**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 “AR”. For transparency, we noted each script used for each analysis in the results section.

*Extracting designated medical events from drug labels*

An algorithm was built using Linguamatics, a natural language processing software, to extract designated medical events (DMEs) (adverse reactions, ARs) 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 XX) were obtained from DailyMed and indexed in Linguamatics. For each AR, 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 ARs in their product label were exported for analysis in PathFX. The data from this analysis are included in *Drugs\_labeled\_for\_AEs.txt*.

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

Drug targets were taken from DrugBank(*1*) (version 5.1.0) and given to the PathFX algorithm as inputs. Prior to this analysis, we had created a library of networks using all drugs in DrugBank but recreated a copy of this analysis available as a python script in the GitHub directory *(/ PathFX/ scripts/ run\_PathFX\_all\_drugBank.py*). This script used code available from the PathFX repository to create networks. Statistical analyses for PathFX are as described in(*2*) and an abbreviated summary is provided below. For subsequent analyses, we copied only the association tables created by PathFX into the GitHub folder: */data/ all\_drugbank\_network\_association\_files/.*

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(*3*) method and is fully elaborated in(*2*). 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.

To find pathway associations to ARs, we searched within the output of significant associations to identify network phenotypes that matched text warnings extracted from drug labels. This analysis is contained in */Code/ read\_drug\_to\_DME\_data.ipynb*. Within this analysis, we calculated the sensitivity and specificity for each AR. A drug-AR association was counted as a true positive or false negative if the drug’s network contained or did not contain a phenotype relevant to the AR listed on the drug’s label. Further, for this AR set, we considered all drugs in DrugBank that did not have the AR listed on their drug label as true 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 AR. We manually combined the raw data, the outputs from sensitivity and specificity analysis, and the results from the pathway analysis into */Code/supp\_1\_true\_positives\_summary.xlsx*.

*Merging and pruning AR pathways*

For each AR, we took the union of all shortest pathways between a drug target and AR-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 (Supplementary File 1). 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 ARs *(/Code/merge\_networks\_for\_DMEs.ipynb*).

We further ranked all network nodes (drug binding and intermediate proteins) by the number of drug-AR 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 AR 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-AR 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 (*Supplementary File 2, supp2\_DME\_merged\_node\_counts.xlsx*). For each AR, we took the top 12 genes and plotted these counts across ARs 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, supp3\_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 ARs, the number of merged pathways is contained in *Supplementary File 1, supp\_1\_true\_positives\_summary.xlsx*. For some ARs, pathways analysis did not uncover an association between the drug’s target(s) and the AR (i.e., the sensitivity = 0, Supplementary File 1). All the genes in the merged pathway constitute an “AR pathway”.

*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 above 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 AR 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 AR pathway gene (discovered above) and were not associated with an AR 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 AR pathway genes: AR-associated genes (ARPs) and proteins along shortest paths between drug targets and AR-associated genes (SPs). We predicted drug combinations for both types of network genes and these results are stored in *supp4\_all\_SP\_drug\_class\_predictions.xlsx* (SPs) and *supp5\_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 AR. We conducted a search of co-mentions of combination drugs and the ARs. Ask Becca to confirm what she did to find the PubMed abstracts. This search yielded a set of PubMed IDs for abstracts that contained sentences that contained co-mentions of the combination drugs and AR phenotypes in the same sentence. Importantly, this set did not contain drugs associated with ARs on their labels and the co-mentions of combination drugs and ARs were not used in the PathFX predictions. Co-mentions in PubMed could represent emerging effects or exceedingly rare relationships to ARs that would not have required the drug to have the AR on its label. We manually read the abstracts to confirm relevance of the abstract and infer directionality of the drug’s effect on the AR (e.g. aggravates the AR or mitigates) (*/data/ Drug-DME\_Eval\_final.xlsx*). We summarized our predictions of potential drug interactions to create tables linking drugs with labeled ARs to potential aggravating or preventative drug interacting partners *(/Code/summarize\_predictions.ipynb, supp6\_summary\_drug\_interactions.xlsx*).

*Considering hypothesis for clinical evaluation*

We leveraged data in TWOSIDES(*4*) 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 or not 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 TWOSIDE 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-AR 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**.

*Electronic Health Record Dataset: Optum Clinformatics Data Mart 8.0*

The Optum dataset is a large US commercial claims dataset containing over 88 million patients largely under the age of 65 and is frequently used for observational studies (*5*). 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 generated 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. 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 AR 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.

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(*6*) tools and the Optum dataset (described previously) to conduct propensity score matching and estimate effect sizes. 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 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 *supp4\_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 XX, suggesting that covariate data was not able to predict whether a patient would be placed in a treatment or comparator group. 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. Similar to above, patient features did not predict treatment assignment and we pursued further estimation. 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 *supp5\_Assembled\_sig\_res\_table.xlsx***.** To conduct this analysis, we used patient language model representations extracted from

(*7*). 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 also used these representations to conduct large-scale propensity matching of patients for each predicted DDI. Propensity score matching restricted our analysis to the comparison of individuals with similar encounters with the health system and mitigated the possible effects of confounding variables. For all DDI studies, we conducted a baseline measurement of the AR risk between the network and non-network class and a second measurement of the AR risk between these classes when the combination drug was also used. To be included in a DDI study, we required that a patient representation included exposure the network class (target cohort, baseline measurement) the non-network class (comparator cohort, baseline measurement), the predicted combination drug with the network class (target cohort, second measurement), or non-network drug class (comparator cohort, second measurement). After identifying a matched cohort, we estimated hazard ratios using Cox regression model for the AR outcome. This procedure is the same as used in {Steinberg:uo}. For all measurements, the p-value represents the likelihood of the estimated hazard ratio relative to the null hypothesis that the hazard ratio is zero.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **drug1** | **drug2** | **AR (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-ARs with PRRs reported in TWOSIDES (*4*).

|  |  |
| --- | --- |
| **Drugs with network association to sepsis and networks contain ADRB2,  “ADBR2-net”** | **Drugs with network association to sepsis and networks does 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.

Table S3.

Covariate balance in sepsis study after matching.

|  |  |
| --- | --- |
| **Drugs with network association to pancreatitis and networks contain TP53, EDRNA, or NFKBIA, “T-E-N-net”** | **Drugs with network association to pancreatitis and networks does 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 | DME | 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.

Chart, bar chart

Description automatically generated

Figure S3.

Cox coefficients measured for 21 of the 58 predicted 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.

Chart, waterfall chart

Description automatically generated

**Fig. S4.**

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

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