UCSF LAUNCHES PHARMACOGENOMICS PROGRAM TO ENHANCE SAFETY FOR GI CANCER PATIENTS

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A novel, pharmacist-led pharmacogenomics (PGx) program at University of California, San Francisco (UCSF) Health is improving safety for gastrointestinal cancer patients by personalizing chemotherapy dosing based on their genetic makeup.

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The program was developed in response to a recognized need to prevent severe drug toxicities that can arise from standard chemotherapy regimens. Aligning with UCSF's core pillars of ensuring patient safety and improving clinical outcomes, the oncology pharmacy team launched this pilot program on July 16, 2024.

The program is led by a team of UCSF oncology pharmacists, Kenric Li, Joon Hwang and Hansen Ho, in collaboration with gastrointestinal (GI) medical oncologists and pharmacogenomics experts at the UCSF School of Pharmacy.

Their work focuses on preemptive testing for dihydropyrimidine dehydrogenase (DPYD) and uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) genetic variants. These specific variants are known to cause life-threatening toxicities in patients receiving common chemotherapy agents such as fluorouracil, capecitabine and irinotecan.

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THE NEED FOR PREEMPTIVE GENETIC TESTING

Historically, the clinical impact of UGT1A1 polymorphisms and DPYD variants on the toxicity and efficacy of irinotecan and fluoropyrimidines has been well-studied.

Approximately 5% to 8% of the general population, particularly those of European descent, carry clinically significant variants in the DPYD gene that lead to reduced or absent DPD enzyme activity.[1,2]

A meta-analysis of over 13,000 patients revealed that DPYD gene variants associated with DPD deficiency had a 25.6 times higher risk of treatment-related death compared to those without

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these variants (2.3% mortality vs. 0.1%).[3]

UGT1A1*28 is the most common variant found in a significant portion of the population. Approximately 10% of North Americans are homozygous, which puts them at the highest risk. Another 30% to 40% are heterozygous.[4,5] These variants are also common in European and African populations.

Despite this, clinical guidance on when and how to use these genetic tests has not been well-defined and established in clinical practice. As a result, many patients were treated with these chemotherapy agents without prior genetic testing, putting them at significant risk for dose-limiting toxicities, diminished quality of life and, ultimately, adverse clinical outcomes. The UCSF oncology pharmacy team identified this gap as a critical area for improvement.

The recent safety announcements from the U.S. Food and Drug Administration and the American Society of Clinical Oncology reinforce the importance of testing for DPYD and UGT1A1,[6,7] which further incentivized the development of this pharmacy consultation service.

PROGRAM GOALS AND PHARMACIST-LED INTERVENTIONS

The program is guided by three clear, patient-centric goals:

▲ Enhance patient outcomes by improving the safety and efficacy of fluoropyrimidine and irinotecan treatments for GI oncology patients at UCSF.

▲ Ensure universal screening by achieving a 100% compliance rate for DPYD and UGT1A1 testing within this patient population.

▲ Expand clinical impact by extending this oncology pharmacist-led consultation service to other solid tumor programs across UCSF Health.

To achieve these goals, the pharmacists designed and implemented a workflow that integrated into the existing clinical practice.

The pharmacy team hopes to expand this pharmacist-led pharmacogenomics consultation service to other solid tumor patient populations within UCSF Health, continuing to advance patient safety and redefine what is possible in personalized cancer care.

▲ **Ordering PGx Testing:** The process begins when an oncologist places an order for a chemotherapy regimen containing fluorouracil, capecitabine or irinotecan through the electronic health record system. A PGx testing panel is automatically included as a recommended order within the treatment plan, simplifying the process for the provider.

▲ **Receiving PGx Results:** Once the test is drawn, the results are available within one to three weeks. Upon completion, the PGx results are automatically routed directly to a dedicated PGx pharmacist's inbox for immediate review.

▲ **Pharmacist Interpretation and Recommendations:** Within 48 hours of receiving the results, a pharmacist conducts a thorough assessment. The pharmacist then writes a comprehensive note in the patient's chart, which includes:

- Documentation of the patient's DPYD and UGT1A1 genotypes;
- Specific, evidence-based recommendations for chemotherapy dosing based on the results; and
- Interpretation of other relevant pharmacogenomic variants included in the panel that affect drug metabolism, such as CYP2C9, CYP2C19 and CYP2D6.

INITIAL OUTCOMES AND CLINICAL IMPACT

Since its launch in July 2024, the program has managed 48 patients, and the initial results underscore the critical need for this type of preemptive testing. The average turnaround time for the PGx panel results was two weeks.

Most notably, approximately 16% of the patients managed required chemotherapy dose adjustments based on the identification of actionable DPYD and/or UGT1A1 variants. This finding demonstrates a significant and immediate clinical impact, as these interventions have likely prevented severe toxicities.

A detailed breakdown of the genetic variants found is as follows:

▲ **DPYD Variants**:

- Normal Metabolizers (NM): 95.8% (46 patients)
- Intermediate Metabolizers (IM): 4.2% (2 patients)
- Poor Metabolizers (PM): 0% (0 patients)

▲ **UGT1A1 Variants:**

- NM: 41.6% (20 patients)
- IM: 47.9% (23 patients)
- PM: 10.4% (5 patients)

The UGT1A1 results were particularly striking, revealing that a significant portion of patients (58.3% combined) had genetic variants that may affect irinotecan metabolism, highlighting a substantial population that benefits from PGx results-guided chemotherapy dosing.

CHALLENGES, LESSONS LEARNED AND FUTURE DIRECTIONS

The implementation of the pharmacy consultation service faced some initial obstacles. A key challenge has been the long turnaround time for the full PGx panel, which has led to limited interest from oncologists. This has resulted in some oncologists preferring to select individual or "à la carte" gene tests for DPYD and UGT1A1 instead of the comprehensive panel.

Furthermore, some oncologists expressed hesitancy in interpreting the

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pharmacogenomic variants on the panel that fall outside of DPYD and UGT1A1, reinforcing the value of a pharmacy consultation service.

In addition, a number of patients had already started their chemotherapy treatment before the PGx results were finalized, a critical issue the team aims to address.

Moving forward, the team plans to identify ways to improve the utilization of PGx testing in cancer patients. Key next steps include collecting and analyzing data on clinical outcomes, such as the incidence of chemotherapy toxicities and the need for dose adjustments, as well as assessing any financial implications for patients.

The pharmacy team hopes to expand this pharmacist-led pharmacogenomics consultation service to other solid tumor patient populations within UCSF Health, continuing to advance patient safety and redefine what is possible in personalized cancer care.

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