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PREDICTING SUICIDALITY USING A COMBINED GENOMIC AND CLINICAL RISK ASSESSMENT

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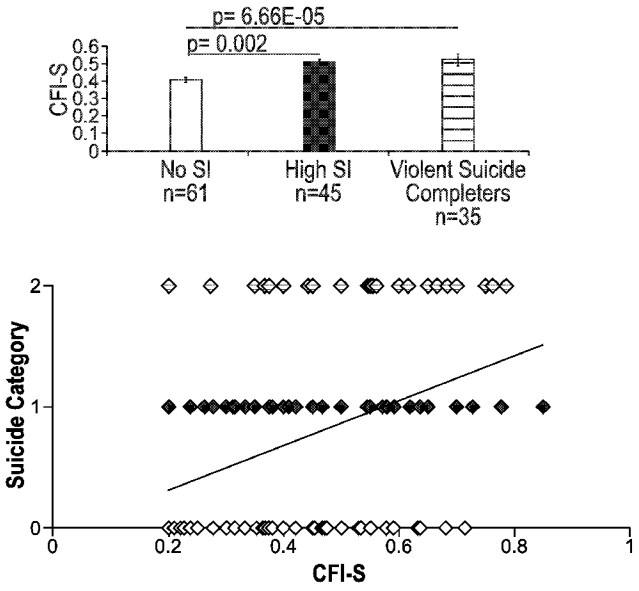
(54) Title: PREDICTING SUICIDALITY USING A COMBINED GENOMIC AND CLINICAL RISK ASSESSMENT

(57) Abstract: Biomarkers and methods for screening expression levels of the biomarkers for predicting suicidality (referred herein to suicidal ideation and actions, future hospitalizations and suicide completion) are disclosed. Also disclosed are quantitative questionnaires and mobile applications for assessing affective state and for assessing socio-demographic and psychological suicide risk factors, and their use to compute scores that can predict suicidality. Finally, an algorithm that combines biomarkers and computer apps for identifying subjects who are at risk for committing suicide is disclosed, as well as methods to mitigate and prevent suicidality based on the biomarkers and computer apps.



Predictor	ANOVA	t-test (Completers vs High SI)	Correlation R	Correlation p-value
CFI-S	6.66E-05	0.223	0.344	1.49E-05

FIG. 3A

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TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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PREDICTING SUICIDALITY USING A COMBINED GENOMIC AND CLINICAL RISK ASSESSMENT

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under OD007363 awarded by National Institutes of Health. The Government has certain rights in the invention.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Application No. 62/278,707 filed January 14, 2016 and U.S. Provisional Application No. 62/174,880 filed on June 12, 2015, both of which are hereby incorporated by reference in their entireties.

BACKGROUND OF THE DISCLOSURE

[0003] The present disclosure relates generally to biomarkers and their use for predicting a subject's risk of suicidality (e.g., suicide ideation and actions, future hospitalization due to suicidality, and suicide completion). More particularly, the present disclosure relates to gene expression biomarkers, and to methods of screening for biomarkers, for identifying subjects who are at risk of committing suicide, as well as for preventing and treating subjects for suicidality. The present disclosure further relates to quantitative clinical information assessments through questionnaires and mobile applications (referred to herein as "apps") for assessing affective state (mood and anxiety), for assessing socio-demographic and psychological suicide risk factors, and for identifying subjects who are at risk of committing suicide. Finally, the present disclosure relates to an algorithm for combining biomarkers and apps for identifying subjects who are at risk for committing suicide.

[0004] Suicide is a leading cause of death in psychiatric patients, and in society at large. Particularly, suicide accounts for one million deaths worldwide each year. Worldwide, one person dies every 40 seconds through suicide, a potentially preventable cause of death. Further, although women have a lower rate of suicide completion as compared to men, due in part to the less-violent methods used, women have a higher rate of suicide attempts. A limiting step in the ability to intervene is the lack of objective, reliable predictors. One cannot just ask individuals if

they are suicidal, as the desire to not be stopped or future impulsive changes of mind may make their self-report of feelings, thoughts and plans unreliable.

[0005] There are currently no objective tools to asses and track changes in suicidal risk without asking the subjects directly. Such tools, however, could prove substantially advantageous as the subjects at risk often choose not to share their suicidal ideation or intent with others, for fear of stigma, hospitalization, or that their plans will be thwarted. The ability to asses and track changes in suicidal risk without asking a subject directly would further allow for intervening prior to suicide attempt and suicide completion by the subject.

[0006] Conventionally, a convergence of methods assessing the subject's internal subjective feelings and thoughts, along with external, more objective, ratings of actions and behaviors, are used *de facto* in clinical practice, albeit not in a formalized and systematic way. Accordingly, there exists a need to develop more quantitative and objective ways for predicting and tracking suicidal states. More particularly, it would be advantageous if objective tools and screening methods could be developed for determining expression levels of biomarkers to allow for determining suicidal risk and other psychotic depressed mood states, as well as monitoring a subject's response to treatments for lessening suicidal risk. The ability to asses and track changes in suicidal risk without asking a subject directly would further allow for intervening prior to suicide attempt and suicide completion by the subject.

BRIEF DESCRIPTION OF THE DISCLOSURE

[0007] The present disclosure is generally related to predicting state (suicidal ideation) and trait - future psychiatric hospitalizations for suicidality. The methods described herein increase the predictive accuracy for specifically identifying subjects who are at risk for committing suicide and for predicting future hospitalization due to suicidality. In one particular aspect, the methods described herein increase the predictive accuracy for specifically identifying subjects who are at risk for committing suicide and for predicting future hospitalization due to suicidality.

[0008] In one aspect, the present disclosure is directed to a method for predicting suicidality in a subject. 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 indicates a risk for suicide.

[0009] In another aspect, the present disclosure is directed to a method for mitigating suicidality 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 suicidality in the subject.

[0010] In another aspect, the present disclosure is directed to a computer-implemented method for assessing mood, anxiety, and combinations thereof in the subject using a computer-implemented method for assessing mood, anxiety, and combinations thereof, the method implemented using a first computer device coupled to a memory device, the method comprising: receiving mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject.

[0011] In another aspect, the present disclosure is directed to a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject using a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject, the method implemented using a first computer device coupled to a memory device, the method comprising: receiving socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to a second computer device; receiving a request from the second

computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject.

[0012] In one aspect, the present disclosure is directed to a method for predicting suicidality in a subject. The method comprises: identifying a difference in the expression level of a blood biomarker in a sample obtained from a subject and a reference expression level of the blood biomarker by obtaining the expression level of the blood biomarker in a sample obtained from a subject; obtaining a reference expression level of a blood biomarker; analyzing the blood biomarker in the sample obtained from the subject and the reference expression level of the blood biomarker to detect the difference between the blood biomarker in the sample and the reference expression level of the blood biomarker; assessing mood, anxiety, and combinations thereof in the subject, using a first computer device coupled to a memory device, wherein the first computer device receives mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; computing, by the first computer device, of the mood information, anxiety information, and combinations thereof, a score that can be used to predict suicidality; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject; assessing socio-demographic/psychological suicidal risk factors in the subject using the first computer device coupled to a memory device, wherein the first computer device receives socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; computing, by the first computer device, of the socio-demographic/psychological suicidal risk factor information, a score that can be used to predict suicidality; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to the second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first

computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject; and predicting suicidality in the subject by the combination of the difference between the expression level of the biomarker in the subject and the reference expression level of the blood biomarker; the assessment of mood, anxiety, and combinations thereof; and the assessment of socio-demographic/psychological suicidal risk factor information.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] 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:

[0014] FIGS. 1A-1C depict the Discovery cohort of Example 1: longitudinal within subject analysis. Phchp### is the study ID for each participant. V# denotes visit number (1, 2, 3, 4, 5, or 6). FIG. 1A depicts suicidal ideation (SI) scoring. FIG. 1B depicts subjects and visits. FIG. 1C depicts PhenoChipping: two-way unsupervised hierarchical clustering of all participant visits in the discovery cohort vs. 18 quantitative phenotypes measuring affective state and suicidality. SASS - Simplified Affective State Scale. A - Anxiety items (Anxiety, Uncertainty, Fear, Anger, Average). M- Mood items (Mood, Motivation, Movement, Thinking, Self-esteem, Interest, Appetite, Average). STAI-STATE is State Trait Anxiety Inventory, State Subscale. YMRS is Young Mania Rating Scale.

[0015] FIGS. 2A-2C depict the Biomarker Discovery, Prioritization and Validation of Example 1. FIG. 2A depicts Discovery – number of probe sets carried forward from the AP and DE analyses, with an internal score of 1 and above. Underline-increased in expression in High SI, bold-decreased in expression in High SI. FIG. 2B depicts Prioritization – CFG integration of multiple lines of evidence to prioritize suicide-relevant genes from the discovery step. FIG. 2C depicts Validation – Top CFG genes validated in the cohort of suicide completers, with a total score of 4 and above. All the genes shown were significantly changed in ANOVA from No SI to High SI to Suicide Completers. *survived Bonferroni correction. SAT1 (x3) had three different probe sets with the same total score of 8.

[0016] FIGS. 3A-3C depict the Convergent Functional Information for Suicide (CFI-S) Scale as analyzed in Example 1. FIG. 3A depicts Validation of scale. CFI-S levels in the

Discovery Cohort and Suicide Completers. FIG. 3B depicts Validation of items. CFI-S was developed independently of any data from this Example by compiling known socio-demographic and clinical risk factors for suicide. It is composed of 22 items that assess the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors known to influence suicidal behavior, and two demographic factors, age and gender. These 22 items are shown here validated in the discovery cohort and suicide completers in a manner similar to that for biomarkers. Additionally, a student's t-test was used to evaluate items that were increased in suicide completers when compared to living participants with high suicidal ideation. FIG. 3C depicts CFI-S predictions for suicidal ideation in the independent test cohort and predicting future hospitalizations due to suicidality.

[0017] FIGS. 4A & 4B depict the testing of Universal Predictor for Suicide (UP-Suicide). UP-Suicide is a combination of the best genomic data (top increased and decreased biomarkers from discovery and prioritization by CFG, and validation in suicide completers), and phenomic data (CFI-S and SASS). The graph in FIG. 4A depicts Area Under the Curve (AUC) for the UP-Suicide predicting suicidal ideation and hospitalizations within the first year in all participants, as well as separately in bipolar (BP), major depressive disorder (MDD), schizophrenia (SZ), and schizoaffective (SZA) participants. Two asterisks indicate the comparison survived Bonferroni correction for multiple comparisons. A single asterisk indicates nominal significance of $p<0.05$. Bold outline indicates that the UP-Suicide was synergistic to its components, i.e. performed better than the gene expression or phenomic markers individually. The table in FIG. 4B summarizes descriptive statistics for all participants together, as well as separately in BP, MDD, SZ, and SZA. Bold indicates the measure survived Bonferroni correction for 200 comparisons (20 genomic and phenomic markers/combinations x 2 testing cohorts for SI and future hospitalizations in the first year x 5 diagnostic categories – all, BP, MDD, SZA, SZ). Pearson correlation data in the suicidal ideation test cohort is shown for HAMD-SI vs. UP-Suicide, as well as Pearson correlation data in the hospitalization test cohort for frequency of hospitalizations for suicidality in the first year, and for frequency of hospitalizations for suicidality in all future available follow-up intervals (that varies among subjects, from 1 year to 8.5 years).

[0018] FIGS. 5A-5C depict prediction of Suicidal Ideation by UP-Suicide. The graph in FIG. 5A (top left) depicts Receiver operating curve identifying participants with suicidal ideation against participants with No SI or intermediate SI. The graph in FIG. 5A (top right) depicts

suicidal ideation prediction. The Y axis contains the average UP-suicide scores with standard error for no SI, intermediate SI, and high SI. The graph in FIG. 5A (bottom right) is a Scatter plot depicting HAMD-SI score on the Y-axis and UP-Suicide score on the X axis with linear trendline. The table in FIG. 5B summarizes the descriptive statistics. ANOVA was performed between groups with no SI, intermediate SI, and high SI. FIG. 5C depicts the number of subjects correctly identified in the test cohort by categories based on thresholds in the discovery cohort. Category 1 means within 1 standard deviation above the average of High SI subjects in the discovery cohort, Category 2 means between 1 and 2 standard deviations above, and so on. Category -1 means within 1 standard deviation below the average of the No SI subjects in the discovery cohort, Category -2 means between 1 and 2 standard deviations below, and so on.

[0019] FIG. 6 depicts the Simplified Affective State Scale (SASS) questionnaire for measuring mood and anxiety.

[0020] FIGS. 7A & 7B depict a screen image of the SASS mobile app (FIG. 7A) and CFI-S mobile app (FIG. 7B).

[0021] FIGS. 8A & 8B summarize biological pathways and diseases as analyzed in Example 1.

[0022] FIG. 9 is a table summarizing the top biomarkers for all diagnoses, the top biomarkers for bipolar disorder, the top biomarkers for depression, the top biomarkers for schizoaffective disorder, and the top biomarkers for schizophrenia as analyzed in Example 1.

[0023] FIGS. 10A-10C depict biomarker discovery as analyzed in Example 2. Discovery cohort: longitudinal within-participant analysis. Phchp### is study ID for each participant. V# denotes visit number (1, 2, 3, 4, 5, or 6). FIG. 10A depicts suicidal ideation (SI) scoring. FIG. 10B depicts participants and visits. FIG. 10C depicts PhenoChipping: two-way unsupervised hierarchical clustering of all participant visits in the discovery cohort vs. 18 quantitative phenotypes measuring affective state and suicidality. SASS- Simplified Affective State Scale. A-Anxiety items (Anxiety, Uncertainty, Fear, Anger, Average). M- Mood items- Mood, Motivation, Movement, Thinking, Self-esteem, Interest, Appetite, Average). STAI-STATE is State Trait Anxiety Inventory, State Subscale. YMRS is Young Mania Rating Scale.

[0024] FIGS. 11A-11C depict biomarker prioritization and validation as analyzed in Example 2. FIG. 11A depicts Discovery – number of probesets carried forward from the AP and

DE analyses, with an internal score of 1 and above. Underline-increased in expression in High SI, bold-decreased in expression in High SI. FIG. 11B depicts the Prioritization- CFG integration of multiple lines of evidence to prioritize suicide -relevant genes from the discovery step. FIG. 11C depicts Validation - Top CFG genes, with a total score of 4 and above, validated in the cohort of suicide completers. All the genes shown were significantly changed and survived Bonferroni correction in ANOVA from No SI to High SI to Suicide Completers. Some genes with (x n) after the symbol had multiple different probesets with the same total score.

[0025] FIGS. 12A & 12B depict Convergent Functional Information for Suicide (CFI-S) Scale as analyzed in Example 2. CFI-S was developed independently of any data from this Example, by compiling known socio-demographic and clinical risk factors for suicide. It is composed of 22 items that assess the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors known to influence suicidal behavior, and two demographic factors, age and gender. FIG. 12A depicts testing of scale in females. Prediction of high suicidal ideation in females in a larger cohort that combines the discovery and test cohorts used for biomarker work. The table depicts individual items and their ability to differentiate between No SI and High SI. FIG. 12B depicts testing of the scale in males, in a larger cohort that combines the discovery and test cohorts used for the biomarker work in Example 1. The table depicts individual items and their ability to differentiate between No SI and High SI.

[0026] FIGS. 13A & 13B depict UP-Suicide predictions of suicidal ideation in the independent test cohort, and predicting future hospitalizations due to suicidality as analyzed in Example 2. FIG. 13A (Top left) depicts receiver operating curve identifying participants with suicidal ideation against participants with No SI or intermediate SI; (Top right): Y axis contains the average UP-Suicide scores with standard error of mean for no SI, intermediate SI, and high SI; (Bottom right): Scatter plot depicting HAMD-SI score on the Y-axis and UP-Suicide score on the X axis with linear trend line; and (Bottom Table) summarizes descriptive statistics. FIG. 13B (Top left) depicts receiver operating curve identifying participants with future hospitalizations due to suicidality against participants without future hospitalizations due to suicidality; (Top right): Y axis contains the average UP-Suicide scores with standard error of mean for no future hospitalizations due to suicidality and participants with future hospitalizations due to suicidality; (Bottom right): Scatter plot depicting frequency of future hospitalizations due

to suicidality on the Y-axis and UP-Suicide score on the X axis with linear trend line; and (Bottom Table) summarizes descriptive statistics.

[0027] FIG. 14 is a table depicting the cohorts used in Example 2.

[0028] FIG. 15 is a table depicting biological pathways and diseases as analyzed in Example 2.

[0029] FIG. 16 is a table depicting UP-suicide predictions as analyzed in Example 2. UP-Suicide is composed of 50 validated biomarkers (18 increased in expression, 32 decreased in expression), along with clinical measures app scores (CFI-S, SASS). SASS is composed of Mood scale and Anxiety scale.

[0030] FIG. 17 depicts convergent functional information for suicide (CFI-S) App testing across genders. Prediction of high suicidal ideation in men and women in a larger cohort that combines the cohorts used in Examples 1 and 2 by gender. CFI-S was developed independently of any data from this disclosure, by compiling known socio-demographic and clinical risk factors for suicide. It is composed of 22 items that assess the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors known to influence suicidal behavior, and two demographic factors, age and gender. The table depicts individual items and their ability to differentiate between No Suicidal Ideation and High Suicidal Ideation. These items provide clinical predictors and targets for psycho-therapeutic intervention.

[0031] FIG. 18 depicts convergent functional information for future hospitalization for suicide (CFI-S) App testing across genders. Particularly, prediction of future hospitalizations for suicidality in men and women in a larger cohort that combines the cohorts used in our studies by gender.

[0032] While the disclosure is susceptible to various modifications and alternative forms, specific embodiments thereof have been shown by way of example in the drawings and are herein described below in detail. It should be understood, however, that the description of specific embodiments is not intended to limit the disclosure to cover all modifications, equivalents and alternatives falling within the spirit and scope of the disclosure as defined by the appended claims.

DETAILED DESCRIPTION

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure belongs. Although any methods and materials similar to or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are described below.

[0034] New data for discovery, prioritization, validation and testing of next generation broader-spectrum blood biomarkers for suicidal ideation and behavior, across psychiatric diagnoses are disclosed. Also disclosed are two clinical information questionnaires in the form of apps, one for affective state (Simplified Affective Scale, SASS) and one for suicide risk factors (Convergent Functional Information for Suicide, CFI-S), that are useful in predicting suicidality. Both of these instruments do not directly ask about suicidal ideation. Also disclosed is a comprehensive universal predictor for suicide (UP-Suicide), composed of the combination of top biomarkers (from discovery, prioritization and validation), along with CFI-S, and SASS, which predicts in independent test cohorts suicidal ideation and future psychiatric hospitalizations for suicidality.

[0035] As disclosed herein, "patient psychiatric information" may include mood information, anxiety information, and other psychiatric symptom information and combinations thereof.

[0036] As used herein, “predicting suicidality in a subject” is used herein to indicate in advance that a subject will attempt suicide and/or complete suicide.

[0037] As known by those skilled in the art, “suicidal ideation” refers to thoughts, feelings, intent, external actions and behaviors about completing suicide. Suicidal ideation can vary from fleeting thoughts to unsuccessful attempts. In some embodiments, the reference expression level of a biomarker can be obtained for a subject who has no suicidal ideation at the time the sample is obtained from the subject, but who later exhibits suicide ideation. As used herein, "suicidality" includes both suicide ideation and suicidal acts.

[0038] As used herein, “a reference expression level of a biomarker” refers to the expression level of a biomarker established for a subject with no suicidal ideation, expression level of a biomarker in a normal/healthy subject with no suicidal ideation as determined by one

skilled in the art using established methods as described herein, and/or a known expression level of a biomarker obtained from literature. The reference expression level of the biomarker can further refer to the expression level of the biomarker established for a high suicide risk subject, including a population of high suicide risk subjects. The reference expression level of the biomarker can also refer to the expression level of the biomarker established for a low suicide risk subject, including a population of low suicide risk subjects. The reference expression level of the biomarker can also refer to the expression level of the biomarker established for any combination of subjects such as a subject with no suicidal ideation, expression level of the biomarker in a normal/healthy subject with no suicidal ideation, expression level of the biomarker for a subject who has no suicidal ideation at the time the sample is obtained from the subject, but who later exhibits suicide ideation, expression level of the biomarker as established for a high suicide risk subject, including a population of high suicide risk subjects, and expression level of the biomarker can also refer to the expression level of the biomarker established for a low suicide risk subject, including a population of low suicide risk subjects. The reference expression level of the biomarker can also refer to the expression level of the biomarker obtained from the subject to which the method is applied. As such, the change within a subject from visit to visit can indicate an increased or decreased risk for suicide. For example, a plurality of expression levels of a biomarker can be obtained from a plurality of samples obtained from the same subject and used to identify differences between the plurality of expression levels in each sample. Thus, in some embodiments, two or more samples obtained from the same subject can provide an expression level(s) of a blood biomarker and a reference expression level(s) of the blood biomarker.

[0039] As used herein, "expression level of a biomarker" refers to the process by which a gene product is synthesized from a gene encoding the biomarker as known by those skilled in the art. The gene product can be, for example, RNA (ribonucleic acid) and protein. Expression level can be quantitatively measured by methods known by those skilled in the art such as, for example, northern blotting, amplification, polymerase chain reaction, microarray analysis, tag-based technologies (e.g., serial analysis of gene expression and next generation sequencing such as whole transcriptome shotgun sequencing or RNA-Seq), Western blotting, enzyme linked immunosorbent assay (ELISA), and combinations thereof.

[0040] As used herein, a "difference" in the expression level of the biomarker refers to an increase or a decrease in the expression of a blood biomarker when analyzed against a reference

expression level of the biomarker. In some embodiments, the "difference" refers to an increase or a decrease by about 1.2-fold or greater in the expression level of the biomarker as identified between a sample obtained from the subject and the reference expression level of the biomarker. In one embodiment, the difference in expression level is an increase or decrease by about 1.2 fold. As used herein "a risk for suicide" can refer to an increased (greater) risk that a subject will attempt to commit suicide and/or complete suicide For example, depending on the biomarker(s) selected, the difference in the expression level of the biomarker(s) can indicate an increased (greater) risk that a subject will attempt to commit suicide and/or complete suicide. Conversely, depending on the biomarker(s) selected, the difference in the expression level of the biomarker(s) can indicate a decreased (lower) risk that a subject will attempt to commit suicide and/or complete suicide.

[0041] In accordance with the present disclosure, biomarkers useful for objectively predicting, mitigating, and/or preventing suicidality in subjects have been discovered. In one aspect, the present disclosure is directed to a method for predicting suicidality in a subject. The method includes obtaining a reference expression level of a blood biomarker; and determining an expression level of the blood biomarker in a sample obtained from the subject. A change in the expression level of the blood biomarker in the sample obtained from the subject as compared to the reference expression level indicates suicidality. In some embodiments, the methods further include obtaining clinical risk factor information and clinical scale data such as for anxiety, mood and/or psychosis from the subject in addition to obtaining blood biomarker expression level in a sample obtained from the subject.

[0042] In one embodiment, the expression level of the blood biomarker in the sample obtained from the subject is increased as compared to the reference expression level of the biomarker. It has been found that an increase in the expression level of particular blood biomarkers in the sample obtained from the subject as compared to the reference expression level of the biomarker indicates a risk for suicide. Suitable biomarkers that indicate a risk for suicide when the expression level increases can be, for example, one or more biomarkers as listed in Table 1 and combinations thereof.

Table 1: Top Candidate Biomarker Genes – increase in expression

Gene Name	Gene Symbol
interleukin 6 (interferon, beta 2)	IL6
spermidine/spermine N1-acetyltransferase 1	SAT1
solute carrier family 4 (sodium bicarbonate cotransporter), member 4	SLC4A4
monoamine oxidase B	MAOB
Glutamate Receptor, Ionotropic, Kainate 2	GRIK2
Rho GTPase activating protein 26	ARHGAP26
B-cell CLL/lymphoma 2	BCL2
cadherin 4, type 1, R-cadherin (retinal)	CDH4
chemokine (C-X-C motif) ligand 11	CXCL11
EMI domain containing 1	EMID1
family with sequence similarity 49, member B	FAM49B
GRB2-Associated Binding Protein 1	GAB1
GRINL1A complex locus 1	GCOM1
hippocalcin-like 1	HPCAL1
mitogen-activated protein kinase 9	MAPK9
nuclear paraspeckle assembly transcript 1 (non-protein coding)	NEAT1
protein tyrosine kinase 2	PTK2
RAS-like, family 11, member B	RASL11B

small nucleolar RNA, H/ACA box 68	SNORA68
superoxide dismutase 2, mitochondrial	SOD2
transcription factor 7-like 2 (T-cell specific, HMG-box)	TCF7L2
v-raf murine sarcoma viral oncogene homolog B	BRAF
chromosome 1 open reading frame 61	C1orf61
Calreticulin	CALR
calcium/calmodulin-dependent protein kinase II beta	CAMK2B
caveolin 1, caveolae protein, 22kDa	CAV1
chromodomain helicase DNA binding protein 2	CHD2
clathrin, light chain A	CLTA
cAMP responsive element modulator	CREM
Cortactin	CTTN
dishevelled associated activator of morphogenesis 2	DAAM2
Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	DAB2
GABA(A) receptor-associated protein like 1	GABARAPL1 GABA(A)
glutamate-ammonia ligase	GLUL
helicase with zinc finger	HELZ
immunoglobulin heavy constant gamma 1 (G1m marker)	IGHG1
interleukin 1, beta	IL1B

jun proto-oncogene	JUN
jun B proto-oncogene	JUNB
lipoma HMGIC fusion partner	LHFP
myristoylated alanine-rich protein kinase C substrate	MARCKS
metallothionein 1E	MT1E
metallothionein 1H	MT1H
metallothionein 2A	MT2A
N-myc downstream regulated 1	NDRG1
nucleobindin 2	NUCB2
PHD finger protein 20-like 1	PHF20L1
phosphatase and tensin homolog	PTEN
reversion-inducing-cysteine-rich protein with kazal motifs	RECK
shisa family member 2	SHISA2
transmembrane 4 L six family member 1	TM4SF1
trophoblast glycoprotein	TPBG
tumor protein D52-like 1	TPD52L1
TSC22 domain family, member 3	TSC22D3
vacuole membrane protein 1	VMP1
ZFP36 ring finger protein	ZFP36
zinc fingers and homeoboxes 2	ZHX2

UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1	B4GALT1
BTB (POZ) domain containing 3	BTBD3
cell adhesion molecule 1	CADM1
chitobiase, di-N-acetyl-	CTBS
DEP domain containing 5	DEPDC5
dystrobrevin, alpha	DTNA
egf-like module containing, mucin-like, hormone receptor-like 2	EMR2
endogenous retrovirus group 3, member 2	ERV3-2
family with sequence similarity 183, member C, pseudogene	FAM183CP
histone cluster 1, H2bo	HIST1H2BO
potassium channel tetramerization domain containing 21	KCTD21
Keratocan	KERA
laminin, beta 1	LAMB1
uncharacterized LOC100289061	LOC100129917
uncharacterized LOC285500	LOC285500
RAB36, member RAS oncogene family	RAB36
uncharacterized LOC283352	RP11-66N7.2
transcription factor Dp-1	TFDP1
TMLHE antisense RNA 1	TMLHE-AS1

superoxide dismutase 2, mitochondrial	SOD2
period circadian clock 1	PER1
Ras association (RalGDS)	RAPH1
spondin 1, extracellular matrix protein	SPON1
forkhead box P1	FOXP1
hepatitis A virus cellular receptor 2	HAVCR2
Rho GTPase activating protein 15	ARHGAP15
gap junction protein, alpha 1, 43kDa	GJA1
hes family bHLH transcription factor 1	HES1
HtrA serine peptidase 1	HTRA1
TIMP metallopeptidase inhibitor 1	TIMP1
erythrocyte membrane protein band 4.1 like 5	EPB41IL5
interleukin 1 receptor, type I	IL1R1
intelectin 1 (galactofuranose binding)	ITLN1
killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4	KIR2DL4
nudix (nucleoside diphosphate linked moiety X)-type motif 10	NUDT10
pyridoxal-dependent decarboxylase domain containing 1	PDXDC1
family with sequence similarity 214, member A	FAM214A
heat shock 60kDa protein 1 (chaperonin)	HSPD1
zinc finger, MYND-type containing 8	ZMYND8
adenylate kinase 2	AK2
AF4/FMR2 family, member 3	AFF3
mitochondrial ribosomal protein S5	MRPS5
v-akt murine thymoma viral oncogene homolog 3	AKT3
aspartate beta-hydroxylase	ASPH
ataxin 1	ATXN1
Brain and reproductive organ-expressed (TNFRSF1A modulator)	BRE
ClpB caseinolytic peptidase B homolog (E. coli)	CLPB
deleted in primary ciliary dyskinesia homolog (mouse)	DPCD
ECSIT signalling integrator	ECSIT

ectonucleoside triphosphate diphosphohydrolase 1	ENTPD1
EPH receptor B4	EPHB4
Fanconi anemia, complementation group I	DANCI
general transcription factor IIIC, polypeptide 3, 102kDa	GTF3C3
inter-alpha-trypsin inhibitor heavy chain family, member 5	ITIH5
kelch-like family member 28	KLHL28
major histocompatibility complex, class I-related	MR1
protein inhibitor of activated STAT, 1	PIAS1
periphilin 1	PPHLN1
retinol dehydrogenase 13 (all-trans/9-cis)	RDH13
strawberry notch homolog 1 (Drosophila)	SBN01
sorting nexin family member 27	SNX27
single-stranded DNA binding protein 2	SSBP2
striatin, calmodulin binding protein	STRN
tetratricopeptide repeat domain 7A	TTC7A
ubiquitin interaction motif containing 1	UIMC1
Z-DNA binding protein 1	ZBP1
zinc finger protein 596	ZNF596
adaptor-related protein complex 3, sigma 2 subunit	AP3S2

In one particularly suitable embodiment, the subject is a male and the blood biomarker that increases in expression level as compared to the reference expression level is selected from solute carrier family 4 (sodium bicarbonate cotransporter), member 4 (SLC4A4), cell adhesion molecule 1 CADM1, dystrobrevin, alpha (DTNA), spermidine/spermine N1-acetyltransferase 1 (SAT1), interleukin 6 (interferon, beta 2) (IL6) and combinations thereof. In another embodiment, the subject is a female and the blood biomarker that increases in expression level as compared to the reference expression level is selected from erythrocyte membrane protein band 4.1 like 5 (EPB41L5), HtrA serine peptidase 1 (HTRA1), deleted in primary ciliary dyskinesia homolog (DPCD), general transcription factor IIIC, polypeptide 3, 102kDa (GTF3C3), period circadian clock 1 (PER1), pyridoxal-dependent decarboxylase domain containing 1 (PDXDC1), kelch-like family member 28 (KLHL28), ubiquitin interaction motif containing 1 (UIMC1), sorting nexin family member 27 (SNX27) and combinations thereof.

[0043] In another embodiment, the expression level of the blood biomarker in the sample obtained from the subject is decreased as compared to the reference expression level of the biomarker. Suitable biomarkers that indicate a risk for suicide when the expression level decreases as compared to the reference expression level have been found to include, for example, one or more biomarkers as listed in Table 2 and combinations thereof.

Table 2: Top Candidate Biomarker Genes – decrease in expression

Gene Name	Gene Symbol
spindle and kinetochore associated complex subunit 2	SKA2
coiled-coil domain containing 136	CCDC136
CD44 molecule (Indian blood group)	CD44
fatty acid desaturase 1	FADS1
FK506 binding protein 5	FKBP5
forkhead box N3	FOXN3
hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	HADHA
adenosylhomocysteinase-like 1	AHCYL1
AKT1 substrate 1 (proline-rich)	AKT1S1
aldehyde dehydrogenase 3 family, member A2	ALDH3A2
B-cell CLL/lymphoma 2	BCL2
	C20orf27
calpain, small subunit 1	CAPNS1
CDC42 effector protein (Rho GTPase binding) 4	CDC42EP4

EH domain binding protein 1	EHBP1
eukaryotic translation initiation factor 5A	EIF5A
fumarate hydratase	FH
glycoprotein M6B	GPM6B
homeobox and leucine zipper encoding	HOMEZ
inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	IKBKB
integrin, beta 4	ITGB4
low density lipoprotein receptor adaptor protein 1	LDLRAP1
uncharacterized LOC728543	LOC728543
mitogen-activated protein kinase kinase 5	MAP2K5
neuromedin B	NMB
platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 (30kDa)	PAFAH1B2
pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1 alpha (TCF1) 2	PCBD2
phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	PIK3C2A
plakophilin 4	PKP4
solute carrier family 5 (sodium/myo-inositol cotransporter), member 3	SLC5A3
spectrin repeat containing, nuclear envelope 2	SYNE2
trans-golgi network protein 2	TGOLN2
trafficking protein, kinesin binding 2	TRAK2
adrenergic, beta, receptor kinase 1	ADRBK1

adenosylhomocysteinase-like 2	AHCYL2
aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	AIMP1
ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e1	ATP6V0E1
BRCA1/BRCA2-containing complex, subunit 3	BRCC3
2',3'-cyclic nucleotide 3' phosphodiesterase	CNP
collagen, type IX, alpha 2	COL9A2
cleavage and polyadenylation specific factor 2, 100kDa	CPSF2
cullin 4B	CUL4B
delta-like 1 (Drosophila)	DLL1
dynein, axonemal, heavy chain 2	DNAH2
dipeptidyl-peptidase 4	DPP4
G2/M-phase specific E3 ubiquitin protein ligase	G2E3
guanylate kinase 1	GUK1
Janus kinase 3	JAK3
lysosomal protein transmembrane 4 beta	LAPTM4B
lysophosphatidic acid receptor 1	LPAR1
membrane associated guanylate kinase, WW and PDZ domain containing 3	MAGI3
myelin basic protein	MBP
microspherule protein 1	MCRS1
myocyte enhancer factor 2C	MEF2C

opioid growth factor receptor	OGFR
protocadherin 9	PCDH9
pleckstrin homology domain containing, family B (evectins) member 1	PLEKHB1
polymerase (RNA) II (DNA directed) polypeptide D	POLR2D
protein kinase, cAMP-dependent, catalytic, alpha	PRKACA
protein kinase C, beta	PRKCB
proteasome (prosome, macropain) subunit, beta type, 4	PSMB4
RAB35, member RAS oncogene family	RAB35
RNA binding motif protein, X-linked	RBMX
ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent)	RNASEL
selenium binding protein 1	SELENBP1
solute carrier family 35, member E1	SLC35E1
synaptosomal-associated protein, 23kDa	SNAP23
transmembrane protein 254	TMEM254
transmembrane protein 259	TMEM259
tensin 1	TNS1
tripartite motif containing 23	TRIM23
tetraspanin 33	TSPAN33
pre-B lymphocyte 3	VPREB3
zinc finger, FYVE domain containing 21	ZFYVE21

zinc finger protein 519	ZNF519
cation channel, sperm associated 3	CATSPER3
chemokine (C-C motif) ligand 28	CCL28
CAP-GLY domain containing linker protein family, member 4	CLIP4
chromosome Y open reading frame 17	CYorf17
DDB1 and CUL4 associated factor 15	DCAF15
EPH receptor A10	EPHA10
v-ets avian erythroblastosis virus E26 oncogene homolog	ERG
heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1	HS3ST3B1
IQ motif containing H	IQCH
kinesin family member 2C	KIF2C
kelch domain containing 3	KLHDC3
uncharacterized LOC100129917	LOC100129917
uncharacterized LOC100996345	LOC100996345
mediator complex subunit 21	MED21
PDX1 C-terminal inhibiting factor 1	PCIF1
plectin	PLEC
RAD23 homolog A (S. cerevisiae)	RAD23A
Rh-associated glycoprotein	RHAG
roundabout, axon guidance receptor, homolog 4 (Drosophila)	ROBO4

ribosomal protein L6 pseudogene 17	RPL6P17
SET domain containing (lysine methyltransferase) 8	SETD8
SH3-domain GRB2-like endophilin B2	SH3GLB2
ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	ST6GALNAC4
testis expressed 10	TEX10
testis expressed 261	TEX261
thymosin beta 15B	TMSB15B
tubulin, gamma complex associated protein 3	TUBGCP3
thioredoxin reductase 2	TXNRD2
ubiquitin specific peptidase 12	USP12
vascular endothelial growth factor B	VEGFB
zinc finger and BTB domain containing 7A	ZBTB7A
glycogen synthase kinase 3 beta	GSK3B
adaptor-related protein complex 1, sigma 2 subunit	AP1S2
catalase	CAT
chromosome 18 open reading frame 54	C19orf54
long intergenic non-protein coding RNA 342	LINC00342
MOB kinase activator 3B	MOB3B
phosphatidylinositol-4-phosphate 5-kinase, type I, beta	PIP5K1B
prolylcarboxypeptidase (angiotensinase C)	PRCP

CD200 receptor 1	CD200R1
CD84 molecule	CD84
centrosomal protein 44kDa	CEP44
carnitine O-octanoyltransferase	CROT
DDB1 and CUL4 associated factor 5	DCAF5
DTW domain containing 2	DTWD2
endoplasmic reticulum protein 27	ERP27
family with sequence similarity 173, member B	FAM173B
glucosidase, alpha; neutral C	GANC
general transcription factor IIIC, polypeptide 2, beta 110kDa	GTF3C2
INO80 complex subunit D	INO80D
inositol polyphosphate-4-phosphatase, type I, 107kDa	INPP4A
Jrk homolog (mouse)	JRK
potassium channel tetramerization domain containing 5	KCTD5
methyltransferase like 15	METTL15
phosphatidylinositol 3-kinase, catalytic subunit type 3	PIK3C3
RNA binding motif protein 48	RBM48
SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 2	SMARCA2
ubiquitin carboxyl-terminal hydrolase L5	UCHL5
vacuolar protein sorting 53 homolog (S. cerevisiae)	VPS53

zinc finger protein 302	ZNF302
capping protein (actin filament) muscle Z-line, alpha 2	CAPZA2
leucine rich repeat containing 8 family, member B	LRRC8B
protein phosphatase, Mg2+	PPM1B
ARP3 actin-related protein 3 homolog (yeast)	ACTR3
SH2 domain containing 1A	SH2D1A
ALG13, UDP-N-acetylglucosaminyltransferase subunit	ALG13
Rho GTPase activating protein 35	ARHGAP35
AT rich interactive domain 4B (RBP1-like)	ARID4B
charged multivesicular body protein 2B	CHMP2B
casein kinase 1, alpha 1	CSNK1A1
ethanolamine kinase 1	ETNK1
F-box and leucine-rich repeat protein 3	FBXL3
HECT and RLD domain containing E3 ubiquitin protein ligase 4	HERC4
jumonji domain containing 1C	JMJD1C
La ribonucleoprotein domain family, member 4	LARP4
muscleblind-like splicing regulator 1	MBNL1
mex-3 RNA binding family member C	MEX3C
nudix (nucleoside diphosphate linked moiety X)-type motif 6	NUDT6
polyhomeotic homolog 3 (Drosophila)	PHC3

peroxiredoxin 3	PRDX3
Pvt1 oncogene (non-protein coding)	PVT1
RAB22A, member RAS oncogene family	RAB22A
solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B3	SLC35B3
small nuclear ribonucleoprotein 27kDa (U4	SNRNP27
USP6 N-terminal like	USP6NL
WW domain containing adaptor with coiled-coil	WAC
wings apart-like homolog (Drosophila)	WAPAL
zinc finger, AN1-type domain 5	ZFAND5
zinc finger protein 117	ZNF117
zinc finger protein 141	ZNF141
zinc finger protein 548	ZNF548
signal sequence receptor, alpha	SSR1

In one particularly suitable embodiment, the subject is a male and the blood biomarker that decreases in expression level as compared to the reference expression level is spindle and kinetochore associated complex subunit 2 (SKA2), CAP-GLY domain containing linker protein family, member 4 (CLIP4), kinesin family member 2C (KIF2C), kelch domain containing 3 (KLHDC3) and combinations thereof. In another embodiment, the subject is a female and the blood biomarker that decreases in expression level as compared to the reference expression level is selected from phosphatidylinositol 3-kinase, catalytic subunit type 3 (PIK3C3), aldehyde dehydrogenase 3 family, member A2 (ALDH3A2), ARP3 actin-related protein 3 homolog (yeast) (ACTR3), B-cell CLL (BCL2), MOB kinase activator 3B (MOB3B), casein kinase 1,

alpha 1 (CSNK1A1), La ribonucleoprotein domain family, member 4 (LARP4), zinc finger protein 548 (ZNF548) and combinations thereof.

[0044] Table 3 further discloses the top biomarkers across gender having expression levels that increase or decrease (as indicated) as compared to the reference expression levels to predict suicidality.

Table 3: Top Universal Biomarkers for Suicide Across Genders

Gene Symbol Gene Name	**Affymetrix Probesets**	**Discovery in Blood (Direction of Change) /Score**	**Validation in Blood ANOVA p-value/Score**	**Significant Prediction of Suicidal Ideation Across All and Best In a Diagnostic Group ROC AUC/ p-value**	**Significant Prediction of Future Hospitalizations for Suicidality Across All and Best in a Diagnostic Group ROC AUC/ p-value**	**Convergent Genetic and Brain Evidence For Involvement in Suicide**	**Other Psychiatric and Related Disorders Evidence**	**Drugs that Modulate the Biomarker in Opposite Direction to Suicide**
BCL2 B-cell CLL/lymphoma 2	203685_at	(D)/1	5.98E-11/4	All 0.609/0.005 Male SZ/SZA 0.68/0.011	Male PTSD 0.83/0.013	5	Aging Alcoholism Anxiety BP Mood Disorders PTSD SZ	Omega-3 Lithium
CD164 CD164 molecule, sialomucin	208654_s_at	(D)/2	3.01E-08/4	All 0.589/0.017 Male BP 0.68/0.020	Male PTSD 0.96/0.0004	4	BP Cocaine Dependence Stress	Clozapine
CD47 CD47 molecule	211075_s_at	(D)/2	1.62E-17/4	All 0.598/0.010 Male SZ/SZA 0.67/0.016	Male PTSD 0.87/0.0048	4	MDD Stress SZ	Clozapine Omega-3
DLG1 discs, large homolog 1 (Drosophila)	202514_at	(D)/1	0.0000844	All 0.58/0.036 Male SZ/SZA 0.65/0.030	Male PTSD 0.9/0.0023	4	Alcoholism BP MDD SZ	Omega-3
DLG1 discs, large	202516_s_at	(D)/1	0.0000000000016/4	All 0.58/0.029	Male PTSD 0.79/	4	Alcoholism BP	Omega-3

homolog 1 (Drosophila)					0.028		MDD SZ	
DYRK2 dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2	202969_at	(D)/1	0.00000000000017/4	All 0.58/0.034 Male SZ/SZA 0.68/0.010	Male PTSD 0.93/0.001	4	Aging BP MDD Sleep Disorders	Clozapine
ITGB1BP1 integrin beta 1 binding protein 1	203336_s_at	(D)/1	0.000000025/4	All 0.57/0.042	Male PTSD 0.83/0.013	4	Alzheimer's Disease BP Mood Disorders SZ	Lithium
APOE apolipoprotein E	203382_s_at	(I)/1	3.44E-09/4	All 0.59/0.021 Male BP 0.71/0.0091		6	Aggression Aging Alcoholism Alzheimer's Disease Autism Dementia Depression-related Longevity MDD Psychosis PTSD SZ	Omega-3
MRPS14 mitochondrial ribosomal protein S14	203800_s_at	(D)/1	0.00000000039/4	Male SZ/SZA 0.69/0.0080	Male PTSD 0.84/0.0093	4	SZ	Omega-3
MRPS14 mitochondrial ribosomal protein S14	203801_at	(D)/1	2.45E-17/4	All 0.60/0.0069 Male SZ/SZA 0.68/0.011	Male PTSD 0.77/0.035	4	SZ	Omega-3
IL6 interleukin 6	205207_at	(I)/1	1.82E-15/4	All 0.58/0.038	Female PTSD 1/0.028	6	Aggression Anxiety BP Cognition Dementia	

							Depression Longevity MDD Mood Disorders Panic Psychosis PTSD Sleep Disorders Stress SZ	
AKAP13 A kinase (PRKA) anchor protein 13	209534_x_at	(I)/1	0.000021/4	Male PTSD 0.78/0.0083	All 0.57/0.047 Male PTSD 0.80/0.022	4	Cocaine Dependence Panic Stress	Clozapine
SECISBP2L SECIS binding protein 2-like	212450_at	(D)/1	0.000063/4	All 0.59/0.021 Male BP 0.71/0.0076	Male PTSD 0.89/0.0034	4	Cocaine Dependence MDD SZ	Clozapine
SOD2 superoxide dismutase 2, mitochondrial	215078_at	(I)/2	2.27E-34/4		Male PTSD 0.85/0.010	5	Longevity MDD Methamphetamine Abuse Mood Disorders SZ	Clozapine
LHFP lipoma HMGIC fusion partner	218656_s_at	(I)/1	0.000000000 40/4	All 0.57/0.05 Male MDD 0.69/0.034	Male MDD 0.79/0.004	4	SZ	Omega-3
SKA2 spindle and kinetochore associated complex subunit 2	225686_at	(D)/1	4.55E-03/2	All 0.62/0.003 Male SZ/SZA 0.75/0.00063	Male PTSD 0.84/0.0093	8	PTSD Stress	
GSK3B	226183_at	(D)/1	2.19E-36/4		Male PTSD	6	Aging	Lithium

glycogen synthase kinase 3 beta					0.84/0.0093		Alcoholism BP Dementia Depression Mood Stabilizers response Lithium response MDD SZ	
ITPKB inositol-trisphosphate 3-kinase B	232526_at	AP (I)/1	0.0000000045/4	All 0.62/0.0019 Male BP 0.76/0.0013	Male PTSD 0.87/0.0048	4	Aging Alcoholism Alzheimer's Disease Autism BP MDD Multiple Sclerosis Stress SZ SZA	Omega-3
MTERF4 mitochondrial transcription termination factor 4	1557966_x_at	(D)/2	6.72E-06/4	All 0.61/0.005 Male SZ/SZA 0.72/0.0019	Male PTSD 0.94/0.0006	4	Stress	
GDI2 GDP dissociation inhibitor 2	200008_s_at	(D)/2	1.52E-11/4	All 0.59/0.013 Male BP 0.67/0.024		4	BP MDD Mood Disorders SZ	Clozapine
PRKAR1A protein kinase, cAMP-dependent, regulatory, type I, alpha	200605_s_at	(D)/2	2.47E-06/4	Male BP 0.72/0.0059	Male PTSD 0.90/0.0023	4	Alcoholism BP Epilepsy Mood Disorders Stress SZ	
NR3C1 nuclear receptor subfamily 3,	201866_s_at	(D)/1	1.64E-03/2	Male BP 0.67/0.029	Male PTSD 0.91/0.0015	5	Alcoholism Anxiety BP	Clozapine

group C, member 1 (glucocorticoid receptor)							Depression Longevity MDD PTSD Response to escitalopram (SSRI) Response to Nortriptyline (TCA) Stress SZ	
ADK adenosine kinase	204119_s_at	DE (D)/4	0.000000020/4	All 0.62/0.0026 Male SZ/SZA 0.66/0.019	Male PTSD 0.84/0.0093	0	Depression	Omega-3
PGK1 phosphoglycerate kinase 1	217383_at	(D)/2	4.07E-07/4	Male SZ/SZA 0.63/0.046		4	Alcoholism BP MDD SZ SZA	Clozapine
ZFYVE21 zinc finger, FYVE domain containing 21	219929_s_at	(D)/2	5.96E-06/4	All 0.58/0.026	All 0.58/0.030 Male MDD 0.78/0.0044	4	SZ	
RBM3 RNA binding motif (RNP1, RRM) protein 3	222026_at	(D)/2	1.73E-05/4		Female PTSD 1/0.028	4	Epilepsy Response to Lithium SZ	Omega-3 Lithium
FAM107B family with sequence similarity 107, member B	223058_at	(D)/2	2.36E-02/2	All 0.58/0.024 Male BP 0.71/0.0079	Male PTSD 0.93/0.001	4	BP MDD Psychosis Response to Lithium Sleep Disorder SZ	Lithium
ECHDC1 enoyl CoA	223087_at	(D)/2	3.35E-09/4	All 0.60/0.009	Male PTSD 0.94/0.0006	4	Addictions BP	

hydratase domain containing 1				Male SZ/SZA 0.66/0.019			PTSD	
TBL1XR1 transducin (beta)-like 1 X-linked receptor 1	235890_at	AP (D)/2	0.000000023/4	Male BP 0.66/0.034	Female PTSD 1/0.028	2	Alcoholism BP Longevity	Clozapine
LONRF2 LON peptidase N-terminal domain and ring finger 2	235977_at	(I)/1	1.48E-03/2	Male BP 0.73/0.0040	Male PTSD 0.77/0.039	5	Stress BP	Omega-3
QKI QKI, KH domain containing, RNA binding	241938_at	(I)/2	1.88E-03/2	Male PTSD 0.77/0.011	All 0.58/0.031	4	BP Longevity MDD PTSD Stress SZ	Omega-3
YWHAH tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta	242325_at	(I)/2	6.65E-11/4	All 0.571/0.047 Male BP 0.66/0.033		4	Alcoholism BP Longevity MDD SZ	Omega-3
SLC4A4 solute carrier family 4 (sodium bicarbonate cotransporter), member 4	210739_x_at	(I)/1	7.74E-05/4	All 0.64/0.00038 Male BP 0.77/0.00094		6	Circadian abnormalities Longevity MDD SZ	
GDI2 GDP dissociation inhibitor 2	200009_at	(D)/1	0.000015/4	All 0.64/0.0006 Male		4	BP MDD Mood Disorders SZ	Clozapine

				SZ/SZA 0.72/0.0028				
UQCRC2 ubiquinol-cytochrome c reductase core protein II	200883_at	(D)/1	0.012/2	All 0.61/0.0035 Male SZ/SZA 0.67/0.013	Male PTSD 0.81/0.017	4	ADHD Alcohol BP MDD Multiple Sclerosis SZ	Omega-3
CTNNB1 catenin (cadherin-associated protein), beta 1, 88kDa	201533_at	(D)/1	0.0023/2	All 0.59/0.018 Male BP 0.74/0.0037	Male PTSD 0.80/0.022	4	MDD PTSD Stress SZ	Clozapine
PSMB4 proteasome (prosome, macropain) subunit, beta type, 4	202243_s_at	(D)/1	6.55E-14/4	All 0.6/0.011 Male SZ/SZA 0.68/0.010	Male PTSD 0.80/0.022	4	BP MDD SZ SZA	
PRKACB protein kinase, cAMP-dependent, catalytic, beta	202742_s_at	(D)/1	0.00042/2	All 0.58/0.028	Male PTSD 0.96/0.0004	4	Alcohol Alzheimer's Disease BP Chronic Fatigue Syndrome	Clozapine
LPAR1 lysophosphatidic acid receptor 1	204036_at	(D)/1	1.35003E-23 4	Male BP 0.68/0.022		4	Aging BP Longevity MDD Mood PTSD SZ	Clozapine Omega-3
HTR2C 5-hydroxytryptamine (serotonin)	207307_at	(I)/1	4.30E-02/2	All 0.583/0.025 Male MDD		6	Affective Disorder Alcohol Antipsychotics BP	Clozapine

receptor 2C, G protein-coupled				0.69/0.035			MDD Mood Disorders Panic Disorder SZ	
CTTN cortactin	214782_at	DE (I)/1	1.042E-19/4	Male BP 0.76/0.0016		4	BP Effect of valproate MDD Stress	Clozapine Omega-3
PDCL3 phosducin-like 3	219043_s_at	(D)/2	1.37E-02/2	All 0.6/0.009 Male SZ/SZA 0.65/0.030	Male PTSD 0.80/ 0.022	5	Sleep Disorders	
SNX6 sorting nexin 6	222410_s_at	DE (D)/1	0.0000068/4	All 0.62/0.0025 Male SZ/SZA 0.65/0.024	Male PTSD 0.86/ 0.0068	4	Panic	0
PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	231854_at	DE (D)/1	2.41E-37/4	All 0.57/0.042 Male BP 0.65/0.047		4	Longevity MDD Stress SZ	Lithium
MBP myelin basic protein	225408_at	(D)/2	8.34E-07/4			4	Alcohol Alzheimer's Disease BP MDD Mood Disorders SZ	Clozapine Omega-3 Lithium
CCDC136 coiled-coil domain containing 136	226972_s_at	(D)/4	3.13E-03/2			4	Psychosis	Clozapine
AIMP1 aminoacyl tRNA	227605_at	(D)/2	1.02E-05/4	All 0.60/0.007	Male PTSD	4		

synthetase complex-interacting multifunctional protein 1				Male SZ/SZA 0.66/0.018	0.93/ 0.001			
PITHD1 PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1	229856_s_at	(D)/4	0.000000067/4	Female BP 0.83/0.031	Male PTSD 0.87/ 0.0048		BP Psychosis SZ	
PCDH9 protocadherin 9	238919_at	(D)/2	6.61E-05/4			4	Aging MDD Psychosis SZ	Clozapine Omega-3
CAPZA2 capping protein (actin filament) muscle Z-line, alpha 2	201238_s_at	(D)/1	0.00029/2	All 0.6/0.0086 Male BP 0.65/0.047	Male PTSD 0.93/ 0.001	4	BP MDD PTSD SZ	
PSME4 Proteasome Activator Subunit 4	237180_at	(I)/1	2.64E-36/4	All 0.6/0.011 Male PTSD 0.79/0.0062		4	Autism	
GABRB1 gamma-aminobutyric acid (GABA) A receptor, beta 1	1557256_a_at	(I)/1	0.012/2	Male BP 0.74/0.0034		4	Alcohol Autism Mood Stabilizers BP MDD SZ SZA	
CNP	1557943_at		0.019/2		Female	4	Alcohol	Clozapine

2',3'-cyclic nucleotide 3' phosphodiesterase		(D)/1			SZ/SZA 1/ 0.029		Epilepsy MDD Multiple Sclerosis Sleep Disorders SZ	Omega-3
RAP1A RAP1A, member of RAS oncogene family	202362_at	(D)/1	0.035/2	All 0.6/0.011 Male BP 0.71/0.0082	Male PTSD 0.83/ 0.013	4	Longevity SZ SZA	
NGFR nerve growth factor receptor	205858_at	(I)/1	2.24E-15/4	All 0.59/0.018 Male SZ/SZA 0.72/0.0020		4	MDD OCD Panic Disorder SZ	
CAMK2B calcium/calmodulin-dependent protein kinase II beta	209956_s_at	DE (I)/1	0.00078/2	All 0.62/0.0017 Male BP 0.74/0.0029		4	Addictions BP SZ	Clozapine
CLN5 ceroid-lipofuscinosis, neuronal 5	214252_s_at	DE (D)/1	1.79E-15/4	All 0.65/0.0002 Male SZ/SZA 0.68/0.010	Male PTSD 0.84/ 0.0093	4		
CLTA clathrin, light chain A	216295_s_at	DE (D)/1	1.74E-15/4	All 0.64/0.0006 Male BP 0.73/0.0049		4	Alzheimer's Disease BP MDD	
DOCK8	232843_s_a	DE	0.0022/2	All	Male PTSD	4	ADHD	

dedicator of cytokinesis 8	t	(D)/1		0.6/0.0079 Male BP 0.78/0.00078	0.76/ 0.044		Longevity	
RARS2 arginyl-tRNA synthetase 2, mitochondrial	232902_s_at	DE (D)/1	0.022/2	All 0.63/0.0014 Male SZ/SZA 0.70/0.0043	Male PTSD 0.86/ 0.0068	4	PTSD BP	
PTK2 protein tyrosine kinase 2	241453_at	DE (I)/1	2.87E-32/4	All 0.61/0.0045 Male MDD 0.69/0.033		4	Alcohol Autism BP Circadian abnormalities MDD Psychosis Stress SZ	0
PLCL1 phospholipase C-like 1	241859_at	(D)/1	0.040/2	Male PTSD 0.78/0.0083		4	Alcohol Psychosis SZ	Clozapine
LPAR1 lysophosphatidic acid receptor 1	204038_s_at	(D)/2	1.66E-04/2			4	Aging BP Longevity MDD Mood Disorders PTSD SZ	Clozapine Omega-3
AK2 adenylate kinase 2	205996_s_at	(D)/2	0.00000011/ 4	All 0.64/0.0005 Male SZ/SZA 0.74/0.0012		2	BP SZ	

APLP2 amyloid beta (A4) precursor-like protein 2	208703_s_at	(D)/2	3.65E-02/2		4	BP Depression Effect of valproate Chronic Fatigue Syndrome	Lithium Omega-3
BACE1 beta-site APP-cleaving enzyme 1	224335_s_at	(I)/1	0.00037/2	All 0.58/0.032 Male BP 0.67/0.024	4	Alzheimer's Disease Cocaine Dependence MDD Psychosis	
ELOVL5 ELOVL fatty acid elongase 5	214153_at	(I)/1	0.0028/2	Male PTSD 0.76/0.012	3	Alcohol Autism BP Circadian abnormalities Cocaine Dependence MDD Mood Disorders	
KIF2C kinesin family member 2C	211519_s_at	(D)/4	0.014/2				

[0045] Particularly suitable subjects are humans. Suitable subjects can also be experimental animals such as, for example, monkeys and rodents, that display a behavioral phenotype associated with suicide, for example, a mood disorder or psychosis. In one particular aspect, the subject is a female human. In another particular aspect, the subject is a male human.

[0046] In another aspect, the subject can further be diagnosed with a psychiatric disorder as known in the art. In particular aspects, the psychiatric disorder can be bipolar disorder, major depressive disorder, schizophrenia, and schizoaffective disorder, post-traumatic stress disorder, and combinations thereof.

[0047] In one embodiment, the subject can be diagnosed as having or as suspected of having bipolar disorder (BP) and the biomarker can be selected from DTNA; HS3ST3B1; CADM1; Unknown gene; KSR1; CD44; DAPP1; OPRM1; SPTBN1; AKT1S1; SAT1; C20orf27; and combinations thereof. As summarized in FIG. 17, the biomarker expression level can increase above a reference expression level of the biomarker or decrease below a reference expression level of the biomarker.

[0048] In another embodiment, the subject can be diagnosed as having or as suspected of having depression (MDD) and the biomarker can be selected from PHF20; EIF1B-AS1; TLN1; NUCKS1; DLK1; BBIP1; BDNF; SKA2; IL10; GATM; PRPF40A; and combinations thereof. As summarized in FIG. 17, the biomarker expression level can increase above a reference expression level of the biomarker or decrease below a reference expression level of the biomarker.

[0049] In another embodiment, the subject can be diagnosed as having or as suspected of having schizoaffective disorder (SZA) and the biomarker can be selected from USP48; NPRL3; TSPYL1; TMSB15B; IL6; TNS1; TNF; S100B; JUN; BATF2; ANXA11; and combinations thereof. As summarized in FIG. 17, the biomarker expression level can increase above a reference expression level of the biomarker or decrease below a reference expression level of the biomarker.

[0050] In another embodiment, the subject can be diagnosed as having or as suspected of having schizophrenia (SZ) and the biomarker can be selected from RP11-389C8.2; CYB561; LOC100128288; CDDC163P; C1orf61; SKA2; BDNF; HTR2A; SLC5A3; ATP6V0E1; JUN; LOC100131662; and combinations thereof. As summarized in FIG. 17, the biomarker expression

level can increase above a reference expression level of the biomarker or decrease below a reference expression level of the biomarker.

[0051] A particularly suitable sample for which the expression level of a biomarker is determined can be, for example, blood, including whole blood, serum, plasma, leukocytes, and megakaryocytes.

[0052] The method can further include assessing mood, anxiety, and other like psychiatric symptoms, and combinations thereof in the subject using questionnaires and/or a computer-implemented method for assessing mood, anxiety, other like psychiatric symptoms, and combinations thereof. In one aspect, the method is implemented using a first computer device coupled to a memory device, the method comprising: receiving mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; computing, by the first computer device, of the mood information, anxiety information, and combinations thereof, a score that can be used to predict suicidality; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject. Suitable mood and anxiety information is described herein in more detail below.

[0053] The method can further include assessing socio-demographic/psychological suicidal risk factors in the subject using a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject, the method implemented using a first computer device coupled to a memory device, the method comprising: receiving socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to a second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the

second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject. Suitable socio-demographic/psychological suicidal risk factors are described herein in more detail below.

[0054] In accordance with the present disclosure, biomarkers useful for objectively predicting future hospitalization due to suicidality in subjects have been discovered. In one aspect, the present disclosure is directed to a method for future hospitalization due to suicidality in a subject. The method includes obtaining a first expression level of a blood biomarker in an initial sample obtained from the subject; and determining a second expression level of the blood biomarker in a subsequent sample obtained from the subject, wherein an increase in the expression level of the blood biomarker in the subsequent sample obtained from the subject as compared to the expression level of the initial sample indicates a higher risk of future hospitalizations due to suicidality. In some embodiments, the methods further include obtaining clinical risk factor information and clinical scale data such as for anxiety, mood and/or psychosis from the subject in addition to obtaining blood biomarker expression level in a sample obtained from the subject.

[0055] Suitable biomarkers for predicting future hospitalization due to suicidality in a subject wherein an increase in the expression level of the blood biomarker occurs can be, for example, the blood biomarker(s) set forth in Table 1.

[0056] In another embodiment, the expression level of the blood biomarker in the sample obtained from the subject is increased as compared to the reference expression level of the biomarker. Suitable biomarkers that indicate a risk for future hospitalization due to suicidality when the expression level increases in males as compared to the reference expression level have been found to include, for example, solute carrier family 4 (sodium bicarbonate cotransporter), member 4 (SLC4A4), cell adhesion molecule 1 CADM1, dystrobrevin, alpha (DTNA), spermidine/spermine N1-acetyltransferase 1 (SAT1), interleukin 6 (interferon, beta 2) (IL6) and combinations thereof. Suitable biomarkers that indicate a risk for future hospitalization due to suicidality when the expression level increases in females as compared to the reference expression level have been found to include, for example, erythrocyte membrane protein band 4.1 like 5 (EPB41L5), HtrA serine peptidase 1 (HTRA1), deleted in primary ciliary dyskinesia homolog (DPCD), general transcription factor IIIC, polypeptide 3, 102kDa (GTF3C3), period circadian clock 1 (PER1), pyridoxal-dependent decarboxylase domain containing 1 (PDXDC1),

kelch-like family member 28 (KLHL28), ubiquitin interaction motif containing 1 (UIMC1), sorting nexin family member 27 (SNX27) and combinations thereof.

[0057] In another embodiment, the expression level of the blood biomarker in the sample obtained from the subject is decreased as compared to the reference expression level of the biomarker. Suitable biomarkers that indicate a risk for future hospitalization due to suicidality when the expression level decreases in males as compared to the reference expression level have been found to include, for example, spindle and kinetochore associated complex subunit 2 (SKA2), CAP-GLY domain containing linker protein family, member 4 (CLIP4), kinesin family member 2C (KIF2C), kelch domain containing 3 (KLHDC3) and combinations thereof. Suitable biomarkers that indicate a risk for future hospitalization due to suicidality when the expression level decreases in females as compared to the reference expression level have been found to include, for example, phosphatidylinositol 3-kinase, catalytic subunit type 3 (PIK3C3), aldehyde dehydrogenase 3 family, member A2 (ALDH3A2), ARP3 actin-related protein 3 homolog (yeast) (ACTR3), B-cell CLL (BCL2), MOB kinase activator 3B (MOB3B), casein kinase 1, alpha 1 (CSNK1A1), La ribonucleoprotein domain family, member 4 (LARP4), zinc finger protein 548 (ZNF548) and combinations thereof.

[0058] Particularly suitable subjects are humans. Suitable subjects can also be experimental animals such as, for example, monkeys and rodents, that display a behavioral phenotype associated with suicide, for example, a mood disorder or psychosis. In one particular embodiment, the subject is a female human. In another particular aspect, the subject is a male human.

[0059] In another aspect, the subject can further be diagnosed with a psychiatric disorder. The psychiatric disorder can be bipolar disorder, major depressive disorder, schizophrenia, and schizoaffective disorder, post-traumatic stress disorder and combinations thereof.

[0060] A particularly suitable sample for which the expression level of a biomarker is determined can be, for example, blood, including whole blood, serum, plasma, leukocytes, and megakaryocytes.

[0061] Suitable biomarkers found to have a difference in expression level include, for example, spermidine/spermine N1-acetyltransferase 1 (SAT1), interleukin 6 (interferon beta 2) (IL6), solute carrier family 4 (sodium bicarbonate cotransporter), member 4 (SLC4A4), spindle

and kinetochore associated complex subunit 2 (SKA2), jun proto-oncogen (JUN), cell adhesion molecule 1 (CADM1), dystrobrevin alpha (DTNA), monoamine oxidase B (MAOB), myristoylated alanine-rich protein kinase C substrate (MARCKS), phosphatase and tensin homolog (PTEN), fatty acid desaturase 1 (FADS1), Rho GTPase activating protein 26 (ARHGAP26), B-cell CLL/lymphoma 2 (BCL2), cadherin 4 type 1 R cadherin (retinal) (CDH4), chemokine (C-X-C motif) ligand 11 (CXCL11), EMI domain containing 1 (EMID1), family with sequence similarity 49 member B (FAM49B), GRINL1A complex locus (GCOM1), hippocalcin-like 1 (HPCAL1), mitogen-activated protein kinase 9 (MAPK9), nuclear paraspeckle assembly transcript 1 (NEAT1), protein tyrosine kinase 2 (PTK2), RAS-like family 11 member B (RASL11B), small nucleolar RNA H/ACA box 68 (SNORA68), superoxide dismutase 2 mitochondrial (SOD2), transcription factor 7-like 2 (T-cell specific HMG-box) (TCF7L2), v-raf murine sarcoma viral oncogene homolog (BRAF), Chromosome 1 Open Reading Frame 61 (C1orf61), calreticulin (CALR), calcium/calmodulin-dependent protein kinase II beta (CAMK2B), caveolin 1 caveolae proein 22kDa (CAV1), chromodomain helicase DNA binding protein 2 (CHD2), cAMP responsive element modulators (CREM), cortactin (CTTN), disheveled associated activator of morphogenesis 2 (DAAM2), Dab mitogen responsive phosphoprotein homolog 2 (DAB2), GABA(A) receptor associated protein like 1 (GABARAPL1), glutamate-ammonia ligase (GLUL), helicase with zinc finger (HELZ), immunoglobulin heavy chain constant gamma 1 (IGHG1), interleukin 1 beta (IL1B), jun B proto-oncogen (JUNB), lipoma HMGIC fusion partner (LHFP), metallothionein 1 E (MT1E), metallothionein 1 H (MT1H), metallothionein 2 (MT2A), N-myc downstream regulated 1 (NDRG1), nucleobindin 2 (NUCB2), PHD finger protein 20-like 1 (PHF20L1), cysteine-rich protein with kazal motifs (RECK), shisa family member 2 (SHISA2), transmembrane 4 L six family member 1 (TM4SF1), trophoblast glycoprotein (TPBG), tumor protein D52-like 1 (TPD52L1), TSC22 domain family member 3 (TSC22D3), vacuole membrane protein 1 (VMP1), ZFP 36 ring finger protein (ZFP36), zink finger FYVE domain containing 21 (ZHX2), histone cluster 1 H2bo (HIST1H2BO), keratocan (KERA), transcription factor Dp-1 (TFDP1), Single-Stranded DNA Binding Protein 2 (SSBP2), Transcription Factor EC (TFEC), Diphosphoinositol Pentakisphosphate Kinase 1 (PPIP5K1), Fibroblast Growth Factor Receptor 1 Oncogene Partner 2 (FGFR1OP2), Zinc Finger MYND-Type Containing 8 (ZMYND8), Interferon Gamma (IFNG), Brain-Derived Neurotrophic Factor (BDNF), cAMP Responsive Element Binding Protein 1 (CREB1), Hes Family BHLH Transcription Factor 1 (HES1), Ankyrin Repeat And MYND Domain Containing 1 (ANKMY1), Aldehyde Dehydrogenase 3 Family Member A2 (ALDH3A2), Heparan Sulfate (Glucosamine) 3-

O-Sulfotransferase 3B1 (HS3ST3B1), Kinase Suppressor Of Ras 1 (KSR1), Dual Adaptor Of Phosphotyrosine And 3-Phosphoinositides (DAPP1), Opioid Receptor Mu 1 (OPRM1), Spectrin Beta Non-Erythrocytic 1 (SPTBN1), PHD Finger Protein 20 (PHF20), EIF1B Antisense RNA 1 (EIF1B-AS1), Talin 1 (TLN1), Nuclear Casein Kinase And Cyclin-Dependent Kinase Substrate 1 (NUCKS1), Delta-Like 1 Homolog (DLK1), BBSome Interacting Protein 1 (BBIP1), Interleukin 10 (IL10), Glycine Amidinotransferase (GATM), PRP40 Pre-MRNA Processing Factor 40 Homolog A (PRPF40A), Ubiquitin Specific Peptidase 48 (USP48), Nitrogen Permease Regulator-Like 3 (NPRL3), Testis-Specific Y-Encoded-Like Protein-Like 1 (TSPYL1), thymosin beta 15B (TMSB15B), Minichromosome Maintenance Complex Component 8 (MCM8), tensin 1 (TNS1), Tumor Necrosis Factor (TNF), S100 Calcium Binding Protein B (S100B), Basic Leucine Zipper Transcription Factor ATF-Like 2 (BATF2), Annexin A11 (ANX11), RP11-389C8.2, Cytochrome B561 (CYB561), LOC100128288 (Uncharacterized LOC100128288), Coiled-Coil Domain Containing 163 Pseudogene (CCDC163P), 5-Hydroxytryptamine (Serotonin) Receptor 2A, G Protein-Coupled (HTR2A), Annexin A11 (ANXA11), Uncharacterized LOC100131662 (LOC100131662), Prolylcarboxypeptidase (Angiotensinase C; PRCP), and combinations thereof. See, FIG. 9 for a list of biomarkers identified as showing a difference in expression level.

[0062] In another aspect, the present disclosure is directed to a method for mitigating suicidality in a subject in need thereof. The method includes: 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 as compared to 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 as compared to the reference expression level of the blood biomarker to mitigate suicidality in the subject. As used herein, "mitigate", "mitigating", and the like refer to making a condition less severe and/or preventing a condition. More particularly, the phrase "mitigate suicidality" refers to reducing suicide ideation in a subject and/or preventing suicide completion.

[0063] Suitable treatments can be a lifestyle modification, administering a therapy, and combinations thereof.

[0064] Suitable therapy can be a nutritional, a drug and psychotherapy.

[0065] Particularly suitable nutritionals can be omega-3 fatty acids, including, by way of example, docosahexaenoic acid (DHA).

[0066] Particularly suitable drugs include, for example, ketamine, lithium, clozapine, selegeline, tocilizumab, siltuximab, enkephalin, methionine, gevokizumab, gallium nitrate, vemurafenib, dabrafenib, oblimersen, rasagiline,(-)-gossypol, navitoclax, gemcitabine/paclitaxel, bortezomib/paclitaxel, ABT-199, paclitaxel/trastuzumab, paclitaxel/pertuzumab/trastuzumab, lapatinib/paclitaxel, doxorubicin/paclitaxel, epirubicin/paclitaxel, paclitaxel/topotecan, paclitaxel, canakinumab, tesevatinib, enzastaurin, fomepizole, miglitol, anakinra, and combinations thereof. Other suitable drugs, as well as biomarkers found to be changed in opposite direction in suicide versus in treatments with omega-3 fatty acids, lithium, clozapine, or antidepressants (MAOIs) as listed in Tables 4 & 5. These biomarkers could potentially be used to stratify patients to different treatment approaches, and monitor their responses.

Table 4: Top candidate biomarker genes - drugs that modulate expression of these markers in the opposite direction in male subjects

Gene symbol/ Gene Name	Discovery (Change) Method/ Score	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Other Drugs
CCDC136 coiled-coil domain containing 136	**(D)** AP4			**(I) Mouse VT** [356]	
CD44 CD44 molecule (Indian blood group)	**(D)** DE2			**(I) Mouse Blood** [356]	
IL6 interleukin 6 (interferon, beta 2)	**(I)** AP2	**(D) Human Blood** [357]			**tocilizumab siltuximab**
SAT1 spermidine/spermine N1-acetyltransferase 1	**(I)** DE2 DE1	**(D) Mouse Blood**[358]			
MAOB monoamine oxidase B	**(I)** DE1				**selegiline**
ARHGAP26 Rho GTPase activating protein 26	**(I)** DE1			**(D) Mouse VT** [356]	
BCL2 B-cell CLL/lymphoma 2	**(D)** DE1		**(I) Human Blood** [153]	**(I) Rat Dentate gyrus Hippocampus** [359]	
EHBP1 EH domain binding protein 1	**(D)** DE 4			**(I) VT** [356]	
FAM49B	**(I)**	**(D)**			

family with sequence similarity 49, member B	AP2	**Mouse Blood**[358]			
HPCAL1 hippocalcin-like 1	**(I)** DE2			**(D) Mouse VT** [356]	
MAPK9 mitogen-activated protein kinase 9	**(I)** DE2			**(D) Mouse VT** [356]	
NEAT1 nuclear paraspeckle assembly transcript 1 (non-protein coding)	**(I)** DE2			**(D) Mouse VT** [356]	
RASL11B RAS-like, family 11, member B	**(I)** AP2			**(D) Mouse Caudate putamen**[356]	
TRAK2 trafficking protein, kinesin binding 2	**(D)** DE2	**(I) Mouse Blood** [358]	**(I) Mouse PFC**[360]		
ADRBK1 adrenergic, beta, receptor kinase 1	**(D)** DE1			**(I) Mouse PFC**[361]	
BRAF v-raf murine sarcoma viral oncogene homolog B	**(I)** DE1				**Vemurafenib Dabrafenib**
CAMK2B calcium/calmodulin-dependent protein kinase II beta	**(I)** DE1			**(D) Mouse striatum** [362]	
CNP 2',3'-cyclic nucleotide 3'	**(D)** AP1	**(I) Mouse**		**(I)**	

phosphodiesterase		**Hippocampus**[358]		**Mouse** AMY [356]	
CTTN cortactin	**(I)** DE1	**(D) Mouse Blood**[358]		**(D) Mouse VT** [356]	
G2E3 G2/M-phase specific E3 ubiquitin protein ligase	**(D)** AP1	**(I) Mouse Hippocampus**[358]			
GABARAPL1 GABA(A) receptor-associated protein like 1	**(I)** DE1	**(D) Mouse Blood**[358]			
HELZ helicase with zinc finger	**(I)** DE1	**(D) Mouse Blood**[358]			
IL1B interleukin 1, beta	**(I)** DE1	**(D) Mouse Blood**[358]			**canakinumab gevokizumab gallium nitrate**
LHFP lipoma HMGIC fusion partner	**(I)** DE1	**(D) Mouse Blood**[358]			
LPAR1 lysophosphatidic acid receptor 1	**(D)** AP1	**(I) Mouse Hippocampus, Blood**[358]		**(I) Mouse** AMY [356]	
MBP myelin basic protein	**(D)** AP1	**(I) Mouse Blood**[358]	**(I) Oligodendrocytes** [363] **Mouse Brain** [360]	**(I) Mouse** AMY **and Blood**[356]	
MEF2C myocyte enhancer factor 2C	**(D)** DE1			**(I) Mouse Hippocampus and VT** [356]	
NDRG1	**(I)**	**(D)**			

N-myc downstream regulated 1	DE1	**Mouse Blood**[358]			
OGFR opioid growth factor receptor	**(D)** DE1				**enkephalin methionine**
PCDH9 protocadherin 9	**(D)** AP1			**(I) Mouse VT** [356]	
PHF20L1 PHD finger protein 20-like 1	**(I)** DE1	**(D) Mouse Blood**[358]		**(D) Mouse Hippocampus** [356]	
PRKCB protein kinase C, beta	**(D)** DE1 AP1		**(I) Mouse PFC**[360] AMY [364]		
RBMX RNA binding motif protein, X-linked	**(D)** DE1	**(I) Mouse** NAC**, Blood**[358]			
RNASEL ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent)	**(D)** AP1	**(I) Mouse Blood**[358]			
SNAP23 synaptosomal-associated protein, 23kDa	**(D)** AP1			**(I) Mouse Blood**[356]	
TM4SF1 transmembrane 4 L six family member 1	**(I)** DE1	**(D) Mouse Blood**[358]			
TSPAN33 tetraspanin 33	**(D)** AP1	**(I) Mouse Blood**[358]		**(I) Mouse VT** [356]	

VMP1 vacuole membrane protein 1	**(I)** DE1	**(D)** **Mouse** **Blood**[358]			
ZFP36 ZFP36 ring finger protein	**(I)** DE1	**(D)** **Mouse** **Blood**[358]	**(D)** **Rat** **Brain** [365]		
BTBD3 BTB (POZ) domain containing 3	**(I)** DE 4	**(D) Mouse** **AMY** [358]			
CADM1 cell adhesion molecule 1	**(I)** DE4			**(D)** **Mouse** **VT** [356]	
CTBS chitobiase, di-N-acetyl-	**(I)** DE 4			**(D) VT** [356]	
LAMB1 laminin, beta 1	**(I)** AP4	**(D) Mouse** **HIP** [358]			
PLEC plectin	**(D)** DE 4			**(I) Mouse VT** [356]	
RAD23A RAD23 homolog A (S. cerevisiae)	**(D)** DE 4	**(I) Mouse** **Blood** [358]			
SETD8 SET domain containing (lysine methyltransferase) 8	**(D)** DE 4	**(I) Mouse Blood** [358]			
TXNRD2 thioredoxin reductase 2	**(D)** AP4			**(I)** **Mouse Blood** [356]	

(I): increase in biomarker expression; (D): decrease in biomarker expression

Table 5: Top candidate biomarker genes - drugs that modulate expression of these markers in the opposite direction in female subjects

Gene Symbol/ Gene Name	Discovery (Change) Method/ Score	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Other Drugs
Out of Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)					
BCL2 B-cell CLL	(D) DE/2		**(I)** FC (Chen, Zeng et al. 1999) **(I)** cerebellar granule cells (Chen and Chuang 1999) **(I)** **Human Blood (Lowthert, Leffert et al. 2012)** **(I)** Astrocyte (Keshavarz, Emamghoreishi et al. 2013) **(I)** HIP (Chen, Rajkowska et al. 2000) **(I)**	**(I)** Hip (Bai, Zhang et al. 2004)	oblimersen, rasagiline,(-)-gossypol, navitoclax, gemcitabine/paclitaxel, bortezomib/paclitaxel, ABT-199, paclitaxel/trastuzumab, paclitaxel/pertuzumab/trastuzumab, lapatinib/paclitaxel, doxorubicin/paclitaxel, epirubicin/paclitaxel, paclitaxel/topotecan, paclitaxel

			Dentate gyrus, HIP(Hammonds and Shim 2009)		
GSK3B glycogen synthase kinase 3 beta	(D) DE/1		**(I)** FC (Fatemi, Reutiman et al. 2009)		enzastaurin
CAT catalase	(D) DE/2		Oxidative Stress BP **(I)** Plasma (de Sousa, Zarate et al. 2014)		fomepizole
JUN jun proto-oncogene	(I) DE/2 DE/1		**(D)** leukocytes (Watanabe, Iga et al. 2014)	**(D)** FC (MacDonald, Eaton et al. 2005)	
MOB3B MOB kinase activator 3B	(D) DE/1	**(I)** PFC (females) (Le-Niculescu, Case et al. 2011)			
NDRG1 N-myc downstream regulated 1	(I) DE/1	**(D)** Blood(Le-Niculescu, Case et al. 2011)			
SPON1 spondin 1, extracellular matrix protein	(D) DE/1			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
FOXP1 forkhead box P1	(I) DE/4	**(D)** Blood(Le-Niculescu, Case et al. 2011)			
HAVCR2 hepatitis A virus cellular receptor 2	(I) DE/4			**(D)** PFC (Jakovcevski,	

				Bharadwaj et al. 2013)	
GJA1 gap junction protein, alpha 1, 43kDa	(I) DE/1	**(D)** HIP (females) (Le-Niculescu, Case et al. 2011)		**(D)** VT (Le-Niculescu, Balaraman et al. 2007)	
CD84 CD84 molecule	(D) DE/2			**(I)** Blood (Le-Niculescu, Balaraman et al. 2007)	
DCAF5 DDB1 and CUL4 associated factor 5	(D) DE/2			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
GANC glucosidase, alpha; neutral C	(D) DE/2				miglitol
IL1R1 interleukin 1 receptor, type I	(I) AP/1				anakinra
INPP4A inositol polyphosphate-4-phosphatase, type I, 107kDa	(D) DE/1			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
JRK Jrk homolog (mouse)	(D) AP/2	**(I)** Brain(Hammamieh, Chakraborty et al. 2014)			
PDXDC1 pyridoxal-dependent decarboxylase domain containing 1	(I) DE/2			**(D)** VT (Le-Niculescu, Balaraman et al. 2007)	
SMARCA2 SWI	(D) DE/1	**(I)** HIP (males) (Le-			

		Niculescu, Case et al. 2011)			
Out of Top Discovery and Prioritization Biomarkers(Non Bonferroni Validated, 65 genes)					
CLTA clathrin, light chain A	(I) DE/4			**(D)** FC (MacDonald, Eaton et al. 2005)	
PPM1B protein phosphatase, Mg2+	(D) DE/4			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
AFF3 AF4/FMR2 family, member 3	(I) AP/4; (I) DE/1	**(D)** Blood (Le-Niculescu, Case et al. 2011)			
WAC WW domain containing adaptor with coiled-coil	(D) DE/4			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
AKT3 v-akt murine thymoma viral oncogene homolog 3	(I) AP/4				enzastaurin
ARID4B AT rich interactive domain 4B (RBP1-like)	(D) DE/4	**(I)** HIP (males) (Le-Niculescu, Case et al. 2011)			
ATXN1 ataxin 1	(I) DE/4	**(D)** Blood(Le-Niculescu, Case et al. 2011)			
BRE	(I)			**(D)**	

Brain and reproductive organ-expressed (TNFRSF1A modulator)	AP/4			VT (Le-Niculescu, Balaraman et al. 2007)	
CSNK1A1 casein kinase 1, alpha 1	(D) DE/4	**(I)** Blood(Le-Niculescu, Case et al. 2011)			
ENTPD1 ectonucleoside triphosphate diphosphohydrolase 1	(I) AP/4	**(D)** Blood(Le-Niculescu, Case et al. 2011)		**(D)** PFC (Jakovcevski, Bharadwaj et al. 2013)	
EPHB4 EPH receptor B4	(I) DE/4				tesevatinib
ETNK1 ethanolamine kinase 1	(D) AP/4	**(I)** PFC (males)(Le-Niculescu, Case et al. 2011)			
ITIH5 inter-alpha-trypsin inhibitor heavy chain family, member 5	(I) AP/4	**(D)** Blood(Le-Niculescu, Case et al. 2011)		**(D)** PFC (Jakovcevski, Bharadwaj et al. 2013)	
LARP4 La ribonucleoprotein domain family, member 4	(D) DE/4			**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	
MBNL1 muscleblind-like splicing regulator 1	(D) DE/4	**(I)** HIP (males) (Le-Niculescu, Case et al. 2011)		**(I)** Blood (Le-Niculescu, Balaraman et al. 2007)	

MR1 major histocompatibility complex, class I-related	(I) DE/4				Anti-Lymphocyte serum
PRDX3 peroxiredoxin 3	(D) DE/4	**(I)** Blood(Le-Niculescu, Case et al. 2011)			
RAB22A RAB22A, member RAS oncogene family	(D) DE/4			**(I)** Blood (Le-Niculescu, Balaraman et al. 2007)	
SNX27 sorting nexin family member 27	(I) AP/4			**(D)** AMY (Le-Niculescu, Balaraman et al. 2007)	
SSBP2 single-stranded DNA binding protein 2	(I) AP/4	**(D)** Blood(Le-Niculescu, Case et al. 2011)		**(D)** VT (Le-Niculescu, Balaraman et al. 2007)	
WAPAL wings apart-like homolog (Drosophila)	(D) DE/4		**(I)** SK-N-AS cells (ATCC derived from a human neuroblastoma cell (Seelan, Khalyfa et al. 2008)	**(I)** VT (Le-Niculescu, Balaraman et al. 2007)	

(I): increase in biomarker expression; (D): decrease in biomarker expression

[0067] More particularly, it has been found that BCL2, JUN, GHA1, ENTPD1, ITIH5, MBNL1, and SSBP2 are changed in expression by the above listed treatments, and in particular therapies such as nutritionals and drugs, suggesting these biomarkers may be core to the anti-suicidal mechanism of these drugs. Further, BCL2, CAT, and JUN may be useful blood pharmacogenomic markers of response to lithium. CD84, MBNL1, and RAB22A may be useful blood pharmacogenomic markers of response to clozapine. NDRG1, FOXP1, AFF3, ATXN1, CSNK1A1, ENTPD1, ITIH5, PRDX3, and SSBP2 may be useful blood pharmacogenomic markers of response to omega-3 fatty acids. Three existing drugs, used for other indications, have been identified as targeting the top suicide biomarkers identified in the present disclosure, and could potentially be re-purposed for testing in treatment of acute suicidality: anakinra (inhibiting ILR1), enzastaurin (inhibiting AKT3), and tesevatinib (inhibiting EPHB4). Additionally, Connectivity Map analyses (FIGS. 34A-34C) identified novel compounds that induce gene expression signatures that are the opposite of those present in suicide, and might generate leads and/or be tested for use to treat/prevent suicidality: betulin (an anti-cancer compound from the bark of birch trees), zalcitabine (an anti-HIV drug), and atractyloside (a toxic glycoside). Other common drugs identified by the Connectivity Map analyses are nafcillin, lansoprazole, mifepristone, LY294002, minoxidil, acetysalicilic acid, estradiol, buspirone, dicloxacillin, corticosterone, metformin, diphenhydramine, haloperidol, metaraminol, yohimbine, trimethadione and fluoxetine (see also Table 6, 7, and 8).

Table 6: Therapeutic Compounds for Suicidality across Gender

Therapeutic compound/Drug	**Score***
fluoxetine	-0.812
betulin	-0.812
dl-alpha tocopherol	-0.821
haloperidol	-0.823
hesperidin	-0.824
calcium folinate	-0.825
harpagoside	-0.826
trimipramine	-0.836
rilmenidine	-0.845
tenoxicam	-0.851
chlorpromazine	-0.852

harman	-0.858
homatropine	-0.863
ramifenazone	-0.864
clozapine	-0.866
diphenhydramine	-0.873
prochlorperazine	-0.874
pirenperone	-0.876
asiaticoside	-0.886
adiphenine	-0.923
verapamil	-0.922
metaraminol	-0.936
vohimbine	-0.958
metformin	-0.983
trimethadione	-1
chlorogenic acid	-1

* Score of -1 means maximum opposite effect.

Table 7: Therapeutic Compounds for Suicidality in Men

Therapeutic compound/drug	**Score***
thiamine	-0.778
homatropine	-0.789
vitexin	-0.794
ergocalciferol	-0.801
tropicamide	-0.801
(-)-atenolol	-0.817
betulin	-0.905
spaglumic acid	-1

* Score of -1 means maximum opposite effect.

Table 8: Therapeutic Compounds for Suicidality in Women

Therapeutic compound/drug	**Score***
mifepristone	-0.797

lansoprazole	-0.888
nafcillin	-0.895
betulin	-1

* Score of -1 means maximum opposite effect.

[0068] In another aspect, the subject can further be diagnosed with a psychiatric disorder. The psychiatric disorder can be any psychiatric disorder known in the art, including, for example, bipolar disorder, major depressive disorder, schizophrenia, and schizoaffective disorder, post-traumatic stress disorder, and combinations thereof.

[0069] In another aspect, the present disclosure is directed to a questionnaire and/or a computer-implemented method for assessing mood, anxiety, and combinations thereof in the subject using a computer-implemented method for assessing mood, anxiety, and the like, and combinations thereof. In one aspect, the method is implemented using a computer device coupled to a memory device. The method implemented using a first computer device coupled to a memory device includes receiving mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject.

[0070] Mood information includes information relating to a subject's mood, motivation, movement, thinking, self-esteem, interest, appetite, and combinations thereof. Anxiety information includes information relating to a subjects anxiety, uncertainty, fear, anger, and combinations thereof. Particular mood and anxiety information assessed can include: determining how good is the subject's mood; determining the subject's motivation, drive, determination to do things right now; determining how high is the subject's physical energy and the amount of moving about that the subject feels like doing right now; determining how high is the subject's mental energy and thinking activity going on in the subject's mind right now; determining how good the subject feels about himself/herself and his/her accomplishments right now; determining how high the subject's interest to do things that are fun and enjoyable right

now; determining how high the subjects appetite and desire for food is right now; determining how anxious the subject is right now; determining how uncertain about things the subject is right now; determining how frightened about things the subject feels right now; determining how angry about things the subject feels right now; determining events or actions the subject thinks are influencing how the subject feels right now; determining additional feelings the subject has right now; and combinations thereof. As illustrated in FIG. 6, the mood and anxiety information can be assessed by having the subject rate each piece of information on a scale of lowest to highest.

[0071] The subject of the method can further be diagnosed as having a psychiatric disorder selected from bipolar disorder, major depressive disorder, schizophrenia, and schizoaffective disorder, post-traumatic stress disorder, and combinations thereof.

[0072] In another aspect, the present disclosure is directed to a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject using a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject, the method implemented using a computer device coupled to a memory device. The method includes: receiving socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to a second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject.

[0073] Socio-demographic and clinical risk factors for suicide includes items for assessing the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors known to influence suicidal behavior, and two demographic factors, age and gender. Socio-demographic/psychological suicidal risk factors assessed can include: lack of coping skills when faced with stress; dissatisfaction with current life; lack of hope for the future; current substance abuse; acute loss/grief; psychiatric illness diagnosed and treated; poor treatment compliance; family history of suicide in blood relatives; personally knowing somebody who committed suicide; history of abuse (such as physical abuse,

sexual abuse, emotional abuse, and neglect); acute/severe medical illness (including acute pain); chronic stress (including perceived uselessness, not feeling needed, and burden to extended kin); history of excessive introversion/conscientiousness (including planned suicide attempts); past history of suicidal acts/gestures; lack of religious beliefs; rejection; lack of positive relationships/social isolation; history of excessive extroversion and impulsive behavior (including rage, anger, physical fights and seeking revenge); lack of children/not in touch with children/not helping care for children; history of command hallucinations of self-directed violence; age (older than 60 years or younger than 25 years); gender; and combinations thereof.

[0074] The socio-demographic/psychological suicidal risk factors can be assessed by having the subject provide an answer to the above factors such as a yes answer, a no answer and a not applicable answer.

[0075] The subject of the method can further be diagnosed as having a psychiatric disorder selected from bipolar disorder, major depressive disorder, schizophrenia, and schizoaffective disorder, post-traumatic stress disorder, and combinations thereof.

[0076] In another aspect, the present disclosure is directed to a method for predicting suicidality in a subject. The method includes: identifying a difference in the expression level of a blood biomarker in a sample obtained from a subject and a reference expression level of the blood biomarker by obtaining the expression level of the blood biomarker in a sample obtained from a subject; obtaining a reference expression level of a blood biomarker; analyzing the blood biomarker in the sample obtained from the subject and the reference expression level of the blood biomarker to detect the difference between the blood biomarker in the sample and the reference expression level of the blood biomarker; assessing mood, anxiety, and combinations thereof, using a first computer device coupled to a memory device, wherein the first computer device receives mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject; assessing socio-demographic/psychological suicidal risk factors in the subject using the first

computer device coupled to a memory device, wherein the first computer device receives socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to the second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject; and predicting suicidality in the subject by the combination of the difference between the expression level of the biomarker in the subject and the reference expression level of the blood biomarker; the assessment of mood, anxiety, and combinations thereof; and the assessment of socio-demographic/psychological suicidal risk factor information.

[0077] As used herein, while the methods are described as using a first and second computer device, it should be understood that more or less than two computer devices may be used to perform the methods of the present disclosure. Particularly, three computer devices, or four computer devices or even five or more computer devices can be used to perform the methods without departing from the scope of the present disclosure.

[0078] In one aspect, the present disclosure is directed to a method for predicting future hospitalization of a subject due to suicidality. The method includes: identifying a difference in the expression level of a blood biomarker in a sample obtained from a subject and a reference expression level of the blood biomarker by obtaining the expression level of the blood biomarker in a sample obtained from a subject; obtaining a reference expression level of a blood biomarker; analyzing the blood biomarker in the sample obtained from the subject and the reference expression level of the blood biomarker to detect the difference between the blood biomarker in the sample and the reference expression level of the blood biomarker; assessing mood, anxiety, and combinations thereof, using a first computer device coupled to a memory device, wherein the first computer device receives mood information, anxiety information, and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, and combinations thereof in the memory device; presenting, by the first computer device, in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer

device for access to the mood information, anxiety information, and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, and combinations thereof to the second computer device to assess mood, anxiety, and combinations thereof in the subject; assessing socio-demographic/psychological suicidal risk factors in the subject using the first computer device coupled to a memory device, wherein the first computer device receives socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to a second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject; and predicting future hospitalization of the subject due to suicidality by the combination of the difference between the expression level of the biomarker in the subject and the reference expression level of the blood biomarker; the assessment of mood, anxiety, and combinations thereof; and the assessment of socio-demographic/psychological suicidal risk factor information.

[0079] Suitable biomarkers for use in the method for predicting suicide ideation in a subject and the method for predicting future hospitalization a subject due to suicidality include those described herein.

[0080] Mood information for use in the method for predicting suicide ideation in a subject and the method for predicting future hospitalization of a subject due to suicidality includes information relating to a subject's mood, motivation, movement, thinking, self-esteem, interest, appetite, and combinations thereof as described herein. Anxiety information includes information relating to a subjects anxiety, uncertainty, fear, anger, and combinations thereof as described herein.

[0081] Socio-demographic and clinical risk factors for suicide for use in the method for predicting suicide ideation in a subject and the method for predicting future hospitalization of a subject due to suicidality include items for assessing the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors

known to influence suicidal behavior, and two demographic factors, age and gender as described herein.

EXAMPLES

Methods

Human blood gene expression experiments and analyses

[0082] *RNA extraction*. Whole blood (2.5–5 ml) was collected into each PaxGene tube by routine venipuncture. PaxGene tubes contain proprietary reagents for the stabilization of RNA. RNA was extracted and processed.

[0083] *Microarrays*. Biotin-labeled aRNAs were hybridized to Affymetrix HG-U133 Plus 2.0 GeneChips (Affymetrix; with over 40 000 genes and expressed sequence tags), according to the manufacturer's protocols. Arrays were stained using standard Affymetrix protocols for antibody signal amplification and scanned on an Affymetrix GeneArray 2500 scanner with a target intensity set at 250. Quality-control measures, including 30/50 ratios for glyceraldehyde 3-phosphate dehydrogenase and β-actin, scale factors, background and Q–values, were within acceptable limits.

[0084] *Analysis*. The participant's SI scores at the time of blood collection (0—no suicidal ideation (SI) compared with 2 and above—high SI) were used. Gene expression differences between the no SI and the high SI visits were analyzed using a within-participant design, then an across-participants summation (FIG. 1C and 10C).

Gene expression analysis in the discovery cohort

[0085] Data was analyzed in two ways: an Absent-Present (AP) approach and a differential expression (DE) approach. The AP approach may capture turning on and off of genes, and the DE approach may capture gradual changes in expression. For the AP approach, Affymetrix Microarray Suite Version 5.0 (MAS5) was used to generate Absent (A), Marginal (M), or Present (P) calls for each probe set on the chip (Affymetrix U133 Plus 2.0 GeneChips) for all participants in the discovery cohort. For the DE approach, all Affymetrix microarray data was imported as Cel. files into Partek Genomic Suites 6.6 software package (Partek Incorporated, St Louis, MO, USA). Using only the perfect match values, a robust multi-array analysis (RMA) was run, background corrected with quantile normalization and a median polish

probe set summarization, to obtain the normalized expression levels of all probe sets for each chip. RMA was performed independently for each of the 6 diagnoses used in the study, to avoid potential artefacts due to different ranges of gene expression in different diagnoses (Niculescu et al. MP 2015). Then the participants' normalized data was extracted from these RMA and assembled for the different cohorts used in the Example.

[0086] *A/P analysis*. For the longitudinal within participant AP analysis, comparisons were made within participant between sequential visits to identify changes in gene expression from Absent to Present that track changes in phene expression (suicidal ideation, "SI") from No SI to High SI. For a comparison, if there was a change from A to P tracking a change from No SI to High SI, or a change from P to A tracking a change from High SI to No SI, that was given a score of +1 (increased biomarker in High SI). If the change was in opposite direction in the gene vs the phene (SI), that was given a score of -1 (decreased biomarker in High SI). If there was no change in gene expression between visits, despite a change of phene expression (suicidal ideation), or a change in gene expression between visits, despite no change in phene expression (suicidal ideation), that was given a score of 0 (not tracking as a biomarker). If there was no change in gene expression and no change in suicidal ideation between visits, that was given a score of +1 if there was concordance (P-P with High SI-High SI, or A-A with No SI-No SI), or a score of -1 if there was the opposite (A-A with High SI-High SI, or P-P with No SI-No SI). If the changes were to M (moderate) instead of P, the values used were 0.5 or –0.5. These values were then summed up across the comparisons in each participant, resulting in a participant score for each gene/probeset in each participant. A perfection bonus was also used. If the gene expression perfectly tracked the suicidal ideation in a participant that had at least two comparisons (3 visits), that probe set was rewarded by a doubling of its participant score. Additionally, a non-tracking correction was used. If there was no change in gene expression in any of the comparisons for a particular participant, that overall participant score for that probe set in that participant was zero.

[0087] *DE analysis*. For the longitudinal within participant DE analysis, fold changes (FC) in gene expression were calculated between sequential visits within each participant. Scoring methodology was similar to that used above for AP. Probe sets that had a FC $\geq$ 1.2 were scored + 1 (increased in High SI) or -1 (decreased in High SI). FC $\geq$ 1.1 were scored +0.5 or -0.5. FC lower than 1.1 were considered no change. The only difference between the DE and the AP analyses was when scoring comparisons where there was no phene expression (SI) change between visits and no change in gene expression between visits (FC lower than 1.1). In that case,

the comparison received the same score as the nearest preceding comparison where there was a change in SI from visit to visit. If no preceding comparison with a change in SI was available, then it was given the same score as the nearest subsequent comparison where there was a change in SI. Also for DE, a perfection bonus and a non-tracking correction was used. If the gene expression perfectly tracked the suicidal ideation in a participant who had at least two comparisons (3 visits), that probe set was rewarded by a doubling of its score. If there was no change in gene expression in any of the comparisons for a particular participant, that overall participant score for that probe set in that participant was zero.

[0088] *Internal score.* Once scores within each participant were calculated, an algebraic sum across all participants was obtained for each probe set. Probe sets were then given internal CFG points based upon these algebraic sum scores. Probe sets with scores above the 33% of the distribution (for increased probe sets and decreased probe sets) received 1 point, those above 50% of the distribution received 2 points, and those above 80% of the distribution received 4 points.

[0089] In Example 1, for AP analyses, 23 probe sets received 4 points, 581 probe sets received 2 points, and 2077 probe sets received 1 point, for a total of 2681 probe sets. For DE analyses, 31 probe sets received 4 points, 1294 probe sets received 2 points, and 5839 probe sets received 1 point, for a total of 7164 probe sets. The overlap between the two discovery methods is shown in FIG. 2A. For Example 2, for AP analyses, 30 probesets received 4 points, 647 probesets with 2 points, and 2596 probesets with 1 point, for a total of 3273 probesets. For DE analyses, 95 probesets received 4 points, 2215 probesets with 2 points, and 7520 probesets with 1 point, for a total of 9829 probesets. The overlap between the two discovery methods for probesets with an internal score of 1 is shown in FIG. 11A.

[0090] Different probe sets may be found by the two methods due to differences in scope (DE capturing genes that were present in both visits of a comparison (i.e. PP, but are changed in expression), thresholds (what makes the 33% change cutoff across participants varies between methods), and technical detection levels (what is considered in the noise range varies between the methods).

[0091] In total, 9413 probe sets were identified with an internal CFG score of 1. Gene names for the probe sets were identified using NetAffyx (Affymetrix) and Partek for Affymetrix HG-U133 Plus 2.0 GeneChips, followed by GeneCards to confirm the primary gene symbol. In

addition, for those probe sets that were not assigned a gene name by NetAffyx or Partek, the UCSC Genome Browser was used to directly map them to known genes, with the following limitations. In case the probe set fell in an intron, that particular gene was assumed to be implicated. Only one gene was assigned to each probe set. Genes were then scored using manually curated CFG databases as described below (FIGS. 2C and 11C).

Convergent Functional Genomics

[0092] *Databases.* Manually curated databases of all the human gene expression (postmortem brain, blood and cell cultures), human genetics (association, copy number variations and linkage), and animal model gene expression and genetic studies published to date on psychiatric disorders was established (Laboratory of Neurophenomics, Indiana University School of Medicine, www.neurophenomics. info). The databases include only primary literature data and do not include review papers or other secondary data integration analyses to avoid redundancy and circularity. These large and constantly updated databases have been used for CFG cross validation and prioritization (FIGS. 2B, 2C, 11B and 11C). For Example 2, data from 442 papers on suicide were present in the databases at the time of the CFG analyses (genetic studies-164, brain studies-192, peripheral fluids- 86).

[0093] *Human postmortem brain gene expression evidence.* Converging evidence was scored for a gene if there were published reports of human postmortem data showing changes in expression of that gene or changes in protein levels in brains from participants who died from suicide.

[0094] *Human blood and other peripheral tissue gene expression data.* Converging evidence was scored for a gene if there were published reports of human blood, lymphoblastoid cell lines, CSF, or other peripheral tissue data showing changes in expression of that gene or changes in protein levels in participants who had a history of suicidality or who died from suicide.

[0095] *Human genetic evidence (association and linkage).* To designate convergence for a particular gene, the gene had to have independent published evidence of association or linkage for suicide. For linkage, the location of each gene was obtained through GeneCards (http://www.genecards.org), and the sex averaged cM location of the start of the gene was then

obtained through http://compgen.rutgers.edu/mapinterpolator. For linkage convergence, the start of the gene had to map within 5 cM of the location of a marker linked to the disorder.

[0096] *CFG scoring*. For CFG analysis (FIGS. 2C and 11C), the external cross-validating lines of evidence were weighted such that findings in human postmortem brain tissue, the target organ, were prioritized over peripheral tissue findings and genetic findings, by giving them twice as many points. Human brain expression evidence was given 4 points, whereas human peripheral evidence was given 2 points, and human genetic evidence was given a maximum of 2 points for association and 1 point for linkage. Each line of evidence was capped in such a way that any positive findings within that line of evidence resulted in maximum points, regardless of how many different studies support that single line of evidence, to avoid potential popularity biases. In addition to the external CFG score, genes were also prioritized based upon the initial gene expression analyses used to identify them. Probe sets identified by gene expression analyses could receive a maximum of 4 points. Thus, the maximum possible total CFG score for each gene was 12 points (4 points for the internal CFG score and 8 points for the external CFG score). The scoring system was decided upon before the analyses were carried out. Twice as much weight was given to external CFG than to internal CFG in order to increase generalizability and avoid fit to cohort of the prioritized genes. It is recognized that other ways of scoring the lines of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes per se. Nevertheless, it is believed that this simple scoring system provides a good separation of genes based on gene expression evidence and on independent cross-validating evidence in the field (FIGS. 2B and 11B).

Pathway Analyses

[0097] IPA 9.0 (Ingenuity Systems, Redwood City, CA, USA), GeneGO MetaCore (Encinitas, CA), and Kyoto Encyclopedia of Genes and Genomes (through the Partek Genomics Suite 6.6 software package) were used to analyze the biological roles, including top canonical pathways, and diseases, of the candidate genes resulting from this work, as well as to identify genes in the dataset that are the target of existing drugs (FIGS. 8, 15 and 17). The analyses was run together for all the AP and DE probe sets with a total CFG score ≥ 4, then for those of them that showed stepwise change in the suicide completers validation cohort, then for those of them that were nominally significant, and finally for those of them that survived Bonferroni correction.

Validation Analyses

[0098] For validation of the candidate biomarker genes, which of the top candidate genes (CFG score of 4 or above) that were stepwise changed in expression from the No SI group to the High SI group to the suicide completers group, were examined. The empirical cutoff of 33% of the maximum possible CFG score of 12 was used, which also permits the inclusion of potentially novel genes with maximal internal CFG score, but no external CFG score. Statistical analyses were performed in SPSS using one-way ANOVA and Bonferonni corrections.

[0099] For the AP analyses, the Affymetrix microarray data files were imported from the participants in the validation cohort of suicide completers into MAS5, alongside the data files from the participants in the discovery cohort.

[0100] For the DE analyses, Cel. files were imported into Partek Genomic Suites. A RMA was then run, background corrected with quantile normalization, and a median polish probe set summarization of all the chips from the validation cohort to obtain the normalized expression levels of all probe sets for each chip. Partek normalizes expression data into a log base of 2 for visualization purposes. Expression data was non-log-transformed by taking 2 to the power of the transformed expression value. The non-log-transformed expression data was then used to compare expression levels of biomarkers in the different groups.

Testing analyses

[0101] The test cohort for suicidal ideation and the test cohort for future hospitalizations analyses were assembled out of data that was RMA normalized by diagnosis. Phenomic (clinical) and gene expression markers used for predictions were z-scored by diagnosis, to be able to combine different markers into panels and to avoid potential artefacts due to different ranges of phene expression and gene expression in different diagnoses. Markers were combined by computing the average of the increased risk markers minus the average of the decreased risk markers. Predictions were performed using R-studio.

[0102] *Predicting Suicidal Ideation.* Receiver-operating characteristic (ROC) analyses between marker levels and suicidal ideation (SI) were performed by assigning participants with a HAMD SI score of 0-1 into the no SI category, and participants with a HAMD-SI score of 2 and greater into the SI category. Additionally, ANOVA was performed between no (HAMD-SI 0),

moderate (HAMD-SI 1), and high SI participants (HAMD-SI 2 and above) and Pearson R (one-tail) was calculated between HAMD-SI scores and marker levels.

[0103] *Predicting Future Hospitalizations for Suicidality.* Analyses for hospitalizations in the first year following testing were conducted on data for all the participants for which data was collected. For each participant in the test cohort for future hospitalizations, the Example visit with highest levels for the marker or combination of markers was selected as index visit (or with the lowest levels, in the case of decreased markers). ROC analyses between marker levels and future hospitalizations were performed based on assigning if participants had been hospitalized for suicidality (suicide ideation, suicide attempts) or not following the index testing visit. Additionally, a one tailed t-test with unequal variance was performed between groups of participants with and without hospitalizations for suicidality. Pearson R (one-tail) correlation was performed between hospitalization frequency (number of hospitalizations for suicidality divided by duration of follow-up) and biomarker score. The correlation analysis for hospitalizations frequency was also conducted for all future hospitalizations due to suicide beyond one year, as this calculation, unlike the ROC and t-test, accounts for the actual length of follow-up, which varied beyond one year from participant to participant.

EXAMPLE 1

[0104] In this Example, male subjects were analyzed for predicting suicidal ideation and future hospitalizations for suicidality.

Human participants

[0105] Data was obtained from four cohorts: one live psychiatric participants discovery cohort (within-participant changes in suicidal ideation; n=37 out of 217); one postmortem coroner's office validation cohort (suicide completers; n=26); and two live psychiatric participants test cohorts–one for predicting suicidal ideation (n=108) and one for predicting future hospitalizations for suicidality (n=157).

[0106] Live psychiatric participants were recruited from the patient population at the Indianapolis VA Medical Center. All participants understood and signed informed consent forms detailing the research goals, procedure, caveats and safeguards. Participants completed diagnostic assessments by an extensive structured clinical interview—Diagnostic Interview for Genetic Studies—at a baseline visit, followed by up to six testing visits, 3–6 months apart or

whenever a hospitalization occurred. At each testing visit, they received a series of psychiatric rating scales, including the Hamilton Rating Scale for Depression-17, which includes a suicidal ideation (SI) rating item (FIGS. 1A-1C), and blood was drawn. Whole blood (10 ml) was collected in two RNA-stabilizing PAXgene tubes, labeled with an anonymized ID number, and stored at -80 degrees C in a locked freezer until the time of future processing. Whole-blood (predominantly lymphocyte) RNA was extracted for microarray gene expression studies from the PAXgene tubes, as detailed below. This Example focused on a male population because of the demographics of the catchment area (primarily male in a VA Medical Center), and to minimize any potential gender-related effects on gene expression, which would have decreased the discriminative power of the analysis given the relatively small sample size.

[0107] The within participant discovery cohort, from which the biomarker data were derived, consisted of 37 male participants with psychiatric disorders, with multiple visits, who each had at least one diametric change in SI scores from no SI to high SI from one testing visit to another testing visit. There was 1 participant with 6 visits, 1 participant with 5 visits, 1 participant with 4 visits, 23 participants with 3 visits each, and 11 participants with 2 visits each, resulting in a total of 106 blood samples for subsequent microarray studies (FIG. 1B).

[0108] The postmortem cohort, in which the top biomarker findings were validated, consisted of a demographically matched cohort of 24 male violent suicide completers obtained through the Marion County coroner's office (FIG. 9). A last observed alive postmortem interval of 24 hours or less was required, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. 14 participants completed suicide by gunshot to head or chest, 8 by hanging, 1 by electrocution and 1 by slit wrist. Next of kin signed informed consent at the coroner's office for donation of tissues and fluids for research. The samples were collected as part of the INBRAIN initiative (Indiana Center for Biomarker Research in Neuropsychiatry).

[0109] The independent test cohort for predicting suicidal ideation consisted of 108 male participants with psychiatric disorders, demographically matched with the discovery cohort with one or multiple testing visits in the lab, with either no SI, intermediate SI, or high SI, resulting in a total of 223 blood samples in whom whole-genome blood gene expression data were obtained.

[0110] The test cohort for predicting future hospitalizations consisted of male participants in whom whole-genome blood gene expression data were obtained at testing visits

over the years as part of a longitudinal study. If the participants had multiple testing visits, the visit with the highest marker (or combination of markers) levels was selected for the analyses. The participants' subsequent number of psychiatric hospitalizations, with or without suicidality, was tabulated from electronic medical records. All participants had at least one year of follow-up or more at the VA Medical Center since the time of the testing visits in the lab. Participants were evaluated for the presence of future hospitalizations for suicidality, and for the frequency of such hospitalizations. A hospitalization was deemed to be without suicidality if suicidality was not listed as a reason for admission, and no SI was described in the admission and discharge medical notes. Conversely, a hospitalization was deemed to be because of suicidality if suicidal acts or intent was listed as a reason for admission, and SI was described in the admission and discharge medical notes.

Medications

[0111] The participants in the discovery cohort were all diagnosed with various psychiatric disorders (e.g., BP, MDD, SZA, SZ, PTSD). The participants were on a variety of different psychiatric medications: mood stabilizer, antidepressants, antipsychotics, benzodiazepines and others. Medications can have a strong influence on gene expression. However, the identification of differentially expressed genes was based on within-participant analyses, which factor out not only genetic background effects but also medication effects, as the participants had no major medication changes between visits. Moreover, there was no consistent pattern in any particular type of medication, or between any change in medications and SI, in the rare instances where there were changes in medications between visits.

Results

[0112] The top increased and decreased biomarkers after the discovery for ideation (CADM1, CLIP4, DTNA, KIF2C), prioritization with CFG for prior evidence (SAT1, SKA2, SLC4A4), and validation for behavior in suicide completers (IL6, MBP, JUN, KLHDC3) steps were tested in a completely independent test cohort of psychiatric participants for prediction of suicidal ideation (n=108), and in a future follow-up cohort of psychiatric participants (n=157) for prediction of psychiatric hospitalizations due to suicidality. The best individual biomarker across psychiatric diagnoses for predicting suicidal ideation was SLC4A4, with 72% accuracy. For bipolar disorder in particular, SLC4A4 predicted suicidal ideation with 93% accuracy, and future hospitalizations with 70 % accuracy. Two new clinical information apps, one for affective state

(Simplified Affective Scale, SASS) and one for suicide risk factors (Convergent Functional Information for Suicide, CFI-S) are disclosed, and how well they predict suicidal ideation across psychiatric diagnoses (85% accuracy for SASS, 89% accuracy for CFI-S). Also disclosed is that the integration of the top biomarkers and the clinical information into a universal predictive measure (UP-Suicide) was able to predict suicidal ideation across psychiatric diagnoses with 92% accuracy. For bipolar disorder, it was able to predict suicidal ideation with 98% accuracy and future hospitalizations with 94 % accuracy.

[0113] For discovery, two differential expression methodologies were used: Absent/Present (AP) (reflecting on/off of transcription) and Differential Expression (DE) (reflecting more subtle gradual changes in expression levels). Genes that tracked suicidal ideation in each participant were identified. Three thresholds were used for increased in expression genes and for decreased in expression genes: ≥ 33% (low), ≥50% (medium), and ≥ 80% (high) of the maximum scoring increased and decreased gene across participants. These differentially expressed genes were then prioritized using a Bayesian-like Convergent Functional Genomics (CFG) approach (FIGS. 2A-2C), integrating all the previously published human genetic evidence, postmortem brain gene expression evidence, and peripheral fluids evidence for suicide available in the field as of September 2014 to identify and prioritize disease relevant genomic biomarkers, extracting generalizable signal out of potential cohort-specific noise and genetic heterogeneity. For validation, genes whose levels of expression were changed stepwise significantly from no suicidal ideation to high suicidal ideation to suicide completion, and who survived Bonferroni correction for multiple comparisons, were carried forward. The overall best biomarkers for suicidal ideation across diagnostic groups was identified. The top genes after discovery were DTNA and KIF2C from AP, CADM1 and CLIP4 from DE. The top genes after prioritization with CFG were SLC4A4 and SKA2 from AP; and SAT1 and SKA2 from DE. The top genes after validation in suicide completers were IL6 and MBP from AP; and JUN and KLHDC3 from DE (FIG. 2C). Notably, the SAT1 finding is a replication and expansion of previously reported results identifying SAT1 as a biomarker for suicidality (Le-Niculescu et al. 2013), and the SKA2 finding is an independent replication of a previous report identifying SKA2 as a biomarker for suicidality (Kaminsky et al. 2014). A number of other genes identified are completely novel in terms of their involvement in suicidality.

[0114] To understand the biology represented by the biomarkers identified, and derive some mechanistic and practical insights, unbiased biological pathway analyses and hypothesis

driven mechanistic queries, overall disease involvement and specific neuropsychiatric disorders queries, and overall drug modulation along with targeted queries for omega-3, lithium and clozapine were conducted. Administration of omega-3s in particular may be a mass-deployable therapeutic and preventive strategy.

[0115] The sets of biomarkers identified have biological roles in immune and inflammatory response, growth factor regulation, mTOR signaling, stress, and perhaps overall the switch between cell survival and proliferation vs. apoptosis (FIG. 8). An extrapolation can be made and model proposed whereas suicide is a whole body apoptosis (or "self-poptosis") in response to perceived stressful life events.

[0116] Evidence for the involvement of the biomarkers for suicidality was also examined for involvement in other psychiatric disorders, allowing for analysis of context and specificity FIGS. 8 and 9). SKA2, HADHA, SNORA68, RASL11B, CXCL11, HOMEZ, LOC728543, AHCYL1, LDLRAP1, NEAT1 and PAFAH1B2 appeared to be relatively specific for suicide, based on the evidence to date. SAT1, IL6, FOXN3 and FKBP5 were less specific for suicide, having equally high evidence for involvement in suicide and in other psychiatric disorders, possibly mediating stress response as a common denominator. CADM1, discovered in this Example as a top biomarker for suicide, had previous evidence for involvement in other psychiatric disorders, such as ASD and BP. Interestingly, it was identified in a previous study as a blood biomarker increased in expression in low mood states in bipolar participants, and it is increased in expression in the current Example in high suicidal ideation states. Increased expression of CADM1 is associated with decreased cellular proliferation and with apoptosis, and this gene is decreased in expression or silenced in certain types of cancers.

[0117] A 22-item scale and app for suicide risk, Convergent Functional Information for Suicidality (CFI-S), was also developed, which integrates information about known life events, mental health, physical health, stress, addictions, and cultural factors that can influence suicide risk. Clinical risk predictors and scales are of high interest in the military and in the general population at large. The scale disclosed herein builds on those excellent prior achievements, while aiming for comprehensiveness, simplicity and quantification similar to a polygenic risk score. CFI-S is able to distinguish between individuals who committed suicide (coroner's cases, information obtained from the next of kin, n=35) and those high risk participants who did not, but had experienced changes in suicidal ideation (e.g., the discovery cohort of psychiatric participants described herein). Items of the CFI-S scale that were the most significantly different

were analyzed. Seven (7) items that were significantly different were identified, 5 of which survived Bonferroni correction: lack of coping skills when faced with stress (p= 3.35E-11), dissatisfaction with current life (p=2.77E-06), lack of hope for the future (4.58E-05), current substance abuse (p=1.25E-04), and acute loss/grief (p= 9.45E-4). The top item was inability to cope with stress, which was independently consistent with the biological mechanistic results discussed above.

[0118] CFI-S provided good accuracy (ROC AUC 0.70, p-value 0.006) at predicting future hospitalizations for suicidality in the first year, across diagnostic groups. CFI-Suicide had very good accuracy (AUC 0.89, p-value 3.53E-13) at predicting suicidal ideation in psychiatric participants across diagnostic groups. Within diagnostic groups, in affective disorders, the accuracy was even higher. CFI-S had excellent accuracy at predicting high suicidal ideation in bipolar participants (AUC 0.97, p-value 1.75E-06) and in depression participants (AUC 0.95, p-value 7.98E-06).

[0119] Previously, the TASS (Total Affective State Scale) was developed and described for measuring mood and anxiety. The wording used in TASS was simplified and a new app was developed for an 11 item scale for measuring mood and anxiety, the Simplified Affective State Scale (SASS). The SASS is a set of 11 visual analog scales (7 for mood, 4 for anxiety) that provides a number ranging from 0 to 100 for mood state and for anxiety state.

[0120] SASS had very good accuracy (AUC 0.85, 9.96E-11) at predicting suicidal ideation in psychiatric participants across diagnostic groups. Within diagnostic groups, in affective disorders, the accuracy was even higher (AUC 0.87) in both bipolar disorder and depression. SASS also had good accuracy (AUC 0.71, p-value 0.008) at predicting future hospitalizations for suicidality in the first year following testing.

[0121] The best single biomarker predictor for suicidal ideation state across all diagnostic groups was SLC4A4, the top increased biomarker from AP CFG prioritization (AUC 0.72, p-value 2.41E-05). Within diagnostic groups, the accuracy was even higher. SLC4A4 had very good accuracy at predicting future high suicidal ideation in bipolar participants (AUC 0.93, p-value 9.45E-06) and good accuracy in schizophrenia participants (AUC 0.76, p-value 0.030). SLC4A4 is a sodium-bicarbonate co-transporter that regulates intracellular pH, and possibly apoptosis. Very little is known to date about its roles in the brain, thus representing a completely novel finding.

[0122] SKA2, the top decreased biomarker from AP and DE CFG, had good accuracy at predicting suicidal ideation across all diagnostic groups (AUC 0.69), and even better accuracy in bipolar participants (AUC 0.76, p-value 0.011) and schizophrenia participants (AUC 0.82).

[0123] The best single top biomarker predictor for future hospitalizations for suicidal behavior in the first year across all diagnostic groups was SAT1, the top increased biomarker from the DE CFG (AUC 0.55). Within diagnostic groups, in affective disorders, the SAT1 prediction accuracies were higher (depression AUC 0.62, bipolar AUC 0.63).

[0124] The a priori primary endpoint was a combined universal predictor for suicide (UP-Suicide), composed of the top biomarkers from discovery, prioritization and validation (n=11), along with CFI-Suicide, and SASS. UP-Suicide is an excellent predictor of suicidal ideation across all disorders in the independent cohort of psychiatric participants (AUC 0.92). UP-Suicide also has good predictive ability for future psychiatric hospitalizations for suicidality in the first year of follow-up (AUC 0.70). The predictive ability of UP-Suicide is notably higher in affective disorder participants (bipolar, depression) (FIGS. 4A & 4B).

EXAMPLE 2

[0125] In this Example, female subjects were analyzed for predicting suicidal ideation and future hospitalizations for suicidality.

Human participants

[0126] Four cohorts were used: one live psychiatric participants discovery cohort (within-participant changes in suicidal ideation; n=12 out of 51); one postmortem coroner's office validation cohort (suicide completers; n=6); and two live psychiatric participants test cohorts–one for predicting suicidal ideation (n=33), and one for predicting future hospitalizations for suicidality (n=24).

[0127] The live psychiatric participants were part of a larger longitudinal cohort that was continuously being collected. Participants were recruited from the patient population at the Indianapolis VA Medical Center and Indiana University School of Medicine through referrals from care providers, the use of brochures left in plain sight in public places and mental health clinics, and through word of mouth. All participants understood and signed informed consent forms detailing the research goals, procedure, caveats and safeguards. Participants completed

diagnostic assessments by an extensive structured clinical interview—Diagnostic Interview for Genetic Studies—at a baseline visit, followed by up to six testing visits, 3–6 months apart or whenever a new psychiatric hospitalization occurred. At each testing visit, they received a series of psychiatric rating scales, including the Hamilton Rating Scale for Depression-17, which includes a suicidal ideation (SI) rating item (FIG. 10A), and the blood was drawn. Whole blood (10 ml) was collected in two RNA-stabilizing PAXgene tubes, labeled with an anonymized ID number, and stored at -80 degrees C in a locked freezer until the time of future processing. Whole-blood (predominantly lymphocyte) RNA was extracted for microarray gene expression studies from the PAXgene tubes, as detailed below. This Exampled focused on a female population.

[0128] The within participant discovery cohort, from which the biomarker data were derived, consisted of 12 female participants with psychiatric disorders and multiple visits in the lab, who each had at least one diametric change in SI scores from no SI to high SI from one testing visit to another. There were 7 participants with 3 visits each, and 5 participants with 2 visits each, resulting in a total of 31 blood samples for subsequent microarray studies (FIGS. 10B and 10C).

[0129] The postmortem cohort, in which the top biomarker findings were validated for behavior, consisted of a demographically matched cohort of 6 female violent suicide completers obtained through the Marion County coroner's office (FIG. 14). A last observed alive postmortem interval of 24 hours or less was required, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. 5 participants completed suicide by gunshot to head or chest, and 1 by asphyxiation. Next of kin signed informed consent at the coroner's office for donation of blood for research. The samples were collected as part of the INBRAIN initiative (Indiana Center for Biomarker Research in Neuropsychiatry).

[0130] The independent test cohort for predicting suicidal ideation (FIG. 14) consisted of 33 female participants with psychiatric disorders, demographically matched with the discovery cohort, with one or multiple testing visits in the lab, with either no SI, intermediate SI, or high SI, resulting in a total of 74 blood samples in whom whole-genome blood gene expression data were obtained (FIG. 14).

[0131] The test cohort for predicting future hospitalizations (FIG. 14) consisted of 24 female participants in whom whole-genome blood gene expression data were obtained at testing visits over the years as part of a longitudinal study. If the participants had multiple testing visits, the visit with the highest marker (or combination of markers) levels was selected for the analyses (so called "high watermark" or index visit). The participants' subsequent number of psychiatric hospitalizations, with or without suicidality (ideation or attempt), was tabulated from electronic medical records. Participants were evaluated for the presence of future hospitalizations for suicidality, and for the frequency of such hospitalizations. A hospitalization was deemed to be without suicidality if suicidality was not listed as a reason for admission, and no SI was described in the admission and discharge medical notes. Conversely, a hospitalization was deemed to be because of suicidality if suicidal acts or intent was listed as a reason for admission, and/or SI was described in the admission and discharge medical notes.

Medications

[0132] The participants in the discovery cohort were all diagnosed with various psychiatric disorders (FIG. 14). Their psychiatric medications were listed in their electronic medical records, and documented at the time of each testing visit. The participants were on a variety of different psychiatric medications: mood stabilizers, antidepressants, antipsychotics, benzodiazepines and others (data not shown). Medications can have a strong influence on gene expression. However, discovery of differentially expressed genes was based on within-participant analyses, which factor out not only genetic background effects but also medication effects, as the participants had no major medication changes between visits. Moreover, there was no consistent pattern in any particular type of medication, or between any change in medications and SI, in the rare instances where there were changes in medications between visits.

Clock Gene Database

[0133] In this Example, a database was compiled of genes associated with circadian function, by using a combination of review papers (Zhang et al. Cell 2009; 139(1):19-210, McCarthy and Welsh Journal of biological rhythms 2012; 27(5):339-352) and searches of existing databases CircaDB (circadb.hogeneschlab.org), GeneCards (www.genecards.org), and GenAtlas (genatlas.medecine.univ-paris5.fr) . Using the data, a total of 1280 genes were identified that show circadian functioning. The genes were classified into "core" clock genes, i.e. those genes that are the main engine driving circadian function (n=18), "immediate" clock genes,

i.e. the genes that directly input or output to the core clock (n=331), and "distant" clock genes, i.e. genes that directly input or output to the immediate clock genes (n=1,119).

Clinical measures

[0134] The Simplified Affective State Scale (SASS) is an 11-item scale for measuring mood and anxiety. The SASS has a set of 11 visual analog scales (7 for mood, 4 for anxiety) that ends up providing a number ranging from 0 to 100 for mood state, and the same for anxiety state. Also developed is an Android app version.

[0135] In some embodiments, the systems and methods described utilize a computer implemented method for assessing suicidal risk factors based upon patient psychiatric information further including mood information, anxiety information, and other psychiatric symptom information. Any and all such patient psychiatric information may be represented as a quantitative rating on a defined analog scale, such as the ratings and scales described above. Further, as used herein, such patient psychiatric information may be processed using an associated processing algorithm. The associated processing algorithm may include calculating mean values for each component of patient psychiatric information and then assigning a suitable weighting to each calculated mean value. The processing algorithm may thus use the quantitative ratings of the patient psychiatric information as inputs to calculate a diagnostic output score. The diagnostic output score may be used to compare to reference scores (from a diagnostic database) associated with patients having psychiatric symptom information (e.g., psychiatric disorder diagnosis or lack thereof) similar to the patient. By such comparison, the diagnostic output score may be assigned a percentile. The diagnostic output score may also be compared to the reference scores in the diagnostic database associated with individuals with no suicidality and high suicidality. Thus, if the diagnostic output score meets or exceeds a high suicidality reference score, a patient may be marked as at risk for suicide. Conversely, if the diagnostic output score meets or falls below a low suicidality reference score, a patient may be marked as not at risk for suicide.

[0136] Convergent Functional Information for Suicidality (CFI-S) is a 22-item scale and Android app for suicide risk, which integrates, in a simple binary fashion (Yes-1, No-0), similar to a polygenic risk score, information about known life events, mental health, physical health, stress, addictions, and cultural factors that can influence suicide risk. The scale was administered at participant testing visits (n= 39), or scored based on retrospective electronic medical record

information and Diagnostic Interview for Genetic Testing (DIGS) information (n=48). When information was not available for an item, it was not scored (NA).

[0137] In other embodiments, the systems and methods described utilize a computer implemented method for assessing suicidal risk factors based upon socio-demographic/psychological suicidal risk factors. Any and all such socio-demographic/psychological suicidal risk factors may be represented as a quantitative rating on a defined analog scale, such as the ratings and scales described above. Further, as used herein, such socio-demographic/psychological suicidal risk factors may be processed using an associated processing algorithm. The associated processing algorithm may include calculating mean values for each component socio-demographic/psychological suicidal risk factor and then assigning a suitable weighting to each calculated mean value. The processing algorithm may thus use the quantitative ratings of the socio-demographic/psychological suicidal risk factors as inputs to calculate a diagnostic output score. The diagnostic output score may be used to compare to reference scores (from a diagnostic database) associated with patients having socio-demographic/psychological suicidal risk factors similar to the patient. By such comparison, the diagnostic output score may be assigned a percentile. The diagnostic output score may also be compared to the reference scores in the diagnostic database associated with individuals with no suicidality and high suicidality. Thus, if the diagnostic output score meets or exceeds a high suicidality reference score, a patient may be marked as at risk for suicide. Conversely, if the diagnostic output score meets or falls below a low suicidality reference score, a patient may be marked as not at risk for suicide.

[0138] In some computer-implemented methods described above and herein, multiple computing devices may interact with one another (e.g., first and second computer devices). To protect data and privacy, such requests and transmissions are made using data encryption.

Combining gene expression and clinical measures

[0139] The Universal Predictor for Suicide (UP-Suicide) construct, the primary endpoint, was decided upon as part of a apriori study design to be broad- spectrum, and combine the top Bonferroni validated biomarkers with the phenomic (clinical) markers (SASS and CFI-S).

Results

Discovery of biomarkers for suicidal ideation

[0140] A whole-genome gene expression profiling was conducted in the blood samples from a longitudinally followed cohort of female participants with psychiatric disorders that predispose to suicidality. The samples were collected at repeated visits, 3–6 months apart. State information about suicidal ideation (SI) was collected from a questionnaire (HAMD) administered at the time of each blood draw. Out of 51 female psychiatric participants (with a total of 123 visits) followed longitudinally in this Example, with a diagnosis of BP, MDD, SZ and SZA, there were 12 participants that switched from a no SI (SI score of 0) to a high SI state (SI score of 2 and above) at different visits, which was the intended discovery group (FIG. 10B). A within-participant design was used to analyze data from these 12 participants and their 31 visits. A within-participant design factors out genetic variability, as well as some medications, lifestyle, and demographic effects on gene expression, permitting identification of relevant signal with Ns as small as 1. Another benefit of a within-participant design may be accuracy/consistency of self-report of psychiatric symptoms ('phene expression'), similar in rationale to the signal detection benefits it provides in gene expression.

[0141] For discovery, two differential expression methodologies were used: Absent/Present (AP) (reflecting on/off of transcription), and Differential Expression (DE) (reflecting more subtle gradual changes in expression levels). The genes that tracked suicidal ideation in each participant were identified in the analyses. Three thresholds were used for increased in expression genes and for decreased in expression genes: $\geq$ 33.3% (low), $\geq$50% (medium), and $\geq$ 80% (high) of the maximum scoring increased and decreased gene across participants. Such a restrictive approach was used as a way of minimizing false positives, even at the risk of having false negatives. For example, there were genes on each of the two lists, from AP and DE analyses, that had clear prior evidence for involvement in suicidality, such as AKAP10 (31.7%) and MED28 (31.8%) from AP, and S100B (31.7%) and SKA2 (31.4%) for DE, but were not included in subsequent analyses because they did not meet the apriori set 33.3% threshold. Notably, SKA2 reproduces the results in males (Example 1).

Prioritization of biomarkers based on prior evidence in the field

[0142] These differentially expressed genes were then prioritized using a Bayesian-like Convergent Functional Genomics (CFG) approach (FIGS. 11B and 11C) integrating all the previously published human genetic evidence, postmortem brain gene expression evidence, and peripheral fluids evidence for suicide in the field available at the time of this analyses (i.e., September 2015). This is a way of identifying and prioritizing disease relevant genomic biomarkers, extracting generalizable signal out of potential cohort-specific noise and genetic heterogeneity. The manually curated databases of the psychiatric genomic and proteomic literature to date were used in CFG analyses. The CFG approach is thus a *de facto* field-wide collaboration.

Validation of biomarkers for behavior in suicide completers

[0143] For validation in suicide completers, 1471 genes were used that had a CFG score of 4 and above, from AP and DE, reflecting either maximum internal score from discovery or additional external literature cross-validating evidence. Out of these, 882 did not show any stepwise change in suicide completers (NC- non-concordant). As such, they may be involved primarily in ideation and not in behavior. The remaining 589 genes (40.0%) had levels of expression that were changed stepwise from no suicidal ideation to high suicidal ideation to suicide completion. 396 of these genes (26.9%) were nominally significant, and 49 genes (50 probesets- two for JUN) (3.33%) survived Bonferroni correction for multiple comparisons (FIG. 11C). These genes are likely involved in suicidal ideation *and* suicidal behavior. (A person can have suicidal ideation without suicidal behavior, but cannot have suicidal behavior without suicidal ideation).

Selection of biomarkers for testing of predictive ability

[0144] For testing, Bonferroni validated biomarkers (49 genes, 50 probesets) were focused on. A secondary analysis of the top scoring biomarkers from both discovery and prioritization (65 genes) was conducted so as to avoid potential false negatives in the validation step due to possible postmortem artefacts or extreme stringency of statistical cutoff. The top CFG scoring genes after the Bonferroni validation step were BCL2 and GSK3B. The top CFG scoring genes from the discovery and prioritization steps were FAM214A, CLTA, HSPD1, and

ZMYND8. Notably, all have co-directional gene expression changes evidence in brains of suicide completers in studies form other groups.

Biological understanding

[0145] Unbiased biological pathway analyses and hypothesis driven mechanistic queries, overall disease involvement and specific neuropsychiatric disorders queries, and overall drug modulation along with targeted queries for omega-3, lithium and clozapine were studied (FIGS. 15 and 17). Administration of omega-3s in particular may be a mass- deployable therapeutic and preventive strategy.

[0146] The sets of biomarkers identified have biological roles in inflammation, neurotrophins, inositol signaling, stress response, and perhaps overall the switch between cell survival and proliferation vs. apoptosis (FIG. 15).

[0147] The involvement of these biomarkers for suicidality in other psychiatric disorders were also analyzed. FAM214A, MOB3B, ZNF548, and ARHGAP35 were relatively specific for suicide, based on the evidence to date in the field, and were also identified co-directionally in the previous male work (Example 1). BCL2, GSK3B, HSPD1, and PER1 were less specific for suicide, having equally high evidence for involvement in suicide and in other psychiatric disorders. BCL2 was also identified co-directionally in Example 1.

[0148] HSPD1, found to be a top biomarker in this Example, increased in expression in suicidality, and was also increased in expression in the blood following anti-depressant treatment. Thus, this may be a useful biomarker for treatment-emergent suicidal ideation (TESI).

[0149] Further, a number of the genes changed in expression in opposite direction in suicide in this Example vs. high mood in Example 1 - SSBP2, ZNF596, suggesting that suicidal participants are in a low mood state. Also, some of the top suicide biomarkers are changed in expression in the same direction as in high psychosis participants in a previous psychosis biomarker study – HERC4, PIP5K1B, SLC35B3, SNX27, KIR2DL4, NUDT10, suggesting that suicidal participants may be in a psychosis-like state. Taken together, the data indicates that suicidality could be viewed as a psychotic dysphoric state. This molecularly informed view is consistent with the emerging clinical evidence in the field.

[0150] A number of top biomarkers identified have biological roles that are related to the core circadian clock (such as PER1), or modulate the circadian clock (such as CSNK1A1), or show at least some circadian pattern (such as HTRA1). To be able to ascertain all the genes in the dataset that were circadian and do estimates for enrichment, a database from literature was compiled of all the known genes that fall into these three categories, numbering a total of 1468 genes. Using an estimate of about 21,000 genes in the human genome, that gives about 7% of genes having some circadian pattern. Out of the 49 Bonferroni validated biomarker genes, 7 had circadian evidence (14.3%), suggesting a 2-fold enrichment for circadian genes.

[0151] Additionally, biological pathway analyses were conducted on the genes that, after discovery and prioritization, were stepwise changed in suicide completers (n=882) and may be involved in ideation and behavior vs. those that were not stepwise changed (n=589), and that may only be involved in ideation. The genes involved in ideation map to pathways related to PI3K signaling. The genes involved in behavior map to pathways related to glucocorticoid receptor signaling. This is consistent with ideation being related to neurotrophic factors, and behavior being related to stress.

Clinical information

[0152] A 22-item scale and app were used for suicide risk, Convergent Functional Information for Suicidality (CFI-S), which scores in a simple binary fashion and integrates information about known life events, mental health, physical health, stress, addictions, and cultural factors that can influence suicide risk. Determining which items of the CFI-S scale were the most significantly different between no and high suicidal ideation live participants was analyzed (FIG. 12A). Seven items were identified that were significantly different: lack of positive relationships/social isolation (p=0.004), substance abuse (p=0.0071), history of impulsive behaviors (p=0.015), lack of religious beliefs (p=0.018), past history of suicidal acts/gestures (p=0.025), rejection (p=0.029), and history of command auditory hallucinations (p=0.045) (FIG. 12B). It is noted that lack of positive relationships/social isolation was the second top item in males as well. Social isolation increases vulnerability to stress, which is independently consistent with the biological marker results.

Testing for predictive ability

[0153] The best single increased (risk) biomarker predictor for suicidal ideation state was EPB41L5 (ROC AUC 0.68, p-value 0.06; Pearson Correlation 0.22, p-value 0.03), an increased in expression, Bonferroni validated biomarker (FIG. 16). This biomarker was also identified co-directionally in Example 1, and has no evidence for involvement in other psychiatric disorders. The best single decreased (protective) biomarker predictor for suicidal ideation is PIK3C3 (ROC AUC 0.65, p-value 0.1; Pearson Correlation -0.21, p-value 0.037), a decreased in expression, Bonferroni validated biomarker (FIG. 16). PIK3C3 is also decreased in expression in postmortem brains in depression.

[0154] The best single increased (risk) biomarker predictor for future hospitalizations for suicidality was HTRA1 (ROC AUC 0.84, p-value 0.01; Cox Regression Hazard Ratio 4.55, p-value 0.01), an increased in expression, Bonferroni validated biomarker (FIG. 16). HTRA1 is also increased in expression in the blood of schizophrenics. The best single decreased (protective) biomarker predictor for future hospitalizations for suicidality was CSNK1A1 (ROC AUC 0.96, p-value 0.0007; Cox Regression Hazard Ratio 620.5, p-value 0.02), a top discovery and prioritization, non-Bonferroni validated biomarker (FIG. 16). This biomarker was also identified co-directionally in Example 1. CSNK1A1 (casein kinase 1, alpha 1) is a circadian clock gene, part of the input into the core clock. It decreased in expression in suicidality, and decreased in postmortem brains of alcoholics. It has further been found to be increased in expression by mood stabilizers and by omega-3 fatty acids. PIK3C3 was also found to be a good predictor for future hospitalizations for suicidality (ROC AUC 0.9, p-value 0.011) (FIG. 16).

[0155] BCL2, the top CFG scoring biomarker from validation, had good accuracy at predicting future hospitalizations for suicidality (ROC AUC 0.89, p-value 0.007; Cox Regression Hazard Ratio 3.08, p-value 0.01) (FIG. 16). In the panel of 50 validated biomarkers, BioM-50, had even better accuracy at predicting future hospitalizations for suicidality (ROC AUC 0.94, p-value 0.002; Cox Regression Hazard Ratio 89.46, p-value 0.02) (FIG. 16). Overall, in women, blood biomarkers seemed to perform better for predicting future hospitalizations for suicidality (trait) than for predicting suicidal ideation (state). This is different than the trend seen in Example 1, where blood biomarkers were somewhat better predictors of state than of trait.

[0156] CFI-S had very good accuracy (ROC AUC 0.84, p-value 0.002; Pearson Correlation 0.39, p-value 0.001) at predicting suicidal ideation in psychiatric participants across

diagnostic groups. The other app, SASS, also had very good accuracy (ROC AUC 0.81, p-value 0.003; Pearson Correlation 0.38, p-value 0.0005) at predicting suicidal ideation in women psychiatric participants. The combination of the apps was synergistic (ROC AUC 0.87, p-value 0.0009; Pearson Correlation 0.48, p-value 0.0001). Thus, even without the benefit of potentially more costly and labor intensive blood biomarker testing, clinically useful predictions could be made with the apps.

[0157] The apriori primary endpoint was a combined universal predictor for suicide (UP-Suicide), composed of CFI-S and SASS, along with the Bonferroni validated biomarkers (n=50) resulting from the sequential discovery for ideation, prioritization with CFG, and validation for behavior in suicide completers steps. UP-Suicide was a good predictor of suicidal ideation (ROC AUC 0.82, p-value 0.003; Pearson Correlation 0.43, p-value 0.0003) (FIGS. 13A, 13B and 16). UP-Suicide also had good predictive ability for future psychiatric hospitalizations for suicidality (ROC AUC 0.78, p-value 0.032; Cox Regression Hazard Ratio 9.61, p-value 0.01).

Discussion

[0158] The present Example identified markers involved in suicidal ideation *and* suicidal behavior, including suicide completion, in females. Markers involved in behavior may be on a continuum with some of the markers involved in ideation, varying in the degree of expression changes from less severe (ideation) to more severe (behavior). One cannot have suicidal behavior without suicidal ideation, but it may be possible to have suicidal ideation without suicidal behavior.

[0159] 50 biomarkers were found to have survived Bonferroni correction (49 genes; one gene, JUN, had two different probesets that validated). Additionally, 65 other biomarkers that were non Bonferroni, but had maximum internal score of 4 in discovery and a CFG score of 6 and above, meaning that in addition to strong evidence in this Example, they also had prior independent evidence of involvement in suicide from other studies, were also studied. These additional biomarkers are likely involved in suicide, but did not make the Bonferroni validation cutoff due to its stringency or potential technical/postmortem artefact reasons (FIGS. 26 and 30).

[0160] Data validating the CFI-S in women in the combined discovery and test cohort of live psychiatric participants was analyzed (FIGS. 12A and 12B) and compared with similar analyses in men (Example 1). The chronic stress of lack of positive relationships/social isolation

was identified as the top differential item in women, which is consistent with biological data from the biomarker side of this Example.

[0161] In assessing anxiety and mood, it was shown that anxiety measures cluster with suicidal ideation and CFI-S, and mood measures are in the opposite cluster, suggesting that the participants have high suicidal ideation when they have high anxiety and low mood (FIG. 10C).

[0162] The rationale for identifying blood biomarkers as opposed to brain biomarkers is a pragmatic one- the brain cannot be readily accessed in live individuals. Other peripheral fluids, such as CSF, require more invasive and painful procedures. Nevertheless, it is likely that many of the peripheral blood transcriptomic changes are not necessarily mirroring what is happening in the brain, and vice-versa. The keys to finding peripheral biomarkers are, first, to have a powerful discovery approach, such as the within-participant design, that closely tracks the phenotype you are trying to measure and reduces noise. Second, cross-validating and prioritizing the results with other lines of evidence, such as brain gene expression and genetic data, are important in order to establish relevance and generalizability of findings. Third, it is important to validate for behavior in an independent cohort with a robust and relevant phenotype, in this case suicide completers. Fourth, testing for predictive ability in independent/prospective cohorts is a must.

[0163] Biomarkers that survive such a rigorous step-wise discovery, prioritization, validation and testing process are likely directly relevant to the disorder studied. As such, whether they are involved in other psychiatric disorders or are relatively specific for suicide, and whether they are the modulated by existing drugs in general, and drugs known to treat suicidality in particular were evaluated.

[0164] A series of biomarkers have been identified that seem to be changed in opposite direction in suicide vs. in treatments with omega-3 fatty acids, lithium, clozapine. These biomarkers could potentially be used to stratify patients to different treatment approaches, and monitor their response.

[0165] BCL2, JUN, GHA1, ENTPD1, ITIH5, MBNL1, and SSBP2 were changed in expression by two of these three treatments, suggesting they may be core to the anti-suicidal mechanism of these drugs. BCL2, CAT, and JUN may be useful blood pharmacogenomic markers of response to lithium. CD84, MBNL1, and RAB22A may be useful blood pharmacogenomic markers of response to clozapine. NDRG1, FOXP1, AFF3, ATXN1,

CSNK1A1, ENTPD1, ITIH5, PRDX3, and SSBP2 may be useful blood pharmacogenomic markers of response to omega-3 fatty acids. Three existing drugs used for other indications have been identified as targeting the top suicide biomarkers identified, and could potentially be re-purposed for testing in treatment of acute suicidality: anakinra (inhibiting ILR1), enzastaurin (inhibiting AKT3), and tesevatinib (inhibiting EPHB4). Additionally, Connectivity Map (ref) analyses identified compounds that induced gene expression signatures that were the opposite of those present in suicide, and might generate leads and/or be tested for use to treat/prevent suicidality: betulin (an anti-cancer compound from the bark of birch trees), zalcitabine (an anti-HIV drug), and atractyloside (a toxic glycoside). Other common drugs identified by the Connectivity Map analyses were nafcillin, lansoprazole, mifepristone, LY294002, minoxidil, acetysalicilic acid, estradiol, buspirone, dicloxacillin, corticosterone, metformin, diphenhydramine, haloperidol, and fluoxetine.

[0166] Of note, a number of biomarkers from the current Example in women reproduced and were co-directional with previous findings in Example 1 (BCL2, ALDH3A2, FAM214A, CLTA, ZMYND8, JUN), whereas others had changes in opposite directions (GSK3B, HSPD1, AK2, CAT), underlying the issue of biological context and differences in suicidality between the two genders.

[0167] Disclosed herein are instruments (biomarkers and applications) for predicting suicidality, that do not require asking the person assessed if they have suicidal thoughts, as individuals who are truly suicidal often do not share that information with people close to them or with clinicians. The widespread use of such risk prediction tests as part of routine or targeted healthcare assessments will lead to early disease interception followed by preventive lifestyle modifications or treatment. Biomarkers identified herein for suicidal ideation are enriched for genes involved in neuronal connectivity and schizophrenia. Biomarkers identified herein also validated for suicide behavior are enriched for genes involved in neuronal activity and mood.

[0168] Worldwide, one person dies every 40 seconds through suicide, a potentially preventable tragedy. A limiting step in the ability to intervene is the lack of objective, reliable predictors. A powerful within-participant discovery approach is disclosed herein in which genes that change in expression between no suicidal ideation and high suicidal ideation states were identified. The methods disclosed herein do not require asking the person assessed if they have thoughts of suicide, as individuals who are truly suicidal often do not share that information with clinicians. The widespread use of such risk prediction tests as part of routine or targeted

healthcare assessments will lead to early disease interception followed by preventive lifestyle modifications and proactive treatment.

[0169] In view of the above, it will be seen that the several advantages of the disclosure are achieved and other advantageous results attained. As various changes could be made in the above methods without departing from the scope of the disclosure, it is intended that all matter contained in the above description and shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

[0170] When introducing elements of the present disclosure or the various versions, embodiment(s) or aspects thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

What is claimed is:

1. A method for predicting suicidality in a subject, the method comprising:

obtaining an expression level of a blood biomarker in a sample obtained from the subject,

obtaining a reference expression level of the blood biomarker; and

identifying a difference between the expression level of the blood biomarker in the sample obtained from the subject and the reference expression level of the 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 indicates a risk for suicide.

2. The method of claim 1, wherein the blood biomarker is selected from the group listed in Table 3 and combinations thereof.

3. The method of claim 1, wherein the expression level of the blood biomarker in the sample obtained from the subject is increased as compared to the reference expression level of the biomarker.

4. The method of claim 3, wherein the blood biomarker is selected from the group listed in Table 1 and combinations thereof.

5. The method of claim 3, wherein the subject is a male, and the blood biomarker is selected from the group consisting of solute carrier family 4 (sodium bicarbonate cotransporter), member 4 (SLC4A4), cell adhesion molecule 1 CADM1, dystrobrevin, alpha (DTNA), spermidine/spermine N1-acetyltransferase 1 (SAT1), interleukin 6 (interferon, beta 2) (IL6), RAS-like family 11 member B (RASL11B), Glutamate Receptor, Ionotropic, Kainate 2 (GRIK2), histone cluster 1, H2bo (HIST1H2BO), GRB2-Associated Binding Protein 1 (GAB1), and combinations thereof.

6. The method of claim 3, wherein the subject is a female, and the blood biomarker is selected from the group consisting of erythrocyte membrane protein band 4.1 like 5 (EPB41L5), HtrA serine peptidase 1 (HTRA1), deleted in primary ciliary dyskinesia homolog (DPCD), general transcription factor IIIC, polypeptide 3, 102kDa (GTF3C3), period circadian clock 1 (PER1), pyridoxal-dependent decarboxylase domain containing 1 (PDXDC1), kelch-like family member 28 (KLHL28), ubiquitin interaction motif containing 1 (UIMC1), sorting nexin

family member 27 (SNX27), Glutamate Receptor, Ionotropic, Kainate 2 (GRIK2) and combinations thereof.

7. The method of claim 1, wherein the expression level of the blood biomarker in the sample obtained from the subject is decreased as compared to the reference expression level of the biomarker.

8. The method of claim 7, wherein the blood biomarker is selected from the group listed in Table 2 and combinations thereof.

9. The method of claim 7, wherein the subject is a male and the blood biomarker is selected from the group consisting of spindle and kinetochore associated complex subunit 2 (SKA2), CAP-GLY domain containing linker protein family, member 4 (CLIP4), kinesin family member 2C (KIF2C), kelch domain containing 3 (KLHDC3), chemokine (C-C motif) ligand 28 (CCL28), v-ets avian erythroblastosis virus E26 oncogene homolog (ERG), fatty acid desaturase 1 (FADS1), and combinations thereof.

10. The method of claim 7, wherein the subject is a female and the blood biomarker is selected from the group consisting of phosphatidylinositol 3-kinase, catalytic subunit type 3 (PIK3C3), aldehyde dehydrogenase 3 family, member A2 (ALDH3A2), ARP3 actin-related protein 3 homolog (yeast) (ACTR3), B-cell CLL (BCL2), MOB kinase activator 3B (MOB3B), casein kinase 1, alpha 1 (CSNK1A1), La ribonucleoprotein domain family, member 4 (LARP4), zinc finger protein 548 (ZNF548), prolylcarboxypeptidase (angiotensinase C) (PRCP), solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B3 (SLC35B3), and combinations thereof.

11. The method of claim 1, wherein the subject has a psychiatric disorder selected from the group consisting of bipolar disorder, major depressive disorder, schizophrenia, schizoaffective disorder, post-traumatic stress disorder and combinations thereof.

12. The method of claim 1 further comprising assessing mood, anxiety, and combinations thereof in the subject using a computer-implemented method for assessing mood, anxiety, and combinations thereof, the method implemented using a first computer device coupled to a memory device, the method comprising:

receiving patient psychiatric information including mood information, anxiety information, other psychiatric symptom information, and combinations thereof, into the first

computer device, wherein each of the patient psychiatric information is represented by a quantitative rating;

storing, by the first computer device, the patient psychiatric information in the memory device;

identifying a processing algorithm associated with the patient psychiatric information;

computing, by the first computer device, a score that can be used to predict suicidality, wherein the score is computed based upon each quantitative rating and the processing algorithm;

identifying, from a diagnostic database, a plurality of reference scores associated with a plurality of patients having reference psychiatric symptom information corresponding to the patient psychiatric symptom information;

determining a patient rating by comparing the score to the plurality of reference scores;

presenting, by the first computer device, in visual form, the patient rating and the patient psychiatric symptom information to a second computer device;

receiving a request from the second computer device for access to the mood information, anxiety information, and combinations thereof; and

transmitting, by the first computer device, the patient rating and the patient psychiatric symptom information to the other computer device to assess mood, anxiety, and combinations thereof in the subject.

13. The method of claim 1 further comprising assessing socio-demographic/psychological suicidal risk factors in the subject using a computer-implemented method for assessing socio-demographic/psychological suicidal risk factors in the subject, the method implemented using a first computer device coupled to a memory device, the method comprising:

receiving socio-demographic/psychological suicidal risk factor information into the first computer device wherein the socio-demographic/psychological suicidal risk factor information is represented by a quantitative rating;

storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device;

identifying a processing algorithm associated with the socio-demographic/psychological suicidal risk factor information;

computing, by the first computer device, a score that can be used to predict suicidality, wherein the score is computed based upon the quantitative rating and the processing algorithm;

identifying, from a diagnostic database, a plurality of reference scores associated with a plurality of patients having reference socio-demographic/psychological suicidal risk factor information corresponding to the socio-demographic/psychological suicidal risk factor information;

determining a patient rating by comparing the score to the plurality of reference scores;

presenting, by the first computer device, in visual form the patient rating and the socio-demographic/psychological suicidal risk factor information to a second computer device;

receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and

transmitting, by the first computer device, the patient rating and the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject.

14. A method for mitigating suicidality in a subject in need thereof, the method comprising:

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 between 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 suicidality in the subject.

15. The method of claim 14, wherein the treatment is selected from lifestyle modification and administering a therapy.

16. The method of claim 15, wherein the therapy is selected from a nutritional, a drug and psychotherapy.

17. The method of claim 16, wherein the nutritional is selected from omega-3 fatty acid.

18. The method of claim 17, wherein the omega-3 fatty acid is docosahexaenoic acid.

19. The method of claim 16, wherein the drug is selected from the group consisting of ketamine, lithium, clozapine, selegeline, tocilizumab, siltuximab, enkephalin, methionine,

gevokizumab, gallium nitrate, vemurafenib, dabrafenib, oblimersen, rasagiline,(-)-gossypol, navitoclax, gemcitabine/paclitaxel, bortezomib/paclitaxel, ABT-199, paclitaxel/trastuzumab, paclitaxel/pertuzumab/trastuzumab, lapatinib/paclitaxel, doxorubicin/paclitaxel, epirubicin/paclitaxel, paclitaxel/topotecan, paclitaxel, canakinumab, tesevatinib, enzastaurin, fomepizole, miglitol, anakinra and combinations thereof.

20. The method of claim 16, wherein the drug is selected from the group consisting of fluoxetine, betulin, dl-alpha tocopherol, hesperidin, calcium folinate, harpagoside, trimipramine, rilmenidine, tenoxicam, chlorpromazine, harman, homatropine, ramifenazone, diphenhydramine, prochlorperazine, pirenperone, asiaticoside, adiphenine, metformin, chlorogenic acid, verapamil, metaraminol, yohimbine, trimethadione and combinations thereof.

21. The method of claim 16, wherein the subject is male, and the drug is selected from the group consisting of thiamine, homatropine, vitexin, ergocalciferol, tropicamide, (-)-atenolol, haloperidol, spaglumic acid and combinations thereof.

22. The method of claim 16, wherein the subject is female, and the drug is selected from the group consisting of mifepristone, lansoprazole, nafcillin, botulin and combinations thereof.

23. The method of claim 15, wherein the lifestyle modification is selected based on socio-demographic/psychological suicidal risk factors identified by a method comprising assessing socio-demographic/psychological suicidal risk factors in the subject using a computer-implemented method for assessing socio-demographic/psychological suicidal risk factor information in the subject, the method implemented using a first computer device coupled to a memory device, the method comprising:

receiving socio-demographic/psychological suicidal risk factor information into the first computer device wherein the socio-demographic/psychological suicidal risk factor information is represented by a quantitative rating;

storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device;

identifying a processing algorithm associated with the socio-demographic/psychological suicidal risk factor information;

computing, by the first computer device, a score that can be used to predict suicidality, wherein the score is computed based upon the quantitative rating and the processing algorithm;

identifying, from a diagnostic database, a plurality of reference scores associated with a plurality of patients having reference socio-demographic/psychological suicidal risk factor information corresponding to the socio-demographic/psychological suicidal risk factor information;

determining a patient rating by comparing the score to the plurality of reference scores;

presenting, by the first computer device, in visual form the patient rating and the socio-demographic/psychological suicidal risk factor information to a second computer device;

receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and

transmitting, by the first computer device, the patient rating and the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject.

24. The method of claim 14, wherein the subject has a psychiatric disorder selected from the group consisting of bipolar disorder, major depressive disorder, schizophrenia, schizoaffective disorder, post-traumatic stress disorder and combinations thereof.

25. A method for predicting suicidality in a subject, the method comprising:

identifying a difference in the expression level of a blood biomarker in a sample obtained from a subject and a reference expression level of the blood biomarker by obtaining the expression level of the blood biomarker in the sample obtained from the subject; obtaining a reference expression level of the blood biomarker; analyzing the blood biomarker in the sample obtained from the subject and the reference expression level of the blood biomarker to detect the difference between the blood biomarker in the sample and the reference expression level of the blood biomarker;

assessing mood information, anxiety information, and combinations thereof, using a first computer device coupled to a memory device, wherein the first computer device receives mood information, anxiety information, and combinations thereof into the computer device; storing, by the computer device, the mood information, anxiety information, and combinations thereof in the memory device; computing, by the computer device, device, of the mood information, anxiety information, and combinations thereof, a score that can be used to predict suicidality; presenting, by the computer device, the score in visual form the mood information, anxiety information, and combinations thereof to a second computer device; receiving a request from the second computer device for access to score of the mood information, anxiety information, and combinations

thereof; and transmitting, by the first computer device, the score of the mood information, anxiety information, and combinations thereof to the other computer device to assess mood, anxiety, and combinations thereof in the subject;

assessing socio-demographic/psychological suicidal risk factor information in the subject using the first computer device coupled to a memory device, wherein the first computer device receives socio-demographic/psychological suicidal risk factor information into the first computer device; storing, by the first computer device, the socio-demographic/psychological suicidal risk factor information in the memory device; computing, by the first computer device, of the socio-demographic/psychological suicidal risk factor information, a score that can be used to predict suicidality; presenting, by the first computer device, in visual form the socio-demographic/psychological suicidal risk factor information to a second computer device; receiving a request from the second computer device for access to socio-demographic/psychological suicidal risk factor information; and transmitting, by the first computer device, the socio-demographic/psychological suicidal risk factor information to the second computer device to assess the socio-demographic/psychological suicidal risk factors in the subject; and

predicting suicidality in the subject by combining the score from difference between the expression level of a blood biomarker or combination of biomarkers in the subject and the reference expression level of the blood biomarker or combination of biomarkers, wherein the score is determined at least partially based upon assessment of mood information, anxiety information, and combinations thereof, and wherein the score is determined at least partially based upon the assessment of socio-demographic/psychological suicidal risk factor information.

Suicidal Ideation (SI)
from Hamilton Rating Scale for Depression (HAMD).
No SI-score of 0; High SI-score of 2 or above

Suicide
0 = Absent
1= Feels life is not worth living
2 = Wishes he were dead or any thoughts of possible death to self
3 = Suicidal ideas or gesture
4 = Attempts at suicide (any serious attempt rates 4)

FIG. 1A

Discovery Cohort

37 psychiatric subjects who have at least one switch between a **No SI state** visit and a High SI state visit.

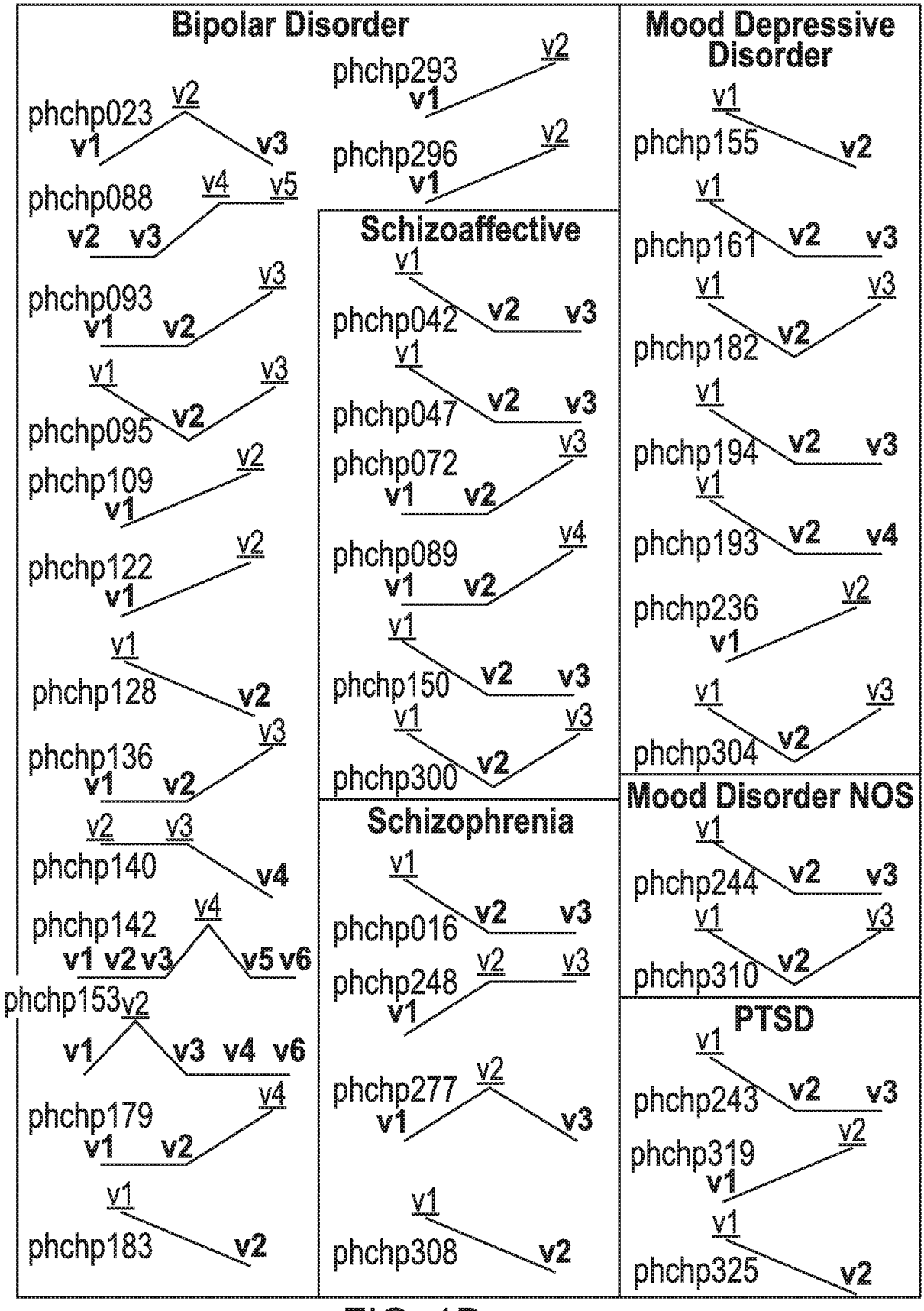


FIG. 1B

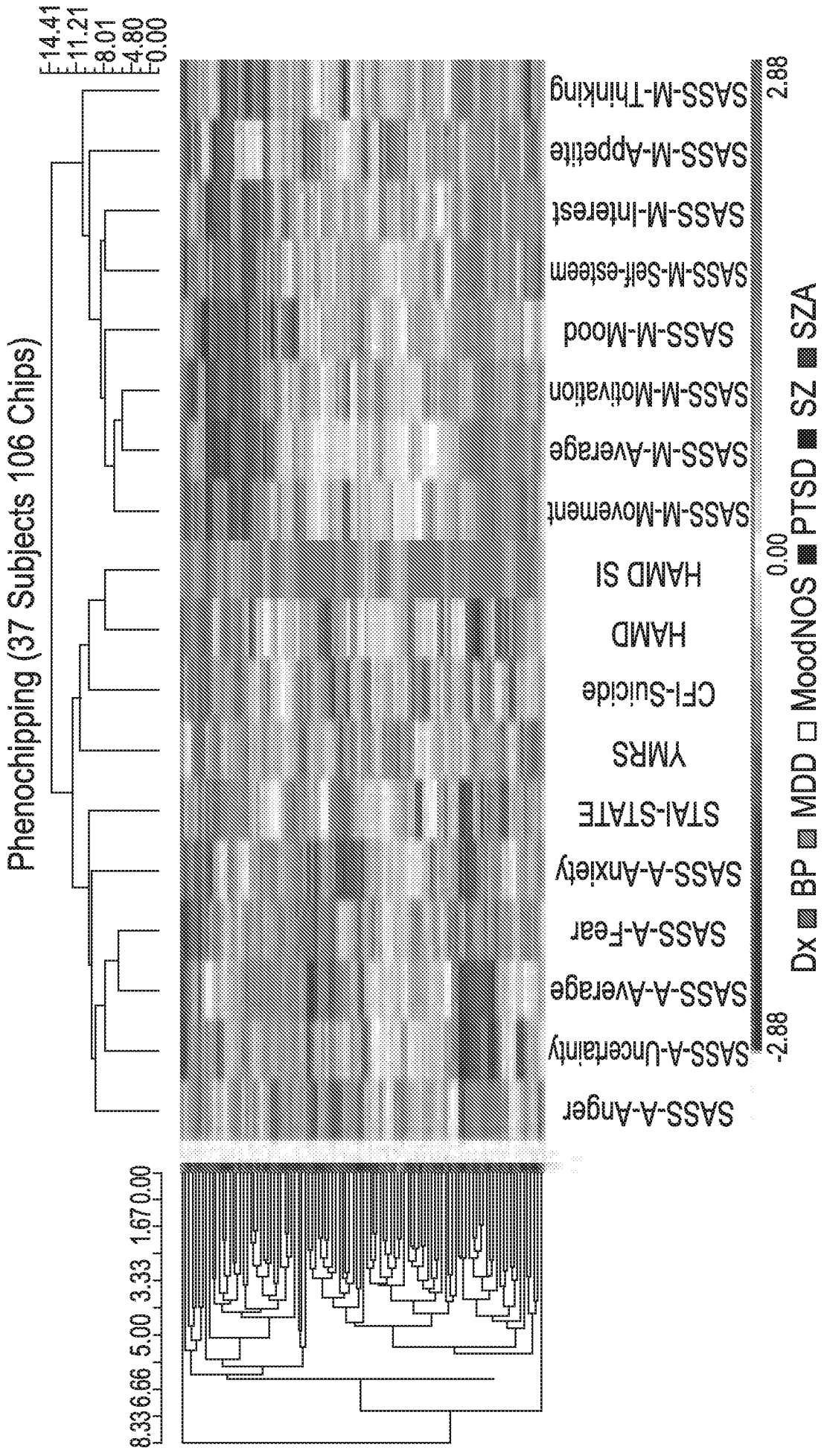

Phenochipping (37 Subjects 106 Chips)
14.41
11.21
8.01
4.80
0.00
8.33 6.66 5.00 3.33 1.67 0.00
SASS-A-Anger
SASS-A-Uncertainty
SASS-A-Average
SASS-A-Fear
SASS-A-Anxiety
STAI-STATE
YMRS
CFI-Suicide
HAMD
HAMD SI
SASS-M-Movement
SASS-M-Average
SASS-M-Motivation
SASS-M-Mood
SASS-M-Self-esteem
SASS-M-Interest
SASS-M-Appetite
SASS-M-Thinking
2.88
0.00
-2.88
Dx BP MDD MoodNOS PTSD SZ SZA

FIG. 1C

Discovery

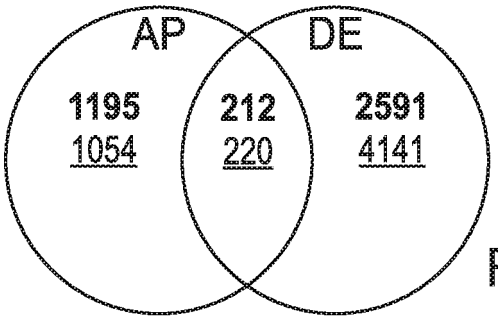


FIG. 2A

Prioritization

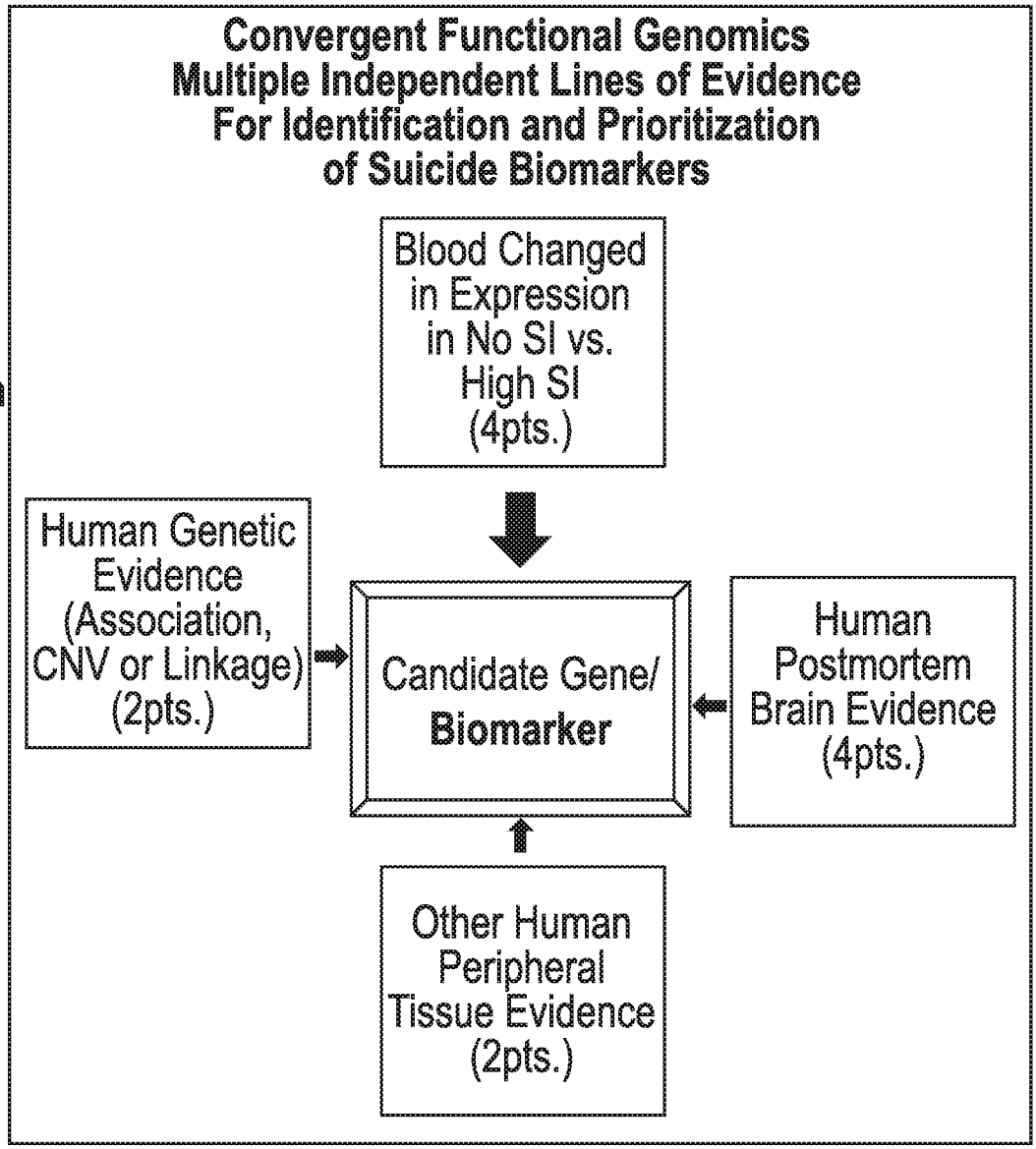


FIG. 2B

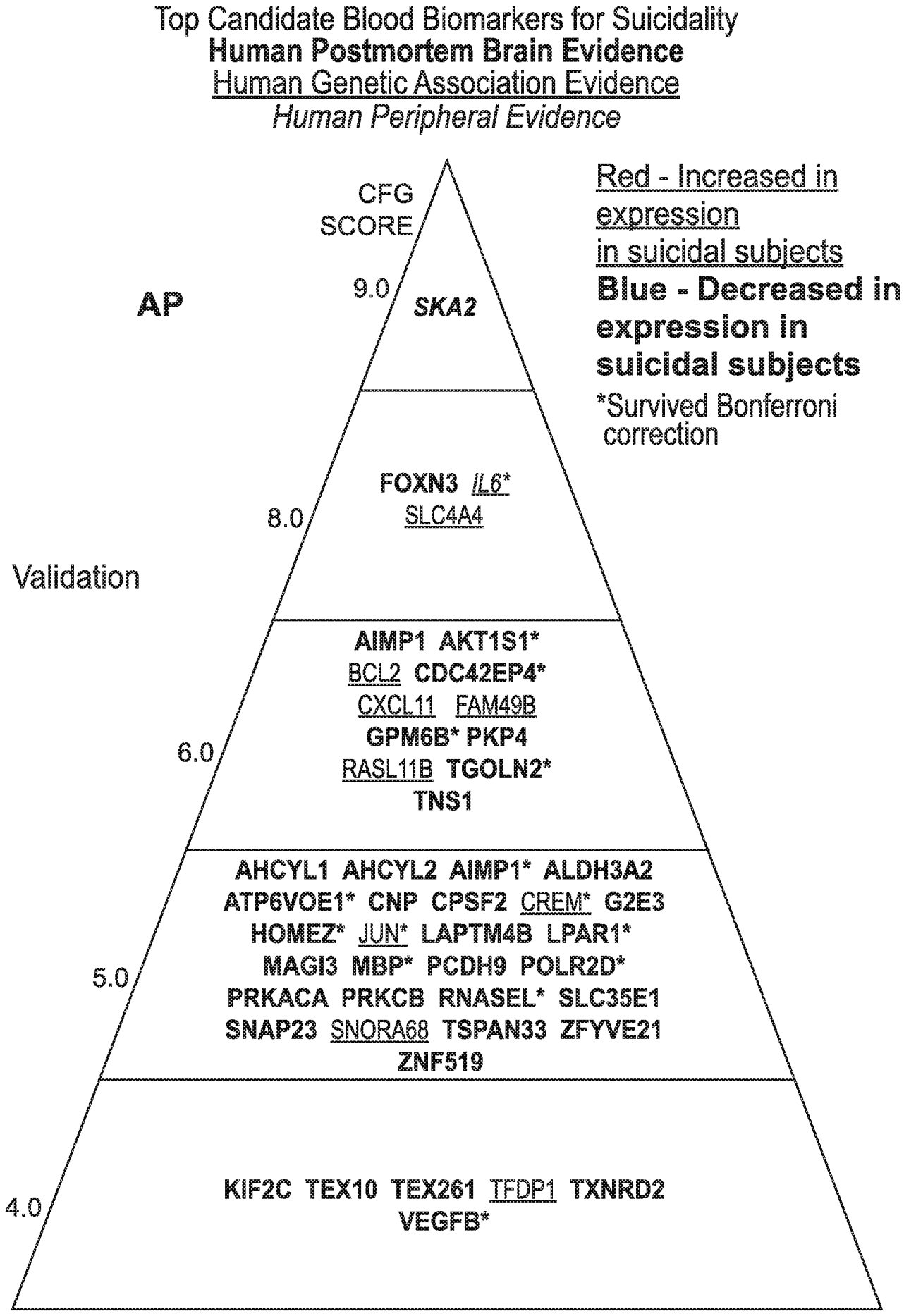

Top Candidate Blood Biomarkers for Suicidality
Human Postmortem Brain Evidence
Human Genetic Association Evidence
Human Peripheral Evidence
CFG SCORE
AP
Validation
9.0
SKA2
8.0
FOXN3 IL6*
SLC4A4
6.0
AIMP1 AKT1S1*
BCL2 CDC42EP4*
CXCL11 FAM49B
GPM6B* PKP4
RASL11B TGOLN2*
TNS1
5.0
AHCYL1 AHCYL2 AIMP1* ALDH3A2
ATP6VOE1* CNP CPSF2 CREM* G2E3
HOMEZ* JUN* LAPTM4B LPAR1*
MAGI3 MBP* PCDH9 POLR2D*
PRKACA PRKCB RNASEL* SLC35E1
SNAP23 SNORA68 TSPAN33 ZFYVE21
ZNF519
4.0
KIF2C TEX10 TEX261 TFDP1 TXNRD2
VEGFB*
Red - Increased in expression in suicidal subjects
Blue - Decreased in expression in suicidal subjects
*Survived Bonferroni correction

FIG. 2C

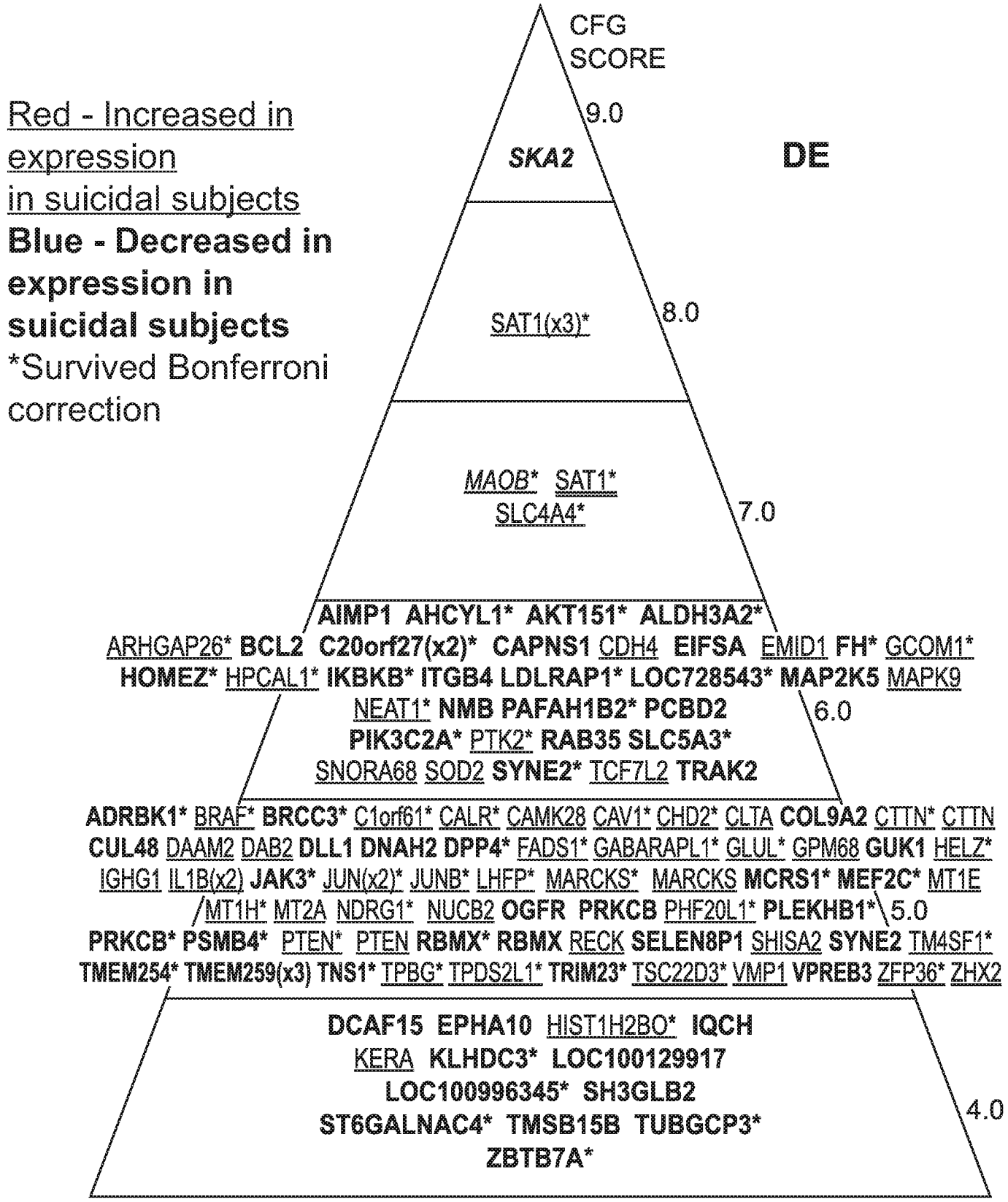
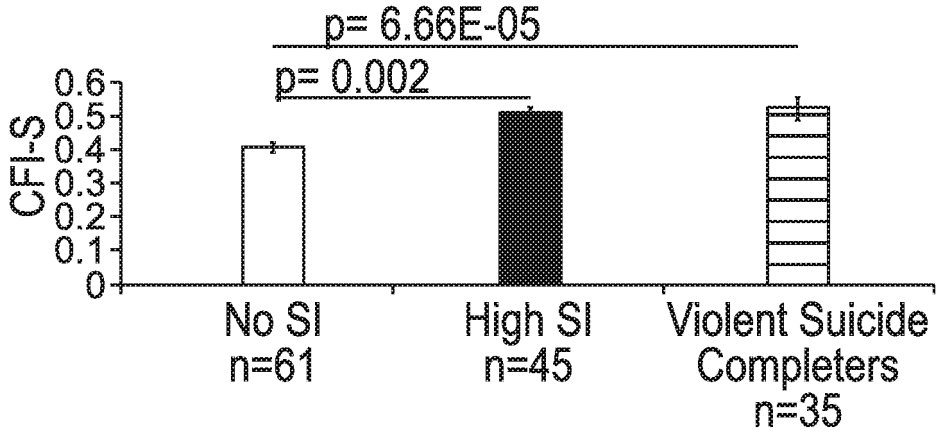
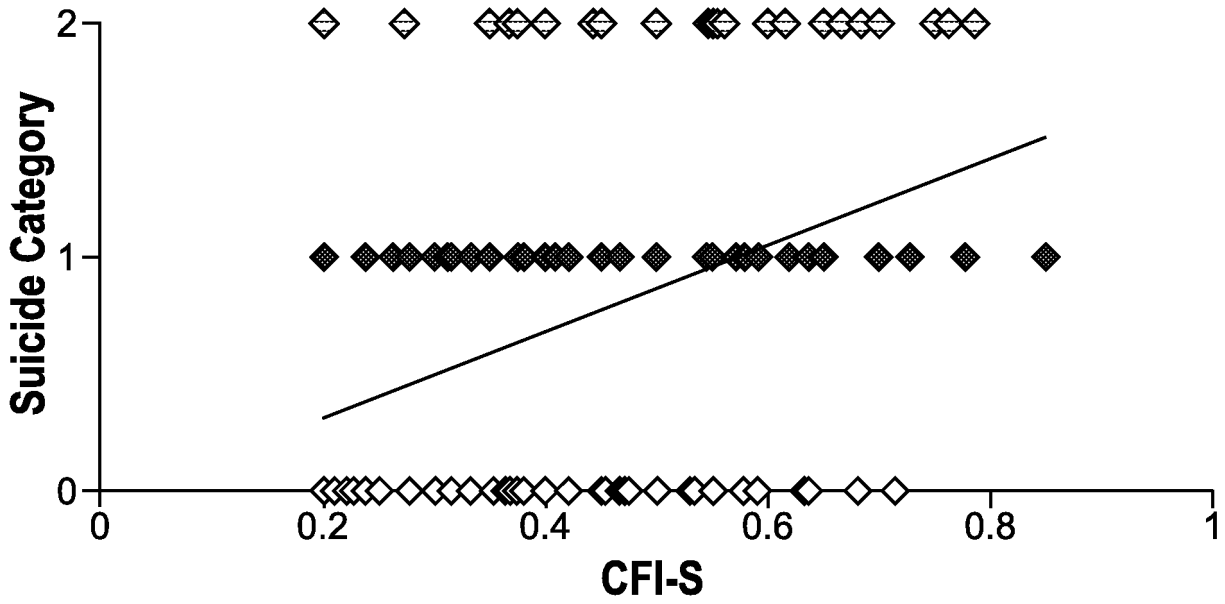

Red - Increased in expression in suicidal subjects
Blue - Decreased in expression in suicidal subjects
*Survived Bonferroni correction
CFG SCORE
DE
9.0
SKA2
8.0
SAT1(x3)*
7.0
MAOB* SAT1* SLC4A4*
6.0
AIMP1 AHCYL1* AKT151* ALDH3A2* ARHGAP26* BCL2 C20orf27(x2)* CAPNS1 CDH4 EIFSA EMID1 FH* GCOM1* HOMEZ* HPCAL1* IKBKB* ITGB4 LDLRAP1* LOC728543* MAP2K5 MAPK9 NEAT1* NMB PAFAH1B2* PCBD2 PIK3C2A* PTK2* RAB35 SLC5A3* SNORA68 SOD2 SYNE2* TCF7L2 TRAK2
5.0
ADRBK1* BRAF* BRCC3* C1orf61* CALR* CAMK28 CAV1* CHD2* CLTA COL9A2 CTTN* CTTN CUL48 DAAM2 DAB2 DLL1 DNAH2 DPP4* FADS1* GABARAPL1* GLUL* GPM68 GUK1 HELZ* IGHG1 IL1B(x2) JAK3* JUN(x2)* JUNB* LHFP* MARCKS* MARCKS MCRS1* MEF2C* MT1E /MT1H* MT2A NDRG1* NUCB2 OGFR PRKCB PHF20L1* PLEKHB1* PRKCB* PSMB4* PTEN* PTEN RBMX* RBMX RECK SELEN8P1 SHISA2 SYNE2 TM4SF1* TMEM254* TMEM259(x3) TNS1* TPBG* TPDS2L1* TRIM23* TSC22D3* VMP1 VPREB3 ZFP36* ZHX2
4.0
DCAF15 EPHA10 HIST1H2BO* IQCH KERA KLHDC3* LOC100129917 LOC100996345* SH3GLB2 ST6GALNAC4* TMSB15B TUBGCP3* ZBTB7A*

FIG. 2C





Predictor	ANOVA	t-test (Completers vs High SI)	Correlation R	Correlation p-value
CFI-S	6.66E-05	0.223	0.344	1.49E-05

FIG. 3A

Validation of items

CFI-S Item	Description	P-Value (One-Way ANOVA) No SI vs High SI vs Completers	Stepwise	T-Test (two tailed)High SI vs Completers
18	Lack of coping skills (cracks under pressure)	3.35E-11	Y	2.42E-05
10	Dissatisfaction with present life	2.77E-06	Y	0.06804
11	Lack of hope for the future	3.28E-05	Y	7.28E-05
12	Current substance abuse	0.000125	Y	0.01273
7	Acute stress: losses, grief	0.000945	Y	0.07253
16	Chronic stress: lack of positive relationships, social isolation	0.0149	Y	0.2897
15	Acute stress: rejection	0.03	Y	0.02242
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	0.0607	Y	0.2097
6	Acute/severe medical illness, pain	0.0892	Y	0.1113
19	Lack of children	0.365	Y	0.2479
22	Gender: Male	No females	No females	No females
4	Personally knowing somebody who committed suicide	No data for completers	No data for completers	No data for completers
1	Psychiatric illness diagnosed and treated	5.06E-15	N	6.02E-06
13	Past history of suicidal acts/gestures	2.40E-05	N	4.46E-05
21	Age: Older >60 or Younger <25	8.89E-05	N	0.000267

FIG. 3B

5	History of abuse: physical, sexual, emotional, neglect	0.0165	N	0.004361
20	History of command hallucinations of self-directed violence	0.0397	N	0.009659
3	Family history of suicide in blood relatives	0.0797	N	0.0242
2	With poor treatment compliance	0.147	N	0.07321
14	Lack of religious beliefs	0.117	N	0.06151
9	History of excessive introversion, conscientiousness	0.303	N	0.2439
8	Chronic stress: perceived uselessness, not feeling needed, burden to extended kin	0.42	N	0.2097

FIG. 3B

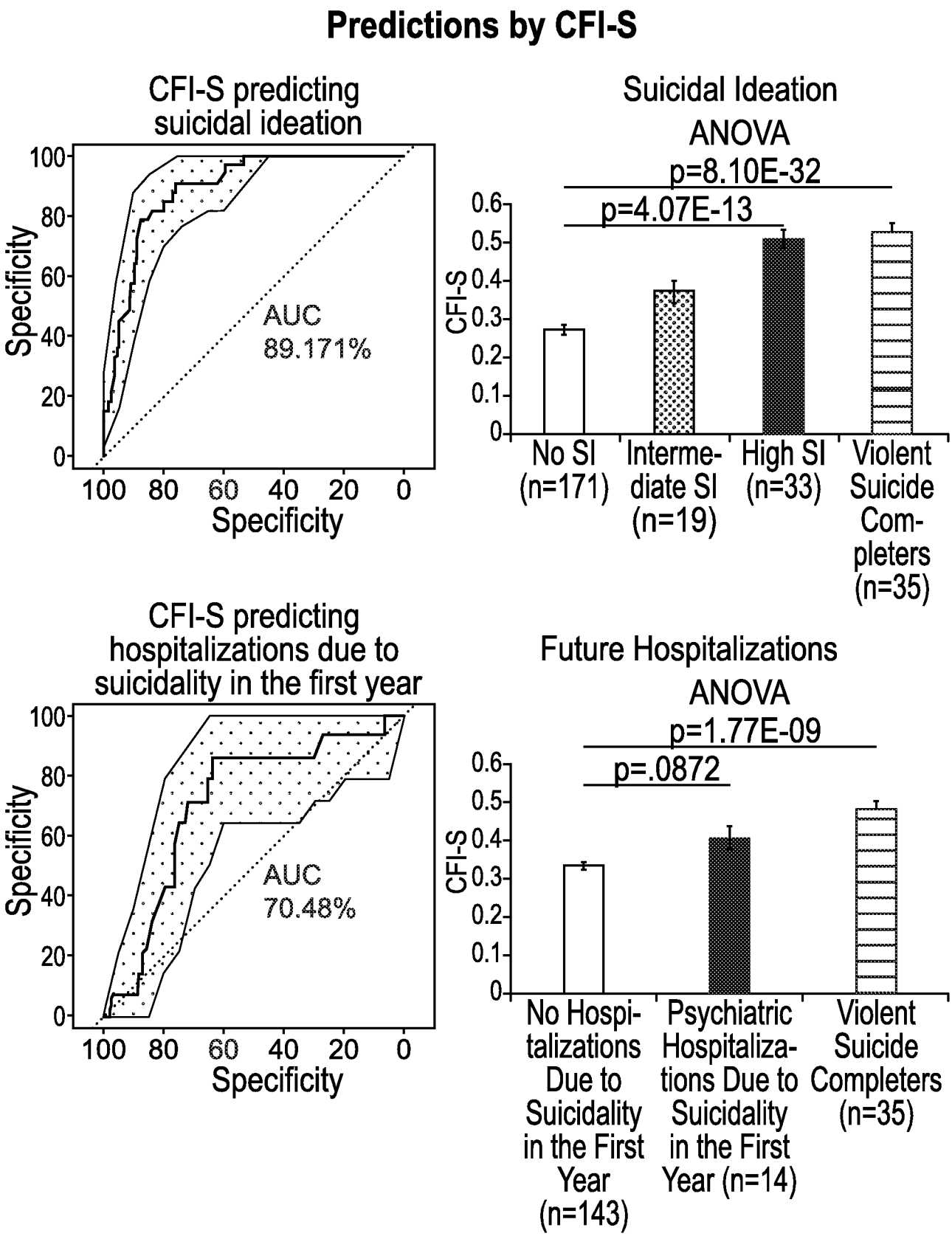

Predictions by CFI-S
CFI-S predicting suicidal ideation
Specificity
Specificity
AUC 89.171%
Suicidal Ideation
ANOVA
p=8.10E-32
p=4.07E-13
CFI-S
No SI (n=171)
Interme-diate SI (n=19)
High SI (n=33)
Violent Suicide Com-pleters (n=35)
CFI-S predicting hospitalizations due to suicidality in the first year
Specificity
Specificity
AUC 70.48%
Future Hospitalizations
ANOVA
p=1.77E-09
p=.0872
CFI-S
No Hospi-talizations Due to Suicidality in the First Year (n=143)
Psychiatric Hospitaliza-tions Due to Suicidality in the First Year (n=14)
Violent Suicide Completers (n=35)

FIG. 3C

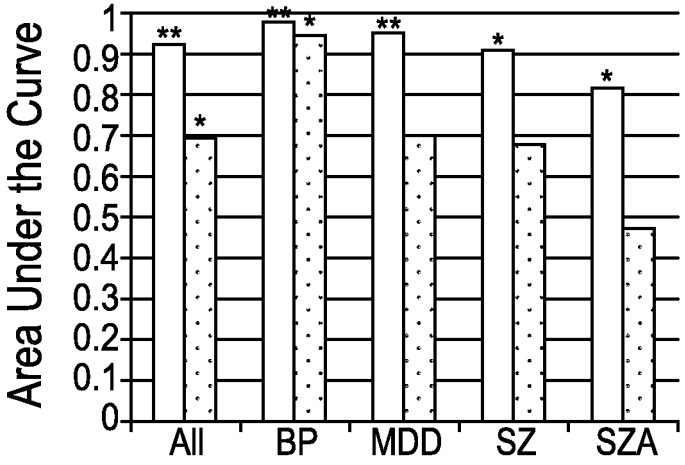
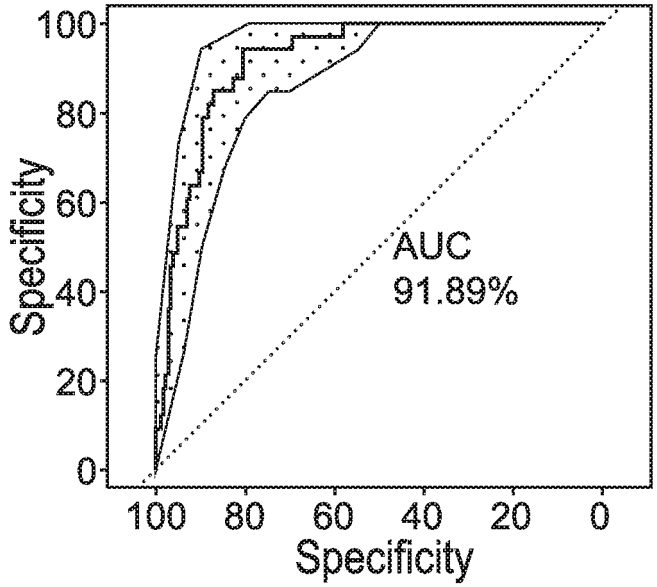


FIG. 4A

	Subjects Total/ High SI	High SI prediction ROC AUC ROC p-value	ANOVA (No SI vs. Intermedi-ate SI vs. High SI)	Correlation R P-value	Subjects Total/ First year hospitalized for suicidality/ All future hospitalized due to suicidality	Predictions First year hospitalized for suicidality ROC AUC ROC p-value	T-test First year hospitalized for suicidality	Correlation R P-value First Year hospitalized for suicidality	Correlation R P-value All future hospitalized due to suicidality
All	108/23	0.919 8.12E-15	6.25E-22	0.60019 3.26E-23	157/18/35	0.695 0.0124	0.0235	0.2093 0.0043	0.1911 0.0083
BP	29/7	0.975 1.19E-06	2.46E-13	0.81626 3.33E-16	50/7/9	0.943 0.002	0.002	0.3692 0.0042	0.2324 0.0522
MDD	25/8	0.949 2.96E-07	NA	0.62052 9.87E-07	23/3/3	*0.700* *0.155*	*0.169*	*0.2118* *0.1660*	*0.1759* *0.2111*
SZ	26/2	0.908 1.46E-03	0.00065	0.48837 5.81E-05	44/5/8	*0.676* *0.173*	*0.287*	*0.1669* *0.1517*	*0.1762* *0.1385*
SZA	28/6	0.814 1.78E-03	0.00271	0.4274 5.68E-04	40/3/15	*0.480* *0.552*	*0.528*	*-0.0082* *0.5209*	*0.1643* *0.1433*

FIG. 4B



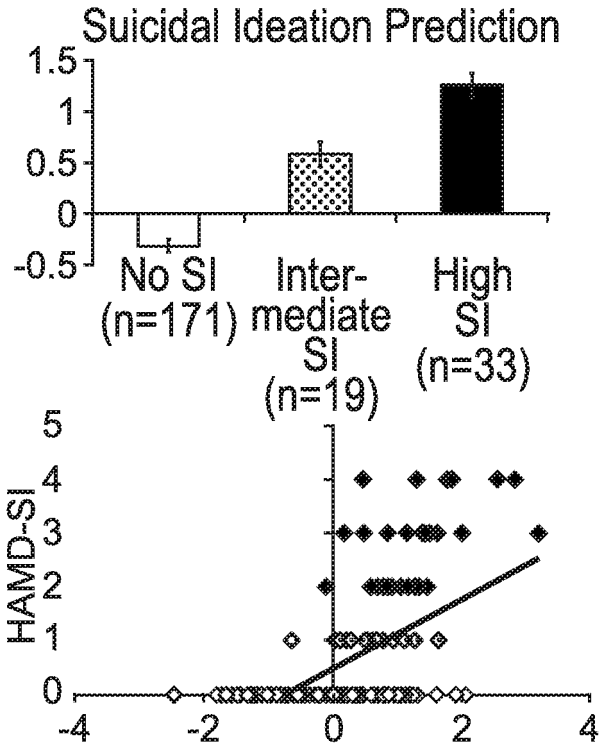
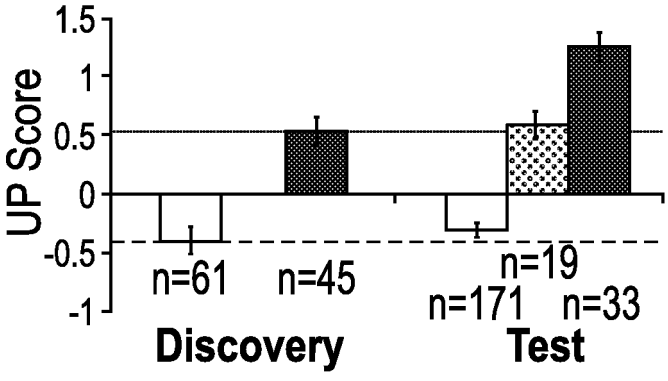


FIG. 5A

Predictor	Dx	Type	ROC AUC	ROC p-value	ANOVA	Correlation R	Correlation p-value
UP-Suicide	All	S	0.91898	8.12E-15	6.25E-22	0.6001871	3.26e-23

FIG. 5B



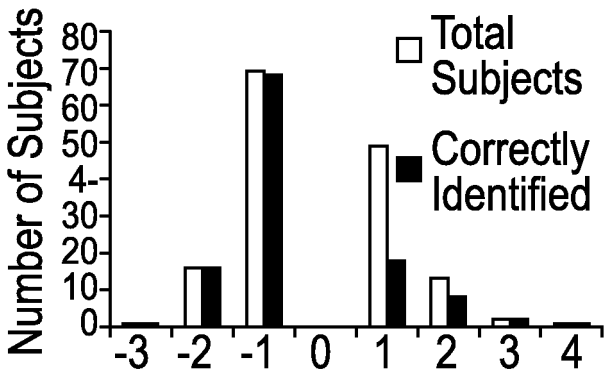


FIG. 5C

Predicting Suicidal Ideation

Sensitivity	Specificity	Balanced Accuracy
88%	81%	84%

Category	Total Subjects	High SI	Intermediate SI	No SI	Positive Predictive Value	Negative Predictive Value
-3	1	0	0	1	100%	100%
-2	16	0	0	16	100%	100%
1	69	0	0	68	99%	100%
0	72	4	6	62	94%	94%
1	49	18	11	20	37%	59%
2	13	8	1	4	62%	69%
3	2	2	0	0	100%	100%
4	1	1	0	0	100%	100%

FIG. 6

Simplifed Affective State Scale (SASS)
For each item, mark the scale with a vertical line where you think you are at this moment in time, compared to lowest and highest you ever remember being:

Mood Subscale

1) Mood

How good is your mood right now?

[----------]
Lowest **Highest**

2) Motivation to do things

How is your motivation, your drive, your determination to do things right now?

[----------]
Lowest **Highest**

3) Movement activity

How high is your physical energy and the amount of moving about that you feel like doing right now?

[----------]
Lowest **Highest**

4) Thinking activity

How high is your mental energy and thinking activity going on in your mind right now?

[----------]
Lowest **Highest**

FIG. 6

5) Self-esteem

How good do you feel about yourself and your accomplishments right now?

[----------]
Lowest **Highest**

6) Interest in pleasurable activities

How high is your interest to do things that are fun and enjoyable right now?

[----------]
Lowest **Highest**

7) Appetite

How high is your appetite and desire for food right now?

[----------]
Lowest **Highest**

Anxiety Subscale

1) Anxiety

How anxious are you right now?

[----------]
Lowest **Highest**

2) Uncertainty

How uncertain about things do you feel right now?

[----------]
Lowest **Highest**

3) Fear

How frightened about things do you feel right now?

FIG. 6

[----------]
Lowest **Highest**

4) Anger

How angry about things do you feel right now?

[----------]
Lowest **Highest**

Comments (optional):
Describe events or actions that you think are influencing how you feel now. Describe any additional feelings you might have at this moment in time:

SASS App

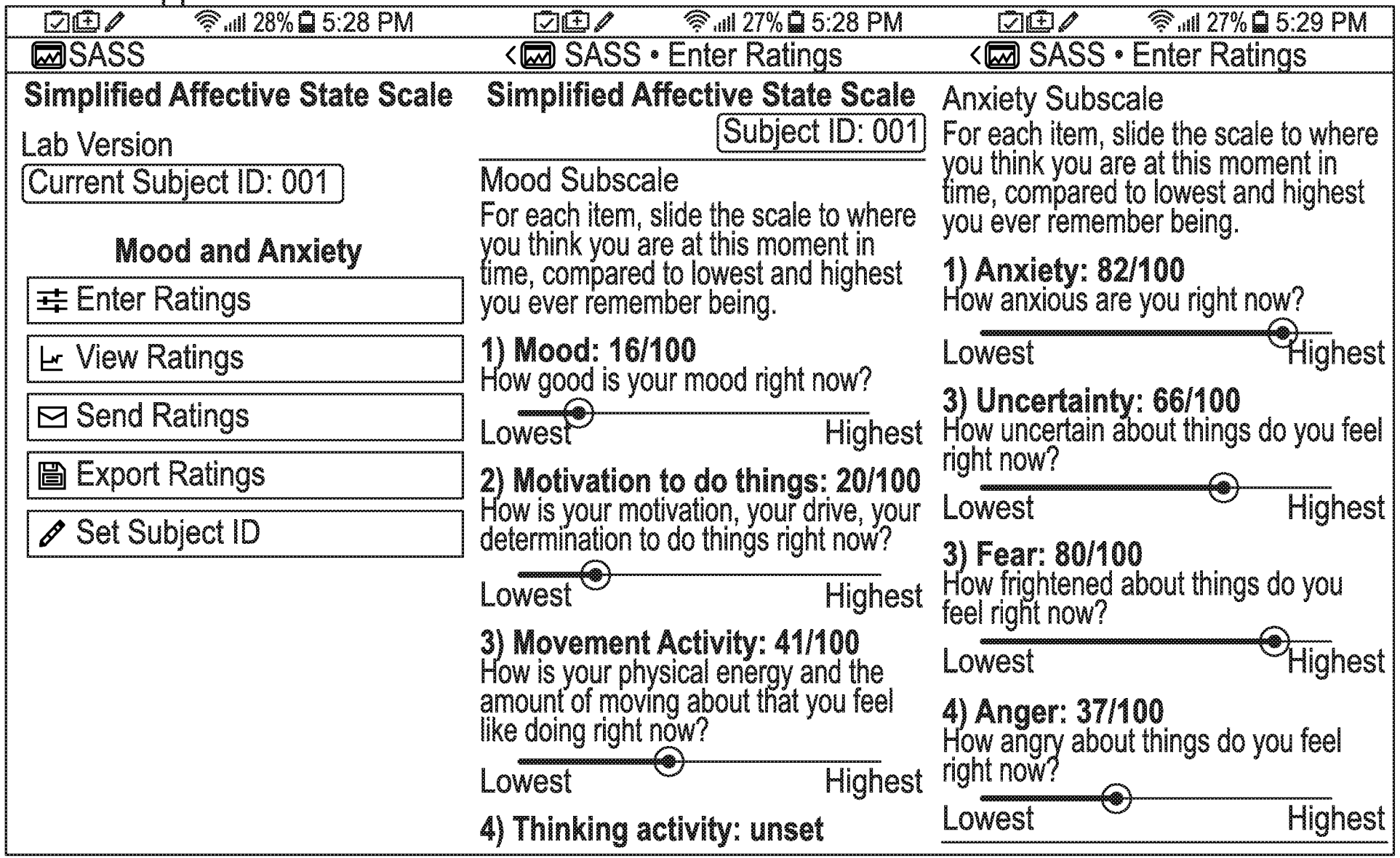


FIG. 7A

SUBSTITUTE SHEET (RULE 26)

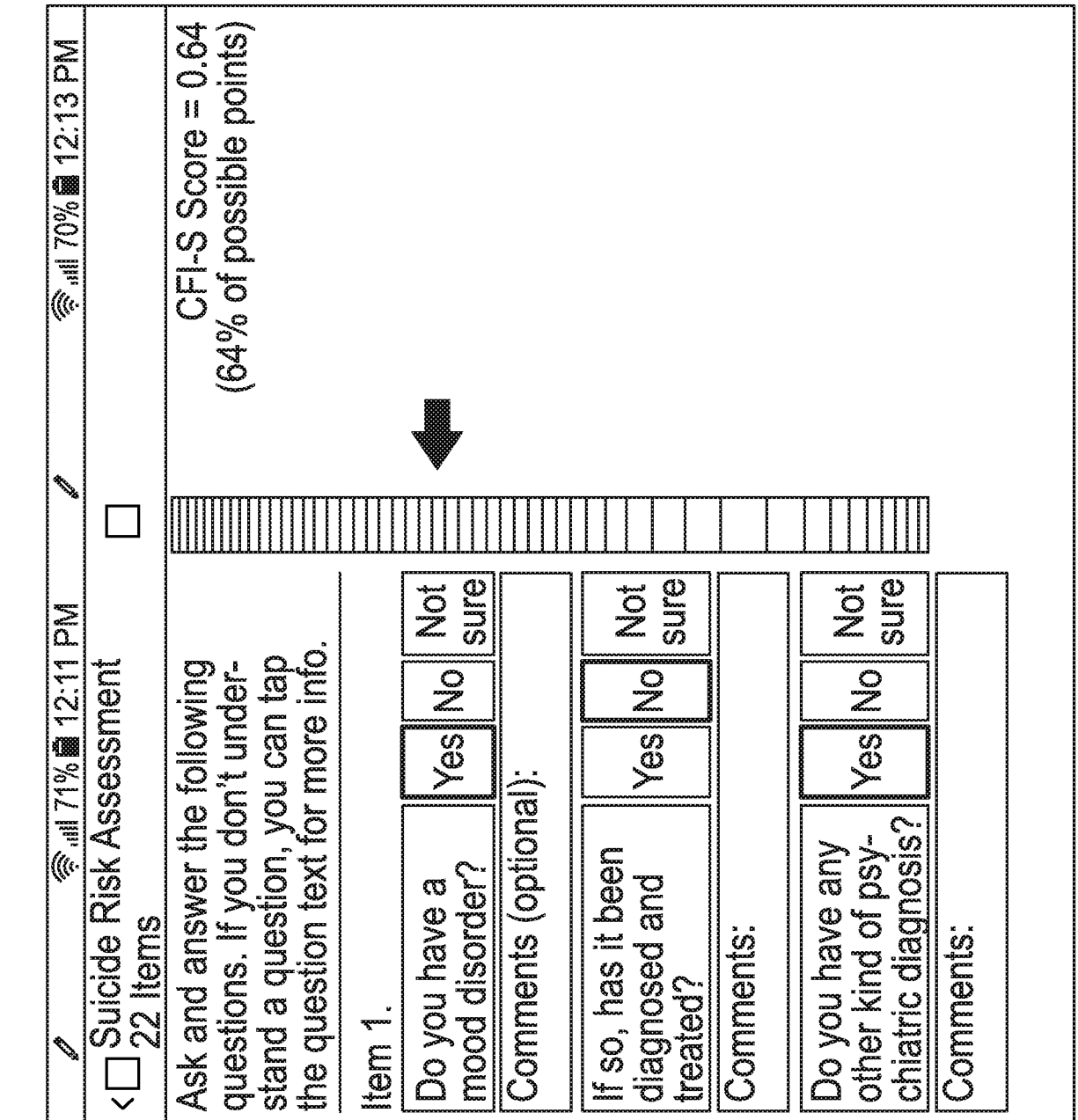

CFI-S App
71% 12:10 PM
Suicide Risk Assessment
Current Subject ID: 001
Last CFI-S Assessment:
11:47 AM, 04/20/2015
Set Subject ID
Select saved Subject ID
Perform CFI-S Assessment
View past assessment results
Take CFI-S without saving score
Settings
Export via excel
Export via email
71% 12:11 PM
Suicide Risk Assessment
22 Items
Ask and answer the following questions. If you don't understand a question, you can tap the question text for more info.
CFI-S Score = 0.64
(64% of possible points)
Item 1.
Do you have a mood disorder?
Yes
No
Not sure
Comments (optional):
If so, has it been diagnosed and treated?
Yes
No
Not sure
Comments:
Do you have any other kind of psychiatric diagnosis?
Yes
No
Not sure
Comments:
70% 12:13 PM

FIG. 7B

FIG. 8A

	Ingenuity Pathways				KEGG Pathways			GeneGO Pathways		
		Top Canonical Pathways	**P-Value**	**Ratio**	**Pathway Name**	**Enrichment Score**	**Enrichment p-value**	**Process Networks**	**Ratio**	**p-value**
Non-Validated in Completers Stepwise (n=208 genes)	1	G-Protein Coupled Receptor Signaling	2.28 E-08	5.7% 15/264	Pathogenic Escherichia coli infection	7.19808	0.000748	Cytoskeleton_ **Regulation of cytoskeleton rearrangement**	16/ 183	5.75E-07
	2	cAMP-mediated signaling	1.51 E-07	5.8% 13/223	Amoebiasis	5.51218	0.004037	Development_ **Neurogenesis_Axonal guidance**	17/ 230	2.65E-06
	3	CREB Signaling in Neurons	6.20 E-06	5.6% 10/179	Dorso-ventral axis formation	4.7856	0.008349	Development_ **Hedgehog signaling**	17/ 254	1.01E-05
	4	Cardiac Hypertrophy Signaling	1.02 E-05	4.7% 11/232	Melanogenesis	4.31121	0.013417	Reproduction_ Progesterone signaling	14/ 214	8.25E-05
	5	Synaptic Long Term Potentiation	2.26 E-05	6.3% 8/127	Influenza A	4.23564	0.014471	Cardiac development_ Wnt_beta-catenin, Notch, VEGF, IP3 and integrin signaling	11/ 150	0.000 1819
		Top Canonical Pathways	**P-Value**	**Ratio**	**Pathway Name**	**Enrichment Score**	**Enrichment p-value**	**Process Networks**	**Ratio**	**p-value**
Validat	1	B Cell Receptor Signaling	1.01	7.2 % 13/	Focal adhesion	10.5307	2.67E-05	Signal transduction_	19/ 177	8.10E-10

FIG. 8A

ed in Compleiters Stepwise (n=204 genes)			E-08	181				**WNT signaling**		
	2	Ovarian Cancer Signaling	3.31 E-08	8.3 % 11/133	Colorectal cancer	10.3054	3.35E-05	Cell cycle_ **G1-S Growth factor regulation**	18/ 195	2.62E-08
	3	Glucocorticoid Receptor Signaling	3.97 E-08	5.3 % 15/281	GABAergic synapse	8.60276	0.000184	Reproduction_ **Gonadotropin regulation**	18/ 199	3.60E-08
	4	Colorectal Cancer Metastasis Signaling	4.00 E-08	5.8 % 14/241	mTOR signaling pathway	8.47678	0.000208	Reproduction_ GnRH signaling pathway	16/ 166	9.05E-08
	5	G12/13 Signaling	1.12 E-07	8.5 % 10/118	Chagas disease (American trypanosomiasis)	7.66796	0.000468	Neurophysiological process_ Transmission of nerve impulse	18/ 212	9.58E-08

FIG. 8B

	Ingenuity				GeneGO		
		Diseases and Disorders	**P-Value**	**# Molecules**	**Diseases**	**pValue**	**Ratio**
Non-Validated in Completers Stepwise (n=208 genes)	1	Neurological disease	5.43E-04 - 8.63E-13	78	Psychiatry and Psychology	1.6E-30	85/1919
	2	Psychological Disorders	1.77E-04 - 2.04E-12	62	Mental Disorders	2.82E-30	78/1614
	3	Skeletal and Muscular Disorders	1.98E-04 - 5.33E-10	60	**Schizophrenia**	3.6E-22	51/914
	4	Organismal Injury and Abnormalities	6.69E-04 - 1.81E-09	184	**Schizophrenia and Disorders with Psychotic Features**	4.37E-22	51/918
	5	Cancer	6.32E-04 - 2.59E-09	182	**Central Nervous System Diseases**	5.41E-22	94/3069
		Diseases and Disorders	**P-Value**	**# Molecules**	**Diseases**	**pValue**	**Ratio**
Validated in Completers Stepwise (n=204 genes)	1	Organismal Injury and Abnormalitie	s 2.11E-04 - 1.23E-13	178	Psychiatry and Psychology	1.77E-23	76/1919
	2	Cancer	2.20E-04 - 5.41E-13	176	Mental Disorders	1.23E-21	67/1614
	3	Neurological Disease	1.31E-04 - 1.07E-12	81	**Mood Disorders**	4.02E-21	47/797
	4	Psychological Disorders	1.31E-04 - 1.07E-12	63	**Depressive Disorder, Major**	1.06E-18	37/546
	5	Tumor Morphology	1.87E-04 - 1.83E-12	38	**Depressive Disorder**	2.44E-18	37/560

FIG. 9

	Males				
Gene Symbol/ Affymetrix Probeset ID	Top Biomarkers All diagnoses	Top Biomarkers Bipolar disorder (BP)	Top Biomarkers Depression (MDD)	Top Biomarkers Schizoaffective disorder (SZA)	Top Biomarkers Schizophrenia (SZ)
Top Discovery AP Increased	DTNA 211493_x_at	DTNA 211493_x_at	PHF20 210500_at	USP48 232621_at	RP11-389C8.2 1556314_a_at
Top Discovery AP Decreased	KIF2C 211519_s_at	HS3ST3B1 1561908_a_at	EIF1B-AS1 1557212_at	NPRL3 210672_s_at	CYB561 210816_s_at
Top Discovery DE Increased	CADM1 237259_at	CADM1 237259_at	TLN1 232763_at	TSPYL1, 1560648_s_at	LOC100128288 1559045_at
Top Discovery DE Decreased	CLIP4 219944_at	Unknown gene 231262_at	NUCKS1 229353_s_at	TMSB15B, 1556964_s_at MCM8, 231827_at	CCDC163P 1559003_a_at
Top Prioritization AP Increased	SLC4A4 210739_x_at	KSR1 213769_at	DLK1 209560_s_at	IL6 205207_at	C1orf61 205103_at
Top Prioritization AP Decreased	SKA2 225686_at	CD44 216056_at	BBIP1 232910_at	TNS1 218863_s_at	SKA2 225686_at
Top Prioritization DE Increased	SAT1 210592_s_at	DAPP1 219290_x_at	BDNF 229353_s_at	TNF 207113_s_at	BDNF 206382_s_at
Top Prioritization DE Decreased	SKA2 225686_at	OPRM1 207989_at	SKA2 225686_at	S100B 1561521_at	HTR2A 211616_s_at
Top Validation AP Increased	IL6 205207_at	SPTBN1 215918_s_at	IL10 207433_at	JUN 201466_s_at	SLC5A3 1553313_s_at
Top Validation AP Decreased	MBP 225408_at	AKT1S1 224982_at	EIF1BAS1 1557212_at	BATF2 228439_at	ATP6V0E1 236527_at
Top Validation DE Increased	JUN 201464_x_at	SAT1 213988_s_at	GATM 1566861_at	JUN 201464_x_at	JUN 201464_x_at
Top Validation DE Decreased	KLHDC3 214383_x_at	C20orf27 218081_at	PRPF40A 226687_at	ANXA11 228727_at	LOC100131662 236973_at

Suicidal Ideation (SI)
from Hamilton Rating Scale for Depression (HAMD).
No SI-score of 0; High SI-score of 2 or above

Suicide
0 = Absent
1= Feels life is not worth living
2 = Wishes he were dead or any thoughts of possible death to self
3 = Suicidal ideas or gesture
4 = Attempts at suicide (any serious attempt rates 4)

FIG. 10A

Discovery Cohort:
12 psychiatric participants who have at least one switch between a **No SI state** visit and a High SI state visit.

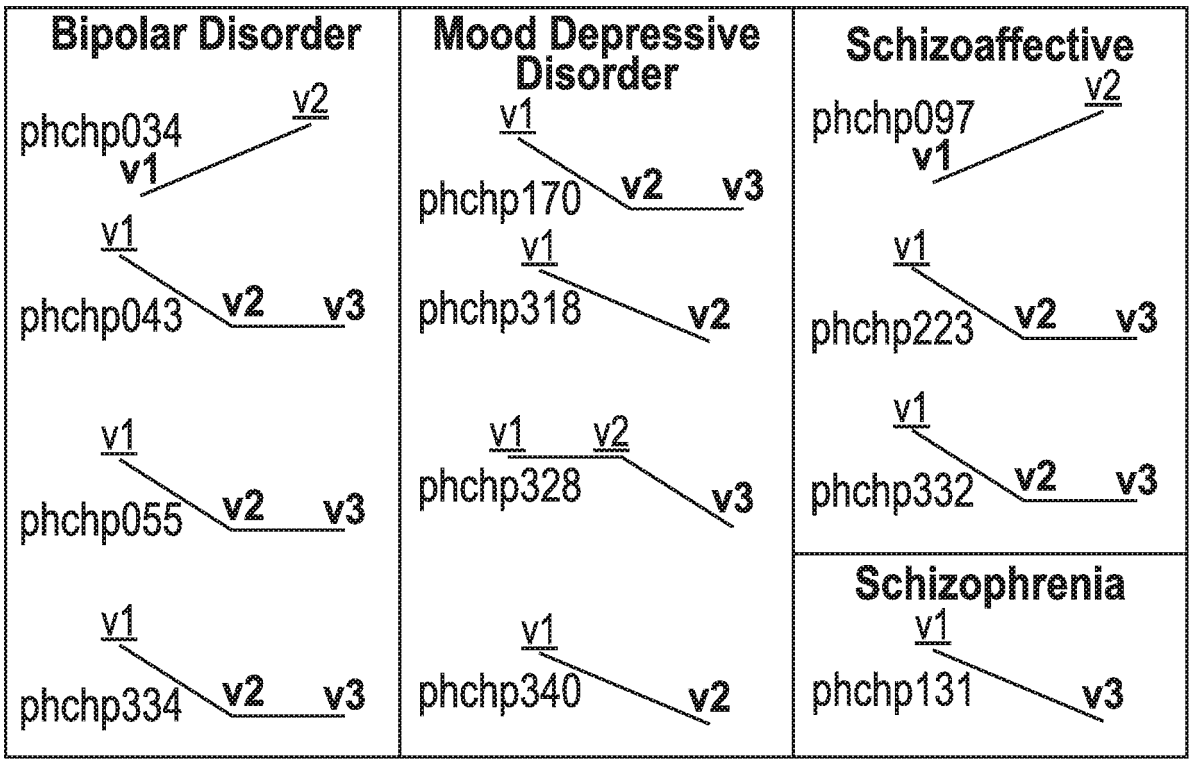


FIG. 10B

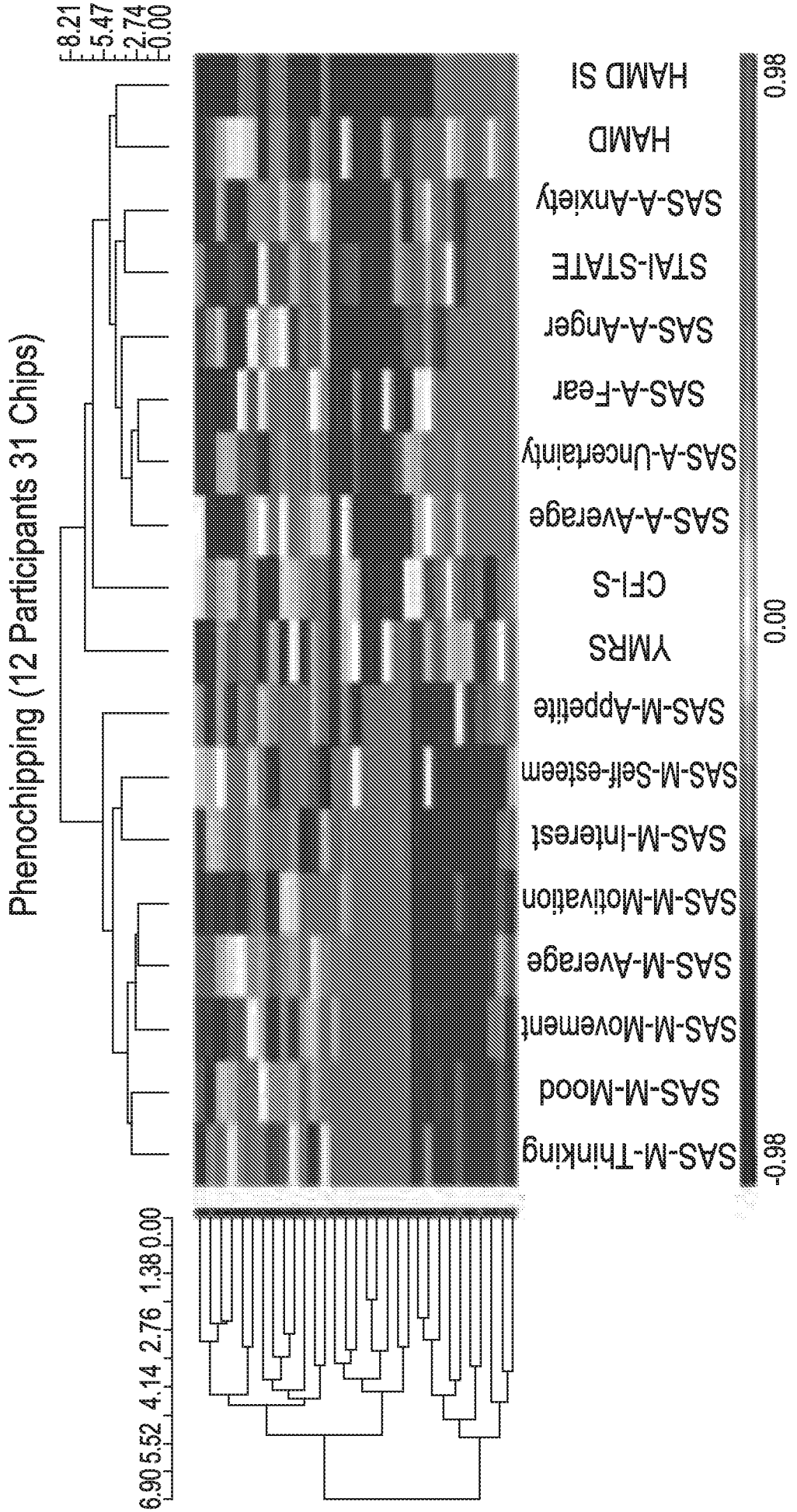

Phenochipping (12 Participants 31 Chips)
8.21
5.47
2.74
0.00
6.90 5.52 4.14 2.76 1.38 0.00
SAS-M-Thinking
SAS-M-Mood
SAS-M-Movement
SAS-M-Average
SAS-M-Motivation
SAS-M-Interest
SAS-M-Self-esteem
SAS-M-Appetite
YMRS
CFI-S
SAS-A-Average
SAS-A-Uncertainty
SAS-A-Fear
SAS-A-Anger
STAI-STATE
SAS-A-Anxiety
HAMD
HAMD SI
0.98
0.00
-0.98
CGI-S Minimum Maximum

FIG. 10C

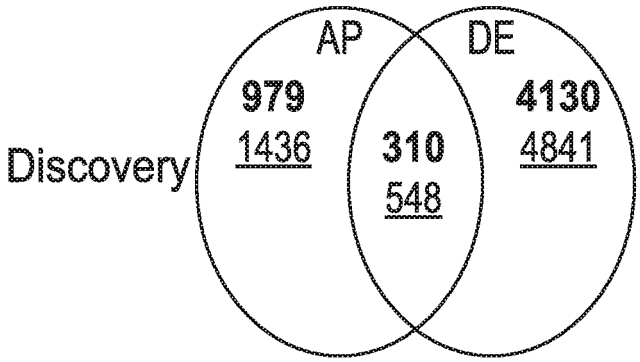


FIG. 11A

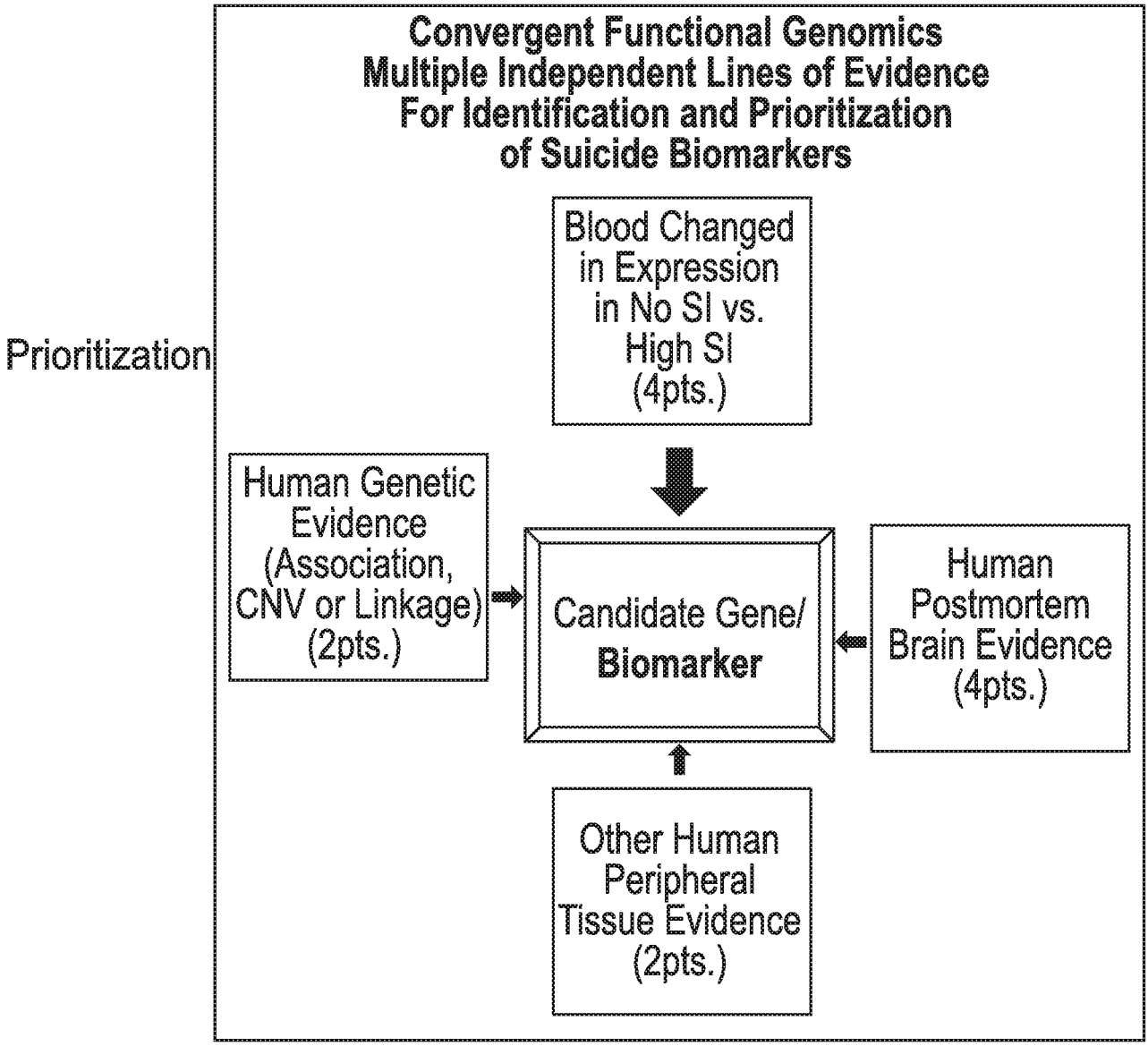


FIG. 11B

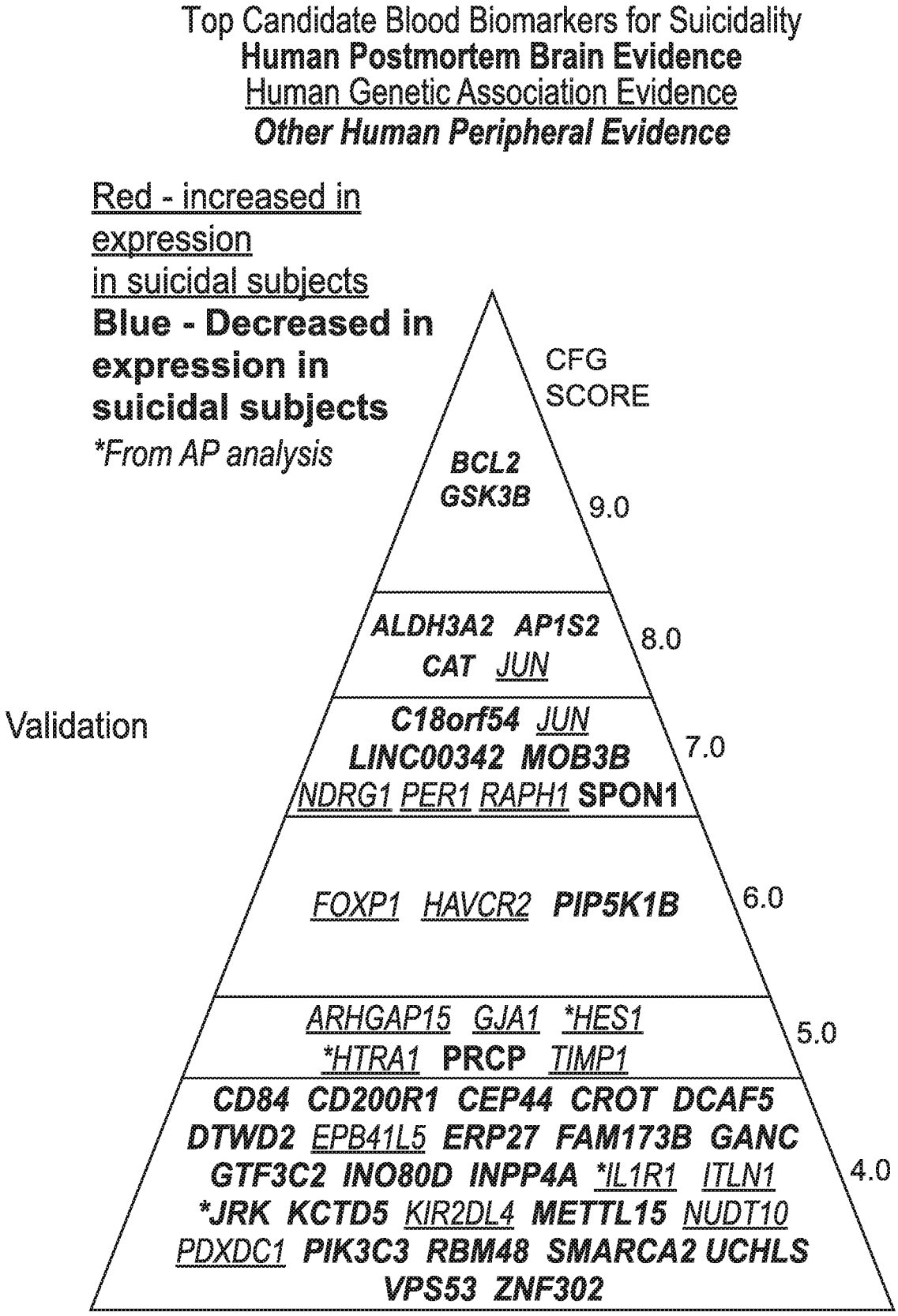
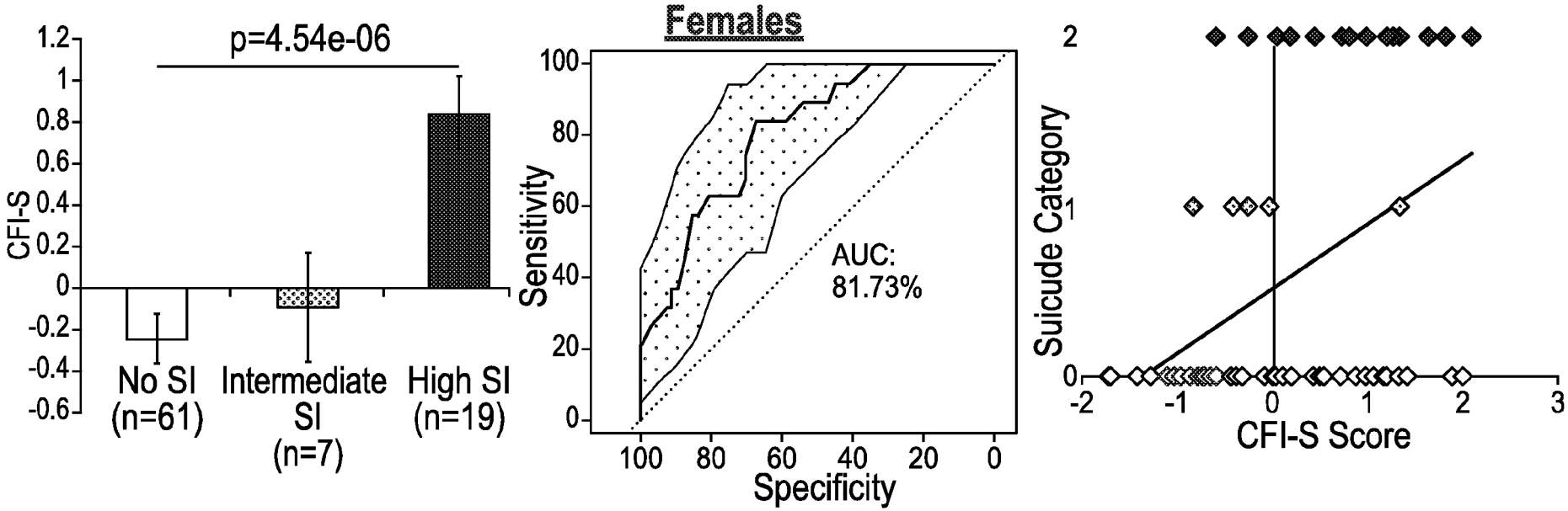

Top Candidate Blood Biomarkers for Suicidality
Human Postmortem Brain Evidence
Human Genetic Association Evidence
Other Human Peripheral Evidence
Red - increased in expression in suicidal subjects
Blue - Decreased in expression in suicidal subjects
*From AP analysis
CFG SCORE
BCL2 GSK3B
9.0
ALDH3A2 AP1S2 CAT JUN
8.0
Validation
C18orf54 JUN LINC00342 MOB3B NDRG1 PER1 RAPH1 SPON1
7.0
FOXP1 HAVCR2 PIP5K1B
6.0
ARHGAP15 GJA1 *HES1 *HTRA1 PRCP TIMP1
5.0
CD84 CD200R1 CEP44 CROT DCAF5 DTWD2 EPB41L5 ERP27 FAM173B GANC GTF3C2 INO80D INPP4A *IL1R1 ITLN1 *JRK KCTD5 KIR2DL4 METTL15 NUDT10 PDXDC1 PIK3C3 RBM48 SMARCA2 UCHLS VPS53 ZNF302
4.0

FIG. 11C

FIG. 12A



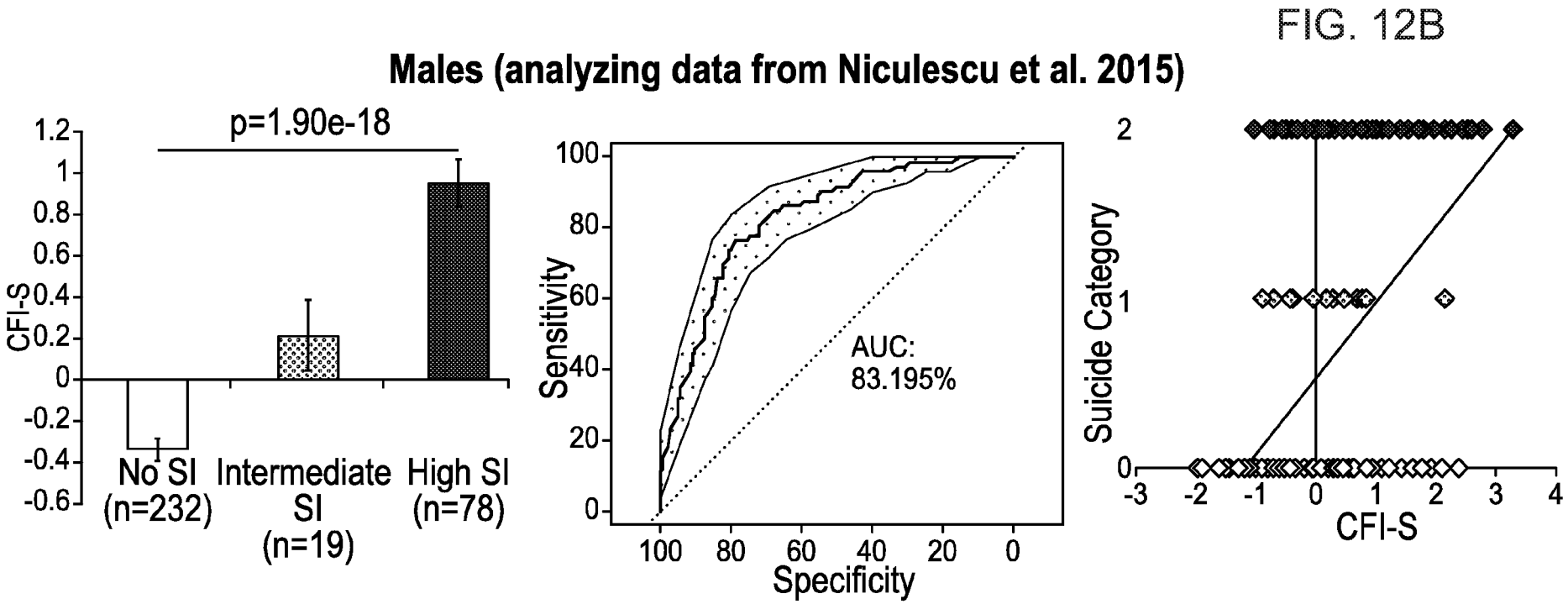
Predictor	AUC	AUC p-value	t-test No vs High SI	Correlation R	Correlation p-value
CFI-S	0.817	1.29e-05	4.54e-06	0.441	9.35e-06

CFI-S Item	Description	Correct direction	T-test (one tailed) High SI vs No SI p-value
16	Chronic stress: lack of positive relationships, social isolation	Y	0.0040
12	Current substance abuse	Y	0.0071
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	Y	0.0147

14	Lack of religious beliefs	Y	0.0175
13	Past history of suicidal acts/gestures	Y	0.0253
15	Acute stress: Rejection (within last 3 months)	Y	0.0294
20	History of command hallucinations of self-directed violence	Y	0.0453
10	Dissatisfaction with life at this moment in time	Y	0.0583
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	0.0635
4	Personally knowing somebody who committed suicide	Y	0.0733
7	Acute stress: losses, grief (within last 3 months)	Y	0.0748
3	Family history of suicide in blood relatives	Y	0.1422
21	Age:Older >60 or Younger <25	Y	0.2374
2	With poor treatment compliance	Y	0.2477
6	Acute/severe medical illness, including acute pain (“I just can’t stand this pain anymore.”) (within last 3 months)	Y	0.2714
5	History of abuse: physical, sexual, emotional, neglect	Y	0.3348
9	History of excessive introversion, conscientiousness (including planned suicide attempts)	Y	0.3388
18	Lack of coping skills when faced with stress (cracks under pressure)	Y	0.3723
19	Lack of children. If has children, not in touch/not helping take care of them	N	0.0714
1	Psychiatric illness diagnosed and treated	All have dx	All have dx
11	Lack of hope for the future	No difference	1
22	Gender: Male	All females	All females

FIG. 12A

FIG. 12B

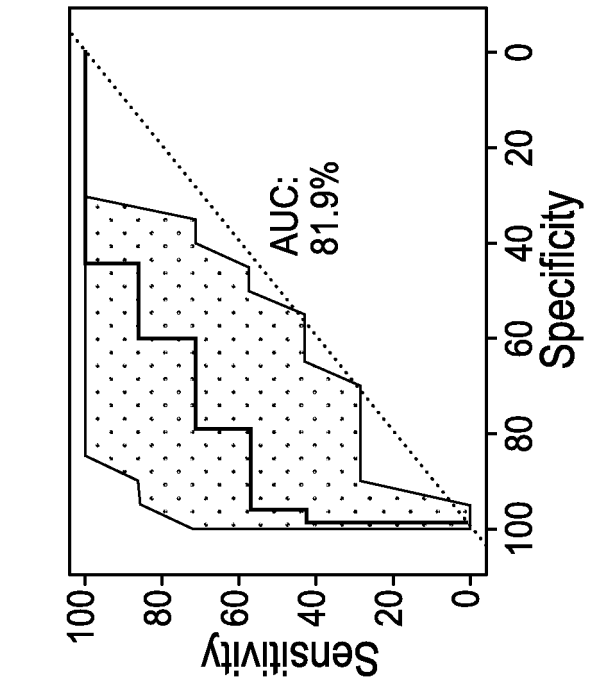


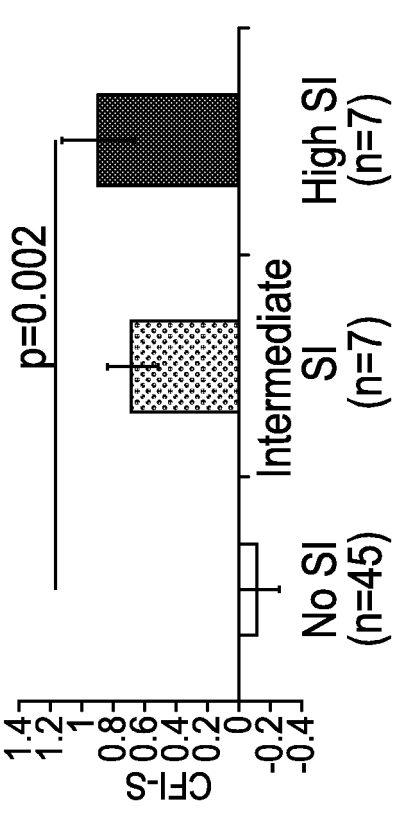
Predictor	AUC	AUC p-value	t-test No vs High SI	Correlation R	Correlation p-value
CFI-S	0.832	1.177E-24	1.90e-18	0.522	1.18e-24

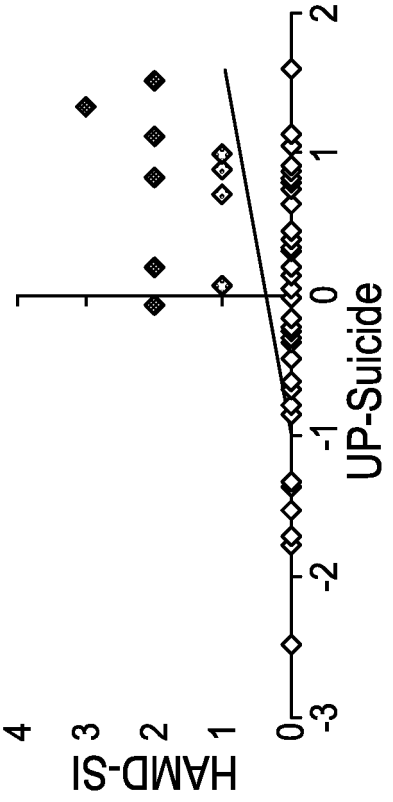
CFI-S Item	Description	Correct direction	T-test (one tailed) High SI vs No SI p-value
13	Past history of suicidal acts/gestures	Y	8.24E-14
16	Chronic stress; lack of positive relationships, social isolation	Y	1.77E-10

10	Dissatisfaction with life at this moment in time	Y	2.12E-08
18	Lack of coping skills when faced with stress (cracks under pressure)	Y	2.93E-07
9	History of excessive introversion, conscientiousness (including planned suicide attempts)	Y	1.73E-06
7	Acute stress: losses, grief (within last 3 months)	Y	0.0005
20	History of command hallucinations of self-directed violence	Y	0.0006
15	Acute stress: Rejection (within last 3 months)	Y	0.0012
3	Family history of suicide in blood relatives	Y	0.0012
2	With poor treatment compliance	Y	0.0013
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	0.0014
11	Lack of hope for the future	Y	0.0063
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	Y	0.0095
4	Personally knowing somebody who committed suicide	Y	0.0216
12	Current substance abuse	Y	0.0216
19	Lack of children. If has children, not in touch/not helping take care of them.	Y	0.0447
6	Acute/severe medical illness, including acute pain (“I just can’t stand this pain anymore.”) (within last 3 months)	Y	0.0568
5	History of abuse: physical, sexual, emotional, neglect	Y	0.752
21	Age: Older >60 or Younger <25	Y	0.0775
14	Lack of religious beliefs	Y	0.0896
1	Psychiatric illness diagnosed and treated	All have dx	All have dx
22	Gender: Male	All males	All males

FIG. 12B

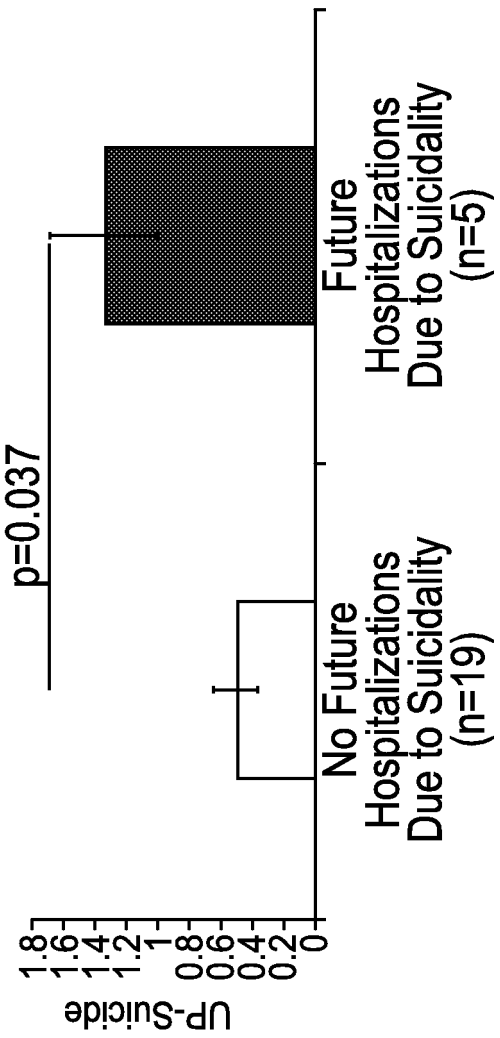


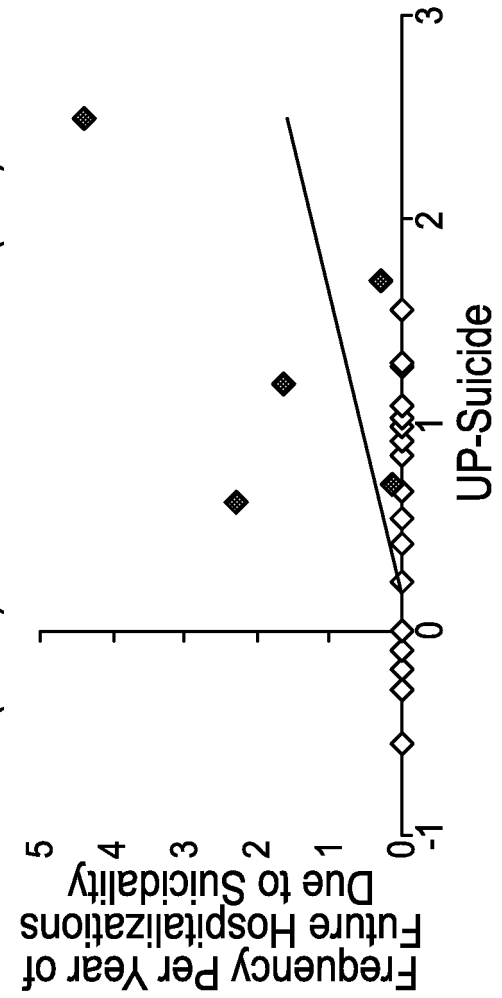


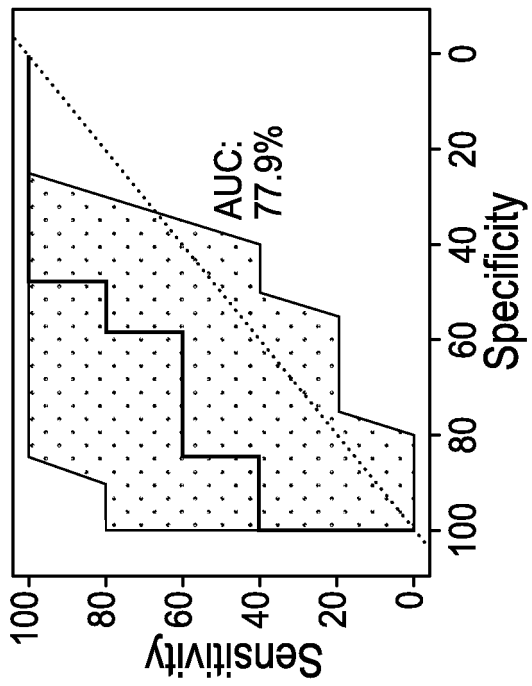


Predictor	Dx	Type	ROC AUC	ROC p-value	ANOVA	Correlation R	Correlation p-value
UP-Suicide	All	S	0.82	0.003	0.002	0.43	0.0003

FIG. 13A







Predictor	Dx	Type	ROC AUC	ROC p-value	t-test	Correlation R	Correlation p-value
UP-Suicide	All	T	0.78	0.032	0.037	0.51	0.006

FIG. 13B

	Partici-pants	Diagnosis	Ethnicity	Age (All Visits) Mean	T-test for age	
Discovery Cohort (Within-Participant Changes in Suicidal Ideation)	12	BP =4 MDD=4 SZA=3 SZ=1	EA=9 AA=2 Asian=1	All=44.39 (11.65) No SI=44.56 High SI=44.15	*T-test for age between No SI and High SI 0.926*	
Independent Valida-tion Cohort for Gene Expression (Suicide Completers)	6	BP=1 MDD=3 PTSD=1 Non-Psychiatric=1	EA=5 AA=1	43.5 (14.24)		*T-test for age with Discovery Cohort P=0.890*
Independent Test-ing Cohort For State Predictions (Suicidal Ideation)	33	<u>All</u> BP=17 MDD=7 SZA=7 SZ=2 <u>No SI</u> BP=13 MDD=4 SZA=6 SZ=2 <u>Intermediate SI</u> BP=3 SZA=1 <u>High SI</u> BP=3 MDD=3 SZA=1	EA=26 AA=5 Asian=1 Mixed=1	All=44.05 (8.81) No SI =43.98 High SI =41.28	*T-test for age between No SI and High SI 0.553*	*T-test for age with Discovery Cohort P=0.887*
Combined Discovery and Testing Cohort For State (Suicidal Ideation) Used for CFI-S analysis (Figure 3)	45	<u>All</u> BP=21 MDD=11 SZA=10 SZ=3 <u>No SI</u> BP=17 MDD=8 SZA=9 SZ=3 <u>Intermediate SI</u> BP=3 SZA=1	EA=35 AA=7 Asian=2 Mixed=1	All=44.15 (9.68) No SI=44.12 High SI =43.15	*T-test for age between No SI and High SI 0.727*	

FIG. 14

		High SI BP=7 MDD=7 SZA=4 SZ=1				
Testing Cohort for Trait Predictions (Future Hospital-izations for Suicid-ality)	24	All BP=10 MDD=9 SZA=3 SZ=2 No Hosp for SI BP=8 MDD=8 SZA=1 SZ=2 Hosp for SI BP=2 MDD=1 SZA=2 SZ=0	EA=19 AA=4 Mixed=1	All=46.51 (6.66) No Hosp for SI =47.2 Hosp for SI =43.4	*T-test for age between No Hosp for SI and Hosp for SI 0.0430*	*T-test for age with Discovery Cohort p=0.354*

FIG. 14

FIG. 15

A.	Ingenuity Pathways				KEGG Pathways			GeneGO Pathways		
	#	Top Canonical Pathways	P-Value	Ratio	Pathway Name	Ratio	Enrichment p-value	Process Networks	Ratio	p-value
Prioritization CFG score ≥4 (n= 1471 genes)	1	B Cell Receptor Signaling	2.88E-13	22.9 % 41/179	Morphine addiction	19/239	9.27E-06	Immune response_BCR pathway	42/137	4.332E-11
	2	Protein Kinase A Signaling	3.61E-13	16.6 % 66/398	Phosphatidylinositol signaling system	18/245	4.20E-05	Apoptosis_Anti-Apoptosis mediated by external signals via MAPK and JAK/STAT	45/179	1.070E-08
	3	PI3K Signaling in B Lymphocytes	5.80E-12	24.8 % 33/133	Neurotrophin signaling pathway	29/545	7.23E-05	Reproduction_Gonadotropin regulation	48/199	1.452E-08
	4	IGF-1 Signaling	7.76E-12	28.3 % 28/99	Amoebiasis	22/363	9.46E-05	Cell cycle_G1-S Growth factor regulation	47/195	2.115E-08
	5	Glucocorticoid Receptor Signaling	1.96E-11	17.8 % 50/281	Insulin signaling pathway	27/520	0.0001855	Development_Hemopoiesis, Erythropoietin pathway	37/136	2.393E-08
Validation Stepwise in Suicide Completers (n=589 genes)	1	Glucocorticoid Receptor Signaling	2.86E-06	7.8 % 22/281	Morphine addiction	9/249	0.0006493	Reproduction_Gonadotropin regulation	24/199	9.843E-07
	2	IGF-1 Signaling	7.18E-06	12.1 % 12/99	Colorectal cancer	9/287	0.0016932	Reproduction_GnRH signaling pathway	20/166	8.256E-06
	3	Renin-Angiotensin Signaling	8.72E-06	11.0 % 13/118	Cocaine addiction	6/155	0.0037291	Reproduction_Progesterone signaling	23/214	1.194E-05
	4	Protein Kinase A Signaling	1.02E-05	6.5 % 26/398	Insulin signaling pathway	12/535	0.0047284	Signal transduction_NOTCH signaling	24/236	1.962E-05
	5	Melanocyte Development and Pigmentation Signaling	1.02E-05	12.8 % 11/86	Inositol phosphate metabolism	6/193	0.0101986	Signal transduction_Androgen receptor signaling cross-talk	12/72	2.241E-05
Validation Nominally significant In Suicide Completers (n= 396 genes)	1	Neurotrophin/TRK Signaling	3.48E-06	12.5 % 9/72	Cocaine addiction	6/155	0.000454	Reproduction_Gonadotropin regulation	16/199	7.748E-05
	2	Glucocorticoid Receptor Signaling	2.68E-05	5.7 % 16/281	Colorectal cancer	7/289	0.002226	Reproduction_GnRH signaling pathway	14/166	1.323E-04
	3	Melanocyte Development and Pigmentation Signaling	1.06E-04	9.3 % 8/86	Wnt signaling pathway	9/495	0.003675	Reproduction_Progesterone signaling	16/214	1.822E-04
	4	G-Protein Coupled Receptor Signaling	1.79E-04	5.3 % 14/264	Notch signaling pathway	5/170	0.004315	Signal transduction_NOTCH signaling	16/236	5.495E-04
	5	Corticotropin Releasing Hormone Signaling	2.23E-04	7.4 % 9/121	Adherens junction	7/340	0.005315	Signal transduction_WNT signaling	13/177	8.738E-04
Validation Bonferroni significant in Suicide Completers (n= 49 genes)	1	IL-17 Signaling	1.34E-05	5.6 % 4/72	Inositol phosphate metabolism	3/196	0.000383	Cell cycle_G1-S Interleukin regulation	6/128	6.400E-06
	2	p53 Signaling	4.52E-05	4.1 % 4/98	Phosphatidylinositol signaling system	3/260	0.000863	Immune response_BCR pathway	5/137	1.387E-04
	3	Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	8.71E-05	2.2 % 5/225	Colorectal cancer	3/293	0.001214	Immune response_Th17-derived cytokines	4/98	4.589E-04
	4	Docosahexaenoic Acid (DHA) Signaling	1.02E-04	6.7 % 3/45	Tryptophan metabolism	2/132	0.004229	Inflammation_IL-2 signaling	4/104	5.752E-04
	5	Ovarian Cancer Signaling	1.48E-04	3.0 % 4/133	Neurotrophin signaling pathway	3/571	0.007844	Cell cycle_G1-S Growth factor regulation	5/195	7.127E-04

Suicidal Ideation Cohort n=33 Participants

Best Blood Biomarkers Predictors

Marker	Participants with Suicidality/ Participants Total	ROC AUC/ p-value	Pearson's Correlation R/p-value	Student's t-test p-value
Out of Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)				
EPB41L5	7 | 33	*0.68/0.06*	0.22/0.03	*0.09*
HAVCR2	7 | 33	0.62/0.15	*0.17/0.07*	0.18
ARHGAP15	7 | 33	0.55/0.34	0.12/0.15	0.22
PIK3C3	7 | 33	0.65/0.1	-0.21/0.037	*0.08368*
GTF3C2	7 | 33	0.64/0.115	-0.11/0.179	*0.07208*
ALDH3A2	7 | 33	0.62/0.142	-0.21/0.036	0.1421
Out of Top Discovery and Prioritization Biomarkers (Non Bonferroni Validated, 65 genes)				
DPCD	7 | 33	*0.67/0.07*	0.21/0.04	0.12
GTF3C3	7 | 33	*0.67/0.07*	0.23/0.02	0.11
ASPH	7 | 33	0.65/0.1	0.07/0.27	0.13
ACTR3	7 | 33	0.62/0.15	-0.19/0.05	0.13
NUDT6	7 | 33	0.62/0.15	-0.07/0.27	0.19
LRRC8B	7 | 33	0.60/0.19	-0.15/0.11	0.13
Panels of Validated Biomarkers (Increased, Decreased, Combined)				
BioM-18	7 | 33	0.37/0.87	0.032/0.39	0.59

FIG. 16

FIG. 16

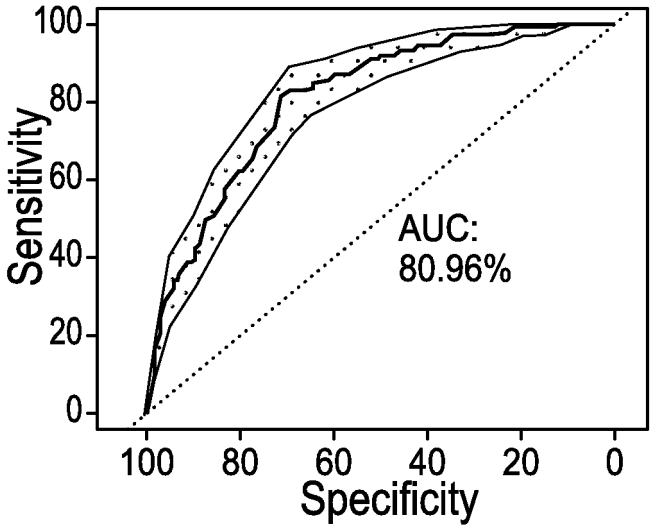
		BioM-32	7 | 33	0.43/0.72	-0.0031/0.49	0.68		
		BioM-50	7 | 33	0.5/0.515	0.02/0.429	0.465		
	Clinical measures	Anxiety	7 | 33	0.72/0.029	0.26/0.011	0.0083		
		Mood	7 | 33	0.78/0.0078	-0.37/0.0006	0.002		
		SASS	7 | 33	0.81/0.0035	0.38/0.0005	5.04E-05		
		CFI-S	7 | 29	0.84/0.002	0.39/0.0013	0.003		
		CFI-S+SASS	7 | 29	0.87/0.00088	0.48/0.0001	0.00027		
	Combined	UP-Suicide	7 | 29	0.82/0.003	0.43/0.0003	0.001467		
		Marker	Participants Hospitalized for Suicidality/ Participants Hospitalized Total	ROC AUC/ p-value	Pearson's Correlation R/p-value	Student's t-test p-value	Cox Regres-sion Hazard Ratio	Cox Regres-sion p-value
Future Hos-pitalizations for Suicidality n=24 Participants	Best Blood Biomarkers Predictors	Out of Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)						
		HTRA1	5 | 24	0.84/0.01	0.62/0.00058	0.02	4.55	0.01
		PER1	4 | 24	0.84/0.018	0.39/0.029	0.1314	1.535	0.1615
		PDXDC1	5 | 24	0.81/0.018	0.64/0.0004	0.04187	2.4436	0.01503
		PIK3C3	3 | 24	0.9/0.011	-0.25/0.115	0.02583	5.995	0.12
		BCL2	4 | 24	0.89/0.007	-0.35/0.047	0.05385	3.0848	0.01
		MOB3B	4 | 24	0.85/0.015	-0.34/0.053	0.000462	*9.572*	*0.09*
		Out of Top Discovery and Prioritization Biomarkers (Non Bonferroni Validated, 65 genes)						

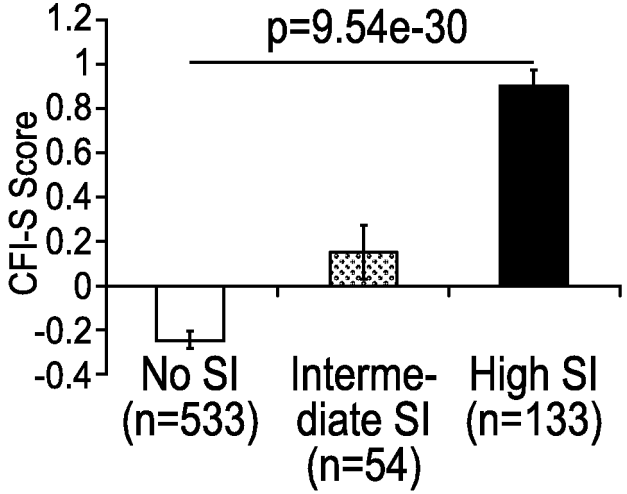
		KLHL28	5	24	0.91/0.002	0.50/0.007	0.003	7.36	0.04
		UIMC1	5	24	0.86/0.006	0.40/0.08	0.04	2.26	0.03
		SNX27	4	24	0.85/0.02	0.73/2.5E-05	0.05	4.27	0.01
		CSNK1A1	4	24	0.96/0.0007	-0.27/0.10	0.0007	620.5	0.02
		LARP4	4	24	0.9/0.005	-0.3/0.08	6.30E-05	37.01	0.11
		ZNF548	5	24	0.83/0.012	-0.31/0.07	0.008	15.94	0.02
		Panels of Validated Biomarkers (Increased, Decreased, Combined)							
		BioM-18	4	24	0.88/0.0088	0.46/0.011	0.033	27.6	0.021
		BioM-32	4	24	0.71/11	*-0.34/0.053*	0.16	10.57	0.23
		BioM-50	5	24	0.94/0.002	0.54/0.003	0.005813	89.459	0.02
	Clinical measures	Anxiety	4	24	0.86/0.01	0.44/0.01	0.0039	*14.4*	*0.061*
		Mood	3	24	0.68/0.18	-0.22/0.16	0.22	33.4	0.1
		SASS	4	24	0.83/0.02	0.39/0.03	0.034	*3.72*	*0.066*
		CFI-S	3	24	0.5/0.52	0.24/0.12	0.38	1.17	0.79
		CFI-S+SASS	4	24	*0.74/0.08*	0.40/0.03	*0.083*	*4.68*	*0.06*
	Combined	UP-Suicide	5	24	0.78/0.032	0.51/0.006	0.03691	9.6068	0.01

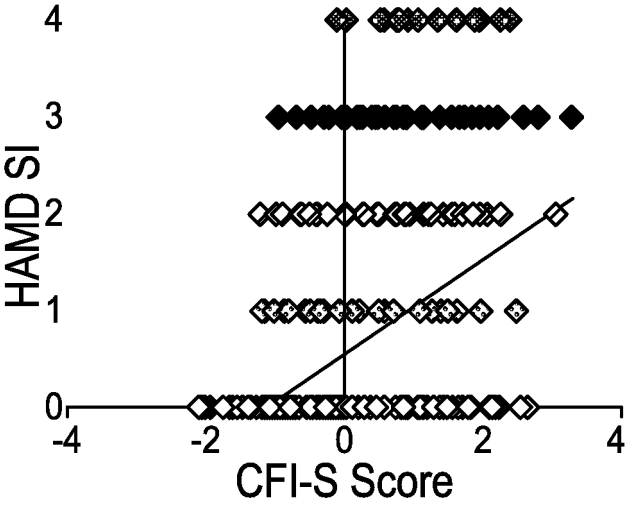
FIG. 16

Prediction of high suicidal ideation

FIG. 17







Predictor	ROC AUC	AUC p-value	t-test	Correlation R	Correlation p-value
CFI-S	0.80959	3.21E-29	9.54E-30	0.443	2.47E-36

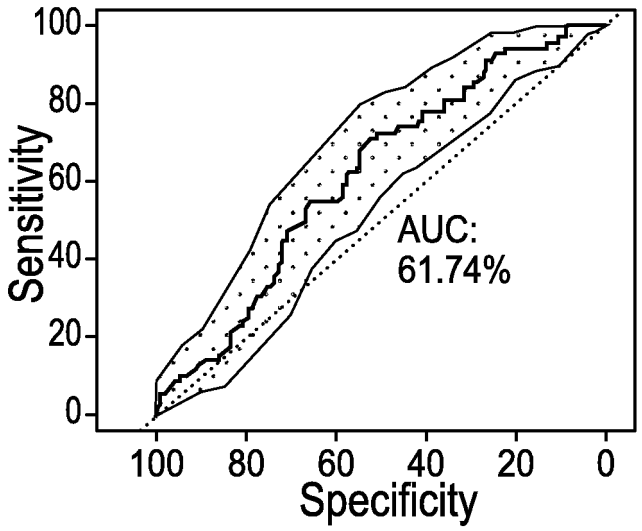
CFI-S Item	Description	Stepwise	T-test (two tailed) High SI vs No SI
13	Past history of suicidal acts/gestures	Y	2.71E-18

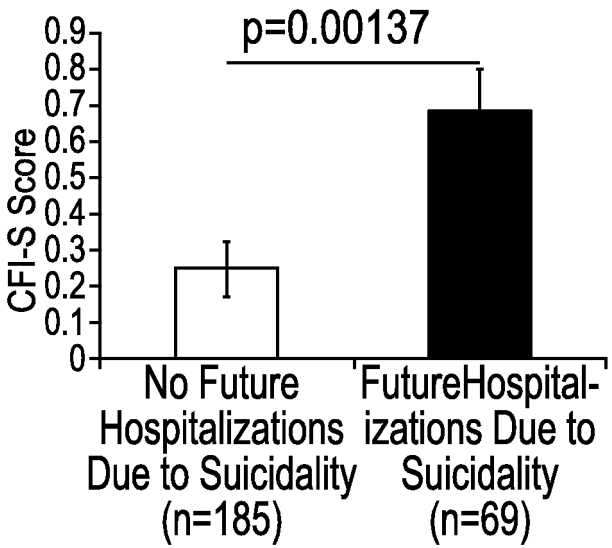
16	Chronic stress: lack of positive relationships, social isolation	Y	3.562E-15
10	Dissatisfaction with present	Y	6.20479E-14
18	Lack of coping skills (cracks under pressure)	Y	2.82E-10
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	5.41467E-06
20	History of command hallucinations of self-directed violence	Y	1.11225-05
9	History of excessive introversion, conscientiousness	Y	1.44517E-05
15	Acute stress: Rejection	Y	1.49128E-05
12	Current substance abuse	Y	1.71401E-05
7	Acute stress: losses, grief	Y	1.90447E-05
11	Lack of hope for the future	Y	5.29E-04
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	Y	0.000540744
14	Lack of religious beliefs	Y	0.000754729
3	Family history of suicide in blood relatives	Y	0.001501435
6	Acute/severe medical illness, pain	Y	0.001551877
2	With poor treatment compliance		0.001716147
4	Personally knowing somebody who committed suicide	Y	0.010376266
5	History of abuse: physical, sexual, emotional, neglect	Y	0.084287799
19	Lack of children	Y	0.393277178
21	Age: Older >60 or Younger <25	N	0.111733842
22	Gender: Male	N	0.992968285
1	Psychiatric illness diagnosed and treated	All have dx	All have dx

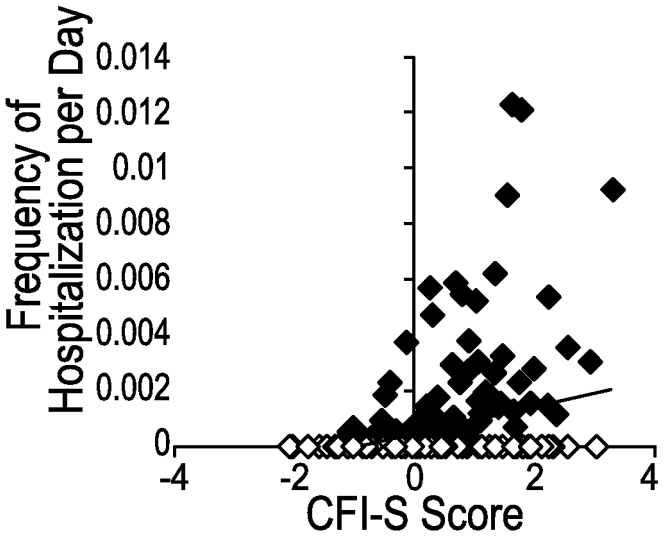
FIG. 17

FIG. 18

Prediction of future hospitalizations for suicidality







Predictor	ROC AUC	AUC p-value	t-test	Correlation R	Correlation p-value
CFI-S	0.617391304	0.002011748	0.0013734	0.298	6.84E-07

CFI-S Item	Description	Stepwise	T-test (two tailed) No SI vs High SI
13	**Past history of suicidal acts/gestures**	**Y**	**8.17E-27**
20	**History of command hallucinations of self-directed violence**	**Y**	**1.84E-05**

15	**Acute stress: Rejection**	**Y**	**3.60E-05**
3	**Family history of suicide in blood relatives**	**Y**	**1.85E-04**
7	**Acute stress: losses, grief**	Y	**1.31E-03**
11	Lack of hope for the future	Y	4.46E-03
16	Chronic stress: lack of positive relationships, social isolation	Y	4.64E-03
18	Lack of coping skills (cracks under pressure)	Y	9.38E-03
10	Dissatisfaction with present life	Y	0.013
6	Acute/severe medical illness, pain	Y	0.0155
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	0.0185
4	Personally knowing somebody who committed suicide	Y	0.0463409
22	Gender: Male	Y	0.0514736
5	History of abuse: physical, sexual, emotional, neglect	Y	0.0904092
12	Current substance abuse	Y	0.100109
14	Lack of religious beliefs	Y	0.2170824
21	Age: Older >60 or Younger <25	Y	0.2578034
2	With poor treatment compliance		0.2851157
9	History of excessive introversion, conscientiousness	Y	0.4891344
19	Lack of children	N	0.2289837
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	N	0.303751
1	Psychiatric illness diagnosed and treated	All have dx	All have dx

FIG. 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/36985

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; G01N 33/96, 33/68, 33/48; G06F 19/18 (2016.01)
CPC - C12Q 1/6809, 1/6813, 1/686; G01N 33/6869, 33/68, 33/48; G06F 19/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C12Q 1/68; G01N 33/96, 33/68, 33/48, 33/53; C40B 40/06; G06F 19/18; A61P 35/00, 48/00; C12P 19/34
CPC: C12Q 1/6809, 1/6813, 1/686; G01N 33/6869, 33/9466, 33/96, 33/68, 33/48; C40B 40/06; G06F 19/18; A61K 31/554, 31/519

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO
Keywords: suicide, depression, treatment, diagnose, computer, gene, expression, level, schizophrenia, antidepressant, demographic, mood, anxiety

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2015/006645 A1 (THE JOHN HOPKINS UNIVERSITY) 15 January 2015; abstract; page 2, lines 31-32; page 6, lines 1-2; page 10, lines 24-33; page 13, lines 12-13; page 14, lines 6-7, 20-21; page 21, lines 3-4; page 21, line 23 - page 22, line 5; page 27, line 23; page 28, lines 20-22; page 40, line 2; page 51, lines 23, 31	1-5, 7-9, 11, 14-16, 19, 24 ---------- 6, 10, 12-13, 17-18, 20-23, 25
Y	(BRENT, D et al.) Pharmacogenomics of Suicidal Events. Pharmacogenomics. June 2010; Vol. 11, No. 6; pages 1-20; abstract; page 4, paragraph 1; page 6, paragraph 4; DOI: 10.2217/pgs.10.64.	6
Y	(STOPKOVA, P et al.) Identification of PIK3C3 Promoter Variant Associated with Bipolar Disorder and Schizophrenia. Biological Psychiatry. 15 May 2004; Vol. 55, No. 10; pages 981-988; abstract; page 986, column 1, paragraph 3	10
Y	US 2012/0269906 A1 (SHEEHAN, DV et al.) 25 October 2012; abstract; paragraphs [0035], [0058], [0089], [0239], [0242], [0251], [0289], [0349], [0431], [0449], [0608]-[0613]; tables 2, 5	12-13, 23, 25
Y	US 2013/0330429 A1 (VUCKOVIC, A) 12 December 2013; paragraphs [0027], [0044]	17-18, 20
Y	(JOHNSON, ERB) Vitamin D and the Occurrence of Depression: Causal Association or Circumstantial Evidence?. Nutrition Reviews. August 2009; Vol. 67, No. 8; pages 1-17; abstract; page 1, paragraph 3; page 7, paragraph 5; DOI: 10.1111/j.1753-4887.2009.00220.x.	21
Y	US 2013/0142776 A1 (ALLERGAN, INC.) 06 June 2013; abstract; paragraph [0014]	22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2016 (16.08.2016)	09 SEP 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774