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Interpretable Machine Learning May Help Personalize Topical Analgesics for Pain Patients

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ABSTRACT

Purpose: *Topical analgesics have gained acceptance in guidelines for the treatment of pain. The Kailo Pain Patch® is a topically applied analgesic adhesive patch, with a recent study showing reduced pain severity and interference scales in comparison to a control group. However, as with any analgesic modality, treatment response is variable. Advances in technology, such as pharmacogenomic evaluation and machine learning (artificial intelligence) have emerged as tools to assist clinicians with selecting the most suitable treatments for a variety of disease states. There is limited data on the use of these technologies for pain management; only limited studies have applied machine learning to personalize the treatment of chronic pain patients. This report analyzed the PREVENT Study using an existing modified interpretable machine learning method to personalize the selection of the most suitable protocol for use of the Kailo Pain Patch® and other topical analgesics.*

Patients and methods: *Data from the IRB-approved observational PREVENT study were used in the present analysis of 128 (89 females,39 males) chronic pain patients and 20 controls answering the Brief Pain (BPI) questionnaire along with additional questions in the baseline and after 30 days of treatment with the Kailo Pain Patch®. An interpretable machine-learning model was used to build pain outcome prediction models. This method is a multi-objective ensemble classification/regression technique, which combines multi-objective evolutionary algorithms with Support Vector Machines, Random Forests, and feature filtering techniques to optimize the classification model and minimize the utilized feature subset. Three basic endpoints were examined as outputs to the prediction models including Total BPI Severity, Total BPI Interference, and Total medication changes in the follow-up period. Both classification and regression models were constructed for these endpoints and a "leave-one-out" cross-validation strategy was used to evaluate the generalization ability, classification, and regression performance of the deployed models.*

Results: *Experimental results showed that the trained models with the proposed machine learning method were able to predict endpoints with extremely high accuracy, with the AUC exceeding 90% and Spearman correlation metric exceeding 0.4 for all endpoints, overcoming the classification and regression performances of other benchmark models, including the recently introduced XGBoost. The interpretable machine learning method was able to reduce the number of significant features to 15 and was able to identify some of the most important characteristics of responders and non-responders allowing for a personalized approach to creating an individualized pain treatment approach. Applying the trained model in a previous IRB-approved Observational Study (OPERA) dataset (631 chronic pain patients) demonstrated that most of the participants (>70%) who did not benefit from other topical analgesics therapies, as well as more than 50% of responders to OPERA study medications, would have noted improvement from the pain patch studied in PREVENT.*

Conclusions: *Artificial intelligence and machine learning technologies are advancing multiple areas in fields of medicine, including pain management. A model has been developed which continues to be refined; here we show use of that model for predicting response to topical analgesic therapies. We will continue to refine these tools and make them available to front-line clinicians through a user-friendly web interface (https://kailo.insybio.com/) that can be used to support analgesic clinical decision making [15 questions].*

Keywords
Personalized medicine, Pain alleviation, Non-opioid treatment, Machine learning, Predictive analytics, Regression, Explainable machine learning, Kailo Pain Patch, Topical analgesics, Random Forests, XGBoost, Support Vector Machines.

Abbreviations
AI: Artificial Intelligence, AUC: Area Under the Curve, KNN: k-nearest neighbors, MSE: Mean Squared Error, ML: Machine learning, PREVENT: Pain Relief: Experiencing and Validity: Evaluating Nano Technology, OPERA: Optimizing Patient Experience and Response to Topical Analgesics, PCA: Principal Component Analysis, ROC: Receiver Operating Characteristic, SVR: Support Vector Regression.

Introduction
Chronic pain causes suffering and affects the quality of life for millions of Americans [1]. The exact mechanism by which pain becomes chronic is unknown but includes causative factors such as degenerative and inflammatory conditions, modulated by genetic, environmental, and lifestyle factors [2]. Each individual has unique pain processing, perception, and analgesic responsiveness [3], with the ultimate goal of acceptable pain relief. To this end, a variety of primary and adjuvant analgesics are utilized, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants [4]. However, oral analgesics have been linked with systemic toxicities and risks like abuse, misuse, and addiction [5]. In contrast, topical analgesics offer pain relief with minimal, if any, systemic adverse effects. Studies have confirmed their effectiveness; they have been found to reduce pain severity, pain interference, and patient overall analgesic drug consumption [6].

Pain-relieving patches are one type of topical therapy. These can be divided into transdermal systems- where the medication is absorbed into the systemic circulation (e.g., fentanyl, nicotine), and topical patches, such as lidocaine and methyl salicylate. In recent years, non-drug patches with analgesic benefit have been introduced into the market. The Kailo Pain Patch®, (Pain Relief Technologies, Salt Lake City, Utah, USA) an over-the-counter (OTC) microtechnology topical pain patch, is one such product [7], although a number of drug and non-drug therapies with variable effectiveness are available.

A mechanism to predict responders of analgesics would be of benefit to clinicians, enabling them to individualize chronic pain management by identifying the most effective analgesic therapy for each patient. To gain insight into potential responders, artificial intelligence (AI) methods have emerged in pain research [8]. Such methods can learn from clinical trial results, identify patterns in the data and extract knowledge from them. As a result, they can be used to stratify subgroups and predict data, such as those patients that may respond favorably to a certain therapy.

AI has been used in aiding diagnoses and outcomes of chronic pain syndromes [9,10]. In recent work, subgroup analyses identified different pain phenotypes and suggested that sleep is a core factor in chronic pain [11]. Emotions are suggested as another chronic pain factor and were used to predict pain after 2 weeks in a mobile app [12]. Machine learning also assisted self-reporting questionnaires to evaluate the outcome of an integrated biopsychosocial chronic pain treatment approach [13].

In another context, postoperative pain management was studied with AI by predicting analgesic consumption to improve perioperative outcomes [14]. Similarly, predicting postoperative analgesic use together with postoperative urinary retention risk prediction was also studied [15], as was prediction of persistent postsurgical pain in women after breast cancer surgery considering presurgical demographic, psychological, and treatment-related factors [16,17]. The use of AI methods in treating chronic pain and neuropathic disorders has been reported on in the literature [18]. Response to a specific drug for neuropathic pain was predicted using baseline demographic and clinical characteristics and changes in pain change [19].

Extensive use of AI methods has been made in opioid research to predict and monitor overdose risk [20]. AI has also been used with genomics data to identify pain patients requiring extremely high opioid doses for their pain [21] but also with quantitative sensory testing data to find response patterns in different pain stimuli [22]. The association of complex pain genotypes with phenotypes was also examined [23].

While there have been attempts in the literature to individualize pain treatments, a straightforward method does not yet exist. An AI analytic approach has been utilized previously to predict chronic pain patient response to topical analgesic treatment [24]. The results suggested that this machine learning model could have predicted in advance at least 10% of patients who would have failed treatment with the studied therapy. An explainable machine learning technique was later introduced [25] and used to predict patients' response to OTC topical analgesics. This revealed a group of super responders with well-defined clinical characteristics who were predicted to get the most benefits from a non-drug Pain Relieving Patch.

In the present paper, we applied a machine learning-based pipeline, enriched with pre- and post-modeling explainability methods, to personalize topical chronic pain treatment by predicting and quantifying the benefits of the non-drug Kailo Pain Patch®.

Material and Methods
Data
In the present analysis, data from the PREVENT study [7] were used to individualize therapy by training and testing prediction models to predict which chronic pain patients would benefit from the pain patch. A detailed description of the active ingredients of the patch, the design of PREVENT study, and additional metadata of the participants are presented in previous peer-reviewed research [7]. There, responses from the Brief Pain Inventory (BPI) validated scale [26] were collected from patients at baseline and

after 30 days of using the pain patch, measuring the changes in 1) pain severity score, 2) pain interference score, 3) medication usage and 4) pain relief before and after the intervention. The PREVENT study was performed in full accordance with the rules of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the principles of the declaration of Helsinki and the international council of Harmonisation/GCP. IntegReview institutional review board approved the study protocol.

The PREVENT dataset was composed of data before and after treatment for 128 chronic pain patients and 20 controls. 97.7% of participants had some improvement in their pain severity and pain interference score; and 71.1% and 50.8% had improvement of more than 2 units in the BPI scale respectively for severity and interference. The treated patients were equally and randomly split into training and test sets with 64 patients each; the control group was kept for validation. All patients replied to questions before (Baseline) and 30-days after the treatment. These BPI questions were categorized as features by encoding categorical variables using the FeatureHasher method of the Scikit-learn package [27] to allow for their integration with number features, ending up with a list of 45 features. Data were scaled to zero means and a standard deviation of 1, and missing values were imputed with the KNN-imputation method using k=5. Leave-one-out cross-validation was used to train and test prediction models on the training set.

Machine Learning Method

To identify outcome prediction models, we treated the prediction problem as a binary classification model designed to evaluate BPI Interference and Severity to identify individuals who are expected to improve their BPI scores by at least 2 units after the intervention. Regarding changes in medication usage, the change in Total drugs in the outcome classification problem was defined as attempting to classify patients who had either an increase or decrease of total drugs after the intervention.

The applied machine learning method is an extension of the machine learning method first introduced in a previous IRB-approved pain study [24] and then expanded with other IRB-approved pain studies using a similar protocol and the BPI validated scale to further improve its ability to train and test accurate regression models with imbalanced datasets minimizing the number of selected features and thus, improving the interpretability of the models. The deployed technique is based on the application of an ensemble dimensionality reduction technique that uses multi-objective optimization heuristic optimization algorithms [28] to perform dimensionality reduction and optimize the classification model by selecting the most suitable classifier among and its optimal parameters in the deployed dataset. The classification models, which are examined, were Support Vector Regression [29] and Random Forest Methods [30]. The deployed evolutionary optimization is a multi-objective Pareto-based technique allowing optimal exploration and exploitation of the search space driven by a combination of fitness functions that evaluate the models based on their classification models, their simplicity, and the number of features that they generate. A detailed description of this multi-objective optimization heuristic algorithm is provided in previous literature [24]. The previous version of this machine learning method was expanded and updated with this new data in an attempt to maximize the spearman correlation of the predicted outcomes against the known quantified outcomes (BPI severity change, BPI interference change, and Total Drugs change after intervention).

Spearman correlation analysis, Principal component analysis, and K-Prototypes clustering [31] were applied to allow the interpretation of the trained outcome prediction models.

Regarding the benchmark methods, the standard SVM and Random Forests models with their parameters optimized using grid search were deployed using the scikit-learn package of python. Moreover, XGBoost [32], a relatively newly introduced machine learning method, was explored for comparative reasons. XGBoost is a library for developing fast and high-performance gradient boosting tree models that have recently outperformed other classification models in difficult machine learning tasks [33,34]. For the comparative results, we have used the same data splitting, feature calculation, normalization, imputation, and cross-validation techniques to reassure a fair comparison.

Results

Statistical Analysis

Differential expression analysis was conducted for the change of both BPI Interference, BPI Severity, and total drugs, after 30 days from intervention (Figure 1). Results of this analysis confirmed that many of the calculated features are informative in predicting the changes after intervention with specific topical analgesic products. It is noteworthy that the higher the baseline BPI Interference and Severity scores, the bigger the decrease in the BPI scores after intervention but the smaller the change in Total medications. Moreover, patients with a diagnosis of chronic pain in the lower extremities were statistically significantly more able to decrease their total medications after the intervention with the usage of the studied patch.

Principal Component and Clustering Analyses

Principal component analysis and k-Prototypes unsupervised clustering was conducted to explore whether the PREVENT study's data can be separated into clusters using the calculated features that can separate responders and not responders (Figure 2). The best clustering, based on the Calinski-Charabazs metric, was shown when six clusters were used. From this analysis, it is obvious that there exists a cluster (light blue) that includes super-responders and a cluster that includes non-responders (dark blue). The non-responders are categorized as patients with a smaller frequency of Moderate Physical Activity, back pain, and smaller use of OTC medications while the responders are categorized as patients with a higher frequency of physical activity, lower extremity pain, and higher usage of OTC medications.

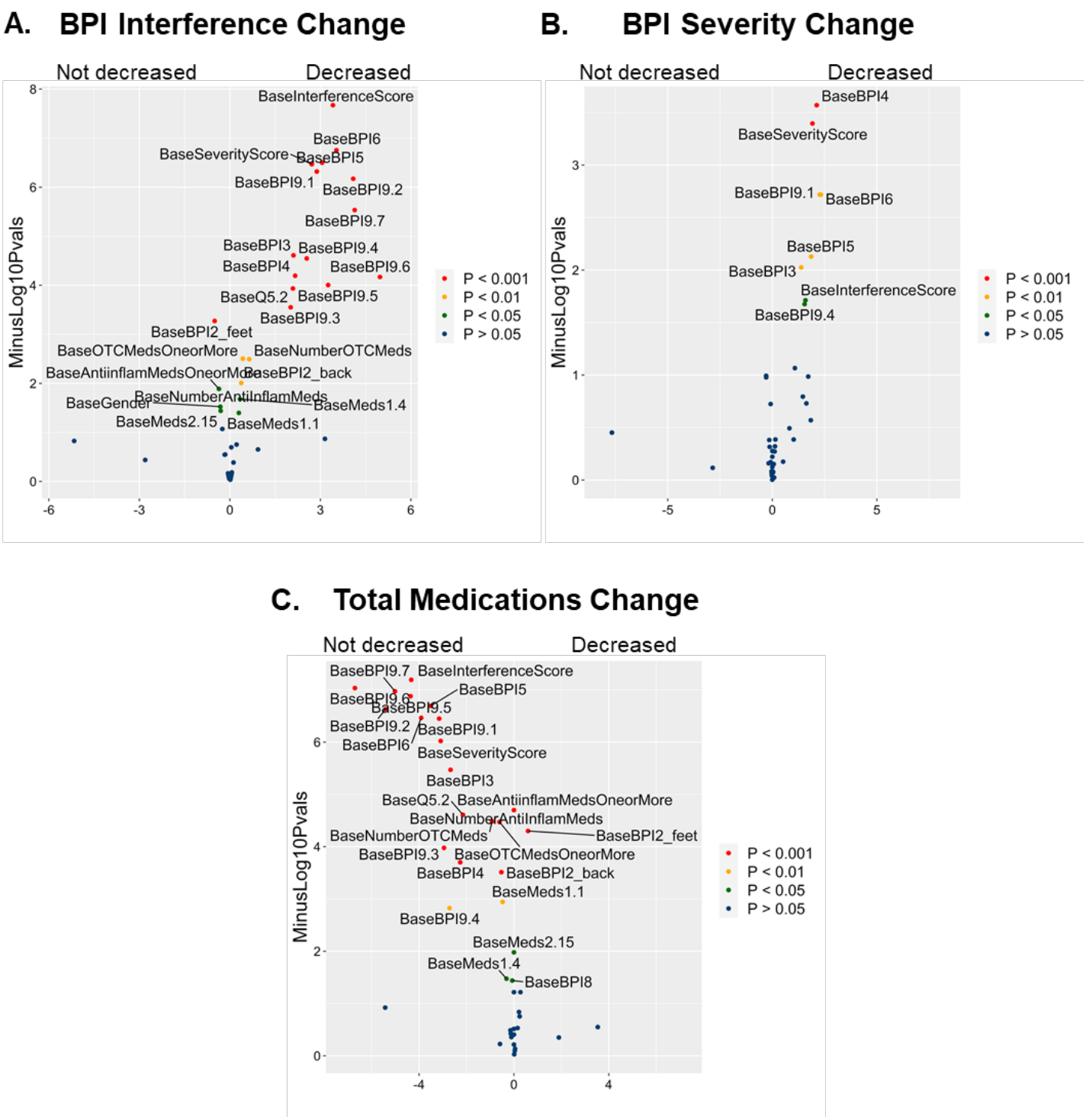

Figure 1: Differential expression analysis of calculated features for A. BPI interference change, B. BPI Severity change, and C. Total medications change after 30 days from intervention with the Kailo Pain Patch®. For continuous features, the non-parametric Mann-Whitney U-test was conducted and for categorical features, the Fisher exact test was conducted.

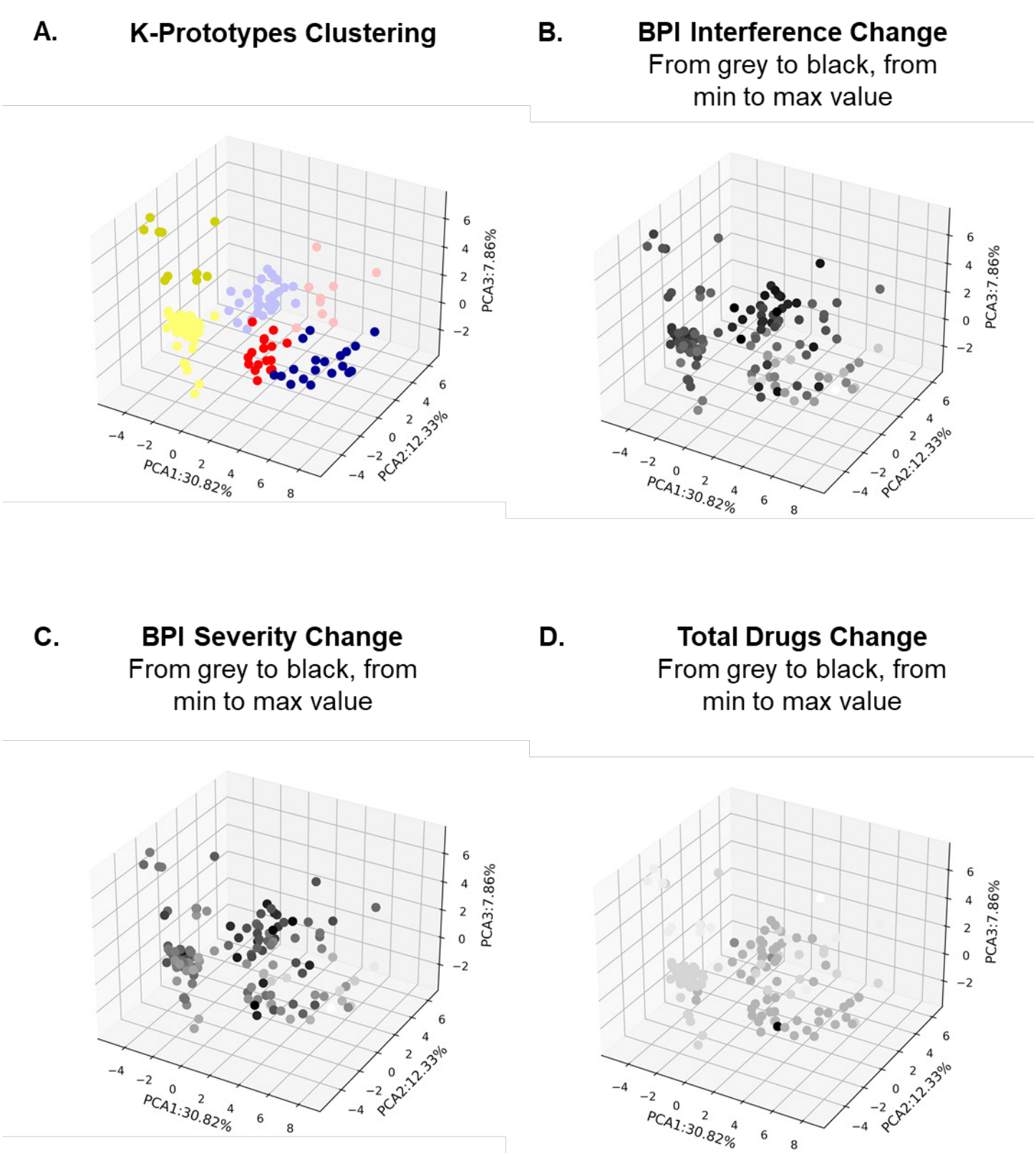

Figure 2: A. K-Prototypes clustering of PREVENT Dataset. Different colors represent the different clusters revealed using the three more important Principal Components and the percentage of the explained variability of each one of these PCAs is depicted in the axis labels. B. 3D representation of the PCAs of the PREVENT Dataset projecting on the samples the BPI Severity Change before and after the treatment. C. 3D representation of the PCAs of the PREVENT Study Dataset projecting on the samples the BPI Interference Change before and after the treatment. D. 3D representation of the PCAs of the PREVENT Dataset projecting on the samples the Total Drugs Change before and after the treatment. The grey to black color scale was used to depict values from min to max respectively.

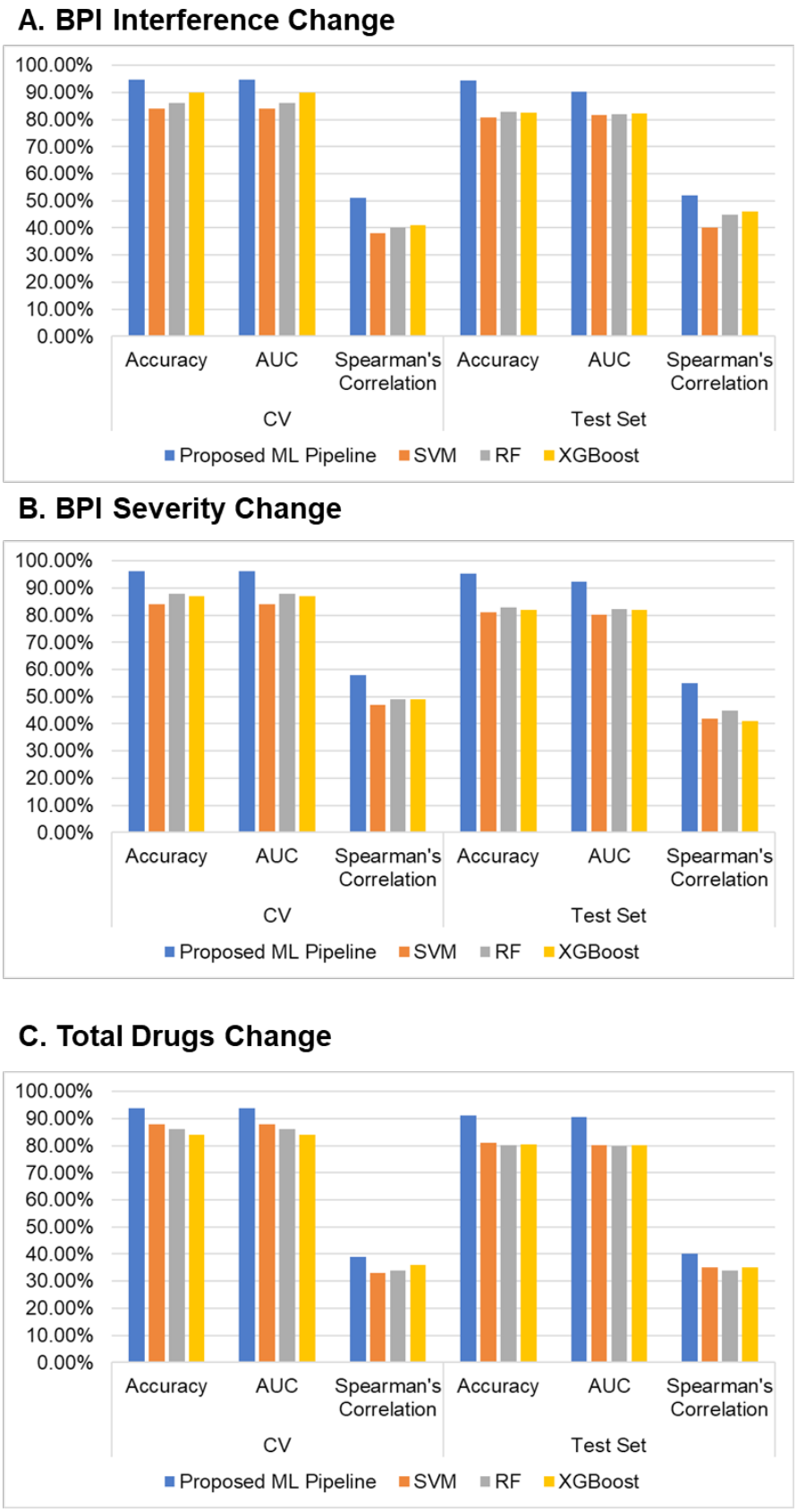

Figure 3: Comparative results of trained machine learning models in predicting A. Total Severity Change, B. Total Interference Change, and C. Total Drugs Change. Evaluation metrics have been calculated in the Training set using Leave-One-Out Cross-Validation (CV) and in the independent Test set. AUC: Area Under the Curve, SVM: Support Vector Machines, RF: Random Forests.

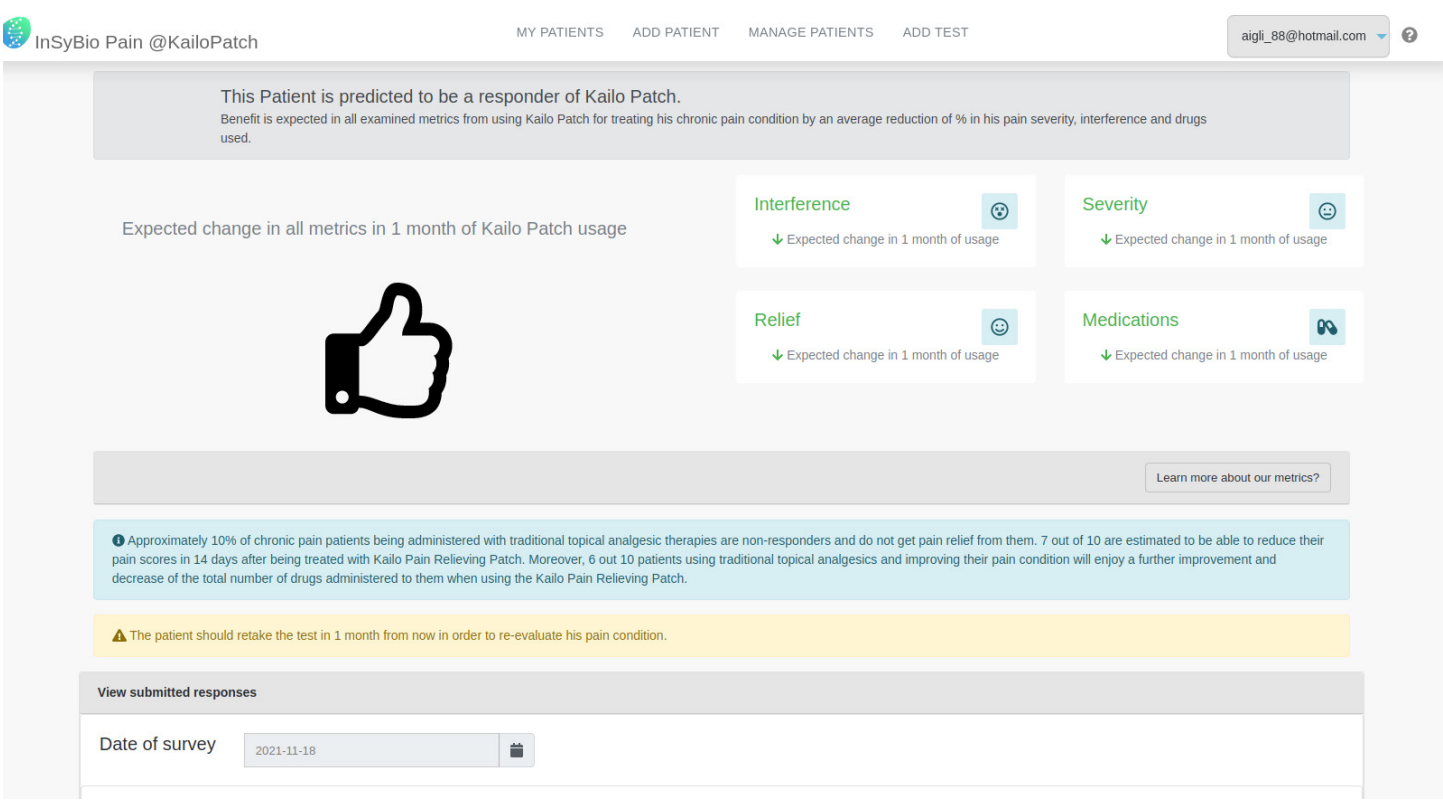

Figure 4: Screenshot of the designed web tool.

Predictive Analytics and Comparative Results

The proposed machine-learning model was applied in the examined dataset using a parameters population size of 50 and a maximum number of generations of 200. Since the proposed method is a heuristic approach, it was applied 10 times in the proposed dataset and Figure 3 presents its average performance in predicting the 3 outcomes of this study. Figure 3 also presents the performance of state-of-the-art regression models, SVR, Random Forests & XGBoost.

Experimental results show the superiority of the proposed machine learning method in all examined metrics with the increase being even more pronounced in the external test set. It is noteworthy, that the proposed model achieved these high predictive metrics by using just 15 features from 11 questions (see Table 1) in opposition to the benchmark methods, which used all the 46 features from the complete questionnaires.

Interpreting Prediction Models

Table 1 presents the selected features and their category. 15 features were selected originating from 11 questions from the Primary complaint/diagnosis and location, the brief pain inventory, and the current medications categories.

Table 1: The final list of selected features from the machine-learning model.

Feature ID	Feature Description	BPI Interference	BPI Severity	BPI Medications
Base Q5.2	Frequency of Moderate Physical Activity			X
Base BPI2_feet	Presence of Pain in Any Position of the Feet	X		X
Base BPI2_back	Presence of Pain in Any Position of the Back	X		X
Base BPI3	Duration of Pain		X	
Base BPI9.1	General Activity Interference			X
Base BPI9.3			X	
Base BPI9.4	Normal work interference	X		
Base BPI9.5	Relations with other people interference			X
Base Meds1.1	Ibuprofen Medication	X		
Base Meds1.4	Tylenol® Medication	X		
Base Meds2.15	Voltaren® Medication		X	
Base OTC Meds One or More	One or More Over-the-Counter Medications	X		
Base Antiinflam Meds One or More	One or more Anti-inflammatory Medications		X	X
Base Total Number Meds	Total number of Medications	X		
Base Severity Score	Baseline BPI Severity		X	X

Web tool for personalizing Chronic Pain Relief with the Kailo Pain Patch®

The obtained models for predicting total interference, total severity, and total drug changes over 30 days using the Kailo Pain Patch® were integrated into a user-friendly web tool (https://kailo.insybio.com/) which includes interfaces for both clinicians and chronic pain patients. This is not a tool intended to automatically generate recommendations about the treatments of chronic pain but can be used as a decision support system for the clinician to identify potential groups of chronic pain patients that might benefit from using the Kailo Pain Patch®. Clinicians can also use this tool to monitor the progress of the symptoms and chronic pain scales of their patients allowing them to make more informed decisions about their suggested treatment protocols. On the other hand, patients can get a recommendation about the probability of belonging to the responder's group of patch users and then seek further advice from their clinician to get a formal recommendation.

Examining the Applicability of the Individualized Prediction Models in Other Cohorts

From a previous published study by these authors [24], a machine learning model was used to identify responders of topical analgesic therapies using previous datasets. In that analysis, approximately 10% of the participants had been predicted not to be suitable for the studied topical analgesic. In the context of the present analysisy, an interpretable machine learning model was developed to predict the specific response of chronic pain patients who used the Kailo Pain Patch®for chronic pain. To explore how this model can be applied with other topical analgesics, we applied the trained model for to the previous studies data. Prediction analysis showed that out of the 9.7% of nonresponders from the topical analgesic therapies in a previous topical anagesic study, 76.76% of them would have presented reduced BPI scores if they were treated with the Kailo Pain Patch®. Moreover, 52.3% of the responders of topical analgesic treatments in a previous study would have further decreased the average of the reductions in BPI scores and the Total number of drugs administered to them.

As an additional test, we applied the trained models to predict the outcomes of the control test set composed of 20 participants with lower than moderate chronic pain. It is noteworthy that the prediction models predicted substantial benefit for only 4/20 participants, validating its specificity.

Discussion and Conclusions

The causes of chronic pain are diverse, but the common denominator is the impact chronic pain has on a patient's quality of life and activities of daily living. The opioid crisis in the USA encouraged identification of new, non-opioid chronic pain analgesic products including over-the-counter drugs, biologics, topical analgesic patches, and other devices. The diversity of chronic pain etiologies, conditions, and symptoms makes it difficult for a clinician to predict which therapy or treatment modality may work for a particular patient. Thus, a precision medicine approach would be extremely valuable to clinicians to identify responders and non-responders when a therapy is under consideration.

In a recent population study (PREVENT), a topical, non-drug pain patch was evaluated in a population of 128 adult patients (89 females, 39 males) with arthritic, neuropathic, or musculoskeletal pain who received patches for 30 days. The results of the study showed that this patch triggers statistically significant benefits to the chronic pain patients in reducing BPI Severity and Interference scores as well as in their total number of drugs used. It is noteworthy that in a control group of 20 participants it was observed that the BPI Interference and Severity Scores did not improve with statistical significance 30 days after the baseline measurements.

However, as expected, it was observed that a minority of chronic pain patients did not benefit from the use of the patch. As observed in Figure 1, many of the questions in the baseline questionnaire can discriminate between responders and non-responders to the Kailo Pain Patch®. In addition, from the PCA analysis conducted (Figure 2), it is noteworthy that there exists one group of patients (dark blue) that does not benefit from the patch. Moreover, there is one group of patients (light blue cluster) who are super responders and have a very high decrease in pain severity and interference scores after getting treated with the pain patch for a month.

Knowing that the questionnaires can discriminate between responders and not responders is not enough since it is required to identify the most accurate prediction models to improve the accuracy in classifying between responders and not responders. Furthermore, the required classification models should use the minimum number of inputs to allow for its incorporation into a usable web interface, minimize the risk of overfitting and raise the interpretability of the model. To achieve the above-mentioned goals, in the present analysis, we modified and used an interpretable machine learning solution that combines a multi-objective optimization algorithm with Support Vector Machines, Random Forests, and other feature filtering methods. This method allowed the identification of accurate regression and classification models for predicting the changes in BPI Severity, BPI Interference, and Total drugs after 1 month of using the patch and whether patients were responders (decrease >20%) or non-responders (decrease< 20%). The proposed method was compared against contemporary machine learning techniques including the recently introduced XGBoost demonstrating a significant improvement in all classification metrics.

The proposed interpretable machine learning technique identified a set of 15 questions that were important for predicting all three outcomes with very high accuracy. These included the frequency of activity of the patients, the location of the pain, the baseline BPI severity score, the number of baseline over-the-counter (OTC) medications as well as responses to specific questions about the duration of pain, the interference of pain with daily activities, and the use of specific medications (e.g. Voltaren®). In summary, patients with a high BPI baseline severity score, who take a high number of OTC medications, including Voltaren®, that have pain in the lower extremities, benefited more from the Kailo Pain Patch®. This can be compared to patients with back pain and taking a high number of anti-inflammatory medications at baseline, who were shown to not be as responsive to the patch. It is noteworthy

that patients with high interference baseline scores were able to reduce their BPI scores after using the pain patches but were not able to substantially decrease the medications they used. Further research is suggested to confirm the results of this analysis and characteristics of responders and non-responders.

Additional analysis using the data from a previous study (OPERA) showed that the Kailo Pain Patch® would have been beneficial for the majority (76.76%) of the chronic pain patients that did not benefit from the treatment in that study. Moreover, the model predicted that more than 50% of the patients who were responders for medications in that previous study would have had a larger positive response if they used the Kailo Pain Patch®. These encouraging results suggested that the Kailo Pain Patch® can be extremely beneficial for specific categories of chronic pain patients and that the use of the proposed machine learning models can contribute to a precision medicine approach to accurately identify responders and super-responders. To further study these precision medicine models, a web tool was developed that can be used by physicians and patients to personalize and evaluate the potential response to topical analgesics that have been studied using these models.

In future analyses to validate the performance of the proposed precision medicine tool, we will incorporate the models into larger population studies, expanding the medications evaluated, adding omics or biochemical measurement features, and incorporating more objective pain quantification methods.

Disclosure

A. Korfiati and S. Mavroudi are the named inventors of the provisional patent (Theofilatos, K., Alexakos, C., Korfiati, A., Dimitrakopoulos, C., & Mavroudi, S. (2018). U.S. Patent Application No. 15/837,407.) submitted to the US Patent Office by InSyBio Ltd which includes the description of the computational framework for predictive biomarkers and building predictive models for diagnosis, prognosis, and treatment.

Jeffrey Gudin MD received compensation from Clarity Science LLC for his role as principal investigator of the PREVENT Study and for providing protocol required services for the study. Peter L Hurwitz is President of Clarity Science LLC, Derek T Dietze received compensation for study statistical analyses of PREVENT data.

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