

Precision Medicine for Schizophrenia and Psychotic Disorders: Objective Assessment, Risk Prediction, Pharmacogenomics, and Repurposed Drugs

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under OD007363 awarded by the National Institutes of Health and CX000139 merit award by the Veterans Administration. The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATION

[0002] This application claims priority to U.S. Patent Application No. 17/351,132, filed on June 17, 2021, the disclosure of which is hereby expressly incorporated by reference in its entirety.

BACKGROUND

[0003] Schizophrenia is a heterogeneous disorder, composed of positive and negative psychotic symptoms. Psychotic symptoms, more broadly, are also often present in other psychiatric disorders. They can be difficult to assess, as they are based on the patient's self-reporting and on the clinician's clinical impression. Continued improvements are needed to adequately diagnose and treat individuals suffering psychotic symptoms.

SUMMARY

[0004] Provided here are newly identified blood gene expression biomarkers for hallucinations, and for delusions. The biomarkers provide a means of assessing state severity, short-term risk, and long-term risk. The biomarkers can also be used for drug repurposing.

[0004a] In one aspect, the present disclosure refers to an *in vitro* method for assessing schizophrenia and other psychotic disorders in general, in particular delusions and risk of developing delusions in an individual, comprising the steps of: (a) quantifying the amounts of RNA biomarkers in a biological sample from the individual, to create a panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to

generate a score for each biomarker; wherein the biomarkers in a first panel (a) comprise one or more of the following RNA biomarkers: Activator Of Transcription and Developmental Regulator 2 (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), GNAS Complex Locus (GNAS), Interleukin 6 Signal Transduce (IL6ST), Chromodomain Helicase DNA Binding Protein 9 (CHD9), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), Actinin Alpha 4 (ACTN4), and Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting delusions or an increased risk for developing delusions; and biomarkers in a second panel (b) comprise one or more of the following RNA biomarkers: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), and (NRP2), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting delusions or an increased risk for developing delusions; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as having delusions or of having an elevated risk for developing delusions, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference.

[0004b] In another aspect, the present disclosure refers to an *in vitro* method for assessing schizophrenia and other psychotic disorders in general, in particular hallucinations and risk of developing hallucinations in an individual, comprising the steps of: (a) quantifying the amounts of one or more RNA biomarkers in the biological sample, to create at least one panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the at least one panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker a first panel and a second panel; wherein the biomarkers in the first panel comprise one or more of the following RNA biomarkers: (PRICKLE1), (NCAM1), (B3GALT5), (ARHGAP18), (PTP4A2), Acylphosphatase 2 (ACYP2),

Reticulon 4 (RTN4), Cullin 4A (CUL4A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), Dystonin (DST), and Discs Large MAGUK Scaffold Protein 1 (DLG1), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting hallucinations or an increased risk for developing hallucinations; and wherein the biomarkers in the second panel comprise one or more of the following RNA biomarkers: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (LAMA4), (KCNV1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting hallucinations or an increased risk for developing hallucinations; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as manifesting hallucinations or of having an elevated risk for developing hallucinations, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference.

[0005] Some examples of the disclosure include methods for treating an individual experiencing or at a heightened risk for developing symptoms such as delusions and/or hallucinations. These symptoms may be indicative of certain psychiatric disorders such as psychosis and/or schizophrenia. Treating involves administered at least one course of treatment, treatment may include psychiatric counseling, administering certain physical intervention, and/or prescribing and/or administering at least one therapeutic compound. Treating may include at least one of the following outcomes, curing, mitigating, managing or otherwise recuing the severity and/or the number of frequency delusions and or hallucinations. In some examples of the disclosure treating

may include identifying individuals with or at an increased risk for developing delusions and/or hallucinations by measuring the level of certain RNA biomarkers as identified in, for example, Tables 2 and 3.

[0006] Some examples of the disclosure include methods for diagnosing an individual experiencing or at a heightened risk for developing symptoms such as delusions and/or hallucinations. These symptoms may be indicative of certain psychiatric disorders such as psychosis and/or schizophrenia. Diagnosing does not require treatment, although it may lead to, or become, part of treating an individual who is manifesting or at an increased risk for manifesting symptom of certain types of mental illness such as psychosis and or schizophrenia. In some examples of the disclosure diagnosing may include identifying individuals with or at an increased risk for developing delusions and/or hallucinations by measuring the level of certain RNA biomarkers as identified in, for example, Tables 2 and 3.

[0007] A first example of the disclosure is a method for treating at least one psychiatric disorder, for example delusions or an increased risk for developing delusions in an individual, comprising the steps of: (a) obtaining a biological sample from an individual and quantifying the amounts of RNA biomarkers in the biological sample, to create a panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker; wherein the biomarkers in the first panel (a) comprise one or more of the following RNA biomarkers: Activator Of Transcription and Developmental Regulator 2 (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), GNAS Complex Locus (GNAS), Interleukin 6 Signal Transducer (IL6ST), Chromodomain Helicase DNA Binding Protein 9 (CHD9), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), Actinin Alpha 4 (ACTN4), and Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting delusions or an increased risk for developing delusions; and biomarkers in a second panel (b) comprise one or more of the following RNA biomarkers: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), and

(NRP2), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting delusions or an increased risk for developing delusions; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as having delusions or of having an elevated risk for developing delusions, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference; (h) treating the individual identified as having delusions or an elevated risk of delusions with at least one treatment selected from the group consisting of: a treatment based on clinical practice guidelines, administering a therapeutically effective amount of at least one therapeutic drug wherein the mode of treatment is on the specific biomarkers scores indicating that individual will benefit from a particular therapy, treating includes curing, mitigating, reducing or even eliminating symptoms of psychotic disorders such as schizophrenia. In some examples of the disclosure samples are taken from an individual two or more time in order to treat, diagnose, and/or monitor the presence of at least one psychotic disorder such as schizophrenia. In some examples, an individual may be treated for symptoms such as delusions or hallucinations without a formal diagnosis of a specific psychotic disorder. In some examples, the individual may be treated with drugs known to treat mental illness and/or drugs repurposed to treat mental illness. Samples from an individual may include any or all of the following, tissue samples, bodily fluids such as blood serum, plasma, saliva, cerebral fluid and the like. The samples may be further processed such as by extraction or purification before being analyzed for the presence of one or more biomarkers of interest.

[0008] In a third example an individual exhibiting symptoms of a psychotic disorder such as those noted the first and second examples may be treated with at least drug selected from the group consisting of: adenosine phosphate, N-acetyl-L-leucine, eldeline, pempidine, verteporfin, C-75, oxprenolol, Prestwick-675, meglumine, guanethidine, pancuronium bromide, karakoline, 15(S)-15-methylprostaglandin E2, hexylcaine, dicoumarol, apramycin, mephenytoin, estriol, 528116.cdx, Cyclopiazonic Acid, SB 218078, BRD-A36630025, Quinacrine hydrochloride, GF-109203X, BRD-A36630025, N9-isopropylolomoucine, BMS-536924, BRD-

K76951091, BRD-K26304855, trichostatin A, ALW-II-38-3, mitoxantrone, HG-6-64-0, alvocidib, SB-216763, and Caffeic acid phenethyl ester. In some examples the drug used to treat the individual may be a drug repurposed from another use, see for example the drugs in Table 4, some repurposed drugs may be identified as efficacious for this purpose because their use correlates in a beneficial change in at least one of the Biomarkers listed in Tables 1 and/or 2.

[0009] A fourth example includes at least portion of the first through the third examples, wherein the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: Activator Of Transcription And Developmental Regulator (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Forkhead Box P1 (FOXP1), GNAS Complex Locus (GNAS), Serine Racemase (SRR), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), and Actinin Alpha 4 (ACTN4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions, or the biomarkers in a second panel (b) comprising one or more biomarkers selected from the group consisting of: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), NRP2, wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions. The males identified in this examples may be treated with at least one therapeutic drug is selected from the group consisting of: flunisolide, apramycin, adenosine phosphate, guanethidine, 15(S)-15-methylprostaglandin E2, meteneprost, methyldopate, hydralazine, rotenone, phthalylsulfathiazole, N-acetyl-L-leucine, eldeline, tocainide, laudanosine, pempidine, 7-aminocephalosporanic acid, Sulfachlorpyridazine, finasteride, 528116.cdx, SB 218078, Quinacrine hydrochloride, N9-isopropylolomoucine, ALW-II-38-3, mitoxantrone, HG-6-64-01, Alvocidib, SB-216763, Syk Inhibitor, Cyclopiazonic Acid, GW 441756, LY 225910, AG 82, doxorubicin, mitomycin, and terfenadine.

[0010] A fifth example includes at least portion of the first through the third examples, wherein the individual is a female and the biomarker is at least one biomarker selected from the group consisting of: Phosphodiesterase 4D Interacting Protein (PDE4DIP), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Transcription Factor 4 (TCF4), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Chromodomain Helicase DNA

Binding Protein 9 (CHD9), (CLCN3), Activator Of Transcription And Developmental Regulator (AUTS2), and (LDB2), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions; and the biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of (FGFR1), (DISC1), (FGFR2), (SPTBN1), (INSR), (GRIK3), Zinc Finger, and BTB Domain Containing 20 (ZBTB20), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions. The females identified in this examples may be treated with at least one therapeutic drug is selected from the group consisting of: erastin, harpagoside, metacycline, amiodarone, furaltadone, metformin, timolol, Repaglinide, sulfafurazole, PNU-0230031, Probenecid, furosemide, fluphenazine, myricetin, sulfacetamide, lomustine, BCB000039, Harmalol, I-BET151, Nyldrin hydrochloride, AMG 9810, Doxorubicin, Mitomycin C, Fludrocortisone acetate, Purvalanol A, Teniposide, Geldanamycin, Importazole, BRD-A36630025, YM-155, Auranofin, 7643453, G-221, BRD-A49680073, BRD-K08547377, and Cladribine.

[0011] A sixth example includes a method of assessing and/or treating schizophrenia and other psychotic disorders in general, and delusions in particular, in an individual, comprising: calculating combined biomarkers and clinical information Up- based on the equation: (Biomarker Panel Score) + (Delusions Score) - (Grooming Score) = Up-Delusions Score; wherein the Biomarker Panel Score is obtained as per the method of claim 1; wherein the Delusions Score is calculated with a clinical rating or self-report scales; wherein the Grooming Score is calculated with a rating scale; assessing the level of delusions of the individual by comparing the individual's Up-Delusions Score to a reference Up-Delusions Score; administering a treatment for delusions to the individual when the individual's Up-Delusions Score is greater than a reference Up-Suicide Score; and monitoring the individual's response to a treatment for delusions by determining changes in the Up-Delusions Score after initiating a treatment.

[0012] A seventh example is a method for assessing and/or treating schizophrenia and other psychotic disorders in general, in particular hallucinations and risk of developing hallucinations in an individual, comprising the steps of: (a) obtaining a biological sample from an individual and quantifying the amounts of one or more RNA biomarkers in the biological sample, to create at least one panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the at least one panel in a clinically relevant population to generate a reference

expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker a first panel and a second panel; wherein the biomarkers in the first panel comprise one or more of the following RNA biomarkers: (PRICKLE1), (NCAM1), (B3GALT5), (ARHGAP18), (PTP4A2), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), Cullin 4A (CUL4A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), Dystonin (DST), and Discs Large MAGUK Scaffold Protein 1 (DLG1), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting hallucinations or an increased risk for developing hallucinations; and wherein the biomarkers in the second panel comprise one or more of the following RNA biomarkers: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (LAMA4), (KCNV1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting hallucinations or an increased risk for developing hallucinations; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as manifesting hallucinations or of having an elevated risk for developing hallucinations, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference; (h) treating the individual identified as having hallucinations or an elevated risk of hallucinations with one or more of the following: 1) a treatment based on clinical practice guidelines, 2) administering a therapeutically effective amount of a therapeutic drug (s), selected based on the specific biomarkers whose scores indicate that they are changed in the individual compared to a reference standard.

[0013] An eighth example is any example from the first through the seventh examples wherein the biomarkers are quantified in samples taken on two or more occasions from the individual. As noted earlier, samples can be taken from tissue or any bodily fluid harboring RNA biomarkers.

[0014] A ninth example is a method of the seventh example wherein each biomarker

is assigned a weighted coefficient based on the biomarkers importance in assessing and predicting hallucinations risk; and the biomarker panel score is based on the weighted coefficients of each of the biomarkers.

[0015] A tenth example is any example from the seventh through the ninth examples, wherein the one or more therapeutic is one or more compounds selected from the group consisting of: clioquinol, pirinixic acid, moxislyte, Prestwick-685, exemestane, azacytidine, C-75, estradiol, tetraethylenepentamine, sparteine, guanethidine, idoxuridine, gliclazide, nitrendipine, N-acetyl-L-aspartic acid, sulfanilamide, doxazosin, pimozide, Proscillaridin, oxetacaine, BRD-K71489689, trichostatin A, A443654, AG 825, Proscillaridin A, Ala-Ala-Phe-CMK, Fluocinolone acetonide, manumycin A, curcumin, BRD-K68548958, CHR 2797, Tyrphostin AG 1478, Wortmannin, HY-50878, 598226, S1003, BRD-A52530684, CGP-60474, Buparlisib, and AS-601245.

[0016] An eleventh example is the method according to the seventh example wherein the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (SH3PXD2A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), (PRICKLE1), (ARHGAP18), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), and Dystonin (DST), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (KCNV1), Mab-21 Like 1 (MAB21L1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations. When the individual is an male the at least one therapeutic compound selected from the group consisting of: digoxigenin, doxazosin, meptazinol, promethazine, cefixime, velnacrine, cetirizine, eldeline, atropine oxide, clioquinol, nicotinic acid, clioquinol, galantamine, rolitetracycline, betahistine, sulconazole, monocrotaline, lanatoside C, Prestwick-1084, Naftidrofuryl, sulfachlorpyridazine, helveticoside, bezafibrate, mifepristone, trichostatin A, manumycin A, NCGC00189555-02, Buparlisib, linifanib, AZD-7762, Dinaciclib, Piretanide, KN-62, Fluticasone propionate, JAK3 Inhibitor VI, Sarmentogenin, Digoxin, Megestrol acetate, Oxymetazoline hydrochloride, U-0126, Tracazolate hydrochloride, Flufenamic acid, Fenofibrate, and U 99194 maleate, may be particularly effective in treating the

individual, although any therapeutically effective drug may be used to treat the individual.

[0017] A twelfth example is the method according to the sixth example wherein the individual is female, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (CELSR2), (KALRN), (B3GALT5), Protein Phosphatase 3 Catalytic Subunit Beta (PPP3CB), (ZFR), (THNSL1), (TNIK), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), and (TNIK), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of GNAS Complex Locus (GNAS), and Catenin Delta 1 (CTNND1), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations. When the individual is a female at least one therapeutic compound selected from the group consisting of: proglumide, quinethazone, esculin, MG-262, GW-8510, haloperidol, guanethidine, deferoxamine, citiolone, meteneprost, amylocaine, CP-944629, Clemizole, IC-86621, Nortriptyline, CP-944629, Tanesprimycin, Prestwick-674, 0317956-0000, and Pioglitazone, may be particularly effective in treating the individual, although any therapeutically effective drug may be used to treat the individual.

[0018] Still another example is a method of treating and or accessing schizophrenia and other psychotic disorders in general, and hallucinations in particular, in an individual, comprising: calculating combined biomarkers and clinical information Up- based on the equation: (Biomarker Panel Score) + (Hallucinations Score) - (Grooming Score) = Up-Hallucinations Score; wherein the Biomarker Panel Score is obtained as per the seventh example; wherein the Hallucinations Score is calculated with a clinical rating or self-report scales; wherein the Grooming Score is calculated with a rating scale; assessing the level of hallucinations of the individual by comparing the individual's Up-Hallucinations Score to a reference Up-Hallucinations Score; administering a treatment for hallucinations to the individual when the individual's Up-Hallucinations Score is greater than a reference Up-Suicide Score; and monitoring the individual's response to a treatment for hallucinations by determining changes in the Up-Hallucinations Score after initiating a treatment.

[0019] Some non-limiting examples of the disclosure include the following examples.

[0020] Example 1, A method for assessing and treating schizophrenia and other psychotic

disorders in general, in particular delusions and risk of developing delusions in an individual, comprising the steps of: (a) obtaining a biological sample from an individual and quantifying the amounts of RNA biomarkers in the biological sample, to create a panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker; wherein the biomarkers in the a first panel (a) comprise one or more of the following RNA biomarkers: Activator Of Transcription and Developmental Regulator 2 (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), GNAS Complex Locus (GNAS), Interleukin 6 Signal Transduce (IL6ST), Chromodomain Helicase DNA Binding Protein 9 (CHD9), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), Actinin Alpha 4 (ACTN4), and Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting delusions or an increased risk for developing delusions; and biomarkers in a second panel (b) comprise one or more of the following RNA biomarkers: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), and (NRP2), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting delusions or an increased risk for developing delusions; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as having delusions or of having an elevated risk for developing delusions, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference; and (h) treating the individual identified as having delusions or an elevated risk of delusions with at least one treatment selected from the group consisting of: a treatment based on clinical practice guidelines, administering a therapeutically effective amount of at least one therapeutic drug wherein the mode of treatment is on the specific biomarkers scores indicating that individual will benefit

from a particular therapy.

[0021] Example 2, the method of example 1, wherein the biomarkers are quantified in samples taken on two or more occasions from the individual.

[0022] Example 3, the method of example 1, wherein each biomarker is assigned a weighted coefficient based on each biomarkers importance in in assessing and predicting delusions risk; and the biomarker panel score is based on the weighted coefficients of each of the biomarkers.

[0023] Example 4, the method of example 1, wherein the biological sample is at least sample from the individual selected from the group consisting of: tissue, a fluid such as cerebrospinal fluid, whole blood, blood serum, plasma, saliva, or other bodily fluid, or an extract or purification therefrom, or a dilution thereof.

[0024] Example 5, the method of example 1, wherein the therapeutic is at least drug selected from the group consisting of: adenosine phosphate, N-acetyl-L-leucine, eldeline, pempidine, verteporfin, C-75, oxprenolol, Prestwick-675, meglumine, guanethidine, pancuronium bromide, karakoline, 15(S)-15-methylprostaglandin E2, hexylcaine, dicoumarol, apramycin, mephenytoin, estriol, 528116.cdx, Cyclopiazonic Acid, SB 218078, BRD-A36630025, Quinacrine hydrochloride, GF-109203X, BRD-A36630025, N9-isopropylolomoucine, BMS-536924, BRD-K76951091, BRD-K26304855, trichostatin A, ALW-II-38-3, mitoxantrone, HG-6-64-0, alvocidib, SB-216763, and caffeic acid phenethyl ester.

[0025] Example 6, the method of example 1, wherein when the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: Activator Of Transcription And Developmental Regulator (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Forkhead Box P1 (FOXP1), GNAS Complex Locus (GNAS), Serine Racemase (SRR), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), and Actinin Alpha 4 (ACTN4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions, or the biomarkers in a second panel (b) comprising one or more biomarkers selected from the group consisting of: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), NRP2, wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions.

[0026] Example 7, the method of example 6, wherein the at least one therapeutic drug is one or more drugs selected from the group consisting of: flunisolide, apramycin, adenosine phosphate, guanethidine, 15(S)-15-methylprostaglandin E2, meteneprost, methyldopate, hydralazine, rotenone, phthalylsulfathiazole, N-acetyl-L-leucine, eldeline, tocainide, laudanosine, pempidine, 7-aminocephalosporanic acid, Sulfachlorpyridazine, finasteride, 528116.cdx, SB 218078, Quinacrine hydrochloride, N9-isopropylolomoucine, ALW-II-38-3, mitoxantrone, HG-6-64-01, Alvocidib, SB-216763, Syk Inhibitor, Cyclopiazonic Acid, GW 441756, LY 225910, AG 82, doxorubicin, mitomycin, and terfenadine.

[0027] Example 8, the method of example 1, wherein when the individual is female, and the biomarkers in the panel comprise one or biomarkers in a first panel (a) comprise one or more of the biomarkers selected from the group consisting of: Phosphodiesterase 4D Interacting Protein (PDE4DIP), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Transcription Factor 4 (TCF4), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Chromodomain Helicase DNA Binding Protein 9 (CHD9), (CLCN3), Activator Of Transcription And Developmental Regulator (AUTS2), and (LDB2), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions; and the biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of (FGFR1), (DISC1), (FGFR2), (SPTBN1), (INSR), (GRIK3), Zinc Finger, and BTB Domain Containing 20 (ZBTB20), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions.

[0028] Example 9, the method of example 8, wherein the at least one therapeutic drug is at least drug selected from the group consisting of: erastin, harpagoside, metacycline, amiodarone, furaltadone, metformin, timolol, Repaglinide, sulfafurazole, PNU-0230031, Probenecid, furosemide, fluphenazine, myricetin, sulfacetamide, lomustine, BCB000039, Harmalol, I-BET151, Nylidrin hydrochloride, AMG 9810, Doxorubicin, Mitomycin C, Fludrocortisone acetate, Purvalanol A, Teniposide, Geldanamycin, Importazole, BRD-A36630025, YM-155, Auranofin, 7643453, G-221, BRD-A49680073, BRD-K08547377, and Cladribine.

[0029] Example 10, a method of assessing and treating schizophrenia and other psychotic disorders in general, and delusions in particular, in an individual, comprising: calculating combined biomarkers and clinical information Up-based on the equation: (Biomarker Panel

Score) + (Delusions Score) - (Grooming Score) = Up-Delusions Score; wherein the Biomarker Panel Score is obtained as per the method of claim 1; wherein the Delusions Score is calculated with a clinical rating or self-report scales; wherein the Grooming Score is calculated with a rating scale; assessing the level of delusions of the individual by comparing the individual's Up-Delusions Score to a reference Up-Delusions Score; administering a treatment for delusions to the individual when the individual's Up-Delusions Score is greater than a reference Up-Suicide Score; and monitoring the individual's response to a treatment for delusions by determining changes in the Up-Delusions Score after initiating a treatment.

[0030] Example 11, a method for assessing and treating schizophrenia and other psychotic disorders in general, in particular hallucinations and risk of developing hallucinations in an individual, comprising the steps of: (a) obtaining a biological sample from an individual and quantifying the amounts of one or more RNA biomarkers in the biological sample, to create at least one panel of RNA biomarkers, (b) quantifying the amounts of the RNA biomarkers in the at least one panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers; (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker a first panel and a second panel; wherein the biomarkers in the first panel comprise one or more of the following RNA biomarkers: (PRICKLE1), (NCAM1), (B3GALT5), (ARHGAP18), (PTP4A2), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), Cullin 4A (CUL4A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), Dystonin (DST), and Discs Large MAGUK Scaffold Protein 1 (DLG1), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting hallucinations or an increased risk for developing hallucinations; and wherein the biomarkers in the second panel comprise one or more of the following RNA biomarkers: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (LAMA4), (KCNV1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting hallucinations or an increased risk for developing hallucinations; (d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel; (e) determining a reference score for the panel in a clinically normal relevant population; (f) identifying a difference between the score of the panel

of biomarker(s) in the sample and the reference score of the panel of biomarker(s); (g) identifying the individual as manifesting hallucinations or of having an elevated risk for developing hallucinations, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference; and (h) treating the individual identified as having hallucinations or an elevated risk of hallucinations with one or more of the following: 1) a treatment based on clinical practice guidelines, 2) administering a therapeutically effective amount of a therapeutic drug (s), selected based on the specific biomarkers whose scores indicate that they are changed in the individual compared to a reference standard.

[0031] Example 12, the method of example 11, wherein the biomarkers are quantified in samples taken on two or more occasions from the individual.

[0032] Example 13, the method of example 11, wherein each biomarker is assigned a weighted coefficient based on the biomarkers importance in assessing and predicting hallucinations risk; and the biomarker panel score is based on the weighted coefficients of each of the biomarkers.

[0033] Example 14, the method of example 11, wherein the biological sample is a tissue sample or a fluid, such as cerebrospinal fluid, whole blood, blood serum, plasma, saliva, or other bodily fluid, or an extract or purification therefrom, or dilution thereof.

[0034] Example 15, the method of example 11, wherein the one or more therapeutic is one or more compounds selected from the group consisting of: clioquinol, pirinixic acid, moxislyte, Prestwick-685, exemestane, azacytidine, C-75, estradiol, tetraethylenepentamine, sparteine, guanethidine, idoxuridine, gliclazide, nitrendipine, N-acetyl-L-aspartic acid, sulfanilamide, doxazosin, pimozone, Proscillaridin, oxetacaine, BRD-K71489689, trichostatin A, A443654, AG 825, Proscillaridin A, Ala-Ala-Phe-CMK, Fluocinolone acetonide, manumycin A, curcumin, BRD-K68548958, CHR 2797, Tyrphostin AG 1478, Wortmannin, HY-50878, 598226, S1003, BRD-A52530684, CGP-60474, Buparlisib, and AS-601245.

[0035] Example 16, the method of example 11, wherein when the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (SH3PXD2A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), (PRICKLE1), (ARHGAP18), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), and Dystonin (DST), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of: (PRL), (SERPING1),

Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (KCNV1), Mab-21 Like 1 (MAB21L1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations.

[0036] Example 17, the method of example 16, wherein the at least one therapeutic is at least one compound selected from the group consisting of: digoxigenin, doxazosin, meptazinol, promethazine, cefixime, velnacrine, cetirizine, eldeline, atropine oxide, clioquinol, nicotinic acid, clioquinol, galantamine, rolitetracycline, betahistine, sulconazole, monocrotaline, lanatoside C, Prestwick-1084, Naftidrofuryl, sulfachlorpyridazine, helveticoside, bezafibrate, mifepristone, trichostatin A, manumycin A, NCGC00189555-02, Buparlisib, linifanib, AZD-7762, Dinaciclib, Piretanide, KN-62, Fluticasone propionate, JAK3 Inhibitor VI, Sarmentogenin, Digoxin, Megestrol acetate, Oxymetazoline hydrochloride, U-0126, Tracazolate hydrochloride, Flufenamic acid, Fenofibrate, and U 99194 maleate.

[0037] Example 18, the method of example 11, wherein when the individual is female, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (CELSR2), (KALRN), (B3GALT5), Protein Phosphatase 3 Catalytic Subunit Beta (PPP3CB), (ZFR), (THNSL1), (TNIK), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), and (TNIK), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of GNAS Complex Locus (GNAS), and Catenin Delta 1 (CTNND1), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations.

[0038] Example 19, the method of example 18, wherein the at least one therapeutic is at least one compound selected from the group consisting of: proglumide, quinethazone, esculin, MG-262, GW-8510, haloperidol, guanethidine, deferoxamine, citiolone, meteneprost, amylocaine, CP-944629, Clemizole, IC-86621, Nortriptyline, CP-944629, Tanespimycin, Prestwick-674, 0317956-0000, and Pioglitazone.

[0039] Example 20, a method of assessing and treating schizophrenia and other psychotic disorders in general, and hallucinations in particular in an individual, comprising: calculating combined biomarkers and clinical information Up- based on the equation: (Biomarker Panel

Score) + (Hallucinations Score) - (Grooming Score) = Up-Hallucinations Score; wherein the Biomarker Panel Score is obtained as per the method of example 11; wherein the Hallucinations Score is calculated with a clinical rating or self-report scales; wherein the Grooming Score is calculated with a rating scale; assessing the level of hallucinations of the individual by comparing the individual's Up-Hallucinations Score to a reference Up-Hallucinations Score; administering a treatment for hallucinations to the individual when the individual's Up-Hallucinations Score is greater than a reference Up-Suicide Score; and monitoring the individual's response to a treatment for hallucinations by determining changes in the Up-Hallucinations Score after initiating a treatment.

BRIEF DESCRIPTION OF THE FIGURES

- [0040]** FIG. 1 A. Cohorts used in study, depicting flow of discovery, prioritization, and validation of biomarkers from each step (N of 74).
- [0041]** FIG. 1 B. Discovery cohort longitudinal within-subject analysis. Phchp### is study ID for each subject. V# denotes visit number.
- [0042]** FIG. 1 C. The clinical phenotypic measure (item from PANSS) used for discovery.
- [0043]** FIG. 1 D. Validation in independent cohort of psychiatric patients with clinically severe psychosis.
- [0044]** FIG. 1 E. Validation in independent cohort of psychiatric patients with clinically severe psychosis.
- [0045]** FIG. 1 F. The 4 step process of discovery, prioritization, validation, and testing.
- [0046]** FIG. 1 G. Schematic illustrating the process of biomarker validation.
- [0047]** FIG. 1 H. Cohorts used in study, depicting flow of discovery, prioritization, and validation of biomarkers from each step.
- [0048]** FIG. 1 I. Discovery cohort longitudinal within-subject analysis. Phchp### is the study identifier (ID) for each subject. V# denotes visit number.
- [0049]** FIG. 1 J. The clinical phenotypic measure (item from PANSS) used for discovery (N of 36).
- [0050]** FIG. 1 K. Validation in independent cohort of psychiatric patients with clinically severe psychosis (N of 36).
- [0051]** FIG. 1 L. The 4 step process of discovery, prioritization, validation, and testing.

CLAIMS

1. An *in vitro* method for assessing schizophrenia and other psychotic disorders in general, in particular delusions and risk of developing delusions in an individual, comprising the steps of:

- (a) quantifying the amounts of RNA biomarkers in a biological sample from the individual, to create a panel of RNA biomarkers,
- (b) quantifying the amounts of the RNA biomarkers in the panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers;
- (c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker;

wherein the biomarkers in a first panel (a) comprise one or more of the following RNA biomarkers: Activator Of Transcription and Developmental Regulator 2 (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), GNAS Complex Locus (GNAS), Interleukin 6 Signal Transduce (IL6ST), Chromodomain Helicase DNA Binding Protein 9 (CHD9), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), Actinin Alpha 4 (ACTN4), and Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting delusions or an increased risk for developing delusions; and

biomarkers in a second panel (b) comprise one or more of the following RNA biomarkers: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), and (NRP2), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting delusions or an increased risk for developing delusions;

(d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel;

(e) determining a reference score for the panel in a clinically normal relevant population;

(f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s);

(g) identifying the individual as having delusions or of having an elevated risk for developing delusions, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference.

2. An *in vitro* method for assessing schizophrenia and other psychotic disorders in general, in particular hallucinations and risk of developing hallucinations in an individual, comprising the steps of:

(a) quantifying the amounts of one or more RNA biomarkers in the biological sample, to create at least one panel of RNA biomarkers,

(b) quantifying the amounts of the RNA biomarkers in the at least one panel in a clinically relevant population to generate a reference expression level for the RNA biomarkers in a panel of RNA biomarkers;

(c) comparing the amounts of the biomarkers in the biological sample from the individual with the amounts of the RNA biomarkers present in the reference standard to generate a score for each biomarker a first panel and a second panel; wherein the biomarkers in the first panel comprise one or more of the following RNA biomarkers: (PRICKLE1), (NCAM1), (B3GALT5), (ARHGAP18), (PTP4A2), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), Cullin 4A (CUL4A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), Dystonin (DST), and Discs Large MAGUK Scaffold Protein 1 (DLG1), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting hallucinations or an increased risk for developing hallucinations; and

wherein the biomarkers in the second panel comprise one or more of the following RNA biomarkers: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (LAMA4), (KCNV1), Catenin Delta 1 (CTNND1), and FAT Atypical Cadherin 4 (FAT4), wherein the expression level of the RNA biomarker(s) in the sample is decreased relative to a reference expression level of the RNA biomarkers in the panel, denoting hallucinations or an increased risk for developing hallucinations;

(d) generating a score for the panel of RNA biomarkers, based on the scores of the biomarker(s) in the panel;

(e) determining a reference score for the panel in a clinically normal relevant population;
(f) identifying a difference between the score of the panel of biomarker(s) in the sample and the reference score of the panel of biomarker(s);

(g) identifying the individual as manifesting hallucinations or of having an elevated risk for developing hallucinations, based on the difference between the biomarker panel score of the individual relative to the biomarker panel score of the reference.

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

4. The method of claim 1 or 2, wherein each biomarker is assigned a weighted coefficient based on each biomarkers importance in assessing and predicting delusions risk or in assessing and predicting hallucinations risk; and the biomarker panel score is based on the weighted coefficients of each of the biomarkers.

5. The method of claim 1, wherein the biological sample is at least sample from the individual selected from the group consisting of: tissue, a fluid such as cerebrospinal fluid, whole blood, blood serum, plasma, saliva, or other bodily fluid, or an extract or purification therefrom, or a dilution thereof.

6. The method of claim 2, wherein the biological sample is a tissue sample or a fluid, such as cerebrospinal fluid, whole blood, blood serum, plasma, saliva, or other bodily fluid, or an extract or purification therefrom, or dilution thereof.

7. The method of claim 1, wherein the therapeutic is at least drug selected from the group consisting of: adenosine phosphate, N-acetyl-L-leucine, eldeline, pempidine, verteporfin, C-75, oxprenolol, Prestwick-675, meglumine, guanethidine, pancuronium bromide, karakoline, 15(S)-15-methylprostaglandin E2, hexylcaine, dicoumarol, apramycin, mephenytoin, estriol, 528116.cdx, Cyclopiazonic Acid, SB 218078, BRD-A36630025, Quinacrine hydrochloride, GF-109203X, BRD-A36630025, N9-isopropylolomoucine, BMS-536924, BRD-K76951091, BRD-K26304855, trichostatin A, ALW-II-38-3, mitoxantrone, HG-6-64-0, alvocidib, SB-216763, and caffeic acid phenethyl ester.

8. The method of claim 1, wherein when the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: Activator Of

Transcription And Developmental Regulator (AUTS2), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Forkhead Box P1 (FOXP1), GNAS Complex Locus (GNAS), Serine Racemase (SRR), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), X-Ray Repair Cross Complementing 6 (XRCC6), RAR Related Orphan Receptor A (RORA), and Actinin Alpha 4 (ACTN4), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions, or

the biomarkers in a second panel (b) comprising one or more biomarkers selected from the group consisting of: Zinc Finger And BTB Domain Containing 20 (ZBTB20), Forkhead Box P1 (FOXP1), Spondin 1 (SPON1), NRP2, wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions, optionally

wherein the at least one therapeutic drug selected from the group consisting of: flunisolide, apramycin, adenosine phosphate, guanethidine, 15(S)-15-methylprostaglandin E2, meteneprost, methyl dopate, hydralazine, rotenone, phthalylsulfathiazole, N-acetyl-L-leucine, eldeline, tocainide, laudanosine, pempidine, 7-aminocephalosporanic acid, Sulfachlorpyridazine, finasteride, 528116.cdx, SB 218078, Quinacrine hydrochloride, N9-isopropylolomoucine, ALW-II-38-3, mitoxantrone, HG-6-64-01, Alvocidib, SB-216763, Syk Inhibitor, Cyclopiazonic Acid, GW 441756, LY 225910, AG 82, doxorubicin, mitomycin, and terfenadine is to be used in therapy of the individual identified as manifesting hallucinations or of having an elevated risk for developing hallucinations.

9. The method of claim 1, wherein when the individual is female, and the biomarkers in the panel comprise one or biomarkers in a first panel (a) comprise one or more of the biomarkers selected from the group consisting of: Phosphodiesterase 4D Interacting Protein (PDE4DIP), Pyruvate Dehydrogenase Phosphatase Catalytic Subunit 1 (PDP1), Transcription Factor 4 (TCF4), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Chromodomain Helicase DNA Binding Protein 9 (CHD9), (CLCN3), Activator Of Transcription And Developmental Regulator (AUTS2), and (LDB2), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased delusions; and

the biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of (FGFR1), (DISC1), (FGFR2), (SPTBN1), (INSR), (GRIK3), Zinc Finger,

and BTB Domain Containing 20 (ZBTB20), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased delusions, optionally

wherein the at least one therapeutic drug selected from the group consisting of: erastin, harpagoside, metacycline, amiodarone, furaltadone, metformin, timolol, Repaglinide, sulfafurazole, PNU-0230031, Probenecid, furosemide, fluphenazine, myricetin, sulfacetamide, lomustine, BCB000039, Harmalol, I-BET151, Nylidrin hydrochloride, AMG 9810, Doxorubicin, Mitomycin C, Fludrocortisone acetate, Purvalanol A, Teniposide, Geldanamycin, Importazole, BRD-A36630025, YM-155, Auranofin, 7643453, G-221, BRD-A49680073, BRD-K08547377, and Cladribine is to be used in therapy of the individual identified as manifesting hallucinations or of having an elevated risk for developing hallucinations.

10. The method of claim 2, wherein the one or more therapeutic selected from the group consisting of: clioquinol, pirinixic acid, moxislyte, Prestwick-685, exemestane, azacytidine, C-75, estradiol, tetraethylenepentamine, sparteine, guanethidine, idoxuridine, gliclazide, nitrendipine, N-acetyl-L-aspartic acid, sulfanilamide, doxazosin, pimozide, Proscillaridin, oxetacaine, BRD-K71489689, trichostatin A, A443654, AG 825, Proscillaridin A, Ala-Ala-Phe-CMK, Fluocinolone acetonide, manumycin A, curcumin, BRD-K68548958, CHR 2797, Tyrphostin AG 1478, Wortmannin, HY-50878, 598226, S1003, BRD-A52530684, CGP-60474, Buparlisib, and AS-601245 is to be used in therapy of the individual identified as manifesting hallucinations or of having an elevated risk for developing hallucinations.

11. The method of claim 2, wherein when the individual is male, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (SH3PXD2A), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), (PRICKLE1), (ARHGAP18), Acylphosphatase 2 (ACYP2), Reticulon 4 (RTN4), and Dystonin (DST), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and

biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of: (PRL), (SERPING1), Ectonucleotide Pyrophosphatase/Phosphodiesterase 2 (ENPP2), (KCNV1), Mab-21 Like 1 (MAB21L1), Catenin Delta 1 (CTNND1), and FAT

Atypical Cadherin 4 (FAT4), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations, optionally wherein the at least one therapeutic selected from the group consisting of: digoxigenin, doxazosin, meptazinol, promethazine, cefixime, velnacrine, cetirizine, eldeline, atropine oxide, clioquinol, nicotinic acid, clioquinol, galantamine, rolitetracycline, betahistine, sulconazole, monocrotaline, lanatoside C, Prestwick-1084, Naftidrofuryl, sulfachlorpyridazine, helveticoside, bezafibrate, mifepristone, trichostatin A, manumycin A, NCGC00189555-02, Buparlisib, linifanib, AZD-7762, Dinaciclib, Piretanide, KN-62, Fluticasone propionate, JAK3 Inhibitor VI, Sarmentogenin, Digoxin, Megestrol acetate, Oxymetazoline hydrochloride, U-0126, Tracazolate hydrochloride, Flufenamic acid, Fenofibrate, and U 99194 maleate is to be used in therapy of the individual identified as manifesting hallucinations or of having an elevated risk for developing hallucinations.

12. The method of claim 2, wherein when the individual is female, and the biomarkers in a first panel (a) comprise one or more biomarkers selected from the group consisting of: (CELSR2), (KALRN), (B3GALT5), Protein Phosphatase 3 Catalytic Subunit Beta (PPP3CB), (ZFR), (THNSL1), (TNIK), Nuclear Receptor Subfamily 4 Group A Member 2 (NR4A2), Zinc Finger E-Box Binding Homeobox 2 (ZEB2), and (TNIK), wherein the expression level of the biomarker(s) in the sample is increased relative to a reference expression level, denoting increased hallucinations; and

biomarkers in a second panel (b) comprise one or more biomarkers selected from the group consisting of GNAS Complex Locus (GNAS), and Catenin Delta 1 (CTNND1), wherein the expression level of the biomarker(s) in the sample is decreased relative to a reference expression level, denoting increased hallucinations, optionally wherein the at least one therapeutic selected from the group consisting of: proglumide, quinethazone, esculin, MG-262, GW-8510, haloperidol, guanethidine, deferoxamine, citiolone, meteneprost, amylocaine, CP-944629, Clemizole, IC-86621, Nortriptyline, CP-944629, Tanespimycin, Prestwick-674, 0317956-0000, and Pioglitazone is to be used in therapy of the individual identified as manifesting hallucinations or of having an elevated risk for developing hallucinations.