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Letter to Editor

# "Personalized Addiction Medicine" May Take Us to the Promised-Land: Coupling Neurogenetic Risk and Nutrigenomic Dopaminergic Activation

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We are entering the era of genomic medicine and neuroimaging as it relates to addiction a subset of Reward Deficiency Syndrome (RDS) [1]. Previously we discussed the importance of providing a common rubric to identify all addictive behaviors drug and non-drug related and potential genetic antecedents [2]. There is a global threat of many addictive like behaviors in all known societies especially as reflected in the legal iatrogenic opioid prescription dilemma [3]. The statistics on heroin fatalities alone has become staggering in the United Sates (see table 1).

Keeping this in mind there is a current need for early diagnosis through genetic testing and the incorporation of inducing "dopamine homeostasis" for long-term therapy. The blocking of dopamine release at the reward center in the brain is favored by the current approved Federal Drug Administration (FDA) list for the treatment of Alcoholism, Heroin dependence and Smoking cessation [4]. However, it can be argued that by doing so in the long-term, the brain is being hijacked of its required dopamine supply, and this in turn can lead to mood changes including suicide ideation. One of us (MSG) proposed the utilization of a powerful D2 agonist known as Bromocyrptine to treat psychostimulant abuse in the 80's but chronic utilization induced a down –regulation of D2 receptors [5]. Many years after this observation it has been very difficult to find an agent that would activate the D2 receptors without subsequent reduction of dopaminergic function [6]. Understanding this conundrum can we find a better solution providing real recovery eliminating unnatural "white knuckle sobriety" [7].

In 2005 Blum received the first USA patent on Nutrigenomics and RDS treatment. This was awarded on the basis of our earlier work showing anti-addiction activity of a nutraceutical consisting of amino-acid precursors and enkephalinase inhibition properties and our discovery of the first polymorphic gene Dopamine D2 Receptor Gene [DRD2] to associate with sever alcoholism [8].

**Drug-poisoning Deaths Involving Heroin:**

**United States, 2000–2013**

**Key findings: Data from the National Vital Statistics System**

**(Mortality)**

**●From 2000 through 2013,the age-adjusted rate for drug-poisoning deaths involving heroin nearly quadrupled from 0.7 deaths per 100,000 in 2000**

**to 2.7 deaths per 100,000 in 2013. Most of the increase occurred after 2010.**

**●The number of drug-poisoning deaths involving heroin was nearly four times higher for men (6,525 deaths)than women (1,732 deaths) in**

**2013.**

**●In 2000, non-Hispanic black persons aged 45–64 had the highest rate for drug-poisoning deaths involving heroin (2.0 per 100,000). In 2013, non-**

**Hispanic white persons aged 18–44 had the highest rate (7.0 per 100,000).**

**●From 2000 through 2013,the age-adjusted rate for drug-poisoning deaths involving heroin increased for all regions of the country, with the greatest increase seen in the Midwest.**

Source: **March 2015**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Centers for Disease Control and Prevention**

**National Center for Health Statistics**

Prior to the later genetic finding we developed the concept of Brain Reward Cascade (BRC) which continues to act as a blue-print for stratification of addiction risk through neurogentics [9]. Many others have continued to provide clear evidence for the role of neurotransmitters in the reward of the brain [10-12] and the importance of dopamine release at specific brain

loci leading to pleasure and anti-stress. As discussed earlier, in 1996 Blum et al also coined the term "Reward Deficiency Syndrome (RDS)" to define a common genetic rubric for both substance and non-substance related addictive behaviors [1,13]. Following many reiterations Blum and associates utilized polymorphic targets of a number of reward genes (serotonergic, Opioidergic, GABAergic and Dopaminergic) to customize KB220 [Neuroadaptogen- amino-acid therapy (NAAT)] by specific algorithms.

Identifying 1,000 obese subjects in the Netherlands a subsequent small subset was administered various KB220 formulae customized according to respective DNA polymorphisms (e.g. serotonin genetic deficits signaled increases in tryptophan etc.). As such individualized dopamine agonist nutrigenomics was utilized differentially for each subject. This novel approach translated to significant decreases in both Body Mass Index (BMI) and weight in pounds [14]. This was followed up in the USA with similar significant effects [15,16]. One very important finding from these and other experiments revealed that carriers of the DRD2 A1 allele (rs1800497) were more responsive to dopamine agonist modalities than carriers of the DRD2 A2 allele (normal compliment of D2 receptor availability) [14,17].

Following these experiments in conjunction with the Institute of Behavioral Genetics, Colorado University, at Boulder, Blum and associates have been successfully developing a panel of genes known as "Genetic Addiction Risk Score ($GARS_{PreDX}$).™ When they selected 10 genes with appropriate variants, a statistically significant association between the ASI- Media Version -alcohol and drug severity scores and $GARS_{PreDX}$™ was found. This observation was found in 273 patients attending seven diverse treatment centers across the United Sates. The selection of specific SNPs seemed crucial because any deviation in altered selection resulted in non-significant association with the ASI-Media version severity scores for both alcohol and drugs.

Independently, it was observed that the Neuroadaptagen-------(rsFMRI) in a putative network that included the dorsal anterior cingulate, medial frontal gyrus, nucleus accumbens, posterior cingulate, occipital cortical areas, and cerebellum[18]. In other unpublished rat work we show that KB220Z significantly activates, above placebo, seed regions of interest including the left nucleus accumbens, cingulate gyrus, anterior thalamic nuclei, hippocampus, pre-limbic and infra-limbic loci. This response induced by KB220Z demonstrates significant functional connectivity, increased brain volume recruitment and enhanced dopaminergic functionality across the brain reward circuitry. This robust yet selective response implies clinical relevance but more research is required.

Considering increase of street use heroin and subsequent fatalities recently noted, and the initiation of prescribing highly addictive opioid pain medications to the multitude of individuals presenting to pain clinics and subsequent induction of iatrogenic legal addiction to for example OxyContin®, we must find better solutions. Indeed, initial genetic screening should help identify potential at risk individuals providing possible alternatives to treatment [19].

We are now paused to propose a Reward Deficiency System Solution™ that promotes early identification and stratification of risk alleles by utilizing $GARS_{PreDX}$ [20] allowing for customized nutrigenomic targeting of these risk alleles by altering NAAT ingredients as an algorithmic function of carrying these polymorphic DNA –SNPS as well as brain electrotherapy, potentially yielding the first ever nutrigenomic solution for addiction and pain. While we are not in the promised -land yet but with continued sophisticated research by the scientific community someday it will indeed take us there.

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## Conflict of Interest

Kenneth Blum, PhD is the holder of a number of US and Foreign patents issued and pending related to Nutrigenomics and Nutraceuticals. Through IGENE LLC., Dr. Blum exclusively licensed the Genetic Addiction Risk Score (GARS)™ to Dominion Diagnostics, LLC. Dr. Blum is also an officer and stock holder of IGENE, LLC and is a paid consultant of Dominion Diagnostics, LLC, IGENE, and Malibu Recovery Center. Dr. Blum is a paid consultant of Dominion Diagnostics, IGENE, Malibu Beach Recovery Center, RDSolutions, and Victory Nutrition International. Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC and is Chief Scientific Advisor of Dominion Diagnostics, LLC. Dr. Gold is a paid consultant by Rivermend Health LLC. Atlanta, GA.

**Contribution of Authors:** The authors equally contributed.

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