

Perspective

The First Exploratory Personalized Medicine Approach to Improve Bariatric Surgery Outcomes Utilizing Psychosocial and Genetic Risk Assessments: Encouraging Clinical Research

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Citation: Thanos, P.K.; Hanna, C.; Mihalkovic, A.; Hoffman, A.B.; Posner, A.R.; Busch, J.; Smith, C.; Badgaiyan, R.D.; Blum, K.; Baron, D.; et al. The First Exploratory Personalized Medicine Approach to Improve Bariatric Surgery Outcomes Utilizing Psychosocial and Genetic Risk Assessments: Encouraging Clinical Research. *J. Pers. Med.* **2023**, *13*, 1164. <https://doi.org/10.3390/jpm13071164>

Academic Editors: Nikolaos Drakoulis and Kenneth P.H. Pritzker

Received: 5 May 2023

Revised: 6 July 2023

Accepted: 10 July 2023

Published: 20 July 2023



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Abstract: It is predicted that by 2030, globally, an estimated 2.16 billion adults will be overweight, and 1.12 billion will be obese. This study examined genetic data regarding Reward Deficiency Syndrome (RDS) to evaluate their usefulness in counselling patients undergoing bariatric surgery and gathered preliminary data on the potential use in predicting short term (6-month) weight loss outcomes. **Methods:** Patients undergoing bariatric surgery ($n = 34$) were examined for Genetic Addiction Risk Severity (GARS) [measures the presence of risk alleles associated with RDS]; as well as their psychosocial traits (questionnaires). BMI changes and sociodemographic data were abstracted from Electronic Health Records. **Results:** Subjects showed Δ BMI ($M = 10.0 \pm 1.05 \text{ kg/m}^2$) and a mean % excess weight loss ($56 \pm 13.8\%$). In addition, 76% of subjects had GARS scores above seven. The homozygote risk alleles for *MAO* (rs768062321) and *DRD1* (rs4532) showed a 38% and 47% prevalence among the subjects. Of the 11 risk alleles identified by GARS, the *DRD4* risk allele (rs1800955), was significantly correlated with change in weight and BMI six months post-surgery. We identified correlations with individual risk alleles and psychosocial trait scores. The *COMT* risk allele (rs4680) showed a negative correlation with EEI scores ($r = -0.4983, p < 0.05$) and PSQI scores ($r = -0.5482, p < 0.05$). The *GABRB3* risk allele (rs764926719) correlated positively with EEI ($r = 0.6161, p < 0.01$) and FCQ scores ($r = 0.6373, p < 0.01$). The *OPRM1* risk allele showed a positive correlation with the DERS score ($r = 0.5228, p < 0.05$). We also identified correlations between DERS and BMI change ($r = 0.61; p < 0.01$). **Conclusions:** These data support the potential benefit of a personalized medicinal approach inclusive of genetic testing and psychosocial trait questionnaires

when counselling patients with obesity considering bariatric surgery. Future research will explore epigenetic factors that contribute to outcomes of bariatric surgery.

Keywords: obesity; bariatric surgery; Reward Deficiency Syndrome; addiction; psychosocial risk factors; genetic risk assessment

1. Introduction

Overweight and obesity were estimated to afflict nearly 1.5 billion adults worldwide in 2008 [1]. By 2030, the respective number of overweight and obese adults was projected to be 1.35 billion and 573 million individuals without adjusting for secular trends. If recent secular trends continue unabated, the absolute numbers were projected to total 2.16 billion overweight and 1.12 billion obese individuals [2]. It is noteworthy that the unwanted burden is greater for much of Asia, Latin America, the Middle East, and Africa due to differences in fat patterning and body composition and the cardiometabolic effects of body mass index (BMI) at levels far below standard BMI overweight cutoffs of 25.

Candidates for metabolic/bariatric surgery show a high prevalence of food addiction (FA). A random-effects meta-analysis was performed with cross-sectional studies to calculate the weighted prevalence of FA at the pre- and postoperative moments. For longitudinal studies, which measured FA at both time points for the same individuals, absolute prevalence reduction (APR) was calculated. Of the 6626 records, 40 studies were included in the meta-analysis. The preoperative weighted prevalence of FA was 32% (95% CI: 27–37%; 33 groups), whereas the postoperative prevalence was 15% (95% CI: 12–18%; 14 groups). Observational data suggest an attenuation in the prevalence of FA among patients that undergo bariatric surgery [3].

Bariatric surgery is the most efficient weight loss treatment for patients unable to achieve or sustain weight loss using non-surgical strategies [4]. A 2020 study reported weight loss of 47% after laparoscopic sleeve gastrectomy (LSG) and 55% after Roux-en-Y gastric bypass (RYGB) [5]. However, in patients undergoing bariatric surgery, there can be recidivism and unintended negative behavioral consequences [6]. For instance, rates of alcohol use disorder (AUD) post-surgery are as high as 28.4% compared to patients' AUD rate of 4.5% preoperatively [7].

Reward Deficiency Syndrome (RDS) is a framework for examining the role of genetics and epigenetics related to addictive behaviors [8,9]. This syndrome encompasses impulsive and compulsive behaviors, such as gambling, binge eating, and alcohol and drug abuse, resulting from hypodopaminergic reward circuitry functioning [10]. The Genetic Addiction Risk Severity (GARS) test was developed as a tool to identify risk variations of particular genes (See Supplementary Table S1): [dopamine receptor-D1 (*DRD1*), dopamine receptor-D4 (*DRD4*), dopamine transporter (*DAT1*), serotonin transporter gene (*5-HTT*)-linked, monoamine oxidase A (*MAOA*), opioid receptor Mu 1 (*OPRM1*), catechol-o-methyltransferase (*COMT*), and gamma-aminobutyric acid receptor subunit beta-3 (*GABRB3*)] that predict vulnerability to pain [11], addiction, and other compulsive behaviors that fall under the umbrella of RDS [12–16]. Understanding an individual's GARS score could provide proactive management for individuals at risk for RDS [12].

Patients who are candidates for bariatric surgery often struggle with body image, sub-optimal quality of life, and symptoms of depression and anxiety [17]. Prior to surgery, psychological assessments to identify these concerns can guide patients to support/interventions to maximize the likelihood of success following bariatric surgery [4,18]. In spite of these proactive interventions, there is variability in bariatric surgery short and long-term outcomes which may be attributed to AUD and other addictions [19]. This observation highlights the importance of identifying individuals who will need more aggressive preparation pre-surgery and post-operative behavioral follow-up [19,20].

The goal of the present study was to utilize a personalized medicine approach for bariatric surgery patients by examining potential genetic and psychosocial markers that may predict which patients undergoing bariatric surgery are at greater risk for recidivism of obesity and negative outcomes.

2. Methods

2.1. Participants

Seventy patients were approached during the last pre-surgery consultation appointment at the Kaleida Health Bariatric Center (Buffalo, NY, USA). After describing the study and providing an informational brochure, 34 subjects provided informed consent. The study was approved by the University at Buffalo's Institutional Review Board. Due to the COVID-19 pandemic, there was an unanticipated lack of in-person follow-up available for patients after surgery resulting in a smaller than anticipated sample size. As a result, sample sizes are not consistent between patients who completed the questionnaire, patients who provided a GARS sample, and patients who could be reached for follow-up appointments at post-op study time points.

2.2. Data Collection

Participants' data collected in the questionnaire were: age, sex, relationship status, education, and income. Additional demographic data and health parameters pre- and post (1, 3, 6 months) bariatric surgery were collected from the electronic health record. Weight loss (kg), change in BMI from preoperative to 6 months post-surgery and percent excess weight loss (%EWL) were calculated. The latter is a standard way for surgeons to assess post bariatric surgery weight changes. The formula for %EWL is: $[(\text{initial weight} - \text{post weight}) / (\text{initial weight} - \text{ideal weight})] \times 100$, where ideal weight corresponded to weight associated with 25 kg/m² BMI [21].

2.3. Psychosocial Questionnaires

Participants were given tablets to complete psychosocial questionnaires privately at the time of the visit or given the option to complete via email/web link remotely. Paper format was also available for those who were uncomfortable using technology. The questionnaire administered was a compilation of several validated scales (see Supplementary Table S2) used to evaluate psychosocial well-being in domains that are relevant to patients with obesity, such as measures of: nutritional habits: Eating Attitudes Test-26 (EAT-26) [22]; Food Cravings Questionnaire-Trait Reduced (FCQ-TR) [23]; Eating Expectancies Inventory (EEI) [24]; food addiction: modified Yale Food Addiction Scale 2.0 (mYFAS 2.0) [25]; binge-eating disorder symptoms: Weight Influenced Self-Esteem Questionnaire (WISE-Q) [26]; depression and anxiety: Difficulties in Emotion Regulation Scale (DERS) [27]; Center for Epidemiologic Studies Depression Scale (CESDS) [28], and chronic stress and life quality: Chronic Stress Index (CSI) [29,30], sleep: Pittsburgh Sleep Quality Index (PSQI) [31]. Questionnaire data were scored according to the corresponding scoring key included for each scale.

2.4. Genetic Addiction Risk Severity (GARS)

The GARS test assessed eleven specific gene polymorphisms known to predict increased susceptibility for substance use disorder (SUD). A cheek swab sample was collected from ($n = 34$) subjects and processed as previously described [32]. Briefly, DNA from the sample was isolated by PCR amplification and assayed for polymorphisms in the following genes: *DRD1*, *OPRM1*, *DRD2*, *DRD3*, *DRD4*, *COMT*, *DAT1*, *DRD4-R*, *GABRB3*, *HTTLPR*, and *MAOA* [14,33]. DNA assay results were analyzed by Geneus Health, (San Antonio, TX, USA) for specific polymorphism markers that have been previously established [33] to predict SUDs as well as RDS. As previously described [13], a risk score for each subject was then calculated based on the genetic analysis.

2.5. Statistical Analysis

Data are expressed as mean ± SD and analyzed and graphed using GraphPad Prism software 8.1.2 (San Diego, CA, USA). Linear regression of correlations between outcome variables were analyzed for ΔBMI and ΔWeight at 3- and 6-months post-surgery as well as for each GARS risk allele tested and psychosocial questionnaire results. Post hoc analysis (Tukey’s HSD test, Sidak’s test) was performed for all significant ANOVA outcomes. The change in weight/BMI for each patient was calculated from the bariatric clinic reports at all study time points. These results were included in a correlational analysis with the GARS scores of all patients who provided a buccal swab. The 3- and 6-month time points were included in the statistical analysis to determine correlation between weight/BMI change and overall GARS score. Correlational analyses were also performed for each of the individual risk alleles implicated by GARS with patients’ change in weight/BMI.

2.6. Ethics

This study was carried out in accordance with and approval by The Institutional Review Board of the University at Buffalo. All subjects were informed about the study, and all provided signed informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of HRP-503.

3. Results

3.1. Baseline Demographic Characteristics

Participants (*n* = 34) were recruited from the Bariatric Program at Kaleida Health, which is designated as a Comprehensive Center under the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program. This study was approved by the IRB at the University at Buffalo. Table 1 summarizes self-reported demographic data via questionnaires and pre-surgery BMI and weight extracted from electronic health records for 26/34 participants. Participants were predominantly female and Caucasian, with >50% reporting a childhood history of overweight/obesity. Table 2 reports the changes in BMI for 24 subjects after undergoing bariatric surgery. Of the subjects, 74% underwent vertical sleeve gastrectomy. The COVID-19 epidemic prevented us from obtaining psychosocial questionnaires and follow-up data in 10 participants.

Table 1. Self-Report Data (Demographics, weight, BMI) (*n* = 26).

Age (years)	M = 47 ± 12, range: 22–72
Sex	90% Female
Race	85% White
Weight (kgs)	M = 118, SD = 20.8
BMI	M = 43, SD = 6.0
Surgery	26% RYGB (bypass) 74% Vertical Sleeve Gastrectomy
Childhood Weight Status	8% Underweight; 38% Healthy Weight; 42% Overweight 12% Obese
Marital Status	27% Single/Never Married; 41% Married/Living with Spouse; 11% Living with Intimate Partner 14% Divorced 7% Widowed
Employment	51% Full-time; 11% Part-time 11% Not employed, but looking 27% Not employed, not looking
Education	96% Graduated from High School/GED 50% College Degree (Associates/Bachelors) 15% College Degree (Masters)

Table 1. Cont.

Income Last Year	27% Less Than \$10,000 27% \$1500–\$55,000 23% \$55,000–\$99,000 12% \$100,000 and over
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Mean patient weight data as well as demographic data from patients based on self-report measures reported preoperatively and Electronic Health Records from the bariatric clinic (*n* = 26).

Table 2. BMI/Weight Loss Outcomes at 6 Months Post-Surgery (*n* = 24).

	Total Population (<i>n</i> = 24)	VSG (<i>n</i> = 19)	RYGB (<i>n</i> = 5)
Mean BMI ± SD	33.3 ± 3.7	32.7 ± 3.6	35.5 ± 4.2
Mean ΔBMI ± SD	10.3 ± 4.3	9.8 ± 4.3	12.1 ± 4.4
%EWL ± SD	56.0 ± 13.8	56.3 ± 14.3	54.5 ± 14.7

Summarized BMI, ΔBMI from preop to 6 months post-op, and percent excess weight loss (%EWL) results from patients of the total study population (*n* = 24) and those who underwent either VSG (*n* = 19) or RYGB surgery (*n* = 5).

3.2. Psychosocial and GARS Data

The psychosocial questionnaires scores are summarized in Table 3. Background information on these scores and their significance are provided in Supplementary Table S2. A majority of patients reported sleep quality, food cravings, depressive-like symptoms, and food addiction scores similar to those reported in previous studies on obese patients [23,25,28,31]. However, the mean score from the modified Yale Food Addiction Scale (mYFAS) was 2.0 which is lower than anticipated, suggesting a less than expected prevalence of food addiction for this cohort. Additionally, the symptom count in our study (1.32 ± 1.23) was lower than previously reported in other studies on individuals with obesity [34,35].

The GARS test results identified copy number of the 11 risk alleles for each patient (*n* = 34), assigned as either homozygote (two copies of the risk allele), heterozygote (one copy of the risk allele), or low risk (no copies of the risk allele). Figure 1 presents the % frequency for each risk allele for each gene of interest. The MAO and DRD1 genes yielded the greatest frequency of homozygote alleles, whereas none of the subjects were homozygous for risk allele genes OPRM1, DRD4 (rs761010487), and DAT1f. A total GARS score of seven or greater qualifies as high risk for alcohol addiction. Our results showed that 76% of subjects fell into the high-risk category for alcohol addiction (Figure 2).

Table 3. Psychosocial Questionnaire Results. Mean (SD).

Eating Attitudes Test-26	Total: 14.9 (8.1)
Food Cravings Questionnaire—Trait Reduced (FCQ-T)	- Domain Control: 2.3 (1.17)
	- Thoughts: 2.1 (1.23)
	- Plans: 2.5 (1.57)
	- Emotions: 2.4 (1.33)
	- Cues: 2.7 (1.54)
Eating Expectancies Inventory	- Manage Negative Affect: 2.91 (2.02)
	- Pleasurable and Useful as a Reward: 3.62 (2.23)
	- Feeling Out of Control: 3.12 (2.11)
	- Enhances Cognitive Competence: 2.69 (1.82)
Modified Yale Food Addiction Scale 2.0	- Alleviates Boredom: 3.35 (2.23)
	Mean Symptom Count (SD): 1.32 (1.23)
	No Food Addiction (%): 61
	Mild (%): 31
	Moderate (%): 4
Weight-Influenced Self Esteem Questionnaire	Severe (%): 4
	M (SD): 1.6 (1.3)

Table 3. Cont.

Eating Attitudes Test-26	Total: 14.9 (8.1)
Difficulties in Emotion Regulation Scale—Short Form	Total Mean (SD): 33.81 (10.96)
	- Total w/o Awareness: 27.5 (10.52)
	- Awareness: 6.35 (2.46)
	- Clarity: 4.61 (1.80)
	- Goals: 7.58 (3.88)
	- Impulse: 4.23 (2.3)
	- Non-acceptance: 5.65 (2.67)
- Strategies: 5.38 (2.89)	
Center for Epidemiological Studies Depression Scale	Total Score (Mean, range): 12.7, 0–35 No Depression (%): 69 Mild Depression (%): 8 Probable Depression (%): 23
Chronic Stress Index	Perceived Everyday Unfair Treatment (Mean Score): 1.8 Major Negative Life Events in Past Year: 1.13
Quality of Life Enjoyment and Satisfaction Questionnaire	M (SD): 3.24 (0.89)
Pittsburgh Sleep Quality Index	M (SD): 8.0 (3.74)

Summary of scored outcomes from self-report psychosocial questionnaires completed by patients prior to surgery (*n* = 26). Mean score totals and subscale scores for each inventory.

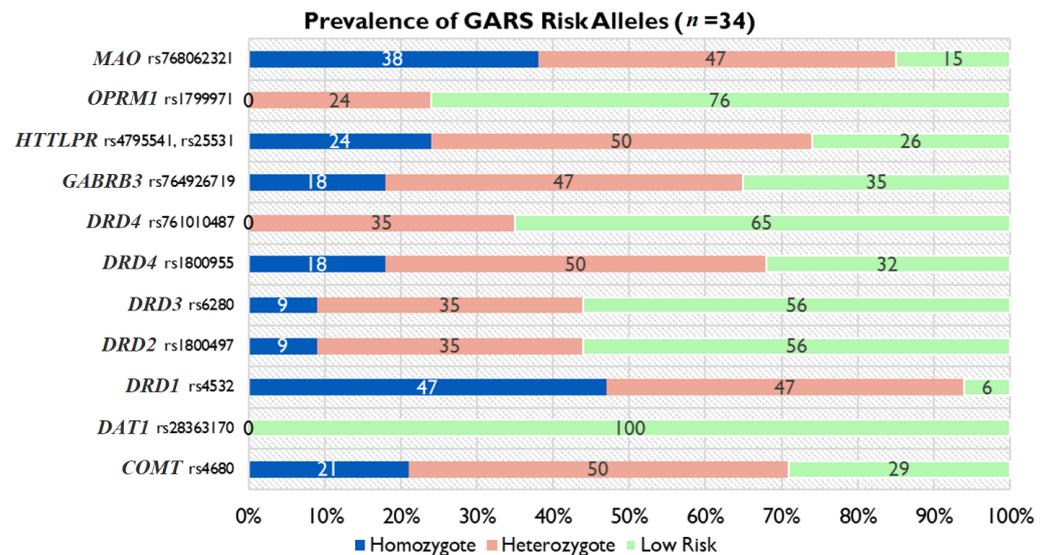


Figure 1. GARS results represented as the percent frequency of gene type for each risk allele analyzed within the patient population (*n* = 34). The homozygote category represents having two copies of the risk allele, heterozygous represents one copy of the risk allele, and the low-risk category represents no copies of the risk allele per gene.

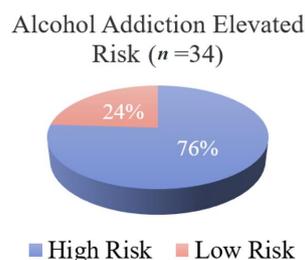


Figure 2. Frequency of patients with a GARS score qualifying them for high risk or low risk of alcohol addiction. Risk category is based on total number of GARS risk alleles.

3.3. Risk Alleles and Association with Weight Loss and Inventory Scores

We analyzed body weight data available preoperatively and at six months post-surgery ($n = 21$) for the 11 risk alleles analyzed. The *DRD4* risk allele (rs1800955) was significantly correlated with preoperative weight ($r = 0.4331$, $p < 0.05$ Figure 3a), change in weight ($r = 0.4726$, $p < 0.05$; Figure 3b), and change in BMI ($r = 0.4577$, $p < 0.05$; Figure 3c).

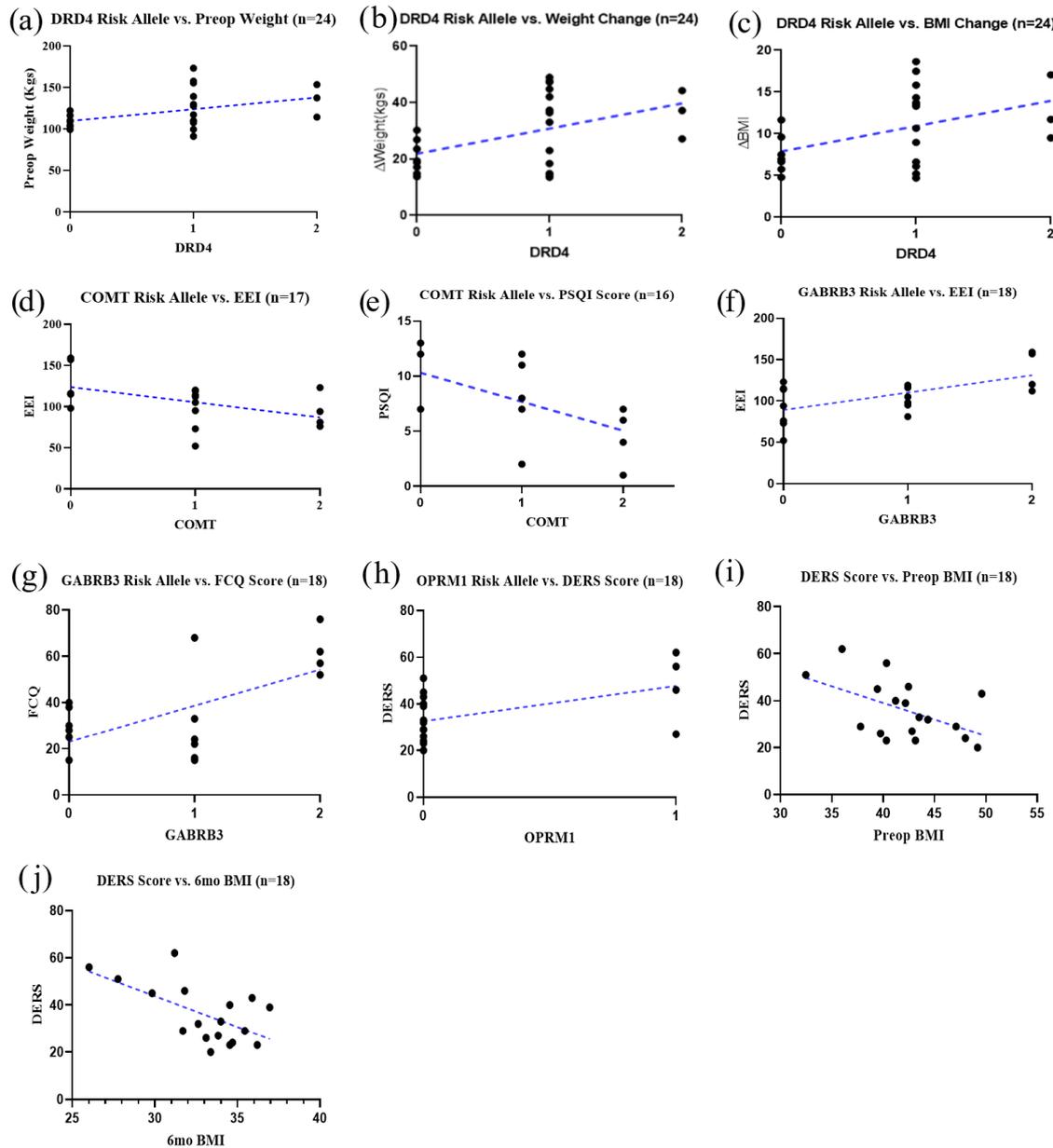


Figure 3. (a–j). BMI and specific psychosocial inventory outcomes are correlated with GARS: (a) *DRD4* risk allele positively correlated with preop weight ($r = 0.4331$, $R^2 = 0.1876$, $p = 0.0345$); (b) *DRD4* risk allele positively correlated with change in weight ($r = 0.4726$, $R^2 = 0.2234$, $p = 0.0197$); (c) *DRD4* risk allele positively correlated with change in BMI ($r = 0.4577$, $R^2 = 0.2095$, $p = 0.0245$); (d) *COMT* risk allele negatively correlated with EEI scores ($r = -0.4983$, $R^2 = 0.2483$, $p = 0.0418$); (e) *COMT* risk allele negatively correlated with PSQI scores ($r = -0.5482$, $R^2 = 0.3005$, $p = 0.0279$); (f) *GABRB3* risk allele positively correlated with EEI scores ($r = 0.6161$, $R^2 = 0.3796$, $p = 0.0084$); (g) *GABRB3* risk allele positively correlated with FCQ scores ($r = 0.6373$, $R^2 = 0.4062$, $p = 0.0044$); (h) *OPRM1* risk allele positively correlated with DERS scores ($r = 0.5228$, $R^2 = 0.2733$, $p = 0.0260$); (i) DERS scores negatively correlated with preop BMI ($r = -0.5142$, $R^2 = 0.2644$, $p = 0.0290$); (j) DERS scores negatively correlated with BMI 6 months post-surgery ($r = -0.6137$, $R^2 = 0.3766$, $p = 0.0068$).

Correlations were examined between the various psychosocial questionnaire scores and individual risk alleles. Results showed a significant negative correlation between the *COMT* risk allele and EEI scores ($r = -0.4983$, $p < 0.05$; Figure 3d). The *COMT* risk allele was also negatively correlated with the PSQI scores, ($r = -0.5482$, $p < 0.05$; Figure 3e). In addition, there was a positive correlation between the *GABRB3* risk allele and EEI scores ($r = 0.6161$, $p < 0.01$; Figure 3f) and a positive correlation with scores on the FCQ ($r = 0.6373$, $p < 0.01$; Figure 3g). Next, the *OPRM1* risk allele was positively correlated with the DERS scores ($r = 0.5228$, $p < 0.05$; Figure 3h). Results also showed that the scores from the DERS were also significantly correlated with BMI before surgery ($r = -0.5142$, $p < 0.01$; Figure 3i) and at 6 months post-surgery ($r = -0.6137$, $p < 0.01$; Figure 3j).

3.4. Heterosis

To determine if heterosis was occurring within the genes evaluated, a student's *t* test was conducted to compare data from patients with no risk allele copies for each gene and patients who were heterozygous for the risk allele of each gene. Heterosis is the adaptive superiority of the heterozygous genotype with respect to one or more characters in comparison with the corresponding homozygote [36]. Moreover, in proposing the term *heterosis* to replace the older term *heterozygosis*, the newer idea aimed to avoid limiting the term to the effects that can be explained by heterozygosity in Mendelian inheritance. Specifically, Heterosis is considered to be an outbreeding enhancement which displays an improved or increased function of any biological quality in a hybrid offspring [37]. An offspring is heterotic if its traits are enhanced as a result of mixing the genetic contributions of its parents. Currently, the actual mechanism for this enhanced improvement or effect is unknown.

The analysis revealed a significant difference in Δ in weight (kg) ($t = 2.400$, $p = 0.03$), Δ in BMI ($t = 2.234$, $p = 0.04$), and %EWL ($t = 2.418$, $p = 0.03$) at six months post-surgery between patients with 0 or 1 copies of the *DRD4* risk allele (Figure 4). Subjects with one copy of the *DRD4* risk allele achieved greater weight loss at the six months post-surgery timepoint, including Δ in BMI and %EWL, than subjects with no copy of this risk allele.

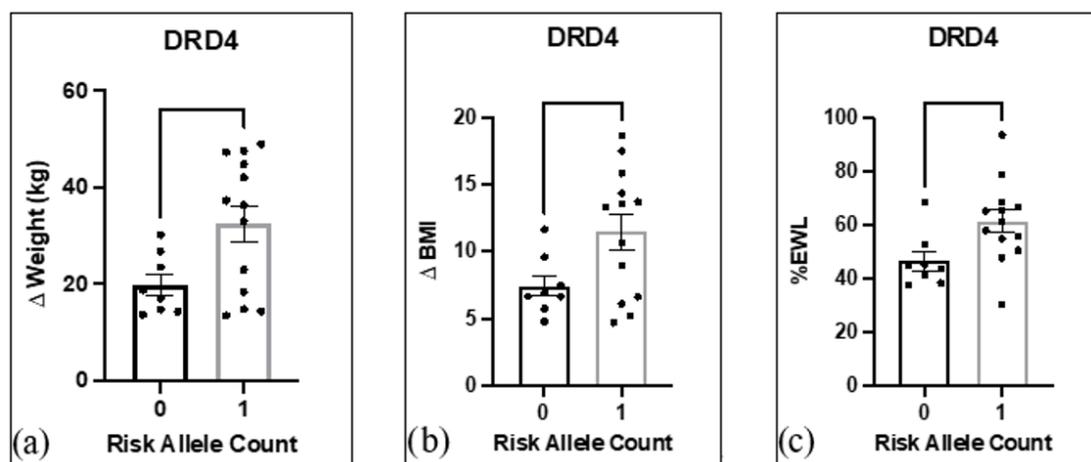


Figure 4. (a–c). Heterosis in *DRD4* gene: (a) significant difference ($t = 2.400$, $p = 0.03$) of mean change in weight at 6 months between patients with 0 and 1 copies of the *DRD4* risk allele; (b) significant difference ($t = 2.234$, $p = 0.04$) of mean change in BMI at 6 months between patients with 0 and 1 copies of the *DRD4* risk allele; (c) significant difference ($t = 2.418$, $p = 0.03$) of %EWL at 6 months between patients with 0 and 1 copies of the *DRD4* risk allele. Data are $M \pm SEM$ Student's *t* test.

4. Discussion

In this study of obese adults undergoing bariatric surgery, we obtained psychosocial inventory scores similar to obese subjects in previous studies [38–41]. As expected, subjects

reported greater eating disorder pathology, sleep disturbances, and food cravings as well as lower life enjoyment and satisfaction than historical non-obese controls [42–45]. There were some inventory score results, however, that were not similar to previous reports in obese subjects. Murray et al. reported that the reduction in food addiction observed six months post-surgery was not maintained at 12 months [46]. In the study by Murray et al., food addiction at 12 months post-surgery was associated with poorer weight loss, eating, and lifestyle behaviors. It is of interest that between baseline and 24 months, YFAS scores decreased ($p = 0.006$) and alcohol intake increased in the surgery group ($p = 0.005$). Significant changes were not observed in the diet or no treatment groups [46].

The genetic results (GARS test) examined the genetic vulnerability for addictive behaviors and RDS as measured by the presence of ten reward genes and eleven risk polymorphisms [13]. The evidence presented provided relevant genetic information that will reinforce targeted therapies to improve recovery and prevent recidivism on an individualized basis, especially in terms of bariatric surgery. The primary driver of RDS is a hypodopaminergic trait (genes) as well as epigenetic states (methylation and deacetylation on chromatin structure). We hypothesize that genetic testing at an early age may be an important strategy to reduce or eliminate pathological substance and behavioral seeking activity post bariatric surgery.

Analysis of the GARS results revealed a diverse genetic profile across study participants. At least one patient from the cohort was homozygous for each of the risk alleles of the genes tested except for the *DRD4* (rs1800955) and *OPRM1* genes, as well as the *DAT1* gene, for which no patient carried the risk allele. The most common homozygous risk alleles present in the study cohort were for the *DRD1* and *MAOA* gene, with a prevalence of 47 and 38 percent, respectively. Using this information, alcohol addiction risk scores were calculated and revealed that 76% of the subjects had an elevated risk for AUD. This outcome highlights the importance of utilizing a personalized approach prior to surgery in order to identify patients that might need additional counselling or intervention after surgery.

The correlational analyses revealed several correlations between GARS and weight changes after bariatric surgery. First, the *DRD4* risk allele (rs1800955) genotype was found to be significantly associated with both BMI and weight change at six months post-surgery. Patients with two copies of the risk allele showed greater change in weight between preop and six months than did patients with no copies of the *DRD4* risk allele. The *DRD4* gene has previously been linked to Attention Deficit Hyperactivity Disorder (ADHD) [47,48]. The D4 receptors in the brain are prominently expressed in the prefrontal cortex, an area that regulates attention, decision-making, and inhibitory control [49]. These receptors are also located in the hippocampus, amygdala, and hypothalamus, where they are involved in the reinforcing properties of food [50]. Each one of these cognitive functions could influence patients' success at dieting and maintaining weight loss after surgery, mediating the positive relationship we identified between greater change in weight and more copies of the *DRD4* risk allele. Our findings indicate that having two copies of the *DRD4* risk allele, as opposed to one or none, could serve as a beneficial genetic predictor for weight loss after surgery. It is possible that the hypodopaminergic functioning associated with this *DRD4* gene polymorphism lowers the reward experienced from food consumption, giving patients an upper hand when it comes to avoiding food and losing weight.

Correlations of each individual GARS gene and psychosocial inventory outcomes also yielded significant outcomes. For instance, we found that scores on the EEI were correlated negatively with the *COMT* gene and positively with the *GABRB3* gene. The inverse relationship seen between EEI scores and copies of the *COMT* risk allele, the Val158Met/rs4680 polymorphism, suggests that patients carrying one or more copies expect less mood and cognitive benefits from eating compared to patients with no copies of this allele who scored higher on the inventory. An important regulator of dopaminergic neurotransmission, *COMT* is a degrading enzyme and metabolizes DA to inactive compounds, especially in prefrontal brain regions [51,52]. Prior studies have uncovered a potential connection be-

tween *COMT* polymorphisms and eating disorder pathology. For instance, an investigation into the influence of the *COMT* polymorphism on behavioral impulsivity in the binge eating disorder found that patients within the BED group that were homozygous for the risk allele showed stronger deficits in inhibitory control [53]. Given the current literature on *COMT* and eating behavior, we expected to see higher scores of eating expectancies in patients with one or more copies of the risk allele. Future data at 12 months post-surgery may reveal more insight into the correlation identified here or present a possible shift in the direction of this relationship.

The significant correlation between EEI scores and the *GABRB3* gene indicates that patients with a homozygous risk allele genotype, the 181 variants of the gene, reported greater expectancies of food to improve their cognitive and emotional states. Disruption in the expression of GABA_A receptors is associated with imbalances in excitatory/inhibitory signaling in the brain that can have profound consequences on cognition, perception, and maintenance of mood [54]. Dysregulation brought on by the *GABRB3* polymorphism involves an increase in GABA transmission that leads to a reduction in DA release at the nucleus accumbens. The EEI discussed here contains items related specifically to affective mood regulation. A major factor influencing negative affect is emotion regulation (ER). Using this framework, a possible explanation for the correlation seen between the *GABRB3* risk allele and increased eating expectancies in our study cohort could be that individuals with dysregulated GABA_A signaling are more likely to use food to regulate their affective states and count on food to improve their mood. Consequently, these individuals may be at greater risk of jeopardizing their maintenance of weight loss after surgery by continuing to rely on food to cope with negative mood states.

The *GABRB3* gene was also significantly correlated with scores on the Food Cravings Questionnaire (FCQ), showing a similar outcome as previously discussed with the EEI. Patients in our study with two copies of the risk allele had scores indicative of greater food cravings compared to patients with one or no copies of the risk allele. Items on the FCQ measure the individuals' perceived ability to control their cravings and the extent to which food occupies their thoughts and influences their emotions. The correlation from this questionnaire adds further support to the hypothesis that homozygous carriers of the *GABRB3* risk allele are at an increased risk of using food to alleviate negative mood states and because of this coping strategy, may over-eat in a manner that leads to weight regain after bariatric surgery.

A negative correlation is presented between the *COMT* gene and scores on the PSQI. The inverse relationship we saw indicates that homozygous carriers of the *COMT* risk allele reported lower scores on the PSQI, associated with good sleep quality, compared to patients with one or no risk alleles. There is some preexisting research on the association between *COMT* polymorphisms and sleep; however, not all studies come to the same conclusion. Investigation into this relationship is based on evidence that individuals homozygous for the Val allele show higher *COMT* activity and lower dopaminergic signaling in the prefrontal cortex than subjects homozygous for the Met allele. Due to the crucial role of *COMT* in metabolizing DA, it has been suggested that the *COMT* gene polymorphism impacts cognitive function, sleep-wake regulation, and sleep pathologies [55]. On the other hand, the current literature has contributed investigations that lack support for the impact of the *COMT* gene polymorphism on arousal regulation and sleep [56]. Given the high rates of sleep apnea among obese populations, examining the possible influence of the Val158Met polymorphism on sleep quality is of relevance and should be further examined.

Additionally, our results revealed a significant correlation between the *OPRM1* gene and scores of the DERS. As previously discussed, emotion regulation is a major factor influencing outcomes after surgery for patients. The A118G polymorphism of the *OPRM1* gene has been associated with lower mRNA transcription and translation and a dampening of opioid signalling efficiency in the brain [57]. Carriers of the G allele resulting from this gene polymorphism have been shown to display increased emotional dysregulation and frequency of mood disturbances and have been shown to warrant potential as a modulator

of sensitivity to stressors [57–59]. These findings help lend an explanation and support to the significant correlations discussed here. No patients in our study were homozygous carriers of the G risk allele; however, heterozygous carriers reported higher scores on the DERS, indicating that they experience greater than normal difficulties in regulating their emotions.

Variations in the genes associated with these neurotransmitters can lead to insensitivity to positive reinforcers. Notably, maternal ingestive behavior can alter the expression of mesocorticolimbic genes implicated in the regulation of dopamine and opioid function in offspring. This finding was reported from a study investigating receptor binding differences in mice prenatally exposed to low protein (LP) or high fat (HF) diets. Results from this experiment showed that LP but not HF offspring had significantly elevated mu-opioid receptor (MOR) and D1R binding in the brain, highlighting the possible outcomes of suboptimal gestational diets and how they may increase risk for obesity, addiction, and ADHD [60].

Self-report outcomes on the DERS were also significantly correlated with pre-surgery and at six months post-surgery BMI. The positive correlations for both study time points suggest that having greater emotional regulation difficulties is associated with a greater BMI. This relationship has been thoroughly examined in previous studies, providing a depth of evidence for the significant correlation of obesity and emotional dysregulation [61–63]. Individual personality and temperament analyzed within the DERS relates to long-term outcomes after bariatric surgery. In fact, certain dispositional tendencies are shown to be less optimal for patients after surgery, highlighting the usefulness of a psychosocial analysis prior to surgery to inform a targeted approach to improving outcomes [64].

While heterosis is an important concept in genetics as evidenced by many studies including the lesson learned with the *DRD2* A1 allele and RDS [12,36], because of high allelic presence of the reward genes as measured in GARS in the general population, we chose to utilize a very conservative approach whereas zero vs. two copies provided highly accurate statistical power. However, our significant finding with the *DRD4* polymorphism further supports a potential heterosis phenomenon.

Limitations

Limitations to this study include a small sample size because of the COVID-19 pandemic. Additionally, the genetic and psychosocial measures of these patients can be considered cofactors. Other epigenetic factors were not considered in this study. These subjects will be monitored for bodyweight data as they relate to genetic and psychosocial data to determine long term outcomes in addition to the present study. It is important to highlight the fact that the GARS test utilized in this study has not been independently validated by scientists across the globe. However, while this is true, it is our contention that currently there are 74 articles listed in Pubmed as of 21 June 2023. The development of this genetic assessment was initiated by Blum's laboratory in 2014 published in *Molecular Neurobiology* [33]. Since that time the same authors have published human trials concerning various applications of GARS in clinical medicine with significantly significant results [11,13,14,16,65–78]. Moreover, since 1990, when our laboratory published the association of the *DRD2* Taq A1 allele and severe alcoholism in *JAMA*, there has been an explosion of genetic candidate association studies, including GWAS. In order to statistically validate the selection of the risk alleles analyzed by GARS, Blum's laboratory applied a strict analysis to studies that investigated the association of each polymorphism with AUD or AUD-related conditions published from 1990 until 2021. The total number of patients evaluated was 74,566. This evaluation calculated the Hardy–Weinberg Equilibrium of each polymorphism in cases and controls. If available, the Pearson's χ^2 test or Fisher's exact test was applied to comparisons of the gender, genotype, and allele distribution. The statistical analyses 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 *DRD2*, *DRD3*, *DRD4*, *DAT1*, *COMT*, *OPRM1*, and *5HTT* at 5% [68]. While most of

the research related to GARS is derived from our laboratory, we are encouraging more independent research to confirm our findings. In addition, large GWAS from Yale recently revealed that for example, in 1.2 million veterans, the top candidate gene to associate with depression was the *DRD2* gene polymorphism tested in GARS [79] was at 1×10^{-7} . In addition, using the same 1.2 million veterans, scientists from Duke performed GWAS and found that the top gene was also the *DRD2* AT 10^{-12} [80]. Additionally, scientists from Washington University also found that the *DRD2* Taq A1 polymorphism in GWAS in over 1 million subjects also identified this loci underlying multiple substance use disorders. In sum, we are very encouraged by these first ever results linking known reward gene risk polymorphisms to a number of metrics related to clinical outcomes post bariatric surgery. Knowledge of precise polymorphic associations can help in the attenuation of: guilt and denial; corroboration of family gene-o-grams; assistance in risk-severity-based decisions about appropriate therapies, including pain medications and risk for addiction; choice of the appropriate level of care placement (i.e., inpatient, outpatient, intensive outpatient, residential); determination of the length of stay in treatment; determination of genetic severity-based relapse and recovery liability and vulnerability; 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 supporting medical necessity for insurance scrutiny. Of course, based on our results herein, we encourage further research to confirm and extend these seemingly very important results. Our futuristic perspective is if these results are subsequently confirmed in much larger studies, we encourage global implementation.

5. Conclusions

The mean change in BMI ($10.3 \text{ kg/m}^2 \pm 4.3$) observed was similar to the six-month weight loss post bariatric surgery reported in the literature. By utilizing genetic testing, we were able to construct a genetic profile for each patient that would inform health care providers and patients regarding individual risk for alcohol and substance abuse. Beyond calculating total risk scores, risk alleles from each gene, we assessed associations with other factors such as patients' change in BMI, % excess weight loss, and psychosocial questionnaire scores. This risk may very well predict other hazardous post-surgery RDS behaviors, such as smoking and gambling. The subsequent information may be then used clinically to counsel patients and potentially provide additional adjunct support and care. The multi-disciplinary approach used here considers how RDS interacts with factors that influence maintenance of weight loss after surgery and overall quality of life. The use of genetic testing in bariatric surgery populations as a predictive measure for risk outcomes is a novel approach which can be incorporated into personalized medicine. This initial study is the first to combine a psychosocial questionnaire and genetic testing as an approach towards identifying negative outcomes after surgery. As a predictive tool, genetic testing continues to show meaningful utility in the ongoing goal of fine-tuning precision medicine and enhancing treatment strategies for patients.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jpm13071164/s1>, Table S1: Psychosocial Questionnaire Inventories; Table S2: GARS Panel.

Author Contributions: P.K.T., L.D.M., T.Q., K.B. and D.B.: study concept and design; A.M. and C.S.: data collection and analysis; A.B.H., A.R.P., J.B., P.K.T., K.B. and T.Q.: data interpretation and statistical analysis; P.K.T., T.Q. and L.D.M.: obtained funding, study supervision. P.K.T., K.B., R.D.B. and C.H.: review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This study was partially supported by the University at Buffalo VPR Buffalo Blue Sky. K.B. along with Marjorie Gondre-Lewis (Howard University) are recipients of R41 MD012318/MD/NIMHD NIH HHS/United States. P.K.T. is the recipient of R21 DA045640/DA/NIDA NIH HHS/United States; R33 DA045640/DA/NIDA NIH HHS/United States.

Institutional Review Board Statement: This study was carried out in accordance with and approval by The Institutional Review Board of the University at Buffalo.

Informed Consent Statement: All subjects were informed about the study, and all provided signed informed consent.

Data Availability Statement: Data is available from the corresponding author. Blum is the inventor of GARS and has assigned patent rights to Igene LLC, and TranspliceGen Holdings LLC.

Acknowledgments: We are indebted to the bariatric program staff, especially NPs and administrative staff. We thank the following individuals who are part of the Obesity Bariatric Research Network: Jamey Tulloch, Ken Leonard, Pamela Novello Smith, and Carroll Harmon.

Conflicts of Interest: Blum is the inventor of the Genetic Addiction Risk Severity (GARS) test and KB220 pro-dopamine variants and through his companies Synaptamine, Inc. and SpliceGen Holdings own all relevant worldwide patents.

Abbreviations

Attention Deficit Hyperactivity Disorder (ADHD), alcohol use disorder (AUD), body mass index (BMI), Center for Epidemiologic Studies Depression Scale (CESDS), catechol-o-methyltransferase (COMT), Chronic Stress Index (CSI), dopamine (DA), dopamine transporter gene (DAT), dopamine receptor-D1 (*DRD1*), dopamine receptor-D4 (*DRD4*), Difficulties in Emotion Regulation Scale (DERS), Eating Attitudes Test-26 (EAT-26), Eating Expectancies Inventory (EEI), emotion regulation (ER), Food Cravings Questionnaire-Trait Reduced (FCQ-TR), gamma-aminobutyric acid receptor subunit beta-3 (*GABRB3*), Genetic Addiction Risk Severity (GARS), high protein (HP), low protein (LP), laparoscopic sleeve gastrectomy (LSG), monoamine oxidase A (*MAOA*), mu-opioid receptor (MOR), modified World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (mWHO-ASSIST), modified Yale Food Addiction Scale 2.0 (mYFAS 2.0), opioid receptor Mu 1 (*OPRM1*), Positron emission tomography (PET), Pittsburgh Sleep Quality Index (PSQI), Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q), reward deficiency syndrome (RDS), Reward Deficiency Syndrome Questionnaire (RDS-Q), Roux-en-Y gastric bypass (RYGB), substance use disorder (SUD), Weight Influenced Self-Esteem Questionnaire (WISE-Q), serotonin transporter gene (*5HTT*), percent excess weight loss (%EWL).

References

1. Carpaij, O.A.; van den Berge, M. The asthma-obesity relationship: Underlying mechanisms and treatment implications. *Curr. Opin. Pulm. Med.* **2018**, *24*, 42–49. [[CrossRef](#)] [[PubMed](#)]
2. Kelly, T.; Yang, W.; Chen, C.S.; Reynolds, K.; He, J. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* **2008**, *32*, 1431–1437. [[CrossRef](#)] [[PubMed](#)]
3. Praxedes, D.R.; Silva-Júnior, A.E.; Macena, M.L.; Gearhardt, A.N.; Bueno, N.B. Prevalence of food addiction among patients undergoing metabolic/bariatric surgery: A systematic review and meta-analysis. *Obes. Rev.* **2022**, *24*, e13529. [[CrossRef](#)] [[PubMed](#)]
4. Wolfe, B.M.; Kvach, E.; Eckel, R.H. Treatment of Obesity: Weight Loss and Bariatric Surgery. *Circ. Res.* **2016**, *118*, 1844–1855. [[CrossRef](#)]
5. Grönroos, S.; Helmiö, M.; Juuti, A.; Tiusanen, R.; Hurme, S.; Löyttyniemi, E.; Ovaska, J.; Leivonen, M.; Peromaa-Haavisto, P.; Mäklin, S.; et al. Effect of Laparoscopic Sleeve Gastrectomy vs. Roux-en-Y Gastric Bypass on Weight Loss and Quality of Life at 7 Years in Patients With Morbid Obesity: The SLEEVEPASS Randomized Clinical Trial. *JAMA Surg.* **2021**, *156*, 137–146. [[CrossRef](#)]
6. Hardman, C.A.; Christiansen, P. Psychological issues and alcohol misuse following bariatric surgery. *Nat. Rev. Endocrinol.* **2018**, *14*, 377–378. [[CrossRef](#)]
7. Ivezaj, V.; Benoit, S.C.; Davis, J.; Engel, S.; Lloret-Linares, C.; Mitchell, J.E.; Pepino, M.Y.; Rogers, A.M.; Steffen, K.; Sogg, S. Changes in Alcohol Use after Metabolic and Bariatric Surgery: Predictors and Mechanisms. *Curr. Psychiatry Rep.* **2019**, *21*, 85. [[CrossRef](#)]
8. Blum, K.; Thanos, P.K.; Wang, G.-J.; Febo, M.; Demetrovics, Z.; Modestino, E.J.; Braverman, E.R.; Baron, D.; Badgaiyan, R.D.; Gold, M.S. The Food and Drug Addiction Epidemic: Targeting Dopamine Homeostasis. *Curr. Pharm. Des.* **2018**, *23*, 6050–6061. [[CrossRef](#)]
9. Gold, M.S.; Blum, K.; Febo, M.; Baron, D.; Modestino, E.J.; Elman, I.; Badgaiyan, R.D. Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti-reward systems. *Front. Biosci.* **2018**, *10*, 309–325.

10. Gondré-Lewis, M.C.; Bassey, R.; Blum, K. Pre-clinical models of reward deficiency syndrome: A behavioral octopus. *Neurosci. Biobehav. Rev.* **2020**, *115*, 164–188. [[CrossRef](#)]
11. Moran, M.; Blum, K.; Ponce, J.V.; Lott, L.; Gondré-Lewis, M.C.; Badgaiyan, S.; Brewer, R.; Downs, B.W.; Fynman, P.; Weingarten, A.; et al. High Genetic Addiction Risk Score (GARS) in Chronically Prescribed Severe Chronic Opioid Probands Attending Multi-pain Clinics: An Open Clinical Pilot Trial. *Mol. Neurobiol.* **2021**, *58*, 3335–3346. [[CrossRef](#)] [[PubMed](#)]
12. Blum, K.; Baron, D.; Lott, L.; Ponce, J.V.; Siwicki, D.; Boyett, B.; Steinberg, B.; Modestino, E.J.; Fried, L.; Hauser, M.; et al. In Search of Reward Deficiency Syndrome (RDS)-free Controls: The “Holy Grail” in Genetic Addiction Risk Testing. *Curr. Psychopharmacol.* **2020**, *9*, 7–21. [[CrossRef](#)] [[PubMed](#)]
13. Blum, K.; Bowirrat, A.; Baron, D.; Lott, L.; Ponce, J.V.; Brewer, R.; Siwicki, D.; Boyett, B.; Gondre-Lewis, M.C.; Smith, D.E.; et al. Biotechnical development of genetic addiction risk score (GARS) and selective evidence for inclusion of polymorphic allelic risk in substance use disorder (SUD). *J. Syst. Integr. Neurosci.* **2020**, *6*. [[CrossRef](#)]
14. Blum, K.; Modestino, E.J.; Gondre-Lewis, M.; Chapman, E.J.; Neary, J.; Siwicki, D.; Baron, D.; Hauser, M.; Smith, D.E.; Roy, A.K.; et al. The Benefits of Genetic Addiction Risk Score (GARS™) Testing in Substance Use Disorder (SUD). *Int. J. Genom. Data Min.* **2018**, *2018*, 115. [[CrossRef](#)] [[PubMed](#)]
15. Blum, K.; Simpatico, T.; Badgaiyan, R.D.; Demetrovics, Z.; Fratantonio, J.; Agan, G.; Febo, M.; Gold, M.S. Coupling Neurogenetics (GARS™) and a Nutritional Based Dopaminergic Agonist to Treat Reward Deficiency Syndrome (RDS): Targeting Polymorphic Reward Genes for Carbohydrate Addiction Algorithms. *J. Reward Defic. Syndr.* **2015**, *1*, 75–80. [[CrossRef](#)]
16. Fried, L.; Modestino, E.J.; Siwicki, D.; Lott, L.; Thanos, P.K.; Baron, D.; Badgaiyan, R.D.; Ponce, J.V.; Giordano, J.; Downs, W.B.; et al. Hypodopaminergia and “Precision Behavioral Management” (PBM): It is a Generational Family Affair. *Curr. Pharm. Biotechnol.* **2020**, *21*, 528–541. [[CrossRef](#)]
17. Sarwer, D.B.; Allison, K.C.; Wadden, T.A.; Ashare, R.; Spitzer, J.C.; McCuen-Wurst, C.; LaGrotte, C.; Williams, N.N.; Edwards, M.; Tewksbury, C.; et al. Psychopathology, disordered eating, and impulsivity as predictors of outcomes of bariatric surgery. *Surg. Obes. Relat. Dis.* **2019**, *15*, 650–655. [[CrossRef](#)]
18. König, I.R.; Fuchs, O.; Hansen, G.; von Mutius, E.; Kopp, M.V. What is precision medicine? *Eur. Respir. J.* **2017**, *50*, 1700391. [[CrossRef](#)]
19. Kotyuk, E.; Magi, A.; Eisinger, A.; Király, O.; Vereczkei, A.; Barta, C.; Griffiths, M.D.; Székely, A.; Kökönyei, G.; Farkas, J.; et al. Co-occurrences of substance use and other potentially addictive behaviors: Epidemiological results from the Psychological and Genetic Factors of the Addictive Behaviors (PGA) Study. *J. Behav. Addict.* **2020**, *9*, 272–288. [[CrossRef](#)]
20. Belligoli, A.; Bettini, S.; Segato, G.; Busetto, L. Predicting Responses to Bariatric and Metabolic Surgery. *Curr. Obes. Rep.* **2020**, *9*, 373–379. [[CrossRef](#)]
21. Brethauer, S.A.; Kim, J.; el Chaar, M.; Pappasavas, P.; Eisenberg, D.; Rogers, A.; Ballem, N.; Kligman, M.; Kothari, S. Standardized outcomes reporting in metabolic and bariatric surgery. *Surg. Obes. Relat. Dis. Med.* **2015**, *11*, 489–506. [[CrossRef](#)] [[PubMed](#)]
22. Garner, D.M.; Olmsted, M.P.; Bohr, Y.; Garfinkel, P.E. The eating attitudes test: Psychometric features and clinical correlates. *Psychol. Med.* **1982**, *12*, 871–878. [[CrossRef](#)] [[PubMed](#)]
23. Meule, A.; Hermann, T.; Kübler, A. A short version of the Food Cravings Questionnaire-Trait: The FCQ-T-reduced. *Front. Psychol.* **2014**, *5*, 190. [[CrossRef](#)] [[PubMed](#)]
24. Fitzsimmons-Craft, E.E.; Keatts, D.A.; Bardone-Cone, A.M. Eating Expectancies in Relation to Eating Disorder Recovery. *Cognit. Ther. Res.* **2013**, *37*, 104. [[CrossRef](#)]
25. Gearhardt, A.N.; Corbin, W.R.; Brownell, K.D. Development of the Yale Food Addiction Scale Version 2.0. *Psychol. Addict. Behav.* **2016**, *30*, 113–121. [[CrossRef](#)]
26. Trottier, K.; McFarlane, T.; Olmsted, M.P.; McCabe, R.E. The Weight Influenced Self-Esteem Questionnaire (WISE-Q): Factor structure and psychometric properties. *Body Image* **2013**, *10*, 112–120. [[CrossRef](#)]
27. Kaufman, E.A.; Xia, M.; Fosco, G.; Yaptangco, M.; Skidmore, C.R.; Crowell, S.E. The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): Validation and Replication in Adolescent and Adult Samples. *J. Psychopathol. Behav. Assess.* **2016**, *38*, 443–455. [[CrossRef](#)]
28. Smarr, K.L.; Keefer, A.L. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res.* **2011**, *63* (Suppl. 11), S454–S466.
29. Schulz, A.J.; Israel, B.A.; Zenk, S.N.; Parker, E.A.; Lichtenstein, R.; Shellman-Weir, S.; Klem, A.B. Psychosocial stress and social support as mediators of relationships between income, length of residence and depressive symptoms among African American women on Detroit’s eastside. *Soc. Sci. Med.* **2006**, *62*, 510–522. [[CrossRef](#)]
30. Schulz, A.J.; Mentz, G.; Lachance, L.; Johnson, J.; Gaines, C.; Israel, B.A. Associations between socioeconomic status and allostatic load: Effects of neighborhood poverty and tests of mediating pathways. *Am. J. Public Health* **2012**, *102*, 1706–1714. [[CrossRef](#)]
31. Buysse, D.J.; Reynolds, C.F., 3rd; Monk, T.H.; Berman, S.R.; Kupfer, D.J. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res.* **1989**, *28*, 193–213. [[CrossRef](#)] [[PubMed](#)]
32. Boór, K.; Rónai, Z.; Nemoda, Z.; Gaszner, P.; Sasvári-Székely, M.; Guttman, A.; Kalász, H. Noninvasive genotyping of dopamine receptor D4 (DRD4) using nanograms of DNA from substance-dependent patients. *Curr. Chem.* **2002**, *9*, 793–797. [[CrossRef](#)] [[PubMed](#)]

33. Blum, K.; Oscar-Berman, M.; Demetrovics, Z.; Barh, D.; Gold, M.S. Genetic Addiction Risk Score (GARS): Molecular neurogenetic evidence for predisposition to Reward Deficiency Syndrome (RDS). *Mol. Neurobiol.* **2014**, *50*, 765–796. [[CrossRef](#)] [[PubMed](#)]
34. Pedram, P.; Wadden, D.; Amini, P.; Gulliver, W.; Randell, E.; Cahill, F.; Vasdev, S.; Goodridge, A.; Carter, J.C.; Zhai, G.; et al. Food addiction: Its prevalence and significant association with obesity in the general population. *PLoS ONE* **2013**, *8*, e74832. [[CrossRef](#)] [[PubMed](#)]
35. Schulte, E.M.; Gearhardt, A.N. Associations of Food Addiction in a Sample Recruited to Be Nationally Representative of the United States. *Eur. Eat Disord. Rev.* **2018**, *26*, 112–119. [[CrossRef](#)]
36. Comings, D.E. Molecular heterosis as the explanation for the controversy about the effect of the DRD2 gene on dopamine D2 receptor density. *Mol. Psychiatry* **1999**, *4*, 213–215. [[CrossRef](#)]
37. Lee, Y.T.; Lee, H.-Y.; Han, C.; Pae, C.-U.; Tae, W.S.; Lee, M.-S.; Joe, S.-H.; Jung, I.-K.; Ham, B.-J. DRD2/ANKK1 TaqI A polymorphism affects corticostriatal activity in response to negative affective facial stimuli. *Behav. Brain Res.* **2011**, *223*, 36–41. [[CrossRef](#)]
38. Cleator, J.; Abbott, J.; Judd, P.; Wilding, J.P.; Sutton, C.J. Correlations between night eating, sleep quality, and excessive daytime sleepiness in a severely obese UK population. *Sleep Med.* **2013**, *14*, 1151–1156. [[CrossRef](#)]
39. Kapadia, S.G.; Wei, C.; Bartlett, S.J.; Lang, J.; Wise, R.A.; Dixon, A.E. Obesity and symptoms of depression contribute independently to the poor asthma control of obesity. *Respir. Med.* **2014**, *108*, 1100–1107. [[CrossRef](#)]
40. Mauri, M.; Rucci, P.; Calderone, A.; Santini, F.; Oppo, A.; Romano, A.; Rinaldi, S.; Armani, A.; Polini, M.; Pinchera, A.; et al. Axis I and II disorders and quality of life in bariatric surgery candidates. *J. Clin. Psychiatry* **2008**, *69*, 295–301. [[CrossRef](#)]
41. Williams-Kerver, G.A.; Schaefer, L.M.; Hawkins, M.A.W.; Crowther, J.H.; Duncan, J. Eating expectancies before bariatric surgery: Assessment and associations with weight loss trajectories. *Surg. Obes. Relat. Dis.* **2019**, *15*, 1793–1799. [[CrossRef](#)] [[PubMed](#)]
42. Abilés, V.; Rodríguez-Ruiz, S.; Abilés, J.; Mellado, C.; García, A.; de la Cruz, A.P.; Fernández-Santaella, M.C. Psychological characteristics of morbidly obese candidates for bariatric surgery. *Obes. Surg.* **2010**, *20*, 161–167. [[CrossRef](#)] [[PubMed](#)]
43. Hayakawa, N.; Tanaka, S.; Hirata, N.; Ogino, S.; Ozaki, N. A battery of self-screening instruments and self-reported body frame could not detect eating disorders among college students. *BMC Res. Notes* **2019**, *12*, 613. [[CrossRef](#)] [[PubMed](#)]
44. Hayashino, Y.; Yamazaki, S.; Takegami, M.; Nakayama, T.; Sokejima, S.; Fukuhara, S. Association between number of comorbid conditions, depression, and sleep quality using the Pittsburgh Sleep Quality Index: Results from a population-based survey. *Sleep Med.* **2010**, *11*, 366–371. [[CrossRef](#)] [[PubMed](#)]
45. Rapaport, M.H.; Clary, C.; Fayyad, R.; Endicott, J. Quality-of-life impairment in depressive and anxiety disorders. *Am. J. Psychiatry* **2005**, *162*, 1171–1178. [[CrossRef](#)]
46. Murray, S.M.; Tweardy, S.; Geliebter, A.; Avena, N.M. A Longitudinal Preliminary Study of Addiction-Like Responses to Food and Alcohol Consumption Among Individuals Undergoing Weight Loss Surgery. *Obes. Surg.* **2019**, *29*, 2700–2703. [[CrossRef](#)] [[PubMed](#)]
47. Li, D.; Sham, P.C.; Owen, M.J.; He, L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum. Mol. Genet.* **2006**, *15*, 2276–2284. [[CrossRef](#)]
48. Ptáček, R.; Kuzelová, H.; Stefano, G.B. Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders. *Med. Sci. Monit.* **2011**, *17*, Ra215–Ra220. [[CrossRef](#)]
49. Patte, K.A.; Davis, C.A.; Levitan, R.D.; Kaplan, A.S.; Carter-Major, J.; Kennedy, J.L. A Behavioral Genetic Model of the Mechanisms Underlying the Link Between Obesity and Symptoms of ADHD. *J. Atten. Disord.* **2020**, *24*, 1425–1436. [[CrossRef](#)]
50. Ariza, M.; Garolera, M.; Jurado, M.A.; Garcia-Garcia, I.; Hernan, I.; Sánchez-Garre, C.; Vernet-Vernet, M.; Sender-Palacios, M.J.; Marques-Iturria, I.; Pueyo, R.; et al. Dopamine genes (DRD2/ANKK1-TaqA1 and DRD4-7R) and executive function: Their interaction with obesity. *PLoS ONE* **2012**, *7*, e41482. [[CrossRef](#)]
51. Avsar, O.; Kuskucu, A.; Sancak, S.; Genc, E. Are dopaminergic genotypes risk factors for eating behavior and obesity in adults? *Neurosci. Lett.* **2017**, *654*, 28–32. [[CrossRef](#)] [[PubMed](#)]
52. Fallgatter, A.J.; Lesch, K.P. 22q11.2 deletion syndrome as a natural model for COMT haploinsufficiency-related dopaminergic dysfunction in ADHD. *Int. J. Neuropsychopharmacol.* **2007**, *10*, 295–299. [[PubMed](#)]
53. Leehr, E.J.; Schag, K.; Brückmann, C.; Plewnia, C.; Zipfel, S.; Nieratschker, V.; Giel, K.E. A Putative Association of COMT Val(108/158)Met with Impulsivity in Binge Eating Disorder. *Eur. Eat Disord. Rev.* **2016**, *24*, 169–173. [[CrossRef](#)] [[PubMed](#)]
54. Liu, Y.; Sun, X.-F.; Ding, M.; Liu, Y.-P.; Zhang, X.-C.; Pang, H.; Xing, J.X.; Xuan, J.F.; Xia, X.; Wang, B.J.; et al. The GABRB3 Polymorphism and its Association with Schizophrenia. *J. Mol. Neurosci.* **2018**, *64*, 75–79. [[CrossRef](#)] [[PubMed](#)]
55. Dauvilliers, Y.; Tafti, M.; Landolt, H.P. Catechol-O-methyltransferase, dopamine, and sleep-wake regulation. *Sleep Med. Rev.* **2015**, *22*, 47–53. [[CrossRef](#)]
56. Jawinski, P.; Tegelkamp, S.; Sander, C.; Häntzsch, M.; Huang, J.; Mauche, N.; Scholz, M.; Spada, J.; Ulke, C.; Burkhardt, R.; et al. Time to wake up: No impact of COMT Val158Met gene variation on circadian preferences, arousal regulation and sleep. *Chronobiol. Int.* **2016**, *33*, 893–905. [[CrossRef](#)]
57. Cimino, S.; Carola, V.; Cerniglia, L.; Bussone, S.; Bevilacqua, A.; Tambelli, R. The μ -opioid receptor gene A118G polymorphism is associated with insecure attachment in children with disruptive mood regulation disorder and their mothers. *Brain Behav.* **2020**, *10*, e01659. [[CrossRef](#)]
58. Daniel, A.M.; Rushing, B.G.; Tapia Menchaca, K.Y. Variation of the human mu-opioid receptor (OPRM1) gene predicts vulnerability to frustration. *Sci. Rep.* **2020**, *10*, 21840. [[CrossRef](#)]

59. Peciña, M.; Love, T.; Stohler, C.S.; Goldman, D.; Zubieta, J.K. Effects of the Mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures. *Neuropsychopharmacology* **2015**, *40*, 957–965. [[CrossRef](#)]
60. Thanos, P.K.; Zhuo, J.; Robison, L.; Kim, R.; Ananth, M.; Choi, I.; Grunseich, A.; Grissom, N.M.; George, R.; Delis, F.; et al. Suboptimal maternal diets alter mu opioid receptor and dopamine type 1 receptor binding but exert no effect on dopamine transporters in the offspring brain. *Int. J. Dev. Neurosci.* **2018**, *64*, 21–28. [[CrossRef](#)]
61. Benzerouk, F.; Djerada, Z.; Bertin, E.; Barrière, S.; Gierski, F.; Kaladjian, A. Contributions of Emotional Overload, Emotion Dysregulation, and Impulsivity to Eating Patterns in Obese Patients with Binge Eating Disorder and Seeking Bariatric Surgery. *Nutrients* **2020**, *12*, 3099. [[CrossRef](#)] [[PubMed](#)]
62. Casagrande, M.; Boncompagni, I.; Forte, G.; Guarino, A.; Favieri, F. Emotion and overeating behavior: Effects of alexithymia and emotional regulation on overweight and obesity. *Eat Weight Disord.* **2020**, *25*, 1333–1345. [[CrossRef](#)] [[PubMed](#)]
63. Fereidouni, F.; Atef-Vahid, M.K.; Fathali Lavasani, F.; Jamshidi Orak, R.; Klonsky, E.D.; Pazooki, A. Are Iranian obese women candidate for bariatric surgery different cognitively, emotionally and behaviorally from their normal weight counterparts? *Eat Weight Disord.* **2015**, *20*, 397–403. [[CrossRef](#)] [[PubMed](#)]
64. Lavender, J.M.; King, W.C.; Kalarchian, M.A.; Devlin, M.J.; Hinerman, A.; Gunstad, J.; Marcus, M.D.; Mitchell, J.E. Examining emotion-, personality-, and reward-related dispositional tendencies in relation to eating pathology and weight change over seven years in the Longitudinal Assessment of Bariatric Surgery (LABS) study. *J. Psychiatry Res.* **2020**, *120*, 124–130. [[CrossRef](#)]
65. Blum, K.; Brodie, M.S.; Pandey, S.C.; Cadet, J.L.; Gupta, A.; Elman, I.; Thanos, P.K.; Gondre-Lewis, M.C.; Baron, D.; Kazmi, S.; et al. Researching Mitigation of Alcohol Binge Drinking in Polydrug Abuse: KCNK13 and RASGRF2 Gene(s) Risk Polymorphisms Coupled with Genetic Addiction Risk Severity (GARS) Guiding Precision Pro-Dopamine Regulation. *J. Pers. Med.* **2022**, *12*, 1009. [[CrossRef](#)]
66. Gupta, A.; Bowirrat, A.; Gomez, L.L.; Baron, D.; Elman, I.; Giordano, J.; Jalali, R.; Badgaiyan, R.D.; Modestino, E.J.; Gold, M.S.; et al. Hypothesizing in the Face of the Opioid Crisis Coupling Genetic Addiction Risk Severity (GARS) Testing with Electrotherapeutic Nonopioid Modalities Such as H-Wave Could Attenuate Both Pain and Hedonic Addictive Behaviors. *Int. J. Environ. Res. Public Health.* **2022**, *19*, 552. [[CrossRef](#)]
67. Vereczkei, A.; Barta, C.; Magi, A.; Farkas, J.; Eisinger, A.; Király, O.; Belik, A.; Griffiths, M.D.; Szekely, A.; Sasvári-Székely, M.; et al. FOXP3 and GDNF Polymorphisms as Common Genetic Factors of Substance Use and Addictive Behaviors. *J. Pers. Med.* **2022**, *12*, 690. [[CrossRef](#)]
68. Blum, K.; Han, D.; Gupta, A.; Baron, D.; Braverman, E.R.; Dennen, C.A.; Kazmi, S.; Llanos-Gomez, L.; Badgaiyan, R.D.; Elman, I.; et al. Statistical Validation of Risk Alleles in Genetic Addiction Risk Severity (GARS) Test: Early Identification of Risk for Alcohol Use Disorder (AUD) in 74,566 Case-Control Subjects. *J. Pers. Med.* **2022**, *12*, 1385. [[CrossRef](#)]
69. Blum, K.; Bowirrat, A.; Gondre Lewis, M.C.; Simpatico, T.A.; Ceccanti, M.; Steinberg, B.; Modestino, E.J.; Thanos, P.K.; Baron, D.; McLaughlin, T.; et al. Exploration of Epigenetic State Hyperdopaminergia (Surfeit) and Genetic Trait Hypodopaminergia (Deficit) During Adolescent Brain Development. *Curr. Psychopharmacol.* **2021**, *10*, 181–196. [[CrossRef](#)]
70. Gilley, E.D.; Bowirrat, A.; Gupta, A.; Giordano, J.; A Dennen, C.; R Braverman, E.; D Badgaiyan, R.; McLaughlin, T.; Baron, D.; Blum, K. The Future is Now for Precision Genomic Addiction Medicine as a Frontline Modality for Inducing “Dopamine Homeostasis” in Reward Deficiency Syndrome (RDS). *Curr. Pharm. Biotechnol.* **2023**. ahead of print. [[CrossRef](#)]
71. Dennen, C.A.; Blum, K.; Bowirrat, A.; Thanos, P.K.; Elman, I.; Ceccanti, M.; Badgaiyan, R.D.; McLaughlin, T.; Gupta, A.; Bajaj, A.; et al. Genetic Addiction Risk Severity Assessment Identifies Polymorphic Reward Genes as Antecedents to Reward Deficiency Syndrome (RDS) Hypodopaminergia’s Effect on Addictive and Non-Addictive Behaviors in a Nuclear Family. *J. Pers. Med.* **2022**, *12*, 1864. [[CrossRef](#)] [[PubMed](#)]
72. Blum, K.; Oscar-Berman, M.; Femino, J.; Waite, R.L.; Benya, L.; Giordano, J.; Borsten, J.; Downs, W.B.; Braverman, E.R.; Loehmann, R.; et al. Withdrawal from Buprenorphine/Naloxone and Maintenance with a Natural Dopaminergic Agonist: A Cautionary Note. *J. Addict. Res. Ther.* **2013**, *4*. [[CrossRef](#)] [[PubMed](#)]
73. Blum, K.; Badgaiyan, R.D.; Agan, G.; Fratantonio, J.; Simpatico, T.; Febo, M.; Haberstick, B.C.; Smolen, A.; Gold, M.S. Molecular Genetic Testing in Reward Deficiency Syndrome (RDS): Facts and Fiction. *J. Reward Defic. Syndr.* **2015**, *1*, 65–68. [[CrossRef](#)] [[PubMed](#)]
74. Gondre-Lewis, M.C.; Elman, I.; Alim, T.; Chapman, E.; Settles-Reaves, B.; Galvao, C.; Gold, M.S.; Baron, D.; Kazmi, S.; Gardner, E.; et al. Frequency of the Dopamine Receptor D3 (rs6280) vs. Opioid Receptor μ 1 (rs1799971) Polymorphic Risk Alleles in Patients with Opioid Use Disorder: A Preponderance of Dopaminergic Mechanisms? *Biomedicines* **2022**, *10*, 870. [[CrossRef](#)]
75. Blum, K.; Lott, L.; Siwicki, D.; Fried, L.; Hauser, M.; Simpatico, T.; Baron, D.; Howedy, A.; Badgaiyan, R.D. Genetic Addiction Risk Score (GARS™) as a Predictor of Substance Use Disorder: Identifying Predisposition Not Diagnosis. *Curr. Trends Med. Diagn. Methods* **2018**, *1*. [[CrossRef](#)]
76. Bajaj, A.; Blum, K.; Bowirrat, A.; Gupta, A.; Baron, D.; Fugel, D.; Nicholson, A.; Fitch, T.; Downs, B.W.; Bagchi, D.; et al. DNA Directed Pro-Dopamine Regulation Coupling Subluxation Repair, H-Wave® and Other Neurobiologically Based Modalities to Address Complexities of Chronic Pain in a Female Diagnosed with Reward Deficiency Syndrome (RDS): Emergence of Induction of “Dopamine Homeostasis” in the Face of the Opioid Crisis. *J. Pers. Med.* **2022**, *12*, 1416. [[CrossRef](#)]
77. Blum, K.; Gondre-Lewis, M.C.; Baron, D.; Thanos, P.K.; Braverman, E.R.; Neary, J.; Elman, I.; Badgaiyan, R.D. Introducing Precision Addiction Management of Reward Deficiency Syndrome, the Construct That Underpins All Addictive Behaviors. *Front. Psychiatry* **2018**, *9*, 548. [[CrossRef](#)]

78. Blum, K.; Baron, D.; Hauser, M.; Henriksen, S.; Thanos, P.K.; Black, C.; Siwicky, D.; Modestino, E.J.; Downs, B.W.; Badgaiyan, S.; et al. Americas' opioid/psychostimulant epidemic would benefit from general population early identification of genetic addiction risk especially in children of alcoholics (COAs). *J. Syst. Integr. Neurosci.* **2019**, *5*, 1–3.
79. Levey, D.F.; Stein, M.B.; Wendt, F.R.; Pathak, G.A.; Zhou, H.; Aslan, M.; Quaden, R.; Harrington, K.M.; Nuñez, Y.Z.; Overstreet, C.; et al. Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nat. Neurosci.* **2021**, *24*, 954–963. [[CrossRef](#)]
80. Hatoum, A.S.; Colbert, S.M.C.; Johnson, E.C.; Huggett, S.B.; Deak, J.D.; Pathak, G.A.; Jennings, M.V.; Paul, S.E.; Karcher, N.R.; Hansen, I.; et al. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nat. Ment. Health* **2023**, *1*, 210–223. [[CrossRef](#)]

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