

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure relates generally to methods for determining and predicting pain. More particularly, the present disclosure relates to methods for objectively determining pain intensity, predicting future emergency department (ED) visits for pain. Also disclosed are methods for identifying drug and natural compounds as candidates for treating pain using biomarker gene expression signatures.

[0007a] In one aspect, the present disclosure is directed to a treatment for example selected from the group listed in Tables 1, 2A, 2B and 7 and combinations thereof for use in a method for treating pain in a subject in need thereof, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s); wherein the treatment is to be administered to reduce the difference between the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s) to mitigate pain in the subject.

[0008] The present disclosure is directed to a method for determining pain intensity in a subject in need thereof. The method comprises: obtaining an expression level of a blood biomarker in a sample obtained from the subject; obtaining a reference expression level of a blood biomarker; and identifying a difference between the expression level of the blood biomarker in a sample obtained from the subject and the reference expression level of a blood biomarker, wherein the difference in the expression level of the blood biomarker in the sample obtained from the subject and the reference expression level of the blood biomarker determines pain intensity. In another aspect, the present disclosure is directed to a method for determining intensity of pain, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from a subject; obtaining a reference expression level of the blood biomarker(s); and identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s), wherein the difference in the expression level of the blood biomarker(s) in the sample obtained from the subject and the reference expression level of the blood biomarker(s) determines the intensity of pain for example wherein the biomarker(s) is/are selected from the group of biomarkers listed in Table 1 and combinations thereof. In one example, the

blood biomarker is a panel of blood biomarkers. The reference level can be an average or reference range in the population (a "cross-sectional" approach), or it can be the level of a sample obtained previously in the subject when the subject was not in need of treating pain (a "longitudinal" approach).

[0009] The present disclosure is directed to a method for identifying a blood biomarker for pain, the method comprising: obtaining a first biological sample from a subject and administering a first pain intensity test to the subject; obtaining a second biological sample from the subject and administering a second pain intensity test to the subject; identifying a first cohort of subjects by identifying subjects having a change from low pain intensity to high pain intensity as determined by a difference between the first pain intensity test and the second pain intensity test; identifying candidate biomarkers in the first cohort by identifying biomarkers having a change in expression between the first biological sample and the second biological sample. In another aspect, the present disclosure is directed to a method for identifying one or more blood biomarker(s) for pain personalized by gender and diagnosis, the method comprising: identifying a first cohort of subjects by identifying subjects having a change from low pain intensity to high pain intensity as determined by a difference between the first pain intensity test and the second pain intensity test; identifying candidate biomarkers in the first cohort by identifying biomarker(s) having a change in expression between the first biological sample and the second biological sample that had been obtained from the subject.

[0010] The present disclosure is directed to a method for predicting future emergency department (ED) visits for pain. The method comprises: obtaining an expression level of a blood biomarker or panel of blood biomarkers in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker or panel of blood biomarkers; identifying a difference in the expression level of the blood biomarkers in the sample and the

reference expression level of the blood biomarkers; wherein the difference in the expression level of the blood biomarkers in the sample obtained from the subject and the reference expression level of the blood biomarkers determines the likelihood of future ED visits for pain. In one example, the blood biomarker is a panel of blood biomarkers. The reference expression level can be that as described herein.

[0010a] In another aspect, the present disclosure is directed to a method for predicting a future medical care facility visit for pain, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from a subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s), wherein the difference in the expression level of the blood biomarker(s) in the sample obtained from the subject and the reference expression level of the blood biomarker(s) determines the likelihood of future medical facility visits for pain for example wherein the biomarker(s) is/are selected from the group of biomarkers listed in Table 1 and combinations thereof.

[0011] The present disclosure is directed to a method for mitigating pain in a subject in need thereof. The method comprises: obtaining an expression level of a blood biomarker in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker; identifying a difference in the expression level of the blood biomarker in the sample and the reference expression level of the blood biomarker; and administering a treatment, wherein the treatment reduces the difference between the expression level of the blood biomarker in the sample and the reference expression level of the blood biomarker to mitigate pain in the subject. In another aspect, the present disclosure is directed to a treatment for example selected from the group listed in Tables 1, 2A, 2B and 7, and combinations thereof for use in a method for mitigating pain in a subject in need thereof, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s); and wherein the treatment is to be administered to reduce the difference between the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s) to mitigate pain in the subject. In one

example, the blood biomarker is a panel of blood biomarkers. The reference expression level can be that as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The disclosure will be better understood, and features, aspects and advantages other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such detailed description makes reference to the following drawings, wherein:

[0013] FIGS. 1A-1G depict Steps 1-3: Discovery, Prioritization and Validation. FIG. 1A depicts Cohorts used in study, depicting flow of discovery, prioritization, and validation of biomarkers from each step. FIG. 1B depicts Discovery cohort longitudinal within-participant analysis. Phchp#### is study ID for each participant. V# denotes visit number. FIG. 1C depicts Discovery of possible subtypes of Pain based on High Pain visits in the discovery cohort. Participants were clustered using measures of mood and anxiety (Simplified Affective State Scale (SASS)), as well as psychosis (PANNS Positive) FIG. 1D depicts Differential gene expression in the Discovery cohort -number of genes identified with differential expression (DE) and absent-present (AP) methods with an internal score of 1 and above. Red/Underlined-increased in expression in High Pain, blue/Bold-decreased in expression in High Pain. At the discovery step probesets are identified based on their score for tracking pain with a maximum of internal points of 6 (33% (2pt), 50% (4pt) and 80% (6pt)). FIG. 1E depicts prioritization with

CLAIMS

What is claimed is:

1. A treatment for example selected from the group listed in Tables 1, 2A, 2B and 7 and combinations thereof for use in a method for treating pain in a subject in need thereof, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s); wherein the treatment is to be administered to reduce the difference between the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s) to mitigate pain in the subject.

2. The treatment for use according to claim 1, wherein the biomarker(s) is/are selected from the group consisting of microfibril associated protein 3 (MFAP3), phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta (PIK3CD), Sushi, Von Willebrand Factor Type A, EGF And Pentraxin Domain Containing 1 (SVEP1), TNF Receptor Superfamily Member 11b (TNFRSF11B), ElaC Ribonuclease Z 2 (ELAC2), and combinations thereof.

3. The treatment for use according to claim 1, wherein the biomarker(s) is decreased in response to the treatment.

4. The treatment for use according to claim 1, wherein the biomarker(s) is increased in response to the treatment.

5. A method for determining intensity of pain, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from a subject; obtaining a reference expression level of the blood biomarker(s); and identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s), wherein the difference in the expression level of the blood biomarker(s) in the sample obtained from the subject and the reference expression level of the blood biomarker(s) determines the intensity of pain for example wherein the biomarker(s) is/are selected from the group of biomarkers listed in Table 1 and combinations thereof.

6. The method of claim 5, wherein the biomarker(s) is/are selected from the group consisting of microfibril associated protein 3 (MFAP3), phosphatidylinositol-4,5-Bisphosphate

3-Kinase Catalytic Subunit Delta (PIK3CD), Sushi, Von Willebrand Factor Type A, EGF And Pentraxin Domain Containing 1 (SVEP1), TNF Receptor Superfamily Member 11b (TNFRSF11B), ElaC Ribonuclease Z 2 (ELAC2), and combinations thereof.

7. The method of claim 5, wherein the expression level of the blood biomarker(s) in the sample obtained from the subject is increased as compared to the reference expression level of the biomarker(s).

8. The method of claim 5, wherein the expression level of the blood biomarker(s) in the sample obtained from the subject is decreased as compared to the reference expression level of the biomarker(s).

9. A method for predicting a future medical care facility visit for pain, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from a subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s), wherein the difference in the expression level of the blood biomarker(s) in the sample obtained from the subject and the reference expression level of the blood biomarker(s) determines the likelihood of future medical facility visits for pain for example wherein the biomarker(s) is/are selected from the group of biomarkers listed in Table 1 and combinations thereof.

10. The method of claim 9, wherein the expression level of the blood biomarker(s) in the sample obtained from the subject is increased as compared to the reference expression level of the biomarker(s).

11. The method of claim 9, wherein the expression level of the blood biomarker(s) in the sample obtained from the subject is decreased as compared to the reference expression level of the biomarker(s).

12. A treatment for example selected from the group listed in Tables 1, 2A, 2B and 7, and combinations thereof for use in a method for mitigating pain in a subject in need thereof, the method comprising: obtaining an expression level of one or more blood biomarker(s) personalized by gender and diagnosis in a sample obtained from the subject; obtaining a reference expression level of the blood biomarker(s); identifying a difference in the expression level of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s); and wherein the treatment is to be administered to reduce the difference between the expression level

of the blood biomarker(s) in the sample and the reference expression level of the blood biomarker(s) to mitigate pain in the subject.

13. The treatment for use according to claim 12, wherein the treatment is selected from the group consisting of SC-560, pyridoxine, methylergometrine, LY-294002, haloperidol, cytosine, cyanocobalamin, betaescin, amoxapine, apigenin and combinations thereof.

14. The treatment for use according to claim 12, wherein the treatment is selected from the group listed in Table 2B, and combinations thereof.

15. A method for identifying one or more blood biomarker(s) for pain personalized by gender and diagnosis, the method comprising: identifying a first cohort of subjects by identifying subjects having a change from low pain intensity to high pain intensity as determined by a difference between the first pain intensity test and the second pain intensity test; identifying candidate biomarkers in the first cohort by identifying biomarker(s) having a change in expression between the first biological sample and the second biological sample that had been obtained from the subject.

16. The method of claim 15 further comprising prioritizing the candidate biomarker(s) by identifying candidate biomarker(s) known to be associated with pain.

17. The method of claim 15, wherein the pain intensity test is selected from the group consisting of Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP), and combinations thereof.