CLINICAL ADVANCEMENT FORECASTING *

Authors TBD
Related Sciences

ABSTRACT

This study examines the extent to which the outcomes of clinical trials can be predicted based on longitudinal properties of drug targets and diseases alone. We find that this is possible by comparing the historical performance of model-based target-disease pair prioritization methods to common baselines. Our primary objective is to demonstrate that statistical learning can effectively optimize such methods with no loss of interpretability. For example, non-negative linear models can produce simple weighting schemes across various types of human, animal and cell model evidence (for targets, diseases and pairings of the two) to identify target-disease pairs that advance beyond phase 2 trials with an average relative risk that is 2x higher than Open Targets composite scores. Other key characteristics of this study include: 1) a comprehensive longitudinal treatment of evidence as well as how it relates to leakage and reverse causality in biomedical research, 2) trial and/or drug details are not used in order to enable ranking for undeveloped targets/diseases, 3) analysis of the space of currently undeveloped, tractable targets with the highest likelihood of clinical success, 3) no data is used outside of Open Targets to ease reproduction and/or deployment, and 4) our method requires no expert knowledge and can easily support the inclusion of more lines of evidence over time, making it easy to operationalize.

1 Introduction

It has been well established that drugs with human genetic evidence linking their respective targets to indications in clinical trials are more likely to succeed [1, 2, 3, 4, 5, 6, 7, 8]. This information has been used to devise many target and target-disease ranking algorithms based primarily on a synthesis of multiple genetic signals alone [9, 10, 11]. It is also possible to expand the breadth of this genetic support to more targets/diseases based on knowledge graphs, protein interactions and/or disease ontologies [12, 13, 14, 15, 16]. To our knowledge, all such expansion methods identify a larger space of opportunities at the expense of expected success rates. This is not a focus of this work as we aim, instead, to establish a framework for identifying targets/diseases with the very highest possible likelihood of success first. This is accomplished by integrating human clinical, genetic/genomic, transcriptomic and proteomic data as well as cell/animal model evidence, pathway information and basic literature metrics from Open Targets [10] in a simple statistical modeling framework. It can be contrasted with far more integrative methods that rely on neural and/or graph models over extensive knowledge graphs [17, 18, 19, 20], which are more complex and difficult to interpret. We believe a desirable middle ground between these approaches and those that aim to combine many orthogonal indicators of success through expert knowledge in heuristic systems [21, 10] would: 1) permit inclusion of many types of evidence from many sources, 2) be highly interpretable, 3) support expert judgement where necessary, and 4) not require manual ranking/weighting schemes.

* *Citation*: **TBD**

A substantial challenge inherent to building such a system is the need to account for the longitudinal nature of knowledge discovery in biomedicine. This is vital because any method that optimizes for likely future clinical success based on historical clinical success may easily be biased by the non-random nature with which evidence is absent otherwise. We use only "temporalized" evidence, i.e. evidence for which timing of its emergence can be determined, and outcomes when training and evaluating our methods before ultimately applying them to present-day evidence with no restrictions on timing. We discuss motivations, prior research and our own analysis on how important this problem is for each source in Section 2.9.

Addressing such problems is common, but not ubiquitous, in studies that attempt to predict clinical trial outcomes using temporalized predictors [22, 23, 24]. The need for this is often clear in that setting where the inclusion of predictors like historical success rates for targets/diseases, trial sponsor track records, eventual patient enrollment, etc. constitute clear information leaks otherwise. This is discussed more in [22] which notes several studies that do not account for this problem, and presents "quasi-prospective" as well as true "prospective" results. The difference between the two is that the former reconstructs timelines for predictors and outcomes based on recorded event dates while the latter relies on frozen predictions that are never evaluated until years later. Nomenclature for these formulations is conflicting though, where this definition of a "quasi-prospective" design is deemed entirely prospective in some cases, e.g. [25]. We will refer to our design in this study as quasi-prospective since this definition is the best fit.

The prior works discussed so far can largely be categorized as either 1) target and target-disease prioritization methods evaluated based on how well they correlate with clinical trial success and 2) clinical trial outcome prediction models. Both are measured against the same outcomes and an important distinction between them lies in how the former methods are **not** directly optimized for those outcomes while the latter methods are. In this study, we attempt to bridge these methodologies by predicting clinical trial advancement for target-disease pairs based solely on information that would be present well in advance of any drug program or individual trial. We then calibrate these predictions to determine what thresholds are necessary to match the observed success rates from benchmarks for genetic support like OMIM [26], ClinVar [27] and GWAS. Finally, we examine how many present-day target-disease pairs are undeveloped (i.e. have never been in clinical trials), have a tractable target and are likely to see success rates matching or exceeding those calibrated benchmarks.

2 Results

In order to model clinical advancement for target-disease (TD) pairs, we first define "advancement" as progression beyond any particular trial phase across all drugs associated with any one TD pair as indicated by the presence of a later-stage trial. All results to follow consider only advancement beyond phase 2 due to limitations described in Section 4. This binary outcome is then predicted based on a list of features shown in Supplementary Table 1. Information for each of these features is only used when it was published before the year **prior** to the first phase 2 trial observed, with an exception for genetic evidence discussed in Section 2.9. A training dataset is then formed by including only TD pairs where this first phase 2 year is between 1990 and 2015. The evaluation dataset then consists of all TD pairs entering phase 2 between 2016 and 2022, with a 2 year offset from the present year (2024) to allow enough time for some trials to complete. While the average phase 2 trial duration may be as low as 2 years [28], other estimates would suggest half of them take longer than 2.9 years [29]. This means a substantial fraction of outcomes are censored, that this is an important parameter to test sensitivity to and that time itself is likely to be a crucial covariate in this formulation. The distribution of these outcomes, the number of associated targets/diseases and a variety of other statistics on this dataset are presented in Supplementary Figure 10.

2.1 Features

The predictors used consist of 27 target-disease pair features, 5 target-specific features and 1 disease-specific feature. These are listed in Supplementary Table 1. The target and disease specific features are chosen carefully such that they are either capable of being associated with years in which events supporting them occurred or result from large-scale, unbiased methods that do not favor well-studied or drugged targets/diseases. Examples of this include target-specific

tissue expression specificity scores computed from Human Protein Atlas [30] and LOEUF [31] scores from gnomAD. Simply put, our dataset combines scores from Open Targets for target-disease evidence and a select subset of target prioritisation [32] fields with almost no modifications, other than to add target and disease specific indicators of maximum trial phases reached and two extra genetic association features.

2.2 Models

We train a variety of models including constrained and unconstrained linear and tree models. The constrained variants of these models force effects of all features to increase monotonically. This is possible with no feature transformations because all scores in Open Targets are constructed such that higher scores are presumed to be advantageous. We also apply these models to our evaluation dataset using several feature ablations in order to assess the value of groups of related features.

In order to compare these models to an Open Targets composite score, we use an equally weighted sum of all scores except for those assigned lower weights in [33]. Scores from these sources are multiplied by the corresponding weight before being summed.

2.3 Performance

Figure 1 demonstrates how well our primary model in this study – a constrained, linear L2-regularized model referred to from here on as "RDG" – ranks TD pairs by comparison to a composite score from Open Targets ("OTS"). The relative risk (RR) metric used in this comparison as well as all others where not specified otherwise is defined as:

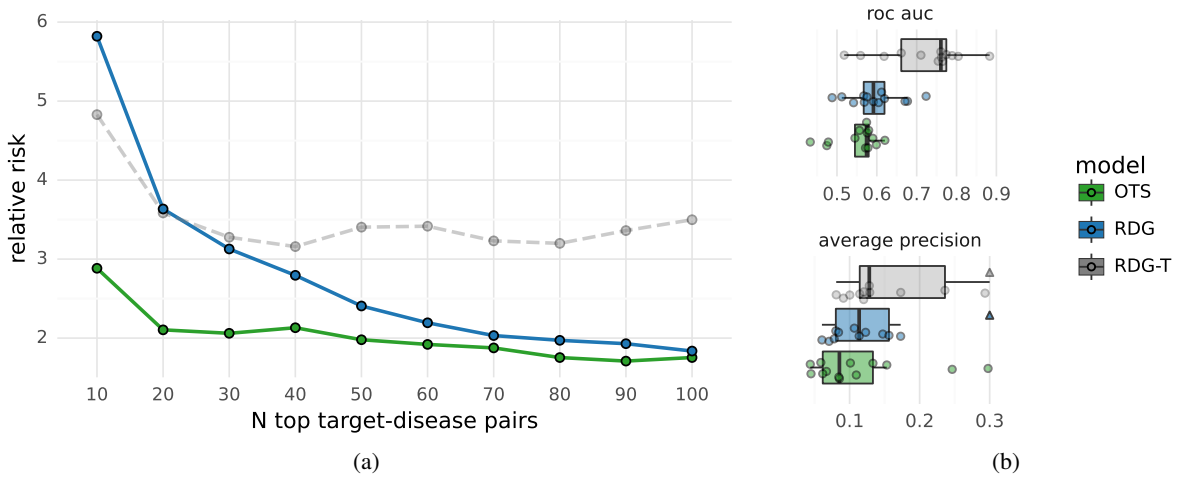
$$\frac{P(advancement|rank >= N)}{P(advancement|rank < N)}. \tag{1}$$

The third ranking method presented in Figure 1, "RDG-T", differs from the RDG model only in that it also uses time since the phase 2 transition as a predictive factor as well as all others. We observe that the use of this information almost universally improves standard performance metrics like ROC (receiver operating characteristic) and AP (average precision), however it adds little to no value in rankings beyond a level where substantial relative risk increases can be observed. In other words, it constitutes an effective but coarse mechanism for ranking TD pairs while lacking the high precision of other factors like genetic support. This is consistent with its nature as a necessary but not sufficient condition for success, and it is likely that much of the value it adds in the tail of lower rankings could be captured and enhanced if other early indicators for the many reasons trials fail [4] were also included (see more on this in Section 4). As a more practical concern, we refrain from focusing on RDG-T, or the similar GBM-T model, because neither is readily applicable to undeveloped TD pairs for which the time since phase 2 transition is not available. They are, however, a useful performance ceiling towards which future work might build towards.

A subset of therapeutic areas was used for this analysis and this is reflected in both the mean estimates and distributions of Figure 1. A full list of these can be seen in Supplementary Figure 8, which also shows the RR estimates used in any summary statistics across therapeutic areas. These were selected based on criteria described in Section 5. Lastly, Supplementary Figure 11 shows RR distributions by model with significances of their differences.

The relative risk estimates from the RDG model were also compared to univariate relative risk scores in Figure 2. This clearly implicates genetic features as being the most precise predictors, albeit with a relatively low frequency compared to others. Similar comparisons for target and disease specific features can be seen in Supplementary Figure 12. These suggest that past clinical success for targets and diseases (independent of pairings) are likely to be highly predictive of advancement as well, while genetic constraint and expression specificity of targets also exhibit modest but significant effects.

In order to establish baseline levels of success and coverage across TD pairs, we refer to several of the univariate features in Figure 2 throughout this study. Specifically, the `omim` and `ot_genetics_portal` features correspond to OMIM and GWAS baselines in the parlance of [2], [1] and [3]. We also use the `eva` feature as a baseline for ClinVar



(a) (b)

Figure 1: **Statistical learning optimizes expected target-disease pair advancement rates using longitudinal evidence**. (a) Equally-weighted average relative risk estimates across 13 therapeutic areas, by number of top rankings and 3 methods: RDG (ours), RDG-T (ours) and Open Targets composite scores. (b) Receiver operating characteristic (ROC) and average precision scores across the same 13 therapeutic areas with no limit on the number of rankings. See Supplementary Figure 8 for raw data underlying (a).

support, which has discriminative capabilities somewhere between these two. The extent to which the RDG model meets or exceeds these benchmarks in both relative risk for advancement and TD pair coverage is illustrated in Figure 3.

One objective of this study is to determine if any model, e.g. RDG, could sort TD pairs with genetic support such that at least some portion of that sorted list had a likelihood of advancement that consistently exceeds what is expected from any one source of genetic support alone. As a hypothetical example, we wanted to determine if the top 50 TD pairs out of 200 with GWAS support were more likely to advance than all 200 overall. We find that this goal is met and exceeded by the RDG model, which actually identifies more TD pairs than those that have either EVA or GWAS support alone at an expected rate of advancement exceeding that of the single source (respectively). This does not appear to be the case with the OMIM baseline, however the lack of examples in our evaluation dataset with OMIM support makes any determination difficult. See Section 2.7 for more on how these benchmarks are employed to contextualize opportunities among undeveloped TD pairs.

2.4 Sensitivity

In order to validate the stability of our findings in Section 2.3, we repeat this analysis across 18 different configurations listed in Supplementary Table 3. This includes 3 separate versions of Open Targets, 3 choices for the year defining the split between training and evaluation data and 2 choices for the length of the minimum advancement window (in years).

We find that the mean RR values from the RDG model consistently exceed the OTS model in all configurations among the very highest rankings (N=10) and also exceed the OTS model in all configurations except for 1 for N between 20 and 60. This data is shown in Supplementary Figure 14. The significance of these differences drops notably after N=40, which can be seen in the distribution of p-values from a Wilcoxon signed-rank test shown in Supplementary Figure 15.

2.5 Predictions

Top predictions from the RDG model over the evaluation dataset are shown in Supplementary Figure 9. This figure demonstrates that there are a significant number of TD pairs with genetic support from many sources and that the combined effects of non-genetic features also substantially influence these rankings.

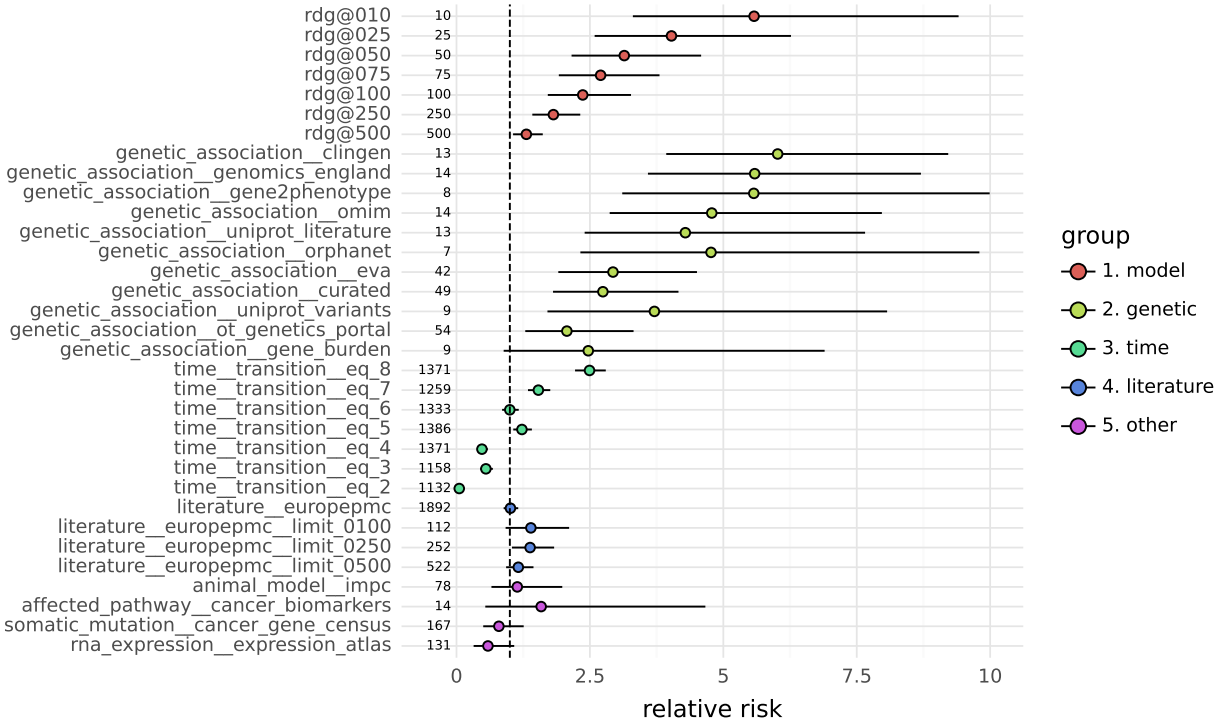


Figure 2: **Performance of individual features and predictive scores as measured by relative risk**. RDG model results denoted by `rdg@N` correspond to results for the `N` top TD pairs. The same convention is used for `literature` evidence and the `time__transition__eq_X` convention denotes RR estimates when the time since the phase 2 transition is equal to `X` years. All other features are assessed based on their existence. The counts along the origin indicate how many TD pairs were used to compute the RR numerator.

2.6 Effects

The coefficients learned by the RDG model, and the average effects they have across the evaluation dataset, are shown in Figure 4. This model most highly prioritizes genetic signals that have the greatest coverage, i.e. associations from GWAS studies through the `ot_genetics_portal` feature and associations from any curated clinical genetics source, i.e. EVA, Orphanet, UniProt, Genomics England, ClinGen and gene2phenotype, via the `curated` feature. Notably, literature and target/disease specific clinical features also have substantial effects, followed by indicators of animal evidence and target genetic constraint / expression specificity. Any features not shown were deflated to have no effect, which is possible in this model due to the non-negativity constraint. One such feature worth emphasizing is transcriptomic evidence from Expression Atlas. We found this somewhat surprising, but it is supported by arguments against transcript over/under expression as an indicator of genes that influence disease rather than the other way around [34].

It is worth noting that the discordance between the coefficients and the average feature effects of Figure 4 arises from both the frequency with which features exist and the distribution of their underlying scores. Scores for many clinical genetics features (e.g. OMIM, Genomics England, UniProt) are very frequently absent or close to 1. By comparison, scores for literature associations are typically far lower, even when limited only to cases where they exist, with a median value of 0.12 (mean=.23) in the evaluation data.

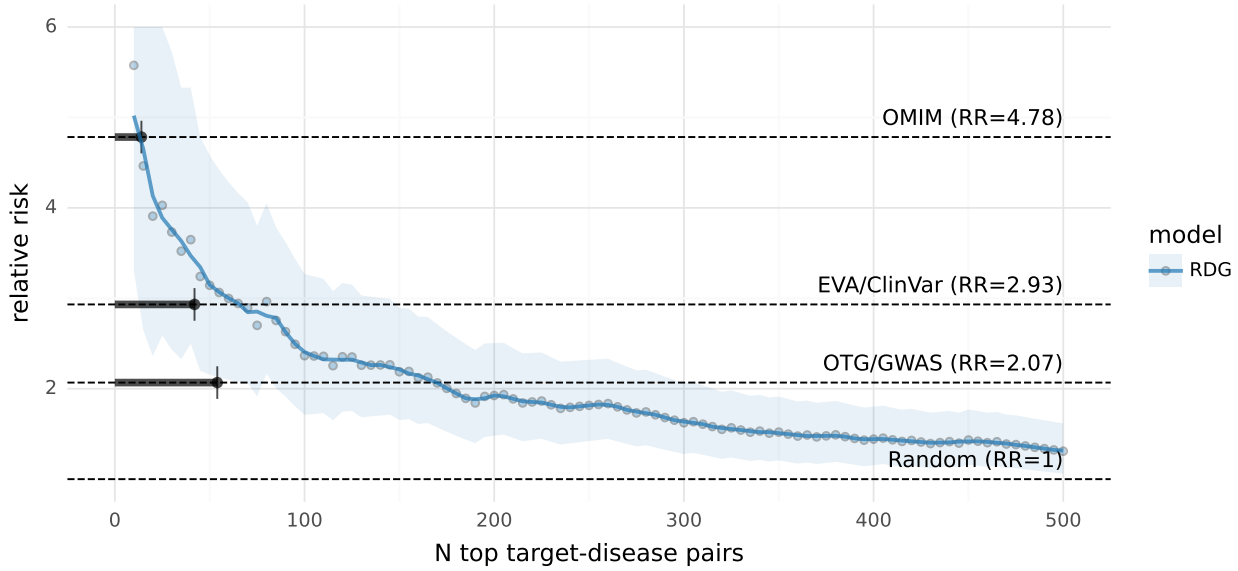


Figure 3: **RDG performance versus genetic support benchmarks across all therapeutic areas**. The RR estimates for each benchmark are based on the presence of the corresponding support across all TD pairs, and the number of pairs for which is present is represented by the horizontal bars extending horizontally from the y-axis. The bounds around the RDG RR estimates correspond to a 90% confidence interval.

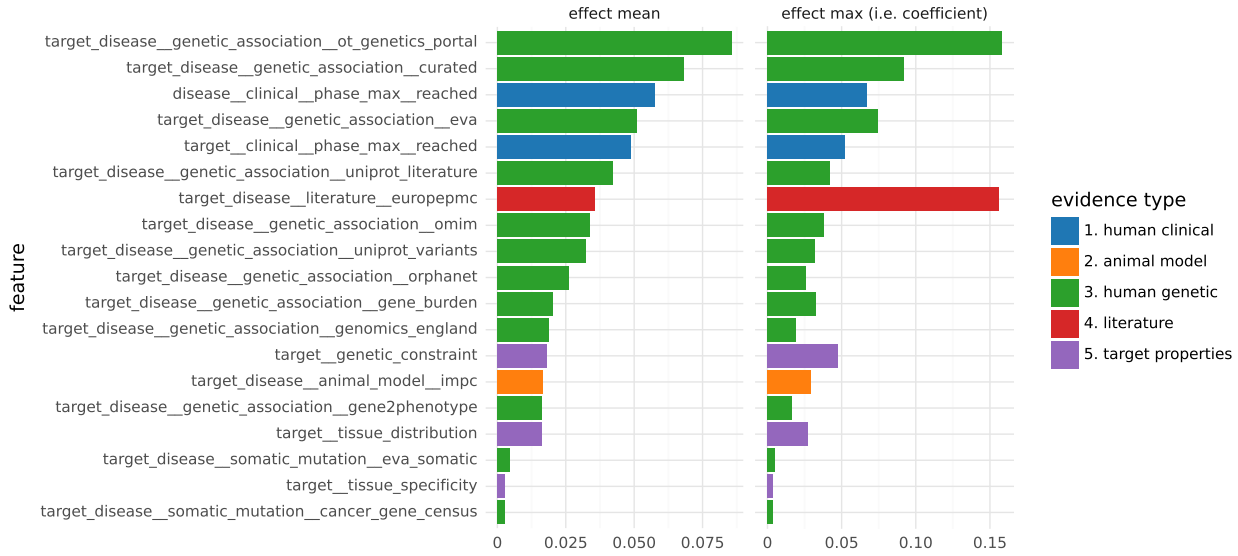


Figure 4: **RDG model feature effects**. The **effect max** values are equivalent to RDG model coefficients for the corresponding feature while the **effect mean** values indicate average values of the product between the coefficient and a particular feature value, when that feature is present.

2.7 Opportunities

A common method for identifying druggable opportunities within a specific disease context involves first ranking TD pairs according to some prioritization methodology followed by filtering or reprioritizing those ranks based on

knowledge of target tractability [35, 36, 11]. We use a similar approach to identify tractable targets associated with TD pairs that have yet to enter clinical trials. To aid in interpreting this approach, we also draw on the results of Figure 3. The data in this figure suggests thresholds for the RDG model that align to expected rates of advancement compared to several genetic support benchmarks. These thresholds are used to bucket undeveloped TD pairs before further bucketing them based on levels of tractability. The tractability buckets in Supplementary Table 2 provide HIGH, MED, and LOW confidence ratings for each type of tractability evidence based on the priorities suggested in [37].

	stage [threshold=EVA]						threshold [stage=NONE]			tractability [stage=NONE, confidence=HIGH, threshold=EVA]			
	ALL	NONE	Phase 1	Phase 2	Phase 3	Phase 4	EVA	OMIM	OTG	AB	OC	PR	SM
therapeutic area													
ALL	9724	8560	165	367	274	358	8560	679	20821	1456	655	14	2408
genetic, familial or congenital disease	4867	4638	32	73	58	66	4638	402	7641	399	271	12	993
cancer or benign tumor	2063	1531	122	209	125	76	1531	96	6506	430	124	0	639
nervous system disease	2093	1923	10	54	49	57	1923	166	3710	153	74	3	446
musculoskeletal or connective tissue disease	1597	1469	15	46	35	32	1469	158	2863	206	129	0	353
gastrointestinal disease	1149	995	22	48	30	54	995	82	3265	257	67	0	334
immune system disease	1294	1114	30	69	36	45	1114	107	2762	339	69	4	290
nutritional or metabolic disease	1491	1409	1	16	16	49	1409	132	2316	94	29	0	310
endocrine system disease	1071	933	17	42	26	53	933	99	2685	184	80	4	287
cardiovascular disease	956	834	7	25	32	58	834	81	1908	126	70	0	315
psychiatric disorder	820	735	2	22	16	45	735	73	1442	59	18	2	168
disorder of visual system	838	823	1	8	3	3	823	87	1289	40	24	0	131
integumentary system disease	733	646	14	35	22	16	646	51	1502	115	40	0	164
hematologic disease	702	589	23	41	31	18	589	45	1394	158	73	1	202
respiratory or thoracic disease	590	472	8	52	33	25	472	23	1552	177	45	0	134
urinary system disease	550	490	5	19	19	17	490	42	1164	94	47	0	121
reproductive system or breast disease	534	452	9	30	18	25	452	33	1240	69	22	6	128
phenotype	353	307	3	10	10	23	307	13	921	74	54	0	142
pancreas disease	326	278	7	9	7	25	278	37	770	65	24	0	96
measurement	7	7	0	0	0	0	7	1	69	1	2	0	3
disorder of ear	5	5	0	0	0	0	5	0	21	1	0	0	1

Figure 5: **Present-day target-disease pair counts by tractability, likelihood of advancement and therapeutic area**. The **stage** panel contains counts by maximum trial phase reached, the **threshold** panel contains counts of pairs with a RDG model score exceeding that of the associated benchmark for only undeveloped pairs, and the **tractability** panel shows pair frequencies among undeveloped pairs exceeding the EVA threshold that also have a HIGH tractability rating as defined in Supplementary Table 2. This corresponds to targets that have all been in clinical development already, except for the **OC** modality in which case it indicates that a target has been approved.

Figure 5 shows the distribution of TD pair counts for select buckets across therapeutic areas as well as across the current maximum phase reached for any one pair. We find that there are ∼2,400 small-molecule-enabled, ∼1,400 antibody-enabled, and 14 PROTAC-enabled TD pairs with a probability of advancement that is nearly 3x other TD pairs based on the EVA threshold RR=2.93 in Figure 3. Top antibody-enabled pairs are shown in Supplementary Figure 13 along with their corresponding genetic and clinical support.

2.8 Algorithms

The primary model for this analysis, RDG, is a constrained, L2-regularized linear regressor. Alternatives to this choice we explore include constrained and unconstrained gradient-boosted machine (GBM) models fit with the LightGBM [38] algorithm as well as unconstrained L2-regularized linear regressors (i.e. RDG with no constraints). The performance of these alternatives, as quantified by relative risk estimates among top predictions, is illustrated in Figure 6.

We conclude from these results that 1) linear models outperform, or are at least not worse, than tree models when time is not used as a predictor and 2) non-negativity constraints in linear models result in greater performance. This

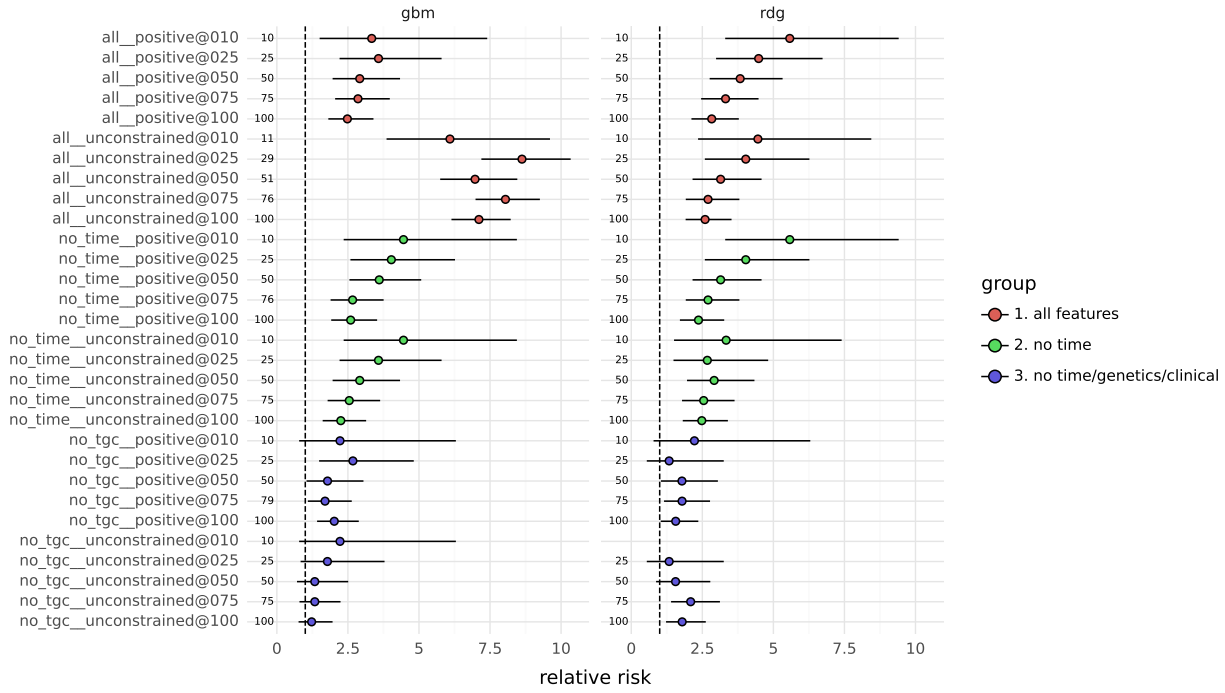


Figure 6: **Performance by algorithm, constraint type and feature grouping**.

is consistent with our expectation that all Open Targets scores should have monotonically increasing effects on the likelihood of success, since they were designed with this intent.

2.9 Inflation

Like most studies of this kind, we assume a "closed-world" [17] over the space of target-disease pairs and any evidence between them. This means that we do not differentiate between evidence that an association for any one pair truly does **not** exist (or is too weak to be relevant under the omnigenic model [39]), and the lack of any attempt to find that evidence in the first place. This also means that our estimate of the prognostic value for any one evidence source is subject to historical trends in biomedical research and the myriad ways that this research can be biased towards particular targets and diseases. We avoid attempting to comprehensively survey these biases in favor of offering an illustrative list of specific examples that are relevant in this study:

1. Mendelian randomization research is biased towards cardiovascular diseases as they have a disproportionate number of known, modifiable exposures [40]
2. Putative protein interactions that do not result from genome-scale or otherwise unbiased assays result in an overrepresentation of successful drug targets in resources like STRING [41], thereby inflating the success of network expansion methods over these databases to identify such targets [14].
3. Transcript expression studies run in late-stage clinical trials for a single indication, e.g. [42] linking SLE to IFN genes, are a degenerate indicator of advancement beyond earlier stage trials when the timing of this evidence is not accounted for.
4. Targets tested against more indications in clinical trials enrich for failures because the marginal cost of testing more indications decreases, but the evidence for these indications is often weaker [12].
5. Herding effects in pharma R&D pipelines around particular drug targets are becoming increasingly clear over time [43] and generate an excess of clinical evidence for those targets.

We also note that the skew in basic drug target research towards those that already have rich annotations and well characterized molecular function [44] as well as the disproportionate representation of particular target families in pharma R&D pipelines [45, 46] and the fact that literature is well known to be biased away from negative results in general [47] are all problematic.

While it is not possible to address all of these issues, we emphasize that there is a clear pattern across the examples in the list above in that they require **past** clinical successes and/or failures to arise in the first place. This suggests that accounting for when evidence first emerged would limit the extent of these problems. We do so in this study based solely on publication dates associated with any one piece of information linking target-disease pairs. This also offers a novel opportunity to attempt to quantify what kind of evidence suffers most from these biases. Figure 7 presents results for this based on a relative risk statistic defined as:

$$\frac{P(A|B)}{P(A|\neg B)} \tag{2}$$

where:

- A is the event that evidence for a TD pair arises after its first early-stage (phase 1 or 2) trial rather than before
- B is the event that a TD pair advances into late-stage trials (phase 3 or 4)

We refer to this as "inflation risk" so as not to confuse it with the relative risk statistic used in all other contexts, and it can be more simply described as the fraction of TD pairs for which evidence arises **after** the beginning of an ultimately successful early-stage trial divided by that same fraction for TD pairs that do not advance to late-stage trials. The intuition for this statistic is that it will be higher if successful trials lead to the generation of evidence of a particular type, and it should be 1 in cases where the emergence of evidence is independent of clinical success. We also measure this potential lack of independence through the more commonly used Fisher's exact test, e.g. [48], and both are presented in Figure 7.

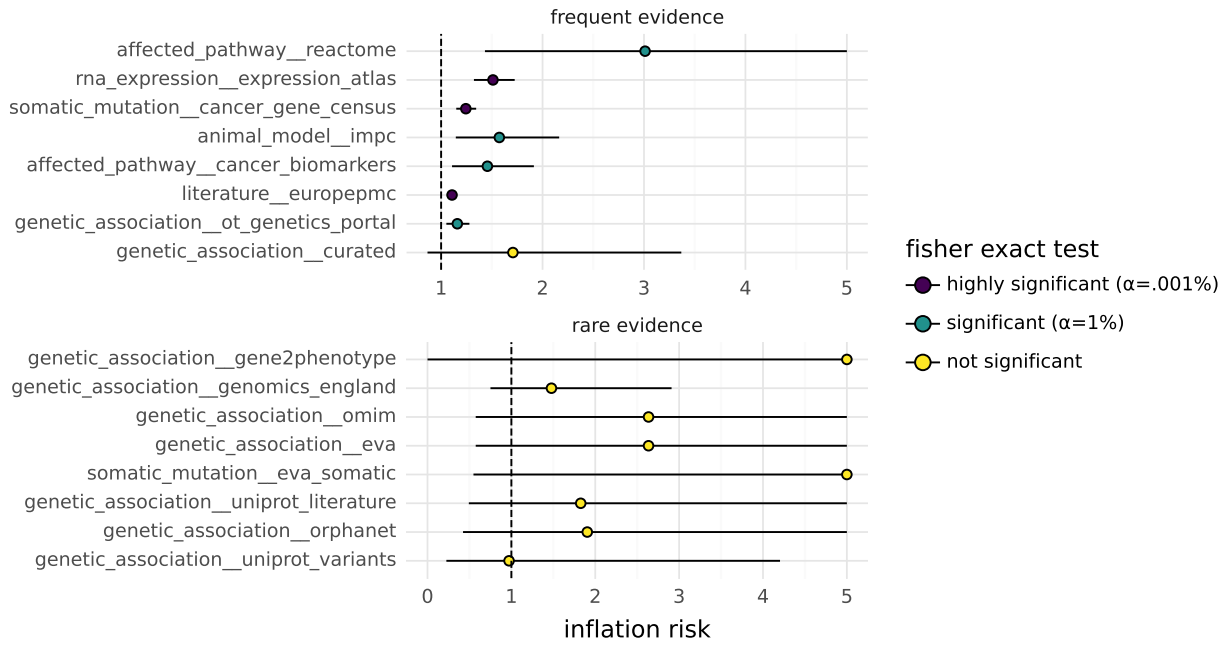


Figure 7: **Clinical success drives evidence discovery**.

We find that evidence from Reactome is the worst offender by this metric, implying that it often only arises for TD pairs after a certain level of clinical success has been attained. We also find that long-running aggregators/curators of published research often focused on individual diseases/phenotypes, like Expression Atlas, IMPC, CGS and Cancer Biomarkers exhibit this form of inflation as well.

Sources of genetic evidence appear to be much less inflated, or have too little data to reach significance. This is to be expected for GWAS evidence arising from genome-wide, phenome-wide biobank consortia, however much of historical GWAS evidence is not phenome-wide. More context on how much this is likely to matter comes from [49] in which it was estimated that as few as 6% of 500 FDA-approved targets for non-cancer drugs arose from programs highly motivated by pre-existing genetic support and that "the remaining 94% were probably identified using conventional pharmacology, biochemistry or molecular biology approaches". We then speculate that if the initiation of new drug programs was not historically motivated highly by the existence of genetic support, then the incentives for pursing new genetic evidence based on clinical and commercial success are likely to be minimized. This, in conjunction with existing precedent [1, 2, 3, 4, 5, 7] and our inflation results, ultimately led us to the use of genetic evidence without temporalization. In other words, we do not treat genetic evidence as longitudinal features like all others associated with TD pairs. A breakdown of which features are treated in which manner is provided in Supplementary Table 1.

3 Conclusion

We have demonstrated that simple machine learning methods applied to longitudinal biomedical evidence from many sources can be used to predict clinical outcomes for combinations of drug targets and diseases, without knowledge of molecular properties or trial design details. We have also shown that these methods are more precise in the extremes of their predictions than composite, heuristic scores like those from Open Targets. They also outperform such baselines by more comprehensive, traditional measures of classifier performance; however, we find this less compelling and easier to accomplish than improving performance among the upper tail of the opportunities implied by the very highest predictions. This framework would also support the addition of new lines of evidence over time well as it is designed to automatically determine the relevance of any new information without intervention. Lastly, we find that the space of present-day, undeveloped targets within a disease context that both exceed baseline levels of tractability and have a high predicted likelihood of clinical advancement is substantial. It is likely to grow quickly as well since the breadth of much of the underlying evidence is expanding rapidly [50, 51, 52].

4 Discussion

- Cover limitations with OT concerning temporalization for both evidence and drug approvals, and why only transitions from phase 2 are relevant for this work
- Discuss the possibility to do prospective evaluation with OT snapshots
- Discuss how typical classifier metrics are inadequate for this problem
- Talk about how the inclusion of time greatly improves performance and suggests it may be possible to fill in this proxy with predictors for more specific early indicators of other reasons trials fail
- We are focusing on prioritizing among targets/indications with genetic support, rather than expanding this space to find opportunities with weaker support
- "There is evidence that a 9.6% vs. 13.8% success rate for drugs from phase 1 trials to approval may mean a $480 million difference in the median research and development cost required to bring a new drug to the market (Wouters, McKee, and Luyten 2020)." [53]
- From [12]: "It is important to bear in mind therefore that what we are measuring when looking at historical trial outcomes is not an unbiased measure of any given gene's true disease associations, but rather a view on how useful a given evidence source or analytical method has been for choosing drug targets based on current and historical drug discovery practices. Dramatic changes in these practices in the future could render some

of our conclusions obsolete, though the fundamental observation that genetic association itself is retained in molecular networks will remain valid."

- Add select tractability and DepMap features?

5 Methods

- Discuss why all target prioritisation data fields are not used due to the potential leakage they may impose (e.g. target families, GO annotations, etc.)
- Describe how therapeutic areas were selected based on having at least 100 TD pairs with target-disease-specific evidence of any kind and with explicit omissions: ("biological_process", "pregnancy or perinatal disease", "injury, poisoning or other complication", "pregnancy or perinatal disease", "medical procedure", "infectious disease", "animal disease")
- Training/evaluation results are limited by temporalization while the present-day predictions are not
- OMIM is defined as EVA associations with publications
- The "genetic_association__curated" field is a union of all genetic association sources other than "gene_burden" and "ot_genetics_portal"
- Mention that the scores for a TD pairs in a year are the maximum score for that source, not the harmonic sum
- Mean imputation is used for target-specific features
- Mention specifics on RDG and GBM implementations, i.e. lightGBM and scikit-learn
- RDG is always trained on all features, but only applied to feature subsets where relevant

6 Supplementary Material

Table 1: Features used in modeling and analysis

	feature	entity	kind
1	disease__clinical__phase_max__reached	disease	temporal
2	target__clinical__phase_max__reached	target	temporal
3	target__genetic_constraint	target	static
4	target__mouse_ko_score	target	static
5	target__tissue_distribution	target	static
6	target__tissue_specificity	target	static
7	target_disease__affected_pathway__cancer_biomarkers	target_disease	temporal
8	target_disease__affected_pathway__crispr	target_disease	temporal
9	target_disease__affected_pathway__crispr_screen	target_disease	temporal
10	target_disease__affected_pathway__progeny	target_disease	temporal
11	target_disease__affected_pathway__reactome	target_disease	temporal
12	target_disease__affected_pathway__slapenrich	target_disease	temporal
13	target_disease__affected_pathway__sysbio	target_disease	temporal
14	target_disease__animal_model__impc	target_disease	temporal
15	target_disease__genetic_association__clingen	target_disease	static
16	target_disease__genetic_association__curated	target_disease	static
17	target_disease__genetic_association__eva	target_disease	static
18	target_disease__genetic_association__gene2phenotype	target_disease	static
19	target_disease__genetic_association__gene_burden	target_disease	static
20	target_disease__genetic_association__genomics_england	target_disease	static
21	target_disease__genetic_association__omim	target_disease	static
22	target_disease__genetic_association__orphanet	target_disease	static
23	target_disease__genetic_association__ot_genetics_portal	target_disease	static
24	target_disease__genetic_association__uniprot_literature	target_disease	static
25	target_disease__genetic_association__uniprot_variants	target_disease	static
26	target_disease__known_drug__chembl	target_disease	temporal
27	target_disease__literature__europepmc	target_disease	temporal
28	target_disease__outcome__advanced	target_disease	temporal
29	target_disease__rna_expression__expression_atlas	target_disease	temporal
30	target_disease__somatic_mutation__cancer_gene_census	target_disease	temporal
31	target_disease__somatic_mutation__eva_somatic	target_disease	temporal
32	target_disease__somatic_mutation__intogen	target_disease	temporal
33	target_disease__time__transition	target_disease	temporal

Table 2: Tractability bucket assignments

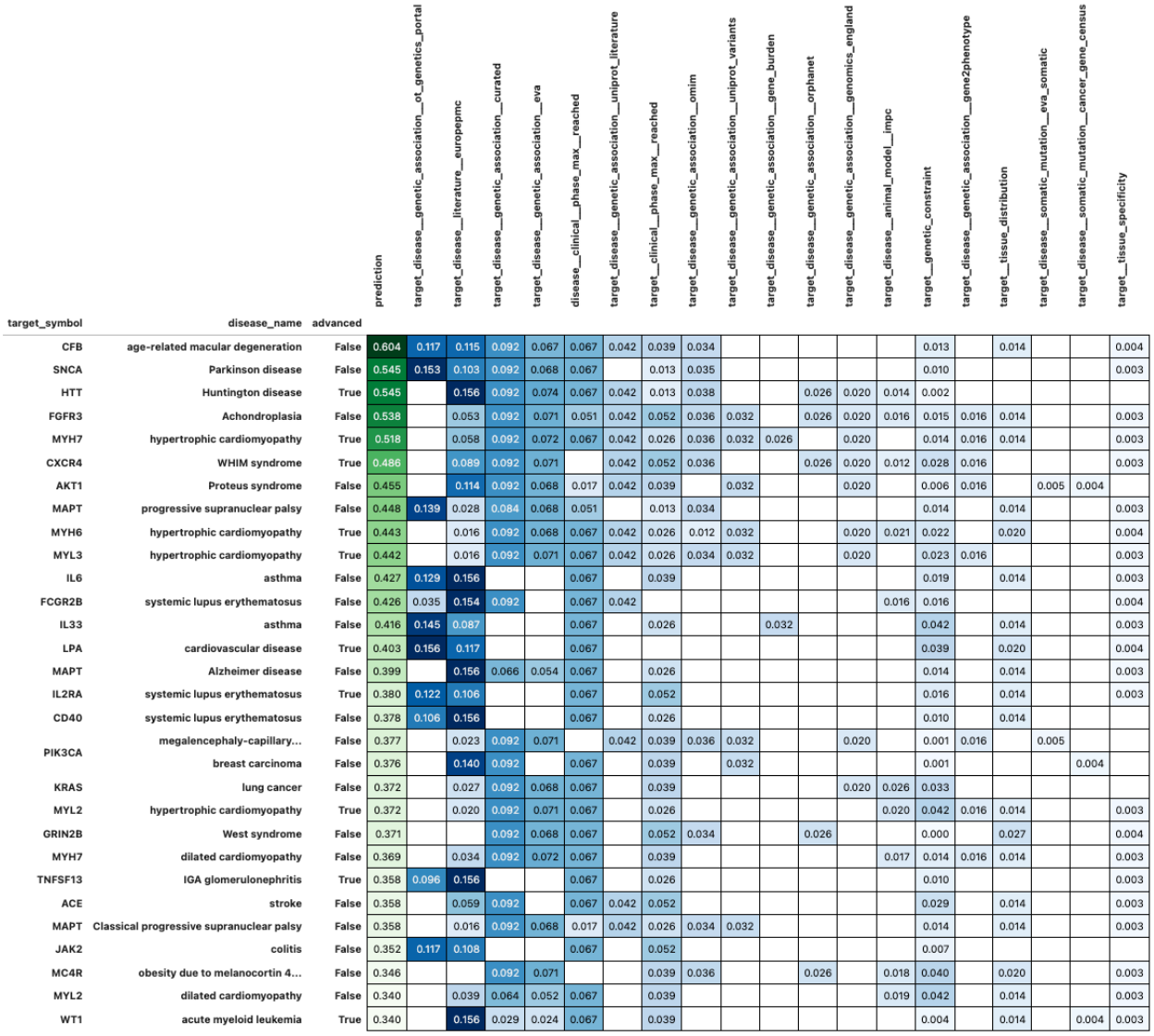
	evidence	modality	confidence
1	Phase 1 Clinical	OC	LOW
2	Advanced Clinical	OC	MED
3	Approved Drug	OC	HIGH
4	GO CC med conf	AB	LOW
5	Human Protein Atlas loc	AB	LOW
6	UniProt SigP or TMHMM	AB	LOW
7	UniProt loc med conf	AB	LOW
8	GO CC high conf	AB	MED
9	UniProt loc high conf	AB	MED
10	Advanced Clinical	AB	HIGH
11	Approved Drug	AB	HIGH
12	Phase 1 Clinical	AB	HIGH
13	Database Ubiquitination	PR	LOW
14	Half-life Data	PR	LOW
15	Small Molecule Binder	PR	LOW
16	Literature	PR	MED
17	UniProt Ubiquitination	PR	MED
18	Advanced Clinical	PR	HIGH
19	Phase 1 Clinical	PR	HIGH
20	Druggable Family	SM	LOW
21	High-Quality Pocket	SM	LOW
22	Med-Quality Pocket	SM	LOW
23	High-Quality Ligand	SM	MED
24	Structure with Ligand	SM	MED
25	Advanced Clinical	SM	HIGH
26	Approved Drug	SM	HIGH
27	Phase 1 Clinical	SM	HIGH

Table 3: Configurations for sensitivity analysis

	open_targets_version	max_training_year	min_time_to_advancement_years
1	23.09	2017	4
2	23.12	2017	2
3	23.09	2015	2
4	23.12	2015	2
5	23.09	2017	2
6	23.06	2015	4
7	23.06	2017	2
8	23.06	2013	2
9	23.06	2015	2
10	23.06	2017	4
11	23.12	2013	4
12	23.09	2015	4
13	23.09	2013	2
14	23.12	2013	2
15	23.09	2013	4
16	23.12	2017	4
17	23.12	2015	4
18	23.06	2013	4

therapeutic_area	n_pairs	OMIM	EVA/ClinVar	OTG/GWAS	OTS@010	OTS@020	OTS@030	OTS@050	OTS@100	RDG@010	RDG@020	RDG@030	RDG@050	RDG@100
average		9.65	5.78	1.95	2.88	2.10	2.06	1.98	1.75	5.82	3.63	3.13	2.41	1.84
all	9010	4.78	2.93	2.07	6.70	3.91	3.35	2.69	2.13	5.58	3.91	3.73	3.14	2.37
cancer or benign tumor	4013		3.69	0.00	2.58	3.91	5.31	3.65	2.68	5.20	5.00	4.40	4.28	3.26
genetic, familial or congenital disease	2035	3.43	2.37	0.68	3.08	1.53	1.02	0.81	0.91	3.08	2.58	1.71	1.23	0.80
nervous system disease	1534	3.64	1.95	0.00	2.54	1.15	1.70	1.54	2.14	2.54	1.26	2.59	2.08	1.56
gastrointestinal disease	1260		0.00	3.48	5.68	4.33	2.68	3.17	2.82	8.72	5.90	3.90	4.34	2.44
immune system disease	1225	21.09	21.44	2.88	6.39	4.30	4.43	2.61	1.99	11.05	5.48	4.43	3.10	2.53
hematologic disease	1023	26.89	27.59	0.00	5.48	2.71	1.79	2.05	1.68	8.44	4.18	3.78	2.22	1.64
endocrine system disease	949	0.00	0.00	11.26	0.00	0.00	2.12	2.88	2.21	10.83	5.36	4.90	2.88	1.77
reproductive system or breast disease	948		0.00	0.00	0.00	0.00	0.00	1.68	1.72	8.79	4.35	3.95	2.99	2.51
musculoskeletal or connective tissue disease	757	8.82	6.67	2.68	4.74	3.62	2.73	2.48	2.18	6.02	5.00	4.76	3.09	2.80
respiratory or thoracic disease	644		0.00	0.00	4.37	2.74	1.80	1.97	1.52	3.22	2.15	2.19	1.51	1.83
cardiovascular disease	617	3.65	1.66	2.09	1.83	1.66	1.48	0.86	0.87	2.21	1.85	1.35	0.93	0.68
integumentary system disease	563			0.00	0.00	0.00	0.82	1.43	1.49	4.37	2.94	1.92	1.76	1.12
urinary system disease	561		3.99	2.29	0.79	1.40	0.92	0.61	0.59	1.19	1.19	0.78	0.86	0.93

Figure 8: **Relative risk scores by method, benchmark and therapeutic area**. The **average** therapeutic area indicates mean values across all others except for **all**, which is an ungrouped estimate across all diseases regardless of therapeutic area.



target_symbol	disease_name	advanced	prediction	target_disease__genetic_association__ot_genetics_portal	target_disease__literature__europepmc	target_disease__genetic_association__curated	target_disease__genetic_association__eva	disease_clinical__phase_max__reached	target_disease__genetic_association__uniprot_literature	target__clinical__phase_max__reached	target_disease__genetic_association__omim	target_disease__genetic_association__uniprot_variants	target_disease__genetic_association__gene_burden	target_disease__genetic_association__orphanet	target_disease__genetic_association__genomics_england	target_disease__animal_model__impc	target__genetic_constraint	target_disease__genetic_association__gene2phenotype	target__tissue_distribution	target_disease__somatic_mutation__eva_somatic	target_disease__somatic_mutation__cancer_gene_census	target__tissue_specificity
CFB	age-related macular degeneration	False	0.604	0.117	0.115	0.092	0.067	0.067	0.042	0.039	0.034						0.013		0.014			0.004
SNCA	Parkinson disease	False	0.545	0.153	0.103	0.092	0.068	0.067		0.013	0.035						0.010					0.003
HTT	Huntington disease	True	0.545		0.156	0.092	0.074	0.067	0.042	0.013	0.038			0.026	0.020	0.014	0.002					
FGFR3	Achondroplasia	False	0.538		0.053	0.092	0.071	0.051	0.042	0.052	0.036	0.032		0.026	0.020	0.016	0.015	0.016	0.014			0.003
MYH7	hypertrophic cardiomyopathy	True	0.518		0.058	0.092	0.072	0.067	0.042	0.026	0.036	0.032	0.026		0.020		0.014	0.016	0.014			0.003
CXCR4	WHIM syndrome	True	0.486		0.089	0.092	0.071		0.042	0.052	0.036			0.026	0.020	0.012	0.028	0.016				0.003
AKT1	Proteus syndrome	False	0.455		0.114	0.092	0.068	0.017	0.042	0.039		0.032			0.020		0.006	0.016		0.005	0.004	
MAPT	progressive supranuclear palsy	False	0.448	0.139	0.028	0.084	0.068	0.051		0.013	0.034						0.014		0.014			0.003
MYH6	hypertrophic cardiomyopathy	True	0.443		0.016	0.092	0.068	0.067	0.042	0.026	0.012	0.032			0.020	0.021	0.022		0.020			0.004
MYL3	hypertrophic cardiomyopathy	True	0.442		0.016	0.092	0.071	0.067	0.042	0.026	0.034	0.032			0.020		0.023	0.016				0.003
IL6	asthma	False	0.427	0.129	0.156			0.067		0.039							0.019		0.014			0.003
FCGR2B	systemic lupus erythematosus	False	0.426	0.035	0.154	0.092		0.067	0.042							0.016	0.016					0.004
IL33	asthma	False	0.416	0.145	0.087			0.067		0.026			0.032				0.042		0.014			0.003
LPA	cardiovascular disease	True	0.403	0.156	0.117			0.067									0.039		0.020			0.004
MAPT	Alzheimer disease	False	0.399		0.156	0.066	0.054	0.067		0.026							0.014		0.014			0.003
IL2RA	systemic lupus erythematosus	True	0.380	0.122	0.106			0.067		0.052							0.016		0.014			0.003
CD40	systemic lupus erythematosus	False	0.378	0.106	0.156			0.067		0.026							0.010		0.014			
PIK3CA	megalencephaly-capillary...	False	0.377		0.023	0.092	0.071		0.042	0.039	0.036	0.032			0.020		0.001	0.016		0.005		
	breast carcinoma	False	0.376		0.140	0.092		0.067		0.039		0.032					0.001				0.004	
KRAS	lung cancer	False	0.372		0.027	0.092	0.068	0.067		0.039					0.020	0.026	0.033					
MYL2	hypertrophic cardiomyopathy	True	0.372		0.020	0.092	0.071	0.067		0.026						0.020	0.042	0.016	0.014			0.003
GRIN2B	West syndrome	False	0.371			0.092	0.068	0.067		0.052	0.034			0.026			0.000		0.027			0.004
MYH7	dilated cardiomyopathy	False	0.369		0.034	0.092	0.072	0.067		0.039						0.017	0.014	0.016	0.014			0.003
TNFSF13	IGA glomerulonephritis	True	0.358	0.096	0.156			0.067		0.026							0.010					0.003
ACE	stroke	False	0.358		0.059	0.092		0.067	0.042	0.052							0.029		0.014			0.003
MAPT	Classical progressive supranuclear palsy	False	0.358		0.016	0.092	0.068	0.017	0.042	0.026	0.034	0.032					0.014		0.014			0.003
JAK2	colitis	False	0.352	0.117	0.108			0.067		0.052							0.007					
MC4R	obesity due to melanocortin 4...	False	0.346			0.092	0.071			0.039	0.036			0.026		0.018	0.040		0.020			0.003
MYL2	dilated cardiomyopathy	False	0.340		0.039	0.064	0.052	0.067		0.039						0.019	0.042		0.014			0.003
WT1	acute myeloid leukemia	True	0.340		0.156	0.029	0.024	0.067		0.039							0.004		0.014		0.004	0.003

Figure 9: **Top RDG model evaluation dataset predictions**. Feature contributions are shown as the product of their underlying values and the RDG coefficients. The **advanced** field indicates whether the associated TD pair advanced beyond phase 2 as of 2024.

split	evaluation							training						
statistic	balance	max_year	min_year	n_diseases	n_pairs	n_pairs_wev	n_targets	balance	max_year	min_year	n_diseases	n_pairs	n_pairs_wev	n_targets
therapeutic_area_name														
all	9.01%	2022	2016	1075	9010	2062	1063	19.76%	2015	1990	1420	25398	3737	1226
cancer or benign tumor	3.89%	2022	2016	400	4013	1148	656	15.69%	2015	1990	478	15303	2267	712
genetic, familial or congenital disease	9.83%	2022	2016	203	2035	378	548	23.12%	2015	1990	286	4745	680	823
nervous system disease	3.98%	2022	2016	200	1534	271	557	21.21%	2015	1990	278	4112	575	759
gastrointestinal disease	3.65%	2022	2016	136	1260	360	418	17.80%	2015	1995	174	4061	572	603
immune system disease	4.90%	2022	2016	136	1225	347	461	16.72%	2015	1992	167	3361	668	650
hematologic disease	3.81%	2022	2016	111	1023	262	389	19.13%	2015	1990	139	3742	476	553
endocrine system disease	3.06%	2022	2016	118	949	289	376	17.65%	2015	1990	140	3372	541	542
reproductive system or breast disease	3.69%	2022	2016	95	948	197	368	16.91%	2015	1990	102	3294	331	486
musculoskeletal or connective tissue disease	8.85%	2022	2016	109	757	195	369	23.20%	2015	1991	168	2190	389	667
respiratory or thoracic disease	9.63%	2022	2016	73	644	174	373	21.76%	2015	1993	81	1769	318	609
cardiovascular disease	27.71%	2022	2016	88	617	121	285	28.67%	2015	1993	116	1444	241	553
phenotype	6.28%	2022	2016	113	605	76	322	29.99%	2015	1994	178	1594	121	497
integumentary system disease	7.28%	2022	2016	85	563	166	293	18.29%	2015	1990	98	1624	268	513
urinary system disease	25.31%	2022	2016	62	561	134	360	21.32%	2015	1992	73	1440	183	412
infectious disease	6.24%	2022	2016	51	529	115	343	19.05%	2015	1991	72	803	76	345
psychiatric disorder	3.25%	2022	2016	65	523	96	257	29.79%	2015	1990	78	1232	211	327
disorder of visual system	5.24%	2022	2016	57	382	47	275	12.44%	2015	1990	67	611	71	292
nutritional or metabolic disease	5.16%	2022	2016	55	310	63	269	45.41%	2015	1992	80	969	169	498
biological_process	28.84%	2022	2016	14	215	18	157	6.13%	2015	1999	12	163	21	152
pancreas disease	1.40%	2022	2016	17	214	89	184	29.53%	2015	1995	26	823	152	391
injury, poisoning or other complication	0.00%	2022	2016	19	123	32	117	15.04%	2015	1997	27	359	29	209
pregnancy or perinatal disease	4.17%	2022	2016	8	24	3	23	78.85%	2015	1996	15	104	4	99

Figure 10: **Training and evaluation dataset summary statistics**.

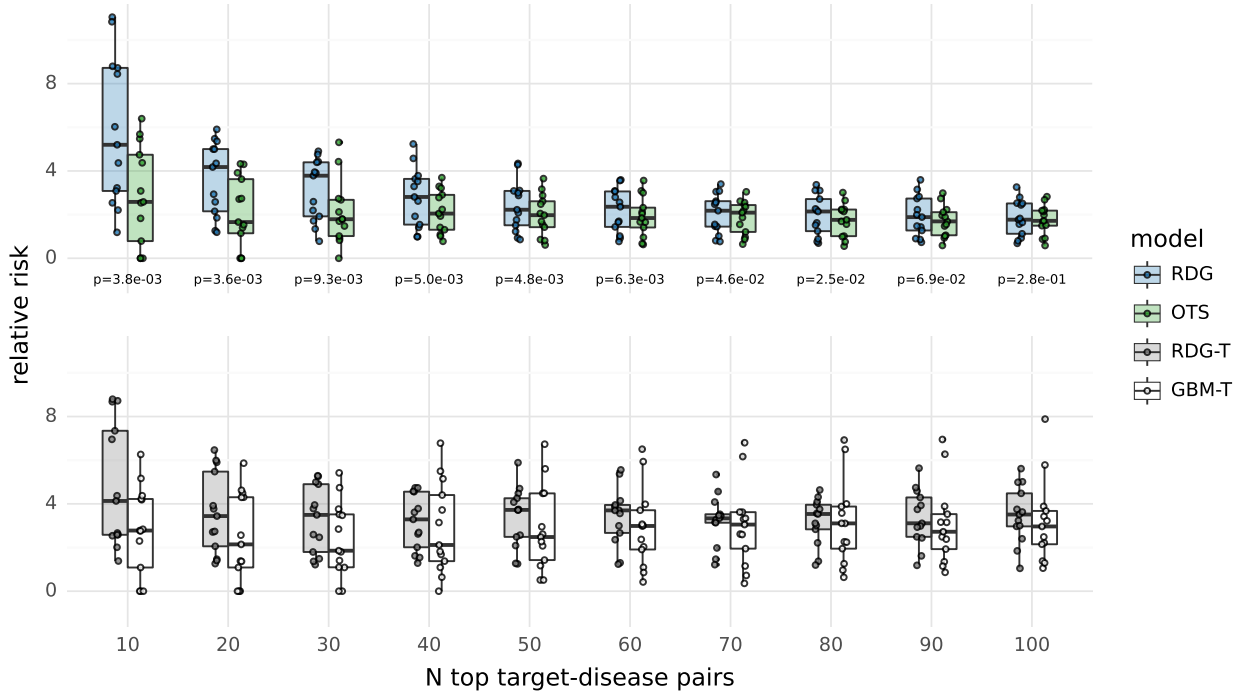


Figure 11: **Relative risk distributions across select therapeutic areas**. P-values are computed from a one-sided Wilcoxon signed-rank test with the alternative that the RDG model RR averages across therapeutic areas exceed OTS averages.

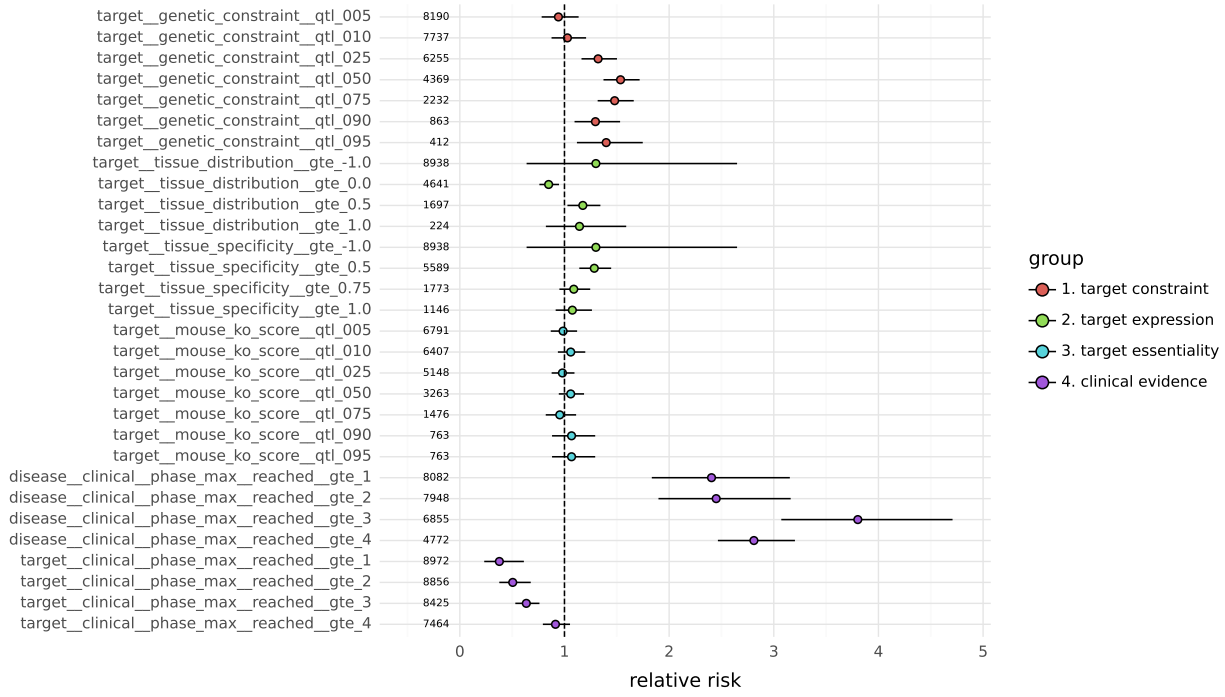
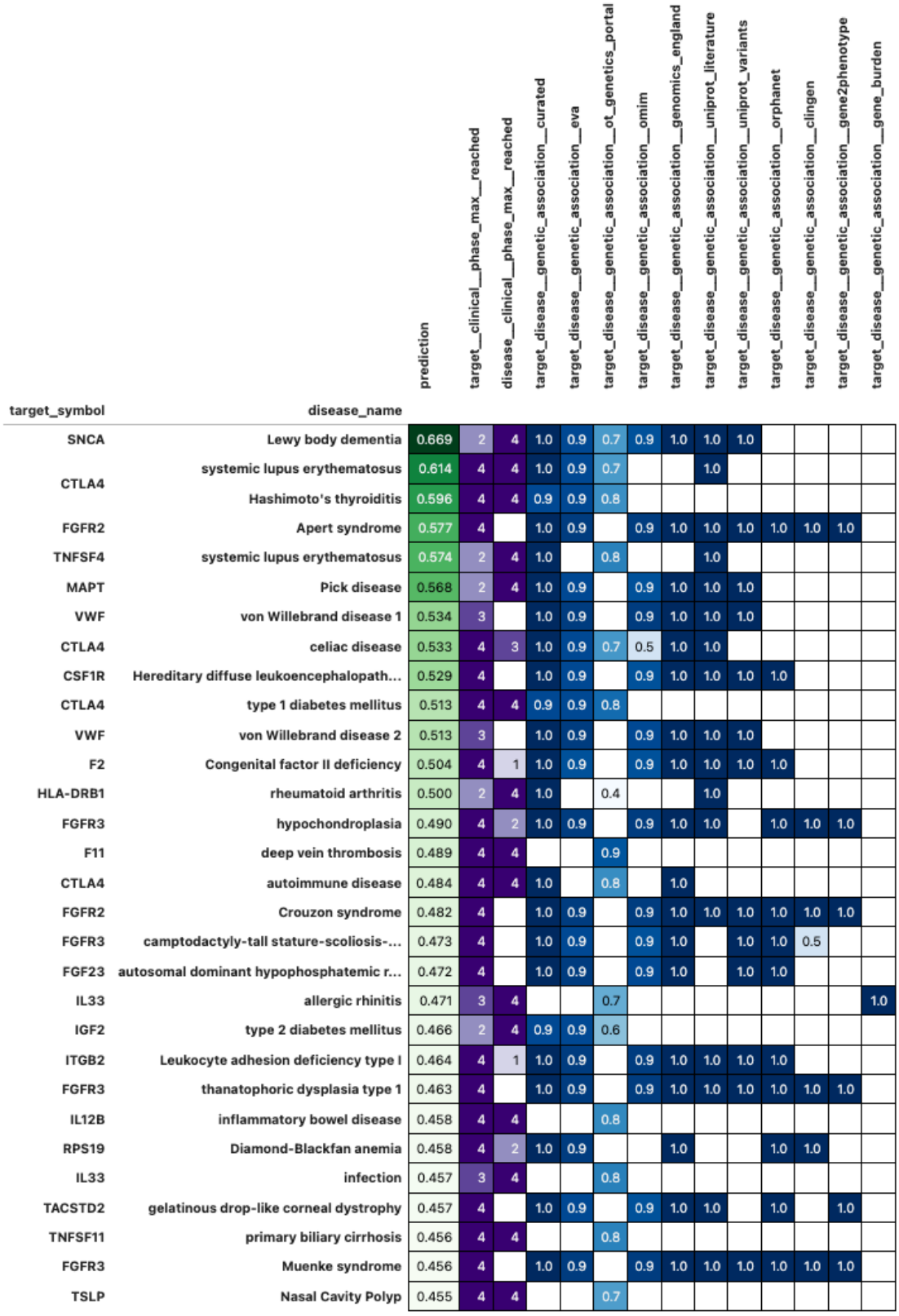


Figure 12: **Relative risk scores for target/disease features**. The features ending with `qtl_Q` denote binary indicators constructed from cases where the feature meets or exceeds quantile `Q` of its distribution. The features ending with `gte_X` denote indicators for when the feature meets or exceeds a specific value `X`.



target_symbol	disease_name	prediction	target__clinical__phase_max__reached	disease__clinical__phase_max__reached	target_disease__genetic_association__curated	target_disease__genetic_association__eva	target_disease__genetic_association__ot_genetics_portal	target_disease__genetic_association__omim	target_disease__genetic_association__genomics_england	target_disease__genetic_association__uniprot_literature	target_disease__genetic_association__uniprot_variants	target_disease__genetic_association__orphanet	target_disease__genetic_association__clingen	target_disease__genetic_association__gene2phenotype	target_disease__genetic_association__gene_burden
SNCA	Lewy body dementia	0.669	2	4	1.0	0.9	0.7	0.9	1.0	1.0	1.0				
CTLA4	systemic lupus erythematosus	0.614	4	4	1.0	0.9	0.7			1.0					
	Hashimoto's thyroiditis	0.596	4	4	0.9	0.9	0.8								
FGFR2	Apert syndrome	0.577	4		1.0	0.9		0.9	1.0	1.0	1.0	1.0	1.0	1.0	
TNFSF4	systemic lupus erythematosus	0.574	2	4	1.0		0.8			1.0					
MAPT	Pick disease	0.568	2	4	1.0	0.9		0.9	1.0	1.0	1.0				
VWF	von Willebrand disease 1	0.534	3		1.0	0.9		0.9	1.0	1.0	1.0				
CTLA4	celiac disease	0.533	4	3	1.0	0.9	0.7	0.5	1.0	1.0					
CSF1R	Hereditary diffuse leukoencephalopath...	0.529	4		1.0	0.9		0.9	1.0	1.0	1.0	1.0			
CTLA4	type 1 diabetes mellitus	0.513	4	4	0.9	0.9	0.8								
VWF	von Willebrand disease 2	0.513	3		1.0	0.9		0.9	1.0	1.0	1.0				
F2	Congenital factor II deficiency	0.504	4	1	1.0	0.9		0.9	1.0	1.0	1.0	1.0			
HLA-DRB1	rheumatoid arthritis	0.500	2	4	1.0		0.4			1.0					
FGFR3	hypochondroplasia	0.490	4	2	1.0	0.9		0.9	1.0	1.0		1.0	1.0	1.0	
F11	deep vein thrombosis	0.489	4	4			0.9								
CTLA4	autoimmune disease	0.484	4	4	1.0		0.8		1.0						
FGFR2	Crouzon syndrome	0.482	4		1.0	0.9		0.9	1.0	1.0	1.0	1.0	1.0	1.0	
FGFR3	camptodactyly-tall stature-scoliosis-...	0.473	4		1.0	0.9		0.9	1.0		1.0	1.0	0.5		
FGF23	autosomal dominant hypophosphatemic r...	0.472	4		1.0	0.9		0.9	1.0		1.0	1.0			
IL33	allergic rhinitis	0.471	3	4			0.7								1.0
IGF2	type 2 diabetes mellitus	0.466	2	4	0.9	0.9	0.6								
ITGB2	Leukocyte adhesion deficiency type I	0.464	4	1	1.0	0.9		0.9	1.0	1.0	1.0	1.0			
FGFR3	thanatophoric dysplasia type 1	0.463	4		1.0	0.9		0.9	1.0	1.0	1.0	1.0	1.0	1.0	
IL12B	inflammatory bowel disease	0.458	4	4			0.8								
RPS19	Diamond-Blackfan anemia	0.458	4	2	1.0	0.9			1.0			1.0	1.0		
IL33	infection	0.457	3	4			0.8								
TACSTD2	gelatinous drop-like corneal dystrophy	0.457	4		1.0	0.9		0.9	1.0	1.0		1.0		1.0	
TNFSF11	primary biliary cirrhosis	0.456	4	4			0.8								
FGFR3	Muenke syndrome	0.456	4		1.0	0.9		0.9	1.0	1.0	1.0	1.0	1.0	1.0	
TSLP	Nasal Cavity Polyp	0.455	4	4			0.7								

Figure 13: **Top ranked undeveloped, tractable target-disease pairs**. The highest scoring TD pairs per the RDG model that have not entered clinical trials despite having a target that has been in trials of an antibody-based drug. All values shown other than **prediction** are raw feature values, unweighted by RDG coefficients.

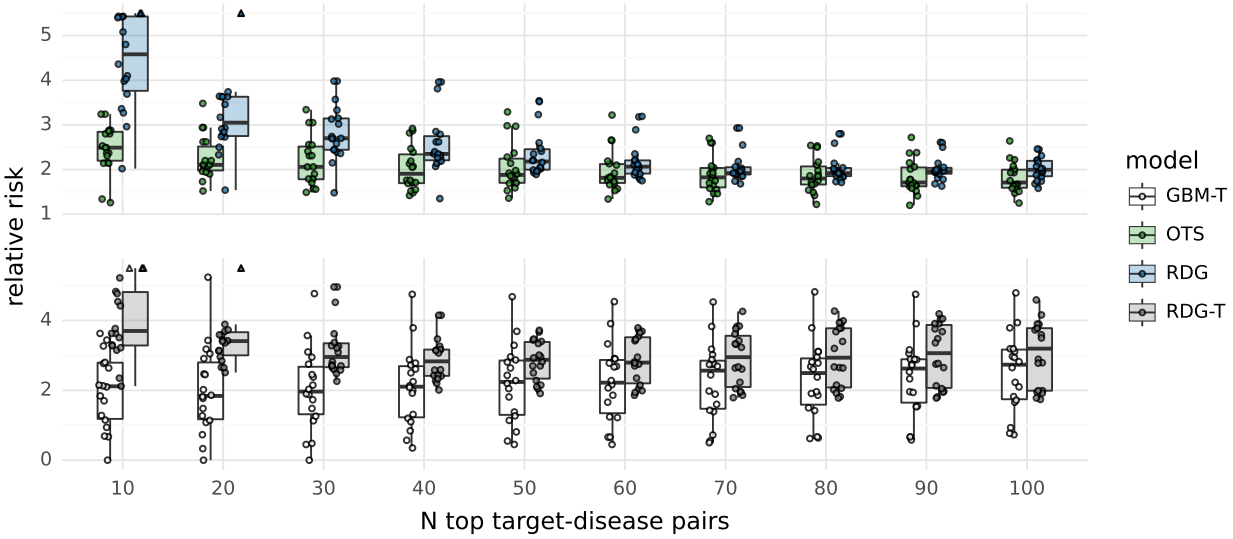


Figure 14: **Relative risk distributions across configurations in sensitivity analysis**. The distribution of the mean RR values displayed for a single configuration in Figure 1 is shown here across 18 configurations.

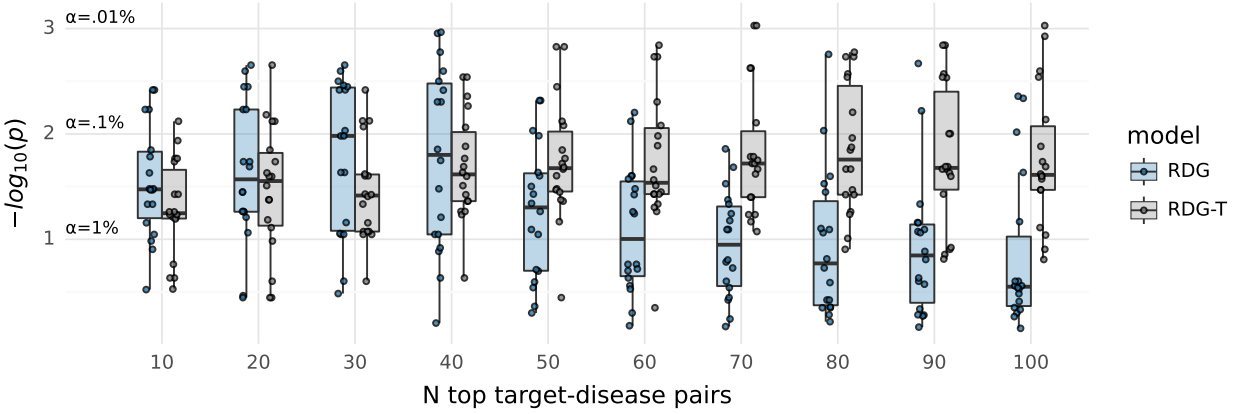


Figure 15: **P-value distributions across configurations in sensitivity analysis**. The distribution of the p-values displayed for a single configuration in Supplementary Figure 11 is shown here across 18 configurations.

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