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Commentary

Benefits of Incorporating Candidate Genetic Screening for Pre-Addiction Vulnerability in the Face of the Opioid Crisis: An Opportunity for Addiction Psychiatry

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Abstract

There were 109,600 premature fatalities due to opioid induced overdoses in 2023. Despite a substantial body of research across the globe related to substance and non-substance behavioral addictions, the USA FDA-approved solutions, which include prescribing powerful opioids to reduce harm or the utilization of the narcotic antagonist, Naltrexone, a mu-opioid receptor blocker that works by the concept of 'psychological extinction" pose significant challenges. The former increase the risk of addiction, while the latter often suffer from poor patient compliance. This has led to an increase in opioid induced fatalities. Our team has continuously promoted early genetic addiction risk testing and pro-dopamine regulation via a nutrigenomic complex known as KB220 with 35 published clinical trials that have shown to induce "dopamine homeostasis" or even "hedonicstasis. Our group developed the statistically validated array of ten reward gene polymorphisms known as Genetic Addiction Risk Severity (GARS) with the primary identification of dopamine dysregulation. Here we review the evidence supporting the coupling of the GARS and KB220 as putative solutions to the ongoing opioid and drug addiction global pandemic. The data supports the use of genetic testing in pain and bariatric clinics, and chemical dependency programs which will help reduce the prescription of opioids and the induction of hedonic homeostasis. This presents a challenging but promising opportunity for the field of addiction psychiatry.

Keywords: Addiction; Dopamine; Reward System; GARS

It is indeed noteworthy that from 1999-2020, at least 932,000 people in the United States died from a drug overdose, and 564,000 of those deaths was due to opioids [1,2]. Importantly since 1999, excluding 2018, opioid induced death rate has soring and unfortunately record-setting [1-13]. Data derived from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) revealed 100,306 drug induced overdose fatalities in 2021. These deaths represent a 28.5 % increase compared to the 78,056 fatalities reported in 2020 [3]. If we continue on this path, we could expect as projected by the current USA drug czar to reach 165,000 by 2025. Indeed, this is a real challenge for addiction psychiatry.

The only FDA approved treatment to help reduce harm avoidance in Opioid Use Disorder (OUD) involves the provision of powerful opioids as a substitution method. Our team has previously argued against this approach, advocating for the short-term use of opioid only in specific cases, such as terminal cancer patients. [13].

Along these lines there is some evidence to suggest the remaining untreated people had an increased risk for mortality, HIV infection and even criminal activity [14]. With this stated, the purpose of this perspective is to provide some novel out of the box thinking to evoke a recapitalization of therapeutic approaches, including genetic screening. We believe followed by intensive clinical and animal studies, the inclusion of testing for pre-addiction and subsequent early identification, could significantly reduce the known 500 billion annual cost [15,16]. Unfortunately, in 2020, 40.3 million inhabitants of the United States were diagnosed primarily by relying on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, (DSM-5), substance use disorder (SUD). However, early-stage SUD or even people born with a number of dysfunctional reward polymorphic genes, lacks an acceptable term like pre-addiction or Reward deficiency Syndrome (RDS) [18].

One of the novel conceptualizations, suggested for inclusion in the DSM, is the "pre-addiction" construct, as it is juxtaposed to "prediabetes" [19-28]. Essentially, this concept as defined by the American Diabetes Association [20], involves individuals having abnormal insulin sensitivity (hemoglobin A1c of 5.7–6.4) and/or glucose tolerance tests (fasting blood glucose of 100-125 mg/dL; oral glucose tolerance test (OGTT) 2-hour blood glucose of 140-199 mg/dL). It needs to be noted that prediabetes is a manifestation of

homeostatic dysfunction, and is linked to hedonistic impairments [23], such as hypodopaminergia in the mesolimbic brain reward circuitry [9], along with dysfunction in other neurotransmitters pathways, including serotonergic, cannabinergic, opioidergic, GABAergic, glutaminergic, and cholinergic abnormalities [24,25], collectively termed RDS [24-28]. It is generally agreed that the construct of "reward" is a key element of mental health. Dysregulation in the neurotransmitter pathways mentioned above, either via genetic or epigenetic factors, can lead to aberrant substance and non -substance behavioral addiction seeking [29-33]. A known hypodopaminergia augments the chances that individuals with these pre-addictive traits (genetic) and/or states (epigenetic), may seek out anything that will provide a temporary alleviation of their unwanted RDS symptoms [34,35]. Indeed, this seeking behavior will exacerbate their neurological and psychiatric co-morbidities [36-38]. Since RDS encompasses co-morbidities that include addictive, compulsive and impulsive behaviors, GWAS have revealed significant gene polymorphisms, especially in dopamine regulatory genes, that are associated with a variety of abnormal behaviors including depression, anxiety, schizophrenia, post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASD) [25,39-43]. Comings [44] reported that incorporating early genetic screening utilizing DNA polymorphic signatures, rather than relying solely on subjective diagnostic interviews, offers significant benefits. Importantly, while the term "pre-addiction" augurs well with the idea of prediabetes, and has preventive relevance for the lay public, in the world of scientific acumen we propose RDS for the scientific and clinical community since it reflects neurochemical alterations as well as modifications in functional connectivity [45,46].

Genetic Addiction Risk Severity (GARS) Screening for RDS

We are hereby proposing the early identification of RDS by embracing the candidate gene approach developed by Blum's group in 2014 known as Genetic Addiction Risk Severity (GARS) test and subsequent implication in the addiction neuroscience field such as revealing pre-addiction liability associated with opioid pain treatment [46] and the RDS Questionnaire [47], identifying pre-addiction or RDS [48,49] early in age. Possible adoption of this genetic risk assessment coupled with attempts to restore dopamine homeostasis (i.e., hedonicstasis) [50-67] may represent a frontline approach in the future of addiction psychiatry.

An important consideration related to this suggestion is the potential to develop a screening tool that stratifies individuals into mild, moderate, or high risk for developing addictive-like behaviors. Drawing from our foundational work [1] and further corroborated by researchers worldwide, the concept of pre-addiction is most accurately understood through the framework of dopamine dysregulation. This framework suggests that pre-addiction is defined by a reduction in dopaminergic activity, stemming from disrupted regulation across key neurotransmitter systems. This dysregulation compromises homeostasis in neurotransmitter release, receptor sensitivity, and neural network function. As of June 2025, PUBMED lists 1,529 relevant articles, with over 47% authored independently of our group. Additionally, 249 articles are indexed under the term "Reward Deficiency Syndrome." While the label "pre-addiction" aligns conceptually with terminology used in early diabetes research, the bulk of scientific evidence points to imbalances, i.e. deficits or excesses, in brain neurotransmitter activity. This is especially pertinent during adolescence, a period marked by significant neurodevelopmental changes, often referred to as a time of "reward dysregulation" [68].

McLellan., *et al*. [21] highlighted that the DSM-5 defines Substance Use Disorders (SUDs) using eleven equally weighted criteria related to impaired control, categorized along a three-stage severity continuum. The term "addiction" is typically reserved for severe SUDs, characterized by six or more symptoms, affecting around 4-5% of adults. In contrast, individuals with mild to moderate SUDs (two to five symptoms) represent a much larger segment, approximately 13% of the population, and are responsible for a greater overall burden of substance-related harm. Recognizing this continuum reinforces the clinical value of tools like the Genetic Addiction Risk Severity (GARS) test in addiction psychiatry.

For instance, Dennen., *et al*. [69] described a genetic panel comprising eleven polymorphisms across ten genes associated with the dopaminergic reward pathway. This panel included six single nucleotide polymorphisms (SNPs) in DRD1, DRD2, DRD3, DRD4,

OPRM1, and COMT; four simple sequence repeats in 5HTT, DAT1, DRD4, and MAOA; and a dinucleotide polymorphism in GABRA3. In a study using this GARS panel with 393 participants, 273 of whom also completed the Addiction Severity Index-Multimedia Version (ASI-MV), results demonstrated that risk was influenced by cumulative gene variations. Individuals with ≥7 polymorphisms associated with reduced dopamine signaling showed significantly higher alcohol severity scores, while those with ≥4 such polymorphisms had higher drug severity scores. These findings support the potential of GARS as a predictive tool for pre-addiction.

Chronic pain affects millions, and prior studies [46,70] using RT-PCR and multiplex PCR/capillary electrophoresis evaluated SNPs in a ten-gene reward panel among 121 chronic opioid users (55 men, 66 women, average ages 54 and 53 years). Inclusion criteria required long-term opioid use with Morphine Milligram Equivalent (MME) ranging from 30-600 mg/day (men) and 20-180 mg/day (women) over 12 months. Notably, 96% of participants had four or more risk alleles, and 73% had seven or more-strongly suggesting high genetic vulnerability to opioid and alcohol addiction. These results advocate for early GARS screening at treatment initiation to reduce the risk of iatrogenic opioid dependence.

A compelling case reported by Bajaj., *et al*. [71] demonstrated the clinical utility of GARS in identifying elevated addiction risk in a woman with chronic pain syndrome. With GARS scores above four, the patient was treated using H-Wave® therapy, a safe, non-addictive alternative to opioids. This personalised theragnostic approach reduced the likelihood of long-term neurobiological harm and opioid-related mortality.

Further, a case series [72] illustrated the benefit of combining GARS with a customized pro-dopaminergic intervention (KB220), tailored to an individual's genetic profile. One female proband achieved sustained recovery over eight months, as verified through drug testing. Her father (a binge drinker) and mother (no SUD) also demonstrated behavioral improvements. GARS testing extended to their children revealed high risk for SUD. This three-generation case underscores the promise of genetically informed interventions in promoting long-term recovery and improved family outcomes.

Another notable application of GARS involves the legal system. While the justice system is founded on principles of free will, it occasionally acknowledges genetic or psychological determinants. One case involved a 35-year-old male (AG) in remission from Alcohol Use Disorder, with five DWI convictions and a prior three-year prison sentence. After GARS testing revealed a hypodopaminergic condition, the court opted for a reduced sentence: five years of standard probation, fines, community service, monitoring, and limited jail time with work release. To date, our team has utilized GARS in around 30 individuals, collectively preventing over 220 years of incarceration, highlighting the potential of genetic evidence in guiding sentencing decisions. This case is the first to illustrate how genetically based "determinism" can influence legal outcomes over the presumption of free will [73].

In our most recent study [74], GARS was used to assess outcomes after bariatric surgery. At six months post-surgery, participants exhibited reduced BMI and excess weight loss. Remarkably, 76% had GARS scores exceeding seven, indicating vulnerability to addictions involving drugs, alcohol, and food. The MAO (rs768062321) and DRD1 (rs4532) homozygous risk alleles were present in 38% and 47% of participants, respectively. Among all 11 alleles screened, DRD4 (rs1800955) was significantly linked to changes in weight and BMI. Additionally, the COMT risk allele (rs4680) showed negative correlations with scores on the Eating Expectancies Inventory ($r = -0.4983$, $p < 0.05$) and Pittsburgh Sleep Quality Index ($r = -0.5482$, $p < 0.05$). These findings further support the translational potential of GARS in tailoring care for individuals at high genetic risk. The GABRB3 risk allele (rs764926719) correlated positively with EEI ($r = 0.6161$, $p < 0.01$) and Food Cravings Questionnaire-Trait Reduced (FCQ) scores ($r = 0.6373$, $p < 0.01$). The OPRM1 risk allele revealed a positive association with the Difficulties in Emotion Regulation Scale (DERS) score ($r = 0.5228$, $p < 0.05$). They also identified correlations between DERS and BMI change ($r = 0.61$; $p < 0.01$). Accordingly, these data support the benefit of personalized genetic screening and psychosocial trait information when considering physician-patient interaction and counseling post bariatric surgery. In a 12-month follow-up results showed that carriers of the DRD2 A1 allele showed the highest compliance to the surgery as evidenced by a reduced BMI [75].

Statistical Validation of Risk Alleles in GARS Test

To develop an accurate test to help identify those at risk for at least AUD, we developed the GARS test, consisting of ten genes and eleven associated risk alleles. Along these lines in order to statistically validate the selection of these risk alleles measured by GARS, we applied strict analysis to studies that investigated the association of each polymorphism with AUD or AUD-related conditions published from 1990 until 2021. Specifically, this statistical analysis calculated the Hardy-Weinberg Equilibrium of each polymorphism in cases and controls. If available, the Pearson's $\chi 2$ test or Fisher's exact test was applied to comparisons of the gender, genotype, and allele distribution. The results found the OR, 95% CI for OR, and a post-risk for 8% estimation of the population's alcoholism prevalence revealed a significant detection. The OR results showed significance for DRD1, DRD2, DRD3, DRD4, DAT1, COMT, OPRM1, and 5HTT at 5% [76].

Odds ratios and likelihood ratios of polymorphisms under consideration.

Gene/Polymorphism	OR	95% CI for OR	Post Risk
Dopamine D1 Receptor (DRD1): rs4532-risk allele G *	1.77	(1.01, 3.10)	-
Dopamine D2 Receptor (DRD2): rs1800497-risk allele A1	1.45	(1.15, 1.90)	0.12
Dopamine D3 Receptor (DRD3): rs6280-risk allele C (Ser9Gly)	3.37	(1.54, 7.40)	0.20
Dopamine D4 Receptor (DRD4): rs1800955-risk allele C (48bp repeat VNTR)	1.56	(1.04, 2.36)	0.10
Dopamine Transporter Receptor (DAT1): SLC6A3 3′-UTR-risk allele A9 (40bp repeat VNTR)	1.18	(1.00, 1.45)	0.10
Catechol-O-Methyltransferase (COMT): rs4680-risk allele G (Val158Met)	1.43	(0.98, 2.10)	0.083
μ-Opioid Receptor (OPRM1): rs1799971-risk allele G (A118G)	1.47	(1.00, 2.18)	0.13
γ-Aminobutyric Acid (GABA) A Receptor, -3 Subunit (GABRB3): CA repeat-risk allele 181*	0.33	(0.14, 0.79)	0.06
Monoamine Oxidase A (MAO-A): 3′ 30bp VNTR-risk allele 4R DNRP *	0.62	(0.15, 2.63)	0.05
Serotonin Transporter Receptor (5HTT) Linked Promoter Region (5HTTLPR) in SLC6A4: rs25531-risk allele S′	1.23	(1.07, 1.40)	0.10

Table 1

*Not enough data. It is noteworthy to point out that for each gene polymorphism, the number of cases and controls has been indicated in table 1.

The Benefits of GARS Testing in SUD

GARS seems to be the only panel of genes with established polymorphisms reflecting the Brain Reward Cascade (BRC) [77] which has been associated with the ASI-MV alcohol and drug risk severity score. Any variations within this pathway, whether genetic or environmental, may result in addictive behaviors. There are a number of benefits that have been reported with the utilization of GARS [77]. These include 1) knowledge of precise polymorphic associations can help in the attenuation of guilt and denial; 2) corroboration of family genograms; 3) assistance in risk-severity-based decisions about appropriate therapies, including pain medications and risk for addiction; 4) choice of the appropriate level of care placement (i.e., inpatient, outpatient, intensive outpatient, residential); 5) determination of the length of stay in treatment; 6) determination of genetic severity-based relapse and recovery liability and vulnerability; 7) determination of pharmacogenetic medical monitoring for better clinical outcomes (e.g., the A1 allele of the DRD2 gene reduces the binding to opioid delta receptors in the brain, thus, reducing Naltrexone's clinical effectiveness); and 8) supporting medical necessity for insurance scrutiny.

Function of Reward Genes in the GARS Test

5HT2A Receptor

Although the current version of the Genetic Addiction Risk Severity (GARS) test does not assess the 1438G/A polymorphism of the 5HT2A receptor, it is expected that future iterations will incor-

porate this SNP. Serotonin (5-hydroxytryptamine or 5-HT), discovered in the 1940s, is a key neurotransmitter. Most 5-HT receptors are G protein-coupled receptors (GPCRs) with seven transmembrane domains, initiating intracellular signaling cascades upon activation, except for 5-HT3, which functions as a ligand-gated ion channel. The 5-HT2A receptor is composed of 471 amino acids in humans, rats, and mice, and is found in both central and peripheral tissues. In the brain, it is found mainly in the cerebral cortex, claustrum, and basal ganglia. This receptor downregulates cyclic AMP (cAMP) synthesis, thereby influencing the release and function of other neurotransmitters such as dopamine (DA), glutamate, gamma-aminobutyric acid (GABA), and enkephalins. The prevalence of 5-HT2A gene polymorphisms differs among populations. For example, the minor allele is found six times less frequently in Black individuals compared to White individuals. Dysfunction in serotonergic genes, including 5-HT2A, has been associated with suicidal ideation, childhood trauma, and criminal behavior [78,79].

5-HTTLPR (Serotonin Transporter-Linked Polymorphic Region)

The serotonin transporter (5-HTT), which is encoded by the SLC6A4 gene on chromosome 17q11.1-q12, is essential for the reabsorption of serotonin. A polymorphism known as 5-HTTLPR influences its activity, with the long (L) allele linked to greater transcriptional efficiency than the short (S) allele. Studies have shown that the L allele increases mRNA expression in human cell cultures. Saiz., *et al*. [80] reported a higher prevalence of -1438G and L allele carriers among alcohol-dependent individuals compared to those with heroin dependence, suggesting these polymorphisms differentiate these disorders. Additionally, 5′ and 3′ SLC6A4 polymorphisms independently affect the risk of suicidal behavior [79]. Interestingly, individuals with genotypes associated with lower 5-HTT expression demonstrate enhanced responses to opioid analgesics, while the S allele has been linked to a heightened risk of chronic pain conditions. Moreover, the S allele is associated with increased vulnerability to alcohol dependence and related comorbidities [81]. In alcohol-dependent patients, relapse risk may be influenced by the presence of the S allele, possibly mediated through intermediate traits such as the Catechol-O-Methyltransferase (COMT) Val158Met polymorphism. Discovered in 1957 by Julius Axelrod, COMT is an extracellular enzyme that degrades catecholamines (DA, norepinephrine, and epinephrine) by transferring a methyl group from S-adenosylmethionine. Serý., *et al*. [82] found a significant association between the Val158Met polymorphism and alcoholism in males, with notable differences in genotype frequencies between alcoholics and controls. The low-activity COMT genotype (A/A) is more common in carriers of the DRD2 A1 allele. Cao., *et al*. [83] identified a higher frequency of the A allele at the −287 A/G polymorphism in heroin-dependent individuals. Rapid DA degradation due to the Val allele leads to lower synaptic dopamine levels, contributing to hypodopaminergia. This association has been reinforced by Vandenbergh., *et al*. [84] and others [85], linking the Val allele to substance use disorders. Li., *et al*. [86] reported that the COMT rs737866 TT genotype correlates with higher novelty seeking and earlier onset of heroin use than CT or CC genotypes. The Val158Met substitution significantly increases DA catabolism, reducing dopaminergic signaling and thus affecting post-synaptic stimulation [87].

Monoamine Oxidase-A (MAOA)

Monoamine oxidase (MAO) is an enzyme located in the mitochondria that catalyses the oxidative deamination of monoamines, such as serotonin, dopamine, and norepinephrine, resulting in the formation of aldehydes and ammonia. Two isoforms exist, namely, MAO-A and MAO-B, both of which are targets for monoamine oxidase inhibitors. MAO-A predominantly metabolizes serotonin, melatonin, norepinephrine, and epinephrine, while MAO-B degrades phenylethylamine and benzylamine. Both isoforms process DA, tyramine, and tryptamine. The MAOA gene is located on the X chromosome and features a polymorphism known as MAOA-uVNTR (variable number tandem repeat) [88], consisting of 30-bp repeats with 2-, 3-, 3.5-, 4-, 5-, or 6-copy variants [89]. Functional studies show the 3.5- and 4-repeat alleles are associated with higher transcriptional activity, whereas the 3-repeat allele shows lower activity [90-94]. Huang., *et al*. [95] explored how DRD2 gene associations with alcoholism are modulated by MAOA polymorphisms. Individuals with both the MAOA 3-repeat allele and the DRD2 A1/A1 genotype had a 3.48-fold increased risk of alcohol dependence with comorbid anxiety and depression, compared to those with the same MAOA allele and the DRD2 A2/A2 genotype [96].

Dopamine D1 Receptor Gene (DRD1)

The dopamine D1 receptor (DRD1), produced by the DRD1 gene, is the most prevalent subtype of dopamine receptor in the human brain, with especially high expression in the caudate-putamen

region. This GPCR activates adenylyl cyclase and cAMP-dependent protein kinases. DRD1 plays key roles in neuronal development, modulation of D2 receptor activity, behavioral regulation, and reinforcement mechanisms. At least two DRD1 transcript variants are initiated at alternative transcription sites. DRD1 is implicated in numerous functions including motor control, social interaction, attentional processes, and reward. Betel., *et al*. [97] identified a higher frequency of the rs686 T allele in individuals with alcohol dependence. A specific DRD1 haplotype (rs686T-rs4532G) was also significantly associated with alcohol use disorder [98]. Furthermore, DRD1-48A>A has been associated with novelty seeking, harm avoidance, and persistence. DRD1 polymorphisms have also been linked to rapid heroin addiction development [99], nicotine dependence [100], and bipolar disorder [101,102].

Dopamine D2 receptor gene (DRD2)

The DRD2 gene produces the D2 subtype of the dopamine receptor, a G protein-coupled receptor that functions by inhibiting adenylyl cyclase activity. There are two known isoforms, with a third variant generated through alternative splicing. In the mouse dentate gyrus, DRD2 surface expression is regulated by the calcium-binding protein NCS-1, which modulates synaptic plasticity, exploration, and memory. The DRD2 gene is one of the most widely studied in psychiatric genetics. Nearly a decade before Arvid Carlsson and others received the Nobel Prize, DRD2 was linked to severe alcoholism [103]. The Taq1A SNP (rs1800497), originally believed to reside in the DRD2 3′ untranslated region, was later found in exon 8 of the neighboring ANKK1 gene. This discovery raised the possibility that the functional impact of Taq1A might be mediated through either or both genes due to shared haplotypes or converging pathways [103-105]. The A1+ genotype (A1/A1 or A1/A2) is associated with up to a 40% reduction in D2 receptor density compared to the A2/A2 genotype [106-108], contributing to hypodopaminergic functioning in the reward circuitry. Additional DRD2 polymorphisms, including rs6277 (C957T), are associated with reward deficiency behaviors such as substance use disorders [109]. Hirvonen., *et al*. [110] demonstrated that the T+ genotype (T/T or T/C) of rs6277 is linked to reduced mRNA translation and receptor density, increasing susceptibility to alcohol dependence, a trait with moderate to high heritability [111,112]. Kazantseva., *et al*. [113,114] found the ANKK1/DRD2 Taq1A variant associated with higher neuroticism in both sexes, and SLC6A3 rs27072 with persistence. Notably, in males only, the A2/A2 genotype was linked to increased novelty seeking and reduced reward dependence.

Dopamine D3 Receptor Gene (DRD3)

The dopamine D3 receptor, encoded by the DRD3 gene in humans, is a subtype of dopamine receptors that is negatively coupled to cyclic AMP signaling. It is thought that DRD3 gene is expressed in older regions of the brain phylogenetically. Different isoforms of the DRD3, resulting from alternative splicing, leads to the transcription of multiple polymorphisms influencing emotional regulation, responses to alcohol and other drugs of abuse.

Vengeliene., *et al*. [115] reported elevated DRD3 mRNA expression in the striatum following one year of voluntary alcohol intake in alcohol-preferring rats. Notably, the Gly9/Gly9 genotype of the DRD3 Ser9Gly polymorphism has been linked to increased traits associated with obsessive personality disorder [116]. Additionally, Retz., *et al*. [117] identified a significant association between the DRD3 polymorphism and impulsivity, as measured by Eysenck's Impulsiveness Questionnaire (EIQ) and the German short form of the Wender Utah Rating Scale (WURS-k), in individuals diagnosed with ADHD. Interestingly, the same study found the Ser9Gly polymorphism to be associated specifically with violent, but not non-violent, ADHD individuals. Among these, heterozygous violent subjects exhibited the highest impulsivity and WURS-k scores, while homozygous individuals showed significantly lower levels, suggesting a potential heterosis effect.

Opiates are known to augment DA neurotransmission [118] Notably, Spangler., *et al*. [118] observed substantial elevations in D3 receptor mRNA expression, an 85% increase in the caudate-putamen and a 165% increase in the ventral midbrain, including the substantia nigra and ventral tegmental area using identical RNA extracts. Most recently, our laboratory, in collaboration with Gondre-Lewis at Howard University, identified a higher prevalence of the polymorphic DRD3 risk allele (rs6280) compared to the μ-opioid receptor gene variant (rs1799971) among African American individuals diagnosed with chronic opioid use disorder Gondre-Lewis., *et al*. [119] suggested that dopamine-related receptors could influence opioid-seeking behavior and nicotine dependence in African Americans [120]. In addition, preclinical data link DRD3 to alcohol [153-155], food [156], caffeine [157] and cocaine intake [158], as well as sleep behavior [159,160].

Dopamine D4 Receptor Gene (DRD4)

The dopamine D4 receptor is encoded by the DRD4 gene, and is located on chromosome 11 at 11p15.5 in humans. Like the DRD2 receptor, DRD4 is a G protein-coupled receptor (GPCR) that inhibits cyclic AMP (cAMP) production upon activation. The DRD4 gene contains several known polymorphisms, including a 48-base pair variable number tandem repeat (VNTR) in exon 3, a 13-base pair deletion in exon 1 (positions 235-247), a C-521T substitution in the promoter region, a Val194Gly substitution, a 12-base pair repeat in exon 1, and a polymorphic 120 bp tandem duplication. The exon 3 VNTR ranges from 2 to 11 repeats, with alleles containing 6 to 10 repeats classified as the "long" variants. Allelic frequencies vary across populations; notably, the 7-repeat (7R) allele is common in the Americas but relatively rare in Asian populations.

The 7R allele of DRD4 has been loosely associated with psychological traits and conditions such as attention-deficit/hyperactivity disorder (ADHD), and is believed to confer reduced responsiveness to dopamine, potentially contributing to altered behavioral regulation. This allele is estimated to have emerged approximately 40,000 years ago. Chen., *et al*. [121,122] found that nomadic groups exhibited higher frequencies of the 7R allele compared to sedentary populations. Furthermore, they observed that populations which migrated over longer distances between 1,000 and 30,000 years ago had a greater prevalence of 7R/long alleles.

DRD4 polymorphisms have been linked, with mixed findings, to various psychiatric and neurological disorders including ADHD, addictive behaviors, eating disorders (e.g., binge-eating, anorexia, bulimia), bipolar disorder, Parkinson's disease, and schizophrenia, with variable associations to novelty seeking traits [123]. Some studies suggest that parenting quality may influence cognitive development in children carrying the 7R allele. Specifically, higher quality parenting has been correlated with improved effortful control in 4-year-olds, possibly mediated by epigenetic mechanisms [124].

Emerging evidence indicates that the 7R VNTR may be associated with increased susceptibility to substance-seeking behavior, potentially due to diminished dopamine sensitivity or resistance, contributing to a state of hypodopaminergia [124–128]. Biederman., *et al*. [129], using survival analysis, reported that by age 25, 76% of individuals carrying the 7R allele met criteria for ADHD, compared to 66% of those without the allele. Additionally, other studies have linked the 7R variant with increased risk for both alcoholism [130] and heroin dependence [131].

Preclinical studies further support the role of DRD4 in modulating behavior related to reinforcement. These include drug-seeking and reward-related responses to food [161], cocaine [161-164], methylphenidate [164,165], and amphetamine [164].

Dopamine Transporter Gene (DAT1)

The dopamine (DA) transporter, also known as the dopamine active transporter (DAT, SLC6A3), functions by reabsorbing dopamine from the synaptic cleft back into the cytosol through a membrane-spanning protein pump. The gene encoding the DAT protein is located on human chromosome 5, spans approximately 64 kilobases, and contains 15 coding exons. After reuptake, dopamine is further sequestered into vesicles by other transporters for future storage and release at the brain's reward center, the nucleus accumbens [132–136]. Dopamine is co-transported across the neuronal membrane along with sodium ions. Additionally, changes in membrane polarity significantly affect transport rates, with depolarization promoting dopamine release at the nucleus accumbens [137,138]. Notably, DAT expression in the brain is highest in the nigrostriatal, mesocortical, and mesolimbic pathways, as well as in the substantia nigra pars compacta [139]. Preclinical studies have demonstrated that DAT plays a role in the intake or preference for substances such as cocaine [166], methylphenidate [167], alcohol [166], and even food [168].

MU opioid receptor gene

The μ-opioid receptors (MOR) are a class of opioid receptors with a high affinity for both beta-endorphins and enkephalins but little to no affinity for dynorphins which bind to kappa receptors in the brain. They are also referred to as μ(mu)-opioid peptide (MOP) or (MOP) receptors. The prototypical μ-opioid receptor agonist is morphine. Moreover, morphine is the primary psychoactive alkaloid in opium and for which the receptor was named, with mu being the first letter of the term Morpheus. One primary action of the mu opioid receptors is its inhibitory role onto the GPCR that stimulates the G alpha subunit thus blocking adenylate cyclase function effectuating reduced cAMP concentration. In humans there are three of the μ-opioid receptors - μ1-3. [140].

The μ-opioid receptors exist for the most part presynaptically, in the periaqueductal gray brain area, and also in dorsal horn and spinal cord. Other areas where they have been located include the external plexiform layer of the olfactory bulb, the nucleus accumbens, cerebral cortex, amygdala and the nucleus of the solitary tract. One important function of the mu opioid receptor is to suppress the GABA presynaptic release which results in an increase in DA release at the nucleus accumbens [141]. The most important regulatory proteins for the MOR are the beta-arrestines and RGS proteins [142,143]. Preclinical studies have shown that MOR levels are associated with feeding [169, 170], and exercise [171].

GABRB3 receptor gene

Gamma-aminobutyric acid receptor subunit beta-3 is a protein that in humans is encoded by the GABRB3 gene. It is located within the 15q12 region in the human genome and spans 250kb. This gene includes 10 exons within its coding region. It is known that via alternative splicing the gene codes for a number of protein isoforms. These isoforms are all subunits in the GABAA receptor a ligand-gated ion channel. In fact, the beta-3 subunit is expressed at different levels within the piriform cortex, olivary body, cerebral cortex, hippocampus, cerebellum, thalamus of the brain at different times of development and maturity. GABRB3 deficiencies are implicated in an array of human neurodevelopmental disorders, such as Autism [144-147]. This gene is located in a gene cluster with two other genes, GABRG3 and GABARA5 [147]. During development, when the GABRB3 subunit functions optimally, its role in the GABAA receptor enables proliferation, migration, and differentiation of precursor cells that lead to the appropriate development of the brain [148]. Because of its inhibitory properties this polymorphism induces a hypodopaminergic trait. GABA signaling has also been shown in preclinical studies to be associated with feeding behavior [163,172,173].

To enhance comprehension, we developed the following table 2 to provide a snapshot of the reward gene polymorphisms measured by the GARS test.

Gene	Risk allele	Comment
Dopamine D1 (DRD)	48A	G normal
Dopamine D2 (DRD2)	A1	A2 normal
Dopamine D3 (DRD3)	C	T normal
Dopamine D4 (DRD4)	7R	4R normal
Dopamine Transporter (DAT1)	9R = Fast uptake 10R = slow uptake	Fast DAT could result in hypodopaminergic and slow could result in hyper dopaminergic
Serotonin Transporter (5HTTLLR)	S	Count S not L
Catechol-O-methyl-transferase (COMT)	G	The G allele = Val substation that causes the enzyme COMT which breaks down Dopamine in the synapse too fast. This could also lead to hypodopaminergic trait. The A = Met = normal
Mu opiate receptor (OPRM1)	G	The G allele G = ASP this contributes to addiction to opiates and alcohol. A = ASN normal. Another name is MOR-Mu opiate receptor
GABA A receptor subunit (GABRA3)	181	This 181 SNP reduces the sensitivity of the GABA receptor and as such increases the chance for alcoholism and other drugs of abuse. It increases risk for stress induction, which can also cause relapse
MAOA uVNTR	4R = Fast uptake 3R = slow uptake	This is a strange gene. It sits on the mitochondria in the neuron. MAO is involved in the breakdown of dopamine and serotonin. The 4R increases the breakdown and 3R slows the breakdown. Since the gene sits on the X chromosome not the Y chromosome females are XX and males are XY. This means that females have two alleles to count, and males only have one
Serotonin 5HTA2 Receptor	C	Alcohol dependent (AD) patients homozygous for C allele had significantly lower age at onset of alcohol problems than subjects having at least one T allele. The results suggest a potential role of the T102C HTR2A polymorphism in development of alcohol dependence
Serotonin 5HTA2 Receptor	1438A allele	Another polymorphism the 5-HT (2A) -1438A allele was significantly more common in patients than controls [0.55 and 0.45, respectively; corrected $P = 0.042$, OR = 1.51 (95 % CI = 1.13–2.03)]

Table 2: RDS-associated SNPs.

Table 2 RDS-associated single nucleotide polymorphisms (SNPs) may be identified through various suitable techniques, including DNA sequencing of individuals diagnosed with one or more Reward Deficiency Syndrome behaviors. Upon validation, these newly identified SNPs may be incorporated into diagnostic panels such as the GARS test. Once validated, the presence of one or more RDS-associated SNPs in nucleic acids obtained from a patient's biological sample can be determined using any appropriate current or future assay. This includes, but is not limited to, site-specific hybridization, restriction enzyme digestion, and DNA sequencing methods. Table 2 outlines a number of preferred RDS-associated SNPs whose detection is applicable to the GARS testing methodology.

GWAS compared to candidate approaches

It is generally agreed that the future of addiction psychiatry using GWAS will provide a window into new therapeutic targets as well as a potential diagnostic tool to unveil ADDICTGENE and other SNPs that load onto the concept of pre-addiction and associated vulnerability. However, there has been strong push back in terms of arguing the importance of the older candidate gene approach. Our laboratory has been a proponent of using the Genetic Addiction Risk Severity (GARS) as one potential way to early identify pre-addiction and futuristic addiction liability [149]. We have come to this conclusion based on a number of recent GWAS and subsequent convergence thereof.

Since 1990, published addiction psychiatry articles have exceeded 11,495. GARS test results have identified risk for reward deficiency behaviors in cohorts from polysubstance and pain clinics, post-surgical bariatrics, and DWI offenders facing prison time. Since Blum *et al* first published in (1990) concerning the association of the DRD2 gene polymorphism and severe alcoholism, confirmation has been mixed and controversial. Recently a meta-analysis of 62 studies revealed a significant link between DRD2 rs 1800497 and Alcohol Use Disorder (AUD). Additionally, research from Yale University showed that a haplotype block of the DRD2 gene A1 allele was associated with AUD and heroin dependence. GWAS studies of depression and suicide in 1.2 million veterans confirmed the first psychiatric candidate gene study finding from Blum., *et al.* 1990; a significant link between the minor DRD2 allele, Taq A1 (rs 1800497 C > T) and severe alcoholism. Moreover, the DRD2 rs1800497 is associated with suicide behaviors robustly at P = 1.77 × 10-7. DNA polymorphic alleles underlying SUD with multiple substances were mapped via chromatin refolding, showing that the DRD2 gene and polymorphism (s) was the top gene signal (DRD2, P = 7.9 × 10-12). Thus, we conclude that GWAS should end the controversy concerning the DRD2 gene being at least one determinant of Reward Deficiency Syndrome (RDS) first reported in the Royal Society of Medicine journaling 1996 [150]. For an updated review of GARS and to help enhance comprehension of these concepts see [151].

Summary

Challenges of genetic testing include the psychological impact on individual, potential misunderstanding of the consequences of genetic predisposition and the risk discrimination. Genetic information can be used to deny persons access to employment, insurance and other essential services. Interestingly, most states have some legislation aimed at preventing discrimination, however, coverage by most state law is spotty. Now with the US Genetic Information Non-Discrimination Act (GINA) of 2008 in place, individuals are protected by federal law. Physicians may find that they have new duties created by reports of genetic test results, including addressing common misunderstandings of the consequences of possessing an affected allele and alerting third parties who may share the patient's genetic endowment [152].

Many of the resulting metabolic conditions in infants are treatable through specialized diets and/or pharmacological interventions. Early detection is critical, as it can prevent mortality, intellectual disability, and other serious complications. Disorders such as phenylketonuria (PKU) and galactosemia require the expertise of pediatric metabolic specialists and nutritionists, who can prescribe and manage highly specific dietary regimens. In these cases, parental education is essential to ensure adherence to dietary restrictions and to perform routine blood and urine monitoring to safeguard the child's health.

Given this established model, could a similar level of clinical expertise and structured intervention be applied to the early identification and management of predisposition to addiction, or

what some have termed pre-addiction? Beyond the ethical debate around labelling, a fundamental question arises: would early identification of pre-addiction, potentially even at birth, provide a meaningful opportunity for preventive intervention?

To this end, an intriguing study by Yanovich., *et al*. [174] sheds light on the interaction between genetic predisposition, environmental stress, and vulnerability to addiction-related behaviors. Using selectively bred mice that were either stress-resilient and socially dominant (Dom) or stress-vulnerable and socially submissive (Sub), the researchers explored the impact of stress on the development of cocaine preference. In a conditioned place preference (CPP) paradigm, Sub mice initially exhibited aversion to cocaine, while Dom mice showed a preference. However, after a four-week regimen of chronic mild stress (CMS), Sub mice demonstrated a dramatic (>400%) increase in cocaine attraction, whereas Dom mice's responses remained unchanged.

Further analysis of hippocampal gene expression revealed striking differences: in Sub mice, both stress and cocaine exposure significantly upregulated corticotropin-releasing hormone (CRH) expression (>100%), whereas in Dom mice, CRH elevation occurred only in response to cocaine. Additionally, stress led to marked reductions in DRD1 (>60%) and DRD2 (>50%) receptor expression in Sub mice, changes that were not observed in the Dom group. These findings suggest that social hierarchy and stress resilience influence dopaminergic regulation in the hippocampus, shaping susceptibility to addiction-like behaviors. The study underscores the potential role of early biological and behavioral markers in identifying individuals at elevated risk for addiction, supporting the broader consideration of early-life screening and intervention in pre-addiction. This demonstration points to the importance of evaluating the genetic trait (DNA polymorphisms) of an individual as measured by GARS, along with the utilization of not only GENOGRAMS to inform the clinician of family history of addictive behaviors (e.g. cocaine) but social rank as well [174].

Conclusion

We are proposing that development of theragnostic approaches targeting hypodopaminergic brain function represents an important and promising novel intervention. Moreover, early identification with GARS in children with the probability that carriers of polymorphic DNA risk antecedents as a pre-addiction trait seems reasonable. The probability that children identified with RDS and subsequent addictive -like behaviors have 74.4% Bayesian Predictive Value must be recognized. It is indeed plausible that these individuals may be more likely to commit crimes as adolescents or develop psychopathologies as adults. Our proposed approach described herein might be cost-effective in terms of averting crime and SUD and promoting normal development, leading to a rewarding and successful adulthood.

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Author Contribution

The initial draft was developed by KM, MSG, PKT, KZT, AP, KB and all co-authors edited provided references and comments and approved the manuscript.

Conflict of Interest

Dr. Blum is the holder of both USA and foreign patents related to GARS and KB220 and has licensed these patents to his company Synaptamine inc.

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