UNIVERSITY OF LJUBLJANA | MF Faculty of Medicine

ESHG

ESHG Pharmacogenomics Course

Book of Abstracts

Portorož, Slovenia
04. – 06. June 2025

ESHG Pharmacogenomics Course
Book of Abstracts

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WELCOME ADDRESS

Dear colleagues,

We are delighted to welcome you to the **ESHG Pharmacogenomics Course,** taking place from June 4th to June 6th, 2025, at Hotel Histrion in Portorož, Slovenia.

This course is designed to provide up-to-date knowledge in pharmacogenomics and genomic medicine, with a focus on their clinical translation. It is intended for a broad audience, including PhD students, postdoctoral researchers, clinical pharmacologists, pharmacists, physicians, healthcare professionals, clinical and molecular geneticists, and genetic counsellors—both in training and certified.

Participants will gain insights into the current state of the art in pharmacogenomics, including next-generation sequencing technologies, as well as biostatistical and bioinformatics approaches that support the advancement of personalized medicine.

A key feature of the course is the opportunity to engage with leading experts from across Europe through lectures, discussions, and interactive sessions. The faculty brings together renowned professionals from various domains of pharmacogenetics and genomic medicine, all recognized for their expertise and teaching excellence. We also encouraged attendees to actively contribute by submitting abstracts for on-site presentation—either as posters or short oral communications—highlighting clinical or genetic case studies.

The course is organized by the Pharmacogenetics Laboratory, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, in collaboration with the European Society of Human Genetics (ESHG). We are pleased to note that ten ESHG fellowships have been awarded to support the participation of students, postdoctoral researchers, and residents in training.

This course is endorsed and supported by European Society of Pharmacogenomics and Personalised Therapy (ESPT), HORIZON-HLTH-2021-CARE-05 project: Improving Safety in Polymedication by Managing Drug-Drug-Gene Interactions (SafePolyMed) and HORIZON-WIDERA-2021-ACCESS-02 project: Pharmacogenomics Hub in a strengthened IMGGE (PharmGenHUB). We also sincerely appreciate the valuable support provided by our corporate partners.

We look forward to an engaging scientific program, set in one of the most beautiful parts of the Slovenian coast.

Welcome to Portorož and enjoy the course!

Prof. dr. Vita Dolžan
Chair of the International Scientific Committee and Organizing Committee

ORGANIZATION

Organized by

Pharmacogenetics Laboratory, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana

International Scientific Committee

- Vita Dolžan (Faculty of Medicine, University of Ljubljana, Slovenia; ESPT, SafePolyMed, PharmGenHub, PerMedZaSe)
- Magnus Ingelman-Sundberg (Karolinska Institutet, Stockholm, Sweden)
- William Newman (Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, United Kingdom; ESHG)
- Cristina Rodriguez-Antona (Spanish National Cancer Research Centre, Madrid, Spain)
- Ron van Schaik (Erasmus Medical Center, Erasmus University Medical Centre, Rotterdam, The Netherlands; ESPT)
- Julia C. Stingl (Heidelberg University Hospital, Germany; SafePolyMed)

Organizing Committee

- Vita Dolžan, chair
- Katja Goričar
- Tanja Blagus
- David Vogrinc
- Teja Muha

Endorsed and supported by

- European Society of Human Genetics – ESHG
- European Society of Pharmacogenomics and Personalised Therapy – ESPT
- ARIS programme P1-0170: Molecular mechanisms of regulation of cellular processes related to some human diseases
- HORIZON-HLTH-2021-CARE-05 project: Improving Safety in Polymedication by Managing Drug-Drug-Gene Interactions – SafePolyMed (GA No. 101057639)
- HORIZON-WIDERA-2021-ACCESS-02 project: Pharmacogenomics Hub in a strengthened IMGGE – PharmGenHUB (GA No. 101059870)
- UL/ARIS 2024-2025 big interdisciplinary project: Personalizirana medicina za zdravo staranje (Personalized Medicine for Healthy Ageing) – PerMedZaSe

GENERAL INFORMATION

CONGRESS VENUE
The event will take place at the **Hotel Histrion**, Obala 2b, Portorož, Slovenia.

REGISTRATION AND INFORMATION DESK
Lobby of the lecture hall Asteria:
Wednesday, 04. 06. 2025 8:00 – 10:00
Thursday, 05. 06. 2025 8:00 – 10:00
Friday, 06. 06. 2025 8:00 – 10:00
The certificate of attendance will be issued at the registration desk.

NAME BADGES
All participants will receive name badges upon registration and are kindly requested to wear badges during all sessions and events of the course.

ESHG FELLOWSHIP RECIPIENTS
Participants that received the ESHG fellowship have to sign the appropriate attendance list every day.

PRESENTATION PREVIEW AND DEPOSITION
Presentation preview point where speakers can check and load their presentations will be available in the lecture hall Asteria, where all lectures will take place. Speakers are kindly requested to upload their presentations during breaks before sessions.

POSTER DISPLAY AREA
Poster session will be held in the lecture hall Asteria.
Presenters are kindly asked to mount their posters on Wednesday, 04. 06. 2025, and remove them on Friday, 06. 06. 2025 by 17:00.
Presenters are responsible for setting and removing the posters. Material for mounting the posters will be available at the venue. Presenters are kindly requested to be present at their poster board for the duration of their allocated poster session.

INTERNET ACCESS
Internet access will be available during the course.

COFFEE BREAKS AND LUNCHES
Coffee breaks will be arranged in the lobby in front of the lecture hall Asteria. Lunches will be served at the restaurant of Hotel Histrion.

SILM POINTS
Participation at the course is awarded with 19 SILM points.

SOCIAL ACTIVITIES FOR ALL REGISTERED PARTICIPANTS
Wednesday, 04. 06. 2025
19:00 Welcome reception, Hotel Histrion

Thursday, 05. 06. 2025
19:00 Conference dinner, Hotel Histrion

Friday, 06. 06. 2025
18:15 A guided tour of Piran
19:30 Dinner in Piran

PROGRAMME OUTLINE

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DETAILED PROGRAMME
WEDNESDAY, 04. 06. 2025

08.00 – 08.30	Registration
08.30 – 10.15	***Session 1:* Introduction to Pharmacogenetics** (Chair: Vita Dolžan)
08.30 – 08.45	**Course Welcome**: **Vita Dolžan** *(Slovenia)*
08.45 – 09.30	**Opening lecture**: Pharmacogenomics, validation of the genetic background – **Magnus Ingelman-Sundberg** *(Sweden)*
09.30 – 10.15	Pharmacogenomics of drug transporters – **Mikko Niemi** *(Finland)*
10.15 – 11.00	Coffee break
11.00 – 12.30	***Session 2:* Pharmacogenomics of Adverse Drug Reactions** (Chair: Erika Cecchin)
11.00 – 11.30	Pharmacogenomics of adverse drug reactions – **Julia C. Stingl** *(Germany)*
11.30 – 12.00	Pharmacogenomics of drug-induced liver injury – **Ann K. Daly** *(UK)*
12.00 – 12.30	Pharmacogenomics in the prediction of cardiovascular drugs adverse reaction – PgxCardioDrug – **Lana Ganoci** *(Croatia)*
12.30 – 14.00	Lunch
14.00 – 15.30	***Session 3:* Cancer Pharmacogenomics** (Chair: Katja Goričar)
14.00 – 14.30	Pharmacogenomics in cancer treatment – **Cristina Rodriguez-Antona** *(Spain)*
14.30 – 15.00	The use of pharmacogenetics to personalize anti-cancer treatment: state of the art and future directions – **Erika Cecchin** *(Italy)*
15.00 – 15.15	Pharmacogenomics of thiopurine drugs in pediatric acute lymphoblastic leukemia: towards personalized therapy in Serbia? – **Branka Zukić** *(Serbia)*
15.15 – 15.30	Tiopurine pharmacogenomics and TDM in Slovenia – **Nataša Karas Kuželički** *(Slovenia)*
15.30 – 16.30	Coffee break and poster viewing
16.30 – 18.30	***Session 4:* Clinical Topics in Pharmacogenomics I** (Chair: Lana Ganoci)
16.30 – 17.00	Pharmacogenetics and psychiatry: impact for suicide prevention – **Adrian Llerena** *(Spain)*
17.00 – 17.30	Integrating pharmacogenomic guided prescribing into primary care: the NHS PROGRESS study – **John McDermott** *(UK)*
17.30 – 17.50	Pharmacogenetic insights into treatment resistance in psychiatry: a clinical perspective – **Milica Pjevac** *(Slovenia)*
17.50 – 18.10	Active pharmacovigilance trial integrating pharmacogenetics, TDM, and drug-drug interaction analyses in oncology – **Diletta Pasin** *(Italy)*
18.10 – 18.30	Weight loss maintenance metabolome and microbiome predictors – **Tingyu Guo** *(UK)*
19.00 –	Welcome reception

THURSDAY, 05. 06. 2025

08.30 – 10.30	***Session 5:* Clinical Topics in Pharmacogenomics II** (Chair: Branka Zukić)
08.30 – 09.00	Pharmacogenomics and polypharmacy in the elderly – **Julia C. Stingl** *(Germany)*
09.00 – 09.30	Pharmacogenetics in treatment of cardiovascular diseases – **Ron van Schaik** *(The Netherlands)*
09.30 – 10.00	Pharmacogenetics lessons from clinical genetics – **Bill Newman** *(UK)*
10.00 – 10.30	Point of care testing in pharmacogenomics – **John McDermott** *(UK)*
10.30 – 11.00	Coffee break
11.00 – 12.30	***Session 6:* Clinical Implementation of Pharmacogenetics I** (Chair: Julia C. Stingl
11.00 – 11.30	Clinical implementation of pharmacogenetics - Finnish experience – **Mikko Niemi** *(Finland)*
11.30 – 12.00	Creation of a national pharmacogenomics program – **Bill Newman** *(UK)*
12.00 – 12.30	Pharmacogenomics clinical implementation in Spain – **Adrian Llerena** *(Spain)*
12.30 – 14.00	Lunch
14.00 – 15.30	***Workshop 1:* Pharmacogenomics Resources** (Chair: Vita Dolžan)
14.00 – 14.30	Bioinformatics tools in pharmacogenomics research – **David Vogrinc, Katja Goričar** *(Slovenia)*
14.30 – 15.00	Pharmacogenes in focus: PharmGKB – **Vita Dolžan, Katja Goričar** *(Slovenia)*
15.00 – 15.30	Educational resources in pharmacogenetics – **Vita Dolžan** *(Slovenia)*
15.30 – 16.30	Coffee break and poster viewing
16.30 – 18.30	***Session 7:* Novel Biomarkers of Treatment Response** (Chair: David Vogrinc)
16.30 – 17.00	Genomic diversity and predictive biomarkers in renal cancer – **Cristina Rodriguez-Antona** *(Spain)*
17.00 – 17.30	Pharmacogenomic and epigenomic biomarkers in radiotherapy – **Katja Goričar** *(Slovenia)*
17.30 – 17.50	Uncovering treatment-responsive immune pathways in multisystem inflammatory syndrome in children (MIS-C) through single-cell multiomics – **Barbara Jenko Bizjan** *(Slovenia)*
17.50 – 18.10	Epigenetic biomarkers of nusinersen treatment in children with SMA – **Jernej Kovač** *(Slovenia)*
18.10 – 18.30	miRNA biomarkers in osteoporosis: a pharmacoepigenetic view of teriparatide response – **Lucija Ana Vrščaj** *(Slovenia)*
19.00	Conference dinner

FRIDAY, 06. 06. 2025

8.30 – 10.00	***Workshop 2:* Extracting Pharmacogenetic Information from NGS Data** (Chair: Branka Zukić)
8.30 – 9.00	PharmGenHUB Project: Population pharmacogenomics in the Western Balkan – **Branka Zukić** *(Serbia)*
9.00 – 9.20	PharmCAT: a bioinformatic tool for clinical pharmacogenomics – **Nikola Kotur** *(Serbia)*
9.20 – 9.40	From BAM to haplotype: using Stargazer for pharmacogenomic data analysis – **Marina Jelovac** *(Serbia)*
9.40 – 10.00	Interpretation of NGS Results: analysis of pharmacogenomic variants – **Vladimir Gašić** *(Serbia)*
10.00 – 11.00	Coffee break and poster viewing
11.00 – 12.30	***Session 8:* Clinical Implementation of Pharmacogenetics II** (Chair: Julia C. Stingl)
11.00 – 11.30	Clinical implementation of pharmacogenetics for routine drug prescription: what are the unmet needs – **Ron van Schaik** *(The Netherlands)*
11.30 – 12.00	Implementation of pharmacogenetics in the oncological clinical practice: from chemotherapy to oral targeted agents – **Erika Cecchin** *(Italy)*
12.00 – 12.30	Implementation of pharmacogenomics testing: lessons learnt from the PREPARE study – **Vita Dolžan** *(Slovenia)*
12.30 – 14.00	Lunch
14.00 – 15.15	***Session 9:* Clinical Implementation of Pharmacogenetics – Discussion Forum** (Chair: Vita Dolžan)
15.15 – 16.00	Coffee break
16.00 – 17.00	***Session 10:* Closing Lectures** (Chair: Vita Dolžan)
16.00 – 16.30	Ongoing challenges in implementing pharmacogenomics in the clinic – **Ann K. Daly** *(UK)*
16.30 – 17.00	Pharmacogenomics, clinical application today and in the future – **Magnus Ingelman-Sundberg** *(Sweden)*
18.00	A guided tour of Piran
19.30	Farewell dinner in Piran

LECTURE ABSTRACTS

WEDNESDAY, 04. 06. 2025

INTRODUCTION TO PHARMACOGENETICS

OPENING LECTURE

Pharmacogenomics, validation of the genetic background

Magnus Ingelman-Sundberg[1]

[1]*Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden*

Pharmacogenomics (PGx) has revolutionized precision medicine by tailoring drug therapies to individual genetic profiles, yet its clinical implementation faces significant challenges. Landmark studies, such as the 2001 HER2 trial for trastuzumab in breast cancer and the PREDICT-1 study for HLA-B*5701 screening in abacavir therapy, underscore PGx's transformative potential in improving outcomes and reducing adverse drug reactions (ADRs). Recent advancements include cost-effective next-generation sequencing, AI-driven predictive algorithms, and polygenic risk scores, alongside better integration of PGx data into electronic health records. However, challenges persist. Current guidelines are still inconsistent, with only 50% of 54 actionable gene-drug pairs reflected in labeling, and just 18% showing concordance across FDA, EMA, CPIC, and DPWG recommendations. Barriers to clinical adoption include limited clinician awareness, complex data interpretation, and insufficient evidence of clinical benefit. To address these, future PGx studies should prioritize high-impact gene-drug pairs, stratify participants by genetic variants, and incorporate robust pharmacokinetic endpoints. Enhanced collaboration between regulatory bodies, academia, and stakeholders like CPIC and DPWG is critical for harmonizing guidelines. AI advancements promise real-time genomic analysis and bias reduction, while comprehensive clinician education and updated drug labeling lists are essential for effective PGx dissemination. By focusing on these areas, PGx can achieve broader clinical uptake, ultimately improving patient safety and therapeutic efficacy across diverse populations.

PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS

Pharmacogenomics of adverse drug reactions

Julia C. Stingl[1]

[1]*University Hospital Heidelberg, Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany*

Introduction: Adverse drug reactions (ADRs) and medication errors are a relevant problem in the context of health and are also of great importance from the point of view of health policy, since they are sometimes associated with considerable follow-up costs for the health care system. Estimates approximately 5%-15% of emergency hospitalizations are due to ADRs. Data in the literature on the incidence of medication errors varies considerably and is dependent on the study conditions, the study population included, and the study country.

Methods: The basis for our evaluation was the recording of a UAW cohort in six central emergency rooms of maximum-care hospitals in Germany. Suspected cases of ADR in patients who came to the hospital emergency department on an emergency basis were documented. Suspected cases of ADR were cases of treatment in adult patients with causality to drug effects was considered "possible", "probable", or "certain" according to WHO-UMC criteria. A biosample for pharmacogenetic analyses was taken if patients gave informed consent.

Results: In the participating emergency departments, 6.5% of all treatment cases were detected as suspected ADRs during the observation period of the feasibility analysis. This rate of suspected ADR cases is comparable to other studies, but once again illustrates the need to consider the aspect of preventability. The majority of the study cases collected involved patients who were, older (median: 73 years) and multimorbid (72.4%). Accordingly, most of the ADR cases were in elderly patients with polymedication (median: 7 drugs). Pharmacogenetic analyses were done in about 1/4 of the total sample in buccal swabs or blood sample. It turned out that pharmacogenetic risk profiles affected prevalence of certain side effects in addition to the patient-specific factors, such as age, gender multimorbidity. Drugs affected by pharmacogenetic polymorphisms were more frequently suspected causing symptoms of adverse drug effects in risk allele carriers than in normal allele carriers.

Conclusion: Certain groups of drugs, such as psychotropic drugs, antithrombotic drugs or antineoplastic and immunomodulatory drugs have a high potential to cause ADRs due to their mechanism of action. Here, a special vigilance on the part of emergency room physicians is required. The knowledge of which drug is affected by pharmacogenetic polymorphism could make a decisive contribution to the recognition of ADRs in the emergency room setting, but also to the selection of drugs for use in certain pharmacogenetic risk groups.

Pharmacogenomics of drug-induced liver injury

Ann K. Daly[1]

[1]*Newcastle University, Translational & Clinical Research Institute, Newcastle upon Tyne, United Kingdom*

Introduction: Idiosyncratic drug-induced liver injury (DILI) is one of the most commonly reported adverse drug reactions and important cause of drug withdrawal from the market. Most patients recover once no longer exposed to the causative drug but up to 10% may develop liver failure requiring liver transplantation. DILI has been linked to a large number of licensed and widely-prescribed drugs. The incidence is drug-dependent and with certain drugs may be as frequent as 1 in every 100 patients but a frequency of 1 in every 10000 to 100000 patients treated is more common.

Content: The presentation will focus on certain antimicrobial drugs which are well established causes of DILI to illustrate typical genetic risk factors. In particular, certain HLA genotypes are the major genetic risk factor with a more minor contribution from other genes linked to immune responses and a small contribution from drug metabolism genes. The examples to be considered will be the following: (i) Flucloxacillin DILI where the major genetic risk factor is carriage of HLA-B*57:01; (ii) Amoxicillin-clavulanate DILI where several HLA alleles and at least 2 other immune genes are risk factors and can be combined to provide a polygenic risk score; (iii) Isoniazid DILI where those positive for alleles associated with the N-acetyltransferase 2 (NAT2) ultraslow metabolizer phenotype show increased risk.

Conclusions: The examples presented show that genetic risk factors for DILI are complex and are highly drug-specific. None of the associations detected to date have sufficient positive predictive value for use prior to drug prescription but have value diagnostically to identify the drug cause and prevent further exposure of the susceptible individual.

Pharmacogenomics in the prediction of cardiovascular drugs adverse reactions – PgxCardioDrug

Lana Ganoci[1,2]

[1]University Hospital Centre Zagreb, Department of Laboratory Diagnostics, Division of Pharmacogenomics and Therapy Individualization, Zagreb, Croatia; [2]University of Zagreb School of Medicine, Department of Pharmacology, Zagreb, Croatia

Introduction: The PGx-CardioDrug study, conducted at the University Hospital Centre Zagreb and the University of Zagreb School of Medicine, investigates the impact of pharmacogenomic variants and drug-drug-gene interactions on predicting adverse drug reactions (ADRs) in patients using cardiovascular medications. This prospective, nested case-control study spans five years, with four years of data currently analysed.

Methods: The study cohort includes patients treated with direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, rivaroxaban), platelet aggregation inhibitors (PAIs: clopidogrel, prasugrel, ticagrelor), and/or statins (atorvastatin, fluvastatin, rosuvastatin, simvastatin). Patients were recruited for 48 months. The cases represent subjects who developed ADRs during the follow-up period: bleeding/inefficacy from DOACs and PAIs, myotoxicity/hepatotoxicity from statins, and other ADRs. Controls are subjects with no ADRs presented during the follow-up period recruited from the same cohort. The relevant ADME gene variants are genotyped by TaqMan real-time PCR: *CYP2C9*, *CYP2C19*, *CYP2C:TG* haplotype, *CYP2D6*, *CYP2J2*7*, *CES1*, *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCG2*, *SLCO1B1*, according to the subjects' therapy. Clinical and laboratory parameters were monitored, and ADRs and drug-drug interactions (DDIs) were assessed.

Results: Among 1885 recruited patients (1207 statins, 717 DOAC, 296 PAI users), 1433 were analysed for drug-gene interactions and ADRs. Observed ADRs and total number in up to now follow-up: statins (atorvastatin n=113/455, rosuvastatin=143/342), DOACs (rivaroxaban n=74/410, apixaban=25/194, dabigatran n=36/113), and PAIs (clopidogrel n=77/296). Potential DDI with increased risk for ADRs were found in groups of statins (n=342/884), DOACs (n=533/648), and PAIs (n=185/262). So far, the study has resulted in five publications, five experimental master's theses and three ongoing PhD theses.

Conclusions: Our findings highlight the potential of pharmacogenomics in individualizing therapy and reducing cardiovascular ADR risk, especially for statins. Further research is needed to refine predictive models and facilitate clinical implementation of pharmacogenomic-guided therapy in cardiovascular medicine.

Acknowledgements: This work is funded by the Croatian Science Foundation (project number UIP-2020-02-8189).

CANCER PHARMACOGENOMICS

Pharmacogenomics in cancer treatment

Cristina Rodriguez-Antona[1]

[1]*Institute for Biomedical Research Sols-Morreale (IIBM), CSIC-UAM, Madrid, Spain*

In cancer treatment, pharmacogenomics has emerged as a transformative approach able to use the patient's genetic profile to tailor treatments and improve clinical outcomes.

Germline variants associated with drug toxicity risk can be used to increase treatment safety, which is critical in oncology, where regimens have narrow therapeutic windows. Key examples include variants in *DPYD, UGT1A1, TPMT*, and *NUDT15*. Furthermore, some germline mutations linked to hereditary syndromes are known to affect drug response and guide treatment selection. For example, mutations in *BRCA1/2* predispose individuals to breast and ovarian cancers but also predict sensitivity to PARP inhibitors, and Lynch syndrome-associated mutations in mismatch repair genes indicate sensitivity to immune checkpoint inhibitors.

Regarding somatic variations, the genomic landscape of each person's specific cancer can inform about drug vulnerabilities, as tumor-specific mutations often dictate the effectiveness of targeted therapies. For instance, *EGFR* mutations in non-small cell lung cancer can guide the use of tyrosine kinase inhibitors. In most cases, biomarker detection is restricted to a specific tumor type, but for some treatments, the indication is independent of the tumor origin, defining "tissue-agnostic" biomarkers. Furthermore, matching a drug treatment to the specific genomic landscape of the patient's tumor is now a reality for many patients, and basket and umbrella trials stratify participants based on specific genetic alterations, allowing for more precise therapies.

Unfortunately, there are many challenges to overcome, such as tumor heterogeneity and drug resistance. But also limited access to genetic testing and disparities in pharmacogenomic data across populations. Furthermore, only a small subset of molecular targets are currently inhibited by drugs, and many common tumor genomic alterations remain undruggable.

In this presentation, examples of cancer pharmacogenomics biomarkers will be highlighted, with a focus on unmet needs.

The use of pharmacogenetics to personalize anti-cancer treatment: state of the art and future directions

Erika Cecchin[1]

[1]*Experimental and Clinical Pharmacology Unit, CRO-Centro di Riferimento Oncologico di Aviano - IRCCS, Aviano, Italy*

More than 21% of admissions to an oncology service are related to the management of adverse drug reactions. Most of them are considered predictable and could be prevented. Analysis of germline genetic polymorphisms can be useful in the early identification of patients at risk of toxicity. To date, only a few gene-drug interactions have been validated for use in clinical oncology practice, such as UGT1A1/ irinotecan (IRI), DPYD/fluoropyrimidine (FP), TPMT/ 6-mercaptopurine, and CYP2D6/ tamoxifen.

The application of TPMT and CYP2D6 in clinical practice is still limited. In contrast, the development of the DPYD test in Europe is a successful example of clinical implementation of a pharmacogenetic test. Regulatory agencies now recommend pre-treatment genotyping for DPYD in Europe, and this was a key step in this process. We recently demonstrated for the first time, in the context of a large randomized clinical trial such as PREPARE, that dose reductions of FP and IRI induced by DPYD and UGT1A1 genotyping in gastrointestinal cancer patients allowed patients to complete their course of treatment, with improved intensity of care. In addition, most oncology patients enrolled in Italy under PREPARE for FP-based prescribing received at least a second prescription managed by an oncologist with PGx guidelines available (at 18 months). This would encourage moving from a single drug-gene interaction analysis to a panel approach to increase cost-effectiveness and improve patient management. The complexity of the genetics of DPYDs encourages the study of rare variants and the application of NGS techniques. Germline genetic variant burden determined by NGS could be a new pharmacogenetic marker to be further studied in the future.

Acknowledgment: All the researchers of Experimental and Clinical Pharmacology Unit at CRO-Aviano and all the oncologists of the Institute.

Pharmacogenomics of thiopurine drugs in pediatric acute lymphoblastic leukemia: towards personalized therapy in Serbia?

Branka Zukić[1]

[1]*Institute of Molecular Genetics and Genetic Engineering, Group for Molecular Biomedicine, Belgrade, Serbia*

Introduction: Acute lymphoblastic leukemia (ALL) in children exemplifies the clinical impact of pharmacogenomics in optimizing treatment and minimizing toxicity. Mercaptopurine (6-MP), a key component of ALL therapy, can cause severe hematotoxicity in patients harboring variants in genes involved in its metabolism.

Methods: In this study, we analyzed genetic variants in *TPMT*, *NUDT15*, *ITPA*, *MDR1*, and *ABCC4* in a cohort of 150 Serbian pediatric ALL patients using PCR-based methods and Sanger sequencing. Functional analyses of *TPMT* expression and 6-MP toxicity were performed both in vitro, using CAT reporter assays, and in vivo, via quantitative real-time PCR.

Results: Variants in *TPMT* exons were detected in 7.5% of ALL patients. Based on these findings, treatment regimens were modified by reducing initial 6-MP doses during the maintenance phase, enabling even heterozygous *TPMT* deficient patients to subsequently tolerate full-protocol dosing.

Functional analysis revealed that the transcriptional activity of the *TPMT* promoter is modulated by the structure of variable number tandem repeats (VNTRs) within the promoter region. Notably, in vivo studies demonstrated a median 280% increase in *TPMT* transcription following 6-MP administration, indicating a positive regulatory effect of the drug on gene expression.

Additionally, polymorphisms in *ITPA*, *MDR1*, and *ABCC4* were identified as potential pharmacogenomic markers. *NUDT15* variants were not associated with toxicity in this cohort. The VNTR region of the *TPMT* promoter emerges as a novel candidate marker for pharmacogenomic stratification.

Conclusions: Our findings support the integration of pharmacogenomic testing into ALL treatment protocols. Tailoring 6-MP dosing based on genetic background reduces early-phase toxicity and facilitates the continuation of full-intensity therapy, thereby improving clinical outcomes in pediatric ALL.

Acknowledgements: This study was funded by the Horizon Europe PharmGenHUB Project (HORIZON-WIDERA-2021-ACCESS-02, European Commission, Grant Agreement No. 101059870).

CLINICAL TOPICS IN PHARMACOGENOMICS I

Pharmacogenetics and psychiatry: impact for suicide prevention

Adrián Llerena[1], Eva Peñas-Lledó[1]

[1]*INUBE Extremadura University Institute for Biosanitary Research, Faculty of Medicine and Health Sciences, Extremadura University Hospital, Unit for Pharmacogenomics and Personalized Medicine, Badajoz, Spain*

Pharmacogenetics allows individualising the prescription in order to optimise the response to drugs based on genetic biomarkers (gBMs). In particular, the determination of gBMs can contribute to improve the effectiveness of mental health prescribing, and to prevent adverse drug reactions (gRAMs) and therapeutic failure. This is especially important considering that ADRs have tripled in the last decade (Koyama et al., 2024). However, despite the various individual contributions, no joint strategy has been developed to enable National Health Systems (NHS) to benefit from the integration of pharmacogenetics into healthcare practice. This may be especially necessary for the prevention of suicide, one of the most relevant health problems today as the first non-natural cause of death, especially relevant in young people (Peñas-Lledó et al., 2011; Peñas-Lledó et al., 2012; Peñas-Lledó et al., 2015a and 2015b).

The objective of this study was to develop a Pilot for the Evaluation of the Implementation of Pharmacogenetics in Mental Health. This will require: 1) to analyse the regulatory framework based on the technical data sheets of the medicines studied, the common portfolio of services of the National Health System, for the generation of a proposal for the implementation. Subsequently, 2) based on the analysis of data from ongoing projects, descriptive variables on diagnosis, pharmacological treatment, presence of ADRs, and frequency of genetic polymorphisms of those defined can be obtained.

The results derived from this study will contribute to implementing a change in the care model thanks to the genotyping of at-risk populations and the incorporation of this pharmacogenetic information in health systems, as currently established in the common portfolio of NHS services and the AEMPS database on pharmacogenetic biomarkers. Its application to suicide prevention is one of the most relevant aspects. Preliminary results will be presented at ESGH Summer School 2025.

Integrating pharmacogenomic guided prescribing into primary care: the NHS PROGRESS study

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Introduction: Leveraging genetic data to support medicines optimisation, a concept known as pharmacogenomics, could lead to improved patient outcomes and reduce healthcare expenditure. Generating pharmacogenetic data in the laboratory is relatively simple, the challenge is making it available to frontline healthcare professionals in a clinically relevant format and a clinically relevant time frame.

Methods: The NHS PROGRESS programme is a national multi-centre implementation study aiming to integrate and assess the impact of pharmacogenetic guided prescribing in primary care in England. Across 18 sites, patients were recruited on prescription of an index medicine (statins, opioids, antidepressants, proton pump inhibitors) and pharmacogenomic guidance was returned, either via a clinical portal or directly integrated into the electronic healthcare record. The primary outcome captured the proportion of patients with an actionable variant related to their index medicine. Changes to prescribing, turnaround times and compliance with guidance were also monitored.

Results: At pre-specified interim analysis (n=500), pharmacogenetic guidance had been returned for all participants, with an average turnround time of 7 days. 95% of participants carried a pharmacogenetic result of interest, and just over 20% participants had their prescription adjusted in line with guidance. The few instances of non-compliance with guidance occurred where recruitment was delayed or where the prescription was issued prior to the return of genetic results.

Conclusions: These findings demonstrate the potential scale and clinical utility of pharmacogenetic testing as an intervention. The PROGRESS programme has piloted an interoperable and scalable model to integrate genomics into routine decision making.

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Pharmacogenetics and polypharmacy in the elderly

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Introduction: Successful outcome in drug therapy is dependent on the drug toxicity profile, but as well on patient vulnerability. Therapies are considered successful when the benefits (efficacy) outweigh the harms (side effects). The "age" factor, along with patient characteristics such as genetics, weight, decreased organ functions, mobility, total body water and sex, has a significant impact on the safety and efficacy of drug therapies. Older adults also often take five or more medications simultaneously, called polymedication, leading to potential drug interactions and increased side effects.

Methods: In clinical pharmacology cohort studies, we analyzed the role of age and polypharmacy for the occurrence of adverse drug reactions. As polypharmacy and pharmacogenetics is interacting, we analyzed the shift in genetically-predicted enzyme activity called phenoconversion, in clinical cohort studies and in TDM data. We analyzed comedication leading to a change in the pharmacogenetically predicted phenotype in drug metabolism. Drugs that share the same metabolism pathway are competing in situations of polypharmacy, and analyses of plasma concentrations of CYP450 enzyme marker drugs were expected to show a decrease in enzyme activity that should be correlated with the number of competing substrates in comedication. Genetically Poor Metabolizers of a CYP450 enzyme, however, may not change in enzyme activity by drug-interactions, as enzyme activity is already zero.

Results: We detected phenoconversion in patients with polypharmacy, and the number of drugs that are metabolized by the same pathway increased the shift in enzyme activity. Pharmacogenetic profiles play an important role here, because in the case that one metabolic pathway is blocked by comedication, other minor pathways get more important. Thus, from TDM data, a synergistic effect of two CYP enzymes involved in drug metabolism was detected in analyses of different combined genotype profiles, but in cases of one enzyme being fully blocked, the influence of pharmacogenetics of the other enzyme got large (even if minor in its role in metabolism of the drug). In elderly patients, drug combinations must be carefully selected considering their aging bodies, pharmacogenetics, and mobility. Especially in the elderly, it is important to make safe and effective personalized therapy decisions.

Pharmacogenetics in treatment of cardiovascular diseases

Ron H. N. van Schaik[1]

[1]*Erasmus MC – University Medical Center, Department of Clinical Chemistry, Rotterdam, The Netherlands*

Introduction: Pharmacogenetic can be used to optimize drug treatment. Whereas initially applications in psychiatry (CYP2D6) and oncology (TPMT) were used, applications in cardiology have increased considerably in our laboratory.

Methods: We analysed test request at our laboratory regarding gene and drug for which requested. We also investigated the desired turn-around-time.

Results: CYP2C19 test requests have increased substantially after 2019. There was a specific need for test results being available within 24 hours. Pharmacogenetics for statins and/or anticoagulation with coumarins are less popular. There is a concern among GPs what to do with patients that have been on clopidogrel for >1 year without having a CYP2C19 genotype.

Conclusions: CYP2C19 testing is increasingly popular and requires fast turn-around-times. Discussions on whether to use lab-based test or switching to near-patient-testing are currently ongoing.

Pharmacogenetics lessons from clinical genetics

William Newman[1]

[1]*Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester, United Kingdom*

Many monogenic disorders are associated with altered responses to medication. In this lecture I will explore some of these conditions including long QT, G6PD deficiency and porphyria in detail. I will explore the pharmacogenetic testing that is now indicated for specific treatments for rare genetic conditions e.g. mavacamten for hypertrophic obstructive cardiomyopathy. I will explore some of the considerations that inform genetic counselling and how relevant these are to the delivery of pharmacogenomics.

Point of care testing in pharmacogenomics

John McDermott[1,2], William Newman[1,2]

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Introduction: Pharmacogenomic testing is context dependent, and in many clinical scenarios a result is required quickly to meaningfully inform clinical practice. In such instances, laboratory testing, relying on centralised infrastructure, may not be sufficiently rapid. This session describes the development and emergency of "point of care" pharmacogenetics.

Methods: We highlight the development of two distinct pharmacogenetic testing technologies. The first to avoid aminoglycoside induced hearing loss in neonates and the second to guide antiplatelet therapy. We also explore how advanced materials might lead to the acceleration of this testing strategy.

Results: Point of care testing technologies can rapidly detect pharmacogenomic variation at the bedside in a clinically meaningful timeframe. These technologies have been successfully implemented in settings across the NHS

Conclusion: Point of care pharmacogenomics offers rapid, accurate and accessible testing approaches for health systems where existing laboratory infrastructure cannot meet the requirements of healthcare professionals and patients.

CLINICAL IMPLEMENTATION OF PHARMACOGENETICS I

Creation of a national pharmacogenomics program

William Newman[1]

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In the UK there have been a number of initiatives over the past five years which are working to implement pharmacogenomics at scale within a public health service. We are moving from a single gene-single drug model to a multi-gene – multi-drug model where pharmacogenetic data are available pre-emptively within the electronic patient record to inform safer and more effective prescribing. This is a multidisciplinary program including pharmacists, doctors, informaticians, laboratory scientists, health economists and implementation scientists. I will describe our proof of concept work in primary care (Progress trial) and potential approaches in acute and other health care settings.

Pharmacogenomics clinical implementation in Spain

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In Spain, the most relevant fact is its integration into the common Heath Care Portfolio of services of the National Health System (NHS) and the generation of a database of the Spanish Agency of Medicines and Health Products (AEMPS), therefore the implementation of pharmacogenetics is now a reality in Spain. This process has a historical development. The initial fact are the conclusions of the Senate Report of Genomic Medicine on 13 February 2019, in point 11, included the need to address 'the variability in the response to drugs in a common situation of polytherapy and pluripathology, and implement the genomic analyses recommended by the AEMPS and the European Medicines Agency (EMA)'.

Following the Senate Report on the Strategy on Genomic and Precision Medicine for the NHS, the IMPaCT Project 'Infrastructure for Precision Medicine associated with Science and Technology' was launched in 2021. The IMPaCT Strategic Plan is configured around three axes that respond to three programmes: Predictive Medicine, Data Science and Genomic Medicine, that contains a work package on Pharmacogenetics (WP05) aimed at establishing the basis for the implementation of pilot projects in which the 5 Spanish Regions are participating. To overcome the barriers to implementation in Spain, the IMPaCT Strategy mentioned above and, as an extension of this, the BioFRAM Project, it is developed.

The objective of the IMPACT PGx project is to evaluate the implementation of a gBM panel. The aim is to propose a clinical implementation panel for subsequent application as a strategy for quaternary prevention of adverse drug reactions (ADRs) in patients with particular relevance in Primary Care. The results of these projects and the strategy for implementing pharmacogenomics in clinical practice will be presented at the EGH.

WORKSHOP 1: PHARMACOGENOMICS RESOURCES

Bioinformatics tools in pharmacogenomics research

David Vogrinc[1], Katja Goričar[1]

[1]*University of Ljubljana, Faculty of Medicine, Institute of Biochemistry and Molecular Genetics, Pharmacogenetics Laboratory, Ljubljana, Slovenia*

Several publicly available bioinformatic tools and databases have been developed to facilitate the interpretation of pharmacogenomics (PGx) data and the implementation into clinical practice. For extraction of required PGx data, a combination of different databases and public repositories is advised. Among others, dbSNP, ClinVar, PharmGKB, PharmVar, DrugBank, DPWG and CPIC are some of the most well-known and frequently used bioinformatic tools and resources in the field of PGx. Each database has specific features and characteristics, with a common goal of providing curated information on gene-drug interactions in the field of precision medicine. Several algorithms are also available for the prediction of functional effects genetic variants in the coding or regulatory regions, such as CADD and PolyPhen, and can be accessed through several databases such as Ensembl and FORGEdb. We will describe the bioinformatic tools that can be used in daily practice and are crucial for the understanding of PGx genetic variability and its role in personalised treatment approach.

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Pharmacogenes in focus: PharmGKB

Vita Dolžan[1], Katja Goričar[1]

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Pharmacogenomics Knowledge Base (PharmGKB)(https://www.pharmgkb.org/) is the most comprehensive online resource in the field of pharmacogenomics. It was developed at the Stanford University with the aim to collect, curate and disseminate knowledge about how human genetic variation affects response to medications, and to provide evidence-based information on clinically actionable gene-drug associations and genotype-phenotype relationships.

The knowledge extracted from primary pharmacogenomic literature is manually curated, annotated, aggregated and integrated into summaries on drug metabolism and action pathways, pharmacogenes, and genetic variants associated with medication response. Clinical annotations provide a summary of all published evidence for the relationship between a particular genetic variant and a medication and a score depicting the level and quality of published evidence for each relationship. Drug label annotations summarize data from medication labels that contain pharmacogenomic information. Most importantly, prescribing information provide evidence-based clinical guidelines for the adjustment of prescribing certain medications based on a person's genetic information. These guidelines were prepared by professional societies such as the Clinical Pharmacogenetic Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and others.

The workshop will provide participants with practical instruction on utilizing PharmGKB to access and interpret various types of pharmacogenomic information, using illustrative patient cases from routine clinical practice.

Educational resources in pharmacogenetics

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Despite the strong body of evidence supporting the role of genetic variability in influencing individual responses to drug therapy—including treatment efficacy and the risk of adverse drug reactions—the integration of pharmacogenomics (PGx) into routine clinical practice remains limited. Lack of knowledge about PGx has been perceived as one of the main barriers in the implementation of PGx in clinical practice.

In several countries, including Slovenia, education on pharmacogenetics is already integrated into undergraduate and graduate study programs in medicine and pharmacy. However, there remains a significant need for continued professional education to ensure that physicians, pharmacists, and other healthcare providers are equipped to apply pharmacogenomic information effectively in clinical decision-making. Equally important is raising awareness among patients and the general public about the potential of pharmacogenomics to improve treatment outcomes.

This workshop will address the diverse educational needs and explore strategies for delivering PGx education to undergraduate and graduate students, healthcare professionals, and patients.

NOVEL BIOMARKERS OF TREATMENT RESPONSE

Genomic diversity and predictive biomarkers in renal cancer

Cristina Rodriguez-Antona[1]

[1]*Institute for Biomedical Research Sols-Morreale (IIBM), CSIC-UAM, Madrid, Spain*

Renal cell carcinoma (RCC) accounts for 2% of all cancer diagnoses, being the 14th most common cancer worldwide. RCC is not a single entity, but it constitutes a heterogeneous group of tumors classified into different histological subtypes, with the most common ones being clear cell RCC (ccRCC; 80%) and papillary RCC (pRCC; 10%). These histologic subtypes not only present different morphologic features but also have unique molecular drivers, prognosis, and treatment response.

RCC is resistant to chemotherapy and radiotherapy, and the survival of the metastatic patients was very poor until the development of targeted medicines. These new drugs that emerged twenty years ago have tripled the survival for these patients. At the moment, there are more than 20 targeted drugs approved for the treatment of advanced/metastatic RCC and grouped as antiangiogenics, mTOR inhibitors, immune checkpoint inhibitors, and, more recently, HIF2alpha inhibitors. Unfortunately, there is a large variability in treatment response among patients. Tumor transcriptional signatures have emerged as promising biomarkers to predict drug response.

This seminar will present current advancements made by us and others to better understand and predict the inter-individual differences in treatment response in patients with ccRCC and pRCC.

Pharmacogenomic and epigenomic biomarkers in radiotherapy

Katja Goričar[1], Tanja Marinko[2,3], Vita Dolžan[1]

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Radiotherapy is one of the three main modalities of oncological treatment, used in various different cancer types. Radiotherapy can improve survival and local disease control as well as reduces the chance of disease recurrence, but also causes acute, often transient, and late, often irreversible, adverse events that can influence patients' quality of life. Several clinical and molecular factors can contribute to the occurrence of adverse events in individual patients, including genetic and epigenetic factors.

Radiogenomic studies have identified several genetic variants that may influence radiotherapy outcome. Key biological pathways involved in the occurrence of radiotherapy adverse events are DNA repair, inflammation and response to oxidative stress or hypoxia. In genome-wide association studies and meta-analyses, *XRCC3*, *XRCC1*, and *TGFB1* emerged as the key genes associated with adverse events of radiotherapy. Good predictors were especially models combining polymorphisms in DNA repair and transforming growth factor beta signaling genes.

Epigenetic factors can also affect radiotherapy outcome. miRNAs, small non-coding RNAs that regulate gene expression on the posttranscriptional level, are frequently differentially expressed in cancer. They can regulate several processes associated with carcinogenesis, including cell cycle, apoptosis, cell proliferation and differentiation. Radiotherapy also leads to changes in miRNA expression in tumor tissue and different biological fluids. Different miRNAs were proposed as potential biomarkers of radiation exposure, including hsa-miR-21 and hsa-miR-34a. Recently, miRNAs were also proposed as a potential treatment target that could be used for tumor radiosensitization.

In conclusion, genetic and epigenetic factors could serve as additional biomarkers of radiotherapy outcome and could enable a more personalized treatment approach in various cancer types, leading to better efficacy and minimizing adverse events.

FRIDAY, 06. 06. 2025
WORKSHOP 2

Extracting pharmacogenetic information from NGS data

Nikola Kotur[1], Marina Jelovac[1], Vladimir Gašić[1], Branka Zukić[1]

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The PharmGenHUB project is a Horizon Europe-funded initiative focused on exploring the pharmacogenomic landscape of populations in the Western Balkan region, including Serbia, Croatia, Montenegro, Bosnia and Herzegovina, and North Macedonia. This project addresses the need for population-specific pharmacogenomic data, which is critical for implementing personalized medicine strategies and optimizing drug safety and efficacy across diverse genetic backgrounds.

Using whole genome sequencing (WGS), the project has generated comprehensive genetic data from individuals across the region. These data were analyzed to identify relevant, actionable pharmacogenetic variants with known influence of drug response and clinical therapy guidelines provided by reputable international resources such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB).

The workshop will present a comprehensive overview of the PharmGenHUB project, including its methodological framework, technical achievements, and preliminary findings. Emphasis will be placed on the development and implementation of NGS technologies, which represent a transformative advancement in pharmacogenomics. The use of the PharmCAT and Stargazer bioinformatic tools were integrated to call star alleles and predict copy number variations in pharmacogenes from NGS data. This pipeline can annotate more than 50 actionable pharmacogenomic variants, offering a high-throughput and reliable approach to personalized drug response profiling. Also, the project employs American College of Medical Genetics and Genomics (ACMG) guidelines to classify the pathogenicity of newly identified variants. This classification is coupled with pharmacogenomic annotations from PharmGKB to interpret the clinical relevance of each variant, especially in the context of specific drug pathways.

The preliminary data generated so far have revealed region-specific drug–pharmacogenomic marker pairs. These findings have the potential to inform national healthcare policies, promote the implementation of pharmacogenomics in routine clinical practice, and contribute to broader European efforts in integrating genomics into public health.

CLINICAL IMPLEMENTATION OF PHARMACOGENETICS II

Clinical implementation of pharmacogenetics for routine drug prescription: what are the unmet needs

Ron H. N. van Schaik[1]

[1]*Erasmus MC – University Medical Center, Department of Clinical Chemistry, Rotterdam, The Netherlands*

Introduction: Using the acquired knowledge on pharmacogenetics (PGx) to provide a laboratory service for routine care has its own challenges. We reflect on 20 years of routine PGx testing.

Methods: We analysed PGx test request at our laboratory for the last 20 years, analysed trents and developed a strategy for the next years

Results: PGx test request increased yearly, starting from 25 requests in 2005 to 32,000 in 2024. During the years, we saw increases (CYP2C19, DPYD, UGT1A1) and decreases (HLA-B*5701) of specific genotypings. In a nation-wide survey of ISO15189 certified laboratories in the Netherlands offering PGx testing, we noticed differences in turn-around-times but also in alleles/gene tested and in a few cases in interpretation.

Conclusions: Harmonization in laboratory testing for PGx, reporting and advising are essential to maintain the diagnostic value of PGx testing.

Implementation of pharmacogenetics in the oncological clinical practice: from chemotherapy to oral targeted agents

Erika Cecchin[1]

[1]*Experimental and Clinical Pharmacology Unit, CRO-Centro di Riferimento Oncologico di Aviano - IRCCS, Aviano, Italy*

Large, prospective implementation studies conducted in Europe have shown that prior application of pharmacogenetics (PGx) to guide therapeutic decisions is feasible and improves patient safety outcomes. However, a review of the activity of laboratories providing PGx testing in Italy demonstrated a high level of heterogeneity in clinical practice. In addition, a thorough review of the RCP of drugs approved by the Italian Drug Agency showed that recommendations on pharmacogenetic testing should be made clearer and more consistent. In this context, the current state of the art of pharmacogenetics implementation in Italy is still limited to a few successful examples, such as DPYD and UGT1A1 for treatment personalization of the anticancer chemotherapeutic agents fluoropyrimidine and irinotecan.

Moving into the era of new targeted oral anticancer drugs, the dose and schedule are still based on the "one-size-fits-all" paradigm, with dose adjustments driven by the appearance of toxicity or lack of efficacy. This results in about 60 percent of patients having plasma drug exposure outside the estimated therapeutic range. Frontline use of PGx may be effective in reducing interindividual variability in both plasma exposure and clinical outcome of patients. However, its application is still lagging for targeted oral agents, and one of the reasons is related to the fact that their metabolism is mainly mediated by CYP3A family enzymes, with the related problem of "missing heritability." In addition, many other factors may interact with a patient's PGx profile, such as concomitant medications or food intake, comorbidities (e.g., obesity, Covid-19), and lifestyle habits (e.g., smoking). There is growing evidence of the clinical benefits of intensified medication assistance in terms of pharmacogenetics, therapeutic drug monitoring (TDM), and co-medication management. We are now enrolling patients treated with targeted oral anticancer drugs in a prospective clinical implementation study (NCT06822959) that integrates PGx with TDM and drug-drug interaction analysis to improve patient management.

Acknowledgment: All the researchers of Experimental and Clinical Pharmacology Unit and all the oncologists of the Institute.

Implementation of pharmacogenomics testing: lessons learnt from the PREPARE study

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The Ubiquitous Pharmacogenomics (U-PGx) project and the PREPARE study implemented pre-emptive, panel-based pharmacogenetic (PGx) testing across seven European countries to generate robust scientific evidence on the impact of PGx-guided therapy on patient outcomes. The PREPARE study offered critical insights into the design, execution, and interpretation of future clinical implementation studies in pharmacogenomics. It identified key barriers to implementation in diverse healthcare settings and provided enabling tools and solutions to support clinical implementation.

The PREPARE study demonstrated that current genotyping technologies allow for rapid and reliable analysis of pharmacogenetic variants, with turnaround times sufficient to inform timely, evidence-based prescribing. Despite the diversity in the health care IT infrastructures across participating countries, a clinical decision support (CDS) system was successfully developed and, where feasible, integrated into electronic health records (EHRs). In settings with less developed digital infrastructure, alternative solutions such as printed reports or portable PGx documentation (e.g., "safety code" cards or pharmacogenetic passports) provided effective solution for delivering PGx information.

However, substantial challenges remain, notably the lack of reimbursement for PGx testing in some countries, limited incorporation of PGx recommendations into clinical guidelines, and low adoption among healthcare providers. These issues are compounded by insufficient awareness, education, and confidence among clinicians regarding the use and interpretation of PGx testing and associated guidelines.

CLOSING LECTURES

Ongoing challenges in implementing pharmacogenomics in the clinic

Ann K. Daly[1]

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Clinical implementation of pharmacogenomics remains patchy, especially in Europe, where there has been excellent progress in certain countries though overall progress across the continent is more limited. This presentation will use the United Kingdom (UK) as an example. In the UK, there has been comprehensive implementation of pharmacogenotyping when it is a regulatory requirement, such as for HLA-B*57:01 prior to abacavir prescription and DPYD for the fluoropyrimidines. Guidance from National Institute for Health and Care Excellence (NICE) and professional societies has assisted in implementation of genotyping for certain additional genes within the UK National Health Service but genotyping for well studied pharmacogenetic polymorphisms such as those in CYP2D6 and SLCO1B1 is not available widely to prescribers. The challenges in widening the availability of well established pharmacogenetic tests in the UK will be considered with the example of warfarin used as an illustration. Pathways towards more general implementation of pharmacogenomics in the near future will be discussed.

SHORT TALK ABSTRACTS

Tiopurine pharmacogenomics and TDM in Slovenia

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Introduction: Thiopurine drugs are the key element of the maintenance therapy of paediatric acute lymphoblastic leukaemia (ALL). Therapeutic drug monitoring (TDM) and pharmacogenetic testing are the basis of the personalisation of the thiopurine therapy. While TDM involves measurement of thiopurine metabolites (6-TGN and 6-MMP), the standard pharmacogenetic testing includes genotyping of *TPMT* and *NUDT15*.

Methods: This exploratory study on the Slovenian population involved 37 children with ALL on the thiopurine therapy and 161 healthy individuals with no exposure to thiopurine drugs. TDM measurement in ALL patients and TPMT activity determination in healthy individuals were done using HPLC method. Genotyping of *TPMT* and *NUDT15* in patients and control group was done using next generation sequencing (NGS) and Sanger sequencing, respectively. We examined the influence of the abovementioned genotypes on the following therapy outcomes in ALL patients: relative cumulative dose of thiopurines (RCD), levels of thiopurine metabolites, WBC and neutrophil count, and liver enzymes levels. In healthy individuals we examined the influence of *TPMT* variants on TPMT activity.

Results: No TPMT*2 and *3 alleles were found in ALL cohort; thus, we screened the entire *TPMT,* and identified 6 SNPs already described in PharmGKB and 58 SNPs of unknown influence on thiopurine therapy outcomes. Of these, rs2518469 was associated with lower TPMT activity and showed a trend towards lower RCD and 6-MMP levels, while rs17839843 was associated with high RCD and 6-MMP. Sequencing of *NUDT15* revealed 8 variants, of which only one was described in PharmGKB (*NUDT15**3). None of the variants was associated with RCD in ALL patients, but variant rs79687000, found only in healthy individuals, was predicted as deleterious and splice altering by two bioinformatic tools.

Conclusions: Deciphering mutational profiles of *TPMT* and *NUDT15* might improve the safety and efficiency of thiopurine therapy in Slovenia.

Acknowledgements: We would like to thank Elvisa Smajlović, Jaka Klemen and Maja Mahorič for the technical assistance.

Pharmacogenetic insights into treatment resistance in psychiatry: a clinical perspective

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Introduction: A substantial proportion of patients with psychiatric disorders do not respond adequately to standard pharmacotherapy. Approximately 30% of patients with depression and up to two-thirds of patients with psychotic disorders remain partially or fully treatment-resistant. Adverse drug reactions (ADRs), polypharmacy, and poor adherence further complicate treatment outcomes. Interindividual pharmacokinetic and pharmacodynamic variability, driven by functional genetic polymorphisms, contributes significantly to these differences in therapeutic response.

Methods: We present two clinical cases of psychiatric illness resistant to psychopharmacotherapy: one with major depressive disorder and one with schizophrenia. In both cases, pharmacogenetic analysis was conducted focusing on *CYP1A2*, *CYP3A4*, *CYP2B6*, *CYP2C19*, and *CYP2D6*. Genotyping was used to identify enzyme activity profiles, which were then used to guide individualized pharmacological strategies.

Results: In the first case, a patient with treatment-resistant depression experienced multiple pharmacotherapy failures due to both inefficacy and numerous adverse drug reactions. Pharmacogenetic testing identified altered metabolism in several cytochrome P450 enzymes. Based on these results, a tailored pharmacological approach was implemented, involving the careful titration of quetiapine and maprotiline. This strategy led to significant clinical improvement and remission within weeks.

In the second case, a patient with schizophrenia did not respond to clozapine and experienced pronounced hypersalivation. Genotyping revealed a CYP1A2 *30/*30 ultrarapid metabolizer phenotype and normal CYP2D6 activity. These findings provided a pharmacokinetic explanation for both the reduced efficacy and increased side effects of clozapine. Subsequent treatment with a high-dose olanzapine regimen (up to 60 mg/day) restored therapeutic efficacy, likely compensating for accelerated drug clearance.

Conclusions: Pharmacogenetic profiling offers valuable insights into the mechanisms underlying treatment resistance in psychiatry. Incorporating genotyping into clinical decision-making may improve outcomes by optimizing drug selection and dosing, particularly in complex or refractory cases.

Acknowledgements: We thank participating clinicians and patients who contributed to these case analyses.

Active pharmacovigilance trial integrating pharmacogenetics, TDM, and drug-drug interaction analyses in oncology

Diletta Pasin[1], Bianca Posocco[1], Sara Gagno[1], Eleonora Cecchin[1,2], Riccardo Cecchin[1], Elena Peruzzi[1], Rossana Roncato[1,2], Angela Buonadonna[3], Lucia Fratino[3], Fabio Puglisi[2,3], Paola Rossi[4], Paolo Baldo[5], Gabriele Stocco[6], Anna Arbo[7], Giuseppe Toffoli[1], Cecchin Erika[1]

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Introduction: Integrating pharmacogenetics (PGx), therapeutic drug monitoring (TDM), and drug–drug interaction (DDI) assessments (MedReview) into routine clinical management of oral anticancer drugs (OADs) holds the potential to optimize their use and enhance adverse drug reaction (ADR) management. A prospective observational clinical trial (NCT06822959) is ongoing at CRO-Aviano and IRCCS Burlo Garofolo (Trieste) to implement an active pharmacovigilance strategy aimed at optimizing OAD therapy. The primary goal is to assess feasibility and compare ADR incidence with standard clinical practice.

Methods: At CRO-Aviano, consenting adult cancer patients eligible for OADs (palbociclib, ribociclib, abemaciclib, olaparib, niraparib, imatinib, sunitinib) underwent PGx analysis and periodic TDM (including dried blood spot sampling where applicable). Co-medications, co-morbidities, adherence, and ADRs were collected through interviews. DDI assessments used Lexicomp, and oncologists received integrated pharmacological counseling reports.

Results: To date, 160 patients (69% of those eligible) were enrolled at CRO-Aviano, with higher rates among those prescribed drugs supported by TDM/PGx guidelines. TDM revealed out-of-range drug exposure in 56% of patients; PGx identified actionable variants in 27%. Clinically relevant DDIs were detected in 24%, including grade D interactions (therapy modification recommended). These findings led to 227 pharmacological consultations. Retrospective ADR review (completed in 29%) showed that 58% experienced clinically relevant toxicity, prompting dose reduction (84%), therapy discontinuation (9%), or treatment change (7%). Eleven ADRs were reported to the Italian Medicines Agency (AIFA). Preliminary data suggest comorbidities (e.g., COVID-19) may be associated with increased exposure or toxicity. Final analysis will follow completion of patient follow-up and will integrate pediatric data from Burlo Garofolo.

Conclusions: This active pharmacovigilance study may support a personalized, integrative pharmacological approach to optimize OAD treatment, identify under-/over-exposure and PGx risks, reduce preventable ADRs, and enhance ADR reporting quality.

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Weight loss maintenance metabolome and microbiome predictors

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Background: Obesity poses many health-related and societal problems—successful weight loss maintenance (WL & WLM) remains challenging. The Finnish ELIPA food intervention study for WLM targeted this challenge while measuring gut microbiome and metabolome changes. We evaluated these omics factors contribution to WLM.

Methods: The 33-week ELIPA study included sampling at four stages: baseline before weight loss (Stage 1: week 0), post-weight loss/pre-maintenance (Stage 2: week 9), mid-maintenance (Stage 3: week 21), and post- maintenance (Stage 4: week 33) Omics velocity profiles (rates of change during WL) were analysed after adjusting for covariates and excluding highly correlated features. Random forest models were used to identify top predictors: one model in the full cohort (anthropometrics, biomarkers, metabolomics), and one in a subset (n=34) including microbiome and transcriptomic data.

Results: Blood test results showed improvements in glucose and insulin levels at 0', 30', and 120' of the OGTT, along with reduced insulin resistance (HOMA-IR) during the weight-loss (WL) period and in the loss/stable tertiles during weight maintenance (WM). Random forest analysis identified key predictors of the three weight trajectories (loss, stable, gain). In the full cohort, triglyceride reduction was the top predictor of weight loss, followed by systolic blood pressure, lysophosphatidylcholine (20:1), and an unknown glycosidic compound. Notably, this unknown glycosidic compound was important across all weight outcomes. In a subset analysis, FRMD6 gene expression changes predicted both weight gain and loss, while shifts in microbiome enterotype cluster 2 were associated with weight gain and maintenance, suggesting these factors may interact with diet or other variables.

Conclusion: Dynamic changes in metabolites, gene expression, and gut microbiome composition during WL are associated with long-term WM outcomes, highlighting potential targets for personalised weight maintenance strategies.

THURSDAY, 05. 06. 2025

Uncovering treatment-responsive immune pathways in multisystem inflammatory syndrome in children (MIS-C) through single-cell multiomics

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Background: Multisystem Inflammatory Syndrome in Children (MIS-C) shows highly variable responses to immunomodulatory therapies—IVIG, corticosteroids, anticoagulation—and emerging biologics. High-resolution single-cell and bulk multiomic profiling can delineate the specific pathways each treatment modulates.

Methods: Nineteen pediatric MIS-C patients at University Children's Hospital Ljubljana were sampled during acute, pre-treatment flare and again 6–12 months into remission. Analyses included plasma cytokine quantification, single-cell RNA and ATAC sequencing (89 154 cells), and bulk RNA-seq.

Results: Integrated multiomic profiling revealed that each frontline therapy counteracts distinct features of acute hyperinflammation. IVIG sharply reduced IFN-γ–driven cytokines (IL-6, IL-18) and chemokines (CXCL10), effectively reversing the cytokine storm. Corticosteroids broadly suppressed pro-inflammatory transcriptional programs across lymphoid and myeloid compartments. Anakinra disrupted the IL-1β/IL-18–driven inflammasome feedback loop, consistent with elevated IL-1RA signatures during flares. Finally, aspirin with low-molecular-weight heparin attenuated endothelial activation and thromboinflammatory signals by opposing VEGF upregulation and chemokine-mediated vascular injury.

Conclusions: By mapping each therapy directly onto the molecular pathways driving MIS-C pathology, our findings provide a mechanistic framework for refining treatment strategies and support future efforts toward personalized immunomodulation.

Epigenetic biomarkers of nusinersen treatment in children with SMA

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Background: Spinal muscular atrophy (SMA) is a genetic motor neuron disease marked by progressive muscle weakness; current therapies include intrathecal nusinersen, onasemnogene abeparvovec gene therapy, and oral splicing modifier risdiplam, yet the impact of these treatments—particularly nusinersen—on the epigenome remains unknown. In this hypothesis-building, exploratory study, we examine genome-wide DNA methylation changes and their potential influence on global gene expression following nusinersen treatment.

Methods: Twenty-four SMA patients received intrathecal nusinersen and provided peripheral blood samples at baseline (0 months {m}), 12 m, and 24 m. Oxford Nanopore–based sequencing of equimollary pooled genomic DNA was used to identify differentially methylated loci (DML) and regions (DMR) across two intervals (0–12 m and 0–24 m), and enrichment analysis (Enrichr) mapped associated genes to canonical signaling pathways.

Results: Between baseline and 12 months, 3.604 DML and 43 DMR were detected, with significant enrichment of Netrin-1 signaling and Notch signaling pathways involved in axon guidance and motor neuron differentiation. From baseline to 24 months, 2.810 DML and 59 DMR remained altered, reflecting sustained epigenetic remodeling of Notch signaling. Comparison of the 12–24 month interval revealed 837 shared DML and 12 shared DMR, underscoring persistent methylation shifts within neurodevelopmental pathways.

Conclusions: Nusinersen therapy induces widespread DNA methylation alterations, particularly within Netrin-1 and Notch signaling networks critical for motor neuron function. These epigenetic changes suggest an additional mechanism of action for nusinersen and warrant further investigation into downstream gene-expression effects.

miRNA biomarkers in osteoporosis: a pharmacoepigenetic view of teriparatide response

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Introduction: Treatment response to teriparatide (TPTD), a potent anabolic therapy for postmenopausal osteoporosis, varies significantly among patients. Identifying predictive biomarkers could enhance personalized treatment strategies. This study aimed to identify the potential of circulating microRNAs (miRNAs) and evaluate them as pharmacoepigenetic biomarkers of TPTD response.

Methods: Candidate miRNAs were identified through transcriptomic analysis of bone mesenchymal stem cells treated with TPTD during osteogenic differentiation. We constructed a miRNA–mRNA interactome to identify key proteins associated with TPTD's mechanism of action. This approach revealed four miRNAs that were selected for further validation: hsa-miR-375-3p, hsa-miR-20b-5p, hsa-miR-133a-3p, and hsa-miR-31-3p. We assessed these miRNAs in serum from 44 postmenopausal women with osteoporosis treated with TPTD for 12 months. Patients were stratified as responders or non-responders based on a ≥3% lumbar spine BMD increase.

Results: The constructed miRNA-mRNA interactome has 465 miRNA and 1341 interactions. These miRNAs were highly enriched in bone signaling pathways, namely Foxo signaling pathway, TGF-ß signaling pathway and Hippo signaling pathwyay. At baseline, responders showed significantly lower levels of miR-375-3p ($P = 0.0002$), miR-133a-3p ($P = 0.085$), and miR-31-3p ($P = 0.0175$). After 6 months, lower levels of miR-375-3p ($P = 0.0031$), miR-20b-5p ($P = 0.0008$), and miR-133a-3p ($P < 0.0001$) were observed in responders. Changes in lumbar spine BMD correlated significantly with miR-375-3p and miR-133a-3p at both time points and with miR-31-3p at baseline.

Conclusions: This two-tiered approach identified and validated miRNAs with the potential to predict response to anabolic osteoporosis therapy. These miRNAs merit further development as biomarkers for personalized osteoporosis treatment.

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POSTER ABSTRACTS

Dissecting the pharmacogenetic landscape of *GLP1R* variants: metabolic and mental health implications

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Introduction: Glucagon-like peptide-1 receptor (GLP-1R) plays crucial role in glucose metabolism and insulin secretion. GLP-1R agonists target GLP-1R while simultaneously bring changes to body weight and mental health, including depression. Missense variants in *GLP1R* gene change response to GLP-1R agonists by affecting the receptor structure and function, potentially leading to side effects. We investigated *GLP1R* gene variants role in glucose metabolism, body mass index (BMI), and depression.

Methods: We analysed 72 coding missense variants in *GLP1R* gene from UK Biobank whole-exome sequencing data, determining their effect on structure via simulations, function via experimental evaluation of MiniGs-coupling/endocytosis, and associations with blood glucose, HbA1c, type 2 diabetes (T2D), BMI, and depressive phenotypes via association analysis with SAIGE, followed by unsupervised hierarchical clustering.

Results: We identified five distinct clusters of *GLP1R* variant structural/functional/phenotypic effects across six metabolic/mental phenotypes, determining their respective pathophysiological effects. Specifically, **ClusterA** 22 variants associated with improvement in metabolic/mental health**. ClusterB** 16 variants **had** positive effects on mental health, but no improvement in metabolic health. **ClusterC** 15 variants showed no improvement in metabolic health, potential issues with mental health. **ClusterD** 12 variants had positive metabolic health effects, but associated with mental health issues. Finally, **ClusterF** 7 variants **lowered adiposity** alongside glycaemic/mental health issues.

Conclusion: We report pharmacogenetic heterogeneity in the effects of *GLP1R* variants on glucose metabolism, adiposity, and mental health. Our findings reveal distinct mechanistic clusters that influence individual responses to GLP-1R mimetics, driven by underlying genetic variation. These insights underscore the importance of pharmacogenetics in guiding stratified treatment strategies for improved efficacy and reduced side effects.

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Assessing miRNAs, mRNA targets, and lncRNAs as biomarkers for spinal muscular atrophy

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Introduction: The advent of therapies for spinal muscular atrophy (SMA) has significantly impacted the clinical course of SMA; however, reliable molecular biomarkers for disease progression and treatment monitoring remain limited. This study analysed the expression profiles of four SMA-associated miRNAs, ten bioinformatically predicted mRNA targets, and two interacting lncRNAs.

Methods: Whole blood samples from 50 SMA patients were analysed to quantify the expression levels of selected RNAs using the RT-qPCR method. Pre-treatment expression levels were analysed for associations with SMA type, ambulatory status, and motor and respiratory function. Longitudinal analyses were performed to assess expression dynamics during nusinersen treatment at 24 months and risdiplam treatment at 6 and 12 months.

Results: Expression of miR-206 was significantly higher in SMA type III patients compared to type II, consistent with the increased levels observed in ambulatory patients compared to non-ambulatory patients. In contrast, miR-1-3p levels were significantly lower in type III patients compared to type II patients. Several transcripts, including miR-133a-3p, miR-133b, miR-206, *HDAC4*, and LINCMD1, showed correlations with motor function; however, only the association with miR-206 remained significant following adjustment for age, disease duration, and *SMN2* copy number. In addition, miR-133a-3p, miR-133b, and miR-206 levels were significantly associated with respiratory function, with associations remaining significant after adjustment. Longitudinal analysis revealed significant downregulation of several transcripts, including miR-206, *PGD, G6PD, TKT, HDAC4, SP1*, LINCMD1, and GJA1 after 24 months of nusinersen treatment. Conversely, risdiplam administration resulted in significant downregulation of miR-133a-3p at 6 months of treatment, with no significant changes observed in other miRNAs, target mRNAs, or lncRNAs at 6 or 12 months.

Conclusions: Dysregulated miRNAs, along with their target mRNAs and interacting lncRNAs, are implicated in SMA pathogenesis and represent promising biomarker candidates for assessing disease severity and treatment monitoring.

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Personalized Medicine for Healthy Aging: the role of pharmacogenomics within the interdisciplinary approach to aging

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Introduction: The society in which we live is ageing and the need to enable and maintain a healthy lifestyle for the elderly population is growing. The project aims to develop tools for personalised assessment of ageing in order to make personalised and general recommendations and to design prevention programmes or 'lifestyle programmes'. A broader aim of the project is also to assess the extent to which such analyses can be implemented in the public health system, taking into account the costs of such analyses and the savings that could be achieved through preventive screening.

Methods: Through an innovative approach combining cutting-edge technologies and digital tools, we aim to obtain a holistic picture of the biological ageing of an individual and the society to which they belong. We will collect and integrate data on a person's family history, lifestyle, physical fitness, dietary habits, social factors, genome, epigenome, pharmacogenome, microbiome and metabolome. We will then create individual digital twins and provide personalised recommendations for healthy ageing.

Results: We expect that by integrating heterogeneous data from a variety of sources, we can more accurately predict biological ageing and the onset of associated diseases for an individual. We have already obtained permission from the National Medical Ethics Committee of the Republic of Slovenia and have conducted a pilot study on a smaller number of individuals. With the long-read ONT PromethION technology for genome sequencing and state-of-the-art analyses tools, we will obtain data on the genome, epigenome and pharmacogenome with a single sequencing analysis.

Conclusions: Using an interdisciplinary approach, we will develop new tools for data analysis, integration as well as digital models for predicting biological aging.

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Pregnancy loss genome-wide association study in UK Biobank replicates associations with common variants at *FAF1* and *PRAG1*

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Background: Pregnancy losses affect 15% of recognised pregnancies. The largest genome-wide association studies (GWAS) on pregnancy loss identified 10 associated loci with sporadic miscarriage (Reynoso et al, 2024, medrxiv:2024.03.20.24304624). Few of these loci are replicated primarily due to challenges in defining the phenotypes. This study investigated pregnancy loss susceptibility using multi-modal data from UK Biobank.

Material and Methods: In UK Biobank European ancestry women, we selected 44,891 cases with self-report or electronic health record (EHR) of pregnancy loss (ICD10: O03, O02.1, N96, O26.2) and 116,060 controls with live birth and no history of pregnancy loss. We performed a GWAS with REGENIE software tool, which accounts for population structure, for 10,880,079 single nucleotide variants (SNVs) with minor allele frequency (MAF)≥0.006 from the genome-wide imputed data, using a ridge regression-based model. We also examined eight previously associated loci that were available in our dataset.

Results: We identified suggestive (P-value<10^{-5}, MAF>0.05) associations at/near genes implicated in pregnancy loss mechanisms, including *DOCK8* (immune response), *TRIM29* (cell differentiation), and *PSMF1* gene (protein turnover). We also replicated two association signals (Bonferroni corrected P-value<0.00625, 8 tests), at *FAF1* (rs10888690-C, effect allele frequency (EAF)=0.41, OR (95%CI) = 1.023 (1.0067-1.039), P-value=0.0052) and *PRAG1* (rs2920991-A, EAF=0.50, OR (95%CI) = 1.023 (1.0073-1.039), P-value=0.0040).

Conclusion: We successfully replicated associations at genes involved in cell cycle regulation and cell morphology regulation, using a more stringent control definition of female participants with live birth and no EHR or self-report of pregnancy loss, despite using less than a quarter of the replication dataset sample size from the original study. Our findings may improve pregnancy loss risk prediction leading to better pharmacogenomic strategy in pregnancy management.

Association of variants in candidate pharmacogenes with response to mercaptopurine and methotrexate drugs in pediatric ALL

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Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Around 20% of patients experience relapse, which results in a fatal outcome in about half of those cases. There is a significant problem with adverse response to therapy, which can leave long-term consequences and in about 3% of cases ends fatally. Pharmacogenetic markers for thiopurines are already used in clinical practice, but this is not the case for other drugs used in the treatment of ALL, including methotrexate. There is a need to further study the effect of pharmacogenetic variants that have the potential to personalize the treatment of ALL. The aim of this study was to determine the association of variants in candidate pharmacogenes with response to mercaptopurine and methotrexate drugs in pediatric ALL.

Methods: PCR and sequencing-based methodology was used to detect variants in following genes: *ITPA, NUDT15, PACSIN2, TPMT, MTHFR, SLCO1B1, SLC19A1 and THYMS*, in a cohort of 43 pediatric ALL patients from the Clinical Hospital Center Rijeka, Croatia. Statistical analyses were performed to investigate their association with markers of response to ALL therapy.

Results: Association analyses have shown that the variant rs1051266 in the *SLC19A1* gene was significantly associated with hepatotoxicity from methotrexate treatment, while the variant rs1127345 in the *ITPA* gene was significantly associated with an incidence of dosage lowering due to poor response to mercaptopurine. No other variants were significantly associated with adverse reactions to these drugs.

Conclusions: Our study has shown that variants in the *SLC19A1* and *ITPA* genes have the potential to affect the response to ALL therapy in a clinical setting. A comprehensive approach combining these and previously established pharmacogenetic markers into a polygenic risk score model to guide treatment protocols could be a further step towards personalized treatment of ALL.

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Influence of *HIF1A* gene variants on cisplatin sensitivity in malignant mesothelioma

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Introduction: Malignant mesothelioma (MM) is a rare, aggressive cancer of pleura and peritoneum that is primarily associated with asbestos exposure. Due to late diagnosis and limited chemosensitivity, the prognosis remains poor. Standard therapies usually include cisplatin in combination with pemetrexed or gemcitabine. The chemoresistance of MM is associated with tumour's ability to adapt to hypoxic environment, which increases the expression of hypoxia-inducible factor 1A (HIF-1A). Elevated levels of HIF-1A may contribute to reduced efficacy of cisplatin. The aim of this study was to investigate the association between *HIF1A* gene polymorphisms and response to cisplatin-based chemotherapy in Slovenian MM patients.

Methods: This retrospective study included 234 patients with histologically confirmed malignant mesothelioma (MM) who received cisplatin/pemetrexed or cisplatin/gemcitabine doublet chemotherapy at the Institute of Oncology in Ljubljana. Genotyping of *HIF1A* rs11549465, rs11549467 and rs2057482 polymorphisms was performed by quantitative allele-specific PCR. Logistic regression, nonparametric tests or the Cox proportional hazards model were used to assess the associations of these polymorphisms with response to chemotherapy.

Results: No significant association was found between *HIF1A* rs11549467 or rs2057482 polymorphisms and chemotherapy treatment outcomes. However, carriers of the rs11549465 CT genotype showed modest but statistically significant reduction in response to chemotherapy after adjusting for weight loss and C-reactive protein (CRP) ($p = 0.044$).

Conclusion: In our study only rs11549465 showed some association with response to cisplatin-based chemotherapy in MM patients, suggesting a minor role of the investigated *HIF1A* polymorphisms in treatment outcomes.

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dPCR application in pharmacogenetics

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Introduction: Pharmacogenetics is transforming personalized medicine by enabling drug therapies to be customized based on an individual's genetic profile. Accurate detection of genetic variations—particularly single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and structural variations—is essential for understanding variable drug responses. Key pharmacogenes such as *CYP2D6, CYP2C19*, and *TPMT* play critical roles in drug metabolism. However, traditional genotyping methods like quantitative PCR (qPCR) and next-generation sequencing (NGS) can face challenges in sensitivity, quantitative accuracy, and clinical turnaround times, limiting their real-time clinical utility**.**

Methods: Digital PCR (dPCR), especially digital droplet PCR (ddPCR), provides absolute quantification, high precision, and improved sensitivity, making it a compelling alternative for pharmacogenetic applications. We reviewed current literature and technological developments regarding dPCR in genotyping, haplotyping, CNV detection, and therapeutic drug monitoring. Key platforms, including Bio-Rad's QX200 and Thermo Fisher's Absolute Q, were assessed in terms of performance, scalability, and clinical integration potential. Advances in multiplexing strategies and assay design were also evaluated.

Results: Our review indicates that dPCR outperforms conventional methods in detecting rare alleles, quantifying complex CNVs, and monitoring gene therapy outcomes. The technology allows for rapid, reproducible measurements with lower input requirements and fewer amplification artifacts. Comparative analyses highlight the QX200's established workflow and the Absolute Q's streamlined, integrated design. However, limitations persist in resolving large structural variants and achieving standardized protocols across laboratories.

Conclusions: Despite current challenges, dPCR is well-positioned to enhance the precision and efficiency of pharmacogenetic testing. Its adoption in clinical settings may support individualized drug therapies, guide dose optimization, and complement NGS for a more comprehensive molecular profile.

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Comprehensive pharmacogenomics profiling of the Serbian population

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Introduction: Pharmacogenomics offers a possibility of anticipating drug response based on individuals' genetic profiles and represents a step toward implementation of personalized treatment through routine genetic testing. Development of high-throughput sequencing technologies aided identification and interpretation of variants in many pharmacogenes simultaneously. Nonetheless, the integration of pharmacogenomics into clinical practice is arduous, partly due to insufficient knowledge of ethnic pharmacogenetic data. The aim of our study was to assemble the most comprehensive pharmacogenomics landscape of the Serbian population so far.

Methods: Genomic data of 881 individuals from Serbia were obtained by clinical and whole exome sequencing. Raw sequencing files were processed using an in-house pipeline for alignment and variant calling. For annotation of pharmacogenetics star alleles and determination of phenotypes, the PharmCAT and Stargazer tools were implemented. Star allele and phenotype frequencies were calculated and compared to the worldwide and European populations. Population differentiation was presented through calculation of the Wright's fixation index.

Results: Results showed that population differentiation was the highest between the Serbian and the worldwide population. In the Serbian population, the most relevant pharmacogenes in terms of star allele frequencies and actionable phenotypes were *CYP2B6*, *NAT2*, *SLCO1B1*, *UGT1A1* and *VKORC1*, that had significantly different distribution compared to other European populations.

Conclusions: In conclusion, significant differences in frequencies of pharmacogenetic phenotypes that influence response to several drug categories including statins and antidepressants indicate that inclusion of data relevant for drug response to genetic reports would be beneficial in the Serbian population. Implementation of pharmacogenetic testing could be achieved through analysis of clinical and whole exome sequencing data.

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Blood DNA methylation signatures for more common forms of pulmonary hypertension

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Introduction: Pulmonary hypertension (PH) describes conditions characterised by increased blood pressure in the pulmonary artery and right heart, leading to premature death by heart failure. PH may be idiopathic but its familial forms are associated with identifiable genetic variants. Epigenetic variation in PH broaches the potential for pharmacological targets and clinically relevant biomarkers, and a means by which to understand disease penetrance. Our recent pilot study [1] from the UK PAH cohort established three significantly associated epigenomic loci hypermethylated in pulmonary arterial hypertension (PAH) (*CTSZ*, *COG6*, and *ZNF678*). Our replication study aims to validate and build upon these findings by conducting an epigenome-wide association study (EWAS) on blood DNA methylation data from individuals with PH of more common aetiologies alongside PAH, and performing a meta-analysis combined with pilot data.

Methods: We performed quality control (QC) on new IlluminaEPICv2.0 methylation data for 375 individuals (415 before QC): 116 symptomatic controls, 64 PAH patients and 195 patients under three further PH diagnostic groups. We used the CPACOR pipeline [2] and the GLINT command-line tool to pre-process the raw methylation data, and EpiSmokEr to infer smoking status. Alongside the pilot study, total number of cases post-QC including all individuals with PH is 688, with 1,242 controls.

Results: We will conduct a case-control analysis combining the total sample data in a meta-analysis and investigate potentially discernible differences in methylation patterns between PH subtypes and potentially explore the clinical implications of such epigenetic mechanisms. We will present the results of our meta-analysis of these two studies.

Conclusion: By expanding the PH analysis, we will produce robust EWAS expanding the knowledge about molecular signatures of this rare condition.

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Utilisation patterns and results of pharmacogenetics tests in treatment of paediatric haematological malignancies during 2019-2024

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Introduction: Pre-emptive pharmacogenetic testing is routinely used for thiopurine-containing dosing regimens in malignant diseases in paediatric cancer population in Finland. We studied the utilisation of pharmacogenetic tests and use of drugs with pharmacogenetic dosing guidelines of patients treated in a paediatric haematological unit of Turku University Hospital, Turku, Finland.

Methods: Patients were identified from electronic health records based on haematological malignancies and being genotyped for *TPMT* or with pharmacogenetic panel test during years 2019 - 2024. From the included patients, pharmacogenetic test results and prescriptions for drugs with pharmacogenetically actionable dosing guideline were recorded. Firstly, we evaluated use *TPMT* test results in dose reductions according clinical treatment protocols and Clinical Pharmacogenetics Implementation Consortium guideline. Secondly, we calculated incidence of other drugs associated with pharmacogenetic dosing guidelines and actionable gene-drug pairs to evaluate significance of testing.

Results: Altogether 40 patients (20 females, 20 males; age range 1-18 years) were included in this study. Patients were mainly diagnosed with acute lymphoblastic leukaemia (n=35), but 5 patients had other malignancies. During the 6-year period, 16 patients were genotyped only for *TPMT* but recently trend has shifted to panel testing, which was used to genotype 24 patients. Three patients were found to have an actionable genotype affecting their TPMT-associated mercaptopurine-treatment. Additionally, actionable genotypes were frequently found in patients genotyped with a panel test, most often in *CYP2C19*, *SLCO1B1* and *VKORC1*. Besides mercaptopurine, most frequently prescribed pharmacogenetically relevant drugs were ondansetron, pantoprazole and ibuprofen.

Conclusions: In Finland, paediatric patients with haematological malignancies treated with thiopurines have routinely been genotyped at least for TPMT during the six-year time. Although relatively few patients had an actionable genotype affecting their mercaptopurine-treatment, results highlight significance of multi-gene panel tests guiding the dosing of other drug treatments as actionable genotypes and drugs other than thiopurines were frequent in this cohort.

Attained and untapped potential of pharmacogenetic panel testing in real-world settings

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Introduction: In recent years pharmacogenetic testing has progressed from single gene tests to multigene panels. The Helsinki University Hospital Diagnostic Center launched a next generation sequencing-based pharmacogenetic panel test in January 2022. The aims of this study were to investigate how widely the pharmacogenetic panel test has been used in the university hospital setting since its launch, whether pharmacogenetic testing reduces gene-drug interactions or hospital costs, how well the test results are taken into account during later clinical encounters, and whether there are patient groups who could potentially benefit from pharmacogenetic testing but are currently not tested.

Methods: This is a retrospective register and biobank study utilizing electronic patient records and pharmacogenetic and other laboratory test results from the HUS Helsinki University Hospital and genome data from the Helsinki Biobank. The study cohort consists of university hospital patients with pharmacogenetic panel test results. Two control cohorts are formed from university hospital patients: one with genome data available from the Helsinki biobank for research use and one without genome data. Each patient enters the cohort during their first encounter with a physician since the start of 2022, and the primary endpoint is a gene-drug interaction during this encounter.

Results: From January 2022 approximately 8,500 Helsinki University Hospital patients had been tested with the pharmacogenetic panel test. Approximately 12% of them also had genome data available in the biobank. In total more than 20,000 patients with a biobank consent had genome data available along with a clinical encounter during the follow-up period. Further results regarding the primary and secondary endpoints will be presented at the course.

Conclusions: Numerous Finnish university hospital patients have existing pharmacogenetic panel test results, which enables physicians to individualize these patients' drug therapy now and in the future.

Association of DNA repair gene polymorphisms with oxidative DNA damage after radiotherapy in ductal carcinoma *in situ*

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Introduction: Ductal carcinoma *in situ* (DCIS) is a non-invasive breast cancer subtype. It is usually treated with surgery followed by adjuvant radiotherapy (RT). RT causes DNA damage either directly or indirectly by increasing oxidative stress within cells. The aim of this study was to determine whether RT affects plasma levels of the oxidative DNA damage biomarker 8-hydroxy-2-deoxyguanosine (8-OHdG) and to investigate the association between single-nucleotide polymorphisms (SNPs) in the DNA repair genes *XRCC1* and *OGG1* are associated with 8-OHdG concentrations in patients with DCIS.

Methods: Our pilot study included 54 DCIS patients undergoing adjuvant RT. Genomic DNA was extracted from blood samples. Genotyping of *XRCC1* (rs2682585, rs1799782, rs25487) and *OGG1* (rs159153, rs1052133, rs293795) SNPs was performed using competitive allele-specific PCR. Oxidative DNA damage in plasma was quantified before and after RT by competitive ELISA for 8-OHdG. Statistical analyses were performed using nonparametric tests.

Results: Concentration of 8-OHdG in plasma did not change significantly after RT (p=0.157). Carriers of two polymorphic *OGG1* rs1052133 alleles had lower 8-hydroxy-2-deoxyguanosine concentration before RT compared to other DCIS patients (p=0.028). In carriers of at least one polymorphic *OGG1* rs159153 (p=0.012) and rs293795 (p=0.033) allele, 8-OHdG concentration increased more after RT compared to carriers of two normal alleles. *XRCC1* polymorphisms were not associated with 8-OHdG concentration.

Conclusions: Our results suggest *OGG1* polymorphisms are associated with plasma oxidative DNA damage levels and might serve as a biomarker of radiosensitivity in DCIS.

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Influence of IL-1β polymorphism rs1143623 on kidney function markers in COVID-19 patients

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Introduction: Interleukin-1 beta (IL-1β) is a key mediator of inflammation implicated in the progression of COVID-19-related organ dysfunction, including kidney impairment. The IL-1β gene polymorphism rs1143623 (C>G) may affect cytokine expression and contribute to interindividual differences in disease outcomes. This study aimed to evaluate the association between rs1143623 and kidney function markers in COVID-19 patients.

Methods: A total of 750 PCR-confirmed COVID-19 patients from the Bosnian population were included and categorized into two groups based on disease severity (mild vs. severe). Genotyping for the IL-1β rs1143623 polymorphism was performed using commercial kits on the Applied Biosystems QuantStudio5 RT-PCR System. Serum levels of urea, creatinine, and uric acid were measured in accordance with standard IFCC protocols. Associations between genotype and kidney markers were assessed using linear regression analysis, adjusted for age and sex.

Results: Linear regression revealed a statistically significant association between the rs1143623 polymorphism and urea levels. Specifically, homozygous carriers of the minor G allele exhibited significantly (p=0.038) lower urea levels (6.70 (5.38-9.53)) compared to carriers of the C allele (7.35 (5.45-11.40)). No significant associations were observed for serum creatinine or uric acid levels in relation to rs1143623 genotype.

Conclusions: Our findings suggest that the IL-1β rs1143623 polymorphism may influence kidney function, particularly urea levels, in COVID-19 patients. This supports the hypothesis that host genetic variation in inflammatory pathways can modulate disease-related metabolic responses. Further studies are warranted to explore the clinical relevance of this association and its potential role in personalized medicine approaches to COVID-19 management.

Uptake of *DPYD* and *UGT1A1* testing in Italy and adherence to pharmacogenetic guidelines

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Aims: Effective pharmacogenetic implementation relies on understanding the current practices of laboratories performing pharmacogenetic testing. This study aimed to evaluate the implementation of pharmacogenetic guidelines and recommendations by Italian laboratories over time, utilizing data from their participation in the EMQN European Molecular Genetics Quality Network (EMQN) Pharmaco-scheme, an external quality assessment (EQA) program established in 2019.

Methods: We began by conducting an overview of the submission trends to the EMQN Pharmaco-scheme across European countries from 2019 to 2023. Subsequently, we performed a detailed year-by-year analysis specifically focusing on Italian laboratories, examining their submission trends to identify emerging patterns over time. Following this, 88 reports focusing on fluoropyrimidine/*DPYD* and irinotecan/*UGT1A1* drug-gene interactions were assessed for genotyping panel selection, methodology, and adherence to guidelines for treatment modification.

Results: Italian laboratories accounted for 45% of all European applications during the five-year study period. A significant increase in *DPYD* and *UGT1A1* testing was observed, with the Italian SIF-AIOM genotyping panel becoming the predominant choice, rising from 0% in 2019 to 97% in 2023. Adherence to at least one guideline (CPIC, DPWG, or SIF-AIOM) increased from 34% in 2021 to 63% in 2023. A significant increase in the adoption of the SIF-AIOM guidelines, uniquely recommending *DPYD*6* testing for post-toxicity assessment, was observed in Italy. Allelic discrimination, particularly using commercial CE-IVD kits, emerged as the preferred genotyping method.

Conclusions: This study provides a snapshot of pharmacogenetic testing practices in Italian laboratories participating in an EQA scheme. It demonstrates a significant improvement in adherence to pharmacogenetic guidelines over time, indicating enhanced awareness and harmonization of clinical pharmacogenetic practice. Participation in External Quality Assessment (EQA) schemes remains crucial for improving pharmacogenetic data use and interpretation.

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PCSK9 Coding Variants Predict Pharmacogenetic Effects of Lipid-Lowering Therapy on Glucose and Type 2 Diabetes Risk

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Introduction: Lipid-lowering medications, particularly statins (HMG-CoA reductase inhibitors), have significantly reduced cardiovascular events and mortality but are linked to an increased risk of type 2 diabetes (T2D). Similarly, inactivating mutations in HMGCR are associated with T2D. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which effectively lower cholesterol, have yielded conflicting data on their role in glucose metabolism and T2D risk. Exploring genetic factors may provide valuable insights to inform clinical practice.

Methods: This study examined the relationship between *PCSK9* missense variants and metabolic traits, including LDL cholesterol, random glucose, and T2D, in 469,835 individuals with whole-exome sequencing data. Statistical methods included single-variant analysis (PLINK), SKAT-O test, and hierarchical clustering to identify potential associations and variant clusters.

Results: Single-variant analysis revealed significant associations between rs374014696 (Ala242Val, OR: 0.51 [0.40–0.65], $p = 1.022 \times 10^{-7}$) and rs773660398 (Ala44Thr, OR: 1.50 [1.26–1.78], $p = 6.735 \times 10^{-6}$) with higher random glucose levels. Clustering analyses identified distinct variant groups. Cluster 1 variants were linked to lower LDL cholesterol and higher glucose. Cluster 2 variants were associated with reduced T2D risk, while Cluster 3 showed a combination of lower LDL, higher glucose, and increased T2D risk. Cluster 4 was associated with increased LDL cholesterol and likely elevated cardiovascular risk.

Conclusions: These findings suggest that certain *PCSK9* missense variants are associated with cholesterol reduction, increased glucose levels, and heightened T2D risk. Genetic profiling may optimise lipid and glucose management strategies, emphasising the need for further studies in diverse populations.

Genomics for a healthier Europe: sequencing, diversity, and data in the 1 + Million Genomes Initiative

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Genetic information is becoming increasingly important in diagnostics, prognosis and disease prevention, especially as whole genome sequencing becomes more affordable. This change enables the identification of genetic and epigenetic factors associated with disease, with most human genome sequences now coming from research and healthcare. Responsible data sharing could increase population diversity in genomic datasets, improve the accuracy of genomic analysis and advance precision medicine. To support this progress, the European Commission is funding the Genomic Data Infrastructure (GDI) project under the 1+ Million Genomes (1+MG) initiative, which aims to collect more than one million European genomes. The objective is to enable secure, federated access to genome data for research, clinical applications and policy-making, while complying with ethical and legal standards in all member states.

Slovenia is also setting up a national node aligned with the European infrastructure to contribute to these efforts. The first use case, the Genome of Europe (GoE) project, focuses on sequencing at least 100,000 healthy individuals — including 500 from Slovenia — to build a reference database of genetic variations in different population groups. An important part of the project is the investigation of pharmacogenomic variants, which represent a specific GoE use case. These variants will be analysed by searching for individual variants to determine allele frequencies in different ancestry groups. This work will help to identify potential inequalities in access to genomic medicine and promote more equitable and informed clinical decision making across all Europe.

Impact of co-medications and *CYP2D6* genotype on tamoxifen efficacy in Moroccan ER+ breast cancer patients

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Estrogen receptor-positive (ER+) breast cancer patients face two significant challenges in tamoxifen therapy. First, the therapeutic efficacy of tamoxifen relies on its bioactivation into active metabolites by the highly polymorphic CYP2D6 enzyme, leading to variability in enzymatic activity among individuals [1]. Second, many breast cancer patients experience depression or tamoxifen-related side effects, necessitating the use of co-medications such as selective serotonin reuptake inhibitors (SSRIs). However, these antidepressants are known CYP2D6 inhibitors, further compounding the impact of genetic polymorphisms on tamoxifen metabolism [2]. This dual challenge presents a critical obstacle for patient management, particularly in Morocco, where limited data exist on the interplay between *CYP2D6* polymorphisms, co-medications, and tamoxifen efficacy [3]. Therefore, our study aims to evaluate the combined influence of *CYP2D6* polymorphisms and co-medications on tamoxifen metabolism and clinical outcomes in Moroccan ER+ breast cancer patients.

In this study, ER+ breast cancer patients receiving tamoxifen therapy are being recruited. *CYP2D6* genotyping is performed to identify genetic variants, while detailed medication histories are reviewed to identify CYP2D6 inhibitors. Plasma concentrations of tamoxifen and its active metabolites are measured using chromatographic techniques. Correlations between genetic profiles, co-medications, pharmacokinetics, and clinical outcomes are analyzed through multivariate statistical modeling.

Although the study is ongoing, it is anticipated to provide critical insights into how genetic and pharmacological factors interact to influence tamoxifen efficacy in Moroccan breast cancer patients. These findings are expected to inform the development of personalized treatment guidelines, optimizing tamoxifen-based therapy and improving patient outcomes.

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The association of transporter genetic variability with plasma bilirubin levels

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Introduction: Bilirubin transporters are involved in absorption and excretion of bilirubin and genetic variation in these transporters can influence plasma bilirubin levels. A critical role is played by hepatic uptake transporters from organic anion transporting polypeptides (OATP, *SLCO*) family; genetic variants in these impair bilirubin clearance eventually increasing plasma levels. Additionally, genetic variants in ATP-binding cassette (ABC) transporters, which mediate bilirubin excretion, can lead to hyperbilirubinemia. Understanding these genetic associations helps explain interindividual variability in bilirubin levels and their implications for drug metabolism, jaundice, and liver function. Our aim was to identify transporter polymorphisms associated with plasma bilirubin levels.

Methods: Our study included 61 patients with cognitive impairment. Plasma total bilirubin concentration was determined using the HUG assay for the nanoscale fluorometric detection of bilirubin in biological fluids. This assay is based on HUG protein, a fusion product of human elastin-like polypeptide (HELP) with the bilirubin-binding fluorescent protein UNaG. Patients were genotyped for 14 polymorphisms in *ABCB1*, *ABCC2*, *ABCG2*, *SLCO1B1*, *SLCO1A2*, *SLCO1B3*, and *SLCO2B1* genes using competitive allele-specific PCR. Nonparametric tests were used for statistical analysis.

Results: In our study, carriers of at least one polymorphic *ABCB1* rs1128503 C allele had lower bilirubin concentration compared to carriers of two normal alleles (P=0.031). When stratifying the patients according to *UGT1A1* rs8175347 genotype, *ABCB1* polymorphisms were associated with bilirubin concentration only in carriers of two *UGT1A1* rs8175347 reference alleles. Carriers of at least one polymorphic *ABCB1* rs1128503 C allele had lower bilirubin concentration also in this cohort (P=0.021). On the other hand, carriers of two polymorphic *ABCB1* rs2032582 alleles had higher bilirubin concentration (P=0.041). The rest of the genes were not associated with bilirubin concentration.

Conclusions: Our results suggest that *ABCB1* polymorphisms are associated with plasma bilirubin concentration, confirming the important role of ABC transporters in bilirubin transport.

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Fluorometric analysis of bile pigments in pleural fluid

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Introduction: Pleural effusions are accumulations of fluid between the parietal and visceral pleura. Analysis of the pleural fluid is necessary for diagnostic evaluation because its volume may increase and its composition may change in response to various pathologic conditions such as infection, neoplasia, myocardial infarction, or liver disease [1]. In this study, we propose to analyze bilirubin and biliverdin as indicators of the rate of heme catabolism to support the assessment of oxidative stress and heme-related disease mechanisms.

Methods: A fluorometric method for measuring bile pigments from nanoM to microM range in pleural fluid, was used [2,3]. Aliquots of pleural fluid (30 µL) were added to HUG solution (0.05 mg/mL in PBS pH 8.5) to obtain a final volume of 3 mL. The diluted samples were then divided into three 0.9 mL aliquots. For the analysis of BR, 200 µL was added directly to the multiwell plate in four replicates, while for BV or BRG, 5 µL of the enzyme solution was added to the other 900-µL aliquots (BVR final concentration 0.1875 mU/µL, NADPH 0.1 mM, or bglucuronidase final concentration 0.08 U/µL) and then added to the multiwell plate. Fluorescence intensity (λex = 485 nm, λem = 528 nm; T = 25°C) was measured after 16 hours.

Results: BR concentrations ranged from 55 nM up to 20 µM, with a median value of 2.4 µM. BV ranged from 4 nM to 1.55 µM, with a median value of 179 nM. BRG was substantially undetectable.

Conclusions: This method for analyzing bile pigments has proven to be both sensitive and accurate. The determination of bile pigments using the HUG method could be integrated with the assessment of other biochemical parameters, potentially expanding the panel of diagnostic markers. Moreover, correlating these findings with specific genetic polymorphisms may enhance disease characterization, aid in prognostic evaluation, and support more targeted therapeutic strategies.

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Exploring the relationship between HLA variants and vedolizumab response in Crohn's disease patients

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Introduction: Vedolizumab is a monoclonal antibody used in Crohn's disease (CD) treatment. So far no validated genetic biomarkers have been identified that reliably predict response to vedolizumab treatment. *HLA* genes play a central role in immunity. Some *HLA* alleles are associated with anti-drug antibody (ADA) development to various drugs that can hinder treatment results. Our aim was to assess whether ADA development *HLA* risk-alleles, particularly *HLA*B*, **DQA1*, **DQB1* and **DRB1* variants influence vedolizumab treatment response.

Methods: Total of 63 CD patients were included in the study (11 analysed using whole genome and 52 using whole exome sequencing). HLA typing was performed using HLA-HD, which is able to call HLA alleles at two-field resolution. ADA development risk-alleles identified from literature, namely *HLA*B*:08. *HLA*DQA1*:05, *HLA*DQB1*:02, *HLA*DRB1*:03, 04, 11 and 15 were analysed for association with vedolizumab patient response, defined as optimal (n=32) or suboptimal (n=31). We tested the association of each potential risk-allele with treatment response by logistic regression.

Results: We found no significant association between *HLA*B*:08 (p = 0.746), **DQA1*:05 (p = 0.22), **DQB1*:02 (p = 0.768) and **DRB1*:03, 04, 11 and 15 (p = 0.415, 0.768, 0.228 and 0.821, respectively) risk-alleles and vedolizumab treatment response in either heterozygous or homozygous form. For *HLA*DRB1*, represented by multiple risk-alleles, we found no association between the presence of any allele and treatment response (p = 0.22). Lastly, we found no association between the presence of any *HLA* risk-allele, nor the number of present risk-alleles and treatment response.

Conclusions: Our findings suggest that specific HLA alleles related to ADA development are not associated with vedolizumab response in a studied group of CD patients. This could indicate that ADA development is not primarily involved in treatment response to vedolizumab.

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PGx profile and patient-reported outcomes of antidepressant drug therapy - results from the ArtiPro project

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Introduction: Patient-reported outcomes (PROs) are increasingly crucial in evaluating drug therapies, capturing patients' perspectives on symptoms, treatment experiences, adverse drug reactions, and overall well-being. This study aimed to investigate patients' perceptions of antidepressant therapy efficacy and safety, and the association of pharmacogenetic (PGx) variants with PROs and adverse drug reactions (ADRs).

Methods: The study assessed 100 psychiatric patients using a questionnaire about current symptoms and possible antidepressant side effects. Of these, 28 patients had PGx profiles relevant to antidepressant drugs, including *ABCB1*, *COMT*, *CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP3A4*, *CYP3A5*, and *SERT*. PGx profiles were analysed with reported outcomes and side effects.

Results: The patients with full PGx profile (n=28) were analysed, with sertraline (54.2%) and escitalopram (20.8%) most prescribed therapy, and 92% of patients were on combination therapy, most often with benzodiazepines. Common side effects were dry mouth (29.2%), increased appetite (25%), dizziness (20.8%), and sleeping disorders (33%). The distribution of CYP2C19 phenotypes was: 50% normal metabolizers (NM), 25% intermediate metabolizers (IM), 16.7% rapid metabolizers (RM), 4.2% ultrarapid metabolizers (UM), and 4.2% poor metabolizers (PM). Notably, CYP2C19 RM/UM phenotypes (5/24) showed a higher incidence of nausea (66.7%) compared to NM/IM (27.8%). CYP2D6 phenotypes: 41.7% NM, 41.7% IM, 12.5% PM, and 42% UM. CYP2B6 phenotypes: 54.2% NM, 41.7% IM, and 4.2% RM. ABCB1 genotype: 33.3% CC, 37.5% CT, and 29.2% TT. SERT (5-HTTLPR) phenotype: 29.2% normal, 45.8% decreased, and 25% low function. Patients with normal SERT function (7/28) showed a better therapeutic response in motivation improvement (71.4% vs 50% in low function).

Conclusions: This small-sized study shows that pharmacogenomic reports and patient-reported outcomes provide complementary insights that allow more personalized and effective antidepressant therapy, reducing the trial-and-error approach often used in psychiatric treatments.

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Exploring host genetic polymorphisms in virus entry genes and its effect on COVID-19 short-term outcomes

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Introduction: Spike (S) glycoprotein plays an important role in the entry of SARS-CoV-2 into host cells. The binding of the S protein to its receptor, angiotensin-converting enzyme 2 (ACE2), leads to exposure of the cleavage site. When a host protease, TMPRSS2, cleaves this site, membrane fusion occurs. *ACE2* and *TMPRSS2* polymorphisms could affect virus recognition and entry into the host cell. Our aim was to investigate potential associations between these polymorphisms and disease severity, duration of hospitalization, and need for ICU treatment.

Methods: Hospitalized COVID-19 patients (N=161) were genotyped for *ACE2* (rs1800764, rs4343, rs2285666, rs1978124) and *TMPRSS2* polymorphisms (rs12329760, rs456298). Statistical analyses included descriptive statistics, the χ^2 test or Fisher's exact test, and the Mann–Whitney U test.

Results: Among the recruited patients, 67.1% were male and 32.9% female with median (min–max) age 62 (23–85) years. Only 2.5% had mild and 11.8% moderate disease, while 65.2% had severe, and 19.9% critical disease. The median (min–max) duration of hospitalization was 10 (3–73) days; 26 (16.1%) patients required ICU treatment. Among the investigated polymorphisms, only *ACE2* rs2285666 showed significant association with duration of hospitalization in the dominant model (p=0.032), with carriers of one or two polymorphic A alleles having shorter hospitalization.

Conclusions: With the exception of *ACE2* rs2285666, none of the other investigated *ACE2* and *TMPRSS2* polymorphisms showed significant association with COVID-19 severity or patient hospitalization. Future studies involving larger patient cohorts with a broader range of disease severities or examining a more extensive panel of polymorphisms may provide a more comprehensive understanding of the relationships between host polymorphisms and COVID-19 severity and short-term outcomes.

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