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CONFERENCE ABSTRACTS

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Personalised and precision medicine

Knowledge and perceptions of individualised medicine among pharmacists in a district hospital at North West Province, South Africa

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Introduction: Individualised medicine is an innovative healthcare approach that uses a patient's genetic profile to help clinicians make informed decisions with regard to the diagnosis, prevention, and treatment of a disease. Pharmacists are experts in medicine who sit in multidisciplinary meetings to give recommendations and share their knowledge on the safe and effective use of medicines. In South Africa (a developing country), there is a need for innovative minds to introduce Individualised medicine to help its health sector. However, despite pharmacy being a growing profession in South Africa, few pharmacists seem to be literate on this innovative healthcare approach.

Purpose: This study served as an investigation to assess pharmacists' knowledge and perceptions of individualised medicine. Identifying gaps in their knowledge could help in recommending for related programmes to be included in the pharmacy curriculum.

Methods: A quantitative, descriptive study was conducted in which a self-administered online questionnaire via Google Forms with five main categories on Individualised medicine was used for data collection. The target population included all the registered hospital pharmacists in a District Hospital in North West Province, South Africa. Descriptive statistics were used to analyse data.

Results: An overall response rate of 80% (n=12) from 15 registered pharmacists was obtained. Most of the participants (83,3%) were familiar with basic principles of human genetics. Only 41,6% of the respondents showed a considerate understanding of genetic abnormalities and their pathophysiology. Furthermore, almost all the respondents (91,6%) were not knowledgeable about pharmacogenomics (how genes affect a patient's response to medicines). Most of the respondents (66,7%) indicated that South Africa has an ailing economy; hence, not everyone can afford Individualised medicine. Regarding the legal aspects, only 33,3% of the respondents agreed that patients' data privacy may be compromised.

Conclusion: Most of the pharmacists were not acquainted with Individualised medicine. To help them become knowledgeable about this, efforts should be made to include academic programmes in the undergraduate and postgraduate pharmacy curricula to teach students about individualised medicine and pharmacogenomics. As the authors are all advancing to this health approach, more research in South Africa should be done to investigate the psychological impact of Individualised medicine on patients and to hear their point of view.

The impact of clustered regularly interspaced short palindromic repeats (CRISPR) in pharmacy

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Background: Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are deoxyribonucleic acid

(DNA) segments present in prokaryotes that contain short repetitive sequences, serving as a defence mechanism against viral DNA. Conditions like Huntington's disease, cancer, cystic fibrosis, type 1 diabetes, and sickle cell anaemia result from genetic mutations. Most of these diseases currently lack effective treatments. CRISPR/Cas technology holds substantial promise as an effective tool to address these conditions.

Purpose: To identify conditions for which CRISPR can be successfully applied in pharmacy practice.

Method: A literature review on CRISPR's role in pharmacy was conducted using PubMed. The review aimed to elucidate CRISPR's multifaceted role in pharmacy, with particular emphasis on its potential in treating chronic and hereditary diseases.

Results: A gene therapy based on CRISPR-Cas9 technology has been approved for the management of sickle cell disease and beta-thalassemia. Advanced detection techniques have been developed for infectious diseases like tuberculosis, HIV, and hepatitis B. CRISPR has been employed in the enhancement of biopharmaceutical production by optimising cell lines due to CRISPR's precision in gene editing, which improves cell survival, protein production, and therapeutic efficacy. In diabetes, CRISPR-Cas9 gene editing corrected genetic mutations in patient-derived cells, resulting in functional insulin-producing beta cells. VCTX210, a CRISPR-based therapy, aims to treat type 1 and insulin-dependent type 2 diabetes. In cardiovascular diseases, CRISPR achieved targeted genome replacement in non-dividing cardiomyocytes, restoring genetic defects. Genome integration in cardiomyocytes using AAV vectors led to the precise modification of heart tissue.

Conclusion: The utilisation of CRISPR technology heralds a new era in precision medicine, offering hope for patients worldwide. Leveraging pharmacists' expertise in drug therapy and patient care can position them as valuable contributors to the successful integration of CRISPR technology in healthcare.

CYP2C19 genetic polymorphisms and response to proton pump inhibitors

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Background: Proton pump inhibitors (PPIs) undergo metabolism primarily by the CYP2C19 enzyme. Genetic polymorphisms in the CYP2C19 enzyme may affect response to PPI therapy.

Purpose: To appraise evidence on the clinical relevance of CYP2C19 genetic variation and response to PPI therapy and to identify priority patient groups for pharmacogenetics (PGx)-guided PPI therapy.

Method: A literature appraisal covering a ten-year period (2012-2022) was conducted using PubMed and ProQuest. Search terms were (proton pump inhibitor) AND ((pharmacogenetic) OR (pharmacogenomic) OR (CYP2C19)). Inclusion criteria were peer-reviewed articles in English that were available as free full-text.

Results: The primary search identified 4,006 records. After applying the inclusion criteria and removing duplicates, 1,076 records were assessed for eligibility, and 108 records were included. Most records were published in 2016 (12%) and 2021 (11%). Eighty-six per cent of the articles focused on CYP2C19 genetic polymorphisms in relation to the efficacy of PPIs, and 14% focused on side effects. Most records were original research articles (63%), of which 87% evaluated the association between CYP2C19 genetic polymorphisms and response to PPIs, which was statistically significant in 67%. The association was mostly identified in Helicobacter pylori infection (37%), with the highest eradication rate in poor metabolisers (PMs), followed by paediatrics (22%), patients experiencing side effects (15%), and patients presenting with oesophagitis (12%), peptic ulcer disease/gastrointestinal bleeding (12%), and gastro-oesophageal reflux disease (10%). More persistent symptoms were reported in rapid metabolisers (RMs) and normal metabolisers (NMs), and higher efficacy was reported in PMs. With respect to side effects, worsening asthma control and increased risk of upper respiratory tract infections were reported in paediatric PMs on lansoprazole. In adults, PMs had an increased risk of chronic migraines compared to NMs and RMs. Genotype-guided PPI therapy to improve outcomes was recommended in 15% of the articles.

Conclusions: This literature appraisal described the application of pharmacogenetic testing for the use of PPIs and identified patient groups where genotype may influence PPI therapy outcomes, hence supporting prioritisation for PGx-guided PPI therapy.

Paediatric obesity: Optimising and individualising dosing strategies using virtual clinical trials

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Introduction: The prevalence of paediatric obesity has increased by approximately 20 % over the past decade, with

estimates suggesting that the number will double by 2035, affecting 208 million boys and 175 million girls globally. Dosing guidelines for obese paediatrics are often derived from obese adults, and complications in the calculation of weight-based dosing methodologies can contribute to non-optimal doses. Current dosing approaches in paediatric obesity have highlighted that over 60 % of drugs administered to obese children result in plasma concentrations outside of the therapeutic range, with clinically significant changes in pharmacokinetics. Given the various physiological changes occurring longitudinally with ageing across the paediatric spectrum (e.g. tissue composition, plasma protein concentrations, metabolism enzyme activity, and glomerular filtration rate), dosing approaches based on the holistic consideration of these physiological changes in the drug pharmacokinetics have gained some traction in adults and, more recently children, through pharmacokinetic modelling approaches using virtual clinical trials. Physiologically based pharmacokinetics (PBPK) modelling, an advanced quantitative approach, helps to understand drug disposition and offers a promising avenue for determining optimal dosing regimens in the paediatric obesity population.

Using amlodipine (and paediatric hypertension) as a clinical case study, this study describes the approach to develop a physiological obesity model to support pharmacokinetic-based dose optimisation in paediatric obesity and compared the impact of weight-based vs fixed dosing across paediatric age groups.

Method: A PBPK modelling approach was implemented using Simcyp® (Simcyp Ltd., a Certara company, Sheffield, UK, Version 21) to develop a virtual paediatric obesity population group and assess pharmacokinetic changes and the optimum dose of amlodipine in the paediatric obesity populations. A total of 9 retrospective clinical studies were used to develop and robustly validate the model in obese paediatrics. Literature-sourced physiological parameters that have been reported to change in obese children were incorporated into the virtual patients, including age-weight-height (WHO/CDC) correlations, haematocrit, plasma proteins, and glomerular filtration rate. Changes in pharmacokinetics were assessed across different age groups in paediatrics with/without obesity as follows: i) 2-6 years, ii) 6-12 years and iii) 12-18 years old across fixed doses of 2.5-10mg or a weight-based dose of 0.20 mg/kg.

Results: Differences in predicted maximum concentration (Cmax) and area-under-the-curve (AUC) were significant between children with and without obesity across the age group 2 to 18 when a fixed dose regimen was used. On the contrary, a weight-based dose regimen showed no difference in Cmax between obese and non-obese from 2 to 9 years old. Thus, when a fixed dose regimen is to be administered, a 1.25 to 1.5-fold increase in dose is required in obese children to achieve the same Cmax concentration as non-obese children, specifically for children aged 5 years and above.

Conclusion: This study demonstrated that the PBPK modelling approach, implemented using virtual clinic trials, could be applied to support personalised dosing in obese paediatric populations.

Knowledge, perceptions, and attitude of physicians and pharmacists practicing in the Philippine General Hospital towards pharmacogenomics and its integration in clinical practice in the Philippines

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Background: Pharmacogenomics (PGx) is the study of how genomic variations influence an individual's response to medications with the ultimate goal of optimising drug therapy plans. However, in the context of the Philippines, this field still has yet to be fully realised.

Purpose: As a first step towards incorporating PGx in clinical practice, this study aims to assess the knowledge, perceptions, and attitudes of physicians and pharmacists practising in the Philippine General Hospital (PGH) towards PGx and its integration into clinical practice in the Philippines.

Method: A cross-sectional questionnaire was disseminated to pharmacists or physicians currently practising in the PGH. Data collected was analysed using descriptive and comparative statistics. A total of 120 respondents participated, 55.8% of which were pharmacists and 44.2% were physicians.

Results: The overall respondents' mean percentage knowledge score is 71.7%, which indicates high knowledge. The overall mean perceptions score indicates positive perceptions (4.8), and the overall mean attitude score indicates positive attitudes (6.8). Prior attendance at an educational activity on PGx positively influences the respondents' knowledge, perceptions, and attitudes. Profession, years of experience, and highest educational attainment also affect the respondents' attitudes. The following perceived barriers were noted: lack of structured education and training in PGx research, facilities or infrastructure which support PGx research/practice, lack of national policies or guidelines for PGx testing, and lack of awareness of PGx. It is worth highlighting, however, that despite the perceived barriers involving the lack of structured education and awareness on PGx, the pharmacists and physicians in this study still demonstrated a high level of knowledge.

Conclusion: Results of the study point to the promising potential for PGx to be implemented into clinical settings, emphasising the need for efforts to be focused on addressing the perceived barriers.

The impact of SLCO1B1 genotype on low density lipoprotein cholesterol lowering effect in statin users with familial hypercholesterolemia: A hospital-based study

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Introduction: Statins are the most potent oral drugs for lowering low-density lipoprotein (LDL) cholesterol and are commonly prescribed for the prevention of coronary heart disease in patients with familial hypercholesterolemia (FH). The reduction of LDL is approximately in the range of 17 to 63 percent among statins, and it is related to the dose. Decreased function of SLCO1B1, a gene that encodes the organic anion transporting polypeptide 1B1 (OATP1B1) that mediates the hepatic uptake of statins, can increase the systemic exposure of statins and is supposed to increase the LDL-lowering effect. However, the impact of the SLCO1B1 genotype on the LDL-lowering effect of statins remains poorly understood. This study aims to estimate the effect of the SLCO1B1 genotype on the reduction of LDL in statin users with FH in a hospital-based population.

Methods: The study population was extracted from the Taiwan Precision Medicine Initiative (TPMI). Participants who had a mutation in the LDLR, PCSK9 or APOB gene and received their first treatment for hyperlipidemia with statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) over 84 days were enrolled. Participants who had received ezetimibe, alirocumab, evolocumab or inclisiran before the index date were excluded. Associations between SLCO1B1 genotype, mutation in the LDLR, PCSK9 or APOB gene, dose adjusted LDL-lowering effect in statin users were analysed.

Results: Ninety-four participants with a mutation in the LDLR or APOB gene and who used statins over a period of 84 days were enrolled. All of the enrolled participants had heterozygous FH, and there was no participant with a PCSK9 gene mutation. These participants were categorised into SLCO1B1 NMs and non-NMs, with 73 (78%) NMs and 21 (22%) non-NMs, which was consistent with the distribution of SLCO1B1 genotype in East Asia. The LDL levels before treatment were 168.4 mg/dL ± 45.9 and 181.8 mg/dL ± 44.6 (p = 0.184) in NM and non-NMs, respectively. There was no difference in the reduction of LDL between NMs and non-NMs (29.4% vs 29.6%, p=0.982). Age, weight and untreated LDL level were associated with the reduction of LDL above 40%, while SLCO1B1 genotype, gender and FH subtype were not correlated. Participants were further categorised into LDLR mutations and APOB mutations, with 30 (32%) having LDLR mutation and 64 (68%) having APOB mutation. The result showed that participants with LDLR mutation had higher HDL levels on the index date than participants with APOB mutation (57.4 mg/dL ± 21.3 vs 47.4 mg/dL ± 21.0, p=0.023), while other lipid profiles showed no difference. There was no difference in the reduction of LDL between LDLR mutations and APOB mutations (24% vs. 32%, p=0.427).

Conclusion: This hospital-based research provides evidence that the SLCO1B1 genotype is not associated with LDL-lowering efficacy in statin users with FH. Nonetheless, further studies with larger sample sizes are needed to evaluate the relationship between SLCO1B1 genotype and statin efficacy in FH patients.

The antidepressant imipramine as an example of drug repurposing in precision-medicine-based cancer treatment

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Introduction: As per DrugBank (accessed Nov 23), there are more than 4,317 approved drugs worldwide, the majority of which possess a single indication despite their biological activity. Drug repurposing involves investigating new applications for already approved drugs or advancing previously studied but unapproved drugs. This constitutes a crucial strategy in drug development, potentially bypassing earlier developmental stages focused on establishing drug safety, which has already been completed. Moreover, it can serve as a cost-effective method for developing countries to access effective patent-free drugs. Numerous reviews suggest that approximately 30% of repurposing endeavours successfully result in an approved market product, compared to about 10% for new drug applications in general. There is substantial evidence highlighting the use of repurposed drugs in treating specific subtypes of cancers characterised by distinct molecular features. The application of drug repurposing in precision medicine aims to optimise efficiency or therapeutic benefit for specific patient groups, particularly through genetic or molecular profiling. In this context, serrated adenocarcinoma (SAC), a subtype of colorectal cancer (CRC) recognised by the WHO, accounts for roughly 10% of CRC cases and is distinguished by its high propensity for metastasis and the absence of molecular targeted

therapy. This research group aimed to identify therapeutic targets for SAC to investigate whether some already FDA/EMA-approved drugs could be repurposed for specifically treating SAC.

Methods: Tumor tissues underwent molecular profiling to determine the overexpression of therapeutic targets in SAC relative to conventional CRC. Subsequently, molecular docking in silico analysis was conducted to identify repurposed drugs capable of targeting these therapeutic targets. Following this, both in vitro and in vivo analyses were conducted to assess the anti-tumoral effects of CRC.

Results: Transcriptomic analysis uncovered the overexpression of the Fascin protein in SAC, indicating its role in driving the aggressive phenotype characteristic of SAC, particularly in tumour invasion and metastasis. Utilising structural bioinformatics and a library of FDA-approved drugs, imipramine, an antidepressant, emerged as a potential Fascin inhibitor. Biophysical and biochemical assays validated this discovery. Subsequent cell culture analysis demonstrated that imipramine hindered CRC cell migration and invasion in a Fascin-dependent manner. In vivo, studies employing two animal models further illustrated imipramine's efficacy in inhibiting tumour growth and metastasis, particularly in tumours exhibiting high Fascin expression. Subsequently, a non-commercial clinical trial was initiated to evaluate imipramine's effectiveness in treating tumours characterised by high fascin expression, including SAC and triple-negative breast cancer. The ongoing clinical trial has confirmed the safety and promise of imipramine for treating these aggressive cancers.

Conclusions: This study delineates the process from identifying molecular targets to conducting non-commercial clinical trials aimed at utilising repurposed drugs for effectively treating cancers in accordance with the principles of precision medicine.

Analysis of ceftazidime-avibactam concentrations in critically ill patients under ECMO support: A prospective single-centre observational study

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Introduction: Optimising antimicrobial treatment in the Intensive Care Unit (ICU) is crucial for improving clinical outcomes and minimising adverse effects and antibiotic resistance. This study aims to describe the outcomes of antimicrobial monitoring in critical patients over the past year.

Materials and Methods: A descriptive observational study was conducted in a tertiary hospital ICU between March 2023 and March 2024. Patients admitted to the ICU with at least one determination of trough plasma concentration (pre-dose) of the following antimicrobials were included: ganciclovir, isavuconazole, linezolid, piperacillin-tazobactam, ceftazidime, meropenem, and teicoplanin. Determinations were classified into three categories: subtherapeutic, therapeutic range, and supratherapeutic (potentially toxic). Continuous variables are expressed as medians (interquartile range), and categorical variables as cases (percentages).

Results: A total of 78 patients were included, 50 (64%) of whom were men, with a median age of 58 (47 - 67) years. A total of 225 concentrations of antimicrobials were measured: isavuconazole 72 (32.0%), meropenem 51 (22.7%), teicoplanin 44 (19.6%), ganciclovir 22 (9.8%), ceftazidime 19 (8.4%), linezolid 12 (5.3%), and piperacillin 5 (2.0%). The median number of determinations per patient was 1 (2-3). The results were classified 44 (19.56%) as subtherapeutic, 116 (51.56%) within the therapeutic range, and 65 (28.89%) were supratherapeutic.

Therapeutic ranges as outlined in the centre's antimicrobial monitoring protocol, developed based on available evidence, were considered. For beta-lactams, minimum inhibitory concentration (MIC) was considered for empiric treatments.

Conclusion: The high percentage of determinations outside the therapeutic range suggests the need for individualised dosing strategies guided by pharmacokinetic monitoring. Alterations in pharmacokinetic parameters described in

critical patients, including changes in the volume of distribution and clearance, could impact this inadequate exposure. Antimicrobial monitoring in the ICU serves as a valuable tool to maximise efficacy and limit the occurrence of adverse effects.

Utilisation of the African genome project for precision medicine and precision drug discovery: A case study of statins

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Introduction: The African genome contains the most genetic variants in the world. In 2020, a study published by the Human Heredity and Health in Africa focusing on single nucleotide polymorphism found that the genotype of 426 African individuals contained more than 3 million variants that were not previously described. A review of the PharmKGB revealed missense mutations that led to clinically relevant effects both on the metabolism and efficacy of many medications. Polymorphisms in drug transporters may contribute to the observed diversity in the response to some drugs in African patients. Specifically, the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene, which encodes a membrane-bound sodium-independent organic anion transporter protein (OATP1B1), has been implicated as a determinant of the efficacy and toxicity of HMG-CoA reductase inhibitors (statins). SLCO1B1 rs4149056 (also known as c.521T>C, Val174Ala or V174A, which reduce uptake/transport activity of the OATP1B1) has been found at markedly higher frequencies in African populations than in non-African populations. This might lead to an increased risk of statin-related myopathy or myalgia when such patients are treated with statins. Furthermore, polymorphism in HMG-CoA reductase (HMGCR), a rate-limiting enzyme involved in cholesterol biosynthesis, has been reported as a determinant of the efficacy of statins.

Method: Firstly, the authors used computational modelling to explore and compare the interaction of rosuvastatin with the wild type and rs4149056 SNP of the OATP1B1 transmembrane transporter protein to gain insight into the potential rate of the drug transportation. Secondly, the authors used recently reported missense SNPs of HMGCR genes rs147043821 and rs193026499 as a foundation for precision drug discovery. The authors examined the effect of the SNPs on the predicted inhibitors of the mutated HMG-CoA reductase using computational modelling.

Results: The authors observed instability OATP1B1 carrier protein which might alter the uptake/transport of rosuvastatin. This might lead to the observed toxicity in patients with the implicated allele. Computational modelling predicted differential binding affinities for inhibitors of the mutated HMG-CoA reductase.

Conclusions: Impaired transport of rosuvastatin by the transporter protein may be responsible for the required dose adjustment for rosuvastatin in the African population with rs4149056 SNP. Differences in the ability of wildtype and mutated HMG-CoA reductase to bind inhibitors make a case for precision drug discovery based on prevailing alleles in a specific population. Overall, the authors demonstrated the value and potential of the output from the African Genome Project to drive Africa-focused precision medicine and precision drug discovery.

The clinical benefits of pharmacogenetic clinical decision support alerts: Experience from Taiwan

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Background: Based on individual genetic markers, finding the appropriate medical decision has evidently become a trend. However, integrating pharmacogenomics (PGx) rules into clinical decision-making presents a significant challenge, as clinicians often lack the time to acquire extensive genetic training. Clinical Decision Support Systems (CDSS) is an essential tool for improving the adoption and clinical application of PGx. By doing so, the authors can maximise therapeutic effects and minimise adverse drug reactions. The authors outline solutions to bridge the existing gaps.

Purpose: This study aims to detail clinician responses, prescription prevalence, and the clinical benefits of genetic data following the standardisation of PGx clinical decision support alerts.

Method: A retrospective analysis was conducted on all PGx alerts issued to a tertiary academic medical centre from January to December 2023, measuring clinician response and acceptance rates. Additionally, the clinical benefits were analysed by examining the therapeutic responses of CYP2C19 patients to Clopidogrel and NUDT15 patients to Azathioprine.

Results: The system encompassed 194 Drug-Gene pairs, with 4195 alerts utilised to assess response rates and acceptance, yielding an average acceptance rate of 65.7%. Clinical benefits include identifying patients at high risk due to CYP2C19 loss-of-function alleles who are taking Clopidogrel, as they have an increased risk of major adverse cardiovascular events (10.17% vs 13.2%, p<0.0001), suggesting a medication change to improve efficacy. Additionally, the system identifies patients who are at a rare but high risk of adverse reactions, successfully reducing by 60% the number of cases where patients with NUDT15 PM experience myelosuppression due to the use of Azathioprine.

Conclusion: The PGx decision support system, through its conspicuous pop-up boxes and simple decision-making phrases, embodies the urgency and accessibility of information. It reminds physicians to consider not only symptoms and diagnoses but also the results of genetic testing to improve patient medication outcomes. This evidence shows that integrating pharmacogenomics-guided treatments into the CDSS facilitates rational therapeutic drug monitoring in this hospital.

Exon-skipping therapy for Duchenne muscular dystrophy: Efficacy, variability, and turnover in skeletal muscle

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Introduction: Exon skipping with Phosphorodiamidate morpholino oligomer (PMO) is a promising therapeutic strategy for Duchenne muscular dystrophy (DMD), and the Food and Drug Administration (FDA) recently gave conditional accelerated approval for four new exon-skipping drugs (eteplirsen, golodirsen, cashmere, and viltolarsen). FDA approvals were based on demonstrated dystrophin production (surrogate endpoint) expected to predict clinical benefit in ongoing clinical trials. All exon-skipping drugs showed good safety and tolerability but yielded highly variable dystrophin restoration in patients. Currently, the authors do not understand the basis of this variability, nor how the restored dystrophin protein elicited by exon skipping influences the dynamics of dystrophin protein synthesis and turnover, and in turn, how this affects the dynamics of other proteins of the dystrophin-associated protein complex (DGC). The authors have designed a series of experiments to understand the factors contributing to the therapeutic efficacy of this new treatment modality.

Methods: Functional (Grip strength, Invitro force contractions), Histological (H&E), Molecular, Biochemical, and imaging techniques in a dystrophin-deficient mdx mouse model.

Results: The authors found that a) dystrophin rescue occurs in a sporadic patchy pattern with high geographic variability across muscle sections. The authors did not find a correlation between residual morpholino drug in muscle tissue and the degree of dystrophin expression; b) high dose monthly PMO administration restores dystrophin expression and increases muscle force; however, the variability of dystrophin expression at both the inter-and intramuscular level remains, and c) sequestration of restored dystrophin protein after exon skipping therapy in muscle leading to a significant extension of its half-life compared to the dynamics of full-length dystrophin in normal muscle. In contrast, DGC proteins show constant turnover attributable to myofiber degeneration and dysregulation of the extracellular matrix in dystrophic muscle.

Conclusion: Additional strategies to optimise PMO uptake, including increased dosing frequencies or combination treatments with other yet-to-be-defined therapies, may be necessary to achieve uniform dystrophin restoration and improve muscle function.

Predicting potential herb-drug interactions between indigenous African plants and variants of CYP2B6 using computational analysis

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Background: Understanding herb-drug interactions (HDIs) is crucial due to the growing popularity of herbal medicines and the increasing likelihood that they could be used in combination with conventional medications. These interactions can modify the pharmacokinetic properties of a drug, which may lead to a subtherapeutic effect or, conversely, adverse effects. Computational approaches can predict HDIs between pharmaceutical drugs and herbal products. Catharanthus roseus and Artemisia afra are African plants that have traditionally been used to treat malaria. They are rich in phytochemicals such as alkaloids, flavonoids, and tannins.

Purpose: This study investigated the possibility that phytochemicals from these plants might inhibit human CYP2B6 and thereby possess the potential for HDIs.

Method: A structure-based in silico method was employed to identify potential CYP2B6 inhibitors by docking selected

phytochemicals of these plants into the active site of the enzyme (PDB ID: 3IBD) using the Discovery Studio 3.1 life sciences molecular modelling suite. Various docking algorithms and scoring functions were first evaluated to find the combination that best identified active inhibitors within a database of active and decoy compounds. This validation step evaluated three metrics: the root mean square deviation (RMSD), enrichment factor (EF) and receiver operating characteristic (ROC) curve. RMSD measured the ability of each docking/scoring combination to correctly redock thirteen co-crystallised ligands onto the active site of CYP2B6, while EF and ROC measured the ability of each combination to identify active inhibitors (n = 14) from among a set of decoy compounds (n = 987). Three docking algorithms (LibDock, LigandFit, CDOCKER) with their native scoring functions and seven additional scoring functions were evaluated.

Results: While none of the docking/scoring combinations had a high RMSD success rate (<42%), the LibDock/Ludi 3 combination was most promising at distinguishing active inhibitors from decoy compounds (EF10%: 2.12, ROC-AUC: 0.782 ± 0.042). Using this combination, the binding of 23 phytochemicals to CYP2B6 was investigated. The results highlighted acacetin (897), isoscopoletin (759), and scopoletin (705) as potential inhibitors of human CYP2B6. These compounds displayed similar Ludi 3 scores to the known inhibitors, ticlodipine (939), 4-benzylpyridine (851), and 4-(4-chlorophenyl) imidazole (742). These findings suggest that these plant-derived phytochemicals.

Conclusion: may have the potential to impact human CYP2B6 drug-metabolising enzymes, potentially leading to reduced treatment efficacy for a range of diseases targeted by CYP2B6 treatments, such as malaria. Computational methods provide insight into these interactions, which could improve drug safety and efficacy.

Herb-drug Interactions of root extracts of Securidaca longipedunculata Fresen (Polygalaceae) with Artemether using CYP2B6 humanised mouse models

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Background: Malaria is a major public health problem, especially in sub-Saharan Africa. This is majorly due to the ever-increasing resistance of malaria causing parasites to antimalarial drugs. Due to limited access to hospitals, people use antimalarial plants in traditional medicine for the treatment of fevers, and if they do not heal, they later seek treatment in hospitals. This leads to herb-drug interactions. The effects of plants used for the treatment of malaria in traditional medicine on the therapeutic activities of the currently used antimalarial drugs are not fully explored. One such plant is Securidaca longipedunculata, which is used in traditional medicine for the treatment of malaria in various African countries.

Purpose: The current study will focus on evaluation of the effects of aqueous and organic root extracts of S. longipedunculata on the metabolism of artemether using CYP2B6 humanised mouse models.

Method: The effects (inhibition or induction) of S. longipedunculata on the metabolism of artemether will be determined using CYP2B6 humanised mice models (CYP2B6 and CYP2B6*6). For induction effects, mice will be treated orally with 100 mg/kg of aqueous and organic root extracts of S. longipedunculata and then after one hour with 15 mg/kg of artemether. Blood collection will be done at selected time points: 0 (predose), 0.08, 0.25, 0.5, 1, 2, 4, 6, 12 and 24 hours. For induction effects, mice will be treated orally with 100 mg/kg of both plant extracts daily at 24 hr intervals. On the 6th day, mice will be orally treated with 100 mg/kg of each extract and then after one hour with 15 mg/kg of artemether. Blood will then be collected at selected time points: 0, 0.08, 0.25, 0.5, 1, 2, 4, 6, 12 and 24 hours. Artemether (ART) will be quantified in plasma using liquid-chromatography mass-spectrometry (LC-MS). Pharmacokinetic parameters will be determined: area under the curve (AUC), time taken to reduce the volume of the drug by half (t1/2), volume of distribution (Vd), clearance (CL), and mean residence time (MRT). Data will be used to determine the maximum concentration (Cmax) and the time taken to reach the maximum concentration (Tmax).

Results: Since metabolism determines the bioavailability and therapeutic effect of orally administered drugs, the current study will provide insight towards the effects of S. longipedunculata on the therapeutic activity of artemether.

Conclusion: The study will provide information on the effects of S. longipedunculata on the co-used antimalarial drug (artemether), therefore contributing knowledge towards the simultaneous use of herb-drug combinations in the treatment of malaria.

Medication experience, pharmacogenomics and health equity: Who stands to gain or lose?

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Introduction: Medication experience (MedXp) is a person's subjective experience related to taking medication in daily

living. The MedXp starts when one encounters the medication, even prior to use. It includes the meaning of that encounter and the totality of the effects thereafter, both positive and negative. Pharmacogenomics (PGx) is a field of investigation that seeks to determine how a person's genes may affect their response to medications to optimise therapy; hence, it is an integral component of precision medicine. A person's response to a medication is, therefore, a part of their MedXp. The appropriate application of PGx into patient care has the potential to enhance MedXp and improve health outcomes, thereby contributing to health equity across all groups. The objective was to illustrate the intersections between MedXp, PGx, and health equity using a case example.

Methods: A review of the literature was conducted to determine the current state of knowledge regarding the relationship between MedXp, PGx, and health equity. A real patient case was examined using an intersectionality lens. The patient, Sam (not real name), an 18-year-old male who self-identified as Black/African American, has sickle cell disease (HbSS) and surgical asplenia with a history of cholecystectomy and anxiety. Sam received PGx testing as part of a research protocol one year prior and was found to have five priority gene results that had Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines at the time of testing. The CPIC publishes peer-reviewed, evidence-based clinical practice guidelines based on gene-drug interactions. Educating Sam and responding to his concerns requires nuanced discussion. Drawing on existing literature, the discussion focused on the benefits and current limitations of PGx application to minoritised racial populations such as Sam's and the associated inequities.

Results: At the intersection of Health Equity and MedXp is the variability in the experiences that individuals and populations have within and outside healthcare driven by structural constructs, and resulting in disparate health outcomes. Such constructs include systemic racism, healthcare access, and persisting race-based medicine (use of race as a biological variable versus social construct). PGx has the potential to leverage knowledge of the influence of genetic variations on medication efficacy and adverse effects to address health inequity. However, it is limited by the underrepresentation of non-European populations in genomic studies, thus affecting the applicability and under-utilisation of recommended guidelines for PGx testing in conditions with well-established benefits. Therapeutic outcomes are therefore influenced by an individual's experiences, genetic information, and structural factors that facilitate or limit accessibility to treatment, as informed by genomic data that is applicable to non-European populations such as Sam's.

Conclusion: PGx is an effective tool in optimising treatment and presents an opportunity to address racial health disparities. However, the under-representation of minoritised racial populations in PGx clinical studies and barriers to access in PGx testing in clinical care pose challenges to achieving health equity in this regard. Increasing the enrollment of populations of non-European ancestry in clinical studies will strengthen the evidence base for the use of genomic data in optimising therapies in these populations.

Matters of the heart: The application of pharmacogenomics in personalised cardiovascular disease therapy

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Background: Patients with the same medical condition, treated with the same medicine, will exhibit different responses. For some patients, the medicine will be effective, while others will experience adverse effects. A patient's age, lifestyle, concomitant disease conditions and medication use, as well as genetics, will influence how a patient responds to medicine therapy. Pharmacogenomics (PGx) is a rapidly progressing field that studies how genetics clinically modifies a patient's response to medicine. For example, pharmacogenomics can have an effect on the pharmacokinetics of medicine by affecting medicine metabolism. The purpose of applying pharmacogenomic principles is to optimise treatment outcomes and minimise adverse effects by selecting the correct medicine at the correct dose for the correct patient, i.e. personalised medicine.

Purpose: The primary aim was to assess the current state of pharmacogenomics in actionable personalised cardiovascular medicine based on the Clinical Pharmacogenetics Implementation Consortium (CPIC) data.

Methods: The CPIC database (https://cpicpgx.org/genes-drugs/) was consulted to identify medicines used to treat cardiovascular disorders that are classified as CPIC level A. In a clinical context, this means that genetic information should be used to change the prescribing of the affected medicine. The identified cardiovascular medicines for which CPIC pharmacogenetics guidelines have been developed were further explored to summarise prescribing change information where the patient's pharmacogenetic information is known, i.e. their metaboliser phenotype.

Results: Comprehensive CPIC guidelines for actionable prescribing changes for clopidogrel, various statins and warfarin have been developed. Clopidrogel is a platelet aggregation inhibitor used to reduce the risk of myocardial infarction (MI) and stroke. The enzyme CYP2C19 catalyses the bioactivation of clopidogrel to the active metabolite of clopidrogel. Antiplatelet therapy recommendations based on polymorphisms in CYP2C219 have been made. For example, in CYP2C19 poor metabolisers, there will be significantly reduced clopidrogel active metabolite formation, increasing the risk for adverse cardiac and cerebrovascular events. The

recommendation is to avoid clopidrogel, and to prescribe prasugrel or ticagrelor at the standard dose. The statins are widely used as an adjunct to dietary modification for lowering LDL and total cholesterol. The musculoskeletal symptoms caused by statins are a common occurrence that has a significant impact on adherence to therapy. Several pharmacogenetic variants have been identified: SLCO1B1, CYP2C9 and ABCG2. Patients with poor SLCO1B1 function, for example, have a high risk of statin-associated musculoskeletal symptoms when atorvastatin (40-80 mg) and rosuvastatin (40 mg) are used, while there is a low risk when treated with fluvastatin (20-40 mg). Warfarin is used in the primary and secondary prevention of venous thromboembolism. Guidelines for CYP2C9, CYP4F2, VKORC1 and rs12777823 have been drawn up. Incorporating genetic information into warfarin prescribing can reduce the risk of bleeding and thromboembolic events.

Conclusions: The pharmacogenetic guidelines that have been drawn up contain valuable information that can directly impact the overall safety, effectiveness and adherence of medicine therapy. Healthcare professionals must be made aware of the information that is available as increased knowledge and awareness is required to optimise therapeutic outcomes in the pursuit and implementation of personalised medicine.

Exploring novel therapeutic strategies for immune checkpoint inhibitor-induced myocarditis through gene expression analysis

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Background: Myocarditis induced by Immune checkpoint inhibitors (ICIs) presents a formidable challenge in contemporary oncology, with mortality rates exceeding 40%. Despite the severity of this adverse event, its rarity — with incidence rates ranging from 0.1 to 1.1% — significantly impedes the accumulation of comprehensive clinical insights. Consequently, the underlying mechanisms of ICI-induced myocarditis and effective treatment strategies remain largely undefined, underscoring the critical need for innovative research approaches.

This study leveraged the power of bioinformatics to bridge this knowledge gap. The authors aim to identify novel therapeutic targets and potential drug candidates that could mitigate or prevent the cardiotoxic effects of ICIs by harnessing publicly available gene expression datasets to pave the way for safer cancer immunotherapy protocols.

Methods: This research methodology employed a meticulous analysis of RNA-seq data derived from the myocardial cells of patients across three distinct groups: patients with ICI-induced myocarditis (n=9, E-MTAB-8867 dataset), patients with dilated cardiomyopathy (n=11), and individuals diagnosed with viral myocarditis (n=5, GSE120567 dataset). These datasets were sourced from the Esteemed Array Express and GEO databases curated by the European Bioinformatics Institute (EBI) and the National Center for Biotechnology Information (NCBI), respectively. Following an exhaustive preprocessing routine, the authors applied advanced statistical methods (the Walt test, with the threshold for significance set to $p = 0.05$ and a false discovery rate (FDR) of 5%) to identify genes uniquely associated with ICI-induced myocarditis. Building on these findings, the authors explored the LINCS database [a comprehensive repository maintained by the National Institutes of Health (NIH) that documents gene expression modifications triggered by an array of chemical compounds] to identify drugs capable of modulating the identified gene expression patterns.

Result: This analysis revealed a profound alteration in the myocardial gene expression landscape attributable to ICI therapy, with 387 genes exhibiting heightened expression and 797 showing reduced activity compared to the dilated and viral myocarditis profiles. Intriguingly, this distinctive genetic signature led to the identification of four promising drug candidates, each with the potential to counteract gene expression aberrations linked to ICI-induced myocarditis.

Discussion: This study represents a significant step forward in the quest for effective countermeasures against cardiotoxicity associated with immune checkpoint inhibition. The authors laid the groundwork for a novel paradigm in the management of ICI-induced myocarditis by integrating gene expression data with drug efficacy profiles. These findings highlight the utility of bioinformatics in uncovering hidden patterns within complex datasets and underscore the potential of this approach in translating genomic insights into tangible therapeutic strategies. The authors plan to refine the list of candidate drugs through rigorous validation processes, employing spontaneous adverse event reports and detailed clinical information databases to ensure the reliability and applicability of these proposed interventions in a clinical setting.