Observational study to calculate addictive risk to opioids: a validation study of a predictive algorithm to evaluate opioid use disorder

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Background: Opioid abuse in chronic pain patients is a major public health issue, with rapidly increasing addiction rates and deaths from unintentional overdose more than quadrupling since 1999.

Purpose: This study seeks to determine the predictability of aberrant behavior to opioids using a comprehensive scoring algorithm incorporating phenotypic risk factors and neuroscience-associated single-nucleotide polymorphisms (SNPs).

Patients and methods: The Proove Opioid Risk (POR) algorithm determines the predictability of aberrant behavior to opioids using a comprehensive scoring algorithm incorporating phenotypic risk factors and neuroscience-associated SNPs. In a validation study with 258 subjects with diagnosed opioid use disorder (OUD) and 650 controls who reported using opioids, the POR successfully categorized patients at high and moderate risks of opioid misuse or abuse with 95.7% sensitivity. Regardless of changes in the prevalence of opioid misuse or abuse, the sensitivity of POR remained >95%.

Conclusion: The POR correctly stratifies patients into low-, moderate-, and high-risk categories to appropriately identify patients at need for additional guidance, monitoring, or treatment changes.

Keywords: opioid use disorder, addiction, personalized medicine, pharmacogenetics, genetic testing, predictive algorithm

Introduction
Opioid abuse in chronic pain patients is a major public health issue, with rapidly increasing addiction rates and deaths from unintentional overdose more than quadrupling since 19991 (National Institute on Drug Abuse). Prescription opioid-related overdoses killed 183,000 people in the USA between 1999 and 2016.2 Furthermore, the US Department of Health and Human Services estimates that opioid abuse, misuse, or dependence plagued >1.9 million people in 2013 alone.3 In addition to the significant human costs, opioid abuse and dependence result in enormous health care costs. In 2012 alone, hospitalizations for opioid abuse and dependence resulted in approximately $15 billion in inpatient charges.4 If that figure is extended to associated infections, the costs increase $700 million.4 Both types of hospitalizations rely primarily on Medicaid for payment, illustrating the financial burden placed on taxpayers.4

The issue of prescription opioid abuse, misuse, and addiction is increasing in the national spotlight, with the White House Initiative in 2011, the US Secretary of Health and Human Services targeted initiative in 2015, and focused efforts by the Center for...
examined the genetic contribution to addiction to alcohol, marijuana, stimulants, and opiates and concluded that genetics contributed 44% of the variance in opioid abuse. These studies and others have identified single-nucleotide polymorphisms (SNPs) in mesocorticolimbic circuits to be associated with OUD. These SNPs lie within four important neurochemical pathways associated with the brain reward pathways— the serotonergic, endorphinergic, GABAergic, and dopaminergic circuits. Variant genes within these cascades have been shown to be predictive of individuals that exhibit aberrant, risky behaviors, such as the abuse of psychoactive substances.

Genetic testing of these markers to inform risks associated with opioid use is already commercially available. The Proove Opioid Risk (POR) profile is a panel test that combines known phenotypic risk factors with validated genetic markers in a patented algorithm to predict risk of OUD with a high degree of sensitivity. The interplay between environment and genetics is widely acknowledged. Therefore, an evaluation of both phenotypic and genetic risk is necessary to achieve predictive accuracy. In fact, a previous study evaluating the POR with both the ORT and SOAPP®-R demonstrated that there was a significant positive correlation among the three tests, but that the POR detected OUD risk determination with higher specificity than either ORT or SOAPP®-R.

The objective of this study was to evaluate the POR algorithm, which was developed in an independent discovery cohort of patients, to establish validated predictive accuracy, and to provide additional evidence to support the performance characteristics of the algorithm.

**Patients and methods**

**Study population**

This multicenter, observational study (study protocols 1JAN15-20CR and 1JAN15-14CR) was reviewed, approved, and overseen by Solutions IRB, an institutional review board licensed by the US Department of Health and Human Services, Office for Human Research Protections. All participants signed informed consent forms prior to data collection.

The study population (Table 1) consisted of 258 patients diagnosed with OUD (defined as the International Statistical Classification of Diseases and Related Health Problems [ICD]-9 series code 304, equivalent to ICD-10 series code F11.20) and 650 control patients. OUD patients were identified solely using ICD codes. OUD diagnosis was independently conducted by patients’ medical professionals at their respective clinics. In addition to diagnostic coding, inclusion criteria for OUD patients involved confirmation of present...
experience of chronic noncancer pain, consumption of opioid medication as part of a pain-management plan, and fluency in English. In this study, OUD is the diagnostic term for OUD, rather than the physiological state of opioid-dependence alone. Control patients were those who were prescribed opioids for chronic pain and were diagnosed with lower back pain (ICD-9 series code 724.2, equivalent to ICD-10 series code M54.5), and no other diagnoses, no history of depression, anxiety, other mental health issues, or history of illicit and prescription drug abuse or misuse. Subjects were 18–89 years of age and predominantly of Caucasian ethnicity. Patients were enrolled from 24 study sites across the USA by site addiction specialists, including experts in internal medicine, family medicine, pain management, orthopedics, neurology, osteopathy, podiatry, mental health, and physical medicine and rehabilitation.

Data collection
Genomic DNA was isolated from buccal swabs obtained from each patient using a proprietary DNA isolation technique and DNA isolation kit (Macherey Nagel GmbH & Co, KG, Duren, Germany), according to the manufacturer’s instructions. Genotyping was performed using predesigned TaqMan® assays (Applied Biosystems, Foster City, CA, USA). Allele-specific fluorescence signals were distinguished by measuring end point 6-FAM or VIC fluorescence intensities at 508 and 560 nm, respectively, and genotypes were generated using Genotyper® Software V 1.3 (Applied Biosystems). The DNA elution buffer was used as a negative control, and K562 cell line DNA (Promega Corporation, Madison, WI, USA) was included in each batch of samples tested as positive control.

Phenotypic information was also collected, including whether patients had a personal history of alcoholism, personal history of illegal drug abuse, personal history of prescription drug abuse, family history of alcoholism, family history of illegal drug abuse, family history of prescription drug abuse, mental health disorders and/or depression, and whether or not they were 16–45 years old. This information was collected in a paper questionnaire that asked patients to give yes or no answers to the phenotypic factors indicated above.

The POR algorithm
A POR score and its associated risk stratification were calculated for each subject. The POR algorithm is a patent-protected, validated measure of opioid risk.25 In short, it combines phenotypic and genotype information to calculate a risk score that correlates with high-, moderate-, or low-risk stratification of opioid dependence,25 such that a score of 1–11 is associated with low-risk, 12–23 with moderate-risk, and ≥24 with high-risk of OUD. Low-risk denotes the subject is at low risk of OUD and the clinician may proceed with prescription opioid therapy; moderate-risk suggests the clinician should proceed with caution and may want to consider more routine urine drug testing and possibly limit the duration of opioid therapy; and high-risk suggests the physician may want to consider an alternative analgesic to improve patient outcomes, consider more routine urine drug testing, limit the duration of opioid therapy, consider titrating the patient off opioid therapy, maintain vigilant awareness of patient outcomes, and possibly consider medically-assisted treatment for detoxification.

The genetic markers used in the algorithm include 11 different SNPs that have been implicated in opioid abuse, misuse, dependence, or addiction (Table 2). Risk alleles for each SNP are weighted more heavily in an additive genetic model, and an overall higher panel score summed across SNPs represents an increased risk of OUD. This approach, which focuses on validated genetic variants, as opposed to comprehensive next-generation sequencing, is the preferred approach of many in the field.26 The phenotypic factors tested include age (whether or not they were 16–45 years old),27,28 personal history of alcohol abuse,23,29 personal history of illegal drug abuse,30 personal history of prescription drug abuse,31 and personal history of other mental health diseases including

<table>
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<th>Table 1 Patient demographics</th>
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<tr>
<td>Population</td>
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<tr>
<td>Opioid dependent, n=258, mean age =36.9 years</td>
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<td>Females, n=126 (49%)</td>
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<td>Males, n=123 (51%)</td>
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<tr>
<td>Overall</td>
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<td>Control group, n=650, mean age =49.7 years</td>
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<td>Females, n=418 (64%)</td>
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<tr>
<td>Males, n=232 (36%)</td>
</tr>
<tr>
<td>Overall %</td>
</tr>
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</table>

Note: *Races categorized as “others”, in statistical analyses.
Abbreviations: A, Asian/Pacific islander; B, black/African-American; D, declined; H, Hispanic; M, mixed; N, not listed; W, white/Caucasian.
Table 2  Proove Opioid Risk test panel markers

<table>
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<th>Protein name</th>
<th>Gene</th>
<th>SNP marker</th>
<th>Associated neuropsychiatric disorders</th>
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<td>Catechol-O-methyltransferase</td>
<td>COMT</td>
<td>rs4680</td>
<td>Alcohol and drug abuse35,36</td>
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<td></td>
<td></td>
<td>Anxiety39</td>
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<td>Dopamine beta-hydroxylase</td>
<td>DBH</td>
<td>rs1611115</td>
<td>Depression48</td>
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<td></td>
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<td>Cocaine addiction39,40</td>
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<tr>
<td>Dopamine D1 receptor</td>
<td>DRD1</td>
<td>rs4532</td>
<td>ADHD41</td>
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<tr>
<td>Ankyrin repeat and kinase domain containing 1/dopamine receptor D2</td>
<td>ANKK1/DRD2</td>
<td>rs1800497</td>
<td>Schizophrenia42</td>
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<tr>
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<tr>
<td>Dopamine transporter SLC6A3</td>
<td>DAT</td>
<td>rs27072</td>
<td>Heroin addiction44</td>
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<tr>
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<td>rs211014</td>
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<td>Opioid receptor, kappa 1</td>
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<td>rs1051660</td>
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<td>Methylenetetrahydrofolate reductase</td>
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<td>Depression41</td>
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</table>

Abbreviations: ADHD, attention deficit hyperactivity disorder; SNP, single-nucleotide polymorphism.

Attention deficit disorder,32 obsessive compulsive disorder,33 bipolar disorder,24 and schizophrenia.34

Statistical analyses
A Mann–Whitney U test was used to determine the statistical significance of the difference between the POR scores of the OUD group and control group. A cross-tab analysis was performed to assess the diagnostic performance of the POR as a comprehensive algorithm for the evaluation of OUD risk. Statistical analyses (implemented in R v3.2.5) included measures of sensitivity (the percentage of OUD patients correctly identified by POR scores), specificity (the percentage of control patients correctly identified by POR scores), positive likelihood ratio (PLR; the likelihood of identifying OUD patients using the POR), and negative likelihood ratio (NLR; the likelihood of identifying controls using the POR). For the risk stratification portion of the analysis, POR scores of OUD patients and controls were divided into low-, moderate-, and high-risk categories. To establish the exact POR scoring parameters for each category, POR scores were compared in OUD patients vs controls.

Results
Distribution of POR scores
The overall distribution of POR scores between patients in the OUD group (n=258) and the patients in the control group (n=650) is shown in Figure 1. The mean POR score for the controls was 17.6 (median =17), with standard deviation of 5.07, whereas the mean POR score for patients with diagnosed OUD was 25.5 (median =26), with standard deviation of 9.05, demonstrating that the POR-predicted risk is increased in patients with diagnosed OUD (p=7.97×10^{-34}).

POR algorithm performance
To assess the performance of the POR for diagnosis of OUD, sensitivities and specificities were calculated across all possible POR scores (Table S1). The area under the curve (AUC) of the receiver operating characteristic (ROC) curve provides information about the accuracy of the test, where an AUC of 1 is equal to 100% accuracy and an AUC of 0.5 is equal to random chance. The AUC of the POR was 0.757 (95% confidence interval: 0.718–0.797), indicating that the POR accurately identified patients in this cohort >75% of the time (Figure 2). The sensitivity of the POR score increased as OUD risk increased, with a sensitivity of 95.3% at a POR score of at least 12 (ie, at moderate and high risk of OUD). At different prevalence rates of OUD, 8% (prevalence of OUD in the general population), 28% (prevalence of OUD in the cohort), and 50% (a balanced prevalence rate), the POR algorithm performs equally well (Figure 3).

Odds of diagnosed OUD
In this cohort, when compared to controls, OUD patients identified by the POR algorithm to be at moderate risk had...
on average 4.17 increased odds of OUD, whereas those in the high-risk category had on average 16.5 increased odds of OUD (Figure 4).

**Likelihood of OUD**

The PLR demonstrates the likelihood that a person with OUD would receive a positive POR test result, while the opposite is true for the NLR, which indicates the likelihood that a person with the condition would receive a negative test result. These
ratios are based on the sensitivity and specificity of the test and do not change based on the prevalence of the disorder of interest. Figure 5 shows small (<2) increases in the likelihood of OUD for the POR scores of 8–19, moderate (2–10) increases in the likelihood of OUD for the POR scores of 20–26, and large (>10) increases in the likelihood of OUD for the POR scores of 27 and up except for the scores of 39–41, which had moderate likelihoods.

**Discussion**

The POR algorithm incorporates genetics and clinical factors to accurately predict a person’s risk of OUD. A previous discovery study demonstrated that the POR predicts risk of OUD with greater specificity than either the ORT or the SOAPP<sup>25</sup>. This study confirms the utility of the POR, with an entirely new cohort of patients. In fact, the odds ratios calculated demonstrate a greatly increased rate of OUD for patients in the moderate- or high-risk category. Those in the moderate-risk category demonstrated an increased 4.17 odds of OUD (ranging from 1.47 to 7.61), and those in the high-risk category had an average of 16.5 increased odds of OUD (ranging from 3.79 to 17.6). Furthermore, based on the ROC curve, the POR is a good model for OUD, with an AUC of >75%. This statistic represents the accuracy of the test and demonstrates that it is capable of stratifying patients into different risk groups.

POR is used as decision tool to understand and act on risks of opioid-associated aberrant behaviors. For patients being evaluated for risk factors associated with a diagnosis of OUD, one would expect this tool to perform with high specificity, so there are few false negatives. The POR algorithm showed high specificity in this validation cohort, with high-risk scores being >90% specific. In contrast, for patients already prescribed opioids or those being screened for opioid use, this tool should capture the patients most at risk so appropriate cautionary measures can be taken. For this scenario, the POR tool should perform with high sensitivity, which may result in false positives, but is less likely to miss patients who are at risk. The POR algorithm showed high specificity in this validation cohort, with high-risk scores being >90% specific. In contrast, for patients already prescribed opioids or those being screened for opioid use, this tool should capture the patients most at risk so appropriate cautionary measures can be taken. For this scenario, the POR tool should perform with high sensitivity, which may result in false positives, but is less likely to miss patients who are at risk. The POR algorithm showed increasing sensitivity with lower scores, with at least 90% sensitivity for scores ≤14, which indicates that patients of moderate-risk scores should be treated with caution. The high sensitivity of moderate-risk scores and the high specificity at high-risk scores validate the profile’s ability to capture, with good sensitivity, patients who should be monitored more closely but do not label patients inappropriately as high risk.

An algorithm that reliably predicts patients most at the risk of opioid addiction is a valuable tool in a clinician’s...
arsenal. By stratifying risk, physicians can appropriately identify those patients at higher risk of OUD and then more safely prescribe opioids in most of the population, which is low risk. This knowledge, as displayed by the POR algorithm, should lead to more rational decision-making by allowing patients access to necessary medication management and avoid exposure to those at elevated risk. The POR algorithm gives physicians the information they need about their most susceptible patients, which not only protects the patient but also protects the physician’s practice as governmental and law enforcement agencies elevate scrutiny on opioid prescribing and the physician. With the dramatic impact of the opioid abuse epidemic, the POR algorithm provides an evidence-based decision-making tool to improve clinical outcomes, reduce deaths and abuse, and potentially reduce health care costs.

Limitations
The limitations of this study include the wide age range of study participants and the reliance on ICD code for diagnosis of OUD. Future studies will include additional objective measures of drug use, including urine drug screening.

Conclusion
This study serves as an additional validation of the POR algorithm in identifying patients at the risk of OUD and concurrently identifying those patients at the lower risk of OUD, for whom opioid treatment may be a good option. There is a delicate balance between managing pain for chronic pain patients and preventing OUD. This algorithm provides clinicians with a tool to identify patients most at risk, reducing stress to the physician, increasing physician confidence in opioid prescribing, and reducing risk to the patient. The precision medicine approach of the POR can be used clinically to address the prescription opioid epidemic to guide health care decisions that increase patient and physician safety while decreasing health care costs.

Acknowledgments
We would like to thank the patients who participated in this study, without whom this study would not be possible. Proove Biosciences provided support for this study. The article has been presented at International Conference on Opioids, June 5–7, 2016, Boston, MA, USA.

Disclosure
AB, SK, BM, and CL are the employees of Proove Biosciences. JB is a former employee of Proove Biosciences. MS and SR are on the Medical Advisory Board of Proove Biosciences. The authors report no other conflicts of interest in this work.

References


Supplementary material

**Table S1** Sensitivities and specificities of the POR algorithm using different cutoffs of POR scores to predict OUD

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**Abbreviations:** OUD, opioid use disorder; POR, Proove Opioid Risk.