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Program in pharmacogenomics at the Ohio State University Medical Center

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Abstract

Established in 2002, the Ohio State University Medical Center Program in Pharmacogenomics, lead by Wolfgang Sadee, is comprised of nearly 50 members dedicated to the discovery, investigation and translation of genetic biomarkers with the primary goal of advancing personalized healthcare. This article describes the research teams, bioinformatics infrastructure, supporting laboratories and Centers for Personalized Healthcare and for Clinical and Translational Science, current molecular genetic studies, translational and clinical pharmacogenomic studies, examples of biomarkers under development, and the future directions of the program.

Established in 2005, the Center for Personalized Healthcare (CPHC) has helped guide critical advancements encompassing the range of personalized medicine, from the medical school's curriculum to patient care and electronic medical records (EMRs). In collaboration with the Institute for Systems Biology in Seattle (WA, USA), Ohio State University Medical Center (OSUMC) is creating predictive, preventive, personalized and participatory (P4) medicine. Directed by Clay Marsh, P4 medicine is organized into six areas: biomedical informatics and information technology; expression genomics, epigenomics and biomarker science; complex adaptive systems work; clinical trials and investigation; consumer-centered and employee health/managed care; and systems engineering and medicine to drive clinical application. CPHC's mission is multifaceted: to propel translational and clinical research in personalized healthcare (PHC), to incorporate PHC research into patient care, and to educate and advocate for the practice of PHC locally, nationally and internationally. It aims to integrate research and technology, facilitating cutting-edge discoveries, and to facilitate high-quality PHC education efforts for patients, students, health professionals and scientists. CPHC intends to combine the unique strengths and resources of each of its members, creating a national consortium of academic medical centers and research institutions with the primary goals of advancing PHC and bridging the research-to-practice gap. Genomic medicine, with the rapid development of sequencing technologies and other high-throughput methodologies, has emerged as the vanguard for tailoring healthcare, disease prevention and individualized therapy. Although human complexity confounds ready implementation of PHC strategies into clinical practice, genetic biomarkers can often provide considerable insight into predicting treatment outcomes, especially for

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pharmacological interventions targeting specific well-described biochemical and signaling pathways critical to disease processes. Pharmacogenomics is one of the earliest clinical applications and fundamental aspects of PHC [1], and this article will focus on describing its implementation at OSUMC.

Center for Clinical & Translational Science

Established in 2008, the Center for Clinical and Translational Science (CCTS) at OSUMC is directed by Rebecca Jackson and fosters research collaborations across the University, the medical center (OSUMC), and Nationwide Children's Hospital; the Center is dedicated to translating scientific discoveries into life-changing disease-prevention strategies, health diagnostics and treatments and offers numerous opportunities for faculty, staff and student researchers to seek assistance with biomedical informatics, biostatistics, clinical research services, community engagement, comparative effectiveness research, education and training, and regulations. Collaboration is promoted through interdisciplinary team-development groups, social networking and scientific meetings. The CCTS offers clinical and translational training programs, sponsored conferences, lectures featuring national and international speakers, mentoring and career-development support. Funding opportunities for pilot projects and professional development are also provided by the CCTS to bolster the translation or research findings into clinical practice.

Pharmacogenomics research

Expression Genetics in Drug Therapy research group

Comprised of scientists from clinical and basic-science departments within the Colleges of Medicine, Pharmacy, Public Health, Veterinary Medicine, Engineering and from OSUMC's Comprehensive Cancer Center (CCC), Heart and Lung Institute and Nationwide Children's Hospital, the Program in Pharmacogenomics is the home of the Expression Genetics in Drug Therapy (XGen) research group, an integral member of the Pharmacogenomics Research Network (PGRN) dedicated to the discovery of clinical biomarkers for guiding individualized pharmacotherapy.

XGen core laboratory

The XGen core laboratory serves to support collaborative research projects with the following capabilities:

- Detection of novel and scoring of known sequence variants (mostly SNPs) with parallel analyses of multiple SNPs in large subject populations;
- Development of novel approaches including next-generation sequencing (RNA and full-genomic) for discovering functional polymorphisms in candidate genes, studying molecular mechanisms and selecting functional polymorphisms for clinical investigation and implementation;
- Development of chemogenomic analyses of large-scale drug–gene interactions, especially applied to oncologic therapies;
- Integration of bioinformatics, providing design guidance for genetic experiments, identification of regulatory SNPs from genomic data, deduction of splice variants from expressed sequence tags, and definition of candidate genes involved in disease susceptibility and response to drug therapy;
- Implementation of traditional, cutting-edge and investigational genotyping panels;

- Assisting in the development of processes for transferring biomarker assay results into patient EMR.

Biomarker discovery & investigation

Several of the functional (regulatory) polymorphisms discovered and/or characterized by XGen are listed in Table 1, and a few are described in greater detail (methodologies employed, results and potential clinical relevance). XGen focuses on regulatory genetic variants (expression, RNA processing and translation) rather than on nonsynonymous SNPs because regulatory variants appear to be more prevalent and many are yet to be discovered.

CYP3A4—The CYP3A4 family of enzymes is involved in the metabolism of nearly half of the most commonly prescribed drugs. XGen has recently discovered a regulatory polymorphism, *CYP3A4*22*, suggesting substantial potential for becoming a predictive biomarker for numerous pharmacotherapy applications. This regulatory SNP was uncovered by measuring allelic mRNA expression in human liver tissues followed by minigene transfections in cell culture, thereby identifying the first relatively frequent *CYP3A4* variant (4–7% minor allele frequency) with 2–5-fold impact on intrahepatic expression. In 235 patients taking stable doses of atorvastatin, simvastatin, or lovastatin for lipid control, heterozygous carriers of the **22* allele required significantly ($p = 0.019$) lower doses (0.2–0.6-fold lower) than wild-type carriers [2]. XGen is further investigating the combined effect of *CYP3A4*22*, *CYP3A5* SNPs and other transport- and metabolism-related SNPs in two large clinical trials in which differences in statin (parent and metabolite) serum concentrations and a variety of clinical outcome measurements (changes in lipid profiles, incidence of cardiovascular and adverse events, and changes in carotid intimal–medial thickness) will be examined. *CYP3A4*22* has been found to significantly affect the metabolism of many other CYP3A substrates: recently investigators have reported findings strongly suggesting its potential as a biomarker for predicting the pharmacokinetics and pharmacodynamics of tacrolimus, cyclosporine, verapamil, saquinavir and potentially any other medication that undergoes significant CYP3A metabolization [3–5].

HTR2A—The serotonin 2A receptor, encoded by *HTR2A*, is a major target for antidepressant and antipsychotic pharmacotherapies. Hundreds of clinical association studies have blindly (without firm knowledge regarding biological relevance) investigated various *HTR2A* variants, and although variability at the *HTR2A* gene locus does affect drug response, the findings to date have been largely inconsistent owing to a lack of known functional genetic variants.

XGen has uncovered multiple novel HTR2A mRNA splice variants and regulatory regions expressed in human brain tissue by utilizing next-generation sequencing of both mRNA and genomic DNA. Several of these provide guidance for the interpretation of clinical association studies related to antidepressants, antipsychotics or mental disorders. One variant (present in up to 75% of the population) modulates the expression of a newly discovered mRNA isoform, subsequently affecting downstream protein expression. Since the variant occurs frequently, gene–gene interactions can be more readily investigated, and epistatic effects that could substantially increase our understanding of genetic causes of disease may be discovered [Smith R *et al.*, Novel HTR2A mRNA splice variants and regulatory regions may help guide clinical association studies of mental disorders or antidepressant and antipsychotic therapies (2012), Manuscript in preparation].

Unraveling ‘missing heritability’, the genetic mechanism contributing to seemingly high population estimates of genetic factors in human phenotypes with a focus on gene–gene environment interactions, is another primary focus of XGen. Once imperative variants in

key genes are validated, existing genome-wide association data can be explored [6]. Citalopram response, for example, has an abundance of associated clinical outcome data but is still in desperate need of improved personalized therapy; efficacy of citalopram response in depression (the STAR*D study) is largely variable and currently few predictive markers are available.

Translational pharmacogenomics

Translating pharmacogenomics into practice is an information-intensive endeavor. Genome-wide SNP analysis, and more recently whole-genome sequencing, yield enormous amounts of data with potential relevance. Integrating that with phenotypic information (contained in EMRs) has great potential for guiding PHC decisions; however, integration of genomic data into clinical practice faces numerous hurdles. Challenges in relating genetics, diseases and therapeutic outcomes are often addressed with bioinformatics approaches [7] requiring large-scale collaborations, often among different institutions, and involving analyses of extremely large datasets. Translating research results into clinical practice also poses multiple bioinformatic challenges including standardizing data and clinical systems integration with the ultimate goal of guiding clinical decisions. The Biomedical Informatics Faculty at OSUMC addresses these challenges through their research across the informatics subdomains of translational bioinformatics, clinical informatics and clinical research informatics [8,9]. Philip Payne (Chair) and Peter Embi (Chief Research Information Officer for OSUMC and Vice Chair) lead OSUMC's Biomedical Informatics Department; 13 full-time faculty, 30 affiliated faculty and over 30 staff work closely with colleagues locally, regionally and nationally to achieve this Department's mission, "To lead the advancement of health and biomedicine through the development, application and dissemination of novel biomedical informatics theories and methods capable of driving biological discovery, generating and translating knowledge and advancing personalized healthcare."

The Coriell Personalized Medicine Collaborative project, an informatics-enabled joint effort between OSUMC and the Coriell Medical Institute, has been designed to evaluate the impact of genomic counseling (using a randomized controlled design) on patient and physician awareness and on management strategies. Patients with chronic illnesses are being enrolled and are providing their medical, medication, lifestyle and family histories. DMET™ Plus and Affymetrix 6.0 platforms are utilized for genetic testing, and secure, web-based interfaces provide personalized risk reports for eight potentially actionable conditions (e.g., Type 2 diabetes; hemochromatosis; age-related macular degeneration) and a single pharmacogenomic report (*CYP2C19* and clopidogrel). Participants are then randomized to receive in-person genomic counseling, provided by a genetic counselor and medical geneticist. Online surveys measure perceived likelihood of disease, risk perception accuracy, numeracy, genetic and genomic knowledge, personalized medicine perceptions, satisfaction with genetic counseling and health-information-seeking behaviors. Additional disease and pharmacogenomic reports (*CYP2D6*, *VKORC1* and *CYP2C9*) are released over the course of the study, and the Coriell Personalized Medicine Collaborative risk reports are incorporated into the participants EMR.

Bioinformatic collaborative efforts among OSUMC investigators and those within the PGRN are pushing to go beyond just making reports available for care decisions; they want to leverage the full capability of computerized systems to provide clinicians with comprehensive decision-making support incorporating discrete data elements representing genetic profiles, EMRs and phenotypic information. For example, a clinician can be alerted and advised to consider alternative therapy when entering an electronic order to initiate clopidogrel therapy in a *CYP2C19*2*-carrying patient. Studies are now underway to

determine whether these types of alerts have the intended impact of influencing and improving medical decision-making.

Pharmacogenomic evaluations in the clinic

The Pharmacoanalytical Shared Resource, supported by the Ohio State University CCC and CCTS, designs and conducts clinical pharmacokinetic and pharmacodynamic studies that enable direct correlation of drug levels with pharmacogenetic markers. Within the CCC, Phase I and II trials are conducted to evaluate safety, pharmacokinetics and efficacy of experimental anticancer therapies in patients with hematologic and solid tumor malignancies. Quantitative analytical assays are developed in the Pharmacoanalytical Shared Resource to measure drug and metabolite levels of experimental agents and US FDA approved drugs. In relatively small trials (approximately 15–50 patients), focused pharmacogenetic hypotheses are tested to directly evaluate specific genotypes in relation to pharmacokinetics or clinical outcomes. Pharmacodynamic correlative studies are also often incorporated to evaluate targeted drug activity.

Emerging as a promising approach for cancer treatment, targeted chemotherapy is based on the assumptions that a tumor carries a driver mutation to which it is ‘addicted’ and optimal therapy will be targeted towards the driver mutation. In non-small-cell lung carcinoma several driver mutations have been identified (*KRAS* 24%, *EGFR* 13%, *ALK* 5%, *TP53* 5%, *PK3Ca* 4%, *CTTNB1* 2%, *BRAF* 2%, *NRAS* 1%, *HER2* 1% and *IDH1* 1%) [10], but the majority of other tumors are as yet uncharacterized. Ongoing research at OSUMC is being conducted to further identify driver mutations and to evaluate targeted therapies by measuring validated and experimental biomarkers.

Future direction for OSUMC Program in Pharmacogenomics

The OSUMC Program in Pharmacogenomics will continue to rely heavily on the numerous resources provided by the CPHC and the NIH-sponsored CCTS and PGRN to move forward in identifying, developing and translating clinically relevant biomarkers for improving patient care.

Numerous genes and polymorphisms have demonstrated influence on the pharmacokinetics and pharmacodynamics of a variety of pharmacotherapies; however, individual genetic polymorphisms are often insufficient to guide therapy, and gene–gene interaction studies are largely lacking in many areas of pharmacogenomic research [11]. For this reason, the Program in Pharmacogenomics at OSUMC has developed the resources and ability to study the combined effect of multiple genes, while also considering other epigenetic regulatory factors. Indeed, drug therapy in itself represents a robust external stimulus that must be considered as an altered environment against which genetic factors can be assessed. Along with combined gene analysis approaches, innovative and integrative bioinformatic strategies will be critical for the success of pharmacogenomics and genomic medicine with the ultimate goal of significantly improving healthcare across the world.

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Highlights

- The Program in Pharmacogenomics at Ohio State University Medical Center (OSUMC) is dedicated to the discovery, investigation and translation of genetic biomarkers with the primary goal of advancing personalized healthcare.
- Supported by the Ohio State University Center for Personalized Healthcare and the NIH-funded Center for Clinical and Translational Science and Pharmacogenomics Research Network (PGRN), the Program in Pharmacogenomics is home of the Expression Genetics in Drug Therapy (XGen) research group.
- XGen continues to develop and utilize novel techniques, including next-generation sequencing, to identify, characterize and validate regulatory genetic variants with significant impact on drug response.
- The Center for Clinical and Translational Science at Ohio State University fosters interdisciplinary research collaborations, supports career development of translational scientists and provides translational scientific resources and infrastructure as well as pilot funding initiatives to catalyze efforts that translate scientific discoveries into life-changing disease-prevention strategies, health diagnostics and treatments.
- The Center for Personalized Healthcare at OSUMC combines the unique strengths and resources of each of its members, creating a national consortium of academic medical centers and research institutions with the primary goals of advancing personalized healthcare and bridging the research-to-practice gap.
- Biomedical informatics at OSUMC is actively developing, applying and disseminating information regarding novel biomedical informatics theories and methods capable of driving biological discovery, generating and translating knowledge and advancing personalized healthcare.
- A university–private sector collaborative effort, the Coriell Personalized Medicine Collaborative project, utilizes novel bioinformatic strategies to evaluate the effect of providing genetic information to the patient and caregiver for guiding medical decision-making.
- The OSUMC Pharmacoanalytical Shared Resource develops quantitative analytic assays to measure drug and metabolite levels in biologic samples and also designs and conducts clinical pharmacokinetic and pharmacodynamic studies that enable direct correlation of drug levels with pharmacogenetic markers.
- Combined (multigene and gene–environment) analyses and innovative integrative bioinformatics strategies will drive the future success of pharmacogenomic research and personalized healthcare at OSUMC and worldwide.

Table 1

Select regulatory polymorphisms identified by Expression Genetics in Drug Therapy research group.

Gene	Polymorphisms	Function, mechanisms
OPRM1	Exonic SNP rs1799971 (A118G, N40D)	Stability and folding of mRNA; protein translation; may affect response to opioid antagonists in treatment of alcoholism
ABCB1	Exonic SNP rs1045642 (3435C>T, **13*)	Stability and folding of mRNA; reduced expression; may affect drug response (e.g., of anti-HIV drugs targeting T lymphocytes)
TPH2	Haplotype containing SNPs rs2171363, rs4760815, rs735115, rs6582078 and rs9325202	Exon 7 splicing, enhanced expression; may modulate response to antidepressant drugs
DRD2	Intronic SNPs rs2283265 and rs1076560	Exon 6 alternative splicing to D2S and D2L; affects cognitive processing, cocaine response, possibly response to antipsychotic therapy and so on
ACE	Promoter SNPs rs7213516, rs7214530 and rs4290	Reduced transcription; may increase risk of coronary artery disease in African–Americans, and possibly response to ACE inhibitors
VKORC1	Promoter SNP rs9923231 (-1639G>A)	Histone modification, transcription; demonstration that -1639G>A is the regulatory variant that should be used in guiding warfarin therapy
CYP3A4	Intronic SNP rs35599367, **22*	RNA folding and nascent RNA, reduced expression; affects metabolism of all CYP3A4 substrates including statins and immunosuppressants
CHRNA5	Enhancer SNPs rs1979905, rs1979906, rs1979907, r880395, rs905740 and rs7164030	Enhanced transcription; may affect nicotine addiction
NAT1	*NAT1*10* and **11*	Enhanced translation, gain of function; protects against skin toxicity caused by sulfamethoxazole in slow NAT2 metabolizers