Supplementary Data
Combinatorial Therapy Discovery using Mixed Integer Linear Programming

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Supplementary Text 1: Processing Drug Interaction and Action Data

We extracted 10,906 unique pairs of adverse drug-drug interaction and all the drug-action direction information from the DrugBank database. There are 37 unique types of drug actions and we manually divided these actions into three categories: positive, negative and unknown. For examples, if a drug is an activator or agonist to a target, we indicated the action of the drug on the target is positive; if a drug is an inhibitor or antagonist to a target, we indicated the action of the drug on the target is negative; if a drug is a binder or have unknown action to a target, we indicated the action of the drug on the target is unknown.

Given an input set of disease genes and required actions, we extracted the associated drugs from the drug-target network. Some drugs could target some input disease genes with right actions, but also could target some other input disease genes with opposite actions. We proposed two solutions to handle drugs with opposite actions on the input genes. The first solution is to remove all the drugs with opposite actions on the input disease genes before search for drug combination. The second solution is to keep all the drugs in the search, but consider input disease genes with opposite drug actions as special off-targets if these genes are covered by the selected drugs with opposite actions. For example, if the user wants to find drug combination to inhibit several oncogenes. The first solution will remove all the drugs that activate these oncogenes before search for drug combination. The second solution will consider these oncogenes as special off-targets if they are activated by the selected drugs. Our online tool allows the user to choose the solutions and to add a different weight to distinguish such special off-targets from the general off-targets. In addition, drugs with the same set of targets, actions, and interacting drugs were merged into a single meta-drug since they are equivalent to our algorithm.

Supplementary Text 2: Mathematical Programming Formulation of MOTSC

Mathematically, MOTSC can be formulated using the Mixed Integer Linear Programming (MILP) as follows:

$$\begin{aligned}
&\text{minimize} && \textstyle\sum_{i=1}^{q} y_i && && (1)\\
&\text{subject to} && (\mathbf{Bx})_j \geq 1 && \text{if } j = 1:p && (2)\\
& && (\mathbf{Bx})_j - y'_i = 0 && \text{if } j = (p+1):(p+q) && (3)\\
& && k y_i - y'_i \geq 0 && && (4)\\
& && y_i - y'_i \leq 0 && && (5)\\
& && y'_i \in \mathbb{Z}^+, y_i, x_j \in \{0,1\} && && (6)
\end{aligned}$$

The formulation has three variables, $\mathbf{x}$, $\mathbf{y}$, and $\mathbf{y}'$. The first two are binary, and the last one is nonnegative. The binary solution vector $\mathbf{x}$ indicates which drugs are selected. The non-negative cost variable y'_i counts the times that the i_{th} off-target gene is covered by the selected drugs. The binary cost vector $\mathbf{y}$ is derived

from $\mathbf{y}'$, $y_i = 1$ if $y'_i \geq 1$; otherwise, $y_i = 0$. The value of y_i indicates whether the i_{th} off-target gene is covered.

The relation between a given disease D and the associated drugs $\mathcal{M}$ can be represented using a binary matrix $\mathbf{B}$. The rows are indexed by the on-targets (p) and off-targets (q), and the columns represent the drugs. $\mathbf{B}_{jm} = 1$ if the j_{th} gene in D is covered by the m_{th} drug in $\mathcal{M}$; otherwise, $\mathbf{B}_{jm} = 0$. The non-zero elements in the product vector of $\mathbf{B}$ and $\mathbf{x}$ indicate the corresponding genes targeted by a selection of drugs.

The intuition of the MILP formulation is the following. The inequality constraint (2) guarantees that any viable solution must cover all the on-target genes. The equality constraint (3) counts the times that an off-target is covered by the selected drug combination. However, $\mathbf{y}'$ cannot be directly used in the objective cost function (1). Thus, the binary cost $\mathbf{y}$ is introduced and related to $\mathbf{y}'$ by the inequality constraints (4) and (5). The inequality constraint (4) requires $y_i = 1$ if $y'_i \geq 1$. For that, the value of k needs to be at least the maximum value of all y'_i. The inequality constraint (5) guarantees that $y_i = 0$ whenever $y'_i = 0$. In this paper, we solved MOTSC problem using the GNU MILP solver GLPK which is based on a branch and cut algorithm.

Supplementary Text 3: Dual Problem of BTSC

PROBLEM 1. (Balanced Target Set Cover Problem, BTSC). Given a disease $D = (T, S)$ and a collection of drugs $\mathcal{M}$, find a subset $\mathcal{C} \subseteq \mathcal{M}$ and $|\mathcal{C}| \leq k$ that minimize the $cost(D, \mathcal{C}) = \alpha|T \setminus (\cup\mathcal{C})| + (1-\alpha)|S \cap (\cup\mathcal{C})|$, where $\cup\mathcal{C} = \cup_{C\in\mathcal{C}} C$, k is the upper bound on the cardinality of the solution set $\mathcal{C}$, and α is the weight balance of the coverage between on-target set T and off-target set S.

The ILP formulation of BTSC can be formulated as:

$$\begin{aligned}
\text{minimize} \quad & \alpha \textstyle\sum_{i=1}^{p}(1-y_i) + (1-\alpha)\sum_{i=p+1}^{p+q} y_i && (7)\\
\text{subject to} \quad & (\mathbf{Bx})_i - y'_i = 0 && (8)\\
& by_i - y'_i \geq 0 && (9)\\
& y_i - y'_i \leq 0 && (10)\\
& \textstyle\sum_{j=1}^{m} x_j \leq k && (11)\\
& (\mathbf{Lx}) \preceq 1 && (12)\\
& y'_i \in \mathbb{Z}^+, y_i, x_j \in \{0,1\}. && (13)
\end{aligned}$$

Constraints (9) and (10) are upper and lower bounds for y'. Constraint (12) is used to avoid drug-drug interation effects. Without loss of generality, constraints (9), (10) and (12) can be dropped for the analysis of the dual problem. The LP relaxation can be formulated as follows:

$$\begin{aligned}
\text{minimize} \quad & \alpha \textstyle\sum_{i=1}^{p}(1-y'_i) + (1-\alpha)\sum_{i=p+1}^{p+q} y'_i && (14)\\
\text{subject to} \quad & (\mathbf{Bx})_i - y'_i = 0 && (15)\\
& \textstyle\sum_{j=1}^{m} x_j \leq k && (16)\\
& y'_i \geq 0, 1 \geq x_j \geq 0. && (17)
\end{aligned}$$

The Lagrangian is

$$L(\mathbf{x}, \lambda_1, \boldsymbol{\lambda_2}, \boldsymbol{\lambda_3}) = \mathbf{w}^\top \mathbf{Bx} + \lambda_1(\mathbf{1}^\top \mathbf{x} - k) - \boldsymbol{\lambda_2}^\top \mathbf{x} + \boldsymbol{\lambda_3}^\top(\mathbf{x} - \mathbf{1}), \tag{18}$$

where $\mathbf{w} = (\underbrace{-\alpha \ldots -\alpha}_{p}, \underbrace{1-\alpha \ldots 1-\alpha}_{q})^\top$ is a weight vector.

Therefore, the dual function is

$$g(\lambda_1, \boldsymbol{\lambda_2}, \boldsymbol{\lambda_3}) = \inf_x L(\mathbf{x}, \lambda_1, \boldsymbol{\lambda_2}, \boldsymbol{\lambda_3}) = -\lambda_1 k - \mathbf{1}^\top \boldsymbol{\lambda_3} + \inf_x (\mathbf{B}^\top \mathbf{w} + \lambda_1 \mathbf{1} - \boldsymbol{\lambda_2} + \boldsymbol{\lambda_3})^\top \mathbf{x}. \tag{19}$$

The infimum of a linear function is $-\infty$, except in the special case when it is identically zero, so the dual function is

$$g(\lambda_1, \lambda_{\mathbf{2}}) = \begin{cases} -\lambda_1 k - \mathbf{1}^\top \lambda_{\mathbf{3}} & \mathbf{B}^\top \mathbf{w} \succcurlyeq -(\lambda_1 + \lambda_{\mathbf{3}}) \\ 0 & \text{otherwise} \end{cases}$$

The Lagrange dual of the LP relaxation is to maximize g over all $\lambda_1 > 0$ and $\lambda_{\mathbf{3}} \succcurlyeq 0$. Again, we can reformulate this explicitly as:

$$\begin{aligned} \text{maximize} \quad & -\lambda_1 k - \mathbf{1}^\top \lambda_{\mathbf{3}} && (20) \\ \text{subject to} \quad & \mathbf{B}^\top \mathbf{w} \succcurlyeq -(\lambda_1 + \lambda_{\mathbf{3}}) && (21) \\ & \lambda_1 \geq 0, \lambda_{\mathbf{3}} \succcurlyeq 0 && (22) \end{aligned}$$

Supplementary Text 4: Dual Problem of MOTSC

Similary, the Lagrange dual problem of the LP relaxation formulation on MOTSC can be deduced as follows:

The Lagrangian is

$$\begin{aligned} L(\mathbf{x}, \mathbf{y}, \mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \mathbf{v}_4, \mathbf{v}_5) = \mathbf{1}^\top \mathbf{y} \quad & + \quad \mathbf{v}_1^\top (1 - \mathbf{B}_T \mathbf{x}) + \mathbf{v}_2^\top (\mathbf{B}_S \mathbf{x} - k\mathbf{y}) \\ & + \quad \mathbf{v}_3^\top (\mathbf{y} - \mathbf{B}_S \mathbf{x}) - \mathbf{v}_4^\top \mathbf{x} - \mathbf{v}_5^\top \mathbf{y} \end{aligned} \tag{23}$$

where matrix $\mathbf{B} = (\mathbf{B}_T; \mathbf{B}_S)$, $\mathbf{B}_T$ is the incidence matrix for all the drugs on disease gene set T, $\mathbf{B}_S$ is the incidence matrix for all the drugs on off-target set S, and $\mathbf{v_1}, \mathbf{v_2}, \mathbf{v_3}, \mathbf{v_4}, \mathbf{v_5}$ are the dual variables. The upper bound on $\mathbf{x}$ and $\mathbf{y}$ are dropped in the LP relaxation.

Therefore, the dual function is

$$\begin{aligned} g(\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \mathbf{v}_4, \mathbf{v}_5) &= \inf_{\mathbf{x},\mathbf{y}} L(\mathbf{x}, \mathbf{y}, \mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3, \mathbf{v}_4, \mathbf{v}_5) \\ &= \mathbf{1}^\top \mathbf{y} + \inf_{\mathbf{x},\mathbf{y}} ((\mathbf{1} - k\mathbf{v}_2 + \mathbf{v}_3 - \mathbf{v}_5)^\top \mathbf{y} + (-\mathbf{B}_T^\top \mathbf{v}_1 + \mathbf{B}_S^\top \mathbf{v}_2 - \mathbf{B}_S^\top \mathbf{v}_3 - \mathbf{v}_4)^\top \mathbf{x}) \end{aligned} \tag{24}$$

The infimum of a linear function is $-\infty$, except in the special case when $\mathbf{1} - k\mathbf{v}_2 + \mathbf{v}_3 \succeq 0$ and $-\mathbf{B}_T^\top \mathbf{v}_1 + \mathbf{B}_S^\top \mathbf{v}_2 - \mathbf{B}_S^\top \mathbf{v}_3 \succeq 0$. Hence, the Lagrange dual of the LP relaxation can be reformulated explicitly as:

$$\begin{aligned} \text{maximize} \quad & \mathbf{1}^T \mathbf{v}_1 && && (25) \\ \text{subject to} \quad & && && \\ & \mathbf{B}_T^T \mathbf{v}_1 - \mathbf{B}_S^T (\mathbf{v}_2 - \mathbf{v}_3) && \preceq 0 && (26) \\ & k\mathbf{v}_2 - \mathbf{v}_3 && \preceq 1 && (27) \\ & \mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3 && \succeq 0 && (28) \end{aligned}$$

We can interpret the dual as maximizing the number of genes in set T such that the number of on-target genes packed in each drug does not exceed the number of off-target genes packed in the same drug. These conditions are guaranteed by inequalities (26) and (27). This problem can also be considered as a generalized Knapsack problem, where each drug is considered as a bag and we want to put maximum number of on-targets in each bag as long as it does not exceed the number of off-targets we put into the same bag.

Supplementary Text 5: Search Parameters

The following are the parameters used by BTSC to predict drug combinations for the six disease gene sets.

Acute Myocardial Infarction (AMI)

1. input genes: AHSP COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6 F10 F2 F2R F7 FGA FGB FGG PLAT PLG PROC PROS1 SERPINC1 TFPI
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 4
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
AHSP		
COL4A1		
COL4A2		
COL4A3		
COL4A4		
COL4A5		
COL4A6		
F10	negative|unknown	positive|negative|unknown
F2	negative|unknown	positive|negative|unknown
F2R	unknown	unknown
F7	unknown	positive|unknown
FGA	negative|unknown	negative|unknown
FGB	negative	negative
FGG	negative	negative
PLAT	unknown	negative|unknown
PLG	positive|unknown	positive|negative|unknown
PROC	positive	positive|negative
PROS1	positive|unknown	positive|negative|unknown
SERPINC1	positive|unknown	positive|unknown
TFPI	negative|unknown	negative|unknown

7. drug selection step: all the drugs

EGFR-PI3K-AKT-mTOR (EPAM)

1. input genes: AKT1 AKT2 EGFR ERBB2 GSK3B MAPK1 MTOR PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 PIK3R2 PIK3R3 PLK1 PTEN TSC1 TSC2
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 5
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
AKT1	unknown	positive|unknown
AKT2	unknown	unknown
EGFR	negative|unknown	negative|unknown
ERBB2	negative	negative
GSK3B	negative|unknown	negative|unknown
MAPK1	negative|unknown	positive|negative|unknown
MTOR	negative	positive|negative
PIK3CA	unknown	unknown
PIK3CB		
PIK3CD	unknown	unknown
PIK3CG	unknown	unknown
PIK3R1	unknown	positive|unknown
PIK3R2		positive
PIK3R3		positive
PLK1	unknown	unknown
PTEN		
TSC1		
TSC2		

7. drug selection step: all the drugs

Hypertension (HTN)

1. input genes: ACE ADRB1 ADRB2 ADRB3 AGT AGTR1 BDKRB2 CLCNKB CYP11B2 ECE1 ECE2 EDN1 EDNRA EDNRB HSD11B2 KCNJ11 KLK1 KNG1 NPPC NR3C2 REN SCNN1A SCNN1B SCNN1G SLC12A1 SLC12A3
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 5
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
ACE	negative|unknown	negative|unknown
ADRB1	negative|unknown	positive|negative|unknown
ADRB2	negative|unknown	positive|negative|unknown
ADRB3	negative|unknown	positive|negative|unknown
AGT		
AGTR1	negative	negative
BDKRB2	negative	negative
CLCNKB		
CYP11B2		
ECE1	unknown	unknown
ECE2		
EDN1		
EDNRA	negative|unknown	negative|unknown
EDNRB	negative	negative
HSD11B2	unknown	unknown
KCNJ11	negative|unknown	positive|negative|unknown
KLK1	unknown	unknown
KNG1		
NPPC		
NR3C2	negative|unknown	positive|negative|unknown
REN	negative|unknown	negative|unknown
SCNN1A	negative	negative
SCNN1B	negative	negative
SCNN1G	negative	negative
SLC12A1	negative|unknown	positive|negative|unknown
SLC12A3	negative|unknown	negative|unknown

7. drug selection step: all the drugs

Type 2 Diabetes Mellitus (T2DM)

1. input genes: AKT2 CRK EIF4E EIF4EBP1 GRB2 HRAS INS INSR IRS1 IRS2 KRAS MAP2K1 MAP2K2 MAPK1 MAPK3 MTOR NRAS PDE3B PDPK1 PIK3CA PIK3CB PIK3R1 PIK3R2 PRKAA1 PRKAA2 PRKAB1 PRKAB2 PRKAG1 PRKAG2 PRKAG3 RAF1 RHEB RPS6 RPS6KB1 RPTOR SHC1 SHC2 SHC3 SOS1 TSC1 TSC2
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 4
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
AKT2	unknown	unknown
CRK		
EIF4E	unknown	unknown
EIF4EBP1		
GRB2	unknown	unknown
HRAS	unknown	unknown
INS	unknown	unknown
INSR	positive|unknown	positive|unknown
IRS1	unknown	unknown
IRS2		
KRAS	unknown	unknown
MAP2K1	unknown	unknown
MAP2K2		
MAPK1	negative|unknown	positive|negative|unknown
MAPK3	negative|unknown	positive|negative|unknown
MTOR	negative	positive|negative
NRAS		
PDE3B	unknown	unknown
PDPK1	unknown	negative|unknown
PIK3CA	unknown	unknown
PIK3CB		
PIK3R1	positive|unknown	positive|unknown
PIK3R2	positive	positive
PRKAA1	positive|unknown	positive|unknown
PRKAA2		
PRKAB1	positive	positive
PRKAB2	positive	positive
PRKAG1		
PRKAG2		
PRKAG3		
RAF1	negative	negative
RHEB	unknown	unknown
RPS6		
RPS6KB1		
RPTOR		
SHC1		
SHC2		
SHC3		
SOS1		
TSC1		
TSC2		

7. drug selection step: all the FDA-approved drugs

Parkinson's Disease (PD)

1. input genes: COMT DDC DRD1 DRD2 DRD3 DRD4 DRD5 MAOA MAOB TH
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 5
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
COMT	negative|unknown	negative|unknown
DDC	negative|unknown	negative|unknown
DRD1	positive|unknown	positive|negative|unknown
DRD2	positive|unknown	positive|negative|unknown
DRD3	positive	positive|negative
DRD4	positive	positive|negative
DRD5	positive|unknown	positive|negative|unknown
MAOA	negative|unknown	negative|unknown
MAOB	negative|unknown	negative|unknown
TH	unknown	unknown

7. drug selection step: all the FDA-approved drugs

Schizophrenia (SZ)

1. input genes: DRD1 DRD2 DRD3 DRD4 DRD5 GABBR1 GABRA1 GABRA6 GABRB2 GABRG2 GABRP GRIA1 GRIA4 GRID1 GRIK3 GRIK4 GRIN1 GRIN2B GRM3 GRM7 HTR1A HTR2A HTR3A HTR4 HTR5A SLC1A2 SLC6A3 SLC6A4
2. exclude adverse drug-drug interaction
3. remove drugs with opposite actions on input genes
4. balance weight α: 0.5
5. number of selected drugs: <= 5
6. drug action selection step (based on available drug action and biological meaning; | indicates and):

genes	selected drug action	available drug action
DRD1	negative|unknown	positive|negative|unknown
DRD2	negative|unknown	positive|negative|unknown
DRD3	negative	positive|negative
DRD4	negative	positive|negative
DRD5	negative|unknown	positive|negative|unknown
GABBR1		positive
GABRA1	negative|unknown	positive|negative|unknown
GABRA6		positive
GABRB2	negative	positive|negative
GABRG2	negative	positive|negative
GABRP		positive
GRIA1	negative|unknown	negative|unknown
GRIA4	unknown	unknown
GRID1	unknown	unknown
GRIK3	unknown	unknown
GRIK4	unknown	unknown
GRIN1	negative|unknown	negative|unknown
GRIN2B	negative|unknown	negative|unknown
GRM3	negative	negative
GRM7	unknown	unknown
HTR1A	negative|unknown	positive|negative|unknown
HTR2A	negative|unknown	positive|negative|unknown
HTR3A	negative|unknown	positive|negative|unknown
HTR4	negative	positive|negative
HTR5A		
SLC1A2	unknown	unknown
SLC6A3	negative|unknown	positive|negative|unknown
SLC6A4	negative|unknown	negative|unknown

7. drug selection step: all the FDA-approved drugs

We note that slightly varying the two parameters (balance weight α and number of selected drugs) does not change the results much. The same parameters (removal of two constraints: balance weight α and number of selected drugs) are used for MOTSC search. The following Supplementary Figures 5-9 are MOTSC search results.

Supplementary Text 6: Performance on Predicting Drug Combinations in DCDB

To our knowledge, there is no gold standard data for the known associations between disease gene sets and drug combinations, so it is difficult to test the performance of our approach in a large scale. However, we tried our best to generate a benchmark dataset using drug combinations derived from DCDB. To do this, we first extracted 185 FDA-approved drug combinations and their targeting diseases from DCDB. We then removed the drug combinations if we cannot find their component drug and/or target information in the DrugBank database. We further removed the drug combinations if we cannot find a decent number of putative genes associated with their targeting diseases through search in Genotator (Wall *et al.*, 2010), OMIM (Hamosh *et al.*, 2005) and literature. The remaining data contains 68 approved drug combinations.

Next, for the 68 approved drug combinations, we extracted their targets from the DrugBank database and divided the targets into on-targets and off-targets as follows. For each approved drug combination, if a target have evidence to be involved in the targeting disease through search in Genotator, OMIM and literature, the target is denoted as an on-target; otherwise, the target is denoted as an off-target. These data were shown in the following table. For each approved drug combination with usage ID (column 1), the table shows its component drugs (column 2), on-targets (column 3) with drug actions (column 4; P=Positive, N=Negative, U=Unknown), and off-targets (column 5). The value in column 6 indicates the cost value associated with the approved drug combination if it is the optimal solution selected by our online tool through search using its on-targets and corresponding drug actions.

Finally, for the 68 approved drug combinations, we performed search using their on-targets and corresponding drug actions to see the extent to which they can be recovered by our online tool. For each predicted drug combination, the component drugs, genes covered, genes not covered, off-targets induced and associated cost value are shown in columns 7-11. If an approved drug combination has the same component drugs as the corresponding predicted drug combination, we indicated that the approved drug combination can be fully recovered (denote "yes" in column 12); if an approved drug combination shares at least two component drugs with the corresponding predicted drug combination, we indicated that the approved drug combination can be partly recovered (denote "partly yes" in column 12); if an approved drug combination shares at most one component drug with the corresponding predicted drug combination, we indicated that the approved drug combination cannot be recovered (denote "no" in column 12). Totally, 59 of 68 (accuracy = 86.8%) approved drug combinations can be fully or partly recovered, while 55 of 68 (accuracy = 80.9%) approved drug combinations can be fully recovered.

We note that although some approved drug combinations cannot be recovered, the corresponding predicted drug combinations are still FDA-approved or well-known drug combinations. For example, for the drug combination with usage ID "DCU0019", the approved drug combination of DB00201 and DB00945 cannot be recovered, but the predicted drug combination of DB00201 and DB00316 is still an FDA-approved drug combination. We also note that the equivalent solutions exist during the optimal drug combination search. In other words, if two or more predicted drug combinations have the same cost value, these predicted drug combinations are equivalent. For each approved drug combination, if the equivalent solutions exist, only one solution close to the approved drug combination was shown in the following table. Currently, the equivalent solutions can be obtained via the iterative search function implemented in our online tool.

Usage ID	Drugs	On-Targets	Actions	Off-Targets	Cost	Predicted Drugs	Covered	Not Covered	Off-Targets	Cost	Coverage
DCU0007	DB00201	ADORA1	N	AKR1C1	2	DB00201	ADORA1		PDE4B	1	partly yes
	DB00316	ADORA2A	N	PDE4B		DB00316	ADORA2A				
	DB00945	PTGS1	N			DB01628	PTGS1				
		PTGS2	N				PTGS2				
		RYR1	U				RYR1				
DCU0008	DB00316	OPRD1	P	AKR1C1	1	DB00316	OPRD1			0	partly yes
	DB00318	OPRK1	P			DB00318	OPRK1				
	DB00945	OPRM1	P			DB00580	OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0012	DB00201	ADORA1	N	PDE4B	1	DB00201	ADORA1		PDE4B	1	yes
	DB00316	ADORA2A	N			DB00316	ADORA2A				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
		RYR1	U				RYR1				
DCU0013	DB00316	OPRD1	P		0	DB00316	OPRD1			0	yes
	DB00318	OPRK1	P			DB00318	OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0015	DB00316	OPRD1	P		0	DB00316	OPRD1			0	yes

	DB00497	OPRK1	P			DB00497	OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0016	DB00316	OPRK1	P		0	DB00316	OPRK1		0	yes	
	DB00652	OPRM1	N			DB00652	OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
		SIGMAR1	P				SIGMAR1				
DCU0017	DB00316	OPRD1	P		0	DB00316	OPRD1		0	yes	
	DB00647	OPRK1	N			DB00647	OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0018	DB00193	CHRM3	N	CHRFAM7A	1	DB00193	CHRM3	CHRFAM7A	1	yes	
	DB00316	GRIN3A	N			DB00316	GRIN3A				
		HTR2C	N				HTR2C				
		OPRD1	P				OPRD1				
		OPRK1	P				OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
		SLC6A2	N				SLC6A2				
		SLC6A4	N				SLC6A4				
DCU0019	DB00201	ADORA1	N	AKR1C1	2	DB00201	ADORA1	PDE4B	1	no	
	DB00945	ADORA2A	N	PDE4B		DB00316	ADORA2A				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
		RYR1	U				RYR1				
DCU0026	DB00497	OPRD1	P	AKR1C1	1	DB00497	OPRD1		0	no	
	DB00945	OPRK1	P			DB00465	OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0027	DB00669	HTR1A	P		0	DB00669	HTR1A		0	yes	
	DB00788	HTR1B	P			DB00788	HTR1B				
		HTR1D	P				HTR1D				
		HTR1F	P				HTR1F				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0030	DB00201	ADORA1	N	ADRA1B	3	DB00201	ADORA1	ADRA1B	3	yes	
	DB00696	ADORA2A	N	ADRA1D		DB00696	ADORA2A	ADRA1D			
		ADRA1A	P	PDE4B			ADRA1A	PDE4B			
		ADRA2A	P				ADRA2A				
		ADRA2B	P				ADRA2B				
		DRD2	P				DRD2				
		HTR1B	P				HTR1B				
		HTR1D	P				HTR1D				
		HTR2A	P				HTR2A				
		RYR1	U				RYR1				
		SLC6A2	N				SLC6A2				
DCU0031	DB00956	OPRD1	P		0	DB00956	OPRD1		0	yes	
	DB01050	OPRM1	P			DB01050	OPRM1				
		PTGS1	U				PTGS1				
		PTGS2	N				PTGS2				
DCU0032	DB00652	ESR1	U	CREB1	1	DB00652	ESR1	CREB1	1	yes	
	DB01183	OPRD1	N			DB01183	OPRD1				
		OPRK1	P|N				OPRK1				
		OPRM1	N				OPRM1				
		SIGMAR1	P				SIGMAR1				
DCU0033	DB00497	OPRD1	P		0	DB00497	OPRD1		0	yes	
	DB01050	OPRK1	P			DB01050	OPRK1				
		OPRM1	P				OPRM1				
		PTGS1	U				PTGS1				
		PTGS2	N				PTGS2				
DCU0036	DB00316	ADRA1A	P		0	DB00316	ADRA1A		0	yes	
	DB00405	ADRA2A	P			DB00405	ADRA2A				
	DB00852	ADRB1	P			DB00852	ADRB1				
		ADRB2	P				ADRB2				
		HRH1	N				HRH1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
		SLC6A2	N				SLC6A2				
		SLC6A3	N				SLC6A3				
		SLC6A4	N				SLC6A4				
DCU0039	DB00321	ADRA1A	N	HRH1	5	DB00321	ADRA1A	HRH1	5	yes	
	DB00475	ADRA1D	N	KCNA1		DB00475	ADRA1D	KCNA1			
		ADRA2A	N	KCND2			ADRA2A	KCND2			
		CHRM1	N	KCND3			CHRM1	KCND3			
		CHRM2	N	KCNQ2			CHRM2	KCNQ2			
		CHRM3	N				CHRM3				
		CHRM4	N				CHRM4				
		CHRM5	N				CHRM5				
		GABRA1	P				GABRA1				
		GABRA2	P				GABRA2				
		GABRA3	P				GABRA3				
		GABRA4	P				GABRA4				
		GABRA5	P				GABRA5				
		GABRA6	P				GABRA6				
		GABRB1	P				GABRB1				
		GABRB2	P				GABRB2				
		GABRB3	P				GABRB3				
		GABRD	P				GABRD				
		GABRE	P				GABRE				
		GABRG1	P				GABRG1				
		GABRG2	P				GABRG2				
		GABRG3	P				GABRG3				
		GABRP	P				GABRP				
		GABRQ	P				GABRQ				
		GABRR1	P				GABRR1				
		GABRR2	P				GABRR2				
		GABRR3	P				GABRR3				
		HTR1A	U				HTR1A				
		HTR2A	N				HTR2A				
		NTRK1	P				NTRK1				
		NTRK2	P				NTRK2				

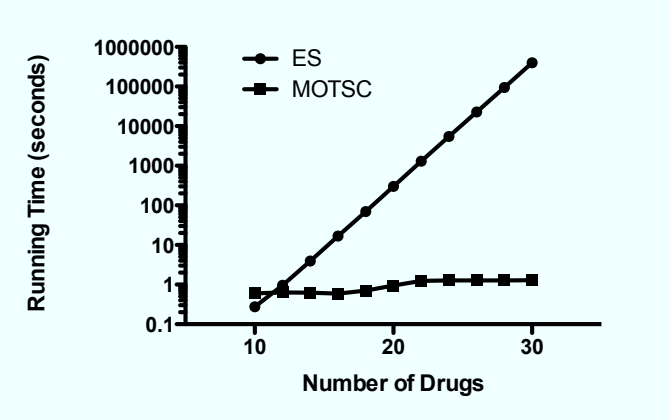
		OPRD1	P				OPRD1				
		OPRK1	P				OPRK1				
		SLC6A2	N				SLC6A2				
		SLC6A4	N				SLC6A4				
DCU0040	DB00321	ADRA1A	N	CALM1	6	DB00321	ADRA1A		HRH1	5	no
	DB00850	ADRA1D	N	HRH1		DB00875	ADRA1D		KCNA1		
		ADRA2A	N	KCNA1			ADRA2A		KCND2		
		CHRM1	N	KCND2			CHRM1		KCND3		
		CHRM2	N	KCND3			CHRM2		KCNQ2		
		CHRM3	N	KCNQ2			CHRM3				
		CHRM4	N				CHRM4				
		CHRM5	N				CHRM5				
		DRD1	N				DRD1				
		DRD2	N				DRD2				
		HTR1A	U				HTR1A				
		HTR2A	N				HTR2A				
		NTRK1	P				NTRK1				
		NTRK2	P				NTRK2				
		OPRD1	P				OPRD1				
		OPRK1	P				OPRK1				
		SLC6A2	N				SLC6A2				
		SLC6A4	N				SLC6A4				
DCU0057	DB00373	ADRA2A	P		0	DB00373	ADRA2A			0	yes
	DB00484	ADRA2B	P			DB00484	ADRA2B				
		ADRA2C	P				ADRA2C				
		ADRB1	N				ADRB1				
		ADRB2	N				ADRB2				
DCU0059	DB00983	ADRB2	P		0	DB00983	ADRB2			0	yes
	DB01222	NR3C1	N			DB01222	NR3C1				
DCU0061	DB00190	COMT	N		0	DB00190	COMT			0	yes
	DB00494	DDC	N			DB00494	DDC				
	DB01235	DRD1	P			DB01235	DRD1				
		DRD2	P				DRD2				
		DRD3	P				DRD3				
		DRD4	P				DRD4				
		DRD5	P				DRD5				
DCU0062	DB00190	DDC	N		0	DB00190	DDC			0	yes
	DB01235	DRD1	P			DB01235	DRD1				
		DRD2	P				DRD2				
		DRD3	P				DRD3				
		DRD4	P				DRD4				
		DRD5	P				DRD5				
DCU0080	DB01050	HRH1	N		0	DB01050	HRH1			0	yes
	DB01075	PTGS1	U			DB01075	PTGS1				
		PTGS2	N				PTGS2				
DCU0096	DB00334	ADRA1A	N	ADRA2B	2	DB00334	ADRA1A		ADRA2B	2	yes
	DB00472	ADRA1B	N	HRH1		DB00472	ADRA1B		HRH1		
		ADRA2A	N				ADRA2A				
		ADRA2C	N				ADRA2C				
		CHRM1	N				CHRM1				
		CHRM2	N				CHRM2				
		CHRM3	N				CHRM3				
		CHRM4	N				CHRM4				
		CHRM5	N				CHRM5				
		DRD1	N				DRD1				
		DRD2	N				DRD2				
		DRD3	N				DRD3				
		DRD4	N				DRD4				
		DRD5	N				DRD5				
		HTR1A	N				HTR1A				
		HTR1B	N				HTR1B				
		HTR1D	N				HTR1D				
		HTR1E	N				HTR1E				
		HTR2A	N				HTR2A				
		HTR2C	N				HTR2C				
		HTR3A	N				HTR3A				
		HTR6	N				HTR6				
		HTR7	N				HTR7				
		SLC6A4	N				SLC6A4				
DCU0102	DB00381	AHR	P	CACNA1B	3	DB00401	AHR	CA1		1	no
	DB01076	CA1	N	CACNA2D3		DB01076	CACNA1C				
		CACNA1C	N	CACNB1			CACNA1D				
		CACNA1D	N				CACNA1S				
		CACNA1S	N				CACNA2D1				
		CACNA2D1	N				CACNB2				
		CACNB2	N				DPP4				
		DPP4	N				HMGCR				
		HMGCR	N								
DCU0103	DB00492	ACE	N		0	DB00492	ACE			0	yes
	DB00999	CA1	N			DB00999	CA1				
		CA12	N				CA12				
		CA2	N				CA2				
		CA4	N				CA4				
		CA9	N				CA9				
		KCNMA1	U				KCNMA1				
		SLC12A3	N				SLC12A3				
DCU0104	DB00542	ACE	N		0	DB00542	ACE			0	yes
	DB00999	CA1	N			DB00999	CA1				
		CA12	N				CA12				
		CA2	N				CA2				
		CA4	N				CA4				
		CA9	N				CA9				
		KCNMA1	U				KCNMA1				
		SLC12A3	N				SLC12A3				
DCU0105	DB00999	CA1	N		0	DB00999	CA1			0	yes
	DB01258	CA12	N			DB01258	CA12				
		CA2	N				CA2				
		CA4	N				CA4				
		CA9	N				CA9				
		KCNMA1	U				KCNMA1				
		REN	N				REN				
		SLC12A3	N				SLC12A3				
DCU0106	DB00594	ACCN1	N	ABP1	1	DB00594	ACCN1		ABP1	1	yes
	DB00999	ACCN2	N			DB00999	ACCN2				
		CA1	N				CA1				
		CA12	N				CA12				

		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		PLAU	N				PLAU			
		SCNN1A	N				SCNN1A			
		SCNN1B	N				SCNN1B			
		SCNN1D	N				SCNN1D			
		SCNN1G	N				SCNN1G			
		SLC12A3	N				SLC12A3			
		SLC9A1	N				SLC9A1			
DCU0107	DB00436	ADRB1	N		0	DB00436	ADRB1		0	yes
	DB01203	ADRB2	N			DB01203	ADRB2			
		CA1	N				CA1			
		CA2	N				CA2			
		CA4	N				CA4			
		KCNMA1	P				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0108	DB00381	ACE	N	CACNA1B	3	DB00401	ACE	CA1	1	no
	DB00542	CA1	N	CACNA2D3		DB00519	CACNA1C			
		CACNA1C	N	CACNB1			CACNA1D			
		CACNA1D	N				CACNA1S			
		CACNA1S	N				CACNA2D1			
		CACNA2D1	N				CACNB2			
		CACNB2	N							
DCU0109	DB00275	AGTR1	N	CACNA1B	3	DB00275	AGTR1	CA1	1	no
	DB00381	CA1	N	CACNA2D3		DB00401	CACNA1C			
		CACNA1C	N	CACNB1			CACNA1D			
		CACNA1D	N				CACNA1S			
		CACNA1S	N				CACNA2D1			
		CACNA2D1	N				CACNB2			
		CACNB2	N							
DCU0110	DB00177	AGTR1	N	CACNA1B	3	DB00177	AGTR1	CA1	1	no
	DB00381	CA1	N	CACNA2D3		DB00401	CACNA1C			
		CACNA1C	N	CACNB1			CACNA1D			
		CACNA1D	N				CACNA1S			
		CACNA1S	N				CACNA2D1			
		CACNA2D1	N				CACNB2			
		CACNB2	N							
DCU0112	DB00999	AGTR1	N		0	DB00999	AGTR1		0	yes
	DB01029	CA1	N			DB01029	CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		JUN	U				JUN			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0113	DB00722	ACE	N		0	DB00722	ACE		0	yes
	DB00999	ACE2	N			DB00999	ACE2			
		CA1	N				CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0114	DB00678	AGTR1	N		0	DB00678	AGTR1		0	yes
	DB00999	CA1	N			DB00999	CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0115	DB00968	ADRA2A	U		0	DB00968	ADRA2A		0	yes
	DB00999	CA1	N			DB00999	CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0116	DB00264	ADRB1	N		0	DB00264	ADRB1		0	yes
	DB00999	ADRB2	N			DB00999	ADRB2			
		CA1	N				CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0117	DB00275	AGTR1	N		0	DB00275	AGTR1		0	yes
	DB00999	CA1	N			DB00999	CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0118	DB00571	ADRB1	N		0	DB00571	ADRB1		0	yes
	DB00999	ADRB2	N			DB00999	ADRB2			
		ADRB3	N				ADRB3			
		CA1	N				CA1			
		CA12	N				CA12			
		CA2	N				CA2			
		CA4	N				CA4			
		CA9	N				CA9			
		HTR1A	U				HTR1A			
		HTR1B	U				HTR1B			
		KCNMA1	U				KCNMA1			
		SLC12A3	N				SLC12A3			
DCU0119	DB00881	ACE	N		0	DB00881	ACE		0	yes
	DB00999	CA1	N			DB00999	CA1			
		CA12	N				CA12			
		CA2	N				CA2			

		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0120	DB00421	AR	N		0	DB00421	AR			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		NR3C2	N				NR3C2					
		SLC12A3	N				SLC12A3					
DCU0121	DB00966	AGTR1	N		0	DB00966	AGTR1			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		PPARG	P				PPARG					
		SLC12A3	N				SLC12A3					
DCU0122	DB00384	CA1	N		0	DB00384	CA1			0	yes	
	DB00999	CA12	N			DB00999	CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SCNN1A	N				SCNN1A					
		SCNN1B	N				SCNN1B					
		SCNN1D	N				SCNN1D					
		SCNN1G	N				SCNN1G					
		SLC12A3	N				SLC12A3					
DCU0123	DB00177	AGTR1	N		0	DB00177	AGTR1			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0124	DB00519	ACE	N	CACNA1B	7	DB00519	ACE	CACNA1A	CACNA2D1	6	no	
	DB00661	CACNA1A	N	CACNA1F		DB00401	CACNA1C	CACNB3				
		CACNA1C	N	CACNA1G			CACNA1D	KCNH2				
		CACNA1D	N	CACNA1I			CACNA1S	KCNJ11				
		CACNA1S	N	CACNB1			CACNB2	SLC6A4				
		CACNB2	N	CACNB4								
		CACNB3	N	SCN5A								
		KCNH2	N									
		KCNJ11	N									
		SLC6A4	U									
DCU0125	DB00584	ACE	N	CACNA2D2	6	DB00401	CACNA1C	ACE		2	no	
	DB01023	CACNA1C	N	CALM1		DB00700	CACNA1D	CACNA1H				
		CACNA1D	N	PDE1A			CACNA1S					
		CACNA1H	N	PDE1B			CACNA2D1					
		CACNA1S	N	TNNC1			CACNB2					
		CACNA2D1	N	TNNC2			NR3C2					
		CACNB2	N									
		NR3C2	N									
DCU0126	DB00584	ACE	N		0	DB00584	ACE			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0127	DB00876	AGTR1	N		0	DB00876	AGTR1			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0128	DB00796	AGTR1	N		0	DB00796	AGTR1			0	yes	
	DB00999	CA1	N			DB00999	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0129	DB00999	ACE	N		0	DB00999	ACE			0	yes	
	DB01197	CA1	N			DB01197	CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		MMP2	N				MMP2					
		SLC12A3	N				SLC12A3					
DCU0130	DB00310	ADRB1	N		0	DB00310	ADRB1			0	yes	
	DB00335	SLC12A1	N			DB00335	SLC12A1					
DCU0131	DB00612	ADRB1	N		0	DB00612	ADRB1			0	yes	
	DB00999	ADRB2	N			DB00999	ADRB2					
		CA1	N				CA1					
		CA12	N				CA12					
		CA2	N				CA2					
		CA4	N				CA4					
		CA9	N				CA9					
		KCNMA1	U				KCNMA1					
		SLC12A3	N				SLC12A3					
DCU0134	DB00373	ADRB1	N		0	DB00373	ADRB1			0	yes	
	DB00869	ADRB2	N			DB00869	ADRB2					
		CA1	N				CA1					

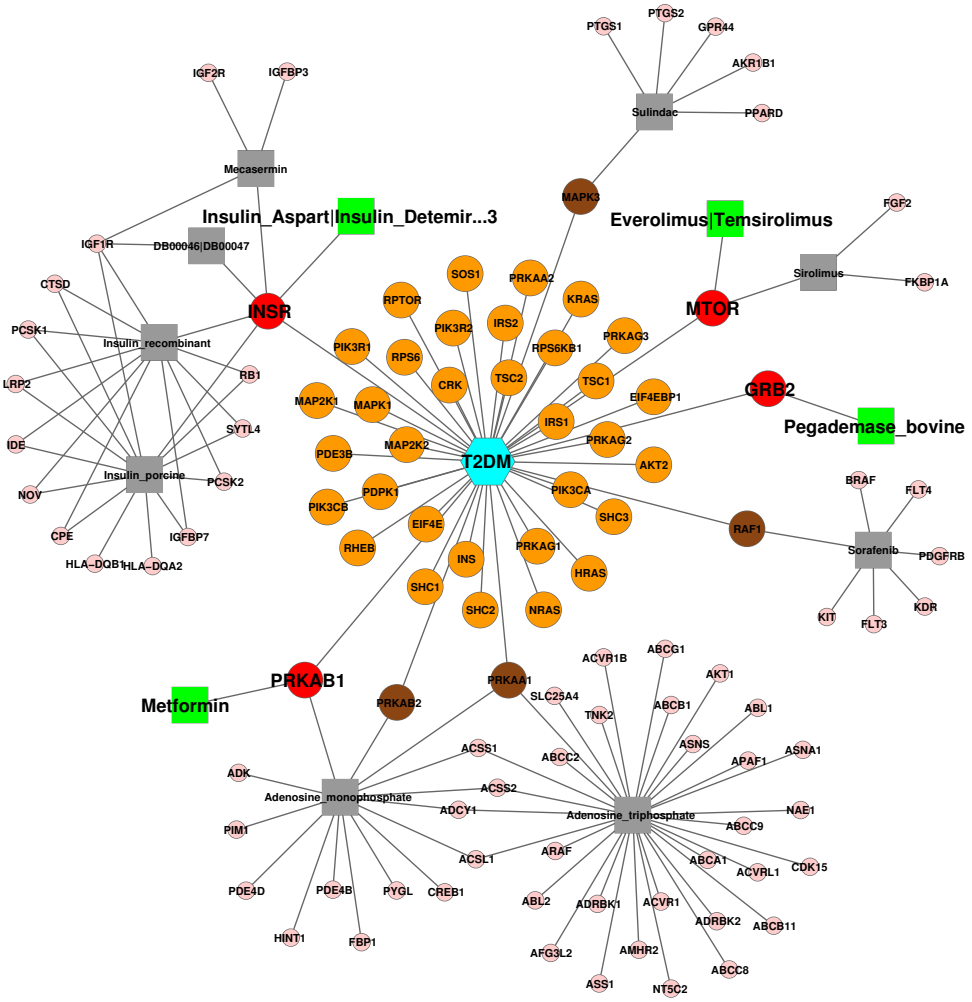
		CA2	N				CA2				
		CA4	N				CA4				
DCU0151	DB00331	PPARG	P		0	DB00331	PPARG		0	yes	
	DB01132	PRKAB1	P			DB01132	PRKAB1				
DCU0152	DB00331	ABCC8	N		0	DB00331	ABCC8		0	yes	
	DB00912	PPARG	P			DB00912	PPARG				
		PRKAB1	P				PRKAB1				
DCU0153	DB00331	ACSL4	N		0	DB00331	ACSL4		0	yes	
	DB00412	PPARG	P			DB00412	PPARG				
		PRKAB1	P				PRKAB1				
DCU0154	DB00331	DPP4	N		0	DB00331	DPP4		0	yes	
	DB01261	PRKAB1	P			DB01261	PRKAB1				
DCU0155	DB00222	ABCC8	P		0	DB00222	ABCC8		0	yes	
	DB01132	KCNJ1	N			DB01132	KCNJ1				
		KCNJ11	N				KCNJ11				
		PPARG	P				PPARG				
DCU0156	DB00222	ABCC8	P		0	DB00222	ABCC8		0	yes	
	DB00412	ACSL4	N			DB00412	ACSL4				
		KCNJ1	N				KCNJ1				
		KCNJ11	N				KCNJ11				
		PPARG	P				PPARG				
DCU0157	DB00331	ABCC8	N		0	DB00331	ABCC8		0	yes	
	DB01067	PPARG	P			DB01067	PPARG				
		PRKAB1	P				PRKAB1				
DCU0158	DB00331	ABCA1	N		0	DB00331	ABCA1		0	yes	
	DB01016	ABCB11	N			DB01016	ABCB11				
		ABCC8	U				ABCC8				
		ABCC9	U				ABCC9				
		CFTR	N				CFTR				
		KCNJ1	N				KCNJ1				
		KCNJ11	U				KCNJ11				
		KCNJ5	N				KCNJ5				
		PRKAB1	P				PRKAB1				
DCU0490	DB00316	OPRD1	P	AKR1C1	1	DB00316	OPRD1		0	partly yes	
	DB00318	OPRK1	P			DB00318	OPRK1				
	DB00945	OPRM1	P			DB00580	OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0491	DB00316	OPRD1	P	AKR1C1	1	DB00316	OPRD1		0	partly yes	
	DB00318	OPRK1	P			DB00318	OPRK1				
	DB00945	OPRM1	P			DB00580	OPRM1				
		PTGS1	N				PTGS1				
		PTGS2	N				PTGS2				
DCU0492	DB00190	DDC	N		0	DB00190	DDC		0	yes	
	DB01235	DRD1	P			DB01235	DRD1				
		DRD2	P				DRD2				
		DRD3	P				DRD3				
		DRD4	P				DRD4				
		DRD5	P				DRD5				
DCU0493	DB00334	ADRA1A	N	ADRA2B	2	DB00334	ADRA1A	ADRA2B	2	yes	
	DB00472	ADRA1B	N	HRH1		DB00472	ADRA1B	HRH1			
		ADRA2A	N				ADRA2A				
		ADRA2C	N				ADRA2C				
		CHRM1	N				CHRM1				
		CHRM2	N				CHRM2				
		CHRM3	N				CHRM3				
		CHRM4	N				CHRM4				
		CHRM5	N				CHRM5				
		DRD1	N				DRD1				
		DRD2	N				DRD2				
		DRD3	N				DRD3				
		DRD4	N				DRD4				
		DRD5	N				DRD5				
		HTR1A	N				HTR1A				
		HTR1B	N				HTR1B				
		HTR1D	N				HTR1D				
		HTR1E	N				HTR1E				
		HTR2A	N				HTR2A				
		HTR2C	N				HTR2C				
		HTR3A	N				HTR3A				
		HTR6	N				HTR6				
		HTR7	N				HTR7				
		SLC6A4	N				SLC6A4				
DCU0494	DB00542	ACE	N		0	DB00542	ACE		0	yes	
	DB00999	CA1	N			DB00999	CA1				
		CA12	N				CA12				
		CA2	N				CA2				
		CA4	N				CA4				
		CA9	N				CA9				
		KCNMA1	U				KCNMA1				
		SLC12A3	N				SLC12A3				
DCU0495	DB00999	ACE	N		0	DB00999	ACE		0	yes	
	DB01197	CA1	N			DB01197	CA1				
		CA12	N				CA12				
		CA2	N				CA2				
		CA4	N				CA4				
		CA9	N				CA9				
		KCNMA1	U				KCNMA1				
		MMP2	N				MMP2				
		SLC12A3	N				SLC12A3				

Simulation Result on MOTSC



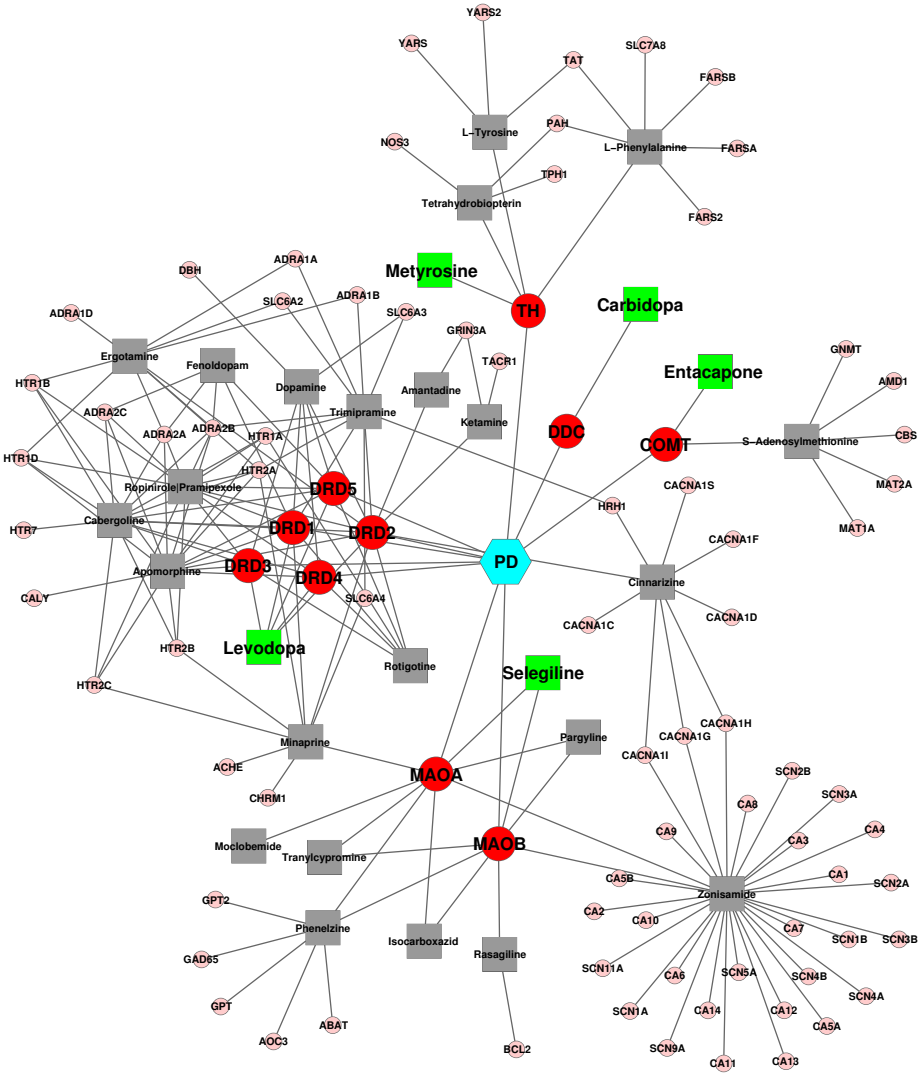
Supplementary Figure 1: Running time difference between MOTSC and ES. The number of associated drugs is simulated from 10 to 30 with a step size equal to 2. Each data point represents the average running time of 10 replicates. For the simulated data with 30 available drugs, ES takes about 4.6 days, while MOTSC only needs 2 seconds.

BTSC Result on T2DM



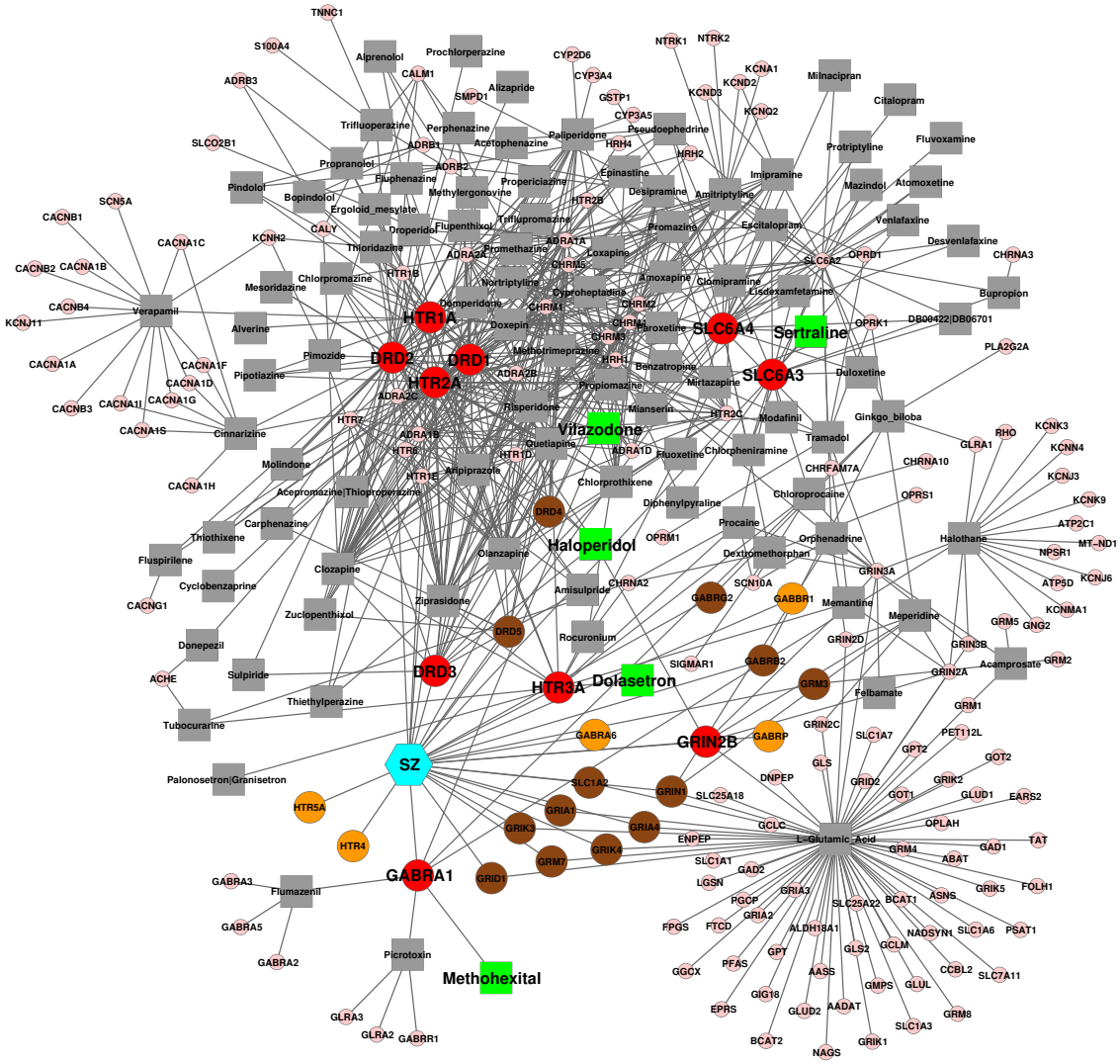
Supplementary Figure 2: The disease-gene-drug network of T2DM. The disease gene set name T2DM is represented using a cyan hexagon and there are 41 genes (red, orange or chocolate circles) in T2DM gene set. Four (green squares) of 13 associated drugs (green or gray squares) selected by BTSC can cover 4 T2DM genes (red circles) with no known off-target. Thirty three genes (orange circles) have no associated drugs and 4 genes (chocolate circles) associated with drugs are not covered by the selected drug combination.

BTSC Result on PD



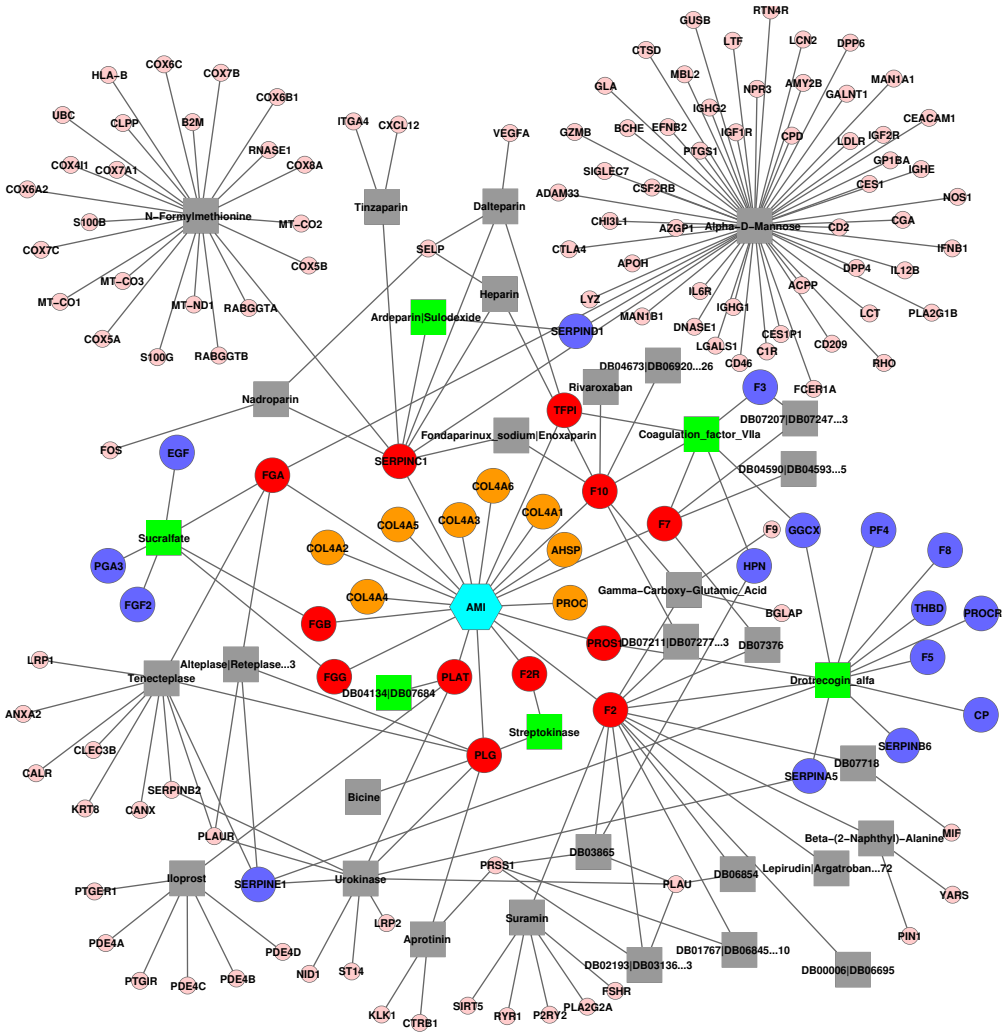
Supplementary Figure 3: The disease-gene-drug network of PD. The disease gene set name PD is represented using a cyan hexagon and there are 10 genes (red, orange or chocolate circles) in PD gene set. Five (green squares) of 28 associated drugs (green or gray squares) selected by BTSC can fully cover 10 PD genes (red circles) with no known off-target.

BTSC Result on SZ



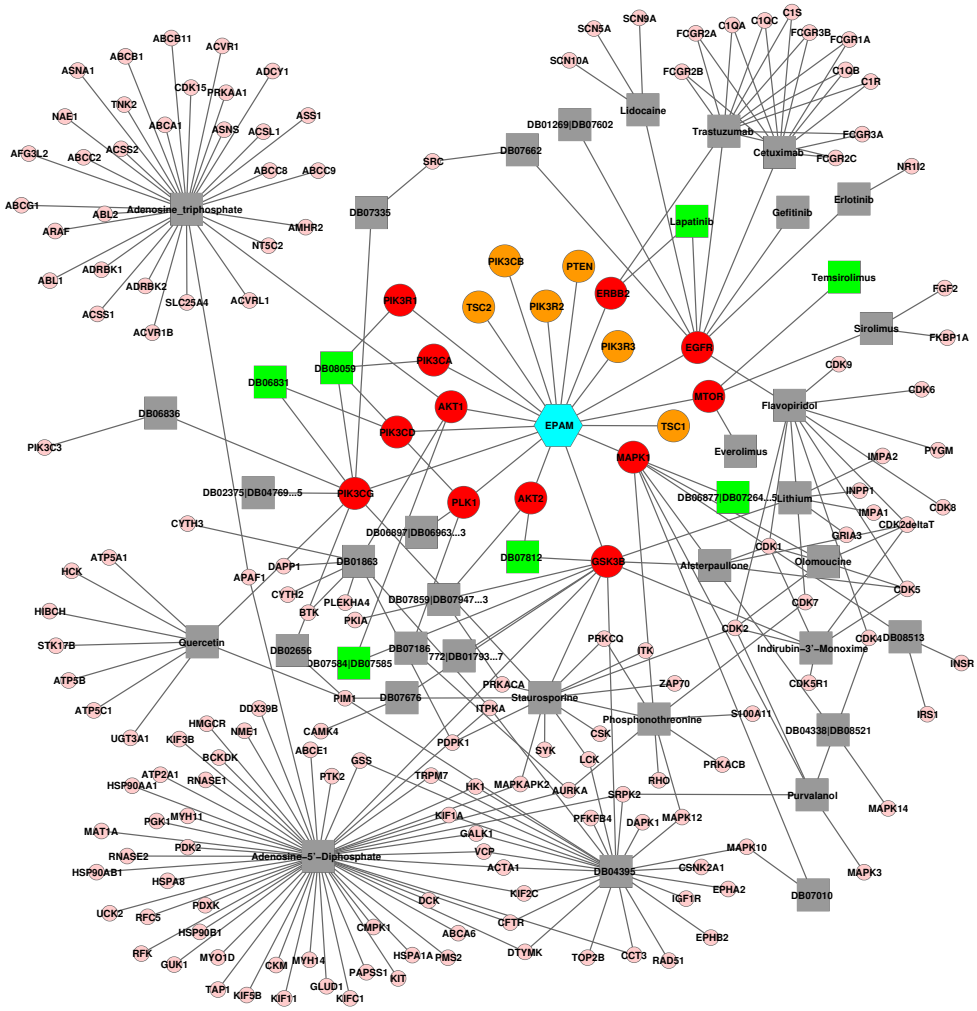
Supplementary Figure 4: The disease-gene-drug network of SZ. The disease gene set name SZ is represented using a cyan hexagon and there are 28 genes (red, orange or chocolate circles) in SZ gene set. Five (green squares) of 102 associated drugs (green or gray squares) selected by BTSC can cover 10 SZ genes (red circles) with no known off-target. Five genes (orange circles) have no associated drugs and 13 genes (chocolate circles) associated with drugs are not covered by the selected drug combination.

MOTSC Result on AMI



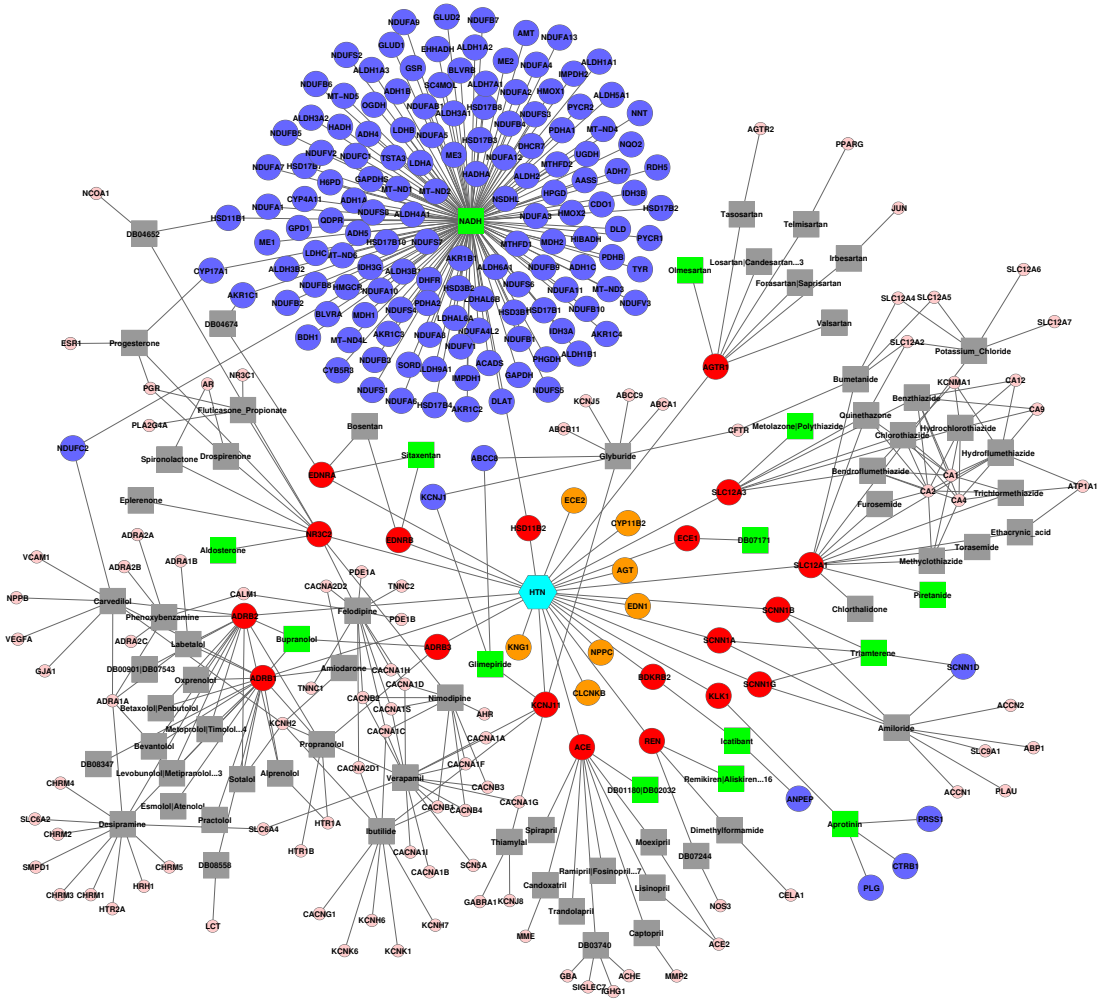
Supplementary Figure 5: The disease-gene-drug network of AMI. Similar result was obtained when we applied MOTSC algorithm to the same set of AMI genes. Streptokinase and DB04134|DB07684 predicted by BTSC are still in MOTSC result. Since MOTSC requires full coverage on the disease gene set, several new drugs were selected, including Ardeparin|Sulodexide, Drotrecogin alfa, Sucralfate, and Coagulation factor VIIa. Among these new drugs, Ardeparin is a low molecular weight heparin anticoagulant, and Sulodexide is a mixture of glycosaminoglycans composed of dermatan sulfate and fast moving heparin. The drug combination predicted by MOTSC still falls in the categories of blood clot dissolvant and anticoagulant, similar to BTSC result.

MOTSC Result on EPAM



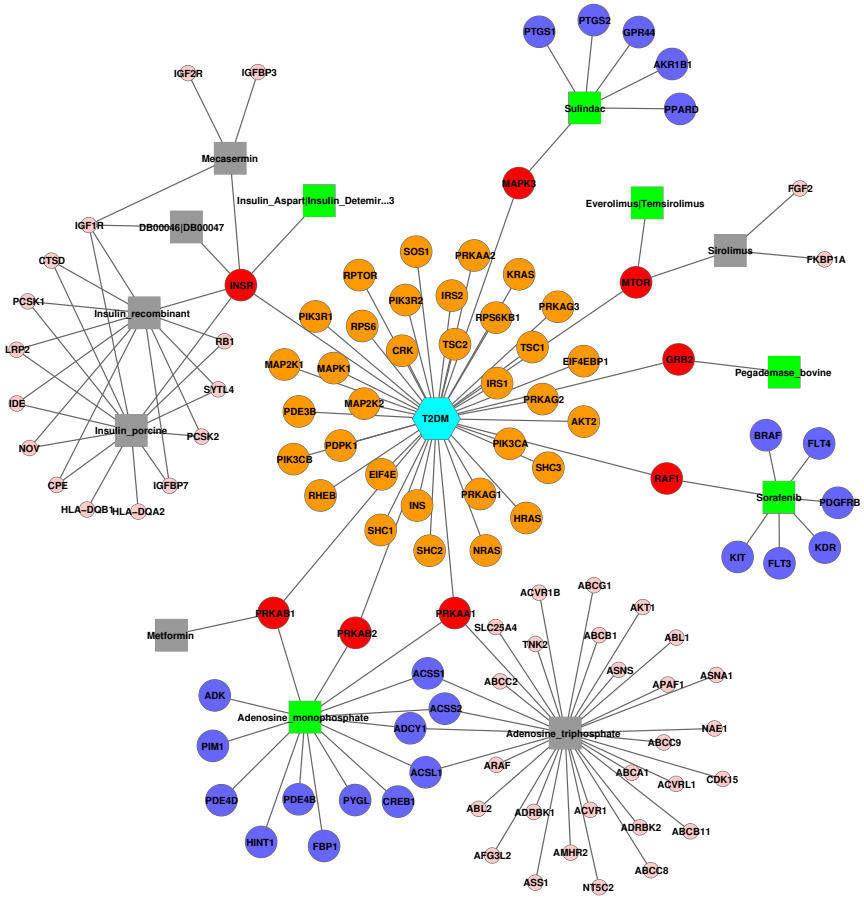
Supplementary Figure 6: The disease-gene-drug network of EPAM. High similarity was observed between the BTSC and MOTSC results. The different selection of drugs is primarily due to the full coverage requirement. Lapatinib, DB08059, DB06831, and DB07812 predicted by BTSC are still in MOTSC result. Several new drugs were selected, including Temsirolimus, DB07584|DB07585, and DB06877|DB07264...5. Among these new drugs, Temsirolimus is an inhibitor of mTOR, and DB07584|DB07585 (pyrrolopyrimidine) is an inhibitor of AKT1 and GSK3β. The drug combination identified by BTSC or MOTSC will offer the hope to better inhibit the whole EPAM pathway.

MOTSC Result on HTN



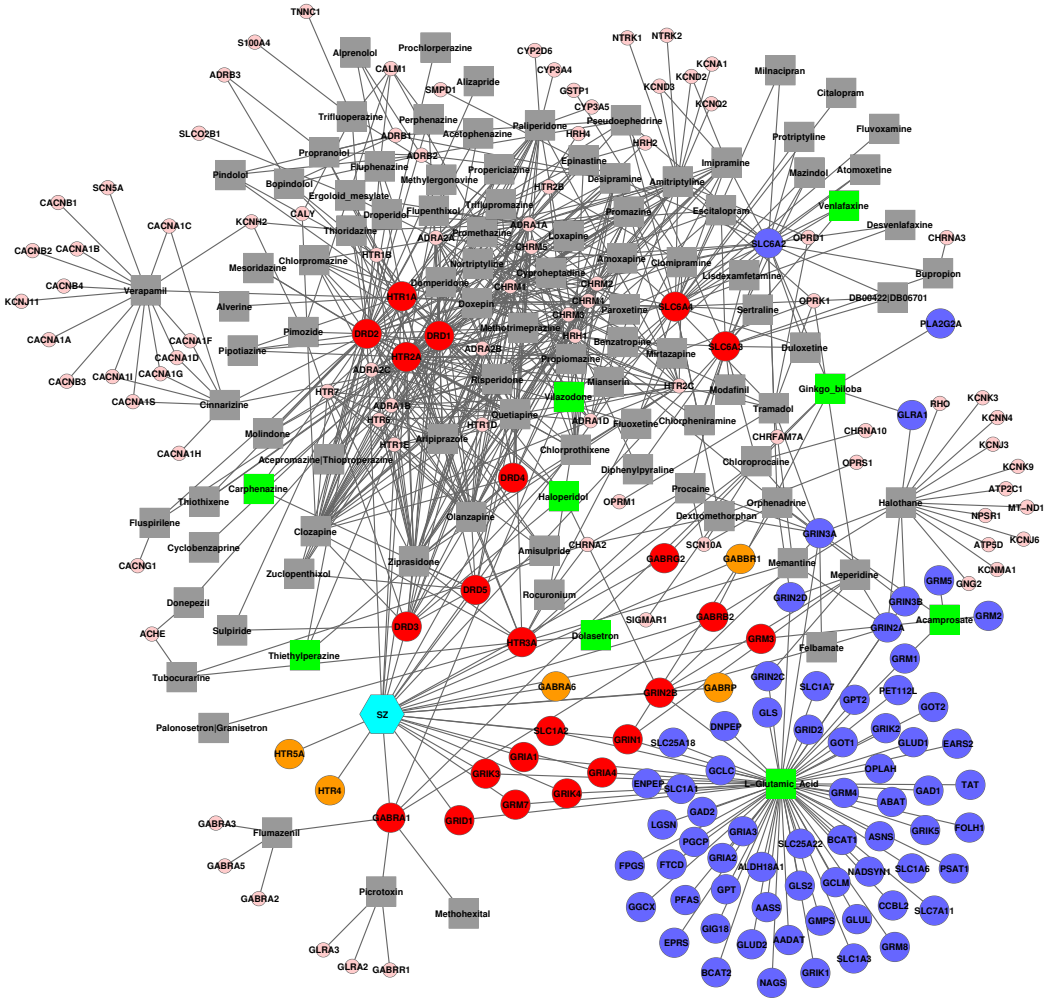
Supplementary Figure 7: The disease-gene-drug network of HTN. Triamterene, Bupranolol, Remikiren, and Sitaxentan predicted by BTSC are still in MOTSC result. Among the new drugs selected, Olmesartan, Metolazone, and Polythiazide are known drugs for the treatment of HTN. A combination tablet containing Metolazone and Triamterene, new drug combination predicted by MOTSC, is reported to be useful in the treatment of HTN (Patent US 4522818 A). The full coverage requirement introduced several more drugs and the selection of NADH, which induced a large number of off-targets. This result demonstrated that BTSC is more flexible and balanced when dealing with real disease gene sets.

MOTSC Result on T2DM



Supplementary Figure 8: The disease-gene-drug network of T2DM. Similar result was obtained when MOTSC algorithm was applied to the same T2DM gene set. Insulin Aspart|Insulin Detemir, Everolimus|Temsirolimus, and Pegademase predicted by BTSC are still in MOTSC result. Several new drugs were selected because of full coverage required by MOTSC. Among the new drugs, Adenosine monophosphate is used for nutritional supplementation and for treating dietary shortage or imbalance. Similar to Metformin, this drug can activate PRKAB1 as well. The use of this drug for treating T2DM is worth further studying.

MOTSC Result on SZ



Supplementary Figure 9: The disease-gene-drug network of SZ. Haloperidol, Dolasetron, and Vilazodone predicted by BTSC are still in MOTSC result. Among the new drugs selected, Carphenazine, and Thiethylperazine are known drugs to treat SZ, while Ginkgo biloba and L-Glutamic Acid can benefit SZ treatment. Haloperidol plus extract of Ginkgo biloba, new drug combination predicted by MOTSC, can improve the treatment of patients with SZ (Zhang *et al.*, 2001, 2006). Similar to HTN, large number of off-targets were induced due to the requirement of full coverage. Application of MOTSC on the five disease gene sets indicates that MOTSC is more applicable if the user has specific requirement that all the input genes must be targeted if there are drugs available. Thus, BTSC and MOTSC provided two complementary ways to identify optimal drug combination.

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