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Background: Pharmacoepidemiologists are becoming involved in clinical studies that have the potential to generate clinically relevant genetic data that could have importance to patients. There are many ethical and policy issues related to the communication of genetic research to participants. Pharmacoepidemiologists need to understand the issues and options that are available to researchers.

Objectives: To evaluate current practice related to the communication of genetic research results and provide a framework for pharmacoepidemiolngists to include options for return of results during study design and to communicate results to study participants.

Methods: The literature (2010–2017) was surveyed and analyzed for genetic studies (RCTS, observational clinical studies) to determine how communication of genetic results was addressed. Additionally, a review of a phase III international clinical trial in late stage ovarian cancer, in which due to emerging scientific evidence, the researchers conducted an exploratory retrospective pharmacogenomic (PGx) study, provided a case that was mined for lessons learned relating to the communication of genetic results.

Results: Of 65 studies reported, 34 were excluded. Of the remaining 31 studies, 29% surveyed physicians, 32% surveyed patients, and 12.9% surveyed families. Among clinical trials, only 4 studies involved communication of genetic results. The phase III exploratory retrospective PGx study demonstrated that carriers of clinically important germ-line BRCA mutations had improved progression-free survival prognosis. However, communicating individual BRCA results was not anticipated during trial design. Despite the significant variation in professional opinion, local guidelines, policies, and clinical practice related to communication of genetic research results to participants, a framework was developed to share aggregate results.

Conclusions: This study provides insights into the evidence and landscape of communicating genetic results in clinical studies to research participants, explores the lessons learned from a large international trial as a case study, and proposes a framework for future decision making in this new era of precision medicine.

436. Early HTA in Pharmacogenomics: A Case Example in Cardiovascular Drugs

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Background: ACE inhibitors (ACEi) are commonly used cardiovascular drugs. In a small percentage (0.2%) of patients, these drugs can cause a severe and possibly lethal adverse drug reaction (ADR), angioedema. A pharmacogenetic test could be used to identify patients at risk for this severe ADR and advise them to use another drug.

Objectives: The aim of this study was to assess the sensitivity, specificity and cost of a hypothetic pharmacogenetic test in order for it to be cost-effective in preventing ACEi-induced angioedema. Furthermore, we assessed the influence of testing only a part of the population carrying risk factors of angioedema.

Methods: A decision tree was used, as angioedema usually occurs within the first year after starting an ACEi and data on long-term risk is scarce. Test characteristics were assessed using Monte Carlo simulations.

Results: With a willingness-to-pay (WTP) threshold of €20.000 and €80.000 per quality-adjusted life year (QALY), a 100% sensitive and specific test may have a maximum cost of €1.30 and €1.95, respectively. A decrease in specificity has a 10-fold higher impact on the incremental cost-effectiveness ratio (ICER) than sensitivity, as additional drug costs of false positives rapidly overcome the benefit of preventing angioedema. In order to warrant a €1,00 price, specificity needs to be >95%, whilst sensitivity may drop to 70%, provided that specificity remains >98%. African Americans have a 3.88 times higher risk of developing angioedema than Caucasians. When only genotyping this population, the maximum test price (100% sensitive and specific) would be €5,04 and €7,57 at a WTP threshold of €20.000 and €80.000, respectively.

Conclusions: A theoretical pharmacogenetic test for ACEi-induced angioedema is only cost-effective at a very high specificity, decent sensitivity and a low price. If only used in patients with a high risk of angioedema, the maximum test price could increase to a somewhat more realistic €5 figure.

437. Drug Interactions with Tamoxifen in a Danish Premenopausal Breast Cancer Cohort

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Background: Tamoxifen treatment roughly halves the recurrence rate among estrogen receptor-positive breast cancer patients. Therapeutic success may hinge on successful biotransformation of tamoxifen to metabolites with higher estrogen receptor affinities. Biotransformation reactions are chiefly catalyzed by CYP2D6, CYP2C19, and CYP3A4. Each of these enzymes can be inhibited by other pharmaceutical substrates.

Objectives: We evaluated whether tamoxifen-treated premenopausal breast cancer patients have a higher recurrence rate if concomitantly exposed to a metabolism-impairing drug.

Methods: We enrolled 5,959 premenopausal women diagnosed with nonmetastatic breast cancer between 2002–2010. We divided the cohort into women with estrogen receptor positive tumors who were treated with tamoxifen (ER+/T+) and women with estrogen receptor negative tumors who were not treated with tamoxifen (ER−/T−). Prescription drug exposures were ascertained with the Danish nationwide prescription registry. We fit Cox regression models to estimate recurrence associations for exposure to pharmaceutical substrates for CYP2D6, CYP2C19, and CYP3A4.

Results: Pharmaceutical inhibition of CYP2D6 and CYP2C19 were not associated with recurrence in the ER+/T+ group (CYP2D6: $HR_{adj} = 0.98$, 95% CI: 0.74, 1.3; CYP2C19: $HR_{adj} = 0.99$, 95% CI: 0.71, 1.4). Pharmaceutical inhibition of CYP3A4 was associated with an increased recurrence hazard among ER+/T+ women (HR = 1.8, 95% CI: 1.1 to 2.0), but not among ER−/T− women.

Conclusions: The positive association for CYP3A4 inhibition was specific to ER+/T+ women, as expected for a predictive marker. However, short-term use of CYP3A4-inhibiting drugs (antifungals and antibiotics) would not overlap much with five years of tamoxifen duration, so this association merits further investigation. All associations warrant study with incorporation of functional variants in the genes encoding these enzymes.

438. Pharmacoepidemiologic-Pharmacodynamic Method to Investigate the Mechanism of Adverse Drug Reaction (ADRs): Application to Movement Disorders ADRs of Antipsychotics

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Background: Pharmacovigilance databases are usually used to detect new potential signals relevant for drug safety. While the identification of adverse drug reactions is of primary importance, understanding their mechanism(s) is essential for optimizing prevention and crisis management.

Objectives: We developed an original method, the Pharmacoepidemiologic-Pharmacodynamic method (PE-PD method) combining both pharmacoepidemiologic data (data from VigiBase, the World Health Organization (WHO) Global Individual Case Safety Report database) and pharmacodynamic data (from IUPHAR database, International Union of Basic and Clinical Pharmacology), to investigate the association between D2, 5HT2A and M1 receptor occupancy and the risks of antipsychotic (AP)-induced movement disorders (MD) in order to explain the pharmacodynamic mechanism of this ADR.

Methods: First, we performed a case/non-case analysis using spontaneous reports from VigiBase®. We thus measured the risk of MD reporting compared to all other ADRs (expressed as a Reporting Odds Ratio, ROR) for first (FGAP) versus second (SGAP) generation APs in general and 49 APs in particular. Second, we performed a linear regression analysis to explore the association between the estimated risk of reporting for individual drugs and their receptor occupancy properties for D2, 5HT2A and M1 receptors. The