**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>.

*Extracting designated medical events from drug labels*

An algorithm was built using Linguamatics, a natural language processing software, to extract DMEs 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 DME, 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 DMEs 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 DMEs*

Drug targets were taken from DrugBank{Wishart:2006cx} 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 uses code available from the PathFX repository to create networks. Statistical analyses for PathFX are as described in{Wilson:2018ko}. For subsequent analyses, we copied only the association tables created by PathFX into the GitHub folder: */data/ all\_drugbank\_network\_association\_files/.*

To find pathway associations to DMEs, 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 DME. A drug-DME 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 DME listed on the drug’s label. Further, for this DME set, we considered all drugs in DrugBank that did not have the DME 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 DME. We manually curated 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 DME pathways*

For each DME, we took the union of all shortest pathways between a drug target and DME-associated genes *(/Code/merge\_networks\_for\_DMEs.ipynb*). For instance, alemtuzumab’s is associated with hemolytic anemia on the drug’s 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 DMEs *(/Code/merge\_networks\_for\_DMEs.ipynb*).

We further ranked all network nodes (drug binding and intermediate proteins) by the number of drug-DME 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 DME 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-DME 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 DME, we took the top 12 genes and plotted these counts across DMEs to look for patterns across genes (*Code/merge\_networks\_for\_DMEs.ipynb, Supplementary File 3, supp3\_DME\_heatmap\_top\_node\_counts.xlsx*).

For example, in tardive dyskinesia, PathFX identified 35 drug pathways that associated the drug’s targets to the tardive dyskinesia phenotype. For all other DMEs, the number of merged pathways is contained in Supplementary File 1, supp\_1\_true\_positives\_summary.xlsx. For some DMEs, pathways analysis did not uncover an association between the drug’s target(s) and the DME (i.e. the sensitivity = 0, Supplementary File 1).

*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. All scripts are included in the ‘code’ folder of the directory. *(/Code/ merge\_networks\_for\_DMEs.ipynb* and */Code/ find\_co\_therapy\_networks.ipynb*).