Blake Wall, MD PGY-2
August 5th, 2022
Mentor: Joshua Motelow, MD

Title: Assessing the prevalence of pertinent pharmacogenomic variants in the PICU

Background

Pharmacogenomic variants affect levels of medications commonly used in the PICU
Pharmacogenomics (PGx) refers to the interaction of the patient's unique genetic code with the metabolism of various medications.[1-3] Genetic variants may affect levels of medications commonly used in the PICU.[1] Utilizing a knowledge of PGx may influence starting doses of medications commonly used in the PICU such as warfarin or proton pump inhibitors.[1; 4; 5] In adult cardiac intensive care units (CICU), the 98% of patients had an actionable or potentially actionable PGx results.[6] Given that the medications used in PICUs differ from those used in an adult CICU, this result may not be applicable. Limited data in pediatric populations with both targeted and broad pharmacogenomic testing indicates changes in management.[1] The prevalence of PGx variants relevant to pediatric intensivists and the utility of WGS compared to WES to call relevant PGx variants are unknown.

Specific Aims

Aim: Assess prevalence of pharmacogenomic variants pertinent in the PICU

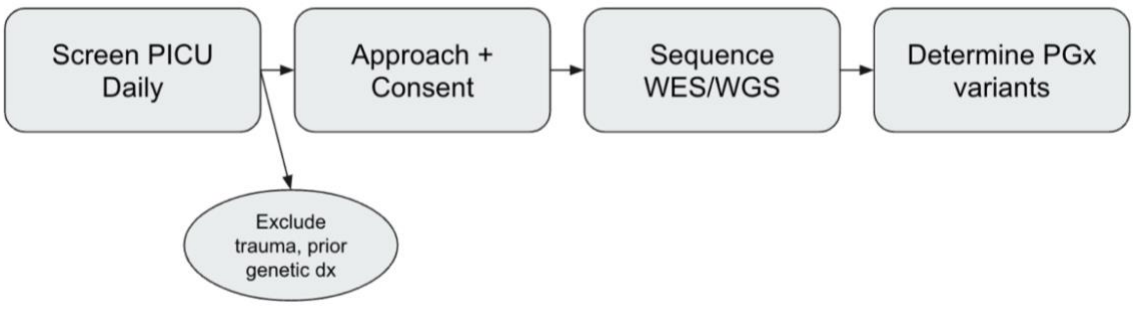
Rationale: Beyond diagnostic variants, genomic data relevant to the pediatric intensivists includes polygenic risk and pharmacogenomic variants. The prevalence of these clinically relevant data is unknown.

Hypothesis: Salient pharmacogenomic variants are common in the PICU.

Hypothesis: Children with critical illness will harbor variants that affect medications important for their care in the PICU.

Experiments: Assess overlap of pharmacogenomic variants detected by WES and affected medications received in PICU with established cohort (285 probands). Perform same analysis among newly sequenced WGS cohort (400 probands).

Approach



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Research Design: Selection and Calling of Pharmacogenomic Variants from WGS
The Pharmacogenomics Knowledgebase (PharmGKB) and PharmVar will be used for variant definitions.[7-11] We will consider star alleles in 15 genes. This is a subset of the 34 Tier 1 Very Important Pharmacogenes (VIPs) for which level 1A () variants defined by PharmGKB exist. We further filtered based on those with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines.[12] Finally, we limited genes to those with variants called by *Stargazer*.[10; 11; 13; 14] The included genes are *CACNA1S*, *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *NUDT15*, *RYR1*, *SLCO1B1*, *TPMT*, *UGT1A1*, and *VKORC1*. These genes harbor variants effecting metabolism of 79 unique drug or drug-combinations including those commonly used in the PICU such as pantoprazole, warfarin, and ondansetron.[5; 15; 16] PGx variants will be extracted from WGS data using *Stargazer*.[82; 83] Of note, *CFTR* was not included because the diagnosis and treatment of cystic fibrosis would likely precede PICU admission.[17]

Research Design: Selection and Calling of Pharmacogenomic Variants from WES
To determine genes and variants detectable by WES, we will follow the methodology described by Lanillos and colleagues.[17] *CYP2C19, CYP3A5, VKORC1,* and *CYP2D6* were not considered in WES data because major actionable alleles are absent from exome data or are CNVs which are challenging to identify in exome data. We assessed the remaining 11 genes (*CACNA1S*, *CYP2B6*, *CYP2C9*, *CYP4F2*, *DPYD*, *G6PD*, *NUDT15*, *RYR1*, *SLCO1B1*, *TPMT*, and *UGT1A1*). This will result in approximately 280 actionable alleles. Actionable alleles will be extracted using freely available code provided by Lanillos and colleagues[17] to identify relevant haplotypes and diplotypes.

Research Design: Medication Administration Data
Medication administration records will be obtained for all probands in this study to identify overlap between medications ordered and clinically relevant PGx variants.

Research Design: Descriptive Statistics
We will describe the overlap of actionable PGx variants and pertinent administered medications in the WES and WGS cohorts. We will provide case presentations of children with critical illness and the means by which PGx variants could have affected care.

Study Subjects
Children with critical illness who are currently in the PICU or have previously been admitted to the PICU. Exclusion criteria is diagnosis of trauma or prior genetic diagnosis.

Confidentiality of Study Data
All data saved on an encrypted device. Data storage and analysis will be performed on an encrypted machine.

Potential Conflict of Interest

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No potential conflicts of interest.

Location of the Study
This is a single-center study. All data will be obtained from the Columbia University Irving Medical Center electronic medical records.

Compensation of Subjects
No compensation will be provided to study subjects.

Potential Challenges, Limitations, and Alternatives
The proposed implementation is unlikely to return results in time to affect care in the PICU. Future directions will focus on (1) rapid return of results, (2) determination of appropriate clinical intervention given clinical information from PGx, and (3) a clinical trial to assess the efficacy of appropriate interventions.

Consideration of Biological Variables, Rigor and Reproducibility, Expected Outcomes, Power Analysis
Both males and females are included in this study. Patients will be included in this study regardless of expected survival. There is no randomization, and the study is unblinded. Descriptive statistics will be used to draw conclusions from the overlap of the actionable PGx variants and pertinent administered medications.

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