Identifying genetic predictors of perioperative opioid use through a prospective cohort of genotyped and phenotyped surgical patients: The Michigan Genomics Initiative

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Introduction: Although multiple psychosocial factors for substance use and dependence have been identified,[1] many genomic studies in this area have been relatively small, limiting their ability to identify additional genetic contributors to studied phenotypes.[2-6] There is also a paucity of genetic studies of prescription opioid use disorders. Consequently, there is a pressing need for large-scale, unbiased, hypothesis-generating genome-wide association studies (GWAS) in this area.

Methods: The Michigan Genomics Initiative is a single-center biorepository effort recruiting participants for future genetic studies of health and treatment outcomes. Elective surgery patients comprise the majority of the cohort. Participants undergo collection of perioperative blood samples and are genotyped using a customized HumanCoreExome GWAS and exome array. Imputation yields dense mapping at over 7.7M common genetic markers. Additionally, participants complete a set of validated patient-reported outcomes measures, including measures of pain severity, 2011 Fibromyalgia Survey Criteria, depression, anxiety, and physical function. All genotyped subjects (more than 42,000 at present) have linked phenotype records containing longitudinal institutional clinical data and national prescription fulfillment data.

Planned Analyses: Three separate GWAS will evaluate the genetic basis for perioperative opioid use: (1) *Preoperative use*: We will study opioid use in the care-seeking population by comparing preoperative opioid-taking cases and non-opioid-taking controls. (2) *New persistent postoperative use*: As many as 6% of opioid-naïve patients provided with routine postoperative opioid prescriptions are still using opioids months after surgery.[7-10] We will examine the genetic basis for this phenotype by comparing opioid-naïve subjects who continue taking opioids 3-6 months after surgery with those who do not progress to persistent use. (3) *Immediate postoperative use*: Using our clinical database, we will assess genetic contributors to postoperative opioid requirements.

Discussion: With sample sizes considerably larger than any prior genomic studies, this initiative aims to advance our understanding of the genetics of perioperative opioid use.