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CONFERENCE ABSTRACTS

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Personalised and precision medicine

Challenges and enablers of pharmaceutical 3D-printing at point-of-care

Elton Gatt, Nicolette Sammut-bartolo, Lilian M. Azzopardi[1]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

Background: Additive manufacturing (AM) using three-dimensional (3D) printing presents a promising opportunity for producing personalised pharmaceutical dosage forms at the point-of-care (POC). By enabling decentralised manufacture in settings such as hospitals, primary care pharmacies and potentially patients' homes, AM could enhance treatment individualisation, improve accessibility and support patient-centred care. Despite these advantages, translation into routine clinical practice remains limited.

This study aimed to identify principal challenges and enabling factors associated with pharmaceutical AM to support safe integration of AM technologies in real-world pharmaceutical scenarios.

Method: A systematic review was conducted in January 2025 to identify challenges and enablers associated with pharmaceutical AM, with emphasis on decentralised and POC applications. Searches were performed across leading electronic databases supplemented by reference list screening and regulatory authority websites. The review followed the PRISMA framework, and eligible studies were appraised using the CASP qualitative checklist.

Data were analysed using inductive thematic analysis, with a subset independently double-coded to ensure inter-rater reliability. A validated structured POC manufacturing gap analysis tool was developed to assess Good Manufacturing Practice (GMP) compliance and readiness for AM implementation within healthcare environments.

Results: The systematic search yielded 49 studies eligible for full-text assessment. Inductive coding identified 161 unique subtheme codes across the dataset, generating 747 coded entries capturing distinct concepts related to pharmaceutical AM. These subthemes were synthesised into ten overarching descriptive themes representing both enabling and limiting factors for implementation.

Key enablers included stakeholder collaboration and professional education, emerging technological developments, future implementation pathways, and the potential of AM to support personalised and patient-centred therapeutic approaches. Major barriers included challenges related to quality control and Quality by Design (QbD) integration, regulatory gaps and uncertainty, technical implementation and scalability limitations, and the ambiguity between pharmaceutical compounding and industrial manufacturing frameworks. Additional constraints related to digital maturity and secure data exchange infrastructure; as well as ethical, legal and social considerations surrounding decentralised pharmaceutical production.

A structured POC manufacturing gap analysis tool was developed, comprising nine sections aligned with the chapters of EudraLex Volume 4, Part I, reflecting core GMP principles. Each section incorporates weighted scoring criteria contributing to an overall compliance score, enabling the assessment of a facility's level of GMP alignment and readiness for safe AM integration.

Conclusion: The findings indicate that adoption of pharmaceutical 3D printing is constrained less by technological capability than by regulatory and infrastructural rigidity. Ambiguity between extemporaneous compounding and industrial manufacturing frameworks represents a critical bottleneck for implementation in decentralised healthcare settings. However, emerging regulatory sandboxes such as hospital exemptions and POC manufacturing frameworks together with harmonised international approaches may provide viable pathways to support responsible innovation. Successful integration of pharmaceutical AM requires

coordinated progress in regulatory clarity, digital infrastructure and operational readiness. Addressing these interconnected barriers depends on collaborative efforts across research, policy development and clinical practice. Ultimately, embedding AM within transparent, patient-centred, and ethically robust governance frameworks is essential to realise its potential for safe, scalable and equitable personalised medicine at the POC.

Standardized ready-to-use natural deep eutectic solvent-impregnated polypropylene fiber units for robust and high-throughput determination of tyrosine kinase inhibitors in biological fluids

Dong Wang[1], Mengrong Li[2]

[1]*Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China, Tianjin, China*

[2]*Tianjin Cancer Hospital Airport Hospital, Tianjin, China, Tianjin, China*

Background: Therapeutic drug monitoring (TDM) of tyrosine kinase inhibitors (TKIs) is essential for individualized dosing due to their narrow therapeutic windows and pronounced pharmacokinetic variability. However, routine TDM is still hindered by sample preparation strategies that rely on labor-intensive workflows, high consumption of toxic organic solvents, and poor procedural standardization, limiting their suitability for high-throughput and green clinical analysis. Therefore, there is a clear need for a standardized, eco-friendly, and ready-to-use sample preparation strategy that enables robust and routine determination of TKIs in plasma, and bridges the gap between green microextraction and standardized clinical application.

Method: Inspired by pharmaceutical blister packaging concepts, a unit-supported liquid-phase microextraction method (NADES-PPF-SLPME) was developed. A hydrophobic natural deep eutectic solvent (NADES), composed of menthol and thymol (2:1 molar ratio), was pre-impregnated onto polypropylene fiber (PPF) and sealed into individual, ready-to-use units. For extraction, one unit was vortexed with 1.0 mL of diluted plasma sample. After a brief water wash to remove matrix interferences, the target analytes were desorbed by vortexing the unit with 150 µL of ethanol. The eluate was directly analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the simultaneous determination of nine TKIs. Density functional theory (DFT) simulations were employed to investigate the extraction mechanism. The method's environmental impact was assessed using five greenness metrics.

Results: A standardized, ready-to-use extraction device inspired by pharmaceutical blister packaging was developed for the determination of nine TKIs in human plasma. Hydrophobic NADES (menthol–thymol) was pre-impregnated into PPF and sealed as individual consumable units, enabling a NADES-PPF-SLPME strategy suitable for high-throughput operation. These units are pre-packaged to ensure stability and solvent retention, eliminating the need for fresh solvent preparation and simplifying the workflow to a “add-vortex-remove” process. DFT revealed that extraction was governed by synergistic hydrogen bonding and π–π stacking interactions between NADES and TKIs. Under Box–Behnken optimized conditions, the method exhibited wide linearity (R^2 ≥ 0.990), low limits of quantification (0.2–1.0 ng/mL), satisfactory recoveries (86.64–110.30%), and acceptable precision (RSD < 14.10%). The standardized units retained extraction efficiencies above 86.47% after three months of storage and enabled reliable quantification of TKIs in real clinical plasma samples.

Conclusion: This work presents a robust, green, and operationally simple “prepare-in-advance, use-on-demand” microextraction strategy. By eliminating on-site solvent handling, centrifugation, and significantly reducing solvent consumption through standardised consumables, the NADES-PPF-SLPME method offers a practical and sustainable solution for high-throughput TDM of TKIs in clinical laboratories.

Predicting drug sensitivity using transcriptomic signatures: Acomputational approach to proposing new drugcombinations for diffuse midline glioma

Nana Amankrah[1]

[1]*Imperial College London, London, United Kingdom*

Background: Diffuse midline gliomas (DMG) are devastating paediatric brain tumours with a median survival of 8-12 months and no effective treatment options. Despite advances in molecular characterisation revealing key mutations like H3K27M in over 80% of cases, therapeutic approaches based on genetic biomarkers have failed to improve outcomes. The rarity of the disease and consequent scarcity of data have made machine learning models unreliable at predicting appropriate treatment. The extensive intra- and inter-tumoural heterogeneity characteristic of DMG suggests that more innovative transcriptomic approaches may be necessary to effectively target diverse cellular populations within these tumours.

Method: This study developed a computational framework integrating transcriptomic profiling with drug sensitivity prediction to identify optimal combination therapies for DMG. Following pre-processing of sequencing reads, drug sensitivity signatures were generated for eight therapeutic agents (alpelisib, avapritinib, corin, FK866, GSK-J4, idasanutlin, infigratinib, trametinib) - selected based on data

availability - and projected onto single-cell RNA sequencing data from both mouse models and patient-derived samples. Systematic combination analysis evaluated all possible drug combinations to identify optimal combinations where the largest proportion of cells – dubbed coverage – across the heterogeneous tumour cell populations, would be sensitive to at least one drug.

Results: Systematic combination analysis revealed that four-drug combinations consistently achieved >99% therapeutic coverage, with optimal regimens including alpelisib + GSK-J4 + idasanutlin + infigratinib.

Conclusion: This study establishes the first computational framework for DMG therapeutic consideration that integrates transcriptomic heterogeneity with drug sensitivity prediction. The demonstration that four-drug combinations can achieve near-universal therapeutic coverage over genetic biomarkers shows fundamental limitations presents in current approaches. While significant experimental validation is required before clinical translation, this computational framework provides essential tools for bridging the gap between our understanding of DMG molecular complexity and the urgent need for effective treatments for children affected by this devastating disease.

Role of genetic markers in anticancer drug-induced peripheral neuropathies: A scoping review based on genomic sequencing technologies

Omid Gholami[1,2], Perla Sader[3,4], Marianne Ruel[5], Lynn Gauthier[2,6], Bruno Megarbane[3,7], Aline Hajj[1,2,8]

[1]Faculty of Pharmacy, Laval University, Quebec, Canada

[2]CHU de Québec- Université Laval Research Center, Oncology Axis, Quebec, Canada

[3]Inserm UMRS-1144, Paris Cité University, Paris, France

[4]Faculty of Medicine, Saint-Joseph University of Beirut, Beirut, Lebanon

[5]Library, Laval University, Quebec, Canada

[6]Department of Family and Emergency Medicine, Faculty of Medicine, Laval University, Quebec, Canada

[7]Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Federation of Toxicology, APHP, Paris, France

[8]INSPECT-LB (Institut National de Santé Publique, d'Épidémiologie Clinique et de Toxicologie-Liban), Beirut, Lebanon

Background: Anticancer drug-induced peripheral neuropathy (ACDIPN) is a common and debilitating adverse effect of cancer therapy that can reduce patients' quality of life and lead to treatment modification or discontinuation. Advances in genomic sequencing technologies, including genome-wide association studies (GWAS), whole-genome sequencing (WGS), and whole-exome sequencing (WES), have enabled the identification of genetic variants associated with susceptibility to this toxicity. Although several systematic reviews have examined the relationship between genetic variations and treatment-induced neuropathy, most have focused on specific anticancer agents. This scoping review therefore aims to provide an updated synthesis of the existing literature by mapping genetic variants associated with ACDIPN across both conventional chemotherapies and emerging targeted therapies using genomic sequencing approaches.

Method: A scoping review was conducted following the methodological framework recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). A systematic literature search was performed in the MEDLINE, EMBASE, Cochrane Library, CINAHL and Web of Science databases. Eligibility criteria and methodological details were defined according to the Joanna Briggs Institute guidelines and described in a published protocol (OSF ID: 10.17605/OSF.IO/Y58RV). Study selection was conducted independently by two reviewers, with disagreements resolved through discussion and consensus. Data extraction was performed using the Covidence® platform. The extracted data included study characteristics, participant demographics, types of anticancer treatments, neuropathy assessment methods, and the genetic variants identified. Additional variables include associated ACDIPN clinical traits such as the presence or absence of sensitive/motor symptoms and neuropathic pain, symptom chronicity, and the impact on quality of life.

Results: Following full-text screening and additional searches conducted through Google Scholar, Semantic Scholar, and the reference lists of included studies, 40 articles up to now were identified for final inclusion and data extraction. Most of the included studies were designed as prospective cohort or case-control studies. In few studies only, the severity and chronicity of ACDIPN were assessed; however, the majority primarily evaluated the presence or incidence of ACDIPN rather than its longitudinal progression or symptom burden. Among the various assessment methods used to evaluate neuropathy, the most frequently applied approach was the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system.

Most of the studies were conducted in populations of European and African American ancestry, with comparatively limited representation of other genetic backgrounds. The reported genetic variants and their associated genes reflect a broad range of biological mechanisms involved in the pharmacokinetics, pharmacodynamics, and pathophysiology of ACDIPN.

The synthesis of these studies will provide a comprehensive mapping of genetic variants associated with ACDIPN identified through GWAS, WGS and WES technologies. It will also highlight the methodological approaches and neuropathy assessment tools most commonly used in the existing literature.

Conclusion: This scoping review will contribute to a better understanding of the genetic determinants underlying ACDIPN. It will also identify current knowledge gaps and research priorities for future investigations. Ultimately, these findings may support personalised medicine strategies to predict and prevent neuropathy in patients undergoing cancer treatment while guiding molecular investigations to identify potential therapeutic targets.

Linking genomic resistance determinants to volatile metabolic signatures in uropathogens by SIFT-MS

Oluseye Chris Olusegun[1], Oliver Gould[1], Ben Delacy Costello[1], Jackie Barnett[1], Katherine Thomas[1]

[1]*University of the West of England, Bristol, United Kingdom*

Background: Urinary tract infections (UTIs) caused by multidrug-resistant E. coli, K. pneumoniae, and P. mirabilis pose a growing problem worldwide. WGS studies have shown that these resistant bacteria possess certain acquired genetic elements, such as blaGES-5, KPC-3, CTX-M-15, qnrB1, along with certain mutations in the genes gyrA and parC, which lead to antibiotic resistance. However, WGS is too slow for point-of-care decisions. These resistance mechanisms alter metabolic pathways within the bacteria, resulting in different volatile organic compounds (VOCs), which can be identified using SIFT-MS technology.

Purpose: To determine if the SIFT-MS method can discriminate between antimicrobial-resistant and -susceptible strains of uropathogens based on VOC patterns and if these findings can be linked to known genomic determinants of resistance.

Method: Six isolates from the university of west of England culture collection were selected for this study: E. coli ATCC 25922 (sensitive) and NCTC 13919 (resistant); K. pneumoniae NCTC 10896 (sensitive) and NCTC 13438 (resistant); P. mirabilis NCIMB 701880 (sensitive) and CC243 (resistant). Genomes obtained using WGS on MicrobesNG were processed for resistance genes, efflux pumps, and porin mutations using ResFinder and CARD. In addition, each isolate was incubated in artificial urine for 5 hours, and headspace VOCs collected during the growth period analysed in triplicate by SIFT-MS using a full-scan mode m/z range of 10–300. Peak areas for each isolate pair were compared using PCA and t-test.

Results: The results of WGS analysis revealed that the resistant isolates had clinically significant acquired genes are not present in the susceptible controls. This included: E. coli isolates with blaGES-5, gyrA(D87N/S83L), parC(S80I) and several efflux regulator genes; K. pneumoniae isolates with KPC-3, ompK37, marA and gyrA(S83I); and P. mirabilis isolates with blaCTX-M-15, blaOXA-1, qnrB1 and aac(6')-Ib-cr genes. SIFT-MS revealed clear separation between resistant and susceptible strains for all three species.

A unified machine learning framework for next-visit tacrolimus concentration prediction and model-informed dose individualisation in renal transplant recipients

Zhaolin Chen[1]

[1]*Anhui Provincial Hospital, Hefei, China*

Background: Tacrolimus is a cornerstone immunosuppressant in kidney transplantation, critical for preventing allograft rejection and ensuring long-term graft survival. However, its clinical utility is constrained by a narrow therapeutic index and substantial inter-individual and intra-individual pharmacokinetic variability, presenting significant challenges for dose optimisation. This study aimed to develop and validate a unified machine learning framework capable of predicting next-visit tacrolimus trough concentrations and supporting model-informed dose individualisation in renal transplant recipients.

Method: A retrospective analysis was conducted of therapeutic drug monitoring (TDM) data collected from 556 kidney transplant recipients, yielding a comprehensive dataset of 5,793 clinical records. A pharmacokinetically-inspired feature engineering approach was developed, specifically incorporating concentration-to-dose ratio dynamics to effectively capture individual patterns of drug clearance over time. To identify the optimal predictive model, eleven distinct prediction approaches were systematically compared, including advanced gradient boosting methods, ensemble techniques, and conventional baseline models. Model performance was rigorously evaluated using patient-level 5-fold cross-validation to ensure generalisability and minimise overfitting.

Results: For next-visit concentration prediction, the tuned ensemble model demonstrated robust performance, achieving a coefficient of determination (R^2) of 0.66 and a mean absolute error (MAE) of 1.57 ng/mL. For dose prediction tasks, the ensemble model exhibited superior accuracy, attaining an R^2 of 0.89 and an MAE of 0.43 mg. SHAP (SHapley Additive exPlanations) analysis revealed that previous tacrolimus concentration, previous concentration-to-dose ratio, historical mean concentration-to-dose ratio, and patient age were the most influential predictors driving model predictions.

Conclusion: The proposed unified framework demonstrates robust and reliable predictive performance for both concentration forecasting and dose adjustment support,

effectively integrating pharmacokinetic principles with machine learning techniques. This approach offers a promising and clinically actionable tool for enhancing tacrolimus TDM and facilitating personalised medicine in renal transplant recipients. Future work should focus on prospective clinical validation and implementation of this framework in routine practice.

Development of explainable machine learning-based predictive models for cisplatin-induced nephrotoxicity using real-world data

Kotoe Kiyomoto[1], Kenji Ikemura[2,3], Masahiro Okuda[2,3]

[1]Department of Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, The University Of Osaka, Osaka, Japan

[2]Department of Pharmacy, The University of Osaka Hospital, Osaka, Japan

[3]Department of Hospital Pharmacy, Graduate School of Medicine, The University of Osaka, Osaka, Japan

Background: Cisplatin–induced nephrotoxicity (CIN) is a serious adverse effect and a major dose-limiting factor that leads to treatment delays and discontinuation. Although preventive strategies such as hydration and forced diuresis have been recommended to mitigate the risk of CIN, approximately one-third of patients receiving cisplatin develop nephrotoxicity. Therefore, early detection and precise prediction of CIN are critical for optimizing the management of patients receiving cisplatin-based chemotherapy. In this study, explainable machine learning–based prediction models for CIN were developed using a large-scale clinical dataset that incorporates demographic characteristics and time-series laboratory data.

Method: A retrospective analysis was conducted of 1,705 patients who received cisplatin for the first time at The University of Osaka Hospital between April 2010 and April 2025. The dataset was divided into training and test sets at an 8:2 ratio. To mitigate class imbalance, weighted learning and the synthetic minority oversampling technique were applied exclusively to the training data. Seven-fold stratified cross-validation was performed within the training data to ensure robust model development and to reduce overfitting. Final models were retrained using the entire training dataset before evaluation. Nephrotoxicity was defined as acute kidney injury of grade ≥1 within 14 days after cisplatin administration according to the Common Terminology Criteria for Adverse Events version 4. Explanatory variables included age, history of diabetes mellitus, concomitant proton pump inhibitor use, cisplatin dose, and longitudinal laboratory values related to renal function, liver function, and electrolytes. Prediction models were developed using random forest (RF), support vector machine (SVM), logistic regression (LR), and artificial neural network (ANN) algorithms. Model performance was evaluated using the independent test dataset, and feature contributions were assessed by performing shapley additive explanations (SHAP) on the same test dataset.

Results: Nephrotoxicity was observed in 551 out of 1,705 patients (32%). Regarding the individual evaluation metrics, the ANN model achieved the highest recall at 0.709. The RF model demonstrated superior accuracy and specificity, scoring 0.742 and 0.792, respectively. In contrast, the LR model excelled with the highest F1.5 score of 0.626 and an area under the receiver operating characteristic curve (AUC-ROC) of 0.791. As minimizing missed cases is critical in the clinical situation, F1.5 and AUC-ROC are the most relevant metrics. Based on these metrics, the LR model exhibited high performance compared with the other models, achieving accuracy of 0.739, recall of 0.645, and specificity of 0.784. SHAP analysis identified baseline serum creatinine (Scr) levels and Scr values at days 4–6 after cisplatin administration as the most influential features, indicating that both pre-treatment renal function and early post-treatment changes in Scr are fundamental indicators for capturing susceptibility to CIN.

Conclusion: In conclusion, this study successfully developed a machine learning-based prediction model for CIN using real-world clinical data. The LR model exhibited robust discriminative performance, enabling improved identification of patients at high risk for CIN. This approach supports individualized preventive strategies and contributes to safe and optimized treatment of cisplatin-based chemotherapy.

Collaboration, evidence, and patient communication: key barriers to pharmacogenetics implementation identified by Dutch Pharmacists

Emma De Brabander[1], Nicole Leibold[1], Therese Van Amelsvoort[1], Roos Van Westrhenen[2,3,4], The Psy-pgx Consortium

[1]Mental Health and Neuroscience Research Institute, Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, Netherlands

[2]Department of Psychiatry, Parnassia Groep BV, Amsterdam, Netherlands

[3]Institute of Psychiatry, Psychology & Neurosciences, King's College London, London, United Kingdom

[4]St. John's National Academy of Health Sciences, Bangalore, India

Background: Over recent years, interest in and application of pharmacogenetics (PGx) has grown. While PGx research and technology have expanded, clinical implementation appears to be slow. Previous research suggests several reasons for this delay in the clinic, including a lack of knowledge on when to initiate PGx and how to apply test results, and high cost of PGx. Interestingly, existing research is often focused on

prescribing physicians and specialists, neglecting an important group of healthcare professionals in the PGx-landscape: pharmacy professionals. Earlier work suggests that pharmacists in the Netherlands consider themselves knowledgeable and capable when it comes to supporting PGx-implementation. Yet, their expertise and potential contribution to clinical implementation remain largely underutilized in PGx practice. To explore this further, we performed an online survey study in Dutch pharmacists. The ultimate objective was to improve understanding of the barriers that hamper the implementation of PGx in Dutch healthcare, from a pharmacist perspective. Here we focused on the qualitative comments provided by respondents in detail to identify practical insights that otherwise would not be measured.

Method: For this analysis we utilised the comments provided by respondents in an open comment study of a larger survey study on PGx aimed at pharmacists and pharmacy professionals. EdB and an independent hospital pharmacist reviewed and categorised comments in overarching themes according to content. Data were stored securely and anonymously on a Maastricht University server.

Results: We identified three main themes, based on comments from 29 respondents: 'collaboration between healthcare professionals', 'evidence and cost-effectiveness', and 'information to patients'. Under the first theme, respondents expressed concerns about the communication and collaboration with (general) practitioners. Especially lack of communication about patient-complaints of lack of treatment response and adverse reactions, which is necessary for healthcare professionals to adequately assess whether PGx could be beneficial, was a serious concern of respondents. Although several respondents noted pharmacists are unable to request a PGx-test themselves in the Netherlands, others mentioned that they do provide advice to the (general) practitioner when asked, highlighting a potential for collaboration. In the second theme, comments primarily described a hesitancy about PGx usefulness in certain situations. According to respondents, PGx implementation should be limited to medications for which sufficient empirical evidence exists, such as anticoagulants and antidepressants. Performing extensive PGx panels was advised against, and therapeutic drug monitoring appeared preferred in circumstances for which drug plasma concentration-outcome relationships have been established. In theme three, the importance of adequate patient-expectation management and information provision were emphasized. Respondents considered PGx to be potentially harmful if costs and benefits are not sufficiently balanced before decision-making. Wrongly interpreted outcomes or catastrophizing non-normal results may lead to unnecessary stress of the patient and discontinuing medication without good reason.

Conclusion: The results highlight practical barriers to PGx implementation faced by Dutch pharmacy professionals, and illustrate the interplay between national healthcare system, healthcare professionals, and the patient. Pharmacy professionals appeared supportive yet cautious of PGx in practice and emphasized the need for improved integration between pharmacy and clinical practice in PGx implementation.

Appropriate proton pump inhibitor use in patients with colorectal cancer may enhance the efficacy of anti-vascular endothelial growth factor therapy

Kenta Yagi[1,2], Fuka Aizawa[2,3], Sato Maki[2], Nana Nakai[2], Akinori Maruo[4], Marin Sagawa[2,4], Takahiro Niimura[2,3], Kei Kawada[2,5], Io Horikawa[2,5], Mitsuhiro Goda[2,6], Yuki Izawa-ishizawa[2,7], Yoshito Zamami[4], Keisuke Ishizawa[2,3,5], Takahisa Yano[1]

[1]Department of Pharmacy, Shimane University Hospital, Izumo-shi, shimane, Japan

[2]Department of Clinical Pharmacology and Therapeutics, University of Tokushima Graduate School of Biomedical Sciences, Tokushima, Tokushima, Japan

[3]Department of Clinical and Translational Science, Tokushima University Hospital, Tokushima, Tokushima, Japan

[4]Department of Pharmacy, Okayama University Hospital, Okayama, Okayama, Japan

[5]Department of Pharmacy, Tokushima University Hospital, Tokushima, Tokushima, Japan

[6]Department of Pharmacotherapy, Graduate School of Biomedical and Heath Sciences, Hiroshima, Hiroshima, Japan

[7]Department of Health and Nutrition, Faculty of Human Life Science, Shikoku University, Tokushima, Tokushima, Japan

Background: Numerous supportive therapeutic drugs are used in cancer treatment. However, their ability to enhance the efficacy of anti-cancer chemotherapeutic agents remains unclear. Vascular endothelial growth factor (VEGF), a protein that increases vascular permeability and promotes angiogenesis, is secreted by various tissues in the body and a key therapeutic target in many diseases. In oncology, VEGF-mediated angiogenesis is associated with cancer progression and metastasis, making it a poor prognostic factor and a therapeutic target for cancer treatment. We discovered that proton pump inhibitors (PPIs), a supportive therapy that suppress gastric acid secretion, exhibit VEGF-inducing effects. In contrast, vonoprazan, which similarly suppresses gastric acid secretion, did not exert VEGF-induced effects. In addition, there was a possibility that estrogen receptor (ER) might mediate this action. However, in a small observational study involving patients with colorectal cancer those receiving PPI therapy showed prolonged treatment efficacy with anti-VEGF agents than those receiving vonoprazan.

Objective: Based on the results of these studies, mechanisms associated with other cancer types may be different from those associated with colorectal cancer. Therefore, we focused on colorectal cancer for further investigations.

Method: Using anonymized processed data from the Japan Medical Data Center (JMDC), we investigated the association between PPI use and anti-VEGF treatment efficacy in patients with colorectal cancer on a large scale. Additionally, we investigated the differences in PPI-induced VEGF-associated gene expression using cell lines from various cancer types to further explore the contribution of estrogen in different cancers and the mechanism by which PPIs induce VEGF expression.

Results: A total of 844 patients were included in this analysis. Patients using PPIs had an approximately 30 days longer duration of bevacizumab treatment than those using vonoprazan. Furthermore, bevacizumab treatment duration in the group that started PPI use more than 30 days before bevacizumab administration was longer than in the group that started PPI use within 30 days. PPIs induced VEGF expression in all cancer cell lines. However, in CRC cells, the PPI-induced VEGF expression was modulated by estrogen ER inhibitors.

Conclusion: The appropriate selection of acid secretion suppressants may enhance the efficacy of cancer treatment. Particularly in colorectal cancer, in which estrogen exposure may be associated with prognosis, PPI-induced ER stimulation could potentially influence the response to bevacizumab therapy. Further investigations into the detailed mechanisms and well-designed prospective clinical trials are warranted.

Improving precision dosing in Kuwait: Building a virtual clinical population

Raj Badhan[1], Mona Alenezi[1,2]

[1]*Aston University, Birmingham, United Kingdom*

[2]*Ministry of Health Kuwait, Sulaibkhat, Kuwait*

Background: Physiologically based pharmacokinetic modelling is a cornerstone of model-informed precision dosing and regulatory decision support, but many widely used platforms are parameterised using North American or European population datasets. Middle Eastern populations remain underrepresented in global modelling frameworks, despite known variability in enzyme abundance, anthropometry, body composition, and disease epidemiology. Kuwait has a distinctive demographic and clinical profile, including high obesity prevalence and metabolic disease burden, alongside limited published quantitative data describing distributions of drug-metabolising enzymes and key physiological covariates. Non-representative default populations may therefore bias exposure predictions, particularly for medicines with narrow therapeutic windows or exposure-response sensitivity. Creating a population digital twin, a synthetic cohort that captures regional physiology, offers a practical route to improve representativeness without requiring immediate large-scale clinical trials for every drug.

Purpose: To develop and verify a Kuwait-specific virtual clinical population suitable for integration into existing modelling platforms to improve dose prediction accuracy for drugs cleared by major hepatic pathways.

Method: Demographic, anthropometric, and clinical chemistry data were collated from publicly available Kuwaiti epidemiological studies and hospital datasets following ethical approval. Population descriptors included age distribution, sex ratio, body mass index distribution, hepatic function markers, and metabolic disease prevalence. Enzyme abundance assumptions for major pathways, including CYP3A4, CYP2D6, and selected UGT isoforms, were derived from literature where available and supplemented by sensitivity analyses to explore plausible variability ranges. A virtual Kuwaiti adult population was constructed by modifying baseline European reference populations to reflect Kuwait-specific distributions of body size and physiology. Model verification used published pharmacokinetic data for probe substrates and clinically relevant medicines with known clearance pathways. Predicted exposure (area under the concentration-time curve and maximum concentration) and clearance were compared with observed data using standard two-fold acceptance criteria. Quality checks included ensuring physiological plausibility across age, sex, and body size strata, and testing whether predicted exposure distributions remained stable across repeated virtual population draws.

Results: The Kuwait-adapted population produced systematic shifts in predicted drug exposure relative to standard European reference populations, particularly for compounds predominantly cleared by CYP3A4. Sensitivity analyses indicated that modest shifts in enzyme abundance parameters can generate clinically relevant exposure differences, especially in individuals with obesity-associated physiological alterations. For selected probe drugs, simulated exposure metrics fell within accepted predictive boundaries when Kuwait-specific anthropometric distributions were incorporated, supporting the feasibility of population tailoring within existing modelling frameworks. The approach also highlights where local data gaps most affect prediction, enabling prioritisation of future measurement studies (for example enzyme abundance sampling or regional clinical chemistry distributions).

Conclusion: Developing a Kuwait-specific virtual population is feasible and measurably influences exposure prediction, supporting more equitable implementation of model-informed precision dosing for underrepresented populations. Expansion of region-specific physiological and enzymatic datasets will be essential to strengthen confidence in dose optimisation for Middle Eastern cohorts and to reduce structural bias in pharmacokinetic evidence generation that underpins global dosing guidance. For pharmacy practice, improved representativeness supports safer initial dosing, reduces reliance on reactive adjustment, and strengthens

clinical justification when applying model outputs in diverse patient groups.

Precision dosing for athletes: Safer and more personalised medicine use in sport

Raj Badhan[1], Neil Clarke[2], Claire May[3]

[1]*Aston University, Birmingham, United Kingdom*

[2]*College of Life Sciences, Birmingham City University, Birmingham, United Kingdom*

[3]*School of Applied Sciences, Brighton University, Brighton, United Kingdom*

Background: Elite athletes represent a physiologically and genetically heterogeneous population. High lean body mass, altered plasma volume, fluctuating hydration status, redistribution of organ blood flow during exercise, altitude exposure, and circadian disruption can influence drug pharmacokinetics. Inter-individual genetic variability in drug-metabolising enzymes and transporters, including CYP2D6, CYP3A4, UGTs and SLCO1B1, may further modify systemic exposure. Despite this, dosing recommendations for clinically indicated medicines are largely extrapolated from general population studies. This work does not aim to enhance performance or circumvent anti-doping frameworks. Instead, it addresses safer and more predictable therapeutic use of approved medicines within World Anti-Doping Agency (WADA) regulations and established Therapeutic Use Exemption (TUE) processes, prioritising therapeutic optimisation and regulatory transparency rather than competitive advantage.

Purpose: To present a Virtual Athlete digital twin framework integrating pharmacokinetic variability and pharmacogenomic factors to support model-informed precision dosing for legitimate medical treatment in athletes.

Method: The Virtual Athlete platform builds on established mechanistic modelling approaches previously applied in paediatrics, obesity, pregnancy and critical care. The framework integrates (1) athlete-specific physiological parameters, including fat-free mass, cardiac output redistribution during exercise, hydration variability, and thermal stress; (2) environmental modifiers such as altitude exposure and long-haul travel; (3) drug-specific properties including absorption kinetics, protein binding, and clearance pathways; and (4) pharmacogenomic variability affecting enzyme and transporter abundance using genotype to phenotype scaling. Simulations estimate exposure metrics including peak concentration, time to peak concentration, area under the concentration-time curve, and accumulation risk under varying physiological and genetic scenarios. The platform models only clinically indicated, permitted medicines and does not evaluate prohibited substances. Dose adjustment recommendations are generated within predefined therapeutic targets, with uncertainty bounds reported to support shared decision-making and clinical accountability. Output reports include attribution of the main drivers of exposure change (for example hydration-related renal clearance shifts versus genotype-related metabolic capacity differences).

Results: Preliminary simulations indicate that dehydration and sustained high-intensity exercise can reduce renal clearance and increase peak exposure for renally eliminated drugs relative to baseline conditions. Genotype-driven variability in CYP2D6 or CYP3A activity further amplifies inter-individual differences, potentially leading to clinically relevant overexposure or subtherapeutic concentrations despite standard dosing. Combined physiological and genetic variability produces exposure ranges substantially wider than those predicted by conventional population averages, highlighting the risk of assuming one-size-fits-all dosing in athletes. Scenario analysis also suggests that altitude and circadian disruption can interact with baseline physiology to change exposure in a time-dependent manner, emphasising the need to consider timing and environment when selecting doses.

Conclusion: The Virtual Athlete digital twin is positioned as a clinical safety and medicines optimisation tool that quantifies the interaction between physiology, environment, and genotype to support informed prescribing for legitimate medical needs. By anticipating variability before treatment rather than reacting to adverse events or therapeutic failure, the approach can strengthen documentation and clinical reasoning for TUE justification where required, while reinforcing WADA compliance. Pharmacists, with expertise in pharmacokinetics, pharmacogenomics, and regulatory governance, are well placed to lead this translational interface between precision medicine and sports healthcare, protecting athlete health while maintaining anti-doping integrity.

Bidirectional link between aging and pain: Mechanisms, health outcomes, and management implications

Sara Pannilunghi[1], Preeti Kachroo[2], Bart Morlion[3]

[1]*Global Medical and Scientific Affairs Senior Scientist, Haleon, Nyon, Switzerland*

[2]*Global Medical and Scientific Affairs Director, Haleon, Nyon, Switzerland*

[3]*Center for Algology & Pain Management, University Hospitals Leuven, Leuven, Belgium*

Background: The interplay between aging and pain perception is complex. Aging modifies nociceptive processing, while chronic pain affects functional, cognitive, and psychosocial health. Despite growing evidence, integrated syntheses spanning both directions remain

limited, constraining development of holistic, age specific pain management strategies essential for improving clinical and pharmacy practice. We synthesize evidence on (1) how aging shapes pain perception and (2) how persistent pain may accelerate biological and functional aging.

Method: We conducted a narrative synthesis of clinical studies (cross sectional and longitudinal studies, systematic review and meta-analysis) identified through PubMed, Embase, and Google Scholar from inception to December 2025. Evidence addressing sensory thresholds, discrimination and temporal summation, pain interference, perceived age, neurocognitive outcomes, mobility and frailty, and biological aging mechanisms were integrated.

Results: Pain presentations shift across the life course, from growth related and reproductive pain in early life to musculoskeletal and degenerative conditions, such as osteoarthritis, in older adulthood. The perception and expression of pain also vary with age. Newborns show heightened nociceptive reactivity but limited ability to communicate pain. Children often display stronger affective responses, whereas adults provide clearer and more localized descriptions. Older adults may underreport symptoms, increasing the risk of missed or delayed diagnosis. The developmental differences also influence pharmacokinetics and pharmacodynamics, requiring age tailored assessment and treatment.

Age-related neurobiological changes further shape pain processing. Perceived age correlates with pain impact, as individuals who feel older than their chronological age tend to report greater disability and psychological distress. Older adults often exhibit higher heat pain thresholds and reduced sensory discrimination due to loss of nociceptors and peripheral nerve fibers. Despite these sensory declines, they often rate thermal pain as more intense and unpleasant and demonstrate increased temporal summation, while pain tolerance remains largely unchanged. Aging is also linked to biological processes that contribute to chronic pain and vulnerability, including inflammaging, oxidative stress, DNA damage, cellular senescence, telomere shortening, neurodegeneration, and mitochondrial dysfunction. These mechanisms, combined with reduced physical activity, increase susceptibility to frailty and increase the overall burden of pain across later life.

A multidimensional pain management approach integrates non pharmacological strategies and pharmacological interventions like acetaminophen or low dose NSAIDs to support healthy aging. Strategies such as mindfulness and cognitive behavioral therapy, yoga and Tai Chi help regulate stress, enhance mobility, reduces frailty, and promotes cognitive health. Adjunctive interventions like sleep optimization enhance recovery. Children and adolescents primarily rely on non pharmacologic measures, with limited analgesics use, adults use tailored multimodal approach, and older adults prioritize self management and non pharmacologic approaches.

Conclusion: Aging alters pain sensitivity, perception and reporting, while chronic pain can accelerate biological and functional aging. Clinicians and pharmacists may benefit from considering a dual approach that incorporates both objective sensory assessment and patient-reported outcomes. This integrated assessment may enable personalized pain management strategies that address both physiological changes and psychosocial impacts, thereby improving patients' care.

Pharmacogenomics standards to promote global uptake

Victoria Cancelliere[1]

[1]*United States Pharmacopeia, Rockville, Maryland, United States*

Background: Pharmacogenomics (PGx), situated at the intersection of genetics and pharmacology, holds significant potential for personalised medicine by utilising individual genetic information to optimise drug selection and dosing. Integrating PGx testing into clinical practice may improve treatment outcomes and reduce adverse drug reactions across a range of medical specialties, including oncology, cardiology, and psychiatry. Despite substantial efforts by clinicians and professional organisations, widespread implementation of PGx remains limited. The United States Pharmacopeia (USP), an independent scientific non-profit organisation, develops public standards used in more than 140 countries to advance patient access to quality medicines. These standards are implemented by healthcare practitioners and are frequently enforced by regulators, accreditors, and payers. At present, no enforceable pharmacogenomics standard exists, which represents a considerable barrier to adoption among providers, payers, and regulators.

Purpose: The aim of this work was to determine how USP might utilise its public health standard-setting expertise to bridge the gap between research, PGx testing, and the broader implementation of clinical pharmacogenomics.

Method: A systematic literature review was conducted using search terms related to PGx nomenclature, laboratory practices, evidence evaluation, and programme implementation. Inclusion criteria encompassed articles published between 2014 and 2024 that reported on randomised controlled trials, systematic reviews, meta-analyses, and narrative reviews. Additional resources were reviewed from PGx-focused organisations, including the Clinical Pharmacogenetics Implementation Consortium (CPIC), Association for Molecular Pathology (AMP), Pharmacogenomics Knowledge Base (PharmGKB), Dutch Pharmacogenetics Working Group (DPWG), and the College of American Pathologists (CAP), as well as regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). A multidisciplinary roundtable was also convened to gather stakeholder insights

regarding health equity considerations in pharmacogenomics.

Results: Evidence Evaluation: Discrepancies were identified in the levels of evidence required to establish gene - drug associations across PGx guidelines. These inconsistencies may contribute to confusion and reduced adoption of PGx recommendations within clinical practice guidelines.

Laboratory Practices: Variability was observed in the consistency and reliability of PGx test results, likely due to reliance on voluntary guidelines. Transparency gaps further complicate clinical decision-making, as laboratories frequently do not disclose allele-selection criteria or test limitations.

Electronic Health Record (EHR) Integration: Significant variation in EHR systems and clinical decision support tools was noted, making workflow integration and interoperability challenging.

Models of Care: Differences in PGx programme structures - such as pre-emptive versus reactive testing and single-gene versus multigene testing - create challenges for payers when determining reimbursement policies.

Conclusion: Several opportunities were identified for USP standards to influence the implementation of pharmacogenomics. USP, as an independent standard-setting body, is well positioned to utilise its expert volunteers and review processes to address these needs. A Personalised Medicines Expert Committee has been established, comprising pharmacogenomics specialists from the United States and Europe representing academia, healthcare systems, and industry. This committee will lead the development of PGx standards to support widespread, equitable adoption of pharmacogenomics in clinical practice.

Repurposing of lansoprazole as a prophylactic agent against oxaliplatin-induced peripheral neuropathy

Akihide Kobayashi[1,2], Kenji Ikemura[1,2], Manami Ueno[3], Eri Wakai[4], Fumihiro Yamane[1,2], Masahiro Okuda[1,2]

[1]Department of Hospital Pharmacy, Graduate School of Medicine, The University of Osaka, Suita, Japan

[2]Department of Pharmacy, The University of Osaka Hospital, Suita, Japan

[3]Department of Hospital Pharmacy, School of Pharmaceutical Sciences, The University of Osaka, Suita, Japan

[4]Laboratory of Clinical Pharmacy 2, College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan

Background: Oxaliplatin (L-OHP), a platinum-based anticancer drug, is widely used to treat various cancers. Because oxaliplatin-induced peripheral neuropathy (OIPN) is a major clinical problem that often limits treatment, effective and safe preventive strategies for OIPN are urgently required. As OIPN is mediated by the accumulation of L-OHP in the dorsal root ganglion (DRG) via organic cation transporter 2 (OCT2/SLC22A2), drugs with OCT2 inhibitory properties may serve as prophylactic agents for OIPN. This study aimed to identify potential prophylactic agents for OIPN through integrated in silico analyses, and subsequently evaluate the protective effects of the identified drugs against OIPN.

Method: We explored potential prophylactic agents for OIPN using an integrated model with the quantitative structure-activity relationship screening for human OCT2 inhibitors and two real-world data analyses of the Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Drug Event Report. In addition, we evaluated the preventive effects of the concomitant administration of candidate agents using an OIPN mouse model, in which four-week-old male C57BL/6J mice were injected intraperitoneally with L-OHP (10 mg/kg) once a week for 6 weeks. OIPN was assessed using the von Frey filament test and the acetone test. At 6 weeks following L-OHP administration, plasma and DRG (L4–L6) were collected, and the platinum concentrations in the plasma and DRG were determined using inductively coupled plasma mass spectrometry. Moreover, we evaluated the effects of cotreatment with candidate preventive agents on L-OHP (10 μM) uptake and the L-OHP-induced decrease in neurite length in primary cultured mouse DRG neurons.

Results: Our integrated in silico model identified lansoprazole, a proton pump inhibitor, as a potential prophylactic agent. In the OIPN mouse model, concomitant lansoprazole (2 mg/kg) drastically suppressed mechanical allodynia ($p < 0.001$) and cold hypersensitivity ($p < 0.001$) after repeated L-OHP administration. Moreover, the concentration of L-OHP in the DRG was significantly decreased by the concomitant administration of lansoprazole ($p < 0.001$). In primary cultured mouse DRG neurons, cotreatment with lansoprazole (10 μM) significantly inhibited L-OHP uptake ($p < 0.01$) and restored the L-OHP-induced decrease in neurite length ($p < 0.001$).

Conclusion: These findings suggest that lansoprazole ameliorates OIPN by inhibiting OCT2-mediated L-OHP uptake in the mouse DRG. Our findings provide important insights for the establishment of novel protective approaches to minimize OIPN.

Discrimination of amphetamine-type stimulant (ATS) dependence and ATS-induced psychosis using a metabolomics approach

Baharudin Ibrahim[1], Ruzmayuddin Mamat[1]

[1]*Universiti Malaya, KUALA LUMPUR, Malaysia*

Background: Amphetamine-type stimulant (ATS) misuse remains a major public health concern, particularly in rehabilitation settings where psychosis is a frequent and debilitating complication. Although ATS-induced psychosis is clinically recognized, its biological underpinnings remain poorly characterized. Current diagnostic approaches rely largely on clinical assessment, with limited objective biomarkers to differentiate ATS dependence from ATS-induced psychosis. Metabolomics offers a systems-level approach to identify biochemical perturbations associated with neuropsychiatric manifestations, potentially addressing an important gap in mechanistic understanding and biomarker development. This study aimed to identify plasma metabolomic signatures capable of differentiating ATS-induced psychosis from ATS dependence without psychosis, and to map discriminant metabolites onto biologically interpretable metabolic pathways. We hypothesized that ATS-induced psychosis would demonstrate coordinated perturbations in amino acid, nitrogen, redox, and neurotransmitter-related metabolic pathways compared with ATS dependence alone.

Method: A cross-sectional comparative metabolomics study was conducted at drug rehabilitation centers known as PUSPEN, recruiting participants from clinical and rehabilitation-associated settings. One hundred Malay male adults were enrolled (n=50 ATS dependence; n=50 ATS-induced psychosis). Group allocation was based on DSM-5 criteria for ATS use disorder with urine-confirmed ATS exposure; psychosis status was clinically diagnosed and psychiatrically confirmed. Polysubstance use was excluded. Standardized plasma samples were analyzed using a proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy workflow. Spectral pre-processing included artefact exclusion, binning, and normalization. Multivariate analyses were performed using SIMCA software, incorporating unsupervised principal component analysis (PCA) and supervised orthogonal partial least squares discriminant analysis (OPLS-DA) with internal validation to minimize overfitting. Model performance was evaluated using R^2Y, Q^2, sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve (AUROC). Identified metabolites were mapped to metabolic pathways for biological interpretation.

Results: The OPLS-DA model demonstrated strong internal discrimination between groups (R^2Y=0.929; Q^2=0.719). Classification performance was high, with sensitivity of 100%, specificity of 98.06%, overall accuracy of 98.08%, and AUROC of 0.916. Discriminatory metabolites included taurine, glycine, L-arginine, glutamic acid, serine, and homovanillic acid. Pathway analysis revealed convergence on interconnected metabolic modules involving glycine/serine metabolism, alanine metabolism, arginine/proline metabolism, glutamate metabolism, ammonia recycling, and the urea cycle. Additional perturbations were observed in redox-related one-carbon and sulphur pathways (including glutathione- and homocysteine-associated metabolism) and energy-linked processes such as the malate–aspartate shuttle.

Conclusion: ATS-induced psychosis appears to be characterized by coordinated disruptions in nitrogen flux, redox regulation, and neurotransmitter-linked metabolism, rather than isolated metabolite changes. These findings provide mechanistic insight into ATS-related neuropsychiatric complications and highlight candidate biomarkers for risk stratification. Future work should include prospective cohort studies, external validation in diverse populations, and integration with other omics platforms to enhance generalizability and clinical translation. This study contributes to a broader strategy aimed at developing objective, precision-based tools for identifying ATS users at risk of psychosis and informing targeted interventions.

Does nonlinear absorption of oral misoprostol challenge guideline-based dosing in late pregnancy cervical ripening? A population pharmacokinetic model to resolve

Zhiheng Yu[1,2], Tianyan Zhou[3], Yangyu Zhao[2]

[1]*Pharmacy Department, Aerospace Center Hospital, Beijing, China*

[2]*Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing, China*

[3]*Department of Pharmaceutics, School of Pharmaceutical Sciences, Peking University, Beijing, China*

Background: Misoprostol is the first-line agent for cervical ripening in late pregnancy, with oral administration increasingly superseding traditional vaginal routes in international clinical guidelines. Current oral dosing regimens are not derived from dose-exposure-response relationships but are empirically extrapolated from vaginal protocols. Dosing intervals (typically 2–4 hours) are based on an elimination half-life of 20–40 minutes, adhering to the principle that the preceding dose must be fully eliminated before subsequent administration. In real-world practice, this approach yields unsatisfactory cervical ripening rates (failure rates of 15–20%) and is concomitant with a high risk of uterine hyperstimulation (approximately 10%).

Purpose: To address this critical gap between guideline recommendations and clinical outcomes, this study utilized prospective cohort data to develop a population

pharmacokinetic (PopPK) model characterizing oral misoprostol disposition in late pregnancy and performed model-informed optimization of dosing regimens.

Method: A prospective cohort of term-pregnant women (37–41 weeks gestation) receiving oral misoprostol for cervical ripening was enrolled. Serial plasma samples were systematically collected following standardized protocols and quantified using a validated HPLC-MS/MS assay (lower limit of quantification: 2.5 pg/mL). A nonlinear mixed-effects (NLME) population pharmacokinetic model was developed using NONMEM® and R software. Covariate analysis employed forward inclusion and backward elimination to identify significant predictors. Model robustness was rigorously assessed through bootstrap validation and internal diagnostic checks. Subsequently, Bayesian estimation was applied to simulate the guideline-recommended dosing regimen, characterize misoprostol pharmacokinetics under current clinical practice, and inform evidence-based regimen optimization.

Results: The study included 87 pregnant women with 228 plasma samples. Contrary to the first-order absorption reported in the literature, the final PopPK model incorporated a lagged absorption time (Tlag), parallel zero-order and first-order absorption kinetics, a one-compartment distribution, and first-order elimination. The observed nonlinear absorption was hypothesized to be primarily influenced by food intake during pregnancy in real-world settings. Following adequate evaluation of the model, simulations of current guideline-recommended dosing regimens were conducted. Results demonstrated that repeated administration of 25 µg every 2 hours or 50 µg every 4 hours led to incomplete drug elimination between doses due to nonlinear absorption, resulting in drug accumulation. Furthermore, simulations identified the Cmax following a 50 µg dose as a safety threshold. Based on this, two optimized regimens (initial-day and subsequent-day dosing) were designed, with a total daily dose cap of 200 µg. Compared to guideline-recommended regimens, the optimized regimens reduced the total cervical ripening duration (9.5 hours vs. 12 hours) while maintaining safety.

Conclusion: This study establishes the first PopPK model for oral misoprostol in late pregnancy cervical ripening. Real-world data revealed nonlinear absorption kinetics, which underpin the drug accumulation observed with current guideline-recommended regimens, thereby increasing safety risks. Model-informed optimization yielded regimens that improved safety while significantly reducing cervical ripening duration.

Case report: A pharmacist-led precision therapy framework for managing invasive fungal infection in csf1r-related leukoencephalopathy post allo-HSCT

Jin Lu[1,2], Mengqi Jia[3], Xinghua Luan[2,4,5,6], Zhongqiu Zhang[1,2], Jingying Wu[4,5,6], Xiaojun Huang[2,4,5,6], Li Yang[1], Xincai Zhao[1,2], Miaomiao Zhou[1,2], Yao Fu[1,2], Quanjun Yang[1,2], Jianping Zhang[1,2], Li Cao[2,4,5,6], Cheng Guo[1,2]

[1]Department of Pharmacy, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[2]Neurology and Genetics Clinical Pharmacy Team, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[3]Department of Clinical Pharmacy, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[4]Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[5]Department of Genetics and Rare Diseases, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

[6]Shanghai Neurological Rare Disease Biobank and Precision Diagnostic Technical Service Platform, Shanghai, China

Background: Hereditary diffuse leukoencephalopathy with spheroids(HDLS), caused by CSF1R mutations, is a rare autosomal dominant leukodystrophy characterized by rapid neurological decline. Hematopoietic stem cell transplantation(HSCT) is a promising treatment, but the risk of post-transplant complications such as invasive fungal disease(IFD) remains underexplored. Microglial dysfunction in CSF1R-related disorder(CRD) may further impair host immune defense.

Method: We describe a Chinese male with a non-hotspot CSF1R mutation(c.2443-1G>C) who underwent allogeneic HSCT. A multidisciplinary team(MDT), including clinical pharmacists, implemented an individualized pharmacological strategy for antifungal management, guided by immune status, infection risk, pharmacokinetics, and next-generation pathogen diagnostics.

Results: Despite prophylaxis with voriconazole and levofloxacin, the patient developed febrile neutropenia and otitis media by day+16. Empirical meropenem therapy was ineffective, prompting escalation to teicoplanin and caspofungin. Pulmonary infection developed; targeted sequencing of bronchoalveolar lavage identified Aspergillus flavus. Antifungal therapy was intensified with voriconazole, resulting in clinical resolution by day+70. Treatment was maintained with good response.

Conclusion: This case demonstrates the complexity of managing IFD in CSF1R-related disorder patients after HSCT.

The interplay between systemic immunosuppression and intrinsic microglial dysfunction may heighten infection susceptibility. Precision antifungal therapy guided by multidisciplinary team expertise and pharmacological monitoring may improve outcomes in this rare and high-risk population.

Discrepancies in vancomycin clearance estimation among patients with low serum creatinine: A pilot study comparing renal function models

Yuki Nakano[1,2], Toshinori Hirai[3], Rintaro Sogawa[1], Hirotsugu Hasuwa[2], Chisato Shimanoe[1]

[1]*Saga University Hospital, Saga, Japan*

[2]*Saiseikai Futsukaichi Hospital, Fukuoka, Japan*

[3]*Institute of Science Tokyo Hospital, Tokyo, Japan*

Background: Vancomycin dosing is commonly guided by population pharmacokinetic (PopPK) models that output clearance (CL) as a function of renal function. In patients with low serum creatinine (Scr), creatinine-based estimates are physiologically heterogeneous. Low Scr may reflect reduced muscle mass despite impaired renal function, or augmented renal clearance (ARC). Muscle mass affects the generation rate of Scr but not cystatin C (Cys-C), but the predictive performance of Cys-C for vancomycin CL prediction in the high renal function range remains uncertain. We evaluated the agreement between observed CL from two steady-state concentrations and PopPK-predicted CL in adults with low Scr, and the factors that influence on agreement.

Method: This single-center retrospective study at Saiseikai Futsukaichi Hospital, Japan screened adults (≥18 years) receiving intravenous vancomycin with therapeutic drug monitoring between January 2019 and December 2024. Patients receiving renal replacement therapy or with unstable renal function (Scr change >±50% or KDIGO-defined acute kidney injury) were excluded. Observed CL was estimated by a modified Sawchuk–Zaske method under a one-compartment model using both peak and trough concentrations at steady-state. Predicted CL was calculated using a PopPK model commonly used in Japan under six scenarios: Ccr (Cockcroft–Gault) alone; Ccr with albumin adjustment; eGFRJapanese, Cys; Ccr with reduced-muscle-mass adjustment; Ccr after rounding Scr to 0.6 mg/dL when Scr<0.6 plus reduced-muscle-mass adjustment; and Ccr with combined albumin and reduced-muscle-mass adjustments. ARC was defined as BSA-indexed Ccr ≥130 mL/min/1.73 m². Agreement was assessed using Deming regression and concordance correlation coefficients (CCC), with Bland–Altman bias and limits of agreement (LoA). The agreement between observed CL and body surface area (BSA) was further examined by age and BMI strata with P for interaction.

Results: The study population consisted of a total of 24 patients with median Scr of 0.44 mg/dL (IQR 0.36–0.52), and 29.2% (n=7) met the ARC criterion. The best overall agreement was Ccr alone (CCC 0.79; 95% CI 0.62–0.89), followed by Ccr with albumin adjustment (CCC 0.77; 95% CI 0.59–0.87). Bland–Altman analysis showed modest mean bias and no apparent proportional bias for these two scenarios, whereas scenarios using eGFRJapanese, Cy and/or Scr rounding showed increasing underestimation at higher CL values, especially in ARC. In sensitivity analyses, the best agreement was Ccr with albumin adjustment in non-ARC (CCC 0.71; 95% CI 0.42–0.87) and Ccr alone in ARC (CCC 0.60; 95% CI 0.26–0.81). Observed CL correlated positively with BSA. The slope was numerically steeper in BMI ≥25 kg/m² than in BMI <25 kg/m² (P for interaction=0.21), and steeper in age <70 years than in age ≥70 years (P for interaction=0.10).

Conclusion: In adults with low Scr, approaches that attenuate high-end renal function estimates (eGFRJapanese, Cys or Scr rounding) tend to underestimate vancomycin CL, particularly under ARC. Ccr-based PopPK predictions showed better agreement with CL derived from two-point steady-state sampling. Two-point sampling–based CL estimation may be practical when higher CL is suspected in case of younger or obese patients.

Cabozantinib serum concentration as a predictor of severe adverse events in patients with metastatic renal cell carcinoma

Takahiro Ito[1], Kotaro Itohara[1], Kazuhiro Yamamoto[1,2], Takuto Hara[3], Yuki Yamanaka[1], Yumi Kitahiro[1], Tomohiro Omura[1], Ikuko Yano[1]

[1]*Department of Pharmacy, Kobe University Hospital, Kobe, Japan*

[2]*Department of Integrated Clinical and Basic Pharmaceutical Sciences, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan*

[3]*Department of Urology, Kobe University Graduate School of Medicine, Kobe, Japan*

Background: Cabozantinib, an oral multi-kinase inhibitor, is used to treat metastatic renal cell carcinoma (mRCC). Cabozantinib frequently causes clinically significant adverse events requiring dose reduction or treatment interruption. Dose adjustment based on therapeutic drug monitoring may help optimize cabozantinib exposure. However, patient factors associated with the safety and efficacy of cabozantinib remain unclear, and the relationship between cabozantinib exposure and clinical outcomes has not been fully elucidated. This study aimed to evaluate the association between cabozantinib serum concentrations and clinical outcomes in patients with mRCC.

Method: In this retrospective study, patients with mRCC who received cabozantinib were included. Cabozantinib serum

concentrations were measured using liquid chromatography-tandem mass spectrometry. Serum samples for cabozantinib concentration measurements were obtained during routine clinical practice at least 8 hours after cabozantinib administration. Adverse events occurring within 28 days after treatment initiation were evaluated and graded according to the Common Terminology Criteria for Adverse Events version 5.0. Serum interleukin-6 (IL-6) levels were measured before treatment initiation using an enzyme-linked immunosorbent assay. Genetic polymorphisms, including CYP3A5*3 (6986A>G), ABCC2 -24C>T, and STAT3 -1697C>G, were analyzed using a TaqMan real-time polymerase chain reaction assay. This study was approved by the ethics committee of Kobe University Hospital (No. B200321).

Results: The initial dose of cabozantinib was 40 mg/day in all patients except one who received 60 mg/day. Among 21 patients whose cabozantinib concentrations were available on days 10-15 after treatment initiation, severe adverse events (grades 3-4 or grade 2 toxicities requiring dose reduction or treatment discontinuation) were observed in 10 patients (47.6%). Cabozantinib serum concentrations showed large interindividual variability [median (range): 972 (307-1966) ng/mL]. The median concentration was significantly higher in patients with severe adverse events than in those without severe adverse events [1268 (765-1966) vs. 414 (307-1374) ng/mL, p = 0.004]. Receiver operating characteristic analysis identified a cutoff concentration of 765 ng/mL for predicting severe adverse events. Multivariate logistic regression analysis showed that IL-6 concentration and genetic polymorphisms were not significant risk factors for severe adverse events. Progression-free survival and time to treatment failure were not significantly different between patients with higher and lower cabozantinib concentrations (p = 0.992 and p = 0.736, respectively).

Conclusion: Among 21 patients, severe adverse events were observed in 10 patients (47.6%) during days 1-28, suggesting the need for careful management of cabozantinib-related toxicities. Maintaining cabozantinib serum concentrations below 765 ng/mL may help avoid the onset of serious adverse events without increasing the risk of disease progression or the treatment failure in patients with mRCC treated with cabozantinib. Monitoring cabozantinib serum concentrations may facilitate treatment optimization in clinical practice.

Comparative evaluation of AUC estimation methods for vancomycin therapeutic drug monitoring: Population pharmacokinetic modelling vs. trough concentrations

Cecilia Maldonado[1,2], Juan Pablo Barboza[1,2], Natalia Guevara[1,2], Martín Umpierrez[1,2]

[1]*Facultad de Quimica, UdelaR, Montevideo, Uruguay*

[2]*Therapeutic Drug Monitoring Service, University Hospital Dr. Manuel Quintela, Universidad de la República, Uruguay, Montevideo, Uruguay*

Background: Vancomycin remains a cornerstone therapy for severe Gram-positive infections, including methicillin-resistant Staphylococcus aureus (MRSA). Contemporary guidelines from the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), formalised in 2020 and reinforced in 2022, recommend monitoring through the 24-hour area under the concentration-time curve (AUC_{0-24}) rather than trough concentrations alone, targeting an AUC/MIC ratio of 400–600 mg·h/L. Despite this, many clinical settings continue relying on trough-only monitoring due to practical barriers, including infrastructure limitations and the logistical burden of multiple blood draws.

Objectives: To evaluate the clinical utility of AUC-guided vancomycin monitoring compared with traditional trough-based monitoring, and to assess whether population pharmacokinetic (popPK) model-based estimation via the TDMx platform provides reliable AUC estimates with reduced sampling requirements relative to the Sanford Guide two-point method.

Method: A two-phase study was conducted at Hospital de Clínicas, Uruguay. Hospitalised patients receiving vancomycin were included; those on dialysis or continuous infusion were excluded. In a retrospective cohort (September–December 2023), only pre-dose concentrations were available. In a prospective cohort (June–August 2024), both pre-dose and post-infusion samples were collected. AUC was estimated using two methods: the Sanford Guide two-point formula (requiring pre-dose and end-of-infusion concentrations) and the TDMx platform, which applies popPK models incorporating individual covariates (age, weight, height, serum creatinine, and urea). Comparisons were performed using the Wilcoxon signed-rank test due to non-normal data distribution.

Results: Sixty-seven patients were included (35 from 2023; 32 from 2024). No statistically significant differences were observed between AUC estimates generated by the Sanford Guide and those produced by TDMx (p=0.38, Wilcoxon statistic=81.0). Similarly, TDMx estimates using only a single pre-dose sample did not differ significantly from those using both pre-dose and post-infusion samples (p=0.501, Wilcoxon statistic=149). Clinically relevant discordances were identified between trough concentrations and AUC-based

categorisation: several patients with pre-dose levels below 15 mg/L presented AUC estimates within the therapeutic range (400–600 mg·h/L), whilst patients above the trough threshold showed AUC values exceeding 600 mg·h/L, suggesting toxicity risk undetected by trough monitoring alone.

Conclusion: AUC estimation via popPK modelling with TDMx is statistically equivalent to the validated Sanford Guide approach whilst requiring only a single blood sample. This has particular relevance in resource-limited clinical settings where multiple sampling is logistically challenging. The findings further demonstrate that trough concentrations alone are insufficient predictors of total drug exposure, reinforcing the need to transition towards individualised, exposure-based vancomycin monitoring in routine clinical practice.

Personalized AML treatment: Integrating obesity-related gene signatures and machine learning to predict drug resistance in acute myeloid leukemia

Man Wang[1], Yan Wang[1], Shaoshuai Yu[1], Li Cao[1]

[1]Affiliated People's Hospital of Jiangsu University, 8 Dianli Rd., Zhenjiang, 212002 People's Republic of China, Zhenjiang, China

Background: Obesity is an all-known risk factor for the development and poor prognosis of acute myeloid leukemia (AML). However, pathways and mechanisms linking obesity to oncogenesis and drug resistance of AML remain poorly understood, hindering the personalization of treatment for these high-risk patients. This study aims to identify key obesity-related genes implicated in AML pathogenesis and drug resistance, and to develop a robust machine learning-based predictive model that can optimize therapeutic strategies for obese patients with AML.

Method: This study integrated transcriptomic and clinical data from publicly available AML cohorts to identify differentially expressed genes associated with body mass index (BMI) and treatment outcomes. Multi machine learning algorithms, including LASSO, SVM-RFE, Random Forest, and XGBoost, was employed to identify AML obesity co-related genes. A genetic algorithm-optimized Naive Bayes model was constructed to predict chemotherapy response. The functional role of the hub gene in promoting resistance was experimentally validated via lentiviral-mediated gain- and loss-of-function studies AML cells.

Results: 8 AML obesity co-related genes (mTORC1, PPARδ, AMPK, FOXO1, PRKACA, CREB3L4, FCGRT, CTSZ) were identified associated with drug resistance in AML. The upregulation of mTORC1 and PPARδ points to a metabolic switch towards lipogenesis and oxidative phosphorylation, providing energy sources for leukemic proliferation. This metabolic rewiring was further supported by the downregulation of AMPK, a master energy sensor whose inactivation indicates a loss of metabolic checkpoint control. Upregulation of FOXO1 and PRKACA was linked to the activation of DNA repair mechanisms and anti-apoptotic signaling, enhancing leukemic cell survival under chemotherapy pressure. The downregulation of CREB3L4 suggests impaired endoplasmic reticulum stress adaptation, potentially rendering cells more reliant on alternative survival pathways. Immune landscape analysis revealed that elevated FCGRT expression correlated positively with the infiltration of immunosuppressive M2 macrophages and negatively with cytotoxic CD8+ T-cell activity, while CTSZ upregulation may contribute to extracellular matrix remodeling and immune evasion. Leveraging this eight-gene signature, our genetic algorithm-optimized Naive Bayes model achieved exceptional predictive performance for AML chemoresistance, demonstrating 92% accuracy and an area under the curve (AUC) of 0.95 in the validation cohort, significantly outperforming conventional models.

Conclusion: This study elucidates a mechanistic framework linking obesity to AML drug resistance through three interconnected axes: metabolic reprogramming (driven by mTORC1/PPARδ upregulation and AMPK downregulation), enhanced DNA repair and survival signaling (via FOXO1/PRKACA), and immune evasion (promoted by FCGRT and CTSZ). The downregulation of AMPK and CREB3L4 further disables key tumor-suppressive barriers, tipping the balance towards oncogenic progression. The GA-Naive Bayes model built on this eight-gene signature offers a robust, clinically-actionable tool for identifying obese AML patients at high risk of treatment failure, thereby supporting the development of personalized therapeutic strategies incorporating metabolic or immunomodulatory agents.

Population pharmacokinetics modeling of kovaltry by real world Data: Free individualized medication guidance for hemophilia patients in China

Xiaoxu Wang[1], Lingling Chen[1], Tiantian Wang[2], Wenjuan Miao[1], Jixin Tian[1], Wei Liu[1], Lei Zhang[1], Jie Wang[2], Yan Cheng[2], Yunhai Fang[2], Renchi Yang[1], Feng Xue[1], Ping Zhang[1]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory, Tianjin, China

[2]Shandong Blood Center, Shandong Hemophilia Treatment Center, Jinan, China

Background: Standard weight-based prophylaxis treatment is unsafe or effective for all patients due to extreme inter-individual variability in FVIII Pharmacokinetics (PK), complicating maintenance of target FVIII coagulating activity. Personalized medication support is essential in China from

both economic and safety perspectives. However, traditional PK methods, requiring complex calculations and numerous blood samples, make PK-tailored individualized prevention challenging. The population pharmacokinetics (PopPK) approach can reduce samples to support precision medication. Kovaltry is one of the most widely used medications for hemophilia patients in China. While several PopPK models for Kovaltry have been reported, their applicability to Chinese patients remains limited due to assay methods, policies or population differences. An urgently needed free PopPK model suitable for more Chinese patients integrated into the Hemophilia Treatment Center Collaboration Network of China (HTCCNC) is required.

Purpose: To develop a PopPK model using real world data in Chinese quantifying the influence between and within patients. Integrating the model into the HTCCNC to support individualized treatment for a larger population of Chinese hemophiliacs to improve quality of life.

Method: 31 Chinese patients' clinical routine prophylactic data were collected and used to develop the model. Phoenix Nonlinear Mixed-Effects (NLME) 8.3 was used to develop the PopPK model and quantify the effect of potential covariates on the PK parameters, including demographics, von Willebrand factor antigens (vWF:Ag) and blood groups. Covariates selection was conducted by stepwise forward inclusion and backward deletion. The visual predictive check (VPC) and bootstrap were conducted to evaluate the robustness and prediction ability of the final model. Meanwhile, external validation was performed using sparse data from 6 real-world prophylactic patients.

Results: Kovaltry conformed with a 2-compartment model in Chinese HA patients. WT and vWF:Ag significantly affected the clearance (CL) of the central compartment (V), while fat-free mass (FFM) affected the distribution volume of peripheral compartment (V2) and V. Our final model demonstrated sufficient reproducibility for evaluating PK parameters via internal and external validation. Through comparison, our model's predicted PK parameters for 6 real-world prophylactic patients are close to those of Web-Application for Population Pharmacokinetic Service (WAPPS). The model enables accurate prediction of individual responses from sparse samples, supporting personalized prophylaxis adjustment in real-world clinical settings and being the first real-world data model integrated into HTCCNC.

Conclusion: This is the first Chinese real-world data predictive model of Kovaltry integrated into HTCCNC. It enables PK-guided prophylaxis, improving patient outcomes and costs for a larger population of Chinese hemophiliacs.

Comparative risk of psychiatric comorbidities between weak opioids in hip OA: Focusing on high-risk subgroups

Yujin Kim[1], Eunjung Choo[2], Sooyoung Shin[2], Yeo Jin Choi[1]

[1]*Kyung Hee University, Seoul, South Korea*

[2]*Ajou University, Suwon, South Korea*

Background: Weak opioids, specifically codeine and tramadol, are frequently prescribed for pain management in patients with hip osteoarthritis. Despite their common use, comparative evidence regarding their differential impact on psychiatric comorbidities remains limited, particularly within clinically vulnerable subgroups. This study aimed to compare the risk of incident psychiatric disorders between codeine and tramadol users, with a specific focus on subgroups defined by comorbidity burden and concomitant medication use.

Method: A nationwide retrospective cohort study was conducted using the Korean Health Insurance Review and Assessment Service database. Patients with hip osteoarthritis (diagnosed between 2014-2017) initiated on either codeine or tramadol were identified. To minimise baseline confounding, 1:4 propensity score matching was employed. The primary outcome was a composite of psychiatric comorbidities, including depression, anxiety, bipolar disorder, schizophrenia, and sleep disorders. Cox proportional hazards regression models were utilised to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Stratified subgroup analyses were performed based on the Charlson Comorbidity Index (CCI) and the use of concomitant psychotropic medications.

Results: In the matched cohort of 22,651 patients, codeine use was associated with a significantly lower risk of composite psychiatric disorders compared with tramadol (aHR 0.86, 95% CI 0.78–0.96). Subgroup analyses revealed that this protective association was more pronounced in patients with a higher comorbidity burden (CCI ≥3; aHR 0.81, 95% CI 0.68–0.96). Codeine use was associated with lower risk of anxiety (aHR 0.74, 95% CI 0.61-0.90), derpession (aHR 0.79,0.65-0.95) and sleep disorder (aHR 0.73, 95% CI 0.56-0.95) in patients with cardiovascular disease. Moreover, Furthermore, the lower risk of psychiatric outcomes with codeine remained consistent among patients who were not concomitantly using benzodiazepines (aHR 0.84, 95% CI 0.74–0.96), antidepressants (aHR 0.82, 95% CI 0.72–0.92), or antipsychotics (aHR 0.85, 95% CI 0.77–0.95). Anxiety was the individual outcome most consistently reduced across the majority of examined subgroups.

Conclusion: The findings suggest that codeine is associated with a more favourable psychiatric safety profile than tramadol in patients with hip osteoarthritis. This association is particularly evident in medically complex patients with high comorbidity levels and those not receiving other centrally

acting medications. These results indicate that clinical decisions regarding opioid selection should incorporate an assessment of the patient's psychiatric risk profile and existing medication regimens to optimise safety in vulnerable populations.

Predictors of serious misuse and dependence for high-risk medications

Yujin Kim[1], Yu Jin Sohn[1], Jin Young Yoo[1], Semi Kim[1], Yeo Jin Choi[1]

[1]*Kyung Hee University, Seoul, South Korea*

Background: The escalating global concern over opioid misuse and dependence necessitates robust monitoring systems to identify high-risk drug-adverse event combinations. In South Korea, while opioid prescriptions have increased, comprehensive analyses of misuse-related reports in the national pharmacovigilance database remain scarce. This study aimed to identify key predictors of serious prescription drug misuse and dependence using nationwide spontaneous reporting data, providing evidence for regulatory decision-making.

Method: A retrospective analysis was conducted using the Korea Adverse Event Reporting System (KAERS) database (2014–2022). Reports related to "drug misuse" and "drug dependence" were identified. Medications were categorized based on their dependence potential. To evaluate the clinical significance, serious cases, defined by death, life-threatening conditions, or prolonged hospitalisation, were compared with non-serious cases. Multivariable logistic regression analysis was performed to identify independent predictors, including patient demographics, reporting personnel, and concomitant medications such as NSAIDs, antidepressants, and antipsychotics. Odds Ratios (ORs) were calculated to assess the strength of associations. We developed and compared multiple machine learning algorithms, including Random Forest and XGBoost, to predict "serious" versus "non-serious" misuse and dependence reports. The models incorporated diverse predictors: demographics, reporting sources, and concomitant medications. Model performance was evaluated using the Area Under the Receiver Operating Characteristic curve (AUROC) and feature importance analysis to identify key contributing factors.

Results: According to the multivariable analysis and feature importance, the concomitant use of antipsychotics (OR 4.97, 95% CI 3.21–7.71) and anticonvulsants (OR 3.42, 95% CI 2.42–4.81) was strongly associated with an increased risk of serious outcomes. Among reporting sources, the general public (OR 4.59, 95% CI 3.04-6.94) showed a distinct reporting pattern compared to physicians. The machine learning approach allowed for the identification of complex polypharmacy patterns that significantly contribute to the severity of dependence-related adverse events. Feature importance analysis revealed that the reporter type was a key predictor of report severity.

Conclusion: This study demonstrates the utility of machine learning in predicting serious outcomes related to medications with high-dependence potential. By leveraging nationwide pharmacovigilance data, these models provide a sophisticated tool for identifying high-risk patient profiles and complex concomitant medication patterns. Furthermore, the integration of patient-reported outcomes (PROs) into the predictive framework ensures that the patient's perspective on functional status and quality of life is prioritised in safety monitoring. These findings offer a robust scientific basis for regulatory agencies to enhance targeted surveillance and develop evidence-based risk-minimisation strategies, ultimately fostering a more patient-centered approach to the safe management of high-dependence risk pharmacotherapy.

A Bayesian network meta-analysis on risk of Parkinson's disease in diabetic patients: Stratified by patient characteristics

Soo Hyeon Lee[1], Yujin Rho[1], Sangyoon Lee[3], Sooyoung Shin[2], Yeo Jin Choi[1]

[1]*Kyung Hee University, Seoul, South Korea*

[2]*Ajou University, Suwon, Korea*

[3]*Union Hospital, Terre Haute, U.S.*

Background: Type 2 diabetes mellitus (T2DM) has been linked to an increased risk of Parkinson's disease (PD), possibly due to shared underlying mechanisms like insulin resistance and neuroinflammation. While various antidiabetic medications are suggested to have neuroprotective effects, their relative efficacy in reducing PD risk remains unclear. This study aimed to compare the risk of PD across different antidiabetic classes and identify the most protective treatments using a network meta-analysis.

Method: A Bayesian network meta-analysis (NMA) were conducted. We searched major databases (PubMed, EMBASE, and Cochrane Library) for longitudinal studies investigating the association between antidaibetics classes and PD risk. The antidiabetic classes included metformin, sulfonylureas (SU), thiazolidinediones (TZD), DPP-4 inhibitors (DPP4i), GLP-1 receptor agonists (GLP-1RA), and SGLT2 inhibitors (SGLT2i). Pooled odds ratios (ORs) and 95% credible intervals (CrIs) were estimated. To determine the relative hierarchy of the medications, Surface Under the Cumulative Ranking (SUCRA) probabilities were calculated.

Results: Nine observational cohort studies of 726,653 patients were included. Based on SUCRA rankings, metformin

was consistently associated with the highest risk of PD across all age, sex, and comorbidity groups. In the stratified analysis, SGLT2i was identified as the most favourable agent, demonstrating the lowest PD risk among older patients (≥75 years), women, and those with a history of CVD. In patients with CVD, the risk of PD was significantly higher with metformin compared to SGLT2i (RR 1.30, 95% CrI 1.10–1.50). GLP-1RA showed the lower risk of PD development in men and individuals <75 years.

Conclusion: This study deonostrates significant differences in the neuroprotective profiles of antidiabetic classes across diverse patient populations. While metformin demonstrated a consistently higher risk profile for PD, newer classes such as SGLT2i and GLP-1RA emerged as superior options for reducing PD risk, with their relative benefits varying by age, sex, and CVD status. These findings provide a scientific basis for personalized antidiabetic therapy, suggesting that clinical selection of antidiabetics should consider the patient's individual risk profile for neurodegenerative diseases.

The impact of specific genetic polymorphisms in optimizing clinical outcomes for patients with substance use disorders

Hebat-allah I. Mandour[1], Nefertiti El-nikhely[2,3], Noha A. Hamdy[1], Mahmoud Agami[4], Aymen H. Abdelshafi[5], Ahmed F. El-yazbi[4,6], Sahar M. El-gowilly[6]

[1]*Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt*

[2]*Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt*

[3]*Molecular Biotechnology, Alamein International University, Alamein, Egypt*

[4]*Research and Innovation Hub, Alamein International University, Alamein, Egypt*

[5]*Addiction Treatment Center, Al-Maamoura Psychiatric Hospital, Alexandria, Egypt*

[6]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt*

Background: Substance use disorder (SUD) represents a complex chronic psychiatric condition influenced by a diverse predisposing factors. Neuropsychopharmacogenomics explores how interindividual genetic variations impact the clinical efficacy and safety of medications utilized in SUD management. While identifying specific genotypes offers a pathway to more effective therapeutic programs, there remains a significant gap in genetic drug-response assessments across diverse populations and limited implementation within the field of addiction medicine.

Objective: This study aimed to screen commonly reported genetic polymorphisms and evaluate their correlation with the variable clinical responses observed during the pharmacotherapeutic treatment of SUD patients in Egypt.

Method: The study cohort was characterized through the collection and analysis of sociodemographic data using frequency and descriptive statistics. Collected patient blood samples were analyzed quantitatively for drug concentrations using an Ultra-High-Performance Liquid Chromatography (UHPLC) system coupled with triple quadrupole mass spectrometry. Targeted genotyping of specific single nucleotide polymorphisms (SNPs) was executed via Polymerase Chain Reaction (PCR) and DNA sequencing, followed by specialized bioinformatic data analysis.

Results: Analysis of 121 patients with SUD identified functional genetic variants such as SNPs in the ABCB1, CYP2C19, and COMT genes that significantly influence metabolic phenotypes. Biostatistical evaluation confirmed a strong association between these genetic profiles and the clinical response to various medications integrated into SUD management protocols in Egypt such as carbamazepine, olanzapine and quetiapine. Descriptive sociodemographic data provided a thorough profile of the study population, while the genomic findings underscored critical limitations in current standardized dosing strategies.

Conclusion: These findings highlight that specific genetic variations are essential determinants of treatment outcome variability in SUD populations. Incorporating pharmacogenomic data into clinical workflows is essential for advancing precision medicine, enhancing patient safety, optimizing therapeutic outcomes, and improving overall treatment adherence within addiction recovery programs.

Evaluation of pharmacogenetic warfarin dosing algorithms in Chinese patients carrying VKORC1/CYP2C9 variant alleles

Jun Wang[1,2], Ning Hou[1,2]

[1]*Shandong Provincial Hospital Affiliated To Shandong First Medical University, Jinan, China*

[2]*Evidence-based Pharmacy Special Committee of Shandong Pharmaceutical Association, Jinan, China*

Background: Warfarin is essential for heart valve replacement patients. VKORC1 and CYP2C9 polymorphisms explain substantial warfarin dose variability. While VKORC1 AA and CYP2C9*1/*1 predominate in Chinese populations, patients with variant alleles (VKORC1 GA/GG or CYP2C9*1/*3, CYP2C9*3/*3) represent dose extremes with increased bleeding or thrombosis risks. Most validation studies focus on common genotypes, leaving a critical gap regarding algorithm performance in this understudied subgroup. This study compared four pharmacogenetic

algorithms—Gage, IWPC, Ohno, and Huang—to identify the most suitable algorithm for Chinese patients with VKORC1/CYP2C9 variant alleles following heart valve replacement.

Method: This single-center retrospective study enrolled patients who underwent heart valve replacement (January 2023–June 2025). Inclusion criteria: age ≥18 years, warfarin initiation post-surgery, VKORC1 GA/GG or CYP2C9*1/*3, CYP2C9*3/*3 genotypes, and stable dose achieved (INR 1.8–2.8 for ≥7 days with unchanged dose). VKORC1 -1639G>A and CYP2C9 were genotyped using fluorescence in situ hybridization sequencing. Demographic data, target INR, concomitant medications, and stable dose were collected. Predictive accuracy was assessed using mean absolute error (MAE) and proportion of predictions within ±20% of actual dose (P20). Subgroup and dose-stratified analyses were performed using mean relative error (MRE).

Results: Of 154 patients (mean age 59.7 ± 10.9 years; 60.1% male), genotype distribution: VKORC1 GA 87 (56.5%), GG 4 (2.6%); CYP2C9*1/*3 64 (41.6%), CYP2C9*3/*3 5 (3.2%). Gage and Huang achieved the lowest MAE (0.51 mg/day), with P20 of 97% and 96%, respectively. Huang provided superior accuracy for VKORC1 GA, VKORC1 GG, and CYP2C9*1/*3. For the rare CYP2C9*3/*3, Gage yielded the lowest MRE, demonstrating best performance in this challenging subgroup.

Conclusion: All algorithms except IWPC demonstrated acceptable accuracy (MAE <1.0 mg/day, P20 >40%) in patients with variant alleles, supporting their clinical utility. Performance was genotype-dependent: Huang excelled for VKORC1 GA, VKORC1 GG, and CYP2C9*1/*3; Gage was superior for CYP2C9*3/*3. These findings inform personalized anticoagulation in Chinese populations and highlight the need for dedicated algorithms for rare genotypes.

Rapid and scalable acoustofluidic enrichment of extracellular vesicles for precision diagnostic and translational workflows

Jianfei Tao[1], Xiaoyan Zhang[2], Hang Qian[2], Xin Yang[2]

[1]*Shanghai Yangsi Hospital, Shanghai, P.R. China*

[2]*Cardiff University, Cardiff, UK*

Background: Extracellular vesicles (EVs) are promising targets for liquid-biopsy biomarker analysis and are also attracting increasing interest as bio-derived therapeutic materials. However, conventional EV isolation and concentration workflows are often slow, equipment-intensive, and difficult to integrate into rapid downstream analytical workflows. Therefore, a fast and gentle enrichment method capable of handling clinically relevant sample volumes could support precision diagnostics and broader pharmaceutical research.#

Purpose: To develop and evaluate an acoustofluidic platform for the rapid enrichment of extracellular vesicle-containing samples from millilitre-scale input volumes, and to assess enrichment performance using nanoparticle tracking analysis and sample integrity using cryo-electron microscopy. This study hypothesises that the simultaneous generation of two orthogonal surface acoustic waves can induce a complex acoustic field within a droplet, resulting in more powerful and more efficient concentration of nanoparticles.

Method: An acoustofluidic device based on combined dual surface acoustic waves was developed and used to concentrate nanoparticles and extracellular vesicles in a 2 mL sample droplet. Device performance was first assessed using fluorescent polystyrene nanoparticles across relevant nanoscale sizes in biofluid-mimicking matrices with varying viscosities. Extracellular vesicles derived from HEK293 human embryonic kidney cells and Du145 prostate cancer cells were then processed. Particle concentration was measured by nanoparticle tracking analysis, with dilution factors corrected before comparison across input, enriched, and residual fractions. Vesicle integrity was further examined by cryo-electron microscopy, and vesicle-associated CD81 was measured using an enzyme-linked immunosorbent assay-based immunolabelling approach. One-way ANOVA was used for normally distributed data, and Kruskal–Wallis tests were used for non-normally distributed data to evaluate statistical significance.

Results: The acoustofluidic platform operated stably and processed 2 mL samples within 2 minutes, reducing the collection volume to approximately 100 µL. Nanoparticle tracking analysis confirmed increased particle concentration in enriched fractions after correction for dilution factors. In HEK293-derived samples, enriched fractions showed approximately 9.8- to 30.0-fold increases in particle concentration relative to input samples, with a median enrichment of about 18-fold. In Du145-derived samples, CD81-positive vesicles increased from 129 to 237 µg mL^{-1} in the concentration zone, whereas the depleted zone contained less than 50 µg mL^{-1}, indicating an approximately 85% difference between zones. Cryo-electron microscopy further indicated preservation of EV structural integrity after processing. These findings support the rapid localisation and pipette retrieval of enriched vesicles while maintaining their biological integrity and function.

Conclusion: This acoustofluidic platform enables the rapid enrichment of extracellular vesicle-containing samples from millilitre-scale inputs into a small collection volume, with quantitative gains demonstrated by nanoparticle tracking analysis and supportive evidence for preservation of extracellular vesicle structure. The method may provide a practical front-end sample-preparation step for precision diagnostic workflows and extracellular vesicle-related pharmaceutical research. Further work should focus on achieving higher recovery, processing larger sample volumes,

improving compatibility with downstream assays in additional biofluids, and enabling fully automated sampling.

Characterization of the plasma concentration of rifampicin in Ghana: Evidence from quantile regression

Michael Opoku-mireku[1], Margaret Lartey[2,3], Awewura Kwara[4], Charles Peloquin[5], Kwadwo Koram[1,6]

[1]Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, Legon, Accra, Ghana

[2]Department of Medicine and Therapeutics, University of Ghana Medical School, Accra, Ghana, Accra, Ghana

[3]Department of Medicine, Korle Bu Teaching Hospital, Accra, Ghana, Accra, Ghana

[4]Division of Infectious Diseases and Global Medicine, University of Florida College of Medicine, Florida, United States

[5]Infectious Disease Pharmacokinetics Laboratory, University of Florida College of Pharmacy, Florida, United States

[6]Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana

Background: Subtherapeutic plasma concentrations of rifampicin, a cornerstone of first-line anti-tuberculosis (TB) therapy, contribute to treatment failure and resistance in high-burden settings like Ghana. Conventional mean regression overlooks exposure heterogeneity. This study aimed to characterize rifampicin peak concentration (Cmax) and its determinants across the distribution using quantile regression.

Method: The study analysed baseline data from 143 adults with drug-susceptible pulmonary TB on WHO-recommended first-line anti-TB drugs enrolled in a cohort study in Ghana. Simultaneous quantile regression models were fitted at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of rifampicin Cmax, adjusting for age, weight, dietary diversity, sex, HIV co-infection, diabetes comorbidity, and concomitant medications. Inference relied on 2,000 bootstrap replications for robust standard errors, with Wald tests assessing inter-quantile heterogeneity.

Results: Rifampicin Cmax showed quantile-dependent variability, with pseudo-R^2 rising from 0.04 (q05) to 0.31 (q95). 94.4% of participants had subtherapeutic Cmax levels (<8µg/ml). Age and weight showed positive associations primarily at upper quantiles (age q75 β=0.045, p=0.007; q95 β=0.098, p=0.001; weight q75 β=0.054, p=0.005; q95 β=0.121, p=0.011), confirmed by inter-quantile tests (age q05 vs q95 p=0.003; weight q05 vs q95 p=0.027). Male sex (q75 β=-1.56, p=0.015; q90 β=-1.48, p=0.036) and concomitant medications (q75 β=-1.19, p=0.039) showed negative mid-upper quantile effects. Diabetes had a quantile-specific effect at q10 (β = 3.28, p = 0.020). No covariates explained lower-tail (q05-q25) variability. In comparison, age (β=0.04, 0.011), weight (β=0.046, 0.013), and male sex (β=-1.36, 0.005) were associated with mean rifampicin Cmax

Conclusion: Quantile regression identified predictors that varied across the rifampicin concentration distribution, revealing substantial heterogeneity in rifampicin exposure among Ghanaian patients with tuberculosis. The findings underscore the limitations of fixed-dose regimens and mean-based analyses. Targeted therapeutic drug monitoring may benefit selected subgroups, but further research is needed to identify predictors of low exposure to inform precision dosing in resource-limited settings.

Subtherapeutic exposure to all four first-line anti-TB drugs and risk of treatment failure or death: A target trial emulation study from Ghana

Michael Opoku-mireku[1], Awewura Kwara[2], Margaret Lartey[3,4], Charles Peloquin[5], Kwadwo Koram[1,6]

[1]Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, Legon, Ghana, Accra, Ghana

[2]Division of Infectious Diseases and Global Medicine, University of Florida, Gainesville, Florida, United States, Florida, United States

[3]Department of Medicine, Korle Bu Teaching Hospital, Accra, Ghana, Accra, Ghana

[4]Department of Medicine and Therapeutics, University of Ghana Medical School, Accra, Ghana, Accra, Ghana

[5]Department of Pharmacotherapy and Translational Research, University of Florida, Gainesville, Florida, United States, Florida, United States

[6]Department of Epidemiology, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana, Accra, Ghana

Background: Despite improved treatment success rates globally, tuberculosis (TB) control in sub-Saharan Africa continues to fall short of End TB targets. In Ghana, treatment success has stagnated between 84% and 87% for over a decade, while the risk of acquired drug resistance among previously treated patients is 19 times higher than in treatment-naïve individuals. Although non-adherence is frequently blamed, emerging evidence suggests that pharmacokinetic variability resulting in subtherapeutic plasma concentrations may play a critical role in poor outcomes and resistance emergence, even among adherent patients. This study used causal inference methods to estimate the effect of concurrent subtherapeutic exposure to all four first-line anti-TB drugs on treatment failure or death.

Method: We conducted a prospective cohort study of 164 adults with GeneXpert-confirmed rifampicin-susceptible pulmonary TB receiving standard WHO weight-band dosing

across five hospitals in Ghana. Peak plasma concentrations (Cmax) of rifampicin, isoniazid, pyrazinamide, and ethambutol were measured at months 1–2 using validated liquid chromatography tandem mass spectrometry. We emulated a target trial comparing two static strategies from the time of pharmacokinetic sampling: (1) achieving therapeutic Cmax for at least one drug versus (2) subtherapeutic Cmax for all four drugs. Using the clone-censor-weight approach with inverse probability of censoring weighting, we estimated the per-protocol analogue risk difference (RD) and risk ratio (RR) for the composite outcome of treatment failure or death by month 6. Sensitivity analyses included inverse probability weighting with regression adjustment, plain inverse probability weighting, and E-value assessment for unmeasured confounding.

Results: Of 164 enrolled participants, 120 had complete pharmacokinetic and outcome data. Twenty percent (24/120) had subtherapeutic concentrations of all four drugs. In weighted analyses, persistent low exposure to all four drugs was associated with a 25.6 percentage-point increase in absolute risk of treatment failure or death (95% CI: 5.7–45.6; p=0.012) and an 8.6-fold higher relative risk (RR 8.64, 95% CI: 2.34–31.92; p=0.001) compared with adequate exposure to at least one drug. Sensitivity analyses were consistent (ATE 19.9%, 95% CI: 2.3–37.5). The E-value of 15.5 (lower bound 5.0) indicated robustness to unmeasured confounding. The number needed to treat was approximately 4.

Conclusion: Concurrent subtherapeutic plasma concentrations of all four first-line anti-TB drugs substantially increase the risk of poor treatment outcomes. These findings highlight an under-recognized pharmacokinetic barrier to TB elimination in high-burden settings and support the urgent evaluation of therapeutic drug monitoring and optimized dosing strategies through randomized trials.

How the fixed dose combination of ibuprofen and acetaminophen delivers moderate to severe pain relief

Richard Petruschke[1], Karin Nicholson[1], Peter Gao[2]

[1]*Haleon, Quakertown, Pennsylvania,, United States*

[2]*Medical Affairs, Haleon, Mississauga, ON,, Canada*

Background: Ibuprofen (IBU) and acetaminophen (APAP) are effective pain relievers. Their maximum over-the-counter (OTC) dose is IBU 400 mg and APAP 1000 mg, both dosed up to every 6 hours and 3 doses daily. A fixed dose combination (FDC) of IBU 125 mg/APAP 250 is available and is dosed 2 tablets every 8 hours daily. The FDC was developed to combine the mechanism of action (MoA) of IBU and APAP. The FDC was evaluated in a robust pharmacokinetic (PK) and clinical study program. The objective of this analysis was to evaluate the factors supporting the effectiveness of the FDC in treating moderate to severe pain.

Method: The FDC was studied in five PK studies, and three clinical studies that used the Dental Pain Model (DPM) (third molar extraction). The PK studies characterized the absorption and distribution of IBU and APAP in the FDC and given alone. The DPM studies evaluated the FDC as a single dose, multidose, and with dose ranging. The studies evaluated pain intensity difference (SPID), time to meaningful pain relief (MPR), and duration of relief (DR). The study subjects all had moderate or severe pain at baseline.

Results: The PK studies confirmed that AUC, Cmax, Tmax, and other PK characteristics were comparable with IBU and APAP in the FDC and when given alone. In the single dose DPM study, 1) mean SPID 0-8 hours was significantly better with FDC (34.3) than APAP (19.4 [p<0.001]), IBU (28.9 [p=0.008]), and PBO (4.1 [p<0.001]); 2) median time (minutes) to MPR was faster with FDC (47.9) than APAP (56.6 [p=0.031]), IBU (65.9 [p=0.003]), and PBO (NA [p<0.001]); 3) median time (minutes) to DR was longer with FDC (629.0) than APAP (449.0 [p<0.001]), IBU (608.5 [p=0.069]), and PBO (107.0 [p<0.001]). In the multidose DPM study, 1) mean SPID 0-24 hours was better with FDC (64.58) than PBO (-7.05 [p<0.001]); 2) median time (minutes) to MPR was faster with FDC (59.2) than PBO (165.9 [p<0.001]); 3) median time (minutes) to DR was longer with FDC (NA) than PBO (82.0 [p<001]). In the dose ranging DPM study, 1) mean SPID 0-8 hour was not significant between FDC and IBU 400 mg, both were significantly better than placebo (p<0.001); 2) median time (minutes) to MPR was not significant between FDC (54.1) and IBU 400 mg (56.2), both were significantly faster than placebo (>720 [p<0.001]); 3) median time (hours) to DR was not significant between FDC (10.1) and IBU 400 mg (10.4), both were significantly longer than placebo (1.6 [p<0.001]).

Conclusion: The studies summarized above demonstrated the effectiveness of the PK and clinical characteristics of the FDC to treat moderate and severe pain. Dental pain is a recognized model for evaluating treatment of acute pain, that can be extrapolated to other common pain types.

Impact of proton pump inhibitors on clinical outcomes during capecitabine therapy in stage II–III colorectal cancer: A real-world pharmacokinetic and mechanistic modeling study

Ching-wen Lin[1], Kai-hsun Lo[1], Tien-yuan Wu[2]

[1]*Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan*

[2]*Taipei Medical University, Taipei, Taiwan*

Background: Proton pump inhibitors (PPIs) are frequently prescribed during chemotherapy to prevent or manage gastrointestinal symptoms. However, their concomitant use with capecitabine has raised concerns regarding potential drug–drug interactions. Pharmacokinetic hypotheses suggest that PPI-induced elevation of gastric pH may reduce capecitabine dissolution and absorption, potentially decreasing systemic exposure and compromising treatment efficacy. Nevertheless, clinical evidence remains inconsistent, and mechanistic explanations for observed outcome differences are limited. Most previous studies relied primarily on observational outcome analyses without integrating pharmacokinetic reconstruction or mechanistic modelling. This study aimed to evaluate the association between concurrent PPI use and clinical outcomes in patients receiving adjuvant capecitabine for stage II–III colorectal cancer, while integrating real-world pharmacokinetic simulation and exploratory mechanistic modelling to generate hypothesis-driven insights.

Method: Electronic medical records from Hsinchu MacKay Memorial Hospital were retrospectively reviewed for patients with stage II–III colorectal cancer who received capecitabine-based adjuvant chemotherapy between 2010 and 2019. Patients were categorised according to the duration of overlap between PPI therapy and capecitabine treatment: no overlap, short-term overlap, and long-term overlap. Individualised pharmacokinetic (PK) simulations were performed using patient-specific parameters derived from body surface area, renal function, and prescribed dosing information. One-compartment models were applied to capecitabine and 5′-deoxy-5-fluorocytidine (5′-DFCR), while flip-flop kinetic models were used for downstream metabolites including 5′-deoxy-5-fluorouridine (5′-DFUR) and 5-fluorouracil (5-FU). Simulated exposure metrics were evaluated alongside clinical outcomes including 3-year and 5-year disease-free survival (DFS) and overall survival (OS). Exploratory mechanistic analyses were further conducted to simulate tumour extracellular pH (pHe) dynamics and tumour-level 5-FU exposure. Machine-learning survival modelling was applied to explore potential interactions between simulated tumour microenvironment changes and predicted clinical outcomes.

Results: A total of 168 patients were included. Across both 3-year and 5-year follow-up periods, no consistent evidence indicated worse DFS or OS among patients receiving concurrent PPIs compared with those without PPI exposure across overlap-duration groups. Pharmacokinetic simulations demonstrated minimal differences in systemic exposure metrics for capecitabine and its metabolites between PPI groups, suggesting that clinically meaningful alterations in systemic drug exposure were unlikely. Exploratory modelling suggested modest increases in simulated tumour extracellular pH and higher predicted cumulative tumour 5-FU exposure in PPI overlap groups compared with the non-PPI group. Machine-learning survival modelling identified a theoretical “beneficial zone” characterised by combined increases in tumour pHe (ΔpHe ≥ 0.14) and cumulative tumour 5-FU AUC of approximately 3000–4000 μmol•h/L, which was associated with lower predicted progression risk within the model framework.

Conclusion: In this real-world cohort of Taiwanese patients receiving adjuvant capecitabine for stage II–III colorectal cancer, concurrent PPI use was not associated with worse long-term survival outcomes or increased chemotherapy-related toxicity. Pharmacokinetic simulations suggested minimal systemic exposure differences between PPI overlap groups. Exploratory mechanistic modelling indicated that PPI-associated modulation of the tumour microenvironment could influence local drug exposure; however, these findings remain hypothesis-generating and require prospective validation. Integrating pharmacokinetic simulation with clinical outcome analysis may provide a useful framework for understanding complex drug–drug interactions in oncology treatment.

Formulation and evaluation of aluminium chloride cream for treatment of hyperhidrosis

Ngozi Udem[1], Ichechiek Ujile[2], Chukwunonso Onwuzuligbo[3]

[1]*University Of Nigeria Teaching Hospital Ituku Ozalla Enugu, Enugu-Port Harcourt Express Way, Nigeria*

[2]*Dermatology Department , University of Port Harcourt Teaching Hosptal, Port Harcourt, Rivers, Nigeria*

[3]*Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Chief Odumegwu Ojukwu University, Igbariam, Anambra state, Nigeria*

Background: Creams are semi solid pharmaceutical dosage forms which are generally oil in water or water in oil emulsions for external application. They may contain active drugs intended to act solely on the surface of the skin to produce local effect like anti-infective, release the medication, which in turn penetrates into the skin or release medication for systemic absorption through the skin. Aluminium Chloride hexahydrate is a potent, topical antiperspirant designed to treat excessive sweating

(hyperhidrosis) of the underarms, hands or feet. Its' mechanism of action is by plugging sweat ducts. It is applied to dry unbroken skin and washed off at night before bedtime. Aluminium Chloride hexahydrate cream, is not commercially available in Nigerian Pharmacies. This research focuses on Formulation and Evaluation of Aluminium Chloride cream for treatment of hyperhidrosis.

Method: Preformulation studies were primarily done to investigate the physiochemical properties of the active pharmaceutical ingredient (API) and to establish its compatibility with other excipients. Aluminium Chloride 20 % cream was prepared by convectional oil-in-water emulsions method using stearic acid as emulsifier and carbomer as viscosity enhancer. Four formulas F1 –F4 were developed for the cream preparation. Evaluation of the cream for colour, odour, loss on drying, pH, spreadability, extrudability, solubility, washability and non-irritancy were carried out. Presence of microbial contaminants such Staphylococcus aureus, Escherichia coli and shigella were also evaluated by microbial assay.. The stability of the cream was also carried out on the product at three temperatures, 20, 30, 45 oC. Case study on the use of Aluminium hydroxide cream on patients with hyperhidrosis were also carried out.

Results: Preformulation studies revealed no colour change nor drug degradation when combined with the excipients used. A white coloured cream with mild sweet characteristic smell was prepared with 20 % Aluminium Chloride. It has pH of 5.8, viscosity of 9000cp, spreadability of 9.7gm.cm/s, and extrudability of 13gm. There were no microbial contamination by staphylococcus aureus, total coliform, shigella and E.coli. The cream were stable in all the temperatures under which they were stored. Dermatology patients treated with aluminium chloride had the excessive sweating resolved with no irritation.

Conclusion: Above data showed successful formulation of Aluminium Chloride cream. The physicochemical and microbiology parameters of the cream showed that it is satisfactory and hence it can be used. The use of 20% Aluminium Chloride treatment of patients with hyperhidrosis with the cream depicted that sweating was resolved within two weeks of case studies.

ECHO - "Expert-Consumer Horizon Optimization": A HCP pilot program advancing future-focused consumer innovation

Chloe Giraldi[1], Beth Fitzsimmons[2], Amaeze Madukah[2], Jasmin Omar[2], Allyn Kaufmann[3]

[1]Haleon, Future Horizons Science & Technology, Wellness & Naturals, Warren, New Jersey, United States

[2]Haleon, Future Horizons Science & Technology, Consumer Science & Product Experience, Weybridge, United Kingdom

[3]Haleon, Future Horizons Science & Technology, Wellness & Naturals, Richmond, Virginia, United States

Background: As the global population ages, people are not only living longer, but also spending more years in poor health, with aging-related conditions contributing substantially to the global disease burden. Biological aging - the gradual loss of cellular and physiological integrity, varies widely across individuals and may be an informative indicator of health resilience and disease risk compared to chronological age.

A component of biological aging involves epigenetic changes, shifts in DNA methylation patterns that form the basis of epigenetic "clocks," which estimate biological age, some of which have demonstrated predictive value for morbidity and mortality. While these biomarkers have shown potential for capturing subtle physiological changes, application in real-world wellness settings still requires careful, evidence-based interpretation.

Given widespread micronutrient inadequacies, nutrition - including diet, lifestyle, and considered use of dietary supplements may offer a practical avenue for consumers to influence biological aging, though evidence continues to evolve. For example, a recent study has provided early indication that daily multivitamin use may impact biological aging using five DNA-based epigenetic clocks.

Consumer-facing digital wellness tools are increasingly translating complex sciences, including epigenetics into everyday insights. Without expert oversight, these tools can be easily misinterpreted. Healthcare Professionals (HCPs), particularly pharmacists at the front line of self-care, are well positioned to provide context, ensure accurate interpretation, and guide evidence-aligned recommendations, yet often lack the time or resources to evaluate these emerging technologies.

To address this gap, the ECHO pilot integrated HCP expertise early in epigenetic-app development to ensure future consumer-facing wellness innovations are scientifically grounded, and capable of supporting behavior-changing recommendations.

Purpose: Assess clarity, scientific credibility, and practical relevance of an epigenetic-based wellness app for HCPs. Identify opportunities to translate aging-biomarker science, including nutrition-related insights into meaningful, actionable consumer experiences.

Leverage internal HCP insights as a cost-efficient alternative to early consumer research.

Method: A qualitative pilot was conducted at Haleon between January and March 2026 involving cross-functional teams from Future Horizons Science & Technology (FHS&T), Consumer Science & Product Experience (CSPX), Product Plus, and Wellness. n=12 HCPs were recruited via internal email and Viva Engage. Participants provided informed consent, explored a non-diagnostic prototype epigenetics app for one week, and completed 45-minute structured online interviews. Interview topics included understanding and clarity, usability, scientific credibility, personal impact, and improvement needs. Interviews were anonymized; findings will be synthesized into a full report.

Results: Pilot is in progress; results are not yet available. We anticipate reporting on qualitative HCP feedback synthesized into themes identifying needs, opportunities, and implications for the design of evidence-aligned epigenetic wellness solutions. Final data will be presented at the meeting.

Conclusion: Early multidisciplinary HCP involvement, including pharmacists, helps ensure epigenetic science is translated into clear, credible, and actionable wellness experiences. This pilot model de-risks innovation, mitigates over-interpretation of emerging technologies, and strengthens development of evidence-based, provider-supported consumer solutions. It also broadens access to more personalized, nutrition- and lifestyle-informed offerings for both consumers and HCPs. Findings will guide early-stage design to responsibly translate biological aging science into consumer-facing digital tools.

The safer dosage regimen for latamoxef in children

Liqin Zhu[1], Wei Liu[2], Ailin Zhang[3], Jingyu Wang[4], Hongyu Chen[3]

[1]*Department of Pharmacy, Tianjin First Central Hospital, Tianjin, China*

[2]*Tianjin Children's Hospital, Tianjin, China*

[3]*First Central Hospital of Tianjin Medical University, Tianjin, China*

[4]*Tianjin University of Traditional Chinese Medicine, Tianjin, China*

Background: :Latamoxef is a semi-synthetic, broad-spectrum oxacephem antibiotic primarily used for infectious diseases in adults and children. However, the use of Latamoxef was limited because of its coagulation disorders and bleeding risks which was correlated with doses. In adults, bleeding risk increases notably at dosage exceeding 4 g/day. In children, the dosage above 100 mg/kg/day relates to lower platelet aggregation. Given these safety concerns, establishing the optimal dosage regimen for children to balancing efficacy with minimized bleeding risk is essential because Latamoxef is one of the limited antibiotic choices in Children.

Method: A physiologically based pharmacokinetic (PBPK) model of latamoxef was established to simulate its pharmacokinetics in healthy adults then extrapolated to children. All models were validated by AUC comparison.

Results: The pharmacokinetic simulations demonstrated good agreement with observed data following intravenous administration of latamoxef across multiple dosing regimens. The fold errors were within the 2-fold error range. Based on model predictions, the dosing regimens of 70mg/kg/d, 60mg/kg/d,50mg/kg/d,40mg/kg/d were respectively suitable for children with 1-3y,3-5y, 5-10y and 10-18y, considering comparable area under the plasma concentration-time curve to that observed in adults.

Conclusion: These individual Latamoxef regimens were predicted to maintain therapeutic efficacy comparable to adults while minimizing the risk of bleeding complications associated with higher exposures. Optimal dosage regimens are beneficial for lower therapeutic risk while ensuring therapeutic efficacy. The extrapolated PK model is interesting to predict dosing regimen in different populations.

Pharmacogenetic Testing in Primary Care Pharmacy Practice: A Scoping Review of Pharmacists' Perspectives and Implementation Barriers

Pegah Adibi[1]

[1]*Dalhousie University, Halifax, Canada*

Background: Pharmacogenetics (PGx), the study of how genetic variation influences drug response, has the potential to improve medication safety and effectiveness by enabling personalised therapy. Pharmacists are well positioned to support the clinical application of PGx in primary care settings through medication management and patient counselling. However, despite its clinical promise, the integration of PGx into routine pharmacy practice remains limited. Understanding pharmacists' perspectives and the barriers they face is essential to inform strategies that support implementation. This scoping review aimed to synthesise existing literature on pharmacists' knowledge, attitudes, and perceptions of PGx testing, and to identify key barriers and facilitators to its implementation in primary care pharmacy practice.

Method: A scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)

guidelines. A comprehensive search of relevant electronic databases was undertaken to identify studies examining pharmacists' perspectives on PGx testing, including their knowledge, attitudes, experiences, and perceived barriers and facilitators to implementation. Following removal of duplicates, 2,619 records were independently screened by title and abstract by two reviewers. Of these, 79 articles progressed to full-text screening, and 26 studies met the inclusion criteria and were included for data extraction. Data were charted and synthesised descriptively to identify recurring themes related to acceptability, feasibility, and educational needs.

Results: Across the 26 included studies, pharmacists demonstrated consistently positive attitudes towards PGx testing and its role in clinical practice. Pharmacists widely recognised PGx as a valuable tool for optimising therapeutic efficacy, preventing adverse drug reactions, and enhancing medication management. Despite this positive perception, several barriers to implementation were consistently reported. The most frequently identified barriers included the cost of PGx testing, concerns regarding the potential misuse of patients' genetic information by insurance providers, and challenges in effectively communicating PGx results to both prescribers and patients. Additionally, pharmacists noted that patients may not fully recognise the benefits of PGx testing, which may limit acceptance and uptake. A prominent and consistent finding across all studies was the presence of significant educational gaps. Pharmacists reported insufficient training and lack of confidence in interpreting and applying PGx results, highlighting a strong need for further education prior to implementation.

Conclusion: This scoping review demonstrates that pharmacists are supportive of the clinical value of PGx testing; however, multiple and interrelated barriers continue to hinder its integration into primary care pharmacy practice. Addressing educational deficiencies, cost-related challenges, ethical and privacy concerns, and communication barriers will be essential to support implementation. These findings provide a foundation for the development of targeted educational programmes, practice guidance, and policy initiatives aimed at enabling pharmacists to play a central role in advancing pharmacogenomics and personalised medicine.

Immunotherapy in hospitalised oncology patients: A real-world study at CHUM

Marie-andrée Fournier[1], Sara Nabeel Issa Shito[2], Anne-julie Lapensée[1], Anne-marie Bégin[1], Maude Beauchamp-vien[1], Anita Ang[1]

[1]*Centre hospitalier de l'Université de Montréal, MONTRÉAL, Canada*

[2]*Faculty of Pharmacie, Université de Montréal, MONTRÉAL, Canada*

Background: Over the past decade, immunotherapy has radically transformed the management of many cancers, particularly through the development of immune checkpoint inhibitors (anti-PD-1, anti-PD-L1 and anti-CTLA-4). However, evidence supporting their use is mainly derived from clinical trials conducted in outpatient settings and frequently excludes patients with poor performance status or acute complications. Despite the increasing use of immunotherapy in hospitalised patients, this population remains under-represented in the literature. These patients often present with advanced disease, functional decline and complex clinical conditions, making therapeutic decision-making challenging. Real-world data are therefore essential to better characterise immunotherapy use and outcomes in hospital settings.

Purpose: To describe the demographic and clinical characteristics of hospitalized patients who received at least one dose of immunotherapy during their hospitalisation at the Centre Hospitalier de l'Université de Montréal (CHUM). Secondary objectives included describing functional status according to the Eastern Cooperative Oncology Group (ECOG), evaluating treatment trajectories following hospitalisation, and estimating progression-free survival (PFS). Exploratory analyses aimed to assess the association between selected clinical factors and patient outcomes.

Method: A retrospective observational study with an adaptive design was conducted at the CHUM among patients hospitalized in medical oncology, gynaecologic oncology, or haematologic oncology who received immunotherapy. This preliminary analysis covered the period from January 1 to December 31, 2024. Targeted therapies included nivolumab, pembrolizumab, atezolizumab, durvalumab, ipilimumab, dostarlimab or cemiplimab, administered alone or in combination with chemotherapy. Data were extracted from electronic medical records and entered into REDCap. Collected variables included demographic characteristics, cancer diagnosis, ECOG performance status, level of care, treatment characteristics and clinical outcomes. PFS was defined as the time from in-hospital immunotherapy administration to initiation of a new line of treatment or death. Descriptive statistical and multivariate Cox regression analyses were performed.

Results: Thirty-seven patients were included, of whom 51.4% were men, with a median age of 64 years. Non-small cell lung

cancer was the most frequent diagnosis (24.3%). Immunotherapy was administered as monotherapy in 59.5% of patients, most commonly pembrolizumab. ECOG performance status was documented in 45.9% of patients and was ≥ 2 in 58.8% of those documented. More than half of the patients (54.1%) progressed to level-of-care D. Median PFS was 70.5 days, and 40.5% (n=15) of patients received any subsequent treatment following hospitalization.

Conclusion: This study provides valuable real-world insight into the clinical profile of hospitalized patients receiving immunotherapy. Despite the limitations related to its retrospective design and the absence of a comparator group, these descriptive data may help inform clinical decision-making and support future research in hospital oncology. Larger studies are needed to better identify factors influencing survival and to optimize care for this vulnerable population.

A machine learning model that predicts a personalised unfractionated heparin dose

Michael Barras[1,2], Hassan Masood[1], Nazanin Falconer[1,2], Kitty St Pierre[2], Ian Scott[1,2]

[1]Princess Alexandra Hospital, Ipswich Rd, Brisbane, Australia

[2]The University of Queensland, Brisbane, Australia

Background: Unfractionated heparin (UFH) is a high-risk medication that is complex to dose. Therapy entails cautious dosing to a narrow therapeutic range, where under-dosing risks thrombotic events and over-dosing bleeding. To dose UFH weight-based nomograms are used. However, this strategy does not fully account for inter-patient variability in response, measured by an activated partial thromboplastin time (APTT).

A local study demonstrated only 23% of patients were in the therapeutic range at 12 hours post dose, despite digital prescribing with clinical decision support. Traditional dosing continues to produce sub-optimal outcomes and is a reactive process. A proactive, data driven, personalised approach is needed. The Princess Alexandra Hospital is one of the largest surgical hospitals in Australia. It provides transplant, vascular, and major orthopaedic surgery requiring extensive use of UFH.

Machine learning (ML), a subdiscipline of artificial intelligence, uses computerised methods to identify patterns in data to develop a model. For high-risk drugs like UFH, ML may help predict the best dose for a patient and prevent adverse outcomes. An international review found few ML studies for UFH, none of which had models that were suitable for hospital use.

Purpose: To develop and validate a ML model that: 1. predicts APTT response to UFH dosing and, 2. recommends personalised dosing to achieve therapeutic targets.

Method: A ML ensemble model was developed using APTT measurements from 3,779 eligible patient encounters over 8-years (2017-2024). It incorporated 33 features including UFH dosing history, patient demographics, vital signs, and pathology results such as haematological markers. Temporal validation was performed on 185 patients from January-June 2025. For dose optimisation, 140 bolus-maintenance combinations per patient were generated and the best model predicted dose to achieve an APTT to the target of 85 seconds was selected. These doses were compared to the actual clinically administered doses for each patient.

Results: The ML model achieved a mean absolute error (MAE) of 17.2 seconds on all data and 24.4 seconds on the temporal validation. The best performance (MAE of 14.3 seconds) was achieved in the therapeutic range (70-100 seconds). For the temporal validation, the observed and predicted APTTs showed strong global calibration (slope = 1.06, bias -3 seconds) with predictions tracking observed APTTs across the entire therapeutic range. Dose recommendations demonstrated clinically appropriate behaviour. For sub-therapeutic patients, 60% of predicted doses were higher than actual doses, while 74% were lower for supra-therapeutic patients.

Conclusion: Temporal validation demonstrated stable model performance and appropriate clinical reasoning in dose recommendations. The next step is a prospective silent trial to assess performance and clinical utility in a live environment. If effective, it is hoped the model can be embedded in a dosing app to aid hospital clinicians. Our research underscores a clear message: more sophisticated dosing strategies are essential to enhance the safety and effectiveness of UFH. Confronted with a medication whose complexities have challenged clinicians around the world for decades, ML offers a pathway to safer, more personalised treatment and a new frontier for dosing in clinical practice.

DPYD Genotyping for Prevention of Fluoropyrimidine Toxicity in Colorectal Cancer Patients in Portugal: a Health Impact Assessment

Maria Luís Cardoso[1], Cristina Costa[1], Alexandra Costa[1], Raquel Fonseca[2], Fátima Lopes[1], Astrid Vicente[1]

[1]National Health Institute Doutor Ricardo Jorge, Lisbon, Portugal

[2]Faculty of Sciences, University of Lisbon, Lisbon, Portugal

Background: Colorectal cancer (CRC) is a major cause of cancer morbidity and mortality in Portugal. Fluoropyrimidines (FP), including 5-fluorouracil and capecitabine, are effective

in CRC treatment, but are associated with severe (grade 3–4) toxicity in up to 30% of patients, which can lead to treatment-related deaths. Reduced activity of the dihydropyrimidine dehydrogenase is a major determinant of toxicity risk, often due to variants in the encoding DPYD gene. Since 2020, the European Medicines Agency (EMA), as well as INFARMED, the National Authority of Medicines and Health Products in Portugal, recommend DPYD testing prior to treatment, to guide individual dosing and improve safety. However, there is no norm enforcing the systematic genotyping of DPYD variants, leading to potential inequalities in patient care outcomes.

Method: A Health Impact Assessment (HIA) evaluated the impact of systematic DPYD genotyping prior to FP therapy in CRC patients in Portugal, compared with current practice (78.6% testing rate in 2023). A multidisciplinary advisory group, including experts in oncology, laboratory clinical genetics, pharmacy, economics, epidemiology, and a patient representative, provided scientific support. A Markov model estimated the impact of systematic testing on severe toxicity, toxicity-related mortality, and 5-year all-cause mortality. The impact of variable implementation across hospital settings on patient outcomes was assessed. Two surveys targeting oncologists and laboratories informed about acceptability and clinical services impact. A structured literature review evaluated the economic impact of DPYD genotyping.

Results: Systematic DPYD genotyping was associated with improved clinical outcomes. In stage III CRC patients, the model estimated a reduction of 2.2% in severe toxicity events and 21.4% in toxicity-related deaths, alongside a 2.1% reduction in 5-year mortality risk.

Equity analysis estimated that smaller hospitals and private institutions, with lower baseline testing rates, would benefit most from systematic DPYD genotyping, with reductions in toxicity-related mortality.

The literature review consistently demonstrated cost savings associated with DPYD genotyping, driven by reductions in hospital admissions and management of severe adverse events. Evidence indicates that upfront testing costs are outweighed by downstream savings and improved outcomes.

Stakeholder consultations showed strong support among oncologists, laboratory professionals and pharmacists. In Portugal, pharmacists specialised in human genetics contribute to DPYD genotyping and results interpretation alongside laboratory clinical scientists, while hospital pharmacists ensure the safe management of FP therapies within hospital pharmacy services.

Conclusion: A shift from recommended to mandatory systematic pre-emptive DPYD genotyping would represent a clinically effective and valuable strategy to reduce FP toxicity and mortality in CRC patients, while also helping to address inequities in access to safer treatment.

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Effectiveness of Pitavastatin in patients with different SLCO1B1/ABCG2 genotypes: Real-world pharmacogenomic association analysis

Hsing Yu Hsu[1], Hsiang-han Kao[2], Shang-yeh Lu[3], Kuan-cheng Chang[4]

[1]Department of pharmacy, China Medical University Hospital, Taichung City, Taiwan

[2]Department of Family Medicine, Taichung Municipal Geriatric Rehabilitation General Hospital, Taichung City, Taiwan

[3]Department of Cardiovascular Medicine, China Medical University Hospital, Taichung City, Taiwan

[4]Department of Cardiovascular Medicine, Taichung Municipal Geriatric Rehabilitation General Hospital, Taichung City, Taiwan

Background: The 2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline recommends SLCO1B1-guided dose limits for pitavastatin primarily to reduce the risk of statin-associated muscle symptoms (SAMS). However, evidence regarding the influence of SLCO1B1 and ABCG2 genetic variation on the lipid-lowering effectiveness of pitavastatin in real-world clinical practice remains limited. We aimed to evaluate the associations between SLCO1B1 and ABCG2 genotypes and treatment response to pitavastatin in a large hospital-based cohort.

Method: We conducted a retrospective cohort study including 8,908 patients receiving pitavastatin therapy at China Medical University Hospital. Genotyping for SLCO1B1 (rs4149056) and ABCG2 (rs2231142) was performed using a validated custom Affymetrix genome-wide array. The primary outcome was LDL-C response, defined as a ≥20% reduction in LDL-C from baseline after at least 28 days of treatment. Multivariable logistic regression models were used to estimate adjusted odds ratios (aORs) controlling for demographic and clinical covariates. Prespecified dose-stratified analyses were performed to explore potential genotype–dose interactions.

Results: Patients with the SLCO1B1 poor-function phenotype demonstrated a significantly lower LDL-C response rate compared with those with normal-function phenotypes (34.4% vs. 46.7%; adjusted OR 0.56, 95% CI 0.34–0.94; p = 0.025). Despite similar relative LDL-C reductions across genotype groups (median reduction approximately −25%; Kruskal–Wallis p = 0.150), individuals with poor-function phenotypes were less likely to achieve absolute LDL-C targets, likely reflecting their higher baseline LDL-C levels. In dose-stratified analyses, the reduced treatment response associated with the poor-function phenotype was more pronounced at doses greater than 2 mg/day, where response rates declined to 36.0% compared with 60.5% among normal-function patients (OR 0.37, 95% CI 0.16–0.84; p = 0.023). In contrast, no clear genotype-related difference in LDL-C response was observed at lower doses. ABCG2 genotype was not independently associated with LDL-C response (aOR 1.00; p = 0.988), and this finding remained consistent across

sensitivity analyses. Creatine phosphokinase (CPK) trajectories did not differ significantly by genotype; however, concomitant use of SLCO1B1 inhibitors was associated with higher CPK levels (median 138 vs. 101 U/L; p = 0.004).

Conclusion: In this large real-world cohort, the SLCO1B1 poor-function phenotype was associated with reduced lipid-lowering response to pitavastatin, with a more pronounced attenuation observed at doses greater than 2 mg/day. These findings provide effectiveness-based evidence that complements the SAMS-focused CPIC recommendations and highlight the potential clinical value of SLCO1B1 genotyping for optimizing pitavastatin therapy. In contrast, ABCG2 genetic variation was not associated with pitavastatin effectiveness, suggesting that pharmacogenomic recommendations derived from rosuvastatin studies may not be directly generalizable to pitavastatin

Impact of NOSIAP genetic variation on interindividual response to exenatide in type 2 diabetes mellitus: Mechanistic and clinical insights

Tao Wang[1], Yuhan Huang[1], Xizhi Li[1], Jia Han[1], Tingting Yang[2], Ke Xu[1]

[1]The Affiliated Hospital Of Xuzhou Medical University, Xuzhou, Jiangsu, China

[2]Xuzhou Medical University, Xuzhou, Jiangsu, China

Background: The interindividual variability in response to glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as exenatide, posed challenges for the management of type 2 diabetes mellitus (T2DM). This variability may be determined by genetic factors, but the role of the gene NOS1AP, which was associated with insulin secretion and response to antidiabetic drugs, remained unclear. Elucidating this relationship could inform individualized treatment strategies.

Objective: This study aimed to investigate the association between the NOS1AP gene polymorphism and the response to exenatide treatment in Chinese patients with T2DM, and to elucidate the related molecular regulatory mechanisms. We hypothesized that NOS1AP mediated insulin secretion stimulated by exenatide through the neuronal nitric oxide synthase (nNOS)/p38 mitogen-activated protein kinase (MAPK)/cAMP response element binding protein (CREB) signaling pathway, and that specific gene variations led to interindividual differences in therapeutic efficacy.

Method: A 6-month prospective study enrolled 100 patients with T2DM treated with exenatide. Genotyping was performed on the rs12742393 and rs10494366 loci of the NOS1AP gene by SNaPshot assay. Glycemic parameters were measured at baseline, 3 months, and 6 months. Complementary mechanistic studies utilized diabetic mice, high-glucose treated INS-1 cells, and isolated mouse islets with NOS1AP knockdown or overexpression. NOS1AP expression was quantified by Western blot, immunofluorescence, and reverse transcription polymerase chain reaction (RT-PCR); insulin secretion was measured by glucose-stimulated insulin secretion (GSIS); and pathway activity was assessed by phosphorylation of nNOS, p38 MAPK, and CREB. Clinical validation was conducted on the levels of NOS1AP in plasma and human pancreatic tissue from 12 patients who underwent pancreatectomy. A predictive model was developed and tested in an independent retrospective cohort of 100 T2DM patients who had used exenatide.

Results: Exenatide reversed the downregulation of NOS1AP induced in mouse pancreatic islets and INS-1 cells. NOS1AP Knockdown attenuated, while NOS1AP overexpression enhanced exenatide-stimulated insulin secretion. Mechanistically, exenatide regulated the nNOS/p38 MAPK/CREB axis in a NOS1AP-dependent manner. Clinically, after 6 months, subjects carrying the rs12742393 C allele (AC/CC) had significantly lower reductions in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and homeostatic model assessment of β-cell function (HOMA-B) compared to AA homozygotes. Subjects carrying the C allele had reduced levels of NOS1AP in plasma and pancreas. In regression models, baseline HbA1c, duration of diabetes, and rs12742393 genotype independently predicted exenatide response.

Conclusion: NOS1AP played a crucial role in regulating insulin secretion induced by exenatide through the nNOS/p38 MAPK/CREB pathway. The NOS1AP rs12742393 C allele was associated with reduced NOS1AP expression and diminished glycemic response to exenatide, providing a mechanistic basis for interindividual variability. Genotyping of this variation could guide individualized treatment with GLP-1RA in patients with T2DM. Future multicenter studies and functional validation in non-cancerous human pancreatic tissues were needed to confirm these findings and explore their broader application in other GLP-1RAs.

Dietary Habits and Mediterranean Diet Adherence in Breath-Hold Divers: Insights for Personalized Nutrition

Natalija Kurmazovic[1], Brizita Djordjevic[1], Sladjana Sobajic[1], Tzortzis Nomikos[2], Manolis Adamakis[3], Vanja Todorovic[1]

[1]Department of Bromatology, University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia

[2]Department of Nutrition and Dietetics, School of Health Sciences & Education, Harokopio University, Kallithea, Greece

[3]National and Kapodistrian University of Athens, Greece, School of Physical Education and Sport Science, Athens, Greece

Background: Breath-hold diving (BHD) induces oxidative stress and inflammation, emphasizing the role of a nutrient-dense diet for enhancing recovery and adaptation. The Mediterranean Diet (MD), rich in antioxidant foods and unsaturated fats, has been linked to reduced inflammation and enhanced endurance and anaerobic performance—key aspects for BHD. However, as carbohydrates are the primary energy source in endurance sports, fat-rich foods may be suboptimal. Foods such as fish, shellfish, nuts, and seeds provide various micronutrients and unsaturated fatty acids including omega-3s, which may support anti-inflammatory response.

Purpose: This study aimed to characterize dietary habits and MD adherence in BH divers.

Method: A cross-sectional study assessed dietary habits in 336 international divers and MD adherence with the antioxidants intake in 16 Greek divers. International divers completed a structured dietary questionnaire via Google Forms, while Greek divers completed validated PREDIMED questionnaire and antioxidant intake questionnaire for athletes.

Results: International cohort comprised 210 men and 126 women (mean age 40.9 ± 9.5 years) and the Greek cohort 13 men and 3 women (mean age 40.0 ± 7.8 years). In the international cohort, 8.3% reported following the MD, with 25% emphasizing antioxidant-rich meals before and 31.3% after training, whereas the Greek cohort demonstrated moderate adherence (PREDIMED score 8.1 ± 1.4/14). Fruit and vegetable intake was higher internationally (89.3% and 93.8% ≥2–3×/week) than in Greeks (43.8% and 56.3% ≥2×/week). Olive oil was the main culinary fat in both groups (74.7% international; 100% Greek), with additional preferences for unrefined (48.5%) and plant/fish fats (60.4%) reported in the international cohort. Fish and shellfish intake was relatively low in both cohorts, with 44.0% of international participants consuming them ≤2–3/week and 81.3% of Greeks consuming them ≤3 times/week. Similarly, nuts and seeds consumption was limited, reported as ≤2–3/week in 28.6% of the international cohort and ≤3 times/week in 62.5% of the Greek cohort. The use of antioxidant supplements included: Vitamin C (66.7% international cohort vs. 75.0% Greek cohort), vitamin E (25.9% vs. 6.3%), selenium (22.3% vs. 0.0%), and beta-carotene (12.5% vs. 6.3%).

Conclusion: Few international divers followed the MD with more of them emphasizing antioxidant intake around training. MD adherence was shown to be moderate in Greek divers. Intake of key MD components—fruit and vegetables—was overall higher in the international cohort. Both groups used olive oil as the main fat source, however, consumption of fish, shellfish, nuts, and seeds, was relatively low in both cohorts. Higher proportion of international divers reported the use of antioxidant supplements. Study limitations include cross-sectional design, self-reported data, selection bias, and a small Greek cohort. Future studies should assess whether higher MD adherence or increased intake of its key components mitigates post-dive oxidative stress and inflammatory response, guiding personalized nutritional strategies to optimize recovery and performance.

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