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Embracing Reward Deficiency Syndrome (RDS) Solution System: A Genomic Thrust

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The mysteries and underlying causes of addictive disorders have spawned a number of important questions which still plague researchers and treatment professionals alike. What populations are susceptible to addictive disorders based upon genetic predisposition? Why are they more susceptible than others? What considerations or adjustments must be made to care plans of certain individuals to maximize their opportunity for recovery?

The Brain Reward Cascade (BRC) first proposed by Blum & Kozlowski in 1989 [1] is an interaction of neurotransmitters and their respective genes to control the amount of dopamine released within the brain. Any variations within this pathway, whether genetic or environmental (epigenetic) [2], may result in addictive behaviors or RDS, which was coined to define addictive behaviors and their genetic components [3].

While there are many studies claiming a genetic association with RDS behavior, not all are scientifically accurate. Another issue in RDS treatment involves 1) compliance or adherence to prescribed treatment medications during treatment; 2) remaining abstinent from all drugs of abuse during treatment. While there is a plethora of very positive experiments involving thousands of studies for many candidate gene associations with all RDS behaviors, there are also negative results [4]. Currently, a number of companies have entered the genetic testing arena in the addiction and pain industrial space claiming "personalized care" [5]. However, we believe these companies have not done their homework in a scientific manner.

These issues include exaggerated claims such as stating that their genetic test is 74% predictive based on only one gene (DRD2) not their panel of genes claimed to be tested [6]; claims suggesting that patient's results are compared to population controls [7]; selection of genes that may be involved in risky behavior but they do not utilize the correct variant in their tests or use very rare variants that do not truly prove addiction risk [8]; never performed research to show whether their "genetic test" significantly predicts anything let alone addiction risk or any associated behaviors [5].

In an attempt to overcome these pitfalls our laboratory has successfully developed the first Genetic Addiction Risk Score ($GARS_{Dx}$)" in conjunction with Dominion Diagnostics, LLC. Certainly genetic risk stratification for RDS prior to or upon entry into chemical dependency programs can provide information central to the implementation of appropriate treatment and relapse prevention [9]. When we selected 10 genes with appropriate variants, a statistically significant association between the ASI- Media Version -alcohol and drug severity scores and $GARS_{Dx}$ was found. While a complete detail of this research is to be submitted elsewhere, in 273 patients attending seven diverse treatment centers the $GARS_{Dx}$ predicted both high alcohol and drug severity as measured by ASI-Media version [10].

Drug abuse and adherence to treatment medications, was investigated in a large sample of patients from chemical dependency programs, using Comprehensive Analysis of Reported Drugs (CARD) data. This *post-hoc* retrospective observational study of data collected in 2010 - 2011 from 10,570 patients reduced to a total

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of 2,919 patients with at least one prescribed treatment medication has been published in PLOSONE. Test results from the first and last analyzed urine samples (5,838 specimens) were used as well as a subset longitudinal analysis [11].

One unpublished important finding related to buprenorphine/naloxone in opiate treatment programs related to both compliance and abstinence issues. Buprenorphine/naloxone was 87.4% [n=1135] compliant. In contrast, abstinence during treatment with Buprenorphine/naloxone was 52.7% [n=609]. In a subset of 17.5% (n=510) a longitudinal analysis of all urine samples revealed significant improvement in compliance and abstinence over the course of treatment. There was a significant reduction of opiate abuse in this population. A promising finding that may have impact on the current FDA 100 patient restriction [12].

Based on this seminal research and unlike other existing genetic tests we are poised to launch the first proven and validated genetic addiction risk score that will have important clinical benefits including medical monitoring for better clinical outcome and pharmaceutical response and assessment of RDS risk [13]. Clinically, the future is here and the treatment of chronic addiction and pain depends on scientifically sound appropriate early genetic risk diagnosis and drug urine screening leading to real personalized care of the patient. Finally, we question the wisdom of utilizing FDA approved Medical Assisted Treatment (MAT) in the long term based on blocking dopaminergic function, instead of dopamine agonistic therapy (DAP) [14,15] as suggested by recent work by many [16-20] involving resting state functional connectivity, for the treatment of all associated RDS behaviors both substance related and non-substance related [21].

Aknowledgement

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