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Editorial

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Addiction Treatment in America: After Money or Aftercare?

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Abstract

There are approximately 14,500 clinics and programs in America that provide treatment for all types of addictive behaviors we call "Reward Deficiency Syndrome (RDS)". While most of these have good intentions to provide needed help to the victims of RDS, we propose herein that most of their efforts, especially during periods of aftercare, are not based on the existing scientific evidence. We use "aftercare" to refer to any form of program or therapy following primary treatment including 12-Step programs. Very few programs actually provide any evidenced-based treatment approaches during this most vulnerable period in recovery. In this trieste we are suggesting that a hypodopaminergic trait (genetic) and/or state (epigenetic) is critical in terms of continued motivation to use/abuse of alcohol or other drugs and can lead to relapse. While there is evidence for the approved FDA drugs to treat drug addiction (e.g. alcohol, opiates, nicotine) these drugs favor a short-term benefit by blocking dopamine. We argue instead for the utilization of long-term benefits that induce "dopamine homeostasis", or in simpler terms "normalcy". We suggest that this could be accomplished through a number of holistic modalities including, but not limited to, dopamine-boosting diets, hyper-oxygenation, heavy metal detoxification, exercise, meditation, yoga, and most importantly, brain neurotransmitter balancing with nutraceuticals such as KB220 variants. We embrace 12-step programs and fellowships but not as a stand-alone modality, especially during aftercare. We also provide some scientific basis for why resting state functional connectivity (rsfMRI) is so important and may be the cornerstone in terms of how to treat RDS. We postulate that since drugs, food, smoking, gambling, and even compulsive sexual behavior could reduce rsfMRI then modalities (following required research), that can restore this impaired cross talk between various brain regions (e.g. Nucleus accumbens, cingulate gyrus, hippocampus etc.) should be incorporated into the aftercare plan in all treatment programs in America. Anything less will ultimately lead to the so called "revolving door" for as many as 90% of treatment participants.

Introduction

Addiction to psychoactive drugs poses a significant threat to the health, social, and economic fabric of communities, families, and nations. The number of substance users is staggering. Global estimates suggest the existence of smokers numbering 1.3 billion, 2 billion alcohol users, and 185 million abusers of other substances [1]. These numbers emphasize the urgent need to develop novel treatments for addiction and advanced methods to evaluate the efficacy of

potential therapeutic agents in the United Sates as well as the rest of the world.

In the United Sates alone there are approximately 14,500 clinics and programs dedicated to providing treatment for Reward Deficiency Syndrome (RDS), for which a definition is to be published (2016) in SAGE Encyclopedia of Abnormal Psychology. With all due respect, we raise the question as to what percentage of these clinics and programs provide meaningful treatment not only during actual attendance of the onsite treatment phase (in-patient, intensive outpatient, opioid replacement programs, outpatient etc.) but during the arduous recovery and aftercare period.

Brief History of Drug Abuse in America

Briefly, drug addiction in America has been considered to be motivated by greed (money), man's desire to escape from his world, and the search for the magic chemical that could help his escape. This has led even to how the pilgrims and every generation has experienced the problems that are inherent with all mind-altering substances. America has always had a battle with whether drug abuse is a health-care concern or a problem for the criminal justice system. Early on, opiate laced alcohol "medicines" gained wide acceptance, as well as use and abuse, in the first half of the 20th century, especially by females.

"Patent medicines", were a concern to the government because of their addictive nature and also a concern to the medical community since they were beginning to establish themselves as the profession of choice for health issues. These two factors were important motivation for the establishment of the Pure Food & Drug Act and the Harrison Act, which made it illegal to import, sell, or possess opiates unless it was under medical auspices. Until 1928, physicians were the only ones who could prescribe opiates, and they could prescribe them for any illness, including opiate addiction. However, in 1928, the Supreme Court outlawed the prescribing of opiates to treat addiction, and we had the start of the development of other methods to treat addiction.

After opiates became government regulated, the Federal Prison System established two prisons in the U. S. for those persons that were addicted to narcotics (defined as opiates, cocaine, and marijuana). These penitentiaries were known as narcotic farms and were also open to non-incarcerated patients. However, only about 20% of their client base was from outside the prison. Addicts were viewed as "experts in malingering, chicanery, and subterfuge" who required a carefully regulated detoxification and a lengthy period of rehabilitation in a controlled residential setting.

From 1935 (the year that Alcoholics Anonymous was founded) to the mid 1950s, treatment consisted of medical detoxification using codeine for mild addictions, subcutaneous morphine and methadone for more serious addictions, as well as group therapy, psychotherapy, and rehabilitative experiences generally involving an effort to instill good work habits and a sense of responsibility. In 1947 Addicts Anonymous, later named Narcotics Anonymous emerged within communities to support addicts' efforts to stay clean through the mutual support of addicts by addicts, in a structure that was a combination of the spiritual teachings and secular lessons in responsibility. By the mid 50s, New York City and Chicago had provided a full range of medical and psychosocial treatments for addicts within their state psychiatric hospitals. With the lack of success and the outspoken publicity from drug addicts who protested the ECT (electroconvulsive therapy routinely prescribed to anyone withdrawing from alcohol and other drugs), the psychiatric community began to shun the delivery of their services to addicts, and until the 1970s the mental health industry did not consider addiction treatment part of their professional "expertise", Through these early beginnings and subsequent new laws including laws involving the utilization of methadone and buprenorphine/naloxone combinations, the current addiction treatment in America was born.

In addition to opiate-like drugs, there were cocaine-based drugs that certainly added profits to the "patent medicines" and the industry, and without doubt, increased drug abuse across the American landscape. Interestingly, chewing coca leaves (a mild stimulant) had been utilized by many worldwide cultures, especially in the Andes, for over a thousand years. However, it had never become popular in the United States until the late 70's early 80's.

Historically, in 1860 cocaine was isolated in a pure form and in 1883 it was used to combat fatigue in Bavarian soldiers. This use was noted by Sigmund Freud who began to use and then later abuse cocaine to help treat his depression and neurotic symptoms. Freud embraced its use in psychiatry, but after a few years there were an increasing number of reports of compulsive use, drug abuse, addiction, and undesirable side effects to cocaine. It's use increased when information on cocaine hit the patent medicine industry in the United Sates, and the substance was touted as even a cure for heroin addiction. Cocaine became very popular especially when it developed into a cheap form called crack. As such it has been considered a major problem by many as the "golden age" of euphoria gained popularity in both urban and rural communities across America.

What about cannabis? Around the 1930's heroin was the drug most Americans focused on as being a taboo, but marijuana was about to share that distinction. Marijuana was being labeled the "devil drug", the "assassin of youth", and the "weed of madness". However, it has been well documented as early as 1629 that marijuana (cannabis) was used by America's early colonists in New England. Even George Washington used it for relief from agonizing pain.

Around the 1800's, Parke-Davis and Squibb produced tincture of cannabis for the family pharmacist to dispense. While as a medicine it was not very popular, marijuana had its devotees as a recreational drug. By 1885 every major American city had its illegal hashish clubs catering to well-to-do clientele.

In the beginning of the twentieth century, marijuana was connected to racial groups and drug abusers. Abuse of marijuana wasn't actually looked at in these early days, but special interests wanted to stigmatize marijuana in order to keep it from interfering with more profitable and more addictive drugs like the opiates run by cartels and organized crime. In fact, before World War II, marijuana literature made

the terms "drug abuse" and "addiction" part of marijuana folklore. Today we are struggling throughout the United Sates with the movement toward legalization not only for medical reasons but for legal recreational use.

Current Concerns of Treatment of Reward Deficiency (Addiction) in America

While we are cognizant of the importance of incorporating FDA approved medical assisted treatment modalities (MAT) that could benefit patients in the short–term, we are concerned about their long-term utilization. Certainly, even on a short-term basis, many patients requiring this medical support are not obtaining treatment because of multiple factors: lack of insurance and the inability to self-pay, unenforceable parity laws, and Federal restrictions for the utilization of buprenorphine/naloxone combinations. These restrictions have been discussed by many, especially from the view of the notable American Society of Addiction Medicine (ASAM) physicians. Any additional lifting of restrictions should follow the evolution of systems that reward and document competency in the integration of prescription medication into treatment, treatment systems, and recovery.

We are aware of the fact that the U.S. has the highest rate of opioid use (*e.g.* morphine) in the world: US 56%; Europe 28%; Canada 6%; Australia/New Zealand 3%; Japan 0.08%; Africa 0.02% and other 6%. [2]. From 2004 to 2011 there has been an 183% increase of hospitalizations for prescription opioid drug use as well as a rise in heroin hospitalizations (700,000 in 2013). The list of FDA approved pharmaceuticals used to treat addiction seems incomplete as it has been limited to those drugs for alcohol, opiates, and nicotine with no approved treatment drugs for psychostimulants, cannabis, or even prescription benzodiazepines. Even more significant, all the approved drugs favor *blocking* dopamine rather than providing "*dopamine homeostasis*" [3].

We are further cognizant that all addictive substances and behaviors (drugs, food, gambling, sex, etc.) share common mechanisms involving dopamine dynamics that are ultimately affected by our genetic code (DNA) and subsequent expression via mRNA transcription as a function of our environment and neuroepigenetics. Thus, expression of the many genes involved in the net release of dopamine must work in concert to provide the brain reward circuitry with just the right amount/function of dopamine throughout our brain. Too little leads to depression while too much leads to schizophrenia.

Importantly, all the providers in this field must understand both neurogenetic and neuroepigentic links to the addictive process and vulnerability/resilience of the patient [4-7]. Without this knowledge by the clinician we are concerned that many treatment centers are not providing adequate care.

Addiction is typically characterized as a disease by experts and government officials including ASAM. Unlike most known diseases, the treatment of addiction in many cases is not based on scientific evidence, nor is it required to be provided by people with any medical education-let alone by actual physicians-according to a well-documented report [8].

In 2008 a 586-page tome published by Columbia University National Center on Addiction and Substance Abuse (CASA) [no longer affiliated with Columbia University], was based on large surveys of treatment providers, people who suffer from addiction, and the general public, as well as a review of more than 7,000 publications on addiction. While updates have been published especially in various books including Joseph Califano's work on adolescents [9], many of the details of the earlier report remain significant. In essence it was found that: 14 states don't require licensing; six states require addiction counselors to have a minimum of a bachelor's degree; one state requires a master's degree; no states have a standard of care; 50% of all patients in the system are referred by the criminal justice system; failure of treatment leads to prison for the patient; and the lack of professional training of most treatment providers means that severity is rarely assessed adequately. In line with what we now know about even the genetics of addiction, that is, carrying certain polymorphisms (*e.g.* dopamine D2 receptor A1 allele present in over 100 million Americans) puts an individual at risk, the CASA report suggests that 16% of the U.S. population suffers from addiction (this includes cigarette smokers) and that an additional 32% are engaged in "risky" substance use.

We agree with the CASA report that most people without definitive diagnosis - which in the future may be avoided by genetic diagnosis for risky behaviors associated with RDS [10] - are therefore slotted into one-size-fits-all programs, typically based on the 12 steps of Alcoholics/Narcotics Anonymous. Since the basic tenant of the self-help programs do not endorse or embrace the use of medications like methadone or buprenorphine to treat opioid addictions or naltrexone (reVia, Vivitrol), both directors of NIDA (Volkow) and NIAAA (Koob) recently argued that these FDA approved drugs work but are underutilized.

While addictive behavior is a complex brain disorder, it can involve virtually every aspect of an individual's functioning - in the family, at work and school, and in the community. It is noteworthy, that recently Blum & Gold and associates [11] pointed out the molecular neurobiology of each step in the 12 step program showing both positive and negative aspects for not only the patient but the provider as well, embracing its utilization for most in recovery. However, it cannot be utilized in isolation, especially in those having high risk types of behaviors including drugs, food, smoking, hypersexuality and gaming due in part to faulty or variant genes and epigenetic hot spots.

Treatment for drug abuse and addiction is delivered in many different settings using a variety of behavioral and pharmacological approaches. In the United States, more than 14,500 specialized drug treatment facilities provide counseling, behavioral therapy, medication, case management, and other types of services to persons with substance use disorders. However, despite the universal understanding that addiction treatment should embrace components focused directly on an individual's drug use as well as other components (such as employment training) focused on restoring the addicted individual to productive membership in the family and society, most facilities are missing a piece of the puzzle, especially

during aftercare.

One example of this conundrum was verified by chatting with an online service linked to a well-publicized now public addiction treatment system in America having good intentions.

The first question posed: **Since Addiction is an inheritable disorder with neuro-epigenetic interactions affecting brain reward circuitry how do you treat all Reward Deficiency as a hypodopaminergic trait/state after a patient is sent into the world of recovery?** The on-line chat person responded: *"We do counseling in the treatment facility, they do detox using drugs that are designed for that procedure".*

The second question**: What dopaminergic agonist do you use? Or do you just use the FDA approved drugs with possible anti-reward properties?** No response from the on-line chat person.

The third question: **What do you do about fixing the genetics during aftercare?** The online chat person responded: *"We address mental health issues that are tied together with addiction. After discharge we have an aftercare plan consisting of continuing care. Not sure there is a way to fix the genetic part; we teach patients relapse prevention skills".*

While understanding the brevity of this online interaction, it is obvious that these answers were not based in acceptable scientific terms. Given that this online event may even constitute a non-human computerized interactive service, the responses provided are not atypical in the field. This assumption is based upon the authors' many years in research, education, training, and clinical interactions with a multitude of active treatment facilities across America.

While the issue of appropriate evidence–based medicine is our primary concern, other barriers to treatment are equally important. Because drug abuse and addiction are major public health problems, a large portion of drug treatment is funded by local, state, and Federal governments. Private and employer-subsidized health plans may also provide coverage for treatment of addiction and its medical consequences. Unfortunately, managed care has resulted in shorter average stays, while a historical lack of or insufficient coverage for substance abuse treatment has curtailed the number of operational programs. The recent passage of parity for insurance coverage of mental health and substance abuse problems developed by A. Kenison Roy III, and a team of ASAM physicians [12], will hopefully improve this state of affairs. Health Care Reform (i.e., the Patient Protection and Affordable Care Act of 2010, "ACA") also stands to increase the demand for drug abuse treatment services and presents an opportunity to study how innovations in service delivery, organization, and financing can improve access to and use of them.

A google search ranked the top ten addiction treatment programs in America in 2015 [13]. A review of their information revealed that only one cited ASAM guidelines as their evidence–based approach, but at least six of the ten relied on the 12-steps as an important aspect of their aftercare policy. None of the top ten programs listed provided any inference for evidence- or neuroscience-based approaches to healing the brain. This is akin to a patient with cardiovascular issues such as heart failure or even tachycardia not to receive any Digoxin.

Understanding Resting State Functional Connectivity in RDS

A major limitation in advancing the development of novel therapeutics for many neuropsychiatric diseases (including substance dependence) is the lack of appropriate methods for analyzing the functional organization of the CNS. The integration of *brain regions* into transient, and sometimes persistent, functional *networks* seems to be part of the organizational principles of the brain [14]. Understanding how the *in vivo* brain is functionally connected during normalcy will likely lead to new understanding of how these functional connections are hampered during disease states. We now know that at rest one part of the brain cross talks with a distant other part of the brain in order to maintain normalcy. This has now been referred to as *"resting state functional connectivity".*

High field functional magnetic resonance imaging (fMRI) using well-validated neuroanatomical analysis methods and animal models provides the strongest direction for (a) understanding the intrinsic functional organization of the CNS and (b) testing compounds that can alter the brains connectivity patterns [15].

One important challenge is the lack of treatment strategies focusing on well-known, highly characterized biochemical pathways regulating brain dopamine systems that are involved in mediating rewarding experiences. Because of rapid and prolonged cellular and intracellular adaptations in response to selective dopamine receptor acting compounds (e.g., desensitization, supersensitivity) many pharmacotherapeutics fail at normalizing dopamine at a neural circuitry level. Normalizing dopamine (dopamine homeostasis) is one promising strategy that is consistent with recent animal models of dependence [16] and with previous theories of the role of dopamine in addiction [17].

Altered Resting State Functional Connectivity and Drug Abuse

Understanding neurophysiological activity between neural structures will increase support for the investigation of functional networks as a novel marker for addictive and other neuropsychiatric disorders. Following the discovery of intrinsic oscillations in blood oxygenation levels dependent (BOLD) signal [18] there have been a number of studies reporting evidence of altered functional connectivity induced by or associated with drug use and dependence [19, 20].

Spontaneous neural oscillations, at very low frequency (below 0.1Hz) that show synchrony between connected anatomical structures have neurobiological and behavioral significance in both human subjects and animals [21]. Correlations in spontaneous resting state activity between specific regions of the cortex and limbic subcortical areas are impacted by drug abuse and are altered in volunteers dependent on alcohol, cocaine, cannabis or heroin [22]. Li et al. [23], among the first to publish this signature of drug abuse, reported a decrease in resting state functional connectivity (rsFC) in the visual and motor cortices following acute cocaine administration in a cohort of long-term cocaine

users. Additional work by this group showed clearly defined reductions in rsFC using five specific mesocorticolimbic "seed" regions [24].

Thus, across several studies in human cocaine users a reduction in rsFC has been shown, particularly in brain structures that are part of the reward system. Reduced rsFC in cocaine users has been correlated with poor performance on cognitive tasks [25] and treatment outcome measures [26]. Similar observations have been reported in heroin users [27]; alcohol users [28]; adolescents with internet gaming addiction [29]; and in pathological gamblers [30].

So understanding this newer concept as espoused by scientists at NIDA, such as Elliot Stein, we are now poised through both genetic testing and neuroimaging techniques to test substances that can enhance rsFC in both humans and animal models. The concept seems quite straight forward: if drugs of abuse including food and even certain risky behaviors induce a reduction of rsFC, then obviously one important goal in the addiction treatment field would be to search for safe non-addicting methods to restore rsFC and as such provide *dopamine homeostasis*.

Paving the Way to Restoring rsFC in RDS

Blum's laboratory along with Marcelo Febo and others have examined functional connectivity patterns between several brain structures and areas of the reward system in the rat under resting conditions. Current experiments were designed to test whether the observed rsFC is altered by administration of a putative dopaminergic agonist, KB220 (core for many variants). This is a natural complex that has been extensively studied in pre-clinical and human trials [31]. As reported in a detailed review article [31] on both animals and humans to date, KB220 variants have been shown to

- enhance brain enkephalin levels in rodents;
- reduce alcohol-seeking behavior in C57/BL mice;
- pharmacogenetically convert ethanol acceptance in preferring mice to non-preferring mice such as DBA/2J;
- reduce drug and alcohol withdrawal symptomatology in humans (i.e. lower need for benzodiazepines, reduced days with withdrawal tremors, evidence of a lower BUD score (building up to drink) and no severe depression on the MMPI;
- reduce stress response in patients in recovery as measured by the skin conductance level (SCL);
- significantly improve Physical Scores and BESS (behavioral, emotional, social and spiritual) scores;
- decrease AMA rates six-fold after detoxification when compared to placebo groups;
- enhance focus in healthy volunteers [32];
- reduce craving for alcohol, heroin, cocaine, nicotine;
- reduce inappropriate sexual behavior;
- reduce post-traumatic stress (PTSD) symptoms, such as lucid nightmares [33, 34];
- modulate theta power in the anterior cingulate cortex in quantitative electroencephalic (qEEG) studies in humans [35, 36];
- significantly reduce relapse rates following intravenous administration [37];
- activate the N. Accumbens as well as the prefrontal-cerebellar-occipital neural network in abstinent heroin addicts utilizing resting state fMRI (a single dose of KB220Z compared to placebo in a pilot study) [38];
- activate the N. Accumbens as well as the prefrontal-cerebellar-occipital neural network.

In addition it, has been found that carriers of the DRD2 A1 allele showed a significant Pearson correlation in terms of enhanced compliance between KB220Z treatment relative to carriers of the normal compliment of DRD2 receptors in known obese patients [39]. In simpler terms carriers of the A1 allele respond better to treatment than carriers of the A2 allele. This suggests that low dopamine function equates to better treatment outcome. In unpublished work we now show the first strong evidence that a putative dopamine agonist nutraceutical (KB220 variant) 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 KB220 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. Clinical outcome is of cause a function of known neurogenetic DNA risk for all addictive behaviors impacted by known environmental induced neuroepigenetic effects [40]. Can we then ask the existing 14,500 treatment centers to consider substances that-rather than blocking dopamine-restore rsFC in the long-term, yielding real dopamine homeostasis.

After Money or Better Aftercare Results?

While as clinicians, scientists, and educators in the addiction industry, we applaud the many treatment centers in America that support the concept of providing a neuroscientific approach to enhance clinical outcome in their respective patients, we are concerned that even with 15,816 articles on the search term "Psychiatric Genetics", 5,156 for "Neurogenetics", 127 for "Epigenetics and Addiction", 514 for "Reward Deficiency", and 4,555 for Dopamine and Addiction," most of the treatment clinics and programs do not embrace healing the hypodopaminergic trait/state of the patient during the vulnerable period known as "aftercare". While some addiction programs utilize MAT especially for opioids (methadone, Burprenorhine/naloxone, etc.), most still only encourage counseling and involvement in 12-step programs. Our question to the entire treatment arena is: in light of the evidence of the genetic and epigenetic aspects of addiction, would they also embrace methods that could promote "dopamine homeostasis"? These known therapies could include meditation [41], yoga [42], dopamine boosting recovery diets [43], exercise [44], hyper-oxygenation [45];

heavy metal detoxification [46]; leaky gut restoration [47]; and certain nutraceuiticals [25].

In an invalidated survey involving hundreds of treatment centers it was found that less than 10% employ these known holistic tactics in their aftercare programs. While the number seems to be increasing and many programs now teach these relapse prevention skills there is no accepted "Standard of Care" especially focused on correctly attaining neurotransmitter balancing in the vulnerable recovering community.

Now not to be ferocious or even slanderous, it is well known that many of the owners of these treatment centers and even pain pill mills are more concerned with financial gain than successful aftercare therapy for their patients. While not discounting the many having good intentions, unfortunately it appears that most would rather see the 90% revolving door to continue, keeping afloat the economic status of their addiction facilities and programs in America. Grass-roots addiction specialists including counselors, practicing nurses, PA's, and Physicians would endorse change if given the unencumbered "freedom" to so.

So following the wise words of David E. Smith, founder of the Haight Ashbury Medical Free Clinic and co-founder of ASAM, *"Love needs Care"* [48] and the new slogan for the devotees of neuroepigenetics like Eric Nestler, "*Lick your Pups*" [49] the addiction landscape will ultimately change for the better.

In summary, we must provide scientifically-based real care for the millions seeking addition treatment in America wherein aftercare becomes as important as initial detoxification for the patient seeking to be free of their unwanted addictions. The new addiction treatment landscape should stand for enhancing the quality of life during recovery and "redeeming joy" by finding ways to induce needed dopamine homeostasis and normalcy.

Conclusion

The plethora of genetic and epigenetic evidence supporting the need for addiction treatment that addresses the hypo-dopaminergic state of the addicted brain, calls for a response from the addiction treatment community that places a priority on treatment that brings about dopamine homeostasis in those who struggle with RDS. While the lack of treatment is frequently cited as the reason for low recovery rates, it is more the lack of *effective* treatment that is at fault. If available treatment is successful for only a small percentage of people seeking recovery, then there is a need for more than additional treatment. There is a need for treatment that works. While acknowledging that addiction is indeed a brain disorder, most addiction professionals have primarily addressed the *consequences* rather than addressing the brain disorder itself or the underlying causes. While this often works in the short-term, in the long-term, during the aftercare period of recovery, relapse happens more often than not.

There is a gap between what is known and what has been done. Addicts have been taught how to *cope* with the symptoms resulting from addiction rather than treating the cause of the symptoms. Evidence-based treatment resources already available are not being utilized: therapies such as dopamine-boosting diets, acupuncture, yoga, and most important, brain neurotransmitter balancing with nutraceuticals such as KB220 variants. In light of the evidence suggesting that RDS is due to a dopamine deficiency, the goal of treatment should be dopamine homeostasis attainable with evidence-based treatment modalities, especially during the aftercare period.

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Conflict of Interest

It is acknowledged that Dr. Blum is the owner of US and foreign patents related to KB220Z. David and Merlene are co-owners of Nupathways Inc. Dr. Blum is a paid consultant of Rivermend Health , Atlanta , GA. Dr. Blum is paid consultant and stock holder of RDSS LLC and Victory nutrition International LLC. Dr. Blum is Chief Scientific Advisor of Dominion Diagnostics, LLC. Dr. Blum is also owner of Igene Inc. There are no other known conflicts.

Authors Contribution

The original draft was developed by KB, DM and MM. MF provided scientific input and RDB provided clinical input to the manuscript.

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