Supplementary manuscript of

Multi-objective optimization based network control principles for identifying personalized drug targets of individual patients with cancer

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## Section S-I: Constructing PGIN by Paired-SSN method

For the paired-SSN method [1], the first step is building the co-expression network based on the tumor sample and the normal sample of an individual patient [2]. Then, We needed to determine whether this edge is used to construct the PGIN according to the P-value of the edge between gene i and gene j in the normal sample network and tumor sample network. The specific conditions are as follows: If the P-value is lower than 0.05 in the tumor sample network (the coexpression relationship between the interaction of two genes is significant) and larger than 0.05 in the normal sample network (not significant), or vice versa , this edge is retained to constitute the PGIN. In addition, we can get P-value of an edge by calculating  and then counting its Z-value of . The  of an edge between gene i and gene j and its Z-score can be calculated :



where n represents the number of reference samples and k represents the k-th patient in the perturbed network.  represents the PCC of an edge between genes i and j in the reference network; and represents the PCC of the edge between genes i and gene j in the perturbed network. Here, we calculated a measure to score the pPCC of edges in the PGIN by integrating gene mutation data across cancer

type-specific data into the PGIN as follows,

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## where Norm represents the min-max normalized function. and respectively is the collection of tumors that exist mutated genes i and gene j after checking for somatic mutations in a given cancer data set; indicates that 10% of the data falls under after sorting a set of data in ascending order.

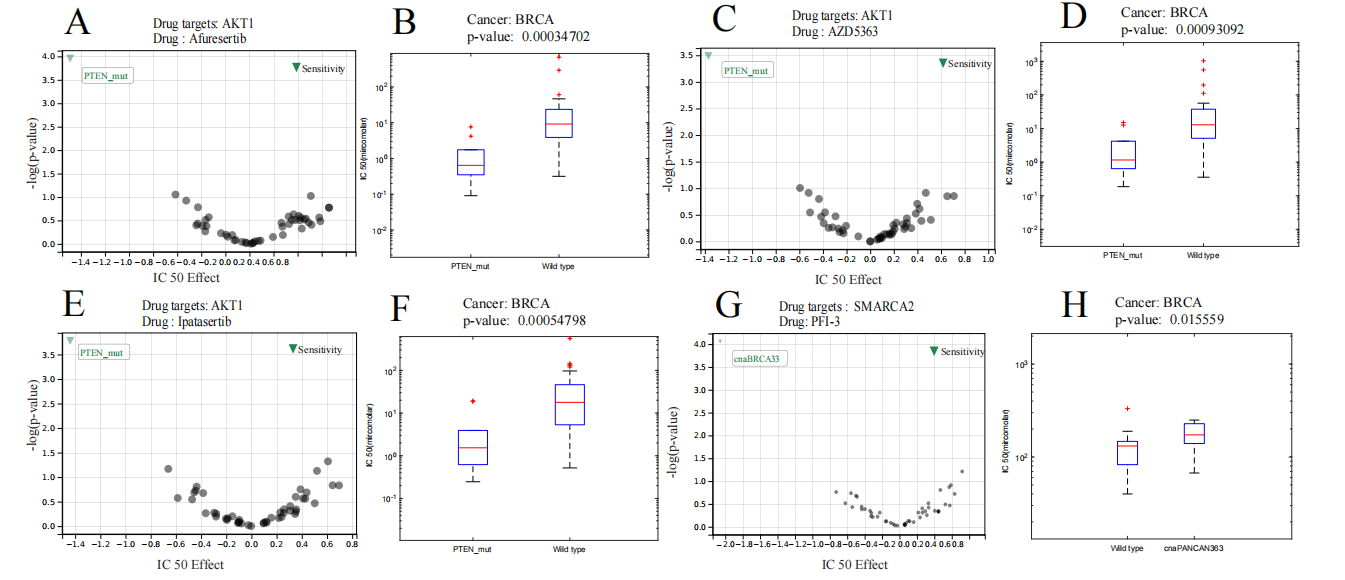
## Section S-II: The the particular parameter setting of all CMOEAs

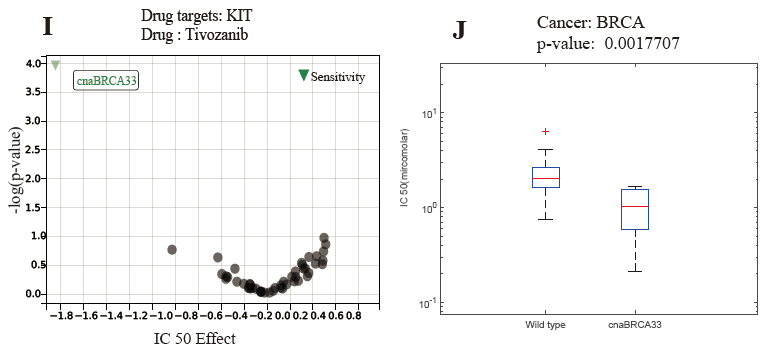
In this work, NSGA-II-CDP [3], CMME [4], CCMO [5], c-DPEA[6], MTCMO[7] and LSCV-MCEA adopt the simulated binary crossover [8]and the polynomial mutation[9] to generate offsprings, while CCMODE adopt the differential evolution [10]and the polynomial mutation to generate offsprings. The general parameters of the algorithms are set as follows:

1. Simulated binary crossover operators: the crossover probability  =1 and the distribution index  = 20;
2. Differential evolution operators: the crossover rate CR = 0.9 and the scaling factor F = 0.5;
3. Polynomial mutation operators: the mutation probability  = 1/n and the distribution index  = 20;

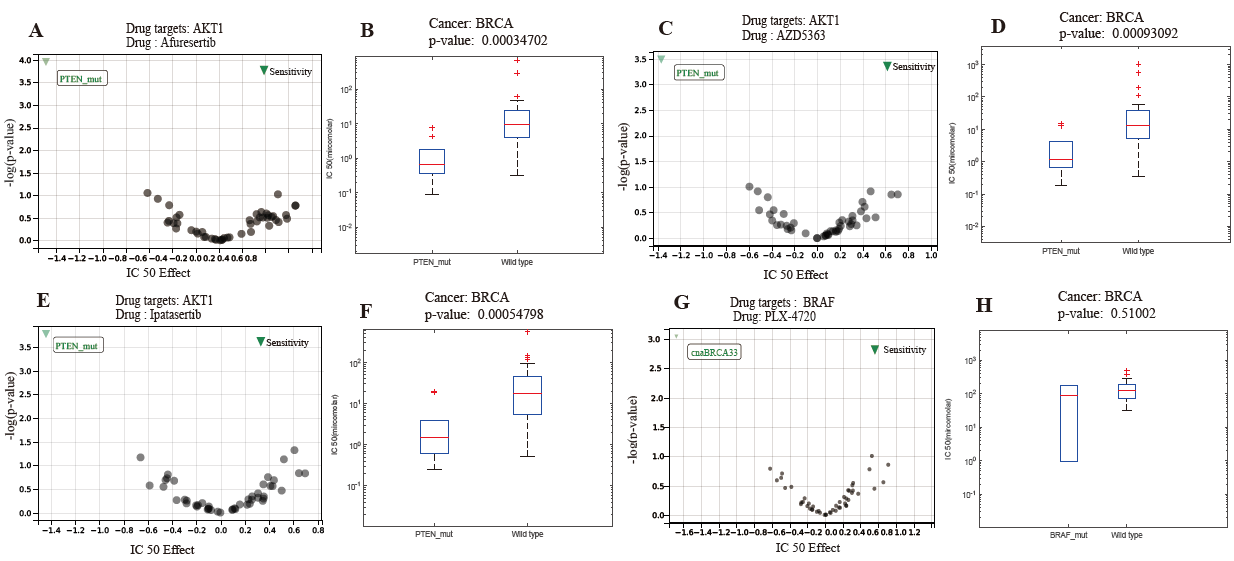
## Section S-III: The biologic significance of patients on three cancer datasets.

To further verify the effectiveness of target genes and corresponding drugs, we queried the drug response datasets (GDSC) as shown in Table 1 of our main manuscript. For BRCA data, we found that three target genes under the framework of MDS, two target genes under the framework of NCUA and two target genes under the framework of DFVS. For instance, **Fig. S1A** shows that the sensitivity of the drug afuresertib, which acts on the drug target AKT1, is significantly correlated with the PTEN mutation cell line in BRCA cancer tissues under the framework of MDS. Furthermore, **Fig. S1**B shows that BRCA cancer cells with the PTEN mutation were significantly inhibited by afuresertib compared with the wildtype cell line, which was consistent with the findings of a previous study[11]. Therefore, afuresertib can be a candidate drug for BRCA patients with PTEN mutation. The sensitivity analysis of other drugs acting on AKT1, SMARCA2 and KIT is also shown in **Fig. S1**. Similar results for NCUA and DFVS are shown in **Fig. S2**.

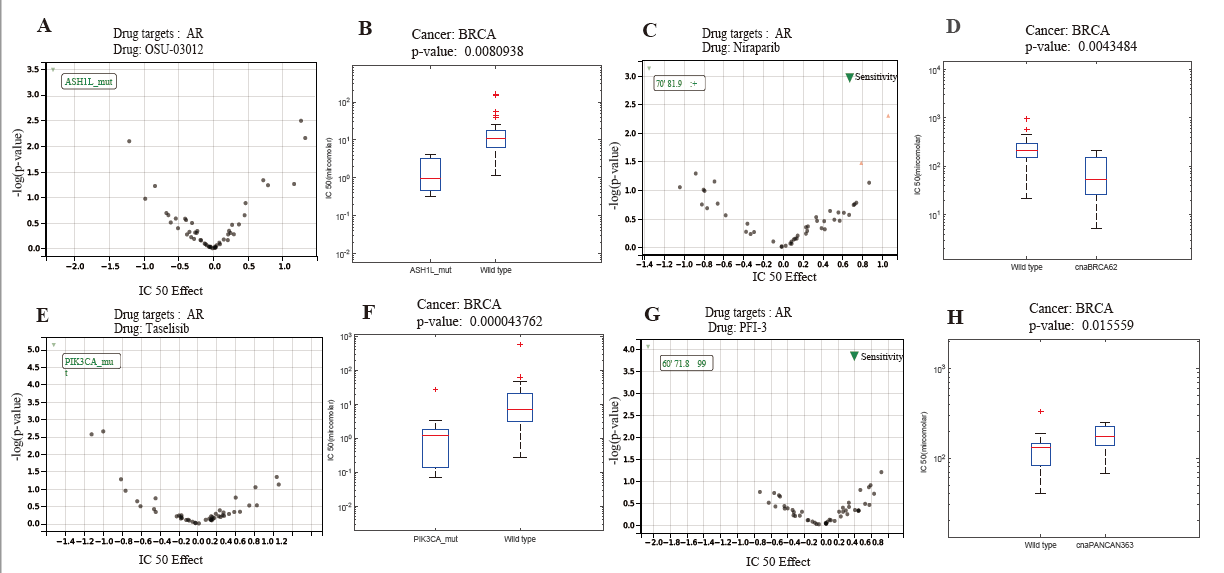


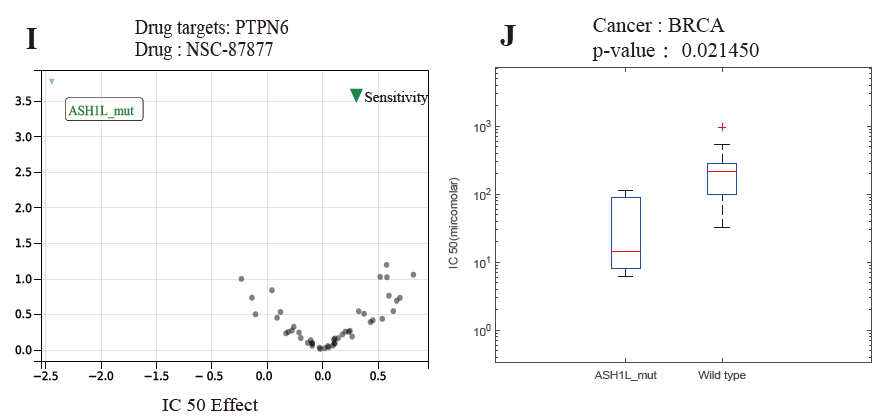


**Fig. S1** The sensitivity of drugs acting on drug targets of BRCA under the framework of MDS. (**A,C,E,G,I**) The volcano plot of drugs acting on drug targets . (**B,D,F,H,J**) The box-plots of IC50 on specific genomic changes cell line and wild type cell line.



**Fig. S2** The sensitivity of drugs acting on drug targets of BRCA under the framework of NCUA. (**A,C,E,G**) The volcano plot of drugs acting on drug targets . (**B,D,F,H**) The box-plots of IC50 on specific genomic changes cell line and wild type cell line.





**Fig. S3** The sensitivity of drugs acting on drug targets of BRCA under the framework of DFVS. (**A,C,E,G,I**) The volcano plot of drugs acting on drug targets . (**B,D,F,H,J**) The box-plots of IC50 on specific genomic changes cell line and wild type cell line.

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