Molecular Psychiatry (2016), 1–18

www.nature.com/mp

IMMEDIATE COMMUNICATION

Towards understanding and predicting suicidality in women: biomarkers and clinical risk assessment

DF Levey[1,2,8], EM Niculescu[1,8], H Le-Niculescu[1], HL Dainton[1], PL Phalen[3], TB Ladd[1,2], H Weber[3], E Belanger[3], DL Graham[3], FN Khan[1], NP Vanipenta[1], EC Stage[1,2], A Ballew[4], M Yard[5], T Gelbart[6], A Shekhar[1], NJ Schork[7], SM Kurian[6], GE Sandusky[5], DR Salomon[6] and AB Niculescu[1,2,3]

Women are under-represented in research on suicidality to date. Although women have a lower rate of suicide completion than men, due in part to the less-violent methods used, they have a higher rate of suicide attempts. Our group has previously identified genomic (blood gene expression biomarkers) and clinical information (apps) predictors for suicidality in men. We now describe pilot studies in women. We used a powerful within-participant discovery approach to identify genes that change in expression between no suicidal ideation (no SI) and high suicidal ideation (high SI) states ($n = 12$ participants out of a cohort of 51 women psychiatric participants followed longitudinally, with diagnoses of bipolar disorder, depression, schizoaffective disorder and schizophrenia). We then used a Convergent Functional Genomics (CFG) approach to prioritize the candidate biomarkers identified in the discovery step by using all the prior evidence in the field. Next, we validated for suicidal behavior the top-ranked biomarkers for SI, in a demographically matched cohort of women suicide completers from the coroner's office ($n = 6$), by assessing which markers were stepwise changed from no SI to high SI to suicide completers. We then tested the 50 biomarkers that survived Bonferroni correction in the validation step, as well as top increased and decreased biomarkers from the discovery and prioritization steps, in a completely independent test cohort of women psychiatric disorder participants for prediction of SI ($n = 33$) and in a future follow-up cohort of psychiatric disorder participants for prediction of psychiatric hospitalizations due to suicidality ($n = 24$). Additionally, we examined how two clinical instruments in the form of apps, Convergent Functional Information for Suicidality (CFI-S) and Simplified Affective State Scale (SASS), previously tested in men, perform in women. The top CFI-S item distinguishing high SI from no SI states was the chronic stress of social isolation. We then showed how the clinical information apps combined with the 50 validated biomarkers into a broad predictor (UP-Suicide), our apriori primary end point, predicts suicidality in women. UP-Suicide had a receiver-operating characteristic (ROC) area under the curve (AUC) of 82% for predicting SI and an AUC of 78% for predicting future hospitalizations for suicidality. Some of the individual components of the UP-Suicide showed even better results. SASS had an AUC of 81% for predicting SI, CFI-S had an AUC of 84% and the combination of the two apps had an AUC of 87%. The top biomarker from our sequential discovery, prioritization and validation steps, BCL2, predicted future hospitalizations due to suicidality with an AUC of 89%, and the panel of 50 validated biomarkers (BioM-50) predicted future hospitalizations due to suicidality with an AUC of 94%. The best overall single blood biomarker for predictions was PIK3C3 with an AUC of 65% for SI and an AUC of 90% for future hospitalizations. Finally, we sought to understand the biology of the biomarkers. BCL2 and GSK3B, the top CFG scoring validated biomarkers, as well as PIK3C3, have anti-apoptotic and neurotrophic effects, are decreased in expression in suicidality and are known targets of the anti-suicidal mood stabilizer drug lithium, which increases their expression and/or activity. Circadian clock genes were overrepresented among the top markers. Notably, PER1, increased in expression in suicidality, had an AUC of 84% for predicting future hospitalizations, and CSNK1A1, decreased in expression, had an AUC of 96% for predicting future hospitalizations. Circadian clock abnormalities are related to mood disorder, and sleep abnormalities have been implicated in suicide. Docosahexaenoic acid signaling was one of the top biological pathways overrepresented in validated biomarkers, which is of interest given the potential therapeutic and prophylactic benefits of omega-3 fatty acids. Some of the top biomarkers from the current work in women showed co-directionality of change in expression with our previous work in men, whereas others had changes in opposite directions, underlying the issue of biological context and differences in suicidality between the two genders. With this study, we begin to shed much needed light in the area of female suicidality, identify useful objective predictors and help understand gender commonalities and differences. During the conduct of the study, one participant committed suicide. In retrospect, when the analyses were completed, her UP-Suicide risk prediction score was at the 100 percentile of all participants tested.

Molecular Psychiatry advance online publication, 5 April 2016; doi:10.1038/mp.2016.31

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Indianapolis Veterans' Affairs Medical Center, Indianapolis, IN, USA; [4]Marion County Coroner's Office, Indianapolis, IN, USA; [5]Indiana Center for Biomarker Research in Neuropsychiatry, Indiana University School of Medicine, Indianapolis, IN, USA; [6]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, USA and [7]J. Craig Venter Institute, La Jolla, CA, USA. Correspondence: Professor AB Niculescu, Psychiatry and Medical Neuroscience, Indiana University School of Medicine, Indianapolis Veterans' Affairs Medical Center, Indiana Center for Biomarker Research in Neuropsychiatry and Laboratory of Neurophenomics, Neuroscience Research Building 200B, 320W. 15th Street, Indianapolis, IN 46202, USA.
E-mail: anicules@iupui.edu
[8]These authors contributed equally to this work.
Received 22 November 2015; revised 27 January 2016; accepted 11 February 2016

INTRODUCTION

'Is there no way out of the mind?'
-Sylvia Plath

Predicting suicidality (suicidal ideation (SI), suicide attempts and suicide completion) in individuals is a difficult task, which is even more challenging in an understudied population like women. Although women have a lower rate of suicide completion than men, due in part to the less-violent methods used, they have a higher rate of suicide attempts.[1] It is reasonable to assume that genetic and biological differences may exist in suicidality between men and women. Studies by gender are a first step toward individualized medicine. We have previously shown in men with psychiatric disorders how blood biomarkers for suicide, alone or in combination with quantitative phenomic data for anxiety and mood, the Simplified Affective State Scale (SASS), and with a risk profile scale we have developed, Convergent Functional Information for Suicide (CFI-S), collected in the form of apps, could have predictive ability for SI, and for future hospitalizations for suicidality.[2] We now present data for discovery, prioritization, validation and testing of blood biomarkers for suicidality in women, across psychiatric diagnoses. We also show the utility of SASS and CFI-S in predicting suicidality in women. Both these type of tools, biomarkers and phenomic data apps, do not directly ask about SI. We demonstrate how our apriori primary end point, a comprehensive universal predictor for suicide (UP-Suicide), composed of the combination of 50 top Bonferroni validated biomarkers, along with SASS, and CFI-S, predicts in independent test cohorts SI and future psychiatric hospitalizations for suicidality. Finally, we uncover biological pathways involved in suicide in women, and potential therapeutics.

MATERIALS AND METHODS

Human participants

We derived our data from four cohorts: one live psychiatric participants discovery cohort; one postmortem coroner's office validation cohort; and two live psychiatric participants test cohorts —one for predicting SI and one for predicting future hospitalizations for suicidality (Figure 1).

The live psychiatric participants are part of a larger longitudinal cohort that we are continuously collecting. Participants are recruited from the patient population at the Indianapolis Veterans' Affairs (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 institutional review board-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 SI rating item (Figure 2a), and the blood was drawn. Whole blood (10 ml) was collected in two RNA-stabilizing PAXgene tubes, labeled with an anonymized ID number, and stored at − 80 °C in a locked freezer until the time of future processing. Whole-blood (predominantly lymphocyte) RNA was extracted for microarray gene expression studies from the PAXgene tubes, as detailed below. We focused this study on a female population. We have recently described a similar study in males,[2] and data from that study are used for gender comparison purposes in this paper.

Our within-participant discovery cohort, from which the biomarker data were derived, consisted of 12 female participants with psychiatric disorders and multiple visits in our laboratory, who each had at least one diametric change in SI scores from no SI to high SI from one testing visit to another. There were 7 participants with 3 visits each, and 5 participants with 2 visits each, resulting in a total of 31 blood samples for subsequent microarray studies (Figure 2 and Supplementary Table S1).

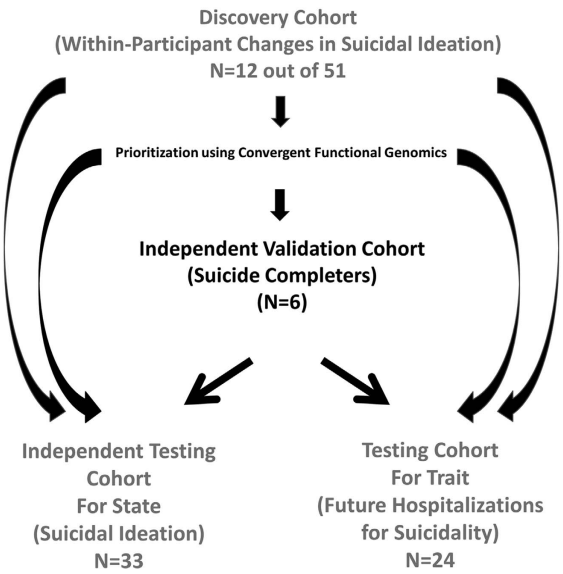


Figure 1. Cohorts used in study depicting, flow of discovery, prioritization, validation and testing of biomarkers from each step.

Our postmortem cohort, in which the top biomarker findings were validated for behavior, consisted of a demographically matched cohort of six female violent suicide completers obtained through the Marion County coroner's office (Table 1 and Supplementary Table S1). We required a last observed alive postmortem interval of 24 h or less, and the cases selected had completed suicide by means other than overdose, which could affect gene expression. Five participants completed suicide by gunshot to head or chest, and one by asphyxiation. Next of kin signed informed consent at the coroner's office for donation of blood for research. The samples were collected as part of our INBRAIN initiative (Indiana Center for Biomarker Research in Neuropsychiatry).

Our independent test cohort for predicting SI (Table 1) consisted of 33 female participants with psychiatric disorders, demographically matched with the discovery cohort, with one or multiple testing visits in our laboratory, with either no SI, intermediate SI or high SI, resulting in a total of 74 blood samples in whom whole-genome blood gene expression data were obtained (Table 1 and Supplementary Table S1).

Our test cohort for predicting future hospitalizations (Table 1 and Supplementary Table S1) consisted of 24 female participants in whom whole-genome blood gene expression data were obtained by us at testing visits over the years as part of our longitudinal study. If the participants had multiple testing visits, then the visit with the highest marker (or combination of markers) levels was selected for the analyses (so-called 'high watermark' or index visit). The participants' subsequent number of psychiatric hospitalizations, with or without suicidality (ideation or attempt), was tabulated from electronic medical records. Participants were evaluated for the presence of future hospitalizations for suicidality, and for the frequency of such hospitalizations. A hospitalization was deemed to be without suicidality if suicidality was not listed as a reason for admission, and no SI was described in the admission and discharge medical notes. Conversely, a hospitalization was deemed to be because of suicidality if suicidal acts or

intent was listed as a reason for admission, and/or SI was described in the admission and discharge medical notes.

Medications

The participants in the discovery cohort were all diagnosed with various psychiatric disorders (Table 1). Their psychiatric medications were listed in their electronic medical records, and documented by us 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, our discovery of differentially expressed genes was based on within-participant analyses, which factor out not only genetic background effects but also medication effects, as the participants had no major medication changes between visits. Moreover, there was no consistent pattern in any particular type of medication, or between any change in medications and SI, in the rare instances where there were changes in medications between visits.

Human blood gene expression experiments and analyses

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 previously described.[3]

Microarrays. Microarray work was carried out using previously described methodology.[4]

Analysis. We have used the participant's SI scores at the time of blood collection (0—no SI compared with 2 and above—high SI). We looked at gene expression differences between the no SI and the high SI visits, using a within-participant design, then an across-participants summation (Figure 2).

Gene expression analyses in the discovery cohort

We analyzed the data in two ways: an Absent-Present (AP) approach, and a differential expression (DE) approach, as in previous work by us on suicide biomarkers.[2,3] 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, we used Affymetrix Microarray Suite Version 5.0 (MAS5) 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, Santa Clara, CA, USA). For the DE approach, we imported all Affymetrix microarray data as .cel files into Partek Genomic Suites 6.6 software package (Partek, St Louis, MO, USA). Using only the perfect match values, we ran a robust multi-array analysis (RMA), 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 of the four diagnoses used in the study, to avoid potential artifacts due to different ranges of gene expression in different diagnoses.[5] Then, the participants normalized data were extracted from these RMAs and assembled for the different cohorts used in the study.

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 (SI) from no SI to high SI. For a comparison, if there was a change from A to P tracking a change from no SI to high SI, or a change from P to A tracking a change from high SI to no SI, that was given a score of +1 (increased biomarker in High SI). If the change was in opposite direction in the gene vs the phene (SI), that was given a score of − 1 (decreased biomarker in High SI). If there was no change in gene expression between visits despite a change of phene expression (SI), or a change in gene expression between visits despite no change in phene expression (SI), that was given a score of 0 (not tracking as a biomarker). If there was no change in gene expression and no change in SI 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, then 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. We also used a perfection bonus. If the gene expression perfectly tracked the SI in a participant that had at least two comparisons (three visits), that probeset was rewarded by a doubling of its overall score. Additionally, we used a non-tracking correction. 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.

DE analysis. For the longitudinal within-participant DE analysis, fold changes (FC) in gene expression were calculated between sequential visits within each participant. Scoring methodology was similar to that used above for AP. Probesets that had a FC $\geqslant$ 1.2 were scored +1 (increased in high SI) or − 1 (decreased in high SI). FC $\geqslant$ 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. For DE also, we used a perfection bonus and a non-tracking correction. If the gene expression perfectly tracked the SI 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.

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 and decreased probesets) received 1 point, those above 50% received 2 points and those above 80% received 4 points. For AP analyses, we have 30 probesets which received 4 points, 647 probesets with 2 points and 2596 probesets with 1 point, for a total of 3273 probesets. For DE analyses, we have 95 probesets which received 4 points, 2215 probesets with 2 points and 7520 probesets with 1 point, for a total of 9829 probesets. The overlap between the two discovery methods for probesets with an internal score of 1 is shown in Figure 2d. Different probesets may be found by the two methods due to differences in scope (DE capturing genes that are present in both visits of a comparison, that is, 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 names 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 name by NetAffyx, we used the UCSC Genome Browser to directly map them to known genes, with the following limitations: (1) in case the

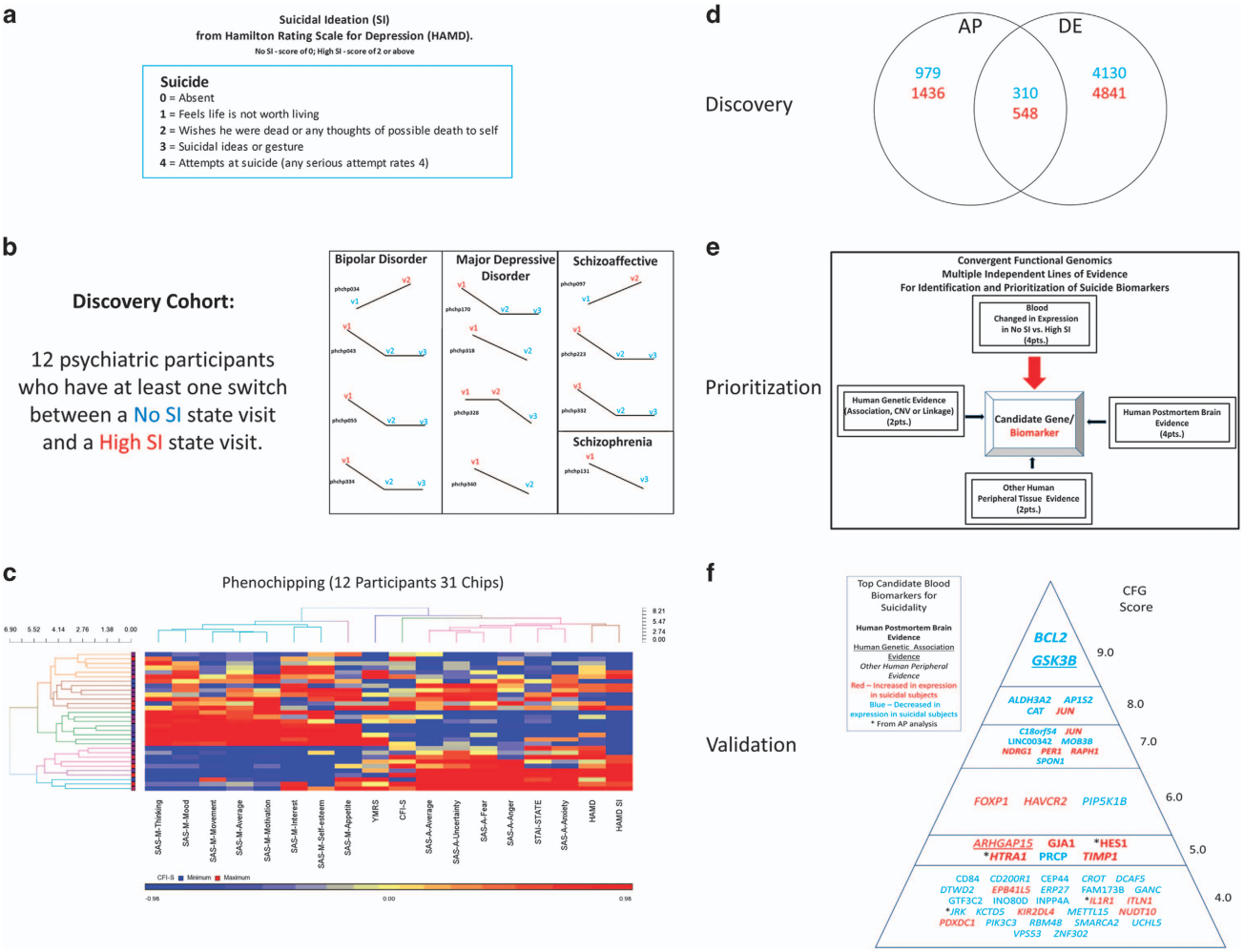


Figure 2. Biomarker discovery, prioritization and validation. Discovery cohort: longitudinal within-participant analysis. Phchp### is study ID for each participant. V# denotes visit number (1, 2 or 3). (**a**) Suicidal ideation (SI) scoring. (**b**) Participants and visits. (**c**) PhenoChipping: two-way unsupervised hierarchical clustering of all participant visits in the discovery cohort vs 18 quantitative phenotypes measuring affective state and suicidality. SASS, Simplified Affective State Scale. A—Anxiety items (Anxiety, Uncertainty, Fear, Anger, Average). M—Mood items (Mood, Motivation, Movement, Thinking, Self-esteem, Interest, Appetite, Average). STAI-STATE is State Trait Anxiety Inventory, State Subscale. YMRS is Young Mania Rating Scale. (**d**) Discovery—number of probesets carried forward from the Absent-Present (AP) and differential expression (DE) analyses, with an internal score of 1 and above. Red—increased in expression in high SI and blue—decreased in expression in high SI; (**e**) Prioritization—CFG integration of multiple lines of evidence to prioritize suicide—relevant genes from the discovery step. (**f**) Validation—Top CFG genes, with a total score of 4 and above, validated in the cohort of suicide completers. All the genes shown were significantly changed and survived Bonferroni correction in ANOVA from no SI to high SI to suicide completers.

probeset fell in an intron, that particular gene was assumed to be implicated; (2) only one gene was assigned to each probeset. Genes were then scored using our manually curated Convergent Functional Genomics (CFG) databases as described below (Figure 2).

Convergent functional genomics

Databases. We have established in our laboratory (Laboratory of Neurophenomics, Indiana University School of Medicine, www.neurophenomics.info) manually curated databases of all the human gene expression (postmortem brain, blood and cell cultures), human genetics (association, copy number variations and linkage), and animal model gene expression and genetic studies published to date on psychiatric disorders. Only the findings deemed significant in the primary publication, by the study authors, using their particular experimental design and thresholds, are included in our databases. Our 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 our CFG cross-validation and prioritization (Figure 2). For this study, data from 442 papers on suicide were present in the databases at the time of the CFG analyses (genetic studies—164, brain studies—192, peripheral fluids—86).

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

Human blood and other peripheral tissue gene expression data. Converging evidence was scored for a gene if there were published reports of human blood, lymphoblastoid cell lines, cerebrospinal fluid or other peripheral tissue data showing changes in expression of that gene or changes in protein levels

Table 1. Cohorts used in study

	Participants	*Diagnosis*	*Ethnicity*	*Age mean (s.d.)*	*T-test for age*	
Discovery cohort (within-participant changes in suicidal ideation)	12	BP = 4 MDD = 4 SZA = 3 SZ = 1	EA = 9 AA = 2 Asian = 1	All = 44.39 (11.65) No SI = 44.56 High SI = 44.15	*T-test for age between no SI and high SI 0.926*	
Independent validation cohort for gene expression (suicide completers)	6	BP = 1 MDD = 3 PTSD = 1 Non-psychiatric = 1	EA = 5 AA = 1	43.5 (14.24)		*T-test for age with discovery cohort P = 0.890*
Independent testing cohort for state predictions (suicidal ideation)	33	All BP = 17 MDD = 7 SZA = 7 SZ = 2 No SI BP = 13 MDD = 4 SZA = 6 SZ = 2 Intermediate SI BP = 3 SZA = 1 High SI BP = 3 MDD = 3 SZA = 1	EA = 26 AA = 5 Asian = 1 Mixed = 1	All = 44.05 (8.81) No SI = 43.98 High SI = 41.28	*T-test for age between no SI and high SI 0.553*	*T-test for age with discovery cohort P = 0.887*
Combined discovery and testing cohort for state (suicidal ideation) used for CFI-S analysis (Figure 3)	45	All BP = 21 MDD = 11 SZA = 10 SZ = 3 No SI BP = 17 MDD = 8 SZA = 9 SZ = 3 Intermediate SI BP = 3 SZA = 1 High SI BP = 7 MDD = 7 SZA = 4 SZ = 1	EA = 35 AA = 7 Asian = 2 Mixed = 1	All = 44.15 (9.68) No SI = 44.12 High SI = 43.15	*T-test for age between no SI and high SI 0.727*	
Testing cohort for trait predictions (future hospitalizations for suicidality)	24	All BP = 10 MDD = 9 SZA = 3 SZ = 2 No Hosp for SI BP = 8 MDD = 8 SZA = 1 SZ = 2 Hosp for SI BP = 2 MDD = 1 SZA = 2 SZ = 0	EA = 19 AA = 4 Mixed = 1	All = 46.51 (6.66) No Hosp for SI = 47.2 Hosp for SI = 43.4	*T-test for age between no Hosp for SI and Hosp for SI 0.0430*	*T-test for age with discovery cohort P = 0.354*

Abbreviation: BP, bipolar; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SZ, schizophrenia; SZA, schizoaffective disorder; SI, suicidal ideation.

in participants who had a history of suicidality or who died from suicide.

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

Table 2. Top biomarkers for suicidality in women

Gene symbol/Gene Name	*Probeset*	*Discovery (change) method/score*	*Prior human genetic evidence*	*Prior human brain expression evidence*	*Prior human peripheral expression evidence*	*Prioritization total CFG score for suicide*	*Validation ANOVA P-value*	*Predictions ROC/P-value*	*Clock function*
Best predictive biomarkers out of validated biomarkers (Bonferroni) (49 genes, 50 probesets)									
BCL2 B-cell CLL/Lymphoma 2	203684_s_at	(D) DE/2	Linkage[38]	(D) PFC[39]	(D) Blood[4]	9.00	**3.95E−06**	SI: 0.48/0.56 Hosp: 0.89/0.007	
ALDH3A2 Aldehyde dehydrogenase 3 family, member A2	202053_s_at	(D) DE/2		(I) PFC, Thalamus[40]	(D) Blood[4]	8.00	**1.62E−06**	SI: 0.63/0.14 Hosp: 0.6/0.29	
MOB3B MOB kinase activator 3B	229568_at	(D) DE/1		(I) ACC[13]	(I) Blood[4]	7.00	**4.69E−06**	SI: 0.55/0.35 Hosp: 0.85/0.015	
PER1 Period circadian clock 1	202861_at	(I) DE/1		(D) PFC[13]	(D) Blood[4]	7.00	**5.32E−12**	SI: 0.45/0.66 Hosp: 0.84/0.018	Clock Core
HAVCR2 Hepatitis A virus cellular receptor 2	1555629_at	(I) DE/4			(D) Blood[4]	6.00	**1.69E−12**	SI: 0.62/0.15 Hosp: 0.8/0.022	
ARHGAP15 Rho GTPase activating protein 15	1561489_at	(I) DE/1	Suicide [41]		(I) Blood[4]	5.00	**3.05E−06**	SI: 0.55/0.34 Hosp: 0.79/0.041	
HTRA1 HtrA serine peptidase 1	201185_at	(I) AP/1		(I) NAC [13]		5.00	**3.17E−07**	SI: 0.36/0.89 Hosp: 0.84/0.01	Clock Distant Output
EPB41L5 erythrocyte membrane protein band 4.1 like 5	229292_at	(I) DE/1	Linkage[42]		(I) Blood [4]	4.00	**4.58E−14**	**SI: 0.68/0.062** Hosp: 0.63/0.24	
GTF3C2 general transcription factor IIIC, polypeptide 2, beta 110kDa	210620_s_at	(D) DE/2			(D) Blood[4]	4.00	**1.68E−07**	SI: 0.64/0.12 Hosp: 0.81/0.05	
PDXDC1 Pyridoxal-dependent decarboxylase domain containing 1	1560013_at	(I) DE/2			(I) Blood[4]	4.00	**1.03E−05**	SI: 0.51/0.46 Hosp:0.81/0.018	
PIK3C3 Phosphatidylinositol 3-kinase, catalytic subunit type 3	232086_at	(D) DE/1	Suicide, Antidepressants [43]		(I) Blood [4]	4.00	**3.14E−08**	**SI: 0.65/0.098 Hosp: 0.9/0.011**	
Best predictive biomarkers out of top discovery and prioritization biomarkers (non-Bonferroni validated, 65 genes)									
LRRC8B Leucine-rich repeat containing 8 family, member B	212976_at	(D) DE/4		(I) PFC[44]		8.00	0.231881	SI: 0.60/0.19 Hosp: 0.69/0.14	
ACTR3 ARP3 actin-related protein 3 homolog (yeast)	213102_at	(D) DE/4	Linkage[42]		(I) Blood[4]	7.00	*0.0045239*	SI: 0.62/0.15 Hosp: 0.73/0.12	
ASPH aspartate beta-hydroxylase	242037_at	(I) DE/4			(I) Blood[4]	6.00	*0.01087*	SI: 0.65/.098 Hosp: 0.8/.022	
CSNK1A1 Casein kinase 1, alpha 1	235464_at	(D) DE/4			(D) Blood[4]	6.00	NC	SI: 0.56/0.32 **Hosp: 0.96/0.0007**	Clock Immediate Input
DPCD Deleted in primary ciliary dyskinesia homolog (mouse)	226009_at	(I) DE/4			(D) Blood [4]	6.00	NC	SI: 0.67/0.067 Hosp: 0.76/0.044	
GTF3C3 General transcription factor IIIC, polypeptide 3, 102kDa	1555439_at	(I) AP/4			(I) Blood[4]	6.00	NC	SI: 0.67/0.075 Hosp: 0.75/.067	
KLHL28 Kelch-like family member 28	220374_at	(I) AP/4			(I) Blood [4]	6.00	NC	SI: 0.64/0.11 Hosp: 0.91/0.002	
LARP4 La ribonucleoprotein domain family, member 4	214155_s_at	(D) DE/4			(D) Blood[4]	6.00	*0.014911*	SI: 0.49/0.55 Hosp: 0.9/0.005	
NUDT6 Nudix (nucleoside diphosphate linked moiety X)-type motif 6	220183_s_at	(D) AP/4			(D) Blood[4]	6.00	NC	SI: 0.62/0.16 Hosp: 0.71/0.14	
SNX27 Sorting nexin family member 27	244349_at	(I) AP/4			(I) Blood[4]	6.00	NC	SI: 0.63/0.13 Hosp: 0.85/0.015	
UIMC1 Ubiquitin interaction motif containing 1	233596_at	(I) DE/4			(I) Blood[4]	6.00	NC	SI: 0.41/0.76 Hosp: 0.86/0.006	
ZNF548 Zinc finger protein 548	1553718_at	(D) DE/4			(D) Blood[4]	6.00	*0.000461*	SI: 0.40/0.82 Hosp: 0.83/0.012	

Abbreviations: ACC, anterior cingulate cortex; AP, Absent-Present; CFG, Convergent Functional Genomics; DE, differential expression; NAC, nucleus accumbens; PFC, pre-frontal cortex; ROC, receiver-operating characteristic. The 3 best predictive markers, increased and decreased, for suicidal ideation (SI) and for hospitalizations (Hosp), from Validated group and from Top Discovery and Prioritization groups, are shown, in order of Total CFG score ($3\times2\times2\times2=24$ possible; in fact 23 as one (PIK3C3) is shared between SI and Hosp. Underlined means changed in the same direction as in prior studies in men:[2] 16 out of the 23 biomarkers listed here (70%) are co-directional in men for the exact same probeset. Evidence in human peripheral expression evidence from column from Niculescu *et al*.[4] shows direction of change of best probeset in men, not necessarily the same one as in women. Two have no prior blood evidence in the field. In validation column, bold means Bonferroni significant, italic means nominally significant. NC means non concordant stepwise. In predictions column, bold are best predictor for SI, and best predictor for future hospitalizations for suicidality (Hosp), and best overall predictor for SI and Hosp.

Table 3. Biological pathways and diseases

A.

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

B.

		Ingenuity			*GeneGO*		
	#	*Diseases and Disorders*	P-*value*	# *Molecules*	*Diseases*	*Ratio*	P-*value*
Prioritization CFG score ≥4 ($n=1471$ genes)	1	Cancer	2.25E−06–2.21E−45	1242	Mental Disorders	256/1610	1.890E−35
	2	Organismal Injury and Abnormalities	2.25E−06–2.21E−45	1242	Psychiatry and Psychology	284/1904	2.194E−34
	3	Gastrointestinal Disease	1.02E−06–5.07E−31	905	Depressive Disorder, Major	120/543	2.660E−29
	4	Reproductive System Disease	1.43E−06–2.31E−24	617	Central Nervous System Diseases	379/3060	8.770E−29
	5	Infectious Diseases	8.30E−07–1.15E−17	246	Depressive Disorder	120/557	3.125E−28
Validation Stepwise in Suicide Completers ($n=589$ genes)	1	Cancer	6.57E−04–6.34E−17	487	Breast Neoplasms	356/8894	3.727E−15

Table 3. (Continued)

B.	*Ingenuity*				*GeneGO*		
	#	*Diseases and Disorders*	*P-value*	*# Molecules*	*Diseases*	*Ratio*	*P-value*
	2	Organismal Injury and Abnormalities	6.57E−04–6.34E−17	492	Breast Diseases	356/8895	3.798E−15
	3	Gastrointestinal Disease	6.23E−04–2.76E−10	355	Psychiatry and Psychology	115/1904	2.268E−14
	4	Reproductive System Disease	6.50E−04–8.34E−09	240	Pathological Conditions, Signs and Symptoms	207/4433	1.078E−13
	5	Infectious Diseases	6.57E−04–6.95E−08	104	Mental Disorders	101/1610	1.146E−13
Validation	1	Cancer	2.36E−03–1.87E−10	325	Depressive Disorder, Major	40/543	1.045E−12
Nominally significant In Suicide	2	Organismal Injury and Abnormalities	2.47E−03–1.87E−10	330	Pathological Conditions, Signs and Symptoms	150/4433	2.002E−12
Completers ($n = 396$ genes)	3	Tumor Morphology	2.29E−03–1.17E−07	36	Depressive Disorder	40/557	2.333E−12
	4	Developmental Disorder	2.47E−03–1.40E−06	69	Breast Neoplasms	245/8894	2.770E−11
	5	Gastrointestinal Disease	2.44E−03–2.43E−06	230	Breast Diseases	245/8895	2.806E−11
Validation	1	Immunological Disease	4.03E−03–1.27E−06	14	Lymphoma, Mantle-Cell	8/196	3.430E−08
Bonferroni significant in Suicide	2	Cancer	4.15E−03–3.97E−06	42	Psychiatry and Psychology	19/1904	1.209E−07
Completers ($n = 49$ genes)	3	Dermatological Diseases and Conditions	4.03E−03–3.97E−06	10	Lymphoma, Non-Hodgkin	12/726	2.323E−07
	4	Hematological Disease	4.03E−03–3.97E−06	5	Mental Disorders	17/1610	3.079E−07
	5	Organismal Injury and Abnormalities	4.15E−03–3.97E−06	42	Leukemia, Myeloid	16/1436	3.667E−07

Abbreviations: CFG, Convergent Functional Genomics; KEGG, Kyoto Encyclopedia of Genes and Genomes. Bold values signify pathways of interest.

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 (Figure 2e), the external cross-validating lines of evidence were weighted such that findings in human postmortem brain tissue, the target organ, were prioritized over peripheral tissue findings and genetic findings, by giving them twice as many points. Human brain expression evidence was given 4 points, whereas human peripheral evidence was given 2 points and human genetic evidence was given a maximum of 2 points for association, and 1 point for linkage. Each line of evidence was capped in such a way that any positive findings within that line of evidence result in maximum points, regardless of how many different studies support that single line of evidence, to avoid potential popularity biases. In addition to our external CFG score, we also prioritized genes based upon the initial gene expression analyses used to identify them. 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) (Table 2 and Supplementary Table S2). The scoring system was decided upon before the analyses were carried out. We sought to give twice as much weight to external score as to internal in order to increase generalizability and avoid fit to cohort of the prioritized genes.[6] It has not escaped our attention that other ways of scoring the lines of evidence may give slightly different results in terms of prioritization, if not in terms of the list of genes *per se*. Nevertheless, we feel this simple scoring system provides a good separation of genes based on gene expression evidence and on independent cross-validating evidence in the field (Figure 2). In the future, with multiple large data sets, machine learning approaches could be used and validated to assign weights to CFG.

Clock gene database

We compiled a database of genes associated with circadian function, by using a combination of review papers[7,8] and searches of existing databases CircaDB (http://circadb.hogeneschlab.org), GeneCards (http://www.genecards.org) and GenAtlas (http://genatlas.medecine.univ-paris5.fr). Using the data we compiled from these sources we identified a total of 1468 genes that show circadian functioning. We further classified genes into 'core' clock genes, that is, those genes that are the main engine driving circadian function ($n = 18$), 'immediate' clock genes, that is, the genes that directly input or output to the core clock ($n = 331$) and 'distant' clock genes, that is, genes that directly input or output to the immediate clock genes ($n = 1119$).

Pathway analyses

IPA (Ingenuity Pathway Analyses, version 24390178, Qiagen, Hilden, Germany), GeneGO MetaCore (Thompson Reuters, New York, NY, USA) and KEGG (Kyoto Encyclopedia of Genes and Genomes) (through the Partek Genomics Suite 6.6 software package) were used to analyze the biological roles, including top canonical pathways, and diseases, of the candidate genes resulting from our work, as well as to identify genes in our data set that are the target of existing drugs (Table 3 and Supplementary Tables S4 and S5). We ran the pathway analyses together for all the AP and DE probesets with a total CFG score of $\geqslant 4$, then for those of them who showed stepwise change in the suicide completers validation cohort, then for those of them who were nominally significant and finally for those of them who survived Bonferroni correction (Table 3).

Validation analyses

For the AP analyses, we imported the Affymetrix microarray .chp data files from the participants in the validation cohort of suicide

completers into MAS5 Affymetrix Expression Console, alongside the data files from the participants in the discovery cohort, to compare expression levels of biomarkers in the validation cohort with those in the no SI and high SI groups in the discovery cohort. We then transferred the AP data to an Excel sheet and transformed A into 0, M into 0.5 and P into 1.

For the DE analyses, we imported Affymetrix microarray .cel files from the participants in the validation cohort of suicide completers into Partek Genomic Suites. We then ran an RMA, background corrected with quantile normalization, and a median polish probeset summarization of all the chips from the validation cohort to obtain the normalized expression levels of all probesets for each chip. Partek normalizes expression data into a log base of 2 for visualization purposes. We non-logtransformed expression data by taking 2 to the power of the transformed expression value. We then used the non-logtransformed expression data to compare expression levels of biomarkers in the validation cohort with those in the no SI and high SI groups in the discovery cohort. We then transferred the expression data to an Excel sheet.

For validation analyses of our candidate biomarker genes, we examined which of the top candidate genes (Total CFG score of 4 or above), separately from AP and from DE, were stepwise changed in expression from the no SI group to the high SI group to the suicide completers group. We used an empirical cutoff of 33.3% of the maximum possible CFG score of 12, which also permits the inclusion of potentially novel genes with maximal internal score but no external evidence score. We imported the Excel sheets with the raw expression data from AP and 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 (stepwise and non-stepwise).

Clinical measures

The SASS is an 11-item scale for measuring mood and anxiety, previously developed and described by us.[4,9] The SASS has a set of 11 visual analog scales (7 for mood and 4 for anxiety) that ends up providing a number ranging from 0 to 100 for mood state, and the same for anxiety state. We have developed an Android app version (Supplementary Figure S2).

CFI-S (Figure 3 and Supplementary Figure S2) is a 22-item scale and Android app for suicide risk,[4] which integrates, in a simple binary manner (Yes—1 and 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.[10,11] The scale was administered at participant testing visits ($n = 39$), or scored based on retrospective electronic medical record information and Diagnostic Interview for Genetic Testing information ($n = 48$). When information was not available for an item, it was not scored (NA).

Combining gene expression biomarkers and clinical measures

The Universal Predictor for Suicide (UP-Suicide) construct, our primary end point, was decided upon as part of our apriori study design to be broad spectrum, and combine our top Bonferroni validated biomarkers with the phenomic (clinical) markers (SASS and CFI-S). It is calculated as the average of three increased markers (BioM-18 averaged increased Bonferroni biomarkers, Anxiety, CFI-S) minus the average of two decreased markers (BioM-32 averaged decreased Bonferroni biomarkers, Mood). All individual markers are Z-scored by diagnosis, to account for different ranges and be able to combine them into a composite predictor.

Testing analyses

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

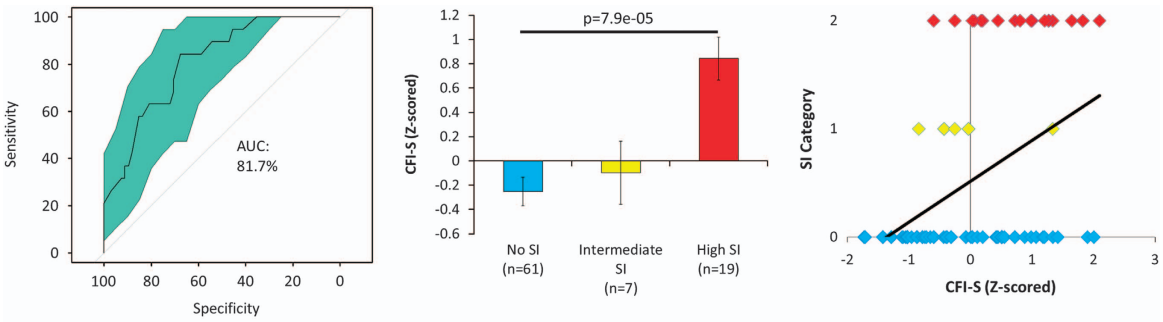
Predicting SI. Receiver-operating characteristic (ROC) analyses between genomic and phenomic marker levels and SI were performed by assigning participants with an HAMD-SI score of 2 and greater into the high SI category. We used the pROC function of the R-studio. We used the z-scored biomarker and app scores, 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 (Table 4 and Figure 4).

Predicting future hospitalizations for suicidality. We conducted analyses for hospitalizations in the years following testing (on average 2.75 years, range 0.3–7.5 years; see Supplementary Table S1). For each participant in the test cohort for future hospitalizations, the study visit with highest levels for the marker or combination of markers was selected as index visit (or with the lowest levels, in the case of decreased markers). ROC analyses between genomic and phenomic marker levels and future hospitalizations were performed as described above, based on assigning if participants had been hospitalized for suicidality (ideation, attempts) or not following the index testing visit. Additionally, a one tailed *t*-test with unequal variance was performed between groups of participants with and without hospitalizations for suicidality. Pearson *R* (one-tail) correlation was performed between hospitalization frequency (number of hospitalizations for suicidality divided by duration of follow-up) and marker scores. We conducted correlation analyses for hospitalizations frequency for all future hospitalizations due to suicidality as this calculation, unlike the ROC and *t*-test, accounts for the actual length of follow-up at our VA, which varied from participant to participant. The ROC and *t*-test might in fact, if anything, underrepresent 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.

RESULTS

Discovery of biomarkers for SI

We conducted whole-genome gene expression profiling in the blood samples from a longitudinally followed cohort of female participants with psychiatric disorders that predispose to suicidality. The samples were collected at repeated visits, 3–6 months apart. State information about SI was collected from a questionnaire (HAMD) administered at the time of each blood draw (Supplementary Table S1). Out of 51 female psychiatric participants (with a total of 123 visits) followed longitudinally in our study, with a diagnosis of BP, MDD, schizophrenia and schizoaffective disorder, there were 12 participants that switched from a no SI (SI score of 0) to a high SI state (SI score of 2 and above) at different visits, which was our intended discovery group (Figure 2). We used a powerful within-participant design to analyze data from these 12 participants and their 31 visits. A within-participant design factors out genetic variability, as well as



Predictor	ROC AUC	AUC p-value	ANOVA	Correlation R	Correlation p-value
CFI-S	0.817	1.29e-05	7.9e-5	0.441	9.35e-06

CFI-S Item	Description	Correct direction	T-test (one tailed) High SI vs. No SI p-value
16	**Chronic stress: lack of positive relationships, social isolation**	**Y**	**0.0040**
12	**Current substance abuse**	**Y**	**0.0071**
17	**History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)**	**Y**	**0.0147**
14	**Lack of religious beliefs**	**Y**	**0.0175**
13	**Past history of suicidal acts/gestures**	**Y**	**0.0253**
15	**Acute stress: Rejection (within last 3 months)**	**Y**	**0.0294**
20	**History of command hallucinations of self-directed violence**	**Y**	**0.0453**
10	Dissatisfaction with life at this moment in time	Y	*0.0583*
8	Chronic stress: perceived uselessness, not feeling needed, burden to extended kin.	Y	*0.0635*
4	Personally knowing somebody who committed suicide	Y	*0.0733*
7	Acute stress: Losses, grief (within last 3 months)	Y	*0.0748*
3	Family history of suicide in blood relatives	Y	0.1422
21	Age: Older >60 or Younger <25	Y	0.2374
2	With poor treatment compliance	Y	0.2477
6	Acute/severe medical illness, including acute pain ("I just can't stand this pain anymore.") (within last 3 months)	Y	0.2714
5	History of abuse: physical, sexual, emotional, neglect	Y	0.3348
9	History of excessive introversion, conscientiousness (including planned suicide attempts)	Y	0.3388
18	Lack of coping skills when faced with stress (cracks under pressure)	Y	0.3723
19	Lack of children. If has children, not in touch /not helping take care of them.	N	0.0714
1	Psychiatric illness diagnosed and treated	All have dx	All have dx
11	Lack of hope for the future	No difference	1
22	Gender: Male	All females	All females

Figure 3. Convergent Functional Information for Suicide (CFI-S) scale testing in women. Prediction of high suicidal ideation in women in a larger cohort that combines the discovery and test cohorts used for biomarker work. CFI-S was developed independently of any data from this study, by compiling known socio-demographic and clinical risk factors for suicide. It is composed of 22 items that assess the influence of mental health factors, as well as of life satisfaction, physical health, environmental stress, addictions, cultural factors known to influence suicidal behavior, and two demographic factors, age and gender. Table depicts individual items and their ability to differentiate between no SI and high SI.

some medications, lifestyle and demographic effects on gene expression, permitting identification of relevant signal with Ns as small as 1.[12] Another benefit of a within-participant design may be accuracy/consistency of self-report of psychiatric symptoms ('phene expression'), similar in rationale to the signal detection benefits it provides in gene expression.

For discovery, we used two methodologies: Absent/Present (reflecting on/off of transcription) and Differential Expression (reflecting more subtle gradual changes in expression levels). The genes that tracked SI in each participant were identified in our analyses. We used three thresholds for increase in expression genes and for decrease in expression genes: $\geqslant$33.3% (low), $\geqslant$50% (medium) and $\geqslant$80% (high) of the maximum scoring increased and decreased gene across participants. Such a restrictive approach was used as a way of minimizing false positives, even at the risk of having false negatives. For example, there were genes on each of the two lists, from AP and DE analyses, that had clear prior evidence for involvement in suicidality, such as AKAP10 (ref. 13) (31.7%) and MED28 (ref. 13) (31.8%) from AP, and S100B[13,14] (31.7%) and SKA2 (ref. 15) (31.4%) for DE, but were not included in our subsequent analyses because they did not meet our apriori set 33.3% threshold. Notably, SKA2 reproduces our results in males,[2] as well as the work from Kaminsky and colleagues.[15,16]

Prioritization of biomarkers based on prior evidence in the field

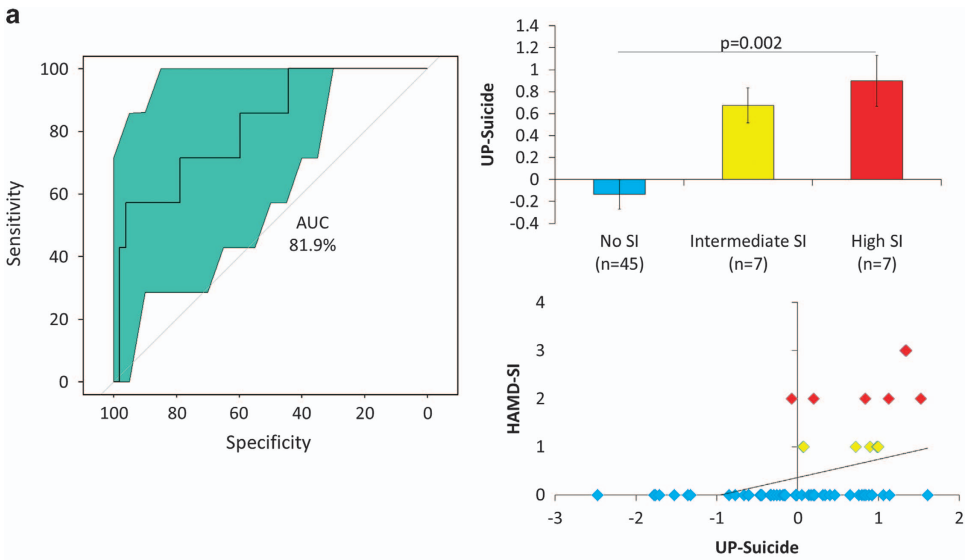
These differentially expressed genes were then prioritized using a Bayesian-like CFG approach (Figure 2) integrating all the

Table 4. Prediction of suicidal ideation and future hospitalizations for suicidality

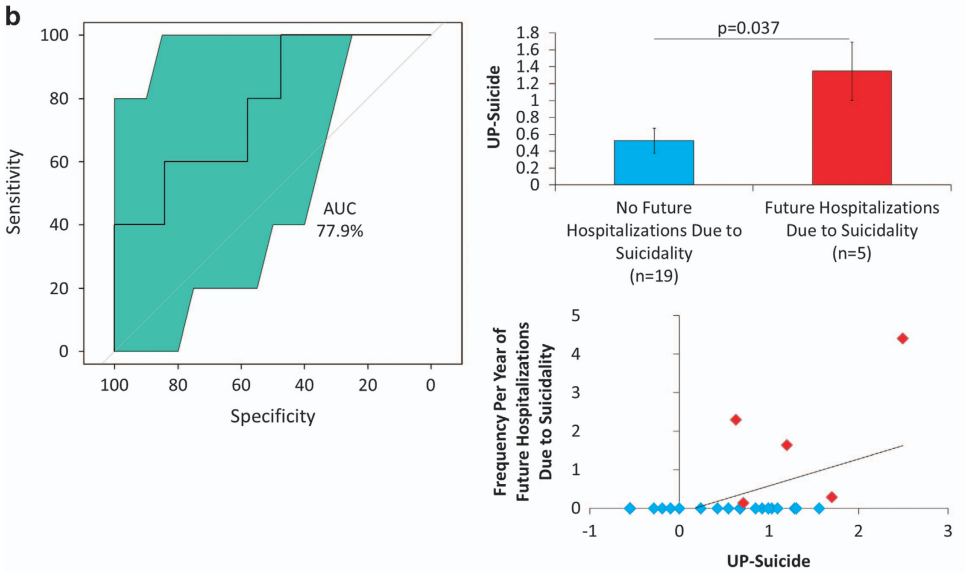
	Marker	*Participants with high SI/Participants total*	*ROC AUC/P-value*	*Pearson's Correlation R/P-value*	*Student's t-test P-value*
Suicidal ideation independent cohort, n = 33					
Best blood biomarker predictors	Out of validated biomarkers (Bonferroni) (49 genes, 50 probesets)				
	EPB41L5	7|33	*0.68/0.06*	**0.22/0.03**	*0.09*
	HAVCR2	7|33	0.62/0.15	*0.17/0.07*	0.18
	ARHGAP15	7|33	0.55/0.34	0.12/0.15	0.22
	PIK3C3	7|33	0.65/0.1	**−0.21/0.037**	*0.08368*
	GTF3C2	7|33	0.64/0.115	−0.11/0.179	*0.07208*
	ALDH3A2	7|33	0.62/0.142	**−0.21/0.036**	0.1421
	Out of top discovery and prioritization biomarkers (Non-Bonferroni Validated, 65 genes)				
	DPCD	7|33	*0.67/0.07*	**0.21/0.04**	0.12
	GTF3C3	7|33	*0.67/0.07*	**0.23/0.02**	0.11
	ASPH	7|33	0.65/0.1	0.07/0.27	0.13
	ACTR3	7|33	0.62/0.15	**−0.19/0.05**	0.13
	NUDT6	7|33	0.62/0.15	−0.07/0.27	0.19
	LRRC8B	7|33	0.60/0.19	**−0.15/0.11**	0.13
	Panels of Validated Biomarkers (Increased, Decreased, Combined)				
	BioM-18	7|33	0.37/0.87	0.032/0.39	0.59
	BioM-32	7|33	0.43/0.72	−0.0031/0.49	0.68
	BioM-50	7|33	0.5/0.515	0.02/0.429	0.465
Clinical measures	**Anxiety**	7|33	**0.72/0.029**	**0.26/0.011**	**0.0083**
	Mood	7|33	**0.78/0.0078**	**−0.37/0.0006**	**0.002**
	SASS	7|33	**0.81/0.0035**	**0.38/0.0005**	**5.04E-05**
	CFI-S	7|29	**0.84/0.002**	**0.39/0.0013**	**0.003**
	CFI-S + SASS	7|29	**0.87/0.00088**	**0.48/0.0001**	**0.00027**
Combined	**UP-Suicide**	7|29	**0.82/0.003**	**0.43/0.0003**	**0.001467**

	Marker	*Participants hospitalized for suicidality/ participants hospitalized total*	*ROC AUC/P-value*	*Pearson's correlation R/ P-value*	*Student's t-test P-value*	*Cox regression hazard ratio*	*Cox regression P-value*
Future hospitalizations for suicidality cohort, n = 24 participants							
Best Blood Biomarker Predictors	Out of Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)						
	HTRA1	5|24	**0.84/0.01**	**0.62/0.00058**	**0.02**	**4.55**	**0.01**
	PER1	4|24	**0.84/0.018**	**0.39/0.029**	**0.1314**	1.535	0.1615
	PDXDC1	5|24	**0.81/0.018**	**0.64/0.0004**	**0.04187**	**2.4436**	**0.01503**
	PIK3C3	3|24	**0.9/0.011**	−0.25/0.115	**0.02583**	5.995	0.12
	BCL2	4|24	**0.89/0.007**	**−0.35/0.047**	**0.05385**	**3.0848**	**0.01**
	MOB3B	4|24	**0.85/0.015**	**−0.34/0.053**	**0.000462**	*9.572*	*0.09*
	Out of top discovery and prioritization biomarkers (Non-Bonferroni Validated, 65 genes)						
	KLHL28	5|24	**0.91/0.002**	**0.50/0.007**	**0.003**	**7.36**	**0.04**
	UIMC1	5|24	**0.86/0.006**	0.40/0.08	**0.04**	**2.26**	**0.03**
	SNX27	4|24	**0.85/0.02**	0.73/2.5E-05	**0.05**	**4.27**	**0.01**
	CSNK1A1	4|24	**0.96/0.0007**	−0.27/0.10	**0.0007**	**620.5**	**0.02**
	LARP4	4|24	**0.9/0.005**	−0.3/0.08	**6.30E-05**	37.01	0.11
	ZNF548	5|24	**0.83/0.012**	−0.31/0.07	**0.008**	**15.94**	**0.02**
	Panels of validated biomarkers (increased, decreased, combined)						
	BioM-18	4|24	**0.88/0.0088**	**0.46/0.011**	**0.033**	**27.6**	**0.021**
	BioM-32	4|24	0.71/11	−0.34/0.053	0.16	10.57	0.23
	BioM-50	5|24	**0.94/0.002**	**0.54/0.003**	**0.005813**	**89.459**	**0.02**
Clinical measures	**Anxiety**	4|24	**0.86/0.01**	**0.44/0.01**	**0.0039**	*14.4*	*0.061*
	Mood	3|24	0.68/0.18	−0.22/0.16	0.22	33.4	0.1
	SASS	4|24	**0.83/0.02**	**0.39/0.03**	**0.034**	*3.72*	*0.066*
	CFI-S	3|24	0.5/0.52	0.24/0.12	0.38	1.17	0.79
	CFI-S + SASS	4|24	*0.74/0.08*	**0.40/0.03**	*0.083*	*4.68*	*0.06*
Combined	**UP-Suicide**	5|24	**0.78/0.032**	**0.51/0.006**	**0.03691**	**9.6068**	**0.01**

Abbreviations: AUC, area under the curve; CFI-S, Convergent Functional Information for Suicidality; ROC, receiver-operating characteristic; SASS, Simplified Affective State Scale; SI, suicidal ideation. Top predictive biomarkers ($n = 23$) from Table 2 are shown, out of the total tested ($n = 115$) from Supplementary Table S2. Also shown are predictions by the panels of Bonferroni validated biomarkers, by the clinical measures/apps and by the combined genomic and clinical predictor, UP-Suicide, for a total of $n = 124$ predictors tested. UP-Suicide is composed of the panels of increased and decreased validated biomarkers (BioM-18 and BioM-32), along with clinical measures app scores from CFI-S and from SASS (Mood and Anxiety). Red—increased marker and blue—decreased marker. Bold—nominally significant. Italic—trend towards significance. *T*-tests are between high SI and no SI, and between hospitalized for suicidality vs not hospitalized for suicidality.



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



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

Figure 4. UP-Suicide predicting suicidal ideation in the independent test cohort, and predicting future hospitalizations due to suicidality. UP-Suicide is composed of the 50 Bonferroni validated biomarkers along with CFI-S scores and SASS (Mood and Anxiety scores). *n* = number of testing visits. (**a**) *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. *Bottom right:* Scatter plot depicting HAMD-SI score on the Y axis and UP-Suicide score on the X axis with linear trend line. *Bottom*: Table summarizing descriptive statistics. (**b**) *Top 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. *Bottom right:* Scatter plot depicting frequency of future hospitalizations due to suicidality on the Y axis and UP-Suicide score on the X axis with linear trend line. *Bottom*: Table summarizing descriptive statistics.

previously published human genetic evidence, postmortem brain gene expression evidence and peripheral fluids evidence for suicide in the field available at the time of our analyses (September 2015). This is a way of identifying and prioritizing disease relevant genomic biomarkers, extracting generalizable signal out of potential cohort-specific noise and genetic heterogeneity. We have built in our laboratory manually curated databases of the psychiatric genomic and proteomic literature to date, for use in CFG analyses. The CFG approach is thus a *de facto* field-wide collaboration. We use in essence, in a Bayesian manner, the whole body of knowledge in the field to leverage findings from our discovery data sets.

Validation of biomarkers for behavior in suicide completers

For validation in suicide completers, we used 1471 genes that had a CFG score of 4 and above, from AP and DE, reflecting either maximum internal score from discovery or additional external literature cross-validating evidence. Out of these, 882 did not show any stepwise change in suicide completers (NC, non-concordant). As such, they may be involved primarily in ideation and not in behavior (Supplementary Table S5). The remaining 589 genes (40.0%) had levels of expression that were changed stepwise from no SI to high SI to suicide completion. In all, 396 of these genes (26.9%) were nominally significant, and 49 genes (50 probesets—two for JUN) (3.33%) survived Bonferroni correction for multiple comparisons (Figure 2f). These genes are likely involved in SI and suicidal behavior. (A person can have SI without suicidal behavior, but cannot have suicidal behavior without SI.)

Selection of biomarkers for testing of predictive ability

For testing, we decided apriori to focus on the Bonferroni validated biomarkers (49 genes, 50 probesets). We also examined in a secondary analysis the top scoring biomarkers from both discovery and prioritization (65 genes), so as to avoid potential false negatives in the validation step due to possible postmortem artifacts or extreme stringency of statistical cutoff (Supplementary Figure S1). The top CFG scoring genes after the Bonferroni validation step were BCL2 and GSK3B. The top CFG scoring genes from the discovery and prioritization steps were FAM214A, CLTA, HSPD1 and ZMYND8. Notably, all have co-directional gene expression changes evidence in brains of suicide completers in studies from other groups (Figure 2, Table 2 and Supplementary Table S2).

Biological understanding

We also sought to understand the biology represented by the biomarkers identified by us, and derive some mechanistic and practical insights. We conducted: (1) unbiased biological pathway analyses and hypothesis-driven mechanistic queries, (2) overall disease involvement and specific neuropsychiatric disorders queries and (3) overall drug modulation along with targeted queries for omega-3, lithium and clozapine (Table 3 and Supplementary Tables S3 and S4). Administration of omega-3s in particular may be a mass-deployable therapeutic and preventive strategy.[18,19]

The sets of biomarkers identified have biological roles in inflammation, neurotrophins, inositol signaling, stress response, and perhaps overall the switch between cell survival and proliferation vs apoptosis (Table 3 and Supplementary Table S5).

We also examined evidence for the involvement of these biomarkers for suicidality in other psychiatric disorders, permitting us to address issues of context and specificity (Supplementary Table S3). FAM214A, MOB3B, ZNF548 and ARHGAP35 seem to be relatively specific for suicide, based on the evidence to date in the field. BCL2, GSK3B, HSPD1 and PER1 are less specific for suicide, having equally high evidence for involvement in suicide and in other psychiatric disorders.

These boundaries and understanding will likely change as additional evidence in the field accumulates. For example, HSPD1, discovered in this work as a top biomarker increased in expression in suicidality, is also increased in expression in the blood following anti-depressant treatment,[20,21] and thus might be a useful biomarker for treatment-emergent suicidal ideation.

A number of the genes are changed in expression in opposite direction in suicide in this study vs high mood in our previous mood biomarker study[22]—SSBP2, ZNF596 (Supplementary Table S3), suggesting that suicidal participants are in a low mood state. Also, some of the top suicide biomarkers are changed in expression in the same direction as in high psychosis participants in a previous psychosis biomarker study of ours[23]—HERC4, PIP5K1B, SLC35B3, SNX27, KIR2DL4 and NUDT10 (Supplementary Table S3), suggesting that suicidal participants may be in a psychosis-like state. Taken together, the data indicate that suicidality could be viewed as a psychotic dysphoric state. This molecularly informed view is consistent with the emerging clinical evidence in the field.[24]

A number of top biomarkers identified by us have biological roles that are related to the core circadian clock (such as PER1), or modulate the circadian clock (such as CSNK1A1), or show at least some circadian pattern (such as HTRA1). To be able to ascertain all the genes in our data set that were circadian and do estimates for enrichment, we compiled from the literature a database 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 our 49 Bonferroni validated biomarker genes, 7 had circadian evidence (14.3%) (Supplementary Table S3), suggesting a two-fold enrichment for circadian genes. Circadian clock abnormalities are related to mood disorders,[8,25] and sleep abnormalities have been implicated in suicide.[26]

Finally, we conducted biological pathway analyses on the genes that, after discovery and prioritization, were stepwise changed in suicide completers ($n = 882$) and may be involved in ideation *and* behavior, vs those that were not stepwise changed ($n = 589$), and that may only be involved in ideation (Supplementary Table S5). The genes involved in ideation map to pathways related to PI3K signaling. The genes involved in behavior map to pathways related to glucocorticoid receptor signaling. This is consistent with ideation *without* behavior being related to neurotrophic factors, and ideation *with* behavior being related to stress.

Clinical information

We used a simple new 22-item scale and app for suicide risk, CFI-S, which scores in a simple binary manner and integrates information about known life events, mental health, physical health, stress, addictions and cultural factors that can influence suicide risk.[10,4,11] Clinical risk predictors and scales are of high interest in the military[27] and in the general population at large.[28] Our scale aims for comprehensiveness, simplicity and quantification similar to a polygenic risk score, and may provide context to the blood biomarker signals. We analyzed which items of the CFI-S scale were the most significantly different between no and high SI live participants (Figure 3). We identified seven items that were significantly different: lack of positive relationships/social isolation ($P = 0.004$), substance abuse ($P = 0.0071$), history of impulsive behaviors ($P = 0.015$), lack of religious beliefs ($P = 0.018$), past history of suicidal acts/gestures ($P = 0.025$), rejection ($P = 0.029$) and history of command auditory hallucinations ($P = 0.045$). Social isolation increases vulnerability to stress, which is independently consistent with our biological marker results.

We also used an 11-item scale for measuring mood and anxiety, the SASS.[4] The SASS is a set of 11 visual analog scales (7 for mood and 4 for anxiety) that ends up providing a number ranging from 0 to 100 for mood state, and the same for anxiety state.

Testing for predictive ability

The best single increased (risk) biomarker predictor for SI state is EPB41L5 (ROC area under the curve (AUC) 0.68, *P*-value 0.06; Pearson Correlation 0.22, *P*-value 0.03), an increase in expression, Bonferroni validated biomarker (Tables 2 and 4). This biomarker was also identified co-directionally in our previous male work,[4] and has no evidence for involvement in other psychiatric disorders. The best single decreased (protective) biomarker predictor for SI is PIK3C3 (ROC AUC 0.65, *P*-value 0.1; Pearson Correlation −0.21, *P*-value 0.037), a decrease in expression,

Bonferroni validated biomarker (Tables 2 and 4). PIK3C3 is also decreased in expression in postmortem brains in depression.[29]

The best single increased (risk) biomarker predictor for future hospitalizations for suicidality is HTRA1 (ROC AUC 0.84, *P*-value 0.01; Cox regression hazard ratio 4.55, *P*-value 0.01), an increase in expression, Bonferroni validated biomarker (Tables 2 and 4). HTRA1 is also increased in expression in the blood of schizophrenics.[30] The best single decreased (protective) biomarker predictor for future hospitalizations for suicidality is CSNK1A1 (ROC AUC 0.96, *P*-value 0.0007; Cox Regression Hazard Ratio 620.5, *P*-value 0.02), a top discovery and prioritization, non-Bonferroni validated biomarker (Tables 2 and 4). This biomarker was also identified co-directionally in our previous male work.[4] CSNK1A1 (casein kinase 1, alpha 1) is a circadian clock gene, part of the input into the core clock. It is decreased in expression in suicidality in our work, and decreased in postmortem brains of alcoholics.[31] Interestingly, it is increased in expression by mood stabilizers[32] and by omega-3 fatty acids.[33] PIK3C3 is also a good predictor for future hospitalizations for suicidality (ROC AUC 0.9, *P*-value 0.011).

BCL2, the top CFG scoring biomarker from validation, has good accuracy at predicting future hospitalizations for suicidality (ROC AUC 0.89, *P*-value 0.007; Cox regression hazard ratio 3.08, *P*-value 0.01). The panel of 50 validated biomarkers, BioM-50, had even better accuracy at predicting future hospitalizations for suicidality (ROC AUC 0.94, *P*-value 0.002; Cox regression hazard ratio 89.46, *P*-value 0.02). Overall, in women, blood biomarkers seemed to perform better for predicting future hospitalizations for suicidality (trait) than for predicting SI (state). This is different from the trend we saw in men,[4] where blood biomarkers were somewhat better predictors of state than of trait. These gender differences are interesting, and merit exploration in additional future comparative studies.

CFI-S has very good accuracy (ROC AUC 0.84, *P*-value 0.002; Pearson Correlation 0.39, *P*-value 0.001) at predicting SI in psychiatric participants across diagnostic groups. The other app, SASS, also has very good accuracy (ROC AUC 0.81, *P*-value 0.003; Pearson Correlation 0.38, *P*-value 0.0005) at predicting SI in women psychiatric participants. The combination of the apps is synergistic (ROC AUC 0.87, *P*-value 0.0009; Pearson Correlation 0.48, *P*-value 0.0001). Thus, even without the benefit of potentially more costly, invasive and labor intensive blood biomarker testing, clinically useful predictions could be made with the apps.

Our apriori primary end point was a combined universal predictor for suicide (UP-Suicide), composed of the scores in CFI-S and in SASS (Mood, Anxiety), along with the Bonferroni validated biomarkers ($n = 50$) resulting from the sequential discovery for ideation, prioritization with CFG, and validation for behavior in suicide completers steps. UP-Suicide is a good predictor of SI (ROC AUC 0.82, *P*-value 0.003; Pearson Correlation 0.43, *P*-value 0.0003) (Table 4 and Figure 4). UP-Suicide also has good predictive ability for future psychiatric hospitalizations for suicidality (ROC AUC 0.78, *P*-value 0.032; Cox Regression Hazard Ratio 9.61, *P*-value 0.01). Overall, while there may *post hoc* appear to be better individual predictors for SI and for future hospitalizations (Table 4), our apriori primary broad-spectrum end point (UP-Suicide) has been successful, may be more robust to effects of fit to cohort, and might be more generalizable to other populations.

DISCUSSION

We carried out systematic studies to identify clinically useful predictors for suicide in women, an understudied population to date. Our work focuses on identifying markers involved in SI *and* suicidal behavior, including suicide completion. Markers involved in behavior may be on a continuum with some of the markers involved in ideation, varying in the degree of expression changes from less severe (ideation) to more severe (behavior). One cannot have suicidal behavior without SI, but it may be possible to have SI without suicidal behavior.

As a first step, we sought to use a powerful but difficult to conduct within-participant design for discovery of blood biomarkers. Such a design is more informative than case–control, case–case or even identical twins designs. The power of a within-participants longitudinal design for multi-omic discovery was first illustrated by Snyder and colleagues[12] in a landmark paper with an $n = 1$. We also have previously demonstrated its power in an initial pilot study in male bipolar participants ($n = 9$ out of 75 showed a switch from a no suicidal ideation to a high suicidal ideation state),[3] and then a larger studies in males with major psychiatric disorders ($n = 37$ out of 217).[4] In this small ($n = 12$ out of 51) but very valuable pilot study in women, we followed a similar path.

Second, we conducted whole-genome gene expression discovery studies in the participants that exhibited the switches, using a longitudinal within-participant design, that factors out genetic variability and reduces environmental variability as well. We have demonstrated the power of such a design in our earlier successful pilot work on suicide biomarkers in men with an $n = 9$.[3] Our current $n = 12$ is comparable (Figure 2). Genes whose levels of expression tracked SI within each participant were identified.

Third, the lists of top candidate biomarkers for SI from the discovery and prioritization step (genes with a CFG score of 4 and above, reflecting genes that have maximal experimental internal evidence from this study and/or additional external literature cross-validating evidence) were additionally validated for involvement in suicidal behavior in a cohort of demographically matched suicide completers from the coroner's office ($n = 6$) (Figure 2).

We ended up with 50 biomarkers that survived Bonferroni correction (49 genes; one gene, JUN, had two different probesets that validated). Additionally, we tested 65 other biomarkers that were non-Bonferroni validated but had maximum internal score of 4 in discovery *and* a CFG score of 6 and above, which means that in addition to strong evidence in this study they also had prior independent evidence of involvement in suicide from other studies. These additional biomarkers are likely involved in suicide but did not make our Bonferroni validation cutoff due to its stringency or potential technical/postmortem artifact reasons (Table 2 and Supplementary Table S2).

Fourth, we describe the use in a female population of the simple and comprehensive phenomic (clinical) risk assessment scale, CFI-S scale,[4] as well as of the companion app to it for use by clinicians and individuals (Supplementary Figure S2). CFI-S was developed independently of any data from this study, by integrating known risk factors for suicide from the clinical literature. It has a total of 20 items (scored in a binary manner—1 for present, 0 for absent, NA for information not available) 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. It also has two demographics risk factors items: age and gender. The result is a simple polyphenic risk score with an absolute range of 0–22, normalized by the number of items on which we had available information, resulting in a score in the range from 0 to 1 (Figure 3 and Supplementary Figure S2). We present data validating the CFI-S in women, in the combined discovery and test cohort of live psychiatric participants (Figure 3). We identified the chronic stress of lack of positive relationships/social isolation as the top differential item between no and high SI in women, which is consistent with biological data from the biomarker side of our study.

Fifth, we also assessed anxiety and mood, using a visual analog SASS, previously described by us,[4,9] for which we now have developed an app version (Supplementary Figure S2). Using a PhenoChipping approach[9] in our discovery cohort of psychiatric participants, we show that anxiety measures cluster with SI and CFI-S, and mood measures are in the opposite cluster, suggesting that our participants have high SI when they have high anxiety

Table 5. Cross-prediction in the other gender

Gene symbol/Gene Name	*Probesets*	*Males Discovery (direction of change) method/internal score (%)*	*Males Participants tested with suicidality/total*	*Males Predictions ROC/P-value*	*Females Discovery (direction of change) method/internal score (%)*	*Females Participants tested with suicidality/total*	*Females Predictions ROC/P-value*
Top biomarkers from males that were co-directional in females							
SLC4A4 Solute carrier family 4 (sodium bicarbonate cotransporter), member 4	210739_x_at	(I) AP/2 (71%)	SI: 33 | 108 Hosp: 32 | 157	**SI: 0.72/2.41E-05** Hosp: 0.44/0.87	(I) DE/0 (20%)	SI: 7 | 33 Hosp: 3 | 24	SI: 0.62/0.15 **Hosp: 0.86/0.03**
SKA2 Spindle and kinetochore associated complex subunit 2	225686_at	(D) DE/1 (34%) AP/1 (42%)	SI: 33 | 108 Hosp: 32 | 157	**SI: 0.69/0.0002** Hosp: 0.46/0.75	(D) DE/0 (6%)	SI: 7 | 33 Hosp: 3 | 24	SI: 0.50/0.51 *Hosp: 0.78/0.07*
Top biomarkers from females that were co-directional in males							
PIK3C3 Phosphatidylinositol 3-kinase, catalytic subunit type 3	232086_at	(D) DE/0 (14%)	SI: 33 | 108 Hosp: 32 | 157	**SI: 0.62/0.01** Hosp: 0.5/0.49	(D) DE/1 (49%)	SI: 7 | 33 Hosp: 3 | 24	*SI: 0.65/0.098* **Hosp: 0.9/0.011**
CSNK1A1 Casein kinase 1, alpha 1	235464_at	(D) AP/0 (21%)	SI: 33 | 108 Hosp: 31 | 157	**SI: 0.63/0.007** Hosp: 0.5/0.53	(D) DE/4 (86%) AP/1 (36%)	SI: 7 | 33 Hosp: 3 | 24	SI: 0.56/0.316 **Hosp: 0.96/0.0007**

Abbreviations: AP, Absent-Present; DE, differential expression; ROC, receiver-operating characteristic; SI, suicidal ideation. Examples of top predictive biomarkers of interest from men[2] and from women (current study) that were changed in expression in the same direction in both genders. These biomarkers were discovered in just one gender, as they were in the other gender below the apriori set threshold for discovery (33.3%). However, they display ability to predict in the other gender as well. SI—predicting suicidal ideation. Hosp—predicting future hospitalizations for suicidality. Bold—*P*-value is significant. Italic—trend towards significance.

and low mood (Figure 2). We would also like to include in the future measures of psychosis, and of stress, to be more comprehensive.

Sixth, we examined how the biomarkers identified by us are able to predict *state* (SI) in a larger independent cohort of women psychiatric participants ($n = 33$ participants).

Seventh, we examined whether the biomarkers are able to predict *trait* (future hospitalizations for suicidal behavior) in women psychiatric participants ($n = 24$).

Last but not least, we demonstrate how our apriori primary end point, a comprehensive universal predictor for suicide (UP-Suicide), composed of the combination of the Bonferroni validated biomarkers ($n = 50$), along with the scores from CFI-S and SASS, predicts state (SI) and trait (future psychiatric hospitalizations for suicidality).

The rationale for identifying blood biomarkers as opposed to brain biomarkers is a pragmatic one—the brain cannot be readily accessed in live individuals. Other peripheral fluids, such as cerebrospinal fluid, require more invasive and painful procedures. Nevertheless, it is likely that many of the peripheral blood transcriptomic changes are not necessarily mirroring what is happening in the brain, and vice-versa. The keys to find peripheral biomarkers[5] are, first, to have a powerful discovery approach, such as our within-participant design, that closely tracks the phenotype you are trying to measure and reduces noise. Second, cross-validating and prioritizing the results with other lines of evidence, such as brain gene expression and genetic data, are important in order to establish relevance to disease and generalizability of findings. Third, it is important to validate for behavior in an independent cohort with a robust and relevant phenotype, in these case suicide completers. Fourth, testing for predictive ability in independent/prospective cohorts is a must (Supplementary Figure S1).

Biomarkers that survive such a rigorous stepwise discovery, prioritization, validation and testing process are likely directly relevant to the disorder studied. As such, we endeavored to study their biology, whether they are involved in other psychiatric disorders or are relatively specific for suicide, and whether they are modulated by existing drugs in general, and drugs known to treat suicidality in particular.

We have identified a series of biomarkers that seem to be changed in opposite direction in suicide vs in treatments with omega-3 fatty acids, lithium and clozapine (Supplementary Table S4). These biomarkers could potentially be used to stratify patients to different treatment approaches, and monitor their response. BCL2, JUN, GHA1, ENTPD1, ITIH5, MBNL1 and SSBP2 are changed in expression by two of these three treatments, suggesting that they may be core to the anti-suicidal mechanism of these drugs. Interestingly, MBNL1, which is decreased in expression in suicidality, was identified as increased in expression in longevity/healthy aging.[34] BCL2, CAT and JUN may be useful blood pharmacogenomic markers of response to lithium. CD84, MBNL1 and RAB22A may be useful blood pharmacogenomic markers of response to clozapine. NDRG1, FOXP1, AFF3, ATXN1, CSNK1A1, ENTPD1, ITIH5, PRDX3 and SSBP2 may be useful blood pharmacogenomic markers of response to omega-3 fatty acids. Three existing drugs used for other indications have been identified as targeting the top suicide biomarkers identified by us (Supplementary Table S4), and could potentially be re-purposed for testing in treatment of acute suicidality: anakinra (inhibiting ILR1), enzastaurin (inhibiting AKT3) and tesevatinib (inhibiting EPHB4). Additionally, Connectivity Map[35] analyses (Supplementary Table S6) identified novel compounds that induce gene expression signatures that are the opposite of those present in suicide, and might generate leads and/or be tested for use to treat/prevent suicidality, including mifepristone, LY294002, acetylsalicylic acid, estradiol, buspirone, corticosterone, metformin, diphenhydramine, haloperidol and fluoxetine (Supplementary Table S6).

a

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		
MOB3B	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		

b

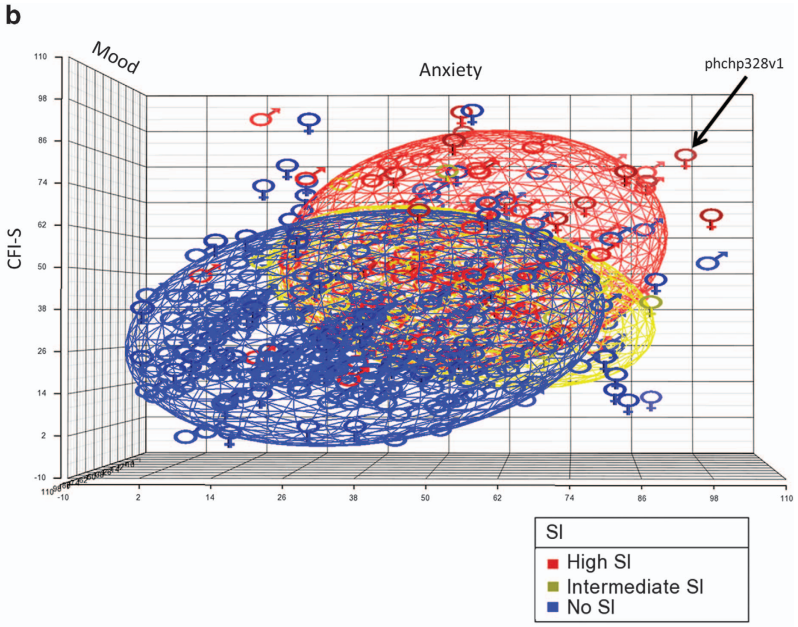


Figure 5. Study participant who committed suicide. Subject phchp328 was a 38-year-old divorced Caucasian female with a long history of MDD, PTSD, BP and polysubstance abuse/dependence. She had multiple psychiatric hospitalizations due to suicidal ideation ($n = 21$) and due to suicidal attempts ($n = 3$), in the 5 years before her suicide. She committed suicide by overdose with pills, leaving behind a suicide note addressed to her mother. (**a**) Percentile for scores on top predictors in all the female subjects in this study ($n = 105$ for biomarkers and $n = 88$ for apps and UP-Suicide). Her panel of Bonferroni validated biomarkers (BioM50) score, apps score (CFI-S+SASS), and UP-Suicide predictor score at a study visit (Visit 1) were at the 100% of the scores of all the psychiatric participant visits tested in this current study. Of note, that testing was conducted during an inpatient hospitalization due to suicidal ideation. While her scores did improve at subsequent outpatient testing visits (Visits 2 and 3), this high watermark score indicated her high risk. After the last testing visit in our study, 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). For decreased biomarkers, a higher percentile corresponds to lower expression values. Only 5 of the 32 predictors (biomarkers, clinical, combined) were discordant between the highest and lowest SI visit (italicized). In all, 17 of the 32 predictors (bold) were stepwise decreased corresponding to her SI scores. One of the biomarkers (HTRA1) was in the 100% of the subjects tested, as was the panel of 50 validated markers (BioM-50), the combination of the clinical measures/apps (CFI-S+SASS), and the combined biomarker panels and clinical/apps predictor (UP-Suicide). (**b**) Tri-dimensional representation of the percentilized scores of the combination of the two apps, CFI-S and SASS (Anxiety and Mood) of all the female participant visits tested in the current study ($n = 87$) and all the male participant visits in our previous work ($n = 317$). A tri-dimensional scatter plot was created using Partek. Tri-dimensional 95% confidence intervals were inserted as ellipsoids, color coded blue, yellow and red for No SI, Intermediate SI and High SI, respectively. Subject phchp328visit1 had the highest Euclidian D (distance from origin), as indicated by the arrow. This is the only subject that completed suicide as far as we know, as of the end of this study in November 2015. BP, bipolar disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

Of note, a number of biomarkers from the current study in women reproduce and are co-directional with our previous findings in men (Table 5, Table 2 and Supplementary Table S2), whereas others had changes in opposite directions (Table 2 and Supplementary Table S2), underlying the issue of biological context and differences in suicidality between the two genders. This avenue merits attention in the field, and detailed future comparative studies, as do studies by diagnostic groups.

Before any testing, we planned to use a comprehensive combination of genomic data (specifically, the top validated biomarkers) and phenomic data (specifically, the CFI-S and the SASS) as the primary end point measure, a broad-spectrum universal predictor (UP-Suicide) for state SI and trait future hospitalizations. It has not escaped our attention that certain single biomarkers, particular phenotypic items, or combinations thereof seem to perform better than the UP-Suicide in one or another type of prediction (see Table 4). However, since such markers and combinations were not chosen by us apriori and such insights derive from testing, we cannot exclude a fit to cohort effect for them and reserve judgement as to their robustness as predictors until further testing in additional independent cohorts, by us and others. What we can put forward for now based on the current work is the UP-Suicide, which seems to be a robust predictor across different scenarios and diagnostic groups.

Our study has a number of limitations. All this work was carried out in psychiatric patients, a high-risk group, and it remains to be seen how such predictors apply to non-psychiatric participants. For the UP-Suicide testing, the prevalence rate for suicidality in our test cohorts was 21% (7 out of 33 for SI and 5 out of 24 for future hospitalizations) (Table 4). Of note, this rate was remarkably similar to our previous work in men.[4] It is to be noted that the incidence of suicidality in the general population is lower, for example at 1.5% in adolescents in an European cohort[36] and estimates of 0.2–2% in the United States,[37] which underlines the rationale

of using a very high-risk group like we did for magnifying and enabling signal detection with a relatively small *N*. Over 40% of the live participants from the discovery cohort (5 out of 12) and independent test cohort (14 out of 33) are non-VA, and all the suicide completers used for validation are from the general population, not VA, so we believe our results have broader relevance. Studies with larger numbers and longer follow-up, currently ongoing, as well as studies in different clinical settings, may provide more generalizability.

The current studies were carried out exclusively in females. Similar work is needed in larger meta-analyses across gender, in participants with and without psychiatric disorders, to find generalizable predictors. Conversely, a narrow focus by gender, diagnosis (or lack of), and perhaps age, may be needed to find more individualized predictors. Such work is ongoing in our group.

In conclusion, we have advanced the biological understanding of suicidality in women, highlighting behavioral and biological mechanisms related to inflammation, neurotrophic factors, circadian clock, stress response and apoptosis. Biomarkers that may track treatment response to lithium and intriguingly, omega-3 fatty acids, have been identified. Of equal importance, we developed instruments (biomarkers and apps) for predicting suicidality, that do not require asking the person assessed if they have suicidal thoughts, as individuals who are truly suicidal often do not share that information with people close to them or with clinicians. We propose that the widespread use of such risk prediction tests as part of routine or targeted health-care assessments will lead to early disease interception followed by preventive lifestyle modifications or treatment. Given the magnitude and urgency of the problem, the importance of efforts to implement such tools cannot be overstated. We note that we have sadly lost one study participant to suicide (Figure 5), that in retrospect was highlighted by UP-Suicide as being the highest risk participant in our study.

Note

Supplementary information is also available from the Niculescu Laboratory website (www.neurophenomics.info).

CONFLICT OF INTEREST

ABN is listed as an inventor on a patent application being filed by Indiana University.

ACKNOWLEDGMENTS

This work is, in essence, a field-wide collaboration. We acknowledge our debt of gratitude for the efforts and results of the many other groups, cited in our paper, who have conducted and published studies (clinical, genetic and biological) in suicidality. With their arduous and careful work, a convergent approach such as ours is possible. We thank David Welsh for advice on clock genes, Joseph Niezer and Tammy Jones for helpful clinical discussions, as well as Meghan Carpenter and Jay Natarajan for help with building literature databases. We also would particularly like to thank the participants who participated in these studies, their families and their caregivers. Without their contribution, such work to advance the understanding of suicide would not be possible. This work was supported by an NIH Directors' New Innovator Award (1DP2OD007363) and a VA Merit Award (2I01CX000139) to ABN.

AUTHOR CONTRIBUTIONS

ABN designed the study and wrote the manuscript. DFL, EN, HLN, HD, PLP, TL and ECS analyzed the data. NV and FNK performed database work. HW, EB and DLG organized, conducted and scored testing in psychiatric participants. AB, MY, AS, GES and ABN organized and carried out postmortem samples collection. TG, NJS, SMK and DRS conducted microarray experiments and provided input on data analyses. All authors discussed the results and commented on the manuscript.

REFERENCES

1 Hawton K. Sex and suicide. Gender differences in suicidal behaviour. *Br J Psychiatry*2000; **177**: 484–485.
2 Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N *et al.* Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Mol Psychiatry* 2015; **20**: 1266–1285.
3 Le-Niculescu H, Levey DF, Ayalew M, Palmer L, Gavrin LM, Jain N *et al.* Discovery and validation of blood biomarkers for suicidality. *Mol Psychiatry* 2013; **18**: 1249–1264.
4 Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N *et al.* Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Mol Psychiatry* 2015; **20**: 1266–1285.
5 Niculescu AB, Levey D, Le-Niculescu H, Niculescu E, Kurian SM, Salomon D. Psychiatric blood biomarkers: avoiding jumping to premature negative or positive conclusions. *Mol Psychiatry* 2015; **20**: 286–288.
6 Niculescu AB, Le-Niculescu H. Convergent Functional Genomics: what we have learned and can learn about genes, pathways, and mechanisms. *Neuropsychopharmacology* 2010; **35**: 355–356.
7 Zhang EE, Liu AC, Hirota T, Miraglia LJ, Welch G, Pongsawakul PY *et al.* A genome-wide RNAi screen for modifiers of the circadian clock in human cells. *Cell* 2009; **139**: 199–210.
8 McCarthy MJ, Welsh DK. Cellular circadian clocks in mood disorders. *J Biol Rhythms* 2012; **27**: 339–352.
9 Niculescu AB, Lulow LL, Ogden CA, Le-Niculescu H, Salomon DR, Schork NJ *et al.* PhenoChipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141B**: 653–662.
10 Borges G, Angst J, Nock MK, Ruscio AM, Kessler RC. Risk factors for the incidence and persistence of suicide-related outcomes: a 10-year follow-up study using the National Comorbidity Surveys. *J Affect Disord* 2008; **105**: 25–33.
11 Nock MK. Future directions for the study of suicide and self-injury. *J Clin Child Adolesc Psychol* **53**2012; **41**: 255–259.
12 Chen R, Mias GI, Li-Pook-Than J, Jiang L, Lam HY, Miriami E *et al.* Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* 2012; **148**: 1293–1307.
13 Sequeira A, Morgan L, Walsh DM, Cartagena PM, Choudary P, Li J *et al.* Gene expression changes in the prefrontal cortex, anterior cingulate cortex and nucleus accumbens of mood disorders subjects that committed suicide. *PLoS One* 2012; **7**: e35367.
14 Falcone T, Fazio V, Lee C, Simon B, Franco K, Marchi N *et al.* Serum S100B: a potential biomarker for suicidality in adolescents? *PLoS One* 2010; **5**: e11089.
15 Guintivano J, Brown T, Newcomer A, Jones M, Cox O, Maher BS *et al.* Identification and replication of a combined epigenetic and genetic biomarker predicting suicide and suicidal behaviors. *Am J Psychiatry* 2014; **171**: 1287–1296.
16 Kaminsky Z, Wilcox HC, Eaton WW, Van Eck K, Kilaru V, Jovanovic T *et al.* Epigenetic and genetic variation at SKA2 predict suicidal behavior and post-traumatic stress disorder. *Transl Psychiatry* 2015; **5**: e627.
17 Mann JJ, Currier D. *Medication in Suicide Prevention Insights from Neurobiology of Suicidal Behavior*, In:Dwivedi Y(ed) The Neurobiological Basis of Suicide: Boca Raton, FL, USA, 2012.
18 Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am J Psychiatry* 2006; **163**: 1100–1102.
19 Lewis MD, Hibbeln JR, Johnson JE, Lin YH, Hyun DY, Loewke JD. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. *J Clin Psychiatry* 2011; **72**: 1585–1590.
20 Hennings JM, Uhr M, Klengel T, Weber P, Putz B, Touma C *et al.* RNA expression profiling in depressed patients suggests retinoid-related orphan receptor alpha as a biomarker for antidepressant response. *Transl Psychiatry* 2015; **5**: e538.
21 Martins-de-Souza D, Maccarrone G, Ising M, Kloiber S, Lucae S, Holsboer F *et al.* Blood mononuclear cell proteome suggests integrin and Ras signaling as critical pathways for antidepressant treatment response. *Biol Psychiatry* 2014; **76**: e15–e17.
22 Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ *et al.* Identifying blood biomarkers for mood disorders using convergent functional genomics. *Mol Psychiatry* 2009; **14**: 156–174.
23 Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C *et al.* Identification of blood biomarkers for psychosis using convergent functional genomics. *Mol Psychiatry* 2011; **16**: 37–58.
24 Kelleher I, Lynch F, Harley M, Molloy C, Roddy S, Fitzpatrick C *et al.* Psychotic symptoms in adolescence index risk for suicidal behavior: findings from 2 population-based case-control clinical interview studies. *Arch Gen Psychiatry* 2012; **69**: 1277–1283.
25 Le-Niculescu H, McFarland MJ, Ogden CA, Balaraman Y, Patel S, Tan J *et al.* Phenomic, convergent functional genomic, and biomarker studies in a

stress-reactive genetic animal model of bipolar disorder and co-morbid alcoholism. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 134–166.
26 Goodwin RD, Marusic A. Association between short sleep and suicidal ideation and suicide attempt among adults in the general population. *Sleep* 2008; **31**: 1097–1101.
27 Schoenbaum M, Kessler RC, Gilman SE, Colpe LJ, Heeringa SG, Stein MB *et al.* Predictors of suicide and accident death in the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS): results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *JAMA Psychiatry* 2014; **71**: 493–503.
28 Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA *et al.* The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168**: 1266–1277.
29 Gaiteri C, Guilloux JP, Lewis DA, Sibille E. Altered gene synchrony suggests a combined hormone-mediated dysregulated state in major depression. *PLoS One* 2010; **5**: e9970.
30 Sainz J, Mata I, Barrera J, Perez-Iglesias R, Varela I, Arranz MJ *et al.* Inflammatory and immune response genes have significantly altered expression in schizophrenia. *Mol Psychiatry* 2013; **18**: 1056–1057.
31 Sokolov BP, Jiang L, Trivedi NS, Aston C. Transcription profiling reveals mitochondrial, ubiquitin and signaling systems abnormalities in postmortem brains from subjects with a history of alcohol abuse or dependence. *J Neurosci Res* 2003; **72**: 756–767.
32 Yu Z, Ono C, Kim HB, Komatsu H, Tanabe Y, Sakae N *et al.* Four mood stabilizers commonly induce FEZ1 expression in human astrocytes. *Bipolar Disord* 2011; **13**: 486–499.
33 Le-Niculescu H, Case NJ, Hulvershorn L, Patel SD, Bowker D, Gupta J *et al.* Convergent functional genomic studies of omega-3 fatty acids in stress reactivity, bipolar disorder and alcoholism. *Transl Psychiatry* 2011; **1**: e4.
34 Sood S, Gallagher IJ, Lunnon K, Rullman E, Keohane A, Crossland H *et al.* A novel multi-tissue RNA diagnostic of healthy ageing relates to cognitive health status. *Genome Biol* 2015; **16**: 185.
35 Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ *et al.* The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* 2006; **313**: 1929–1935.
36 Wasserman D, Hoven CW, Wasserman C, Wall M, Eisenberg R, Hadlaczky G *et al.* School-based suicide prevention programmes: the SEYLE cluster-randomised, controlled trial. *Lancet* 2015; **385**: 1536–1544.
37 Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev* 2008; **30**: 133–154.
38 Butler AW, Breen G, Tozzi F, Craddock N, Gill M, Korszun *et al.* A genomewide linkage study on suicidality in major depressive disorder confirms evidence for linkage to 2p12. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 1465–1473.
39 Smalheiser NR, Lugli G, Rizavi HS, Torvik VI, Turecki G, Dwivedi Y. MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. *PLoS One* 2012; **7**: e33201.
40 Fiori LM, Bureau A, Labbe A, Croteau J, Noel S, Merette C *et al.* Global gene expression profiling of the polyamine system in suicide completers. *Int J Neuropsychopharmacol* 2011; **14**: 595–605.
41 Dick DM, Meyers J, Aliev F, Nurnberger J Jr., Kramer J, Kuperman S *et al.* Evidence for genes on chromosome 2 contributing to alcohol dependence with conduct disorder and suicide attempts. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 1179–1188.
42 Hesselbrock V, Dick D, Hesselbrock M, Foroud T, Schuckit M, Edenberg H *et al.* The search for genetic risk factors associated with suicidal behavior. *Alcohol Clin Exp Res* 2004; **28**: 70 S–76 S.
43 Menke A, Domschke K, Czamara D, Klengel T, Hennings J, Lucae S *et al.* Genome-wide association study of antidepressant treatment-emergent suicidal ideation. *Neuropsychopharmacology* 2012; **37**: 797–807.
44 Sequeira A, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero RA Jr. *et al.* Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Arch Gen Psychiatry* 2006; **63**: 35–48.

Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Supplementary Information:

Figure S1 Sequential flow of biomarker discovery, prioritization, validation and testing.

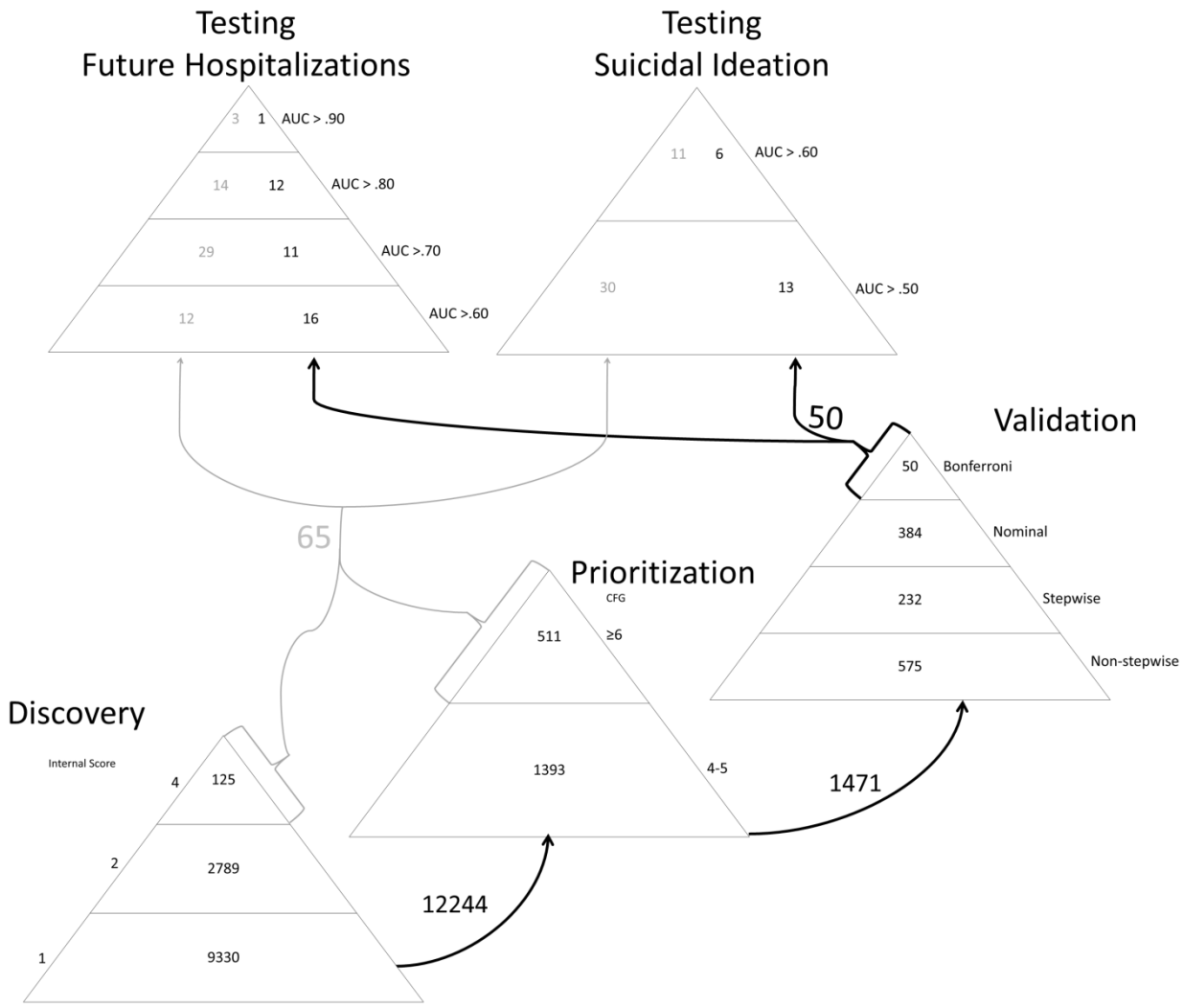


Figure S2. SASS and CFI-S questionnaires and apps.

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

Mood Subscale

1) Mood

How good is your mood right now?

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

2) Motivation to do things

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

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

3) Movement activity

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

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

4) Thinking activity

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

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

5) Self-esteem

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

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

6) Interest in pleasurable activities

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

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

7) Appetite

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

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

Anxiety Subscale

1) Anxiety

How anxious are you right now?

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

2) Uncertainty

How uncertain about things do you feel right now?

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

3) Fear

How frightened about things do you feel right now?

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

4) Anger

How angry about things do you feel right now?

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

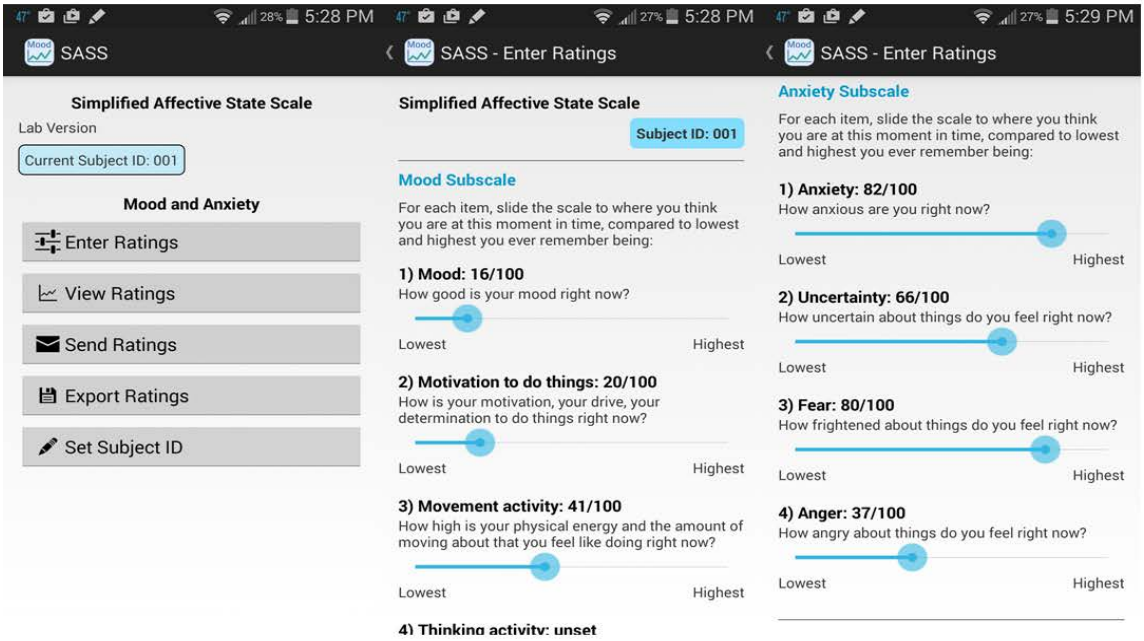
Comments (optional):
Describe events or actions that you think are influencing how you feel now. Describe any additional feelings you might have at this moment in time:

Convergent Functional Information for Suicide (CFI-S) Scale. Items are scored 1 for Yes, 0 for No. Total Score has a maximum possible of 22. Final Score (normalized) 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.

Items	Yes	No	NA	Domain	Type Increased Reasons (IR) Decreased Barriers (DB)
1. Psychiatric illness diagnosed and treated				Mental Health	IR
2. With poor treatment compliance				Mental Health	DB
3. Family history of suicide in blood relatives				Mental Health	IR
4. Personally knowing somebody who committed suicide				Cultural Factors	DB
5. History of abuse: physical, sexual, emotional, neglect				Life Satisfaction	IR
6. Acute/severe medical illness, including acute pain (“I just can’t stand this pain anymore.”) (within last 3 months)				Physical Health	IR
7. Acute stress: Losses, grief (within last 3 months)				Environmental Stress	IR
8. Chronic stress: perceived uselessness, not feeling needed, burden to extended kin.				Environmental Stress	IR
9. History of excessive introversion, conscientiousness (including planned suicide attempts)				Mental Health	IR
10. Dissatisfaction with life at this moment in time				Life Satisfaction	IR
11. Lack of hope for the future				Life Satisfaction	IR
12. Current substance abuse				Addictions	DB
13. Past history of suicidal acts/gestures				Mental Health	DB
14. Lack of religious beliefs				Cultural Factors	DB
15. Acute stress: Rejection (within last 3 months)				Environmental Stress	IR
16. Chronic stress: lack of positive relationships, social isolation				Environmental Stress	DB
17. History of excessive extroversion and impulsive behaviors (including rage, anger, physical fights, seeking revenge)				Mental Health	DB
18. Lack of coping skills when faced with stress (cracks under pressure)				Mental Health	DB
19. Lack of children. If has children, not in touch /not helping take care of them.				Life Satisfaction	DB

20. History of command hallucinations of self-directed violence				Mental Health	IR
21. Age: Older >60 or Younger <25				Age	IR
22. Gender: Male				Gender	DB

SASS App



CFI-S App

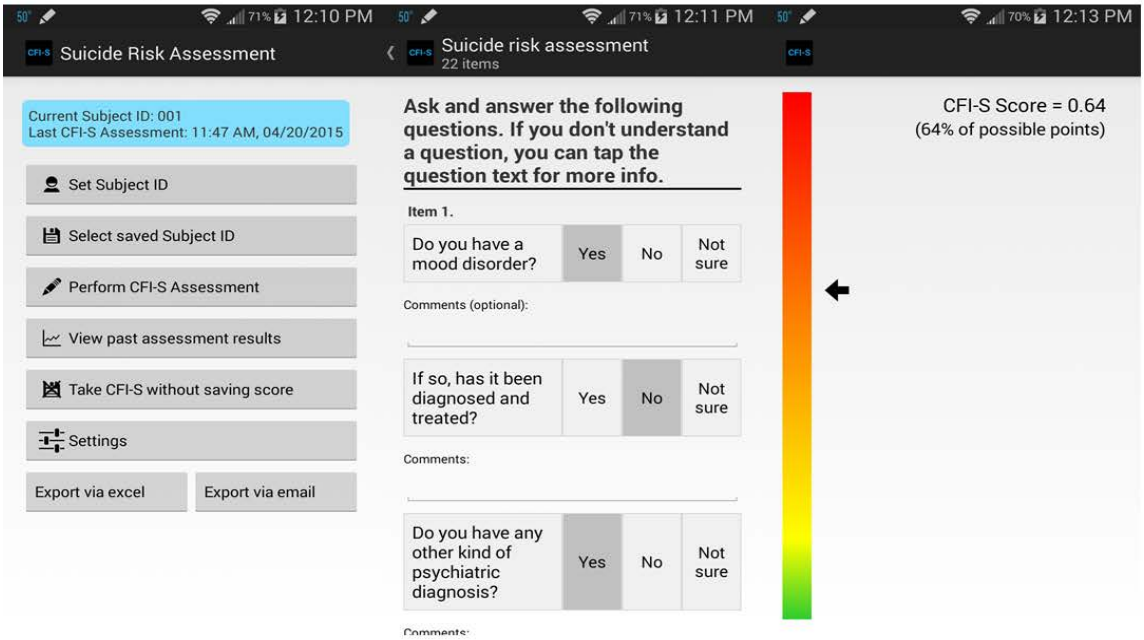


Table S1. Detailed Demographics

Cohort 1: Discovery Cohort (n=12) (31 visits)						
Participant ID visit	Veteran Status	Diagnosis	Age	Gender	Ethnicity	HAMD SI
phchp034v1	NON-VA	BP	51	F	Asian American	0
phchp034v2	NON-VA	BP	52	F	Asian American	3
phchp043v1	NON-VA	BP	30	F	Caucasian	2
phchp043v2	NON-VA	BP	31	F	Caucasian	0
phchp043v3	NON-VA	BP	31	F	Caucasian	0
phchp055v1		BP	46	F	Caucasian	4
phchp055v2		BP	46	F	Caucasian	0
phchp055v3		BP	46	F	Caucasian	0
phchp097v1	NON-VA	SZA	25	F	Caucasian	0
phchp097v2	NON-VA	SZA	26	F	Caucasian	2
phchp131v1		SZ	54	F	African American	3
phchp131v3		SZ	56	F	African American	0
phchp170v1	NON-VA	MDD	26	F	Caucasian	2
phchp170v2	NON-VA	MDD	26	F	Caucasian	0
phchp170v3	NON-VA	MDD	26	F	Caucasian	0
phchp223v1	NON-VA	SZA	60	F	Caucasian	2
phchp223v2	NON-VA	SZA	60	F	Caucasian	0
phchp223v3	NON-VA	SZA	61	F	Caucasian	0
phchp318v1		MDD	57	F	Caucasian	2
phchp318v2		MDD	57	F	Caucasian	0
phchp328v1		MDD	37	F	Caucasian	3
phchp328v2		MDD	38	F	Caucasian	2
phchp328v3		MDD	38	F	Caucasian	0
phchp332v1		SZA	47	F	African American	4
phchp332v2		SZA	48	F	African American	0
phchp332v3		SZA	48	F	African American	0
phchp334v1		BP	50	F	Caucasian	4
phchp334v2		BP	50	F	Caucasian	0
phchp334v3		BP	51	F	Caucasian	0
phchp340v1		MDD	51	F	Caucasian	2
phchp340v2		MDD	51	F	Caucasian	0

Coroner's Office Validation Cohort –Toxicology

Cohort 2: Coroner's Office Validation Cohort -gene expression data (n=6)					
Subject ID visit	Psych [1]Dx	Age	Gender	Ethnicity	Cause of Death
INBRAIN020	Depression	55	F	Caucasian	Single GSW to chest
INBRAIN026	None	57	F	Caucasian	Single GSW to head
INBRAIN029	PTSD	36	F	Caucasian	Asphyxiation (duct tape)
INBRAIN032	Bipolar	44	F	Caucasian	Single GSW to head
INBRAIN034	Depression	50	F	Caucasian	Single GSW to chest
INBRAIN050	Depression	19	F	African American	Single GSW under chin

Coroner's Office Validation Cohort - Toxicology	
Subject ID visit	Toxicology
INBRAIN020	clonazepam 6.7 7-aminoclonazepam 32.9 duloxetine 68.7 trazodone 0.21
INBRAIN026	CAFFEINE POSITIVE
INBRAIN029	NA
INBRAIN032	CAFFEINE POSITIVE
INBRAIN034	Oxazepam 54.5 Temazepam 395 Gabapentin 1 Zolpidem 571 Temazepam >2500 Oxazepam>2500 Hydrocodone 88 Hydromorphine 161
INBRAIN050	NA

Cohort 3: Test Cohort for Suicidal Ideation (n=33) (74 visits)						
Participant ID visit	Veteran Status	Diagnosis	Age	Gender	Ethnicity	HAMD SI
phchp018v1	NON-VA	SZA	54	F	Caucasian	0
phchp028v1	NON-VA	BP	50	F	Asian	1
phchp028v2	NON-VA	BP	50	F	Asian	1
phchp035v1	NON-VA	BP	36	F	Caucasian	0
phchp035v2	NON-VA	BP	37	F	Caucasian	0
phchp035v3	NON-VA	BP	37	F	Caucasian	0
phchp037v1	NON-VA	BP	52	F	Caucasian	0
phchp063v1	NON-VA	SZ	46	F	African American	0
phchp071v1	NON-VA	SZA	50	F	African American	0
phchp074v1		SZA	46	F	African American	0
phchp074v2		SZA	46	F	African American	0
phchp074v3		SZA	46	F	African American	0
phchp076v1		SZA	41	F	African American	2
phchp076v2		SZA	41	F	African American	1
phchp076v3		SZA	41	F	African American	1
phchp084v1		BP	49	F	Caucasian	0
phchp084v2		BP	49	F	Caucasian	0
phchp084v3		BP	50	F	Caucasian	0
phchp106v1		BP	28	F	Mixed	0
phchp106v2		BP	28	F	Mixed	0
phchp106v3		BP	29	F	Mixed	0
phchp130v1		MDD	42	F	Caucasian	0
phchp130v2		MDD	42	F	Caucasian	0
phchp130v3		MDD	42	F	Caucasian	0
phchp141v1		BP	47	F	Caucasian	1
phchp141v2		BP	47	F	Caucasian	0
phchp141v3		BP	47	F	Caucasian	1
phchp156v1		BP	35	F	Caucasian	2
phchp160v1	NON-VA	SZA	41	F	Caucasian	0
phchp160v2	NON-VA	SZA	41	F	Caucasian	0
phchp160v3	NON-VA	SZA	41	F	Caucasian	0
phchp164v1		MDD	48	F	Caucasian	0
phchp164v2		MDD	49	F	Caucasian	0
phchp164v3		MDD	49	F	Caucasian	0
phchp172v1	NON-VA	BP	24	F	Caucasian	0
phchp172v2	NON-VA	BP	24	F	Caucasian	0
phchp172v3	NON-VA	BP	25	F	Caucasian	0

phchp177v1		SZ	39	F	Caucasian	0
phchp177v2		SZ	39	F	Caucasian	0
phchp180v1	NON-VA	BP	47	F	Caucasian	0
phchp180v2	NON-VA	BP	47	F	Caucasian	0
phchp180v3	NON-VA	BP	47	F	Caucasian	0
phchp181v1	NON-VA	BP	28	F	Caucasian	0
phchp181v3	NON-VA	BP	28	F	Caucasian	0
phchp181v4	NON-VA	BP	29	F	Caucasian	0
phchp204v1	NON-VA	BP	49	F	Caucasian	0
phchp204v2	NON-VA	BP	49	F	Caucasian	0
phchp204v3	NON-VA	BP	49	F	Caucasian	0
phchp232v1	NON-VA	SZA	38	F	Caucasian	0
phchp232v2	NON-VA	SZA	38	F	Caucasian	0
phchp232v3	NON-VA	SZA	38	F	Caucasian	0
phchp239v1	NON-VA	SZA	54	F	African American	0
phchp239v2	NON-VA	SZA	54	F	African American	0
phchp239v3	NON-VA	SZA	54	F	African American	0
phchp240v1		MDD	55	F	Caucasian	0
phchp240v2		MDD	55	F	Caucasian	0
phchp240v3		MDD	56	F	Caucasian	0
phchp254v1		MDD	49	F	Caucasian	0
phchp254v2		MDD	49	F	Caucasian	0
phchp254v3		MDD	50	F	Caucasian	0
phchp258v1		BP	52	F	Caucasian	0
phchp258v2		BP	52	F	Caucasian	0
phchp285v1		BP	56	F	Caucasian	0
phchp285v2		BP	56	F	Caucasian	1
phchp291v1		BP	45	F	Caucasian	0
phchp291v2		BP	46	F	Caucasian	0
phchp291v3		BP	47	F	Caucasian	0
phchp294v1	NON-VA	BP	20	F	Caucasian	2
phchp307v1		MDD	53	F	Caucasian	2
phchp330v1		BP	45	F	Caucasian	3
phchp338v1		BP	51	F	Caucasian	0
phchp338v2		BP	51	F	Caucasian	0
phchp353v1		MDD	45	F	Caucasian	2
phchp355v1		MDD	50	F	Caucasian	3

Cohort 4: Testing cohort for future hospitalizations for suicidality (n=24) (59 chips)									
Participant ID visit	Diagnosis	Age	Gender	Ethnicity	Years Followed	Number of All Future Hospitalizations Due to Suicidality		Hospitalizations Frequency Due to Suicidality	
						SI	SA	SI	SA
phchp055v1	BP	46	F	Caucasian	3.482192	0	1	0	0.287175
phchp055v2	BP	46	F	Caucasian	3.175342	0	0	0	0
phchp055v3	BP	46	F	Caucasian	2.893151	0	0	0	0
phchp074v1	SZA	46	F	African American	1.882192	0	0	0	0
phchp074v2	SZA	46	F	African American	1.583562	0	0	0	0
phchp074v3	SZA	46	F	African American	1.326027	0	0	0	0
phchp076v1	SZA	41	F	African American	7.490411	2	0	0.267008	0
phchp076v2	SZA	41	F	African American	7.210959	1	0	0.138678	0
phchp076v3	SZA	41	F	African American	6.991781	1	0	0.143025	0
phchp084v1	BP	49	F	Caucasian	7.032877	0	0	0	0
phchp084v2	BP	49	F	Caucasian	6.835616	0	0	0	0
phchp084v3	BP	50	F	Caucasian	6.567123	0	0	0	0
phchp106v1	BP	28	F	Mixed	5.446575	0	0	0	0
phchp106v2	BP	28	F	Mixed	5.205479	0	0	0	0
phchp106v3	BP	29	F	Mixed	4.961644	0	0	0	0
phchp130v1	MDD	42	F	Caucasian	4.939726	0	0	0	0
phchp130v2	MDD	42	F	Caucasian	4.641096	0	0	0	0
phchp130v3	MDD	42	F	Caucasian	4.386301	0	0	0	0
phchp131v1	SZ	54	F	African American	1.671233	0	0	0	0
phchp131v2	SZ	55	F	African American	1.358904	0	0	0	0
phchp131v3	SZ	56	F	African American	1.112329	0	0	0	0
phchp141v1	BP	47	F	Caucasian	4.60274	0	0	0	0
phchp141v2	BP	47	F	Caucasian	4.336986	0	0	0	0
phchp141v3	BP	47	F	Caucasian	4.090411	0	0	0	0
phchp156v1	BP	35	F	Caucasian	1.778082	0	0	0	0
phchp164v1	MDD	48	F	Caucasian	3.906849	0	0	0	0
phchp164v2	MDD	49	F	Caucasian	3.578082	0	0	0	0
phchp164v3	MDD	49	F	Caucasian	3.309589	0	0	0	0
phchp177v1	SZ	39	F	Caucasian	3.912329	0	0	0	0
phchp177v2	SZ	39	F	Caucasian	3.613699	0	0	0	0
phchp240v1	MDD	55	F	Caucasian	3.252055	0	0	0	0
phchp240v2	MDD	55	F	Caucasian	2.641096	0	0	0	0

phchp240v3	MDD	56	F	Caucasian	2.282192	0	0	0	0
phchp254v1	MDD	49	F	Caucasian	2.353425	0	0	0	0
phchp254v2	MDD	49	F	Caucasian	1.739726	0	0	0	0
phchp254v3	MDD	50	F	Caucasian	1.336986	0	0	0	0
phchp258v1	BP	52	F	Caucasian	2.863014	0	0	0	0
phchp258v2	BP	52	F	Caucasian	2.252055	0	0	0	0
phchp291v1	BP	45	F	Caucasian	2.468493	0	0	0	0
phchp291v2	BP	46	F	Caucasian	2.084932	0	0	0	0
phchp291v3	BP	47	F	Caucasian	0.391781	0	0	0	0
phchp318v1	MDD	57	F	Caucasian	2.369863	0	0	0	0
phchp318v2	MDD	57	F	Caucasian	0.660274	0	0	0	0
phchp328v1	MDD	37	F	Caucasian	1.30411	5	0	3.834034	0
phchp328v2	MDD	38	F	Caucasian	1.008219	4	0	3.967391	0
phchp328v3	MDD	38	F	Caucasian	0.613699	3	0	4.888393	0
phchp330v1	BP	45	F	Caucasian	1.2	0	0	0	0
phchp332v1	SZA	47	F	African American	0.871233	2	0	2.295597	0
phchp332v2	SZA	48	F	African American	0.619178	2	0	3.230088	0
phchp332v3	SZA	48	F	African American	0.561644	0	0	0	0
phchp334v1	BP	50	F	Caucasian	1.065753	2	0	1.876607	0
phchp334v2	BP	50	F	Caucasian	0.816438	2	0	2.449664	0
phchp334v3	BP	51	F	Caucasian	0.534247	0	0	0	0
phchp338v1	BP	51	F	Caucasian	0.89863	0	0	0	0
phchp338v2	BP	51	F	Caucasian	0.556164	0	0	0	0
phchp340v1	MDD	51	F	Caucasian	0.923288	0	0	0	0
phchp340v2	MDD	51	F	Caucasian	0.627397	0	0	0	0
phchp353v1	MDD	45	F	Caucasian	0.29863	0	0	0	0
phchp355v1	MDD	50	F	Caucasian	0.539726	0	0	0	0

Table S2. Top candidate biomarker genes -evidence for involvement in suicidality.

The top 49 genes (50 probesets) from validation (Bonferroni significant), as well as 65 genes that were top scoring in both discovery (internal score of 4) and prioritization (CFG score of 6 and above) but were non Bonferroni validated. Underlined gene symbol means co-directionality of the exact same probeset with biomarkers findings from our previous work in males (Niculescu et al. 2015)[2]. 82 out of 115 probesets were co-directional (71%). *Italic- nominally significant.* **Bold p-value is Bonferroni significant after validation in suicide completers.**

Gene Symbol/Gene Name	Probesets	Discovery (Change) Method/ Score	Prior human genetic evidence	Prior human Brain expression evidence	Prior human peripheral expression evidence	Prioritization Total CFG Score For Suicide	Validation ANOVA p-value
Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)							
BCL2 B-cell CLL/Lymphoma 2	203684_s_at	(D) DE/2	Linkage [3]	(D) PFC [4]	(D) Blood[5]	9	**3.95E-06**
GSK3B glycogen synthase kinase 3 beta	226183_at	(D) DE/1	Suicide [6]	(D) PFC [7] [8]	(I) Blood[5]	9	**2.26E-05**
ALDH3A2 aldehyde dehydrogenase 3 family, member A2	202053_s_at	(D) DE/2		(I) BA4, BA44, THALAMUS [9]	(D) Blood[5]	8	**1.62E-06**
AP1S2 adaptor-related protein complex 1, sigma 2 subunit	203299_s_at	(D) DE/1	Linkage [10]	(I) BA 8/9 ; (D) BA 44, BA 11 Suicide [10]	(D) Blood[5]	8	**2.52E-05**
CAT catalase	238363_at	(D) DE/2		(D) BA47 [11]	(I) Blood[5]	8	**5.04E-07**
JUN jun proto-oncogene	201466_s_at 201465_s_at	(I) DE/2 DE/1		(D) HIP [12]	(I) Blood[5]	8 7	**1.14E-11** **1.72E-14**
C18orf54 chromosome 18 open reading frame 54	244324_at	(D) DE/1		(D) HIP [12]	(I) Blood[5]	7	**2.79E-06**
LINC00342 long intergenic non-protein coding RNA 342	1560661_x_at	(D) DE/2	Linkage [13]	(D) DLFPC [14]		7	**1.67E-06**
MOB3B MOB kinase activator 3B	229568_at	(D) DE/1		(I) ACC [14]	(I) Blood[5]	7	**4.69E-06**
NDRG1 N-myc downstream regulated 1	200632_s_at	(I) DE/1		(I) NAC [14]	(I) Blood[5]	7	**3.07E-07**
PER1 period circadian clock 1	202861_at	(I) DE/1		(D) DLFPC [14]	(D) Blood[5]	7	**5.32E-12**
RAPH1 Ras association (RalGDS	1552482_at	(I) DE/1		(I) BA11 [15]	(I) Blood[5]	7	**7.44E-10**
SPON1 spondin 1, extracellular matrix protein	213993_at	(I) DE/1		(D) PFC [16] (I) DLFPC [14]	(I) Blood[5]	7	**1.02E-05**
FOXP1 forkhead box P1	223937_at	(I) DE/4			(D) Blood[5]	6	**7.03E-07**
HAVCR2 hepatitis A virus cellular receptor 2	1555629_at	(I) DE/4			(D) Blood[5]	6	**1.69E-12**
PIP5K1B phosphatidylinositol-4-phosphate 5-	205632_s_at	(D) DE/4			(I) Blood[5]	6	**1.83E-05**

kinase, type I, beta							
ARHGAP15 Rho GTPase activating protein 15	1561489_at	(I) DE/1	Suicide [13]		(I) Blood[5]	5	**3.05E-06**
GJA1 gap junction protein, alpha 1, 43kDa	201667_at	(I) DE/1		(D) HIP [12] PFC [16 17]		5	**1.96E-06**
HES1 hes family bHLH transcription factor 1	203394_s_at	(I) AP/1		(D) DLPFC, AMY [18]		5	**7.65E-10**
HTRA1 HtrA serine peptidase 1	201185_at	(I) AP/1		(I) NAC [14]		5	**3.17E-07**
PRCP prolylcarboxypeptidase (angiotensinase C)	242636_at	(D) DE/1		(D) HIP [12]		5	**2.36E-08**
TIMP1 TIMP metallopeptidase inhibitor 1	201666_at	(I) DE/1		(I) HIP [19] (D) PFC [16]		5	**7.00E-07**
CD200R1 CD200 receptor 1	1553395_a_at	(D) DE/2			(D) Blood[5]	4	**1.45E-05**
CD84 CD84 molecule	230391_at	(D) DE/2			(D) Blood[5]	4	**1.74E-05**
CEP44 centrosomal protein 44kDa	231850_x_at	(D) DE/4				4	**6.71E-08**
CROT carnitine O-octanoyltransferase	231102_at	(D) DE/2			(I) Blood[5]	4	**7.62E-06**
DCAF5 DDB1 and CUL4 associated factor 5	224696_s_at	(D) DE/2			(I) Blood[5]	4	**1.37E-05**
DTWD2 DTW domain containing 2	231277_x_at	(D) DE/2			(I) Blood[5]	4	**1.87E-09**
EPB41L5 erythrocyte membrane protein band 4.1 like 5	229292_at	(I) DE/1	Linkage [20]		(I) Blood [5]	4	**4.58E-14**
ERP27 endoplasmic reticulum protein 27	227450_at	(D) DE/2			(D) Blood [5]	4	**9.54E-08**
FAM173B family with sequence similarity 173, member B	225670_at	(D) DE/2			(D) Blood[5]	4	**2.25E-05**
GANC glucosidase, alpha; neutral C	235714_at	(D) DE/2			(I) Blood[5]	4	**1.40E-08**
GTF3C2 general transcription factor IIIC, polypeptide 2, beta 110kDa	210620_s_at	(D) DE/2			(D) Blood[5]	4	**1.68E-07**
IL1R1 interleukin 1 receptor, type I	215561_s_at	(I) AP/1	Linkage [13]		(D) Blood[5]	4	**5.47E-08**
INO80D	227924_at	(D)			(D)	4	**6.58E-06**

INO80 complex subunit D		DE/2			Blood[5]		
INPP4A inositol polyphosphate-4-phosphatase, type I, 107kDa	235695_at	(D) DE/1	Linkage [13]		(D) Blood[5]	4	**1.79E-05**
ITLN1 intelectin 1 (galactofuranose binding)	223597_at	(I) DE/2			(I) Blood[5]	4	**6.69E-07**
JRK Jrk homolog (mouse)	37872_at	(D) AP/2			(D) Blood[5]	4	**4.25E-06**
KCTD5 potassium channel tetramerization domain containing 5	218474_s_at	(D) DE/2			(D) Blood[5]	4	**2.05E-07**
KIR2DL4 killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4	208426_x_at	(I) DE/2			(D) Blood[5]	4	**1.61E-11**
METTL15 methyltransferase like 15	238773_at	(D) DE/2			(D) Blood[5]	4	**2.16E-06**
NUDT10 nudix (nucleoside diphosphate linked moiety X)-type motif 10	241596_at	(I) DE/2			(D) Blood[5]	4	**7.99E-07**
PDXDC1 pyridoxal-dependent decarboxylase domain containing 1	1560013_at	(I) DE/2			(I) Blood[5]	4	**1.03E-05**
PIK3C3 phosphatidylinositol 3-kinase, catalytic subunit type 3	232086_at	(D) DE/1	Suicide, Antidepressants [21]		(I) Blood[5]	4	**3.14E-08**
RBM48 RNA binding motif protein 48	232661_s_at	(D) DE/2			(I) Blood[5]	4	**7.89E-07**
SMARCA2 SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 2	206543_at	(D) DE/1	Linkage [3]		(D) Blood[5]	4	**2.46E-05**
UCHL5 ubiquitin carboxyl-terminal hydrolase L5	1570145_at	(D) DE/2			(I) Blood[5]	4	**9.05E-11**
VPS53 vacuolar protein sorting 53 homolog (S. cerevisiae)	235882_at	(D) DE/2			(I) Blood[5]	4	**3.41E-09**
ZNF302 zinc finger protein 302	228392_at	(D) DE/2			(D) Blood[5]	4	**7.64E-06**

Top Discovery and Prioritization Biomarkers(Non Bonferroni Validated, 65 genes)							
CLTA clathrin, light chain A	216296_at	(I) DE/4		(I) PFC [22]	(I) Blood[5]	10	
FAM214A family with sequence similarity 214, member A	236237_at	(I) DE/4		(I) ACC [14]	(I) Blood[5]	10	
HSPD1 heat shock 60kDa protein 1 (chaperonin)	241716_at	(I) DE/4		(I) AMY [23]	(D) Blood[5]	10	*0.021922*
ZMYND8 zinc finger, MYND-type containing 8	214795_at	(I) AP/4		(I) ACC [14]	(I) Blood[5]	10	
AK2 adenylate kinase 2	212172_at	(I) AP/4	Suicide [24]		(D) Blood[5]	8	
CAPZA2 capping protein (actin filament) muscle Z-line, alpha 2	201238_s_at	(D) DE/4		(I) PFC [23]		8	0.116785
LRRC8B leucine rich repeat containing 8 family, member B	212976_at	(D) DE/4		(I) PFC [15]		8	0.231881
PPM1B protein phosphatase, Mg2+	209296_at	(D) DE/4		(I) NAC [14]		8	*0.002299*
ACTR3 ARP3 actin-related protein 3 homolog (yeast)	213102_at	(D) DE/4	Linkage [20]		(I) Blood[5]	7	*0.0045239*
AFF3 AF4/FMR2 family, member 3	244696_at	(I) AP/4	Linkage [13]		(D) Blood[5]	7	
MRPS5 mitochondrial ribosomal protein S5	237560_at	(I) AP/4	Linkage [3] {Willour, 2007 #37863}		(D) Blood[5]	7	
SH2D1A SH2 domain containing 1A	211211_x_at	(D) DE/4	Linkage [9] {Zubenko, 2004 #37861}		(D) Blood[5]	7	
AKT3 v-akt murine thymoma viral oncogene homolog 3	240568_at	(I) AP/4			(D) Blood[5]	6	
ALG13 ALG13, UDP-N-acetylglucosaminyltransferase subunit	205584_at	(D) DE/4			(I) Blood[5]	6	*0.046957*
ARHGAP35 Rho GTPase activating protein 35	229397_s_at	(D) DE/4			(D) Blood[5]	6	*0.00160014*
ARID4B AT rich interactive domain 4B (RBP1-like)	221230_s_at	(D) DE/4			(I) Blood[5]	6	
ASPH aspartate beta-		(I)			(I) Blood[5]	6	*0.01087*

hydroxylase	242037_at	DE/4					
ATXN1 ataxin 1	1565804_at	(I) DE/4			(I) Blood[5]	6	
BRE Brain and reproductive organ-expressed (TNFRSF1A modulator)	1556817_a_at	(I) AP/4			(I) Blood[5]	6	
CHMP2B charged multivesicular body protein 2B	202538_s_at	(D) DE/4			(I) Blood[5]	6	*0.022703*
CLPB ClpB caseinolytic peptidase B homolog (E. coli)	1566581_at	(I) AP/4			(D) Blood[5]	6	*0.025268*
CSNK1A1 casein kinase 1, alpha 1	235464_at	(D) DE/4			(D) Blood[5]	6	
DPCD deleted in primary ciliary dyskinesia homolog (mouse)	226009_at	(I) DE/4			(D) Blood[5]	6	
ECSIT ECSIT signalling integrator	218225_at	(I) DE/4			(D) Blood[5]	6	
ENTPD1 ectonucleoside triphosphate diphosphohydrolase 1	243111_at	(I) AP/4			(I) Blood[5]	6	
EPHB4 EPH receptor B4	202894_at	(I) DE/4			(D) Blood[5]	6	
ETNK1 ethanolamine kinase 1	224453_s_at	(D) AP/4			(D) Blood[5]	6	
FANCI Fanconi anemia, complementation group I	213008_at	(I) DE/4			(I) Blood[5]	6	*0.000897*
FBXL3 F-box and leucine-rich repeat protein 3	225132_at	(D) DE/4			(I) Blood[5]	6	*0.00127*
GTF3C3 general transcription factor IIIC, polypeptide 3, 102kDa	1555439_at	(I) AP/4			(I) Blood[5]	6	NC
HERC4 **HECT and RLD** domain containing E3 ubiquitin protein ligase 4	225988_at	(D) DE/4			(D) Blood[5]	6	*0.042192*
ITIH5 inter-alpha-trypsin inhibitor heavy chain family, member 5	1553243_at	(I) AP/4			(I) Blood[5]	6	
JMJD1C jumonji domain containing 1C	221763_at	(D) DE/4			(I) Blood[5]	6	0.191525

KLHL28 kelch-like family member 28	220374_at	(I) AP/4			(I) Blood[5]	6	
LARP4 La ribonucleoprotein domain family, member 4	214155_s_at	(D) DE/4			(D) Blood[5]	6	*0.014911*
MBNL1 muscleblind-like splicing regulator 1	201153_s_at	(D) DE/4			(D) Blood[5]	6	*0.009769*
MEX3C mex-3 RNA binding family member C	222567_s_at	(D) DE/4			(D) Blood[5]	6	*0.00603*
MR1 major histocompatibility complex, class I-related	207566_at	(I) DE/4			(D) Blood[5]	6	
NUDT6 nudix (nucleoside diphosphate linked moiety X)-type motif 6	220183_s_at	(D) AP/4			(D) Blood[5]	6	
PHC3 polyhomeotic homolog 3 (Drosophila)	1552644_a_at	(D) DE/4 (I) DE/1			(I) Blood[5]	6	
PIAS1 protein inhibitor of activated STAT, 1	1558418_at	(I) DE/4			(I) Blood[5]	6	
PPHLN1 periphilin 1	234459_at	(I) DE/4			(I) Blood[5]	6	
PRDX3 peroxiredoxin 3	201619_at	(D) DE/4			(I) Blood[5]	6	*0.000225*
PVT1 Pvt1 oncogene (non-protein coding)	1562153_a_at	(D) DE/4			(D) Blood[5]	6	*0.000433*
RAB22A RAB22A, member RAS oncogene family	218360_at	(D) DE/4			(I) Blood[5]	6	
RDH13 retinol dehydrogenase 13 (all-trans/9-cis)	225449_at	(I) AP/4			(D) Blood[5]	6	
SBNO1 strawberry notch homolog 1 (Drosophila)	229528_at	(I) DE/4			(I) Blood[5]	6	
SLC35B3 solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B3	231003_at	(D) DE/4			(I) Blood[5]	6	*3.34E-05*
SNRNP27 small nuclear ribonucleoprotein 27kDa (U4	212440_at	(D) DE/4			(D) Blood[5]	6	
SNX27	244349_at	(I)			(I)	6	

sorting nexin family member 27		AP/4			Blood[5]		
SSBP2 single-stranded DNA binding protein 2	1557814_a_at	(I) AP/4			(I) Blood[5]	6	
STRN striatin, calmodulin binding protein	1569813_at	(I) AP/4			(I) Blood[5]	6	
TTC7A tetratricopeptide repeat domain 7A	224924_at	(I) DE/4			(I) Blood[5]	6	
UIMC1 ubiquitin interaction motif containing 1	233596_at	(I) DE/4			(I) Blood[5]	6	
USP6NL USP6 N-terminal like	204761_at	(D) DE/4			(D) Blood[5]	6	*0.007614*
WAC WW domain containing adaptor with coiled-coil	230154_at	(D) DE/4			(D) Blood[5]	6	*8.53E-05*
WAPAL wings apart-like homolog (Drosophila)	212267_at	(D) DE/4			(D) Blood[5]	6	*0.002521*
ZBP1 Z-DNA binding protein 1	208087_s_at	(I) DE/4			(D) Blood[5]	6	
ZFAND5 zinc finger, AN1-type domain 5	210275_s_at	(D) DE/4			(D) Blood[5]	6	*0.042362*
ZNF117 zinc finger protein 117	207605_x_at	(D) DE/4			(D) Blood[5]	6	
ZNF141 zinc finger protein 141	206931_at	(D) DE/4			(D) Blood[5]	6	
ZNF548 zinc finger protein 548	1553718_at	(D) DE/4			(D) Blood[5]	6	*0.000461*
ZNF596 zinc finger protein 596	240324_at	(I) AP/4			(I) Blood[5]	6	
AP3S2 adaptor-related protein complex 3, sigma 2 subunit	213215_at	(I) DE/4				4	
SSR1 signal sequence receptor, alpha	200890_s_at	(D) DE/4				4	*0.000923*

Table S3. Top candidate biomarker genes – evidence for involvement in other psychiatric and non-psychiatric disorders (aging, pain). Underlined gene symbol means concordant with findings from our previous mood and psychosis biomarker studies (mood-opposite direction, psychosis-same direction). Alc- alcoholism; BP- Bipolar; SZ- schizophrenia. ASD- Autism spectrum disorders; ALZ- Alzheimer; PTSD-Post Traumatic Stress Disorder.

Gene Symbol/Gene Name	Probesets	Discovery (Change) Method/ Score	Prioritization CFG Score For Suicide	Validation ANOVA p-value	Circadian clock function	Prior human genetic evidence	Prior human Brain expression evidence	Prior human peripheral expression evidence	CFG Score For Other Disorders
Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)									
BCL2 B-cell CLL/Lymphoma 2	203684_s_at	(D) DE/2	9.00	**3.95E-06**		**Anxiety**[25] **BP**[26 27] **BP, SZ**[28]	**(I) Aging** PFC [29] **(D) BP** FC [30] **PTSD** DLPFC [31]	**(I) Alc** Blood [32] **Pain** Vertebral disc [33] **(D) BP** lymphoblast [26] **Mood stabilizers** Blood [34]	8.00
GSK3B glycogen synthase kinase 3 beta	226183_at	(D) DE/1	9.00	**2.26E-05**	**Clock Immediate Input**	**BP** [35 36 37] **MDD** [38] **Mood Stabilizers** [3 9] **MDD**[40 41] **SZ**[42 43]	**(D) Alc** HTH [44] **BP** Brain [45] DLPFC [46 47] ACC [46] **SZ** HIP [48 49] DLPFC [50 43] Thalamus[51] Temporal Cortex [52] **(I) MDD** HTH (I) [44] ACC, DLPFC [46]	**(I) MDD** Fibroblast[53] **(D) Mood stabilizers** platelets[54] **Mild Cognitive Impairment** Blood [55] **BP** platelets[54]	8.00
ALDH3A2 aldehyde dehydrogenase 3 family, member A2	202053_s_at	(D) DE/2	8.00	**1.62E-06**			**(D) BP** Brain [45]		4.00
AP1S2 adaptor-related protein complex 1, sigma 2 subunit	203299_s_at	(D) DE/1	8.00	**2.52E-05**			**(D) BP** Brain [45 56] **SZ,SZA** DLPFC [57]		4.00
CAT catalase	238363_at	(D) DE/2	8.00	**5.04E-07**			**(I) Mood Disorders NOS** ACC [58] **PTSD** DLPFC BA46 [31] **BP** ACC ,DLPFC[46]	**(I) BP** Plasma [59] **(D) SZ** Red Blood Cell[60] **SZ** Fibroblasts[61]	8.00

							(D) **MDD** BA47 [11]; ACC,DLPFC [46]		
JUN jun proto-oncogene	201466_s_at 201465_s_at,	(I) DE/2 DE/1	8.0 7.0	**1.14E-11** **1.72E-14**			**(I)** **MDD** BA2 [62] AMY [63] **SZ** cerebellar vermis [64] middle temporal gyrus [65] thalamus [66]	**SZ** Fibroblasts [67] **Neurological Pain** vertebral disc [33] **(D)** **Stress, Lithium** Leukocytes [68] **SZ** Blood [67]	6.00
C18orf54 chromosome 18 open reading frame 54	244324_at	(D) DE/1	7.00	**2.79E-06**					0.00
LINC00342 long intergenic non-protein coding RNA 342	1560661_x_at	(D) DE/2	7.00	**1.67E-06**					0.00
MOB3B MOB kinase activator 3B	229568_at	(D) DE/1	7.00	**4.69E-06**					0.00
NDRG1 N-myc downstream regulated 1	200632_s_at	(I) DE/1	7.00	**3.07E-07**	**Clock** **Distant** **Output**		**SZ** ACC (BA 24) [56] (I) **SZ** APFC [69]		4.00
PER1 period circadian clock 1	202861_at	(I) DE/1	7.00	**5.32E-12**	**Clock** **Core**	**ASD** [70] **Depression** [71] **Stress/Alc** [7 2]	**(Unspecified)** **MDD** DLPFC [73] **(D)** **BP** ACC [44] **(I)** **SZ** middle temporal gyrus [65]	**(I)** **BP** buccal mucosa cells [74] **MDD** leukocytes [75] **(D)** **SZ** Lymphocyte [76] **Alc** Blood [77]	8.00
RAPH1 Ras association (RalGDS	1552482_at	(I) DE/1	7.00	**7.44E-10**	**Clock** **Distant** **Output**		**(I)** **MDD** BA11 [15]	**(D)** **MDD** Blood [78 79] **(I)** **(MDD)** Fibroblast [53]	6.00
SPON1	213994_s_at	(D)	7.00	**1.02E-05**				**(I)**	8.00

spondin 1, extracellular matrix protein		DE/1				**Antidepressants** [80]	**(D)** **SZ** PFC (BA 46/10) [16]	**PTSD** Blood [81] **(D)** **SZ** Fibroblasts [61]	
FOXP1 forkhead box P1	223937_at	(I) DE/4	6.00	**7.03E-07**	**Clock Immediate Output**	**Alc** [82] **ASD** [83] **BP** [84] **SZ** [85]	**(I)** **MDD** AMY and cingulate cortex [86]	**(D)** **Circadian Abnormalities** Blood [87]	8.00
HAVCR2 hepatitis A virus cellular receptor 2	1555629_at	(I) DE/4	6.00	**1.69E-12**				**(I)** **PTSD** Blood [81] **SZ** Blood [88]	2.00
PIP5K1B phosphatidylinositol-4-phosphate 5-kinase, type I, beta	205632_s_at	(D) DE/4	6.00	**1.83E-05**			**(D)** **BP** Brain [45]	**(D)** **Delusions** Blood [89] **(I)** **SZ** Fibroblasts [61]	6.00
ARHGAP15 Rho GTPase activating protein 15	1561489_at	(I) DE/1	5.00	**3.05E-06**		**ASD** [90] **SZ** [85] **Alcohol** [13]			2.00
GJA1 gap junction protein, alpha 1, 43kDa	201667_at	(I) DE/1	5.00	**1.96E-06**			**(I)** **Alc** PFC [91] frontal **(D)** **Alc** [92] **MDD** Locus coeruleus foreBrain [93] **SZ** PFC BA 46/10) [16] supragenual (BA24) ACC [94]	**(I)** **Neurological Pain** vertebral disc [33]	6.00
HES1 hes family bHLH transcription factor 1	203394_s_at	(I) AP/1	5.00	**7.65E-10**					0.00
HTRA1 HtrA serine peptidase 1	201185_at	(I) AP/1	5.00	**3.17E-07**	**Clock Distant Output**		**(D)** **Alc** FC [92]	**(I)** **SZ** Blood [95]	6.00
PRCP prolylcarboxypeptidase (angiotensinase C)	242636_at	(D) DE/1	5.00	**2.36E-08**				**(D)** **Chronic Stress** Blood monocytes [96] **SZ** Fibroblasts [61] Blood [88]	2.00

TIMP1 TIMP metallopeptidase inhibitor 1	201666_at	(I) DE/1	5.00	**7.00E-07**			**(I)** **Alc** HIP [97] **ASD** cerebral cortex [98] **BP** FC [99] **MDD** HIP [19] DLPFC [100] **(D)** **BP** PFC BA 46/10 [16] **BP,MDD** Pituitary [101] **Alc** Frontal, motor cortex [102]	**(I)** **SZ** Plasma (I) [103] **(Unspecified)** **Antidepressants** BLOOD [104]	6.00
CD200R1 CD200 receptor 1	1553395_a_at	(D) DE/2	4.00	**1.45E-05**		**ASD, SZ** [105]			2.00
CD84 CD84 molecule	230391_at	(D) DE/2	4.00	**1.74E-05**				**(I)** **BP** Whole Blood [106] **Psychosis** Blood [89] **(D)** **ALZ** BMC [107] **Circadian abnormalities** Whole Blood [87]	2.00
CEP44 centrosomal protein 44kDa	231850_x_at	(D) DE/4	4.00	**6.71E-08**					0.00
CROT carnitine O-octanoyltransferase	231102_at	(D) DE/2	4.00	**7.62E-06**	**Clock** **Distant** **Output**	**Personality Disorder, Cynicism** [108]			2.00
DCAF5 DDB1 and CUL4 associated factor 5	224696_s_at	(D) DE/2	4.00	**1.37E-05**				**(D)** **Circadian abnormalities** Whole Blood [87]	2.00
DTWD2 DTW domain containing 2	231277_x_at	(D) DE/2	4.00	**1.87E-09**					0.00
EPB41L5 erythrocyte membrane protein band 4.1 like 5	229292_at	(I) DE/1	4.00	**4.58E-14**					0.00
ERP27 endoplasmic reticulum protein 27	227450_at	(D) DE/2	4.00	**9.54E-08**					0.00
FAM173B family with sequence similarity 173,	225670_at	(D) DE/2	4.00	**2.25E-05**			**(D)** **Alcohol** [97]		4.00

member B									
GANC glucosidase, alpha; neutral C	235714_at	(D) DE/2	4.00	**1.40E-08**		**ASD** [109]			2.00
GTF3C2 general transcription factor IIIC, polypeptide 2, beta 110kDa	210620_s_at	(D) DE/2	4.00	**1.68E-07**			**(D)** **MDD** AMY, cingulate cortex [86]		4.00
IL1R1 interleukin 1 receptor, type I	215561_s_at	(I) AP/1	4.00	**5.47E-08**		**Alc** [110]	**(I)** **Alcohol** NAC [111] HIP [97] **BP** Brain [45] FC [112] **(D)** **BP,SZ** DLPFC [113] **SZ** PFC [114] **SZ** PFC [114]	**(I)** **SZ** serum [115] [116] **Psychological Distress** peripheral Blood cells [117] **Stress** Leukocyte [118] **MDD** [119] **(D)** **SZ** PBMC [120]	7.00
INO80D INO80 complex subunit D	227924_at	(D) DE/2	4.00	**6.58E-06**					0.00
INPP4A inositol polyphosphate-4-phosphatase, type I, 107kDa	235695_at	(D) DE/1	4.00	**1.79E-05**		**Bipolar Psychosis** [121]	**(D)** **BP** Brain [45] **(I)** **SZ** supragenual (BA24) ACC [94]	**(D)** **BP** Lymphocyte [122]	8.00
ITLN1 intelectin 1 (galactofuranose binding)	223597_at	(I) DE/2	4.00	**6.69E-07**					0.00
JRK Jrk homolog (mouse)	37872_at	(D) AP/2	4.00	**4.25E-06**					0.00
KCTD5 potassium channel tetramerization domain containing 5	218474_s_at	(D) DE/2	4.00	**2.05E-07**				**(I)** **BP** Whole Blood [106]	2.00
KIR2DL4 killer cell immunoglobulin-like receptor, two domains, long cytoplasmic tail, 4	208426_x_at	(I) DE/2	4.00	**1.61E-11**				**SZ** Blood [95] **(I)** **Delusions** Blood [89] **Tourette Syndrome** Blood [123]	2.00
METTL15 methyltransferas	238773_at	(D) DE/2	4.00	**2.16E-06**					0.00

e like 15									
NUDT10 nudix (nucleoside diphosphate linked moiety X)-type motif 10	241596_at	(I) DE/2	4.00	**7.99E-07**				**(I)** **Hallucinations** Blood [89]	2.00
PDXDC1 pyridoxal-dependent decarboxylase domain containing 1	1560013_at	(I) DE/2	4.00	**1.03E-05**		**SZ** [124]			2.00
PIK3C3 phosphatidylinositol 3-kinase, catalytic subunit type 3	232086_at	(D) DE/1	4.00	**3.14E-08**		**BP** [125] **SZ** [126] **BP, SZ** [28, 127]	**(D)** **MDD** AMY, ACC [86]		6.00
RBM48 RNA binding motif protein 48	232661_s_at	(D) DE/2	4.00	**7.89E-07**					0.00
SMARCA2 SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 2	206543_at	(D) DE/1	4.00	**2.46E-05**		**SZ** [128] [129] [130] **Aging** [131] *CNV* **SZ** [132]	**(I)** **BP** FC [99] **SZ** DLPFC [133] DLPFC BA46 [134] **(D)** **SZ** PFC [129] **BP** Brain [45]	**(I)** **BP** Lymphocyte [76]	8.00
UCHL5 ubiquitin carboxyl-terminal hydrolase L5	1570145_at	(D) DE/2	4.00	**9.05E-11**			**(D)** **BP** Brain [45]	**(I)** **Antidepressants** Blood [135]	5.00
VPS53 vacuolar protein sorting 53 homolog (S. cerevisiae)	235882_at	(D) DE/2	4.00	**3.41E-09**			**(D)** **BP** Brain [45]	**(I)** **MDD** Fibroblast [53]	6.00
ZNF302 zinc finger protein 302	228392_at	(D) DE/2	4.00	**7.64E-06**			**(D)** **MDD** AMY, cingulate cortex [86] **(I)** **SZ** DLPFC [136]		4.00
Top Discovery and Prioritization Biomarkers(Non Bonferroni Validated, 65 genes)									
CLTA clathrin, light chain A	216296_at	(I) DE/4	10.00				**(I)** **MDD** FC [22] **(D)** **BP** Brain [45]	**(D)** **ALZ** Blood [107]	6.00
FAM214A family with sequence similarity 214, member A	236237_at	(I) DE/4	10.00						0.00

HSPD1 heat shock 60kDa protein 1 (chaperonin)	241716_at	(I) DE/4	10.00	*0.021922*		**SZ** [137]	**(D) Alc** FC [92] **(I) BP** parietal cortex [138] **MDD** AMY and cingulate cortex [86] **PTSD** DLPFC [31]	**(I) Antidepressants** Blood [135] MNC [139] **(D) Circadian Abnormalities** Blood [87] **SZ** Blood [140] **Mood Disorder NOS** Fetal Brain cultured in cortisol treatment 3weeks [141]	8.00
ZMYND8 zinc finger, MYND-type containing 8	214795_at	(I) AP/4	10.00				**(I) SZ** DLPFC [136]		4.00
AK2 adenylate kinase 2	212172_at	(I) AP/4	8.00		**Clock Distant Output**		**(D) BP,SZ** PFC (BA46) [142]		4.00
CAPZA2 capping protein (actin filament) muscle Z-line, alpha 2	201238_s_at	(D) DE/4	8.00	0.116785			**(D) BP** ACC [56]; Brain [45] **SZ** Thalamus [51]	**(D) BP, MDD,SZ** CSF [143] **PTSD** Blood [81]	6.00
LRRC8B leucine rich repeat containing 8 family, member B	212976_at	(D) DE/4	8.00	0.231881			**(D) BP** Brain [45] **(I) MDD** BA11 [15] **SZ** DPFC (BA 46) [134]	**(D) Mood State** Blood [144]	6.00
PPM1B protein phosphatase, Mg2+	209296_at	(D) DE/4	8.00	*0.002299*	**Clock Immediate Input**		**(D) Alc** FC [145]		4.00
ACTR3 ARP3 actin-related protein 3 homolog (yeast)	213102_at	(D) DE/4	7.00	*0.004524*			**(I) BP** ACC (BA 24) [56]; Brain **SZ** ACC [146] **(D) BP** [45] PFC [147] **SZ,SZA** DLPFC [57] **SZA** APFC [69]	**(I) BP** Blood [106]	6.00
AFF3 AF4/FMR2 family, member 3	244696_at	(I) AP/4	7.00			**SZ** [85]	**(D) BP** Brain [45]	**(I) BP** Blood [106]	8.00
MRPS5 mitochondrial ribosomal	237560_at	(I) AP/4	7.00				**(D) Alc** HIP [97]	**(I) PTSD** Blood [81]	6.00

protein S5									
SH2D1A SH2 domain containing 1A	211211_x_at	(D) DE/4	7.00				**(I)** **BP** APFC [69]	**(I)** **PTSD** Blood [81] **Antidepressants** Blood [135]	6.00
AKT3 v-akt murine thymoma viral oncogene homolog 3	240568_at	(I) AP/4	6.00			**SZ** [148] [149] [137] **Longevity** [150]	**(D)** **BP** Brain [45]		6.00
ALG13 ALG13, UDP-N-acetylglucosaminyltransferase subunit	205584_at	(D) DE/4	6.00	*0.046957*			**(D)** **BP** Brain [45]	**(I)** **BP** Blood [106]	6.00
ARHGAP35 Rho GTPase activating protein 35	229397_s_at	(D) DE/4	6.00	*0.0016*					0.00
ARID4B AT rich interactive domain 4B (RBP1-like)	221230_s_at	(D) DE/4	6.00						0.00
ASPH aspartate beta-hydroxylase	242037_at	(I) DE/4	6.00	*0.01087*				**(I)** **MDD** Blood [151]	2.00
ATXN1 ataxin 1	1565804_at	(I) DE/4	6.00			**ADHD** [152] **Alc** [82] **BP** [153 154 84] **SZ** [155 156] [126 153 42]	**(D)** **Alc** Frontal, motor cortex [102]	**(I)** **Mood State** Blood [144] **Pain** vertebral disc [33] **Social Isolation** leukocytes [157] **(D)** **Delusions/ Hallucinations** Blood [89] **Chronic Stress** BLOOD monocytes [96]	6.00
BRE Brain and reproductive organ-expressed (TNFRSF1A modulator)	1556817_a_at	(I) AP/4	6.00			**BP** [158] **Longevity** [159]	**(D)** **BP** Brain [45]		6.00
CHMP2B charged multivesicular body protein 2B	202538_s_at	(D) DE/4	6.00	*0.022703*			**(I)** **MDD** AMY and cingulate cortex [86]		4.00
CLPB ClpB caseinolytic peptidase B homolog (E. coli)	1566581_at	(I) AP/4	6.00	*0.025268*					0.00
CSNK1A1 casein kinase 1, alpha 1	235464_at	(D) DE/4	6.00		**Clock Immediate Input**		**(D)** **Alc** temporal cortex [160] **(Unspecified)** **MDD** thalamus [51]	**(I)** **Mood stabilizers** Human astrocyte-derived cells U-87 MG (I) [161] **(D)**	6.00

								Mood State Blood [144]	
DPCD deleted in primary ciliary dyskinesia homolog (mouse)	226009_at	(I) DE/4	6.00				**(D) BP** Brain [45]	**(I) PTSD** Blood [81] **(D) BP** Whole Blood [106]	6.00
ECSIT ECSIT signalling integrator	218225_at	(I) DE/4	6.00				**(D) BP** Brain [45]	**(I) BP** Blood [106]	6.00
ENTPD1 ectonucleoside triphosphate diphosphohydrolase 1	243111_at	(I) AP/4	6.00					**(I) SZ** Blood mononuclear cells [162]	2.00
EPHB4 EPH receptor B4	202894_at	(I) DE/4	6.00				**(I) BP** DPFC (BA 46) [163] **SZ** DLPFC (BA 46) [163]		4.00
ETNK1 ethanolamine kinase 1	224453_s_at	(D) AP/4	6.00				**(D) BP** Brain [45] **(I) MDD** AMY and cingulate cortex [86]		4.00
FANCI Fanconi anemia, complementation group I	213008_at	(I) DE/4	6.00	*0.000897*			**(D) MDD** DLPFC [164]	**(D) Delusions** Blood [89]	6.00
FBXL3 F-box and leucine-rich repeat protein 3	225132_at	(D) DE/4	6.00	*0.00127*	**Clock Immediate Input**		**(D) Alc** superior FC [145] **(I) Alz** Occipital lobe [165]	**(I) BP** Blood [106] **(D) SZ** Fibroblasts [61]	6.00
FGFR1OP2 FGFR1 oncogene partner 2	223262_s_at	(D) DE/4	6.00				**(D) BP** Brain [45]	**(I) BP** Blood [106]	6.00
GTF3C3 general transcription factor IIIC, polypeptide 3, 102kDa	1555439_at	(I) AP/4	6.00				**(I) SZ** PFC [166]	**(D) Circadian abnormalities** Blood [87]	6.00
HERC4 HECT and RLD domain containing E3 ubiquitin protein ligase 4	225988_at	(D) DE/4	6.00	*0.042192*			**(D) Alc** HIP [97]	**(D) Delusions** Blood [89] **(I) BP** Blood [106]	6.00
ITIH5 inter-alpha-trypsin inhibitor heavy chain family, member 5	1553243_at	(I) AP/4	6.00			**BP** [84] **Alc** [167]	**(D) BP** Brain [45]	**(I) PTSD** Blood [81]	8.00
JMJD1C jumonji domain containing 1C	221763_at	(D) DE/4	6.00	0.191525		**Anxiety, BP** [168]		**(I) BP** Blood [106] **(D) PTSD** Blood [81]	4.00

KLHL28 kelch-like family member 28	220374_at	(I) AP/4	6.00				**(D)** **Alc** HIP [97]	**(I)** **BP** Blood [106]	6.00
LARP4 La ribonucleoprotein domain family, member 4	214155_s_at	(D) DE/4	6.00	*0.014911*				**(D)** **Mood State** Blood [144] **Circadian abnormalities** Blood [87]	2.00
MBNL1 muscleblind-like splicing regulator 1	201153_s_at	(D) DE/4	6.00	*0.009769*		**BP** [169]	**(I)** **MDD** AMY and cingulate cortex [86] **SZ** DLPFC - BA 46 [170]	**(D)** **BP** Blood [106] **MDD** Blood [151] **(I)** **Longevity** [171]	8.00
MEX3C mex-3 RNA binding family member C	222567_s_at	(D) DE/4	6.00	*0.00603*				**(I)** **Alc** Blood [32] **PTSD** Blood [81] **(D)** **BP** Blood [106]	2.00
MIER1 mesoderm induction early response 1, transcriptional regulator	225475_at	(D) DE/4	6.00	*0.031445*					0.00
MR1 major histocompatibility complex, class I-related	207566_at	(I) DE/4	6.00						0.00
NUDT6 nudix (nucleoside diphosphate linked moiety X)-type motif 6	220183_s_at	(D) AP/4	6.00					**(I)** **SZ** serum [172]	2.00
PHC3 polyhomeotic homolog 3 (Drosophila)	1552644_a_at	(D) DE/4	6.00						0.00
PIAS1 protein inhibitor of activated STAT, 1	1558418_at	(I) DE/4	6.00		**Clock** **Distant** **Output**		**(D)** **MS** Subcortical,periventricular,medial subcortical white matter [173]	**(D)** **Alc** Blood [32]	6.00
PPHLN1 periphilin 1	234459_at	(I) DE/4	6.00					**(D)** **BP** Whole Blood [106]	2.00
PRDX3 peroxiredoxin 3	201619_at	(D) DE/4	6.00	*0.000225*			**(I)** **SZA** APFC [69] **SZ** PFC [174] **(D)**	**(D)** **Chronic Stress** Blood monocytes [96]	6.00

							Alc Superior Frontal Gyrus [175] **BP** Brain [45] **MDD** Pituitary [101] **BP, MDD** APFC [69]		
PVT1 Pvt1 oncogene (non-protein coding)	1562153_a_at	(D) DE/4	6.00	*0.000433*		**Psychosis** [176] **SZ,BP** [177]			2.00
RAB22A RAB22A, member RAS oncogene family	218360_at	(D) DE/4	6.00						0.00
RDH13 retinol dehydrogenase 13 (all-trans/9-cis)	225449_at	(I) AP/4	6.00				**(D)** **PTSD** DLPFC BA46 [31]		4.00
SBNO1 strawberry notch homolog 1 (Drosophila)	229528_at	(I) DE/4	6.00			**SZ** [178] [137]	**(I)** **Alc** superior FC [145]	**(I)** **SZ** Fibroblasts [61]	8.00
SLC35B3 solute carrier family 35 (adenosine 3'-phospho 5'-phosphosulfate transporter), member B3	231003_at	(D) DE/4	6.00	*3.34E-05*	**Clock** **Distant** **Output**		**(I)** **BP** Brain [45]	**(D)** **Delusions** Blood [89]	6.00
SNRNP27 small nuclear ribonucleoprotein 27kDa (U4	212440_at	(D) DE/4	6.00				**(I)** **MDD** AMY, cingulate cortex [86]		4.00
SNX27 sorting nexin family member 27	244349_at	(I) AP/4	6.00				**(D)** **Alc** HIP [97] **SZ** STG [179]	**(I)** **Delusions/** **Hallucinations** Blood [89] **(D)** **BP** Blood [106]	6.00
SSBP2 single-stranded DNA binding protein 2	1557814_a_at	(I) AP/4	6.00				**(D)** **BP** Brain [45] **(I)** **MDD** AMY and cingulate cortex [86]	**(D)** **Mood State** Blood [144]	6.00
STRN striatin, calmodulin binding protein	1569813_at	(I) AP/4	6.00				**(D)** **Alc** HIP [97]	**(I)** **MDD** leukocytes [180]	6.00
TTC7A tetratricopeptide repeat domain 7A	224924_at	(I) DE/4	6.00			**MDD** [40]			2.00
UIMC1 ubiquitin interaction motif containing 1	233596_at	(I) DE/4	6.00						0.00

USP6NL USP6 N-terminal like	204761_at	(D) DE/4	6.00	*0.007614*				**(D)** **Mood State** Blood [144]	2.00
WAC WW domain containing adaptor with coiled-coil	230154_at	(D) DE/4	6.00	*8.53E-05*		**ASD** [83]	**(Unspecified)** **BP** ACC (BA 24) [56]		6.00
WAPAL wings apart-like homolog (Drosophila)	212267_at	(D) DE/4	6.00	*0.002521*				**(I)** **Mood stabilizers** SK-N-AS cells [181]	2.00
ZBP1 Z-DNA binding protein 1	208087_s_at	(I) DE/4	6.00				**(I)** **Alc** HIP [97]	**(I)** **SZ** LCLs [182] Blood leukocytes (Stress, PTSD, Post-Traumatic Stress Disorder) 0	6.00
ZFAND5 zinc finger, AN1-type domain 5	210275_s_at	(D) DE/4	6.00	*0.042362*					0.00
ZNF117 zinc finger protein 117	207605_x_at	(D) DE/4	6.00				**(I)** **MDD** FC [183]		4.00
ZNF141 zinc finger protein 141	206931_at	(D) DE/4	6.00						0.00
ZNF548 zinc finger protein 548	1553718_at	(D) DE/4	6.00	*0.000461*					0.00
ZNF596 zinc finger protein 596	240324_at	(I) AP/4	6.00					**(D)** **Mood State** Blood [144]	2.00

Table S4. Top candidate biomarker genes - drugs that modulate these markers in the opposite direction. FC- frontal cortex. HIP-Hippocampus. AMY- amygdala. VT-ventral tegmentum. Underlined-potential pharmacogenomics marker.

Gene Symbol/ Gene Name	Discovery (Change) Method/ Score	Prioritization Total CFG Score For Suicide	Validation ANOVA p-value	Modulated by Omega-3	Modulated by Lithium	Modulated by Clozapine	Other Drugs
Out of Validated Biomarkers (Bonferroni) (49 genes, 50 probesets)							
BCL2 B-cell CLL	(D) DE/2	9.00	**3.95E-06**		**(I)** FC [184] **(I)** cerebellar granule cells [185] **(I)** **Human Blood** [34] **(I)** Astrocyte [186] **(I)** HIP [187] **(I)** Dentate gyrus, HIP[188]	**(I)** Hip [189]	oblimersen,rasagiline,(-)-gossypol,navitoclax,gemcitabine/paclitaxel,bortezomib/paclitaxel,ABT-199,paclitaxel/trastuzumab,paclitaxel/pertuzumab/trastuzumab,lapatinib/paclitaxel,doxorubicin/paclitaxel,epirubicin/paclitaxel,paclitaxel/topotecan,paclitaxel
GSK3B glycogen synthase kinase 3 beta	(D) DE/1	9.00	**2.26E-05**		**(I)** FC [190]		enzastaurin
CAT catalase	(D) DE/2	8.00	**5.04E-07**		BP **(I)** Plasma [59]		fomepizole
JUN jun proto-oncogene	(I) DE/2 DE/1	8.00	**1.14E-11** **1.72E-14**		**(D)** leukocytes[68]	**(D)** FC [191]	
MOB3B MOB kinase activator 3B	(D) DE/1	7.00	**4.69E-06**	**(I)** PFC (females) [192]			
NDRG1 N-myc downstream regulated 1	(I) DE/1	7.00	**3.07E-07**	**(D)** Blood[192]			
SPON1 spondin 1, extracellular matrix protein	(D) DE/1	7.00	**1.02E-05**			**(I)** VT [193]	
FOXP1 forkhead box P1	(I) DE/4	6.00	**7.03E-07**	**(D)** Blood[192]			
HAVCR2 hepatitis A virus cellular receptor 2	(I) DE/4	6.00	**1.69E-12**			**(D)** PFC [194]	
GJA1 gap junction protein, alpha 1, 43kDa	(I) DE/1	5.00	**1.96E-06**	**(D)** HIP (females) [192]		**(D)** VT [193]	
CD84 CD84 molecule	(D) DE/2	4.00	**1.74E-05**			**(I)** Blood [193]	
DCAF5 DDB1 and	(D) DE/2	4.00	**1.37E-05**			**(I)** VT	

CUL4 associated factor 5						[193]	
GANC glucosidase, alpha; neutral C	(D) DE/2	4.00	**1.40E-08**				miglitol
IL1R1 interleukin 1 receptor, type I	(I) AP/1	4.00	**5.47E-08**				anakinra
INPP4A inositol polyphosphate -4- phosphatase, type I, 107kDa	(D) DE/1	4	**1.79E-05**			**(I)** VT [193]	
JRK Jrk homolog (mouse)	(D) AP/2	4.00	**4.25E-06**	**(I)** Brain[195]			
PDXDC1 pyridoxal-dependent decarboxylase domain containing 1	(I) DE/2	4.00	**1.03E-05**			**(D)** VT[193]	
SMARCA2 SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 2	(D) DE/1	4.00	**2.46E-05**	**(I)** HIP (males) [192]			
Out of Top Discovery and Prioritization Biomarkers(Non Bonferroni Validated, 65 genes)							
CLTA clathrin, light chain A	(I) DE/4	10.00				**(D)** FC[191]	
PPM1B protein phosphatase, Mg2+	(D) DE/4	8.00	*0.002299*			**(I)** VT[193]	
AFF3 AF4/FMR2 family, member 3	(I) AP/4; (I) DE/1	7.00		**(D)** Blood [192]			
WAC WW domain containing adaptor with coiled-coil	(D) DE/4	7.00	*8.53E-05*			**(I)** VT[193]	
AKT3 v-akt murine thymoma viral oncogene homolog 3	(I) AP/4	6.00					enzastaurin
ARID4B AT rich interactive domain 4B (RBP1-like)	(D) DE/4	6.00		**(I)** HIP (males) [192]			
ATXN1 ataxin 1	(I) DE/4	6.00		**(D)** Blood[192]			
BRE Brain and reproductive organ-expressed (TNFRSF1A	(I) AP/4	6.00				**(D)** VT[193]	

modulator)							
CSNK1A1 casein kinase 1, alpha 1	(D) DE/4	6.00		**(I)** Blood[192]			
ENTPD1 ecton ucleoside triphosphate diphosphohydr olase 1	(I) AP/4	6.00		**(D)** Blood[192]		**(D)** PFC[194]	
EPHB4 EPH receptor B4	(I) DE/4	6.00					tesevatinib
ETNK1 ethanolamine kinase 1	(D) AP/4	6.00		**(I)** PFC (males)[192]			
ITIH5 inter-alpha-trypsin inhibitor heavy chain family, member 5	(I) AP/4	6.00		**(D)** Blood[192]		**(D)** PFC[194]	
LARP4 La ribonucleoprot ein domain family, member 4	(D) DE/4	6.00	*0.014911*			**(I)** VT[193]	
MBNL1 muscleblind-like splicing regulator 1	(D) DE/4	6.00	*0.009769*	**(I)** HIP (males) [192]		**(I)** Blood[193]	
MR1 major histocompatibi lity complex, class I-related	(I) DE/4	6.00					antiLymphocyte serum
PRDX3 peroxiredoxin 3	(D) DE/4	6.00	*0.000225*	**(I)** Blood[192]			
RAB22A RAB22A, member RAS oncogene family	(D) DE/4	6.00				**(I)** Blood[193]	
SNX27 sorting nexin family member 27	(I) AP/4	6.00				**(D)** AMY[193]	
SSBP2 single-stranded DNA binding protein 2	(I) AP/4	6.00		**(D)** Blood[192]		**(D)** VT[193]	
WAPAL wings apart-like homolog (Drosophila)	(D) DE/4	6.00	*0.002521*		**(I)** SK-N-AS cells (ATCC derived from a human neuroblastoma cell [181]	**(I)** VT[193]	

Table S5 Biological Pathways and Diseases. Suicidal ideation markers non-validated for behavior in completers (n=886) vs. suicidal ideation markers that were stepwise validated for behavior in completers (n=595).

A.	Ingenuity Pathways				KEGG Pathways			GeneGO Pathways		
	#	Top Canonical Pathways	P-Value	Ratio	Pathway Name	Ratio	Enrichment p-value	Process Networks	Ratio	p-value
Non-Validated Stepwise in Completers (n=882 genes) Biomarkers for IDEATION only	1	PI3K Signaling in B Lymphocytes	6.05 E-13	20.3 % 27/133	Amoebiasis	17/368	2.95E-05	Immune response_BCR pathway	30/137	5.123E-09
	2	B Cell Receptor Signaling	3.08 E-11	16.2 % 29/179	Glioma	15/300	3.69E-05	Cytoskeleton_Regulation of cytoskeleton rearrangement	33/183	1.357E-07
	3	Role of NFAT in Cardiac Hypertrophy	3.91 E-10	15.1 % 28/186	Pancreatic cancer	15/366	0.0003	Signal transduction_WNT signaling	31/177	6.413E-07
	4	Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	1.05 E-09	11.9 % 36/302	Focal adhesion	24/771	0.000318	Signal transduction_Neuropeptide signaling pathways	28/155	1.189E-06
	5	Amyotrophic Lateral Sclerosis Signaling	2.78 E-09	18.7 % 20/107	Phosphatidylinositol signaling system	12/251	0.000324	Cell cycle_G1-S Growth factor regulation	32/195	1.875E-06
	#	Top Canonical Pathways	P-Value	Ratio	Pathway Name	Ratio	Enrichment p-value	Process Networks	Ratio	p-value
Validation Stepwise in Completers (n=589 genes) Biomarkers for IDEATION and BEHAVIOR	1	Glucocorticoid Receptor Signaling	2.86 E-06	7.8 % 22/281	Morphine addiction	9/249	0.0006493	Reproduction_Gonadotropin regulation	24/199	9.843E-07
	2	IGF-1 Signaling	7.18 E-06	12.1 % 12/99	Colorectal cancer	9/287	0.0016932	Reproduction_GnRH signaling pathway	20/166	8.256E-06
	3	Renin-Angiotensin Signaling	8.72 E-06	11.0 % 13/118	Cocaine addiction	6/155	0.0037291	Reproduction_Progesterone signaling	23/214	1.194E-05
	4	Protein Kinase A Signaling	1.02 E-05	6.5 % 26/398	Insulin signaling pathway	12/535	0.0047284	Signal transduction_NOTCH signaling	24/236	1.962E-05
	5	Melanocyte Development and Pigmentation Signaling	1.02 E-05	12.8 % 11/86	Inositol phosphate metabolism	6/193	0.0101986	Signal transduction_Androgen receptor signaling cross-talk	12/72	2.241E-05

B.		**Ingenuity**			**GeneGO**		
		Diseases and Disorders	**P-Value**	**# Molecules**	**Diseases**	**pValue**	**Ratio**
Non-Validated Stepwise in Completers (n=886 genes) **Biomarkers for IDEATION only**	1	Cancer	1.33E-04E - 2.55E-23	440	Mental Disorders	1.44E-25	166/1610
	2	Organismal Injury and Abnormalities	1.33E-04E - 2.55E-23	440	Psychiatry and Psychology	3.23E-24	182/1904
	3	Gastrointestinal Disease	9.09E-05 - 2.12E-18	333	Central Nervous System Diseases	1.43E-22	247/3060
	4	Reproductive System Disease	2.80E-05 - 7.72E-18	244	Neurodegenerative Diseases	1.98E-22	189/2087
	5	Infectious Diseases	3.72E-05 - 6.69E-15	109	Depressive Disorder, Major	1.31E-21	80/543
		Diseases and Disorders	**P-Value**	**# Molecules**	**Diseases**	**pValue**	**Ratio**
Validation Stepwise in Completers (n=592 genes) **Biomarkers for IDEATION and BEHAVIOR**	1	Cancer	6.51E-04 - 6.47E-17	489	Breast Neoplasms	2.361E-15	359/8894
	2	Organismal Injury and Abnormalities	6.92E-04 - 6.47E-17	494	Breast Diseases	2.407E-15	359/8895
	3	Gastrointestinal Disease	6.27E-04 - 6.91E-10	354	Psychiatry and Psychology	3.842E-14	115/1904
	4	Reproductive System Disease	2.60E-04 - 1.51E-08	237	Pathological Conditions, Signs and Symptoms	1.247E-13	208/4433
	5	Infectious Diseases	6.92E-04 - 9.45E-8	104	Mental Disorders	1.833E-13	101/1610

Table S6 Drugs that have similar and opposite gene expression profile to our suicide biomarkers.

Connectivity Map (cmap) (Broad/MIT)[196] results. Cmap comprises a collection of genome-wide transcriptional expression data from cultured human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of functional connections between drugs, genes and diseases through the transitory feature of common gene-expression changes [196], [197]. Score of 1 means maximum similarity, score of -1 means maximum opposite effect. Red (most)/pink (other commonly used medications) that mimic effects of suicidality, i.e. may induce suicidality. **Green (most)/light green other commonly used medications) that do the opposite to suicide, i.e. may be tested for or used to generate leads to treat/prevent suicidality.** A. Validated Bonferroni biomarkers. B. Top biomarkers from validation, as well as discovery and prioritization (Table S2). C. Validated nominally significant biomarkers.

A. Validated Bonferroni Significant Biomarkers (49 Genes)

rank	batch	cmap name	dose	cell	score
1	683	lycorine	12 µM	PC3	1
3	645	lycorine	12 µM	HL60	0.947
6	726	digoxigenin	10 µM	MCF7	0.924
7	715	digoxin	5 µM	PC3	0.923
10	767	fluphenazine	10 µM	MCF7	0.914
12	506	thioridazine	10 µM	MCF7	0.9
14	504	felodipine	10 µM	MCF7	0.889
17	636	tamoxifen	7 µM	MCF7	0.86
22	502	felodipine	10 µM	MCF7	0.854
6081	622	mifepristone	9 µM	HL60	-0.797
6097	665	**lansoprazole**	11 µM	HL60	-0.888
6098	658	nafcillin	9 µM	HL60	-0.895
6100	665	betulin	9 µM	HL60	-1

B. Top Biomarkers (114 Genes)

rank	batch	cmap name	dose	cell	score
1	631	7-aminocephalosporanic acid	15 µM	HL60	1
7	647	methotrexate	9 µM	MCF7	0.902
9	661	ribavirin	16 µM	HL60	0.894
10	664	fluticasone	8 µM	HL60	0.888
15	1074	pioglitazone	10 µM	MCF7	0.859
20	659	ganciclovir	16 µM	HL60	0.834
21	645	flunisolide	9 µM	HL60	0.834
35	695	simvastatin	10 µM	MCF7	0.805
6049	650	troglitazone	10 µM	HL60	-0.8
6059	635	rifampicin	5 µM	HL60	-0.812
6061	732	ondansetron	12 µM	PC3	-0.813
6062	636	tetracycline	8 µM	MCF7	-0.817

6063	665	**lansoprazole**	11 µM	HL60	-0.821
6064	707	dicloxacillin	8 µM	MCF7	-0.824
6067	630	**buspirone**	9 µM	HL60	-0.83
6072	650	**estradiol**	100 nM	HL60	-0.839
6080	650	**acetylsalicylic acid**	100 µM	HL60	-0.868
6083	750	**LY-294002**	10 µM	HL60	-0.881
6092	694	minoxidil	19 µM	MCF7	-0.92
6097	650	**LY-294002**	10 µM	HL60	-0.96
6100	694	zalcitabine	19 µM	MCF7	-1

C. Validated Nominally Significant Biomarkers (396 genes)

rank	batch	cmap name	dose	cell	score
1	665	pivampicillin	9 µM	HL60	1
6	648	metoprolol	6 µM	HL60	0.902
18	630	cefalexin	11 µM	HL60	0.852
20	749	dexpropranolol	14 µM	HL60	0.843
23	750	valproic acid	200 µM	HL60	0.831
6079	634	**fluoxetine**	12 µM	HL60	-0.772
6082	602	haloperidol	10 µM	HL60	-0.791
6085	629	**diphenhydramine**	14 µM	HL60	-0.799
6091	630	prochlorperazine	7 µM	HL60	-0.832
6092	629	**metformin**	24 µM	HL60	-0.837
6095	665	**lansoprazole**	11 µM	HL60	-0.873
6098	631	corticosterone	12 µM	HL60	-0.919
6100	649	atractyloside	5 µM	HL60	-1

Literature Cited

1. Vargas JL, Sainz M, Roldan C, Alvarez I, de la Torre A. Analysis of electrical thresholds and maximum comfortable levels in cochlear implant patients. *Auris, nasus, larynx* 2013; **40**(3)**:** 260-265.

2. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N *et al.* Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Mol Psychiatry* 2015; **20**(11)**:** 1266-1285.

3. Butler AW, Breen G, Tozzi F, Craddock N, Gill M, Korszun A *et al.* A genomewide linkage study on suicidality in major depressive disorder confirms evidence for linkage to 2p12. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**(8)**:** 1465-1473.

4. Smalheiser NR, Lugli G, Rizavi HS, Torvik VI, Turecki G, Dwivedi Y. MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects. *PLoS One* 2012; **7**(3)**:** e33201.

5. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N *et al.* Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular psychiatry* 2015.

6. Jimenez E, Arias B, Mitjans M, Goikolea JM, Roda E, Saiz PA *et al.* Genetic variability at IMPA2, INPP1 and GSK3beta increases the risk of suicidal behavior in bipolar patients. *Eur Neuropsychopharmacol* 2013; **23**(11)**:** 1452-1462.

7. Ren X, Rizavi HS, Khan MA, Dwivedi Y, Pandey GN. Altered Wnt signalling in the teenage suicide brain: focus on glycogen synthase kinase-3beta and beta-catenin. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum* 2013; **16**(5)**:** 945-955.

8. Pandey GN, Dwivedi Y, Rizavi HS, Teppen T, Gaszner GL, Roberts RC *et al.* GSK-3beta gene expression in human postmortem brain: regional distribution, effects of age and suicide. *Neurochem Res* 2009; **34**(2)**:** 274-285.

9. Fiori LM, Bureau A, Labbe A, Croteau J, Noel S, Merette C *et al.* Global gene expression profiling of the polyamine system in suicide completers. *Int J Neuropsychopharmacol* 2011; **14**(5)**:** 595-605.

10. Fiori LM, Zouk H, Himmelman C, Turecki G. X chromosome and suicide. *Molecular psychiatry* 2011; **16**(2)**:** 216-226.

11. Klempan TA, Sequeira A, Canetti L, Lalovic A, Ernst C, ffrench-Mullen J *et al.* Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. *Molecular psychiatry* 2009; **14**(2)**:** 175-189.

12. Labonte B, Suderman M, Maussion G, Lopez JP, Navarro-Sanchez L, Yerko V *et al.* Genome-wide methylation changes in the brains of suicide completers. *Am J Psychiatry* 2013; **170**(5)**:** 511-520.

13. Dick DM, Meyers J, Aliev F, Nurnberger J, Jr., Kramer J, Kuperman S *et al.* Evidence for genes on chromosome 2 contributing to alcohol dependence with conduct disorder and suicide attempts. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2010; **153B**(6)**:** 1179-1188.

14. Sequeira A, Morgan L, Walsh DM, Cartagena PM, Choudary P, Li J *et al.* Gene expression changes in the prefrontal cortex, anterior cingulate cortex and nucleus accumbens of mood disorders subjects that committed suicide. *PloS one* 2012; **7**(4)**:** e35367.

15. Sequeira A, Gwadry FG, Ffrench-Mullen JM, Canetti L, Gingras Y, Casero RA, Jr. *et al.* Implication of SSAT by gene expression and genetic variation in suicide and major depression. *Arch Gen Psychiatry* 2006; **63**(1)**:** 35-48.

16. Kim S, Choi KH, Baykiz AF, Gershenfeld HK. Suicide candidate genes associated with bipolar disorder and schizophrenia: an exploratory gene expression profiling analysis of post-mortem prefrontal cortex. *BMC Genomics* 2007; **8:** 413.

17. Ernst C, Nagy C, Kim S, Yang JP, Deng X, Hellstrom IC *et al.* Dysfunction of astrocyte connexins 30 and 43 in dorsal lateral prefrontal cortex of suicide completers. *Biol Psychiatry* 2011; **70**(4)**:** 312-319.

18. Monsalve EM, Garcia-Gutierrez MS, Navarrete F, Giner S, Laborda J, Manzanares J. Abnormal expression pattern of Notch receptors, ligands, and downstream effectors in the dorsolateral prefrontal cortex and amygdala of suicidal victims. *Mol Neurobiol* 2014; **49**(2)**:** 957-965.

19. Hoyo-Becerra C, Huebener A, Trippler M, Lutterbeck M, Liu ZJ, Truebner K *et al.* Concomitant interferon alpha stimulation and TLR3 activation induces neuronal expression of depression-related genes that are elevated in the brain of suicidal persons. *PloS one* 2013; **8**(12)**:** e83149.

20. Hesselbrock V, Dick D, Hesselbrock M, Foroud T, Schuckit M, Edenberg H *et al.* The search for genetic risk factors associated with suicidal behavior. *Alcohol Clin Exp Res* 2004; **28**(5 Suppl)**:** 70S-76S.

21. Menke A, Domschke K, Czamara D, Klengel T, Hennings J, Lucae S *et al.* Genome-wide association study of antidepressant treatment-emergent suicidal ideation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2012; **37**(3)**:** 797-807.

22. Zhurov V, Stead JD, Merali Z, Palkovits M, Faludi G, Schild-Poulter C *et al.* Molecular pathway reconstruction and analysis of disturbed gene expression in depressed individuals who died by suicide. *PLoS One* 2012; **7**(10)**:** e47581.

23. Kekesi KA, Juhasz G, Simor A, Gulyassy P, Szego EM, Hunyadi-Gulyas E *et al.* Altered functional protein networks in the prefrontal cortex and amygdala of victims of suicide. *PLoS One* 2012; **7**(12)**:** e50532.

24. Coon H, Darlington T, Pimentel R, Smith KR, Huff CD, Hu H *et al.* Genetic risk factors in two Utah pedigrees at high risk for suicide. *Translational psychiatry* 2013; **3:** e325.

25. Sipila T, Kananen L, Greco D, Donner J, Silander K, Terwilliger JD *et al.* An association analysis of circadian genes in anxiety disorders. *Biological psychiatry* 2010; **67**(12)**:** 1163-1170.

26. Machado-Vieira R, Pivovarova NB, Stanika RI, Yuan P, Wang Y, Zhou R *et al.* The Bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. *Biological psychiatry* 2011; **69**(4)**:** 344-352.

27. Soeiro-de-Souza MG, Salvadore G, Moreno RA, Otaduy MC, Chaim KT, Gattaz WF *et al.* Bcl-2 rs956572 polymorphism is associated with increased anterior cingulate cortical glutamate in euthymic bipolar I disorder. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2013; **38**(3)**:** 468-475.

28. Yu H, Bi W, Liu C, Zhao Y, Zhang D, Yue W. A hypothesis-driven pathway analysis reveals myelin-related pathways that contribute to the risk of schizophrenia and bipolar disorder. *Progress in neuro-psychopharmacology & biological psychiatry* 2014; **51:** 140-145.

29. Erraji-Benchekroun L, Underwood MD, Arango V, Galfalvy H, Pavlidis P, Smyrniotopoulos P *et al.* Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. *Biological psychiatry* 2005; **57**(5)**:** 549-558.

30. Kim HW, Rapoport SI, Rao JS. Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. *Neurobiology of disease* 2010; **37**(3)**:** 596-603.

31. Su YA, Wu J, Zhang L, Zhang Q, Su DM, He P *et al.* Dysregulated mitochondrial genes and networks with drug targets in postmortem brain of patients with posttraumatic stress disorder (PTSD) revealed by human mitochondria-focused cDNA microarrays. *Int J Biol Sci* 2008; **4**(4)**:** 223-235.

32. Beech RD, Qu J, Leffert JJ, Lin A, Hong KA, Hansen J *et al.* Altered expression of cytokine signaling pathway genes in peripheral blood cells of alcohol dependent subjects: preliminary findings. *Alcoholism, clinical and experimental research* 2012; **36**(9)**:** 1487-1496.

33. Gruber HE, Hoelscher GL, Ingram JA, Hanley EN, Jr. Genome-wide analysis of pain-, nerve- and neurotrophin -related gene expression in the degenerating human annulus. *Molecular pain* 2012; **8:** 63.

34. Lowthert L, Leffert J, Lin A, Umlauf S, Maloney K, Muralidharan A *et al.* Increased ratio of anti-apoptotic to pro-apoptotic Bcl2 gene-family members in lithium-responders one month after treatment initiation. *Biology of mood & anxiety disorders* 2012; **2**(1)**:** 15.

35. Szczepankiewicz A, Skibinska M, Hauser J, Slopien A, Leszczynska-Rodziewicz A, Kapelski P *et al.* Association analysis of the GSK-3beta T-50C gene polymorphism with schizophrenia and bipolar disorder. *Neuropsychobiology* 2006; **53**(1)**:** 51-56.

36. Lachman HM, Pedrosa E, Petruolo OA, Cockerham M, Papolos A, Novak T *et al.* Increase in GSK3beta gene copy number variation in bipolar disorder. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2007; **144B**(3)**:** 259-265.

37. Jimenez E, Arias B, Mitjans M, Goikolea JM, Roda E, Ruiz V *et al.* Association between GSK3beta gene and increased impulsivity in bipolar disorder. *Eur Neuropsychopharmacol* 2014; **24**(4)**:** 510-518.

38. Kripke DF, Nievergelt CM, Tranah GJ, Murray SS, Rex KM, Grizas AP *et al.* FMR1, circadian genes and depression: suggestive associations or false discovery? *J Circadian Rhythms* 2013; **11**(1)**:** 3.

39. McCarthy MJ, Wei H, Marnoy Z, Darvish RM, McPhie DL, Cohen BM *et al.* Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients. *Translational psychiatry* 2013; **3:** e318.

40. Lewis CM, Ng MY, Butler AW, Cohen-Woods S, Uher R, Pirlo K *et al.* Genome-wide association study of major recurrent depression in the U.K. population. *Am J Psychiatry* 2010; **167**(8)**:** 949-957.

41. Inkster B, Nichols TE, Saemann PG, Auer DP, Holsboer F, Muglia P *et al.* Association of GSK3beta polymorphisms with brain structural changes in major depressive disorder. *Archives of general psychiatry* 2009; **66**(7)**:** 721-728.

42. Mozhui K, Wang X, Chen J, Mulligan MK, Li Z, Ingles J *et al.* Genetic regulation of Nrxn1 [corrected] expression: an integrative cross-species analysis of schizophrenia candidate genes. *Translational psychiatry* 2011; **1:** e25.

43. Blasi G, Napolitano F, Ursini G, Di Giorgio A, Caforio G, Taurisano P *et al.* Association of GSK-3beta genetic variation with GSK-3beta expression, prefrontal cortical thickness, prefrontal physiology, and schizophrenia. *The American journal of psychiatry* 2013; **170**(8)**:** 868-876.

44. Gonzalez R, Bernardo C, Cruz D, Walss-Bass C, Thompson PM. The relationships between clinical characteristics, alcohol and psychotropic exposure, and circadian gene expression in human postmortem samples of affective disorder and control subjects. *Psychiatry Res* 2014; **218**(3)**:** 359-362.

45. Chen H, Wang N, Zhao X, Ross CA, O'Shea KS, McInnis MG. Gene expression alterations in bipolar disorder postmortem brains. *Bipolar disorders* 2013; **15**(2)**:** 177-187.

46. Vawter MP, Tomita H, Meng F, Bolstad B, Li J, Evans S *et al.* Mitochondrial-related gene expression changes are sensitive to agonal-pH state: implications for brain disorders. *Molecular psychiatry* 2006; **11**(7)**:** 615, 663-679.

47. Nakatani N, Hattori E, Ohnishi T, Dean B, Iwayama Y, Matsumoto I *et al.* Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. *Human molecular genetics* 2006; **15**(12)**:** 1949-1962.

48. Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biol Psychiatry* 2005; **57**(3)**:** 252-260.

49. Nadri C, Dean B, Scarr E, Agam G. GSK-3 parameters in postmortem frontal cortex and hippocampus of schizophrenic patients. *Schizophrenia research* 2004; **71**(2-3)**:** 377-382.

50. Kozlovsky N, Shanon-Weickert C, Tomaskovic-Crook E, Kleinman JE, Belmaker RH, Agam G. Reduced GSK-3beta mRNA levels in postmortem dorsolateral prefrontal cortex of schizophrenic patients. *J Neural Transm* 2004; **111**(12)**:** 1583-1592.

51. Chu TT, Liu Y, Kemether E. Thalamic transcriptome screening in three psychiatric states. *Journal of human genetics* 2009; **54**(11)**:** 665-675.

52. Polesskaya OO, Sokolov BP. Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *Journal of neuroscience research* 2002; **67**(6)**:** 812-822.

53. Garbett KA, Vereczkei A, Kalman S, Wang L, Korade Z, Shelton RC *et al.* Fibroblasts from patients with major depressive disorder show distinct transcriptional response to metabolic stressors. *Translational psychiatry* 2015; **5:** e523.

54. Pandey GN, Ren X, Rizavi HS, Dwivedi Y. Glycogen synthase kinase-3beta in the platelets of patients with mood disorders: effect of treatment. *Journal of psychiatric research* 2010; **44**(3)**:** 143-148.

55. Marksteiner J, Humpel C. Glycogen-synthase kinase-3beta is decreased in peripheral blood mononuclear cells of patients with mild cognitive impairment. *Exp Gerontol* 2009; **44**(6-7)**:** 370-371.

56. Zhao Z, Xu J, Chen J, Kim S, Reimers M, Bacanu SA *et al.* Transcriptome sequencing and genome-wide association analyses reveal lysosomal function and actin cytoskeleton remodeling in schizophrenia and bipolar disorder. *Molecular psychiatry* 2015; **20**(5)**:** 563-572.

57. Arion D, Corradi JP, Tang S, Datta D, Boothe F, He A *et al.* Distinctive transcriptome alterations of prefrontal pyramidal neurons in schizophrenia and schizoaffective disorder. *Molecular psychiatry* 2015.

58. Deo AJ, Huang YY, Hodgkinson CA, Xin Y, Oquendo MA, Dwork AJ *et al.* A large-scale candidate gene analysis of mood disorders: evidence of neurotrophic tyrosine kinase receptor and opioid receptor signaling dysfunction. *Psychiatr Genet* 2013; **23**(2)**:** 47-55.

59. de Sousa RT, Zarate CA, Jr., Zanetti MV, Costa AC, Talib LL, Gattaz WF *et al.* Oxidative stress in early stage Bipolar Disorder and the association with response to lithium. *Journal of psychiatric research* 2014; **50:** 36-41.

60. Raffa M, Fendri C, Ben Othmen L, Slama H, Amri M, Kerkeni A *et al.* The reduction of superoxide dismutase activity is associated with the severity of neurological soft signs in patients with schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry* 2012; **39**(1)**:** 52-56.

61. Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S *et al.* Modelling schizophrenia using human induced pluripotent stem cells. *Nature* 2011; **473**(7346)**:** 221-225.

62. Aston C, Jiang L, Sokolov BP. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry* 2005; **10**(3)**:** 309-322.

63. Sibille E, Wang Y, Joeyen-Waldorf J, Gaiteri C, Surget A, Oh S *et al.* A molecular signature of depression in the amygdala. *The American journal of psychiatry* 2009; **166**(9)**:** 1011-1024.

64. Todorova VK, Elbein AD, Kyosseva SV. Increased expression of c-Jun transcription factor in cerebellar vermis of patients with schizophrenia. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2003; **28**(8)**:** 1506-1514.

65. Aston C, Jiang L, Sokolov BP. Microarray analysis of postmortem temporal cortex from patients with schizophrenia. *Journal of neuroscience research* 2004; **77**(6)**:** 858-866.

66. Kyosseva SV. Differential expression of mitogen-activated protein kinases and immediate early genes fos and jun in thalamus in schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry* 2004; **28**(6)**:** 997-1006.

67. Cattane N, Minelli A, Milanesi E, Maj C, Bignotti S, Bortolomasi M *et al.* Altered gene expression in schizophrenia: findings from transcriptional signatures in fibroblasts and blood. *PloS one* 2015; **10**(2)**:** e0116686.

68. Watanabe S, Iga J, Nishi A, Numata S, Kinoshita M, Kikuchi K *et al.* Microarray analysis of global gene expression in leukocytes following lithium treatment. *Human psychopharmacology* 2014; **29**(2)**:** 190-198.

69. Gottschalk MG, Wesseling H, Guest PC, Bahn S. Proteomic enrichment analysis of psychotic and affective disorders reveals common signatures in presynaptic glutamatergic signaling and energy metabolism. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum* 2014; **18**(2).

70. Nicholas B, Rudrasingham V, Nash S, Kirov G, Owen MJ, Wimpory DC. Association of Per1 and Npas2 with autistic disorder: support for the clock genes/social timing hypothesis. *Molecular psychiatry* 2007; **12**(6)**:** 581-592.

71. Utge SJ, Soronen P, Loukola A, Kronholm E, Ollila HM, Pirkola S *et al.* Systematic analysis of circadian genes in a population-based sample reveals association of TIMELESS with depression and sleep disturbance. *PloS one* 2010; **5**(2)**:** e9259.

72. Dong L, Bilbao A, Laucht M, Henriksson R, Yakovleva T, Ridinger M *et al.* Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking. *The American journal of psychiatry* 2011; **168**(10)**:** 1090-1098.

73. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP *et al.* Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America* 2013; **110**(24)**:** 9950-9955.

74. Novakova M, Prasko J, Latalova K, Sladek M, Sumova A. The circadian system of patients with bipolar disorder differs in episodes of mania and depression. *Bipolar disorders* 2015; **17**(3)**:** 303-314.

75. Gouin JP, Connors J, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Atkinson C *et al.* Altered expression of circadian rhythm genes among individuals with a history of depression. *Journal of affective disorders* 2010; **126**(1-2)**:** 161-166.

76. Middleton FA, Pato CN, Gentile KL, McGann L, Brown AM, Trauzzi M *et al.* Gene expression analysis of peripheral blood leukocytes from discordant sib-pairs with schizophrenia and bipolar disorder reveals points of convergence between genetic and functional genomic approaches. *Am J Med Genet B Neuropsychiatr Genet* 2005; **136**(1)**:** 12-25.

77. Huang MC, Ho CW, Chen CH, Liu SC, Chen CC, Leu SJ. Reduced expression of circadian clock genes in male alcoholic patients. *Alcoholism, clinical and experimental research* 2010; **34**(11)**:** 1899-1904.

78. Pajer K, Andrus BM, Gardner W, Lourie A, Strange B, Campo J *et al.* Discovery of blood transcriptomic markers for depression in animal models and pilot validation in subjects with early-onset major depression. *Translational psychiatry* 2012; **2:** e101.

79. Redei EE, Andrus BM, Kwasny MJ, Seok J, Cai X, Ho J *et al.* Blood transcriptomic biomarkers in adult primary care patients with major depressive disorder undergoing cognitive behavioral therapy. *Translational psychiatry* 2014; **4:** e442.

80. Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S *et al.* A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *Arch Gen Psychiatry* 2009; **66**(9)**:** 966-975.

81. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW *et al.* Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the National Academy of Sciences of the United States of America* 2013; **110**(20)**:** 8302-8307.

82. Juraeva D, Treutlein J, Scholz H, Frank J, Degenhardt F, Cichon S *et al.* XRCC5 as a risk gene for alcohol dependence: evidence from a genome-wide gene-set-based analysis and follow-up studies in Drosophila and humans. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2015; **40**(2)**:** 361-371.

83. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D *et al.* The contribution of de novo coding mutations to autism spectrum disorder. *Nature* 2014; **515**(7526)**:** 216-221.

84. Nurnberger JI, Jr., Koller DL, Jung J, Edenberg HJ, Foroud T, Guella I *et al.* Identification of pathways for bipolar disorder: a meta-analysis. *JAMA psychiatry* 2014; **71**(6)**:** 657-664.

85. Aberg KA, McClay JL, Nerella S, Clark S, Kumar G, Chen W *et al.* Methylome-wide association study of schizophrenia: identifying blood biomarker signatures of environmental insults. *JAMA psychiatry* 2014; **71**(3)**:** 255-264.

86. Gaiteri C, Guilloux JP, Lewis DA, Sibille E. Altered gene synchrony suggests a combined hormone-mediated dysregulated state in major depression. *PloS one* 2010; **5**(4)**:** e9970.

87. Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R *et al.* Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proceedings of the National Academy of Sciences of the United States of America* 2013; **110**(12)**:** E1132-1141.

88. Glatt SJ, Stone WS, Nossova N, Liew CC, Seidman LJ, Tsuang MT. Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B**(8)**:** 869-887.

89. Kurian SM, Le-Niculescu H, Patel SD, Bertram D, Davis J, Dike C *et al.* Identification of blood biomarkers for psychosis using convergent functional genomics. *Molecular psychiatry* 2011; **16**(1)**:** 37-58.

90. Wong CC, Meaburn EL, Ronald A, Price TS, Jeffries AR, Schalkwyk LC *et al.* Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. *Molecular psychiatry* 2014; **19**(4)**:** 495-503.

91. Iwamoto K, Bundo M, Yamamoto M, Ozawa H, Saito T, Kato T. Decreased expression of NEFH and PCP4/PEP19 in the prefrontal cortex of alcoholics. *Neuroscience research* 2004; **49**(4)**:** 379-385.

92. Lewohl JM, Wang L, Miles MF, Zhang L, Dodd PR, Harris RA. Gene expression in human alcoholism: microarray analysis of frontal cortex. *Alcohol Clin Exp Res* 2000; **24**(12)**:** 1873-1882.

93. Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD *et al.* Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. *Molecular psychiatry* 2011; **16**(6)**:** 634-646.

94. Focking M, Lopez LM, English JA, Dicker P, Wolff A, Brindley E *et al.* Proteomic and genomic evidence implicates the postsynaptic density in schizophrenia. *Molecular psychiatry* 2015; **20**(4)**:** 424-432.

95. Sainz J, Mata I, Barrera J, Perez-Iglesias R, Varela I, Arranz MJ *et al.* Inflammatory and immune response genes have significantly altered expression in schizophrenia. *Mol Psychiatry* 2013; **18**(10)**:** 1056-1057.

96. Miller GE, Chen E, Sze J, Marin T, Arevalo JM, Doll R *et al.* A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. *Biological psychiatry* 2008; **64**(4)**:** 266-272.

97. McClintick JN, Xuei X, Tischfield JA, Goate A, Foroud T, Wetherill L *et al.* Stress-response pathways are altered in the hippocampus of chronic alcoholics. *Alcohol* 2013; **47**(7)**:** 505-515.

98. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S *et al.* Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature* 2011; **474**(7351)**:** 380-384.

99. Bezchlibnyk YB, Wang JF, McQueen GM, Young LT. Gene expression differences in bipolar disorder revealed by cDNA array analysis of post-mortem frontal cortex. *Journal of neurochemistry* 2001; **79**(4)**:** 826-834.

100. Kang HJ, Adams DH, Simen A, Simen BB, Rajkowska G, Stockmeier CA *et al.* Gene expression profiling in postmortem prefrontal cortex of major depressive disorder. *J Neurosci* 2007; **27**(48)**:** 13329-13340.

101. Stelzhammer V, Alsaif M, Chan MK, Rahmoune H, Steeb H, Guest PC *et al.* Distinct proteomic profiles in post-mortem pituitary glands from bipolar disorder and major depressive disorder patients. *Journal of psychiatric research* 2015; **60:** 40-48.

102. Leclercq C, Ferro-Luzzi A. Total and domestic consumption of salt and their determinants in three regions of Italy. *Eur J Clin Nutr* 1991; **45**(3)**:** 151-159.

103. Domenici E, Wille DR, Tozzi F, Prokopenko I, Miller S, McKeown A *et al.* Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. *PLoS One* 2010; **5**(2)**:** e9166.

104. Guilloux JP, Bassi S, Ding Y, Walsh C, Turecki G, Tseng G *et al.* Testing the predictive value of peripheral gene expression for nonremission following citalopram treatment for major depression. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2015; **40**(3)**:** 701-710.

105. Ersland KM, Christoforou A, Stansberg C, Espeseth T, Mattheisen M, Mattingsdal M *et al.* Gene-based analysis of regionally enriched cortical genes in GWAS data sets of cognitive traits and psychiatric disorders. *PloS one* 2012; **7**(2)**:** e31687.

106. Beech RD, Lowthert L, Leffert JJ, Mason PN, Taylor MM, Umlauf S *et al.* Increased peripheral blood expression of electron transport chain genes in bipolar depression. *Bipolar disorders* 2010; **12**(8)**:** 813-824.

107. Maes OC, Xu S, Yu B, Chertkow HM, Wang E, Schipper HM. Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. *Neurobiology of aging* 2007; **28**(12)**:** 1795-1809.

108. Merjonen P, Keltikangas-Jarvinen L, Jokela M, Seppala I, Lyytikainen LP, Pulkki-Raback L *et al.* Hostility in adolescents and adults: a genome-wide association study of the Young Finns. *Translational psychiatry* 2011; **1:** e11.

109. Salyakina D, Ma DQ, Jaworski JM, Konidari I, Whitehead PL, Henson R *et al.* Variants in several genomic regions associated with asperger disorder. *Autism research : official journal of the International Society for Autism Research* 2010; **3**(6)**:** 303-310.

110. Saiz PA, Garcia-Portilla MP, Florez G, Corcoran P, Arango C, Morales B *et al.* Polymorphisms of the IL-1 gene complex are associated with alcohol dependence in Spanish Caucasians: data from an association study. *Alcoholism, clinical and experimental research* 2009; **33**(12)**:** 2147-2153.

111. Flatscher-Bader T, van der Brug M, Hwang JW, Gochee PA, Matsumoto I, Niwa S *et al.* Alcohol-responsive genes in the frontal cortex and nucleus accumbens of human alcoholics. *Journal of neurochemistry* 2005; **93**(2)**:** 359-370.

112. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Molecular psychiatry* 2010; **15**(4)**:** 384-392.

113. Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weickert C. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. *Translational psychiatry* 2014; **4:** e365.

114. Toyooka K, Watanabe Y, Iritani S, Shimizu E, Iyo M, Nakamura R *et al.* A decrease in interleukin-1 receptor antagonist expression in the prefrontal cortex of schizophrenic patients. *Neuroscience research* 2003; **46**(3)**:** 299-307.

115. de Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS *et al.* Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. *Schizophrenia research* 2014; **154**(1-3)**:** 23-29.

116. Chan MK, Krebs MO, Cox D, Guest PC, Yolken RH, Rahmoune H *et al.* Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. *Translational psychiatry* 2015; **5:** e601.

117. Morita K, Saito T, Ohta M, Ohmori T, Kawai K, Teshima-Kondo S *et al.* Expression analysis of psychological stress-associated genes in peripheral blood leukocytes. *Neurosci Lett* 2005; **381**(1-2)**:** 57-62.

118. Ohmori T, Morita K, Saito T, Ohta M, Ueno S, Rokutan K. Assessment of human stress and depression by DNA microarray analysis. *J Med Invest* 2005; **52 Suppl:** 266-271.

119. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine* 2009; **71**(2)**:** 171-186.

120. Bergink V, Burgerhout KM, Weigelt K, Pop VJ, de Wit H, Drexhage RC *et al.* Immune system dysregulation in first-onset postpartum psychosis. *Biological psychiatry* 2013; **73**(10)**:** 1000-1007.

121. Goes FS, Hamshere ML, Seifuddin F, Pirooznia M, Belmonte-Mahon P, Breuer R *et al.* Genome-wide association of mood-incongruent psychotic bipolar disorder. *Translational psychiatry* 2012; **2:** e180.

122. Matigian N, Windus L, Smith H, Filippich C, Pantelis C, McGrath J *et al.* Expression profiling in monozygotic twins discordant for bipolar disorder reveals dysregulation of the WNT signalling pathway. *Molecular psychiatry* 2007; **12**(9)**:** 815-825.

123. Lit L, Gilbert DL, Walker W, Sharp FR. A subgroup of Tourette's patients overexpress specific natural killer cell genes in blood: a preliminary report. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2007; **144B**(7)**:** 958-963.

124. Ikeda M, Aleksic B, Kirov G, Kinoshita Y, Yamanouchi Y, Kitajima T *et al.* Copy number variation in schizophrenia in the Japanese population. *Biological psychiatry* 2010; **67**(3)**:** 283-286.

125. Stopkova P, Saito T, Papolos DF, Vevera J, Paclt I, Zukov I *et al.* Identification of PIK3C3 promoter variant associated with bipolar disorder and schizophrenia. *Biological psychiatry* 2004; **55**(10)**:** 981-988.

126. Glessner JT, Reilly MP, Kim CE, Takahashi N, Albano A, Hou C *et al.* Strong synaptic transmission impact by copy number variations in schizophrenia. *Proc Natl Acad Sci U S A* 2010; **107**(23)**:** 10584-10589.

127. Carrard A, Salzmann A, Perroud N, Gafner J, Malafosse A, Karege F. Genetic association of the Phosphoinositide-3 kinase in schizophrenia and bipolar disorder and interaction with a BDNF gene polymorphism. *Brain and behavior* 2011; **1**(2)**:** 119-124.

128. Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM *et al.* Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 2008; **320**(5875)**:** 539-543.

129. Koga M, Ishiguro H, Yazaki S, Horiuchi Y, Arai M, Niizato K *et al.* Involvement of SMARCA2/BRM in the SWI/SNF chromatin-remodeling complex in schizophrenia. *Human molecular genetics* 2009; **18**(13)**:** 2483-2494.

130. Loe-Mie Y, Lepagnol-Bestel AM, Maussion G, Doron-Faigenboim A, Imbeaud S, Delacroix H *et al.* SMARCA2 and other genome-wide supported schizophrenia-associated genes: regulation by REST/NRSF, network organization and primate-specific evolution. *Human molecular genetics* 2010; **19**(14)**:** 2841-2857.

131. Walter S, Atzmon G, Demerath EW, Garcia ME, Kaplan RC, Kumari M *et al.* A genome-wide association study of aging. *Neurobiology of aging* 2011; **32**(11)**:** 2109 e2115-2128.

132. Szatkiewicz JP, O'Dushlaine C, Chen G, Chambert K, Moran JL, Neale BM *et al.* Copy number variation in schizophrenia in Sweden. *Molecular psychiatry* 2014; **19**(7)**:** 762-773.

133. Vawter MP, Atz ME, Rollins BL, Cooper-Casey KM, Shao L, Byerley WF. Genome scans and gene expression microarrays converge to identify gene regulatory loci relevant in schizophrenia. *Hum Genet* 2006; **119**(5)**:** 558-570.

134. Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD *et al.* Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* 2001; **98**(8)**:** 4746-4751.

135. Hennings JM, Uhr M, Klengel T, Weber P, Putz B, Touma C *et al.* RNA expression profiling in depressed patients suggests retinoid-related orphan receptor alpha as a biomarker for antidepressant response. *Translational psychiatry* 2015; **5:** e538.

136. Glatt SJ, Everall IP, Kremen WS, Corbeil J, Sasik R, Khanlou N *et al.* Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. *Proc Natl Acad Sci U S A* 2005; **102**(43)**:** 15533-15538.

137. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**(7510)**:** 421-427.

138. Jurata LW, Bukhman YV, Charles V, Capriglione F, Bullard J, Lemire AL *et al.* Comparison of microarray-based mRNA profiling technologies for identification of psychiatric disease and drug signatures. *Journal of neuroscience methods* 2004; **138**(1-2)**:** 173-188.

139. Martins-de-Souza D, Maccarrone G, Ising M, Kloiber S, Lucae S, Holsboer F *et al.* Blood mononuclear cell proteome suggests integrin and Ras signaling as critical pathways for antidepressant treatment response. *Biological psychiatry* 2014; **76**(7)**:** e15-17.

140. Herberth M, Koethe D, Cheng TM, Krzyszton ND, Schoeffmann S, Guest PC *et al.* Impaired glycolytic response in peripheral blood mononuclear cells of first-onset antipsychotic-naive schizophrenia patients. *Molecular psychiatry* 2011; **16**(8)**:** 848-859.

141. Salaria S, Chana G, Caldara F, Feltrin E, Altieri M, Faggioni F *et al.* Microarray analysis of cultured human brain aggregates following cortisol exposure: implications for cellular functions relevant to mood disorders. *Neurobiology of disease* 2006; **23**(3)**:** 630-636.

142. Iwamoto K, Bundo M, Kato T. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis. *Human molecular genetics* 2005; **14**(2)**:** 241-253.

143. Maccarrone G, Ditzen C, Yassouridis A, Rewerts C, Uhr M, Uhlen M *et al.* Psychiatric patient stratification using biosignatures based on cerebrospinal fluid protein expression clusters. *Journal of psychiatric research* 2013; **47**(11)**:** 1572-1580.

144. Le-Niculescu H, Kurian SM, Yehyawi N, Dike C, Patel SD, Edenberg HJ *et al.* Identifying blood biomarkers for mood disorders using convergent functional genomics. *Molecular psychiatry* 2009; **14**(2)**:** 156-174.

145. Liu J, Lewohl JM, Harris RA, Iyer VR, Dodd PR, Randall PK *et al.* Patterns of gene expression in the frontal cortex discriminate alcoholic from nonalcoholic individuals. *Neuropsychopharmacology* 2006; **31**(7)**:** 1574-1582.

146. Clark D, Dedova I, Cordwell S, Matsumoto I. A proteome analysis of the anterior cingulate cortex gray matter in schizophrenia. *Molecular psychiatry* 2006; **11**(5)**:** 459-470, 423.

147. Nakatani N, Ohnishi T, Iwamoto K, Watanabe A, Iwayama Y, Yamashita S *et al.* Expression analysis of actin-related genes as an underlying mechanism for mood disorders. *Biochemical and biophysical research communications* 2007; **352**(3)**:** 780-786.

148. Juraeva D, Haenisch B, Zapatka M, Frank J, Investigators G, Group P-GSW *et al.* Integrated pathway-based approach identifies association between genomic regions at CTCF and CACNB2 and schizophrenia. *PLoS genetics* 2014; **10**(6)**:** e1004345.

149. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S *et al.* Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 2013; **45**(10)**:** 1150-1159.

150. Deelen J, Uh HW, Monajemi R, van Heemst D, Thijssen PE, Bohringer S *et al.* Gene set analysis of GWAS data for human longevity highlights the relevance of the insulin/IGF-1 signaling and telomere maintenance pathways. *Age (Dordr)* 2013; **35**(1)**:** 235-249.

151. Jansen R, Penninx BW, Madar V, Xia K, Milaneschi Y, Hottenga JJ *et al.* Gene expression in major depressive disorder. *Molecular psychiatry* 2015.

152. Rizzi TS, Arias-Vasquez A, Rommelse N, Kuntsi J, Anney R, Asherson P *et al.* The ATXN1 and TRIM31 genes are related to intelligence in an ADHD background: evidence from a large collaborative study totaling 4,963 subjects. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2011; **156**(2)**:** 145-157.

153. Fallin MD, Lasseter VK, Avramopoulos D, Nicodemus KK, Wolyniec PS, McGrath JA *et al.* Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. *American journal of human genetics* 2005; **77**(6)**:** 918-936.

154. Johnson C, Drgon T, McMahon FJ, Uhl GR. Convergent genome wide association results for bipolar disorder and substance dependence. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**(2)**:** 182-190.

155. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I *et al.* Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009; **460**(7256)**:** 753-757.

156. Culjkovic B, Stojkovic O, Savic D, Zamurovic N, Nesic M, Major T *et al.* Comparison of the number of triplets in SCA1, MJD/SCA3, HD, SBMA, DRPLA, MD, FRAXA and FRDA genes in schizophrenic patients and a healthy population. *Am J Med Genet* 2000; **96**(6)**:** 884-887.

157. Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol* 2007; **8**(9)**:** R189.

158. Cichon S, Muhleisen TW, Degenhardt FA, Mattheisen M, Miro X, Strohmaier J *et al.* Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am J Hum Genet* 2011; **88**(3)**:** 372-381.

159. Sebastiani P, Solovieff N, Dewan AT, Walsh KM, Puca A, Hartley SW *et al.* Genetic signatures of exceptional longevity in humans. *PloS one* 2012; **7**(1)**:** e29848.

160. Sokolov BP, Jiang L, Trivedi NS, Aston C. Transcription profiling reveals mitochondrial, ubiquitin and signaling systems abnormalities in postmortem brains from subjects with a history of alcohol abuse or dependence. *Journal of neuroscience research* 2003; **72**(6)**:** 756-767.

161. Yu Z, Ono C, Kim HB, Komatsu H, Tanabe Y, Sakae N *et al.* Four mood stabilizers commonly induce FEZ1 expression in human astrocytes. *Bipolar disorders* 2011; **13**(5-6)**:** 486-499.

162. Gardiner EJ, Cairns MJ, Liu B, Beveridge NJ, Carr V, Kelly B *et al.* Gene expression analysis reveals schizophrenia-associated dysregulation of immune pathways in peripheral blood mononuclear cells. *Journal of psychiatric research* 2013; **47**(4)**:** 425-437.

163. Shao L, Vawter MP. Shared gene expression alterations in schizophrenia and bipolar disorder. *Biological psychiatry* 2008; **64**(2)**:** 89-97.

164. Martins-de-Souza D, Guest PC, Harris LW, Vanattou-Saifoudine N, Webster MJ, Rahmoune H *et al.* Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. *Translational psychiatry* 2012; **2:** e87.

165. Yokota T, Mishra M, Akatsu H, Tani Y, Miyauchi T, Yamamoto T *et al.* Brain site-specific gene expression analysis in Alzheimer's disease patients. *Eur J Clin Invest* 2006; **36**(11)**:** 820-830.

166. Harris LW, Lockstone HE, Khaitovich P, Weickert CS, Webster MJ, Bahn S. Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. *BMC Med Genomics* 2009; **2:** 28.

167. Kalsi G, Kuo PH, Aliev F, Alexander J, McMichael O, Patterson DG *et al.* A systematic gene-based screen of chr4q22-q32 identifies association of a novel susceptibility gene, DKK2, with the quantitative trait of alcohol dependence symptom counts. *Human molecular genetics* 2010; **19**(12)**:** 2497-2506.

168. Kerner B, Rao AR, Christensen B, Dandekar S, Yourshaw M, Nelson SF. Rare Genomic Variants Link Bipolar Disorder with Anxiety Disorders to CREB-Regulated Intracellular Signaling Pathways. *Front Psychiatry* 2013; **4:** 154.

169. Hattori E, Toyota T, Ishitsuka Y, Iwayama Y, Yamada K, Ujike H *et al.* Preliminary genome-wide association study of bipolar disorder in the Japanese population. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**(8)**:** 1110-1117.

170. Dean B, Keriakous D, Scarr E, Thomas EA. Gene expression profiling in Brodmann's area 46 from subjects with schizophrenia. *Aust N Z J Psychiatry* 2007; **41**(4)**:** 308-320.

171. Sood S, Gallagher IJ, Lunnon K, Rullman E, Keohane A, Crossland H *et al.* A novel multi-tissue RNA diagnostic of healthy ageing relates to cognitive health status. *Genome Biol* 2015; **16:** 185.

172. Jaros JA, Martins-de-Souza D, Rahmoune H, Rothermundt M, Leweke FM, Guest PC *et al.* Protein phosphorylation patterns in serum from schizophrenia patients and healthy controls. *J Proteomics* 2012; **76 Spec No.:** 43-55.

173. Tajouri L, Mellick AS, Tourtellotte A, Nagra RM, Griffiths LR. An examination of MS candidate genes identified as differentially regulated in multiple sclerosis plaque tissue, using absolute and comparative real-time Q-PCR analysis. *Brain Res Brain Res Protoc* 2005; **15**(2)**:** 79-91.

174. Smalla KH, Mikhaylova M, Sahin J, Bernstein HG, Bogerts B, Schmitt A *et al.* A comparison of the synaptic proteome in human chronic schizophrenia and rat ketamine psychosis suggest that prohibitin is involved in the synaptic pathology of schizophrenia. *Mol Psychiatry* 2008; **13**(9)**:** 878-896.

175. Etheridge N, Lewohl JM, Mayfield RD, Harris RA, Dodd PR. Synaptic proteome changes in the superior frontal gyrus and occipital cortex of the alcoholic brain. *Proteomics Clin Appl* 2009; **3**(6)**:** 730-742.

176. Kanazawa T, Ikeda M, Glatt SJ, Tsutsumi A, Kikuyama H, Kawamura Y *et al.* Genome-wide association study of atypical psychosis. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2013; **162B**(7)**:** 679-686.

177. Byrne EM, Psychiatric Genetics Consortium Major Depressive Disorder Working G, Raheja UK, Stephens SH, Heath AC, Madden PA *et al.* Seasonality shows evidence for polygenic architecture and genetic correlation with schizophrenia and bipolar disorder. *J Clin Psychiatry* 2015; **76**(2)**:** 128-134.

178. Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L *et al.* Increased exonic de novo mutation rate in individuals with schizophrenia. *Nature genetics* 2011; **43**(9)**:** 860-863.

179. Bowden NA, Scott RJ, Tooney PA. Altered gene expression in the superior temporal gyrus in schizophrenia. *BMC Genomics* 2008; **9:** 199.

180. Yi Z, Li Z, Yu S, Yuan C, Hong W, Wang Z *et al.* Blood-based gene expression profiles models for classification of subsyndromal symptomatic depression and major depressive disorder. *PloS one* 2012; **7**(2)**:** e31283.

181. Seelan RS, Khalyfa A, Lakshmanan J, Casanova MF, Parthasarathy RN. Deciphering the lithium transcriptome: microarray profiling of lithium-modulated gene expression in human neuronal cells. *Neuroscience* 2008; **151**(4)**:** 1184-1197.

182. Sanders AR, Goring HH, Duan J, Drigalenko EI, Moy W, Freda J *et al.* Transcriptome study of differential expression in schizophrenia. *Human molecular genetics* 2013; **22**(24)**:** 5001-5014.

183. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA *et al.* Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Molecular psychiatry* 2011; **16**(7)**:** 751-762.

184. Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH *et al.* The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *Journal of neurochemistry* 1999; **72**(2)**:** 879-882.

185. Chen RW, Chuang DM. Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression. A prominent role in neuroprotection against excitotoxicity. *J Biol Chem* 1999; **274**(10)**:** 6039-6042.

186. Keshavarz M, Emamghoreishi M, Nekooeian AA, J JW, Zare HR. Increased bcl-2 Protein Levels in Rat Primary Astrocyte Culture Following Chronic Lithium Treatment. *Iran J Med Sci* 2013; **38**(3)**:** 255-262.

187. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *Journal of neurochemistry* 2000; **75**(4)**:** 1729-1734.

188. Hammonds MD, Shim SS. Effects of 4-week treatment with lithium and olanzapine on levels of brain-derived neurotrophic factor, B-cell CLL/lymphoma 2 and phosphorylated cyclic adenosine monophosphate response element-binding protein in the sub-regions of the hippocampus. *Basic & clinical pharmacology & toxicology* 2009; **105**(2)**:** 113-119.

189. Bai O, Zhang H, Li XM. Antipsychotic drugs clozapine and olanzapine upregulate bcl-2 mRNA and protein in rat frontal cortex and hippocampus. *Brain Res* 2004; **1010**(1-2)**:** 81-86.

190. Fatemi SH, Reutiman TJ, Folsom TD. Chronic psychotropic drug treatment causes differential expression of Reelin signaling system in frontal cortex of rats. *Schizophr Res* 2009; **111**(1-3)**:** 138-152.

191. MacDonald ML, Eaton ME, Dudman JT, Konradi C. Antipsychotic drugs elevate mRNA levels of presynaptic proteins in the frontal cortex of the rat. *Biological psychiatry* 2005; **57**(9)**:** 1041-1051.

192. Le-Niculescu H, Case NJ, Hulvershorn L, Patel SD, Bowker D, Gupta J *et al.* Convergent functional genomic studies of omega-3 fatty acids in stress reactivity, bipolar disorder and alcoholism. *Translational psychiatry* 2011; **1:** e4.

193. Le-Niculescu H, Balaraman Y, Patel S, Tan J, Sidhu K, Jerome RE *et al.* Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 2007; **144B**(2)**:** 129-158.

194. Jakovcevski M, Bharadwaj R, Straubhaar J, Gao G, Gavin DP, Jakovcevski I *et al.* Prefrontal cortical dysfunction after overexpression of histone deacetylase 1. *Biological psychiatry* 2013; **74**(9)**:** 696-705.

195. Hammamieh R, Chakraborty N, Gautam A, Miller SA, Muhie S, Meyerhoff J *et al.* Transcriptomic analysis of the effects of a fish oil enriched diet on murine brains. *PloS one* 2014; **9**(3)**:** e90425.

196. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ *et al.* The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science* 2006; **313**(5795)**:** 1929-1935.

197. Lamb J. The Connectivity Map: a new tool for biomedical research. *Nat Rev Cancer* 2007; **7**(1)**:** 54-60.