

Prospective, Longitudinal Study to Evaluate the Clinical Utility of a Predictive Algorithm to Detect Opioid Use Disorder in Chronic Pain Patients

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Received date: May 16, 2017; Accepted date: June 02, 2017; Published date: June 09, 2017

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Abstract

A prospective, longitudinal study was conducted to determine the clinical utility of an algorithm-based precision medicine profile designed to assess risk associated with opioid use disorder in 5,315 patients in a clinical setting. Specifically, we sought to assess how physicians were using the profile and how its use affected patient outcomes. Ninety percent of all clinicians surveyed reported some benefit to their patient care, with the most utilization for changing the prescribed opioid and the most significant benefits from discontinuing opioids. Patients who received profile-guided care reported on average a 42% reduction in pain, and almost 40% of patients had >50% reduction in pain.

Keywords: Chronic pain; Precision medicine; Personalized medicine; Opioids; Pain management; Opioid use disorder

Introduction

The World Health Organization estimates that up to 22% of patients in primary care clinics suffer from chronic pain [1] and in the United States, chronic pain affects 11% of adults [2]. Since the 1990s, spurred by several studies that reported that opioids pose little addiction harm and pressured to not undertreat pain in patients, physicians have gradually adopted opioids as the mainstay of chronic pain management [3]. The Centers for Disease Control and Prevention (CDC) reports that opioid prescriptions increased by 300% in recent years while data from the RADARS (Researched Abuse, Diversion and Addiction-Related Surveillance) System programs show that opioid prescriptions increased from 47 million per quarter in 2006 to 60 million per quarter in 2011 and stayed so until 2013 [4,5]. From 2002 to 2011, an estimated 25 million Americans used opioids for non-medical purposes [6].

Opioid-related abuse and deaths have also escalated with prescription numbers. From 2004 to 2011, opioid abuse related emergency medical cases almost tripled, with 420,040 emergency department visits in 2011 [7]. In 2013, about 1.9 million people abused or were dependent on prescription opioid pain medication [8]. Opioid-related overdose deaths tripled between 2000 and 2014 in the United States, with more than 165,000 deaths in the period and about 28,000 deaths in 2014 [9,10]. Between 2004 and 2011, rates of drug diversion, opioid abuse, and opioid use among college students all at least doubled. Opioid abuse costs the economy between \$53 - \$72 billion annually [11].

These statistics reflect the conundrum in which physicians find themselves, particularly those in the United States. Physicians need to alleviate pain in patients while avoiding opioid abuse. Surveys of primary care physicians reveal that most felt stress from the risk of opioid abuse and addiction in their patients; younger physicians were particularly distressed and lacked confidence in making opioid-related

decisions [12]. Notably, about half of the physicians felt they lacked adequate training in prescribing opioids. In another survey, authors found that while most physicians support using clinical tests and regulations to curb opioid abuse, only one-third of them believed that such interventions would work [13]. More education and training in opioid-related interventions were especially welcomed [14].

Opioid use disorder (OUD) is the diagnostic term for chronic opioid abuse and dependence, which includes using opioids for longer than intended, an increased tolerance to opioids, having an uncontrollable craving for opioids and using opioids despite detrimental effects to one's physical, emotional, and social well-being. To prevent OUD, physicians are advised to check for and monitor opioid risk in patients. A variety of tools are available. Patient self-reported questionnaires like the Opioid Risk Tool (ORT), and Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP[®]-R) use family, social and medical history to evaluate the risk of aberrant opioid behavior and addiction [15,16]. Although easy to use, these subjective questionnaires pose variable reliability [17]. Regardless of how accurate patients answer the questions, physicians still have only a 50% chance of predicting the development of OUD [18]. For more objective information, physicians can run random urine drug tests (UDT) to monitor medication metabolites in urine, or query the database of the Prescription Drug Monitoring Program (PDMP) for drug prescription records [19]. Although there is no conclusive evidence that such checks and interventions reduce opioid-related deaths, a drop in opioid prescriptions, abuse and deaths have been observed [5].

In view of the high burden of OUD on healthcare and the economy, tools that help physicians assess opioid risks are greatly needed. The profile is a patent-protected algorithm that evaluates a patient's risk for OUD based on a panel of SNP genotypes and phenotypic factors selected from the ORT [20-22]. Several studies of pain patients demonstrate that the profile identifies those at high risk of OUD with greater accuracy, sensitivity and specificity than either the ORT or SOAPP[®]-R [20-22]. In this study, we further evaluate the clinical utility and actionability of the profile through examination of how physicians

use the profile results to guide treatment and evaluating patient outcomes.

Methods

Study population

A prospective, longitudinal study was conducted to assess the utility of precision medicine testing in 5,315 patients across 76 clinics in the USA. This study was reviewed, approved, and overseen by Solutions IRB (Protocols 1JUL14-62CR, 1JAN15-14CR, 1JAN15-20CR), an institutional review board licensed by the United States Department of Health and Human Services, Office for Human Research Protections. All participants signed informed consent forms prior to data collection. The research sites were stratified into four different specialty groups: Family Medicine/Primary Care/Internal Medicine, Neurology/Psychiatry, Orthopedic Surgery, and Pain Medicine/PMR/Anesthesiology. Per protocol, exclusion criteria were significant diminished mental capacity, recent febrile illness that precludes or delays participation by more than one month, pregnancy or lactation, incomplete gene report, invalid profile score, participation in a clinical study that may interfere with participation in this study, and anything that would place the individual at increased risk or preclude full compliance.

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; Germany), according to the manufacturer's instructions. Genotyping was performed using pre-designed TaqMan[®] assays (Applied Biosystems; Foster City, CA). Allele-specific fluorescence signals were distinguished by measuring endpoint 6-FAM or VIC fluorescence intensities at 508 nm and 560 nm, respectively, and genotypes were generated using Genotyper[®] Software V 1.3 (Applied Biosystems; Foster City, CA). The DNA Elution Buffer was used as a negative control, and K562 Cell Line DNA (Promega Corporation; Madison, WI), was included in each batch of samples tested as positive control.

Age and behavioral information was also collected, including whether subjects had a personal or family history of alcoholism, illegal drug abuse, prescription drug abuse, mental health disorders and/or depression.

Physicians who requested a profile assessment for their patients were given questionnaires for their patients' baseline and follow-up study visits to document their actions, decisions, and perceptions regarding the utility of the precision medicine tests. Baseline visits were conducted when physicians received their patients' profile results. A follow-up visit occurred approximately one month later. During both the baseline and follow-up visits, physicians completed the questionnaires, which consisted of a 12-item checklist of actions or decisions that the physician might have made using profile guidance (Supplementary Table 2). Physicians could also describe any other decisions not listed. The questionnaire queried the physicians for any dosage or medication selection changes they made for the patients and their patients' response to medication, and evaluated the degree to which the profile benefitted both clinical decision making and patient care on a 5-point scale: 1=no benefit; 5=significant benefit.

To assess patient outcomes, patients were asked approximately one month after receiving guided decisions from their physicians to assess their pain levels before and after receiving care using the pain numerical rating scale (NRS). The NRS ranges from 0-10, where 0 is "no pain," and is "agonizing" pain. NRS scores of 7-10 correspond to severe pain, 4-6 to moderate pain and 1-3 to mild pain [10,23].

The profile algorithm

A profile score and its associated OUD risk stratification were calculated for each subject. The profile algorithm is a patent-protected, validated measure of opioid use disorder risk [20-22]. In short, it combines phenotypic and genotypic information to calculate a risk score that correlates to low-, moderate- or high-risk stratifications of opioid use disorder [20-22]. A profile score of 1-11 is associated with low risk, 12-23 with moderate risk, and ≥ 24 with high risk. The genetic markers used in the algorithm include 11 different single nucleotide polymorphisms (SNPs) that have been implicated in opioid abuse, misuse, dependence, or addiction (Table 1). This approach, which focuses on validated genetic variants, as opposed to comprehensive next-generation sequencing, is the preferred approach of many in the field [24]. The phenotypic factors tested include an age of 16-45 years [25,26], personal history of alcohol abuse, personal history of illegal drug abuse, personal history of prescription drug abuse [27-30], and personal history of other mental health diseases including attention deficit disorder, obsessive compulsive disorder [31], bipolar disorder [32], and schizophrenia [33]. The algorithm is 42% genetic information and 58% phenotypic information [20-22].

Protein Name	Gene	SNP	Associated Neuro-Psychiatric Disorders
Catechol-O-Methyltransferase	COMT	rs4680	Alcohol and Drug Abuse [39,40]
			Anxiety [41]
			Depression [42]
Dopamine Beta-Hydroxylase	DBH	rs1611115	Cocaine Addiction [43,44]
			ADHD
			Schizophrenia [45]
Dopamine D1 Receptor	DRD1	rs4532	Depression [46]
			Heroin Addiction [47]

Ankyrin Repeat and Kinase Domain Containing 1/Dopamine Receptor D2	ANKK1/DRD2	rs1800497	Alcohol and Cocaine Dependence [48]
Dopamine D4 Receptor	DRD4	rs3758653	Anxiety [49,50]
Dopamine Transporter SLC6A3	COMT	rs27072	Methamphetamine Addiction [51]
Gamma Aminobutyric Acid Receptor A, gamma2 subunit	GABRG2	rs211014	Alcohol Abuse [52]
Opioid Receptor, Kappa 1	OPRK1	rs1051660	Mood Disorders [53]
			Alcohol Dependence [54]
Methylenetetrahydrofolate Reductase	MTHFR	rs1801133	Bipolar Disorder Depression [55]
Opioid Receptor, Mu 1	OPRM1	rs1799971	Heroin Addiction [56]
Serotonin Receptor 2A	HTR2A	rs7997012	Drug Abuse [39]
			Depression [57]
Phenotypic Traits	Risk Factors		
Age	16-45 years old		
Personal history	Mental health disorders [27,39,58,59]		
	Depression [28,29,60]		
	Alcoholism [24,61]		
	Illicit drug use [25,62]		
	Prescription drug abuse [63]		

Table 1: PROOVE opioid risk test panel markers.

Statistical methods

For each patient, an aggregate rating of the benefit of the profile was calculated, as there was no difference in the mean or distribution of scores across visits. Chi-squared test was used to assess any differences in sex and if physicians used the profile to guide decisions. The Student's t-test was used to assess any differences in age and if physicians used the profile to guide decisions. The Wilcoxon rank-sums test was used to assess the difference in physicians' average ratings by those who used the profile to guide decisions. Ordinal logistic regression was used to test for associations between profile-predicted risk of opioid abuse and ratings, and between ratings and specific decisions, adjusting for possible confounders: age, sex, race, and clinic specialty. The Wilcoxon signed rank sums test for paired

data was used to test for significant differences in before and after pain NRS scores. All tests were two-sided, and $p \leq 0.05$ was considered significant. Statistical analysis was performed with R Statistical Software version 3.2.3.

Results

Study population

A total of 5,315 patients were assessed in the study (Table 2). There was no sex bias and patient ages were normally distributed around a mean age of 57 years old.

Specialty	Total Patients	Low (%)	Moderate (%)	High (%)
Pain Medicine/Physical Medicine and Rehabilitation/Anesthesiology	2822	47.8	47.7	4.5
Family Medicine/Primary Care/Internal Medicine	2066	48.5	46.7	4.8
Orthopedic Surgery	396	66.7	32.1	1.3
Neurology/Psychiatry	31	19.4	61.3	19.4

Table 2: Opioid risk categories of patients from 76 clinics assessed by the profile, clinics were grouped according to specialties. Orthopedic surgery had the greatest proportion of patients in the low risk category, while neurology/psychiatry had the highest proportion in the high risk category.

Opioid risk category distribution of patients by specialty

Among the four categories of clinics, patients in Orthopedic Surgery had primarily low-risk profile test results (66.7%), while over 50% of the patients from the other three categories of clinics, including pain medicine, primary care and neurology, had moderate- to high-risk results.

An average benefit rating (referred to as rating from here on) was calculated across both visits in order to have one rating per patient. There were no significant differences between the ratings of each follow-up visit. Physicians rated the benefit of the profile an average of 3.5 on a scale of 1-5 (1: no benefit, 5: significant benefit; Table 3), with 90% of physicians reporting that the test provided some benefit, and 27% reporting significant benefit.

Profile use by physicians

Physicians rated the benefit of the profile for clinical decision-making and patient care during the baseline and follow up study visits.

Specialty	Total Patients	Rating Distribution (%)					Mean Rating
		1	2	3	4	5	
Pain Medicine/Physical Medicine and Rehabilitation/ Anesthesiology	2822	11.3	8.2	16.7	36.5	27.3	3.6
Family/Primary Care/Internal Medicine	2066	9.4	20	27.8	19.6	23.2	3.3
Orthopedic Surgery	396	2.5	2.5	21.5	34.1	39.4	4.1
Neurology/Psychiatry	31	0	0	0	3.2	96.8	5

Table 3: Benefit ratings of the profile tool by physicians, physicians from 76 clinics used the profile and rated its benefit for clinical decision making and patient care on a scale of 1-5 (1=no benefit; 5=significant benefit), clinics were grouped according to specialties, the mean benefit rating differed by specialty, with significant differences in reported benefit between the 4 groups of practices, at least 90% of physicians thought the profile provided some benefit, with 27% indicating they felt the test provided significant benefit.

Action/Decision	n=5,315 patients			Adjusted model: age+sex+race +specialty		
	Count "Yes"	Percent "Yes"	Avg. Rating Yes/No	OR	P-value	
No changes were implemented (i.e., not guided)	3,242	61	3.1/3.9	0.31	7.34 × 10 ⁻¹⁰⁷	***
n=2,595 patients (guided only)						
Confidence in medical regimen	1,852	71.4	4.0/3.7	2	1.81 × 10 ⁻¹⁵	***
Discontinued opioids	78	3	4.4/3.9	3.6	1.17 × 10 ⁻⁶	***
Changed opioid or dosage	455	17.5	4.2/3.9	1.66	1.39 × 10 ⁻⁶	***
Advised another provider	66	2.5	4.0/3.9	2.15	3.16 × 10 ⁻³	***
Initiated opioid	40	1.5	4.3/3.9	2.13	0.019	*
Changed urine toxicology test frequency	28	1.1	4.3/3.9	2.14	0.059	Trending
Spent more time with patient	1,769	68.1	4.0/3.9	1.01	0.92	

Table 4: Benefit of profile-specific guidance in clinical management, any answer of “yes” on survey questions indicated that the physician used the profile to guide decisions, overall, physicians who made any decision rated the benefit of the profile higher than physicians who did report any guidance, odds ratios (OR) are proportional odds that may be interpreted as the average odds comparing consecutive ratings (i.e., the overall average of the odds of having a rating of 5 versus 4, 4 versus 3 and etc.), an OR<1 indicates that the decision correlated with decreased ratings, the OR of 0.31 for physicians who made no changes indicates that physicians who used the profile to guide decisions rated the profile to be on average 3.2 times higher (1/0.31) than physicians who made no changes, significance levels are indicated as * =p ≤ 0.05, *** =p ≤ 0.001 and trending” =p ≤ 0.10.

The mean benefit ratings of the profile were dependent on 3 variables: clinic specialty, profile risk stratification results, and whether profile results were used to guide clinical decisions (Table S1).

Orthopedic Surgery and Neurology/Psychiatry physicians rated the profile more favourably than those in Pain Medicine and Family Medicine; physicians treating patients with a high profile score rated

the benefit of profile more favourably ($p=1.37 \times 10^{-5}$); and physicians rated the profile as more beneficial by 0.8 points when used for making specific clinical actions or decisions ($p=1.93 \times 10^{-93}$; Figure 1). In particular, the benefit of the profile to patient care was greater if physicians discontinued or initiated an opioid prescription, made a change to an opioid prescription or dosage, advised another provider to make changes in the patient's prescriptions, and/or used the results to verify and document their medical regimen with more confidence (Table 4). After adjusting for any confounding due to age, sex, race, and clinic specialties, physicians who implemented profile guidance still rated the profile to be on average 3.2 times more beneficial for patient care than physicians who did not follow profile guidance (Table 4).

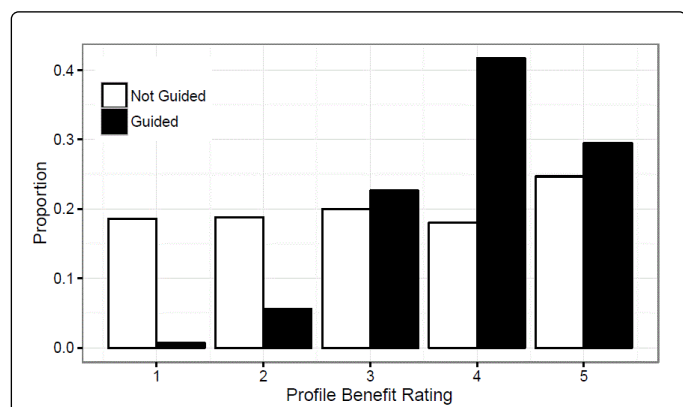


Figure 1: Benefit to clinical care as a function of guidance, physicians who used the profile to make guided clinical decisions indicated greater benefit to their patient's clinical improvement (mean rating \pm std. dev): Not guided, 3.1 ± 1.4 , $n=2,720$; Guided 3.9 ± 0.9 , $n=2,595$, specifically, physicians who used the test rated it 0.8 points higher for patient benefit ($p=1.93 \times 10^{-93}$).

Patient outcomes after receiving profile-guided decisions

Overall, patients improved significantly after receiving guided care from their physicians. Patients' pain NRS before profile-guided care was 6.7 (on a scale of 0-10, where 0 was "no pain" and 10 was "agonizing" pain), compared to 3.9 after receiving care—a 42% reduction of pain ($n=1,134$, $p=5.27 \times 10^{-152}$). Almost 40% of patients had >50% reduction, and 91% reported at least some reduction of pain. Additionally, 13% of patients reported 100%, or complete reduction of pain. Whereas, no patients reported higher pain, and only 8.6% reported no change in pain (Figure 2).

Discussion

The prevalence of OUD in primary care ranges from 3% - 26%, and physicians prescribing opioids are under stringent scrutiny from federal and state regulations [24,32,34]. Although strict policies are meant to curb opioid abuse, they inadvertently place huge stress on physicians who thread the fine line between treating chronic pain and preventing opioid abuse. Guidelines for opioid prescribing for chronic pain management recommend physicians evaluate the patients for opioid risk factors. The profile is a patent-protected tool that predicts patient risk of OUD based on a combination of genetic and phenotypic information. Compared to other tests based exclusively on self-report, the profile can better identify and stratify opioid use disorder in

patients Previous studies 20-22 have demonstrated that the profile identifies those at risk of OUD with high sensitivity (>95%) and specificity (~90%). Furthermore, previous studies have found that the profile performs with Receiver Operating Characteristic (ROC) Area under the Curve (AUC) measurements ranging from 0.75-0.97, which demonstrates that the profile correctly identifies those at risk of OUD between 75% and 97% of the time [20-22]. This is in contrast with published studies describing the specificity of the SOAPP[®]-R 52%, [35] and the sensitivities of the SOAPP ranging from 72% to 80% [35,36] and the ORT 45% [36]. The published AUC of the SOAPP-R ranges from 0.67-0.76, [37] which are lower than the AUC of the profile, in all cases except one.

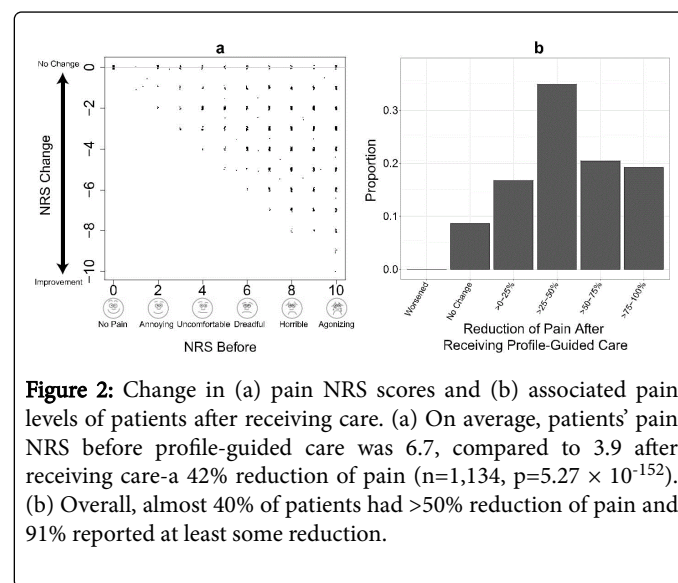


Figure 2: Change in (a) pain NRS scores and (b) associated pain levels of patients after receiving care. (a) On average, patients' pain NRS before profile-guided care was 6.7, compared to 3.9 after receiving care—a 42% reduction of pain ($n=1,134$, $p=5.27 \times 10^{-152}$). (b) Overall, almost 40% of patients had >50% reduction of pain and 91% reported at least some reduction.

Analyzing rating patterns sheds light on how physicians use and appreciate the profile. In this study, 90% of physicians agreed that the profile benefited their practice, with 27% reporting a significant benefit to patient care. Physicians rated the benefit of the profile an average of 3.5 on a 1-5 point scale ("5" indicates that physicians received significant benefits from using profile). Physicians rated the benefit of the profile more favorably for high-risk patients. While it may be intuitive that the result would be most useful for taking action in high-risk cases, we found that the specialty of the clinic makes a difference in the utility of the profile. The trend towards higher benefit in high-risk cases was driven by physicians specializing in pain medicine and those in primary care. For orthopedic surgeons, though not significant, the trend towards higher benefit of the test for treatment decision support leaned towards the low-risk test result. This may be because orthopedic surgeons, unlike pain management physicians, are using the profile as a screening test for surgical cases. Pain management clinics, on the other hand, may be more focused on making differential opioid utilization decisions based on high-risk cases.

Furthermore, physicians reported the profile as more beneficial to patient care—0.8 points higher on a 5-point scale—when they used the tool to guide a treatment decision. The clinical actions that attributed most towards physician reported benefit (raising benefit score by 0.5 points or more) were discontinuing opioids, changing frequency of urine toxicology tests, and changing the opioid selection or dosage. These results demonstrate the benefit of using the profile over other methods used to predict aberrant behavior to opioids.

In both the baseline and follow-up visits, between 23%-34% of physicians felt that the profile facilitated confidence in their medical regimen. Physicians who responded so tended to rate profile more favourably. Although these responses are not direct clinical effects, they indicate that the nebulous nature of prescribing opioids based on self-report can benefit from a more objective, documented assessment. Moreover, a physician's confidence in their prescribing or diagnostic practices can strongly affect doctor-patient interactions. If and how opioid therapy works for a patient depends on a myriad of factors, and one factor in the success of opioid therapy-particularly in terms of avoiding aberrant opioid behaviors-hinges on effective and honest communication between physicians and patients. CDC guidelines recommend physicians discuss opioid risks and benefits in transparent and realistic terms with patients [19]. Other practitioners encourage physicians to win patients' cooperation through empathy and establishing trust [38,39]. Higher confidence and spending more time with patients would help physicians make better opioid prescribing decisions through the establishment of stronger doctor-patient relationships.

Pain is a huge burden on healthcare. In 2010, pain direct and indirect costs exceeded \$560-635 billion than those of injury, cardiovascular disease and respiratory (Gaskin, 2012). Incorporation of the profile in physician decisions to guide treatment of pain can have immense impact on healthcare costs. Along with establishing improved provider-patient relationships, profile-guided treatment resulted in improved patient outcomes through decreased pain. Patients whose physician used the profile to guide treatment experienced an average pain decrease of 2.8 points on the NRS, equivalent to an average decrease from moderately-high to low pain levels.

Conclusion

A patent-protected opioid risk assessment profile combining known genetic risk factors with proven phenotypic risk factors, is beneficial and relevant for physicians in clinics. Physicians rated the profile favorably, with 90% stating the profile was beneficial to clinical decision-making and patient care, and 27% of them indicating that the profile resulted in significant improvements in their patients' status. The actions ranked most highly by physicians included: making decisions regarding opioid prescriptions and increasing confidence in opioid prescribing-resulting in improved patient-physician relationships. Most importantly, patients whose physicians used the profile to guide treatment experienced a reduction in overall pain. The results of this study demonstrate the clinical utility of the profile in a naturalistic, multi-specialty setting.

Acknowledgement

The authors would like to acknowledge Yao Hua Law, Ph.D. for drafting the manuscript. The authors also gratefully acknowledge all patients and physicians who agreed to take part in the study, without whose participation and cooperation this work would not have been possible.

Disclosure and Conflicts of Interest

This study was sponsored by Proove Biosciences Inc.; KL is a member of the Proove Biosciences Medical Advisory Board. JB is a former employee of Proove Biosciences. CL, SK, BM and AB are employees of Proove Biosciences.

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