decision support strategy to personalize antihypertensive treatment in routine care.
Design: Hypermarker is a pragmatic, adaptive, open-label strategy trial embedded in routine clinical practice across four European sites in the Netherlands, the United Kingdom, Spain, and Germany. The

study will enroll 400 adults with uncontrolled hypertension and a clinical indication for starting or intensifying treatment, while using no more than two antihypertensive drugs. The intervention combines clinical characteristics with metabolomic profiles generated from plasma samples to support shared treatment decisions on drug class selection. Participants are randomized to standard care or the pharmacometabolomic-guided strategy. Home blood pressure monitoring is performed twice daily to establish baseline values and assess response over four weeks after treatment review. In phase two, the algorithm is refined using accumulating cohort and trial data, after which all participants may transition to the updated strategy and repeat four weeks of monitoring.

Results: Model development uses clinical data and pharmacometabolomic profiles derived from samples from more than 4,000 patients to identify predictors of antihypertensive treatment response. The clinical validation phase has been initiated, with the first patient enrolled in March 2026 and four patients included to date. This marks the transition to prospective evaluation in routine clinical practice.

Conclusions: Hypermarker will evaluate whether pharmacometabolomic guidance can improve treatment selection and support more precise hypertension management in routine practice.

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