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**The impact of social and genetic risk factors on the onset of comorbid problems in persons with substance use disorders.**

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Persons with substance use disorders (SUD) often suffer from multiple additional comorbidities, including other psychiatric conditions and physical health problems. Researchers have explored this overlap in electronic health records (EHR) using phenome wide association studies (PheWAS) to characterize the vast pleiotropic impact of genetic risk for SUD, which could reflect both a shared genetic liability (biological pleiotropy) or a causal chain of events (mediated pleiotropy). These PheWAS have shown that the impact of genetic risk for SUD-related traits span all bodily systems and have serious implications for public health.

In the current analysis, we move beyond the focus of lifetime diagnosis in PheWAS to characterize whether different aspects of genetic risk, in the form of polygenic scores (PGS), are associated with more rapid onset of comorbid diagnoses appearing in their EHR after the first record of SUD. Harnessing the longitudinal nature of the All of Us Research Programs' EHR data, we will explore whether PGSs for psychiatric and substance use disorders, social determinants of health, and lifestyle factors are associated with earlier onset of these comorbidities by performing a phenome-wide survival analysis. Our analyses will inform the degree to which genetic and environmental risk factors are important in the progression of SUD related medical problems (e.g., suicidal thoughts and behaviors, drug induced psychosis, viral hepatitis, etc.).