

1 **Machine learning guided association of adverse drug reactions with *in vitro* target-based**
2 **pharmacology**

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24 **Abstract**

25 Adverse drug reactions (ADRs) are one of the leading causes of morbidity and mortality in health
26 care. Understanding which drug targets are linked to ADRs can lead to the development of safer
27 medicines. Here, we analyze *in vitro* secondary pharmacology of common (off) targets for 2134
28 marketed drugs. To associate these drugs with human ADRs, we utilized FDA Adverse Event
29 Reports and developed random forest models that predict ADR occurrences from *in vitro*
30 pharmacological profiles. By evaluating Gini importance scores of model features, we identify 221
31 target-ADR associations, which co-occur in PubMed abstracts to a greater extent than expected
32 by chance. Among these are established relations, such as the association of *in vitro* hERG
33 binding with cardiac arrhythmias, which further validate our machine learning approach. Evidence
34 on bile acid metabolism supports our identification of associations between the Bile Salt Export
35 Pump and renal, thyroid, lipid metabolism, respiratory tract and central nervous system disorders.
36 Unexpectedly, our model suggests PDE3 is associated with 40 ADRs. These associations provide
37 a comprehensive resource to support drug development and human biology studies.

38 **Keywords**

39 Adverse drug reactions, adverse event report, FAERS, secondary pharmacology, machine
40 learning, statistical modeling, drug discovery & development, drug safety.

41 Toxicity is one of the major causes of termination, withdrawal, or labeling of a drug candidate or
42 drug, other than lack of efficacy¹⁻³. There is an urgent need to better identify toxic on- and off-
43 target effects on vital organ systems especially for cardiovascular, renal, hepatic and central
44 nervous system (CNS)-related toxicities; furthermore, there is a desire to reduce cost and labor
45 in preclinical assays and drug testing on non-human species⁴⁻⁶. *In vitro* pharmacological assays
46 have been widely used to screen for possible off-targets and potential adverse effects and
47 eliminate compounds that are not safe enough in the drug development stage as early as possible
48^{5,7}. However, systematic prediction of compound safety and potential adverse events associated
49 with a compound is still a challenge for the pharmaceutical industry.

50
51 Machine learning can be very insightful for many different stages of drug discovery and
52 development, such as automation in pharmacology assays, clinical trials, and basic science
53 research. Previous studies have focused on predicting structure-function relationships based on
54 chemical structure of small molecules and potency assays that probe the physicochemical
55 properties of compounds to estimate associations with off-targets⁸. However, the diversity of
56 structures that interact with targets, even when they are well described like human Ether-a-go-
57 go-related gene (hERG), make it challenging to produce reliable models⁹. Several papers provide
58 small, hand-curated databases providing up to 70 pharmacological targets (i.e. receptors, ion
59 channels, transporters, etc.) with established links to adverse side effects based on a scientific
60 literature search^{5,7,10,11}. Mirams et al. recently described how integration of data from multiple ion
61 channels (e.g. hERG, sodium, L-type calcium) provided improved *in silico* prediction of
62 torsadogenic risk¹². Chen et al. proposed a machine learning approach to predict adverse drug
63 reaction (ADR) outcomes for given patient characteristics and drug usage¹³. Another study
64 highlights importance of predicting the likelihood of clinical trial side effects using human genetic
65 studies of drug-targeted proteins¹⁴. From a pharmacogenomics perspective, predicting drug-
66 target interactions using pharmacological similarities of drugs and the US Food and Drug
67 Administration (FDA) Adverse Event Reporting System (FAERS¹⁵) can be beneficial for drug
68 repositioning and repurposing¹⁶.

69
70 FAERS is a voluntary, post-marketing pharmacovigilance tool that can be used to monitor the
71 clinical performance of drugs. In this study, we explore an alternative use of FAERS data to predict
72 compound safety using Medical Dictionary for Regulatory Activities (MedDRA[®]¹⁷) terms, which
73 we envision to be useful for future preclinical studies. Our machine learning approach is different
74 from the aforementioned approaches because we not only predict adverse drug reaction

75 occurrences of drugs but most importantly also extract biologically meaningful target-ADR links.
76 Using an *in vitro* secondary pharmacology database of more than 2,000 marketed or withdrawn
77 drugs (see Methods), we built a random forest model to predict drug-ADR and target-ADR
78 associations. We validate drug-ADR predictions through systematic Side Effect Resource
79 (SIDER) drug label analysis and 221 target-ADR predictions through systematic literature co-
80 occurrence analysis. Furthermore, we find canonical target-ADR associations, such as hERG
81 binding causing cardiac arrhythmias. We also encountered unexpected associations which
82 warrant further investigations, such as a link between Phosphodiesterase 3 (PDE3) and several
83 ADRs, including congenital renal and urinary tract disorders. We conclude our study with potential
84 targets that are associated with cardiovascular and renal ADRs to demonstrate the utility and
85 possible impact of this method in drug development and preclinical safety sciences by enabling
86 prediction of ADRs from *in vitro* pharmacological profiles.

87 **Results**

88 **Systematic *in vitro* pharmacology of marketed and withdrawn drugs**

89 To link gene targets to ADR occurrence, we utilized *in vitro* pharmacology assay data for 2134
90 marketed or withdrawn drugs, generated by Novartis, and ADR reports from FAERS (Figure 1A,
91 Supplementary Table 1). Withdrawn drugs and their assay data are also included due to the fact
92 that they are associated with a plethora of ADRs, and thereby constitute an important resource
93 for our predictive approach. Figure 1B summarizes the top 50% of frequently occurring primary
94 indications, classified by the Anatomical Therapeutic Chemical (ATC) codes, of the 2134 drugs
95 using a word cloud. The categories that have the highest number of compounds are antibacterial,
96 ophthalmological, and antineoplastic drugs. The *in vitro* pharmacology assay data includes AC_{50}
97 values for each drug at up to 218 different assays for 184 gene targets (see Supplementary Table
98 2 for a list of target assays). There are 6 classes of these 184 gene targets, with the majority
99 (47%) of targets falling into G protein-coupled receptors (GPCRs) (Figure 1C), which is a
100 dominant, widely studied drug target family, broadly represented by marketed drugs¹⁸. Figure 1D
101 is a heatmap visualization of the *in vitro* pharmacology assay data, where each row is a drug,
102 grouped by their ATC anatomical main group terms¹⁹, and each column is a target assay, grouped
103 by target class. It consists of AC_{50} values of drugs for target assays. The heatmap is not a
104 complete data matrix; 70% of drug-assay combinations have not been tested, i.e. these

105 combinations have NA value for AC₅₀. Nevertheless, our data indicate relatively uniform assaying
106 with respect to the different drug classes.

107 **Analysis of adverse event reports from FAERS connects drugs with human ADRs**

108 We queried FAERS¹⁵ using openFDA²⁰ for 2134 marketed or withdrawn drugs in October 2018
109 (FAERS Q4_2018 version; covering all reports from January 2004 to October 2018) and retrieved
110 671143 adverse event reports using our data extraction criteria (Figure 2A). We only included
111 reports which were submitted by physicians and were annotated as the primary suspect drug²¹.
112 There are 464 drugs that did not have a matching name in FAERS, 341 drugs that did not have
113 any adverse event reports, and 1329 drugs with at least 1 adverse event report. We developed a
114 significance test based on a binomial null distribution and false discovery rate (FDR) multiple
115 testing correction to determine if the observed ADR occurrence was significantly high to be
116 classified as an association (or alternatively no association) between ADR and drug (see Methods
117 for detail). The resulting drug-ADR associations corresponded strongly (odds ratio = 11, χ^2 -test,
118 p-value < 10⁻¹⁶) with those identified with ERAM (Empirical-Bayes Regression-adjusted Arithmetic
119 Mean), an established Bayesian method based on the proportional reporting ratio adjusted for
120 covariates and concomitant drugs^{22,23}. Overall, we observe a positive trend between the number
121 of adverse event reports and the number of ADR associations (Figure 2B). Antineoplastic and
122 immunomodulatory drugs (Figure 2B, blue, N=155) have many ADR associations while the extent
123 of ADR association for antihypertensive drugs (Figure 2B, red, N=35) varies more widely. As an
124 example, we visualized our drug-ADR associations (Figure 2C), in which ADRs are grouped by
125 MedDRA System Organ Class (SOC) level terms and drugs are grouped by ATC anatomical main
126 group terms¹⁹, revealing that ADRs are widespread across organs caused by antineoplastic and
127 immunomodulating agents (Figure 2C, label L), as well as nervous system drugs (Figure 2C, label
128 N).

129

130 **Random forest model learns relationship between *in vitro* pharmacology and reported 131 ADRs in humans**

132 We deployed a machine learning approach to predict ADRs for a given drug from their *in vitro*
133 secondary pharmacology profiles (Figure 3A). We consider this a multi-label classification
134 problem because a given drug can cause multiple ADRs based on its possible engagement with
135 multiple targets and because a single target may be associated with multiple ADRs. We
136 discretized and one-hot encoded our *in vitro* pharmacology assay data (AC₅₀ values) into 3

137 classes: highly active ($AC_{50} < 3 \mu\text{M}$), active ($3 \mu\text{M} \leq AC_{50} \leq 30 \mu\text{M}$) and inactive ($AC_{50} > 30 \mu\text{M}$),
138 which reflect commonly used ranges in the field⁴. In total, 413 features (assay information) were
139 used to predict 321 High Level Group Term (HLGT) ADRs or 26 System Organ Class (SOC)
140 ADRs for each drug. The observed drug-ADR associations from FAERS, as described above,
141 constitute the dependent variable that the model is learning. We constructed a unifying binary
142 relevance random forest model, which consists of 321 random forest HLGT ADR models. The
143 models were first trained and tested, using 5-fold cross validation where each fold is selected
144 sequentially (Figure 3B). We used 1329 drugs for model construction because these drugs had
145 at least 1 adverse event report in FAERS Q4_2018. The remaining 805 drugs, which did not have
146 any ADR reports, were excluded for training or cross-validation. The model predictions are in
147 probability format, which is used later for target-ADR predictions, and in boolean format (Figure
148 3A), to enable assessment of model performance via accuracy; macro-precision; macro-recall;
149 Matthew's correlation coefficient (MCC), a performance measure that takes class imbalance into
150 account; and area under the receiver operating characteristic curve (macro-AUROC) (Figure 3B).
151 The unifying random forest model performance of SOC ADRs and HLGT ADRs using the full
152 training set (1329 drugs) and the 5-fold cross validation sets (266 drugs, averaged) are depicted
153 in Figure 3B. Accuracy ranges from 0.82 to 0.98, macro-precision ranges from 0.5 to 0.85, macro-
154 recall ranges from 0.29 to 0.74, MCC ranges from 0.37 to 0.83, and macro-AUROC ranges from
155 0.80 to 0.96. Compared to SOC level (21 ADR terms), the finer grain HLGT level (321 ADR terms)
156 had proportionally fewer drug-ADR associations; additionally, the performance of the HLGT and
157 SOC models are comparable. We therefore proceeded with the HLGT level models for further
158 investigation.

159
160 For 55 of the 321 HLGT ADRs, the corresponding random forest models simply predicted zero
161 for all drugs as mostly none (and at most 4) of the 1329 drugs with adverse event reports were
162 associated with those ADRs (Supplemental Table 3). Since these models were not predictive, we
163 did not consider them for further analyses. For the remaining 266 ADRs, we could determine
164 performance metrics (Figure 3C). Accuracy and precision were high, ranging between 0.9 and 1,
165 whilst the recall and MCC range more widely (Figure 3C). This variability occurs for ADRs that
166 have only a few drugs associated with them (Figure 3D). As the number of associated drugs
167 increases, the models learn to better distinguish true positives from false negatives so that their
168 recall and MCC values increase (Figure 3D).

169

170 **Predictive power of the random forest model for multiple FAERS reporting time periods**

171 To test if our random forest model framework is sensitively dependent on the FAERS reporting
172 period, we constructed new random forest models and performed 5-fold cross validations for both
173 SOC and HLGT levels using FAERS data from 2 different time points: Q4_2014 (including all
174 reports from January 2004 to December 2014) and Q2_2019 (including all reports from January
175 2004 to June 2019). For proper comparison, the model constructions and cross validations were
176 identical to our above described “main” model based on FAERS Q4_2018. Overall, the
177 performance metrics (accuracy, MCC, macro-precision, macro-recall, macro-AUROC) of both
178 SOC and HLGT level models are comparable between Q4_2014, Q4_2018 and Q2_2019
179 (Supplementary Table 4). This analysis demonstrates that our random forest modeling framework
180 has a comparable predictive power despite changes in the FAERS reporting time period;
181 therefore, it is not sensitive to different versions of FAERS.

182

183 **Chronological validation of predicted drug-ADR associations**

184 To validate the predictive power of our random forest modeling framework further, we performed
185 a chronological validation analysis, through identification of initial false predictions (false positives
186 and false negatives) from the random forest model trained on FAERS Q4_2014 that become
187 validated in the subsequent time period 2015-2019. The random forest model trained on Q4_2014
188 data has 421 (0.1% of a total of N=433671 model predictions) false positive drug - ADR
189 associations, i.e. based on a drug’s pharmacology profile the model predicted a probability > 0.5
190 (Figure 3A) for an ADR even though there was no association observed from the adverse event
191 reports up until 2014. However, when compared to the observed Q2_2019 FAERS data, which
192 also include adverse event reports from the time period 2014-2019, 3.1% (13) of the false
193 positives turned into (true positive) observed drug-ADR associations, which is 4.4-fold more than
194 expected by chance (χ^2 -test: p-value = 2×10^{-5}). Similarly, the Q4_2014 random forest model made
195 8519 false negative predictions, of which 2.2% (184), 40-fold more than expected by chance (χ^2 -
196 test: p-value < 10^{-16}), turned into true negative predictions when compared to the Q2_2019
197 observed drug-ADR associations. This analysis indicates that significant proportions of our model
198 predictions on drug-ADR associations that were initially “false predictions” are chronologically
199 validated through accumulation of new adverse events reports over time.

200

201 **Random forest model predicts expected ADR profiles for anti-hypertensive drugs**

202 As another demonstration of model validation, we analyzed the ADR profiles of 6 subclasses of
203 antihypertensive drugs: adrenergic alpha, adrenergic beta, ACE inhibitors, angiotensin AT2

204 inhibitors, calcium channel blockers and diuretics (Supplementary Table 5). The signature of the
205 anti-hypertensive drug subclass represents a set of ADRs that were common to all drugs in this
206 subclass. Each antihypertensive drug subclass has a unique ADR fingerprint in the Q4_2018
207 FAERS version which was closely predicted by our random forest model (Figure 3E). The
208 accuracy ranged from 0.984 to 1, with perfect specificity and precision (Supplementary Table 6).
209 The sensitivity ranged from 0.882 to 1, except for the diuretics sub-class, which had a sensitivity
210 of 0.167. This may be because diuretics target the kidney, and not the cardiovascular system as
211 the rest of the anti-hypertensive drugs do. Of note, the adrenergic alpha and adrenergic beta
212 receptor subclasses maintain distinct profiles in the predicted data. Specifically, the model
213 correctly predicts that adrenergic alpha receptor drugs are associated with suicidal and self
214 injurious behaviors, which has been reported in the literature^{24,25}.

215

216 **Random forest model validation through comparison with drug label ADRs**

217 To demonstrate the predictive power of our random forest model on a test set of drugs that were
218 not used for model construction, we utilized the model to predict drug-ADR associations for 805
219 drugs that did not have any reported ADRs in the FAERS Q4_2018 version, either because there
220 was no match with the drug name or there were no ADR reports for that drug submitted to FAERS.
221 For validation, we queried the Side Effect Resource (SIDER) database²⁶, which is independent
222 from FAERS and contains drug-ADR pairs extracted from FDA drug labels by text mining²⁶. For
223 these 805 drugs, we obtained 95 drug matches, which were further reduced to 75 drugs that did
224 not share active ingredients with drugs in the training set. Overall, 57% of positive drug-ADR pairs
225 (i.e. drugs where the model predicts ADRs) were reported in SIDER, compared to 9% of negative
226 pairs (N = 24075; χ^2 -test: p-value < 10^{-16} ; Supplementary Table 7). For instance, methysergide,
227 a 5-HT receptor antagonist used to treat migraine and cluster headaches, has predicted ADRs
228 from 6 HLG categories, all of which are supported by specific ADRs from SIDER (Figure 3F).
229 "Cardiovascular disorders with murmurs" appears in the Warnings and Precautions section of the
230 label. Other adverse events under gastrointestinal symptoms and CNS symptoms from SIDER
231 were confirmed in the Adverse Events section. Oxprenolol, a lipophilic beta blocker used for
232 treating angina pectoris, abnormal heart rhythms and high blood pressure, has predicted ADRs
233 from 3 HLG categories. The specific SIDER ADRs of bradycardia, dizziness and asthenia were
234 also confirmed in the label from the Electronic Medicines Compendium
235 (<https://www.medicines.org.uk/emc/product/3235>; accessed 09/11/2019). Overall, our random

236 forest model proves to be a powerful tool to predict both on- and off-target related drug-ADR
237 associations from *in vitro* pharmacological drug profiles.

238

239 **Random forest model predicts 221 target-ADR associations**

240 To predict which target genes are associated with which ADRs, we utilized the Gini importance
241 score to rank features for their importance in random forest models for each ADR (Figure 4A).
242 For a given ADR, we selected assays that had multiple AC₅₀ features represented in the top 5%
243 of Gini scores ranking (see Methods for detail). We then generated ADR probability predictions
244 for an *in silico* compound that is assumed to target only the selected assay with an AC₅₀ value
245 corresponding to a represented feature. We also assumed no available data for all other assays.
246 Using this *in silico* AC₅₀ profile as an input to the ADR model, we could generate the ADR
247 probability. By assessing differences in ADR probabilities (two sample t-test, FDR corrected p-
248 value < 0.1) between different AC₅₀ classes, e.g. highly active (0-3 µM) vs inactive (>30 µM), we
249 predict positive or negative correlations, collectively termed associations, between the selected
250 target assay and ADR. Unsurprisingly, some ADRs did not generate any target associations.

251

252 To find biologically meaningful associations, we first filtered out HLGTT terms belonging to SOC
253 classes that are not specific to human body parts or only procedural or intervention related (see
254 Methods for detail). Secondly, we filtered out terms that fall under the SOC class neoplasms,
255 since genes are often severely misregulated in cancers and therefore not representative of
256 neoplasm-related ADRs in the organ where the tumor resides. After filtering, we found 221
257 statistically significant target-ADR associations (Figure 4B, full details including p-values in
258 Supplementary Table 8); 51 out of 184 target assays and 132 out of 321 ADRs are represented
259 (Figure 4B). In the following sections we investigate these associations in more detail.

260

261 **Systematic literature validation of target-ADR associations**

262 To validate our ADR-target predictions, we performed a systematic literature co-occurrence
263 analysis. First, we mapped all genes corresponding to the assays and HLGTT level ADRs to their
264 respective MeSH terms (Supplementary Table 9). Next, we queried PubMed for the publication
265 identifiers linked to these MeSH terms and determined the number of publications that
266 corresponded to both a gene and HLGTT term (i.e. co-occurrence). We found at least one co-

267 occurrence publication for 66% (145) of 219 predicted unique gene-HLGT Mesh pairs, which was
268 higher (Fisher Exact test: odds ratio=1.8, p-value= 6×10^{-5}) than for all possible negative unique
269 gene-HLGT pairs (N=26705). In order to control for the fact that some ADRs and genes are
270 studied more intensively than others, we also compared our set of positive predictions to a
271 negative control set (N=4890) formed by permuted pairs from the positive set and obtained similar
272 results (Fisher Exact test: odds ratio=1.5, p-value= 3×10^{-3}). Furthermore, as quantified by the co-
273 occurrence “lift” over the reporting probability when assuming independence, $\frac{P(A,T_{co-occurrence})}{P(A)P(T)}$
274 (see Methods for details), we found 4-fold higher co-occurrence median lift values for our
275 predictions compared to all negative pairs (Mann Whitney U-test: p-value= 2×10^{-5}), and 3-fold
276 higher lift than permuted negative pairs (Mann Whitney U-test: p-value= 3×10^{-4}). We conclude that
277 our target-ADR identification method provides association predictions that are supported by the
278 literature in higher proportion than random selection of target-ADR pairs.

279

280 **Evidence for targets that are predicted to cause cardiovascular-related ADRs**

281 To further validate our model’s ability to predict target-ADR associations, we investigated a group
282 of cardiovascular ADRs. We found that hERG binding was associated with cardiac arrhythmias
283 and heart failure (Table 1). hERG encodes for a subunit of the cardiac potassium ion channel and
284 contributes to cardiac electrical activity, which is necessary to regulate the heartbeat. The
285 mechanism of action for drug-induced arrhythmias by blocking hERG has been described in
286 numerous human ²⁷ and animal studies ²⁸, as well as structural modeling ²⁹ studies (Table 1).
287 Consistently, our systematic PubMed queries found 753 co-occurrence publications in support of
288 this predicted association and 6 co-occurrences for hERG binding increasing the risk of heart
289 failure. We did not find an ADR probability associated within the range of 0-3 μM AC₅₀ of hERG
290 binding, likely because such strong binding to hERG is a common reason for deprioritizing drug
291 candidates in development ³⁰.

292

293 The model predictions also suggest that PDE3 inhibition is associated with cardiac valve disorders
294 (Table 1, 3 co-occurrence publications). PDE3 inhibition is used clinically to treat dilated
295 cardiomyopathy ³¹, which encapsulates valvular heart disorder. However, the PDE3 therapeutic
296 window is narrow, partially due to complex signaling networks ³², and careful dosing is required
297 to avoid increased mortality in response to treatment.

298

299 Furthermore, our model predicts that adenosine transporter (AdT) inhibition increases the risk of
300 pericardial disorders (Table 1). For this scenario, we did not find direct supporting evidence in the
301 literature, however there is evidence that disturbed adenosine homeostasis in pathological
302 cardiac conditions could result in pericardial effusion or pericarditis ³³.

303

304 The model suggests that glucocorticoid receptor (GR) binding is more likely to lead to myocardial
305 disorders if the drug has high affinity for GR (Table 1, 8 co-occurrence publications). This is
306 supported by the finding that glucocorticoid treatment of patients with rheumatoid arthritis
307 increased the risk of myocardial infarction ³⁴. Furthermore, it is known that dysregulation of
308 glucocorticoids can give rise to cardiotoxicity ³⁵.

309

310 Taken together, this investigation of genes associated with cardiovascular ADRs confirms the
311 well-known association of hERG with cardiac arrhythmia, and also highlights ADR associations
312 that would merit further experimental investigation.

313

314 **COX-2, PDE3, and hERG associations with kidney related ADRs**

315 Another important class of ADRs are related to the kidney (Figure 4B, label: renal). We found
316 COX-2 associated with nephropathies (Table 2), which has been well recognized (398 co-
317 occurrence publications) and evidenced previously ³⁶⁻³⁸. Interestingly, another model prediction
318 is PDE3 sensitivity correlating with congenital renal and urinary tract disorders (Table 2).
319 According to a mouse model study ³⁹, PDE3 inhibition could be a contributing factor in Polycystic
320 Kidney Disease (PKD), as PDE3 protein levels are already lower in PKD than WT kidneys. Lastly,
321 we found an unexpected association between hERG and renal disorders (excluding nephropathy)
322 (Table 2). One study has found a loss of hERG function in renal cell carcinoma ⁴⁰. In humans,
323 hERG expression in the kidney is much lower than in the heart ⁴¹. Therefore, we conclude that a
324 link between hERG and renal disorders remains a prediction that warrants further investigation.

325

326 **PDE3 and nuclear hormone receptors AR, ERα, and PR are overrepresented in ADR** 327 **associations**

328 To investigate if the number of different drugs tested for a target assay is predictive to the number
329 of ADRs associated with that target (Figure 4C), we calculated their Spearman correlation

330 coefficient and found a moderate correlation ($\rho=0.5$; Figure 4C). However, some targets had
331 considerably more associated ADRs than other targets that were tested a similar number of times,
332 indicating that more frequently performed assays do not necessarily result in a higher number of
333 associated ADRs (Figure 4C). Out of all target assays, PDE3 was associated with the most ADRs
334 (40) (Figure 4C), falling in a wide range of SOC classes (Figure 4B, Supplementary Table 8).
335 Furthermore, nuclear hormone receptors for androgen (AR), estrogen (ERa) and progesterone
336 (PR) binding assays also have disproportionately many ADR associations, compared to their
337 frequency of testing (Figure 4C). As expected, AR (7/14 ADRs), ERa (9/10 ADRs) but not PR
338 (0/17 ADRs) are associated with sexual reproductive organ and pregnancy-related ADRs (Figure
339 4B, Supplementary Table 8). Androgen is produced in the adrenal gland⁴² and we predict a link
340 between AR with adrenal gland disorders, with evidence in mouse studies⁴³. Interestingly, the
341 model predicted 6 ocular ADRs associated to PR, including vision disorders, anterior eye
342 structural change (deposit and degeneration), infections, irritations and inflammations and
343 structural changes (Figure 4B, Supplementary Table 8), for which we could find supporting
344 evidence⁴⁴.

345

346 **GABA_A receptor associations with psychoactive ADRs**

347 GABA_A receptor is the primary target of benzodiazepines (BZD), a drug class known to be
348 psychoactive with potential of addiction⁴⁵. Consistently, our model predicts that this ligand-gated
349 chloride ion channel assay is associated with 14 ADRs, 13 of which are neurologically and
350 psychiatrically related, including disturbances in thinking and perception, sleep disorders,
351 depression and suicidal behaviors (Figure 4B, Supplementary Table 8).

352

353 **Bile salt export pump BSEP associations with ADRs in various organs**

354 BSEP, encoded by *ABCB11* and a member of the superfamily of ATP-binding cassette (ABC)
355 transporters, is most highly expressed in the liver⁴¹. Drugs that target BSEP are often associated
356 with hepatotoxicity⁴⁶. However, initially, we did not find a BSEP association with hepatic and
357 hepatobiliary disorders. To investigate this false negative prediction, we noted that the dynamic
358 range of the BSEP assay specifically extends up to 300 μM because the first pass effect for orally
359 delivered drugs results in high concentrations in the liver⁴⁷; as a result, most of our data falls into
360 the 'inactive' (>30 μM class). Consistently, the BSEP inactive feature had the highest Gini score
361 for this HLG term, while its two active features had much lower Gini scores, falling outside of the

362 top 5%. To take the extended dynamic range into account, we altered the BSEP assay class
363 boundaries to 0-30 μM , 30-300 μM and >300 μM and retrained the random forest model. In this
364 case, we did find BSEP associated with hepatic and hepatobiliary disorders (Table 3, 354
365 publication co-occurrences), according to our association criteria (Figure 4A). We repeated this
366 procedure whilst replacing the first class boundary (30 μM) with 100 μM and found the same
367 association again, indicating the robustness of our results. Interestingly, with our original AC_{50}
368 discretizations (Figure 1D), we found BSEP associated with 7 other ADRs from various organ
369 classes (Table 3), much more than other targets that were assayed at a similar frequency (Figure
370 4C). This suggests that compounds potent against BSEP ($\text{AC}_{50} < 30 \mu\text{M}$) could cause adverse
371 effects in addition to hepatotoxicity, which already occurs at lower potency. We found BSEP
372 associated with urolithiasis and with disorders of the thyroid gland, upper respiratory tract
373 disorders (excl infections), lipid metabolism and central nervous system (Table 3). Since BSEP
374 expression is much lower in these organs ⁴¹, we searched the literature for evidence including a
375 substrate of BSEP, bile acid. We could find previous studies linking bile acid to these disorders
376 (Table 3), which suggests an indirect relation between BSEP and these ADRs through bile acid
377 metabolism. Lastly, we found BSEP associated with foetal complications and pregnancy
378 conditions (Table 3), both supported through prior studies that link BSEP with transient neonatal
379 cholestasis and intrahepatic cholestasis of pregnancy, respectively ^{48,49}.

380

381 Discussion

382 In this study we have taken a machine learning approach to predict human ADRs from the *in vitro*
383 secondary pharmacology profiles of a large number of marketed and withdrawn drugs. Several
384 prior studies focus on predicting ADRs directly from chemical drug structure ^{50,51}. However,
385 utilizing functional information such as *in vitro* pharmacological targeting of common (off) targets
386 represents a viable alternative to bridge the complex relationship between drugs and their effects
387 in the human body ⁴.

388

389 Our random forest model performance metrics are good considering the sparse coverage (2134
390 drugs) over a large input space (3^{184} possibilities) and partial overlap with ADR reporting for these
391 drugs, making ADR occurrence prediction effectively a one shot learning task. Importantly,
392 optimizing test performance was not the main objective of this study. Instead, we endeavored to
393 find biologically meaningful target-ADR associations. To achieve this without relying on test
394 performance, we trained on all data and made use of Gini scores to robustly select relevant

395 features for ADR probability predictions. Our novel method for target-ADR associations was able
396 to recapitulate well recognized causal relations, such as hERG with cardiac arrhythmias. For
397 others, we were able to find literature evidence in animal or *in vitro* studies but our study is, to our
398 knowledge, a first in human report. Another fraction of target-ADR associations represents
399 predictions of novel, unexpected or little known associations, such as Adenosine Transporter
400 (AdT) and pericardial disorders, for which we could find little evidence other than our analysis of
401 adverse event reports. Similar to genome-wide association studies, our quantitative methodology
402 extracts statistically significant relations from human population data. With this framework in mind,
403 our 221 associations form a rich resource that can be used for further mechanistic studies in the
404 drug discovery process.

405
406 Our random forest model is agnostic to molecular mechanisms; therefore, resulting associations
407 could arise from indirect regulation. A likely example is the bile transporter BSEP, which is
408 associated with numerous ADRs, although it is most highly expressed in the liver and kidney. We
409 have related our findings to evidence that misregulation of its substrate, bile acid, could result in
410 disorders related to kidney stones, lipid metabolism, thyroid gland, respiratory system, and central
411 nervous system. This also indicates the strength of our approach, which can relate genes to
412 physiological processes unbiasedly in humans, without any interventions or large scale genome-
413 wide association studies, but solely with voluntary adverse event reporting.

414
415 While we recommend this approach to find target-ADR associations to impact safety awareness
416 in drug discovery, we are also aware of the limitations. Firstly, the presented analyses are limited
417 by the input data. The *in vitro* data matrix is incomplete (targets in the *in vitro* pharmacology panel
418 cover a small fraction of the biological target space and not all drugs were tested in all assays).
419 We recognize that the present set of targets is biased towards the GPCR target family with limited
420 representation of other therapeutic or ADR-associated targets such as ion channels and kinases.
421 Also, data are influenced by prior knowledge; for example, more than 87% of all drugs in the set
422 were tested for hERG activity. High affinity (lower AC_{50} value) for hERG is associated with higher
423 probability for QT prolongation for human and non-human preclinical species^{27,28}. As discussed
424 earlier, there are not many drugs with a hERG AC_{50} value in the highly active class (0-3 μ M),
425 which is a commonly encountered roadblock for drug candidates to progress towards clinical trials
426³⁰. Only about 10% of all drugs fall into the highly active class in our assay data. To limit feature
427 engineering, our AC_{50} discretization into three classes (Figure 1D) was kept uniform across all
428 assays. Notably for the BSEP assay only, the dynamic range extends up to 300 μ M and as a

429 result most of our data falls into the 'inactive' (>30 μ M) class. Consequently, we initially did not
430 find the expected association with hepatotoxicity. We rectified this by reclassifying the BSEP
431 assay data according to levels required for hepatotoxicity of BSEP inhibition^{52,53} and indeed
432 recovered the expected association.

433
434 Secondly, *in vitro* potency is a very simplified marker of clinical effect, and does not take into
435 account prolonged dosing, comorbidity or pharmacokinetic/pharmacodynamic relationships (e.g.
436 therapeutic window). For 9 of 184 assays, non-human proteins were assayed (e.g. rat brain was
437 used as a source for the benzodiazepine receptor) which may not be a direct correlate of the
438 human protein. Further development of the model would require addition of parameters on
439 occupancy and pharmacodynamic components for more precision and enhanced predictive
440 value.

441
442 Thirdly, the FAERS database has limitations. For example, drug-ADR associations may be
443 mislabeled, e.g. anti-hypertensives are often reported as associated with hypertension as an
444 ADR, rather than as the indication. This and other limitations are discussed by Maciejewski et al.
445²¹ with suggestions and methodology for further refinement of the method. Additionally, the
446 FAERS database does not contain information on the total number of patients exposed to a
447 particular drug, nor is it necessarily a reflection of the true incidence or frequency of ADRs.

448
449 This work retains several uncertainties. One of the most critical might be the prediction of
450 congenital ailments, which are hard to prove. The one example we would like to highlight is the
451 PDE3 enzyme association with congenital renal disorders association. While the association is
452 correct, the modality has to be clarified: PDE3 inhibitors are proposed to ameliorate certain forms
453 of chronic kidney disease⁵⁴, instead of causing it. Thus, predictions of congenital disorders should
454 be considered but confirmed by checking the modality of the effects.

455
456 We investigated one-to-one associations between targets and ADRs because these relationships
457 are biologically meaningful and have utility in preclinical drug development. However, in some
458 cases, a given ADR can be a prerequisite for others (e.g. hypotension leading to reflex
459 tachycardia). We leave a model extension to incorporate these dependencies as future work. For
460 target-ADR associations, we utilized our random forest model for a single drug at a time. One can
461 repurpose our model to predict possible ADRs from combination drug therapies and likelihood of
462 drug-drug interactions. In principle, this can be extended for combination therapies by merging

463 the *in vitro* data from the individual compounds. Offside and Twosides databases can be used for
464 validation ⁵⁵. Similarly, our model can be utilized for drug repositioning and repurposing, using
465 similar target-ADR profiles. In conclusion, our random forest model and the target ADR
466 associations provide a validated, comprehensive resource to support drug development and
467 future human biology studies.
468

469 **Methods**

470 ***In vitro* secondary pharmacology assays for marketed drugs**

471 AC₅₀ values of 2134 marketed drugs (Supplementary Table 1) were measured in up to 218
472 different *in vitro* secondary pharmacology assays. Compounds were obtained from the Novartis
473 Institutes of Biomedical Research (NIBR) compound library and tested in a panel of *in vitro*
474 biochemical and cell-based assays at Eurofins and at NIBR in concentration-response (8
475 concentrations, half-log dilutions starting at 30 μM). Assay formats varied from radioligand binding
476 to isolated protein to cellular assays. Example protocols may be found at
477 <https://www.eurofinsdiscoveryservices.com/cms/cms-content/services/in-vitro-assays/> .

478 Normalized concentration response curves were fitted using a four parameter logistic equation
479 with internally developed software (Helios). The equation used is for a one site sigmoidal dose
480 response curve Y as a function of tested concentrations X: $Y(X)=A+(B-A)/(1+(X/C)^D)$, with fitted
481 parameters A=min(Y), B=max(Y), C=AC₅₀ and exponent D. By default, A is fixed at 0, whereas B
482 is not fixed.

483
484 If a drug was not tested against a specific assay, the AC₅₀ value was set to NA (not available).
485 AC₅₀ values from similar assays with the same gene target were merged to reduce the NA data
486 and features in the random forest model; this procedure resulted in 184 different target assays
487 (Supplementary Table 2). In case any merged assays had multiple AC₅₀ values for the same drug,
488 we averaged these geometrically to take into account variation over orders of magnitudes. In
489 figures 1D and 2C, the drugs are classified according to their annotated Anatomical Therapeutic
490 Chemical (ATC) code ¹⁹. In case of multiple ATC codes, we assigned the most frequent level 1
491 code.

492

493 **Mining adverse event reports of marketed drugs using OpenFDA**

494 In this study, we utilized openFDA to acquire FAERS reports related to the query compounds^{15,20}.
495 This Elasticsearch-based API provides a raw download access to a large volume of structured
496 datasets, including adverse events reports from FAERS.

497
498 We used generic compound names (e.g. “Amoxicillin”) to query through the openFDA interface,
499 accessed programmatically using Python. In order to maximize the coverage over FDA datasets,
500 we normalized generic names to uppercase format followed by a name similarity metric to filter
501 out unrelated records in our analysis. We included reports when the Jaro similarity between the
502 query generic name and reported compound name was equal or greater than 0.8. To illustrate, to
503 query “3alpha-Androstanediol”, we acquired reports including “3 α -Androstanediol”,
504 “Androstanediol”, “3-alpha-Androstanediol” as different lexical variations of the generic name and
505 collated the resulting adverse event reports.

506
507 As the FAERS database contains information voluntarily submitted by healthcare professionals,
508 consumers, lawyers and manufacturers, adverse event reports may be duplicated by multiple
509 parties per event, and may be more likely to contain incorrect information if submitted by a non-
510 medical professional. To reduce reporting bias and increase report information accuracy, we only
511 analyzed reports submitted by physicians (data field: ‘qualification’ = 1). In this subset of adverse
512 event reports, the data were further filtered by reported drug characterization, which indicates
513 how the physician characterized the role of the drug in the patient’s adverse event. A drug can be
514 characterized as a primary suspect drug, holding a primary role in the cause of the adverse event
515 (data field: ‘drugcharacterization’ = 1); a concomitant drug (‘drugcharacterization’ = 2); or an
516 interacting drug (‘drugcharacterization’ = 3). Here, we included only primary suspect drug reports.
517 Without this restriction, model performances did not improve. We obtained all adverse events
518 reports corresponding to the query compound that passed through the aforementioned filters.

519
520 Adverse event report descriptions are coded as medical terms of MedDRA terminology¹⁷. Medical
521 observations can be reported using 5 hierarchical levels of medical terminology, ranging from a
522 very general System Organ Class term (e.g. gastrointestinal disorders) to a very specific Lowest
523 Level Term (e.g. feeling queasy). Each term is linked to only one term on a higher level. For each
524 report, we recorded all MedDRA Reaction terms (data field: “reactionmeddrapt”) at the Preferred
525 Term level and mapped these Preferred Terms to Higher Level Group Term and System Organ
526 Class level. For each (ADR term, drug) tuple, we then calculated the ADR occurrence, defined as

527 the following fraction: number of adverse event reports containing that ADR term relative to the
528 total number of ADR reports for that drug.

529
530 For different FAERS versions (Q4_2014, Q4_2018 and Q2_2019), we used the same query
531 except the time parameter TO, which was set to 12/30/2014 for the Q4_2014 query. For other
532 two queries, we didn't set the limit parameter which was filled with the query time by default (query
533 date was 10/10/2018 for Q4_2018 and 08/12/2019 for Q2_2019).

534

535 **Random forest models**

536 To construct and train our models (Figure 3A), we used AC_{50} values for a panel of target assays
537 for marketed drugs (model input; independent variable) and ADR occurrences of the compounds
538 (model output/predictions; dependent variable). Since there may be several ADRs associated
539 with any given drug, we considered this a multi-label learning problem. We took a “first-order
540 strategy”, i.e. we assume there is no correlation between different ADRs, and a “divide and
541 conquer” strategy, i.e. we decompose our multi-label learning task into n independent binary
542 classification problems, where n is the number of different ADR terms in our output data ($n = 26$
543 for SOC and $n = 321$ for HLGTL level respectively). We built a random forest⁵⁶ binary classifier for
544 each ADR using Binary Relevance with the random forest modeling option in mlr package⁵⁷ and
545 utiml package in R⁵⁸.

546
547 To define the features for the random forest models, we discretized and one-hot encoded our
548 input AC_{50} values. Discretization was essential to limit the number of features and enhance the
549 predictive power of the model. We defined 3 classes (levels) of AC_{50} ranges for each target assay.

- 550 ● Highly active class: AC_{50} in $[0, 3 \mu\text{M})$
- 551 ● Active class: AC_{50} in $[3 \mu\text{M}, 30 \mu\text{M}]$
- 552 ● Inactive class: AC_{50} greater than $30 \mu\text{M}$

553 If the AC_{50} value is NA, the values for all Classes are 0. Each drug has AC_{50} values for 184
554 (merged) assays, so there are $184 \times 3 = 552$ binary features to represent our input data. Features
555 consisting of only 0 values were removed, resulting in 413 input features used for model
556 construction.

557
558 The observed ADR occurrences were discretized into binary dependent variables. To achieve
559 this, first let N_d be the total number of ADR reports for a given drug. The probability to observe an
560 ADR occurrence $O^{\text{ADR}} = X / N_d$ at random is equivalent to choosing that ADR X times out of N_d

561 with X distributed binomially: $X \sim \text{bin}(N_d, p=1/n)$. Here, n represents the total number of ADRs as
562 defined above. Under this null distribution, we calculate the p -values for all observed ADR
563 occurrences O^{ADR} for a given drug, and then perform a Benjamini-Hochberg False Discovery Rate
564 (FDR) correction (using the Python statsmodels package). If an FDR-corrected p -value is < 0.01 ,
565 then the ADR value for that drug is 1, reflecting an association; 0 otherwise.

566
567 All random forest models were first trained using 5-fold cross validation and each fold is selected
568 sequentially. 1063 drugs were used for training and 266 drugs were used for testing in each fold.
569 Then, the drugs with at least 1 ADR report are used as a training set. For a given (drug) input of
570 AC_{50} values and ADR, the random forest model output, termed ADR probability, can be
571 interpreted as the probability that the ADR is associated with the drug. To enable direct
572 comparison of model predictions with binarized ADR occurrences, we binarized these ADR
573 probabilities with a simple threshold value of 0.5. These binary values were used for training,
574 cross validation and to calculate classification performance metrics (Figure 3B,C). All models
575 have been constructed the same way regardless of different FAERS versions.

576
577 We evaluated our models based on five metrics: accuracy, Matthew's correlation coefficient
578 (MCC), macro-precision, macro-recall and area under the receiver operating characteristic curve
579 (macro-AUROC). These metrics are calculated using their definitions below, except 2 metrics: (1)
580 MCC, which is calculated using mltools package in R (<https://github.com/ben519/mltools>) and (2)
581 AUROC, which is calculated using precrec package in R⁵⁹.

- 582 • Accuracy = $(TP + TN) / (TP + TN + FP + FN)$
- 583 • Precision = $TP / (TP + FP)$
- 584 • Recall = $TP / (TP + FN)$
- 585 • MCC = $(TP * TN - FP * FN) / \text{SQRT}((TP + FP) * (TP + FN) * (TN + FP) * (TN + FN))$
- 586 • AUROC = $\int_{x=0}^1 TPR(FPR^{-1}(x)) dx$

587 where TPR (true positive rate = $TP / (TP + FN)$) and FPR (false positive rate = $FP / (FP + TN)$).
588 The corresponding metrics for each ADR model (Figure 3C, 3D) are accuracy, precision, recall,
589 and MCC, which is calculated using mltools package in R (<https://github.com/ben519/mltools>).

590
591 **Determination of target-ADR associations**
592 To find associations between gene target assays and ADRs (Figure 4), we first generated ADR
593 probabilities specific to a given assay. As a model input, one out of its three random forest input
594 features' value was set to 1 and all others to 0. This simulates the scenario of an *in silico*

595 compound that is potent with an AC_{50} value in the range corresponding to the positive feature
596 only. We then utilized the ADR's random forest model, pre-trained on all available marketed drug
597 data (see previous section), to calculate the resulting ADR probability. We repeated this
598 procedure for each feature of all assays and each ADR.

599
600 To select the predictive features for a given ADR, we ordered the pre-trained random forest
601 model's input features according to their Gini importance score⁶⁰ and denote the top 5% as
602 significant features. Our criteria for a gene (target assay) - ADR pair were:

- 603 • For a given ADR: at least 2 out of 3 assay features need to be significant in order to make
604 a reliable comparison between the ADR probabilities with respect to AC_{50} values.
- 605 • At least one of the ADR probabilities of the significant features has to be larger than zero.

606
607 We filtered out target-ADR pairs if the ADR term maps to the following SOC classes, which are
608 not specific to body parts or underlying human biology:

- 609 • general disorders and administration site conditions
- 610 • injury, poisoning and procedural complications
- 611 • investigations
- 612 • neoplasms benign, malignant and unspecified (incl cysts and polyps)
- 613 • poisoning and procedural complications
- 614 • social circumstances
- 615 • surgical and medical procedures

616 To ensure the reproducibility of the target-ADR pair selection procedure, we repeated the random
617 forest model training with different seeds for a total of 5 times. We then took the union of the 5
618 sets of target-ADR pairs and discarded pairs that were only found once out of 5 runs. Finally, to
619 determine if the mean ADR probabilities between the selected AC_{50} classes were statistically
620 significantly different, we performed a two-sample t-test with sample sizes equal to the number of
621 times a class was selected (ranging from 2 to 5 times) using the Python scikit.stats package. In
622 case all three AC_{50} classes were represented, we tested the highly active versus inactive class.
623 We then performed a Benjamini-Hochberg FDR correction. If the FDR-corrected p-value is < 0.1 ,
624 then the target-ADR pair is considered a statistically significant association (Figure 4B,
625 Supplementary Table 8).

626

627 To evaluate the relation between the HLGT level ADR term hepatic and hepatobiliary disorders
628 and target assay BSEP, we also trained and analyzed two random forest models as described
629 above to find target-ADR pairs but with only the BSEP assay data discretized with class
630 boundaries [0, 30 μ M), [30, 300 μ M] and >300 μ M or [0, 100 μ M), [100, 300 μ M] and >300 μ M.

631
632 **Side Effect Resource (SIDER) analysis**
633 The Side Effect Resource (SIDER; version 4.1) was downloaded
634 (<http://sideeffects.embl.de/download/>; accessed 09/16/2019). The file meddra_all_se.tsv.gz
635 contains drug-ADR pairs extracted from drug labels using text mining²⁶. The supplied MedDRA
636 preferred term (PT) was mapped to HLGT used for the random forest modeling. The file
637 drug_atc.txt provides mappings from drug names as used in SIDER to Anatomical Therapeutic
638 Chemical (ATC) codes. ATC codes for the 805 drugs in the test set were obtained from the NIBR
639 compound database, and matched to ATC codes from SIDER. For drugs that could not be
640 matched via ATC codes, additional matches were obtained by mapping the compound name, first
641 trying the name in its entirety (e.g. “butriptyline hydrochloride”, then on the first word in the drug
642 name (e.g. “butriptyline”). All matches, whether obtained on ATC codes or by drug name, were
643 reviewed manually for accuracy.

644
645 **Systematic validation of predicted target-ADR association using PubMed database**
646 We built a query based on 254 unique HLGT level ADR terms and 106 unique target genes
647 (corresponding to the assays), for which we could find a corresponding MeSH term
648 (Supplementary Table 9), to retrieve linked publication identifiers (PMIDs) from the PubMed
649 database. All PMIDs were acquired by submitting a query for every MeSH entity separately via
650 the PubMed API engine, a search engine that provides access to the MEDLINE database of
651 references and abstracts on life sciences and biomedical articles. Next, we determined the PMIDs
652 for a gene-ADR pair as the intersection of the two PMID sets of each corresponding MeSH term
653 query. Furthermore, for each possible gene-ADR pair we determined whether it was part of the
654 221 predicted associations from the Random Forest model or not. In this way, we obtained 219
655 unique positive gene-ADR pairs and a total 26705 unique negative pairs. Lastly, we generated a
656 set of negative pairs corresponding to all permutation pairs from the 39 unique genes and 131
657 unique ADRs that are part of the positive set, resulting in 4890 unique negative pairs in this
658 negative control set. To assess any statistical overrepresentation, we calculated the number of
659 pairs with at least one co-occurrence publication for both negative and positive sets and assessed
660 significance with a Fisher Exact test (Python function `scipy.stats.fisher_exact`). Furthermore, we

661 calculated the co-occurrence “lift” over the reporting probability when assuming independence,
662 defined as $lift := \frac{P(A,T_{co-occurrence})}{P(A)P(T)} = \frac{N(A,T)*N_{pubmed}}{N(A)N(T)}$, with $N_{pubmed} = 29138919$ the total
663 number of PMIDs in the Pubmed database in 2019
664 (https://www.nlm.nih.gov/bsd/licensee/2019_stats/2019_LO.html). $N(A, T)$, $N(A)$, and $N(T)$ are
665 respectively the number of retrieved PMIDs for a unique gene-ADR pair, ADR, or gene target
666 separately. To assess the location differences of the above described positive versus negative
667 distribution of lift values, we performed a Mann Whitney U test (Python function
668 `scipy.stats.mannwhitneyu`, `two-sided`, `continuity correction=True`).

669 **Figure Legends**

670

671 **Figure 1. Major elements of the target-ADR association analysis**

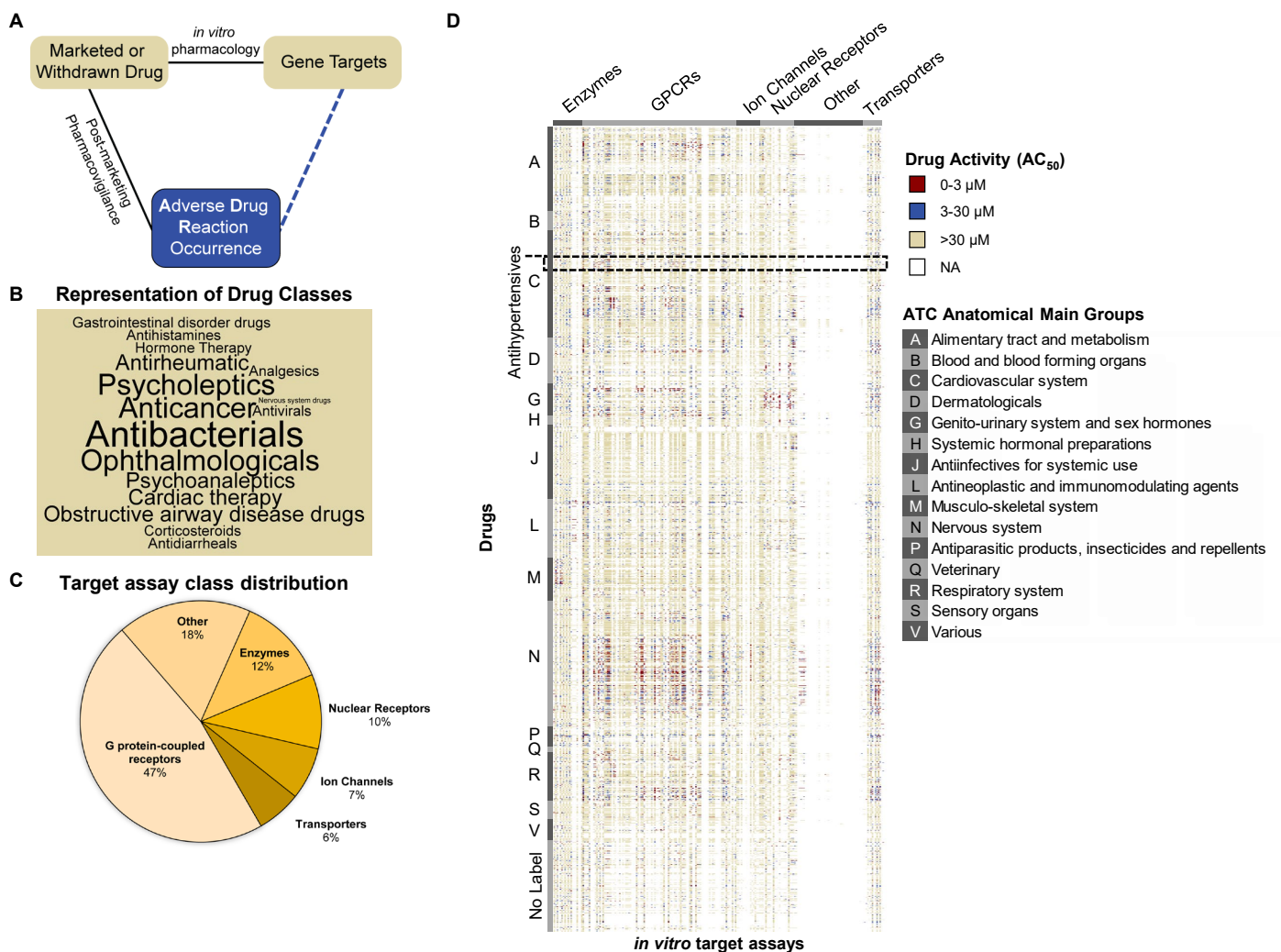
672 **A. Schematic outline of target-ADR pair determinations.** The observed relations (solid lines)
673 between drugs and adverse drug reactions (ADRs) are determined by post-marketing
674 pharmacovigilance and between drugs and their (off) targets by *in vitro* pharmacology. This
675 approach enables prediction of associations (dashed line) between targets and ADRs through
676 random forest modeling.

677 **B. Representation of drug classes in word cloud.** The cloud displays the top 50% most
678 frequently occurring drug classes, representing 2134 drugs, in the Novartis *in vitro* pharmacology
679 data warehouse. Size of the font of the drug class reflects the number of associated drugs.

680 **C. Target class distribution in the Novartis *in vitro* secondary pharmacology assay panel.**
681 The 184 targets in the Novartis assay panel cover 6 target classes. Almost half of the target
682 assays belong to the G protein-coupled receptor (GPCR) class.

683 **D. Novartis target panel potency (AC₅₀) heatmap.** The profile consists of the AC₅₀ values of
684 184 target assays for 2134 drugs. We considered an AC₅₀ value less than 3 μM as highly active
685 (red), between 3 μM and 30 μM as active (blue), and greater than 30 μM as inactive (yellow). No
686 data for a drug-target pair is labeled as NA (white). Drugs are grouped (vertically) by their
687 Anatomical Therapeutic Chemical (ATC) codes. Assays are grouped (horizontally) by target class.

FIGURE 1



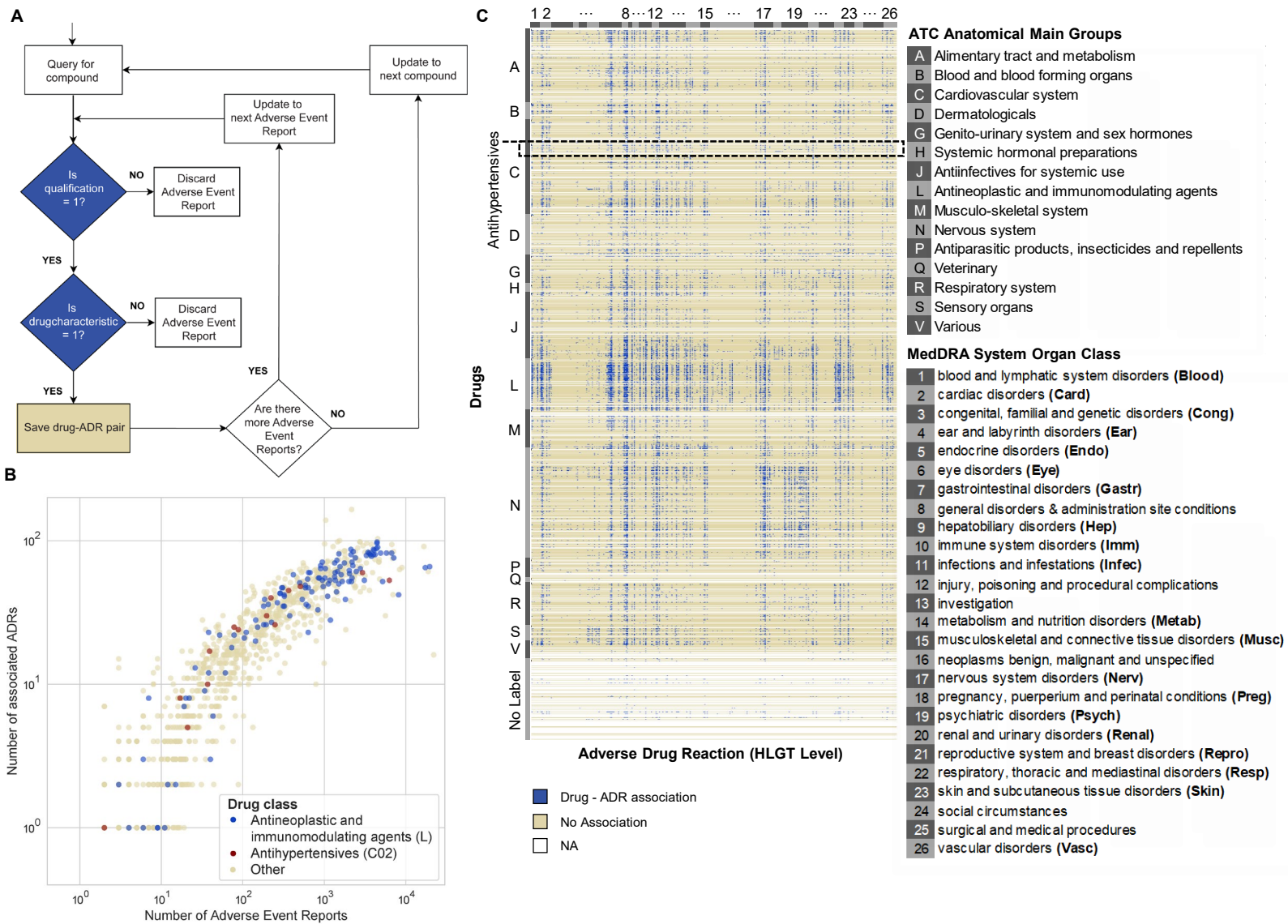
688 **Figure 2. Retrieval of Adverse Event Reports from the FDA Adverse Event Reporting**
689 **System (FAERS) database**

690 **A. Flow chart of the programmatic strategy for Adverse Event Report retrieval from FAERS**
691 **by using openFDA.** 'is qualification = 1' is a positive filter for adverse event reports that were
692 reported by physicians. 'is drugcharacterization' = 1 is a positive filter for drugs that are annotated
693 as the primary suspect drug, which hold a primary role in the cause of the adverse event.

694 **B. Scatter plot of the number of associated ADRs for drugs as a function of the number of**
695 **adverse event reports retrieved for each drug ($N_{\text{drugs}} = 1329$).** Drugs without any reported ADR
696 are not shown.

697 **C. Heatmap of ADR profiles (discretized as used for input of random forest model) for all**
698 **marketed drugs used in this study ($N_{\text{drugs}} = 2134$).** Drugs are clustered (vertically) according to
699 their ATC drug classes (A-V, or No label if without any ATC code) and HLG (high level group
700 term) ADRs are grouped (horizontally) according to the parent System Organ Class (SOC) level
701 listed in the legend.

FIGURE 2



702 **Figure 3. Application of the random forest model to characterize drug-ADR associations**

703 **A. Schematic representation of the machine learning approach.** Using input data, which is a
704 discretized AC_{50} *in vitro* pharmacological profile, we built a separate random forest model for each
705 adverse drug reaction (ADR) that predicts the probability of a drug causing that ADR. For training
706 we used all drugs for which we could retrieve FAERS Q4_2018 adverse event reports ($N_{\text{drugs}} =$
707 1329).

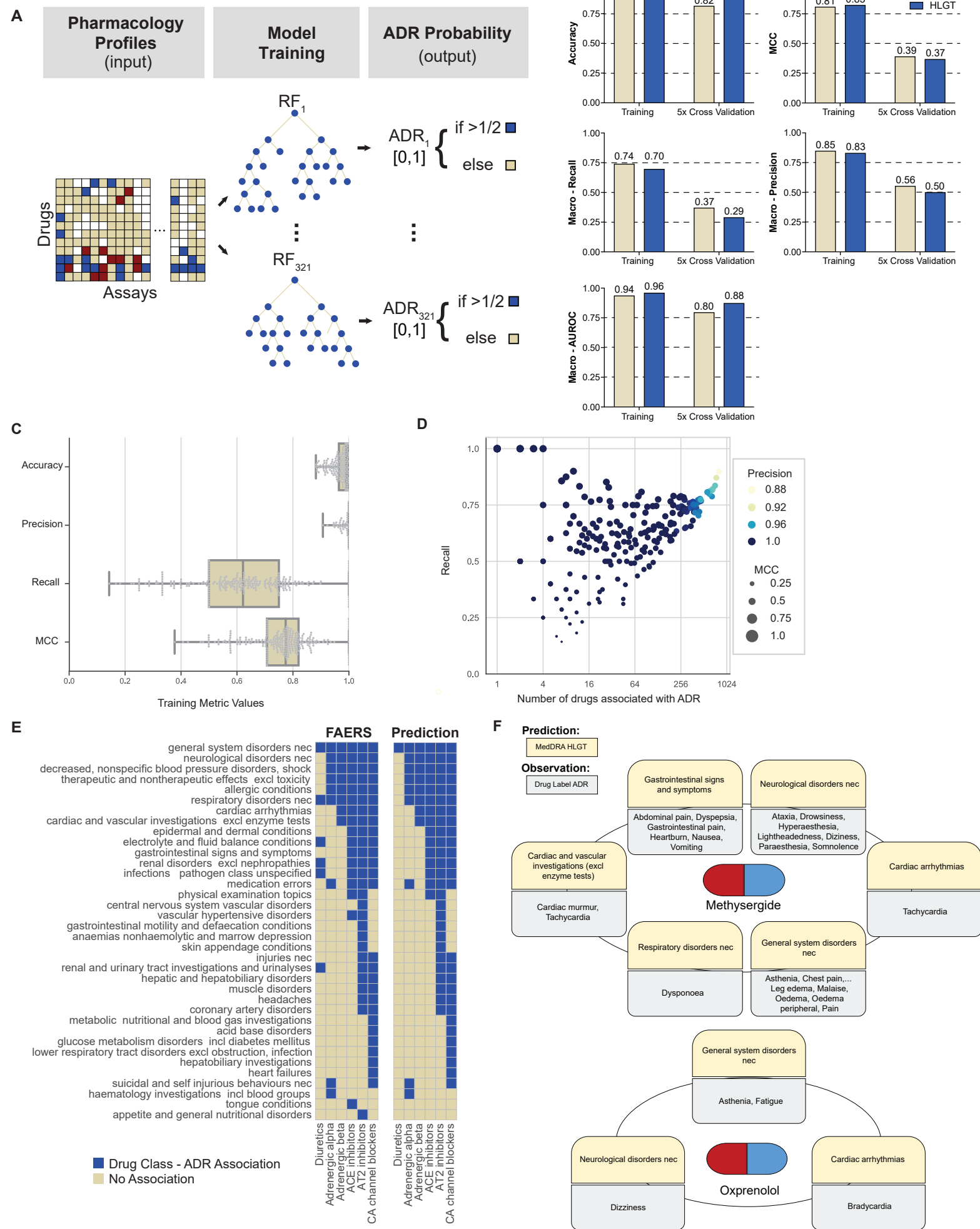
708 **B. Summary statistics of overall model performance.** We developed two unified random forest
709 models based on two hierarchical levels of organ class specifications. The high level group term
710 (HLGT; blue) unified random forest model consists of 321 ADR random forest models whereas
711 the system organ class (SOC; yellow) unified random forest model consists of 26 ADR random
712 forest models. The performance of the HLGT and SOC models is similar, except in few cases
713 when the HLGT model outperforms the SOC model. (MCC: Matthew's correlation coefficient,
714 AUROC: area under receiver operating characteristic). Training reflects performance after model
715 training on all 1329 drugs (see A). 5-fold cross validation results are averaged over each fold (all
716 metrics for each fold are detailed in Supplementary Table 4).

717 **C. Box plots indicating the distributions of the training performance metrics** (as in B) for all
718 random forest models of each individual HLGT ADR ($N_{\text{ADRs}} = 266$).

719 **D. Scatter plot of the random forest models' recall (all metrics as in C) as a function of**
720 **number of associated ADRs**, which served as positive training examples. Colors indicate model
721 precision and circle size reflects the MCC.

722 **E. ADR predictions for anti-hypertensive drugs with different pharmacological targets.** For
723 a set of 22 antihypertensive drugs, we visualized the association between the drugs and HLGT-
724 level ADRs (left). Using the ADR random forest models, we predicted the differences in ADR
725 associations between antihypertensive drugs representing various pharmacological targets (right;
726 overall 36 of the HLGT terms are visualized). True negative predictions (285 HLGT-level ADRs)
727 were omitted from this visualization.

728 **F. Examples of model validation using methysergide and oxprenolol.** The random forest
729 model predicted associations of methysergide with 6 of 321 HLGTs (yellow) which were validated
730 by comparison of ADRs from its drug label (grey) using the SIDER database. One or more of the
731 ADRs corresponding to each HLGT category were confirmed in the drug label.



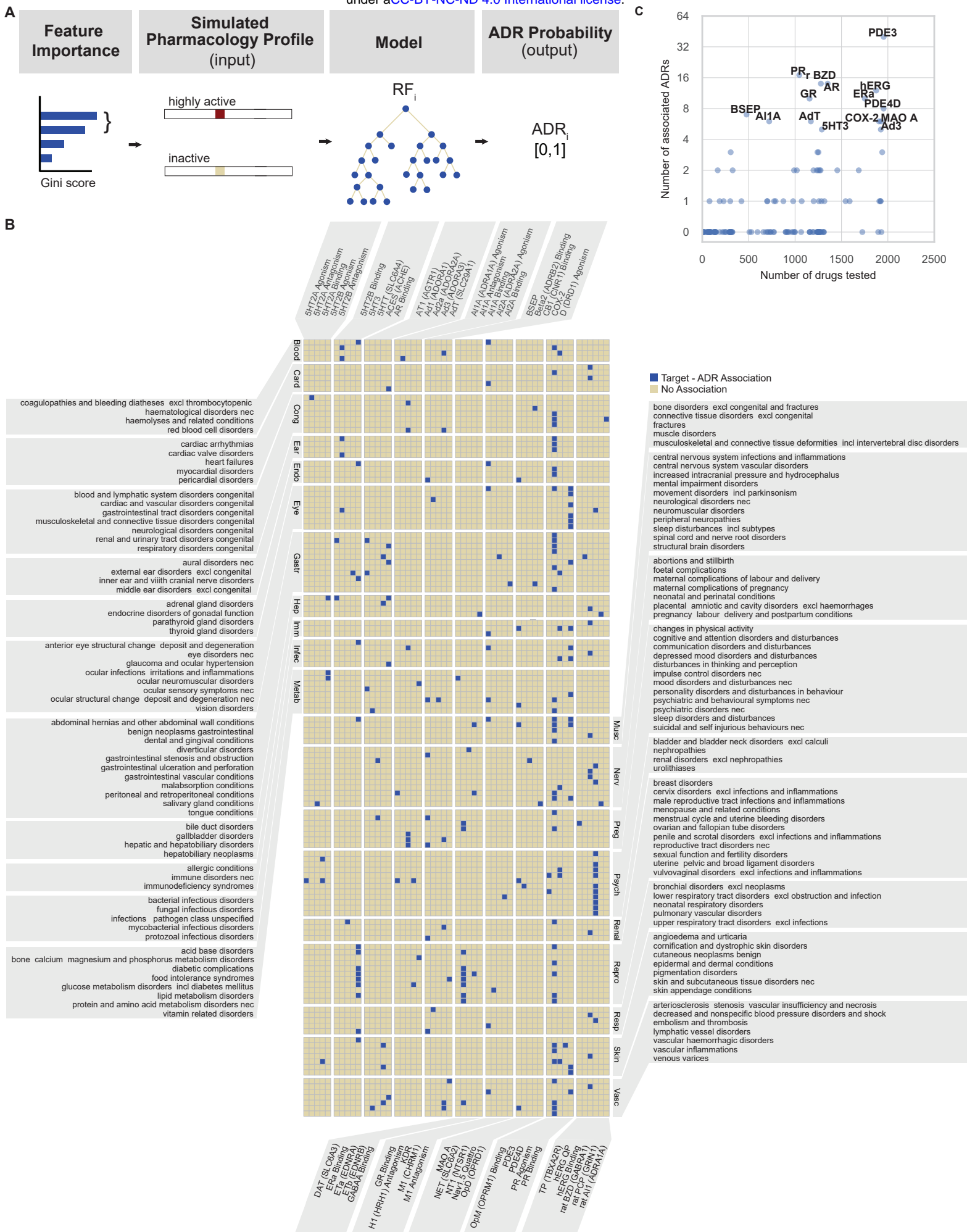
732 **Figure 4. Random forest model predicts target-ADR associations**

733 **A. Schematic outline of the *in silico* ADR-target predictions.** For an ADR of interest, we
734 determined the top 5% of features from the corresponding trained random forest model, ranked
735 according to their Gini importance scores, which measures their contribution to the predictive
736 power of the model. If at least two features (e.g. as depicted: highly active and inactive) from the
737 same target assay are within that top 5%, we determined the ADR probabilities for the simulated
738 cases where an *in silico* compound would target those assay AC₅₀ classes only. The ADR
739 probabilities of those simulated cases can then be compared to determine the concentration
740 dependence of the ADR probability. If there is a non-zero correlation between AC₅₀ values and
741 ADR probabilities, we conclude that there is an association between the respective ADR and
742 target. For full details, see the Methods.

743 **B. Heatmap showing the resulting 221 predicted target-ADR associations (blue).** Target
744 (gene symbol) assays are listed alphabetically (horizontal), and HLG_T ADRs (vertical) are
745 grouped according to their parent SOC level (as detailed in Figure 2C). For a full description of all
746 target-ADR associations and their ADR probabilities, see Supplementary Table 8.

747 **C. Scatter plot of each target (assay, N=184) showing the number of ADR associations as**
748 **a function of number of assayed drugs.**

FIGURE 4



749 **Table 1** Predicted associations between targets and cardiac ADRs.

750 High Level Group Terms (HLGT; MedDRA) associations with targets and Adverse Drug Reaction
 751 (ADR) probability in three concentration ranges (third column). Evidence of the ADR-target pairs
 752 were obtained from peer reviewed publications (fourth column). The number of publications linked
 753 to both an HLGT ADR and target gene was obtained via a systematic literature co-occurrence
 754 analysis (fifth column). hERG: human Ether-a-go-go-Related Gene associated potassium
 755 channel; PDE3: phosphodiesterase-3 enzyme; GR: glucocorticoid receptor; AdT: Adenosine
 756 transporter; COX-2: cyclooxygenase enzyme, type 2.

Cardiac Disorder HLGT	Target	ADR Probability			Literature evidence human (h), animal (a), <i>in vitro</i> (v)	Co-occurrence (number)
		0-3 μM	3-30 μM	>30 μM		
cardiac arrhythmias	hERG (Binding)	-	0.03	0.002	h ²⁷ a ²⁸ v ²⁹	753
cardiac valve disorders	PDE3	0.05	-	0	h ^{31,32}	3
heart failures	hERG (Binding)	-	0.005	0	h ⁶¹	6
myocardial disorders	GR (Binding)	0.02	-	0.005	h ^{34,35}	8
pericardial disorders	AdT	-	0.01	0	a ³³	0

757

758 **Table 2** Predicted renal ADR - target associations (detailed legend in Table 1).

Renal Disorder HLGT	Target	ADR Probability			Literature evidence human (h); animal (a), <i>in vitro</i> (v)	Co-occurrence (number)
		0-3 μM	3-30 μM	>30 μM		
nephropathies	COX-2	0.003	-	0	h ³⁶ a ^{37,38}	398
renal and urinary tract disorders congenital	PDE3	0.004	-	0	h ^{54,62} a ^{39,63}	0
renal disorders excl nephropathies	hERG (Binding)	-	0.01	0.0007	h ⁴⁰ a ⁶⁴	2

759

760 **Table 3** Predicted ADR associations with inhibition of the Bile Salt Export Pump (BSEP)
 761 transporter (detailed legend in Table 1).

HLGT	Target	ADR Probability			Literature evidence	Co-occurrence (number)
		0-3 μM	3-30 μM	>30 μM	human (h); animal (a)	
central nervous system vascular disorders	BSEP	-	0.09	0.008	for BSEP and bile acid) a ⁶⁵	2
foetal complications	BSEP	0.01	-	0	h ⁴⁸	7
pregnancy labour delivery and postpartum conditions	BSEP	-	0.1	0	h ⁴⁹	0
lipid metabolism disorders	BSEP	-	0.2	0	h ^{66,67}	5
thyroid gland disorders	BSEP	-	0.07	0	a ^{68,69}	1
upper respiratory tract disorders excl infections	BSEP	0.1	-	0	h ⁷⁰ a ⁷¹	0
urolithiases	BSEP	-	0.07	0	h ⁷²	0
		0-30 μM	30-300 μM	>300 μM		
hepatic and hepatobiliary disorders	BSEP	-	0.2	0.09	h ⁴⁶	354

762

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768

769 **Author contributions**

770 R.I., S.A., A.X.C., S.F., B.K., D.A. and L.U. conceived the study. D.A., A.F. and L.U. provided
771 the Novartis *in vitro* pharmacology data, advice and mentorship. S.A., R.I., A.X.C., S.F., B.K.,
772 W.D.M. and J.S. performed data analysis. S.A. developed the random forest modeling. R.I.
773 developed the formalism for target-ADR association inference. S.F., R.I. and A.X.C. developed
774 the query of OpenFDA. J.S. performed the SIDER analysis. S.F., J.S. and R.I. performed the
775 systematic PubMed query. S.A., R.I., and A.X.C. wrote the paper and designed the figures with
776 input from all the authors.

777

778 **Conflict of interest**

779 Authors declare no conflict of interest.

780

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