Precision prescribing with pharmacogenomics

An interview with **Philip Empey and Peter Silvester**

According to the U.S. Food & Drug Administration, pharmacogenomics is an important part of precision medicine. FDA has an interest in determining how a person's genetic makeup may affect their response to a drug, and how this can assist healthcare providers in "choosing a drug that is more likely to work, avoiding drugs that might have side effects, adjusting the dose of a drug, or determining if closer monitoring is needed."

To realize this potential source of data, the University of Pittsburgh partnered with Thermo Fisher Scientific to establish a new Pharmacogenomics (PGx) Center of Excellence in the School of Pharmacy that aims to discover and validate medication response predictors in patients, overcome implementation barriers, and demonstrate the value of genetic testing to guide medication prescribing in routine clinical practice. Pharmacogenomics is the study of how genetic variation impacts medication responses.

Alan Sachs, chief scientific officer at Thermo Fisher Scientific, noted, "Pharmacogenomics envisions the widespread use of genetic testing to predict how patients may respond to particular medications. Together with the University of Pittsburgh, we realized that no single entity had stepped forward to work toward establishing the clinical utility of this approach at population scale, and this was the impetus for launching the new Center of Excellence."

We interviewed Philip Empey and Peter Silvester to discuss the establishment of the PGx Center of Excellence between the two organizations. Philip Empey, associate director for pharmacogenomics in the Institute for Precision Medicine and faculty in the School of Pharmacy and the Clinical and Translational Institute, will lead the Center. Peter Silvester serves as Senior Vice President and President of Life Sciences Solutions at Thermo Fisher Scientific, with a remit that includes leading the businesses responsible for developing products and workflows for genetic analysis and strategy related to the Center.

Dr Empey and Mr Silvester have agreed to discuss the partnership with us. Let's start with questions about its value, its current role, and its future impact.

Q Peter, can you please tell us what led Thermo Fisher to partner with University of Pittsburgh to establish the Center?

A We first engaged in a dialogue on precision medicine in late 2016, in part, to gain insights from leading clinical research institutes on practical approaches to the implementation of personalized healthcare. We firmly believe in the importance of a digitally integrated multi-omics approach to precision medicine. In fact, we were engaged with the University of Pittsburgh and their affiliated hospital system, University of Pittsburgh Medical Center [UPMC], on multiple fronts in genomics and targeted proteomics.

Earlier that same year, the University of Pittsburgh was awarded $4.2M in funding by the NIH, as part of the All of Us Research Program, which is aimed at enrolling one million participants as a first step in understanding factors influencing health and disease. In parallel, the University of Pittsburgh's Clinical and Translational Science Institute (CTSI), was in the early stages of developing a large institutional biorepository, now called Pitt+Me Discovery.

Our multi-omics vision was shared by Steve Reis, the Director of the CTSI and Principal Investigator of the All of Us grant, and we began mapping out a critical path, which we agreed should start with PGx. Accordingly, Philip Empey, who led the PreCISE-Rx PGx clinical implementation and research initiative at the University of Pittsburgh and UPMC, was identified to lead and advance this project.

The PGx Center of Excellence is the first academic-industry collaboration focused on PGx at this scale. As a partner in developing the technologies, including microarray, qPCR, next generation sequencing and mass spectrometry, along with unique capabilities in clinical and commercial development, manufacturing and logistics, we envisioned a collaboration that would extend from basic and translational research to clinical implementation and scale-up. The Center underscores the firm commitment of both organizations to establish PGx as a key application of personalized precision healthcare.

We have organized our efforts into three workstreams:
1) Development of state-of-the-art PGx methodologies and analytics,
2) Further improvement of patient outcomes through clinical implementation, and
3) Advancement of technology awareness and adoption through education.

> *"The PGx field requires bold initiatives to bring stakeholders together to make a transformative leap forward like the PGx Center of Excellence"*
>
> Philip Empey

Q Phil, could you please provide your perspective on the partnership and the value to programs at the Center?

A Precision medicine aims to improve health by leveraging technologies that can translate scientific discoveries into care tailored for each person. PGx has become a leading use case as the wealth of clinical data has started to associate genomic variation with altered drug response. PGx can reveal a disease or drug-response signature of variants prevalent in a population, which is of particular value as panel-based genetic testing becomes rapidly less expensive. Further, many groups, including our own, have shown PGx-guided prescribing is feasible through demonstration projects. But, additional evidence of clinical utility in real-world populations is still needed to drive payer reimbursement and barriers to universal implementation. The PGx field requires bold initiatives like the PGx Center of Excellence to bring stakeholders together to make a transformative leap forward.

As Peter noted, the PGx Center of Excellence represents the first "at scale" US academic-industry collaborative genomics implementation program focused on PGx. We aim to test >150,000 subjects preemptively through this new research initiative and return relevant results to drive clinical care. The collaboration is expected to show the value of true population-scale, preemptive PGx testing by enabling rapid technology deployment and scale-up; delivering innovation and best practices in the use of genomic data; and, above all, providing precision medicine proof points in a high-profile heath provider organization.

Q Phil, what is the relationship between the Center and UPMC?

A The PGx Center of Excellence is catalyzing UPMC efforts in Pharmacy and within the Institute of Precision Medicine to develop best practices in precision medicine clinical services and the use of genomic data in routine clinical care. As both a health care provider and insurer, we have the rare opportunity for researchers to link genetics, prescribing, outcomes, and utilization data in a very large cohort to evaluate precision prescribing enabled by PGx.

Q Peter, how do you do see the business value of the partnership to Thermo Fisher?

A Clinical providers, research institutions, pharmaceutical companies, diagnostic labs, government agencies, payers and companies like Thermo Fisher are part of the global precision medicine ecosystem. All contributors are essential to implementing precision healthcare at scale.

The Pharmacogenomics Center of Excellence team advancing research, clinical, and educational initiatives at the University of Pittsburgh. Left to right (seated): Karryn Crisamore, Philip Empey, Inmaculada Hernandez; (standing): Lin Huang, James Stevenson, Carlo Iasella, Linda Prebehalla and James Coons. Missing from photo is Lucas Berenbrok and Ryley Uber.

As such, we are working closely with the University of Pittsburgh and more broadly with precision medicine efforts across the globe to demonstrate the clinical utility and economic value of preemptive PGx testing to improve the efficacy in delivering the right drug to the right patient and avoiding or minimizing adverse effects. The NCBI recently cited that in the US alone, 7-9K people die each year as a result of medication errors, and the total cost of medication associated errors is in excess of $40B annually (https://www.ncbi.nlm.nih.gov/books/NBK519065/).

Clearly, there is an opportunity for PGx testing to lower the cost of healthcare due to mis-prescribed drugs or ineffective dosing, but more importantly, to improve patient outcomes. Our contribution of technology in these partnerships enables and encompasses higher accuracy of PGx testing, improved content, enhanced speed and scale of testing, global accessibility, and, of course, lower cost per test.

Q Phil, how do you see the Center and partnership adding to your clinical and education programs (e.g., *PreCISE-Rx* and Test2Learn) already up and running at the University of Pittsburgh?

A They are highly-synergistic. We launched the *PreCISE-Rx* (Pharmacogenomics-guided Care to Improve the Safety and Effectiveness of Medications) initiative in 2015 to implement *CYP2C19* PGx testing in our cardiac catheterization laboratory at UPMC Presbyterian Hospital. Our research has shown genotyped-guided care is associated with

"Programs which engage all stakeholders – academia, industry, clinicians and patients – to deliver real-world evidence and economic value models to policy makers, regulatory agencies and payers, are what is needed to catalyze the adoption of precision medicine"

Peter Silvester

improved outcomes. To date, over 2500 patients have received testing as a standard-of-care to tailor anti-platelet prescribing. For this targeted roll-out, we've successfully deployed novel clinical grade testing, electronic health care record integration, clinical decision support, and pharmacist-led clinical services.

Test2Learn (www.test2learn.org) is our award-winning genomics education program where providers can undergo personal genomic testing as a self-study engagement tool to advance their own education.

Taken together, these assets form a critical foundational infrastructure for PGx implementations. The Center and partnership add industry-leading omics testing expertise and technologies.

Q To what extent will the Center's bioinformatics, data analytics, and related IT capabilities advance PGx testing?

A Informatics and data analytics are core components of the initiative. The Center works closely with clinical informatics professionals both at UPMC and in the University of Pittsburgh's Clinical and Translational Science Institute (CTSI) as well as in PittPharmacy's pharmacoanalytics program. The Center's informatics expertise drives development of clinical decision support and educational solutions. Genomic data structure and reporting strictly follows standardized nomenclature advanced by Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines.

The Center has already received grant funding to apply novel machine learning and artificial intelligence approaches to predict prescribing and to identify the key clinical variables that will produce the best return of value for PGx testing. These capabilities are intended to generalize answers regarding "who to test" in the future and to expand the case for treatment and reimbursement by associating drug efficacy with newly-discovered genotypes.

Q Peter, does Thermo Fisher plan to leverage knowledge generated by the Center?

A From a business perspective, we operate under jointly developed guidelines for IP and commercialization. Both parties are interested in advancing the field, specifically in accelerating the translation of PGx into routine clinical practice.

We anticipate potential innovations in assays, methods and analytics through our partnership, which will inform and complement new design, development and/or optimization of our PGx platforms.

Q Peter, in follow-up, is Thermo Fisher looking to "clone" this model in other regions of the US or in other countries?

A Of course. Both Thermo Fisher and the University of Pittsburgh are committed to sharing our learnings to help facilitate widespread implementation of PGx into routine clinical practice in the future. Many of our partners would like to establish a global network to share best practices for implementation, and among other areas, establish economic models, clinician and patient education, standardization and guidelines. Thermo Fisher is working with ⟩

other groups on large-scale PGx programs, as well as partnerships with pharma in preemptive genomic genotyping. However, as mentioned previously, this is the first large-scale program we are implementing with an academic partner.

Q Phil, could you explain how Thermo Fisher's PGx platforms will be integrated into the Center – strategically and tactically?

A The Center will deploy Thermo Fisher 's portfolio of PGx testing solutions including the PharmacoScan™ Solution. Instrumentation has already been installed in the CAP/CLIA-accredited UPMC Genome Center. High-density population testing (4,627 markers within 1,191 genes) is expected to yield concise PGx signatures that associate with novel and known phenotypes within specific cohorts.

Research efforts using these individual and population genotypes along with drug prescribing and EHR-based phenotyping data will advance Center translational and clinical research. In the future, targets deemed actionable will undergo additional validation to enable clinical reporting within the consent framework and UPMC governance. For those targets successfully validated, discrete results will be documented in UPMC EHRs and results will be returned to patients and providers with educational support.

Q Phil, this program has both clinical and research components, which could address the precision medicine community needs for examples of real-world evidence and economic modeling to demonstrate value. Can you elaborate on some of the research questions you hope to address having a diverse 150K+ cohort?

A We are excited about the opportunity for research in a cohort of this size. Beyond the primary aims of investigating clinical utility and economics of preemptive testing (overall and within specific subpopulations defined by medication prescribing patterns), we'll also look to address additional research questions that may involve the study of extreme phenotypes to discover potential novel genotype-phenotype associations. Further, we'll work to independently confirm genotype-phenotype associations involving gene-drug pairs where data involving efficacy or adverse drug reactions

phenotypes are currently just below the current evidentiary standard for actionability.

To advance testing, we've already compared PGx arrays, whole genome sequencing, and external reference lab results to understand concordance and will continue to evaluate the performance of testing in difficult genome regions. Similarly, we'll evaluate innovative genetics services, adherence, activation, downstream research engagement, and satisfaction.

Q Follow-up: How is your program designed to provide this to the community?

A A priori economic modeling using clinical analytics data and subsequent downstream validation is planned. We further have a rich history of innovation in information technology development and interoperability solutions. The development of extensible real-world informatics and novel care models (e.g. new pharmacist-led PGx services) is expected.

Q Peter, how do you see the long-term value of the program?

A I believe this effort has the potential to transform the treatment and management of disease and will fast-track the search for the right answers at both the individual and population level. Within ten years, we anticipate broad adoption of PGx in routine clinical setting. Routine clinical utilization of PGx data in the patient EHR will help pharmacists and clinicians guide medication decisions. Potentially, PGx testing could be performed at birth and available for use throughout the patient's lifetime.

Q Phil, how do you see the long-term value of the program? Where do you see the Center in the 5- to 10-year frame?

A I believe the long-term value will be derived from the research, the economic proof-points, and the dissemination of successful implementation approaches. The

expertise brought together by this partnership, the experience-generated, and Center's leadership will drive innovation and will likely stimulate other large investments to advance PGx. Overall, I believe in five years we'll have advanced a broader adoption of PGx, particularly preemptive testing and advances in testing technology and approaches to the safe and effective return of results.

I expect we'll see that the routine application of PGx has improved medication outcomes. Emerging data suggest patients already seek genetic data that may help explain their medication experiences. Locally, we've already seen great enthusiasm during early recruitment efforts. The Center will support greater provider and patient awareness and understanding of PGx through education. Ultimately, when successful, I expect our results will have advanced policy decisions regarding how to appropriately use testing and genetic data for research and clinical care. The value of the program will therefore extend well beyond the initial (large) cohort envisioned.

JPM:
Thank you, we greatly appreciated your insights on this emerging opportunity. JoPM

Dr. Philip Empey, associate director for pharmacogenomics in the Institute for Precision Medicine and faculty in the School of Pharmacy and the Clinical and Translational Institute, is leading the Center. Dr. Empey's translational research program focuses on pharmacokinetics, drug transporters, pharmacogenomics. He teaches at the graduate level in the Schools of Pharmacy, Medicine, and Nursing and has an interest in innovative approaches to transform education.

Mr. Peter Silvester serves as Senior Vice President and President of Life Sciences Solutions at Thermo Fisher Scientific. Mr. Silvester provides executive oversight of Thermo Fisher's biosciences, genetic sciences and clinical next-generation sequencing businesses as well as life sciences finance, legal, HR, licensing and commercial supply functions. He is a Board Member of Coriell Life Sciences and Executive Board Member of Biocom.

Highlights of Program

■ Pharmacogenomics Center of Excellence – First academic-industry collaboration focused on PGx at scale

■ Accelerate translation of PGx into routine clinical practice

■ Samples from 150,000 individuals to determine the value of implementing a pre-emptive PGx approach in a large health care system

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