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Toward Precision Medicine in Addiction Treatment

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Advances in technologies used to analyze the sequence and structure of DNA have pushed medicine to the threshold of a new era of precision medicine. Instead of attacking cancers, for instance, using the hit-or-miss therapies of previous decades, therapies in many cases can now be more precisely targeted based on the genetics of the individual or the tumor. Ongoing research identifying specific gene variants underlying an individual's unique response to substances of abuse is setting the stage for this type of precision medicine in the treatment of substance use disorders as well.

Among the new technologies enabling a precision medicine approach to addiction are genome-wide association studies, which rapidly scan complete DNA from many individuals to find variations associated with specific conditions. For example, recent NIDA-funded research using this technology identified a gene variant, or single-nucleotide polymorphism (SNP), associated with therapeutic methadone dose in African American but not European American opioid-dependent individuals.[1] Methadone is a highly effective treatment for opioid addiction when it is used at the correct dose, but individuals vary widely in their response to and metabolism of this medication. This results in significant variability in the effective dose, and finding the right dose for an individual patient can be time-consuming. Too low a dose may fail to prevent relapse to opioids, whereas too high a dose may be dangerous, and until now there have been no biomarkers available to guide the physician in establishing the right dose.

The SNP (rs73568641) identified in this study[1] lies upstream of a gene that codes for the mu-opioid receptor OPRM1, although thus far the mechanism by which the SNP affects an individual's response to opioids is unknown. This opioid receptor mediates both the addictive and pain-relieving properties of opioids, and the researchers found that this SNP has implications beyond addiction treatment. The SNP was found to be associated with not only higher effective dose of methadone for addiction treatment but also, in a separate study sample of children, with a higher dose of morphine necessary to provide post-surgical analgesia, again specifically in African Americans. As is now well known, pain and addiction have become closely intertwined in a medical system that still largely relies on opioids for treating many pain conditions. Thus this finding has major implications not only for precision opioid addiction treatment but also for the precision treatment of pain.

Smoking cessation is also poised to benefit from a precision medicine approach. Research over the past several years has identified variants in many genes that correlate with smoking-related variables, including age at first use, cessation success, risk of relapse after quitting, and responsiveness to treatment. This research is beginning to provide biomarkers that can be used to help guide treatment decisions.

For example, specific gene variants related to the functioning of the α5 nicotinic cholinergic receptor (CHRNA5) predict individuals smoking more heavily, quitting later, and being more likely to relapse than other individuals. In one study, those with the high-risk gene variants were three times more likely to respond to cessation pharmacotherapies than those without these variants.[2] In 2014, the same researchers found something similar for the gene *CYP2A6*, which codes for an enzyme that metabolizes nicotine in the body.[3] Different variants render nicotine inactive in the body at different rates, and people who metabolize nicotine more quickly have been shown to smoke more cigarettes per day and to have poorer success at quitting than those with slower nicotine metabolism. The researchers found that nicotine replacement therapy was specifically effective at improving success in quitting, as measured by reduction in relapse risk over 90 days, for fast metabolizers, whereas it had no effect on slow metabolizers. On the other hand, patients' response to bupropion was not affected by their *CYP2A6* genotype.

Nicotine metabolism as mediated by *CYP2A6* has lately been linked to specific changes in the brain associated with nicotine addiction. Recently, researchers at NIDA's Intramural Research Program and the University of Toronto found that in smokers, but not nonsmokers, *CYP2A6* variants correlated with differences in functional connectivity strength in the dorsal anterior cingulate cortex and ventral striatum.[4] The fact that these differences only appeared in smokers supports the idea that smoking causes connectivity changes in the brain and suggests that these changes are affected by the concentration of nicotine, which is determined by the individual's rate of nicotine metabolism. These findings obviously have important implications for predicting smoking behavior and for designing individualized treatments for smoking cessation.

Precision medicine aims not only to produce better targeted treatments but also to produce better targeted prevention interventions. Using previously compiled information on a large set of SNPs with the greatest association with success at quitting smoking, NIDA-funded researchers compiled a "polygenic score"—an estimate of the combined likelihood

of quit success conferred by multiple gene variants—for 556 young adults and found an association between their scores and responsiveness to a smoking prevention intervention received in elementary-school.[5] Overall age of smoking initiation was later in young adults who had received the intervention than in those who did not, but the difference was greatest in those with the lowest inherited risk for tobacco use and nicotine addiction, as indicated by a high polygenic score. This gene-by-environment interaction effect suggested that genetic protective factors may be enhanced by enriched environments such as those provided by a school-based intervention.

One of the biggest roadblocks to developing a precision medicine approach involves the imbalance between our present ability to gather data and our ability to analyze it. Thanks to advances in DNA sequencing technology, for example, it is now less expensive to sequence whole genomes than it is to analyze the data produced. New Big Data initiatives like NIDA's Addictome Project are intended to develop the needed data and analytics infrastructure to address this bottleneck.[6] With such tools, and as more and more genetic variants relevant to addiction and related processes such as pain are identified, we can move closer to a world in which prevention and treatment of substance use disorders can be targeted in a truly individualized, personalized fashion to maximize successful prevention and treatment outcomes.

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