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RealOmics-Centered Translational Pipeline for Drug Repurposing in Methamphetamine Use Disorder

Methamphetamine use disorder (MUD) remains a major public health challenge, with no FDA approved pharmacotherapies and limited success from traditional single target drug discovery approaches. To address this gap, we developed an integrated translational drug repurposing pipeline that leverages large scale molecular and clinical data to efficiently bridge gene discovery and clinical validation. Multi omic signals—including genetic, transcriptomic, epigenomic, and proteomic data—were integrated across substance use disorders using the Multiplex Embedding of Networks for Team based Omics Research (MENTOR) framework, identifying mechanistically coherent gene modules comprising 688 genes.

We applied the RTI RealOmics platform to systematically link and prioritize disease implicated genes to existing FDA approved compounds, generating actionable gene–compound pairs for translational prioritization. Of the 688 MENTOR identified genes, 107 were targeted by at least one FDA approved drug and yielding a total of 716 unique compounds. Gene–compound pairs were annotated with pharmacologic, safety, and translational feasibility features relevant to EHR based target trial emulation and randomized clinical trials, including bioavailability, specificity, pharmacodynamics, and molecular mechanism. After applying prioritization filters, 85 compounds emerged as high confidence repurposing candidates, including agents with prior evidence in MUD (prazosin), supporting the validity of our translational pipeline.

RealOmics identified multiple novel gene–compound pairs supported by convergent multi omic evidence and, for select targets, robust preclinical validation. To assess real world translational feasibility, we evaluated prescribing prevalence and observed that at least two of the top eight candidates have been dispensed to more than 380,000 and 94,000 unique patients, in the Veteran Aging Cohort Study National database, demonstrating the feasibility of EHR based target trial emulation. Ongoing work will prioritize EHR based target trial emulation, with top candidates advancing toward prospective early phase clinical trials. Together, this framework establishes RealOmics as a scalable bridge from systems biology to causal clinical inference and experimental validation for MUD and related substance use disorders.

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