

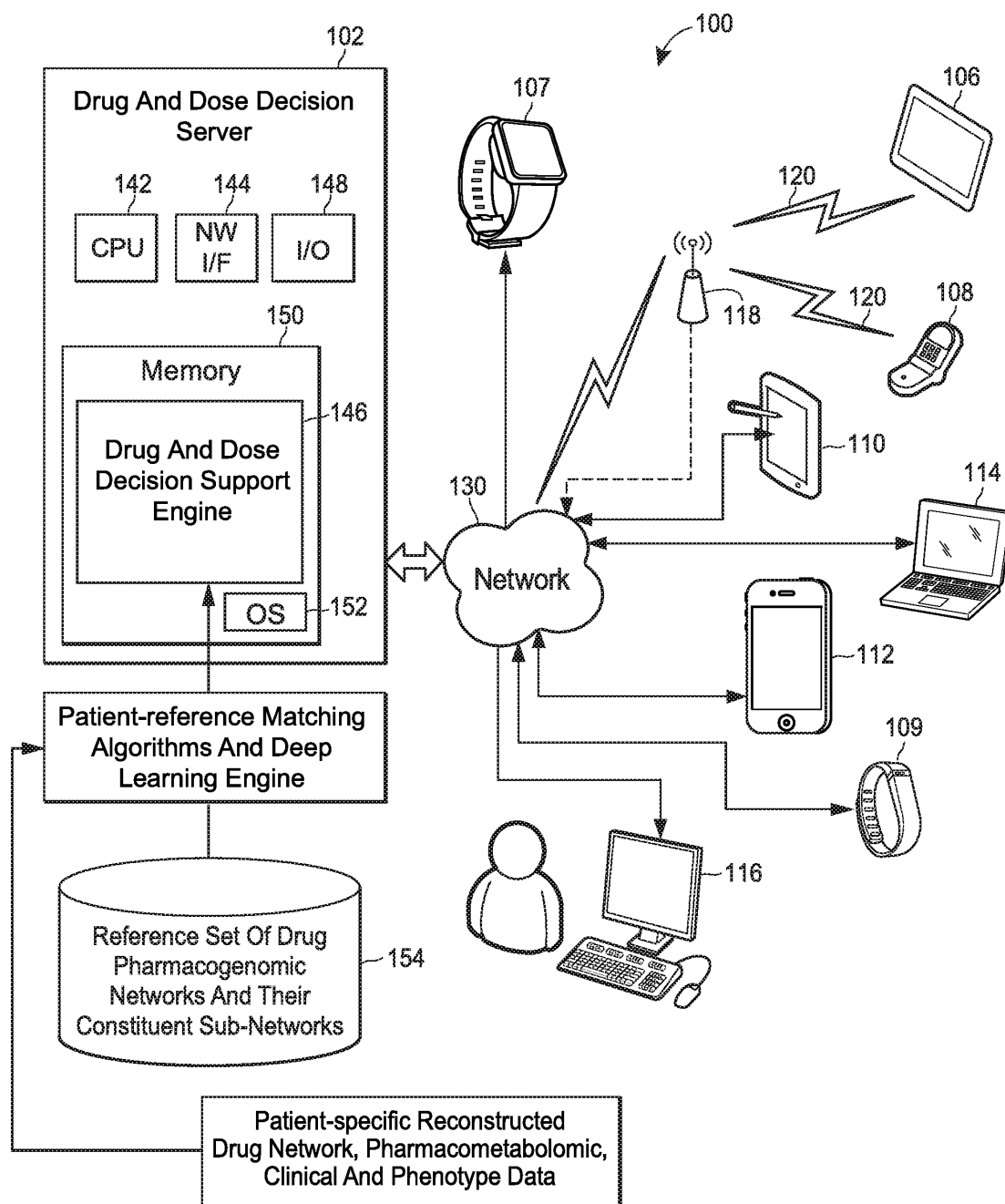
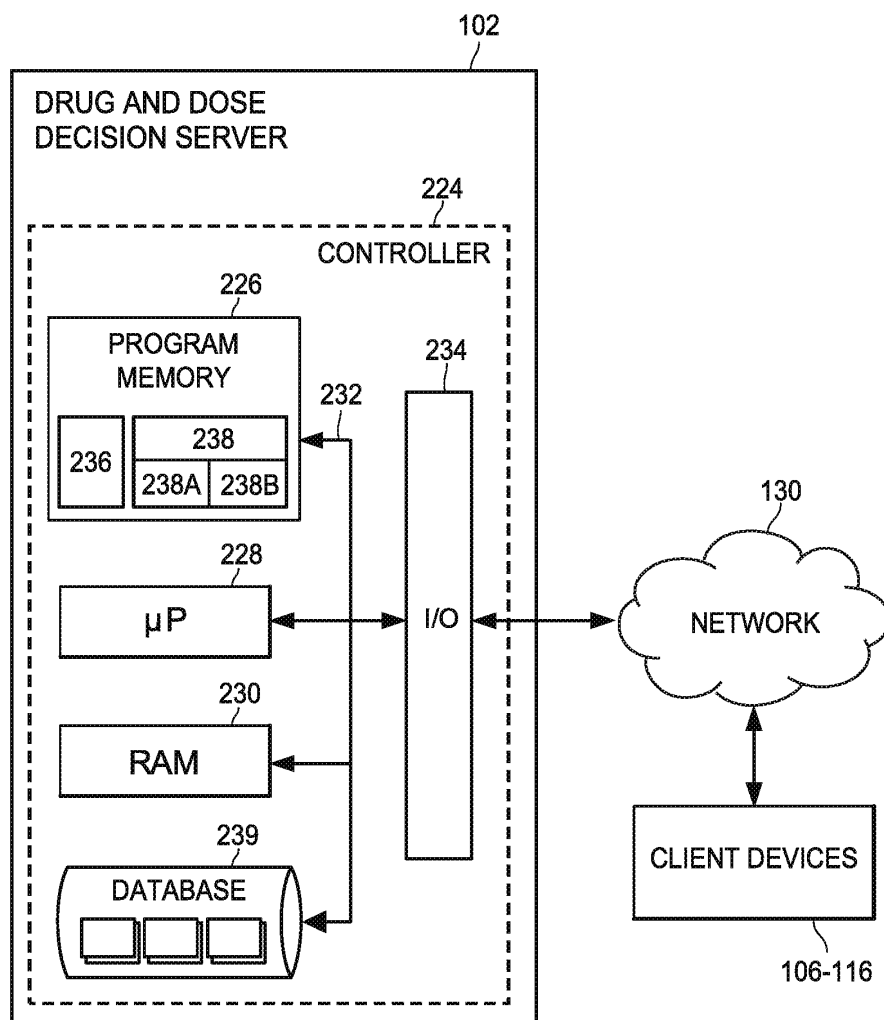


FIG. 1A

**FIG. 1B**

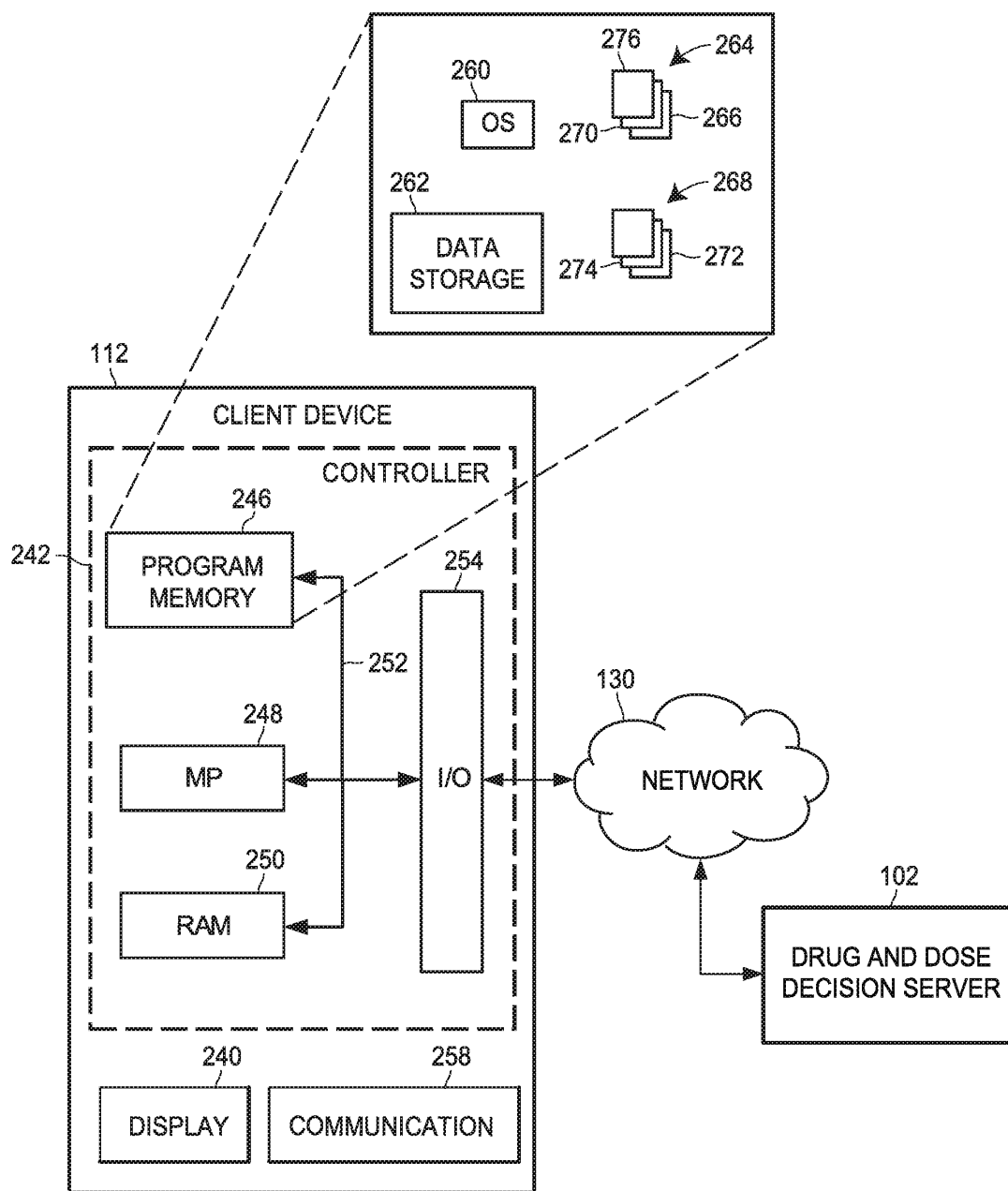


FIG. 1C

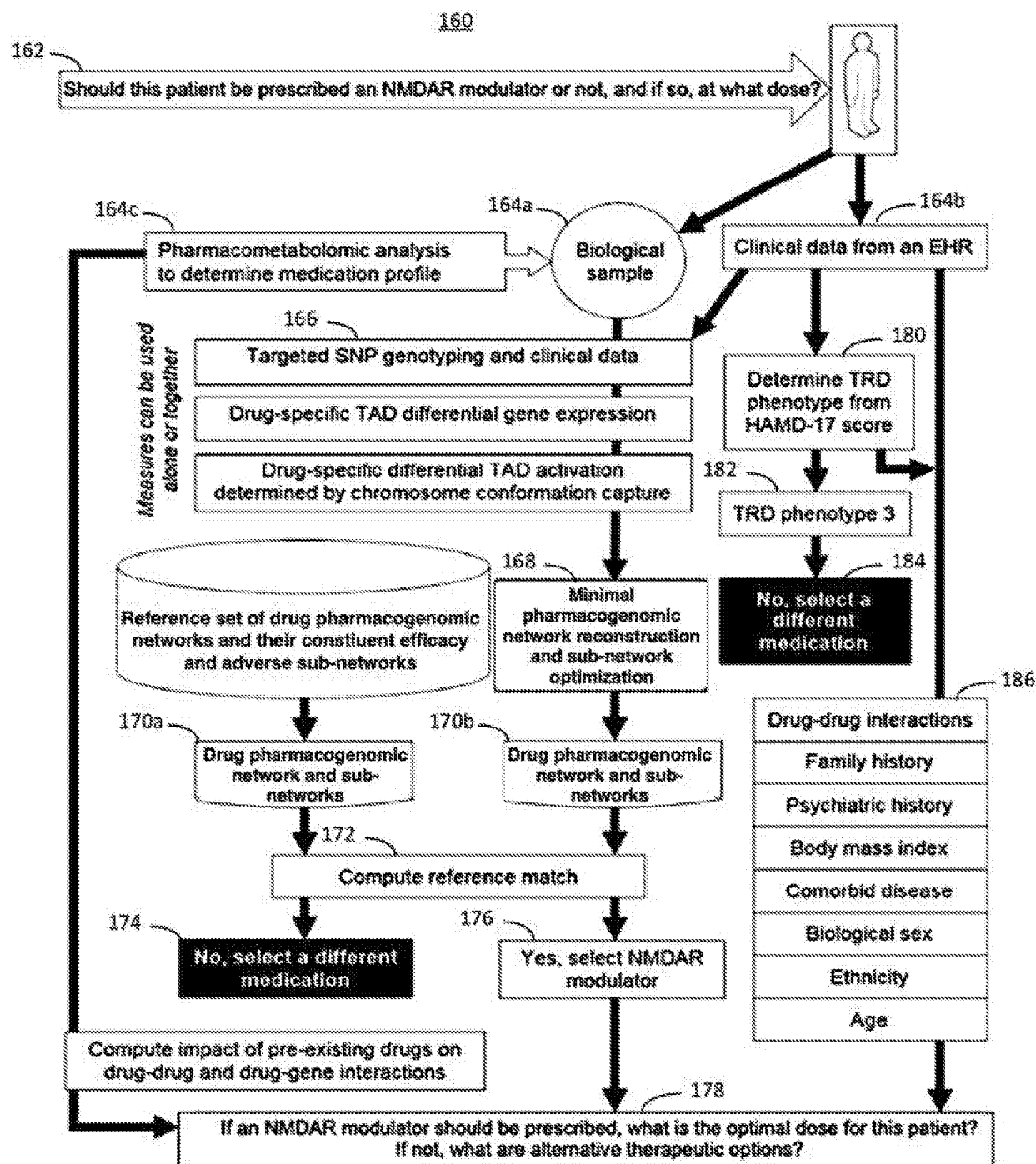


FIG. 1D

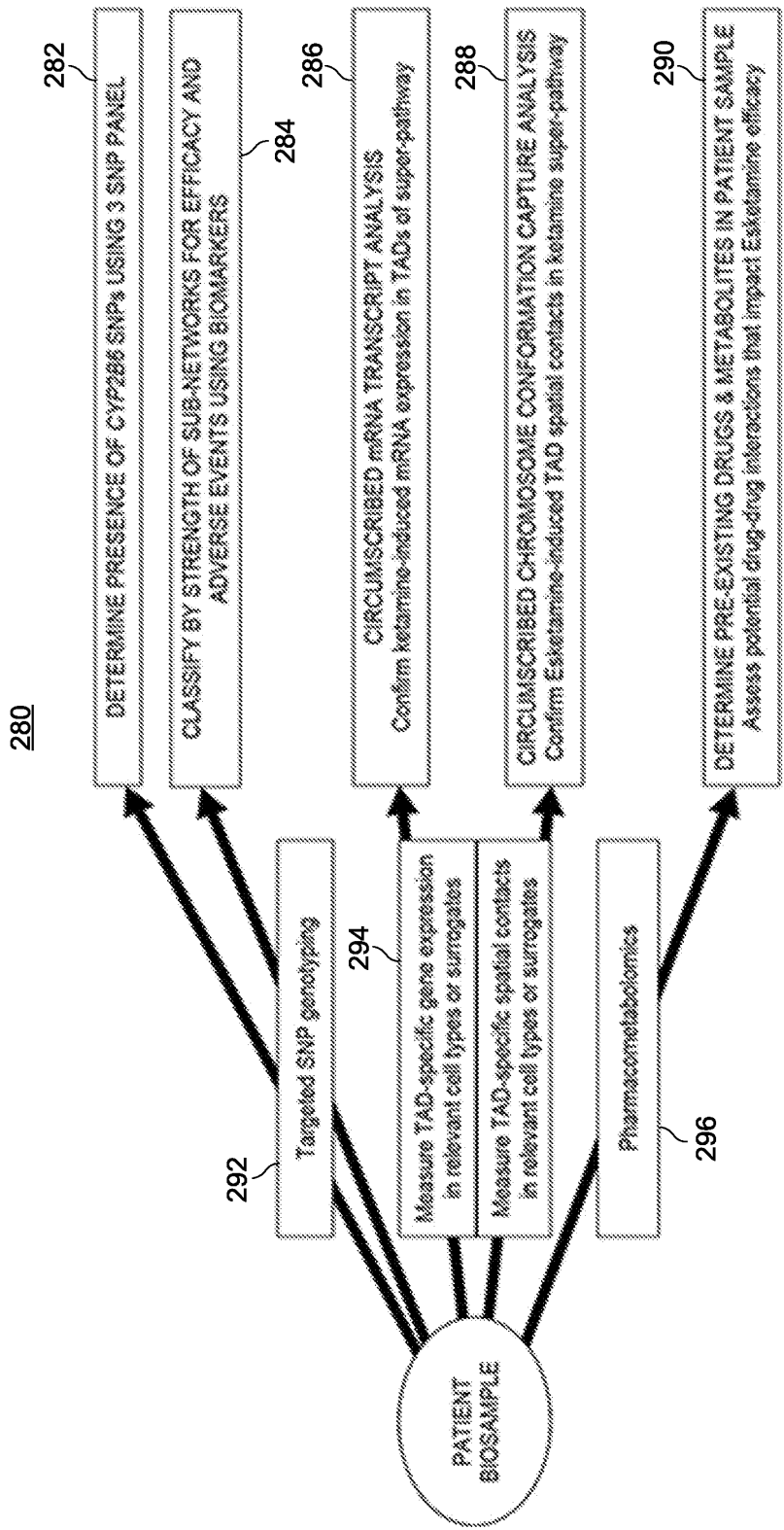


FIG. 2

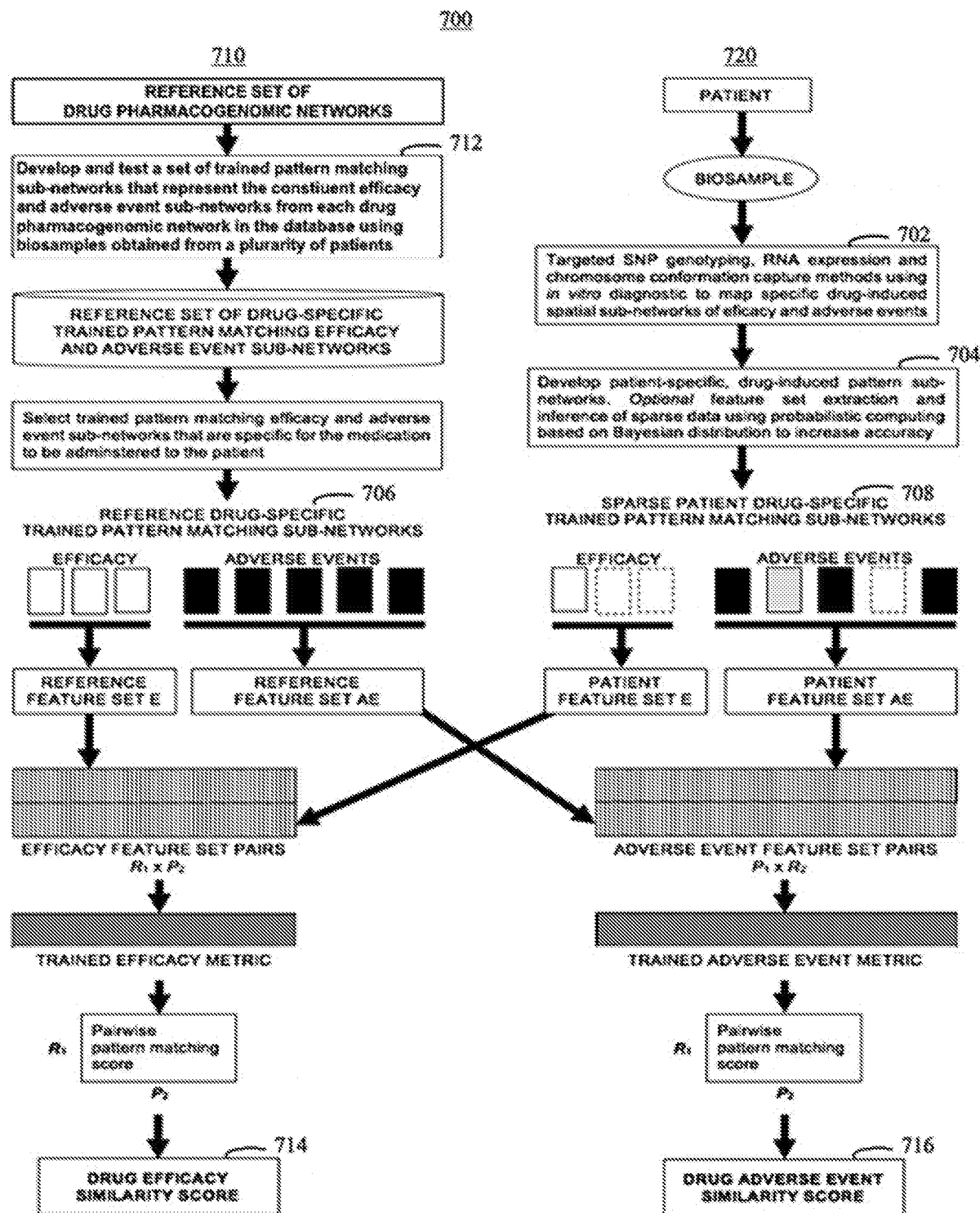


FIG. 4

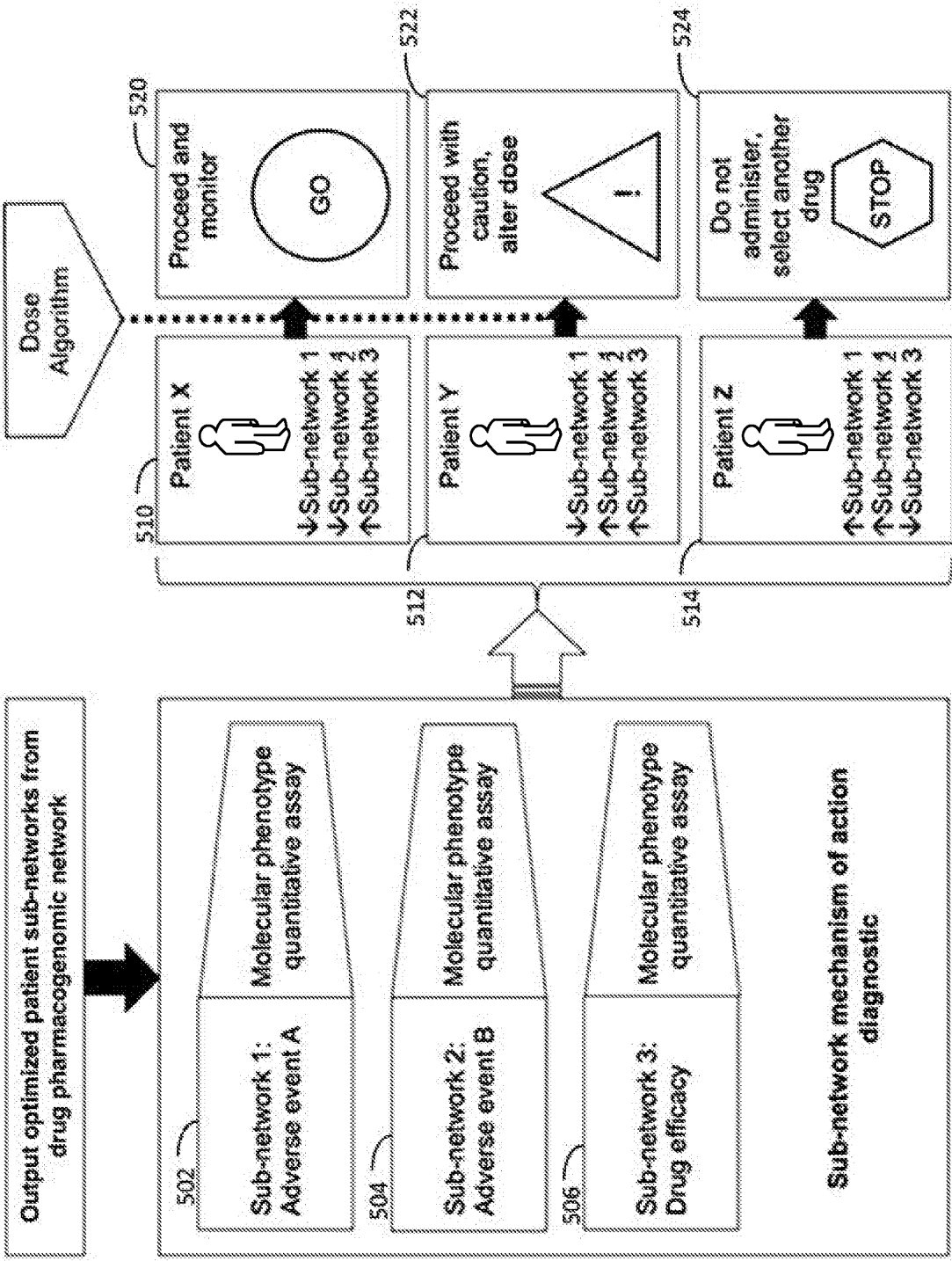


FIG. 5

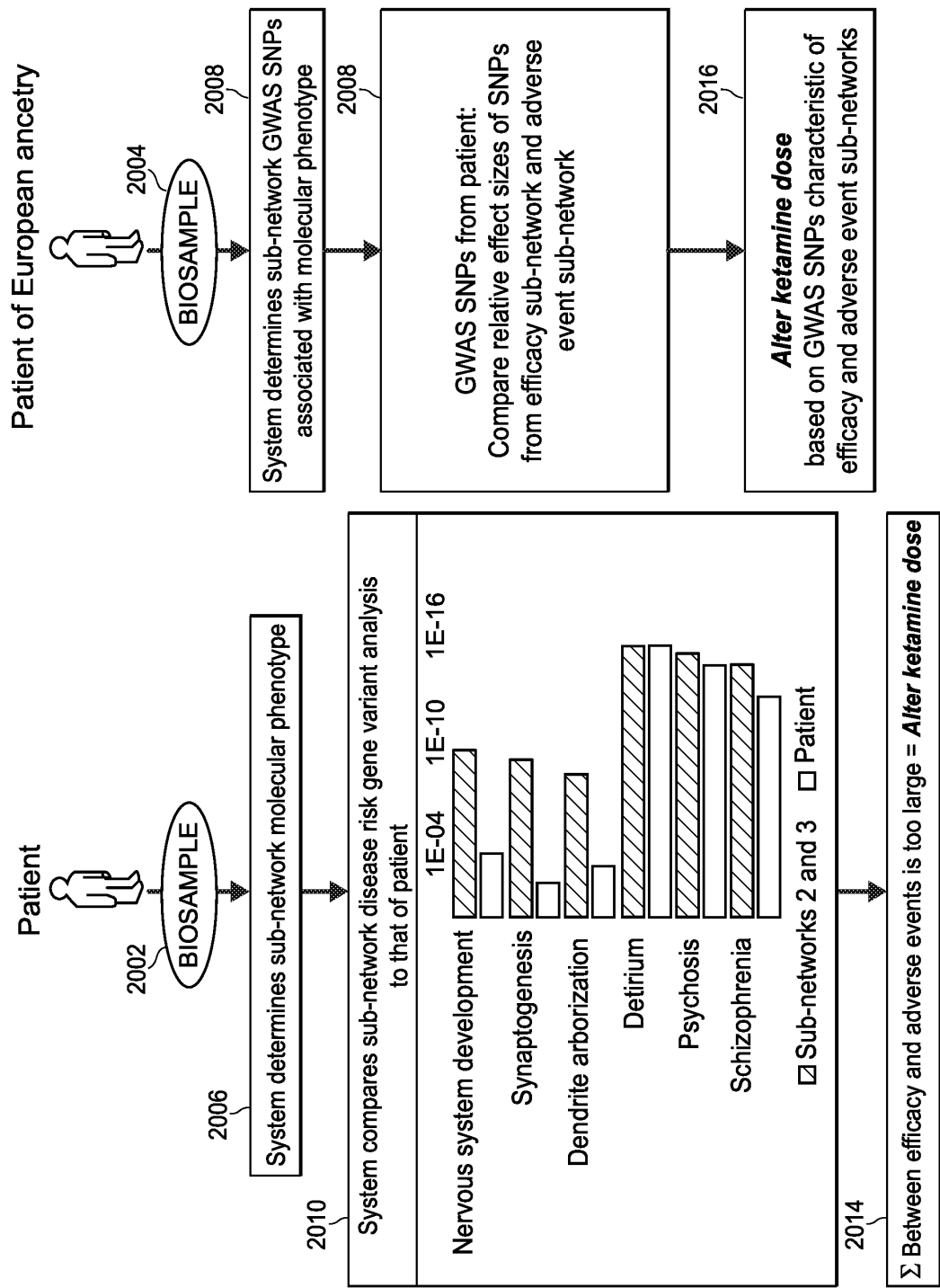


FIG. 6

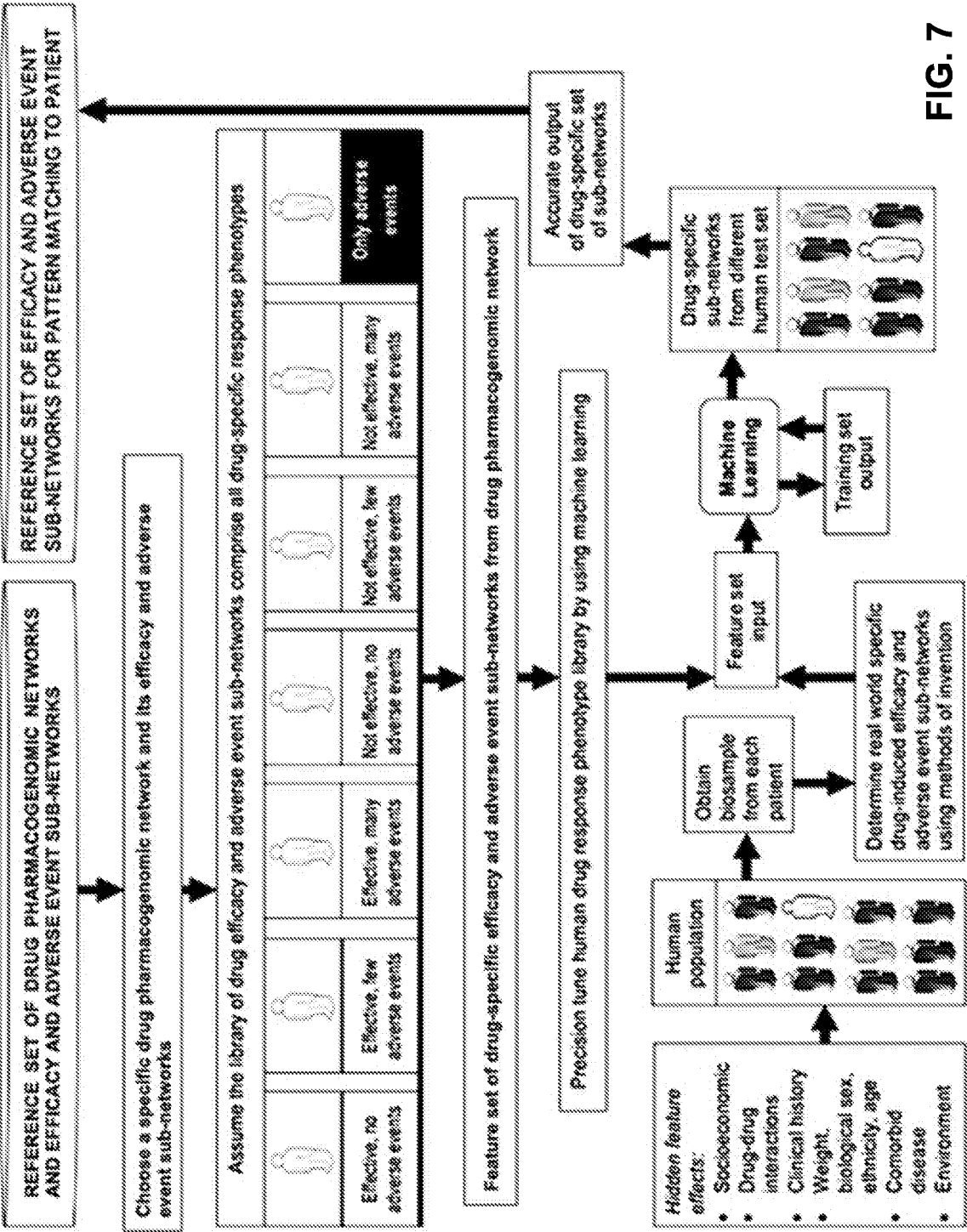


FIG. 7

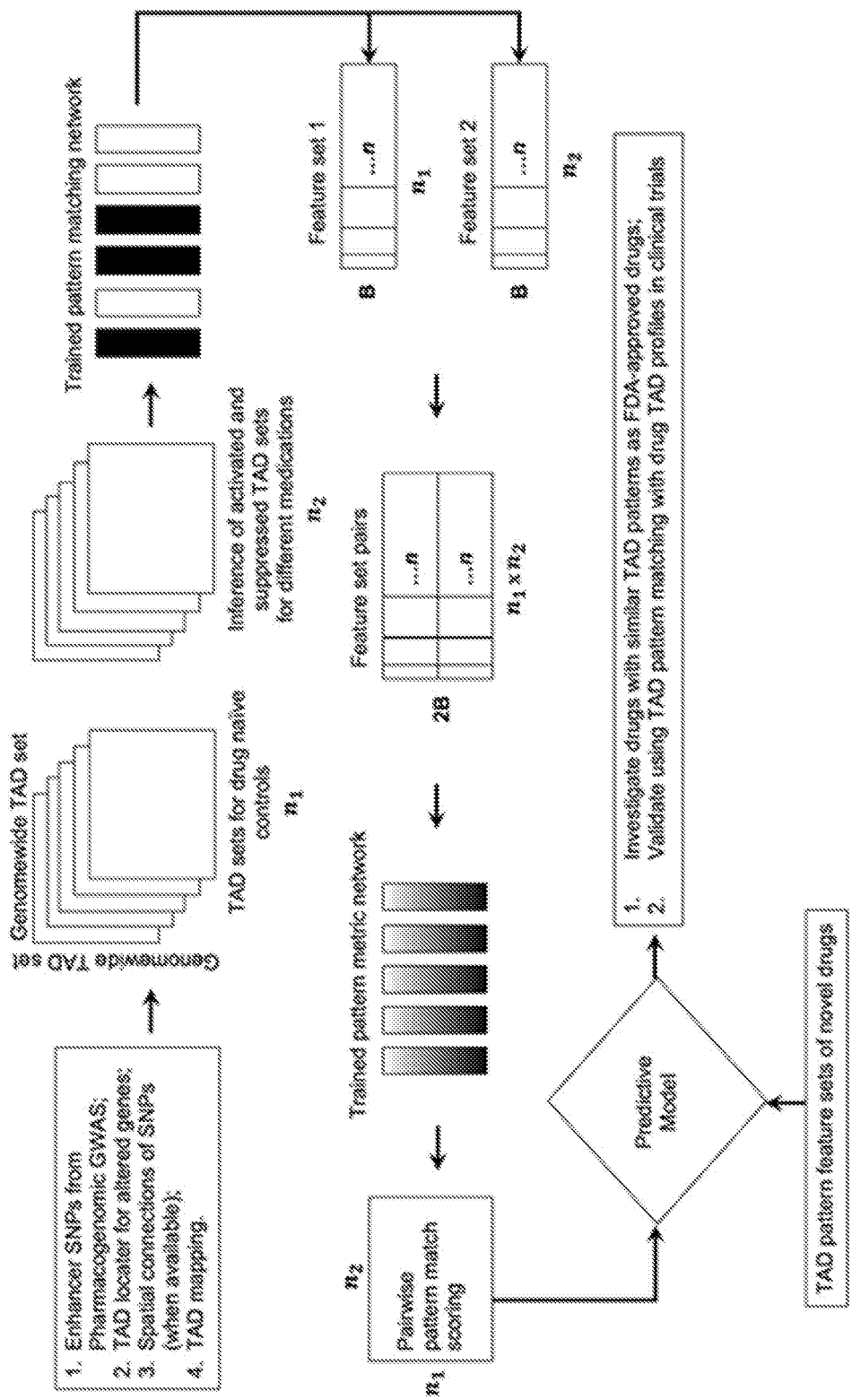


FIG. 8

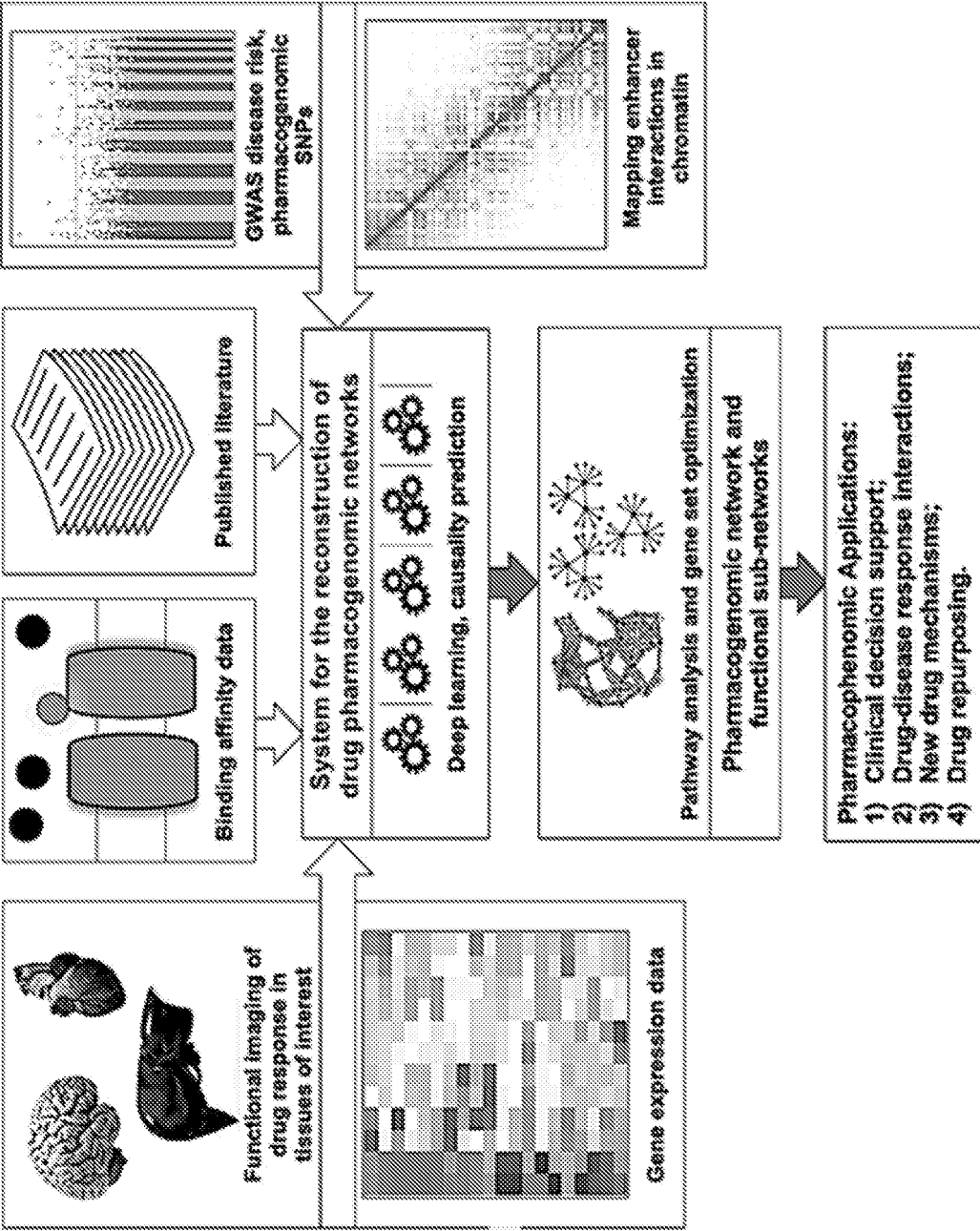


FIG. 9A

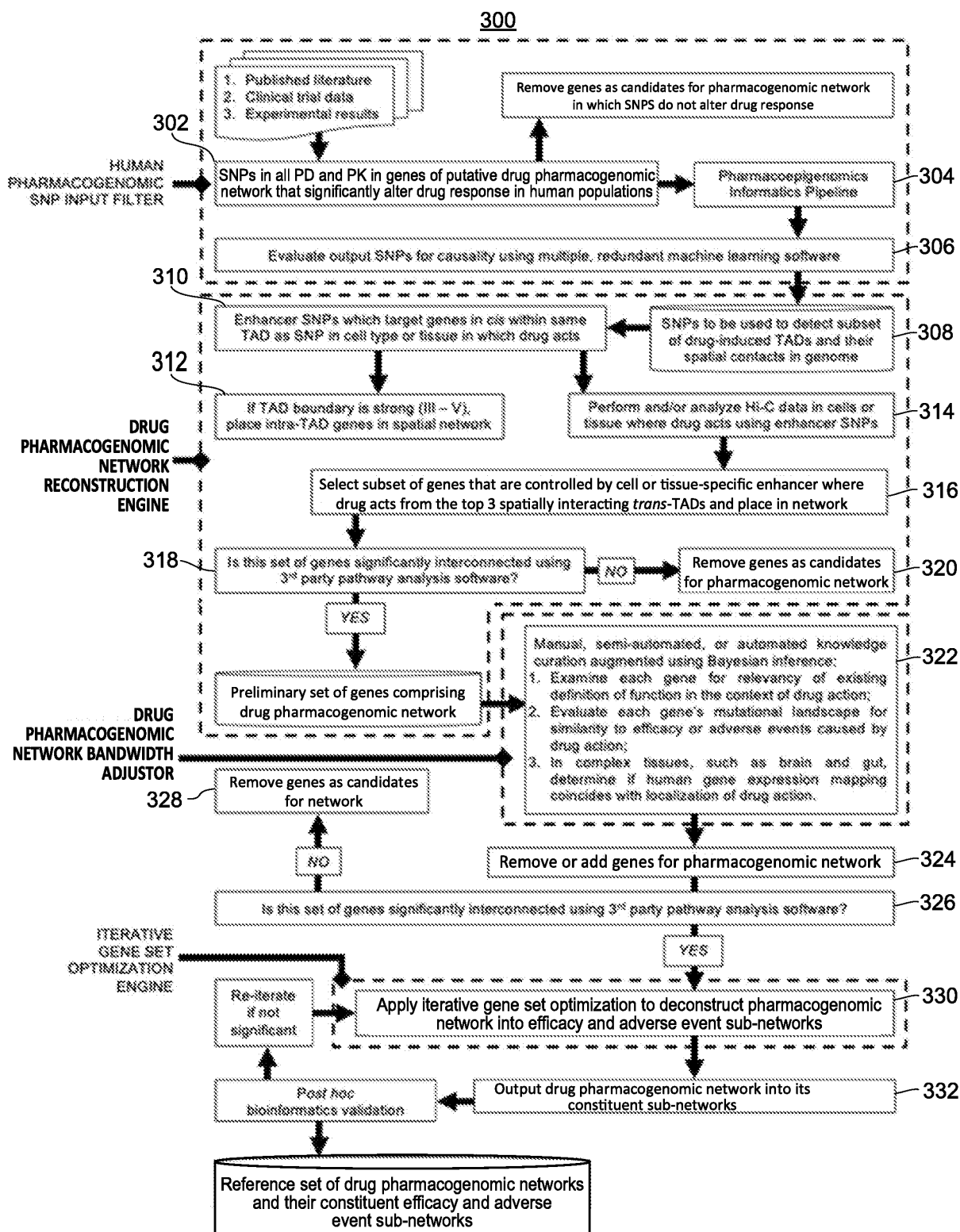


FIG. 9B

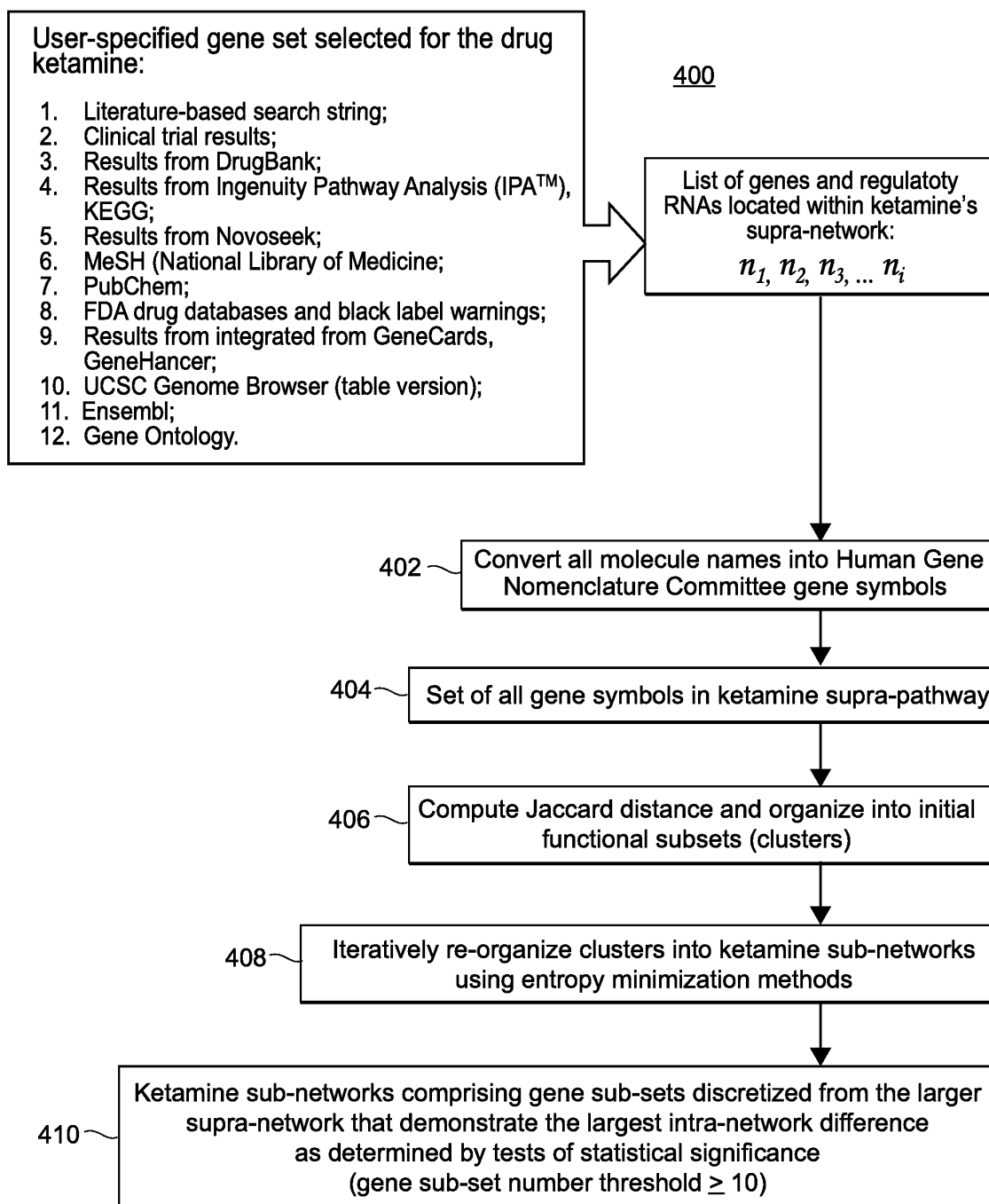


FIG. 10

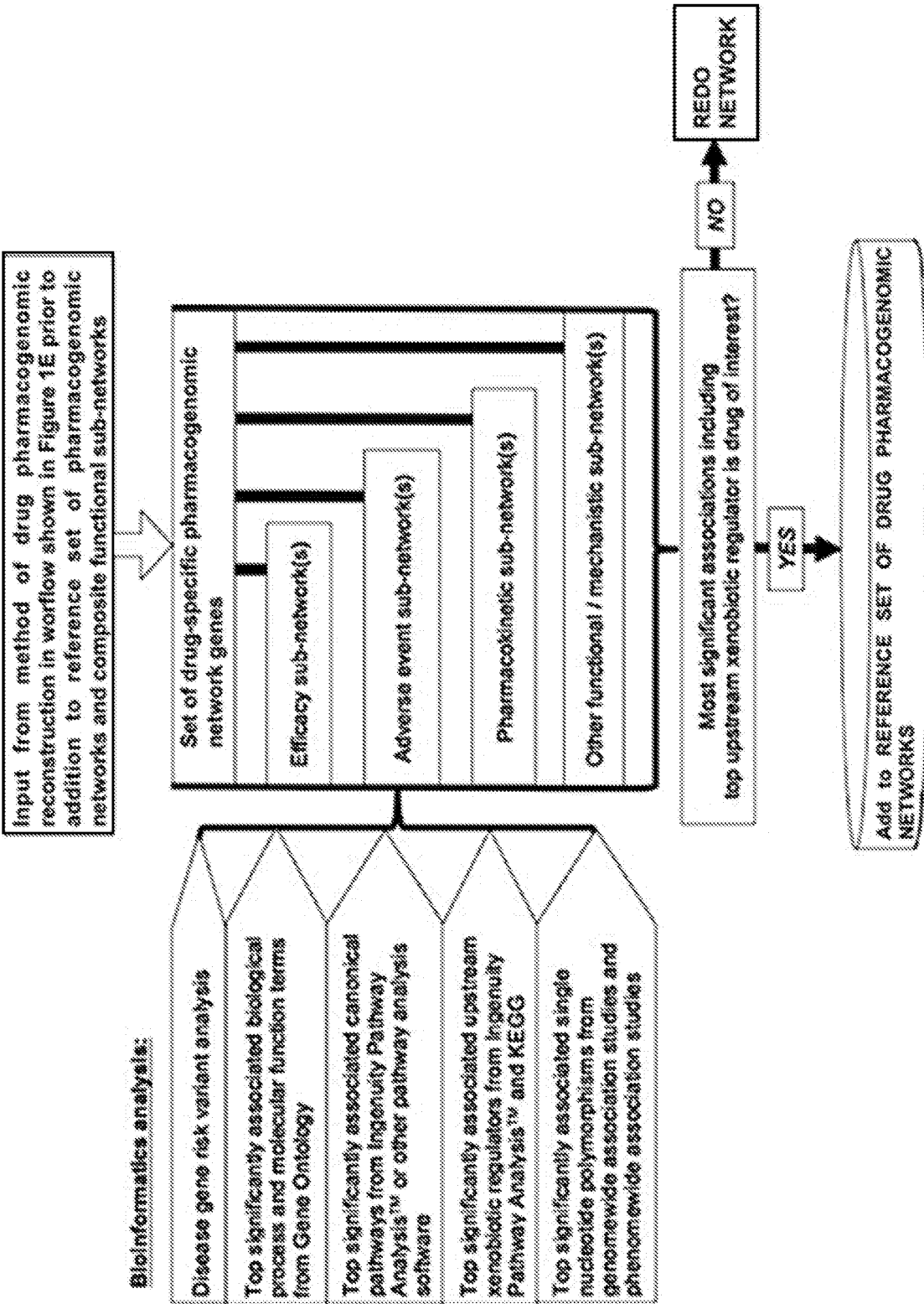


FIG. 11

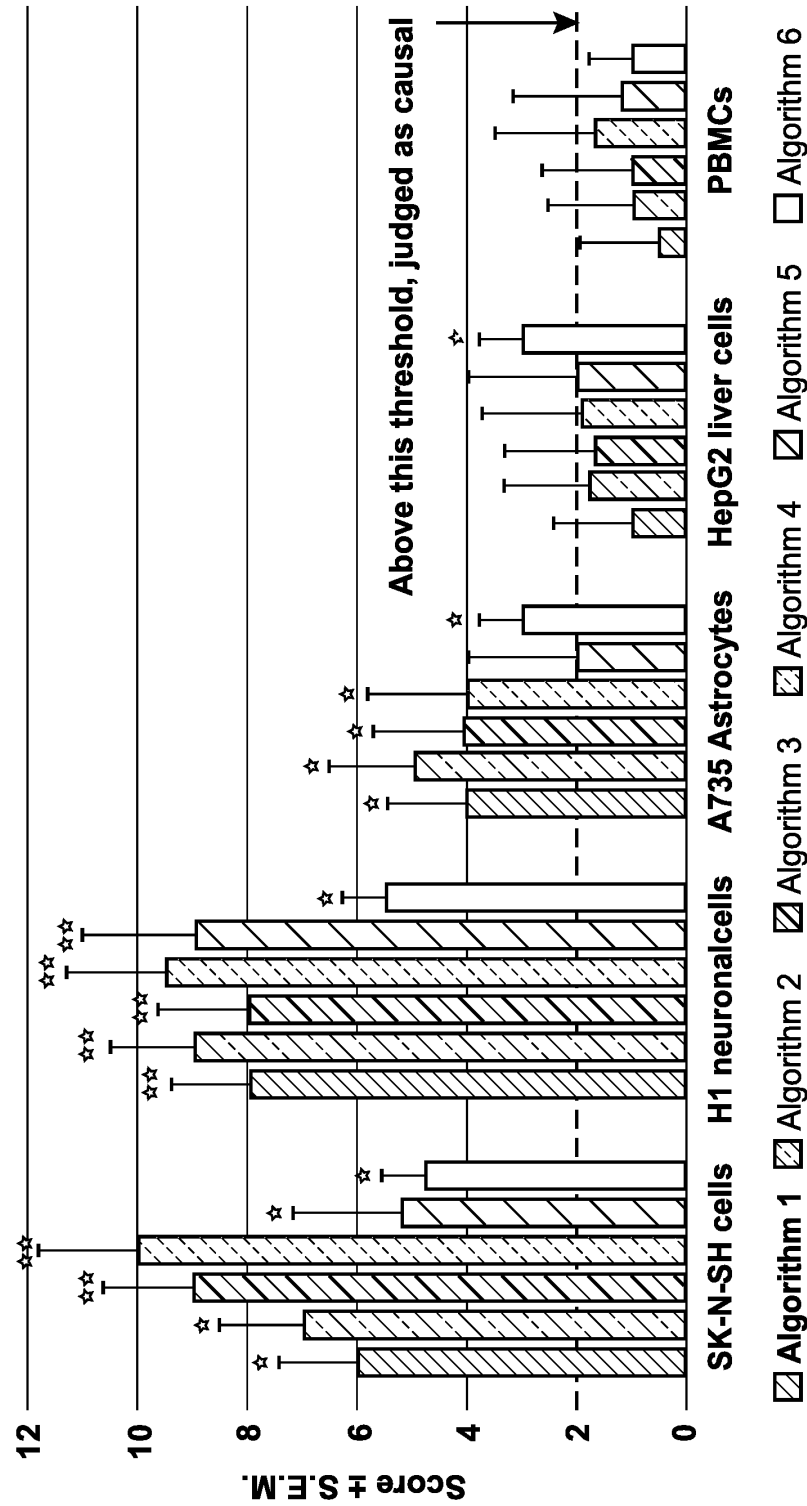


FIG. 12

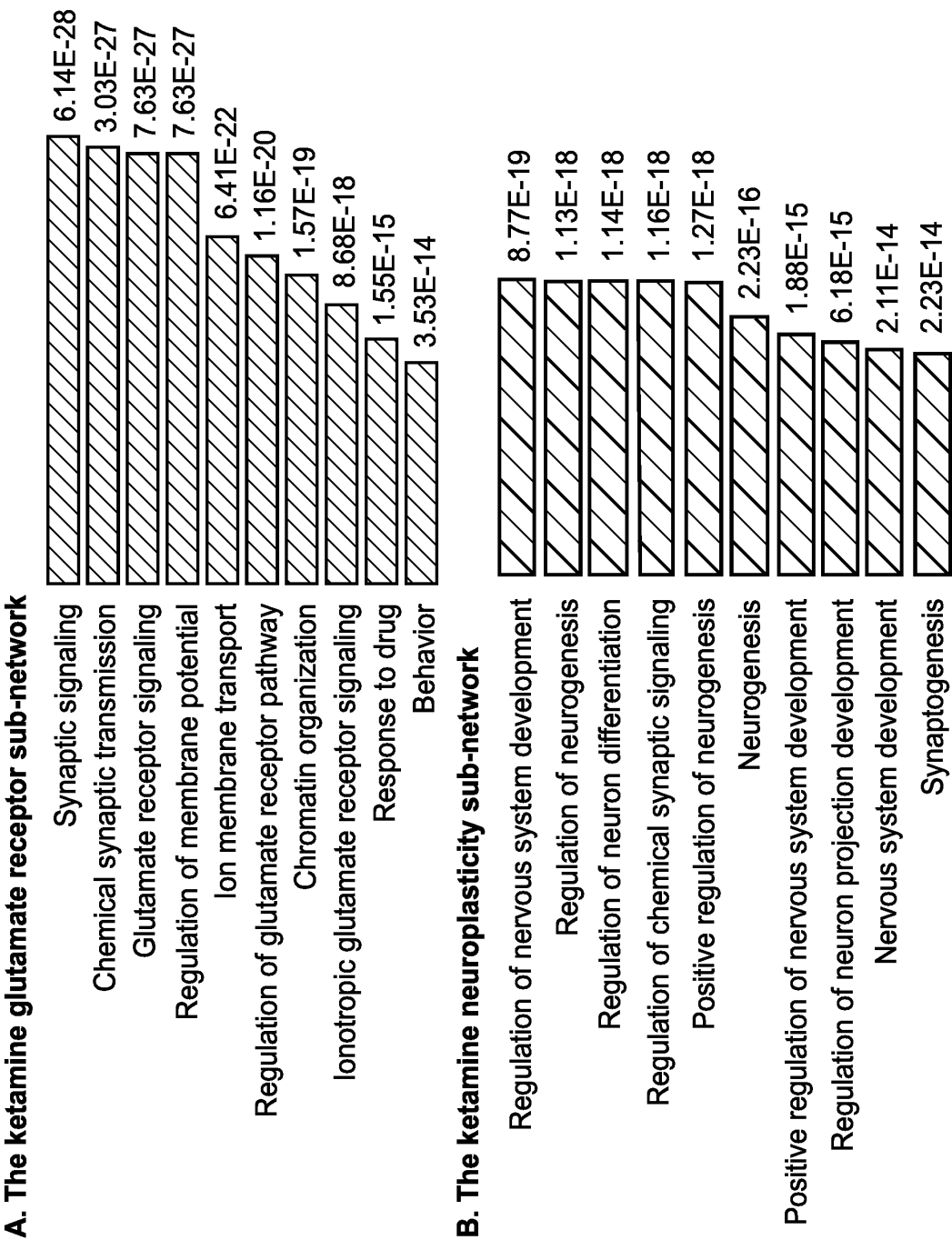


FIG. 13

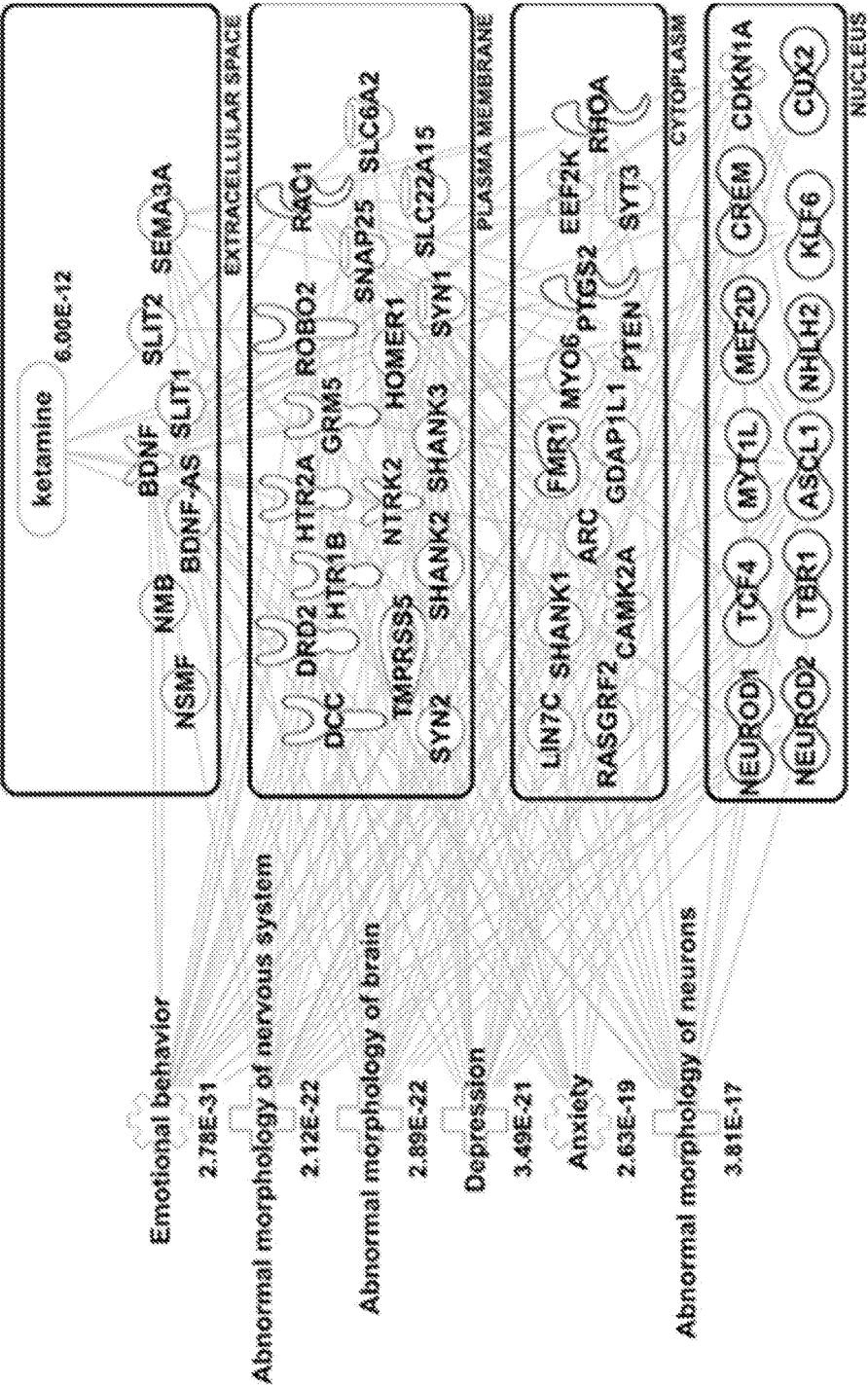
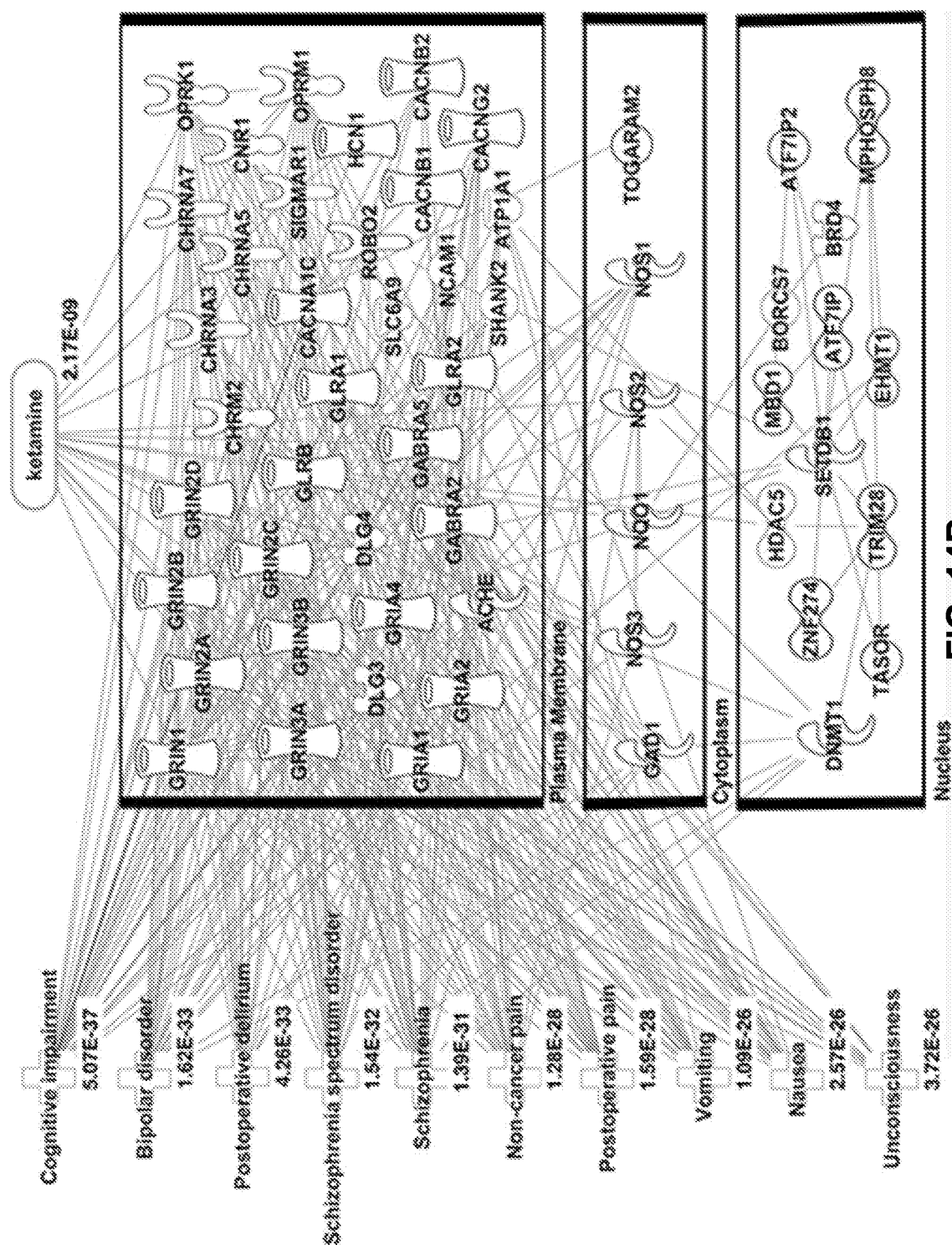


FIG. 14A



Symbol	Entrez Gene Name
ARC	activity regulated cytoskeleton associated protein
ASCL1	achaete-scute family bHLH transcription factor 1
BDNF	brain derived neurotrophic factor
BDNF-AS	BDNF antisense RNA
CAMK2A	calcium/calmodulin dependent protein kinase II alpha
CDKN1A	cyclin dependent kinase inhibitor 1A
CREM	cAMP responsive element modulator
CUX2	cut like homeobox 2
DCC	DCC netrin 1 receptor
DRD2	dopamine receptor D2
EEF2K	eukaryotic elongation factor 2 kinase
FMR1	fragile X mental retardation 1
GDAP1L1	ganglioside induced differentiation associated protein 1 like 1
GRM5	glutamate metabotropic receptor 5
HOMER1	homer scaffold protein 1
HTR1B	5-hydroxytryptamine receptor 1B
HTR2A	5-hydroxytryptamine receptor 2A
KLF6	Kruppel like factor 6
LIN7C	lin-7 homolog C, crumbs cell polarity complex component
LOC105379109	
MEF2D	myocyte enhancer factor 2D
MYO6	myosin VI
MYT1L	myelin transcription factor 1 like
NEUROD1	neuronal differentiation 1
NEUROD2	neuronal differentiation 2
NHLH2	nescient helix-loop-helix 2
NMB	neuromedin B
NSMF	NMDA receptor synaptonuclear signaling and neuronal migration factor
NTRK2	neurotrophic receptor tyrosine kinase 2
PTEN	phosphatase and tensin homolog
PTGS2	prostaglandin-endoperoxide synthase 2
RAC1	Rac family small GTPase 1
RASGRF2	Ras protein specific guanine nucleotide releasing factor 2
RHOA	ras homolog family member A
ROBO2	roundabout guidance receptor 2
RP11_360A181	
SEMA3A	semaphorin 3A
SHANK1	SH3 and multiple ankyrin repeat domains 1
SHANK2	SH3 and multiple ankyrin repeat domains 2
SHANK3	SH3 and multiple ankyrin repeat domains 3
SLC22A15	solute carrier family 22 member 15
SLC6A2	solute carrier family 6 member 2
SLIT1	slit guidance ligand 1
SLIT2	slit guidance ligand 2
SNAP25	synaptosome associated protein 25
SYN1	synapsin I
SYN2	synapsin II
SYT3	synaptotagmin 3
TBR1	T-box, brain 1
TCF4	transcription factor 4

FIG. 15

Symbol	Entrez Gene Name
ACHE	acetylcholinesterase (Cartwright blood group)
ATF7IP	activating transcription factor 7 interacting protein
ATF7IP2	activating transcription factor 7 interacting protein 2
ATP1A1	ATPase Na ⁺ /K ⁺ transporting subunit alpha 1
BORCS7	BLOC-1 related complex subunit 7
BRD4	bromodomain containing 4
CACNA1C	calcium voltage-gated channel subunit alpha1 C
CACNB1	calcium voltage-gated channel auxiliary subunit beta 1
CACNB2	calcium voltage-gated channel auxiliary subunit beta 2
CACNG2	calcium voltage-gated channel auxiliary subunit gamma 2
CHRM2	cholinergic receptor muscarinic 2
CHRNA3	cholinergic receptor nicotinic alpha 3 subunit
CHRNA5	cholinergic receptor nicotinic alpha 5 subunit
CHRNA7	cholinergic receptor nicotinic alpha 7 subunit
CNR1	cannabinoid receptor 1
DLG3	discs large MAGUK scaffold protein 3
DLG4	discs large MAGUK scaffold protein 4
DNMT1	DNA methyltransferase 1
EHMT1	euchromatic histone lysine methyltransferase 1
GABRA2	gamma-aminobutyric acid type A receptor alpha2 subunit
GABRA5	gamma-aminobutyric acid type A receptor alpha5 subunit
GAD1	glutamate decarboxylase 1
GLRA1	glycine receptor alpha 1
GLRA2	glycine receptor alpha 2
GLRB	glycine receptor beta
GRIA1	glutamate ionotropic receptor AMPA type subunit 1
GRIA2	glutamate ionotropic receptor AMPA type subunit 2
GRIA4	glutamate ionotropic receptor AMPA type subunit 4
GRIN1	glutamate ionotropic receptor NMDA type subunit 1
GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B
GRIN2C	glutamate ionotropic receptor NMDA type subunit 2C
GRIN2D	glutamate ionotropic receptor NMDA type subunit 2D
GRIN3A	glutamate ionotropic receptor NMDA type subunit 3A
GRIN3B	glutamate ionotropic receptor NMDA type subunit 3B
HCN1	hyperpolarization activated cyclic nucleotide gated potassium channel 1
HDAC5	histone deacetylase 5
MBD1	methyl-CpG binding domain protein 1
MPHOSPH8	M-phase phosphoprotein 8
NCAM1	neural cell adhesion molecule 1
NOS1	nitric oxide synthase 1
NOS2	nitric oxide synthase 2
NOS3	nitric oxide synthase 3
NQO1	NAD(P)H quinone dehydrogenase 1
OPRK1	opioid receptor kappa 1
OPRM1	opioid receptor mu 1
ROBO2	roundabout guidance receptor 2
SETDB1	SET domain bifurcated histone lysine methyltransferase 1
SHANK2	SH3 and multiple ankyrin repeat domains 2
SIGMAR1	sigma non-opioid intracellular receptor 1
SLC6A9	solute carrier family 6 member 9
TASOR	transcription activation suppressor
TOGARAM2	TOG array regulator of axonemal microtubules 2
TRIM28	tripartite motif containing 28
ZNF274	zinc finger protein 274

FIG. 16

Symbol	Entrez Gene Name
ANAPC2	anaphase promoting complex subunit 2
CYP2A6 (<i>includes others</i>)	cytochrome P450 family 2 subfamily A member 6
CYP2B6	cytochrome P450 family 2 subfamily B member 6
CYP3A4	cytochrome P450 family 3 subfamily A member 4
DLG4	discs large MAGUK scaffold protein 4
EEF2K	eukaryotic elongation factor 2 kinase
ESR1	estrogen receptor 1
GRIA1	glutamate ionotropic receptor AMPA type subunit 1
GRIA4	glutamate ionotropic receptor AMPA type subunit 4
GRIN1	glutamate ionotropic receptor NMDA type subunit 1
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B
MYO6	myosin VI
ROBO2	roundabout guidance receptor 2
SHANK2	SH3 and multiple ankyrin repeat domains 2
TCERG1	transcription elongation regulator 1

FIG. 17

Inputs required for the algorithm	Independent predictors of Esketamine dose	R ² after rank and entry in cohort model	P-value in cohort
CYP2B6 SNP rs3745274*	+100%	1	25%
Biological sex (Female, pre-menopausal)	-25%	2	34%
CYP2B6 SNP rs3786547*	-22%	4	40%
Clopidogrel (Plavix®) use	-22%	5	45%
CYP2B6 SNP rs11083595*	-19%	6	50%
Height, weight (Body Surface Area, BSA or BMI)	-11% per 0.25m ²	7	52%
Current smoker	-20%	8	53%
Nicotine use other than tobacco	-11%	9	53.4%
Suicide attempt(s) and/or family history of suicide (first degree relative)	-17%	10	53.8%
Age	-7% per decade	11	54%
Family history of alcohol use disorder (first degree relative)	-10%	12	54.4%
Ethnicity	-10% (Non-Hispanic white)	13	54.7 %
Ticlopidine (Ticlid®) use	-20%	14	54.9%
Previous psychiatric hospitalization	-15%	15	55%

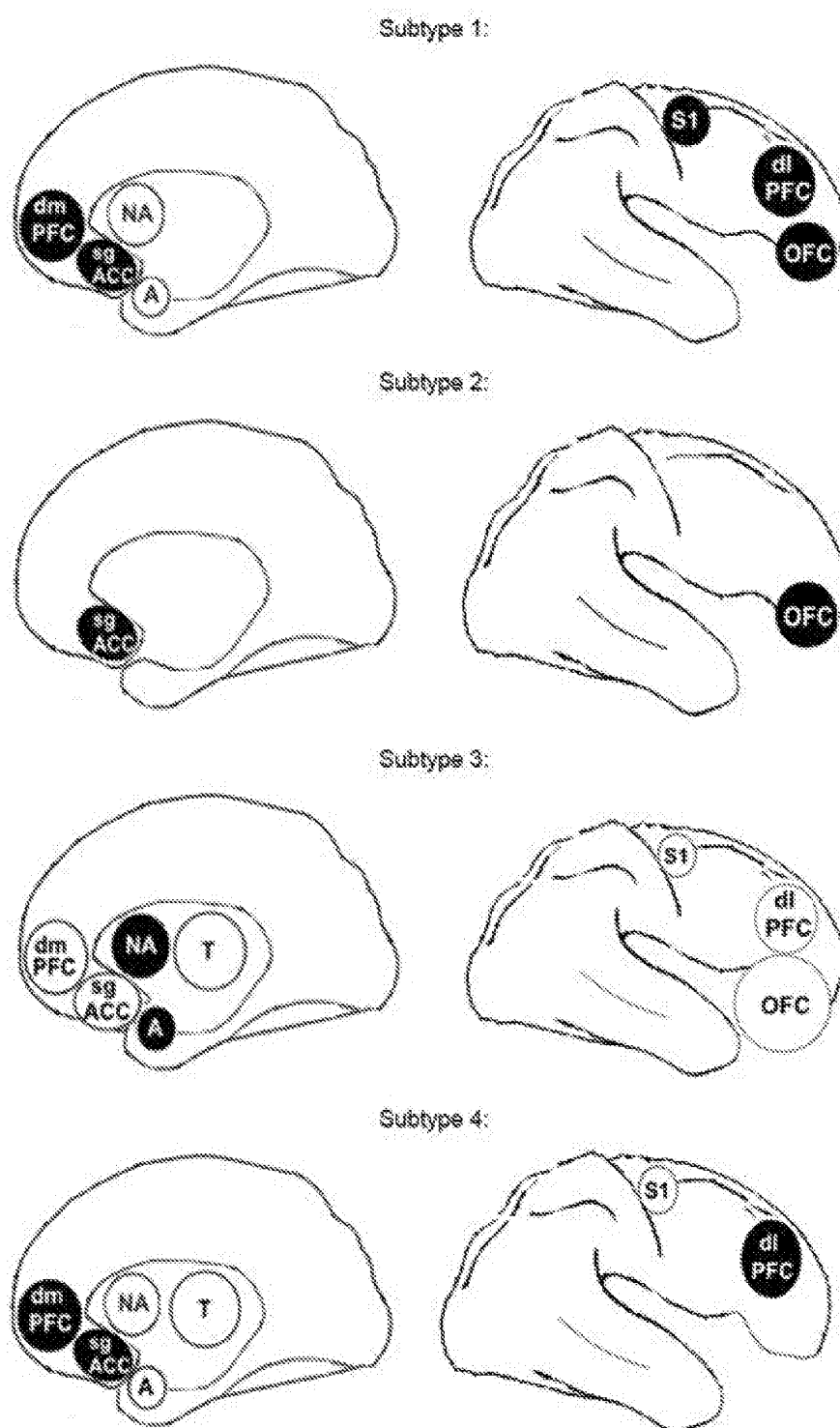
FIG. 18A

Accuracy metric	Pharmacogenomics	Clinical	P-value
R ² (SD)	54% (5%)	17% (4%)	<0.001
Median (mean) absolute prediction error, mg/day	1.0 (1.4)	1.6 (1.9)	<0.001

FIG. 18B

FIG. 19

% of TRD patients	Symptoms in rank order (HAMD-17)	Network connectivity predicted by from TMS and neuroimaging	Behavioral traits	Associated clinical values
1 23.6%	Anxiety Anergia, fatigue	- Reduced connectivity in frontoamygdala networks, which regulate fear-related behavior and reappraisal of negative emotional stimuli - Reduced connectivity in anterior cingulate and orbitofrontal areas supporting motivation and incentive-salience evaluation	- Poor impulse control - Desires never satisfied - Highest scores on neuroticism of the different subtypes	- Co-diagnosis of generalized anxiety disorder (GAD) and recurrent depression; - Natural language processing (NLP) of psychiatric notes on "neuroticism"; - HAMD-17 rating – "neuroticism";
2 22.7%	Anergia, fatigue Anhedonia	Reduced connectivity in anterior cingulate and orbitofrontal areas supporting motivation and incentive-salience evaluation	- Score lower on HAMD and other depression rating scales than other biotypes - Loneliness	- NLP of clinical notes or HAMD-17 rating – "loneliness"; - ICD codes for chronic fatigue syndrome, fibromyalgia and neuropathic pain.
3 20.0%	Anhedonia PMR (Psychomotor retardation) PMA (Psychomotor agitation)	- Hyperconnectivity in thalamic and frontostriatal networks with exception of the nucleus accumbens; - Hyperactive subgenulate anterior cingulate cortex (sgACC); - Hyperactive neurons of lateral orbitofrontal cortex, which supports non-reward / punishment system and substitutes for the Nucleus accumbens-based reward system in these patients.	- High impulse control - Introversive - Highest educational attainment and "successful" - Exaggerated focus and rumination on finances, job - Self-deprivation – food, clothes, bathing ("punishing")	- Measures of educational attainment based on college degrees, post-graduate education; - In longitudinal EHR, loss in body weight; - HAMD-17 rating – "PMR, PMA"; - Failure to respond to the drug mirtazapine in pharmacotherapy regimens.
4 33.6%	Anxiety Anhedonia Guilt PMR (Psychomotor retardation) Early insomnia Middle insomnia Hypochondria Suicidal ideation, family history.	- Reduced connectivity in frontoamygdala networks which regulate fear-related behavior and reappraisal of negative emotional stimuli - Hyperconnectivity in thalamic and frontostriatal networks, which support reward processing, adaptive motor control and action initiation	- Poor impulse control - Extroversion - Constant attempts to validate self-worth based on praise from others - Tendency towards bipolar disorder and dysfunctional moods	- Co-diagnosis of generalized anxiety disorder (GAD) and recurrent depression; - Co-diagnosis of bipolar spectrum disorders and/or hypomania; NLP or structured data showing "suicidal ideation," - Lithium-responsive.

**FIG. 20**

Subtype	Selection of ketamine as antidepressant?	Antidepressants, other psychotropic medications and options to which TRD patients should be switched if not ketamine
1	Yes	• Fluoxetine • Lamotrigine • Lithium • Valproic acid
2	Yes	• Amitriptyline, if not already proven ineffective in patient or cohort • Recommend transcranial magnetic stimulation (TMS) with proper anatomical positioning • Recommend cognitive behavioral therapy
3	No, based on innate hyperactivity of the subgenulate cingulate, prefrontal and orbitofrontal cortices.	• Amitriptyline, if not already proven ineffective in patient or cohort • Mirtazapine, if not already proven ineffective in patient or cohort • Recommend transcranial magnetic stimulation (TMS) with proper anatomical positioning
4	Yes	• Clonazepam • Escitalopram, if not already proven ineffective in patient or cohort • Lamotrigine • Lithium • Quetiapine • Sertraline, if not already proven ineffective in patient or cohort • Valproic acid • Zolpidem extended release (if not on Quetiapine pharmacotherapy) • Recommend transcranial magnetic stimulation (TMS) with proper anatomical positioning • Recommend behavioral dialectical therapy

FIG. 21

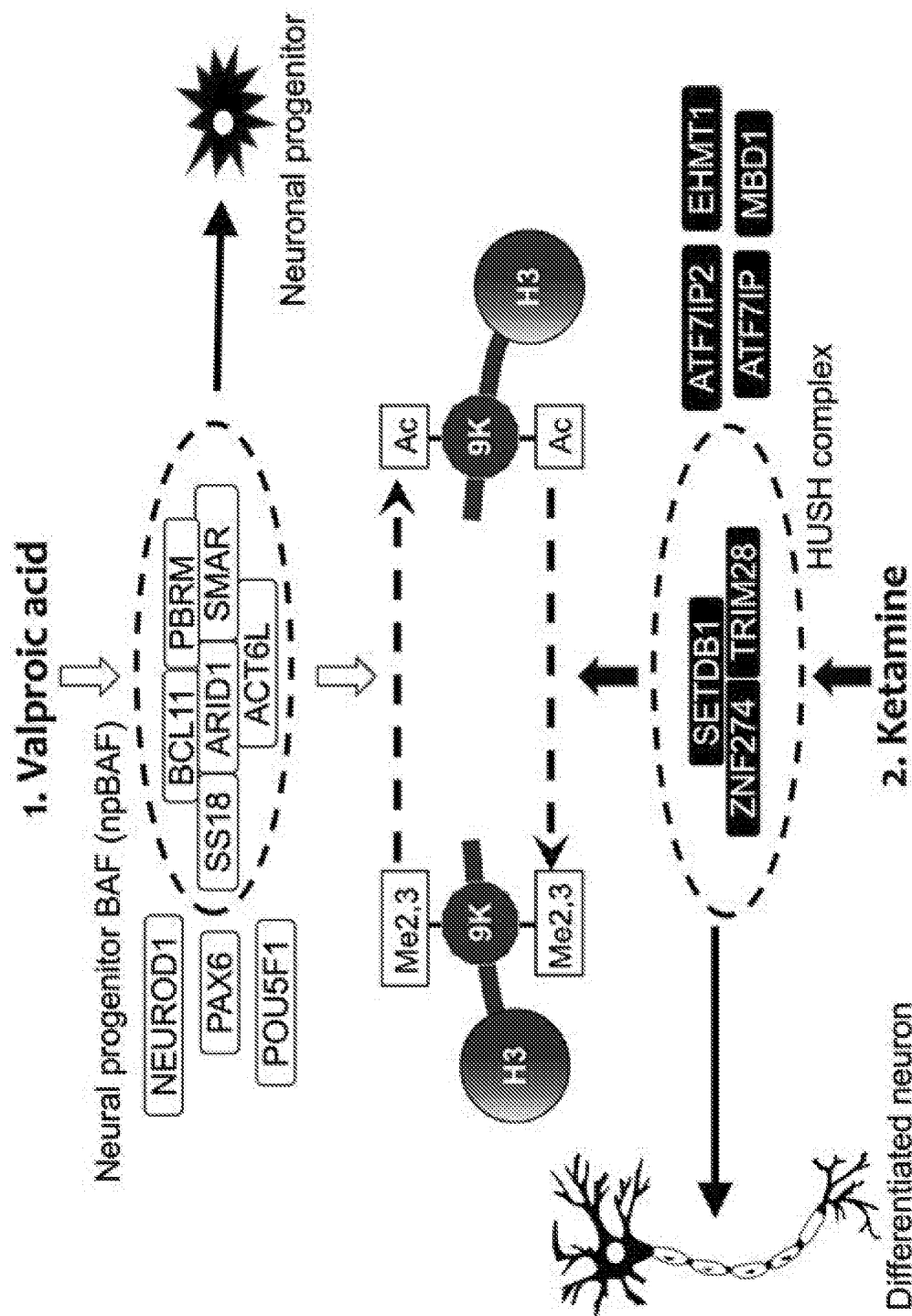


FIG. 22

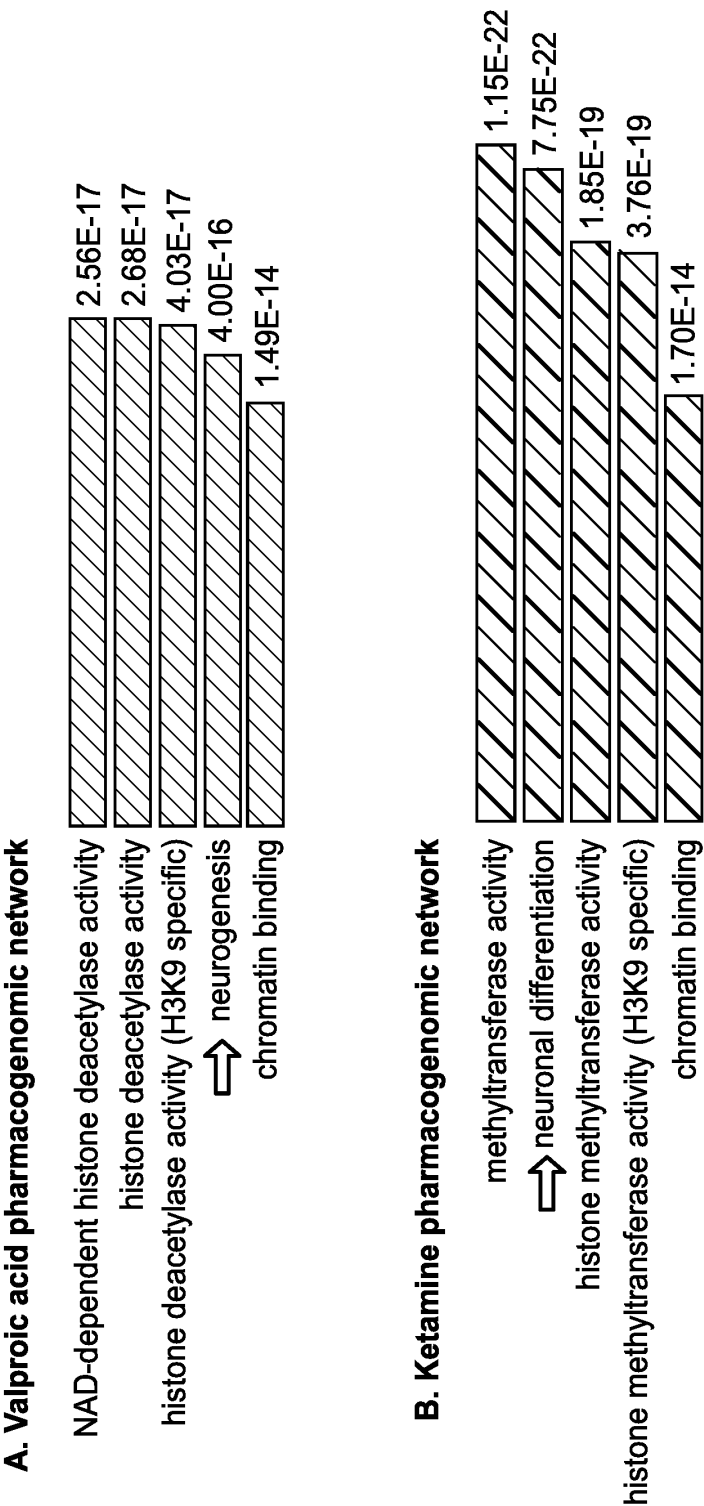


FIG. 23

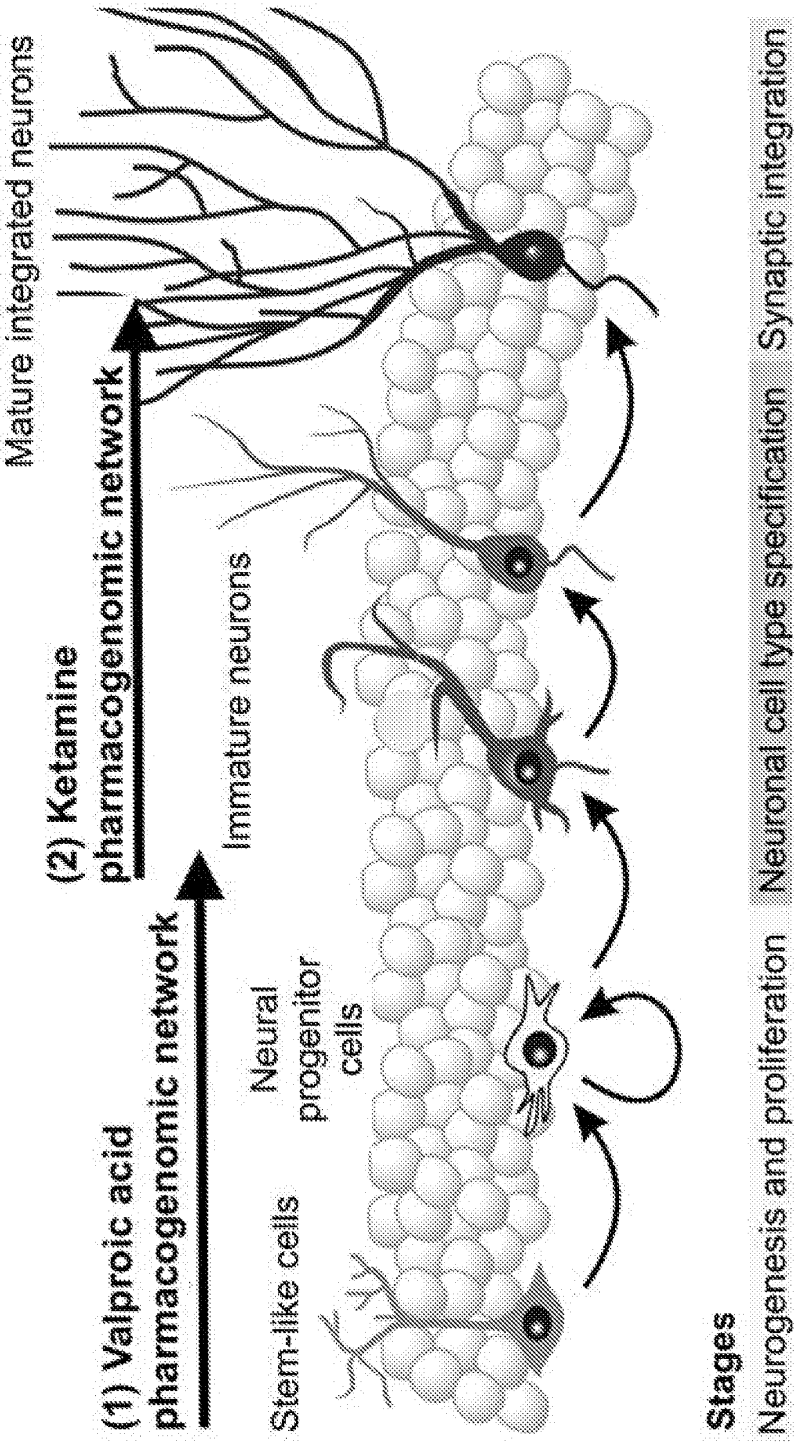


FIG. 24