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## **Heritability Estimate of Postoperative Total Morphine Equivalents in New Persistent Opioid Users**

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Excess opioid prescriptions following surgery represents an important source of prescription opioid misuse among opioid-naïve individuals and plays an important role in the opioid epidemic. The quantity of opioids prescribed following common surgeries varies widely, and often, opioids are overprescribed. Many patients continue to use opioids more than 90 days post-surgery for poorly known reasons. Further, the genetic component of persistent postoperative opioid use is unknown. Here, we estimated the array heritability of total morphine milligram equivalents (MME) in 2,368 opioid-naïve non-Hispanic white patients from the Kaiser Permanente Northern California Genetic Epidemiology Research in Adult Health and Aging (GERA) cohort, who continued to use opioids more than 90 days after surgery. The GERA cohort includes both genome-wide genotype data and extensive clinical and pharmacy data, captured through electronic health records, with long periods of follow-up. For each patient, the total MME filled between 91 to 365 days post-surgery was assessed, based on the number of opioid prescription fills, days supplied, and opioid drug. The median (1st - 3rd quartiles) postoperative total MME was 950.0 (300.0 - 2,400.0). To estimate the heritability of postoperative total MME based on genome-wide array data of unrelated individuals, we used a linkage disequilibrium (LD) Score regression method. LD Score regression analysis resulted in a heritability estimate of 0.33 (SE=0.22) for postoperative total MME. These findings suggest an important genetic component for persistent postoperative opioid use among opioid-naïve patients who continue to use opioids more than 90 days post-surgery.