Title: A network paradigm predicts drug synergistic effects using downstream protein-protein interactions

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One Sentence Summary: We predicted and tested clinical effects of drug combinations using protein-protein interaction network drug classification.

Abstract: In some cases, drug combinations affect adverse outcome phenotypes by binding the same protein; however, drug-binding proteins are associated through protein-protein interaction networks within the cell, suggesting that drug phenotypes may result from long-range, network effects. We first used protein-protein interaction network analysis to classify drugs based on proteins downstream of their targets and next predicted drug combination effects where drugs shared network proteins but had distinct binding proteins (e.g., targets, enzymes, or transporters). By classifying drugs using their downstream proteins, we had an 80.7% sensitivity for predicting rare drug combination effects documented in gold-standard datasets. We further measured the effect of predicted drug combinations on adverse outcome phenotypes using novel observational studies in the electronic health record. We tested predictions for 60 network-drug classes on 7 adverse outcomes and measured changes in clinical outcomes for predicted combinations. These

results demonstrate a novel paradigm for anticipating drug synergistic effects using proteins downstream of drug targets.

Main Text:

INTRODUCTION

Many drug-drug interactions (DDIs) associated with adverse effects occur from a shared binding protein, where drugs share similar targets, enzymes, carrier, or transporter proteins. For example, one drug can inhibit an enzyme that is responsible for metabolism of another drug substrate. However, not all DDIs are explained by this mechanism. Regulatory guidances recommend clinical (*1*) and in vitro experiments(*2*) to evaluate a drug's potential for drug interactions; these recommendations emphasize the study of drug metabolizing enzymes and transporters that are relevant to other marketed therapies. DrugBank's drug-drug interaction database (*3*, *4*) curates DDIs based on shared protein mechanisms and PharmGKB (*5*) curates drug-gene interactions, but neither consider the effects of proteins downstream of drug targets. In contrast, evidence suggests that drugs synergize through pathway effects without shared binding proteins. For example, the combined use of the chemotherapeutic drugs paclitaxel and carboplatin reduced hematopoietic toxicity experienced with carboplatin alone yet the combination did not affect the pharmacokinetics of either single drug (*6*), suggesting a non-shared-protein mechanism.

Using *in silico* methods, such as protein-protein interaction (PPI) network models, to anticipate drug effects is attractive because of the relative ease and scale of these methods for making predictions. These approaches have successfully predicted opportunities for drug repurposing (*7-10*), for treating co-morbid conditions (*11*), for identifying drug-drug interactions (DDIs) (*12*, *13*) and for understanding disease mechanisms (*14*). Already, there is mounting evidence that

single and combination drug effects propagate through protein networks. Yet, downstream PPIs are not routinely used to anticipate drug effects in regulatory and industry settings because of the propensity of these models to over-predict drug phenotypes. We recently developed a per-phenotype PPI network approach that improved prediction performance 50% and increased average precision 76-95% when anticipating single drug adverse events, compared to global approaches (*in press*, doi: https://doi.org/10.1101/2020.12.15.422844). Interestingly, downstream proteins, relative to drug targets, were highly weighted in predicting a drug's adverse outcome. Further, downstream proteins distinguished true from false positive predictions and were integral to preventing over-prediction. Because drug effects propagate through networks and our previous discovery that downstream proteins were predictive of drug adverse outcomes, we hypothesized that downstream proteins could be predictive of DDIs when drugs did not share binding proteins.

We explored the extent to which protein-protein interactions downstream from the targets of two drugs were sufficient to predict DDIs in cases where the drugs had distinct binding proteins (motivated in **Fig. 1.**) (We refer to drug targets, enzymes, carriers, or transporters as "targets" in the rest of this analysis.) To complete this analysis, we generated a novel set of drug-adverse-reaction (ADR) pairs by extracting these relationships from the drugs' labels. Informed by the success of our per-phenotype PPI approach, we used meta-analysis to prioritize proteins downstream of targets of drugs labeled with the same ADR and re-classified drugs using these network proteins. We then predicted DDIs for drugs using their network class. We validated predicted combinations using novel observational studies in the electronic health record and demonstrated an ability to detect rare DDIs using protein interactions downstream of their targets. Although we used ADRs as a case study, our network paradigm is broadly applicable to

all biological phenotypes, suggesting a relatively simple, and useful approach for anticipating drug synergistic effects generally.

RESULTS

Network analysis of single drugs with the same ADR

We first discovered PPI associations between a drug's target(s) and adverse drug reactions listed in the drug product's FDA-approved drug labeling. Specifically, we focused our investigation on a list of designated medical events which are adverse drug reactions (ADRs) of high priority in regulatory review. We used a natural language processing method to extract ADRs from the warnings, boxed warnings, adverse reactions, and precautions sections of the drugs' labels. This analysis yielded associations between 1,970 drugs and 34 ARs. This provided a unique dataset for interrogating network proteins of drugs associated with ADRs.

For network analysis, we restricted our analysis to 1,136 drugs that had drug-binding proteins listed in DrugBank(*3*) and further restricted to 970 drugs whose targets were connected in our PPI network(*8*). We used the PathFX algorithm (*8*) to create networks for these drugs (**Fig. 2., Sup. File 1.**). Compared to other PPI network models, PathFX used the amount and quality of evidence supporting PPIs around drug targets to prioritize downstream proteins and then used statistical enrichment to discover phenotypes enriched in the drug's network. Importantly, PathFX was naïve to a drug's true set of phenotypes (e.g., an ADR from the drug label or the drug's intend-to-treat disease) and instead used the corpus of evidence to anticipate drug network associations (further discussed in methods). PathFX discovered network associations for 424 drugs to 24 ARs.

This analysis discovered downstream proteins that were common to multiple drug-ADR pairs and distinct to ADRs (**Fig 3A.**, **Sup. File 2.**, **Sup. File 3.**). For example, for drugs labeled with sepsis, their networks shared drug-binding and downstream proteins (**Fig. 3B**). Because of these patterns, we reclassified drugs based on shared downstream proteins (**Fig. 2B**). For instance, multiple drugs associated with sepsis contained the adrenoreceptor beta 2 (ADRB2) downstream of their drug targets; this yielded two new classes for sepsis-associated drugs: "ADBR2 network" drugs and "non-ADBR2 network" drugs. We repeated this reclassification for all shared downstream proteins across all 24 ARs and tracked two types of network proteins for classification – ADR-associated network proteins (ARPs) or any protein on a shortest-path between a drug target and ADR protein (SPs). We discovered 172 network classes (each corresponding to 172 "non-Gene-net" classes) across 12 ADRs or 1,623 classes across 24 ADRs using ARPs, or SPs, respectively.

Next, using non-ADR drugs, we predicted novel DDIs for each network class where non-ADR drugs had target proteins downstream in the network class. For instance, ADBR2 is a target for the drug albuterol and albuterol is not associated with sepsis on its label. We predicted that "ADBR2 network" drugs would interact with albuterol to affect sepsis outcomes. In total, we predicted 18,988 drug-drug-ADR combinations using ARPs (51,605 combinations using SPs) from network classification. We further removed predicted DDIs if the drugs shared any target proteins because we were motivated to understand DDI effects due to downstream proteins. This yielded 6,098 drug-drug-ADR triplets using ARPs (19,741 triplets using SPs) representing 5,246 unique drug-drug pairs using ARPs (11,904 unique pairs using SPs) for further consideration (some drug-drug pairs were associated with multiple ADRs).

Literature, TWOSIDES evidence supports combination effects and suggests directionality

We estimated the sensitivity of our method by using TWOSIDES(*15*, *16*), a well-regarded dataset for drug combination effects. TWOSIDES uses the FDA Adverse Event Reporting System (FAERS) to detect DDIs based on the relative reporting rates of combination drugs as compared to single drugs while controlling for confounding variables(*15*, *16*). Predicted DDIs in TWOSIDES indicated combinations prescribed in the real world. For reference, TWOSIDES contained 42,920,391 drug-drug-ADR sets reported for 211,990 unique drug-drug pairs. Of note, TWOSIDES contained DDIs for 12,726 unique ADRs and included many more and milder side effects than our analysis (e.g., diarrhea, headache). We next counted our total drug-drug predictions and drug-drug-ADR triplets tracking both ARPs and SPs (**Table 1**). We first filtered our predictions by drug-drug combinations documented in TWOSIDES, reasoning that if a drug combination was reported in TWOSIDES, the combination was likely prescribed in the real world. To estimate the sensitivity of our method, we counted predicted drug-drug-ADR triplets documented in TWOSIDES (**Table 1**). From these results, using ARPs relative to SPs generated a higher sensitivity for detecting DDIs (80.7% vs 50.2%).

Our PathFX analysis identified non-directional associations and motivated us to pursue complementary data sources. For instance, our network analysis discovered an association between the drug paroxetine that had sepsis on its label, a non-sepsis-labeled drug, albuterol, and the ADR, sepsis, but our analysis didn't indicate whether co-administering albuterol with paroxetine would reduce or worsen sepsis. We used the literature to infer the directionality of drug effects. Specifically, we used sentences to identify if a combination drug would worsen or mitigate the drug-induced ADR. We searched for combo-drug-ADR relationships within PubMed abstracts using natural language processing. Using emerging results from the literature was important because it did not replicate data used in the network analysis. We manually

curated sentences containing mention of combo drugs and ADRs to understand how the combo drug may affect the ADR. For instance, the beta-2 agonist albuterol, binds the ADRB2 protein, which is downstream in the interaction network of three drugs that are associated with sepsis on their drug labels (paroxetine, atropine, and cocaine). Albuterol is not associated with sepsis on its drug label, yet in our search of published abstracts, we discovered that albuterol is associated with sepsis in a rat model. Specifically, we discovered and manually validated the following sentence to support further consideration of these combinations study: *"This study showed for the first time that oral administration of albuterol exerted protective effects on CLP-induced sepsis and related lung injury in rats"* (*17*). The full list of predicted drug-drug-ADR combinations, their relevant network proteins, and manually curated literature evidence are provided in **Sup. Files 4** (predictions for SPs) and **5** (predictions for ARPs)**.**

We further investigated predicted drug-drug-ADR combinations with clinical data using published databases and novel observational studies. To consider feasibility of detecting drug combination effects in patient data, we again referenced TWOSIDES (*18*), and investigated the proportional reporting ratios (PRRs) reported for the 368 combinations discovered using ARPs. PRRs were a sufficient proxy for ADR severity of predicted DDIs. Indeed, predicted combination effects were discovered in TWOSIDES (**Table 2**, full results in **Sup. File 4**). Further, because PathFX networks do not contain directional pathway information, measuring a drug-combination effect in TWOSIDES suggested that drug combinations may increase risk for ADRs in the real world.

We also pursued multiple novel observational studies to test our hypotheses and used two approaches to conduct this analysis. For these analyses, we used the deidentified Optum Clinformatics dataset v7 that included over 88 million US patients, both privately insured and

Medicare beneficiaries, largely under the age of 65. We accessed a version of the Optum dataset standardized to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM); standardized data models have decreased heterogeneity between datasets and improved consistency in underlying data(*19*). We leveraged the Observational Health Data Sciences and Informatics (OHDSI) network tools, specifically CohortMethod to measure ADR outcomes for patients exposed to our predicted combinations. CohortMethod is a software package that facilitates extracting patient data from the EHR, conducting large-scale propensity matching for controlling confounding variables, and estimating outcome models, such as Cox regression (example applications (*20*) (*21*)). The LEGEND study is one relevant application where CohortMethod measured cardiovascular outcomes across first-line anti-hypertensive drugs(*20*). Our approach was conceptually similar, however, we aggregated drugs into network classes instead of by their chemical structures or therapeutic use classes. We first used CohortMethod to test two network DDI predictions to validate our ability to detect DDIs in the real world. We used a customized pipeline to analyze the 58 network classes that encompassed the 368 drug-drug-ADR triplets documented in TWOSIDES.

Altered sepsis outcomes for network-classified drugs in a novel observational study

We first investigated the effect of albuterol on beta-2 adrenergic receptor 2 (ADRB2) network drugs. PathFX identified network associations for 29 drugs with sepsis listed on the drugs' labels. From this 29-drug set, two drugs, paroxetine, and atropine, contained ADRB2, an albuterol (also known as salbutamol) drug target, downstream in their networks and did not share other target proteins with albuterol. Of the remaining 27 drugs, 18 drugs did not contain albuterol-binding proteins downstream in their networks nor share drug target proteins with albuterol. These 18 drugs were considered the "non-ADRB2-net" class (**Table S2**). We

hypothesized that concomitant use of albuterol would alter risk of sepsis for ADBR2-network drugs relative to non-ADBR2-network drugs.

For the first measurement, we measured the risk of sepsis for patients on ADBR2-network ("target" cohort) or non-ADBR2-network ("comparator" cohort) drugs. For the second measurement, we measured the risk of sepsis for patients with an overlapping exposure to albuterol+ADBR2-network drugs ("target" cohort) or albuterol+ non-ADBR2-network ("comparator" cohort) drugs. To select patients with an overlapping exposure, we required patients have an albuterol "DRUG ERA" that started between the start and end of an exposure to either the ADBR2-network or non-ADBR2-network drugs and risk for sepsis was observed for 30 days following the start of the second drug exposure. The drug era is considered a sufficient proxy to estimate an exposure to an active ingredient and the details of this data table are further explained in *Materials and Methods.* We further used large-scale propensity matching to estimate confounding and then matched patients based on their propensity score to estimate risk. Propensity matching aggregates all available patient data in the health record including commonly-considered confounders such age, diagnoses, demographics as well as other data such as number of visits, time to visits, that also reflect patient characteristics (*18*, *22*, *23*). After matching, we discovered good covariate balance between the target and comparator cohorts and sufficient patient attrition for measuring outcomes (**Fig. S1., Table S3.**).

We measured the risk of sepsis between these two drug classes without a combination therapy and with co-administration of albuterol (**Fig. 4**., **Table 3**). The risk of sepsis occurring in the ADBR2-net class is increased compared to the non-ADBR2-net class when albuterol is used concurrently: Hazard Ratio (HR)=0.792 with the combination compared to HR=0.525 without the combination; this yielded an HR-ratio of 1.51. The risk of sepsis from paroxetine or atropine

(ADBR2-network class) was less than non-ADBR2-network class drugs, however, the combined use of albuterol with paroxetine or atropine increased the risk of sepsis compared to non-ADBR2-network class. We did not discover literature evidence supporting sepsis outcomes in combined use of atropine or paroxetine with albuterol. A retrospective chart review supported that albuterol and atropine were both therapeutic options for systematic bradycardia (*24*), suggesting that patients may have overlapping exposures to these drugs. A clinical trial in infants suffering from chronic lung disease observed that salbutamol (a synonym of albuterol) had no observable effect on patient sepsis (*25*), further supporting that albuterol isn't associated with sepsis when used alone.

Altered pancreatitis outcomes for network-classified drugs in a novel observational study

We next investigated the effect of aspirin (also known as acetylsalicylic acid) prescribed in combination with drug network classes associated with aspirin target proteins. This analysis was like the analysis of albuterol, except that we classified pancreatitis-associated drugs by aspirin target proteins. We discovered downstream network proteins for 80 drugs with pancreatitis listed on their labels. From this 80-drug set, eight drug networks contained at least one of the following aspirin target proteins – tumor protein p53 (TP53), endothelin receptor type A (EDRNA), or nuclear factor of kappa light chain gene enhancer of B-cells, inhibitor alpha (NFKBIA) – and did not share other aspirin target proteins. We classified these eight drugs as the "T-E-N-net" class. Of the remaining 72 drugs, 28 drugs did not share aspirin target proteins or have downstream connections to aspirin target proteins. We classified these 28 drugs as the "non-T-E-N-net" class. All drugs in both classes are listed in **Table S4**. We hypothesized that aspirin would increase the risk of pancreatitis when co-administered with the T-E-N-net class but not with the non-T-E-N-net class.

As above, we extracted patients from the Optum dataset to be used in the target/comparator cohorts if they had an exposure to the T-E-N-net/non-T-E-N-net classes, respectively. We defined combined exposure cohorts as mentioned previously, except that patients were required to have a drug exposure to aspirin that overlapped with an exposure to the T-E-N-net or non-T-E-N-net classes. We also used propensity score analysis and patient-matching to calculate the relative risk of pancreatitis with the aspirin combination. Again, we had sufficient patient attrition and covariate balance to pursue further analysis (**Fig. S2., Table S5.**).

After designing cohorts and looking for covariate balance, we measured hazard ratios for patients in these groups (**Fig. 4**., **Table 3**) using cox proportional hazards. The risk of pancreatitis occurring in the T-E-N-net class increased relative to the non-T-E-N-net class when aspirin is used concurrently: HR = 1.01 with the combination compared to HR=0.580 without the combination; this yielded an HR-ratio of 1.74. The T-E-N-net class had a lower risk of pancreatitis compared to the non-T-E-N-net class, and the addition of aspirin increased the risk of the T-E-N-net class compared to the non-T-E-N-net class. The change in risk of drugs with network associations to the combo drug in these two cases encouraged us to pursue further validation. Aspirin inhibits prostaglandins and inhibits pancreas ductal permeability (*26*), suggesting that aspirin could exacerbate pancreatitis when used in combination with other drugs associated with this ADR. While insufficient to make conclusions, at least one study referenced the concomitant use of aspirin and aripiprazole (a T-E-N-net class drug) and documented an occurrence of pancreatitis; the report documented a 50-year old woman experiencing pancreatitis when aspirin and aripiprazole were used concomitantly, though the case report concluded that the pancreatitis may have been due to a third medication (*27*). Our network classification

predicted a DDI of pancreatitis for combined use of aspirin and aripiprazole, suggesting an alternative explanation for the patient's pancreatitis outcome.

Novel observational studies for 58 additional DDI classes discovered using ARPs

We sought validation for an additional 58 network-class DDIs predicted from using ARPs because these predictions had higher sensitivity for anticipating effects in TWOSIDES (**Table S6** and **Sup. File 5**). For these 58 predictions, we estimated a hazard ratio using Cox regression on a 1-1 propensity score matched cohort with a caliper of 0.1. We used a logistic regression propensity score model trained on low dimensional CLMBR patient representations (*28*). Precomputed CLMBR representations enabled more rapid cohort definitions and HR-ratio estimation than CohortMethod. Like before, we included patients in our baseline/combo analysis if they had exposure to drugs in the network or non-network classes with/without the predicted combo drug, respectively. We measured HRs between network and non-network drug classes with and without drug combinations.

Like the two cases outlined above, we measured the relative risk between the net-GENE and non-net-GENE classes with and without the predicted combination drug for the 58 remaining class predictions (**Table S6**). Not surprisingly because our drug interaction predictions are rare, we were unable to generate sufficient patient cohorts to measure HRs for all predicted classes. For 21 of the 58 total classes, we had sufficient patients to measure HRs between the net-GENE and non-net-GENE classes and for 8 of these cases, there were also sufficient patients to measure HRs between drug classes with the predicted combination drugs (**Fig. S3**). However, we removed one class prediction because the predicted combination drug's indication was too similar to the side effect. For the 7 remaining classes we measured the change in Cox coefficient to estimate effects of the predicted DDIs. (**Table 4, Fig. S4**). These DDI effects were moderate

with HR-ratios that ranged from 0.85-1.17. The highest HR-ratio, 1.17, was measured for drug-induced hypertension associated with proopiomelanocortin (POMC) network class drugs used in combination with loperamide, an ingredient used to treat diarrhea. The lowest HR-ratio, 0.85, was measured for from drug-induced hypertension associated with prostaglandin E receptor 4 (PTGER4) network class drugs used in combination with misoprostol, an ingredient once used to treat stomach ulcers. This result suggests a protective effect of misoprostol for the PTGER4 network drug class.

DISCUSSION

We predicted drug-drug interactions (DDIs) using network classification and validated our predictions using DDI databases and novel observational studies. We first extracted a novel dataset of drug-adverse reaction (ADR) pairs using data extracted from drug labels. This dataset was crucial to our analysis and will be valuable to other investigations of drug ADRs. We used network analysis to discover downstream proteins associated with ADRs, reclassified drugs by their downstream proteins, and predicted DDIs based on network classification. We demonstrated high sensitivity for detecting rare DDIs using ARPs for classification, further supporting that rare or emerging drug-drug effects may arise when drugs do not share protein targets. Compared to other network approaches, our analysis was, to our knowledge, unique in the requirement that we excluded drugs with shared protein targets. This allowed us to exclusively explore DDIs that resulted from downstream effects and not a shared protein mechanism. We validated DDI predictions for albuterol and aspirin based on network classification and 58 additional DDI effects using novel observational studies. Overall, these results provide evidence for investigating downstream proteins for anticipating DDIs and that

protein-protein interactions between drugs' targets are sufficient for identifying drug combination effects.

Fortunately, rigorous regulatory review and good clinical practices prevent the use of many harmful drug combinations, and this limited our ability to extensively validate every prediction. We could not measure DDI effect sizes for all network predictions, yet we found evidence for rare drug combinations. Nonetheless, *in silico* network analysis is relatively cheap and efficient and could aid in therapeutic development where anticipation of ADRs is essential for therapeutic development. Further, our predictions are not documented in routinely used DDI data sources and integration of these predictions could inform clinical care or further research efforts. Our discovery of drug combinations that mitigated ADR outcomes suggested a new paradigm for managing drug induced ADRs; specifically, that mitigating therapies could be prescribed based on drug network class. Similarly, *in silico* network analysis which predicts therapies to mitigate side effects could also inform safety analysis plans for clinical development.

Our results also have implications for advancing protein-protein interaction (PPI) networks for anticipating drug effects. There is sufficient evidence that PPI networks can anticipate drug effects and be used predictively for identifying repurposing opportunities. However, our analysis is distinct because of our emphasis on attribution; we aimed to ascribe drug effects to specific downstream proteins. Classifying drugs by their downstream proteins and measuring relative ADR risk in the presence of secondary drugs is evidence that drug effects could be attributed to downstream proteins discovered from PathFX network analysis. Further experimental validation would be required to investigate these hypotheses. However, it suggests that PPI methods are useful not just for pattern discovery (e.g., drug A's network is like drug B's network) but also for

predicting mechanistic effects (e.g., drug A's ADR outcome is mediated by the downstream protein Y).

Our study expands a growing body of knowledge that drugs can exert synergistic effects without sharing drug-binding proteins, which may lead to a better understanding of adverse drug reactions and rational design of new therapeutic combinations. Drug synergy is a broad field where many frameworks are used to anticipate drug effects (*29*, *30*). Some approaches leverage "supra-additive" effects of drugs used in combination (*31*, *32*), yet these measurements often rely on complex and relatively costly high-throughput screens(*33*). While the performance of computational synergy prediction algorithms has increased, these effects have yielded little success in the clinic (*30*, *34*). A community competition for synergy prediction noted that drugs with high experimental synergy contained drug targets in the same pathway and further, that well-predicted drug synergies occurred when combination drug targets were downstream of a shared protein (*30*). While we used drug induced ADRs as the focus of this investigation, analysis of proteins downstream of drug targets could improve prediction of drug synergistic effects on disease outcomes.

MATERIALS AND METHODS

Data and code availability

The data and code used in this manuscript and referenced in this section are available at https://github.com/jenwilson521/Designated-Medical-Event-Pathways. Note: In the computational analysis, we used "DME" as shorthand for "ADR". For transparency, we noted each script used for each analysis in the results section. Patient data from the electronic health record analysis is not made available to respect patient privacy and data use agreements.

Extracting adverse reaction phenotypes from drug labels

An algorithm was built using Linguamatics, a natural language processing software, to extract designated medical events (DMEs) (adverse drug reactions, ADRs) as MedDRA Preferred Terms from the black box warning, warnings & precautions, and adverse reactions sections of FDA product labels. All available FDA product labels (as of December 2017) were obtained from DailyMed and indexed in Linguamatics. For each ADR, the related MedDRA Preferred Term, Lower Level Term, and colloquial terms were searched (i.e., "SJS" was an additional term searched for "Stevens-Johnson syndrome"). Drugs with one or more ADRs in their product label were exported for analysis in PathFX. The data from this analysis are included in *supp1_Drugs_labeled_for_AEs.txt*.

PathFX modeling of marketed drugs and identification of pathway associations to ARs

To find pathway associations to ADRs, we used the PathFX algorithm(*8*) to identify network relationships between drug targets and ADR-associated proteins. Compared to other methods, PathFX used a data-driven approach to discover network associations, the algorithm generated "white-box" predictions of drug associations, and demonstrated high specificity in predicting drug-ADR effects(*8*). We used drug targets from DrugBank(*3*) (version 5.1.0) as inputs to PathFX. This analysis yielded a dataset of drug-ADR associations and downstream proteins associated with ADRs from drug labels. A summary of the PathFX algorithm approach and detailed description of the analysis and results is included in the *Supplemental Materials and Methods.*

Network meta-analysis

We next used meta-analysis to identify downstream proteins shared between drugs with the same ADR. PathFX contained multiple phenotypes associated with ADRs from a drug label (e.g., "Hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency" and "Hemolytic anemia" were both considered as a prediction of "anemia"), and we collapsed these phenotypes when investigating each ADR. For a full description of the meta-analysis and pathways considered, please see the *Supplemental Materials and Methods.*

Network images and heatmaps

To create network images, we wrote a custom python script for creating images with drugs oriented above drug-binding proteins and phenotypes. The script used the merged networks created previously and created a layered array where drugs were plotted in the topmost layer, drug targets in the second layer, intermediate and downstream proteins in the third layer, and ADR phenotypes in the fourth, and bottom layer. All scripts are included in the 'code' folder of the directory. *(/Code/ merge_networks_for_DMEs.ipynb* and */Code/ find_co_therapy_networks.ipynb*).

Identifying novel co-therapies and determining directionality of effect

We again used drug-protein binding data from DrugBank to identify drugs that bound an ADR pathway gene (discovered previously) and were not associated with an ADR on their drug label *(/Code/find_predicted_cotherapies.ipynb, /char_data/ charac_novel_combinations.py,* and */Code/ charac_novel_combos_using_int.py*). We tracked two types of ADR pathway genes: ADR-associated genes (ARPs) and proteins along shortest paths between drug targets and ADR-associated genes (SPs). We predicted drug combinations for both types of network genes and these results are stored in *supp5_all_SP_drug_class_predictions.xlsx* (SPs) and *supp6_Assembled_sig_res_table.xlsx* (ARPs). The ARPs were a subset of the SP set.

We then sought separate data that could validate the predicted combination drug's association to the ADR. We conducted a search of co-mentions of combination drugs and the ADRs. The rule-based natural language processing tool Linguamatics was used to identify MEDLINE abstracts that contained sentences with co-mentions of drugs and ADRs in December 2018, yielding a set of PubMed IDs for relevant abstracts. This search yielded a set of PubMed IDs for abstracts that contained sentences that contained co-mentions of the combination drugs and ADR phenotypes in the same sentence. Importantly, this set did not contain drugs associated with ADRs on their labels and the co-mentions of combination drugs and ADRs were not used in the PathFX predictions. Co-mentions in PubMed could represent emerging effects or exceedingly rare relationships to ADRs that would not have required the drug to have the ADR on its label. We manually read the abstracts to confirm relevance of the abstract and infer directionality of the drug's effect on the ADR (e.g., aggravates the ADR or mitigates) (*/data/ Drug-DME_Eval_final.xlsx*). We summarized our predictions of potential drug interactions to create tables linking drugs with labeled ADRs to potential aggravating or preventative drug interacting partners *(/Code/summarize_predictions.ipynb, supp7_summary_drug_interactions.xlsx*).

Considering hypothesis for clinical evaluation

We leveraged data in TWOSIDES(*18*) as a filter for predicted drug combinations. TWOSIDES used data from the FDA Adverse Event Reporting (FAERs) system for identifying adverse outcomes that were statistically associated with combinations of drugs. We searched TWOSIDES for our predicted combinations to assess whether drug combinations were observed clinically and to get an estimate of the potential effect size of a drug combination on an adverse outcome. We used the scripts */char_data/charac_novel_combinations.py* and */Code/ charac_novel_combos_using_int.py* to investigate if TWOSIDES supported our predicted drug

combinations for ARPs and SPs. We leveraged drug synonyms from DrugBank (*contained in /data/drugbank_vocabulary.csv*) to find match drug combinations from TWOSIDES with our predicted DDIs. We later filtered drug combinations that overlapped from our predictions and TWOSIDES if the predicted ARs were synonymous.

We next aggregated predicted DDIs by network class. We used drug-drug-network protein-ADR data from */data/cotherapy/potential_co_therapies.xlsx* and the filtered drug-drug combinations from TWOSIDES to generate predictions for our expanded observational studies. These predictions are contained in /*char_data/network_mechanisms_for_ehr_ml.xlsx* and are summarized in **Table S6**.

Novel observation studies using the Optum Clinformatics Dataset

We pursued 60 novel observational studies using the Optum Clinformatics dataset using best practices for propensity matching patients to control confounding. Importantly, we used a deidentified dataset that did not require IRB approval. A full description of the dataset and methods are provided in the *Supplemental Materials and Methods.*

Supplementary Materials

Materials and Methods

Summary of PathFX analysis

Application of PathFX to understand drug-ADR relationships mediated by downstream proteins

Extended explanation of network meta-analysis

Electronic Health Record Dataset: Optum Clinformatics Data Mart 7.0

Novel observational study for assessing aspirin and albuterol combinations using CohortMethod

Novel observational studies for additional network predictions

Fig. S1. Attrition diagram after performing patient matching in sepsis study.

Fig. S2. Attrition diagram after performing patient matching in pancreatitis study.

Fig. S3. Cox coefficients measured for 21 of the 58 predicted class effects**.**

Fig. S4. Changes in the cox coefficient for 8 predicted classes with combination drugs compared to without the combination drug.

Table S1. Predicted drug-drug-ADRs with PRRs reported in TWOSIDES (*18*)

Table S2. Drugs used in sepsis DDI study.

Table S3. Covariate balance in sepsis study after matching.

Table S4. Drugs used in pancreatitis DDI study.

Table S5. Covariate balance in pancreatitis study after matching.

Table S6. Remaining 58 class predicted DDIs, network classes and drugs contained in each class.

Data file S1. ADRs extracted from drug labels (supp1_Drugs_labeled_for_AEs.txt)

Data file S2. Drug-network ADR associations discovered from PathFX (supp2_true_positives_summary.xlsx)

Data file S3. Analysis of common downstream, ADR-associated proteins (supp3_DME_merged_node_counts.xlsx)

Data file S4. Top ADR-associated network proteins used in heatmap (supp4_DME_heatmap_top_node_counts.xlsx)

Data file S5. DDI predictions from all-shortest-path (SPs) (supp5_all_SP_drug_class_predictions.xlsx)

Data file S6. DDI predictions from ADR-associated-proteins (ARPs) and HER analysis results (supp6_Assembled_sig_res_table.xlsx)

Data file S7. Summary from literature search of directionality of DDI effects. (supp7_summary_drug_interactions.xlsx)

References and Notes

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Visualization: JLW

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Writing – original draft: JLW

Writing – review & editing: JLW, ES, RR, NS, RBA, KG

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Data and materials availability: All data are available in the main text or the supplementary materials.

Figures

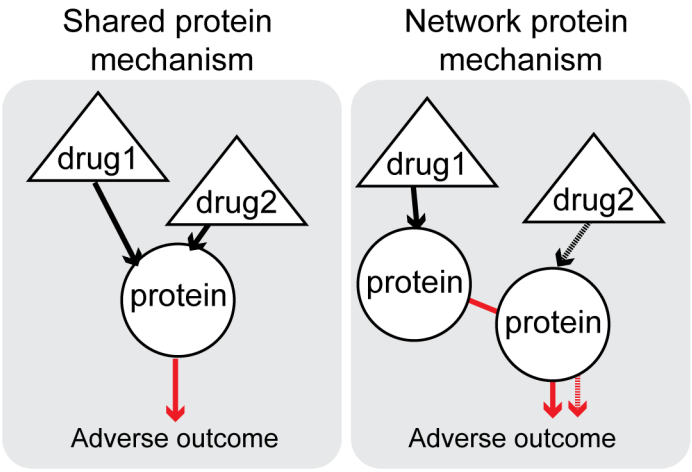

Fig. 1. **A downstream-protein paradigm for detecting drug-drug interactions is distinct from a shared-protein paradigm**. In a shared protein mechanism, two drugs share a protein target (transporter, metabolizing enzyme, etc.), and this competition causes an adverse outcome. In a network protein mechanism, protein-protein interactions connect drugs' target proteins. A DDI is caused when a second drug targets a protein downstream of the original drug. Downstream proteins can be used to reclassify drugs.

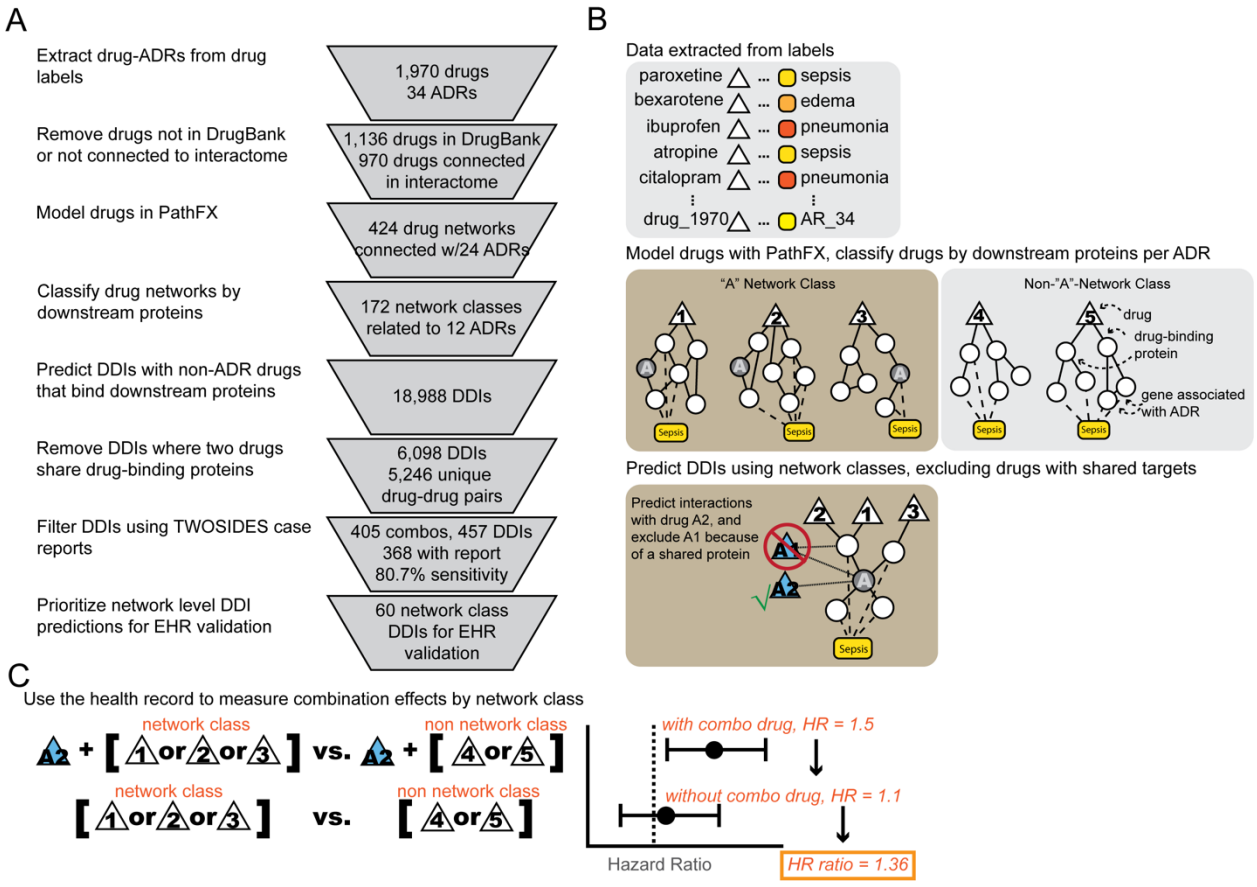

Fig. 2. Project workflow used pathway modeling and electronic health record analysis to assess DDIs predicted by network class. (**A**) Starting with drug-ADR relationships from drug labels, we used PPI modeling and network classification to predict DDIs (workflow demonstrated for ARPs). We filtered predicted DDIs using TWOSIDES for further validation. (**B**) The starting drug-ADR dataset comprised 1970 drugs associated with 34 different adverse drug reactions (ADRs). For the 970 drugs with targets connected to our interactome, we constructed networks and looked for downstream associations to ADRs. We used downstream AR-associated proteins (ARPs) to define network classes and predicted DDIs where non-ADR drugs targeted downstream proteins. The figure depicts a hypothetical "GENE A" class based on the downstream protein, "A". (**C**) We validated predicted DDIs by measuring hazard ratios

between “network” and “non-network” classes with (top row) and without (bottom row) the predicted combination drug and take the ratio of HRs to estimate the DDI effect. Hypothetical example shown to depict experimental set-up.

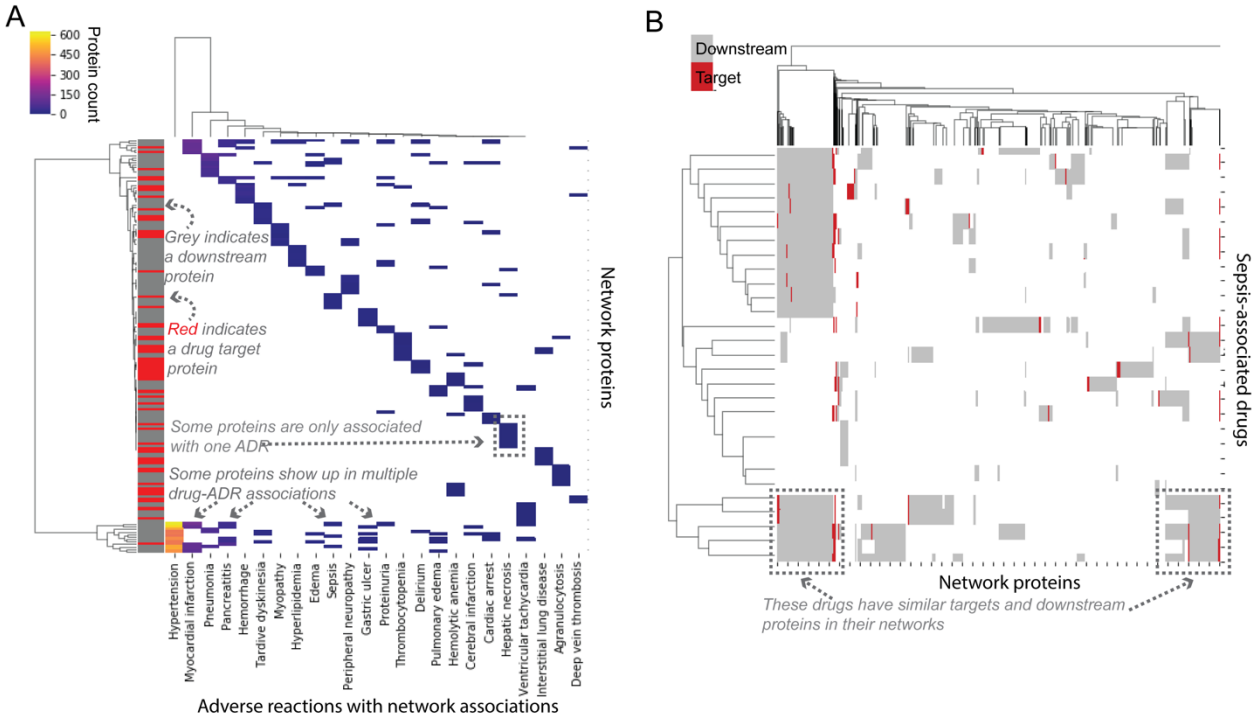

Fig. 3. Drug networks have common target and downstream proteins across and within ADRs. (**A**) The most common target (red) and downstream (grey) proteins (rows) for all drug networks associated with 24 ADRs (columns). Protein count indicates in how many drug networks the protein appears (**B**) Target (red) and downstream (grey) proteins (columns) for all sepsis-associated drugs networks (rows).

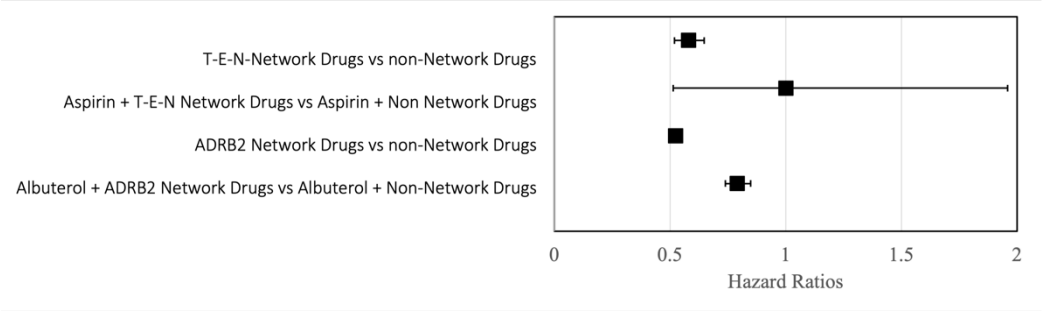

Fig. 3. Hazard ratio estimates for ADBR2 and T-E-N network classes. We estimated the between class effects with and without a combination drug for two predicted DDI effects.

	ADR-associated proteins (ARPs)	Proteins on a shortest path between drug target and ADR-gene (SPs)
Drug pairs documented in TWOSIDES / Total predicted drug pairs	405 / 5,246 (7.7%)	964/11,904 (8.1%)
Drug-drug-ADR triplet in TWOSIDES / Predicted drug-drug-ADR triplets	368 / 456 (80.7%)	786 / 1,565 (50.2%)

Table 1. Sensitivity of DDI prediction using network classification.

Combo drug	DME-associated drug	Adverse event search term	TWOSIDES condition name	PRR
aspirin	aripiprazole	pancreatitis	pancreatitis chronic	20
			pancreatitis relapsing	20
			pancreatitis acute	12.1053
			pancreatitis	7.56757
	atropine		pancreatitis	5
	pramipexole		pancreatitis	1.5
			pancreatitis acute	0.5
	ropinirole		pancreatitis chronic	2.5
			pancreatitis	1.09091
albuterol (albuterol)	atropine	sepsis	sepsis	5
			urosepsis	10

Table 2. TWOSIDES supports predicted drug combination effects. PRR = proportional reporting ratio as published in(*18*).

Comparison	HR	lower 0.95	upper 0.95
Pancreatitis			
T-E-N-Network Drugs vs non-Network Drugs	0.580	0.519	0.648
Aspirin + T-E-N-Network Drugs_vs_Aspirin + non-Network Drugs	1.001	0.514	1.959
Sepsis			
ADRB2-network Drugs vs non-Network Drugs	0.525	0.499	0.552
Albuterol + ADRB2-Network Drugs_vs_Albuterol + non-Network Drugs	0.792	0.739	0.848

Table 3. Adverse event hazard ratios are altered in drugs predicted to have combination network effects.

With Combo Drug		*Without Combo Drug*						
HR	**P-value**	**HR**	**P-value**	**HR Ratio**	**AR**	**Combo Drug**	**Downstream Protein**	**ExpNum**
1.09	4.61E-01	0.93	6.33E-04	1.17	Hypertension	Loperamide	POMC	Exp22
1.00	1.00E+00	0.88	6.65E-02	1.14	Pancreatitis	Sucralfate	EGF	Exp35
1.17	2.86E-03	1.15	9.72E-13	1.01	Hypertension	Sucralfate	EGF	Exp17
1.13	1.29E-02	1.12	1.48E-12	1.01	Edema	Aliskiren	REN	Exp2
1.00	1.00E+00	1.02	6.74E-01	0.98	Myopathy	Sucralfate	EGF	Exp29
1.08	6.94E-01	1.20	9.55E-21	0.90	Hypertension	Gentamicin	LRP2	Exp8
0.96	5.24E-01	1.12	3.48E-08	0.85	Hypertension	Misoprostol	PTGER4	Exp18

Table 4. Additional HR ratios estimated from EHR-ML analysis. Network and non-network class drugs are listed in Table S6 and are referenced by the experimental number ("ExpNum").

Materials and Methods

Summary of PathFX analysis

PathFX used drug-binding proteins as inputs to first identify a relevant protein-protein interaction network around these targets, and next used the full list of network genes/proteins to identify phenotypes associated with these genes/proteins relative to the entire interactome. The original interaction network published with PathFX contained an edge score for all protein interactions. The edge score reflected the amount and quality of evidence (e.g., the number of publications, and the type of experimental analysis used to discover the interaction) and all scores are normalized from 0-1. A higher score reflects more and greater quality of evidence that the proteins interact. This scoring was based on the MIScore(*35*) method and is fully elaborated in(*8*). PathFX used a depth-first search to discover protein-protein interactions around a drugs' target(s). The depth first search stops when a path score falls below the empirically derived threshold. This path score threshold was derived by measuring path uniqueness per network gene across a wide range of thresholds. At each threshold, and for each gene, the uniqueness of a path was measured as the difference between the path's score and the average of all path scores for a gene. Path scores greater than the average were considered unique and path scores below the average were considered not unique. The empirical threshold was selected by counting the proportion of total unique paths in the network. At high score thresholds (e.g., 0.99) very few path scores exceeded this threshold and very few paths were unique. As we measured lower values (e.g., 0.7) many more paths were discovered, but the proportion of paths above the average path score for a gene peaked and then diminished. We formulated the scoring this way because highly connected, and highly studied genes (e.g., ubiquitin or tumor protein P53 (TP53)) could be compared to their own averages. This would generate a stricter threshold for including

highly studied genes without penalizing network gene with fewer interacting partners. In the originally PathFX publication, this score was set to 0.77. Unique to our approach, this path score was not optimized for capturing drug-disease associations but was set to minimize biases such as hub bias when including protein interactions in a drug pathway. Conceptually, this path score represented an interaction distance where we had the strongest support from the corpus of underlying data to support that a downstream protein was likely relevant to a drug-induced effect.

After prioritizing downstream proteins, PathFX used a multiple hypothesis corrected Fisher's exact test to identify biological phenotypes enriched in the drug's network. This analysis created a table of phenotype associations, a p-value for the strength of those associations, and network genes associated with the phenotype. Importantly, PathFX was naive to the drug's labeled phenotypes when discovering associations and only uncovered phenotype connections based on the supporting data.

Application of PathFX to understand drug-ADR relationships mediated by downstream proteins

We used PathFX(*8*) to discover networks for all drugs in DrugBank *(* analysis contained */ PathFX/ scripts/ run_PathFX_all_drugBank.py*). We uploaded the association tables created by PathFX into the GitHub folder: */data/ all_drugbank_network_association_files/.* We next investigated whether downstream proteins connected drug targets to ADR-associated proteins. We calculated the sensitivity and specificity for each ADR. A drug-ADR association was counted as a true positive or false negative if the drug's network contained or did not contain an ADR-related phenotype from the drug's label. Further, for this ADR set, we considered all drugs in DrugBank that did not have the ADR listed on their drug label as negatives. We investigated the pathways for these drugs and considered the drugs as false positives or true negatives if the

pathway contained or did not contain a phenotype relevant to the ADR. Our analysis of PathFX results is contained in */Code/ read_drug_to_DME_data.ipynb*. We manually combined the raw data, the outputs from sensitivity and specificity analysis, and the results from the pathway analysis into */Code/supp2_true_positives_summary.xlsx*.

Extended explanation of network meta-analysis

For each ADR, we took the union of all shortest pathways between a drug target and ADR-associated genes *(/Code/merge_networks_for_DMEs.ipynb*). For instance, the drug, alemtuzumab, is associated with hemolytic anemia on its label. Alemtuzumab's pathway was associated with the phenotypes, 'autoimmune hemolytic anemia' because the pathway contained the genes, FCGR3B, CD3G, IGHV2-5, and FCGR3A, and 'hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency' because the pathway contained the genes FCGR2B, FCGR2A, FCGR2C, CD3G, and IGHV2-5 (**Data file S1**). We found all shortest pathways between alemtuzumab's drug targets and these genes. We repeated this process for all true positive drug pathways for hemolytic anemia and took the union of these shortest paths to create the merged pathway for hemolytic anemia. We repeated this process for all ADRs *(/Code/merge_networks_for_DMEs.ipynb*).

We further ranked all network nodes (drug binding and intermediate proteins) by the number of drug-ADR pathways in which they occurred. For the alemtuzumab example, the gene CD3G is counted twice because it is involved in the pathway between alemtuzumab and two ADR phenotypes ('autoimmune hemolytic anemia' and 'hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency'). The total count for CD3G was 7 because it also occurred in the pathways for the drugs, natalizumab, rituximab, and pegademase. The full list of drug-ADR pathways for CD3G includes: Natalizumab:Hemolytic anemia, nonspherocytic, due

to glucose phosphate isomerase deficiency; Rituximab:Hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency; Alemtuzumab:Autoimmune hemolytic anemia; Rituximab:Autoimmune hemolytic anemia; Natalizumab:Autoimmune hemolytic anemia; Pegademase bovine:Hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency; and Alemtuzumab:Hemolytic anemia, nonspherocytic, due to glucose phosphate isomerase deficiency (**Data file S2**, *supp3_DME_merged_node_counts.xlsx*). For each ADR, we took the top 12 genes and plotted these counts across ADRs to look for patterns across genes using the seaborn and pandas modules in python for creating heatmaps (*Code/merge_networks_for_DMEs.ipynb, Supplementary File 3, supp4_DME_heatmap_top_node_counts.xlsx, plotted in* ***Fig 3***).

For example, in tardive dyskinesia, PathFX identified 35 cases where drug pathways contained an association to the tardive dyskinesia phenotype. For all other ADRs, the number of merged pathways is contained in **Data file S1**, *supp2_true_positives_summary.xlsx*. For some ADRs, pathways analysis did not uncover an association between the drug's target(s) and the ADR (i.e., the sensitivity = 0, **Data file S1**). All the genes in the merged pathway constitute an "ADR pathway".

Electronic Health Record Dataset: Optum Clinformatics Data Mart 7.0

The Optum Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN) is a de-identified database from a large national insurance provider. The dataset contains over 88 million patients largely under the age of 65 and is frequently used for observational studies (*20*) We used a version of Optum standardized to OHDSI's Observational Medical Outcomes Partnership (OMOP) common data model version 5 (https://github.com/OHDSI/CommonDataModel). The

OMOP CDM used standard vocabulary concepts to map to international coding systems into a consolidated data resource.

Novel observational study for assessing aspirin and albuterol combinations using CohortMethod

Accessing data in the CDM format enabled us to produce anonymized code that is sufficiently standardized to enable deployment on other health record datasets in the CDM format. Anonymized code does not contain any server access information or any patient data that would jeopardize data security and facilitates reproducibility. All the anonymized SQL and R code used for the first two observational studies is contained in */Code/CohortMethod_and_SQL.* We used the following code to execute the following searches in the electronic health record:

- *count_dmes_outcomes.sql*: identified patients with ADR diagnoses from the CONDITION_OCCURENCE table. For pancreatitis and sepsis, we used the concept ids 4192640 and 132797 which mapped to the SNOMED terms, “pancreatitis”, and “sepsis”, respectively. In both cases, we included descendent concepts of either primary term.
- *count_drug_eras_singleDrug.sql*: identified patients exposed to a predicted combination drug from the DRUG_ERA table (see below).
- *count_drug_eras_from_list.sql*: identified patients exposed to network or non-network class drugs from the DRUG_ERA table (see below).
- *look_for_overlaps.sql*: identified patients that had overlapping drug exposures of classified drugs and predicted combination drugs.

- look_for_subsequent_outcomes.sql: identified patients with an adverse outcome CONDITION_OCCURENCE following exposure to a classified drug or combination of drugs. This search was largely for feasibility of estimating Hazard Ratios.

The DRUG_ERA is a derived data table used in OMOP CDM databases. The eras are derived from drug exposure data using standardized algorithms. They reflect a continuous exposure to a single compound and can be derived from multiple drug exposure data types: for pharmacy prescriptions, a drug era begins at the start of the prescription and ends at the time of the last dispensed dose, for procedure drugs they reflect the date of administration, and drug eras may be combined if the gap between subsequent exposures is less than or equal to 30 days (https://www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:drug_era).

To test these hypotheses, we used CohortMethod(*36*) tools and the Optum dataset (described previously) to conduct propensity score matching and estimate effect sizes. For transparency, the analyses for the sepsis and pancreatitis studies are contained in *count_drug_combo_exposures_sepsis.R* and *count_drug_combo_exposures_pancreatitis.R*, respectively.

For the sepsis study, we started with 29 drugs where their networks were associated with sepsis. Of these 29, 2 drug networks contained ADRB2, which is a target of the predicted combo drug, albuterol. These 2 drugs also did not share any of the albuterol drug targets. Of the remaining 27 drug networks, 18 drugs did not share drug-binding targets with albuterol and did not contain any albuterol-binding genes in their networks. All drugs are listed in **Table S2** and **Data file S5**, *supp5_all_SP_drug_class_predictions.xlsx*.

Instead of manually defining patient covariates, we used the built-in function to create a propensity score that leveraged the totality of data for a given patient to reduce confounding. For

this analysis the area under the curve (AUC) for the propensity model was 0.99. We used two methods to assess treatment vs. comparator effects: inverse propensity weighting (IPW) and matching. In IPW, we used the entire patient population and weighted patient subsets based on their propensity score to balance the representation of patient subsets in the overall estimation. In the matching approach, we used a subset of the patient population, and estimated the drug effects only on patients who are matched between the treatment and comparator groups based on their propensity scores (the propensity score is a sufficient proxy for shared confounding variables). We ultimately used matching to define patient cohorts as this was the best comparison of patients with similar clinical features. The patient attrition diagram and covariate balance table after matching are contained in **Fig S1** and **Table S3**, respectively.

We repeated this analysis procedure for the pancreatitis study. For this analysis, we started with 80 drugs where their networks were associated with pancreatitis. Of these 80, 8 drugs contained either TP53, EDRNA, or NFKBIA, which are targets of the predicted combo drug aspirin. These 8 drugs also did not bind any of aspirin's drug targets. Of the remaining 72 drug networks, 28 drugs did not share drug-binding targets with aspirin and did not contain any aspirin-binding genes in their networks. All drugs are listed below in **Table S4**. We used the same propensity score matching function and the AUC for the propensity model was 0.90. The attrition diagram after patient matching and the cohort covariate balance table are contained in **Fig S2** and **Table S5,** respectively**.** In both studies, we observed patients for a 30-day risk window after the second, combination drug era was initiated.

Novel observational studies for additional network predictions

We pursued clinical validation of an additional 58 predicted DDIs from the ARP predictions because these had a greater sensitivity in the TWOSIDES dataset. To prioritize these

combinations, we started with the 457 DDIs that were supported by a case report in TWOSIDES. We grouped these DDIs by network class (using downstream network proteins discovered by PathFX) and converted DrugBank identifiers to Anatomical Therapeutic Chemical (ATC) codes. We mapped DrugBank identifiers to all ATC codes but excluded combination products from the analysis. All network, non-network classes and drugs contained in these classes are included in **Table S6** and **Data file S6**, *supp6_Assembled_sig_res_table.xlsx***.** To conduct this analysis, we used a custom, more scalable pipeline using low dimension CLMBR patient representations (*28*). These representations are a consolidated record of patient encounters with the health system – visits, diagnoses, drug exposures – and have been shown to outperform other patient representations on multiple clinical prediction tasks. Having precomputed patient representations allowed us to efficiently conduct multiple DDI studies because these representations could be reused across analyses.

We used these representations to conduct large-scale propensity matching of patients for each predicted DDI. Propensity score matching reduces confounding by limiting the analysis to similar patients. For all DDI studies, we conducted a baseline measurement of the ADR risk between the network and non-network class and a second measurement of the ADR risk between these classes when the combination drug was also used. To be included in a DDI study, each patient needs to have been exposed to drugs in either the network or non-network class and then be exposed to the predicted combination drug or a comparator. After identifying a matched cohort, we estimated hazard ratios using Cox regression model for the ADR outcome. This procedure is the same as used in CohortMethod (https://github.com/OHDSI/CohortMethod). For all measurements, the p-value represents the likelihood of the estimated hazard ratio relative to the null hypothesis that the hazard ratio is 1.

drug1	drug2	ADR (PathFX)	TWOSIDES condition name	PRR	PRR error	mean reporting freq
aspirin	nabumetone	gastric ulcer	gastric ulcer	5.556	0.556	0.010
dronabinol	gabapentin	pancreatitis	pancreatitis	4.167	0.526	0.030
aspirin	ibuprofen	gastric ulcer	gastric ulcer	10.460	0.149	0.013
aspirin	ibuprofen	gastric ulcer	gastric ulcer haemorrhage	8.421	0.240	0.005
aspirin	ibuprofen	gastric ulcer	gastric ulcer perforation	18.000	0.394	0.003
dabigatran etexilate	clonidine	myocardial infarction	acute myocardial infarction	6.667	0.910	0.010
dabigatran etexilate	clonidine	myocardial infarction	myocardial infarction	0.690	0.512	0.019
dabigatran etexilate	cyclobenzaprine	myocardial infarction	acute myocardial infarction	10.000	0.810	0.028
dabigatran etexilate	cyclobenzaprine	myocardial infarction	myocardial infarction	1.200	0.602	0.028
dabigatran etexilate	diphenhydramine	myocardial infarction	myocardial infarction	0.455	1.017	0.011
epinephrine	metoprolol	gastric ulcer	gastric ulcer	3.333	1.153	0.003
epinephrine	metoprolol	gastric ulcer	gastric ulcer haemorrhage	10.000	1.413	0.003
dabigatran etexilate	pramipexole	myocardial infarction	myocardial infarction	2.222	0.541	0.048
candesartan	dabigatran etexilate	myocardial infarction	acute myocardial infarction	5.000	0.497	0.016
candesartan	dabigatran etexilate	myocardial infarction	myocardial infarction	1.667	0.295	0.034
dabigatran etexilate	losartan	myocardial infarction	acute myocardial infarction	4.444	0.423	0.010
dabigatran etexilate	losartan	myocardial infarction	myocardial infarction	0.606	0.323	0.013
dabigatran etexilate	donepezil	myocardial infarction	acute myocardial infarction	3.333	1.152	0.005
dabigatran etexilate	donepezil	myocardial infarction	myocardial infarction	0.952	0.518	0.021
dabigatran etexilate	hydroxyzine	myocardial infarction	myocardial infarction	1.111	1.045	0.017
dabigatran etexilate	telmisartan	myocardial infarction	acute myocardial infarction	7.143	0.582	0.021
dabigatran etexilate	telmisartan	myocardial infarction	myocardial infarction	0.426	0.719	0.008
dabigatran etexilate	doxazosin	myocardial infarction	acute myocardial infarction	6.667	0.910	0.010

dabigatran etexilate	doxazosin	myocardial infarction	myocardial infarction	0.426	0.718	0.010
aspirin	thalidomide	gastric ulcer	gastric ulcer	3.846	0.525	0.005
dabigatran etexilate	imipramine	myocardial infarction	myocardial infarction	10.000	1.375	0.100
olanzapine	dabigatran etexilate	myocardial infarction	myocardial infarction	10.000	1.397	0.043
memantine	promethazine	delirium	delirium	3.333	1.148	0.014
dabigatran etexilate	escitalopram	myocardial infarction	acute myocardial infarction	3.333	0.814	0.008
dabigatran etexilate	escitalopram	myocardial infarction	myocardial infarction	0.690	0.512	0.017
dronabinol	mirtazapine	pancreatitis	pancreatitis	10.000	0.806	0.047
dronabinol	mirtazapine	pancreatitis	pancreatitis acute	5.000	1.218	0.016
dabigatran etexilate	trazodone	myocardial infarction	acute myocardial infarction	2.500	1.115	0.006
dabigatran etexilate	trazodone	myocardial infarction	myocardial infarction	0.556	0.722	0.013
dabigatran etexilate	disopyramide	myocardial infarction	myocardial infarction	2.000	1.080	0.030
dabigatran etexilate	mirtazapine	myocardial infarction	acute myocardial infarction	8.000	0.665	0.028
dabigatran etexilate	mirtazapine	myocardial infarction	myocardial infarction	2.000	0.439	0.042
valsartan	dabigatran etexilate	myocardial infarction	acute myocardial infarction	7.692	0.419	0.013
valsartan	dabigatran etexilate	myocardial infarction	myocardial infarction	0.526	0.361	0.011
dabigatran etexilate	heparin	myocardial infarction	acute myocardial infarction	15.000	0.638	0.052
dabigatran etexilate	tramadol	myocardial infarction	acute myocardial infarction	6.667	0.454	0.016
dabigatran etexilate	tramadol	myocardial infarction	myocardial infarction	0.825	0.365	0.016
dabigatran etexilate	amitriptyline	myocardial infarction	acute myocardial infarction	5.000	0.861	0.017
dabigatran etexilate	amitriptyline	myocardial infarction	myocardial infarction	0.645	0.723	0.017
quetiapine	dronabinol	pancreatitis	pancreatitis	5.000	0.852	0.043
dabigatran etexilate	citalopram	myocardial infarction	acute myocardial infarction	4.444	0.598	0.012
dabigatran etexilate	citalopram	myocardial infarction	myocardial infarction	1.552	0.354	0.027
dabigatran etexilate	ropinirole	myocardial infarction	myocardial infarction	0.417	1.015	0.010
dabigatran etexilate	ropinirole	sepsis	sepsis	1.667	0.757	0.020
dronabinol	diphenoxylate	pancreatitis	pancreatitis	35.000	0.788	0.140

dabigatran etexilate	metoclopramide	myocardial infarction	acute myocardial infarction	6.667	0.907	0.019
dabigatran etexilate	metoclopramide	myocardial infarction	myocardial infarction	0.667	0.723	0.019
epinephrine	lidocaine	myopathy	stress cardiomyopathy	10.000	0.816	0.004
epinephrine	lidocaine	myopathy	cardiomyopathy	7.778	0.503	0.009
epinephrine	lidocaine	myopathy	congestive cardiomyopathy	2.500	1.117	0.001
epinephrine	lidocaine	myopathy	ischaemic cardiomyopathy	10.000	1.414	0.001
dabigatran etexilate	olmesartan	myocardial infarction	acute myocardial infarction	0.833	1.039	0.003
dabigatran etexilate	olmesartan	myocardial infarction	myocardial infarction	0.375	0.585	0.008
erlotinib	sorafenib	neuropathy	optic ischaemic neuropathy	10.000	1.413	0.004
erlotinib	sorafenib	neuropathy	polyneuropathy	2.500	1.116	0.004
aspirin	caffeine	gastric ulcer	gastric ulcer	13.684	0.300	0.025
aspirin	caffeine	gastric ulcer	gastric ulcer haemorrhage	25.000	0.836	0.005
dabigatran etexilate	nortriptyline	myocardial infarction	myocardial infarction	10.000	1.398	0.042
dabigatran etexilate	irbesartan	myocardial infarction	acute myocardial infarction	8.333	0.602	0.017
dabigatran etexilate	irbesartan	myocardial infarction	myocardial infarction	1.500	0.352	0.031
aspirin	meloxicam	gastric ulcer	gastric ulcer	8.205	0.238	0.013
aspirin	meloxicam	gastric ulcer	gastric ulcer haemorrhage	11.667	0.393	0.006
aspirin	meloxicam	gastric ulcer	gastric ulcer perforation	20.000	1.225	0.001
sulfasalazine	aspirin	sepsis	neutropenic sepsis	70.000	1.068	0.010
sulfasalazine	aspirin	sepsis	staphylococcal sepsis	2.500	1.117	0.001
sulfasalazine	aspirin	sepsis	streptococcal sepsis	10.000	1.414	0.001
sulfasalazine	aspirin	sepsis	bacterial sepsis	10.000	1.414	0.001
sulfasalazine	aspirin	sepsis	sepsis	3.600	0.272	0.025

Table S1. Predicted drug-drug-ADRs with PRRs reported in TWOSIDES (*18*).

Drugs with network association to sepsis and their networks contain ADRB2, "ADBR2-net"	**Drugs with network association to sepsis and their networks do NOT contain ADRB2, "non-ADBR2-net"**

atropine, paroxetine	abatacept, canakinumab, certolizumab pegol, diphenoxylate, eculizumab, etanercept, gabapentin, glycine, golimumab, goserelin, infliximab, menthol, pramipexole, sulfasalazine, sumatriptan, ketoprofen, niacin, memantine

Table S2. Drugs used in sepsis DDI study.

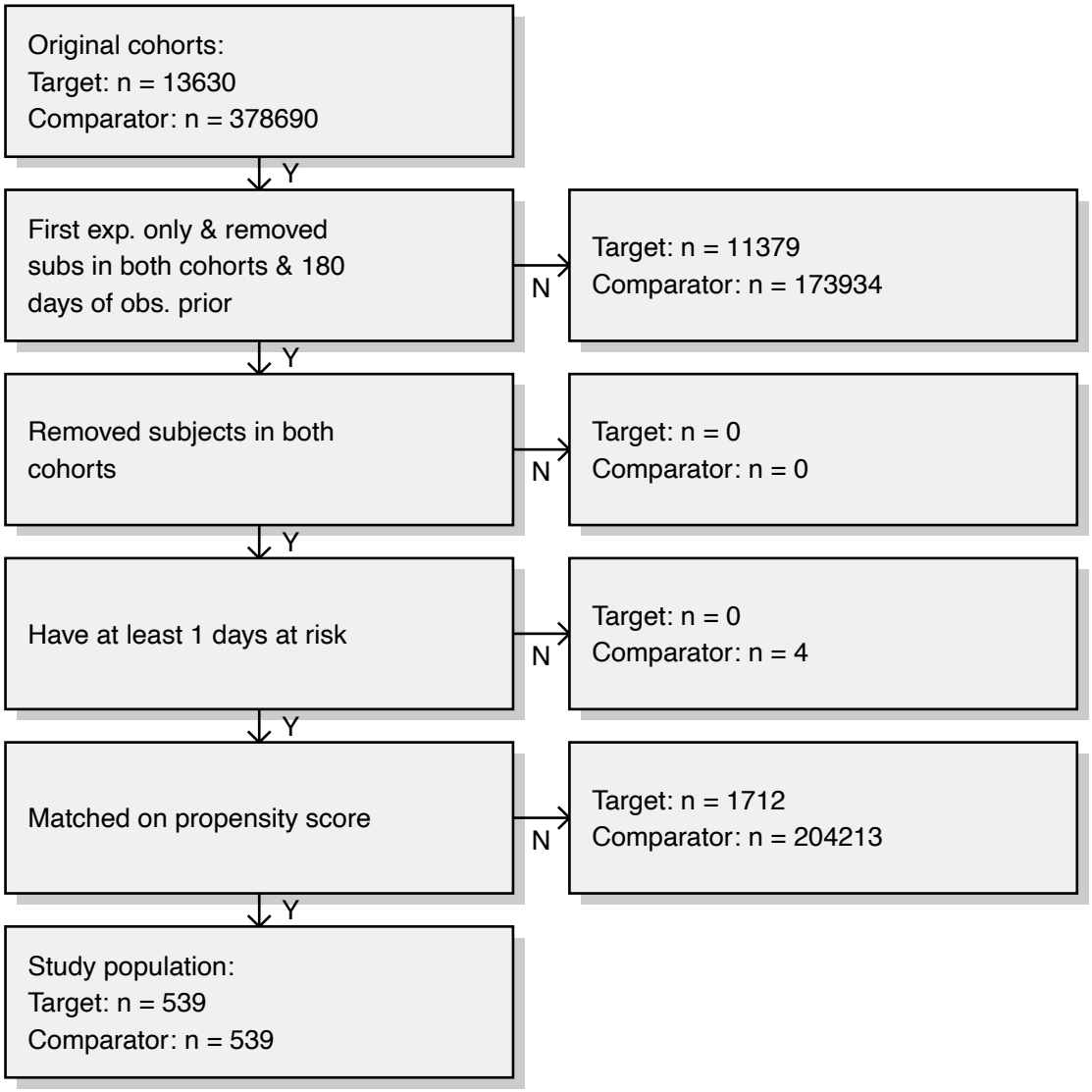

Fig. S1. Attrition diagram after performing patient matching in sepsis study.

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
0 - 4	4.6	0	0.31	2.8	3.3	-0.03
5 - 9	6.3	0.1	0.36	4.3	5.8	-0.07
10 - 14	1.9	0.4	0.14	2.4	1.9	0.04
15 - 19	1.7	0.9	0.07	1.3	1.1	0.02
20 - 24	1.6	1	0.06	0.2	0.9	-0.1
25 - 29	1.8	1.3	0.04	1.3	0.7	0.06
30 - 34	3.3	2.3	0.06	2.2	1.9	0.03
35 - 39	3.4	3.7	-0.02	2	1.7	0.03
40 - 44	5.7	5.4	0.01	3.7	2.8	0.05
45 - 49	7.6	7.7	0	3.9	4.5	-0.03
50 - 54	9.4	10.1	-0.03	5.2	5.2	0
55 - 59	11.3	11.9	-0.02	5.8	6.9	-0.05
60 - 64	9.2	11.3	-0.07	8.2	9.6	-0.05
65 - 69	7.6	12.5	-0.16	8.3	7.2	0.04
70 - 74	5.5	11	-0.2	7.2	10.9	-0.13
75 - 79	8	9.1	-0.04	13.2	10.6	0.08
80 - 84	6.2	7.3	-0.05	14.1	13.2	0.03
85 - 89	5	4	0.05	13.9	11.9	0.06
Gender: female	65.7	69.5	-0.08	59.4	59.7	-0.01
Medical history: General						
Acute respiratory disease	47.4	42.4	0.1	40.3	44.2	-0.08
Attention deficit hyperactivity disorder	1.7	1.8	-0.01	1.7	2	-0.03
Chronic liver disease	2.5	3.5	-0.06	2.4	2.2	0.01
Chronic obstructive lung disease	15.9	26.4	-0.26	23.2	25.8	-0.06
Crohn's disease	1.6	0.9	0.06	0.7	1.9	-0.1
Dementia	7.5	4.4	0.13	20.6	21.5	-0.02
Depressive disorder	16.9	26.7	-0.24	21.9	22.8	-0.02
Diabetes mellitus	16.2	32.9	-0.4	27.5	27.3	0
Gastroesophageal reflux disease	24.7	26.7	-0.05	25.2	29.1	-0.09
Gastrointestinal hemorrhage	6	5.2	0.04	7.6	8	-0.01
Human immunodeficiency virus infection	0.2	0.4	-0.04		0.2	

Hyperlipidemia	33.7	53.4	-0.4	41	41	0
Hypertensive disorder	41	61.8	-0.43	56.4	57	-0.01
Lesion of liver	0.9	1.6	-0.06	1.5	2.6	-0.08
Obesity	7.2	17	-0.3	7.8	9.8	-0.07
Osteoarthritis	21.5	45.8	-0.53	31.2	29.1	0.04
Pneumonia	11	10.6	0.01	20.2	22.8	-0.06
Psoriasis	0.6	2.4	-0.15	0.9	1.5	-0.05
Renal impairment	8.4	15.6	-0.22	21	20.2	0.02
Rheumatoid arthritis	2	6.7	-0.24	3.3	4.1	-0.04
Schizophrenia	0.4	0.8	-0.04	1.1	1.7	-0.05
Ulcerative colitis	1.4	0.9	0.04	1.3	0.4	0.1
Urinary tract infectious disease	18.9	18.6	0.01	28	29.5	-0.03
Viral hepatitis C	0.7	1.5	-0.07	0.6	0.6	0
Visual system disorder	45	37.7	0.15	63.5	70.9	-0.16
Medical history: Cardiovascular disease						
Atrial fibrillation	5.7	8.9	-0.12	12.1	14.3	-0.07
Cerebrovascular disease	5.4	7.7	-0.1	12.8	13.9	-0.03
Coronary arteriosclerosis	11.6	18.5	-0.2	22.3	22.3	0
Heart disease	27.9	38.2	-0.22	43.6	47.3	-0.07
Heart failure	8.4	13.6	-0.17	17.8	21	-0.08
Ischemic heart disease	8.2	11.7	-0.12	12.8	12.6	0.01
Peripheral vascular disease	16	25.2	-0.23	33.2	31.4	0.04
Pulmonary embolism	0.9	1.8	-0.07	1.7	2.4	-0.05
Venous thrombosis	3.1	4.6	-0.08	6.3	8.3	-0.08
Medical history: Neoplasms						
Hematologic neoplasm	1.4	2.2	-0.06	3.2	3.7	-0.03
Malignant lymphoma	0.4	0.9	-0.05	1.1	0.6	0.06
Malignant neoplasm of anorectum	0.1	0.3	-0.05			
Malignant neoplastic disease	9.6	12.7	-0.1	16.3	14.1	0.06
Malignant tumor of breast	1.8	2.6	-0.05	2	1.5	0.04
Malignant tumor of colon	0.2	0.7	-0.07	0.6	0.6	0
Malignant tumor of lung	0.9	1.4	-0.05	2.8	1.3	0.11
Malignant tumor of urinary bladder	0.5	0.5	0.01	0.7	0.9	-0.02
Primary malignant neoplasm of prostate	1.1	1.1	0	1.5	2.4	-0.07
Medication use						
Agents acting on the renin-angiotensin system	28.7	44	-0.32	35.4	34.5	0.02

Antibacterials for systemic use	79	71.2	0.18	75	80.1	-0.12
Antidepressants	39.1	54	-0.3	44.2	42.5	0.03
Antiepileptics	58.9	22.5	0.8	21	25.2	-0.1
Antiinflammatory and antirheumatic products	26.4	40.4	-0.3	24.5	25	-0.01
Antineoplastic agents	2.2	4.7	-0.14	3.5	5.4	-0.09
Antipsoriatics	0.7	1.2	-0.05	1.5	1.7	-0.01
Antithrombotic agents	11.2	18.4	-0.2	16.5	18.9	-0.06
Beta blocking agents	26.5	34.4	-0.17	38.6	37.7	0.02
Calcium channel blockers	17.1	24.2	-0.18	22.8	21.2	0.04
Diuretics	29.1	41.6	-0.26	36.5	35.6	0.02
Drugs for acid related disorders	39.9	43	-0.06	39.5	45.1	-0.11
Drugs for obstructive airway diseases	59.8	54.8	0.1	60.9	60.7	0
Drugs used in diabetes	12.5	27.5	-0.38	20.6	20.4	0
Immunosuppressants	3.6	6.7	-0.14	4.3	7.1	-0.12
Lipid modifying agents	29.1	46.2	-0.36	34.9	35.8	-0.02
Opioids	31.7	44.8	-0.27	36	35.1	0.02
Psycholeptics	73.5	43	0.65	46.8	50.5	-0.07
Psychostimulants, agents used for adhd and nootropics	7.7	6.5	0.05	5	4.8	0.01

Table S3. Covariate balance in sepsis study after matching.

Drugs with network association to pancreatitis and their networks contain TP53, EDRNA, or NFKBIA, "T-E-N-net"	**Drugs with network association to pancreatitis and their networks do NOT contain aspirin-binding proteins, "non-T-E-N-net"**
acamprosate, aripiprazole, atropine, droxidopa, pergolide, pilocarpine, pramipexole, ropinirole	aliskiren, amoxapine, benazepril, blinatumomab, busulfan, danazol, diphenoxylate, enalaprilat, fosinopril, gabapentin, hydroflumethiazide, isopropyl alcohol, lanreotide, levodopa, menthol, octreotide, olmesartan, oxaliplatin, pasireotide, pentazocine, prilocaine, quinapril, Ramipril, riluzole, tenecteplase, tramadol, trandolapril, vandetanib

Table S4. Drugs used in pancreatitis DDI study.

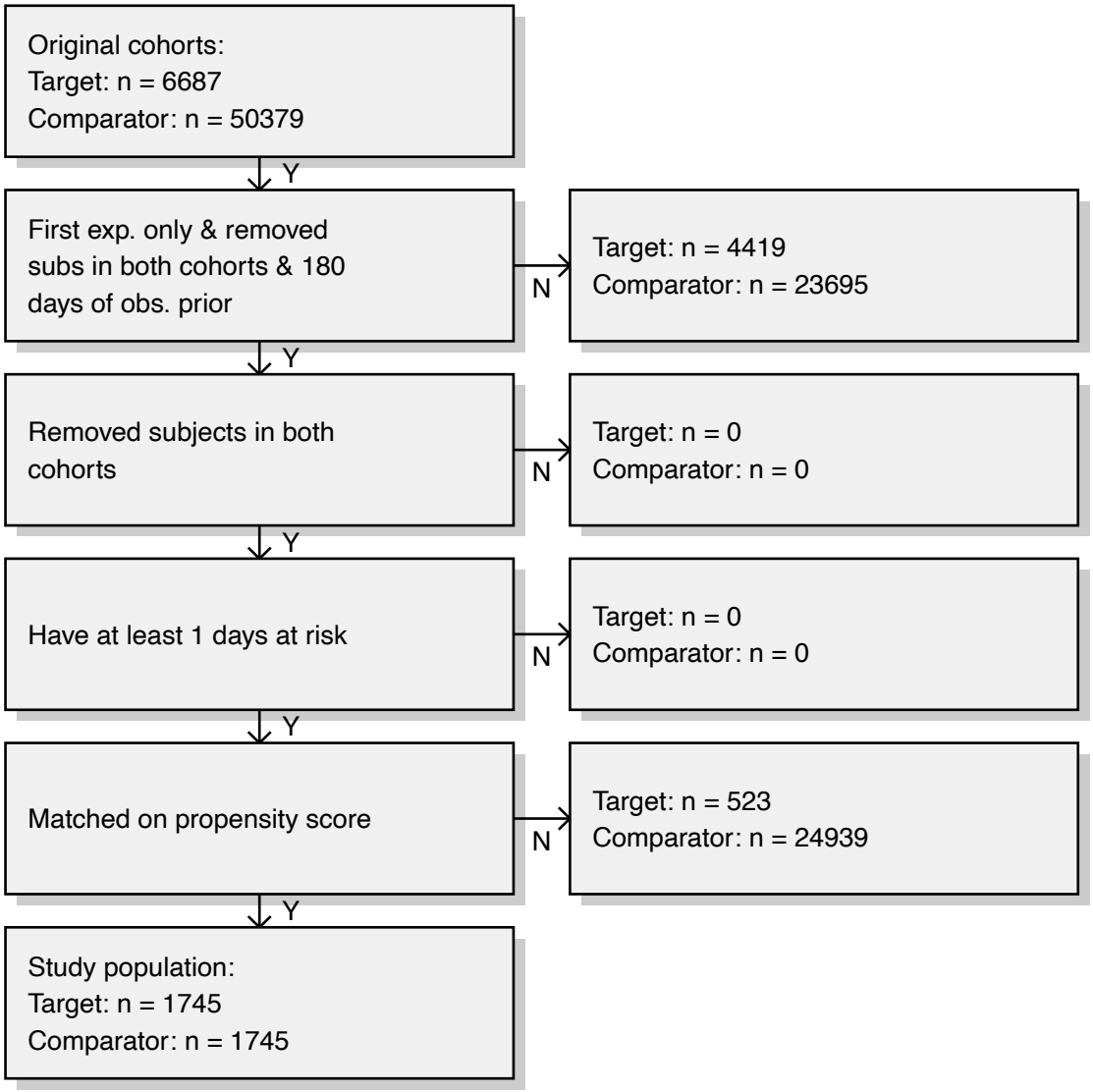

Fig. S2. Attrition diagram after performing patient matching in pancreatitis study.

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
0 - 4		0				
5 - 9		0				
10 - 14	0.3	0	0.06	0.2	0.1	0.03
15 - 19	0.9	0.2	0.1	1	0.6	0.05

20 - 24	1.1	0.6	0.06	1.2	1	0.02
25 - 29	1.5	1.2	0.03	1.5	1.8	-0.02
30 - 34	3.2	2.2	0.06	2.8	3.8	-0.05
35 - 39	5	3.4	0.08	4.8	5.6	-0.04
40 - 44	7.3	5.7	0.06	7.2	7	0.01
45 - 49	11.7	10	0.06	10.6	11.8	-0.04
50 - 54	12.7	13.6	-0.03	12.8	12.4	0.01
55 - 59	15.9	17.3	-0.04	16	17.1	-0.03
60 - 64	15.3	15.2	0	15.3	13.3	0.06
65 - 69	7.8	9.4	-0.06	7.6	8.2	-0.02
70 - 74	5.1	7.4	-0.1	5.6	5.5	0
75 - 79	6.4	7.6	-0.04	7.3	5.4	0.08
80 - 84	4.3	4.8	-0.02	4.4	4.5	-0.01
85 - 89	1.5	1.5	0	1.6	1.7	-0.01
Gender: female	72.1	59	0.28	69.9	71.3	-0.03
Medical history: General						
Acute respiratory disease	38.2	31	0.15	36.7	38.3	-0.03
Attention deficit hyperactivity disorder	4.3	1.3	0.19	4	4.2	-0.01
Chronic liver disease	3.3	2.8	0.03	3.5	3.3	0.01
Chronic obstructive lung disease	11	9.1	0.06	11.6	11.3	0.01
Crohn's disease	0.9	0.5	0.05	0.7	0.9	-0.02
Dementia	2.7	2.2	0.03	3	3.2	-0.01
Depressive disorder	39.6	17.5	0.51	38.7	46.4	-0.16
Diabetes mellitus	18.7	30.3	-0.27	20.8	19.3	0.04
Gastroesophageal reflux disease	22.2	18.5	0.09	20.6	23.5	-0.07
Gastrointestinal hemorrhage	4.7	3.9	0.04	3.9	5.1	-0.06
Human immunodeficiency virus infection	0.4	0.4	0	0.5	0.6	-0.02
Hyperlipidemia	48.9	53.1	-0.08	49.4	47.8	0.03
Hypertensive disorder	50.7	65.4	-0.3	52.7	50.5	0.04
Lesion of liver	1.1	1.1	0	1.1	1.7	-0.04
Obesity	13	13.3	-0.01	13.4	13.5	-0.01
Osteoarthritis	33.2	36.8	-0.08	33.9	35.1	-0.02
Pneumonia	5.2	5.1	0	5.8	5.7	0.01
Psoriasis	1.8	1.3	0.04	1.9	1.3	0.05
Renal impairment	8.6	10.1	-0.05	9.3	9.8	-0.02
Rheumatoid arthritis	2.8	3	-0.01	2.7	3.6	-0.05

Schizophrenia	1.3	0.3	0.11	1.4	1.6	-0.01
Ulcerative colitis	0.6	0.5	0.02	0.6	0.7	-0.01
Urinary tract infectious disease	16.7	13.4	0.09	16.8	16.5	0.01
Viral hepatitis C	1.2	1.2	0	1.2	1.3	-0.01
Visual system disorder	34.5	30.9	0.08	35.6	36.3	-0.02
Medical history: Cardiovascular disease						
Atrial fibrillation	3.7	4.2	-0.03	3.9	4.1	-0.01
Cerebrovascular disease	10.3	10.9	-0.02	10.8	11.9	-0.03
Coronary arteriosclerosis	12.7	15.9	-0.09	13	13	0
Heart disease	29.6	32.9	-0.07	29.9	29.3	0.01
Heart failure	5.7	7.7	-0.08	5.8	7.6	-0.07
Ischemic heart disease	8.2	10.6	-0.08	8.5	8.7	0
Peripheral vascular disease	16.9	19.2	-0.06	18.1	16.6	0.04
Pulmonary embolism	0.6	0.7	-0.02	0.7	0.9	-0.01
Venous thrombosis	2.9	2.8	0.01	2.8	2.8	0
Medical history: Neoplasms						
Hematologic neoplasm	1.3	1.4	-0.01	1.4	1.7	-0.02
Malignant lymphoma	0.2	0.5	-0.05	0.3	0.4	-0.02
Malignant neoplasm of anorectum	0.1	0.2	-0.03	0.1	0.2	-0.03
Malignant neoplastic disease	9.7	9	0.02	9.7	9.7	0
Malignant tumor of breast	2	1.6	0.03	1.9	2.3	-0.03
Malignant tumor of colon	0.6	0.5	0.01	0.5	0.6	-0.01
Malignant tumor of lung	0.4	0.4	-0.01	0.3	0.6	-0.03
Malignant tumor of urinary bladder	0.4	0.3	0.01	0.4	0.3	0.02
Primary malignant neoplasm of prostate	1.2	1.1	0.01	1.3	0.6	0.07
Medication use						
Agents acting on the renin-angiotensin system	29.9	32.2	-0.05	30.9	29	0.04
Antibacterials for systemic use	69.9	59.4	0.22	68.3	70.3	-0.04
Antidepressants	68.3	39.3	0.61	66.6	73.9	-0.16
Antiepileptics	41.4	16.7	0.56	35.2	41.2	-0.12
Antiinflammatory and antirheumatic products	38	39.7	-0.03	38.2	40.1	-0.04
Antineoplastic agents	2.3	2.4	-0.01	2.3	3.3	-0.06
Antipsoriatics	0.9	0.9	0.01	0.9	1.1	-0.03
Antithrombotic agents	37.3	32.5	0.1	36.2	38.3	-0.04

Beta blocking agents	32.5	33.8	-0.03	33.4	32.3	0.02
Calcium channel blockers	17.2	29.5	-0.29	18.7	17.2	0.04
Diuretics	30.4	39.7	-0.2	32	29.9	0.05
Drugs for acid related disorders	36.6	30.4	0.13	35	38.3	-0.07
Drugs for obstructive airway diseases	33.2	26.7	0.14	32.1	34.2	-0.04
Drugs used in diabetes	14.9	26.5	-0.29	16.7	14.9	0.05
Immunosuppressants	4.4	3.7	0.04	4.3	5.4	-0.05
Lipid modifying agents	39.2	46	-0.14	39.9	39.7	0
Opioids	32.4	26.6	0.13	31.9	32.7	-0.02
Psycholeptics	61.5	36.6	0.51	57.6	63.4	-0.12
Psychostimulants, agents used for adhd and nootropics	33.6	18.1	0.36	30.4	33.8	-0.07

Table S5. Covariate balance in pancreatitis study after matching.

Exp Num	ADR	Combo Drug	Downstream Protein	Network Drugs	Non Network Drugs
exp1	Delirium	Calcium	CALM3	Memantine	Quetiapine,Aripiprazole,Buspirone,Nefazodone,Imipramine,Codeine,Dextromethorphan,Ziprasidone,Oxycodone,Dronabinol,Fentanyl,Nortriptyline,Oxcarbazepine
exp2	Edema	Aliskiren	REN	Quinapril,Perindopril,Lisinopril,Ramipril,Benazepril,Fosinopril	Quetiapine,Pramipexole,Olmesartan,Telmisartan,Insulin Detemir,Modafinil,Repaglinide,Eprosartan,Carvedilol,Pentoxifylline,Levocetirizine,Ropinirole,Irbesartan
exp3	Edema	Bosentan	EDNRA	Olmesartan,Telmisartan	Quinapril,Perindopril,Lisinopril,Ramipril,Fosinopril,Pramipexole,Infliximab,Ampicillin,Benazepril,Quetiapine,Insulin Detemir,Dicyclomine,Carvedilol,Pentoxifylline,Treprostinil,Erythromycin,Levocetirizine,Ropinirole,Epoprostenol
exp4	Hypertension	Plerixafor	CXCR4	Hydromorphone,Diphenhydramine	Allopurinol,Dexamethasone,Ondansetron,Metoprolol,Cetirizine,Oxycodone,Sargramostim,Sorafenib,Morphine,Gabapentin
exp5	Hypertension	Macitentan	EDNRB	Cetirizine	Losartan,Trazodone,Iloprost,Allopurinol,Metoprolol,Tiotropium,Tramadol,Formoterol,Salmeterol,Hydrocodone,Insulin Glargine

exp6	Hypertension	Bosentan	EDNRB	Dicyclomine,Pramipexole,Cetirizine,Metoclopramide	Iloprost,Dexamethasone,Oxybutynin,Solifenacin,Metoprolol,Ibuprofen,Dopamine,Risperidone,Oxycodone,Indomethacin,Ropinirole,Zidovudine,Azathioprine,Insulin Glargine,Gabapentin,Diphenhydramine,Hydromorphone,Niacin,Ketoprofen,Insulin Detemir,Amitriptyline,Imatinib,Estradiol,Ticagrelor,Salmeterol,Mometasone,Fentanyl,Ranitidine,Losartan,Quetiapine,Escitalopram,Epinephrine,Allopurinol,Buprenorphine,Diphenoxylate,Propranolol,Azelastine,Dextromethorphan,Pilocarpine,Darbepoetin alfa,Clonidine,Famotidine,Tizanidine,Paroxetine,Haloperidol,Hydrocodone,Triamcinolone,Doxepin,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Tramadol,Febuxostat,Cyclobenzaprine,Promethazine,Formoterol,Levonorgestrel,Citalopram,Sotalol,Cinacalcet,Morphine
exp7	Hypertension	Ambrisentan	EDNRB	Pramipexole,Metoclopramide,Cetirizine,Pseudoephedrine,Midodrine	Aripiprazole,Testosterone,Iloprost,Buspirone,Oxybutynin,Solifenacin,Metoprolol,Cyproheptadine,Donepezil,Ziprasidone,Ibuprofen,Risperidone,Oxycodone,Repaglinide,Indomethacin,Sumatriptan,Dicyclomine,Ropinirole,Oxcarbazepine,Azathioprine,Insulin Glargine,Gabapentin,Diphenhydramine,Hydromorphone,Niacin,Ketoprofen,Terazosin,Insulin Detemir,Prasugrel,Amitriptyline,Imatinib,Estradiol,Timolol,Salmeterol,Mometasone,Fentanyl,Modafinil,Ketamine,Ranitidine,Nortriptyline,Olanzapine,Losartan,Quetiapine,Memantine,Escitalopram,Allopurinol,Cevimeline,Levodopa,Buprenorphine,Diphenoxylate,Propranolol,Azelastine,Teriparatide,Pilocarpine,Darbepoetin alfa,Clonidine,Famotidine,Dronabinol,Tizanidine,Paroxetine,Hydrocodone,Ketorolac,Nabumetone,Triamcinolone,Doxepin,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Tramadol,Febuxostat,Oxymetazoline,Promethazine,Formoterol,Cyclobenzaprine,Citalopram,Sotalol,Cinacalcet,Morphine,Darifenacin,Travoprost

exp8	Hypertension	Gentamicin	LRP2	Epinephrine,Diphenhydramine,Terbutaline,Tiotropium,Amitriptyline,Promethazine,Scopolamine,Salmeterol,Rocuronium,Paroxetine	Dexamethasone,Oxybutynin,Metoprolol,Etomidate,Donepezil,Ibuprofen,Dopamine,Repaglinide,Risperidone,Oxycodone,Indomethacin,Ropinirole,Zidovudine,Tinzaparin,Azathioprine,Insulin Glargine,Gabapentin,Dalteparin,Hydromorphone,Ketoprofen,Imatinib,Phenylephrine,Estradiol,Timolol,Octreotide,Mometasone,Fentanyl,Ranitidine,Ketamine,Ticagrelor,Olanzapine,Losartan,Quetiapine,Nalbuphine,Escitalopram,Atropine,Allopurinol,Ephedrine,Sufentanil,Metoclopramide,Levodopa,Buprenorphine,Propranolol,Darbepoetin alfa,Succinylcholine,Remifentanil,Clonidine,Famotidine,Cyclopentolate,Carboplatin,Droperidol,Sunitinib,Haloperidol,Ketorolac,Hydrocodone,Drospirenone,Triamcinolone,Trazodone,Naloxone,Mirtazapine,Ondansetron,Adenosine,Codeine,Tramadol,Cetirizine,Cyclobenzaprine,Oxaliplatin,Citalopram,Sotalol,Cinacalcet,Morphine
exp9	Hypertension	Macitentan	EDNRA	Cetirizine	Losartan,Iloprost,Allopurinol,Metoprolol,Tiotropium,Tramadol,Formoterol,Salmeterol,Hydrocodone,Insulin Glargine
exp10	Hypertension	Bosentan	EDNRA	Dicyclomine,Pramipexole,Cetirizine,Metoclopramide	Iloprost,Dexamethasone,Oxybutynin,Metoprolol,Ibuprofen,Dopamine,Risperidone,Oxycodone,Indomethacin,Ropinirole,Zidovudine,Azathioprine,Insulin Glargine,Gabapentin,Diphenhydramine,Hydromorphone,Niacin,Ketoprofen,Insulin Detemir,Amitriptyline,Ticagrelor,Estradiol,Imatinib,Salmeterol,Mometasone,Fentanyl,Ranitidine,Losartan,Quetiapine,Escitalopram,Epinephrine,Allopurinol,Buprenorphine,Diphenoxylate,Propranolol,Dextromethorphan,Darbepoetin alfa,Famotidine,Tizanidine,Haloperidol,Hydrocodone,Triamcinolone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Tramadol,Febuxostat,Cyclobenzaprine,Formoterol,Levonorgestrel,Sotalol,Cinacalcet,Morphine

exp11	Hypertension	Ambrisentan	EDNRA	Pramipexole,Metoclopramide,Cetirizine,Pseudoephedrine,Midodrine	Aripiprazole,Testosterone,Iloprost,Buspirone,Oxybutynin,Metoprolol,Donepezil,Ziprasidone,Ibuprofen,Risperidone,Oxycodone,Repaglinide,Indomethacin,Sumatriptan,Ropinirole,Oxcarbazepine,Azathioprine,Insulin Glargine,Gabapentin,Diphenhydramine,Hydromorphone,Niacin,Ketoprofen,Insulin Detemir,Prasugrel,Amitriptyline,Imatinib,Estradiol,Timolol,Salmeterol,Mometasone,Fentanyl,Ranitidine,Ketamine,Nortriptyline,Olanzapine,Losartan,Quetiapine,Memantine,Escitalopram,Allopurinol,Cevimeline,Levodopa,Buprenorphine,Diphenoxylate,Propranolol,Teriparatide,Darbepoetin alfa,Famotidine,Dronabinol,Tizanidine,Hydrocodone,Ketorolac,Nabumetone,Triamcinolone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Tramadol,Febuxostat,Cyclobenzaprine,Formoterol,Sotalol,Cinacalcet,Morphine,Darifenacin,Travoprost

exp12	Hypertension	Hydrochlorothiazide	KCNMA1	Aripiprazole,Iloprost,Nefazodone,Ziprasidone,Terazosin,Amitriptyline,Modafinil,Paliperidone,Midodrine,Nortriptyline,Clozapine,Quetiapine,Epinephrine,Loxapine,Imipramine,Ergotamine,Clonidine,Doxepin,Oxymetazoline,Cabergoline,Dextroamphetamine	Leuprolide,Buspirone,Acitretin,Metoprolol,Ibuprofen,Dopamine,Regadenoson,Oxcarbazepine,Dalteparin,Pramipexole,Mefloquine,Bosutinib,Eletriptan,Fentanyl,Dihydroergotamine,Losartan,Atropine,Terbutaline,Azelastine,Dextromethorphan,Darbepoetin alfa,Famotidine,Paroxetine,Clemastine,Droperidol,Trimipramine,Butorphanol,Haloperidol,Drospirenone,Desipramine,Naloxone,Riboflavin,Ondansetron,Tramadol,Formoterol,Levonorgestrel,Sotalol,Morphine,Frovatriptan,Etonogestrel,Trihexyphenidyl,Cyproheptadine,Risperidone,Degarelix,Rocuronium,Amphetamine,Salsalate,Indacaterol,Azathioprine,Tinzaparin,Lanreotide,Hydromorphone,Niacin,Rizatriptan,Hyoscyamine,Ponatinib,Naltrexone,Regorafenib,Octreotide,Salmeterol,Lurasidone,Allopurinol,Cevimeline,Sufentanil,Tocilizumab,Diphenoxylate,Carboplatin,Sorafenib,Sunitinib,Hydrocodone,Amoxapine,Trazodone,Mirtazapine,Codeine,Oxaliplatin,Darifenacin,Dasatinib,Testosterone,Oxybutynin,Zolmitriptan,Lisdexamfetamine,Solifenacin,Amantadine,Etomidate,Desogestrel,Scopolamine,Sargramostim,Fluphenazine,Ropinirole,Gabapentin,Ketoprofen,Prasugrel,Imatinib,Timolol,Mometasone,Rotigotine,Ranitidine,Ephedrine,Metoclopramide,Levodopa,Buprenorphine,Propranolol,Eculizumab,Pilocarpine,Pentazocine,Dronabinol,Tizanidine,Tiotropium,Goserelin,Cyclobenzaprine,Cetirizine,Febuxostat,Adenosine,Donepezil,Vandetanib,Dexamethasone,Maprotiline,Bromocriptine,Asenapine,Oxycodone,Acamprosate,Repaglinide,Tofacitinib,Indomethacin,Zidovudine,Insulin Glargine,Brompheniramine,Diphenhydramine,Insulin Detemir,Ticagrelor,Phenylephrine,Estradiol,Dicyclomine,Ketamine,Naratriptan,Memantine,Escitalopram,Cabozantinib,Piroxicam,Bivalirudin,Teriparatide,Succinylcholine,Perphenazine,Remifentanil,Progesterone,Ketorolac,Nabumetone,Triamcinolone,Nepafenac,Pseudoephedrine,Promethazine,Citalopram,Triptorelin,Sumatriptan,

					Cinacalcet,Almotriptan,Travoprost,Pertuzumab
exp13	Hypertension	Bendroflumethiazide	KCNMA1	Losartan,Aripiprazole,Quetiapine,Amitriptyline,Olanzapine,Clozapine	Leuprolide,Testosterone,Dexamethasone,Oxybutynin,Solifenacin,Metoprolol,Donepezil,Ibuprofen,Risperidone,Scopolamine,Oxycodone,Rocuronium,Indomethacin,Sumatriptan,Ropinirole,Tinzaparin,Azathioprine,Insulin Glargine,Gabapentin,Dalteparin,Pramipexole,Ketoprofen,Insulin Detemir,Imatinib,Modafinil,Estradiol,Timolol,Salmeterol,Mometasone,Fentanyl,Ranitidine,Ticagrelor,Nortriptyline,Escitalopram,Epinephrine,Metoclopramide,Allopurinol,Piroxicam,Terbutaline,Levodopa,Buprenorphine,Imipramine,Propranolol,Dextromethorphan,Teriparatide,Darbepoetin alfa,Remifentanil,Clonidine,Carboplatin,Sorafenib,Sunitinib,Haloperidol,Paroxetine,Nabumetone,Triamcinolone,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Goserelin,Codeine,Tramadol,Cetirizine,Cabergoline,Formoterol,Promethazine,Oxaliplatin,Citalopram,Sotalol,Morphine,Travoprost

exp14	Hypertension	Misoprostol	PTGER3	Aripiprazole,Buspirone,Dexamethasone,Oxycodone,Ropinirole,Gabapentin,Pramipexole,Diphenhydramine,Hydromorphone,Ketoprofen,Niacin,Rizatriptan,Amitriptyline,Fentanyl,Olanzapine,Nortriptyline,Quetiapine,Metoclopramide,Levodopa,Buprenorphine,Diphenoxylate,Propranolol,Hydrocodone,Mirtazapine,Ondansetron,Codeine,Morphine	Leuprolide,Testosterone,Oxybutynin,Solifenacin,Metoprolol,Amantadine,Ziprasidone,Ibuprofen,Risperidone,Repaglinide,Indomethacin,Sumatriptan,Salsalate,Azathioprine,Insulin Glargine,Terazosin,Insulin Detemir,Modafinil,Estradiol,Timolol,Salmeterol,Mometasone,Dicyclomine,Ranitidine,Clozapine,Losartan,Memantine,Escitalopram,Allopurinol,Piroxicam,Tocilizumab,Azelastine,Dextromethorphan,Teriparatide,Pentazocine,Clonidine,Famotidine,Carboplatin,Sorafenib,Progesterone,Tizanidine,Ketorolac,Nabumetone,Sunitinib,Triamcinolone,Doxepin,Haloperidol,Trazodone,Tiotropium,Cetirizine,Tramadol,Pseudoephedrine,Promethazine,Formoterol,Oxaliplatin,Levonorgestrel,Citalopram,Sotalol,Cyclobenzaprine,Donepezil,Paroxetine
exp15	Hypertension	Dinoprostone	PTGER3	Fentanyl	
exp16	Hypertension	Bimatoprost	PTGER3	Quetiapine,Memantine,Metoclopramide,Dexamethasone,Mirtazapine,Niacin,Levodopa,Ondansetron,Olanzapine,Codeine,Amitriptyline,Oxycodone,Fentanyl,Morphine,Hydrocodone,Gabapentin	Naphazoline,Leuprolide,Testosterone,Aripiprazole,Oxybutynin,Solifenacin,Metoprolol,Ibuprofen,Repaglinide,Sumatriptan,Ropinirole,Azathioprine,Insulin Glargine,Pramipexole,Diphenhydramine,Hydromorphone,Insulin Detemir,Modafinil,Ticagrelor,Estradiol,Timolol,Salmeterol,Mometasone,Dicyclomine,Ranitidine,Clozapine,Losartan,Escitalopram,Atropine,Allopurinol,Buprenorphine,Diphenoxylate,Propranolol,Azelastine,Teriparatide,Pilocarpine,Darbepoetin alfa,Clonidine,Famotidine,Tizanidine,Sunitinib,Progesterone,Paroxetine,Ketorolac,Nabumetone,Triamcinolone,Trazodone,Tiotropium,Cetirizine,Tramadol,Promethazine,Formoterol,Citalopram,Sotalol,Cyclobenzaprine,Donepezil,Travoprost

exp17	Hypertension	Sucralfate	EGF	Epinephrine,Diphenhydramine,Oxybutynin,Solifenacin,Hyoscyamine,Tiotropium,Imipramine,Ziprasidone,Pseudoephedrine,Pilocarpine,Scopolamine, Dicyclomine,Salmeterol, Promethazine,Sotalol,Paroxetine,Sorafenib	Leuprolide,Aripiprazole,Buspirone, Metoprolol,Ibuprofen,Dopamine,Oxcarbazepine,Pramipexole,Eletriptan,Fentanyl,Losartan,Atropine,Terbutaline ,Azelastine,Dextromethorphan,Darbepoetin alfa,Famotidine,Haloperidol,Drospirenone,Naloxone,Ondansetron,Tramadol,Formoterol,Morphine,Cyproheptadine,Risperidone,Azathioprine,Hydromorphone,Niacin,Rizatriptan,Octreotide,Clozapine,Quetiapine,Allopurinol ,Tocilizumab,Diphenoxylate,Carboplatin,Sunitinib,Hydrocodone,Trazodone,Mirtazapine,Codeine,Oxaliplatin, Darifenacin,Dasatinib,Testosterone,Zolmitriptan,Amantadine,Ropinirole,Gabapentin,Ketoprofen,Terazosin,Amitriptyline,Imatinib,Timolol,Midodrine,Ranitidine,Olanzapine,Metoclopramide,Levodopa,Buprenorphine,Propranolol,Eculizumab,Pentazocine,Dronabinol,Tizanidine,Doxepin,Goserelin, Cetirizine,Cyclobenzaprine,Febuxostat,Donepezil,Dexamethasone,Oxycodone,Repaglinide,Indomethacin,Insulin Glargine,Insulin Detemir,Modafinil,Ticagrelor,Estradiol,Nortriptyline,Memantine,Escitalopram,Piroxicam,Teriparatide,Perphenazine,Progesterone,Ketorolac,Nabumetone,Triamcinolone,Oxymetazoline, Citalopram,Sumatriptan,Cinacalcet,Dextroamphetamine,Travoprost

exp18	Hypertension	Misoprostol	PTGER4	Quetiapine,Aripiprazole,Ondansetron,Propranolol,Amitriptyline,Teriparatide,Pseudoephedrine,Salmeterol,Famotidine,Olanzapine	Leuprolide,Testosterone,Buspirone,Dexamethasone,Oxybutynin,Solifenacin,Metoprolol,Amantadine,Donepezil,Ziprasidone,Ibuprofen,Risperidone,Oxycodone,Repaglinide,Indomethacin,Sumatriptan,Salsalate,Ropinirole,Azathioprine,Insulin Glargine,Gabapentin,Pramipexole,Diphenhydramine,Hydromorphone,Niacin,Rizatriptan,Ketoprofen,Terazosin,Insulin Detemir,Modafinil,Estradiol,Timolol,Dicyclomine,Mometasone,Fentanyl,Ranitidine,Nortriptyline,Clozapine,Losartan,Memantine,Escitalopram,Metoclopramide,Allopurinol,Piroxicam,Tocilizumab,Levodopa,Buprenorphine,Diphenoxylate,Azelastine,Dextromethorphan,Pentazocine,Clonidine,Carboplatin,Sorafenib,Progesterone,Tizanidine,Ketorolac,Nabumetone,Sunitinib,Triamcinolone,Doxepin,Haloperidol,Trazodone,Hydrocodone,Mirtazapine,Tiotropium,Codeine,Tramadol,Cetirizine,Promethazine,Formoterol,Oxaliplatin,Levonorgestrel,Citalopram,Sotalol,Cyclobenzaprine,Morphine,Paroxetine
exp19	Hypertension	Pramlintide	RAMP2	Amitriptyline	Metoprolol,Ibuprofen,Repaglinide,Oxycodone,Gabapentin,Insulin Glargine,Niacin,Insulin Detemir,Salmeterol,Ranitidine,Losartan,Quetiapine,Escitalopram,Metoclopramide,Allopurinol,Clonidine,Paroxetine,Hydrocodone,Trazodone,Tiotropium,Tramadol,Promethazine,Citalopram

exp20	Hypertension	Oxytocin	OXTR	Losartan,Quetiapine,Leuprolide,Escitalopram,Epinephrine,Dexamethasone,Oxybutynin,Tramadol,Amitriptyline,Phenylephrine,Promethazine,Clonidine,Paroxetine,Olanzapine	Iloprost,Solifenacin,Metoprolol,Etomidate,Donepezil,Ibuprofen,Dopamine,Risperidone,Oxycodone,Rocuronium,Zidovudine,Azathioprine,Tinzaparin,Insulin Glargine,Gabapentin,Hydromorphone,Niacin,Insulin Detemir,Imatinib,Estradiol,Octreotide,Fentanyl,Salmeterol,Ranitidine,Nalbuphine,Atropine,Allopurinol,Ephedrine,Sufentanil,Metoclopramide,Buprenorphine,Propranolol,Teriparatide,Darbepoetin alfa,Succinylcholine,Remifentanil,Sorafenib,Haloperidol,Butorphanol,Ketorolac,Hydrocodone,Drospirenone,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Cetirizine,Formoterol,Levonorgestrel,Citalopram,Morphine

exp21	Hypertension	Sucralfate	FGF2	Sunitinib,Sorafenib	Leuprolide,Aripiprazole,Buspirone,Metoprolol,Ibuprofen,Dopamine,Oxcarbazepine,Dalteparin,Pramipexole,Eletriptan,Fentanyl,Losartan,Atropine,Terbutaline,Imipramine,Azelastine,Dextromethorphan,Darbepoetin alfa,Famotidine,Paroxetine,Haloperidol,Drospirenone,Naloxone,Ondansetron,Tramadol,Formoterol,Sotalol,Morphine,Cyproheptadine,Risperidone,Azathioprine,Hydromorphone,Niacin,Rizatriptan,Hyoscyamine,Octreotide,Salmeterol,Clozapine,Quetiapine,Epinephrine,Allopurinol,Tocilizumab,Diphenoxylate,Carboplatin,Hydrocodone,Trazodone,Mirtazapine,Codeine,Oxaliplatin,Darifenacin,Testosterone,Oxybutynin,Zolmitriptan,Solifenacin,Amantadine,Scopolamine,Ropinirole,Gabapentin,Ketoprofen,Terazosin,Cinacalcet,Amitriptyline,Imatinib,Timolol,Midodrine,Ranitidine,Olanzapine,Metoclopramide,Levodopa,Buprenorphine,Propranolol,Eculizumab,Pilocarpine,Pentazocine,Dronabinol,Tizanidine,Doxepin,Tiotropium,Goserelin,Cetirizine,Febuxostat,Donepezil,Dexamethasone,Ziprasidone,Repaglinide,Oxycodone,Indomethacin,Insulin Glargine,Diphenhydramine,Insulin Detemir,Ticagrelor,Modafinil,Estradiol,Dicyclomine,Nortriptyline,Memantine,Escitalopram,Piroxicam,Teriparatide,Perphenazine,Progesterone,Ketorolac,Nabumetone,Triamcinolone,Oxymetazoline,Pseudoephedrine,Promethazine,Citalopram,Sumatriptan,Cyclobenzaprine,Dextroamphetamine,Travoprost

exp22	Hypertension	Loperamide	POMC	Terbutaline,Hyoscyamine,Eculizumab,Teriparatide,Dicyclomine,Tizanidine,Octreotide,Famotidine,Sotalol,Droperidol,Tinzaparin	Leuprolide,Aripiprazole,Buspirone,Nefazodone,Ibuprofen,Dopamine,Oxcarbazepine,Dalteparin,Pramipexole,Fentanyl,Losartan,Atropine,Azelastine,Dextromethorphan,Darbepoetin alfa,Clonidine,Paroxetine,Clemastine,Haloperidol,Desipramine,Drospirenone,Naloxone,Ondansetron,Tramadol,Levonorgestrel,Morphine,Cyproheptadine,Risperidone,Amphetamine,Azathioprine,Hydromorphone,Niacin,Rizatriptan,Ponatinib,Regorafenib,Clozapine,Quetiapine,Epinephrine,Allopurinol,Tocilizumab,Diphenoxylate,Carboplatin,Sorafenib,Sunitinib,Hydrocodone,Trazodone,Mirtazapine,Codeine,Oxaliplatin,Darifenacin,Dasatinib,Testosterone,Oxybutynin,Zolmitriptan,Solifenacin,Amantadine,Scopolamine,Sargramostim,Ropinirole,Gabapentin,Ketoprofen,Terazosin,Cinacalcet,Amitriptyline,Imatinib,Mometasone,Midodrine,Olanzapine,Metoclopramide,Levodopa,Buprenorphine,Propranolol,Pilocarpine,Dronabinol,Doxepin,Tiotropium,Goserelin,Cetirizine,Febuxostat,Donepezil,Vandetanib,Dexamethasone,Ziprasidone,Repaglinide,Oxycodone,Indomethacin,Zidovudine,Insulin Glargine,Brompheniramine,Diphenhydramine,Insulin Detemir,Ticagrelor,Phenylephrine,Estradiol,Modafinil,Nortriptyline,Memantine,Escitalopram,Cabozantinib,Piroxicam,Progesterone,Ketorolac,Nabumetone,Triamcinolone,Oxymetazoline,Pseudoephedrine,Promethazine,Citalopram,Sumatriptan,Cyclobenzaprine,Dextroamphetamine,Travoprost,Pertuzumab
exp23	Hypertension	Eptifibatide	ITGB3	Tenecteplase	Metoprolol,Ibuprofen,Dopamine,Gabapentin,Insulin Glargine,Diphenhydramine,Hydromorphone,Prasugrel,Ticagrelor,Phenylephrine,Salmeterol,Fentanyl,Ranitidine,Epinephrine,Atropine,Allopurinol,Metoclopramide,Bivalirudin,Clonidine,Famotidine,Paroxetine,Hydrocodone,Ondansetron,Promethazine,Morphine

exp24	Hypertension	Oxytocin	OXT	Losartan,Quetiapine,Leuprolide,Escitalopram,Epinephrine,Oxybutynin,Tramadol,Amitriptyline,Phenylephrine,Promethazine,Clonidine,Paroxetine,Olanzapine	Iloprost,Dexamethasone,Solifenacin,Metoprolol,Etomidate,Donepezil,Ibuprofen,Dopamine,Risperidone,Oxycodone,Rocuronium,Zidovudine,Tinzaparin,Azathioprine,Insulin Glargine,Gabapentin,Hydromorphone,Niacin,Insulin Detemir,Imatinib,Estradiol,Octreotide,Fentanyl,Salmeterol,Ranitidine,Nalbuphine,Atropine,Allopurinol,Ephedrine,Sufentanil,Metoclopramide,Buprenorphine,Propranolol,Teriparatide,Darbepoetin alfa,Succinylcholine,Remifentanil,Sorafenib,Haloperidol,Butorphanol,Ketorolac,Hydrocodone,Drospirenone,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Cetirizine,Formoterol,Levonorgestrel,Citalopram,Morphine
exp25	Hypertension	Alglucosidase alfa	M6PR	Diphenhydramine	Ephedrine,Ondansetron,Metoprolol,Propranolol,Cetirizine,Ibuprofen,Amitriptyline,Fentanyl,Famotidine,Ranitidine,Gabapentin
exp26	Hypertension	Pramlintide	RAMP1	Amitriptyline	Metoprolol,Ibuprofen,Repaglinide,Oxycodone,Gabapentin,Insulin Glargine,Niacin,Insulin Detemir,Salmeterol,Ranitidine,Losartan,Quetiapine,Escitalopram,Metoclopramide,Allopurinol,Clonidine,Paroxetine,Hydrocodone,Trazodone,Tiotropium,Tramadol,Promethazine,Citalopram

exp27	Hypertension	Montelukast	CYSLTR1	Leuprolide,Atropine,Pramipexole,Metoclopramide,Terazosin,Cyproheptadine,Hyoscyamine,Cetirizine,Pseudoephedrine,Phenylephrine,Scopolamine,Dicyclomine,Midodrine,Dextroamphetamine	Aripiprazole,Buspirone,Iloprost,Acitretin,Nefazodone,Metoprolol,Ibuprofen,Dopamine,Oxcarbazepine,Dalteparin,Eletriptan,Fentanyl,Losartan,Terbutaline,Imipramine,Ergotamine,Azelastine,Dextromethorphan,Darbepoetin alfa,Clonidine,Famotidine,Paroxetine,Clemastine,Haloperidol,Butorphanol,Desipramine,Drospirenone,Naloxone,Riboflavin,Ondansetron,Tramadol,Formoterol,Levonorgestrel,Sotalol,Morphine,Frovatriptan,Etonogestrel,Trihexyphenidyl,Risperidone,Carbinoxamine,Amphetamine,Salsalate,Indacaterol,Azathioprine,Hydromorphone,Niacin,Rizatriptan,Ponatinib,Naltrexone,Octreotide,Salmeterol,Vigabatrin,Clozapine,Quetiapine,Lurasidone,Epinephrine,Allopurinol,Cevimeline,Tocilizumab,Diphenoxylate,Carboplatin,Sorafenib,Sunitinib,Hydrocodone,Trazodone,Mirtazapine,Codeine,Oxaliplatin,Darifenacin,Dasatinib,Testosterone,Oxybutynin,Zolmitriptan,Lisdexamfetamine,Solifenacin,Amantadine,Desogestrel,Fluphenazine,Ropinirole,Gabapentin,Ketoprofen,Prasugrel,Paliperidone,Amitriptyline,Timolol,Imatinib,Mometasone,Ranitidine,Olanzapine,Mirabegron,Levodopa,Buprenorphine,Propranolol,Eculizumab,Pilocarpine,Pentazocine,Dronabinol,Tizanidine,Doxepin,Tiotropium,Goserelin,Cyclobenzaprine,Febuxostat,Donepezil,Dexamethasone,Bromocriptine,Ziprasidone,Asenapine,Oxycodone,Repaglinide,Tofacitinib,Indomethacin,Zidovudine,Insulin Glargine,Brompheniramine,Diphenhydramine,Insulin Detemir,Ticagrelor,Modafinil,Estradiol,Nortriptyline,Naratriptan,Memantine,Escitalopram,Piroxicam,Teriparatide,Perphenazine,Progesterone,Ketorolac,Nabumetone,Triamcinolone,Oxymetazoline,Promethazine,Citalopram,Sumatriptan,Cinacalcet,Almotriptan,Travoprost

exp28	Hypertension	Zafirlukast	CYSLTR1	Cetirizine	Aripiprazole,Buspirone,Dexamethasone,Oxybutynin,Solifenacin,Metoprolol,Ziprasidone,Ibuprofen,Risperidone,Oxycodone,Ropinirole,Gabapentin,Insulin Glargine,Pramipexole,Diphenhydramine,Amitriptyline,Estradiol,Salmeterol,Mometasone,Fentanyl,Ranitidine,Losartan,Quetiapine,Escitalopram,Epinephrine,Metoclopramide,Allopurinol,Terbutaline,Buprenorphine,Diphenoxylate,Azelastine,Clonidine,Famotidine,Tizanidine,Paroxetine,Hydrocodone,Nabumetone,Triamcinolone,Trazodone,Mirtazapine,Ondansetron,Tiotropium,Codeine,Tramadol,Pseudoephedrine,Promethazine,Formoterol,Citalopram,Sumatriptan,Cyclobenzaprine,Morphine
exp29	Myopathy	Sucralfate	EGF	Lidocaine	Phenytoin,Fluoxetine,Prednisone,Niacin,Abiraterone,Ziprasidone,Imatinib,Hydrochlorothiazide,Rosuvastatin,Erlotinib
exp30	Myopathy	Dobutamine	ADRB2	Lidocaine	Phenytoin,Fluoxetine,Prednisone,Rocuronium,Hydrochlorothiazide,Rosuvastatin
exp31	Pancreatitis	Cinacalcet	CASR	Valsartan,Gabapentin	Ramipril,Losartan,Lisinopril,Quinapril,Quetiapine,Pramipexole,Thalidomide,Benazepril,Propofol,Levodopa,Ibuprofen,Ropinirole,Aliskiren,Estradiol,Enalapril,Fosinopril,Diclofenac,Hydrochlorothiazide,Atenolol,Acetaminophen
exp32	Pancreatitis	Dronabinol	CNR1	Diphenoxylate,Gabapentin	Aripiprazole,Dexamethasone,Ibuprofen,Risperidone,Ropinirole,Morphine,Estradiol,Octreotide,Atenolol,Hydrochlorothiazide,Losartan,Quetiapine,Propranolol,Enalapril,Clonidine,Paroxetine,Caffeine,Erlotinib,Acetaminophen,Lisinopril,Thalidomide,Benazepril,Mirtazapine,Tramadol,Oxaliplatin,Citalopram,Valsartan,Donepezil,Dasatinib

exp33	Pancreatitis	Dronabinol	CNR2	Diphenoxylate,Gabapentin	Aripiprazole,Dexamethasone,Ibuprofen,Risperidone,Ropinirole,Morphine,Estradiol,Octreotide,Atenolol,Hydrochlorothiazide,Losartan,Quetiapine,Propranolol,Enalapril,Clonidine,Paroxetine,Caffeine,Erlotinib,Acetaminophen,Lisinopril,Thalidomide,Benazepril,Mirtazapine,Tramadol,Oxaliplatin,Citalopram,Valsartan,Donepezil,Dasatinib
exp34	Pancreatitis	Tinzaparin	CXCL12	Morphine,Dexamethasone	Ramipril,Ibuprofen,Gabapentin,Ketoprofen,Atenolol,Olanzapine,Hydrochlorothiazide,Propofol,Losartan,Quetiapine,Propranolol,Enalapril,Erythromycin,Paroxetine,Erlotinib,Acetaminophen,Lisinopril,Thalidomide,Mirtazapine,Telmisartan,Oxaliplatin,Citalopram,Valsartan,Diclofenac
exp35	Pancreatitis	Sucralfate	EGF	Quetiapine,Aripiprazole,Nadolol,Mirtazapine,Propranolol,Atenolol	Ramipril,Dexamethasone,Donepezil,Ibuprofen,Sulfasalazine,Risperidone,Ropinirole,Gabapentin,Pramipexole,Olmesartan,Ketoprofen,Trandolapril,Aliskiren,Estradiol,Octreotide,Fosinopril,Olanzapine,Hydrochlorothiazide,Propofol,Clozapine,Losartan,Memantine,Busulfan,Atropine,Levodopa,Diphenoxylate,Pentazocine,Pilocarpine,Enalapril,Erythromycin,Paroxetine,Caffeine,Erlotinib,Acetaminophen,Quinapril,Lisinopril,Naloxone,Thalidomide,Benazepril,Telmisartan,Tramadol,Oxaliplatin,Citalopram,Valsartan,Diclofenac,Morphine,Sulindac,Dasatinib
exp36	Pancreatitis	Ketamine	TACR1	Atropine	Ramipril,Quetiapine,Lisinopril,Ketoprofen,Diclofenac,Ibuprofen,Pentazocine,Atenolol,Morphine,Hydrochlorothiazide,Propofol,Gabapentin,Acetaminophen
exp37	Pneumonia	Plerixafor	CXCR4	Gabapentin,Prochlorperazine	Dexamethasone
exp38	Pneumonia	Drotrecogin alfa	PF4	Fentanyl,Dexamethasone	

exp39	Pneumonia	Sulindac	PTGDR2	Quetiapine,Tiotropium,Tramadol,Risperidone,Fentanyl,Hydrocodone,Gabapentin	Quinapril,Infliximab,Dexamethasone,Adalimumab,Tocilizumab,Paroxetine,Mirtazapine,Codeine,Ibuprofen,Golimumab,Sulfasalazine,Etanercept,Amitriptyline,Promethazine,Clopidogrel,Prochlorperazine,Sumatriptan,Ropinirole
exp40	Pneumonia	Loperamide	POMC	Treprostinil	Aripiprazole,Dexamethasone,Zolmitriptan,Amantadine,Ibuprofen,Ziprasidone,Risperidone,Sulfasalazine,Clopidogrel,Maraviroc,Ropinirole,Gabapentin,Tinzaparin,Adalimumab,Amitriptyline,Octreotide,Fentanyl,Clozapine,Quetiapine,Infliximab,Memantine,Tocilizumab,Pilocarpine,Etanercept,Paroxetine,Hydrocodone,Doxepin,Quinapril,Aldesleukin,Mirtazapine,Balsalazide,Tiotropium,Codeine,Tramadol,Golimumab,Promethazine,Prochlorperazine,Sumatriptan,Certolizumab pegol
exp41	Pneumonia	Theophylline	ADORA2B	Pramipexole	Aripiprazole,Dexamethasone,Amantadine,Ibuprofen,Ziprasidone,Risperidone,Sulfasalazine,Clopidogrel,Ropinirole,Gabapentin,Adalimumab,Amitriptyline,Octreotide,Fentanyl,Clozapine,Quetiapine,Infliximab,Memantine,Tocilizumab,Buprenorphine,Dextromethorphan,Pilocarpine,Etanercept,Paroxetine,Hydrocodone,Doxepin,Quinapril,Mirtazapine,Tiotropium,Codeine,Tramadol,Promethazine,Prochlorperazine,Sumatriptan
exp42	Pneumonia	Trastuzumab	EGFR	Quetiapine,Mirtazapine,Tiotropium,Amitriptyline,Promethazine,Paroxetine,Olanzapine	Quinapril,Pramipexole,Dexamethasone,Metoclopramide,Buprenorphine,Tinzaparin,Codeine,Tramadol,Ibuprofen,Dextromethorphan,Fentanyl,Clopidogrel,Prochlorperazine,Sumatriptan,Hydrocodone,Gabapentin,Clozapine
exp43	Pneumonia	Cetuximab	EGFR	Mirtazapine,Tiotropium,Amitriptyline,Promethazine,Paroxetine	Quinapril,Metoclopramide,Dexamethasone,Buprenorphine,Tinzaparin,Codeine,Hydrocodone,Ibuprofen,Tramadol,Pilocarpine,Dextromethorphan,Octreotide,Fentanyl,Clopidogrel,Prochlorperazine,Ropinirole,Gabapentin

exp44	Pneumonia	Panitumumab	EGFR	Promethazine,Tiotropium	Metoclopramide,Dexamethasone,Mirtazapine,Buprenorphine,Tinzaparin,Codeine,Tramadol,Ibuprofen,Amitriptyline,Fentanyl,Clopidogrel,Prochlorperazine,Paroxetine,Hydrocodone,Gabapentin
exp45	Pneumonia	Alteplase	PLG	Ibuprofen	Metoclopramide,Dexamethasone,Buprenorphine,Codeine,Tramadol,Amitriptyline,Promethazine,Fentanyl,Clopidogrel,Prochlorperazine,Paroxetine,Hydrocodone,Gabapentin
exp46	Sepsis	Tamsulosin	ADRA1D	Pramipexole,Goserelin,Atropine	Infliximab,Memantine,Ticlopidine,Ibrutinib,Niacin,Ketoprofen,Diphenoxylate,Sulfasalazine,Golimumab,Eculizumab,Etanercept,Fentanyl,Tofacitinib,Sumatriptan,Abatacept,Certolizumab pegol,Gabapentin
exp47	Sepsis	Doxazosin	ADRA1D	Pramipexole	Infliximab,Memantine,Ticlopidine,Niacin,Ketoprofen,Diphenoxylate,Sulfasalazine,Golimumab,Eculizumab,Etanercept,Fentanyl,Sumatriptan,Abatacept,Certolizumab pegol,Gabapentin
exp48	Sepsis	Carvedilol	ADRA1D	Goserelin	Canakinumab,Infliximab,Memantine,Ticlopidine,Ibrutinib,Niacin,Ketoprofen,Diphenoxylate,Sulfasalazine,Golimumab,Eculizumab,Etanercept,Fentanyl,Tofacitinib,Sumatriptan,Abatacept,Certolizumab pegol,Gabapentin
exp49	Sepsis	Terazosin	ADRA1D	Ropinirole	Infliximab,Memantine,Ticlopidine,Ibrutinib,Niacin,Diphenoxylate,Sulfasalazine,Eculizumab,Etanercept,Fentanyl,Sumatriptan,Gabapentin
exp50	Sepsis	Metoprolol	ADRB2	Atropine	Ibrutinib,Sulfasalazine,Tofacitinib,Abatacept,Ropinirole,Gabapentin,Pramipexole,Ketoprofen,Niacin,Fentanyl,Infliximab,Memantine,Cevimeline,Diphenoxylate,Eculizumab,Etanercept,Aminophylline,Canakinumab,Ticlopidine,Aldesleukin,Goserelin,Golimumab,Sumatriptan,Certolizumab pegol

exp51	Sepsis	Atenolol	ADRB2	Atropine	Ibrutinib,Sulfasalazine,Tofacitinib,Abatacept,Ropinirole,Gabapentin,Pramipexole,Ketoprofen,Niacin,Fentanyl,Infliximab,Memantine,Cevimeline,Diphenoxylate,Eculizumab,Etanercept,Aminophylline,Canakinumab,Ticlopidine,Aldesleukin,Goserelin,Golimumab,Sumatriptan,Certolizumab pegol
exp52	Sepsis	Terbutaline	ADRB2	Paroxetine	Aminophylline,Infliximab,Ketoprofen,Sulfasalazine,Etanercept,Fentanyl,Sumatriptan,Gabapentin
exp53	Sepsis	Bisoprolol	ADRB2	Atropine	Ibrutinib,Sulfasalazine,Tofacitinib,Abatacept,Ropinirole,Gabapentin,Pramipexole,Niacin,Ketoprofen,Fentanyl,Infliximab,Memantine,Diphenoxylate,Eculizumab,Etanercept,Canakinumab,Ticlopidine,Goserelin,Golimumab,Sumatriptan,Certolizumab pegol
exp54	Sepsis	Dobutamine	ADRB2	Atropine	Fentanyl,Gabapentin
exp55	Sepsis	Pirbuterol	ADRB2	Paroxetine	Niacin,Fentanyl,Sumatriptan,Ropinirole,Gabapentin
exp56	Sepsis	Tinzaparin	CXCL12	Paroxetine,Fentanyl,Gabapentin	Infliximab,Goserelin
exp57	Sepsis	Dabigatran etexilate	F2	Ropinirole	Infliximab,Memantine,Ticlopidine,Niacin,Ketoprofen,Diphenoxylate,Sulfasalazine,Etanercept,Fentanyl,Sumatriptan,Gabapentin
exp58	Sepsis	Loperamide	POMC	Pramipexole,Goserelin,Atropine,Gabapentin	Infliximab,Aldesleukin,Ibrutinib,Sulfasalazine,Golimumab,Etanercept,Certolizumab pegol

Table S6. Remaining 58 class predicted DDIs, network classes and drugs contained in each class.

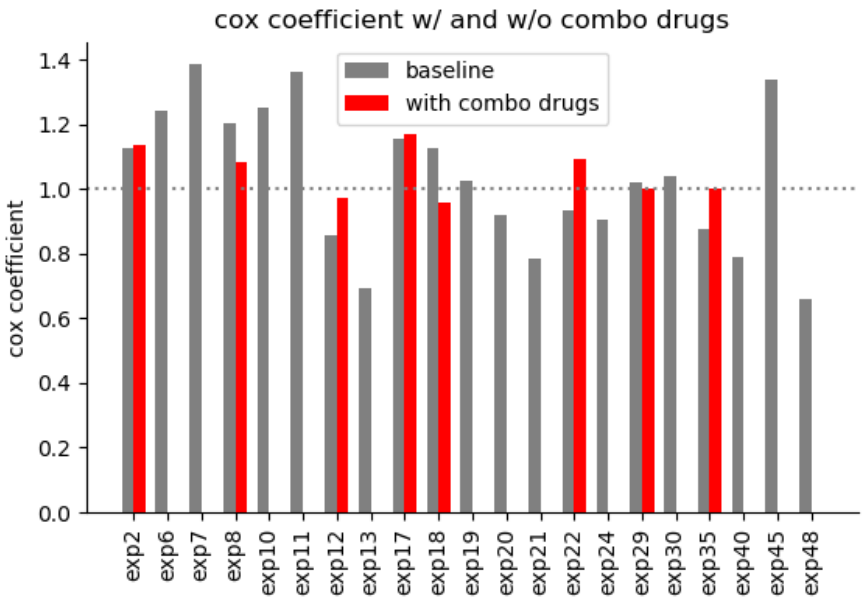

Fig S3. Cox coefficients measured for 21 of the 58 predicted class effects. We measured Cox coefficients for network class effects where there were sufficient patients exposed to the target and comparator drug classes (grey bars) and for the 8 classes where there were sufficient patients

exposed to the combination drug and either the target or comparator drug classes (red bars). Experimental numbers correspond with network classifications in **Table S6**.

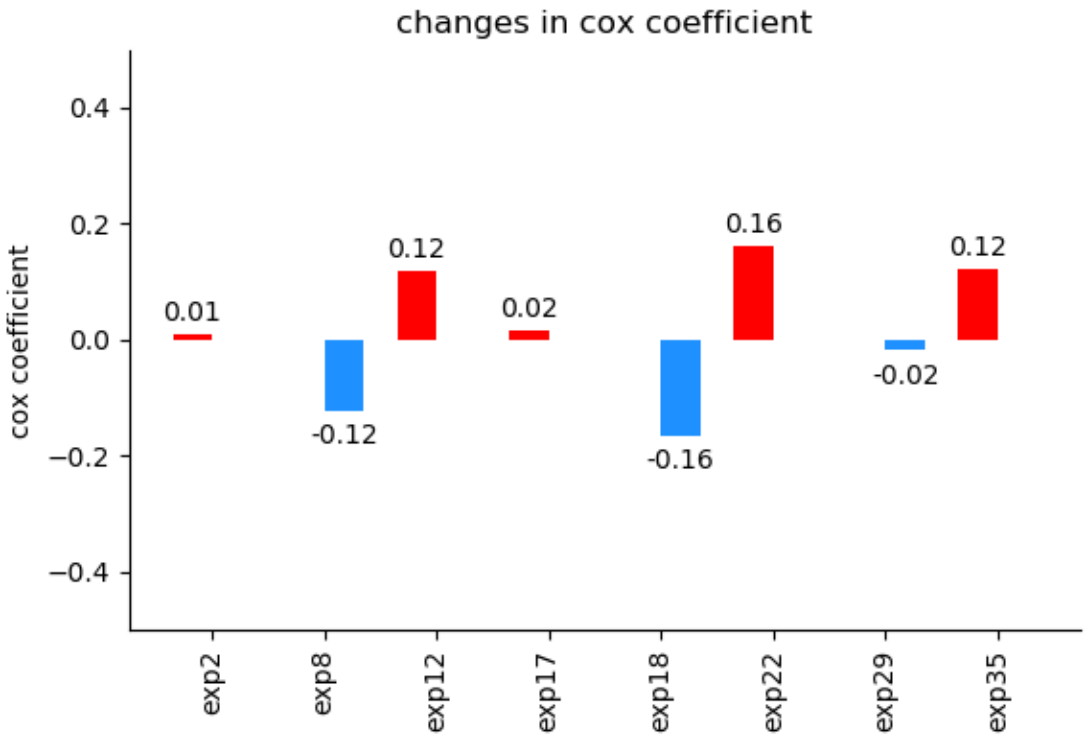

Fig. S4. Changes in the cox coefficient for 8 predicted classes with combination drugs compared to without the combination drug. Increased/decreased risk for the ADR is represented in red/blue bars respectively. Experimental numbers correspond with network classifications in **Table S6**.