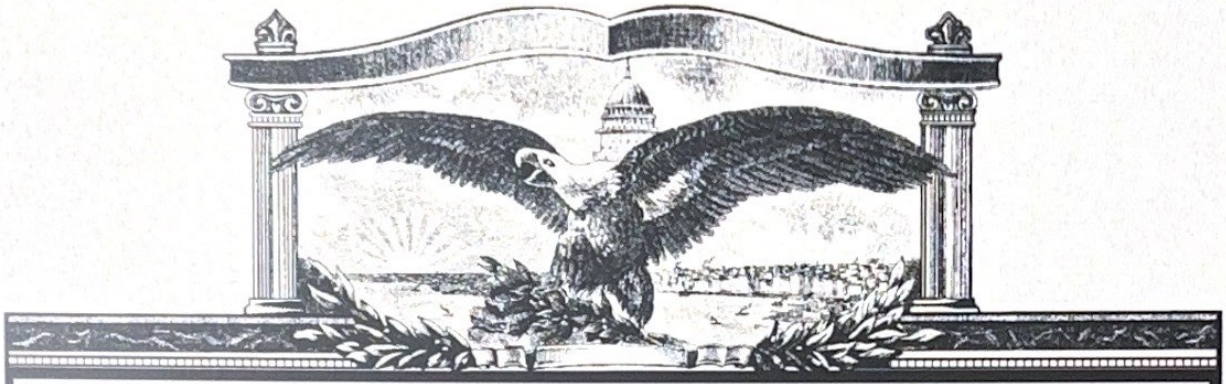

UNITED STATES PATENT

Granted on March 21, 2023

Prof. Alexander B. Niculescu, MD, PhD

INVENTOR

US 11,608,532 B2

PRECISION MEDICINE FOR TREATING AND PREVENTING SUICIDALITY

The present disclosure relates generally to discovery of novel compounds involved in the treatment and prevention of suicidality by bioinformatics drug repurposing using novel genes expression biomarkers involved in suicidality. Disclosed are methods for assessing severity, determining future risk, matching with a drug treatment, and measuring response to treatment, for suicidality. Also disclosed are new methods of use for drugs and natural compounds repurposed for use in preventing and treating suicidality. These methods include computer-assisted methods analyzing the expression of panels of genes, clinical measures, and drug databases. Detailed herein are methods using a universal approach, in everybody, as well as personalized approaches by gender, and by diagnosis. The discovery describes compounds for use in everybody (universal), as well as personalized by gender (males, females), diagnosis (bipolar, depression), gender and diagnosis combined (male bipolar, male depression), male PTSD, male SZ/SZA), and subtypes of suicidality (high anxiety, low mood, combined (affective), and high psychosis (non-affective). Also disclosed are methods for identifying which subjects should be receiving which treatment, using genes expression biomarkers for patient stratification and measuring response to treatment. The disclosure also relates to algorithms, universal and personalized by gender and diagnosis. The algorithms combine biomarkers as well as clinical measures for suicidality and for mental state, in order to identify subjects who are at risk of committing suicide, as well as to track responses to treatments...

The United States of America

The Director of Patents and Trademarks has received an application for a patent for a new and useful invention. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law. Therefore, this

UNITED STATES PATENT

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of the patent, subject to the payment of maintenance fees as provided by law.

Katherine Kelly Vidal

Director of the United States Patent and Trademark Office

US011608532B2

(12) **United States Patent**
Niculescu

(10) **Patent No.: US 11,608,532 B2**
(45) **Date of Patent: Mar. 21, 2023**

(54) **PRECISION MEDICINE FOR TREATING AND PREVENTING SUICIDALITY**

(71) Applicants: **Indiana University Research and Technology Corporation**, Indianapolis, IN (US); **United States Government as Represented by the Department of Veterans Affairs**, Washington, DC (US)

(72) Inventor: **Alexander Bogdan Niculescu**, Indianapolis, IN (US)

(73) Assignees: **Indiana University Research and Technology Corporation**, Bloomington, IN (US); **The United States Government as Reprecented by the Department of Veterans Affairs**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/677,414**

(22) Filed: **Nov. 7, 2019**

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US 2020/0318188 A1 Oct. 8, 2020

Related U.S. Application Data

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(51) **Int. Cl.**

C12Q 1/6883	(2018.01)
G16H 10/60	(2018.01)
G16H 50/20	(2018.01)
G16B 50/30	(2019.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**

CPC ***C12Q 1/6883*** (2013.01); ***G16B 50/30*** (2019.02); ***G16H 10/60*** (2018.01); ***G16H 50/20*** (2018.01); *A61K 45/06* (2013.01); *C12Q 2600/158* (2013.01); *G01N 2800/52* (2013.01); *G01N 2800/60* (2013.01)

(58) **Field of Classification Search**

CPC C12Q 1/6883; G16B 50/30; G16H 50/20; G01N 2800/60

See application file for complete search history.

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Primary Examiner — Olga N Chernyshev

(74) *Attorney, Agent, or Firm* — Faegre Drinker Biddle & Reath LLP

(57) **ABSTRACT**

The present disclosure relates generally to discovery of novel compounds involved in the treatment and prevention of suicidality by bioinformatics drug repurposing using novel genes expression biomarkers involved in suicidality. Disclosed are methods for assessing severity, determining future risk, matching with a drug treatment, and measuring response to treatment, for suicidality. Also disclosed are new methods of use for drugs and natural compounds repurposed for use in preventing and treating suicidality. These methods include computer-assisted methods analyzing the expression of panels of genes, clinical measures, and drug databases. Detailed herein are methods using a universal approach, in everybody, as well as personalized approaches by gender, and by diagnosis. The discovery describes compounds for use in everybody (universal), as well as personalized by gender (males, females), diagnosis (bipolar, depression), gender and diagnosis combined (male bipolar, male depression), male PTSD, male SZ/SZA), and subtypes of suicidality (high anxiety, low mood, combined (affective), and high psychosis (non-affective). Also disclosed are methods for identifying which subjects should be receiving which treatment, using genes expression biomarkers for patient stratification and measuring response to treatment. The disclosure also relates to algorithms, universal and personalized by gender and diagnosis. The algorithms combine biomarkers as well as clinical measures for suicidality and for mental state, in order to identify subjects who are at risk of committing suicide, as well as to track responses to treatments. The disclosure further relates to determining subtypes of suicidality. Such subtypes may delineate groups of individuals that are more homogenous in terms of biology, behavior, and response to treatment.

7 Claims, 42 Drawing Sheets
(7 of 42 Drawing Sheet(s) Filed in Color)

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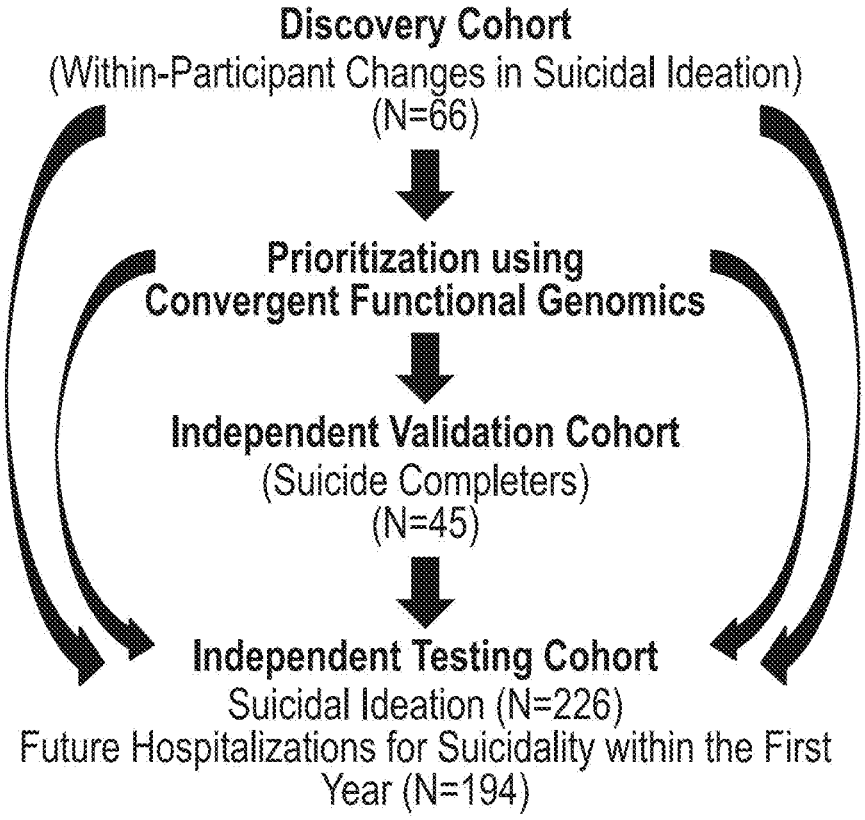

Discovery Cohort
(Within-Participant Changes in Suicidal Ideation)
(N=66)
Prioritization using
Convergent Functional Genomics
Independent Validation Cohort
(Suicide Completers)
(N=45)
Independent Testing Cohort
Suicidal Ideation (N=226)
Future Hospitalizations for Suicidality within the First
Year (N=194)

FIG. 1A

Discovery Cohort :
49 male and 17 female psychiatric participants
who have at least one switch between a
No SI state visit and a High SI state visit.

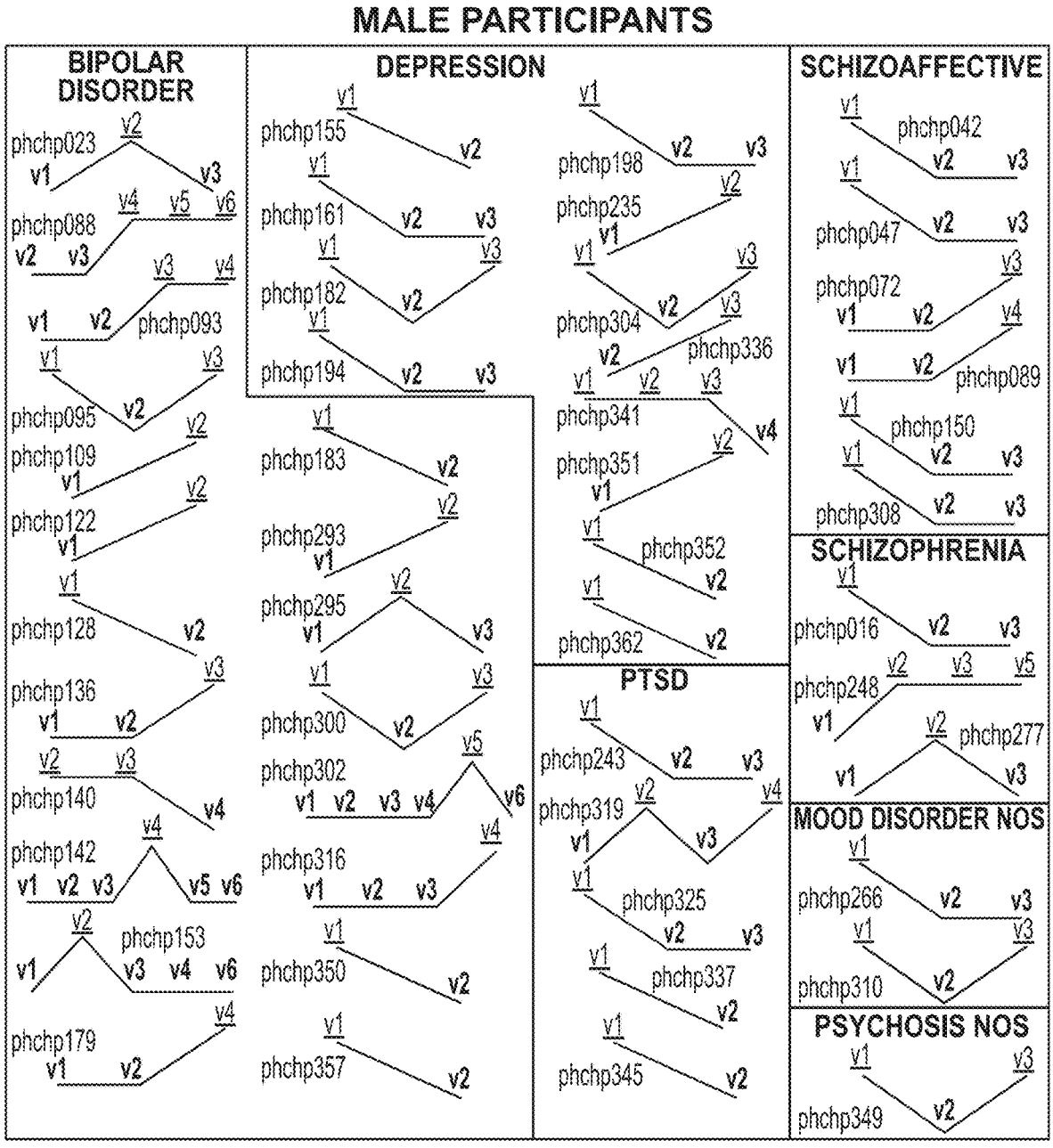


FIG. 1B

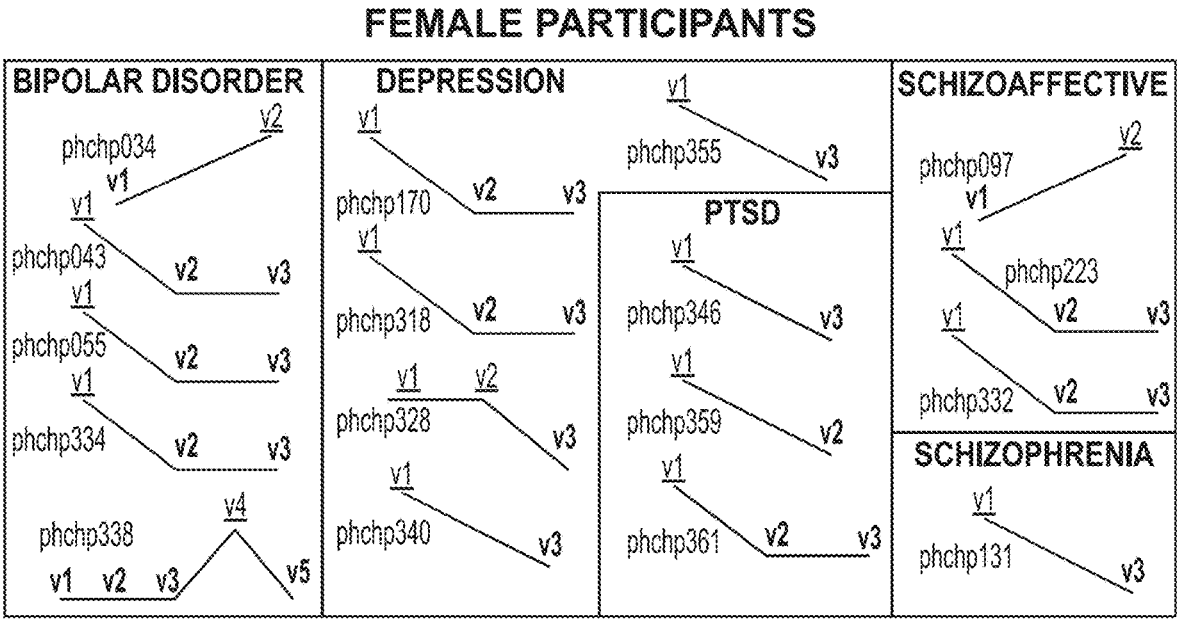

FEMALE PARTICIPANTS
BIPOLAR DISORDER
phchp034
phchp043
phchp055
phchp334
phchp338
DEPRESSION
phchp170
phchp318
phchp328
phchp340
phchp355
PTSD
phchp346
phchp359
phchp361
SCHIZOAFFECTIVE
phchp097
phchp223
phchp332
SCHIZOPHRENIA
phchp131
Suicidal Ideation (SI)
from Hamilton Rating Scale for Depression (HAMD).
No SI - score of 0; High SI - score of 2 or above

FIG. 1B Cont.

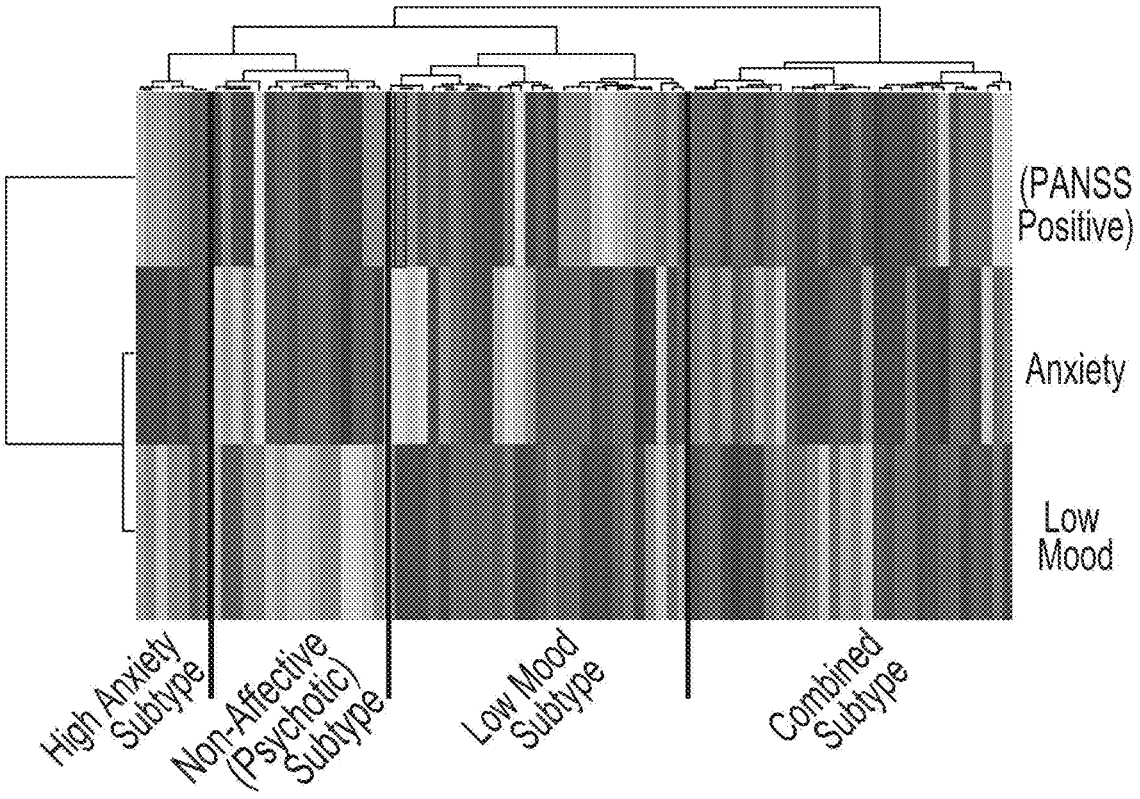

(PANSS Positive)
Anxiety
Low Mood
High Anxiety Subtype
Non-Affective (Psychotic) Subtype
Low Mood Subtype
Combined Subtype

FIG. 1C

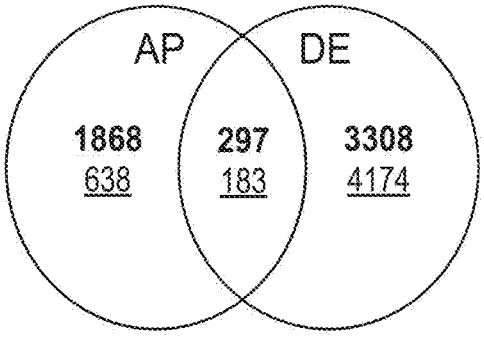

AP
DE
1868
638
297
183
3308
4174

FIG. 1D

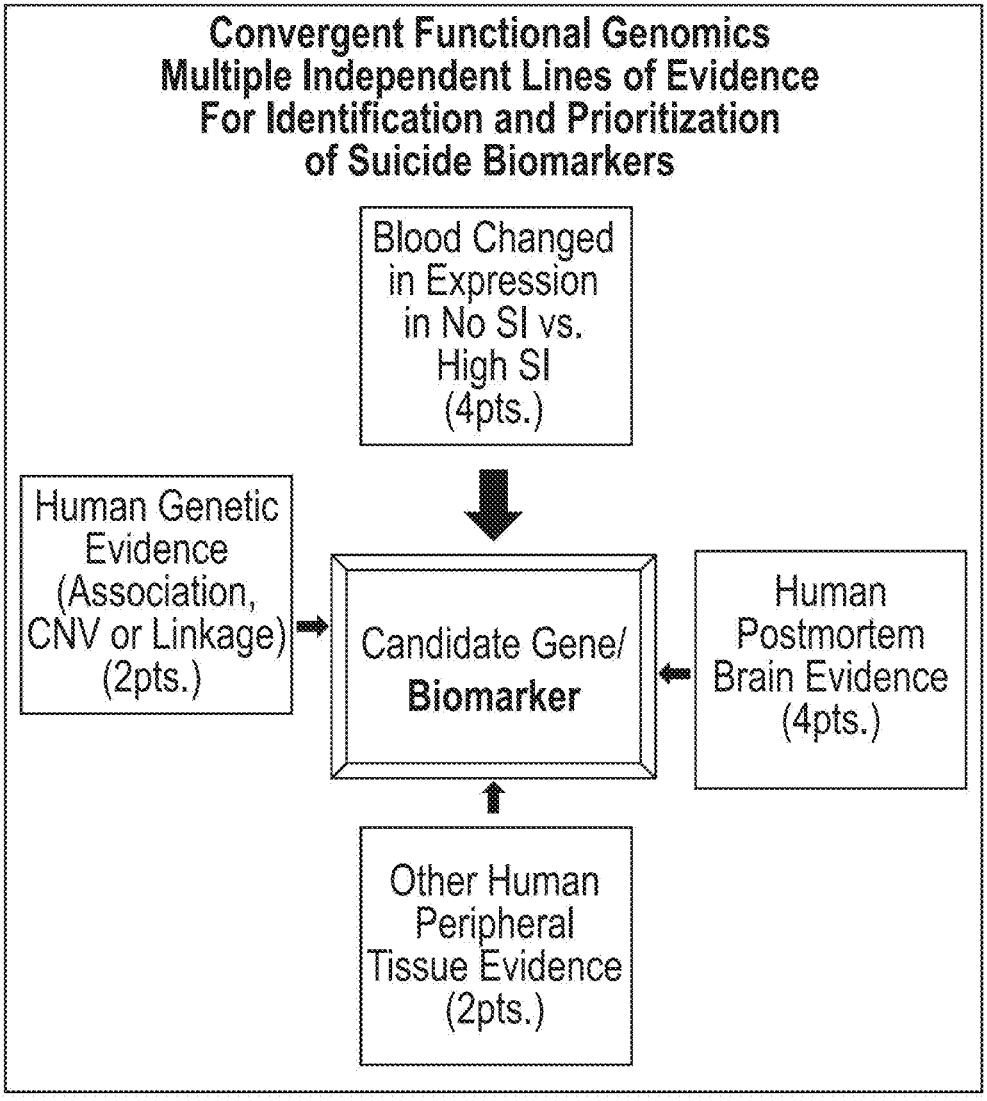

Convergent Functional Genomics
Multiple Independent Lines of Evidence
For Identification and Prioritization
of Suicide Biomarkers
Blood Changed in Expression in No SI vs. High SI (4pts.)
Human Genetic Evidence (Association, CNV or Linkage) (2pts.)
Candidate Gene/ Biomarker
Human Postmortem Brain Evidence (4pts.)
Other Human Peripheral Tissue Evidence (2pts.)

FIG. 1E

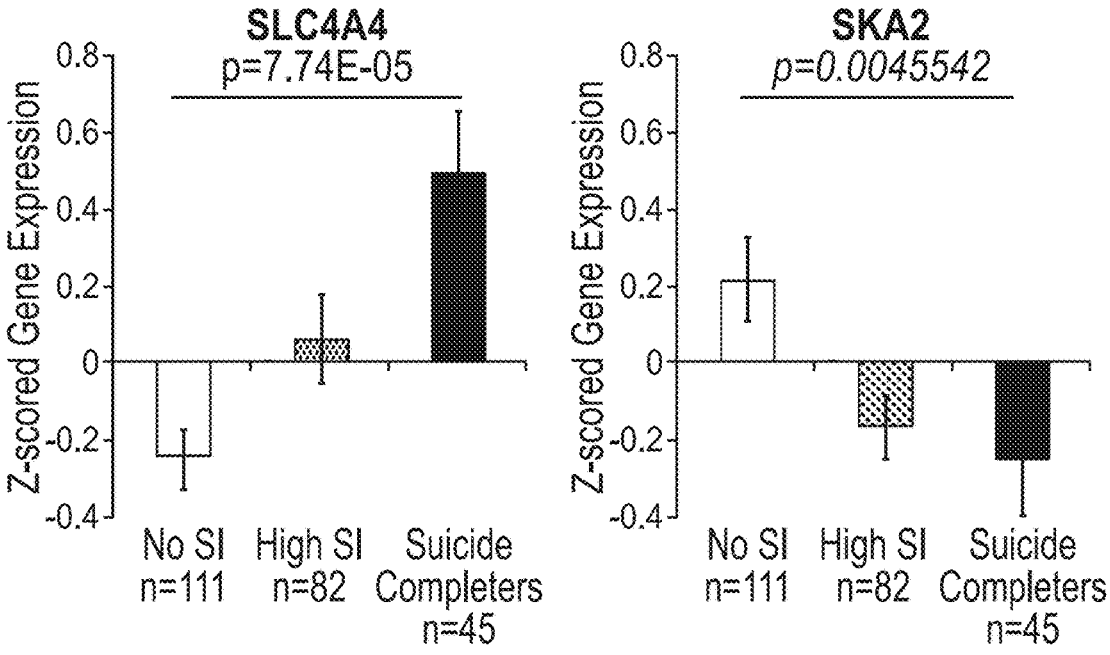

SLC4A4
p=7.74E-05
Z-scored Gene Expression
0.8
0.6
0.4
0.2
0
-0.2
-0.4
No SI n=111
High SI n=82
Suicide Completers n=45
SKA2
p=0.0045542
Z-scored Gene Expression
0.8
0.6
0.4
0.2
0
-0.2
-0.4
No SI n=111
High SI n=82
Suicide Completers n=45

FIG. 1F

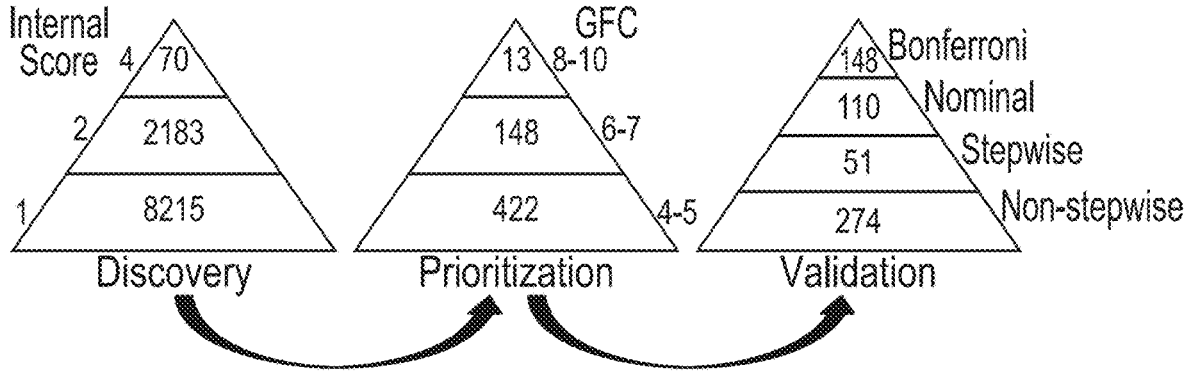
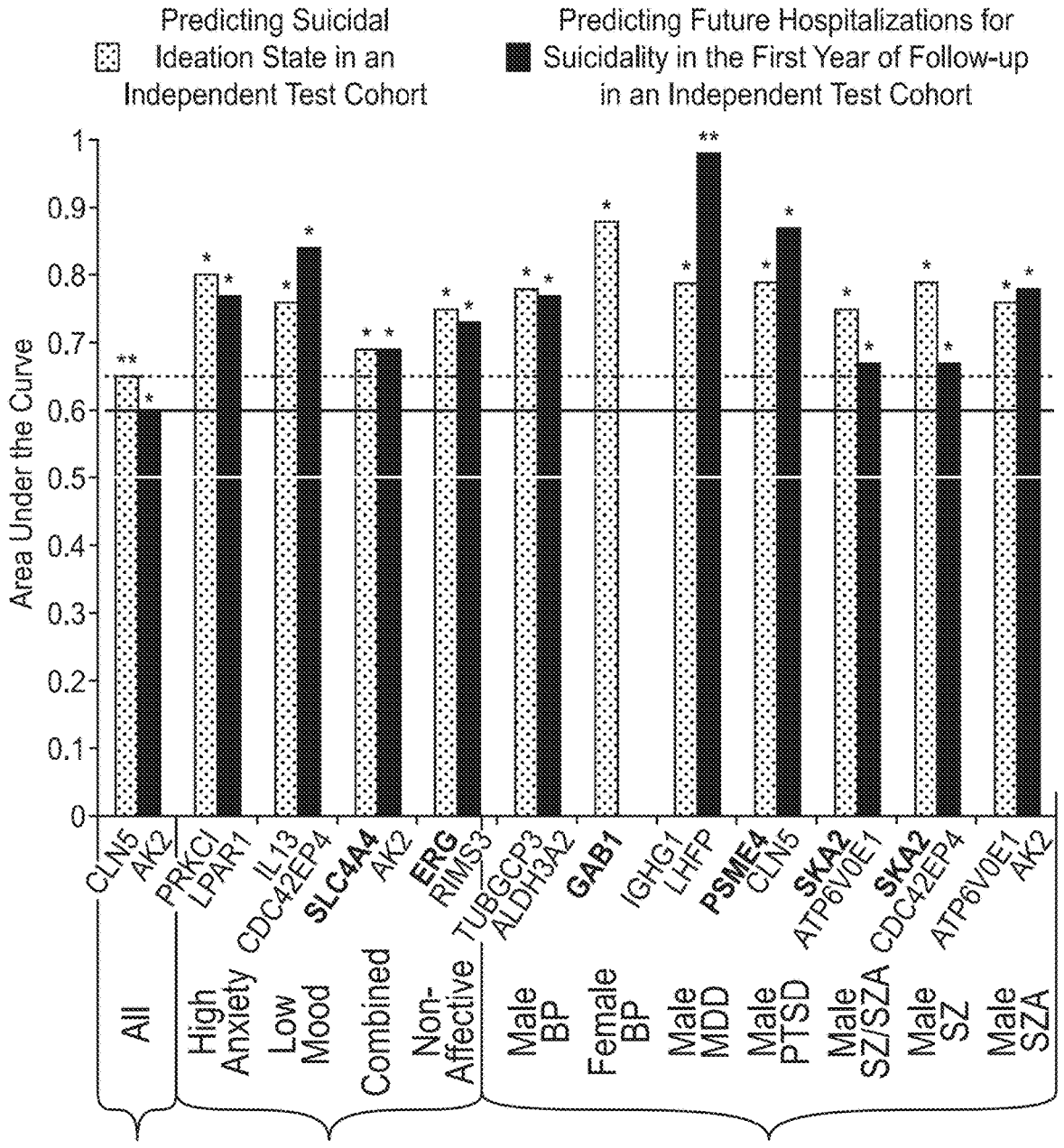

Internal Score
4
70
2
2183
1
8215
Discovery
GFC
13
8-10
148
6-7
422
4-5
Prioritization
148
Bonferroni
110
Nominal
51
Stepwise
274
Non-stepwise
Validation

FIG. 1G



AUCs	All	Subtypes						Personalized (Gender/Dx)											
≥ 0.7	0	0	3	5	7	3	0	0	2	4	15	1	6	0	6	7	7	19	7	0	17	0	15	9
≥ 0.6	16	0	3	5	31	3	38	12	2	8	47	1	6	0	6	7	10	19	38	4	17	2	25	17
≥ 0.5	52	6	3	5	31	3	39	12	2	8	47	1	6	0	6	7	10	19	38	4	17	2	25	17

FIG. 2

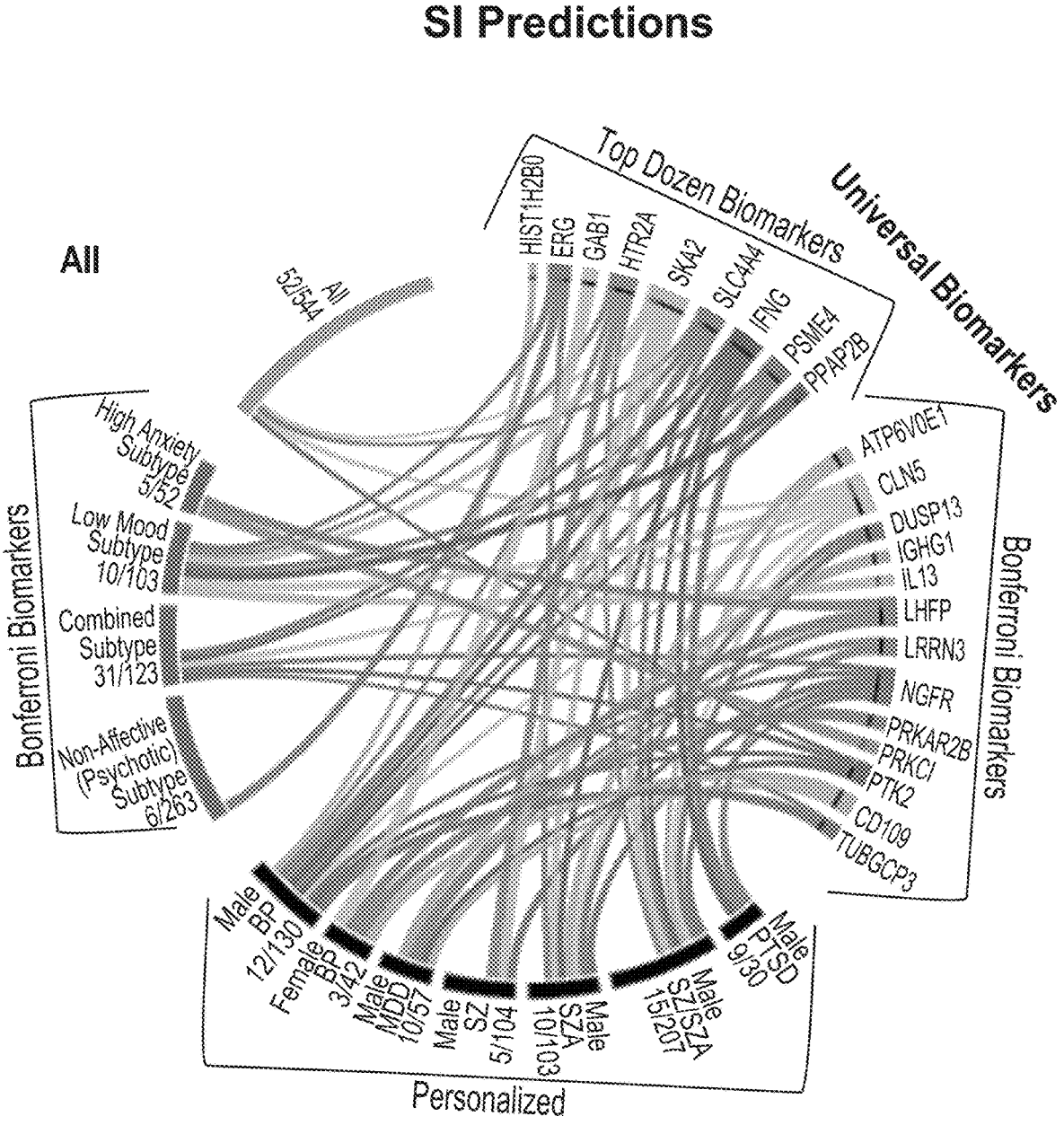

SI Predictions
All
All
52/544
Top Dozen Biomarkers
Universal Biomarkers
HIST1H2B0
ERG
GAB1
HTR2A
SK42
SLC4A4
IFNG
PSME4
PPAP2B
Bonferroni Biomarkers
High Anxiety Subtype 5/52
Low Mood Subtype 10/103
Combined Subtype 31/123
Non-Affective (Psychotic) Subtype 6/263
ATP6V0E1
CLN5
DUSP13
IGHG1
IL13
LHFP
LRRN3
NGFR
PRKAR2B
PRKCI
PTK2
CD109
TUBGCP3
Bonferroni Biomarkers
Male BP 12/130
Female BP 3/42
Male MDD 10/57
Male SZ 5/104
Male SZA 10/103
Male SZ/SZA 15/207
Male PTSD 9/30
Personalized

FIG. 3A

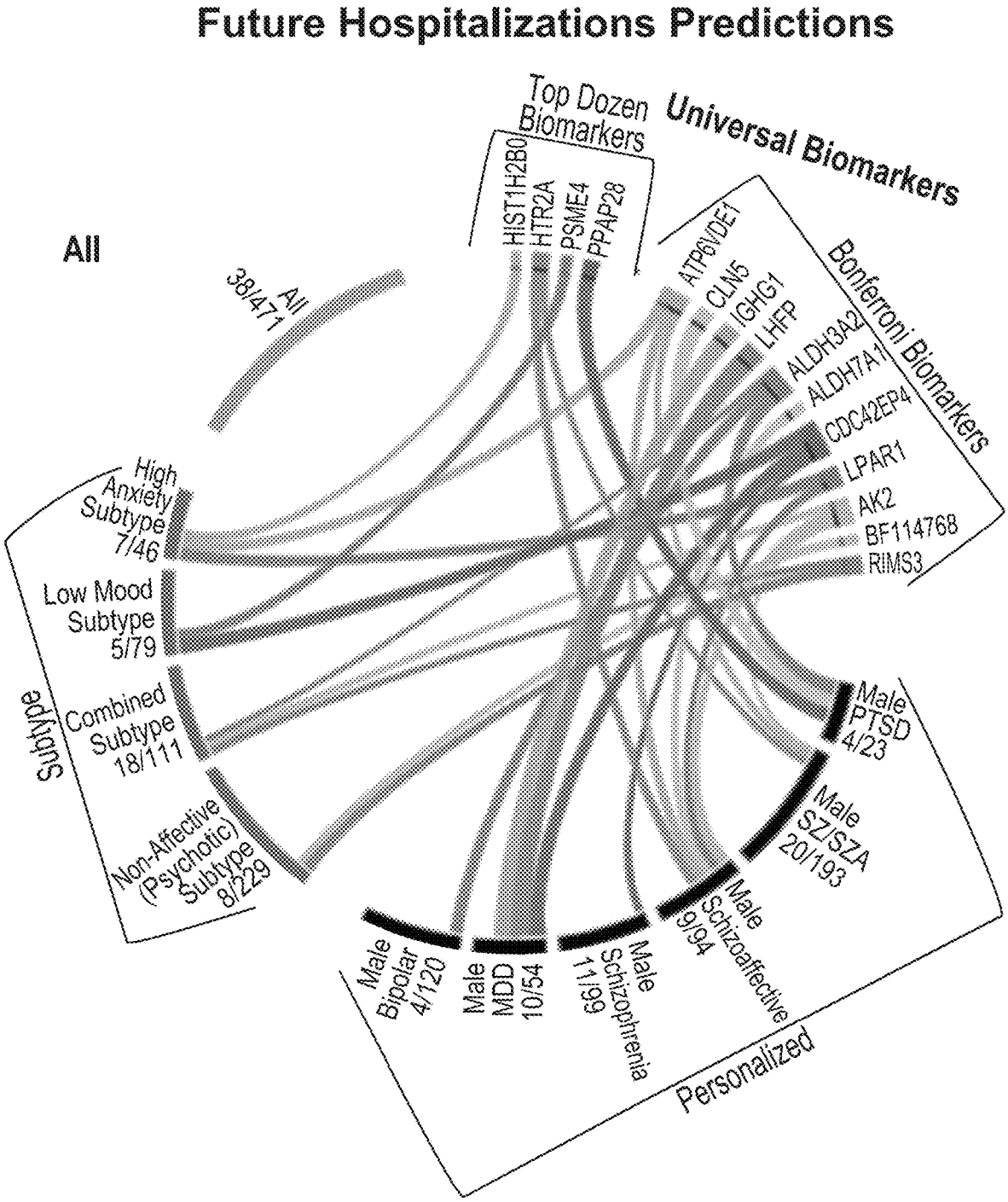

Future Hospitalizations Predictions
All
All
38/471
Top Dozen Biomarkers
HIST1H2B0
HTR2A
PSME4
PPAP28
Universal Biomarkers
ATP6V0E1
CLN5
IGHG1
LHFP
Bonferroni Biomarkers
ALDH3A2
ALDH7A1
CDC42EP4
LPAR1
AK2
BF114768
RIMS3
Subtype
High Anxiety Subtype 7/46
Low Mood Subtype 5/79
Combined Subtype 18/111
Non-Affective (Psychotic) Subtype 8/229
Male PTSD 4/23
Male SZ/SZA 20/193
Male Schizoaffective 9/94
Male Schizophrenia 11/99
Male MDD 10/54
Male Bipolar 4/120
Personalized

FIG. 3B

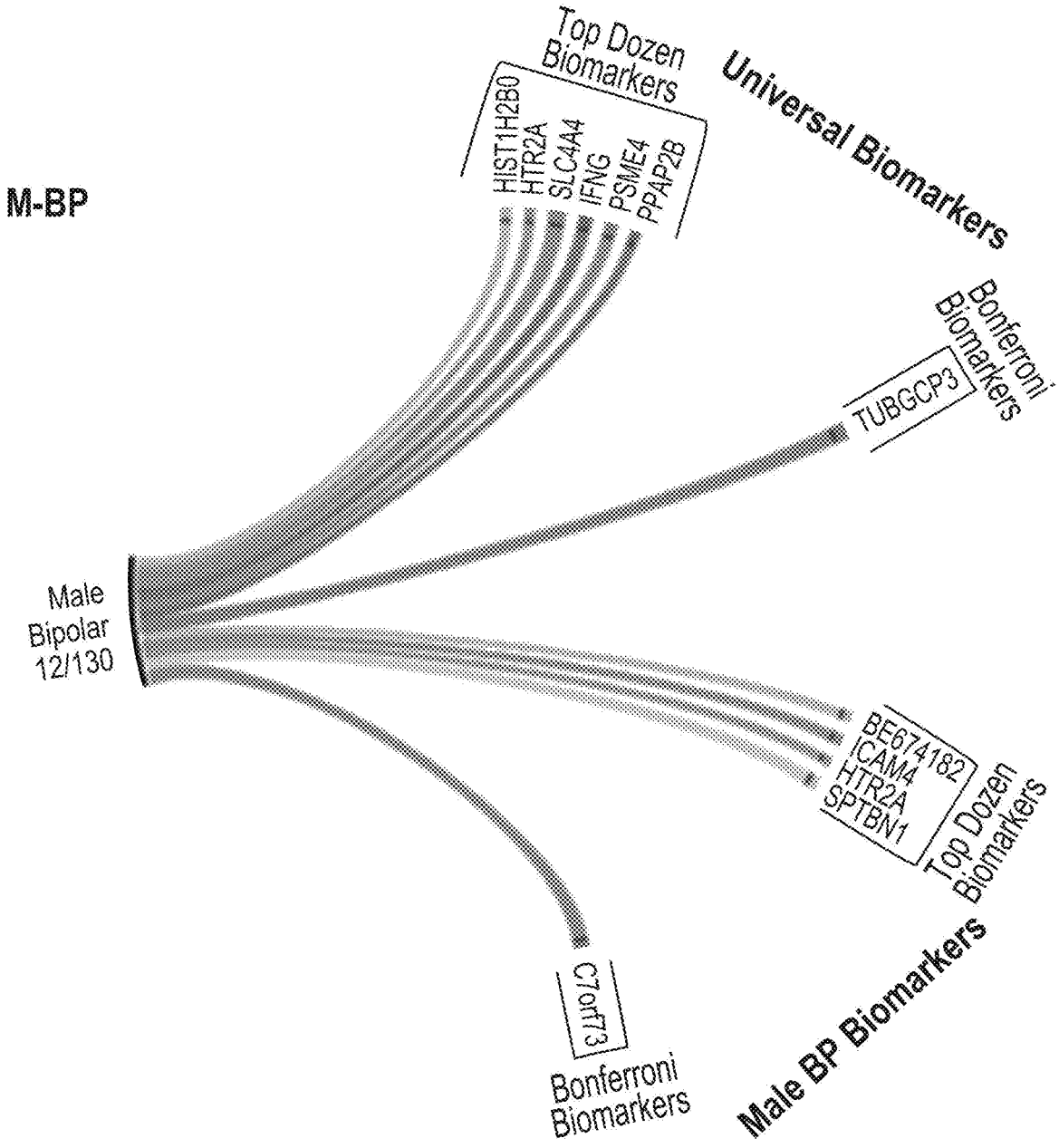

M-BP
Male
Bipolar
12/130
Top Dozen
Biomarkers
HIST1H2BO
HTR2A
SLC4A4
IFNG
PSME4
PPAP2B
Universal Biomarkers
Bonferroni
Biomarkers
TUBGCP3
BE674182
ICAM4
HTR2A
SPTBN1
Top Dozen
Biomarkers
C10orf3
Bonferroni
Biomarkers
Male BP Biomarkers

FIG. 3C

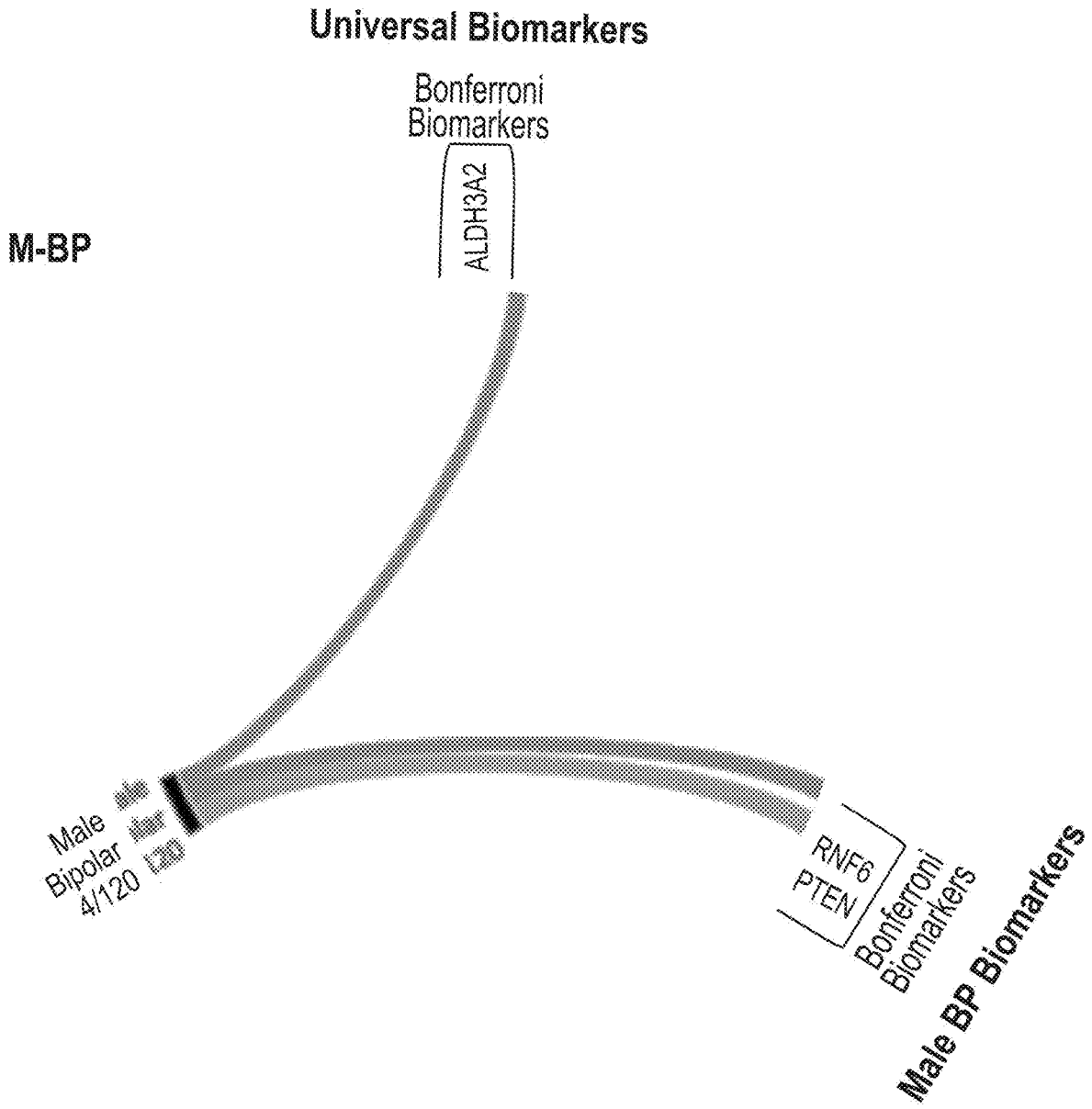

Universal Biomarkers
Bonferroni Biomarkers
ALDH3A2
M-BP
Male Bipolar 4/120
RNF6
PTEN
Bonferroni Biomarkers
Male BP Biomarkers

FIG. 3D

SI Sate Predictions

Universal Biomarkers	Genes	All(52/544)	High Anxiety (5/52)	Low Mood (10/103)	Combined Subtype (31/123)	Non-Affective (6/263)	Male BP (12/130)	Female BP (3/42)	Male MDD (10/57)	Male SZ (5/104)	Male SZA (10/103)	MaleSZSZA (15/207)	Male PTSD (9/30)
Top Dozen	ERG			0.68/2.77E-02		0.75/1.93E-02					0.66/4.96E-02		
Top Dozen	GAB1							0.88/1.49E-02					
Top Dozen	HIST1H2BO						0.67/2.78E-02						
Top Dozen	HTR2A			0.66/4.74E-02			0.65/4.45E-02			0.79/1.58E-02		0.65/2.52E-02	
Top Dozen	IFNG				0.61/3.03E-02		0.71/9.22E-03				0.68/3.14E-02	0.66/1.75E-02	0.72/2.72E-02
Top Dozen	PPAP2B			0.75/4.15E-03			0.65/4.56E-02						
Top Dozen	PSME4			0.68/3.47E-02			0.69/1.41E-02						0.79/6.82E-03
Top Dozen	SKA2	0.61/3.35E-03		0.74/5.91E-03						0.79/1.35E-02	0.73/8.07E-03	0.75/5.97E-04	
Top Dozen	SLC4A4	0.64/3.83E-04			0.69/6.13E-04		0.77/9.27E-04					0.66/1.85E-02	
Bonferroni	ATP6V0E1										0.76/3.76E-03	0.68/9.28E-03	
Bonferroni	CD109							0.81/3.73E-02	0.73/1.11E-02				
Bonferroni	CLNS	0.65/1.86E-04		0.75/4.43E-03	0.68/1.27E-03		0.65/3.91E-02				0.68/3.47E-02	0.68/9.51E-03	
Bonferroni	DUSP13										0.72/9.96E-03	0.71/3.67E-03	
Bonferroni	IGHG1								0.79/2.47E-03				
Bonferroni	IL13			0.76/3.51E-03									
Bonferroni	LHFP		0.78/1.95E-02					0.79/4.60E-02	0.69/3.32E-02				
Bonferroni	LRRN3								0.68/3.56E-02				0.77/1.11E-02
Bonferroni	NGFR				0.66/4.27E-03		0.66/3.55E-02			0.72/4.96E-02	0.72/9.96E-03	0.72/1.92E-03	
Bonferroni	PRKAR2B							0.84/2.69E-02					
Bonferroni	PRKCI		0.8/1.55E-02										
Bonferroni	PTK2	0.61/4.53E-03			0.64/1.04E-02		0.66/3.64E-02		0.69/3.24E-02				
Bonferroni	TUBGCP3				0.61/3.28E-02		0.78/7.44E-04						
Male BP Biomarkers	**GENES**						**Male BP (12/130)**						
Bonferroni	C7orf73						0.75/2.38E-03						
Top Dozen	SPTBN1						0.72/6.62E-03						
Top Dozen	ICAM4						0.67/2.83E-02						
Top Dozen	BE674182						0.66/3.33E-02						
Top Dozen	HTR2A						0.65/4.45E-02						

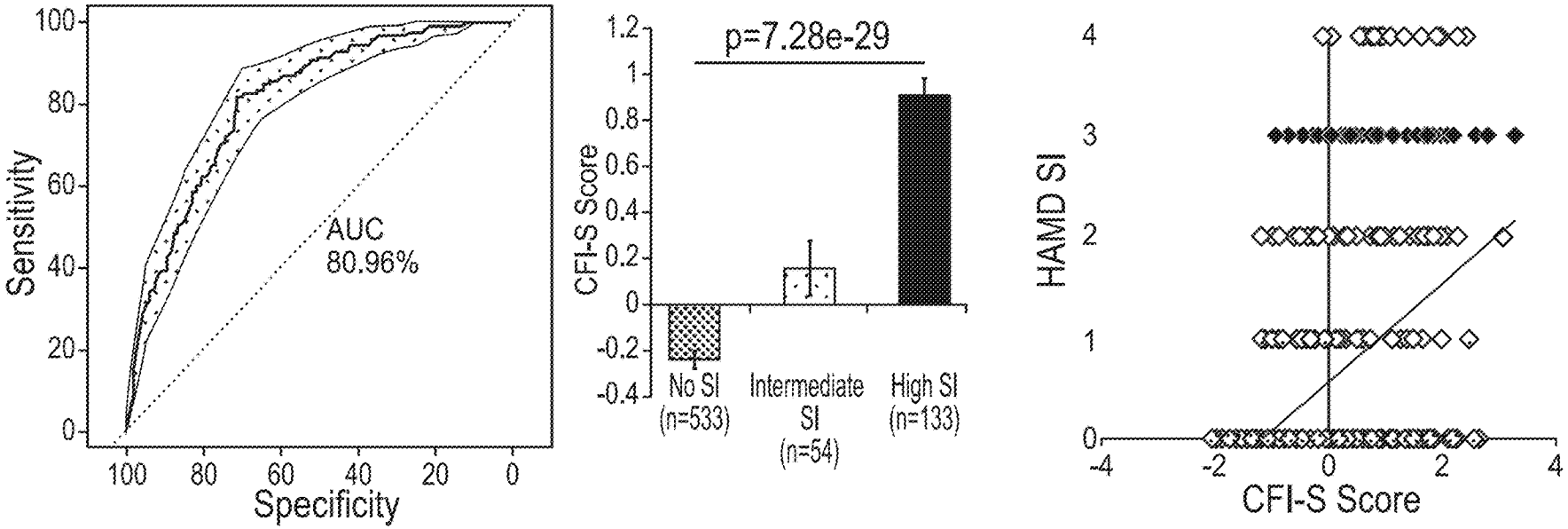
FIG. 3E

Future Hospitalizations Predictions													
Universal Biomarkers	Genes	All(38/471)	High Anxiety (7/46)	Low Mood (5/79)	Combined Subtype (18/111)	Non-Affective (8/229)	Male BP (4/120)	Female BP (na)	Male MDD (5/54)	Male SZ (11/99)	Male SZA (9/94)	MaleSZSZA (20/193)	Male PTSD (4/23)
Top Dozen	HIST1H2BO		0.71/4.20E-02										
Top Dozen	HTR2A										0.72/1.47E-02	0.65/1.67E-02	
Top Dozen	PPAP2B												0.83/2.13E-02
Top Dozen	PSME4			0.72/4.73E-02									
Bonferroni	AK2				0.68/6.72E-03						0.78/2.70E-03	0.64/2.34E-02	
Bonferroni	ALDH3AE				0.63/4.65E-02		0.77/3.38E-02						0.83/2.13E-02
Bonferroni	ALDH7A1										0.72/1.47E-02		
Bonferroni	ATP6VDE1		0.78/1.55E-02								0.73/1.21E-02	0.67/6.53E-03	
Bonferroni	BF114768					0.69/3.36E-02							
Bonferroni	CDC42EP4			0.84/6.28E-03					0.84/5.84E-03	0.67/3.15E-02			
Bonferroni	CLN5												0.87/1.16E-02
Bonferroni	IGHG1								0.9/1.64E-03				
Bonferroni	LHFP								0.98/2.54E-04				
Bonferroni	LPAR1		0.77/1.33E-02								0.7/2.22E-02		
Bonferroni	RIMS3				0.66/1.88E-02	0.73/1.37E-02							
Male BP Biomarkers	GENES						Male BP (12/130						
Bonferroni	PTEN						0.90/3.27E-03						
Bonferroni	RNF6						0.81/1.58E-02						

FIG. 3E cont.

Suicidal Ideation Predictions

FIG. 4A



Predictor	ROC AUC	AUC p-value	t-test	Correlation R	Correlation p-value
CFI-S	0.810	3.20E-29	p=7.28e-29	0.443	2.47E-36

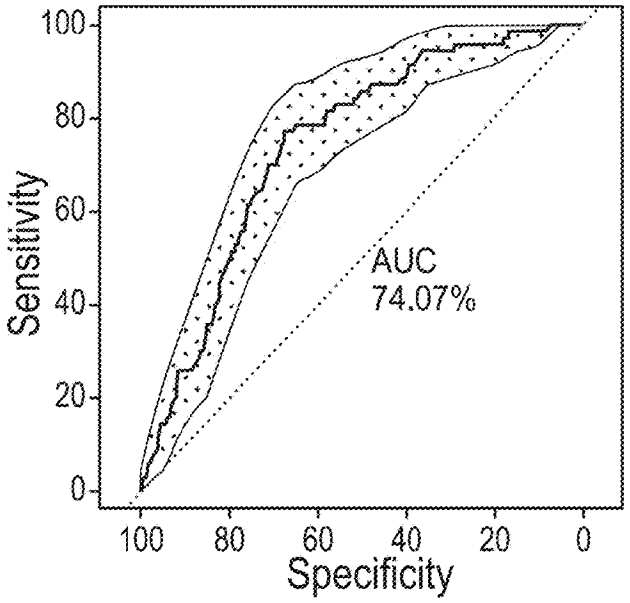
Item	Description	Stepwise	T-test (one tailed) No SI vs High SI
13	Past history of suicidal acts/gestures	Y	1.36E-18
16	Chronic stress; lack of positive relationships, social isolation	Y	1.78E-15

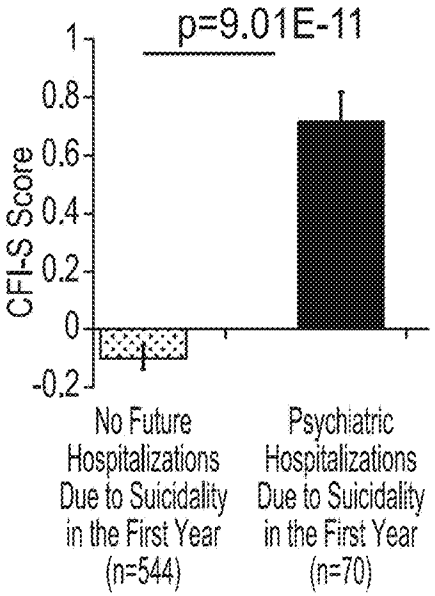
10	Dissatisfaction with present life	Y	3.10E-14
18	Lack of coping skills (cracks under pressure)	Y	1.41E-10
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	2.71E-06
20	History of command hallucinations of self-directed violence	Y	5.56E-06
9	History of excessive introversion, conscientiousness	Y	7.23E-06
15	Acute stress: rejection	Y	7.46E-O6
12	Current substance abuse	Y	8.57E-06
7	Acute stress: losses, grief	Y	9.52E-06
11	Lack of hope for the future	Y	2.65E-04
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	Y	2.70E-04
14	Lack of religious beliefs	Y	3.77E-04
3	Family history of suicide in blood relatives	Y	7.51E-04
6	Acute/severe medical illness, pain	Y	7.76E-04
2	With poor treatment compliance	Y	8.58E-04
4	Personally knowing somebody who committed suicide	Y	0.005188
5	History of abuse: physical, sexual, emotional, neglect	Y	0.042144
19	Lack of children	Y	0.196639
21	Age: Older >60 or Younger <25	N	0.055867
22	Gender: Male	N	0.496484
1	Psychiatric illness diagnosed and treated	All have dx	All have dx

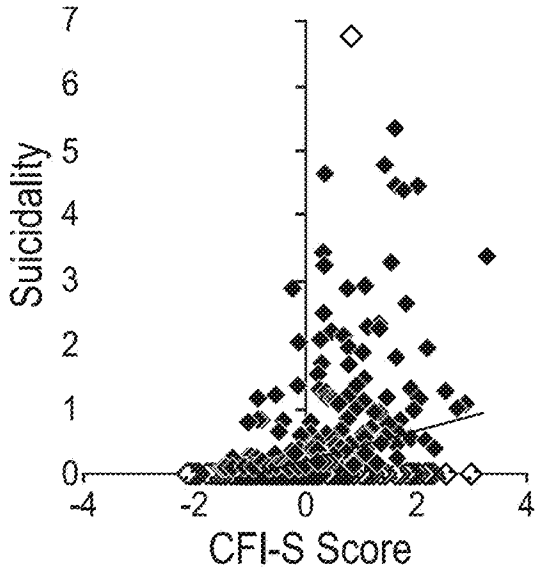
FIG. 4A cont.

Future Hospitalizations Predictions

FIG. 4B







Predictor	ROC AUC	AUC p-value	t-test	Correlation R	Correlation p-value
CFI-S	0.741	2.69E-11	9.01E-11	0.305	6.66E-16

Item	Description	Stepwise	T-test (one tailed) No SI vs High SI
13	Past history of suicidal acts/gestures	Y	5.00E-14
20	History of command hallucinations of self-directed violence	Y	5.91E-05

16	Chronic stress; lack of positive relationships, social isolation	Y	142E-04
15	Acute stress: rejection	Y	4.09E-04
6	Acute/severe medical illness, pain	Y	3.78E-03
9	History of excessive introversion, conscientiousness	Y	6.47E-03
10	Dissatisfaction with present life	Y	8.63E-03
11	Lack of hope for the future	Y	0.010596577
7	Acute stress: losses, grief	Y	0.011549309
18	Lack of coping skills (cracks under pressure)	Y	0.014967478
2	With poor treatment compliance	Y	0.025120503
3	Family history of suicide in blood relatives	Y	0.042731464
22	Gender: Male	Y	0.047852304
12	Current substance abuse	Y	0.069034807
5	History of abuse: physical, sexual, emotional, neglect	Y	0.104299343
4	Personally knowing somebody who committed suicide	Y	0.153942173
8	Chronic stress: perceived uselessness, not feeeling needed, burden to extended kin	Y	0.156594082
21	Age: Older >60 or Younger <25	Y	0.168685211
14	Lack of religious beliefs	Y	0.236253954
17	History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)	Y	0.288722724
19	Lack of children	N	0.489134681
1	Psychiatric illness diagnosed and treated	All have dx	All have dx

FIG. 4B cont.

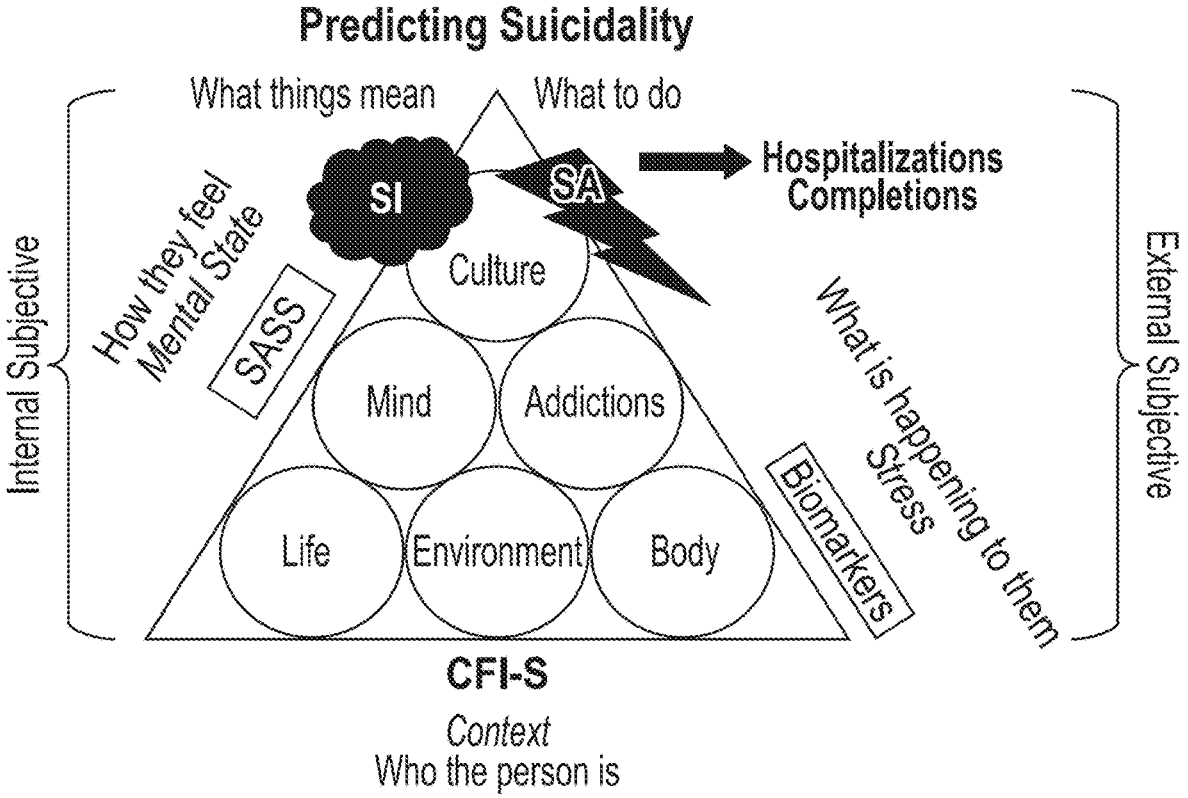
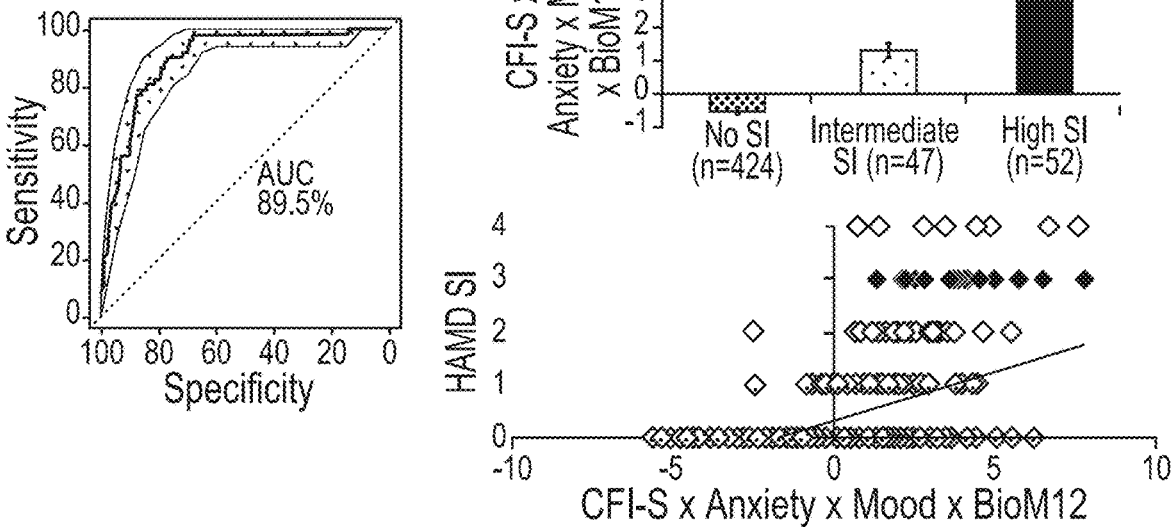
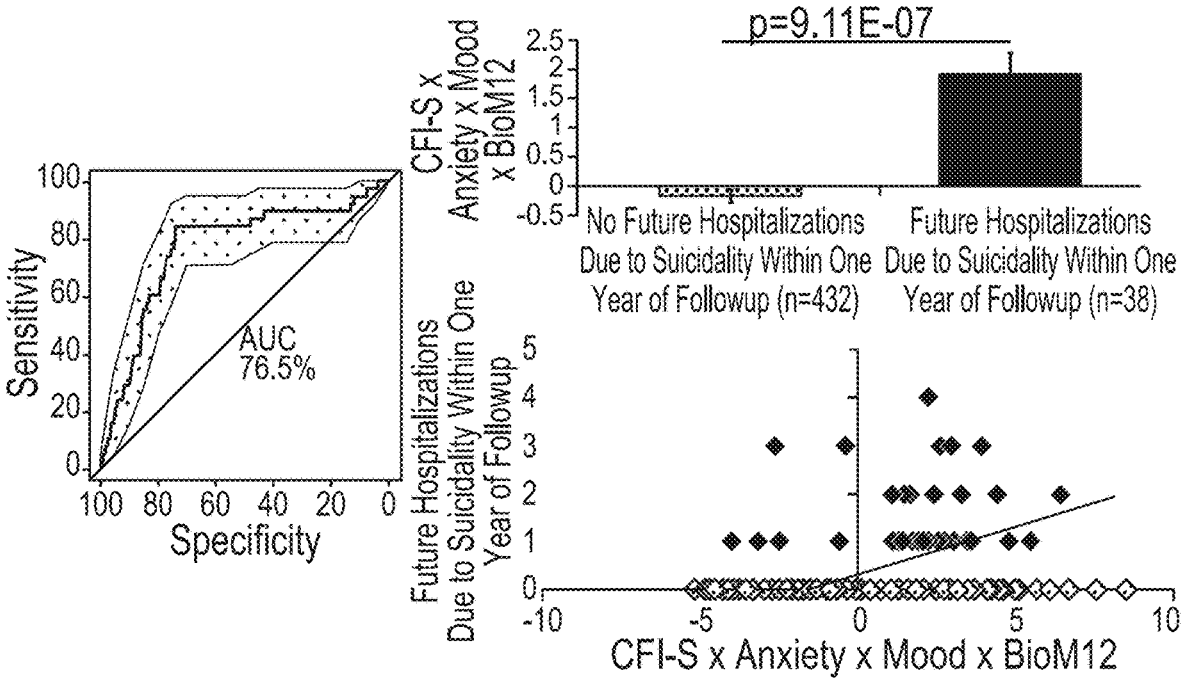

Predicting Suicidality
What things mean
What to do
SI
SA
Hospitalizations
Completions
How they feel
Mental State
SASS
Culture
Mind
Addictions
Life
Environment
Body
What is happening to them
Stress
Biomarkers
Internal Subjective
External Subjective
CFI-S
Context
Who the person is

FIG. 5A

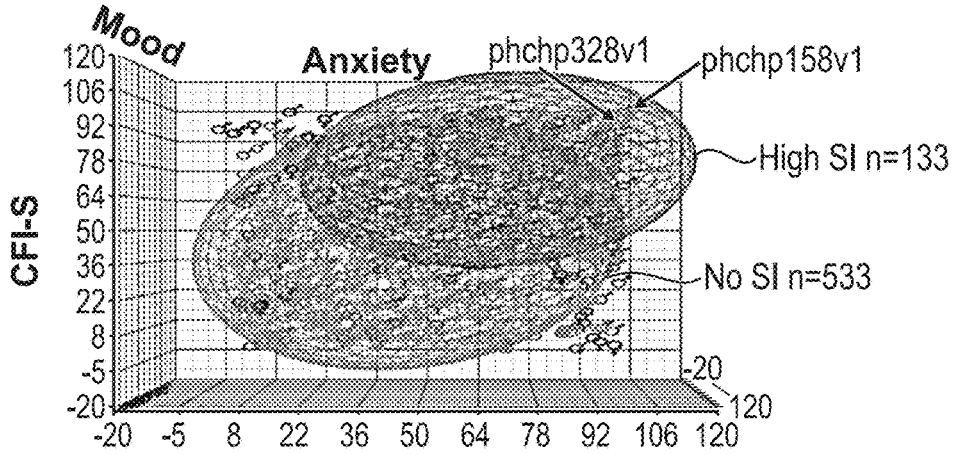


Predictor	Predicting	ROC AUC	AUC p-value	ANOVA	Correlation R	Correlation p-value
CFI-S x Anxiety x Mood x BioM12	High SI	0.90	3.87E-21	9.43E-33	0.501463	5.91E-35



Predictor	Predicting	ROC AUC	AUC p-value	T-test	Correlation R	Correlation p-value
CFI-S x Anxiety x Mood x BioM12	Future Hospitalizations for Suicidality	0.77	2.87E-08	9.11E-07	0.228367	2.81E-07

FIG. 5B



Dimensions	Test Results Variable(s)	ROC AUC	Std. Error	AUC p-value	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
1D	CFIS	0.81	0.019	6.42E-29	0.772	0.847
2D	CFIS x Anxiety	0.833	0.019	4.16E-33	0.796	0.869
3D	CFIS x Anxiety x Mood	0.841	0.018	8.01E-35	0.807	0.876
4D	CFIS x Anxiety x Mood x BioM12	0.849	0.019	2.37E-36	0.812	0.886

Participant 15B			Participant 32							
Predictors	Visit 1 High SI HAMD-SI 4	+2 H	Visit 1 High SI HAMD-SI 3 (T-14 months)%	+1 H	Visit 2 High SI HAMD-SI 2 (T-10 months)%	+1 H	Visit 3 No SI HAMD-SI 0 (T-5 months)%	+4 H	T Suicide
ARRB1	34.4		59.5		56.7		93.1		
LDLRAP1	21.4		99.8		59.3		29.8		
IFNG	91.4		88.5		76.6		18.2		
ERG	36.8		30.7		16.3		45.9		
CCL28	40.6		76.5		70.8		39.4		
SKA2	64.8		99.9		59.5		29.7		
SLC4A4	92.3		92.7		89.7		42.5		
PPAP2B	62.9		89.2		36.7		83.9		
HIST1H2BO	87.6		97.5		44.2		39		
PSME4	67.8		35.1		83.5		56.7		
GAB1	53.1		89.6		98.1		11.4		
HTR2A	8.6		62.7		43.6		57.4		
BioM12	70.3		99.4		90.3		46.1		
Mood	100		91.3		47.8		10.2		
CFIS	99		94.9		90.9		79.4		
Anxiety	99.1		99		94.1		73.1		
CFIS x Anxiety x Mood	100		99.4		87.7		56.6		
CFIS x Anxiety x Mood x BioM12	99.3		100		94.1		56.8		

FIG. 5C

Predictors	Visit 1 High SI HAMD-SI 3 (T- 14 months) %	+ 1 H	Visit 2 High SI HAMD-SI 2 (T- 10 months) %	+ 1 H	Visit 3 No SI HAMD-SI 0 (T- 5 months) %	+ 4 H	T Suicide
EPB41L5	*39.03*		*19.68*		*100*		
HAVCR2	62.85		34.2		17.67		
ARHGAP15	29.17		33.26		25.67		
HTRA1	**100**		40.46		20.6		
PER1	69.72		26.62		20.98		
PDXDC1	*17.75*		*62.26*		*100*		
PIK3C3	81.07		65.73		56.85		
GTF3C2	*42.63*		*51.89*		*81.08*		
ALDH3A2	81.47		66.03		55.81		
BCL2	71.02		40.43		61.61		
MO83B	86.13		65.50		23.66		
DPCD	*33.51*		*46.59*		*44.6*		
GTF3C3	23.14		62.60		17.21		
ASPH	57.87		16.57		7.95		
KLHL28	59.17		86.01		37.19		
UIMC1	46.25		60.38		13.84		
SNX27	40.27		100		20.41		
ACTR3	78.33		80.32		61.09		
NUDT6	*65.18*		*80.59*		*73.34*		
LRRC8B	86.34		89.48		70.00		
CSNK1A1	93.4		93.83		78.25		
LARP4	90.63		91.63		71.60		
ZNF548	83.18		69.06		34.55		
BioM18	82.99		32.54		17.85		
BioM32	95.40		85.90		29.51		
BioM50	**100**		62.49		21.16		
Anxiety	96.00		84.18		59.80		
CFI-S	87.15		79.83		65.19		
Mood	83.61		50.86		21.43		
SASS	97.13		72.27		42.75		
CFI-S +SASS	**100**		72.24		40.62		
UP-Suicide	**100**		72.14		36.80		

Figure 5D

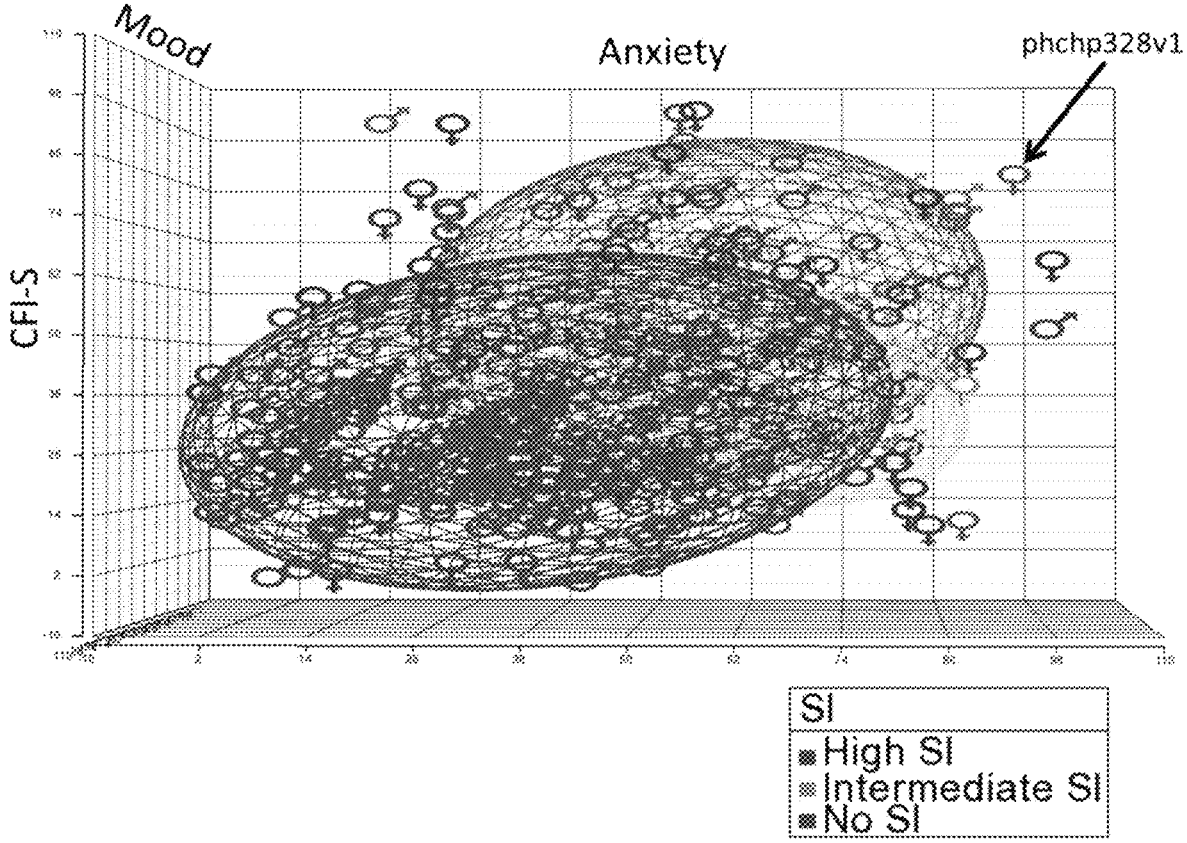

Mood
Anxiety
phchp328v1
CFI-S
SI
High SI
Intermediate SI
No SI

FIG. 5E

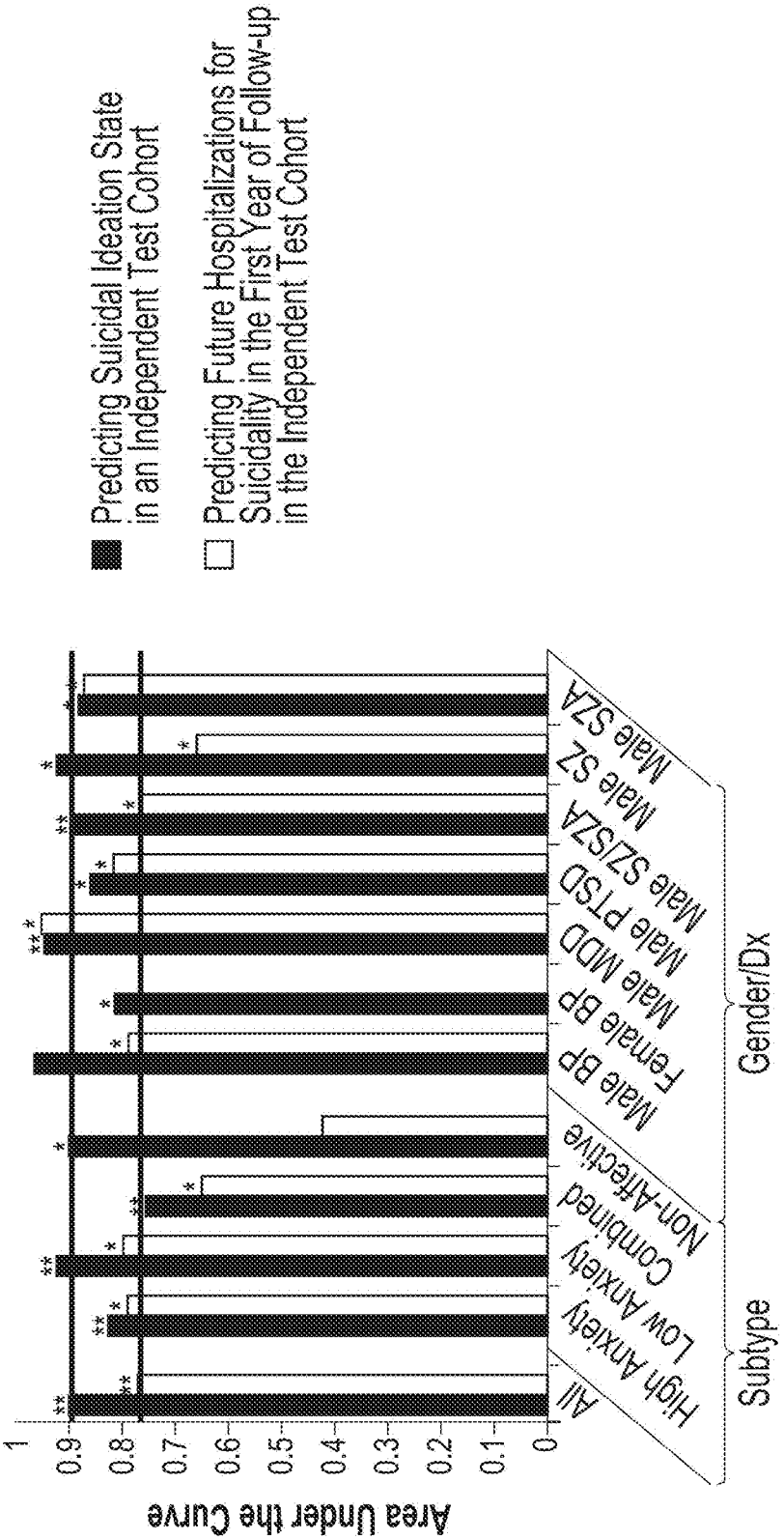

Predicting Suicidal Ideation State in an Independent Test Cohort
Predicting Future Hospitalizations for Suicidality in the First Year of Follow-up in the Independent Test Cohort
Area Under the Curve
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
All
High Anxiety
Low Anxiety
Combined
Non-Affective
Male BP
Female BP
Male MDD
Male PTSD
Male SZ/SZA
Male SZ
Male SZA
Subtype
Gender/Dx

FIG. 6

	Subjects Total/ High SI	High SI prediction ROC AUC ROC p-value	t-test (High SI vs. No SI)	Correlation R P-value	Subjects Total/ First year hospitalized for suicidality/All future hospitalized for 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 for suicidality
All	544/52	**0.8954 3.87E-21**	**3.42E-19**	**0.5015 5.91E-35**	470/38/98	**0.7654 2.87E-08**	**9.11E-07**	**0.2284 2.81E-07**	**0.2803 1.72E-10**
High Anxiety Subtype	50/5	0.8222 9.53E-03	1.22E-02	0.3457 6.97E-03	46/7/13	0.7912 7.52E-03	4.14E-03	0.2933 2.40E-02	0.1685 1.24E-01
Low Mood Subtype	99/10	**0.9191 7.42E-06**	**3.61E-06**	**0.4268 5.28E-05**	78/5/13	0.8 1.27E-02	1.15E-02	0.2756 7.29E-03	0.1808 4.99E-02
Combined Subtype	119/31	**0.7548 1.29E-05**	1.89E-05	**0.4672 4.25E-08**	111/18/38	0.6511 2.15E-02	1.87E-02	0.1712 3.62E-02	0.2077 1.33E-02
Non-Affective Subtype	252/6	0.9004 4.04E-04	3.94E-02	**0.3319 3.39E-08**	229/8/34	0.4242 7.67E-01	6.72E-01	-0.0139 5.83E-01	0.0322 3.12E-01
Male Bipolar	128/12	**0.9605 8.03E-08**	**4.79E-07**	**0.6322 6.05E-16**	120/4/9	0.7888 2.51E-02	6.30E-02	0.1927 1.75E-02	0.2765 1.07E-03
Female Bipolar	31/3	0.8095 4.12E-02	5.03E-02	0.4005 1.28E-02	NA/NA/NA	NA NA	NA	NA NA	NA NA
Male Depression	57/10	**0.9404 7.02E-06**	4.35E-05	**0.6067 2.83E-07**	54/5/6	0.951 4.88E-04	**1.83E-07**	0.363 3.49E-03	0.3059 1.16E-02
Male PTSD	28/9	0.8596 1.24E-03	1.29E-03	0.6643 5.78E-05	23/4/14	0.8158 2.58E-02	2.72E-03	0.3493 5.12E-02	0.5951 5.30E-04
Male Schizophrenia/ Schizoaffective	206/15	**0.8918 2.22E-07**	**5.80E-08**	**0.4356 3.01E-11**	193/20/52	0.7598 7.20E-05	9.50E-04	**0.315 4.05E-06**	**0.3345 7.79E-07**
Male Schizophrenia	103/5	0.9204 7.86E-04	5.21E-04	0.389 2.44E-05	99/11/21	0.6612 4.12E-02	1.03E-01	0.2334 1.00E-02	0.3595 1.03E-04
Male Schizoaffective	103/10	0.8763 4.84E-05	3.01E-05	**0.4714 2.50E-07**	94/9/31	0.8719 1.28E-04	7.79E-05	0.3939 4.28E-05	0.3788 7.67E-05

FIG. 6 cont.

FIG. 7

Gene Symbol/ Gene Name	Probesets	Step 1 Discovery in Blood (Direction of Change) Method/ Score	Step 2 Convergent Functional Genomics (CFG) Evidence For In-volvement in Suicide Score	Step 3 Validation in Blood ANOVA p-value/ Score	Step 4 Significant Prediction of Suicidal Ideation All Best in Subtypes Best in Individualized Gender/Dx ROC AUC/p-value	Step 4 Significant Prediction of First Year Hospitalizations for Suicidality All Best in Subtypes Best in Individualized Gender/DxROC AUC/p-value	Step 5 Other Psychiatric and Related Disorders Evidence	Step 6 Drugs that Modulate the Biomarkers in Opposite Direction to Suicide	CFE Poly-evid-ence Score
APOE apolipo-protein E	203382_s_at	(I) DE/1	6	3.44E-09/4	All: 0.58/2.26E-02 Combined Subtype: 0.62/1.99E-02 M-BP: 0.71/9.02E-03	M-PTSD 0.78/4.43E-02	Aggression, Aging, Alcohol, Alzheimer's Disease, ASD, Dementia, Depression-related, Longevity, MDD, Psychosis, PTSD, SZ	Omega-3	19
IL6 interleukin 6	205207_at	(I) AP/1	6	1.82E-15/4	All: 0.58/3.74E-02 Combined Subtype: 0.61/3.98E-02	M-PTSD 0.82/2.58E-02	Aggression, Antipsychotics Anxiety, BP, Cognition, Dementia, Depression, Longevity, MDD, Mood Neurological, Panic, Personality, SZ/SZA,	Antipsychotics, Antidepressants, Tocilizumab, Siltuximab	19

							PTSD, Sleep, Stress, SZ		
CD164 CD164 molecule, sialomucin	208654_s_at	(D) DE/2	4	3.01E-08/4	All: 0.59/1.80E-02 M-BP: 0.68/1.94E-02	M-PTSD 0.86/1.43E-02	BP, Cocaine Dependence, Stress	Clozapine	18
CD47 CD47 molecule	211075_s_at	(D) DE/2	4	1.62E-17/4	All: 0.6/9.71E-03 Depressed Subtype: 0.68/2.99E-02 M-SZA: 0.69/2.19E-02	M-PTSD 0.79/3.72E-02	MDD, Stress, SZ	Clozapine Omega-3	18
HTR2A 5-hydroxy-tryptamine (serotonin) receptor 2A, G protein-coupled	244130_at	(I) DE/2	8	NS	Depressed Subtype: 0.66/4.74E-02 M-SZ: 0.79/1.58E-02	M-SZA 0.72/1.47E-02	Alcohol, Anxiety, BP, MDD, SZ, OCD Response to Antidepressants	Clozapine, Lithium, Valproate, Antipsychotics, Antidepressants	18
PGK1 phospho-glycerate kinase 1	217383_at	(D) DE/2	4	4.07E-07/4	M-SZA: 0.73/8.31E-03	M-SZA 0.71/1.84E-02	Alcohol, BP, MDD, SZ, SZA	Clozapine Diazepam	18
PKP4 plakophilin 4	201929_s_at	(D) DE/1	5	3.82E-08/4	Combined Subtype: 0.62/2.59E-02 M-SZ: 0.75/2.93E-02	Combined Subtype: 0.68/8.75E-03	Alcohol, BP, MDD, SZ/SZA, SZ	Valproate	18
ACP1 acid phos-phatase 1, soluble	1554808_at	(D) DE/1	6	3.82E-11/4		M-MDD 0.74/3.79E-02	BP, SZ	Omega-3, SSRIs, Olanzapine	17
DYRK2 dual-specificity tyrosine-(Y)-phosphorylа-	202969_at	(D) DE/1	4	1.67E-13/4	All: 0.58/3.37E-02 Combined Subtype: 0.61/3.00E-02 M-SZ/SZA: 0.68/9.85E-03	M-PTSD 0.82/2.58E-02	Aging, BP, MDD, Sleep	Clozapine	17

FIG. 7 cont.

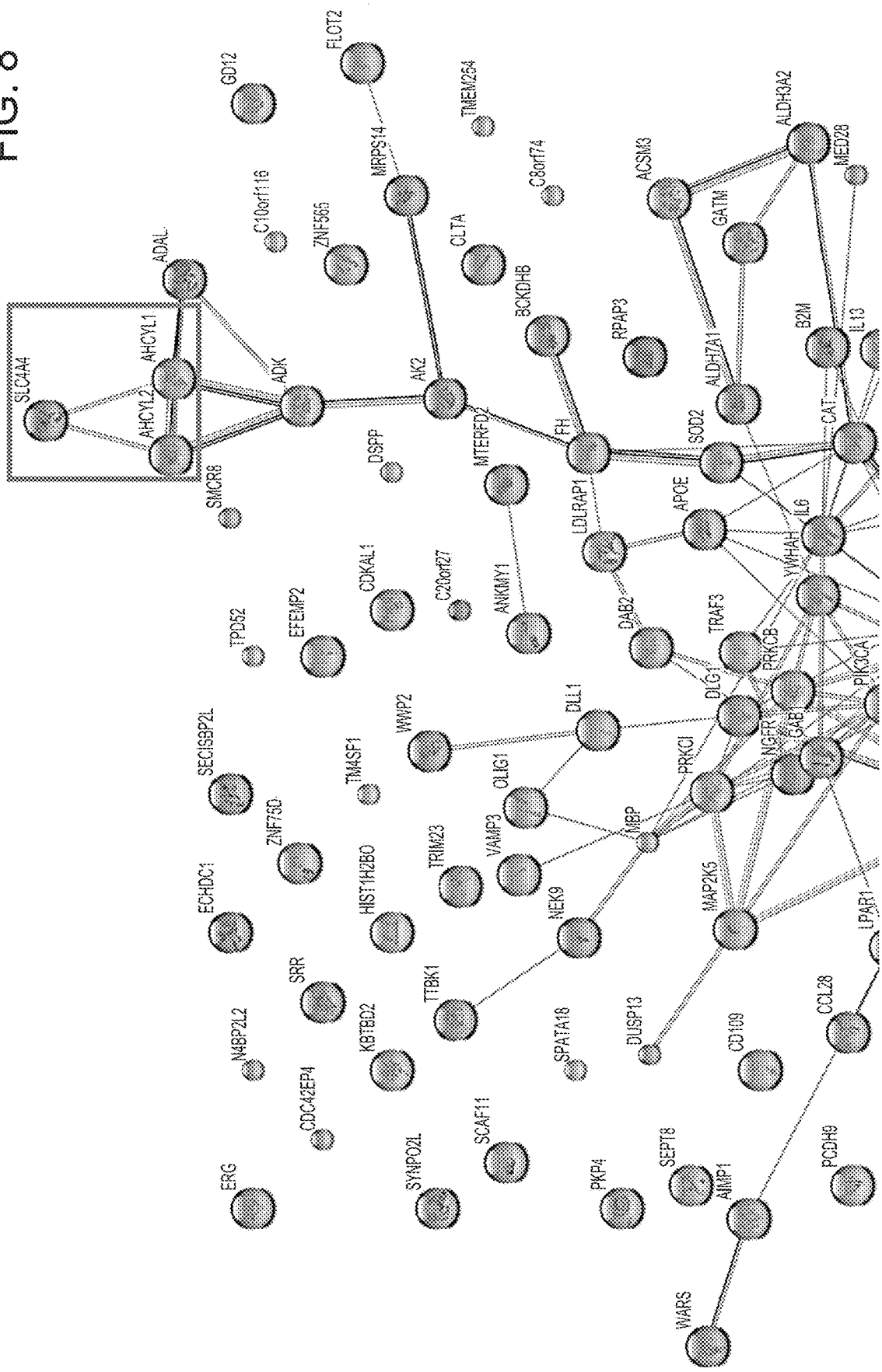
tion regulated kinase 2									
GATM L-arginine: glycine amidino-transferase	1566861_at	(I) DE/1	4	1.80E-12/4	Combined Subtype: 0.6/4.84E-02 M-BP: 0.68/1.94E-02	M-PTSD 0.78/4.43E-02	Alzheimer's Disease, BP, MDD, PTSD	Omega-3	17
GSK3B glycogen synthase kinase 3 beta	226183_at	(D) DE/1	6	2.19E-36/4	M-SZA: 0.68/3.47E-02		Aging, Alcohol, BP, Dementia, Depression, Mood Stabilizers, Lithium response, MDD, SZ	Lithium, SSRI, Antipsychotics	17
IFNG interferon, gamma	210354_at	(D) AP/1	8	NS	All: 0.6/1.01E-02 Combined Subtype: 0.61/3.03E-02 M-PTSD: 0.73/2.72E-02	M-PTSD 0.82/2.58E-02	SZ, MDD, PTSD, Anxiety, SZ/SZA	Antipsychotics	17
ITGB1BP1 integrin beta 1 binding protein 1	203337_x_at	(D) DE/1	4	1.11E-08/4	Depressed Subtype: 0.67/4.21E-02 M-SZ: 0.78/1.64E-02	Non-Affective Subtype 0.7/2.59E-02	Alzheimer's Disease, BP, Mood, SZ	Lithium	17
LHFP lipoma HMGIC fusion partner	218656_s_at	(I) DE/1	4	3.97E-10/4	All: 0.57/5.00E-02 Anxious Subtype: 0.78/1.95E-02 F-BP: 0.79/4.60E-02	M-MDD 0.98/2.54E-04	SZ	Omega-3	17
LPAR1 lysophos-phatidic acid receptor 1	204036_at	(D) AP and DE/1	4	1.35E-23/4	M-BP: 0.68/2.13E-02	Anxious Subtype 0.77/1.33E-02	Aging, BP, Longevity, MDD, Mood, PTSD, SZ	Clozapine, Omega-3, Antidepressants	17

FIG. 7 cont.

PRKCI protein kinase C, iota	209677_at	(D) DE/1	4	2.71E-05/4	Anxious Subtype: 0.8/1.55E-02	Combined Subtype: 0.64/2.64E-02	BP, Circadian abnormalities Cocaine Dependence, MDD, SZ	Ingenol mebutate	17
SKA2 spindle and kinetochore associated complex subunit 2	225686_at	(D) DE/1	8	4.55E-03/2	All: 0.61/3.35E-03 Depressed Subtype: 0.74/5.91E-03 M-SZ: 0.79/1.35E-02	M-PTSD 0.84/1.75E-02	PTSD, Stress		17
SLC4A4 sodium bicarbonate cotran-sporter	210739_x_at	(I) AP/1	6	7.74E-05/4	All: 0.64/3.83E-04 Combined Subtype: 0.69/6.13E-04 M-BP: 0.77/9.27E-04		Circadian abnormalities, Longevity, MDD, SZ	Valproate	17

FIG. 7 cont.

FIG. 8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MED28
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C8orf74
ACSM3
ZNF565
GATM
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AHCYL1
BCKDHB
RPAP3
B2M
IL13
SLC4A4
ADK
AK2
ALDH7A1
AHCYL2
DSPP
MTERFD2
FH
SOD2
CAT
SMCR8
APOE
IL6
LDLRAP1
CDKAL1
C20orf27
ANKMY1
YWHAH
TPD52
EFEMP2
DAB2
TRAF3
PRKCB
PIK3CA
SECISBP2L
WWP2
DLL1
DLG1
GAB1
NGFR
TM4SF1
OLIG1
PRKCI
ZNF750
VAMP3
MBP
ECHDC1
TRIM23
HIST1H2BD
NEK9
MAP2K5
LPAR1
SRR
TTBK1
N4BP2L2
KBTBD2
SPATA18
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ERG
PKP4
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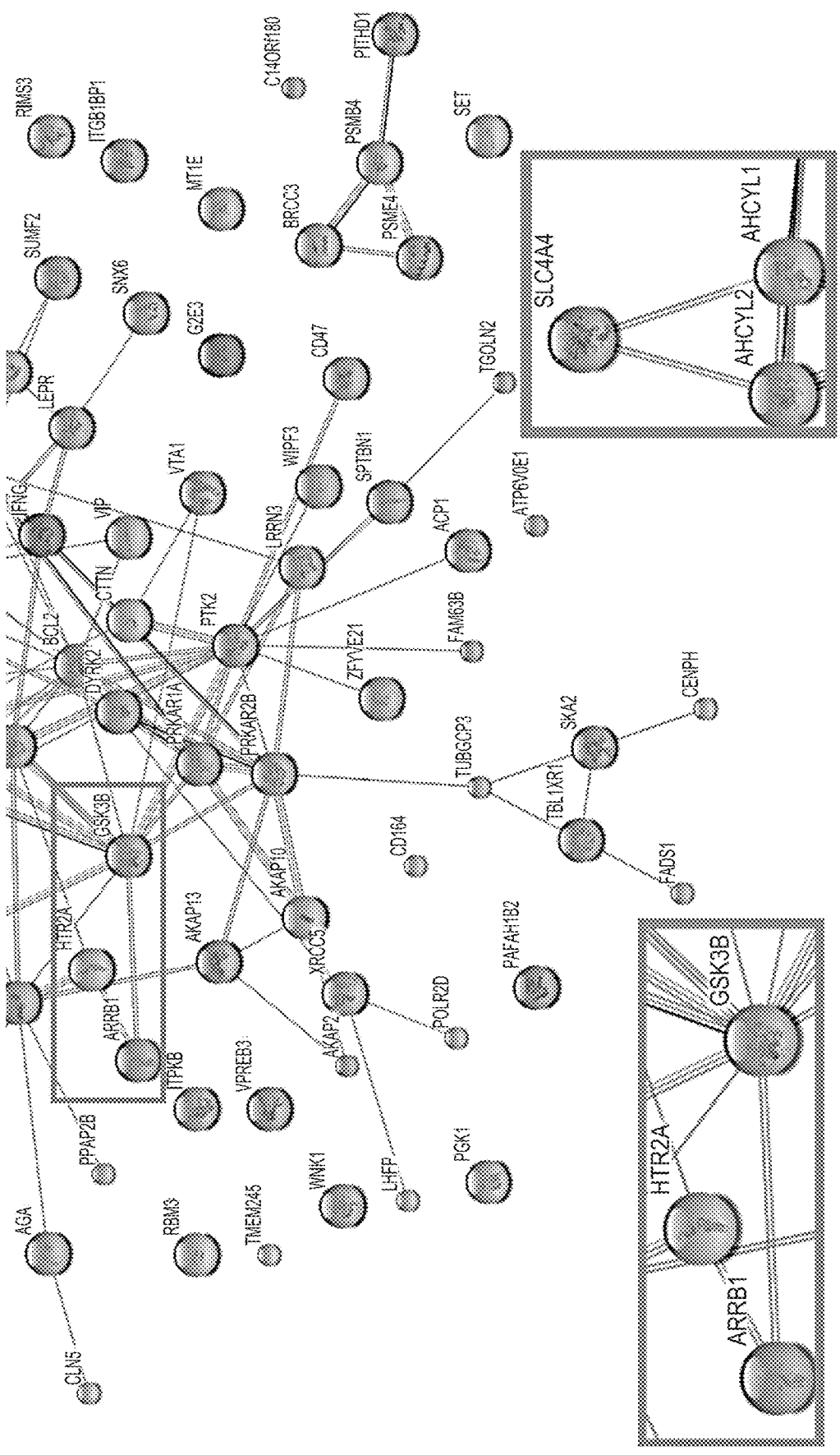
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SPTBN1
ATP6V0E1
LRRN3
ACP1
CTTN
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BCL2
DYRK2
FAM63B
ZFYVE21
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SKA2
TUBGCP3
TBL1XR1
GSK3B
CD164
FADS1
AKAP10
HTR2A
AKAP13
XRCC5
PAFAH1B2
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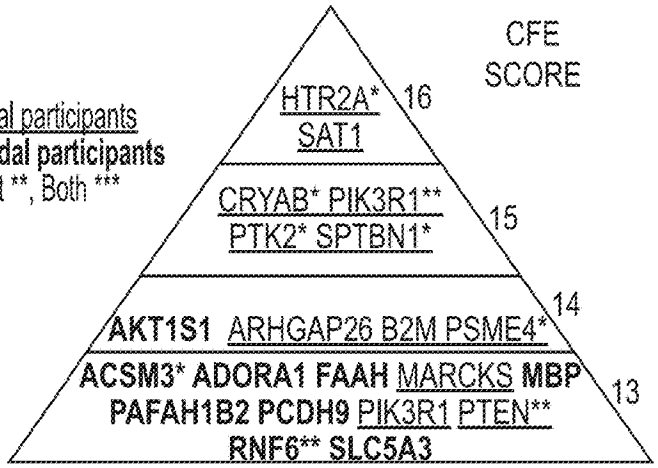
POLR2D
ITPKB
VPREB3
PPAP2B
WNK1
PGK1
LHFP
AGA
RBM3
TMEM245
CLN5
SLC4A4
AHCYL1
AHCYL2
GSK3B
HTR2A
ARRB1

FIG. 8 cont.

FIG. 9

Male Bipolar Biomarkers
Red – Increased in expression in suicidal participants
Blue – decreased in expression in suicidal participants
Significant predictions for: State*, Trait **, Both ***



Gene Symbol/ Gene name	Probesets	Step 1 Discovery in Blood (Direction of Change) Method/ Score	Step 2 Convergent Functional Genomics (CFG) Evidence For In-volvement in Suicide Score	Step 3 Validation in Blood ANOVA p-value/ Score	Step 4 Significant Prediction of Suicidal Ideation in Male Bipolars ROC AUC/p-value	Step 4 Significant Prediction of First Year Hospitaliza-tions for Suicidality in Male Bipolars ROC AUC/p-value	Step 5 Other Psychiatric and Related Disorders Evidence	Step 6 Drugs that Modulate the Biomarker in Opposite Direction to Suicide	CFE Poly-evid-ence Score
HTR2A 5-Hydroxytrypt-amine Receptor 2A	244130_at	(I) DE/2	8.00	NS	0.65/4.45E-02	NA	Alcohol, Anxiety, BP, MDD, SZ, OCD	Clozapine, Lithium, Valproate, Antipsychotics, Antidepressants	16
SAT1 spermidine/ spermine N1-acetyl-transferase 1	210592_s_at	(I) DE/2	6.00	4.00E-33/4	NA	NA	MDD, Anxiety, Mood Disorders, NOS	Omega-3	16

CRYAB crystallin, alpha B	209283_at	(I) DE/1	4.00	3.49E-05	0.65/4.41E-02	NA	Autism, Alcohol, PTSD, SZA, BP, SZ, Insomnia, Social Isolation, Siress, MDD	Lithium, Clozapine, Methamphet-amine	15
PIK3R1 Phosphoinositide-3-Kinase Regulatory Subunit 1	239476_at	(I) DE/1	4.00	2.79E-12	NA	0.81/1.64E-02	Schizophrenia, MDD, Relaxation Response, PTSD, BP, Longevity, Stress, Insomnia, Anxiety	Mood Stabilizers	15
PTK2 Protein Tyrosine Kinase 2	241453_at	(I) DE/2	4.00	4.29E-16/4	0.66/3.64E-02	NA	Alcohol, ASD, BP, Circadian abnormalities, MDD, Neurological, SZ/SZA, Stress, SZ	CT-707	15
SAT1 spermidine/ spermine N1-acetyl-transferase 1	203455_s_at	(I) DE/1	6.00	9.99E-29/4	NA	NA	MDD, Anxiety, Mood Disorders, NOS	Omega-3	15
SAT1 spermidine/ spermine N1-acetyl-transferase 1	213988_s_at	(I) DE/2	6.00	4.06E-34	NA	NA	MDD, Anxiety, Mood Disorders, NOS	Omega-3	15
SPTBN1 spectrin, beta, non-erythrocytic 1	215918_s_at	(I) AP/1	4.00	6.7E-32	0.72/6.62E-03	NA	Aging, BP, Longevity, MDD, SZ	Clozapine Omega-3, **Diazepam**	15
AKT1S1 AKT1 substrate 1 (proline-rich)	1555821_a_at	(D) DE/2	4.00	8.69E-09/4	NA	NA	Circadian abnormalities, Aging	Omega-3 fatty acids	14
AKT1S1 AKT1 substrate 1 (proline-rich)	224982_at	(D) AP/1 and DE/2	4.00	8.04E-11/4	NA	NA	Circadian abnormalities, Longevity	Omega-3 fatty acids	14
ARHGAP26 Rho GTPase activating protein 26	205068_s_at	(I) DE/1	5.00	7.99E-08/4	NA	NA	BP, MDD, Panic Disorder, SZ	Clozapine	14

FIG. 9 cont.

B2M beta-2-microglobulin	232311_at	(I) DE/2	4.00	5.43E-06/4	NA	NA	Alcohol Effect of valproate, MDD, SZ	Omega-3	14
PSME4 Proteasome Activator Subunit 4	237180_at	(I) DE/2	4.00	2.02E-16/4	0.69/1.41E-02	NA	ASD, MDD		14
ACSM3 acyl-CoA synthetase medium-chain family member 3	210377_at	(D) DE/1	4.00	2.31E-10/4	0.69/1.35E-02	NA	MDD, Mood		13
ADORA1 adenosine A1 receptor	205481_at	(D) DE/1	4.00	1.19E-07/4	NA	NA	Alcohol, SZ, BP, Mood, Stimulants, Depression	Clozapine	13
FAAH fatty acid amide hydrolase	204231_s_at	(D) DE/1	4.00	7.47E-12/4	NA	NA	Alcohol, SZ, BP, MDD, Pain, Placebo, PTSD, Stress, Hallucinogens, Social Isolation		13
MARCKS Myristoylated alanine-rich protein kinase C substrate	213002_at	(I) DE/1	4.00	7.35E-08/4	NA	NA	BP, SZ, MDD, Yohimbine, Alcohol, Pain Disorder	Lithium	13
MBP myelin basic protein	225408_at	(D) AP/1	4.00	3.26E-06/4	NA	NA	Alcohol, Alzheimer's Disease, BP, MDD, Mood, Neurological, SZ	Clozapine Omega-3, Lithium	13
PAFAH1B2 platelet-activating factor acetylhydro-lase 1b, catalytic subunit 2 (30kDa)	210160_at	(D) DE/1	4.00	4.85E-09/4	NA	NA	MDD	Lithium, PCP, Clozapine	13
PCDH9 Protocadherin 9	238919_at	(D) AP/1	4.00	4.52E-05/4	NA	NA	Aging, MDD, SZ/SZA, SZ	Clozapine Omega-3	13

FIG. 9 cont.

PIK3R1 phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	212240_s_at	(I) DE/1	4.00	7.11E-14/4	NA	NA	SZ, MDD, Relaxation Response, PTSD, BP, Longevity, Stress, Alchol, Insomnia, Anxiety	Amygdala mood stabilizers	13
PTEN phosphatase and tensin homolog	222176_at	(I) DE/1	4.00	4.88E-05/4	NA	09/3.27E-03	SZ, MDD, BP, PTSD, Longevity, Stress		13
RNF6 ring finger protein (C3H2C3 type) 6	210932_s_at	(D) DE/1	4.00	1.25E-05/4	NA	0.82/1.58E-02	BP, Social Isolation		13
SLC5A3 sodium/myo-inositol cotransporter	213167_s_at	(D) DE/1	4.00	4.89E-14/4	NA	NA	Chronic Stress, MDD, Alcohol	Lithium	13

FIG. 9 cont.

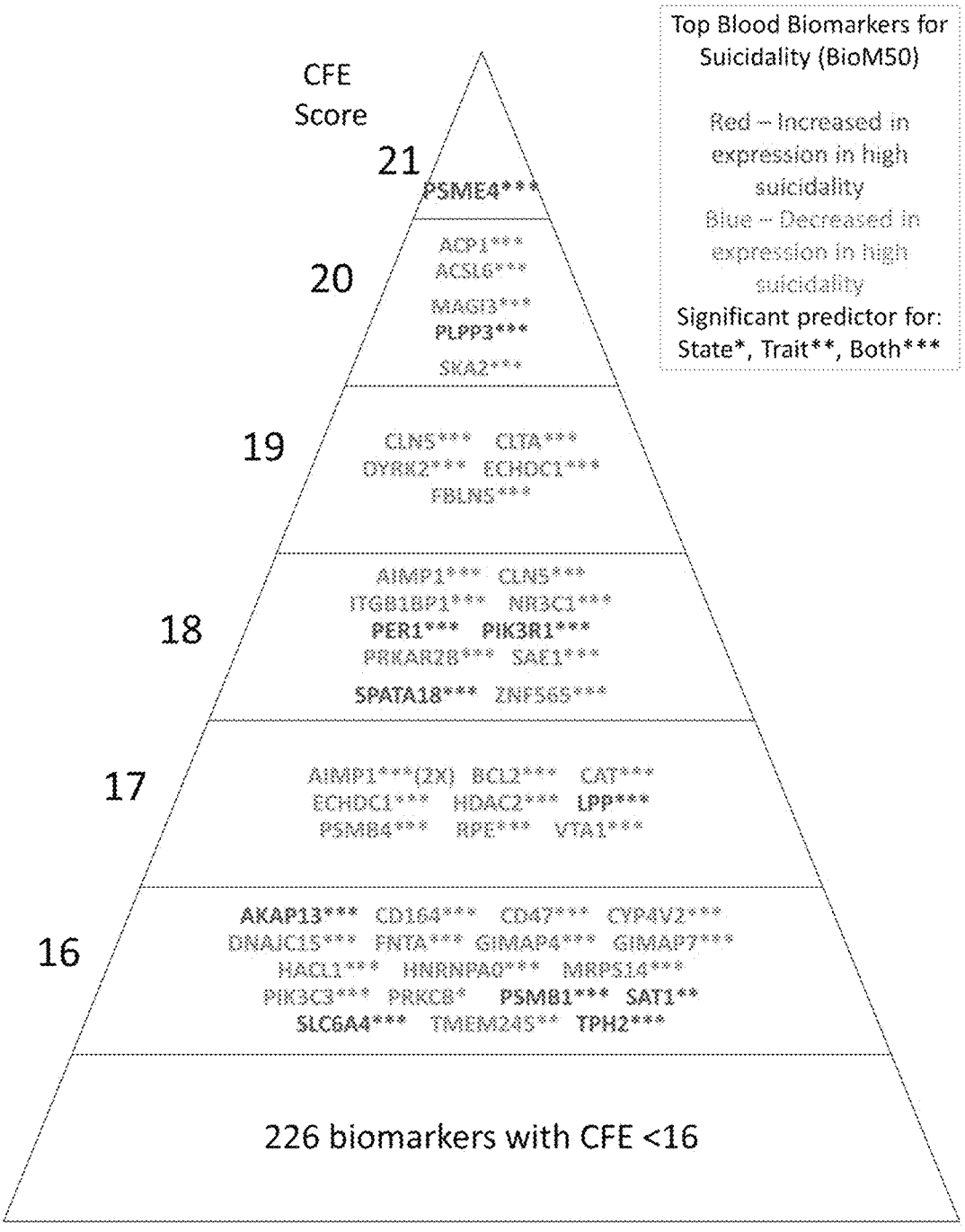
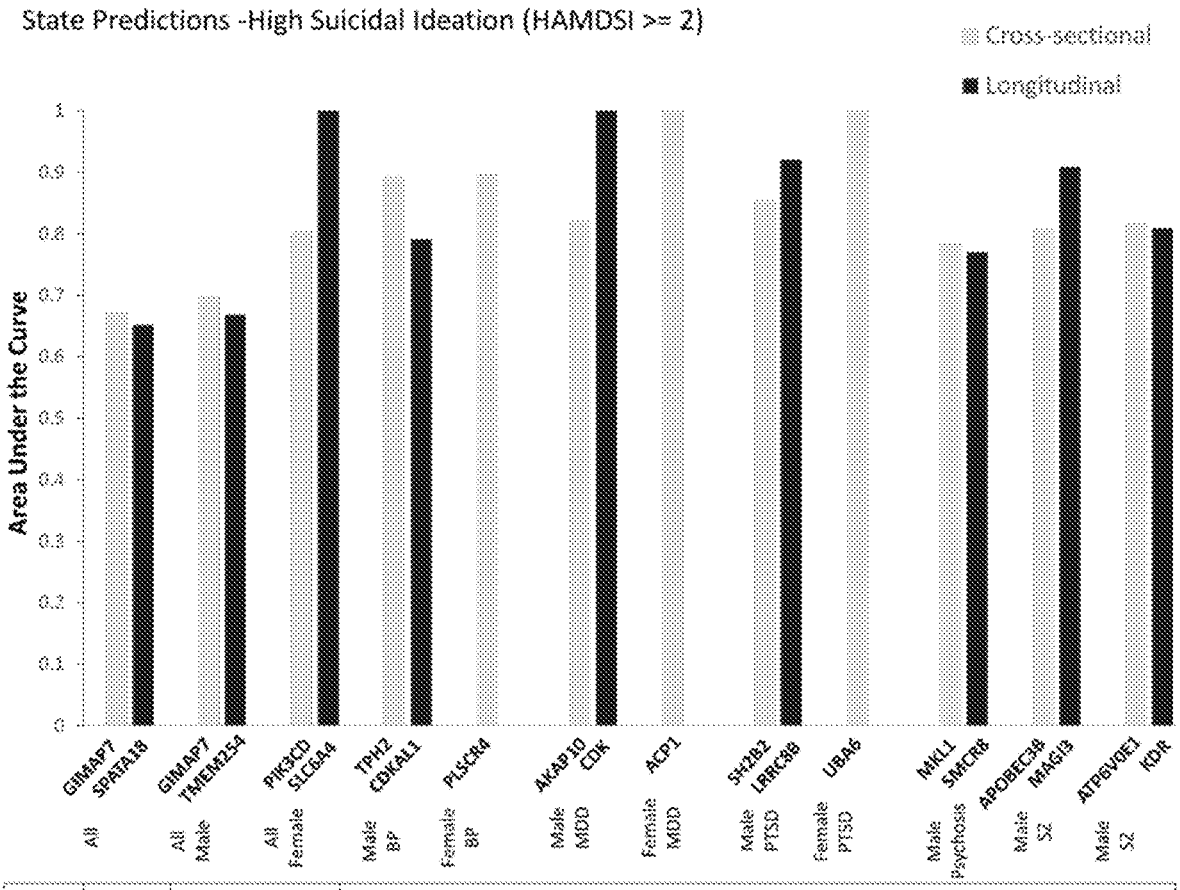
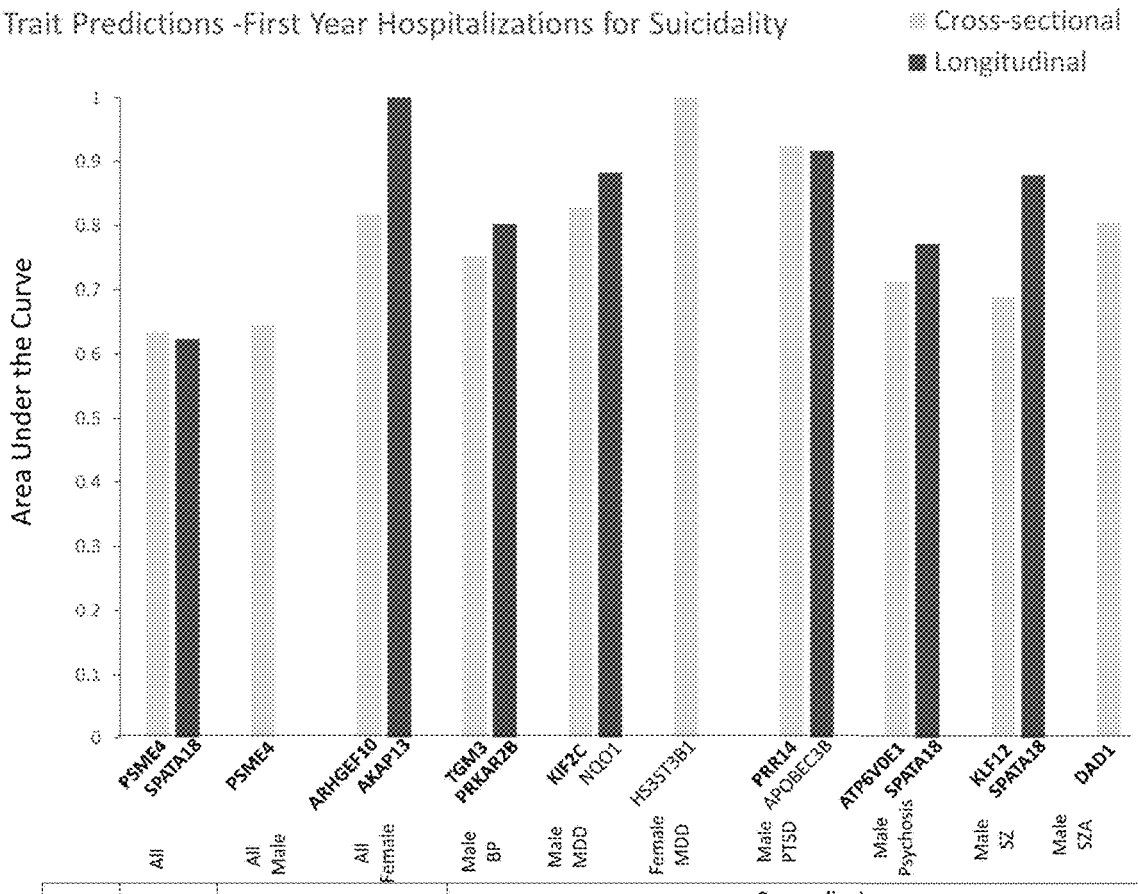


FIG. 10 CFE Pyramid for Top BioM 50



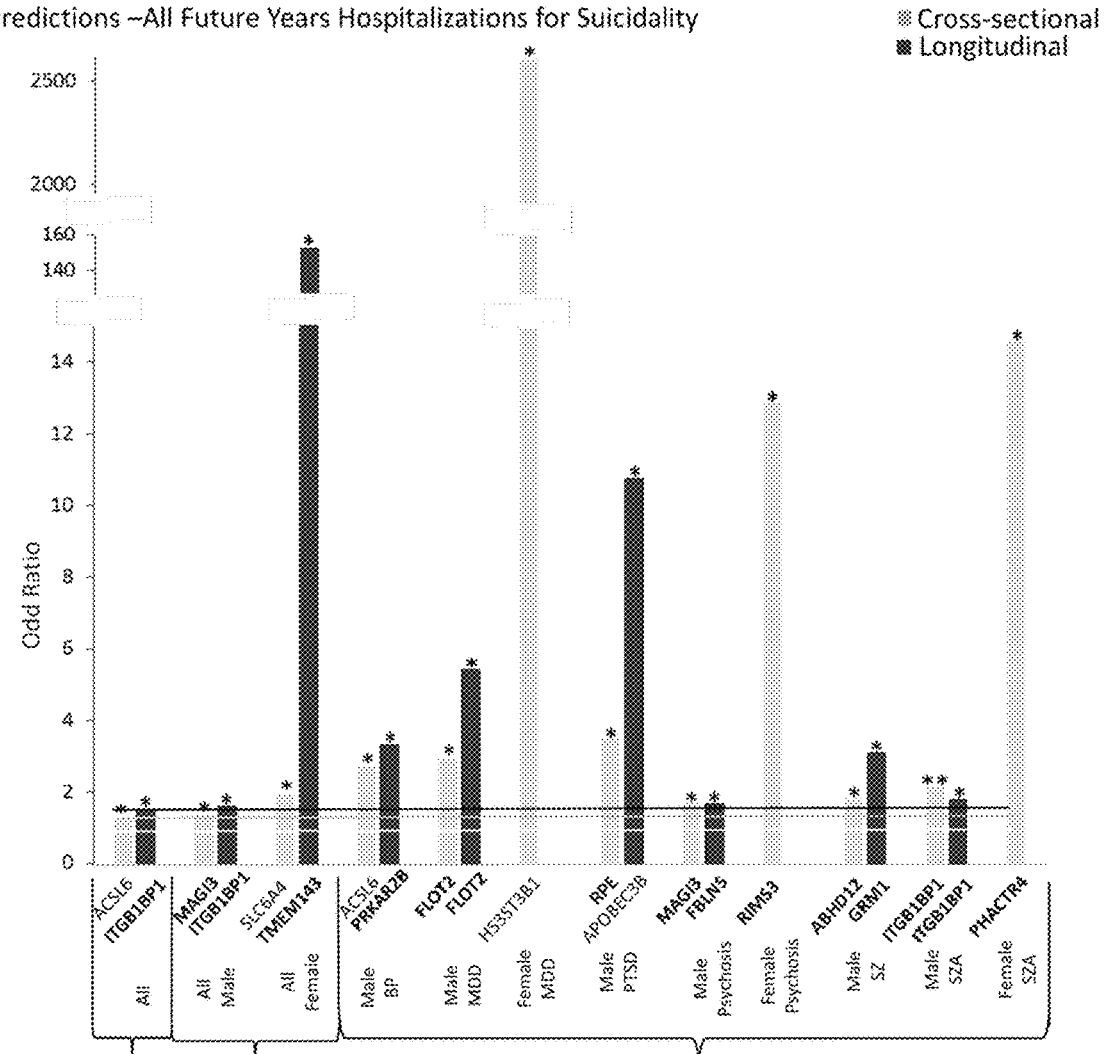
AUCs	All		Gender		Personalized (Gender/Dx)									
≥ 0.7	0	0	0	0	15	3	103	3	10	7	8	34	17	7	2	27	17	31	71	49	1
≥ 0.6	69	4	115	7	19	3	160	3	10	8	8	34	17	7	2	106	17	31	71	77	1
≥ 0.5	146	4	154	7	19	3	160	3	10	8	8	34	17	7	2	106	17	31	71	77	1

FIG. 11A



AUCs	All	Gender		Personalized (Gender/Dx)						
≥ 0.7	0 0	0	2 8	3 2	11 1	7	35 2	1 4	0 10	16
≥ 0.6	1 2	3	2 8	7 2	11 1	7	35 2	18 4	7 10	40
≥ 0.5	9 2	12	2 8	7 2	11 1	7	35 2	18 4	7 10	40

FIG. 11B



Odds Ratio	All		Gender			Personalized (Gender/Dx)													
≥ 2.0	0	0	0	0	0	8	4	2	6	11	6	15	12	0	0	3	0	16	1	0	4
≥ 1.5	0	1	0	6	3	8	21	4	14	11	6	36	13	1	10	3	6	28	5	5	4
≥ 1.0	22	23	32	40	3	8	28	4	14	11	6	37	13	22	10	3	21	29	26	5	4

FIG. 11C

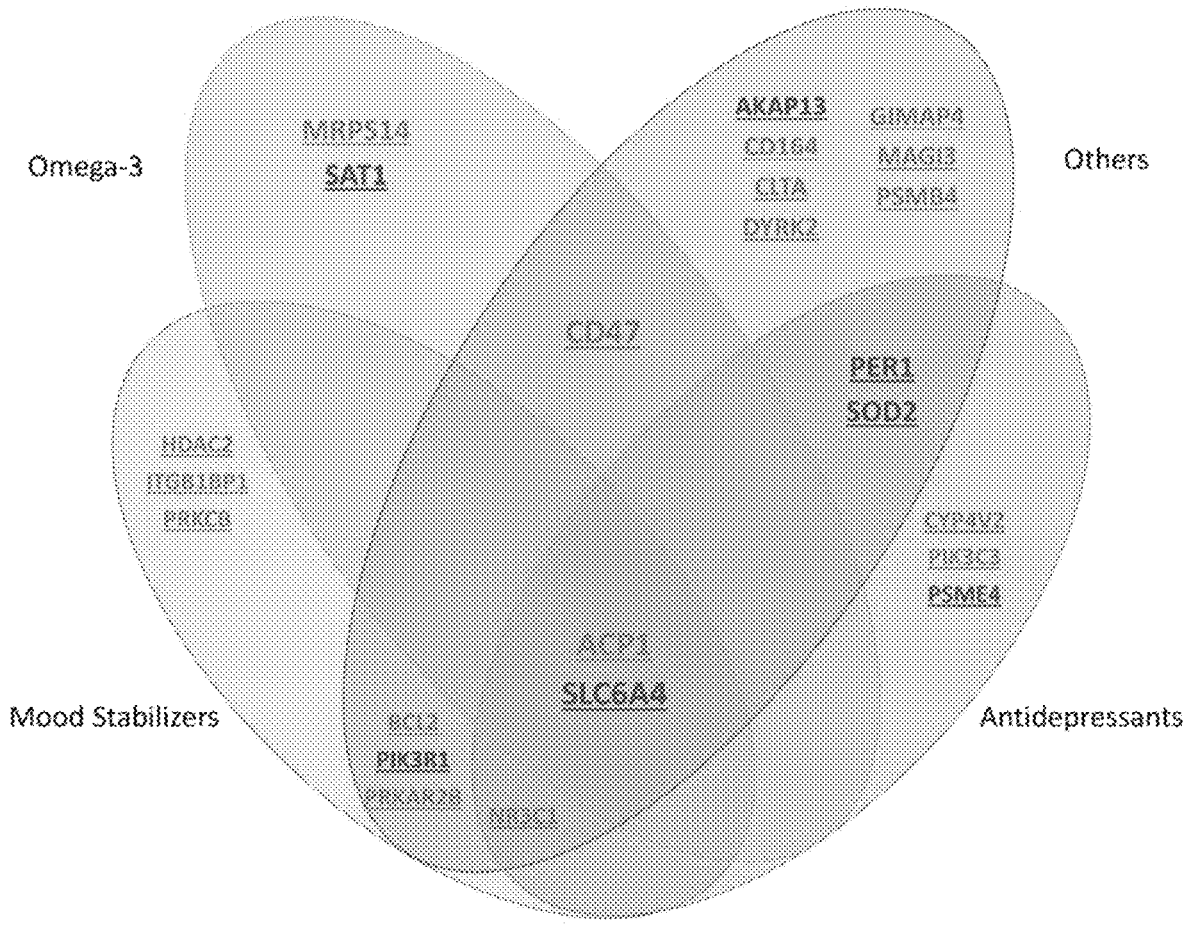
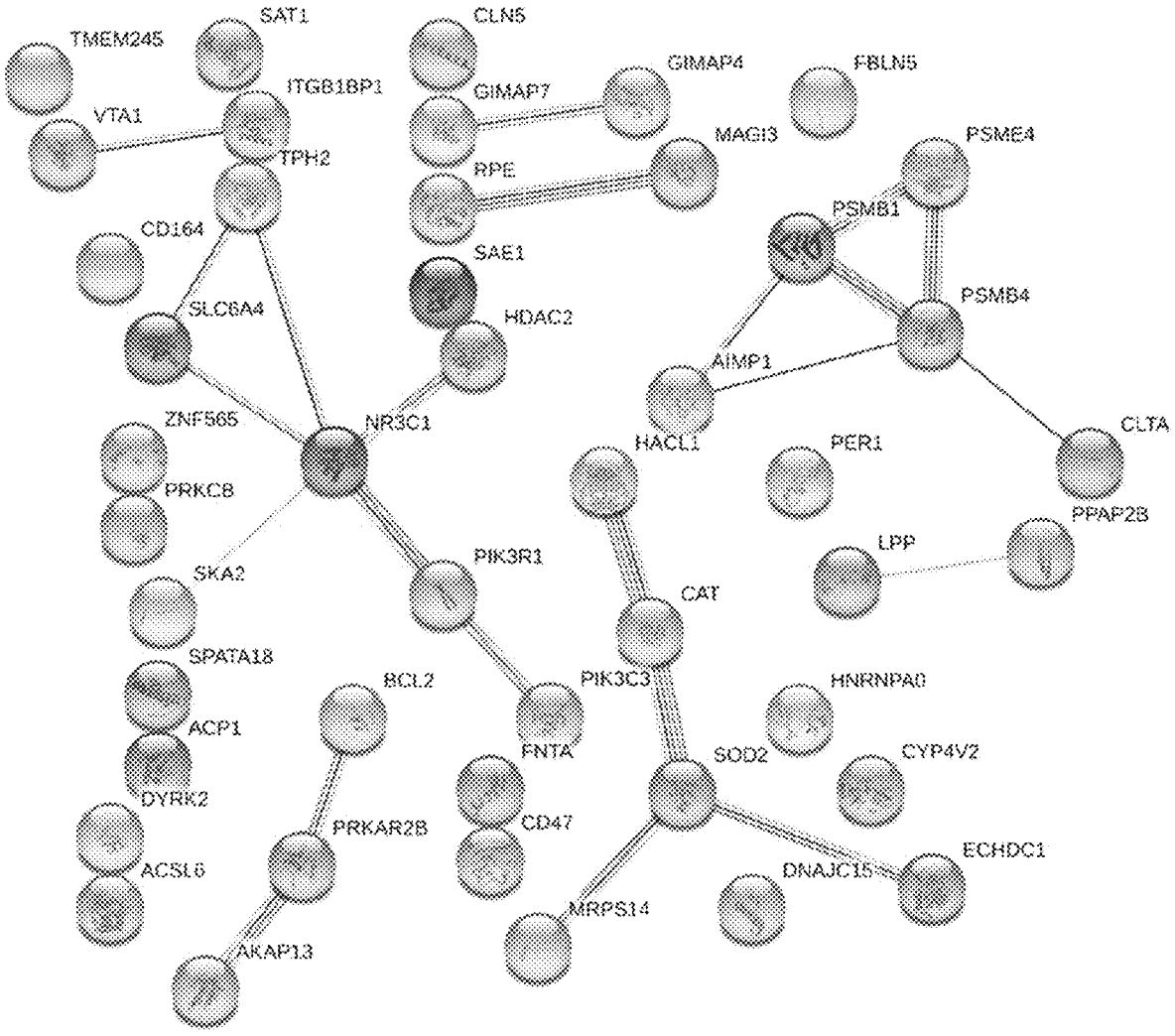

Omega-3
Others
Mood Stabilizers
Antidepressants
MRPS14
SAT1
AKAP13
CD164
CJTA
DYRK2
GINS4P4
MAGI3
PSME4
CD47
PER1
SOD2
HDAC2
ITGB1BP1
PRKCB
CYP4V2
PIK3C3
PSME4
AC13
SLC6A4
PIK3R1

FIG. 12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ACP1
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ACSL6
AKAP13
PRKAR2B
BCL2
CLN5
GIMAP7
GIMAP4
FBLN5
MAGI3
RPE
SAE1
HDAC2
NR3C1
PIK3R1
FNTA
CD47
PSME4
PSMB1
PSMB4
AIMP1
HACL1
PER1
CLTA
PPAP2B
LPP
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HNRNPA0
SOD2
CYP4V2
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DNAJC15
MRPS14

FIG. 13

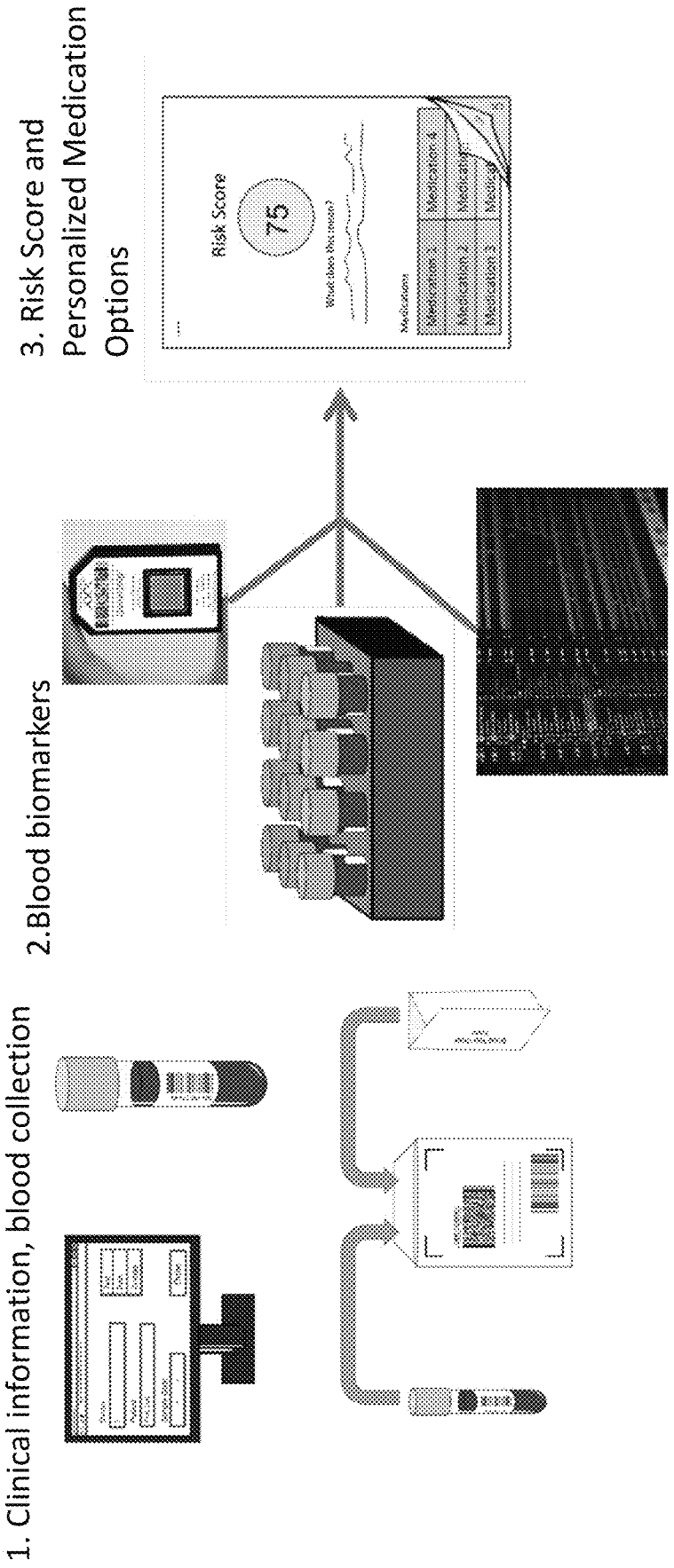
1. Clinical information, blood collection
2.Blood biomarkers
3. Risk Score and Personalized Medication Options
Risk Score
75
Medication 1
Medication 2
Medication 3
Medication 4

FIG. 14

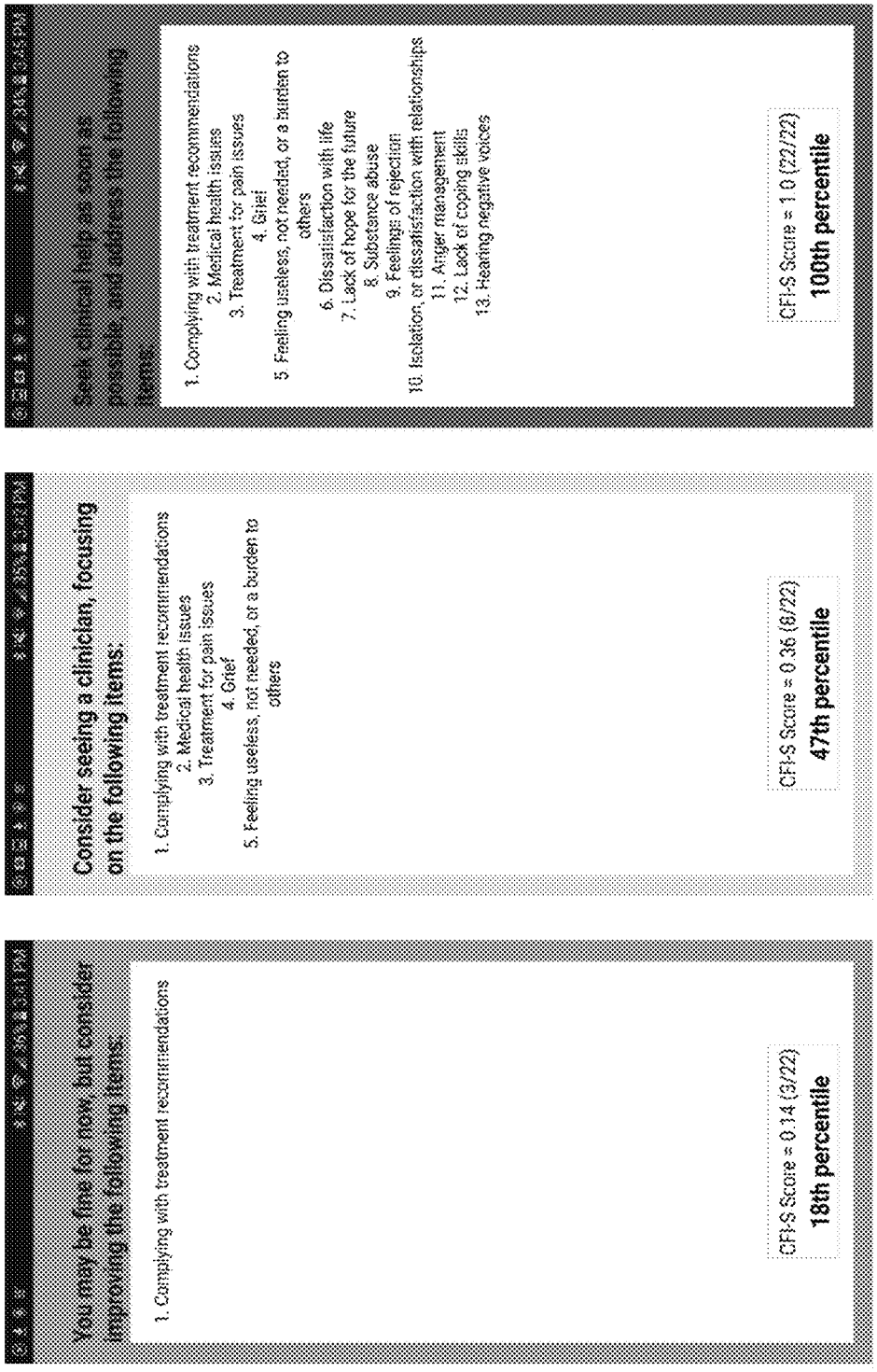
Low Risk
Intermediate Risk
High Risk
You may be fine for now but consider improving the following items:
1. Complying with treatment recommendations
CFI-S Score = 0.14 (3/22)
18th percentile
Consider seeing a clinician, focusing on the following items:
1. Complying with treatment recommendations
2. Medical health issues
3. Treatment for pain issues
4. Grief
5. Feeling useless, not needed, or a burden to others
CFI-S Score = 0.36 (8/22)
47th percentile
Seek clinical help as soon as possible, and address the following items:
1. Complying with treatment recommendations
2. Medical health issues
3. Treatment for pain issues
4. Grief
5 Feeling useless, not needed, or a burden to others
6. Dissatisfaction with life
7. Lack of hope for the future
8. Substance abuse
9. Feelings of rejection
10. Isolation, or dissatisfaction with relationships
11. Anger management
12. Lack of coping skills
13. Hearing negative voices
CFI-S Score = 1.0 (22/22)
100th percentile

FIG. 15

PRECISION MEDICINE FOR TREATING AND PREVENTING SUICIDALITY

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of and claims priority to PCT Application serial number PCT/US2018/032540, filed May 14, 2018, which claims priority to U.S. Provisional Application No. 62/505,197 filed on May 12, 2017, the contents of both of which are incorporated herein by reference in their entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under OD007363 awarded by the National Institutes of Health and 2IO1CX000139 merit award by the Veterans Administration. The government has certain rights in the invention.

BACKGROUND OF THE DISCLOSURE

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.

There are currently no objective tools to assess 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 assess 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.

SUMMARY

Based on the foregoing, objective and precise identification of individuals at risk, ways of monitoring response to treatments, and novel preventive therapeutics need to be discovered, employed, and widely deployed. Particularly, objective and quantitative markers would permit better and more precise assessment, tracking, and prediction of suicidal risk, which would enable preventive therapeutic interventions. Accordingly, the present disclosure is directed to identifying universal predictors, and in some embodiments, personalized predictors for suicidality. The present disclosure is generally directed at methods for assessing suicidality and early identification of risk for future suicidality, as well as methods for matching patients and drugs for prevention and mitigation of suicidality, and for monitoring response to treatment. Further, the present disclosure describes new methods of use for drugs and natural compounds repurposed for treating suicidality. All the above-mentioned methods are computer-assisted methods analyzing the expression of panels of genes, clinical measures, and drug databases. A universal approach in everybody, as well as a personalized approach by gender, and by diagnosis, are disclosed.

The present disclosure relates generally to compounds for mitigating suicidality. Particularly, novel drugs and natural compounds for treating and preventing suicidality (e.g., suicide ideation and actions, future hospitalization due to suicidality, and suicide completion) have now been identified through bioinformatics drug repurposing methods using novel gene expression biomarkers. The disclosure describes compounds for use in everybody (universal), as well as personalized by gender (males, females), diagnosis (bipolar, depression), and gender and diagnosis combined (male bipolar, male depression). Further, the present disclosure relates to gene expression biomarkers and their use for deciding in a particular person which drug or natural compound to use (precision medicine) for treating and preventing suicidality (e.g., suicide ideation and actions, future hospitalization due to suicidality, and suicide completion), as well as for tracking response to the drug or natural compound (pharmacogenomics). More particularly, the present disclosure relates to an algorithm composed of clinical measures and biomarkers for identifying subjects who are at risk of committing suicide, as well as for monitoring response to treatment. In some embodiments, the biomarkers used herein have been found to be more universal in nature, working across psychiatric diagnoses and genders. Such biomarkers may reflect and/or be a proxy for the core biology of suicide. In other embodiments, the present disclosure relates to biomarkers identified using a personalized approach; that is, by psychiatric diagnosis and/or gender, with a focus on bipolar males, the highest risk group. Such a personalized approach may be more sensitive to gender differences and to the impact of psychiatric co-morbidities and medications.

The present disclosure further relates to determining subtypes of suicidality using an app (SASS), based on mental state at the time of high suicidal ideation, and identified four subtypes: high anxiety, low mood, combined, and non-affective (psychotic). Such subtypes may delineate groups of individuals that are more homogenous in terms of biology and behavior.

The present disclosure further relates to a checklist of socio-demographic and psychological factors that influence the likelihood of becoming suicidal (CFI-S), with contributions from six domains (life events, mental health, physical health, environmental factors, cultural factors, and addictions). It can provide a likelihood score for an individual attempting that behavior (suicide) in the future. The items that are positive on the checklist can have differences in importance embodied as weight coefficients, based on specificity for suicide (Table 1), and based on empirical data, such as rank order in predictive datasets (FIGS. **4**A & **4**B). They also vary from individual to individual. As such, there is an individualized profile that can be affected by targeted interventions to prevent that behavior (suicide).

TABLE 1

Convergent Functional Information for Suicidality (CFI-S 30) Scale
Items are scored 1 for Yes, 0 for No. Total Score has a maximum possible of 30. Final Score is Total Score divided by number of items that were scored (as for some items information might not be available (NA) so they are not scored), and multiplied by 100.

Items	Yes = 1	No = 0	NA	Domain	Weights for sensitivity/ Importance to behavior 3 is most important, 2 intermediate, 1 less important	Type Increased Reasons (IR) Decreased Barriers (DB)	Weights for specificity2 is Specific for Suicidality, 1 is non-specific	Weighted Score
1. Psychiatric illness diagnosed and treated				Mental Health	x2	IR	x1	
2. With poor treatment compliance				Mental Health	x2	DB	1	
3. Family history of suicide in blood relatives				Mental Health	x2	IR	x2	
4. Personally knowing somebody who committed suicide				Cultural Factors	x2	DB	x2	
5. History of abuse growing up: physical, sexual, emotional, neglect				Life Satisfaction	x3	IR	x1	
6. Acute/severe medical illness, including acute pain ("I just can't stand this pain anymore.") (within last 3 months)				Physical Health	x1	IR	x1	
7. Acute stress: Losses, grief (within last 3 months)				Environmental Stress	x1	IR	x1	
8. Chronic stress: perceived uselessness, not feeling needed, burden to extended kin.				Environmental Stress	x1	IR	x1	
9. History of excessive introversion, conscientiousness (including planned suicide attempts)				Mental Health	x2	IR	x1	
10. Dissatisfaction with life at this moment in time				Life Satisfaction	x3	IR	x1	
11. Lack of hope for the future				Life Satisfaction	x3	IR	x1	
12. Current substance abuse				Addictions	x3	DB	x1	
13. Past history of suicidal acts/gestures				Life Satisfaction	x3	DB	x2	
14. Lack of religious beliefs				Cultural Factors	x2	DB	x1	
15. Acute stress: Rejection (within last 3 months)				Environmental Stress	x1	IR	x1	
16. Chronic stress: lack of positive relationships, social isolation				Environmental Stress	x1	DB	x1	
17. History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights)				Mental Health	x2	DB	x1	
18. Lack of coping skills when faced with stress (cracks under pressure)				Mental Health	x2	DB	x1	
19. Lack of children. If has children, not in touch/ not helping take care of them.				Life Satisfaction	x3	DB	x1	
20. History of command hallucinations of self-directed violence				Mental Health	x2	IR	x2	
21. Age: Older >60 or Younger <25				Age	x1	IR	x1	

TABLE 1-continued

Convergent Functional Information for Suicidality (CFI-S 30) Scale
Items are scored 1 for Yes, 0 for No. Total Score has a maximum possible of 30. Final Score is Total Score divided by number of items that were scored (as for some items information might not be available (NA) so they are not scored), and multiplied by 100.

Items	Yes = 1	No = 0	NA	Domain	Weights for sensitivity/ Importance to behavior 3 is most important, 2 intermediate, 1 less important	Type Increased Reasons (IR) Decreased Barriers (DB)	Weights for specificity2 is Specific for Suicidality, 1 is non-specific	Weighted Score
22. Gender: Male or Transgender				Gender	1	DB	1	
23. Persistent reduced (<5 hrs/night), excessive (>11 hrs/night) or fragmented sleep (within the last 3 months)				Mental Health	x2	IR	x1	
24. History of head trauma/traumatic brain injury				Physical Health	x1	DB	x1	
25. Owns/has easy access to guns or to multiple medications				Cultural Factors	x2	DB	x2	
26. History of exposure to trauma as an adult: combat, accidents, violence, rape				Life Satisfaction/ Environmental Stress	x3	IR	x1	
27. Is an artist or entertainer, or works in the healthcare field as a provider of clinical care				Cultural Factors	x2	DB	x1	
28. History of revenge behaviors				Mental Health	x2	DB	x1	
29. History of feeling very guilty				Mental Health	x2	DB	x1	
30. Does not easily confide or seek help from others				Cultural Factors	x2	DB	x1	

Total score = (Sum of Weighted score/Number of items scored) x 100

Biomarkers underlying propensity to behaviors can also be identified, as described in the present disclosure. They can be viewed as a checklist of biological measures. Again, the items/biomarkers that are positive/changed in levels on the checklist can have different weights of importance embodied as weight coefficients, based on specificity for suicide as reflected in a convergent functional genomics (CFG) score obtained during their discovery, prioritization and validation, (Table 1), and also based on other empirical data, such as strength in predictive datasets (FIGS. **2** and **3**A-**3**D). They also vary from individual to individual. There is an individualized profile that can be affected by targeted interventions, such as matched nutraceuticals and medications, as described in our invention.

Besides the checklists of factors that influence behavior (such as CFI-S in the case of suicide), and the checklist of biomarkers that indicate propensity to a behavior, such as panels of predictive biomarkers, the state of mind of an individual is a major factor influencing whether a behavior will happen or not. So a checklist of measures of the mind domains (anxiety and mood (for example measured with SASS), psychosis (for example measured with PANSS Positive Scale), and a direct assessment of the severity of suicidal ideation (for example measured with the suicide item in HAMD (HAMD-SI), would be informative to include in the overall algorithm to predict suicidality, and as targets for intervention to facilitate or prevent behaviors.

BRIEF DESCRIPTION OF THE DISCLOSURE

The present disclosure is generally directed at methods for assessing suicidality and early identification of risk for future suicidality, as well as methods for matching patients and drugs for prevention and mitigation of suicidality, and for monitoring response to treatment. The present disclosure is further related to drugs for mitigating suicidality in subjects. Particular drugs have been found that can mitigate suicidality in subjects universally; that is, drugs that can be used for mitigating suicidality across psychiatric diagnoses, genders and subtypes of suicidality. Some drugs, however, have been found that can be used more effectively for mitigating suicidality dependent on gender, psychiatric diagnoses, subtypes and combinations thereof.

Additionally, the present disclosure relates to biomarkers and their use for predicting a subject's risk of suicidality. In some embodiments, the biomarkers used herein have been found to be more universal in nature, working across psychiatric diagnoses, genders and subtypes. In other embodiments, the present disclosure relates to biomarkers identified using a personalized approach; that is, by psychiatric diagnosis, gender and subtype.

The present disclosure further relates to determining subtypes of suicidality based on mental state at the time of high suicidal ideation, and identified four subtypes: high anxiety, low mood, combined, and psychotic (non-affective)

such to delineate groups of individuals that are more homogenous in terms of biology and behavior.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

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:

FIGS. **1**A-**1**G depict Discovery, Prioritization and Validation methodology used in the Examples. (FIG. **1**A) Cohorts used in the Examples, depicting flow of discovery, prioritization, and validation, and testing of biomarkers from each step. (FIG. **1**B) 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. **1**C) Discovery of subtypes of suicidality based on high suicidal ideation visits in the discovery cohort. Subjects were clustered using measures of mood and anxiety (SASS), as well as psychosis (PANS S Positive). (FIG. **1**D) Differential gene expression in the Discovery cohort-number of genes identified with DE and AP methods with an internal score of 1 and above. Underlined-increased in expression in High SI, no underline—decreased in expression in High SI. At the discovery step probesets were identified based on their score for tracking suicidal ideation with a maximum of internal points of 4 (33% (1 pt), 50% (2 pt) and 80% (4 pt)). (FIG. **1**E) Prioritization with CFG for prior evidence of involvement in suicide. In the prioritization step probesets were converted to their associated genes using Affymetrix annotation and GeneCards. Genes were prioritized and scored using CFG for Suicide evidence with a maximum of 8 external points. Genes scoring at least 4 points out of a maximum possible of 12 total internal and external score point were carried to the validation step. (FIG. **1**F) Validation in an independent suicide completers cohort from the coroner's office. In the validation step biomarkers were assessed for stepwise change from the discovery groups of participants with no SI, to high SI, to suicide completion, using ANOVA. Stringent Bonferroni correction is calculated for the total number of probesets analyzed. (FIG. **1**G) Discovery, Prioritization and Validation scores for the cohorts in the Examples.

FIG. **2** depicts the best universal individual biomarkers for predicting suicidality out of the top dozen and Bonferroni validated biomarkers.

FIGS. **3**A-**3**D depict the best biomarkers predicting suicidality as found in the Examples. Best individual biomarkers out of top dozen and Bonferroni validated. FIG. **3**A is a circos plot depicting the best individual biomarker predictions for suicidal ideation state in the independent cohort (across all subjects, in subtypes, and personalized by gender and diagnosis), using universal biomarkers. FIG. **3**B is a circos plot depicting the best individual biomarker predictions for future hospitalizations for suicidality in the first year following testing in the independent cohort (across all subjects, in subtypes, and personalized by gender and diagnosis), using universal biomarkers. FIG. **3**C is a circos plot depicting the best individual biomarker predictions for suicidal ideation state in the independent male bipolar sub-cohort, using universal biomarkers and male bipolar biomarkers. FIG. **3**D is a circos plot depicting the best individual biomarker predictions for future hospitalizations for suicidality in the first year following testing in the independent male bipolar sub-cohort, using universal biomarkers and male bipolar biomarkers. The circumference bands represent and are proportional to the number of participants in each cohort. The ribbons represent and are proportional to the AUC of the predictions. Table underneath the figures displays the actual numerical results. Only biomarkers whose AUC p-values are at least nominally significant are shown.

FIG. **3**E The predictive ability of the biomarkers from FIGS. **3**A-**3**D, shown in numerical fashion (AUC, p-value), in all (universal), by subtypes, and by gender and diagnosis.

FIGS. **4**A & **4**B depict Convergent Functional Information for Suicide (CFI-S) Testing. Testing in a large cohort that combines the discovery and test cohorts used for biomarker work. CFI-S was developed independently of any data from the Examples, by compiling known socio-demographic and clinical risk factors for suicide. It is composed of a short version with 22 items, and a longer version with 30 items (Table 1), that assess the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, and cultural factors known to influence suicidal behavior, as well as two demographic factors, age and gender. FIG. **4**A depicts prediction of high suicidal ideation (HAMD SI>=2). FIG. **4**B depicts prediction of future hospitalizations due to suicidality within one year of follow up. Table under FIG. **4**A depicts individual items and their ability to differentiate between No SI and High SI. Table under FIG. **4**B depicts participants with and without future hospitalizations due to suicidality.

FIGS. **5**A-**5**C depict predicting suicidality using a broad-spectrum predictor (UP-Suicide), combining phenomic measures and the top dozen biomarkers. FIG. **5**D-**5**E depict broad-spectrum predictor (UP-Suicide), combining phenomic measures and the top dozen biomarkers in a single research participant (phchp328). FIG. **5**A depicts the UP-Suicide model. FIG. **5**B depicts UP-Suicide predicting suicidal ideation in the independent test cohort, and predicting future hospitalizations due to suicidality in the first year following testing. UP-Suicide is composed of the top increased and decreased biomarkers from each step of discovery, prioritization, and validation, for a total of 12, along with CFI-S scores and SASS (Mood and Anxiety scores). n=number of testing visits. Top left 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. Scatter plot depicting HAMD-SI score on the Y-axis and UP-Suicide score on the X axis with linear trend line. The table below FIG. **5**B top left receiver operating curve and top right summarizes descriptive statistics. Bottom left 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. 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. The table below FIG. **5**B bottom left receiver operating curve and bottom right summarizes descriptive statistics. FIG. **5**C is a dimensional view of risk stratification using clinical information measures, and example of two high risk participants. A tri-dimensional scatter plot was created using Partek. Tri-dimensional 95%

confidence intervals were inserted as ellipsoids, color coded blue and red, for No SI and High SI, respectively. Euclidian D (distance from origin) is depicted for the 2 subjects, as indicated by the arrows. Percentiles for scores on top predictors in all the subjects' visits in this Example are depicted in the table underneath the plot. Participant phchp158 was a divorced African American male in his late 20s with a long history of schizoaffective disorder, bipolar type, and *Cannabis* abuse. He was tested once (v1) while hospitalized for a suicide attempt by hanging. In the five years following testing, he had two additional hospitalizations for suicidality: one for suicidal ideation, one for attempt by overdose. He also had two hospitalizations for psychosis exacerbation without suicidality during this time span. Moved out of state, lost to follow-up since December 2015. Participant phchp328 (FIGS. **5**D and **5**E) was a Caucasian female in her late 30s with a long history of depression, PTSD, borderline personality disorder, and polysubstance abuse/dependence. She was first tested while in-patient for suicidal ideation. Over the next year, she subsequently had six psychiatric hospitalizations for suicidality: five due to suicidal ideation and one due to a suicidal attempt by overdose. She also had one hospitalization for opioid withdrawal and depression during this time span. She committed suicide by overdose with pills, leaving behind a suicide note addressed to her mother. Her UP-Suicide score at Visit 1, composed of the panel of top dozen biomarkers (BioM12) scores and phenomic measures scores (CFI-S, SASS), was at the 100% of the scores of all the psychiatric participant visits in the Example. Of note, that testing was conducted during an in-patient hospitalization due to suicidal ideation. While her scores improved at subsequent outpatient testing visits (Visits 2 and 3), this high watermark score indicated her high risk. After the last testing visit for the Example, she had four subsequent psychiatric hospitalizations: three due to suicidal ideation, one for opioid withdrawal/detox (the last one), ending 2 weeks before date of committing suicide (T). FIG. **5**D provides percentiles for scores on top predictors in the subjects' visits. FIG. **5**E is a dimensional view of risk stratification using clinical information measures, and example of two high risk participants. A tri-dimensional scatter plot was created using Partek. Tri-dimensional 95% confidence intervals were inserted as ellipsoids, color coded blue and red, for No SI and High SI, respectively.

FIG. **6** depicts UP-Suicide across all, by subtypes, and personalized by gender/diagnosis. UP-Suicide is composed of the panel of the top dozen universal biomarkers, CFI-S, and SASS (Anxiety, Mood). Plot 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 subtypes, and by gender and diagnosis (Gender/Dx). Two asterisks indicate the comparison survived Bonferroni correction for all the multiple comparisons depicted. 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 biomarkers or phenomic data individually. The table below contains descriptive statistics for all participants together, as well as separately by subtypes, and by gender/dx. Bold indicates the measure survived Bonferroni correction for all the multiple comparisons depicted. Pearson correlation data is also shown in the suicidal ideation test cohort 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 (which varies among participants, from 0.40 to 10.42 years).

FIG. **7** depicts universal biomarkers—Convergent Functional Evidence for Involvement in Suicidality. Top dozen and Bonferroni validated biomarkers. Post-hoc summation of all the evidence form discovery, validation, prioritization and testing, along with evidence for being a target of drugs and for involvement in other psychiatric disorders. This prioritization highlights for future studies biomarkers that may have broad applicability in the field, for diagnostics and therapeutics.

FIG. **8** depicts a STRING analysis depicting interactions between universal biomarkers. Top Dozen and Bonferroni combined lists.

FIG. **9** depicts Male Bipolar Biomarkers—Convergent Functional Evidence for Involvement in Suicidality. Top Dozen and Bonferroni biomarkers. Post-hoc summation of all the evidence form discovery, validation, prioritization and testing, along with evidence for involvement in other psychiatric disorders and for being a target of drugs. This prioritization highlights, for future studies, biomarkers that may have broad applicability in the field, for diagnostics and therapeutics. BP—bipolar, MDD—major depressive disorder, SZ—schizophrenia, PTSD—post-traumatic stress disorder, ASD—autism spectrum disorder;

FIG. **10** is a schematic diagram depicting top blood biomarkers for suicidality (BioM50) in accordance with embodiments of the present disclosure;

FIGS. **11**A-**11**C depict the best Single Biomarkers Predictors for Suicidality State, and for Trait (Future Hospitalizations for Suicidality) from top candidate biomarkers from each of the Steps 1-3 (Discovery, Prioritization, Validation-Bold). FIG. **11**A depicts state predictions-high suicidal ideation (HAMDSI>=2). FIG. **11**B depicts trait predictions-first year hospitalizations for suicidality. FIG. **11**C depicts trait predictions-all future years hospitalizations for suicidality. Bar graphs show the best predictive biomarkers in each group. * Nominally significant $p<0.05$. The tables underneath FIGS. **11**A-**11**C display the actual number of biomarkers for each group whose ROC AUC p-values (FIGS. **11**A-B) and Cox Odds Ratio p-values (FIG. **11**C) are at least nominally significant. Some gender and diagnosis group are missing from the graph as they did not have any significant biomarkers. Cross-sectional is based on levels at one visit. Longitudinal is computed based on levels at multiple visits (integrates levels at most recent visit, maximum levels, slope into most recent visit, and maximum slope). Dividing lines represent the cutoffs for a test performing at chance levels (white), and at the same level as the best biomarkers for all subjects in cross-sectional (gray) and longitudinal (black) based predictions. All biomarkers performed better than chance. Biomarkers performed better when personalized by gender and diagnosis;

FIG. **12** is a schematic diagram depicting the matching of patients to drugs, the pharmacogenomics for suicidality. FIG. **12** depicts the top biomarkers, from the BioM 50 panel, with modulation capabilities by existing drugs in the opposite direction to suicidality. Such biomarkers can be used to target treatments to different patients, and to measure response to that treatment. The higher the proportion/percentile of biomarkers for a certain drug/class, the more indicated that drug would be for treatment. When biomarkers for multiple different drug/classes are changed in an individual, a prioritization based on the proportion/percentile of biomarkers for each class can be used to choose the drug or combination of drugs (targeted rational polypharmacy);

FIG. **13** depicts a STRING analysis depicting interactions between Top CFE BioM 50 Biomarkers (n=46 top genes, 50 probesets). The links between nodes depict various types of evidence of interaction (see (https://string-db.org). The STRING interaction analysis revealed at least 3 biological networks (centered on NR3C1, PSMB4, and SOD2), which represent biomarkers and networks/pathways which can be targets for new drug development;

FIG. **14** depicts a schematic diagram of generating risk score and personalized medication options based on a panel of biomarkers, according to embodiments of the disclosed methods;

FIG. **15** depicts a representation of a report providing a risk score and personalized treatment options, according to embodiments of the disclosed methods.

DETAILED DESCRIPTION

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.

The present disclosure is generally directed at methods for assessing suicidality and early identification of risk for future suicidality, as well as methods for matching patients and drugs for prevention and mitigation of suicidality, and for monitoring response to treatment. The methods may further include the generation of a report providing a risk score and/or personalized treatment options. Further, the present disclosure generally is directed to drugs for mitigating suicidality in subjects. Particular drugs have been found that can mitigate suicidality in subjects universally; that is, drugs that can be used for mitigating suicidality across psychiatric diagnoses and genders. Some drugs, however, have been found that can be used more effectively for mitigating suicidality dependent on gender, psychiatric diagnoses, and combinations thereof.

In additional embodiments, the present disclosure is directed to blood gene expression biomarkers that are more universal in nature; that is, blood biomarkers that can be used for predicting suicidality across psychiatric diagnoses and genders. Accordingly, a longitudinal within-participant design and large cohorts were used.

Additionally, subtypes of suicidality were identified based on mental state (anxiety, mood, psychosis) at the time of high suicidal ideation.

Furthermore, the predictive ability of the biomarkers discovered were examined, in a completely independent cohort, in all the participants in it, as well as divided by subtypes, and personalized by gender and diagnosis.

The top biomarkers were combined with scores from a clinical information measure of suicide risk (CFI-S), as well as anxiety and mood (SASS), to obtain a broader spectrum predictor (UP-Suicide) that puts the biomarkers in the context of the person and his/her mental state. This list was then leveraged for therapeutics and drug discovery purposes to see if some of the biomarkers identified could be modulated by existing compounds used to treat suicidality, and also to conduct bioinformatics drug repurposing analyses to discover new drugs and natural compounds that may be useful for treating suicidality.

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

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.

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.

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.

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.

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.

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 universal method for predicting suicidality in a subject; that is, a method for predicting suicidality across all psychiatric diagnoses and for either gender. 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.

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 Tables 3A-3G and combinations thereof.

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 Tables 3A-3G and combinations thereof.

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, and in another particular aspect, the subject is a male bipolar human. In yet another particular aspect, the subject is a male depressed human.

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.

The method can further include assessing mood, anxiety, psychosis and other like psychiatric symptoms, and combinations thereof in the subject using questionnaires and/or a computer-implemented method for assessing mood, anxiety, psychosis, 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, psychosis information and combinations thereof into the first computer device; storing, by the first computer device, the mood information, anxiety information, psychosis information and combinations thereof in the memory device; computing, by the first computer device, of the mood information, anxiety information, psychosis 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, psychosis 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, psychosis information and combinations thereof; and transmitting, by the first computer device, the mood information, anxiety information, psychosis information and combinations thereof to the second computer device to assess mood, anxiety, psychosis and combinations thereof in the subject. Suitable mood and anxiety information is described herein in more detail below.

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.

In accordance with embodiments of the present disclosure, as specifically seen in FIG. **14**, clinical information and blood may be collected, one or more blood biomarkers may be assessed, alone or in panel form, and a risk score and personalized medication options may be generated. In a variation, the risk score and/or personalized medication options may be presented in a report. As seen in FIG. **15**, another report, based on clinical and socio-demographic data, may provide, a CFI-S score, percentile, a risk rating, and treatment recommendations. In an example, the reports are electronic, and processed via a computer device, system or an app. In another example, the reports are printed on paper.

Additionally, in accordance with another aspect of the present disclosure, biomarkers useful for objectively pre-

dicting future hospitalization due to suicidality in subjects have been discovered. In one aspect, the present disclosure is directed to a universal method for future hospitalization due to suicidality in a subject; that is, a method for predicting future hospitalization due to suicidality across all psychiatric diagnoses and genders. 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 a blood biomarker expression level in a sample obtained from the subject.

In another aspect, the present disclosure is directed to further mitigating suicidality in the subject(s) identified above. 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, upon 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, 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.

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

Suitable therapy can be a nutritional, a drug and psychotherapy.

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

In some embodiments, the therapies can include drugs and natural compounds that have now been found to be effective in mitigating suicidality either universally or for a specific gender and/or psychiatric diagnosis. Exemplary repurposed drugs and natural compounds are found in Tables 6-18.

Various functions and advantages of these and other embodiments of the present disclosure will be more fully understood from the examples shown below. The examples are intended to illustrate the benefits of the present disclosure, but do not exemplify the full scope of the disclosure.

EXAMPLES

In this Example, blood biomarkers from three cohorts of subjects were analyzed.

Materials and Methods

Cohorts

Three independent cohorts were examined: discovery cohort (a live psychiatric participants cohort), validation cohort (a postmortem coroner's office cohort), and testing cohort (also referred to herein as "test cohort") (an independent live psychiatric participants test cohort for predicting suicidal ideation, and for predicting future hospitalizations for suicidality) (FIG. **1**A).

The live psychiatric participants are part of a larger longitudinal cohort of adults that are continuously being collected. Participants are 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, per IRB approved protocol. 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. **1**B). Further, 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° C. in a locked freezer until the time of future processing. Whole-blood RNA was extracted for microarray gene expression studies from the PAXgene tubes, as detailed below.

The participant discovery cohort, from which the biomarker data were derived, consisted of 66 participants (49 males, 17 females) with psychiatric disorders and multiple testing visits, 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 2 participants with 6 visits each, 3 participants with 5 visits each, 5 participants with 4 visits each, 34 participants with 3 visits each, and 22 participants with 2 visits each resulting in a total of 193 blood samples for subsequent gene expression microarray studies (FIG. **1**B and Table 2).

The postmortem validation cohort, in which the top biomarker findings were validated for behavior, consisted of 38 male and 7 female violent suicide completers obtained through the Marion County coroner's office (Table 2). A last observed alive postmortem interval of 24 h or less was required, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. Thirty-one participants completed suicide by gunshot to head or chest, 12 by asphyxiation, 1 by slit wrist, and 1 by electrocution. Next of kin signed informed consent at the coroner's office for donation of blood for research.

The independent test cohort for predicting suicidal ideation (Table 2) consisted of 184 male and 42 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 226 blood samples in which whole-genome blood gene expression data were obtained (FIG. **1**A and Table 2).

The test cohort for predicting future hospitalizations (FIG. **1**A and Table 2) is a subset (170 males, 24 females) of the independent test cohort for which a longitudinal follow-up with electronic medical records was available. 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 due to suicidality if suicidal acts or intent were listed as a reason for admission, and/or SI was described in the admission and discharge medical notes.

TABLE 2

Demographics					
Universal	Subjects	Gender	Diagnosis	Ethnicity	Age Mean (SD)
Discovery					
Discovery Cohort (Longitudinal Within-Subject Changes in Suicidal Ideation)	66	Male = 49 Female = 17	BP = 25 MDD = 17 SZA = 9 SZ = 4 PTSD = 8 MOOD = 2 PSYCH = 1	EA = 51 AA = 14 Asian = 1	47.94 (9.47)
Validation					
Independent Validation Cohort for Gene Expression (Suicide Completers)	45	Male = 38 Female = 7	NP = 19 MDD = 19 BP = 2 SZ = 1 AX = 1 Alcoholism = 1 ADHD = 1 PTSD = 1	EA = 37 AA = 7 Hispanic = 1	40.69 (16.93)
Testing All					
Independent Testing Cohort For Predicting State (Suicidal Ideation at Time of Assessment)	226	Male = 184 Female = 42	BP = 68 MDD = 32 SZA = 53 SZ = 45 PTSD = 19 MOOD = 5 PSYCH = 4	EA = 148 AA = 73 Asian = 1 Hispanic = 3 Mixed = 1	All 50.26 (9.47) No SI 51.1 Intermediate SI 49 High SI 44.3
Independent Testing Cohort For Predicting Trait (Hospitalizations for Suicidality in the Year Following Assessment)	194	Male = 170 Female = 24	BP = 72 MDD = 44 SZA = 50 SZ = 46 PTSD = 24 MOOD = 8 PSYCH = 3	EA = 167 AA = 76 Hispanic = 3 Mixed = 1	All = 50.04 (9.11) No Hosp for SI = 50.52 Hosp for SI = 46.24
Subtypes					
High Anxiety Subtype	46	Male = 40 Female = 6	BP = 13 MDD = 10 SZA = 9 SZ = 11 PTSD = 2 MOOD = 1	EA = 27 AA = 19	All 50.96 (7.63) No SI 52.1 (n = 44) Intermediate SI 52.5 (n = 4) High SI 39.4 (n = 5)
Low Mood Subtype	76	Male = 57 Female = 19	BP = 21 MDD = 17 SZA = 15 SZ = 15 PTSD = 6 MOOD = 1 PSYCH = 1	EA = 53 AA = 20 Hispanic = 2 Asian = 1	All 51.53 (10.04) No SI 51.44 (n = 58) Intermediate SI 51.81 (n = 14) High SI 51.9 (n = 8)
Combined Subtype	86	Male = 61 Female = 25	BP = 30 MDD = 11 SZA = 21 SZ = 11 PTSD = 11 MOOD = 2	EA = 63 AA = 21 Hispanic = 1 Mixed = 1	All 47.95 (9.36) No SI 50.79(n = 56) Intermediate SI 45.43 (n = 18) High SI 43.06 (n = 25)

TABLE 2-continued

Demographics					
Non-Affective (Psychotic) Subtype	141	Male = 121 Female = 20	BP = 40 MDD = 17 SZA = 35 SZ = 32 PTSD = 10 MOOD = 4 PSYCH = 3	EA = 86 AA = 52 Hispanic = 2 Mixed = 1	All 50.71 (9.49) No SI 50.89 (n = 132) Intermediate SI 51.67 (n = 6) High SI 42.33 (n = 6)

Male Bipolar	Subjects	Gender	Diagnosis	Ethnicity	Age Mean (SD)
Discovery					
Male Bipolar Discovery Cohort (Within-Subject Changes in Suicidal Ideation)	20	Male = 20	BP = 20	EA = 20	48.12 (9.10)
Validation					
Male Independent Validation Cohort for Gene Expression (Suicide Completers)	38	Male = 38	NP = 18 MDD = 16 BP = 1 SZ = 1 AX = 1 Alcoholism = 1	EA = 31 AA = 6 Hispanic = 1	40.82 (17.31)
Testing					
Male Bipolar Independent Testing Cohort For Predicting State (Suicidal Ideation at Time of Assessment	49	Male = 49	BP = 49	EA = 43 AA = 5 Hispanic = 1	All 49.16 (10.01) No SI 50.19 Intermediate SI 48.73 High SI 40.42
Male Bipolar Independent Testing Cohort For Predicting Trait (Hospitalizations for Suicidality in the Year Following Assessment)	44	Male = 44	BP = 44	EA = 39 AA = 4 Hispanic = 1	All = 48.88 (10.23) No Hosp for SI = 48.76 Hosp for SI = 52.25

Medications. The participants in the discovery cohort were all diagnosed with various psychiatric disorders (Table 2). 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, the discovery of differentially expressed genes was based on within-participant analyses, which factor out not only genetic background effects but also minimizes medication effects, as the participants rarely had 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.

Blood Gene Expression Experiments

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 as described in Le-Niculescu et al., Mol Psychiatry 2013; 18(12): 1249-1264.

Microarrays. Microarray work was carried out using methodology described in Niculescu et al., Mol Psychiatry 2015; 20(11): 1266-1285.

Biomarkers

Discovery Cohort

The participant's suicidality score from the item in the Hamilton Rating Scale for Depression (HAMD SI) assessed at the time of blood collection (FIG. 1G) was used. The gene expression differences were analyzed between the no SI (a score of 0) and the high SI (a score of 2 and above) visits, using a powerful within-participant design, then an across-participants summation (FIG. 1F).

The 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 (MASS) was used to generate Absent (A), Marginal (M), or Present (P) calls for each probeset on the chip (Affymetrix U133 Plus 2.0 GeneChips) for all participants in the discovery cohort (Affymetrix Inc., Santa Clara, Calif.). 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, Mich., USA). Using only the perfect match values, a robust multi-array analysis (RMA) was conducted, background corrected with quantile normalization and a median polish probeset summarization, to obtain the normalized expression levels of all

probesets for each chip. RMA was performed independently for each gender and diagnosis subgroup used in the Example, to avoid potential artefacts due to different ranges of gene expression in different gender and diagnoses. Then the participants' normalized data was extracted from these gender and diagnosis RMAs and assembled for the different cohorts used in the Example.

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) from No SI to High SI, as described in Niculescu et al., Mol Psychiatry 2015; 20(11): 1266-1285 and Levey et al., Mol Psychiatry 2016; 21(6): 768-785. For a comparison between two sequential visits, 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 versus the phene (which is 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 (SI levels), or a change in gene expression between visits despite no change in phene expression (SI levels), 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 an overall 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 probeset was rewarded by a doubling of its overall 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 score for that probeset in that participant was zero. An R script was developed to conduct the calculations, and the analysis was double-checked manually using formulas/macros in Excel.

DE analysis. For the longitudinal within-participant DE analysis, fold changes (FC) in gene expression were calculated between sequential visits within each participant, as described in Niculescu et al., Mol Psychiatry 2015; 20(11): 1266-1285 and Levey et al., Mol Psychiatry 2016; 21(6): 768-785. Scoring methodology was similar to that used above for AP. Probesets that had a FC≥1.2 were scored +1 (increased in High SI) or −1 (decreased in High SI). FC≥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. A perfection bonus and a non-tracking correction were also used for the DE analysis. If the gene expression perfectly tracked the suicidal ideation in a participant that had at least two comparisons (3 visits), that probeset 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 score for that probeset in that participant was zero. An R script was developed to conduct the calculations, and the analysis was double-checked manually using formulas/macros in Excel.

Internal score. Once scores within each participant were calculated, an algebraic sum across all participants was obtained, for each probeset. Probesets were then given internal points based upon these algebraic sum scores. Probesets with scores above the 33.3% of the maximum score (for increased probesets, respectively for decreased probesets) received 1 point, those above 50% received 2 points, and those above 80% received 4 points. For AP analyses, 35 probesets received 4 points, 754 probesets received 2 points, and 2197 probesets received 1 point, for a total of 2986 probesets. For DE analyses, 35 probesets received 4 points, 1477 probesets received 2 points, and 6450 probesets received 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. **1**D. Different probesets may be found by the two methods due to differences in scope (DE is also capturing genes that are present in both visits of a comparison, i.e. PP, but are changed in expression), thresholds (what makes the 33.3% change cutoff across participants varies between methods), and technical detection levels (what is considered in the noise range varies between the methods).

Gene Symbol for the probesets were identified using NetAffyx (Affymetrix) for Affymetrix HG-U133 Plus 2.0 GeneChips, followed by GeneCards to confirm the primary gene symbol. In addition, for those probesets that were not assigned a gene symbol by NetAffyx, GeneAnnot (https://genecards.weizmann.ac.il/geneannot/index.shtml) was used to obtain a gene symbol for these uncharacterized probesets, followed by GeneCard. Genes were then scored using manually curated CFG databases as described below (FIG. **1**E).

Prioritization Using Convergent Functional Genomics (CFG)

Databases. Manually curated databases were established of the human gene expression/protein expression studies (postmortem brain, peripheral tissue/fluids: CSF, blood and cell cultures), human genetic studies (association, copy number variations and linkage), and animal model gene expression and genetic studies, published to date on psychiatric disorders. Only the findings deemed significant in the primary publication, using the particular experimental design and thresholds, are included in the databases. 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 in the CFG cross validation and prioritization platform (FIG. **1**E). For this Example, data from 454 papers on suicide were present in the databases at the time of the CFG analyses (genetic studies-170, brain studies-197, peripheral fluids-87).

Human postmortem brain gene expression/protein 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.

Human blood, CSF, and other peripheral tissue gene expression/protein expression evidence. Converging evidence was scored for a gene if there were published reports of human blood, lymphoblastoid cell lines, cerebrospinal fluid, 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.

Human genetic evidence (association, 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 physical positions (bp) of each gene were 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/map_interpolator.shtml. For linkage convergence, the start of the gene had to map within 5 cM of the location of a marker linked to the disorder.

CFG scoring. For CFG analysis (FIG. **1**E), 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/fluid 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 prioritized based upon the initial gene expression analyses used to identify them, giving them an internal score. Probesets 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 score and 8 points for the external CFG score) (Tables 3A-3F). The scoring system was decided upon before the analyses were carried out. Twice as much weight was given to the external score as compared to the internal score in order to increase generalizability and avoid fit to cohort of the prioritized genes. This scoring system provides a good separation of genes based on gene expression evidence and on independent cross-validating evidence in the field (FIG. **1**E). In the future, with multiple large datasets, machine learning approaches could be used and validated to assign weights to CFG.

TABLE 3

Affymetrix Probe Set ID	Gene Symbol	Direction of Change in Suicidality	Analysis	Top Dozen Biomarker from:	Top Predictor Biomarker for:
A: Universal Biomarkers for Suicidality - Top Dozen and Top Predictor Biomarkers. D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression					
224240_s_at	CCL28	D	AP	Discovery	
213541_s_at	ERG	D	DE	Discovery	
242572_at	GAB1	I	AP	Discovery	
214540_at	HIST1H2BO	I	DE	Discovery	
210354_at	IFNG	D	AP	Prioritization	
225686_at	SKA2	D	DE	Prioritization	
210739_x_at	SLC4A4	I	AP	Prioritization	Suicidal ideation state - cross-sectional
218832_x_at	ARRB1	D	AP	Validation	
57082_at	LDLRAP1	D	DE	Validation	
212226_s_at	PPAP2B	I	AP	Validation	
2215078_at	SOD2	I			Future hospitalizations for suicidality - all future years - cross-sectional
203680_at	PRKAR2B	D			Future hospitalizations for suicidality - all future years - longitudinal
209534_x_at	AKAP13	I			Future hospitalizations for suicidality - all future years - longitudinal
237180_at	PSME4	I	DE	Validation	Future hospitalizations for suicidality - in the first year - cross-sectional
209000_s_at	SEPT8	I			Future hospitalizations for suicidality - in the first year - longitudinal
218062_x_at	CDC42EP4	D			Future hospitalizations for suicidality - in the first year - cross-sectional
214252_s_at	CLN5	D			Suicidal ideation state - cross-sectional Future hospitalizations for suicidality - all future years - cross-sectional
232526_at	ITPKB	I			Suicidal ideation state - longitudinal
209677_at	PRKCI	D			Suicidal ideation state - longitudinal
244130_at	HTR2A	I	DE	Prioritization	Suicidal ideation state - longitudinal
B. Biomarkers for Suicidality in Males - Top Dozen and Top Predictor Biomarkers. D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression					
227351_at	C16orf52	D	AP	Discovery	
203032_s_at	FH	D	DE	Discovery	
214540_at	HIST1H2BO	I	DE	Discovery	
242538_at	TFDP1	I	AP	Discovery	
225686_at	SKA2	D	AP, DE	Prioritization	
210739_x_at	SLC4A4	I	AP	Prioritization	
241811_x_at	SLC6A4	I	DE	Prioritization	
57082_at	LDLRAP1	D	DE	Validation	
210592_s_at	SAT1	I	DE	Validation	
209386_at	TM4SF1	I	AP	Validation	
239991_at	ZMYND8	D	AP	Validation	

TABLE 3-continued

218174_s_at	TMEM254	D			Suicidal ideation state - longitudinal
200009_at	GDI2	D			Suicidal ideation state - cross-sectional
207194_s_at	ICAM4	D			Future hospitalizations for suicidality - in first year - cross-sectional
203336_s_at	ITGB1BP1	D			Future hospitalizations for suicidality - all future years - longitudinal
201460_at	MAPKAPK2	I			Suicidal ideation state - cross-sectional Future hospitalizations for suicidality - all future years - cross-sectional
237180_at	PSME4	I			Future hospitalizations for suicidality - in first year - cross-sectional
224758_at	C7orf73	D			Future hospitalizations for suicidality - in first year - longitudinal
214252_s_at	CLN5	D			Future hospitalizations for suicidality - all future years - cross-sectional
244677_at	PER1	I			Future hospitalizations for suicidality - all future years - longitudinal

C. Biomarkers for Suicidality in Females - Top Dozen and Top Predictor Biomarkers.
D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression

1566183_at	Hs.637764	I	AP	Discovery	Suicidal ideation state
243713_at	Hs.661328	I	DE	Discovery	
217369_at	IGHG1	D	AP	Discovery	
1556842_at	LOC286087	D	DE	Discovery	
244019_at	T89845	I	AP	Discovery	
219025_at	CD248	I	AP	Prioritization	
236804_at	COMT	I	AP	Prioritization	
244130_at	HTR2A	I	DE	Prioritization	
210354_at	IFNG	D	AP	Prioritization	
210354_at	IFNG	D	DE	Prioritization	
240226_at	AA828246	I	DE	Validation	
1568903_at	Hs.736359	D	AP	Validation	
201185_at	HTRA1	I	AP	Validation	
220005_at	P2RY13	D	DE	Validation	
210486_at	ANKMY1	D			Suicidal ideation state - cross-sectional
1569022_a_at	PIK3C2A	I			Future hospitalizations for suicidality - in first year - longitudinal Future hospitalizations for suicidality - all future years - longitudinal
215078_at	SOD2	I			Future hospitalizations for suicidality - all future years - longitudinal

Affymetrix Probe Set ID	Gene Symbol	Direction of Change in Suicidality	Analysis	Top Dozen Biomarker from:	Top Bonferroni Predictor Biomarker for:

D. Biomarkers for Suicidality in Bipolar Disorder - Top Dozen and Top Bonferroni Predictor Biomarkers.
D—Decreased, I—Increased. A—Absent/Present, DE—Differential Expression

236879_at	BF114768	I	DE	Discovery	
1562416_at	FLNB	I	AP	Discovery	
231262_at	Hs.147375	D	DE	Discovery	
1557984_s_at	RPAP3	D	AP	Discovery	
239683_at	CLYBL	D	AP	Prioritization	
244130_at	HTR2A	I	DE	Prioritization	
207519_at	SLC6A4	D	DE	Prioritization	
1563357_at	TNF	I	AP	Prioritization	
218081_at	C20orf27	D	DE	Validation	
203394_s_at	HES1	I	AP	Validation	
214144_at	POLR2D	D	AP	Validation	
213988_s_at	SAT1	I	DE	Validation	
232526_at	ITPKB	I			Suicidal ideation state - cross-sectional
224758_at	C7orf73	D			Suicidal ideation state - cross-sectional
208889_s_at	NCOR2	D			Suicidal ideation state - longitudinal
214433_s_at	SELENBP1	D			Future hospitalizations for suicidality - in first year - cross-sectional Future hospitalizations for suicidality - all future years - cross-sectional
219862_s_at	NARF	I			Future hospitalizations for suicidality - in first year - cross-sectional
201466_s_at	JUN	I			Future hospitalizations for suicidality - in first year - longitudinal
237180_at	PSME4	I			Future hospitalizations for suicidality - all future years - cross-sectional

Affymetrix Probe Set ID	Gene Symbol	Direction of Change in Suicidality	Analysis	Top Dozen Biomarker from:	Top Predictor Biomarker for:

E. Biomarkers for Suicidality in Depression - Top Dozen and Top Predictor Biomarkers.
D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression

35201_at	HNRNPL	D	DE	Discovery	
1556828_at	MNATI	I	DE	Discovery	
218509_at	PLPPR2	I	AP, DE	Discovery	
222351_at	PPP2R1B	D	AP	Discovery	

TABLE 3-continued

219243_at	GIMAP4	D	DE	Discovery and Validation	
1554808_at	ACP1	D	AP	Prioritization	
239367_at	BDNF	I	DE	Prioritization	
209560_s_at	DLK1	I	AP, DE	Prioritization	
206462_s_at	NTRK3	I	AP, DE	Prioritization	
225686_at	SKA2	D	DE	Prioritization	
236527_at	ATP6V0E1	D	AP	Validation	
1554264_at	CKAP2	I	AP	Validation	Future hospitalizations for suicidality
201465_s_at	JUN	I	DE	Validation	
241453_at	PTK2	I			Suicidal ideation state - cross-sectional Future hospitalizations for suicidality - in first year - cross-sectional
214085_x_at	GLIPR1	D			Suicidal ideation state - cross-sectional
232633_at	XRCC5	D			Suicidal ideation state - longitudinal
1554610_at	ANKMY1	D			Future hospitalizations for suicidality - in first year - cross-sectional Future hospitalizations for suicidality - all future years - cross-sectional
204850_s_at	DCX	D			Future hospitalizations for suicidality - in first year - longitudinal

F. Biomarkers for Suicidality in Males with Bipolar Disorder - Top Dozen and Top Predictor Biomarkers.
D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression

239711_at	ADAL	D	AP	Discovery	Future hospitalizations for suicidality
237259_at	BE674182	I	DE	Discovery	
208299_at	CACNA1I	I	AP	Discovery	
207194_s_at	ICAM4	D	DE	Discovery	
239683_at	CLYBL	D	AP	Prioritization	
214619_at	CRHR1	D	DE	Prioritization	
244130_at	HTR2A	I	DE	Prioritization	
213769_at	KSR1	I	AP	Prioritization	
218081_at	C20orf27	D	DE	Validation	
214144_at	POLR2D	D	AP	Validation	
213988_s_at	SAT1	I	DE	Validation	
215918_s_at	SPTBN1	I	AP	Validation	Suicidal ideation state - cross-sectional
224758_at	C7orf73	D			Suicidal ideation state - cross-sectional
234332_at	NUB1	I			Suicidal ideation state - longitudinal
205481_at	ADORA1	D			Suicidal ideation state - longitudinal
222176_at	PTEN	I			Future hospitalizations for suicidality - in first year - cross-sectional
214433_s_at	SELENBP1	D			Future hospitalizations for suicidality - in first year - cross-sectional
237180_at	PSME4	I			Future hospitalizations for suicidality - all future years - cross-sectional
210377_at	ACSM3	D			Future hospitalizations for suicidality - all future years - cross-sectional

Affymetrix Probe Set ID	Gene Symbol	Direction of Change in Suicidality	Analysis	Top Dozen Biomarker from:	Top Bonferroni Predictor Biomarker for:

G. Biomarkers for Suicidality in Males with Depression - Top Dozen and Top Predictor Biomarkers.
D—Decreased, I—Increased. AP—Absent/Present, DE—Differential Expression

234681_s_at	CHD6	I	AP	Discovery	
223974_at	DLGAP1-AS2	I	DE	Discovery	
35201_at	HNRNPL	D	DE	Discovery	
237951_at	R02328	I	DE	Discovery	
215263_at	ZXDA	D	AP	Discovery	
209560_s_at	DLK1	I	AP	Prioritization	
214170_x_at	FH	D	DE	Prioritization	
236587_at	LRRC6	I	DE	Prioritization	
217033_x_at	NTRK3	D	AP	Prioritization	
236527_at	ATP6V0E1	D	AP	Validation	
213524_s_at	G0S2	I	DE	Validation	
226687_at	PRPF40A	D	DE	Validation	
209841_s_at	LRRN3	D			Suicidal ideation state - cross-sectional
241453_at	PTK2	I			Suicidal ideation state - cross-sectional
210192_at	ATP8A1	I			Suicidal ideation state - longitudinal Future hospitalizations for suicidality - all future years - longitudinal
228305_at	ZNF565	D			Suicidal ideation state - longitudinal
1554610_at	ANKMY1	D			Future hospitalizations for suicidality - in first year - cross-sectional Future hospitalizations for suicidality - all future years - cross-sectional

TABLE 3-continued

205898_at	CX3CR1	D	Future hospitalizations for suicidality - in first year - longitudinal
213524_s_at	G0S2	I	Future hospitalizations for suicidality - all future years - cross-sectional

Affymetrix Probe Set ID	Gene Symbol	Direction of Change in Suicidality	Top Predictor Biomarker for:
H. Biomarkers for Suicidality in Males with Post-Traumatic Stress Disorder (PTSD) - Top Predictor Biomarkers. D—Decreased, I—Increased.			
237180_at	PSME4	I	Suicidal ideation state - cross-sectional
			Future hospitalizations for suicidality - all future years - cross-sectional
209841_s_at	LRRN3	D	Suicidal ideation state - cross-sectional
209677_at	PRKCI	D	Suicidal ideation state - longitudinal
229331_at	SPATA18	I	Suicidal ideation state - longitudinal
			Future hospitalizations for suicidality - in first year - longitudinal
			Future hospitalizations for suicidality - all future years - longitudinal
214252_s_at	CLN5	D	Future hospitalizations for suicidality - in first year - cross-sectional
212226_s_at	PPAP2B	I	Future hospitalizations for suicidality - in first year - cross-sectional
202259_s_at	N4BP2L2	D	Future hospitalizations for suicidality - all future years - cross-sectional
238919_at	PCDH9	D	Future hospitalizations for suicidality - all future years - longitudinal
I. Biomarkers for Suicidality in Males with Schizophrenia/Schizoaffective Disorder - Top Predictor Biomarkers. D—Decreased, I—Increased.			
205996_s_at	AK2	D	Suicidal ideation state - cross-sectional
205858_at	NGFR	I	Suicidal ideation state - cross-sectional
			Suicidal ideation state - longitudinal
236527_at	ATP6V0E1	D	Suicidal ideation state - longitudinal
			Future hospitalizations for suicidality - in first year - cross-sectional
218062_x_at	CDC42EP4	D	Future hospitalizations for suicidality - in first year - longitudinal
229331_at	SPATA18	I	Future hospitalizations for suicidality - in first year - longitudinal
1557966_x_at	MTERF4	D	Future hospitalizations for suicidality - all future years - cross-sectional
212226_s_at	PPAP2B	I	Future hospitalizations for suicidality - all future years - cross-sectional
213321_at	BCKDHB	D	Future hospitalizations for suicidality - all future years - longitudinal
J. Biomarkers for Suicidality in High Anxiety Subtype - Top Predictor Biomarkers. D—Decreased, I—Increased.			
209677_at	PRKCI	D	Suicidal ideation state - cross-sectional
			Future hospitalizations for suicidality - all future years - longitudinal
218656_s_at	LHFP	I	Suicidal ideation state - cross-sectional
204036_at	LPAR1	D	Future hospitalizations for suicidality - in first year - cross-sectional
214540_at	HIST1H2BO	I	Future hospitalizations for suicidality - in first year - cross-sectional
			Future hospitalizations for suicidality - all future years - cross-sectional
236879_at	BF114768	I	Future hospitalizations for suicidality - all future years - longitudinal
216765_at	MAP2K5	D	Future hospitalizations for suicidality - all future years - cross-sectional
K. Biomarkers for Suicidality in Low Mood Subtype - Top Predictor Biomarkers. D—Decreased, I—Increased.			
209534_x_at	AKAP13	I	Suicidal ideation state - longitudinal
231772_x_at	CENPH	D	Suicidal ideation state - longitudinal
207844_at	IL13	I	Suicidal ideation state - cross-sectional
214252_s_at	CLN5	D	Suicidal ideation state - cross-sectional
230191_at	TTBK1	D	Future hospitalizations for suicidality - in first year - longitudinal
237180_at	PSME4	I	Future hospitalizations for suicidality - in first year - longitudinal
			Future hospitalizations for suicidality - all future years - cross-sectional
231854_at	PIK3CA	D	Future hospitalizations for suicidality - in first year - cross-sectional
214782_at	CTTN	I	Future hospitalizations for suicidality - in first year - cross-sectional
211633_x_at	IGHG1	D	Future hospitalizations for suicidality - all future years - longitudinal
L. Biomarkers for Suicidality in the High Psychosis (Non-Affective) Subtype - Top Predictor Biomarkers. D—Decreased, I—Increased.			
231854_at	PIK3CA	D	Suicidal ideation state - cross-sectional
204730_at	RIMS3	D	Future hospitalizations for suicidality - in first year - cross-sectional
215078_at	SOD2	I	Future hospitalizations for suicidality - in first year - cross-sectional
229856_s_at	PITHD1	D	Future hospitalizations for suicidality - all future years - longitudinal
215078_at	SOD2	I	Future hospitalizations for suicidality - all future years - longitudinal
			Future hospitalizations for suicidality - all future years - cross-sectional
203336_s_at	ITGB1BP1	D	Future hospitalizations for suicidality - all future years - cross-sectional
M. Biomarkers for Suicidality in the Combined (Affective) Subtype - Top Predictor Biomarkers. D—Decreased, I—Increased.			
209677_at	PRKCI	D	Suicidal ideation state - longitudinal
			Future hospitalizations for suicidality - all future years - longitudinal
566861_at	GATM1	I	Suicidal ideation state - longitudinal
214782_at	CTTN	I	Future hospitalizations for suicidality - in first year - longitudinal
228305_at	ZNF565	D	Future hospitalizations for suicidality - in first year - longitudinal
201929_s_at	PKP4	D	Future hospitalizations for suicidality - in first year - cross-sectional
236879_at	BF114768	I	Future hospitalizations for suicidality - all future years - longitudinal

TABLE 3-continued

1557966_x_at	MTERF4	D	Future hospitalizations for suicidality - all future years - cross-sectional
232526_at	ITPKB	I	Future hospitalizations for suicidality - all future years - cross-sectional

Validation Analyses

For the AP analyses, the Affymetrix microarray .chp data files from the participants in the coroner validation cohort of suicide completers were imported into the MASS Affymetrix Expression Console, alongside the data files from the No SI and High SI groups in the live discovery cohort. The AP data was transferred to an Excel sheet and transformed: A into 0, M into 0.5, and P into 1. All data was then Z-scored together by gender. If a probeset would have showed no variance and thus gave a non-determined (0/0) value in Z-scoring in a gender, the values were excluded from that probeset for that gender from the analysis. All probesets, however, did show variance in this Example.

For the DE analyses, Affymetrix microarray .cel files were imported from the participants in the validation cohort of suicide completers into Partek Genomic Suites. An RMA was run by gender, background corrected with quantile normalization, and a median polish probeset summarization of the chips from the validation cohort was conducted to obtain the normalized expression levels of all probesets for each chip. The No SI and High SI groups from the discovery cohort were RMA by gender and diagnosis, as described above for Discovery. 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, and the non-log transformed coroner validation cohort expression data was transferred to an Excel sheet, alongside data from the No SI and High SI groups from the discovery cohort. All data was then Z-scored together by gender.

Validation analyses of the candidate biomarker genes were conducted separately for AP and for DE. The top candidate genes (total CFG score of 4 or above), were stepwise changed in expression from the No SI group to the High SI group to the suicide completers group. A CFG score of 4 or above reflects an empirical cutoff of 33.3% of the maximum possible CFG score of 12, which permits the inclusion of potentially novel genes with maximal internal score of 4, but no external evidence score. The Excel sheets with the Z-scored by gender expression data from AP were imported, respectively from DE, into Partek, and statistical analyses were performed using a one-way ANOVA for the stepwise changed probesets, and stringent Bonferroni corrections for all the probesets tested in AP and DE (stepwise and non-stepwise) (FIG. **1**F).

Discovery and Validation in Male Bipolars

For male bipolar disorders, the discovery and validation were conducted as described above except that only male bipolar subjects from the discovery cohort (n=20 subjects, 65 visits) were used for discovery, and male suicide completers (n=38) were used for validation.

Phenotypic Measures

SASS. The Simplified Affective State Scale (SASS) is an 11-item scale for measuring mood state (SMS) and anxiety state (SAS), previously developed and described in Niculescu et al., Mol Psychiatry 2015; 20(11): 1266-1285 and Niculescu et al., American journal of medical genetics Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics 2006; 141B (6): 653-662. The SASS has a set of 11 visual analog scales (7 for mood, 4 for anxiety) each item ranging from 0 to 100 for mood state, and the same for anxiety state. The averaged 7 items for mood give the Mood score, and the averaged 4 items for anxiety give the Anxiety score.

CFI-S. Convergent Functional Information for Suicidality (CFI-S) (FIG. **4**A) 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 (263), or scored based on retrospective electronic medical record information and Diagnostic Interview for Genetic Testing (DIGS) information (457). When information was not available for an item, it was not scored (NA). The average of the score of the items for which there was information gives us the CFI-S score.

Subtypes

In order to identify possible subtypes of suicidality, a two-way unsupervised hierarchical clustering of the high SI visits in the discovery cohort, based on measures of anxiety and mood (from the SASS), as well as psychosis (PANS S Positive) was used. The mood item was inverted for the purposes of this analysis so that higher values indicate low mood. This clustering was used to identify four distinct subtypes of suicidality/high suicidal ideation: a high anxiety subtype, a low mood subtype, a combined affective subtype, and a non-affective (psychotic) subtype (FIG. **1**C).

The insight from the discovery cohort was used to divide the independent test cohort into the four subtypes, using anxiety and mood measures from SASS, which are on a scale of 0 to 100. The high anxiety subtype participant visits had anxiety above 50 and low mood below 50, the low mood subtype had low mood below 50 and anxiety below 50, the combined affective subtype had low mood above 50 and anxiety above 50, and the non-affective subtype had low mood below 50 and anxiety below 50.

Combining Biomarkers and Phenotypic Measures

The Universal Predictor for Suicidality (UP-Suicide) construct, the primary endpoint, was decided upon as part of the apriori study design. It combines the top biomarkers with the phenomic (clinical) measures (CFI-S score, Mood and Anxiety scores from SASS). It is calculated as the simple algebraic summation of the components included (averaged panel of biomarkers (BioM), CFI-S, Mood, Anxiety). All individual biomarkers and clinical measure scores are Z-scored by gender and diagnosis, to normalize for different ranges of values and be able to combine them into a composite predictor (UP-Suicide). Decreased biomarkers, and Mood, have a minus sign in front of them.

Diagnostics

The test cohort for predicting suicidal ideation (state), and the subset of it that is a test cohort for predicting future hospitalizations for suicidality (trait), were assembled out of data that was RMA normalized by gender and diagnosis. The cohort was completely independent, there was no subject overlap with the discovery cohort. Phenomic (clinical) and gene expression markers used for predictions were Z-scored by gender and diagnosis, to be able to combine different markers into panels and to avoid potential artefacts due to different ranges of expression in different gender and diagnoses. Markers were combined by simple summation of the

increased risk markers minus the decreased risk markers. Predictions were performed using R-studio. For cross-sectional analyses, marker expression levels were used, z-scored by gender and diagnosis. For longitudinal analyses, four measures were combined: marker expression levels, slope (defined as ratio of levels at current testing visit vs. previous visit, divided by time between visits), maximum levels (at any of the current or past visits), and maximum slope (between any adjacent current or past visits). For decreased markers, the minimum, rather than the maximum, was used for level calculations. All four measures were Z-scored then combined in an additive fashion into a single measure. The longitudinal analysis was carried out in a sub-cohort of the testing cohort consisting of participants that had at least two test visits.

Predicting High Suicidal Ideation State. Receiver-operating characteristic (ROC) analyses between genomic and phenomic marker levels and suicidal ideation (SI) were performed by assigning participants with a HAMD-SI score of 2 and greater into the high SI category. The pROC function of the R studio was used. The Z-scored biomarker and phene scores were used, running them in this ROC generating program against the "diagnostic" groups in the independent test cohort (high SI vs. the rest of subjects). Additionally, ANOVA was performed between no SI (HAMD-SI 0), intermediate (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 (Tables 4A & 4B, FIGS. **5**A-**5**C & FIG. **6**).

TABLE 4

Diagnostics. Biomarkers, Phenes, and Combined Predictions.
Red - top increased biomarker predictor; Blue - top decreased biomarker predictor. Underlined are individual biomarkers from the Top Dozen list, the others are from the Bonferroni list. For Universal, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM148, reflecting the number of markers in the panel. For Male Bipolar, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM54, reflecting the number of markers in the panel. Italic - a priori primary endpoint (UP-Suicide).

A. Suicidal Ideation State
Bold - p-value of AUC survives correction for multiple testing for predictions. ROC AUC is apriori primary predictive tool.

Predictors	Cohort	Participants with high SI/Participants total	ROC AUC/ p-value	Suicidality Severity (HAMD SI Score) Correlation R/ p-value	T-test p-value
		Universal Best Biomarkers			
SLC4A4	All	52/544	0.64/3.83E−04	0.13/1.54E−03	1.50E−03
CLN5	All	52/544	**0.65/1.86E−04**	−0.11/6.13E−03	3.90E−04
BioM 148 Panel (Bonferroni List)	All	52/544	0.61/6.18E−03	0.069/5.33E−02	1.77E−02
BioM 12 Panel (Top Dozen List)	All	52/544	0.61/3.66E−03	0.12/3.02E−03	3.08E−03
BioM 2 Panel (SLC4A4 and CLN5)	All	52/544	**0.66/4.92E−05**	0.14/7.82E−04	1.90E−04
		Phenes			
Mood	All	52/544	**0.77/5.93E−11**	−0.38/3.17E−20	1.95E−10
Anxiety	All	52/544	**0.77/3.43E−11**	0.31/8.60E−14	2.03E−12
Mood and Anxiety (SASS)	All	52/544	**0.81/5.55E−14**	0.40/3.66E−22	3.57E−14
CFI-S	All	52/523	**0.86/9.98E−18**	0.43/1.03E−24	5.46E−16
Mood and Anxiety and CFI-S	All	52/523	**0.89/2.59E−20**	0.49/1.60E−33	1.08E−18
		Phenes and Biomarkers			
Mood and Anxiety and CFI-S and BioM 148	All	52/523	**0.89/1.36E−20**	0.49/2.84E−33	2.88E−18
Mood and Anxiety and CFI-S and BioM 12(UP-Suicide)	*All*	*52/523*	*0.90/3.87E−21*	*0.50/5.91−35*	*3.42E−19*
Mood and Anxiety and CFI-S and BioM2	All	52/523	**0.89/4.56E−21**	0.50/4.07E−34	2.83E−18
		Male Bipolar Best Biomarkers			
SPTBN1	M-BP	12/130	0.72/6.62E−03	0.21/8.54E−03	9.05E−03
C7orf73	M-BP	12/130	0.75/2.38E−03	−0.17/2.76E−02	1.08E−04
BioM 54 Panel (Bonferroni List)	M-BP	12/130	0.49/5.29E−01	0/4.90E−01	7.12E−01
BioM 12 Panel (Top Dozen List)	M-BP	12/130	0.57/2.08E−01	0.08/1.78E−01	8.79E−02
BioM 2 (SPTBN1 and C7orf73)	M-BP	12/130	0.80/3.54E−04	0.23/4.77E−03	6.62E−05
		Phenes			
Mood	M-BP	12/130	0.8/3.65E−04	−0.47/6.83E−09	1.65E−03
Anxiety	M-BP	12/130	0.86/2.19E−05	0.41/7.09E−07	1.91E−05
Mood and Anxiety (SASS)	M-BP	12/130	0.86/1.66E−05	0.5/7.15E−10	5.66E−05
CFI-S	M-BP	12/128	0.92/1.10E−06	0.5/6.11E−10	1.31E−06
Mood and Anxiety and CFI-S	M-BP	12/128	0.94/2.82E−07	0.61/1.24E−14	3.01E−06

TABLE 4-continued

Diagnostics. Biomarkers, Phenes, and Combined Predictions.
Red - top increased biomarker predictor; Blue - top decreased biomarker predictor. Underlined are individual biomarkers from the Top Dozen list, the others are from the Bonferroni list. For Universal, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM148, reflecting the number of markers in the panel. For Male Bipolar, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM54, reflecting the number of markers in the panel. Italic - a priori primary endpoint (UP-Suicide).

Phenes and Biomarkers					
Mood and Anxiety and CFI-S and BioM 54	M-BP	12/128	0.93/5.30E−07	0.61/1.78E−14	5.54E−06
Mood and Anxiety and CFI-S and BioM 12	*M-BP*	*12/128*	*0.95/1.62E−07*	*0.62/1.92E−15*	*8.31E−07*
Mood and Anxiety and CFI-S and BioM 2	M-BP	12/128	0.97/5.14E−08	0.64/2.29E−16	2.59E−07

B. Future Hospitalizations for Suicidality in the First Year Following Assessment in the Independent Test Cohort
Bold - p-value of AUC survives correction for multiple testing for predictions. ROC AUC is our apriori primary predictive tool. HAMD SI is the suicide rating question from the Hamilton Rating Scale for Depression. *Smaller cohort, as not everybody had HAMD SI information.

Predictors	Cohort	Participants with future hospitalizations for suicidality within the first year/Particpants total	ROC AUC/ p-value	Frequency of future hospitalizations for suicidality within the first year Correlation R/p-value	T-test p-value	Cox Regression Hazard Ratio/ P-value
Universal Best Biomarkers						
PSME4	All	38/471	0.59/2.62E−02	0.08/4.12E−02	6.20E−02	1.23/1.56E−01
AK2	All	38/471	0.60/2.31E−02	−0.06/9.70E−02	9.39E−03	1.35/7.22E−02
BioM 148 Panel (Bonferroni List)	All	38/471	0.52/3.37E−01	−0.02/6.67E−01	4.18E−01	1.09/8.27E−01
BioM 12 Panel (Top Dozen List)	All	38/471	0.58/4.20E−02	0.05/1.47E−01	5.02E−02	1.88/1.41E−01
BioM 2 Panel (PSME4 and AK2)	All	38/471	0.65/1.10E−03	0.10/1.29E−02	1.35E−03	1.68/0.018
Phenes						
Mood	All	38/471	0.65/1.00E−03	−0.16/3.63E−04	1.03E−03	1.69/1.47E−03
Anxiety	All	38/471	**0.69/3.70E−05**	0.16/3.43E−04	2.30E−04	1.82/2.62E−04
Mood and Anxiety (SASS)	All	38/471	**0.71/9.78E−06**	0.18/4.89E−05	7.73E−05	1.45/8.11E−05
CFI-S	All	38/470	**0.75/1.79E−07**	0.2/5.11E−06	1.40E−06	2.02/7.11E−07
Mood and Anxiety and CFI-S	All	38/470	**0.76/6.34E−08**	0.22/4.18E−07	2.22E−06	1.40/1.13E−07
HAMD SI	All	35/458*	**0.81/5.27E−10**	0.40/1.57E−19	2.64E−06	2.10/1.11E−15
Mood and Anxiety and CFI-S and HAMD SI	All	35/458*	**0.82/9.96E−11**	0.35/4.11E−15	4.34E−08	1.36/1.83E−13
Phenes and Biomarkers						
Mood and Anxiety and CFI-S and BioM 148	All	38/470	**0.76/6.65E−08**	0.21/1.29E−06	2.29E−06	1.37/2.01E−07
Mood and Anxiety and CFI-S and BioM 12 (UP-Suicide)	*All*	*38/470*	*0.77/2.87E−08*	*0.23/2.81E−07*	*9.11E−07*	*1.40/5.31E−08*
Mood and Anxiety and CFI-S and BioM 2	All	38/470	**0.76/3.87E−08**	0.24/1.17E−07	1.02E−06	1.39/3.98E−08
Mood and Anxiety and CFI-S and HAMD SI and BioM 2	All	35/458*	**0.82/9.38E−11**	0.35/3.20E−15	3.39E−08	1.35/1.83E−13
Male Bipolars Best Biomarkers						
PTEN	M-BP	4/120	0.9/3.27E−03	0.22/6.76E−03	3.12E−02	1.73/2.73E−02
RNF6	M-BP	4/120	0.82/1.58E−02	−0.14/5.89E−02	9.14E−03	6.24/7.19E−02
BioM 54 Panel (Bonferroni List)	M-BP	4/120	0.75/4.23E−02	0.11/1.23E−01	4.71E−02	4.58/2.52E−01
BioM 12 Panel (Top Dozen List)	M-BP	4/120	0.56/3.41E−01	0.05/2.85E−01	3.08E−01	2.57/5.73E−01
BioM 2 (PTEN and RNF6)	M-BP	4/120	0.94/1.50E−03	0.23/5.17E−03	3.06E−03	2.68/1.19E−02
Phenes						
Mood	M-BP	4/120	0.69/1.04E−01	−0.14/6.08E−02	1.75E−01	2.10/1.32E−01
Anxiety	M-BP	4/120	0.70/9.29E−02	0.12/9.74E−02	1.12E−01	1.87/2.09E−02
Mood and Anxiety (SASS)	M-BP	4/120	0.72/7.19E−02	0.15/5.27E−02	1.34E−01	1.52/1.18E−01
CFI-S	MBP	4/120	0.80/2.10E−02	0.15/5.22E−02	3.46E−03	1.95/1.21E−01
Mood and Anxiety and CFI-S	M-BP	4/120	0.78/2.77E−02	0.18/2.36E−02	6.78E−02	1.41/5.54E−02

TABLE 4-continued

Diagnostics. Biomarkers, Phenes, and Combined Predictions.
Red - top increased biomarker predictor; Blue - top decreased biomarker predictor. Underlined are individual biomarkers from the Top Dozen list, the others are from the Bonferroni list. For Universal, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM148, reflecting the number of markers in the panel. For Male Bipolar, the panel of Top Dozen biomarkers is called BioM 12, and the panel of Bonferroni biomarkers is called BioM54, reflecting the number of markers in the panel. Italic - a priori primary endpoint (UP-Suicide).

Phenes and Biomarkers						
Mood and Anxiety and CFIS and BioM 54	M-BP	4/120	0.81/1.64E−02	0.2/1.61E−02	5.13E−02	1.45/4.04E−02
Mood and Anxiety and CFI-S and BioM 12 (UP-Suicide Male BP)	*M-BP*	*4/120*	*0.79/2.59E−02*	*0.19/1.88E−02*	*7.92E−02*	*1.44/4.72E−02*
Mood and Anxiety and CFI-S and BioM 2	M-BP	4/120	0.86/7.02E−03	0.25/3.48E−03	2.22E−02	1.55/1.18E−2

Predicting Future Hospitalizations for Suicidality in First Year Following Testing. Analyses for predicting hospitalizations for suicidality in the first year following each testing visit were conducted in subjects that had at least one year of follow-up in the VA system, for which there was access to complete electronic medical records. ROC analyses between genomic and phenomic marker levels at a specific testing visit and future hospitalizations were performed as described above, based on assigning if participants had been hospitalized for suicidality (ideation, attempts) or not within one year following a testing visit. Additionally, a one tailed t-test with unequal variance was performed between groups of participant visits with and without future 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 marker levels.

A correlation analyses for hospitalization frequency for all future hospitalizations due to suicidality was also conducted, including those occurring beyond one year of follow-up, in the years following testing (on average 4.90 years per participant, range 0.40 to 10.42 years), as this calculation, unlike the ROC and t-test, accounts for the actual length of follow-up, which varied from participant to participant. The ROC and t-test might in fact, if used, under-represent the power of the markers to predict, as the more severe psychiatric patients are more likely to move geographically and/or be lost to follow-up.

Therapeutics

The individual top biomarkers known to be modulated by existing drugs were analyzed using the CFG databases, and using Ingenuity Drugs analyses (Tables 5A-5G). Drugs and natural compounds which are an opposite match for the gene expression profile of panels of the top biomarkers (top dozen biomarkers, Bonferroni corrected) were also analyzed using the Connectivity Map (Broad Institute, MIT) (Tables 6-18). For the top dozen universal biomarker panel, 7 of 12 probesets were present of the array used for the Connectivity Map; for the Bonferroni universal biomarker panel, 102 out of 148 probesets; for the top dozen male bipolar panel, 8 out of 12 probesets; and for the Bonferroni male bipolar panel, 31 out of 56 probesets.

TABLE 5

Gene Symbol Gene Name	(Direction of Change in Suicidality) Analysis/ Internal Score	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Modulated by other Antidepressants	Modulated by other Mood Stabilizers	Modulated by other Antipsychotics	Modulated by other Drugs
A. Top Universal Biomarkers for Suicidality - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide.								
CCL28 chemokine (C-C motif) ligand 28	(D) AP/4				Paroxetine			
HTR2A 5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	(I) DE/2			Yes	Buspirone, mirtazapine, amitriptyline	Valproate	Haloperidol Paliperidone, Risperidone, Iloperidone, asenapine, cariprazine, thioproperazine, lurasidone, opipramol, quetiapine, olanzapine,	
IFNG interferon, gamma	(D) AP/1						Olanzapine, Risperidone, Quetiapine, Aripiprazole	
ITGB1BP1 integrin beta 1 binding protein 1	(D) DE/1		Yes					

TABLE 5-continued

LHFP lipoma HMGIC fusion partner	(I) DE/1	Yes						
PTK2 protein tyrosine kinase 2	(I) DE/1							CT-707
SLC4A4 solute carrier family 4 (sodium bicarbonate cotransporter), member 4	(I) AP/1					Valproate		

Gene Symbol Gene Name	Direction of Change in Suicidality Analysis/ Internal Score	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Modulated by other Antidepressants	Modulated by other Mood Stabilizers	Modulated by other Antipsychotics	Modulated by other Drugs
B. Top Biomarkers for Suicidality in Males - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide								
AGT Angiotensinogen	I AP/1			Yes				
GDI2 GDP Dissociation Inhibitor 2	D DE/1			Yes				Benzodiazepines
IL6 Interleukin 6	I AP/2			Yes	Yes		Yes	tocilizumab, siltuximab
ITGB1BP1 Integrin Subunit Beta 1 Binding Protein 1	D DE/1		Yes					
PRKACB Protein Kinase CAMP-Activated Catalytic Subunit Beta	D AP/4			Yes				
SAT1 Spermidine/Spermine N1-Acetyltransferase 1	I DE/1	Yes						
SLC4A4 Solute Carrier Family 4 Member 4	I AP/2					Valproate		
SLC6A4 Solute Carrier Family 6 Member 4	I DE/2	Yes			Yes SSRIs SNRIs			bicifadine, DOV-102,677, SLV-314
TM4SF1 Transmembrane 4 L Six Family Member 1	I AP/1	Yes	Yes					
ZMYND8 Zinc Finger MYND-Type Containing 8	D AP/1	Yes						
C. Top Biomarkers for Suicidality in Females - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide								
BDNF Brain Derived Neurotrophic Factor	I DE/2	Yes			Fluoxetine		Haloperidol	Mifepristone
HS6ST2 Heparan Sulfate 6-O-Sulfotransferase 2	I DE/1			Yes				
HTR2A 5-Hydroxytryptamine Receptor 2A	I DE/2		Yes	Yes	Buspirone, mirtazapine, amitriptyline	Valproate	Haloperidol Paliperidone, Risperidone, Iloperidone, asenapine, cariprazine, thioproperazine, lurasidone, opipramol, quetiapine, olanzapine,	
IFNG Interferon Gamma	D AP/1			Yes			Yes	
NTRK3 Neurotrophic	I DE/2			Yes				TSR-011, entrectinib,

TABLE 5-continued

Receptor Tyrosine Kinase 3								PLX7486, DS-6051b
TPR Translocated Promoter Region, Nuclear Basket Protein	D AP/4					Valproate		
Gene Symbol Gene Name	(Direction of Change in Suicidality) Analysis/ Internal Score	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Modulated by other Antidepressants	Modulated by other Mood Stabilizers	Modulated by other Antipsychotics	Modulated by other Drugs
D. Top Biomarkers for Suicidality in Bipolar Disorder - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide								
HTR2A 5-Hydroxytryptamine Receptor 2A	(I) DE/2		Yes	Yes	Buspirone, mirtazapine, amitriptyline	Valproate	Haloperidol Paliperidone, Risperidone, Iloperidone, asenapine, cariprazine, thioproperazine, lurasidone, opipramol, quetiapine, olanzapine,	
ITPKB Inositol-Trisphosphate 3-Kinase B	(I) AP/2	Yes						
PIK3R1 Phosphoinositide-3-Kinase Regulatory Subunit 1	(I) DE/1		Yes					
SAT1 Spermidine/Spermine N1-Acetyltransferase 1	(I) DE/1	Yes						
SLC6A4 Solute Carrier Family 6 Member 4	(D) DE/1		Yes	Yes	Fluoxetine			bicifadine, DOV-102,677, SLV-314
TM4SF1 Transmembrane 4 L Six Family Member 1	(I) AP/1	Yes	Yes					
TNF Tumor Necrosis Factor	(I) DE/1 (I) AP/1				Sertraline Venlafaxine			, etanercept, infliximab, certolizumab, golimumab, thalidomide
E. Top Biomarkers for Suicidality in Depression - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide								
BDNF Brain Derived Neurotrophic Factor	(I) DE/1	Yes			Fluoxetine		Haloperidol	Mifepristone
DLK1 Delta Like Non-Canonical Notch Ligand 1	(I) AP/2 (I) DE/1	Yes						
NTRK3 Neurotrophic Receptor Tyrosine Kinase 3	(I) AP/2 (I) DE/1			Yes				TSR-011, entrectinib, PLX7486, DS-6051b
ACP1 Acid Phosphatase 1, Soluble	(D) AP/1	Yes			Fluoxetine		Olanzapine	
TSPYL1 TSPY Like 1	(D) AP/1	Yes				Valproate		
CD47 CD47 Molecule	(D) AP/2 (D) DE/1	Yes		Yes				
GLIPR1 GLI Pathogenesis Related 1	(D) DE/1					Valproate		

TABLE 5-continued

GEM	(I)			Yes				
GTP Binding Protein Overexpressed In Skeletal Muscle	AP/1							
JUN	(I)		Yes	Yes	Fluoxetine			
Jun Proto-Oncogene, AP-1 Transcription Factor Subunit	DE/1							
GIMAP4	(D)							Benzodiazepines
GTPase, IMAP Family Member 4	DE/4							
HNRNPL	(D)			Yes				
Heterogeneous Nuclear Ribonucleoprotein L	DE/4							

F. Top Biomarkers for Suicidality in Males with Bipolar Disorder - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide

HTR2A	(I)		Yes	Yes	Buspirone,	Valproate	Haloperidol	
5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	DE/2				mirtazapine, amitriptyline		Paliperidone, Risperidone, Iloperidone, asenapine, cariprazine, thioproperazine, lurasidone, opipramol, quetiapine, olanzapine,	
SPTBN1	(I)	Yes						
spectrin, beta, non-erythrocytic 1	AP/1							

G. Top Biomarkers for Suicidality in Males with Depression - Pharmacogenomics for potential stratification and monitoring response to treatment. Biomarker genes that are targets of existing drugs and modulated by them in opposite direction to suicide

DLK1	(I)	Yes						
Delta Like Non-Canonical Notch Ligand 1	AP/2							
NTRK3	(D)				Fluoxetine			TSR-011,
Neurotrophic Receptor Tyrosine Kinase 3	AP/2							entrectinib, PLX7486, DS-6051b
CD47	D	Yes		Yes				
CD47 Molecule	AP/2							
PTK2	I							CT-707
Protein Tyrosine Kinase 2	DE/1							
TSPYL1	D	Yes				Valproate		
TSPY Like 1	AP/1							
HNRNPL	(D)			Yes				
Heterogeneous Nuclear Ribonucleoprotein L	DE/4							

TABLE 6

Repurposed Drugs for Suicidality Treatment in Everybody (Universal)

compound name	dose	cell	score	gene expression signature
dapsone	16 μM	HL60	−1	Top Predictor Biomarkers
ebselen	15 μM	PC3	−1	Top Dozen Biomarkers
chlorogenic acid	11 μM	HL60	−1	Bonferroni Biomarkers
clemastine	9 μM	HL60	−0.983	Top Predictor Biomarkers
metformin	24 μM	HL60	−0.983	Bonferroni Biomarkers
piracetam	28 μM	MCF7	−0.973	Top Dozen Biomarkers
dihydroergocristine	6 μM	MCF7	−0.946	Top Dozen Biomarkers
amoxapine	13 μM	MCF7	−0.927	Top Dozen Biomarkers
metformin	24 μM	HL60	−0.925	Top Predictor Biomarkers
lisuride	12 μM	PC3	−0.922	Top Dozen Biomarkers
homatropine	11 μM	HL60	−0.917	Top Predictor Biomarkers
ritodrine	12 μM	HL60	−0.916	Top Predictor Biomarkers
merbromin	5 μM	HL60	−0.904	Top Predictor Biomarkers
naproxen	16 μM	MCF7	−0.903	Top Dozen Biomarkers
dl-alpha tocopherol	9 μM	HL60	−0.885	Top Predictor Biomarkers
chlorpromazine	11 μM	HL60	−0.877	Top Predictor Biomarkers
diphenhydramine	14 μM	HL60	−0.873	Bonferroni Biomarkers

TABLE 6-continued

Repurposed Drugs for Suicidality Treatment in Everybody (Universal)

compound name	dose	cell	score	gene expression signature
genistein	10 μM	PC3	−0.869	Top Dozen Biomarkers
fluoxetine	12 μM	HL60	−0.851	Top Predictor Biomarkers
adiphenine	11 μM	HL60	−0.847	Top Predictor Biomarkers
chlorogenic acid	11 μM	HL60	−0.842	Top Predictor Biomarkers
yohimbine	10 μM	MCF7	−0.842	Top Predictor Biomarkers
prazosin	10 μM	PC3	−0.838	Top Predictor Biomarkers
amitriptyline	13 μM	HL60	−0.827	Top Predictor Biomarkers
calcium folinate	8 μM	MCF7	−0.825	Bonferroni Biomarkers

Using Universal Biomarker Signatures, as identified herein, Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold—known antidepressant/psychotropic.

Italic—natural compound

TABLE 7

Repurposed Drugs for Suicidality Treatment in Males

compound name	dose	cell	score	gene expression signature
clemastine	9 μM	HL60	−1	Top Predictor Biomarkers
metformin	24 μM	HL60	−1	Bonferroni Biomarkers
chlorpromazine	11 μM	HL60	−0.997	Top Predictor Biomarkers
thiamine	12 μM	MCF7	−0.989	Top Dozen Biomarkers
hydrochlorothiazide	13 μM	MCF7	−0.984	Top Dozen Biomarkers
LY-294002	100 nM	MCF7	−0.981	Top Predictor Biomarkers
naringin	7 μM	MCF7	−0.963	Top Dozen Biomarkers
betulin	9 μM	HL60	−0.952	Top Dozen Biomarkers
ritodrine	12 μM	HL60	−0.941	Top Predictor Biomarkers
fluvastatin	9 μM	PC3	−0.935	Top Predictor Biomarkers
dapsone	16 μM	HL60	−0.913	Top Predictor Biomarkers
ranitidine	11 μM	MCF7	−0.908	Top Dozen Biomarkers
diphenhydramine	14 μM	MCF7	−0.906	Top Dozen Biomarkers
mephenesin	22 μM	MCF7	−0.905	Top Predictor Biomarkers
thiamphenicol	11 μM	HL60	−0.904	Top Predictor Biomarkers
dizocilpine	12 μM	MCF7	−0.9	Top Predictor Biomarkers
metformin	24 μM	HL60	−0.885	Top Predictor Biomarkers
droperidol	11 μM	HL60	−0.85	Top Predictor Biomarkers
lisuride	12 μM	MCF7	−0.85	Top Predictor Biomarkers
vitexin	9 μM	PC3	−0.842	Top Predictor Biomarkers
risperidone	10 μM	MCF7	−0.841	Top Predictor Biomarkers
fluoxetine	12 μM	HL60	−0.831	Bonferroni Biomarkers

Using the identified Male Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold—known antidepressant/psychotropic.

Italic—natural compound

TABLE 8

Repurposed Drugs for Suicidality Treatment in Females

compound name	dose	cell	score	gene expression signature
estradiol	100 nM	HL60	−1	Bonferroni Biomarkers
pizotifen	9 μM	HL60	−1	Top Dozen Biomarkers
rosiglitazone	10 μM	HL60	−1	Top Dozen Biomarkers
orlistat	10 μM	MCF7	−0.972	Top Dozen Biomarkers
nefopam	14 μM	MCF7	−0.953	Bonferroni Biomarkers
biperiden	11 μM	MCF7	−0.941	Bonferroni Biomarkers
fluoxetine	12 μM	HL60	−0.927	Bonferroni Biomarkers
cyanocobalamin	3 μM	MCF7	−0.896	Top Dozen Biomarkers
vitexin	9 μM	MCF7	−0.895	Top Dozen Biomarkers
hesperetin	13 μM	PC3	−0.883	Top Dozen Biomarkers
kawain	17 μM	MCF7	−0.883	Bonferroni Biomarkers
ergocalciferol	10 μM	HL60	−0.832	Bonferroni Biomarkers

Using the identified Female Biomarkers Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold—known antidepressant/psychotropic.

Italic—natural compound

TABLE 9

Repurposed Drugs for Suicidality Treatment in Bipolar Disorder

compound name	dose	cell	score	gene expression signature
phenelzine	17 μM	MCF7	−1	Top Predictor Biomarkers
methocarbamol	17 μM	PC3	−1	Top Dozen Biomarkers
baclofen	19 μM	PC3	−1	Bonferroni Biomarkers
mepenzolate bromide	10 μM	PC3	−0.993	Top Predictor Biomarkers
lobelanidine	11 μM	MCF7	−0.992	Top Predictor Biomarkers
genistein	10 μM	MCF7	−0.985	Top Dozen Biomarkers
lactobionic acid	11 μM	MCF7	−0.974	Top Dozen Biomarkers
fluocinonide	8 μM	PC3	−0.968	Top Predictor Biomarkers
apigenin	15 μM	PC3	−0.957	Top Predictor Biomarkers
betahistine	17 μM	MCF7	−0.948	Top Dozen Biomarkers
levonorgestrel	13 μM	PC3	−0.933	Top Predictor Biomarkers
amoxapine	13 μM	PC3	−0.932	Top Dozen Biomarkers
(+/−)-catechin	14 μM	MCF7	−0.931	Top Predictor Biomarkers
apigenin	15 μM	PC3	−0.93	Bonferroni Biomarkers
fenoprofen	7 μM	PC3	−0.923	Top Predictor Biomarkers
carisoprodol	15 μM	MCF7	−0.919	Bonferroni Biomarkers
benfotiamine	9 μM	PC3	−0.918	Bonferroni Biomarkers
felodipine	10 μM	MCF7	−0.917	Bonferroni Biomarkers
nifedipine	12 μM	MCF7	−0.914	Bonferroni Biomarkers
0175029-0000	10 μM	PC3	−0.913	Top Predictor Biomarkers
nifuroxazide	15 μM	HL60	−0.91	Top Predictor Biomarkers
cotinine	23 μM	MCF7	−0.862	Top Dozen Biomarkers
ergocalciferol	10 μM	MCF7	−0.86	Top Dozen Biomarkers
resveratrol	18 μM	MCF7	−0.857	Top Predictor Biomarkers
hesperetin	13 μM	PC3	−0.854	Top Dozen Biomarkers

Using the identified Bipolar Biomarkers Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.
Bold—known antidepressant/psychotropic.
Italic—natural compound

TABLE 10

Repurposed Drugs for Suicidality Treatment in Depression

compound name	dose	cell	score	gene expression signature
hyoscyamine	14 μM	HL60	−1	Top Dozen Biomarkers
metrizamide	5 μM	HL60	−1	Top Dozen Biomarkers
nadolol	13 μM	MCF7	−1	Bonferroni Biomarkers
mebhydrolin	5 μM	HL60	−0.969	Top Dozen Biomarkers
rofecoxib	10 μM	MCF7	−0.966	Top Dozen Biomarkers
gabapentin	23 μM	MCF7	−0.958	Top Dozen Biomarkers
thiamazole	35 μM	MCF7	−0.953	Top Dozen Biomarkers
celecoxib	10 μM	MCF7	−0.952	Top Dozen Biomarkers
nimodipine	10 μM	MCF7	−0.951	Bonferroni Biomarkers
estradiol	10 nM	MCF7	−0.949	Top Dozen Biomarkers
ginkgolide A	10 μM	PC3	−0.946	Top Dozen Biomarkers
harmine	16 μM	HL60	−0.931	Top Dozen Biomarkers

TABLE 10-continued

Repurposed Drugs for Suicidality Treatment in Depression

compound name	dose	cell	score	gene expression signature
nifedipine	12 μM	PC3	−0.929	Top Dozen Biomarkers
SC-58125	10 μM	MCF7	−0.929	Top Dozen Biomarkers
noscapine	10 μM	MCF7	−0.924	Top Dozen Biomarkers
thiamine	12 μM	MCF7	−0.922	Top Dozen Biomarkers
diphenhydramine	14 μM	HL60	−0.861	Bonferroni Biomarkers
metformin	24 μM	HL60	−0.84	Bonferroni Biomarkers

Using the identified Depression Biomarkers Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.
Bold - known antidepressant/psychotropic.
Italic - natural compound

TABLE 11

Repurposed Drugs for Suicidality Treatment in Males with Bipolar Disorder

compound name	dose	cell	score	gene expression signature
betonicine	25 μM	MCF7	−1	Top Predictor Biomarkers
betulin	9 μM	HL60	−1	Top Dozen Biomarkers
Prestwick-692	7 μM	MCF7	−1	Top Dozen Biomarkers
chlorphenesin	16 μM	HL60	−1	Bonferroni Biomarkers
naproxen	16 μM	PC3	−0.96	Bonferroni Biomarkers
biperiden	11 μM	PC3	−0.948	Top Dozen Biomarkers
carteolol	12 μM	HL60	−0.946	Top Dozen Biomarkers
baclofen	19 μM	PC3	−0.94	Bonferroni Biomarkers
harmaline	14 μM	MCF7	−0.932	Top Dozen Biomarkers
carteolol	12 μM	HL60	−0.907	Top Dozen Biomarkers
amylocaine	15 μM	MCF7	−0.9	Top Predictor Biomarkers
estradiol	10 nM	MCF7	−0.894	Top Dozen Biomarkers
acacetin	14 μM	PC3	−0.882	Bonferroni Biomarkers
alpha-ergocryptine	7 μM	MCF7	−0.862	Bonferroni Biomarkers
myosmine	27 μM	MCF7	−0.846	Top Predictor Biomarkers
zuclopenthixol	9 μM	MCF7	−0.839	Top Predictor Biomarkers
benfotiamine	9 μM	PC3	−0.839	Bonferroni Biomarkers

TABLE 11-continued

Repurposed Drugs for Suicidality Treatment in Males with Bipolar Disorder

compound name	dose	cell	score	gene expression signature
valproic acid	500 μM	PC3	−0.832	Top Predictor Biomarkers
resveratrol	18 μM	HL60	−0.826	Top Dozen Biomarkers
azacyclonol	15 μM	MCF7	−0.814	Top Predictor Biomarkers
allantoin	25 μM	PC3	−0.811	Top Dozen Biomarkers

Using the identified Bipolar Males Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.

A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 12

Repurposed Drugs for Suicidality Treatment in Males with Depression

compound name	dose	cell	score	gene expression signature
suloctidil	12 μM	PC3	−1	Top Predictor Biomarkers
vincamine	11 μM	MCF7	−1	Top Dozen Biomarkers
ciprofibrate	14 μM	HL60	−1	Bonferroni Biomarkers
methanthelinium bromide	10 μM	HL60	−0.996	Bonferroni Biomarkers
amantadine	10 μM	MCF7	−0.967	Bonferroni Biomarkers
estradiol	10 nM	ssMCF7	−0.956	Top Dozen Biomarkers
fenspiride	13 μM	PC3	−0.945	Top Dozen Biomarkers
nimodipine	10 μM	PC3	−0.939	Top Dozen Biomarkers
lansoprazole	11 μM	HL60	−0.931	Bonferroni Biomarkers
famotidine	12 μM	MCF7	−0.923	Top Dozen Biomarkers
cyclopenthiazide	11 μM	HL60	−0.917	Top Predictor Biomarkers
cyclopenthiazide	11 μM	HL60	−0.91	Top Dozen Biomarkers
fluvoxamine	9 μM	MCF7	−0.903	Top Dozen Biomarkers
adipiodone	4 μM	HL60	−0.902	Top Predictor Biomarkers
calcium folinate	8 μM	HL60	−0.902	Bonferroni Biomarkers
trichostatin A	1 μM	MCF7	−0.892	Top Predictor Biomarkers
docosahexaenoic acid ethyl ester	100 μM	PC3	−0.889	Top Dozen Biomarkers
metformin	10 μM	MCF7	−0.882	Top Dozen Biomarkers
calcium folinate	8 μM	HL60	−0.869	Top Predictor Biomarkers
chlorogenic acid	11 μM	HL60	−0.864	Bonferroni Biomarkers
dosulepin	12 μM	HL60	−0.831	Top Predictor Biomarkers
thioproperazine	6 μM	HL60	−0.831	Top Predictor Biomarkers
rolipram	15 μM	PC3	−0.811	Top Predictor Biomarkers
citalopram	1 μM	MCF7	−0.787	Top Predictor Biomarkers

Using Our Depression Males Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 13

Repurposed Drugs for Suicidality Treatment in Males with Post-Traumatic Stress Disorder (PTSD)

compound name	dose	cell	score	gene expression signature
hemicholinium	7 μM	PC3	−1	Top Predictor Biomarkers
epitiostanol	13 μM	PC3	−0.974	Top Predictor Biomarkers
pirenperone	10 μM	HL60	−0.913	Top Predictor Biomarkers
tretinoin	13 μM	PC3	−0.901	Top Predictor Biomarkers
betamethasone	10 μM	PC3	−0.901	Top Predictor Biomarkers
tolnaftate	13 μM	MCF7	−0.895	Top Predictor Biomarkers
atractyloside	5 μM	HL60	−0.884	Top Predictor Biomarkers
prochlorperazine	7 μM	HL60	−0.878	Top Predictor Biomarkers
tolazoline	20 μM	MCF7	−0.866	Top Predictor Biomarkers
fulvestrant	10 nM	HL60	−0.858	Top Predictor Biomarkers
procainamide	15 μM	HL60	−0.844	Top Predictor Biomarkers
pioglitazone	10 μM	PC3	−0.839	Top Predictor Biomarkers
calcium folinate	8 μM	MCF7	−0.838	Top Predictor Biomarkers
merbromin	5 μM	HL60	−0.831	Top Predictor Biomarkers
adipiodone	4 μM	HL60	−0.831	Top Predictor Biomarkers

TABLE 13-continued

Repurposed Drugs for Suicidality Treatment in Males with Post-Traumatic Stress Disorder (PTSD)

compound name	dose	cell	score	gene expression signature
benzbromarone	9 μM	HL60	−0.83	Top Predictor Biomarkers
prazosin	10 μM	PC3	−0.828	Top Predictor Biomarkers

Using the identified PTSD Males Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 14

Repurposed Drugs for Suicidality Treatment in Males with Schizophrenia and Schizoaffective Disorder (SZ/SZA)

compound name	dose	cell	score	gene expression signature
asiaticoside	4 μM	HL60	−1	Top Predictor Biomarkers
procainamide	15 μM	HL60	−0.959	Top Predictor Biomarkers
3-hydroxy-DL-kynurenine	18 μM	HL60	−0.946	Top Predictor Biomarkers
mafenide	18 μM	HL60	−0.913	Top Predictor Biomarkers
metformin	24 μM	HL60	−0.899	Top Predictor Biomarkers
trimipramine	10 μM	HL60	−0.895	Top Predictor Biomarkers
ramifenazone	14 μM	HL60	−0.885	Top Predictor Biomarkers
lithocholic acid	11 μM	HL60	−0.881	Top Predictor Biomarkers
chlorogenic acid	11 μM	HL60	−0.878	Top Predictor Biomarkers
hydrastinine	16 μM	HL60	−0.875	Top Predictor Biomarkers
diphenhydramine	14 μM	HL60	−0.874	Top Predictor Biomarkers
clozapine	12 μM	HL60	−0.868	Top Predictor Biomarkers

Using the identified SZ/SZA Males Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 15

Repurposed Drugs for Suicidality Treatment in the High Anxiety Subtype

compound name	dose	cell	score	gene expression signature
ethaverine	9 μM	PC3	−1	Top Predictor Biomarkers
moracizine	9 μM	HL60	−0.969	Top Predictor Biomarkers
dl-alpha tocopherol	9 μM	HL60	−0.944	Top Predictor Biomarkers
cefalotin	10 μM	PC3	−0.933	Top Predictor Biomarkers
calcium folinate	8 μM	PC3	−0.855	Top Predictor Biomarkers
indoprofen	14 μM	PC3	−0.854	Top Predictor Biomarkers
ethoxyquin	18 μM	PC3	−0.825	Top Predictor Biomarkers
mesalazine	26 μM	MCF7	−0.824	Top Predictor Biomarkers
valproic acid	500 μM	MCF7	−0.822	Top Predictor Biomarkers
orphenadrine	13 μM	PC3	−0.82	Top Predictor Biomarkers
thioridazine	10 μM	HL60	−0.819	Top Predictor Biomarkers
risperidone	10 μM	HL60	−0.812	Top Predictor Biomarkers
trifluoperazine	10 μM	HL60	−0.811	Top Predictor Biomarkers
thioproperazine	6 μM	PC3	−0.804	Top Predictor Biomarkers
chlorpromazine	11 μM	HL60	−0.791	Top Predictor Biomarkers

Using the Top Predictor Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 16

Repurposed Drugs for Suicidality Treatment in the Low Mood Subtype

compound name	dose	cell	score	gene expression signature
streptomycin	3 μM	MCF7	−1	Top Predictor Biomarkers
isoetarine	12 μM	MCF7	−0.988	Top Predictor Biomarkers
carbimazole	21 μM	HL60	−0.947	Top Predictor Biomarkers

TABLE 16-continued

Repurposed Drugs for Suicidality Treatment in the Low Mood Subtype

compound name	dose	cell	score	gene expression signature
IC-86621	1 μM	PC3	−0.944	Top Predictor Biomarkers
dapsone	16 μM	HL60	−0.94	Top Predictor Biomarkers
bumetanide	11 μM	MCF7	−0.909	Top Predictor Biomarkers
pergolide	10 μM	PC3	−0.906	Top Predictor Biomarkers
sulindac	11 μM	PC3	−0.905	Top Predictor Biomarkers
bemegride	26 μM	MCF7	−0.904	Top Predictor Biomarkers
yohimbine	10 μM	MCF7	−0.894	Top Predictor Biomarkers
cotinine	23 μM	MCF7	−0.892	Top Predictor Biomarkers
prochlorperazine	7 μM	HL60	−0.891	Top Predictor Biomarkers
chlorprothixene	11 μM	MCF7	−0.885	Top Predictor Biomarkers
sulindac	11 μM	PC3	−0.88	Top Predictor Biomarkers
ramifenazone	14 μM	HL60	−0.874	Top Predictor Biomarkers
boldine	12 μM	HL60	−0.874	Top Predictor Biomarkers
dl-alpha tocopherol	9 μM	HL60	−0.87	Top Predictor Biomarkers
nordihydroguaiaretic acid	1 μM	ssMCF7	−0.858	Top Predictor Biomarkers
serotonin	19 μM	PC3	−0.854	Top Predictor Biomarkers
diphenhydramine	14 μM	HL60	−0.852	Top Predictor Biomarkers

Using the Top Predictor Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 17

Repurposed Drugs for Suicidality Treatment in the High Psychosis (Non-Affective) Subtype

compound name	dose	cell	score	gene expression signature
PF-01378883-00	10 μM	MCF7	−0.975	Top Predictor Biomarkers
ketotifen	9 μM	MCF7	−0.959	Top Predictor Biomarkers
levamisole	17 μM	MCF7	−0.938	Top Predictor Biomarkers
tenoxicam	12 μM	HL60	−0.934	Top Predictor Biomarkers
ifosfamide	15 μM	MCF7	−0.933	Top Predictor Biomarkers
naloxone	11 μM	MCF7	−0.931	Top Predictor Biomarkers
timolol	9 μM	MCF7	−0.928	Top Predictor Biomarkers
metformin	24 μM	HL60	−0.926	Top Predictor Biomarkers
iocetamic acid	7 μM	HL60	−0.922	Top Predictor Biomarkers
rofecoxib	10 μM	MCF7	−0.921	Top Predictor Biomarkers
pepstatin	6 μM	MCF7	−0.913	Top Predictor Biomarkers
isocarboxazid	17 μM	PC3	−0.909	Top Predictor Biomarkers
tinidazole	16 μM	MCF7	−0.908	Top Predictor Biomarkers
mefexamide	13 μM	PC3	−0.907	Top Predictor Biomarkers
etodolac	14 μM	MCF7	−0.907	Top Predictor Biomarkers
myricetin	13 μM	MCF7	−0.899	Top Predictor Biomarkers
promazine	12 μM	MCF7	−0.897	Top Predictor Biomarkers
nomegestrol	11 μM	MCF7	−0.884	Top Predictor Biomarkers
lobelanidine	11 μM	MCF7	−0.881	Top Predictor Biomarkers
diphenhydramine	14 μM	HL60	−0.878	Top Predictor Biomarkers

Using the Top Predictor Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.

Bold - known antidepressant/psychotropic.

Italic - natural compound

TABLE 18

Repurposed Drugs for Suicidality Treatment in the Combined (Affective) Subtype

compound name	dose	cell	score	gene expression signature
trimipramine	10 μM	HL60	−1	Top Predictor Biomarkers
proguanil	14 μM	HL60	−1	Top Predictor Biomarkers
cyclopenthiazide	11 μM	HL60	−0.961	Top Predictor Biomarkers
lansoprazole	11 μM	HL60	−0.941	Top Predictor Biomarkers
ozagrel	15 μM	HL60	−0.939	Top Predictor Biomarkers
asiaticoside	4 μM	HL60	−0.928	Top Predictor Biomarkers
metformin	24 μM	HL60	−0.92	Top Predictor Biomarkers
corticosterone	12 μM	HL60	−0.907	Top Predictor Biomarkers
chlorogenic acid	11 μM	HL60	−0.904	Top Predictor Biomarkers
ondansetron	12 μM	HL60	−0.876	Top Predictor Biomarkers
betulin	9 μM	HL60	−0.875	Top Predictor Biomarkers

TABLE 18-continued

Repurposed Drugs for Suicidality Treatment in the Combined (Affective) Subtype

compound name	dose	cell	score	gene expression signature
pirenperone	10 μM	HL60	−0.872	Top Predictor Biomarkers
adiphenine	11 μM	HL60	−0.855	Top Predictor Biomarkers
felbinac	19 μM	MCF7	−0.853	Top Predictor Biomarkers
finasteride	11 μM	HL60	−0.843	Top Predictor Biomarkers
rilmenidine	8 μM	HL60	−0.833	Top Predictor Biomarkers
ritodrine	12 μM	HL60	−0.826	Top Predictor Biomarkers
dexamethasone	9 μM	PC3	−0.819	Top Predictor Biomarkers
cyclic adenosine monophosphate	12 μM	HL60	−0.806	Top Predictor Biomarkers
fluoxetine	12 μM	HL60	−0.805	Top Predictor Biomarkers

Using the Top Predictor Biomarker Signatures Matching to the Connectivity Map (Cmap) to identify compounds that have opposite gene expression effects to suicide.
A score of −1 means perfect opposite effect.
Bold - known antidepressant/psychotropic.
Italic - natural compound

Understanding

Pathway Analyses

IPA (Ingenuity Pathway Analyses, version 24390178, Qiagen), David Functional Annotation Bioinformatics Microarray Analysis (National Institute of Allergy and Infectious Diseases), and Kyoto Encyclopedia of Genes and Genomes (KEGG) (through DAVID) were used to analyze the biological roles, including top canonical pathways, and diseases, of the candidate genes, as well as to identify genes in that dataset that are the targets of existing drugs (Table 19). The pathway analyses were conducted for the combined AP and DE probesets with a total internal and external CFG prioritization score >4 that showed stepwise change in the suicide completers validation cohort and survived Bonferroni correction (130 genes, 148 probesets) (Table 4). For male bipolars, there were 50 genes, 54 probesets.

TABLE 19

Biological Pathways and Diseases
A. Universal biomarkers

Universal	DAVID GO Functional Annotation Biological Processes					KEGG Pathways			
Pathways	#	Term	Count	%	P-Value	Term	Count	%	P-Value
Validation Bonferroni Significant in Suicide Completers (n = 130 genes)	1	Regulation of neurogenesis	8	6.6	2.10E−04	Tryptophan metabolism	4	0.2	1.10E−02
	2	Negative regulation of apoptosis	11	9	2.60E−04	Neurotrophin signaling pathway	6	0.3	1.40E−02
	3	Negative regulation of programmed cell death	11	9	2.90E−04	Insulin signaling pathway	6	0.3	1.90E−02
	4	Negative regulation of cell death	11	9	3.00E−04	Butanoate metabolism	3	0.2	5.90E−02
	5	Regulation of cell morphogenesis	7	5.7	3.90E−04	Endocytosis	6	0.3	6.10E−02

		Ingenuity Pathways		
	Universal Pathways	Top Canonical Pathways	P-Value	Overlap
	Validation Bonferroni Significant in Suicide Completers (n = 130 genes)	Protein Kinase A Signaling	4.36E−06	0.03112/386
		IGF-1 Signaling	2.86E−05	0.06235/582
		Gap Junction Signaling	4.66E−05	0.0457/155
		Renin-Angiotensin Signaling	5.52E−05	0.0556/109
		Hepatic Cholestasis	5.93E−05	0.0437/161

TABLE 19-continued

Biological Pathways and Diseases
A. Universal biomarkers

Universal	DAVID					Ingenuity			
Diseases		Term	Count	%	P-Value		Diseases and Disorders	P-Value	# Molecules
Validation Bonferroni Significant in Suicide Completers (n = 130 genes)	1	diabetes, type 1	9	7.4	1.40E−03	1	Infectious Diseases	1.01E−03-1.31E−07	35
	2	breast cancer	9	7.4	1.40E−02	2	Organismal Injury and Abnormalities	1.66E−03-7.72E−07	89
	3	hypertension	7	5.7	1.60E−02	3	Developmental Disorder	1.10E−03-9.64E−07	28
	4	oxidized LDL	2	1.6	2.30E−02	4	Cancer	1.66E−03-1.38E−06	83
	5	brain aging	2	1.6	2.30E−02	5	Cardiovascular Disease	1.66E−03-1.70E−06	18

B. Male Bipolar biomarkers

Male Bipolar	DAVID GO Functional Annotation Biological Processes					KEGG Pathways			
Pathways	#	Term	Count	%	P-Value	Term	Count	%	P-Value
Validation Bonferroni significant in Suicide Completers (n = 50 genes)	1	negative regulation of neuron differentiation	7	14.6	9.30E−06	mTOR signaling pathway	3	6.2	1.60E−02
	2	negative regulation of neurogenesis	7	14.6	3.60E−05	Small cell lung cancer	3	6.2	3.20E−02
	3	negative regulation of nervous system development	7	14.6	5.50E−05	Leukocyte transendothelial migration	3	6.2	5.80E−02
	4	positive regulation of protein localization to plasma membrane	4	8.3	1.10E−04	Sphingolipid signaling pathway	3	6.2	6.00E−02
	5	positive regulation of protein localization to cell periphery	4	8.3	1.10E−04	NA	NA	NA	NA

B. Male Bipolar biomarkers

		Ingenuity Pathways		
	Male Bipolar Pathways	Top Canonical Pathways	P-Value	Overlap
	Validation Bonferroni significant in Suicide Completers (n = 50 genes)	G-Protein Coupled Receptor Signaling	1.14E−14	0.11329/256
		CREB Signaling in Neurons	1.98E−14	0.1424/171
		Neuropathic Pain Signaling In Dorsal Horn Neurons	4.82E−13	0.1818/100
		14-3-3-mediated Signaling	7.79E−12	0.15418/117
		Gap Junction Signaling	1.50E−11	0.12920/155

Male Bipolar	DAVID					Ingenuity			
Diseases	#	Term	Count	%	P-Value	#	Diseases and Disorders	P-Value	# Molecules
Validation Bonferroni significant	1	plasma HDL cholesterol (HDL-C) levels	5	10.4	4.80E−03	1	Cancer	6.89E−03-1.18E−05	46

TABLE 19-continued

				Biological Pathways and Diseases A. Universal biomarkers					
in Suicide Completers (n = 50 genes)	2	Type 2 Diabetes | edema | rosiglitazone	13	27.1	1.30E-02	2	Gastrointestinal Disease	6.89E-03-1.18E-05	41
	3	Eczema	2	4.2	2.70E-02	3	Organismal Injury and Abnormalities	6.89E-03-1.18E-05	46
	4	Neoplasms	3	6.2	6.00E-02	4	Reproductive System Disease	6.89E-03-1.57E-05	20
	5	healthy oldest-old	2	4.2	6.50E-02	5	Hematological Disease	5.30E-03-2.55E-05	20

STRING Analysis

In order to examine potential network interactions between the biomarkers, the Search Tool for the Retrieval of Interacting Genes (STRING v10, string-db.org) was used. To run the analyses, the lists of genes were entered into the search box and *Homo Sapiens* was selected as the organism. The default (medium confidence) setting was used. (FIGS. **8** & **9**).

CFG Beyond Suicide

A CFG approach was also used to examine evidence from other psychiatric and related disorders, for the top dozen biomarker genes and Bonferroni validated biomarker genes.

Clock Gene Database

For informational non-CFG scoring purposes, the suicide biomarker genes for involvement in the circadian clock were annotated. A database of genes associated with circadian function were compiled by using a combination of review papers (Zhang et al. 2009, McCarthy and Welsh 20129, 10) and searches of existing databases CircaDB (circadb.hogeneschlab.org), GeneCards (www.genecards.org), and GenAtlas (genatlas.medecine.univ-paris5.fr). Using the data compiled from these sources, a total of 1468 genes were identified that show circadian functioning. Genes were further 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).

Convergent Functional Evidence (CFE)

A convergent functional evidence (CFE) score tabulated all the evidence from discovery (up to 4 points), prioritization (up to 8 points), validation (up to 4 points), testing (2 points for SI predictions, 2 points for hospitalizations predictions), other psychiatric and related disorders (2 points), and drug evidence (2 points). The goal was to highlight, based on the totality of the data and of the evidence in the field to date, biomarkers that have all around evidence: track suicidality, predict suicidality, are reflective of psychiatric pathology, and are potential drug targets. Such biomarkers merit priority evaluation in future clinical trials.

Additionally, a convergent functional evidence (CFE) score was computed with all the evidence from discovery (up to 4 points), prioritization (up to 8 points), testing (High Suicide State and Trait Suicide Hospitalization Future (up to 4 points each if significantly predicts in all subjects, 2 points if predicts by gender, 1 points if predicts in gender/diagnosis subgroups). The goal was to highlight, based on the totality of the data and of the evidence in the field to date, biomarkers that have all-around evidence for tracking suicidality in discovery and validation steps, as well as to permit an objective assessment of state, and predict future clinical events (hospitalizations for suicidality) in the clinical utility testing step.

Results

From Universal to Subtypes and Personalized

Discovery

A powerful within-participant discovery approach to identify genes that: 1. change in expression in blood between no suicidal ideation (no SI) and high suicidal ideation (high SI) states, 2. track the SI state across visits in a participant, and 3. track the SI state in multiple participants. A longitudinally followed cohort of participants was used that showed diametric changes in SI between at least two testing visits (n=66 participants out of a cohort of 293 men and women psychiatric disorder participants followed longitudinally, with diagnoses of bipolar disorder, depression, mood disorder nos, schizophrenia, schizoaffective disorder, psychosis nos, and PTSD). Using a 33% of maximum raw score threshold (internal score of 1 pt), 10,468 unique probesets from AP and DE were found. (FIG. **1**D). These were carried forward to the prioritization step. This represents approximately a 5-fold enrichment of the 54,625 probesets on the Affymetrix array.

It was then examined in the discovery cohort whether subtypes of suicidality can be identified based on mental state at the time of high suicidal ideation visits, using two way hierarchical clustering with anxiety, mood, and psychosis measures. The SI state self-report may be more reliable in this cohort, as the subjects demonstrated the aptitude and willingness to report different, and diametric, SI states. Four potential subtypes of suicidality were found: high anxiety, low mood, co-morbid, and non-affective (psychotic) (FIG. **1**C). These subtypes need to be tested in independent cohorts for practical utility, diagnostic and therapeutic.

Prioritization

A Convergent Functional Genomics (CFG) approach was used to prioritize the candidate biomarkers identified in the discovery step (internal score of >=1 pt.) by using all of the published prior independent evidence in the field (FIG. **1**E). There were 583 probesets that had a CFG score (combined internal and external score) of 4 and above. These were carried forward to the validation step. This represents approximately a 100-fold enrichment of the probesets on the Affymetrix array.

Validation

Next, suicidal behavior was validated for these prioritized biomarkers in a demographically matched cohort of men and women suicide completers from the coroner's office (n=45), by assessing which markers were stepwise changed in expression from no SI to high SI to suicide completers (FIG. **1**G). 274 probesets were non-stepwise changed, and 309 were stepwise changed. Of these, 148 survived Bonferroni

correction for all the 583 probesets validated. This represents approximately a 500-fold enrichment of the probesets on the Affymetrix array.

Diagnostics

Diagnostic ability of the "universal" top dozen biomarkers (composed of the top increased and decreased biomarkers from AP and from DE from each step: discovery based on all participants, prioritization, and validation in all the coroner's cases) was tested, as well as all of the biomarkers that survived Bonferroni correction after the validation step (Table 3), in a completely independent test cohort of men and women psychiatric disorder participants (n=226), for prediction of suicidal ideation state, as well as for prediction of future psychiatric hospitalizations due to suicidality (FIGS. **3**A-**3**D). Universal biomarkers that work across gender and diagnoses were successfully identified. Their predictive ability was also analyzed in participants in the independent cohort grouped by the subtypes described above, as well as grouped by a more personalized approach, by psychiatric diagnosis and gender. The universal approach was compared to the subtypes approach and the personalized approach, and it was shown that the subtype and personalized approaches permitted enhanced precision of predictions for different biomarkers (FIGS. **3**A-**3**D). For example, for suicidal ideation prediction in the independent test cohort, SLC4A4, a top increased in expression biomarker, had an AUC of 64% (p=3.83E-04) across all subjects, 69% (6.13E-04) in the combined subtype, and 77% (9.72E-04) in male bipolars. SKA2, a top decreased in expression biomarker, had an AUC of 61% (p=3.35E-03) across all subjects, 74% (5.91E-03) in the low mood subtype, and 79% (1.35E-02) in male schizophrenics.

Additionally, two previously described clinical instruments in the form of apps, the Simplified Affective State Scale (SASS) that measures anxiety and mood, and the Convergent Functional Information for Suicidality (CFI-S) that measures risk for suicide indirectly, were used without asking about suicidal ideation. The scores from these apps showed good predictive ability for both state (suicidal ideation) and trait (future hospitalizations) (Table 4).

A panel of the dozen top biomarkers was combined with measures of anxiety and mood (SASS), and with the suicide risk scale (CFI-S), into a broad spectrum universal predictor (UP Suicide). The UP Suicide provides the biomarkers with mental state (SASS) and personal history context (CFI-S), enhancing precision of predictions (FIGS. **5**A-**5**C and **6**). Across all subjects in the independent test cohort, UP Suicide 12 had an AUC of 90% (3.87E-21) for state (suicidal ideation) prediction as well as an AUC of 77% (p=2.87E-08) for trait (future hospitalizations for suicidality) predictions. The results for predicting suicidal ideation were even stronger in the low mood subtype (AUC of 92%, p=7.42E-06) and in male bipolars, the highest risk group (AUC 96%, p=8.03E-08). For predicting future hospitalizations, the results were stronger in the high anxiety subtype (AUC 79%, p=7.52E-03), and in male depression (AUC 95%, p=4.88E-04).

Therapeutics

Pharmacogenomics. For phenomenology, the top CFI-S items distinguishing high SI from no SI states were past history of suicidality, social isolation, and dissatisfaction with one's life. The top CFI-S items distinguishing those that had future hospitalizations for suicidality vs. those that did not were past history of suicidality, command auditory hallucinations, and social isolation (FIGS. **4**A & **4**B). This provides empirical evidence that, in general, reducing social isolation is a good behavioral therapeutic intervention for preventing suicidality. In different individuals different CFI-S items are positive, providing avenues for tailored and targeted (psycho)therapeutic interventions.

A number of individual top biomarkers are targets of medications in current clinical use for treating suicidality, such as lithium (HTR2A, GSK3B, ITGB1BP1, BCL2), clozapine (IL6, CD164, CD47, HTR2A, PGK1, DYRK2, IFNG, LPAR1), and omega-3 fatty acids (APOE, CD47, ACP1, GATM, LHFP, LPAR1) (Tables 4A-4G). In particular, HTR2A and CRYAB are at the overlap of lithium and clozapine, and MBP is at the overlap of all three treatments. Omega-3 fatty acids may be a widely depoyable preventive treatment, with minimal side-effects, including in women who are or may become pregnant.

Bioinformatics drug repurposing analyses using the gene expression biosignature of panels of top biomarkers identified new potential therapeutics for suicidality, such as ebselen (a lithium mimetic), piracetam (a nootropic), chlorogenic acid (a polyphenol from coffee), and metformin (an antidiabetic and possible longevity promoting drug) (Tables 6-18).

Understanding

Biological Pathways. Biological pathway analyses using the Bonferroni validated biomarkers was conducted, which suggested that neurotrophic factors, programmed cell death, and insulin signaling are involved in the biology of suicide (Table 19).

Networks and Interactions. STING analyses revealed groups of directly interactive genes, in particular HTR2A/ARRB1/GSK3B, and SLC4A4/AHCYL1/AHCYL2 (FIG. **8**), These networks may have biological significance and be targeted therapeutically.

A number of top biomarkers identified have biological roles that are related to the circadian clock (Table 20). To be able to ascertain all the genes in the dataset that were circadian and do estimates for enrichment, from the literature, a database 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 154 top biomarker genes, 18 had circadian evidence (11.7%) (Table 20), suggesting a 1.7 fold enrichment for circadian genes. Circadian clock abnormalities are related to mood disorders, and sleep abnormalities have been implicated in suicide.

Enrichment in suicide completers. Of the candidate biomarkers from the Prioritization step, 125/430 of the DE ones (29.1%) and 37/180 of the AP ones (20.6%) were Bonferroni validated in suicide completers. There is a 1.4 fold enrichment in DE vs. AP, which suggests that completion of suicide may be due more to an incremental change in expression of genes rather than the complete turning on and off of genes.

Overall evidence. For the top biomarkers identified, combining all the available evidence from this Example and published literature into a convergent functional evidence (CFE) score (FIG. **7**), leads to a prioritization of biomarkers for future studies in this field.

TABLE 20

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

Gene Symbol/ Gene Name	Probesets	Step 1 Discovery in Blood (Direction of Change) Method/ Score	Step 2 Convergent Functional Genomics (CFG) Evidence For Involvement in Suicide Score	Step 3 Validation in Blood ANOVA p-value/ Score	Step 4 Significant Prediction of Suicidal Ideation All Best in Subtypes Best in Individualized Gender/Dx ROC AUC/ p-value
APOE apolipoprotein E	203382_s_at	(I) DE/1	6	3.44E−09/4	All 0.58/2.26E−02 Combined Subtype 0.62/1.99E−02 M-BP 0.71/9.02E−03
IL6 interleukin 6	205207_at	(I) AP/1	6	1.82E−15/4	All 0.58/3.74E−02 Combined Subtype 0.61/3.98E−02
CD164 CD164 molecule, sialomucin	208654_s_at	(D) DE/2	4	3.01E−08/4	All 0.59/1.80E−02 M-BP 0.68/1.94E−02
CD47 CD47 molecule	211075_s_at	(D) DE/2	4	1.62E−17/4	All 0.6/9.71E−03 Low Mood Subtype 0.68/2.99E−02 M-SZA 0.69/2.19E−02
HTR2A 5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	244130_at	(I) DE/2	8	NS	Low Mood Subtype 0.66/4.74E−02 M-SZ 0.79/1.58E−02
PGK1 phosphoglycerate kinase 1	217383_at	(D) DE/2	4	4.07E−07/4	M-SZA 0.73/8.31E−03
PKP4 plakophilin 4	201929_s_at	(D) DE/1	5	3.82E−08/4	Combined Subtype 0.62/2.59E−02 M-SZ 0.75/2.93E−02
ACP1 acid phosphatase 1, soluble	1554808_at	(D) DE/1	6	3.82E−11/4	
DYRK2 dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2	202969_at	(D) DE/1	4	1.67E−13/4	All 0.58/3.37E−02 Combined Subtype 0.61/3.00E−02 M-SZ/SZA 0.68/9.85E−03
GATM glycine amidinotransferase (L-arginine: glycine amidinotransferase)	1566861_at	(I) DE/1	4	1.80E−12/4	Combined Subtype 0.6/4.84E−02 M-BP 0.68/1.94E−02
GSK3B glycogen synthase kinase 3 beta	226183_at	(D) DE/1	6	2.19E−36/4	M-SZA 0.68/3.47E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

IFNG interferon, gamma	210354_at	(D) AP/1	8	NS	All 0.6/1.01E−02 Combined Subtype 0.61/3.03E−02 M-PTSD 0.73/2.72E−02
ITGB1BP1 integrin beta 1 binding protein 1	203337_x_at	(D) DE/1	4	1.11E−08/4	Low Mood Subtype 0.67/4.21E−02 M-SZ 0.78/1.64E−02
LHFP lipoma HMGIC fusion partner	218656_s_at	(I) DE/1	4	3.97E−10/4	All 0.57/5.00E−02 Anxious Subtype 0.78/1.95E−02 F-BP 0.79/4.60E−02
LPAR1 lysophosphatidic acid receptor 1	204036_at	(D) AP and DE/1	4	1.35E−23/4	M-BP 0.68/2.13E−02
PRKCI protein kinase C, iota	209677_at	(D) DE/1	4	2.71E−05/4	Anxious Subtype 0.8/1.55E−02
SKA2 spindle and kinetochore associated complex subunit 2	225686_at	(D) DE/1	8	4.55E−03/2	All 0.61/3.35E−03 Low Mood Subtype 0.74/5.91E−03 M-SZ 0.79/1.35E−02
SLC4A4 solute carrier family 4 (sodium bicarbonate cotransporter), member 4	210739_x_at	(I) AP/1	6	7.74E−05/4	All 0.64/3.83E−04 Combined Subtype 0.69/6.13E−04 M-BP 0.77/9.27E−04
BCL2 B-cell CLL/lymphoma 2	203685_at	(D) DE/1	5	5.98E−11/4	All 0.61/4.90E−03 M-SZ 0.76/2.73-02 Low Mood Subtype 0.67/4.02E−02
ECHDC1 enoyl CoA hydratase domain containing 1	223087_at	(D) DE/2	4	3.35E−09/4	All 0.6/9.14E−03 Combined Subtype 0.64/1.04E−02 M-SZA 0.68/3.14E−02
GDI2 GDP dissociation inhibitor 2	200008_s_at	(D) DE/2	4	1.52E−11/4	All 0.59/1.26E−02 M-BP 0.67/2.39E−02
MTERF4 mitochondrial transcription termination factor 4	1557966_x_at	(D) DE/2	4	6.72E−06/4	All 0.61/4.64E−03 Low Mood Subtype 0.67/4.21E−02 M-SZ 0.76/2.64E−02
PCDH9 protocadherin 9	238919_at	(D) AP/2	4	6.61E−05/4	Combined Subtype 0.6/4.45E−02
TGOLN2 trans-golgi network protein 2	203834_s_at	(D) AP/1	5	1.37E−11/4	
YWHAH tyrosine 3-monooxygenase/ tryptophan 5-monooxygenase activation protein, eta	242325_at	(I) DE/2	4	6.65E−11/4	All 0.57/4.92E−02 F-BP 0.79/4.60E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

ACSM3 acyl-CoA synthetase medium-chain family member 3	210377_at	(D) DE/1	4	9.67E−06/4	All 0.58/2.90E−02 M-BP 0.69/1.35E−02
AGA aspartylglucosaminidase	204333_s_at	(D) DE/1	4	1.51E−06/4	Combined Subtype 0.62/2.07E−02
AKAP13 A kinase (PRKA) anchor protein 13	209534_x_at	(I) DE/1	4	2.06E−05/4	Low Mood Subtype 0.68/3.14E−02 M-PTSD 0.78/8.75E−03
AKAP2 A kinase (PRKA) anchor protein 2	202759_s_at	(D) DE/1	4	5.17E−07/4	Combined Subtype 0.6/4.23E−02
ALDH7A1 aldehyde dehydrogenase 7 family, member A1	20895l_at	(I) DE/1	4	1.58E−07/4	All 0.58/3.55E−02 M-BP 0.68/2.09E−02
ATP6V0E1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1	214244_s_at	(D) DE/1	4	7.84E−07/4	M-SZA 0.76/3.76E−03
ATP6V0E1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1	236527_at	(D) AP/1	4	5.91E−13/4	M-SZA 0.72/1.29E−02
BRCC3 BRCA1/BRCA 2-containing complex, subunit 3	216521_s_at	(D) DE/1	4	1.71E−12/4	All 0.58/3.74E−02 M-BP 0.72/6.47E−03
CAT catalase	211922_s_at	(D) DE/1	4	1.28E−11/4	All 0.57/3.84E−02 Low Mood Subtype 0.67/4.02E−02 M-BP 0.7/1.14E−02
CTTN cortactin	214782_at	(I) DE/1	4	1.04E−19/4	Combined Subtype 0.61/3.33E−02 M-BP 0.76/1.54E−03
DLG1 discs, large homolog 1 (*Drosophila*)	202516_s_at	(D) DE/1	4	1.61E−12/4	All 0.58/2.91E−02 Low Mood Subtype 0.7/2.02E−02
DUSP13 dual specificity phosphatase 13	219963_at	(I) AP/1	4	5.27E−08/4	M-SZA 0.73/9.96E−03
ECHDC1 enoyl CoA hydratase domain containing 1	219974_x_at	(D) DE/1	4	4.00E−14/4	All 0.59/1.38E−02 M-BP 0.65/4.48E−02 Combined Subtype 0.6/4.34E−02
EFEMP2 EGF containing fibulin-like extracellular matrix protein 2	209356_x_at	(I) AP/1	4	2.38E−05/4	Low Mood Subtype 0.66/4.96E−02
G2E3 G2/M-phase specific E3 ubiquitin protein ligase	223256_at	(D) DE/1	4	5.19E−09/4	Low Mood Subtype 0.67/3.56E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

GDI2 GDP dissociation inhibitor 2	200009_at	(D) DE/1	4	1.47E−05/4	All 0.64/5.93E−04 M-BP 0.74/2.76E−03 Low Mood Subtype 0.69/2.43E−02
IGHG1 —	211633_x_at	(D) AP and DE/1	4	6.55E−11/4	M-MDD 0.79/2.47E−03
IL13 interleukin 13	207844_at	(I) DE/1	4	3.38E−08/4	Low Mood Subtype 0.76/3.51E−03
ITGB1BP1 integrin beta 1 binding protein 1	203336_s_at	(D) DE/1	4	2.54E−08/4	All 0.57/4.15E−02
ITPKB inositol-trisphosphate 3-kinase B	232526_at	(I) AP/1	4	4.46E−09/4	All 0.62/1.90E−03 M-BP 0.76/1.31E−03 Combined Subtype 0.68/1.76E−03
LRRN3 leucine rich repeat neuronal 3	209841_s_at	(D) DE/1	4	6.69E−10/4	All 0.58/2.37E−02 M-PTSD 0.77/1.11E−02
MRPS14 mitochondrial ribosomal protein S14	203800_s_at	(D) DE/1	4	3.95E−10/4	M-SZA 0.72/1.15E−02
MRPS14 mitochondrial ribosomal protein S14	203801_at	(D) DE/1	4	2.45E−17/4	All 0.6/6.89E−03 M-SZ 0.72/4.66E−02 Low Mood Subtype 0.69/2.63E−02
N4BP2L2 NEDD4 binding protein 2-like 2	202259_s_at	(D) DE/1	4	8.33E−10/4	Low Mood Subtype 0.66/4.63E−02
PIK3CA phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	231854_at	(D) DE/1	4	2.41E−37/4	All 0.57/4.23E−02 M-BP 0.65/4.64E−02 Non-Affective Subtype 0.74/2.24E−02
PPAP2B phosphatidic acid phosphatase type 2B	212226_s_at	(I) AP/1	4	2.76E−17/4	All 0.58/3.64E−02 M-BP 0.65/4.56E−02 Low Mood Subtype 0.75/4.15E−03
PRKAR2B protein kinase, cAMP-dependent, regulatory, type II, beta	203680_at	(D) DE/1	4	3.83E−09/4	F-BP 0.84/2.69E−02
PSMB4 proteasome (prosome, macropain) subunit, beta type, 4	202243_s_at	(D) DE/1	4	6.55E−14/4	All 0.6/1.07E−02 M-SZA 0.71/1.67E−02
PSME4 Proteasome Activator Subunit 4	237180_at	(I) DE/1	4	2.64E−36/4	All 0.6/1.11E−02 M-PTSD 0.79/6.82E−03 Low Mood Subtype 0.68/3.47E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

PTK2 protein tyrosine kinase 2	241453_at	(I) DE/1	4	2.87E−32/4	All 0.61/4.53E−03 M-MDD 0.69/3.24E−02 Combined Subtype 0.64/1.04E−02
SECISBP2L SECIS binding protein 2-like	212450_at	(D) DE/1	4	6.30E−05/4	All 0.59/2.05E−02 M-BP 0.71/7.49E−03 Low Mood Subtype 0.68/3.47E−02
SEPT8 septin 8	209000_s_at	(I) DE/1	4	4.56E−09/4	All 0.58/2.31E−02 M-BP 0.69/1.52E−02 Combined Subtype 0.63/1.53E−02
SNX6 sorting nexin 6	222410_s_at	(D) DE/1	4	6.82E−06/4	All 0.62/2.46E−03 M-PTSD 0.69/4.93E−02 Low Mood Subtype 0.72/1.15E−02
SOD2 superoxide dismutase 2, mitochondrial	215078_at	(I) DE/2	5	2.27E−34/4	
VTA1 vesicle (multivesicular body) trafficking 1	223021_x_at	(D) DE/1	4	3.95E−08/4	All 0.57/4.16E−02 M-SZ/SZA 0.64/3.26E−02 Combined Subtype 0.6/4.29E−02
WIPF3 WAS/WASL interacting protein family, member 3	241600_at	(D) DE/1	4	1.24E−07/4	
ZNF565 zinc finger protein 565	228305_at	(D) DE/1	4	4.20E−16/4	All 0.59/1.31E−02 M-SZA 0.75/4.43E−03 Low Mood Subtype 0.69/2.50E−02
ADK adenosine kinase	204119_s_at	(D) DE/4	0	1.99E−08/4	All 0.62/2.58E−03 M-PTSD 0.69/4.93E−02 Combined Subtype 0.64/8.60E−03
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	227605_at	(D) AP/2	4	1.02E−05/4	All 0.6/7.31E−03 M-SZA 0.72/1.06E−02 Combined Subtype 0.66/3.69E−03
AK2 adenylate kinase 2	212174_at	(D) DE/2	2	3.19E−06/4	All 0.59/1.71E−02 M-SZ 0.76/2.64-02 Combined Subtype 0.62/2.35E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

AK2 adenylate kinase 2	205996_s_at	(D) DE/2	2	1.15E−07/4	All 0.64/5.39E−04 M-SZ 0.75/2.93E−02 Combined Subtype 0.62/2.04E−02
CD109 CD109 molecule	226545_at	(I) DE/2	2	2.16E−09/4	F-BP 0.81/3.73E−02
DSPP dentin sialophosphoprotein	221681_s_at	(D) DE/2	4	7.04E−09/4	All 0.57/4.26E−02
HIST1H2BO histone cluster 1, H2bo	214540_at	(I) DE/4	0	5.37E−14/4	M-BP 0.67/2.78E−02
LEPR leptin receptor	211355_x_at	(D) DE/2	4	4.79E−05/4	
MAP2K5 mitogen-activated protein kinase kinase 5	216765_at	(D) AP/2	4	1.74E−08/4	M-SZA 0.67/3.56E−02
MBP myelin basic protein	225408_at	(D) AP/2	4	8.34E−07/4	
MED28 mediator complex subunit 28	222636_at	(D) AP/2	4	1.30E−09/4	
PITHD1 PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1	229856_s_at	(D) AP/4	0	6.61E−08/4	F-BP 0.83/3.00E−02
PRKAR1A protein kinase, cAMP-dependent, regulatory, type I, alpha	200605_s_at	(D) DE/2	4	2.47E−06/4	M-BP 0.72/5.84E−03
RBM3 RNA binding motif (RNP1, RRM) protein 3	222026_at	(D) DE/2	4	1.73E−05/4	
RIMS3 regulating synaptic membrane exocytosis 3	204730_at	(D) AP/4	0	6.47E−08/4	
SCAF11 SR-related CTD-associated factor 11	206989_s_at	(D) DE/2	4	1.71E−10/4	All 0.6/8.62E−03 M-BP 0.77/8.78E−04 Combined Subtype 0.64/9.60E−03
TBL1XR1 transducin (beta)-like 1 X-linked receptor 1	235890_at	(D) AP/2	2	2.34E−08/4	M-BP 0.66/3.36E−02 Combined Subtype 0.62/2.48E−02
ZFYVE21 zinc finger, FYVE domain containing 21	219929_s_at	(D) AP/2	4	5.96E−06/4	All 0.58/2.56E−02
ADIRF adipogenesis regulatory factor	203571_s_at	(I) DE/1	4	6.58E−14/4	M-SZ/SZA 0.66/2.22E−02 Low Mood Subtype 0.71/1.58E−02
AGA aspartylglucosaminidase	216064_s_at	(D) DE/1	4	2.41E−06/4	

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

AHCYL1 adenosylhomocysteinase-like 1	207464_at	(D) DE/1	4	3.53E−11/4	
AKAP10 A kinase (PRKA) anchor protein 10	205045_at	(D) AP/1	4	4.05E−05/4	All 0.58/3.79E−02 M-MDD 0.76/5.91E−03
ALDH3A2 aldehyde dehydrogenase 3 family, member A2	202053_s_at	(D) DE/1	4	3.52E−06/4	
ANKMY1 ankyrin repeat and MYND domain containing 1	1554610_at	(D) DE/1	4	6.19E−15/4	M-PTSD 0.69/4.93E−02
ARRB1 arrestin, beta 1	218832_x_at	(D) AP/1	4	5.26E−17/4	
B2M beta-2-microglobulin	232311_at	(I) DE/1	4	5.80E−12/4	
BCKDHB branched chain keto acid dehydrogenase E1, beta polypeptide	213321_at	(D) DE/1	4	1.72E−11/4	
BRCC3 BRCA1/BRCA 2-containing complex, subunit 3	221196_x_at	(D) DE and AP/1	4	6.11E−12/4	M-BP 0.73/4.69E−03 Low Mood Subtype 0.69/2.50E−02
CAT catalase	201432_at	(D) DE/1	4	3.39E−14/4	M-BP 0.69/1.54E−02 Low Mood Subtype 0.7/1.97E−02
CDC42EP4 CDC42 effector protein (Rho GTPase binding) 4	218062_x_at	(D) AP/1	4	1.48E−05/4	
CLN5 ceroid-lipofuscinosis, neuronal 5	214252_s_at	(D) DE/1	4	1.79E−15/4	All 0.65/1.86E−04 M-SZ/SZA 0.68/9.51E−03 Low Mood Subtype 0.75/4.43E−03
CLTA clathrin, light chain A	20405 0_s_at	(D) DE/1	4	7.07E−11/4	All 0.6/7.10E−03 M-BP 0.68/2.18E−02 Combined Subtype 0.62/2.48E−02
CLTA clathrin, light chain A	216295_s_at	(D) DE/1	4	1.74E−15/4	All 0.64/6.31E−04 M-SZ 0.77/2.20E−02 Combined Subtype 0.67/2.41E−03
DAB2 Dab, mitogen-responsive phosphoprotein, homolog 2 (*Drosophila*)	201279_s_at	(I) DE/1	4	6.28E−07/4	All 0.59/1.99E−02 M-PTSD 0.72/3.02E−02
FADS1 fatty acid desaturase 1 /// microRNA 1908	208964_s_at	(I) DE/1	4	3.12E−11/4	M-PTSD 0.7/4.07E−02

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

NGFR nerve growth factor receptor	205858_at	(I) DE/1	4	2.24E−15/4	All 0.59/1.81E−02 M-SZA 0.73/9.96E−03 Combined Subtype 0.66/4.27E−03
OLIG1 oligodendrocyte transcription factor 1	228170_at	(D) DE/1	4	9.88E−16/4	
PAFAH1B2 platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 □Z	210160_at	(D) DE/1	4	6.61E−18/4	
POLR2D polymerase (RNA) II (DNA directed) polypeptide D	214144_at	(D) AP/1	4	1.38E−13/4	M-SZ/SZA 0.63/4.45E−02 Low Mood Subtype 0.66/4.42E−02
PRKCB protein kinase C, beta	227824_at	(D) DE and AP/1	4	2.40E−13/4	
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8	227304_at	(D) DE/1	4	1.37E−13/4	All 0.58/2.35E−02 M-SZ 0.76/2.54E−02 Low Mood Subtype 0.69/2.37E−02
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8	227305_s_at	(D) DE/1	4	5.56E−12/4	M-BP 0.67/2.53E−02
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8	238434_at	(D) DE/1	4	2.88E−10/4	
SPTBN1 spectrin, beta, non-erythrocytic 1	200672_x_at	(D) DE/1	4	4.56E−07/4	
TM4SF1 transmembrane 4 L six family member 1	209386_at	(I) DE/1	4	1.28E−12/4	
TPD52 tumor protein D52	201691_s_at	(D) DE/1	4	5.67E−12/4	Low Mood Subtype 0.73/7.59E−03
TTBK1 tau tubulin kinase 1	230191_at	(D) DE/1	4	4.81E−07/4	
VAMP3 vesicle-associated membrane protein 3	211749_s_at	(D) DE/1	4	7.97E−07/4	
WARS tryptophanyl-tRNA synthetase	200628_s_at	(D) AP/1	4	2.00E−05/4	Anxious Subtype 0.73/4.84E−02
WNK1 WNK lysine deficient protein kinase 1	202940_at	(D) AP/1	4	2.38E−12/4	

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

XRCC5 X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)	208643_s_at	(D) DE/1	4	3.71E−22/4	Combined Subtype 0.61/4.03E−02
ZNF75D zinc finger protein 75D	1553225_s_at	(D) AP/4	1	5.40E−14/4	All 0.58/2.79E−02 M-BP 0.73/4.80E−03 Combined Subtype 0.6/4.61E−02
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	202542_s_at	(D) DE/4	4	1.48E−05/4	All 0.59/1.31E−02 M-SZA 0.71/1.45E−02 Low Mood Subtype 0.69/2.25E−02
FAM63B family with sequence similarity 63, member B	214691_x_at	(D) DE/4	0	6.24E−11/4	
FH fumarate hydratase	203032_s_at	(D) DE/2	4	8.14E−20/4	
TMEM254 transmembrane protein 254	218174_s_at	(D) DE/2	4	4.56E−15/4	Combined Subtype 0.63/1.67E−02
TUBGCP3 tubulin, gamma complex associated protein 3	215739_s_at	(D) DE/2	2	3.48E−24/4	M-BP 0.78/7.44E−04 Combined Subtype 0.61/3.28E−02
UQCC1 ubiquinol-cytochrome c reductase complex assembly factor 1	222470_s_at	(D) DE/4	0	6.99E−33/4	All 0.57/4.27E−02
VIP vasoactive intestinal peptide	206577_at	(D) DE/1	5	3.76E−14/4	
AHCYL2 adenosylhomocysteinase-like 2	212814_at	(D) AP/1	4	6.28E−05/4	
C20orf27 chromosome 20 open reading frame 27	218081_at	(D) DE/1	4	3.56E−35/4	
C8orf74 chromosome 8 open reading frame 74	1569245_at	(D) DE/1	6	6.63E−08/4	
DLL1 delta-like 1 (*Drosophila*)	227938_s_at	(D) DE/1	4	2.72E−10/4	
FLOT2 flotillin 2	211299_s_at	(D) AP/1	4	1.17E−10/4	
MAP2K5 mitogen-activated protein kinase kinase 5	211370_s_at	(D) DE/1	4	4.24E−05/4	
MT1E metallothionein 1E	212859_x_at	(I) DE/1	4	2.38E−09/4	

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

MTERF4 mitochondrial transcription termination factor 4	214364_at	(D) AP/1	4	3.38E−09/4	
NEK9 NIMA-related kinase 9	212299_at	(D) DE/1	4	1.08E−09/4	M-BP 0.69/1.75E−02
SRR serine racemase	222844_s_at	(D) DE/1	4	1.36E−18/4	
SYNPO2L synaptopodin 2-like	219804_at	(I) DE/1	4	1.12E−09/4	Low Mood Subtype 0.69/2.50E−02
TMEM245 transmembrane protein 245	223006_s_at	(D) DE/1	4	2.10E−08/4	
TRAF3 TNF receptor-associated factor 3	221571_at	(D) DE/1	4	1.61E−25/4	
TRIM23 tripartite motif containing 23	210995_s_at	(D) DE/1	4	3.24E−21/4	
ADAL adenosine deaminase-like	239711_at	(D) AP/4	0	1.23E−05/4	
ANKMY1 ankyrin repeat and MYND domain containing 1	210486_at	(D) AP/2	4	6.98E−04/2	M-SZ/SZA 0.67/1.66E−02 Combined Subtype 0.67/2.08E−03
BF114768 —	236879_at	(I) DE/4	0	1.61E−23/4	
CDKAL1 CDK5 regulatory subunit associated protein 1-like 1	214877_at	(D) DE/4	0	3.66E−14/4	
CENPH centromere protein H	231772_x_at	(D) DE/4	0	4.47E−15/4	M-SZ 0.72/4.96E−02 Low Mood Subtype 0.69/2.40E−02
ERG V-Ets avian erythroblastosis virus E26 oncogene homolog	213541_s_at	(D) DE/4	0	NS	M-SZA 0.66/4.96E−02 Non-Affective Subtype 0.75/1.93E−02
KBTBD2 kelch repeat and BTB (POZ) domain containing 2	223585_x_at	(D) DE/2	2	2.77E−06/4	
LDLRAP1 low density lipoprotein receptor adaptor protein 1	221790_s_at	(D) DE/4	4	1.97E−32/4	
RPAP3 RNA polymerase II associated protein 3	1557984_s_at	(D) AP/4	0	1.06E−05/4	
SET SET nuclear proto-oncogene /// SET pseudogene 4 ///SET-like protein	215780_s_at	(D) DE/4	0	1.19E−05/4	

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

WWP2 WW domain containing E3 ubiquitin protein ligase 2	1552737_s_at	(D) AP/4	0	3.71E−06/4	
C14orf180 chromosome 14 open reading frame 180	1558420_at	(I) DE/1	4	3.21E−10/4	
LDLRAP1 low density lipoprotein receptor adaptor protein 1	57082_at	(D) DE/1	4	1.49E−38/4	
SPATA18 spermatogenesis associated 18	229331_at	(I) DE/1	4	1.10E−06/4	
VPREB3 pre-B lymphocyte 3	220068_at	(D) DE/1	4	1.79E−11/4	
CCL28 chemokine (C-C motif) ligand 28	224240_s_at	(D) AP/4	0	NS	
GAB1 GRB2 Associated Binding Protein 1	242572_at	(I) AP/4	0	NS	F-BP 0.88/1.49E−02
SUMF2 sulfatase modifying factor 2	225002_s_at	(D) DE/4	0	1.69E−08/4	

Gene Symbol/ Gene Name	Step 4 Significant Prediction of First Year Hospitalizations for Suicidality All Best in Subtypes Best in Individualized Gender/Dx ROC AUC/ p-value	Step 5 Other Psychiatric and Related Disorders Evidence	Step 6 Drugs that Modulate the Biomarker in Opposite Direction to Suicide	CFE Polyevidence Score
APOE apolipoprotein E	M-PTSD 0.78/4.43E−02	Aggression Aging Alcohol Alzheimer's Disease ASD Dementia Depression-related Longevity MDD SZ/SZA PTSD SZ	Omega-3	19
IL6 interleukin 6	M-PTSD 0.82/2.58E−02	Aggression Antipsychotics Anxiety BP Cognition Dementia Depression Longevity MDD Mood	Antipsychotics Antidepressants Tocilizumab Siltuximab	19

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

		Neurological Panic Personality SZ/SZA PTSD Sleep Stress SZ		
CD164	M-PTSD	BP	Clozapine	18
CD164 molecule, sialomucin	0.86/1.43E−02	Cocaine Dependence Stress		
CD47	M-PTSD	MDD	Clozapine	18
CD47 molecule	0.79/3.72E−02	Stress SZ	Omega-3	
HTR2A	M-SZA	Alcohol	Clozapine	18
5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	0.72/1.47E−02	Anxiety BP MDD SZ OCD Response to Antidepressants	Lithium Valproate Paliperidone, Risperidone Loxapine, Quetiapine Olanzapine, Nefazodone Mirtazapine Ziprasidone Aripiprazole	
PGK1	M-SZA	Alcohol	Clozapine	18
phosphoglycerate kinase 1	0.71/1.84E−02	BP MDD SZ SZA	Diazepam	
PKP4	Combined	Alcohol	Valproate	18
plakophilin 4	Subtype 0.68/8.75E−03	BP MDD SZ/SZA SZ		
ACP1 acid	M-MDD	BP	Omega-3	17
phosphatase 1, soluble	0.74/3.79E−02	SZ	SSRIs Olanzapine	
DYRK2	M-PTSD	Aging	Clozapine	17
dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2	0.82/2.58E−02	BP MDD Sleep		
GATM	M-PTSD	Alzheimer's	Omega-3	17
glycine amidinotransferase (L-arginine: glycine amidinotransferase)	0.78/4.43E−02	Disease BP MDD PTSD		
GSK3B		Aging	Lithium	17
glycogen synthase kinase 3 beta		Alcohol BP Dementia Depression Mood Stabilizers Lithium response MDD SZ	SSRI Antipsychotics	
IFNG	M-PTSD	SZ	Antipsychotics	17
interferon, gamma	0.82/2.58E−02	MDD PTSD Anxiety SZ/SZA		
ITGB1BP1	Non-Affective	Alzheimer's	Lithium	17
integrin beta 1 binding protein 1	Subtype 0.7/2.59E−02	Disease BP Mood SZ		
LHFP	M-MDD	SZ	Omega-3	17
lipoma HMGIC fusion partner	0.98/2.54E−04			

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

LPAR1 lysophosphatidic acid receptor 1	Anxious Subtype 0.77/1.33E−02	Aging BP Longevity MDD Mood PTSD SZ	Clozapine Omega-3 Antidepressants	17
PRKCI protein kinase C, iota	Combined Subtype 0.64/2.64E−02	BP Circadian abnormalities Cocaine Dependence MDD SZ	Ingenol mebutate	17
SKA2 spindle and kinetochore associated complex subunit 2	M-PTSD 0.84/1.75E−02	PTSD Stress		17
SLC4A4 solute carrier family 4 (sodium bicarbonate cotransporter), member 4		Circadian abnormalities Longevity MDD SZ	Valproate	17
BCL2 B-cell CLL/lymphoma 2		Aging Alcohol Anxiety BP Mood PTSD SZ	Lithium Oblimersen Paclitaxel	16
ECHDC1 enoyl CoA hydratase domain containing 1	M-PTSD 0.84/1.75E−02	Addictions BP PTSD		16
GDI2 GDP dissociation inhibitor 2		BP MDD Mood SZ	Clozapine	16
MTERF4 mitochondrial transcription termination factor 4	Non-Affective Subtype 0.67/4.71E−02	Stress		16
PCDH9 protocadherin 9		Aging MDD SZ/SZA SZ	Clozapine Omega-3	16
TGOLN2 trans-golgi network protein 2	Combined Subtype 0.64/3.41E−02	BP Cocaine Dependence MDD Stress SZ	Clozapine	16
YWHAH tyrosine 3-monooxygenase/ tryptophan 5-monooxy genase activation protein, eta		Alcohol BP Longevity MDD SZ	Omega-3 Clozapine	16
ACSM3 acyl-CoA synthetase medium-chain family member 3	M-PTSD 0.79/3.72E−02	MDD Mood		15
AGA aspartylglucosaminidase		MDD SZ	Haloperidol Antidepressants	15
AKAP13 A kinase (PRKA) anchor protein 13		Cocaine Dependence Other Substances/ Addictions	Clozapine Diazepam Haloperidol	15

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

		Panic Stress		
AKAP2 A kinase (PRKA) anchor protein 2		MDD	Clozapine	15
ALDH7A1 aldehyde dehydrogenase 7 family, member A1	M-SZA 0.72/1.47E−02	BP SZ Stress		15
ATP6V0E1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1	Anxious Subtype 0.76/1.55E−02 M-SZA 0.73/1.21E−02	Alcohol BP MDD Stress		15
ATP6V0E1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1	M-SZA 0.68/3.86E−02	Alcohol BP MDD Stress		15
BRCC3 BRCA1/BRCA 2-containing complex, subunit 3	Combined Subtype 0.63/3.85E−02	Sleep BP		15
CAT catalase	M-SZA 0.70/2.29E−02	BP Longevity MDD Mood PTSD SZ		15
CTTN cortactin		BP Effect of valproate MDD Stress	Clozapine Omega-3 Valproate	15
DLG1 discs, large homolog 1 (*Drosophila*)		Alcohol BP MDD SZ	Omega-3 Clozapine	15
DUSP13 dual specificity phosphatase 13		SZ/SZA	Olanzapine	15
ECHDC1 enoyl CoA hydratase domain containing 1	M-PTSD 0.79/3.72E−02	Addictions BP PTSD		15
EFEMP2 EGF containing fibulin-like extracellular matrix protein 2		Neurological	Clozapine	15
G2E3 G2/M-phase specific E3 ubiquitin protein ligase		Cocaine Dependence	Omega-3	15
GDI2 GDP dissociation inhibitor 2		BP MDD Mood SZ	Clozapine	15
IGHG1 —	M-MDD 0.9/1.64E−03	ASD BP Mood SZ/SZA Stress SZ SZA		15
IL13 interleukin 13		MDD SZ	CAT-354	15
ITGB1BP1 integrin beta 1 binding protein 1		Alzheimer's Disease BP	Lithium	15

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

		Mood SZ		
ITPKB inositol- trisphosphate 3- kinase B		Aging Alcohol Alzheimer's Disease ASD BP MDD Multiple Sclerosis Stress SZ SZA	Omega-3	15
LRRN3 leucine rich repeat neuronal 3		Bipolar disorder (Effect of Mood Stibilizers)	Mood stabilizers	15
MRPS14 mitochondrial ribosomal protein S14		SZ	Omega-3	15
MRPS14 mitochondrial ribosomal protein S14		SZ	Omega-3	15
N4BP2L2	M-PTSD 0.8/3.11E−02	BP MDD SZ		15
NEDD4 binding protein 2-like 2				
PIK3CA phosphatidylinositol- 4,5-bisphosphate 3- kinase, catalytic subunit alpha		Longevity MDD Stress SZ	Lithium	15
PPAP2B phosphatidic acid phosphatase type 2B	M-PTSD 0.83/2.13E−02	SZ/SZA SZ		15
PRKAR2B protein kinase, cAMP- dependent, regulatory, type II, beta		Alcohol Antipsychotics BP MDD PTSD SZ	Clozapine Valproate	15
PSMB4 proteasome (prosome, macropain) subunit, beta type, 4		BP MDD SZ SZA	Diazepam	15
PSME4 Proteasome Activator Subunit 4	All 0.59/2.62E−02 Low Mood Subtype 0.72/4.73E−02	ASD		15
PTK2 protein tyrosine kinase 2		Alcohol ASD BP Circadian abnormalities MDD Neurological SZ/SZA Stress SZ	CT-707	15
SECISBP2L SECIS binding protein 2-like		Cocaine Dependence MDD SZ	Clozapine	15
SEPT8 septin 8	M-SZA 0.68/4.14E−02	Alcohol Epilepsy Mood SZ		15

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

SNX6 sorting nexin 6	M-PTSD 0.83/2.13E−02	Panic		15
SOD2 superoxide dismutase 2, mitochondrial		Longevity MDD methamphetamine SZ/SZA Mood SZ	Clozapine Antidepressants	15
VTA1 vesicle (multivesicular body) trafficking 1	M-SZA 0.67/4.55E−02	BP MDD SZ SZA		15
WIPF3 WAS/WASL interacting protein family, member 3	M-MDD 0.82/9.58E−03	SZ	Clozapine	15
ZNF565 zinc finger protein 565	All 0.6/2.36E−02 M-SZA 0.67/4.81E−02 Anxious Subtype 0.71/3.93E−02	SZ		15
ADK adenosine kinase		Depression	Omega-3	14
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	M-PTSD 0.82/2.58E−02 Non-Affective Subtype 0.68/3.83E−02			14
AK2 adenylate kinase 2	All 0.59/3.29E−02 Non-Affective Subtype 0.71/2.05E−02	BP SZ		14
AK2 adenylate kinase 2	All 0.6/2.31E−02 M-SZA 0.78/2.70E−03 Combined Subtype 0.68/6.72E−03	BP SZ		14
CD109 CD109 molecule	M-MDD 0.76/2.90E−02	Response to paroxetine (SSRI)		14
DSPP dentin sialophosphoprotein		SZ Circadian abnormalities		14
HIST1H2BO histone cluster 1, H2bo	Anxious Subtype 0.71/4.20E−02	Stress		14
LEPR leptin receptor		Alcohol Cocaine Dependence MDD Mood Other Substances/ Addictions	Antidepressants Recombinant-methionyl human leptin	14
MAP2K5 mitogen-activated protein kinase kinase 5		Agoraphobia BP MDD Methamphetamine dependence Other Substances/ Addictions		14

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

MBP myelin basic protein		Alcohol Alzheimer's Disease BP MDD Mood Neurological SZ	Clozapine Omega-3 Lithium	14
MED28 mediator complex subunit 28	M-PTSD 0.83/2.13E−02	Alcohol BP PTSD		14
PITHD1 PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1	M-PTSD 0.78/4.43E−02	BP SZ/SZA SZ		14
PRKAR1A protein kinase, cAMP-dependent, regulatory, type I, alpha		Alcohol BP Epilepsy Mood Stress SZ		14
RBM3 RNA binding motif (RNP1, RRM) protein 3		Epilepsy Response to Lithium (Bipolar) SZ	Omega-3 Valproate	14
RIMS3 regulating synaptic membrane exocytosis 3	Non-Affective Subtype 0.73/1.37E−02	Alcohol Antipsychotics BP SZ	Clozapine Haloperidol	14
SCAF11 SR-related CTD-associated factor 11		BP Mood		14
TBL1XR1 transducin (beta)-like 1 X-linked receptor 1		Alcohol BP Longevity	Clozapine	14
ZFYVE21 zinc finger, FYVE domain containing 21		SZ		14
ADIRF adipogenesis regulatory factor		BP		13
AGA aspartyl glucosaminidase		MDD SZ	Haloperidol Antidepressants	13
AHCYL1 adenosylhomocysteinase-like 1		SZ	Omega-3	13
AKAP10 A kinase (PRKA) anchor protein 10		BP		13
ALDH3A2 aldehyde dehydrogenase 3 family, member A2	M-PTSD 0.83/2.13E−02 Combined Subtype 0.63/4.65E−02	BP		13
ANKMY1 ankyrin repeat and MYND domain containing 1	M-MDD 0.76/2.71E−02			13
ARRB1 arrestin, beta 1	M-SZA 0.69/3.35E−02 Combined	Alcohol MDD Personality		13

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

	Subtype 0.65/2.19E−02	Response to paroxetine (SSRI) Stress		
B2M beta-2-microglobulin		Alcohol Effect of valproate MDD SZ	Omega-3	13
BCKDHB branched chain keto acid dehydrogenase E1, beta polypeptide	All 0.59/3.90E−02 M-SZ 0.67/3.74E−02 Non-Affective Subtype 0.7/2.53E−02	MDD SZ/SZA		13
BRCC3 BRCA1/BRCA 2-containing complex, subunit 3		Sleep BP		13
CAT catalase		BP Longevity MDD Mood PTSD SZ		13
CDC42EP4 CDC42 effector protein (Rho GTPase binding) 4	All 0.59/2.91E−02 M-MDD 0.85/5.84E−03 Low Mood Subtype 0.84/5.28E−03	Aging Alcohol MDD		13
CLN5 ceroid-lipofuscinosis, neuronal 5	M-PTSD 0.87/1.16E−02			13
CLTA clathrin, light chain A		Alzheimer's Disease BP MDD		13
CLTA clathrin, light chain A		Alzheimer's Disease BP MDD		13
DAB2 Dab, mitogen-responsive phosphoprotein, homolog 2 (*Drosophila*)		SZ/SZA		13
FADS1 fatty acid desaturase 1 /// microRNA 1908		Aging Antipsychotics SZ		13
NGFR nerve growth factor receptor		MDD OCD Panic Disorder SZ		13
OLIG1 oligodendrocyte transcription factor 1	Non-Affective Subtype 0.69/3.08E−02	Agreeableness SZ		13
PAFAH1B2 platelet-activating factor acetylhydrolase 1b, catalytic subunit 2		Lithium effect	Lithium	13

□Z

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

POLR2D polymerase (RNA) II (DNA directed) polypeptide D		BP		13
PRKCB protein kinase C, beta		Aging ASD BP MDD PTSD Stress SZ	Lithium Ingenol mebutate	13
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8		MDD Anxiety		13
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8		MDD Anxiety		13
SMCR8 Smith-Magenis syndrome chromosome region, candidate 8	Combined Subtype 0.63/4.42E−02	MDD Anxiety		13
SPTBN1 spectrin, beta, non-erythrocytic 1		Aging BP Longevity MDD SZ	Clozapine Omega-3 Diazepam	13
TM4SF1 transmembrane 4 L six family member 1		SZ BP	Lithium Omega- Antipschotic	13
TPD52 tumor protein D52		BP Mood Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome SZ		13
TTBK1 tau tubulin kinase 1		SZ	Clozapine	13
VAMP3 vesicle-associated membrane protein 3		Alcohol lithium effect MDD Stress valproate effect	Lithium	13
WARS tryptophanyl-tRNA synthetase		Alcohol SZ		13
WNK1 WNK lysine deficient protein kinase 1		Alcohol BP Cocaine Dependence MDD SZ	Omega-3 SSRI	13
XRCC5 X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining)		Alcohol BP Longevity MDD		13

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

ZNF75D zinc finger protein 75D	Circadian abnormalities Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome		13
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1			12
FAM63B family with sequence similarity 63, member B	BP Mood Sleep SZ	Clozapine	12
FH fumarate hydratase	BP MDD Stress		12
TMEM254 transmembrane protein 254			12
TUBGCP3 tubulin, gamma complex associated protein 3	BP		12
UQCC1 ubiquinol-cytochrome c reductase complex assembly factor 1	BP		12
VIP vasoactive intestinal peptide	Alcohol BP MDD SZ		12
AHCYL2 adenosylhomocysteinase-like 2	ASD		11
C20orf27 chromosome 20 open reading frame 27	BP MDD		11
C8orf74 chromosome 8 open reading frame 74			11
DLL1 delta-like 1 (*Drosophila*)	BP PTSD SZ		11
FLOT2 flotillin 2	SZ		11
MAP2K5 mitogen-activated protein kinase kinase 5	Agoraphobia BP MDD Methamphetamine dependence Other Substances/ Addictions		11
MT1E metallothionein 1E	BP SZ SZ/SZA		11
MTERF4 mitochondrial transcription termination factor 4	Stress		11
NEK9 NIMA-related kinase 9			11

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.

SRR serine racemase		SZ	11
SYNPO2L synaptopodin 2-like			11
TMEM245 transmembrane protein 245		BP MDD Stress	11
TRAF3 TNF receptor-associated factor 3		BP MDD Neurological Stress SZ SZA	11
TRIM23 tripartite motif containing 23		BP SZ	11
ADAL adenosine deaminase-like		Mood Circardian abnormalities	10
ANKMY1 ankyrin repeat and MYND domain containing 1			10
BF114768 —	Non-Affective Subtype 0.69/3.36E−02		10
CDKAL1 CDK5 regulatory subunit associated protein 1-like 1		Alcohol BP SZ	10
CENPH centromere protein H			10
ERG V-Ets avian erythroblastosis virus E26 oncogene homolog	Low Mood Subtype 0.82/8.29E−03	Alcohol	10
KBTBD2 kelch repeat and BTB (POZ) domain containing 2	M-SZA 0.7/2.43E−02		10
LDLRAP1 low density lipoprotein receptor adaptor protein 1			10
RPAP3 RNA polymerase II associated protein 3		SZ/SZA	10
SET SET nuclear proto-oncogene /// SET pseudogene 4 ///SET-like protein		Alzheimer's Epilepsy	10
WWP2 WW domain containing E3 ubiquitin protein ligase 2		Alcohol SZ	10
C14orf180 chromosome 14 open reading frame 180			9

TABLE 20-continued

Convergent Functional Evidence (CFE). Universal Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are tabulated and shown.			
LDLRAP1 low density lipoprotein receptor adaptor protein 1			9
SPATA18 spermatogenesis associated 18			9
VPREB3 pre-B lymphocyte 3			9
CCL28 chemokine (C-C motif) ligand 28	Circardian abnormalities Mood	SSRI	8
GAB1 GRB2 Associated Binding Protein 1	Alcohol BP Delusions Hallucinations		8
SUMF2 sulfatase modifying factor 2			8

Biological pathway analyses were conducted using the top biomarkers, which suggest that neurotrophic factors, programmed cell death, and insulin signaling are involved in the biology of suicide (Table 19).

For the top biomarkers identified, combining all the available evidence from this current Example and the published literature, into a convergent functional evidence (CFE) score (FIG. **7**), leads to a prioritization of biomarkers for future studies in the field.

Example 2

As a comparator to the universal approach across gender and diagnoses, in this Example, a within-participant longitudinal biomarker discovery analyses in male bipolars only, the largest subgroup (n=20 participants, 65 testing visits) in our discovery cohort, was conducted.

Male bipolars are the highest risk group for suicide clinically, and have been the focus of earlier suicide biomarker studies, with an N that was less than half of the current one (n=9). The discovery step was followed by prioritization, and by validation in male suicide completers. Some of the previous biomarker findings in bipolar disorder (Tables 3B and FIGS. **3**C & **3**D) were reproduced and examined in this Example. The top dozen biomarkers (Table 3B), and all the biomarkers that survived Bonferroni correction after the validation, for prediction of suicidal ideation and for prediction of future psychiatric hospitalizations due to suicidality in the male bipolar subgroup (n=49) in the independent test cohort (FIGS. **3**C & **3**D & **9**).

TABLE 21

Universal Biomarkers - Predictions In Male Bipolars					
A. Predicting Suicidal Ideation State In Independent Sub-Cohort Of Male Bipolars					
Markers	Cohort	Participants with high SI/ Participants total	ROC AUC/ p-value	Suicidality Severity (HAMD SI Score) Correlation R/ p-value	T-test p-value
Male Bipolar					
Best Biomarkers					
SLC4A4	M-BP	12/130	0.77/9.27E−04	0.24/3.20E−03	1.06E−03
TUBGCP3	M-BP	12/130	0.78/7.44E−04	−0.21/7.99E−03	1.46E−04
BioM 148 Panel (Bonferroni List)	M-BP	12/130	0.7/1.27E−02	0.17/2.81E−02	4.06E−03
BIOM 12 (Top Dozen List)	M-BP	12/130	0.73/4.07E−03	0.19/1.72E−02	5.48E−03
BioM 2 (SLC4A4 and TUBGCP3)	M-BP	12/130	0.80/2.97E−04	0.26/1.63E−03	8.59E−05
Phenes					
Mood	M-BP	12/130	0.8/3.65E−04	−0.47/6.83E−09	1.65E−03
Anxiety	M-BP	12/130	0.86/2.19E−05	0.41/7.09E−07	1.91E−05
Mood and Anxiety	M-BP	12/130	0.86/1.66E−05	0.5/7.15E−10	5.66E−05

TABLE 21-continued

Universal Biomarkers - Predictions In Male Bipolars					
CFI-S	M-BP	12/128	0.92/1.10E−06	0.5/6.11E−10	1.31E−06
Mood and Anxiety and CFI-S	M-BP	12/128	0.94/2.82E−07	0.61/1.24E−14	3.01E−06
Phenes and Biomarkers					
Mood and Anxiety and CFI-S and BioM 148	M-BP	12/128	0.95/1.55E−07	0.62/1.71E−15	1.21E−06
Mood and Anxiety and CFI-S and BioM 12	M-BP	12/128	0.96/8.03E−08	0.63/6.05E−16	4.79E−07
Mood and Anxiety and CFI-S and BioM 2	M-BP	12/128	0.96/9.58E−08	0.62/2.20E−15	3.91E−07

B. Prediction Of Future Hospitalizations For Suicidality Within First Year Of Testing Visit In Independent Sub-Cohort Of Male Bipolars

Biomarker	Cohort	Participants with future hospitalizations for suicidality within the first year/Particpants total	ROC AUC/ p-value	Frequency of future hospitalizations for suicidality within the first year Correlation R/ p-value	T-test p-value	Cox Regression Hazard Ratio/ P-value
			Male Bipolar			
Best Biomarkers						
PPAP2B	M-BP	4/120	0.74/5.08E−02	0.11/1.15E−01	7.74E−02	1.52/2.28E−01
ALDH3A2	M-BP	4/120	0.77/3.38E−02	−0.15/5.25E−02	4.15E−02	2.43/1.02E−01
BioM 148 Panel (Bonferroni List)	M-BP	4/120	0.52/4.48E−01	0.01/4.56E−01	4.66E−01	1.13/9.18E−01
BIOM 12 (Top Dozen List)	M-BP	4/120	0.67/1.21E−01	0.08/1.95E−01	1.85E−01	2.65/3.76E−01
BioM 2 (PPAP2B and ALDH3A2)	M-BP	4/120	0.77/2.97E−02	0.15/5.50E−02	5.59E−02	6.29/6.95E−02
Phenes						
Mood	M-BP	4/120	0.69/1.04E−01	−0.14/6.08E−02	2.75E−01	2.10/1.32E−01
Anxiety	M-BP	4/120	0.7/9.29E−02	0.12/9.74E−02	1.12E−01	1.87/2.09E−01
Mood and Anxiety	M-BP	4/120	0.72/7.19E−02	0.15/5.27E−02	1.34E−01	1.52/1.18E−01
CFIS	M-BP	4/120	0.80/2.10E−02	0.15/5.22E−02	3.46E−03	1.95/1.21E−01
Mood and Anxiety and CFIS	M-BP	4/120	0.78/2.77E−02	0.18/2.36E−02	6.78E−02	1.41/5.54E−02
Phenes and Biomarkers						
Mood and Anxiety and CFI-S and BioM 148	M-BP	4/120	0.77/3.49E−02	0.18/2.56E−02	8.84E−02	1.38/6.06E−02
Mood and Anxiety and CFI-S and BioM 12	M-BP	4/120	0.79/2.51E−02	0.19/1.75E−02	6.30E−02	1.42/4.35E−02
Mood and Anxiety and CFI-S and BioM 2	M-BP	4/120	0.84/1.13E−02	0.22/7.95E−03	3.67E−02	0.96/8.38E−01

C. Prediction Of All Future Hospitalizations For Suicidality Following Testing In Independent Sub-Cohort Of Male Bipolars

Predictors	Cohort	Participants with future hospitalizations for suicidality/ Participants total	Frequency of future hospitalizations for suicidality Correlation R/ p-value	Cox Regression/ P-value
Best Biomarkers				
		Male Bipolar		
Best Biomarkers				
TM4SF1	Male Bipolar	9/121	0.11/1.07E−01	1.41/2.78E−01
ADAL	Male Bipolar	9/121	−0.17/3.14E−02	1.42/3.98E−01
BioM 148 Panel (Bonferroni List)	Male Bipolar	9/121	−0.04/6.74E−01	1.15/8.61E−01
BIOM 12 (Top Dozen List)	Male Bipolar	9/121	0.04/3.43E−01	7.97/2.44E−01
BioM 2 (TM4SF1 and ADAL)	Male Bipolar	9/121	0.18/2.21E−02	1.32/5.25E−01

TABLE 21-continued

Universal Biomarkers - Predictions In Male Bipolars				
Phenes				
Mood	Male Bipolar	9/121	−0.07/2.30E−01	1.86/6.72E−02
Anxiety	Male Bipolar	9/121	0.31/3.27E−04	4.00/1.10E−03
Mood and Anxiety	Male Bipolar	9/121	0.21/9.74E−03	1.77/2.71E−03
CFI-S	Male Bipolar	9/121	0.25/2.91E−03	2.78/7.90E−04
Mood and Anxiety and CFI-S	Male Bipolar	9/121	0.27/1.17E−03	1.6/1.11E−04
Phenes and Biomarkers				
Mood and Anxiety and CFI-S and BioM 148	Male Bipolar	9/121	0.26/2.04E−03	1.55/1.47E−04
Mood and Anxiety and CFI-S and BioM 12	Male Bipolar	9/121	0.28/1.07E−03	0.96/7.12E−01
Mood and Anxiety and CFI-S and BioM 2	Male Bipolar	9/121	0.32/1.55E−04	0.98/8.10E−01

Bold - p-value of Correlation survives correction for multiple testing.
Correlation is our apriori primary measure.
HAMD SI is the suicide rating question from the Hamilton Rating Scale for Depression.
* Smaller cohort, as not everybody had HAMD SI information.

This Example was successful in the identification of predictive biomarkers that might be more specific for suicidality in male bipolars. Also examined was whether biomarkers discovered using just male bipolar subjects yielded even better predictors for male bipolar subjects than using the universal biomarkers. It was found that to be the case for trait (hospitalizations) predictions (FIG. 3D). For the top male bipolar biomarkers identified, a number of individual top biomarkers are targets of medications in current clinical use for treating suicidality. Bioinformatics drug repurposing analyses using the gene expression biosignature of panels of top biomarkers identified new potential therapeutics for suicidality in male bipolars. The top compounds identified include betulin (a natural plant compound with anticancer properties), carteolol (a non-specific beta-blocker used for glaucoma), alpha-ergocryptine (an ergot alkaloid and non-specific serotonin agonist used for migraines), and baclofen (a derivative of GABA used as a muscle relaxant). Combining all the available evidence from this Example and the published literature, into a convergent functional evidence (CFE) score, leads to a prioritization of biomarkers for future studies in the field.

TABLE 22

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

Gene Symbol/ Gene Name	Probesets	Step 1 Discovery in Blood (Direction of Change)/ Score	Step 2 Convergent Evidence For Involvement in Suicide	Step 3 Validation in Blood ANOVA p-value/ Score	Step 4 Significant Prediction of Suicidal Ideation in Male Bipolars ROC AUC/ p-value	Step 4 Significant Prediction of First Year Hospitalizations for Suicidality in Male Bipolars ROC AUC/p-value
HTR2A 5-Hydroxytryptamine Receptor 2A	244130_at	(I) DE/2	8.00	NS	0.65/ 4.45E−02	NA
SAT1 spermidine/ spermine N1-acetyltransferase 1	213988_s_at	(I) DE/2	6.00	4.06E−34/4	NA	NA
SAT1 spermidine/ spermine N1-acetyltransferase 1	210592_s_at	(I) DE/2	6.00	4.00E−33/4	NA	NA
CRYAB crystalline, alpha B	209283_at	(I) DE/1	4.00	3.49E−05	0.65/ 4.41E−02	NA
PIK3R1 Phosphoinositide-3-Kinase Regulatory Subunit 1	239476_at	(I) DE/1	4.00	2.97E−12	NA	0.81/ 1.64E−02
PTK2 Protein Tyrosine Kinase 2	241453_at	(I) DE/2	4.00	4.29E−16/4	0.66/ 3.64E−02	NA

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

SAT1 spermidine/ spermine N1-acetyltransferase 1	203455_s_at	(I) DE/1	6.00	9.99E−29/4	NA	NA
SPTBN1 spectrin, beta, non-erythrocytic 1	215918_s_at	(I) AP/1	4.00	6.7E−32/4	0.72/ 6.62E−03	NA
AKT1S1 AKT1 substrate 1 (proline-rich)	1555821_a_at	(D) DE/2	4.00	8.69E−09/4	NA	NA
AKT1S1 AKT1 substrate 1 (proline-rich)	224982_at	(D) AP/1 and DE/2	4.00	8.04E−11/4	NA	NA
ARHGAP26 Rho GTPase activating protein 26	205068_s_at	(I) DE/1	5.00	7.99E−08/4	NA	NA
B2M beta-2-microglobulin	232311_at	(I) DE/2	4.00	5.43E−06/4	NA	NA
PSME4 Proteasome Activator Subunit 4	237180_at	(I) DE/2	4.00	2.02E−16/4	0.69/ 1.41E−02	NA
ACSM3 acyl-CoA synthetase medium-chain family member 3	210377_at	(D) DE/1	4.00	2.31E−10/4	0.69/ 1.35E−02	NA
ADORA1 adenosine A1 receptor	205481_at	(D) DE/1	4.00	1.19E−07/4	NA	NA
FAAH fatty acid amide hydrolase	204231_s_at	(D) DE/1	4.00	7.47E−12/4	NA	NA
MARCKS Myristoylated alanine-rich protein kinase C substrate	213002_at	(I) DE/1	4.00	7.35E−08/4	NA	NA
MBP myelin basic protein	225408_at	(D) AP/1	4.00	3.26E−06/4	NA	NA
PAFAH1B2 platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 (30 kDa)	210160_at	(D) DE/1	4.00	4.85E−09/4	NA	NA
PCDH9 Protocadherin 9	238919_at	(D) AP/1	4.00	4.52E−05/4	NA	NA
PIK3R1 phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	212240_s_at	(I) DE/1	4.00	7.11E−14/4	NA	NA
PTEN phosphatase and tensin homolog	222176_at	(I) DE/1	4.00	4.88E−05/4	NA	0.9/ 3.27E−03
RNF6 ring finger protein (C3H2C3 type) 6	210932_s_at	(D) DE/1	4.00	1.25E−05/4	NA	0.82/ 1.58E−02
SLC5A3 solute carrier family 5 (sodium/myoinositol cotransporter), member 3	213167_s_at	(D) DE/1	4.00	4.89E−14/4	NA	NA

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

C20orf27 chromosome 20 open reading frame 27	218081_at	(D) DE/2	4.00	1.09E−34/4	NA	NA
C7orf73 Chromosome 7 open reading frame 73	224758_at	(D) DE/2	4.00	4.72E−06/4	0.75/ 2.38E−03	NA
CLYBL Citrate Lyase Beta Like	239683_at	(D) AP/4	4.00	0.009/2	NA	NA
EZR ezrin	208623_s_at	(I) DE/1	5.00	3.92E−11/4	NA	NA
ICAM4 intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)	207194_s_at	(D) DE/4	0.00	3.81E−08/4	0.67/ 2.83E−02	NA
NEAT1 nuclear paraspeckle assembly transcript 1 (non-protein coding)	224565_at	(I) DE/2	4.00	9.99E−20/4	NA	NA
NUB1 Negative regulator of ubiquitin-like proteins 1	234332_at	(I) DE/4	0.00	8.11E−10/4	NA	0.75/ 4.78E−02
PGBD2 PiggyBac Transposable Element Derived 2	238004_at	(D) AP/4	0.00	1.25E−05/4	0.72/ 6.77E−03	NA
C8orf74 chromosome 8 open reading frame 74	1569245_at	(D) DE/1	6.00	3.82E−08/4	NA	NA
CALR calreticulin	212953_x_at	(I) DE/1	4.00	1.12E−10/4	NA	NA
CRHR1 Corticotropin-Releasing Hormone Receptor 1	214619_at	(D) DE/1	6.00	NS	NA	NA
DLL1 delta-like 1 (*Drosophila*)	227938_s_at	(D) DE/1	4.00	1.17E−09/4	NA	NA
FADS1 fatty acid desaturase 1	208963_x_at	(I) AP/1	4.00	1.58E−05/4	NA	NA
KLK7 Kallikrein Related Peptidase 7	239381_at	(D) AP/1	4.00	2.79E−05/4	NA	NA
MED28 mediator complex subunit 28	222635_s_at	(D) DE/1	4.00	1.63E−15/4	NA	NA
NDUFS1 NADH:Ubiquinone Oxidoreductase Core Subunit S1	239268_at	(D) DE/1	4.00	3.72E−11/4	NA	NA
POLR2D polymerase (RNA) II (DNA directed) polypeptide D	214144_at	(D) AP/1	4.00	2.1E−08/4	NA	NA
PPAP2B phosphatidic acid phosphatase type 2B	212230_at	(I) DE/1	4.00	2.49E−06/4	NA	NA
SELENBP1 selenium binding protein 1	214433_s_at	(D) DE/1	4.00	7.24E−05/4	NA	NA
TRIM23 tripartite motif containing 23	210995_s_at	(D) DE/1	4.00	3.98E−19/4	NA	NA
WARS tryptophanyl-tRNA synthetase	200628_s_at	(D) AP/1	4.00	3.8E−06/4	NA	NA

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

ADAL Adenosine Deaminase-Like	239711_at	(D) AP/4	0.00	4.53E−08/4	NA	NA
ATP13A2 ATPase type 13A2	218608_at	(D) DE/2	4.00	4.75E−08/4	NA	NA
CNOT3 CCR4-NOT transcription complex, subunit 3	211141_s_at	(D) DE/4	0.00	4.05E−16/4	NA	NA
JMJD1C jumonji domain containing 1C	228793_at	(I) DE/4	0.00	3.6E−06/4	NA	NA
KSR1 kinase suppressor of ras 1	213769_at	(I) AP/4	4.00	NS	NA	NA
RPAP3 RNA polymerase II associated protein 3	1557984_s_at	(D) AP/4	0.00	4.34E−06/4	NA	NA
SORBS1 sorbin and SH3 domain containing 1	211705_s_at	(D) DE/2	2.00	8.95E−11/4	NA	NA
TDG thymine-DNA glycosylase	203742_s_at	(I) DE/2	2.00	1.04E−16/4	NA	NA
ZNF302 zinc finger protein 302	218490_s_at	(D) AP/4	0.00	3.87E−05/4	NA	NA
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	202542_s_at	(D) DE/1	4.00	1.73E−05/4	NA	NA
FIGNL1 fidgetin-like 1	222843_at	(D) AP/1	4.00	2.08E−05/4	NA	NA
MRTO4 mRNA turnover 4 homolog (*S. cerevisiae*)	235783_at	(D) DE/1	4.00	7.52E−16/4	NA	NA
BF114768	236879_at	(I) DE/4	0.00	2.62E−12/4	NA	NA
BE674182	237259_at	(I) DE/4	0.00	NS	0.66/ 3.33E−02	NA
CACNA1I calcium channel, voltage-dependent, T type, alpha 1I subunit	208299_at	(I) AP/4	0.00	NS	NA	NA

Gene Symbol/ Gene Name	Step 5 Other Psychiatric and Related Disorders Evidence	Step 6 Drugs that Modulate the Biomarker in Opposite Direction to Suicide	CFE Polyevidence Score
HTR2A 5-Hydroxytryptamine Receptor 2A	Alcohol Anxiety BP MDD SZ OCD Response to Antidepressants	Clozapine Lithium Valproate Paliperidone, Risperidone, lurasidone, clozapine, doxepin, desipramine, , clomipramine, loxapine, quetiapine, olanzapine, nefazodone, mirtazapine, amitriptyline lisuride, sertindole, ziprasidone, mesoridazine, thioridazine, aripiprazole, methysergide, dihydroergotamine, apomorphine, ergotamine, azatadine	16

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

SAT1 spermidine/ spermine N1-acetyltransferase 1	MDD Anxiety Mood Disorders NOS	Omega 3	16
SAT1 spermidine/ spermine N1-acetyltransferase 1	MDD Anxiety Mood Disorders NOS	Omega 3	16
CRYAB crystalline, alpha B	Autism Alcohol PTSD SZA BP SZ Insomnia Social Isolation Stress MDD	Lithium Clozapine Methamphetamine	15
PIK3R1 Phosphoinositide-3-Kinase Regulatory Subunit 1	Schizophrenia MDD Relaxation Response PTSD BP Longevity Stress Alcohol Insomnia Anxiety	Mood Stabilizers	15
PTK2 Protein Tyrosine Kinase 2	Alcohol ASD BP Circadian abnormalities MDD Neurological SZ/SZA Stress SZ	CT-707	15
SAT1 spermidine/ spermine N1-acetyltransferase 1	MDD Anxiety Mood Disorders NOS	Omega 3	15
SPTBN1 spectrin, beta, non-erythrocytic 1	Aging BP Longevity MDD SZ	Clozapine Omega-3 Diazepam	15
AKT1S1 AKT1 substrate 1 (proline-rich)	Circadian abnormalities Aging	Omega-3 fatty acids	14
AKT1S1 AKT1 substrate 1 (proline-rich)	Circadian abnormalities Longevity	(I) Brain Omega-3 fatty acids[195]	14
ARHGAP26 Rho GTPase activating protein 26	BP MDD Panic Disorder SZ	Clozapine	14
B2M beta-2-microglobulin	Alcohol Effect of valproate MDD SZ	Omega-3	14
PSME4 Proteasome Activator Subunit 4	ASD MDD		14
ACSM3 acyl-CoA synthetase medium-chain family member 3	MDD Mood		13

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

ADORA1 adenosine A1 receptor	Alcohol SZ BP Mood, Stimulants Depression	(I) Ventral tegmentum Clozapine[194]	13
FAAH fatty acid amide hydrolase	Alcohol SZ BP MDD Pain Placebo PTSD Stress Hallucinogens Social Isolation	(D)FAAH Hippocampus (males) Omega-3[193]	13
MARCKS Myristoylated alanine-rich protein kinase C substrate	BP SZ MDD Yohimbine Alcohol Panic Disorder	(D) Cerebral Cortex (right) Lithium[199]	13
MBP myelin basic protein	Alcohol Alzheimer's Disease BP MDD Mood Neurological SZ	Clozapine Omega-3 Lithium	13
PAFAH1B2 platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 (30 kDa)	MDD	Lithium PCP Clozapine	13
PCDH9 Protocadherin 9	Aging MDD SZ/SZA SZ	Clozapine Omega-3	13
PIK3R1 phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	SZ MDD Relaxation Response PTSD BP Longevity Hallucinogens Stress Alcohol Insomnia Anxiety	(D) Amygdala mood stabilizers[198]	13
PTEN phosphatase and tensin homolog	SZ MDD BP PTSD Longevity Hallucinogens Stress Yohimbine Alcohol Stimulants Anxiety		13
RNF6 ring finger protein (C3H2C3 type) 6	BP Social Isolation		13
SLC5A3 solute carrier family 5 (sodium/myoinositol cotransporter), member 3	Chronic Stress MDD Alcohol	frontal cortex Lithium[197]	13
C20orf27 chromosome 20 open reading frame 27	BP MDD		12
C7orf73 Chromosome 7 open reading frame 73			12

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

CLYBL Citrate Lyase Beta Like	MDD Delusions Stimulants ADHD Longevity Alcohol		12
EZR ezrin	SZ Mood Disorders NOS Stimulants Anxiety Alcohol		12
ICAM4 intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)	MDD		12
NEAT1 nuclear paraspeckle assembly transcript 1 (non-protein coding)		Clozapine	12
NUB1 Negative regulator of ubiquitin-like proteins 1		(D) NUB1 Ventral tegmentum Clozapine[194]	12
PGBD2 PiggyBac Transposable Element Derived 2	BP Mood State		12
C8orf74 chromosome 8 open reading frame 74			11
CALR calreticulin	SZ MDD Relaxation Response Pain Longevity Stimulants SZA Alcohol Chronic Stress		11
CRHR1 Corticotropin- Releasing Hormone Receptor 1	SZ MDD Pain Panic Disorder ASD Depression Alcohol Substances/Addictions SSRI PTSD Anxiolytics BP Aggression SNRI Longevity Stress Alcohol Antipsychotics Anxiety	"Ventral tegmentum (D) (Treatments, Cognition, Antipsychotics)[194] Amygdala (D) (Addictions, Alcohol, Alcohol)[201] Amygdala (paradigm 3) (I) (Addictions, Alcohol, Alcohol)[202]	11
DLL1 delta-like 1 (*Drosophila*)	BP PTSD SZ		11
FADS1 fatty acid desaturase 1	Aging Antipsychotics SZ		11
KLK7 Kallikrein Related Peptidase 7	BP Mood State		11
MED28 mediator complex subunit 28	Alcohol BP PTSD		11
NDUFS1 NADH: Ubiquinone Oxidoreductase Core Subunit S1	Alcohol SZ Circadian abnormalities		11

TABLE 22-continued

Convergent Functional Evidence (CFE). Male bipolar Top Dozen and Bonferroni biomarkers. Only predictions with a significant p-value for the ROC AUC are shown. Those that do not have a significant p-value are marked NA.

POLR2D polymerase (RNA) II (DNA directed) polypeptide D	BP	11
PPAP2B phosphatidic acid phosphatase type 2B	SZ/SZA SZ	11
SELENBP1 selenium binding protein 1	SZ Psychosis Circadian abnormalities ASD	11
TRIM23 tripartite motif containing 23	BP SZ	11
WARS tryptophanyl- tRNA synthetase	Alcohol SZ	11
ADAL Adenosine Deaminase-Like	Circadian abnormalities Mood	10
ATP13A2 ATPase type 13A2		10
CNOT3 CCR4-NOT transcription complex, subunit 3	BP Hallucinogens	10
JMJD1C jumonji domain containing 1C	BP PTSD Anxiety Hallucinogens	10
KSR1 kinase suppressor of ras 1	Hallucinogens MDD	10
RPAP3 RNA polymerase II associated protein 3	SZ/SZA	10
SORBS1 sorbin and SH3 domain containing 1	ASD SZ Longevity Mood Disorders NOS MDD BP	10
TDG thymine-DNA glycosylase	Alcohol Chronic Stress	10
ZNF302 zinc finger protein 302	MDD SZ Post-Traumatic Stress Disorder	10
AIMP1 aminoacyl tRNA synthetase complex- interacting multifunctional protein 1		9
FIGNL1 fidgetin-like 1		9
MRTO4 mRNA turnover 4 homolog (*S. cerevisiae*)		9
BF114768		8
BE674182		6
CACNA1I calcium channel, voltage- dependent, T type, alpha 1I subunit	MDD SZ	6

Example 3

A list/panel of 50 biomarkers (BioM50) was generated from the biomarkers with the best evidence from discovery, prioritization, validation, and testing in independent cohorts, obtained with additional data, longer follow-up, and longitudinal analyses (Table 23, FIG. **10**).

In this Example, the following abbreviations were utilized: validation: DE—differential expression, AP—Absent/Present. NS—Non-stepwise; Step 4 Predictions: C—cross-sectional (using levels from one visit), L—longitudinal (using levels, slope, as well as maximum levels and maximum slope from multiple prior visits); M—Males, F—Females. MDD—depression, BP—bipolar, SZ—schizophrenia, SZA—schizoaffective, PSYCHOSIS—schizophrenia and schizoaffective combined, PTSD-post-traumatic stress disorder. In ALL, by Gender, and personalized by Gender and Diagnosis. Score for predictions: 4 pts if in ALL, 2 pts Gender, 1 pts Gender/Dx. Bold name genes are also Bonferroni significant at Step 3 validation.

To generate the BioM50, the raw gene expression data was first Z-scored by gender and diagnosis, for normalization purposes. Then, each of the biomarkers in the panel was multiplied by a weight coefficient corresponding to their CFE (convergent functional evidence) score, and then an additive score of the 50 weighted biomarkers was obtained. This score can be used for (1) objective assessment of suicidality state and (2) predictive purposes for future clinical worsening, as reflected in hospitalizations for suicidality. Two types of analyses can be performed: cross-sectional, and longitudinal (Table 23, FIGS. **11**A-**11**C).

As depicted in FIGS. **11**A-**11**C, for cross-sectional analyses, biomarker expression levels were used, z-scored by gender and diagnosis. For longitudinal analyses, four measures were combined: biomarker expression levels, slope (defined as ratio of levels at current testing visit vs. previous visit, divided by time between visits), maximum levels (at any of the current or past visits), and maximum slope (between any adjacent current or past visits). For decreased biomarkers, the minimum rather than the maximum was used for level calculations. All four measures were Z-scored, then combined in an additive fashion into a single measure. This type of longitudinal analysis can be carried out in patients that have at least two test visits.

The BioM-50 score of a new patient tested was compared against the scores of previously tested patients with known severity and outcomes. The thresholds were set based on averages of previous data, and on previous ROC AUC curves, choosing values for sensitivity and specificity. A report was generated with a raw score, a % score, and a risk classification (low, intermediate, high).

BioM50 scores can also be used in combination with quantitative phenotypic data from questionnaires/apps (such as CFI-S, SASS, others), in the UP-Suicide algorithm.

The biomarkers from the BioM50 panel can be used to (3) match patients to medications (Table 23, FIG. **12**). Some biomarkers have corresponding known drugs or classes of drugs, that have an opposite effect to suicidality on their direction of change (pharmacogenomics). Such biomarkers can be used to target treatments to different patients, and to (4) measure response to that treatment. The higher the proportion/percentile of biomarkers for a certain drug/class, the more indicated that drug would be for treatment. When biomarkers for multiple different drug/classes are changed in an individual, a prioritization based on the proportion/percentile of biomarkers for each class can be used to choose the drug or combination of drugs (targeted rational polypharmacy).

The gene expression signature of the 50 biomarkers (BioM50) was used to identify repurposed drugs, for (5) new method of use in suicidality treatment and prevention (Table 24). The biological networks where these 50 biomarkers map offer additional targets for new drug development (FIG. **13**).

For the top biomarkers identified, combining all the available evidence from this current Example and the published literature, into a convergent functional evidence (CFE) score (Table 23), leads to a prioritization of biomarkers for future studies in the field.

TABLE 23

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

Gene Symbol/ Gene Name	Probeset	Discovery in Longitudinally Followed Patients Step 1 Discovery in Blood (Direction of Change tracking High Suicidal Ideation) Method/Score/% 4 pts	Step 2 Prioritization External CFG Evidence for Involvement in Suicide Score 8 pt	Validation in Suicide Completers Step 3 Validation Anova p-value 4 pts
PSME4 Proteasome Activator Subunit 4	237180_at	(I) DE/1 46.2%	4.00	3.81E−12 Bonferroni/4
ACP1 acid phosphatase 1, soluble	201630_s_at	(D) DE/2 55.2%	6.00	4.03E−05 Bonferroni/4
ACSL6 acyl-CoA synthetase long-chain family member 6	211207_s_at	(D) DE/4 94.8%	2.00	6.92E−02 Nominal/2

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

MAGI3 membrane associated guanylate kinase, WW and PDZ domain containing 3	226770_at	(D) AP/2 56%	4.00	4.02E−12 Bonferroni/4
PLPP3 phospholipid phosphatase 3	212226_s_at	(I) DE/1 36.9% (I) AP/2 53.1%	4.00	1.65E−05 Bonferroni/4
SKA2 spindle and kinetochore associated complex subunit 2	225686_at	(D) AP/1 34.5%	8.00	4.74E−03 Nominal/2
SOD2 superoxide dismutase 2, mitochondrial	215078_at	(I) DE/2 73.8%	4.00	6.26E−11 Bonferroni/4
CLN5 ceroid-lipofuscinosis, neuronal 5	214252_s_at	(D) DE/2 60.4%	4.00	1.66E−11 Bonferroni/4
CLTA clathrin, light chain A	204050_s_at	(D) DE/2 62.5%	4.00	5.13E−07 Bonferroni/4
DYRK2 dual specificity tyrosine-(Y)-phosphorylation regulated kinase 2	202969_at	(D) DE/2 56.3%	4.00	2.29E−09 Bonferroni/4
ECHDC1 ethylmalonyl-CoA decarboxylase 1	223087_at	(D) DE/2 74%	4.00	2.12E−07 Bonferroni/4
FBLN5 fibulin 5	203088_at	(D) DE/2 52.1%	6.00	1.05E−11 Bonferroni/4
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	227605_at	(D) DE/2 53.1% (D) AP/1 41.4%	4.00	8.98E−13 Bonferroni/4
CLN5 ceroid-lipofuscinosis, neuronal 5	204084_s_at	(D) DE/1 41.7%	4.00	6.03E−15 Bonferroni/4
ITGB1BP1 integrin beta 1 binding protein 1	203336_s_at	(D) DE/2 57.3%	4.00	9.47E−06 Bonferroni/4
NR3C1 nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	201866_s_at	(D) DE/2 53.1%	6.00	2.83E−06 Bonferroni/4
PER1 period circadian clock 1	244677_at	(I) DE/1 37.7%	4.00	3.52E−18 Bonferroni/4

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

PIK3R1 Phospho-inositide-3-Kinase Regulatory Subunit 1	244181_at	(I) DE/1 36.2%	4.00	7.33E−08 Bonferroni/4
PRKAR2B protein kinase, cAMP-dependent, regulatory, type II, beta	203680_at	(D) DE/2 66.7%	6.00	7.27E−06 Bonferroni/4
SAE1 SUMO1 activating enzyme subunit 1	1555618_s_at	(D) DE/4 86.5%	0.00	3.33E−05 Bonferroni/4
SPATA18 spermato-genesis associated 18	229331_at	(I) DE/2 54.6%	4.00	1.39E−05 Bonferroni/4
ZNF565 zinc finger protein 565	228305_at	(D) DE/1 49%	4.00	3.43E−10 Bonferroni/4
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	202542_s_at	(D) DE/2 78.1%	4.00	3.55E−05 Bonferroni/4
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	202541_at	(D) DE/1 34.4%	4.00	4.06E−05 Bonferroni/4
BCL2 B-cell CLL/ lymphoma 2	203685_at	(D) DE/2 55.2%	6.00	1.55E−07 Bonferroni/4
CAT catalase	211922_s_at	(D) DE/2 59.4%	4.00	1.03E−08 Bonferroni/4
ECHDC1 ethylmalonyl-CoA decarboxylase 1	219974_x_at	(D) DE/2 59.4%	4.00	2.94E−09 Bonferroni/4
HDAC2 histone deacetylase 2	201833_at	(D) DE/4 82.3%	0.00	9.15E−08 Bonferroni/4
LPP LIM domain containing preferred translocation partner in lipoma	241879_at	(I) DE/1 36.2%	4.00	8.45E−11 Bonferroni/4
PSMB4 proteasome subunit beta 4	202243_s_at	(D) DE/2 51%	6.00	5.97E−08 Bonferroni/4
RPE ribulose-5-phosphate-3-epimerase	221770_at	(D) DE/2 68.8%	2.00	2.79E−09 Bonferroni/4
VTA1 vesicle (multivesicular body) trafficking 1	223021_x_at	(D) DE/2 52.1%	4.00	1.01E−06 Bonferroni/4

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

AKAP13 A kinase (PRKA) anchor protein 13	209534_x_at	(I) DE/1 46.2%	4.00	1.61E−07 Bonferroni/4
CD164 CD164 molecule, sialomucin	208654_s_at	(D) DE/2 64.6%	4.00	3.65E−07 Bonferroni/4
CD47 CD47 molecule	211075_s_at	(D) DE/2 62.5%	4.00	6.65E−11 Bonferroni/4
CYP4V2 cytochrome P450, family 4, subfamily V, polypeptide 2	226745_at	(D) DE/2 50%	2.00	6.31E−07 Bonferroni/4
DNAJC15 DnaJ (Hsp40) homolog, subfamily C, member 15	230305_at	(D) DE/2 63.5%	4.00	3.94E−08 Bonferroni/4
FNTA farnesyl-transferase, CAAX box, alpha	209471_s_at	(D) DE/4 90.6%	0.00	2.15E−09 Bonferroni/4
GIMAP4 GTPase, IMAP family member 4	219243_at	(D) DE/2 77.1%	2.00	1.90E−17 Bonferroni/4
GIMAP7 GTPase, IMAP family member 7	228071_at	(D) DE/2 71.9%	2.00	7.51E−08 Bonferroni/4
HACL1 2-hydroxyacyl-CoA lyase 1	223211_at	(D) DE/1 46.9%	4.00	8.93E−09 Bonferroni/4
HNRNPA0 heterogeneous nuclear ribonucleo-protein A0	201054_at	(D) DE/2 53.1%	2.00	2.83E−10 Bonferroni/4
MRPS14 mitochondrial ribosomal protein S14	203801_at	(D) DE/2 50%	4.00	1.18E−11 Bonferroni/4
PIK3C3 phosphatidyl-inositol 3-kinase, catalytic subunit type 3	232086_at	(D) DE/2 63.5%	3.00	1.43E−16 Bonferroni/4
PRKCB protein kinase C, beta	207957_s_at	(D) DE/2 51%	6.00	1.04E−11 Bonferroni/4
PSMB1 proteasome subunit beta 1	214289_at	(I) DE/1 39.2% (I) AP/2 54.7%	6.00	2.51E−07 Bonferroni/4
SAT1 spermidine/ spermine N1-acetyltransferase 1	213988_s_at	(I) DE/1 39.2%	6.00	1.66E−20 Bonferroni/4

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

SLC6A4 solute carrier family 6 (neurotransmitter transporter), member 4	241811_x_at	(I) DE/2 70%	8.00	NS
TMEM245 transmembrane protein 245	223007_s_at	(D) DE/2 50%	4.00	1.89E−09 Bonferroni/4
TPH2 tryptophan hydroxylase 2	1555332_at	(I) DE/1 33.8%	8.00	1.36E−01 Nominal/2

	Clinical Utility of our Biomarkers 1. Assessment of State, 2. Prediction of Future Risk, 3. Matching to Treatments Testing/Demonstration in Independent Clinical Cohorts				
Gene Symbol/ Gene Name	Step 4 Best Significant Predictions of State High Suicidal Ideation ROC AUC/ p-value 4 pts ALL 2 pts Gender 1 pts Gender/Dx	Step 4 Best Significant Predictions of Trait First Year Hosp with Suicidality OR/OR p-value 4 pts ALL 2 pts Gender 1 pts Gender/Dx	Step 4 Best Significant Predictions of Trait All Future Years Hosp with Suicidality OR/OR p-value 4 pts ALL 2 pts Gender 1 pts Gender/Dx	Matching to Treatments (Pharmaco genomics) Drugs that Modulate the Biomarker in opposite Direction to Suicide	CFE Score
PSME4 Proteasome Activator Subunit 4	**ALL** **C:** (54/320) 0.61/6.46E−03 **Gender** **Males** **C:** (46/247) 0.61/7.56E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.69/1.97E−02 **M-PTSD** **C:** (9/19) 0.79/1.69E−02	**ALL** **C:** (51/359) 0.64/9.99E−04 **Gender** **Males** **C:** (45/307) 0.65/8.54E−04 **Gender Dx** **M-MDD** **C:** (7/41) 0.72/3.19E−02 **M-PTSD** **C:** (6/24) 0.85/5.65E−03	**ALL** **C:** (140/477) 1.21/3.53E−03 **L:** (74/287) 1.31/3.89E−02 **Gender** **Females** **L:** (5/42) 6.08/4.17E−02 **Gender** **Males** **C:** (129/409) 1.2/5.01E−03 **Gender Dx** **M-BP** **C:** (23/108) 1.33/4.02E−02 **M-MDD** **C:** (13/52) 1.55/3.03E−02 **M-PTSD** **C:** (12/28) 2.01/1.12E−02 **M-SZA** **C:** (37/99) 1.24/4.48E−02 **M-SZA** **L:** (19/57) 1.6/3.56E−02	Antidepressants	21
ACP1 acid phosphatase 1, soluble	**ALL** **C:** (54/320) 0.63/1.77E−03 **Gender** **Males**		**ALL** **L:** (74/287) 1.36/4.24E−02 **Gender** **Males**	Omega-3 fatty acids Lithium Antidepressants Antipsychotics Psychotherapy	20

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	C: (46/247) 0.65/6.92E−04 **Gender Dx** **M-BP** **C:** (12/82) 0.74/4.69E−03 **M-PSYCHOSIS** **C:** (15/107) 0.69/8.50E−03 **M-PTSD** **C:** (9/19) 0.73/4.32E−02 **M-PTSD** **L:** (5/10) 0.92/1.41E−02 **M-SZ** **L:** (3/32) 0.79/4.96E−02 **M-SZA** **C:** (10/50) 0.69/3.45E−02		**L:** (69/245) 1.44/2.21E−02 **Gender Dx** **M-PTSD** **C:** (12/28) 1.81/3.91E−02 **M-SZ** **L:** (17/62) 1.94/3.46E−02		
ACSL6 acyl-CoA synthetase long-chain family member 6	**ALL** **C:** (54/320) 0.6/1.17E−02 **Gender** **Males** **C:** (46/247) 0.65/1.04E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.79/6.84E−04 **M-PSYCHOSIS** **C:** (15/107) 0.63/4.94E−02 **M-PTSD** **C:** (9/19) 0.84/5.68E−03	**ALL** **C:** (51/359) 0.59/2.50E−02 **Gender** **Males** **C:** (45/307) 0.59/2.40E−02	**ALL** **C:** (140/477) 1.26/1.28E−02 **Gender** **Males** **C:** (129/409) 1.26/1.57E−02 **Gender Dx** **M-BP** **C:** (23/108) 2.72/3.09E−02		20
MAGI3 membrane associated guanylate kinase, WW and PDZ domain containing 3	**ALL** **C:** (54/320) 0.6/1.30E−02 **Gender** **Males** **C:** (46/247) 0.61/9.81E−03 **L:** (16/133) 0.64/3.34E−02 **Gender Dx** **M-BP** **C:** (12/82) 0.68/2.38E−02 **M-PSYCHOSIS** **C:** (15/107) 0.78/3.04E−04 **M-PSYCHOSIS** **L:** (6/56)	**Gender** **Males** **C:** (45/307) 0.58/4.79E−02 **Gender Dx** **M-PSYCHOSIS** **C:** (21/134) 0.65/1.39E−02 **M-SZ** **C:** (12/67) 0.66/3.87E−02	**ALL** **C:** (140/477) 1.26/5.13E−03 **L:** (74/287) 1.44/1.47E−02 **Gender** **Males** **C:** (129/409) 1.35/1.04E−03 **L:** (69/245) 1.52/7.94E−03 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.69/2.39E−04 **M-PSYCHOSIS** **L:** (36/119) 1.6/2.71E−02	Antipsychotics	20

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	0.72/4.25E−02 **M-SZ** **C:** (5/57) 0.79/1.60E−02 **M-SZ** **L:** (3/32) 0.91/1.09E−02 **M-SZA** **C:** (10/50) 0.78/3.30E−03		**M-SZ** **C:** (31/101) 1.82/3.27E−03 **M-SZ** **L:** (17/62) 2.46/1.53E−02 **M-SZA** **C:** (37/99) 1.52/2.15E−02	
PLPP3 phospholipid phosphatase 3	**ALL** **C:** (54/320) 0.58/3.75E−02 **Gender** **Males** **C:** (46/247) 0.59/2.61E−02 **Gender Dx** **M-BP** C: (12/82) 0.68/2.69E−02 **M-PSYCHOSIS** **C:** (15/107) 0.65/3.43E−02	**Gender** **Males** **C:** (45/307) 0.59/2.86E−02 **Gender Dx** **M-BP** **C:** (8/92) 0.73/1.76E−02 **M-PSYCHOSIS** **C:** (21/134) 0.61/4.83E−02 **M-SZA** **C:** (9/67) 0.69/3.73E−02	**ALL** **C:** (140/477) 1.17/1.50E−02 **Gender** **Males** **C:** (129/409) 1.22/2.90E−03 **Gender Dx** **M-BP** **C:** (23/108) 1.4/1.85E−02 **M-PSYCHOSIS** **C:** (68/200) 1.18/4.01E−02 **M-SZA** **C:** (37/99) 1.28/1.73E−02	20
SKA2 spindle and kinetochore associated complex subunit 2	**ALL** **C:** (54/320) 0.61/6.70E−03 **Gender** **Males** **C:** (46/247) 0.65/8.03E−04 **Gender Dx** **M-BP** **C:** (12/82) 0.68/2.61E−02 **M-MDD** **L:** (2/14) 0.92/3.39E−02 **M-PSYCHOSIS** **C:** (15/107) 0.74/1.77E−03 **M-PSYCHOSIS** **L:** (6/56) 0.72/4.02E−02 **M-SZ** **C:** (5/57) 0.79/1.60E−02 **M-SZ** **L:** (3/32) 0.86/2.09E−02 **M-SZA** **C:** (10/50) 0.7/2.77E−02	**Gender Dx** **M-SZA** **C:** (9/67) 0.71/1.97E−02	**ALL** **C:** (140/477) 1.17/4.49E−02 **Gender** **Males** **C:** (129/409) 1.22/2.39E−02 **Gender Dx** **M-BP** **C:** (23/108) 2.05/1.67E−02	20

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

SOD2 superoxide dismutase 2, mitochondrial	**Gender Males C:** (46/247) 0.58/4.93E−02 **Gender Dx M-PSYCHOSIS C:** (15/107) 0.66/2.37E−02	**ALL C:** (51/359) 0.6/1.43E−02 **Gender Males C:** (45/307) 0.61/8.62E−03 **Gender Dx M-BP C:** (8/92) 0.68/4.96E−02 **M-PTSD C:** (6/24) 0.75/3.59E−02	**ALL C:** (140/477) 1.24/3.68E−03 **Gender Females L:** (5/42) 3.28/3.25E−02 **Gender Males C:** (129/409) 1.25/3.21E−03 **Gender Dx M-BP C:** (23/108) 1.47/1.95E−02	Antidepressants Antipsychotics	20
CLN5 ceroid-lipofuscinosis, neuronal 5	**ALL C:** (54/320) 0.64/4.17E−04 **Gender Males C:** (46/247) 0.66/2.71E−04 **Gender Dx M-BP C:** (12/82) 0.74/4.02E−03 **M-PSYCHOSIS C:** (15/107) 0.71/4.39E−03 **M-PSYCHOSIS L:** (6/56) 0.71/4.76E−02 **M-SZ C:** (5/57) 0.73/4.53E−02 **M-SZ L:** (3/32) 0.83/3.27E−02 **M-SZA C:** (10/50) 0.72/1.85E−02	**Gender Dx M-SZA C:** (9/67) 0.68/4.03E−02	**ALL C:** (140/477) 1.23/9.78E−03 **L:** (74/287) 1.4/2.71E−02 **Gender Males C:** (129/409) 1.27/5.59E−03 **L:** (69/245) 1.49/1.39E−02 **Gender Dx M-BP C:** (23/108) 1.65/2.60E−02		19
CLTA clathrin, light chain A	**ALL C:** (54/320) 0.59/2.08E−02 **Gender Males C:** (46/247) 0.6/1.77E−02 **Gender Dx M-BP C:** (12/82) 0.71/1.01E−02	**Gender Dx M-SZA C:** (9/67) 0.68/4.54E−02	**ALL L:** (74/287) 1.3/4.49E−02 **Gender Males L:** (69/245) 1.33/3.35E−02	Antipsychotics	19

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	M-PSYCHOSIS **C:** (15/107) 0.68/1.40E−02 **M-SZA** **C:** (10/50) 0.69/3.45E−02				
DYRK2 dual specificity tyrosine-(Y)-phosphorylation regulated kinase 2	**ALL** **C:** (54/320) 0.6/7.73E−03 **L:** (17/174) 0.62/4.85E−02 **Gender Males** **C:** (46/247) 0.64/1.34E−03 **L:** (16/133) 0.66/2.10E−02 **Gender Dx M-BP** **C:** (12/82) 0.73/5.26E−03 **M-PSYCHOSIS** **C:** (15/107) 0.73/2.49E−03 **L:** (6/56) 0.74/2.82E−02 **M-SZ** **C:** (5/57) 0.73/4.26E−02 **Gender Dx M-SZ** **L:** (3/32) 0.89/1.52E−02 **Gender Dx M-SZA** **C:** (10/50) 0.74/1.13E−02	**Gender Dx M-PTSD** **C:** (6/24) 0.78/2.28E−02	**ALL** **L:** (74/287) 1.39/2.99E−02 **Gender Males** **L:** (69/245) 1.46/1.67E−02 **Gender Dx M-PTSD** **C:** (12/28) 2.08/2.36E−02 **L:** (8/16) 2.73/3.54E−02 **M-SZ** **L:** (17/62) 1.81/4.16E−02	Antipsychotics	19
ECHDC1 ethylmalonyl-CoA decarboxylase 1	**ALL** **C:** (54/320) 0.62/2.09E−03 **Gender Males** **C:** (46/247) 0.64/1.49E−03 **Gender Dx M-BP** **C:** (12/82) 0.68/2.38E−02 **M-PSYCHOSIS** **C:** (15/107) 0.67/1.53E−02	**Gender Dx M-PTSD** **C:** (6/24) 0.76/3.10E−02	**ALL** **C:** (140/477) 1.18/3.14E−02 **Gender Males** **C:** (129/409) 1.18/3.75E−02 **Gender Dx M-PTSD** **C:** (12/28) 2.14/2.62E−02		19

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	M-SZ **L:** (3/32) 0.82/3.77E−02 **M-SZA** **C:** (10/50) 0.71/2.34E−02			
FBLN5 fibulin 5	**Gender Dx** **M-SZA** **C:** (10/50) 0.69/3.45E−02	**ALL** **C:** (51/359) 0.6/1.13E−02 **Gender** **Males** **C:** (45/307) 0.64/1.50E−03 **Gender Dx** **M-PSYCHOSIS** **C:** (21/134) 0.65/1.50E−02 **M-PTSD** **C:** (6/24) 0.73/4.78E−02 **M-SZ** **L:** (5/36) 0.74/4.31E−02	**Gender** **Males** **C:** (129/409) 1.21/1.96E−02 **Gender** **Males** **L:** (69/245) 1.45/1.62E−02 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.36/1.00E−02 **L:** (36/119) 1.68/1.04E−02 **M-SZ** **C:** (31/101) 1.46/3.22E−02 **M-SZ** **L:** (17/62) 2.17/1.36E−02	19
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	**ALL** **C:** (54/320) 0.62/2.41E−03 **L:** (17/174) 0.63/3.58E−02 **Gender** **Males** **C:** (46/247) 0.67/2.25E−04 **L:** (16/133) 0.65/2.36E−02 **Gender Dx** **M-BP** **C:** (12/82) 0.73/5.06E−03 **M-PSYCHOSIS** **C:** (15/107) 0.71/5.55E−03 **M-PTSD** **L:** (5/10) 0.92/1.41E−02 **M-SZA** **C:** (10/50) 0.76/6.24E−03		**ALL** **C:** (140/477) 1.17/3.79E−02 **Gender** **Males** **C:** (129/409) 1.22/1.86E−02 **Gender Dx** **M-BP** **C:** (23/108) 1.44/5.00E−02 **M-PSYCHOSIS** **C:** (68/200) 1.3/2.48E−02 **M-SZ** **C:** (31/101) 1.46/4.63E−02	18
CLN5 ceroid-lipofuscinosis, neuronal 5	**ALL** **C:** (54/320) 0.62/3.63E−03 **Gender** **Males** **C:** (46/247)	**Gender Dx** **M-PSYCHOSIS** **C:** (21/134) 0.63/2.91E−02 **M-SZA** **C:** (9/67)	**ALL** **C:** (140/477) 1.22/1.37E−02 **L:** (74/287) 1.36/3.95E−02 **Gender**	18

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	0.63/2.17E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.72/7.61E−03 **M-PSYCHOSIS** **C:** (15/107) 0.7/6.31E−03 **M-PSYCHOSIS** **L:** (6/56) 0.71/4.76E−02 **M-SZ** **L:** (3/32) 0.84/2.82E−02 **M-SZA** **C:** (10/50) 0.75/7.65E−03	0.76/5.89E−03	**Males** **C:** (129/409) 1.26/5.59E−03 **L:** (69/245) 1.43/2.18E−02 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.34/9.29E−03 **L:** (36/119) 1.63/2.07E−02 **M-SZ** **L:** (17/62) 2.14/1.66E−02 **M-SZA** **C:** (37/99) 1.43/1.72E−02		
ITGB1BP1 integrin beta 1 binding protein 1	**ALL** **C:** (54/320) 0.57/4.27E−02 **Gender** **Males** **C:** (46/247) 0.61/1.17E−02		**ALL** **C:** (140/477) 1.26/3.93E−03 **L:** (74/287) 1.51/6.20E−03 **Gender** **Males** **C:** (129/409) 1.31/1.49E−03 **L:** (69/245) 1.61/3.09E−03 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.28/2.19E−02 **M-SZA** **C:** (37/99) 2.17/1.06E−04 **L:** (19/57) 1.8/2.44E−02	Lithium	18
NR3C1 nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	**ALL** **C:** (54/320) 0.58/4.00E−02 **Gender** **Males** **C:** (46/247) 0.58/4.91E−02 **Gender Dx** **F-MDD** **C:** (2/11) 0.89/4.95E−02 **M-BP** **C:** (12/82) 0.69/1.91E−02		**Gender** **Males** **L:** (69/245) 1.38/3.05E−02	Valproate Antidepressants Antipsychotics	18
PER1 period circadian clock 1	**ALL** **C:** (54/320) 0.62/3.51E−03 **Gender** **Females**	**Gender Dx** **M-PSYCHOSIS** **C:** (21/134) 0.64/1.94E−02	**ALL** **C:** (140/477) 1.16/2.89E−02 **L:** (74/287)	Antidepressants Anxiolytics	18

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	C: (8/73) 0.75/1.19E−02 **Gender** **Males** **C:** (46/247) 0.6/2.19E−02 **Gender Dx** F-MDD **C:** (2/11) 1/1.69E−02 **M-BP** **C:** (12/82) 0.68/2.24E−02 **M-SZ** **C:** (5/57) 0.73/4.80E−02		1.49/3.57E−03 **Gender** **Males** **C:** (129/409) 1.15/4.75E−02 **L:** (69/245) 1.53/3.28E−03 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.3/7.61E−03 **L:** (36/119) 1.52/1.87E−02 **Gender Dx** **M-SZ** **C:** (31/101) 1.43/1.26E−02		
PIK3R1 Phospho-inositide-3-Kinase Regulatory Subunit 1	**Gender Dx** **M-PTSD** **C:** (9/19) 0.76/3.02E−02	**ALL** **C:** (51/359) 0.58/4.10E−02 **Gender** **Females** **L:** (1/31) 1/4.68E−02 **Gender Dx** **F-MDD** **C:** (3/17) 0.91/1.78E−02	**ALL** **L:** (74/287) 1.27/4.23E−02 **Gender Dx** **F-MDD** **C:** (3/17) 2.93/3.98E−02 **M-PTSD** **C:** (12/28) 1.7/2.41E−02 **M-PTSD** **L:** (8/16) 1.94/4.50E−02	Lithium Psychotherapy	18
PRKAR2B protein kinase, cAMP-dependent, regulatory, type II, beta	**Gender Dx** **F-BP** **C:** (3/32) 0.84/2.82E−02	**Gender Dx** **M-BP** **C:** (8/92) 0.68/4.55E−02 **Gender Dx** **M-BP** **L:** (3/57) 0.8/4.00E−02	**ALL** **L:** (74/287) 1.44/2.15E−02 **Gender** **Males** **L:** (69/245) 1.4/3.74E−02 **Gender Dx** **M-BP** **C:** (23/108) 1.63/2.48E−02 **L:** (11/68) 3.34/4.09E−02	Valproate Antipsychotics	18
SAE1 SUMO1 activating enzyme subunit 1	**Gender** **Females** **C:** (8/73) 0.71/2.60E−02 **Gender Dx** F-MDD **C:** (2/11) 0.89/4.95E−02	**ALL** **C:** (51/359) 0.58/3.97E−02 **Gender** **Males** **C:** (45/307) 0.58/4.26E−02 **Gender Dx** **M-BP** **C:** (8/92) 0.68/4.29E−02 **M-MDD** **C:** (7/41) 0.7/4.81E−02	**ALL** **C:** (140/477) 1.17/3.25E−02 **Gender** **Males** **C:** (129/409) 1.2/1.82E−02 **Gender Dx** **M-MDD** **C:** (13/52) 2.4/1.56E−03 **M-MDD** **L:** (6/29) 2.76/2.76E−02		18

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

SPATA18 spermatogenesis associated 18	**ALL** **C:** (54/320) 0.59/2.23E−02 **L:** (17/174) 0.65/2.04E−02 **Gender Males** **C:** (46/247) 0.58/3.76E−02 **L:** (16/133) 0.63/4.78E−02 **Gender Dx M-PSYCHOSIS** **L:** (6/56) 0.72/4.25E−02 **M-PTSD** **L:** (5/10) 0.84/3.79E−02	**ALL** **L:** (19/200) 0.62/3.92E−02 **Gender Dx M-PSYCHOSIS** **L:** (7/70) 0.77/9.66E−03 **M-SZ** **L:** (5/36) 0.88/3.73E−03		18
ZNF565 zinc finger protein 565	**ALL** **C:** (54/320) 0.58/4.07E−02 **Gender Males** **C:** (46/247) 0.61/1.04E−02 **Gender Dx M-PSYCHOSIS** **C:** (15/107) 0.71/4.88E−03 **M-SZA** **C:** (10/50) 0.75/8.17E−03	**Gender Dx M-SZA** **C:** (9/67) 0.7/2.68E−02	**ALL** **C:** (140/477) 1.18/2.99E−02 **L:** (74/287) 1.34/4.22E−02 **Gender Males** **C:** (129/409) 1.21/1.67E−02 **L:** (69/245) 1.44/1.88E−02 **Gender Dx M-PSYCHOSIS** **C:** (68/200) 1.23/4.28E−02 **L:** (36/119) 1.51/3.57E−02 **M-SZ** **L:** (17/62) 1.91/2.16E−02 **M-SZA** **C:** (37/99) 1.46/2.62E−02	18
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	**ALL** **C:** (54/320) 0.6/1.20E−02 **Gender Males** **C:** (46/247) 0.63/2.43E−03 **Gender Dx M-PSYCHOSIS** **C:** (15/107) 0.72/2.86E−03 **M-SZ** **L:** (3/32) 0.84/2.82E−02 **M-SZA**	**Gender Dx M-SZA** **C:** (9/67) 0.69/3.17E−02	**Gender Males** **C:** (129/409) 1.19/3.60E−02 **L:** (69/245) 1.36/4.76E−02 **Gender Dx M-BP** **C:** (23/108) 1.77/2.21E−02 **M-PTSD** **C:** (12/28) 1.8/4.33E−02	17

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	C: (10/50) 0.74/9.32E−03				
AIMP1 aminoacyl tRNA synthetase complex-interacting multifunctional protein 1	**ALL** **C:** (54/320) 0.62/2.92E−03 **Gender** **Males** **C:** (46/247) 0.65/6.19E−04 **Gender Dx** **M-BP** **C:** (12/82) 0.68/2.10E−02 **M-PSYCHOSIS** **C:** (15/107) 0.69/1.03E−02 **M-SZ** **L:** (3/32) 0.82/3.77E−02 **M-SZA** **C:** (10/50) 0.7/2.47E−02		**ALL** **C:** (140/477) 1.2/2.64E−02 **L:** (74/287) 1.36/4.65E−02 **Gender** **Males** **C:** (129/409) 1.25/1.31E−02 **L:** (69/245) 1.41/3.38E−02 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.38/1.31E−02 **M-SZA** **C:** (37/99) 1.51/1.70E−02		17
BCL2 B-cell CLL/ lymphoma 2	**ALL** **C:** (54/320) 0.64/7.17E−04 **Gender** **Males** **C:** (46/247) 0.65/5.80E−04 **Gender Dx** **M-BP** **C:** (12/82) 0.74/4.69E−03 **M-PSYCHOSIS** **C:** (15/107) 0.69/8.50E−03 **M-SZ** **C:** (5/57) 0.78/2.11E−02 **L:** (3/32) 0.85/2.43E−02		**Gender Dx** **M-SZ** **C:** (31/101) 1.37/4.28E−02	Lithium Valproate Antipsychotics	17
CAT catalase	**ALL** **C:** (54/320) 0.62/2.24E−03 **Gender** **Females** **C:** (8/73) 0.73/1.70E−02 **Gender** **Males** **C:** (46/247) 0.6/1.58E−02 **Gender Dx** F-MDD **C:** (2/11) 0.94/2.97E−02 **M-BP**	**Gender** **Males** **C:** (45/307) 0.58/4.90E−02 **Gender Dx** **M-MDD** **C:** (7/41) 0.72/3.58E−02 **M-SZA** **C:** (9/67) 0.72/1.65E−02	**Gender Dx** **M-MDD** **C:** (13/52) 2.02/1.68E−02		17

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	C: (12/82) 0.75/3.44E−03				
ECHDC1 ethylmalonyl-CoA decarboxylase 1	**ALL** **C:** (54/320) 0.61/4.99E−03 **Gender Males** **C:** (46/247) 0.61/9.52E−03 **Gender Dx M-BP** **C:** (12/82) 0.67/2.94E−02 **M-SZA** **C:** (10/50) 0.67/4.95E−02	**Gender Dx M-SZA** **C:** (9/67) 0.7/2.91E−02	**Gender Males** **C:** (129/409) 1.18/3.76E−02 **L:** (69/245) 1.41/2.93E−02		17
HDAC2 histone deacetylase 2	**ALL** **C:** (54/320) 0.64/6.78E−04 **Gender Males** **C:** (46/247) 0.64/1.10E−03 **Gender Dx M-BP** **C:** (12/82) 0.71/9.10E−03 **M-PSYCHOSIS** **C:** (15/107) 0.68/1.13E−02 **M-SZA** **C:** (10/50) 0.67/4.71E−02	**Gender Dx M-PTSD** **C:** (6/24) 0.75/3.59E−02	**ALL** **L:** (74/287) 1.38/2.95E−02 **Gender Males** **L:** (69/245) 1.45/1.73E−02 **Gender Dx M-BP** **C:** (23/108) 1.6/1.61E−02	Lithium	17
LPP LIM domain containing preferred translocation partner in lipoma	**ALL** **C:** (54/320) 0.62/2.14E−03 **Gender Females** **C:** (8/73) 0.72/2.20E−02 **Gender Males** **C:** (46/247) 0.61/1.07E−02 **Gender Dx F-BP** **C:** (3/32) 0.84/2.82E−02 **M-PTSD** **C:** (9/19) 0.74/3.62E−02	**Gender Females** **L:** (1/31) 1/4.68E−02 **Gender Dx M-PTSD** **C:** (6/24) 0.82/9.82E−03	**Gender Females** **L:** (5/42) 3.02/3.56E−02 **Gender Dx** F-MDD **C:** (3/17) 3.33/3.37E−02 **M-MDD** **L:** (6/29) 2.21/3.20E−02 **M-PTSD** **C:** (12/28) 1.92/7.27E−03		17
PSMB4 proteasome subunit beta 4	**ALL** **C:** (54/320) 0.59/1.87E−02 **Gender Males** **C:** (46/247)	**Gender Dx M-SZA** **C:** (9/67) 0.7/3.04E−02		Benzodiazepines	17

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	0.63/2.91E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.7/1.50E−02 **M-PSYCHOSIS** **C:** (15/107) 0.71/4.63E−03 **M-SZA** **C:** (10/50) 0.76/5.44E−03				
RPE ribulose-5-phosphate-3-epimerase	**ALL** **C:** (54/320) 0.6/1.15E−02 **Gender** **Males** **C:** (46/247) 0.62/5.61E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.7/1.47E−02 **M-PSYCHOSIS** **C:** (15/107) 0.66/2.50E−02 **M-SZ** **L:** (3/32) 0.84/2.82E−02	**Gender Dx** **M-PTSD** **C:** (6/24) 0.91/1.68E−03 **Gender Dx** **M-PTSD** **L:** (4/13) 0.89/1.54E−02	**ALL** **L:** (74/287) 1.4/3.01E−02 **Gender** **Males** **L:** (69/245) 1.45/2.37E−02 **Gender Dx** **M-PTSD** **C:** (12/28) 3.51/6.74E−03 **L:** (8/16) 3.93/8.53E−03		17
VTA1 vesicle (multivesicular body) trafficking 1	**ALL** **C:** (54/320) 0.6/1.26E−02 **Gender** **Males** **C:** (46/247) 0.61/1.00E−02 **Gender Dx** **M-BP** **C:** (12/82) 0.68/2.31E−02 **M-PSYCHOSIS** **C:** (15/107) 0.68/1.19E−02 **M-SZ** **L:** (3/32) 0.84/2.82E−02 **M-SZA** **C:** (10/50) 0.72/1.74E−02	**Gender Dx** **M-SZA** **C:** (9/67) 0.72/1.72E−02	**Gender** **Males** **L:** (69/245) 1.43/3.26E−02		17
AKAP13 A kinase (PRKA) anchor protein 13	**Gender Dx** **M-PTSD** **C:** (9/19) 0.76/3.02E−02	**Gender** **Females** **L:** (1/31) 1/4.68E−02 **Gender Dx** **M-PTSD** **C:** (6/24) 0.78/2.28E−02	**ALL** **L:** (74/287) 1.3/2.13E−02 **Gender** **Females** **L:** (5/42) 3.36/2.31E−02 **Gender** **Males** **L:**	Antipsychotics	16

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

			(69/245) 1.26/4.34E−02 **Gender Dx** **M-PTSD** **C:** (12/28) 1.67/3.09E−02		
CD164 CD164 molecule, sialomucin	**ALL** **C:** (54/320) 0.61/3.94E−03 **Gender** **Males** **C:** (46/247) 0.62/5.70E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.72/7.34E−03 **M-SZ** **L:** (3/32) 0.82/3.77E−02	**Gender Dx** **M-PTSD** **C:** (6/24) 0.81/1.39E−02	**Gender Dx** **M-PTSD** **C:** (12/28) 2.15/1.91E−02	Antipsychotics	16
CD47 CD47 molecule	**ALL** **C:** (54/320) 0.6/1.03E−02 **Gender** **Males** **C:** (46/247) 0.63/2.94E−03 **M-BP** **C:** (12/82) 0.67/3.22E−02 **M-PSYCHOSIS** **C:** (15/107) 0.69/7.89E−03 **M-SZ** **L:** (3/32) 0.8/4.33E−02 **M-SZA** **C:** (10/50) 0.74/9.32E−03	**Gender Dx** **M-SZA** **C:** (9/67) 0.68/4.54E−02	**Gender Dx** **M-PTSD** **C:** (12/28) 1.87/3.94E−02	Omega-3 fatty acids Antipsychotics	16
CYP4V2 cytochrome P450, family 4, subfamily V, polypeptide 2	**ALL** **C:** (54/320) 0.57/4.20E−02 **Gender** **Males** **C:** (46/247) 0.61/1.14E−02 **Gender Dx** **M-BP** C: (12/82) 0.77/1.58E−03 **M-PSYCHOSIS** **C:** (15/107) 0.68/1.36E−02 **M-SZA** **C:** (10/50) 0.78/3.82E−03		**ALL** **C:** (140/477) 1.25/8.55E−03 **Gender** **Males** **C:** (129/409) 1.26/7.94E−03 **Gender Dx** **M-BP** **C:** (23/108) 1.68/2.19E−02 **M-PSYCHOSIS** **C:** (68/200) 1.32/2.05E−02 **M-SZA** **C:** (37/99) 1.42/2.59E−02	Antidepressants	16

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

DNAJC15 DnaJ (Hsp40) homolog, subfamily C, member 15	**ALL C:** (54/320) 0.57/4.69E−02 **Gender Males C:** (46/247) 0.59/2.93E−02 **Gender Dx M-PTSD C:** (9/19) 0.77/2.27E−02	**Gender Dx M-PTSD C:** (6/24) 0.76/2.87E−02	**Gender Dx M-PTSD C:** (12/28) 2.37/2.03E−02		16
FNTA farnesyl-transferase, CAAX box, alpha	**ALL C:** (54/320) 0.6/9.25E−03 **Gender Males C:** (46/247) 0.63/3.64E−03 **Gender Dx M-BP C:** (12/82) 0.74/4.52E−03 **M-PSYCHOSIS C:** (15/107) 0.65/3.10E−02 **M-SZ L:** (3/32) 0.83/3.27E−02		**ALL L:** (74/287) 1.35/4.46E−02 **Gender Males L:** (69/245) 1.43/2.51E−02		16
GIMAP4 GTPase, IMAP family member 4	**ALL C:** (54/320) 0.6/8.98E−03 **Gender Males C:** (46/247) 0.62/4.62E−0 **Gender Dx M-BP C:** (12/82) 0.73/5.67E−03		**ALL C:** (140/477) 1.19/1.94E−02 **L:** (74/287) 1.49/1.00E−02 **Gender Males C:** (129/409) 1.21/1.57E−02 **L:** (69/245) 1.55/5.93E−03 **Gender Dx M-PTSD L:** (8/16) 2.45/3.52E−02	Benzodiazepines	16
GIMAP7 GTPase, IMAP family member 7	**ALL C:** (54/320) 0.67/3.59E−05 **Gender Males C:** (46/247) 0.7/1.36E−05 **Gender Dx M-BP C:** (12/82) 0.78/1.22E−03 **M-PSYCHOSIS C:** (15/107) 0.66/2.08E−02		**ALL C:** (140/477) 1.22/1.48E−02 **Gender Males C:** (129/409) 1.23/1.55E−02 **Gender Dx M-BP C:** (23/108) 1.54/3.90E−02 **M-PSYCHOSIS C:** (68/200) 1.27/3.91E−02		16

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	M-PTSD **C:** (9/19) 0.84/5.68E−03 **M-SZ** **L:** (3/32) 0.86/2.09E−02		**M-PTSD** **L:** (8/16) 2.42/3.55E−02		
HACL1 2-hydroxyacyl-CoA lyase 1	**Gender** **Males** **C:** (46/247) 0.62/6.04E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.66/3.83E−02 **M-PSYCHOSIS** **C:** (15/107) 0.72/2.70E−03 **M-SZA** **C:** (10/50) 0.76/6.68E−03	**Gender Dx** **M-SZA** **C:** (9/67) 0.68/3.88E−02	**ALL** **C:** (140/477) 1.19/2.11E−02 **L:** (74/287) 1.35/3.32E−02 **Gender** **Males** **C:** (129/409) 1.24/8.47E−03 **L:** (69/245) 1.42/1.71E−02 **Gender Dx** **M-PSYCHOSIS** **C:** (68/200) 1.26/3.24E−02 **M-SZ** **L:** (17/62) 1.92/3.45E−02		16
HNRNPA0 heterogeneous nuclear ribonucleo-protein A0	**ALL** **C:** (54/320) 0.6/9.17E−03 **Gender** **Males** **C:** (46/247) 0.61/9.34E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.75/3.18E−03 **M-PSYCHOSIS** **C:** (15/107) 0.71/5.55E−03 **M-SZ** **C:** (5/57) 0.75/3.34E−02 **M-SZ** **L:** (3/32) 0.79/4.96E−02 **M-SZA** **C:** (10/50) 0.69/3.45E−02		**ALL** **L:** (74/287) 1.35/4.70E−02 **Gender** **Males** **L:** (69/245) 1.38/3.73E−02		16
MRPS14 mitochondrial ribosomal protein S14	**ALL** **C:** (54/320) 0.61/6.26E−03 **Gender** **Males** **C:** (46/247) 0.64/1.76E−03 **Gender Dx** **M-BP**		**Gender** **Males** **C:** (129/409) 1.2/3.06E−02 **Gender** **Males** **L:** (69/245) 1.41/2.99E−02 **Gender Dx**	Omega-3 fatty acids	16

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

	C: (12/82) 0.72/8.78E−03 **M-PSYCHOSIS** **C:** (15/107) 0.71/4.51E−03 **M-SZ** **C:** (5/57) 0.73/4.80E−02 **L:** (3/32) 0.79/4.96E−02 **M-SZA** **C:** (10/50) 0.71/1.96E−02		**M-BP** **C:** (23/108) 1.51/4.23E−02		
PIK3C3 phosphatidyl-inositol 3-kinase, catalytic subunit type 3	**ALL** **C:** (54/320) 0.58/3.62E−02 **Gender Dx** F-MDD **C:** (2/11) 0.94/2.97E−02 **M-BP** **C:** (12/82) 0.65/4.92E−02	**Gender Dx** **M-PTSD** **C:** (6/24) 0.83/8.20E−03 **Gender Dx** **M-SZA** **C:** (9/67) 0.7/2.79E−02	**Gender** **Males** **L:** (69/245) 1.38/3.36E−02 **Gender Dx** **M-PSYCHOSIS** **L:** (36/119) 1.57/2.66E−02 **M-PTSD** **C:** (12/28) 1.94/3.19E−02	Antidepressants	16
PRKCB protein kinase C, beta	**ALL** **C:** (54/320) 0.61/3.96E−03 **Gender** **Males** **C:** (46/247) 0.61/8.52E−03 **Gender Dx** **M-BP** **C:** (12/82) 0.76/2.21E−03			Lithium	16
PSMB1 proteasome subunit beta 1	**Gender** **Females** **C:** (8/73) 0.75/1.19E−02 **Gender Dx** F-MDD **C:** (2/11) 1/1.69E−02 **M-PTSD** **C:** (9/19) 0.8/1.37E−02 **L:** (5/10) 0.92/1.41E−02	**Gender Dx** F-MDD **C:** (3/17) 0.88/2.58E−02	**Gender Dx** **M-BP** **L:** (11/68) 1.94/2.90E−02 **M-SZA** **L:** (19/57) 1.56/3.41E−02		16
SAT1 spermidine/spermine N1-acetyltransferase 1		**ALL** **C:** (51/359) 0.59/1.62E−02 **Gender** **Males** **C:** (45/307) 0.59/3.02E−02 **Gender Dx** **M-SZ**	**Gender Dx** **M-SZ** **C:** (31/101) 1.43/2.42E−02	Omega-3 fatty acids	16

TABLE 23-continued

CFE. Convergent Functional Evidence (CFE) Score: Prioritization of Top Biomarkers for Suicidality (resulting in a panel of n = 50 biomarkers, from 46 genes). Some genes have more than one biomarker probeset. The CFE score for each biomarker is based on the totality of evidence from our studies (Discovery, Prioritization, Validation, and Clinical Utility Testing). These biomarkers may be a panel, with the score for 50 biomarkers panel (BioM 50) computed in an additive way, with each biomarker in the panel having the CFE score as a weight coefficient.

		C: (12/67) 0.68/2.58E−02			
SLC6A4 solute carrier family 6 (neurotransmitter transporter), member 4	**ALL** **C:** (54/320) 0.63/1.73E−03 **Gender Males** **C:** (46/247) 0.66/3.89E−04 **M-BP** **C:** (12/82) 0.7/1.57E−02 **M-PSYCHOSIS** **C:** (15/107) 0.67/1.56E−02 **M-SZ** **C:** (5/57) 0.77/2.42E−02		**Gender Females** **C:** (11/68) 1.94/2.25E−02	Omega-3 fatty acids Lithium Antidepressants Remifentanil Exposure therapy	16
TMEM245 transmembrane protein 245		**Gender Males** **C:** (45/307) 0.58/4.98E−02 **Gender Dx M-BP** **C:** (8/92) 0.72/2.08E−02	**ALL** **C:** (140/477) 1.2/1.50E−02 **Gender Males** **C:** (129/409) 1.21/1.71E−02		16
TPH2 tryptophan hydroxylase 2	**ALL** **C:** (54/320) 0.65/2.98E−04 **Gender Males** **C:** (46/247) 0.68/6.60E−05 **Gender Dx M-BP** **C:** (12/82) 0.89/7.93E−06 **M-PSYCHOSIS** **C:** (15/107) 0.69/8.29E−03 **M-SZA** **C:** (10/50) 0.75/8.17E−03		**Gender Dx M-BP** **C:** (23/108) 1.36/4.64E−02	Antipsychotics Physical and Cognitive stimulation	16

TABLE 24

New drug Discovery/Repurposing. A. Top CFE BioM 50 Connectivity Map (CMAP) database discovery. Query for signature was done using exact Affymetrix probesets and direction of change. Drugs that have opposite gene expression profile effects to suicidality biomarkers signatures. A score of −1 indicates the perfect match, i.e. the best potential therapeutic for treating suicide. B. Top CFE BioM 50 NIH LINCS database discovery. Using the L1000CDS2 (LINCS L1000 Characteristic Direction Signature Search Engine) tool. Query for signature was done using gene symbols and direction of change. Shown are compounds Reversing direction of change in suicidality.

A. Top CFE BioM 50 CMAP Discovery
(n = 46 unique genes; 5 increased and 25 decreased were present in HG-U133A array used by CMAP)

Rank	CMAP name	Score
1	trimethoprim	−1
2	ethoxyquin	−0.979
3	haloperidol	−0.966
4	terazosin	−0.947
5	pepstatin	−0.921
6	diethylstilbestrol	−0.919
7	nifenazone	−0.905
8	metrizamide	−0.902
9	prazosin	−0.87
10	baclofen	−0.864

B. Top CFE BioM 50 LINCS Discovery
(n = 46 unique genes; 12 increased and 34 decreased).

Rank	Drug	Score
1	Daunorubicin hydrochloride	0.1143
2	BRD-K06666320	0.1143
3	WZ-3105	0.1143
4	Piretanide	0.0857
5	Syk Inhibitor	0.0857
6	vorinostat	0.0857
7	DACTINOMYCIN	0.0857
8	trichostatin A	0.0857
9	Tiotidine	0.0857
10	troglitazone	0.0857

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.

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 treating suicidality and mitigating suicidality risk in a subject in need thereof, comprising the steps of:

determining an expression level of at least a fist panel of blood biomarkers or a second panel of blood biomarkers in a sample from the subject;

wherein the first panel of biomarkers in the panel comprise; Apolipoprotein E (APOE), anchor protein 13 (AKAP13), aldehyde dehydrogenase 7 family, member A1 (ALDH7A1), adipogenesis regulatory factor (ADIRF), beta-2-microglobulin (B2M), Gene Accession No. BF114768, CD109 molecule (CD109), Cortactin (CTTN), chromosome 14 open reading frame 180 (C14ORF180), Dab, mitogen-responsive phosphoprotein, homolog 2 (*Drosophila*) (DAB2), dual specificity phosphatase 13 (DUSP13), EGF containing fibulin-like extracellular matrix protein 2 (EFEMP2), fatty acid desaturase 1 (FADS1), GRB2 Associated Binding Protein 1 (GAB1), glycine amidinotransferase (L-arginine: glycine amidinotransferase) (GATM), 5-Hydroxytryptamine Receptor 2A (HTR2A), Histone Cluster 1 H2B Family Member O (HIST1H2BO), Interleukin 6 (IL6), interleukin 13 (IL13), inositol-trisphosphate 3-kinase B (ITPKB), Lipoma HMGIC fusion partner (LHFP), LIM domain containing preferred translocation partner in lipoma (LPP), metallothionein 1E (MT1E), Nerve Growth Factor Receptor (NGFR), Proteasome Activator Subunit 4 (PSME4), proteasome subunit beta 1 (PSMB1), phospholipid phosphatase 3 (PLPP3), period circadian clock 1 (PER1), Phosphoinositide-3-Kinase Regulatory Subunit 1 (PIK3R1), phosphatidic acid phosphatase type 2B (PPAP2B), protein tyrosine kinase 2 (PTK2), spermidine/spermine N1-acetyltransferase 1 (SAT1), septin 8 SEPT8, solute carrier family 4 (sodium bicarbonate cotransporter), member (SLC4A4), superoxide dismutase 2, mitochondrial (SOD2), spermatogenesis associated 18 (SPATA18), synaptopodin 2-like (SYNPO2L), Transmembrane 4 L Six Family Member 1 (TM4SF1), tryptophan hydroxylase 2 (TPH2), and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (YWHAH),

wherein the second panel of biomarkers comprises acid phosphatase 1, soluble (ACP1), acyl-CoA synthetase long-chain family member 6 (ACSL6), adenylate kinase 2 (AK2), arrestin, beta (ARRB1), aminoacyl tRNA synthetase complex-interacting multifunctional protein 1 (AIMP1), acyl-CoA synthetase medium-chain family member 3 (ACSM3), aspartylglucosaminidase (AGA), A kinase (PRKA) anchor protein 2 (AKAP2), A kinase (PRKA) anchor protein 10 (AKAP10), ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e1 (ATP6VOE1), adenosine kinase (ADK), ankyrin repeat and MYND domain containing (ANKMY1), adenosylhomocysteinase-like 1 (AHCYL1), adenosylhomocysteinase-like 2 (AHCYL2), adenosine deaminase-like (ADAL), ceroid-lipofuscinosis, neuronal 5 (CLN5), chromosome 20 open reading frame 27 (C20ORF27), chromosome 8 open reading frame 74 (C8ORF74), CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1), centromere protein H (CENPH), delta-like 1 (*Drosophila*) (DLL1), dual specificity tyrosine-(Y)-phosphorylation regulated kinase 2 (ECHDC1), ERG, fibulin 5 (FBLN5), farnesyltransferase, CAAX box, alpha (FNTA), family with sequence similarity 63, member B (FAM63B), fumarate hydratase (FH), flotillin 2 (FLOT2), GDP dissociation inhibitor 2 (GDI2), glycogen synthase kinase 3 beta (GSK3B), G2/M-phase specific E3 ubiquitin protein ligase (G2E3), histone deacetylase 2 (HDAC2), heterogeneous nuclear ribonucleoprotein A0 (HNRNPA0), 2-hydroxyacyl-CoA lyase 1 (HACL1), IGHG1, kelch repeat and BTB (POZ) domain containing 2 (KBTBD2) GTPase, IMAP family member 7 (GIMAP7), GTPase, IMAP family member 4 (GIMAP4), interferon, gamma (IFNG), Integrin beta-1-binding protein 1 (ITGB1BP1), low density lipoprotein receptor adaptor protein 1 (LDLRAP1), leptin receptor (LEPR), lysophosphatidic acid receptor 1 (LPAR1), leucine rich repeat neuronal 3 (LRRN3), membrane associated guanylate kinase, WW and PDZ domain containing 3 (MAGI3), mitogen-activated protein kinase 5 (MAP2K5), mediator complex subunit 28

(MED28), myelin basic protein (MBP), mitochondrial ribosomal protein S14 (MRPS14), mitochondrial transcription (MTERF4), nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor (NR3C1), NEDD4 binding protein 2-like 2 (N4BP2L2), NIMA-related kinase 9 (NEK9), oligodendrocyte transcription factor 1 (OLIG1), proteasome subunit beta 4 (PSMB4), protein kinase C, beta (PRKCB), PIK3C3 phosphatidylinositol 3-kinase, catalytic subunit type 3, (PIK3CA), protein kinase, cAMP-dependent, regulatory, type II, beta (PRKAR2B), protein kinase, cAMP-dependent, regulatory, type I, alpha (PRKAR1A), phosphoglycerate kinase 1 (PGK1), plakophilin 4 (PKP4), protein kinase C, iota (PRKCI), protocadherin 9 (PCDH9), PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1 (PITHD1), platelet-activating factor acetylhydrolase 1b, catalytic subunit 2 (30 kDa (PAFAH1B2), polymerase (RNA) II (DNA directed) polypeptide D (POLR2D), ribulose-5-phosphate-3-epimerase (RPE), RNA binding motif (RNP1, RRM) protein 3 (RBM3), regulating synaptic membrane exocytosis 3 (RIMS3), RNA polymerase II associated protein 3 (RPAP3), spindle and kinetochore associated complex subunit 2 (SKA2), SUMO1 activating enzyme subunit 1 (SAE1,) SECIS binding protein 2-like (SECISBP2L), sorting nexin 6 (SNX6), SR-related CTD-associated factor 11 (SCAF11), SCMR8, spectrin, beta, non-erythrocytic 1 (SPTBN1), serine racemase (SRR), SET nuclear proto-oncogene///SET pseudogene 4///SET-like protein (SET), sulfatase modifying factor 2 (SUMF2), tumor protein D52 (TPD52), tau tubulin kinase 1 (TTBK1), transmembrane protein 245 (TMEM245), TMEM254, (TMEM254), tubulin, gamma complex associated protein 3 (TUBGCP3), TNF receptor-associated factor 3 (TRAF3), tripartite motif containing 23 (TRIM23), ubiquinol-cytochrome c reductase complex assembly factor 1 (UQCC1), vesicle (multivesicular body) trafficking 1 (VTA1), vesicle-associated membrane protein 3 (VAMP3), vasoactive intestinal peptide (VIP), tryptophanyl-tRNA synthetase (WARS), WAS/WASL interacting protein family, member 3 (WIPF3), WNK lysine deficient protein kinase 1 (WNK1), WWP2 WW [MMK1]domain containing E3 ubiquitin protein ligase 2 (WWP2), pre-B lymphocyte 3 (VPREB3), X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining) (XRCC5), zinc finger protein 565 (ZNF565), zinc finger, FYVE domain containing 21 (ZFYVE21), and zinc finger protein 75D (ZNF75D),

identifying a subject as having suicidality risk wherein the expression level of the blood biomarkers in the first panel is increased relative to a reference expression level, or, wherein the expression level of the blood biomarkers in the second panel is decreased relative to a reference expression level; and, administering to the subject identified as having suicidality a drug to treat the suicidality.

2. The method of claim **1**, wherein the biomarkers are quantified in samples taken on two or more occasions from the individual.

3. The method of claim **1**, wherein the biological sample is selected from the group consisting of; a tissue or a bodily fluid, cerebrospinal fluid, whole blood, blood serum, plasma, and saliva, or an extract of the sample.

4. The method of claim **1**, further including the step of treating the subject with at least one therapeutic agent selected from the group consisting of: dissociatives, mood stabilizers; antipsychotics; antidepressants; omega-3 fatty acids; and anxiolytics.

5. The method of claim **1**,

further including the step of treating:

a subject who exhibits changes in ACP1, BCL2, CRYAB, GSK3B, HDAC2, HTR2A, ITGB1BP1, MBP, NR3C1, PIK3R1, PRKAR2B, PRKCB, and SLC6A4 with a mood stabilizer;

a subject who exhibits changes in ACP1, AKAPI13, BCL2, CD164, CD47, CLTA, CRYAB, DYRK2, HTR2A, IFNG, IL6, LPAR1, MAGI3, MBP, NR3CI1, PGK1, PRKAR2B, SOD2, and TPH2 with an antipsychotic;

a subject who exhibits changes in ACP1, CD47, ACP1, GATM, LPAR1, MBP, MRPS14, and SLC6A4, with omega-3 fatty acids;

a subject who exhibits changes in ACP1, CYP4V2, NR3C1, PER1, PIK3C3, PSME4, SLC6A4, and SOD2, are treated with an antidepressant;

a subject who exhibits changes in GIMAP4, PER1, and PSMB4 with an anxiolytics; and

a subject who exhibits changes in one or more of ACP1, PIK3R1, SLC6A4, and TPH2 with CBT.

6. The method of claim **1**,

further including the step of: treating a subject who exhibits changes in ACP1, CD47, ACPI, GATM, LPAR1, MBP, MRPS14, and SLC6A4, with omega-3 fatty acids.

7. The method of claim **1**, further including the step: of treating the subject with at least one therapeutic selected from the group consisting of: chlorogenic acid, ebselen, metformin, piracetam, oxybuprocaine, sertaconazole, fenbufen, alprostadil, tolmetin, tenoxicam, merbromin, adiphenine, ozagrel, procainamide, asiaticoside, carbimazole, ramifenazone, dl-alpha tocopherol, diphenhydramine, betulin, calcium folinate, dapsone, clemastine, dihydroergocristine, amoxapine, lisuride, homatropine, ritodrine, merbromin, naproxen, chlorpromazine, genistein, fluoxetine, yohimbine, prazosin, amitriptyline, trimethoprim, ethoxyquin, haloperidol, terazosin, pepstatin, diethylstilbestrol, nifenazone, metrizamide, baclofen, Daunorubicin hydrochloride, BRD-K06666320, WZ-3105, Piretanide, Syk Inhibitor, vorinostat, DACTINOMYCIN, trichostatin A, Tiotidine, and troglitazone.

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