OpenTargetsBaselDatathonRNotebook

November 20, 2018

1 BioData Basel Open Targets Datathon

Matthew R. Nelson
November 19, 2018

1.1 Introduction

There has been exponential growth in the genetic and genomic data being produced to yield new insights into biology, and particularly with the intent to understand the role of genes and proteins and pathways in disease. Despite this, selecting protein targets for drug discovery still seems more of an art, guided by intuition and influenced by cognitive biases, than a reproducible science. Open Targets was established to bring the data and science together in a pre-competitive environment to help foster better early discovery decision making. In this dual session, we will introduce and engage the participants to the science of target selection. In this datathon, you will be introduced to the evidence types Open Targets is currently using to established relationships between genes and disease to aid in selecting and validating prospective drug targets.

You will be introduced to several genomic and gene-disease data sources. You are tasked with exploring methods for using these data for predicting drug development success. Insights and feedback from among the participants will be collated and shared, and may be used in future development of the Open Targets platform.

Prior to the datathon, you are encouraged to download the data files, view the example analysis notebooks available in R and Python, and review the data documentation. A brief summary will be provided during the introductory session and researchers from Open Targets and GSK will be on hand to answer any questions you may have.

At the datathon, you will be divided into small groups where you can work individually or jointly to explore these data, their relationships to development outcomes, and methods of modeling them to predict outcomes. At the end of the datathon, groups will be invited to share their experiences and discuss potential next steps. You are welcome to use whatever analysis tools you prefer for this analysis exercise.

1.2 Data Import

The three primary datathon files are summarized below. You can find a more complete description of each data file and the variables within them at the datathon Wiki site.

Note about neoplasm versus non-neoplasm indications: Because the genomic evidence that may be important for neoplasms may be very different than for non-neoplasms, we restrict this summary of the data to non-neoplasm data only.

```
In [133]: ## Load packages to use
          library(ggplot2) # Plotting functions
          library(tidyr) # Use gather() for reformatting to long-skinny
          library(dplyr) # Using chaining (%>%) and several dplyr verbs
```

1.2.1 Pharmaprojects data

The first data file, Pprojects_drugs_TTlabel.csv, is derived from Informa Pharmaprojects, a commercial database tracking the development of over 68,000 drugs over the past several decades. Researchers at GSK have carefully processed and curated this database to create a summary of all target-indication pairs (T-I) that have entered clinical development, tracking the furthest stage of development achieved. A T-I is considered successful if any drug annotated to act through the selected target was approved for the accompanying indication. Further details are available on the See the datathon Wiki site for details. The objective of this datathon is to identify the genomic factors that predict successful T-Is (for example, see the related paper by Nelson et al. 2015). Informa has permitted us to make these data freely available to the datathon participants during the course of this datathon. They must be permanently deleted after the datathon work is completed, as agreed in the survey. We have identified 80%/20% of T-Is as a training set and test set. We encourage any participants interested in exploring predictive models to use them as such.

```
In [134]: pp.data = read.csv("Pprojects_drugs_TTlabel.csv",
                             na.strings = c("NA", ""), header = TRUE) %>%
            filter(DiseaseType %in% "Non-Neoplasm") %>%
            rename(key = target_indication)
```

```
In [135]: summary(pp.data)
```

```
                          key              ensembl_gene_id       disease_id
 ENSG00000000971-EFO_0000253 :   1   ENSG00000113580:  97   EFO_0000685: 171
 ENSG00000001626-EFO_0000555 :   1   ENSG00000073756:  85   EFO_0000676: 158
 ENSG00000001626-HP_0002014  :   1   ENSG00000095303:  79   EFO_0000198: 138
 ENSG00000001626-Orphanet_586:   1   ENSG00000065989:  63   EFO_0003843: 128
 ENSG00000001630-EFO_0003914 :   1   ENSG00000184588:  61   EFO_0000270: 126
 ENSG00000003436-EFO_0001420 :   1   ENSG00000105650:  59   EFO_0000249: 113
 (Other)                     :7874   (Other)        :7436   (Other)    :7046
   entrez_id            MeSH_ID            DiseaseType
 Min.   :        2   D001172: 171   Neoplasm    :   0
 1st Qu.:     1815   D011565: 158   Non-Neoplasm:7880
 Median :     3596   D009190: 138
 Mean   :    35198   D001249: 126
 3rd Qu.:     5743   D000544: 113
 Max.   :100133941   D003924: 110
                     (Other):7064
           Clinical.Label_PP             Furthest.Phase
 Clinical Failure    :4160   Clinical Phase I  :1635
 In Progress Clinical:1820   Clinical Phase II :3290
 Succeeded           :1900   Clinical Phase III:1005
                             Succeeded         :1900
                             Withdrawn         :  50
```

```
     Therapeutic.Direction Indication.with.First.Clinical.Outcome.for.Target
 Activator       :1768      N:7165
 Inhibitor       :4435      Y: 715
 Mixed or Unknown:1677
```

```
                           Types.of.Assets Suggested.Dataset.Utility
 Non-Selective Assets              :2835   Neither :7167
 Selective and Non-Selective Assets:1635   Test    : 154
 Selective Assets                  :3410   Training: 559
```

1.2.2 Open Targets Evidence Scores

The second dataset includes the evidence scores that are available through the Open Targets Portal. See the datathon Wiki pages for details.

The data file provided includes target evidence scores for all target-indication combinations available in the Open Targets database (over 2.4 million). As the focus of this exercise is to predict clinical success of target-indication pairs, I have imported the large data file and saved the overlap with Pharmaprojects as a separate, much smaller data set.

```
In [136]: ## Create a small dataset matched to pp.data
          #ot.data.all = read.csv("gene_disease_associations_with_expression.csv.gz",
          #                       na.strings = c("NA", ""), header = TRUE)
          # dim(ot.data.all)
          # 2405593 38
          write.table(subset(ot.data.all, target_indication %in% pp.data$key),
                      file = "PP_gene_disease_associations.csv",
                      sep = ",", na = "NA",
                      row.names = FALSE)
```

```
In [137]: names(ot.data.all)
```

1. 'target_indication' 2. 'entrez_id' 3. 'ensembl_gene_id' 4. 'symbol' 5. 'disease_id' 6. 'disease_label' 7. 'therapeutic_area' 8. 'is_direct' 9. 'overall_score' 10. 'genetic_association' 11. 'somatic_mutation' 12. 'known_drug' 13. 'rna_expression' 14. 'affected_pathway' 15. 'animal_model' 16. 'literature' 17. 'expression_atlas' 18. 'uniprot' 19. 'gwas_catalog' 20. 'phewas_catalog' 21. 'eva' 22. 'uniprot_literature' 23. 'genomics_england' 24. 'gene2phenotype' 25. 'reactome' 26. 'slapenrich' 27. 'progeny' 28. 'phenodigm' 29. 'cancer_gene_census' 30. 'eva_somatic' 31. 'uniprot_somatic' 32. 'intogen' 33. 'chembl' 34. 'europepmc' 35. 'tissue_label' 36. 'source' 37. 'max_fold_change' 38. 'expression_score'

Now we can simply import the smaller dataset to make re-running this notebook much simpler.

```
In [138]: ot.data <- read.csv("PP_gene_disease_associations.csv",
                               na.strings = c("NA", ""), header = TRUE) %>%
                     rename(key = target_indication)
          dim(ot.data)
          summary(ot.data)
```

1. 5121 2. 38

```
                            key         entrez_id
ENSG00000000971-EFO_0000253   :   1   Min.   :        2
ENSG00000001626-EFO_0000555   :   1   1st Qu.:     1815
ENSG00000001626-HP_0002014    :   1   Median :     3587
ENSG00000001626-Orphanet_586  :   1   Mean   :    29466
ENSG00000003436-Orphanet_903  :   1   3rd Qu.:     5743
ENSG00000003436-Orphanet_98878:   1   Max.   :100133941
(Other)                       :5115
       ensembl_gene_id     symbol           disease_id
ENSG00000073756:  72   PTGS2  :  72   EFO_0000685: 150
ENSG00000113580:  68   NR3C1  :  68   EFO_0000676: 135
ENSG00000095303:  57   PTGS1  :  57   EFO_0000270: 116
ENSG00000232810:  51   TNF    :  51   EFO_0003843: 115
ENSG00000149295:  46   DRD2   :  46   EFO_0000198: 103
ENSG00000102468:  35   HTR1A  :  35   EFO_0000249:  98
(Other)        :4792   (Other):4792   (Other)    :4404
                 disease_label                                therapeutic_area
rheumatoid arthritis    : 150   phenotype                            : 754
psoriasis               : 135   nervous system disease; other disease: 596
asthma                  : 116   cardiovascular disease               : 475
pain                    : 115   nervous system disease               : 276
myelodysplastic syndrome: 103   respiratory system disease           : 267
Alzheimers disease      :  98   (Other)                              :2528
(Other)                 :4404   NA's                                 : 225
is_direct    overall_score       genetic_association somatic_mutation
False: 310   Min.   :0.0000118   Min.   :0.00000     Min.   :0.000000
True :4811   1st Qu.:0.0572183   1st Qu.:0.00000     1st Qu.:0.000000
             Median :0.2250000   Median :0.00000     Median :0.000000
             Mean   :0.4675443   Mean   :0.06141     Mean   :0.004013
             3rd Qu.:1.0002227   3rd Qu.:0.00000     3rd Qu.:0.000000
             Max.   :1.5124629   Max.   :1.49404     Max.   :1.008904

  known_drug     rna_expression      affected_pathway   animal_model
Min.   :0.0000   Min.   :0.0000000   Min.   :0.00000   Min.   :0.000000
1st Qu.:0.0000   1st Qu.:0.0000000   1st Qu.:0.00000   1st Qu.:0.000000
Median :0.2000   Median :0.0000000   Median :0.00000   Median :0.000000
Mean   :0.3863   Mean   :0.0001652   Mean   :0.01001   Mean   :0.008673
```

```
3rd Qu.:1.0000   3rd Qu.:0.0000000   3rd Qu.:0.00000   3rd Qu.:0.000000
Max.   :1.0000   Max.   :0.0471697   Max.   :1.00000   Max.   :0.314590

  literature      expression_atlas       uniprot         gwas_catalog
Min.   :0.00000   Min.   :0.0000000   Min.   :0.00000   Min.   :0.00000
1st Qu.:0.01480   1st Qu.:0.0000000   1st Qu.:0.00000   1st Qu.:0.00000
Median :0.04150   Median :0.0000000   Median :0.00000   Median :0.00000
Mean   :0.05209   Mean   :0.0001652   Mean   :0.01761   Mean   :0.02406
3rd Qu.:0.06873   3rd Qu.:0.0000000   3rd Qu.:0.00000   3rd Qu.:0.00000
Max.   :0.32125   Max.   :0.0471697   Max.   :1.00000   Max.   :1.00000

phewas_catalog           eva          uniprot_literature genomics_england
Min.   :0.0000000   Min.   :0.00000   Min.   :0.00000    Min.   :0.00000
1st Qu.:0.0000000   1st Qu.:0.00000   1st Qu.:0.00000    1st Qu.:0.00000
Median :0.0000000   Median :0.00000   Median :0.00000    Median :0.00000
Mean   :0.0001925   Mean   :0.02103   Mean   :0.02324    Mean   :0.02421
3rd Qu.:0.0000000   3rd Qu.:0.00000   3rd Qu.:0.00000    3rd Qu.:0.00000
Max.   :0.1942961   Max.   :1.00000   Max.   :1.00000    Max.   :1.00000

gene2phenotype        reactome          slapenrich          progeny
Min.   :0.000000   Min.   :0.000000   Min.   :0.000000   Min.   :0
1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0
Median :0.000000   Median :0.000000   Median :0.000000   Median :0
Mean   :0.006444   Mean   :0.006444   Mean   :0.003566   Mean   :0
3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0
Max.   :1.000000   Max.   :1.000000   Max.   :0.802229   Max.   :0

  phenodigm        cancer_gene_census  eva_somatic        uniprot_somatic
Min.   :0.000000   Min.   :0.000000   Min.   :0.0000000   Min.   :0.0000000
1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.0000000   1st Qu.:0.0000000
Median :0.000000   Median :0.000000   Median :0.0000000   Median :0.0000000
Mean   :0.008673   Mean   :0.003568   Mean   :0.0007907   Mean   :0.0001085
3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.0000000   3rd Qu.:0.0000000
Max.   :0.314590   Max.   :0.808287   Max.   :0.8131173   Max.   :0.5555556

   intogen              chembl         europepmc
Min.   :0.0000000   Min.   :0.0000   Min.   :0.00000
1st Qu.:0.0000000   1st Qu.:0.0000   1st Qu.:0.01480
Median :0.0000000   Median :0.2000   Median :0.04150
Mean   :0.0001085   Mean   :0.3863   Mean   :0.05209
3rd Qu.:0.0000000   3rd Qu.:1.0000   3rd Qu.:0.06873
Max.   :0.4166667   Max.   :1.0000   Max.   :0.32125

                             tissue_label          source
Unspecified                        :4662   GTExv6     : 459
Lung                               :  44   Unspecified:4662
Small Intestine - Terminal Ileum   :  34
Nerve - Tibial                     :  29
```

```
Skin - Not Sun Exposed (Suprapubic):  29
Adipose - Subcutaneous            :  25
(Other)                           : 298
max_fold_change   expression_score
Min.   :    0.0   Min.   :0.00000
1st Qu.:    0.0   1st Qu.:0.00000
Median :    0.0   Median :0.00000
Mean   :   32.3   Mean   :0.04283
3rd Qu.:    0.0   3rd Qu.:0.00000
Max.   :23708.3   Max.   :0.99000
```

```
In [139]: subset(ot.data, key %in% "ENSG00000105650-MP_0001845")
```

key	entrez_id	ensembl_gene_id	symbol	disease_id	disease_label
ENSG00000105650-MP_0001845	5143	ENSG00000105650	PDE4C	MP_0001845	inflammation

1.2.3 Additional Gene Characteristics of Interest

In addition to the current Open Targets evidence scores, we include a number of other genomic characteristics that may be insightful in differentiating between effective and ineffective mechanisms. See the datathon Wiki pages for details.

```
In [140]: #gene.data.all <- read.csv("gene_info_qtq.csv",
          #                          na.strings = c("NA", ""), header = TRUE)
          #write.table(subset(gene.data.all, entrez_id %in% pp.data$entrez_id),
          #            file = "PP_gene_info_qtq.csv", sep = ",", na = "NA",
          #            row.names = FALSE)
```

```
In [141]: gene.data <- read.csv("PP_gene_info_qtq.csv",
                                na.strings = c("NA", ""), header = TRUE) %>%
            select(-X, -hgnc_id, -ensembl_gene_id, -uniprot_id)
          dim(gene.data)
          length(unique(gene.data$entrez_id))
          summary(gene.data)
```

1. 40518 2. 16
1108

```
    symbol        entrez_id                              locus_type
JAK2   :  248   Min.   :        2   endogenous retrovirus     :    7
TGFB1  :  231   1st Qu.:     1815   gene with protein product :40486
CTNNB1 :  218   Median :     3757   immunoglobulin gene       :   17
AKT1   :  179   Mean   :    96704   RNA, micro                :    5
SIRT1  :  177   3rd Qu.:     6387   RNA, misc                 :    1
(Other):39464   Max.   :100133941   T-cell receptor gene      :    1
NA's   :    1                       T-cell receptor pseudogene:    1
             locus_group          go_id
```

```
non-coding RNA     :    6   GO:0005886:  842
other              :   25   GO:0005515:  775
protein-coding gene:40486   GO:0005829:  456
pseudogene         :    1   GO:0005576:  390
                            GO:0005887:  358
                            (Other)   :37686
                            NA's      :   11
                                 go_label     evidence_type
plasma membrane                      :  842   IEA    :10934
protein binding                      :  775   IDA    : 9039
cytosol                              :  456   TAS    : 7854
extracellular region                 :  390   ISS    : 3414
integral component of plasma membrane:  358   IMP    : 3058
(Other)                              :37686   (Other): 6208
NA's                                 :   11   NA's   :   11
reported_count                protein_class                 target_class
Min.   :  1.000   Enzyme              : 3789   Enzyme_all_others   : 7315
1st Qu.:  1.000   Unclassified protein: 3346   Kinase_Protein      : 6689
Median :  1.000   Secreted protein    : 2175   Extracellular Ligand: 4568
Mean   :  1.673   Membrane receptor   : 1548   Receptor_all_others : 4324
3rd Qu.:  1.000   Transcription factor:  693   7TM_Group1          : 3613
Max.   :453.000   (Other)             :22284   (Other)             :14001
NA's   :11        NA's                : 6683   NA's                :    8
   topology_type    target_location               ExAC_LoF
Membrane  : 4314   Exposed  :15753   Intolerant to LoF:14716
MultiTM   : 8653   Nucleus  : 8200   Missing          :  794
Secreted  : 7519   Free     : 7519   Tolerant to LoF  : 6810
SingleTM  : 6962   Organelle: 4123   Unclassified     :18190
Unattached:13062   Cytoplasm: 3255   NA's             :    8
NA's      :    8   (Other)  : 1660
                   NA's     :    8
pc_mouse_gene_identity GTEX_median_all_tissues
Min.   :  0.00         Min.   :    0.00
1st Qu.: 77.62         1st Qu.:    0.50
Median : 88.10         Median :    3.77
Mean   : 83.37         Mean   :   28.21
3rd Qu.: 94.59         3rd Qu.:   17.74
Max.   :100.00         Max.   :10056.00
NA's   :8              NA's   :8
                           description
Janus kinase 2                   :  248
transforming growth factor beta 1:  231
catenin beta 1                   :  218
AKT serine/threonine kinase 1    :  179
sirtuin 1                        :  177
(Other)                          :39457
NA's                             :    8
```

Most of the descriptors in this data set have a single value for each gene:

```
In [142]: apply(gene.data, 2, function(x) length(unique(paste(gene.data$symbol, x))))
```

symbol 1108 **entrez_id** 1108 **locus_type** 1108 **locus_group** 1108 **go_id** 37167 **go_label** 37167 **evidence_type** 6620 **reported_count** 3886 **protein_class** 1124 **target_class** 1108 **topology_type** 1108 **target_location** 1108 **ExAC_LoF** 1108 **pc_mouse_gene_identity** 1108 **GTEX_median_all_tissues** 1108 **description** 1108

In this analysis, I'm not doing anything sophisticated with the various GO terms. To simplify this, I create an analysis version by reducing this data set to the first occurance of each each gene.

```
In [143]: ugene.data <- gene.data %>%
              subset(!duplicated(symbol))
```

1.2.4 Merge all data sets into single data frame for analysis

```
In [144]: all.data <- pp.data %>%
              filter(Clinical.Label_PP %in% c("Clinical Failure",
                                              "Succeeded")) %>%
              inner_join(ot.data) %>%
              left_join(ugene.data) %>%
              mutate(clinical.outcome =
                     droplevels(recode_factor(Clinical.Label_PP,
                                              `Clinical Failure` = "Failure",
                                              `Succeeded` = "Success")))
          dim(all.data)
          summary(all.data)
```

```
Joining, by = c("key", "ensembl_gene_id", "disease_id", "entrez_id")
Warning message:
"Column `key` joining factors with different levels, coercing to character vector"Warning messa
"Column `ensembl_gene_id` joining factors with different levels, coercing to character vector"W
"Column `disease_id` joining factors with different levels, coercing to character vector"Joinin
Warning message:
"Column `symbol` joining factors with different levels, coercing to character vector"
```

1. 4064 2. 61

```
     key              ensembl_gene_id     disease_id          entrez_id
 Length:4064        Length:4064        Length:4064        Min.   :        2
 Class :character   Class :character   Class :character   1st Qu.:     1813
 Mode  :character   Mode  :character   Mode  :character   Median :     3557
                                                          Mean   :    33352
                                                          3rd Qu.:     5742
                                                          Max.   :100133941


    MeSH_ID           DiseaseType              Clinical.Label_PP
 D001172: 130   Neoplasm    :   0   Clinical Failure    :2772
 D011565: 114   Non-Neoplasm:4064   In Progress Clinical:   0
```

```
D001249: 104                       Succeeded          :1292
D000544:  73
D003924:  73
D006973:  68
(Other):3502
           Furthest.Phase      Therapeutic.Direction
Clinical Phase I  : 777   Activator       : 847
Clinical Phase II :1506   Inhibitor       :2247
Clinical Phase III: 455   Mixed or Unknown: 970
Succeeded         :1292
Withdrawn         :  34
```

```
Indication.with.First.Clinical.Outcome.for.Target
N:3542
Y: 522
```

```
                          Types.of.Assets Suggested.Dataset.Utility
Non-Selective Assets             :1241   Neither :3542
Selective and Non-Selective Assets:1243   Test    : 117
Selective Assets                 :1580   Training: 405
```

```
   symbol                             disease_label
Length:4064        rheumatoid arthritis     : 130
Class :character   psoriasis                : 114
Mode  :character   asthma                   : 104
                   pain                     : 102
                   Alzheimers disease       :  73
                   type II diabetes mellitus:  73
                   (Other)                  :3468
                             therapeutic_area is_direct    overall_score
phenotype                            : 649    False: 255   Min.   :0.0000118
nervous system disease; other disease: 520    True :3809   1st Qu.:0.0630852
cardiovascular disease               : 409                 Median :0.2618932
nervous system disease               : 216                 Mean   :0.5074321
respiratory system disease           : 213                 3rd Qu.:1.0052498
(Other)                              :1861                 Max.   :1.5124629
NA's                                 : 196
genetic_association somatic_mutation    known_drug     rna_expression
Min.   :0.00000     Min.   :0.00000   Min.   :0.0000   Min.   :0.0000000
1st Qu.:0.00000     1st Qu.:0.00000   1st Qu.:0.0000   1st Qu.:0.0000000
```

```
Median :0.00000     Median :0.00000   Median :0.2000   Median :0.0000000
Mean   :0.06101     Mean   :0.00383   Mean   :0.4293   Mean   :0.0001741
3rd Qu.:0.00000     3rd Qu.:0.00000   3rd Qu.:1.0000   3rd Qu.:0.0000000
Max.   :1.49404     Max.   :1.00890   Max.   :1.0000   Max.   :0.0313116

affected_pathway   animal_model       literature      expression_atlas
Min.   :0.00000   Min.   :0.00000   Min.   :0.00000   Min.   :0.0000000
1st Qu.:0.00000   1st Qu.:0.00000   1st Qu.:0.01505   1st Qu.:0.0000000
Median :0.00000   Median :0.00000   Median :0.04229   Median :0.0000000
Mean   :0.01128   Mean   :0.00908   Mean   :0.05269   Mean   :0.0001741
3rd Qu.:0.00000   3rd Qu.:0.00000   3rd Qu.:0.06923   3rd Qu.:0.0000000
Max.   :1.00000   Max.   :0.31459   Max.   :0.32125   Max.   :0.0313116

   uniprot         gwas_catalog     phewas_catalog           eva
Min.   :0.00000   Min.   :0.00000   Min.   :0.0000000   Min.   :0.00000
1st Qu.:0.00000   1st Qu.:0.00000   1st Qu.:0.0000000   1st Qu.:0.00000
Median :0.00000   Median :0.00000   Median :0.0000000   Median :0.00000
Mean   :0.01854   Mean   :0.02333   Mean   :0.0002309   Mean   :0.02072
3rd Qu.:0.00000   3rd Qu.:0.00000   3rd Qu.:0.0000000   3rd Qu.:0.00000
Max.   :1.00000   Max.   :1.00000   Max.   :0.1942961   Max.   :1.00000

uniprot_literature genomics_england  gene2phenotype        reactome
Min.   :0.00000    Min.   :0.00000   Min.   :0.000000   Min.   :0.00000
1st Qu.:0.00000    1st Qu.:0.00000   1st Qu.:0.000000   1st Qu.:0.00000
Median :0.00000    Median :0.00000   Median :0.000000   Median :0.00000
Mean   :0.02338    Mean   :0.02436   Mean   :0.006398   Mean   :0.00689
3rd Qu.:0.00000    3rd Qu.:0.00000   3rd Qu.:0.000000   3rd Qu.:0.00000
Max.   :1.00000    Max.   :1.00000   Max.   :1.000000   Max.   :1.00000

  slapenrich          progeny    phenodigm       cancer_gene_census
Min.   :0.000000   Min.   :0   Min.   :0.00000   Min.   :0.000000
1st Qu.:0.000000   1st Qu.:0   1st Qu.:0.00000   1st Qu.:0.000000
Median :0.000000   Median :0   Median :0.00000   Median :0.000000
Mean   :0.004391   Mean   :0   Mean   :0.00908   Mean   :0.003492
3rd Qu.:0.000000   3rd Qu.:0   3rd Qu.:0.00000   3rd Qu.:0.000000
Max.   :0.802229   Max.   :0   Max.   :0.31459   Max.   :0.808287

 eva_somatic        uniprot_somatic        intogen              chembl
Min.   :0.0000000   Min.   :0.0000000   Min.   :0.0000000   Min.   :0.0000
1st Qu.:0.0000000   1st Qu.:0.0000000   1st Qu.:0.0000000   1st Qu.:0.0000
Median :0.0000000   Median :0.0000000   Median :0.0000000   Median :0.2000
Mean   :0.0004735   Mean   :0.0001367   Mean   :0.0001367   Mean   :0.4293
3rd Qu.:0.0000000   3rd Qu.:0.0000000   3rd Qu.:0.0000000   3rd Qu.:1.0000
Max.   :0.8131173   Max.   :0.5555556   Max.   :0.4166667   Max.   :1.0000

  europepmc                                    tissue_label
Min.   :0.00000   Unspecified                        :3684
1st Qu.:0.01505   Lung                               :  35
```

```
Median :0.04229   Nerve - Tibial                     :  24
Mean   :0.05269   Heart - Left Ventricle             :  23
3rd Qu.:0.06923   Skin - Not Sun Exposed (Suprapubic):  23
Max.   :0.32125   Artery - Aorta                     :  22
                  (Other)                            : 253
        source     max_fold_change    expression_score
GTExv6     : 380   Min.   :    0.00   Min.   :0.00000
Unspecified:3684   1st Qu.:    0.00   1st Qu.:0.00000
                   Median :    0.00   Median :0.00000
                   Mean   :   26.72   Mean   :0.04472
                   3rd Qu.:    0.00   3rd Qu.:0.00000
                   Max.   :10791.95   Max.   :0.98000

                     locus_type                locus_group          go_id
endogenous retrovirus     :   0   non-coding RNA     :   0   GO:0009897: 190
gene with protein product :4058   other              :   6   GO:0005737: 181
immunoglobulin gene       :   6   protein-coding gene:4058   GO:0004252: 154
RNA, micro                :   0   pseudogene         :   0   GO:0000187: 128
RNA, misc                 :   0                              GO:0005088:  86
T-cell receptor gene      :   0                              (Other)   :3324
T-cell receptor pseudogene:   0                              NA's      :   1
                                          go_label    evidence_type
external side of plasma membrane              : 190   IEA    :1260
cytoplasm                                     : 181   IDA    : 790
serine-type endopeptidase activity            : 154   TAS    : 749
activation of MAPK activity                   : 128   ISS    : 465
Ras guanyl-nucleotide exchange factor activity:  86   IMP    : 256
(Other)                                       :3324   (Other): 543
NA's                                          :   1   NA's   :   1
reported_count              protein_class                target_class
Min.   : 1.000   Secreted protein  : 239   7TM_Group1          : 998
1st Qu.: 1.000   Oxidoreductase    : 229   Enzyme_all_others   : 545
Median : 1.000   Membrane receptor : 220   Receptor_all_others : 444
Mean   : 1.191   Enzyme            : 188   Ion Channel         : 385
3rd Qu.: 1.000   Serotonin receptor: 147   Extracellular Ligand: 306
Max.   :15.000   (Other)           :2753   Kinase_Protein      : 247
NA's   :1        NA's              : 288   (Other)             :1139
   topology_type       target_location              ExAC_LoF
Membrane  : 358   Cytoplasm    : 210   Intolerant to LoF:1175
MultiTM   :1751   Exposed      :2186   Missing          :  96
Secreted  : 593   Free         : 593   Tolerant to LoF  : 702
SingleTM  : 612   Mitochondrion: 152   Unclassified     :2091
Unattached: 750   Nucleus      : 432
                  Organelle    : 491
                  Unknown      :   0
pc_mouse_gene_identity GTEX_median_all_tissues
Min.   :  0.00         Min.   :   0.00
1st Qu.: 77.87         1st Qu.:   0.11
```

```
Median : 87.42         Median :   0.87
Mean   : 82.67         Mean   :  10.76
3rd Qu.: 93.51         3rd Qu.:   5.41
Max.   :100.00         Max.   :1488.58

                                      description   clinical.outcome
prostaglandin-endoperoxide synthase 2        :  69   Failure:2772
nuclear receptor subfamily 3 group C member 1:  64   Success:1292
prostaglandin-endoperoxide synthase 1        :  55
tumor necrosis factor                        :  49
dopamine receptor D2                         :  41
5-hydroxytryptamine receptor 1A              :  33
(Other)                                      :3753
```

```
In [145]: write.csv(all.data, "all_data.csv", na = "")
```

1.3 Data Exploration

In this section, we perform some basic exploratory data visualizations and summaries to understand the score and evidence distributions and their relationships with clinical success.

1.3.1 Quantitative Open Targets scores

Put data into a long format to permit trellised ggplots

```
In [146]: id.vars = c('key', 'symbol', 'disease_label')
          outcome.vars = c('Clinical.Label_PP', 'Furthest.Phase',
                           'Therapeutic.Direction', 'clinical.outcome')
          ot.scores = c('overall_score', 'genetic_association',
                        'known_drug', 'rna_expression', 'expression_score',
                     'affected_pathway', 'animal_model', 'literature')
          otsrc.scores = c('expression_atlas', 'uniprot', 'gwas_catalog',
                           'phewas_catalog',
                           'eva', 'uniprot_literature', 'genomics_england',
                           'gene2phenotype',
                           'reactome', 'slapenrich', 'phenodigm', 'europepmc')
          gene.qvars = c('pc_mouse_gene_identity', 'GTEX_median_all_tissues')
          gene.cvars = c('protein_class', 'target_class', 'topology_type',
                         'target_location', 'ExAC_LoF')
```

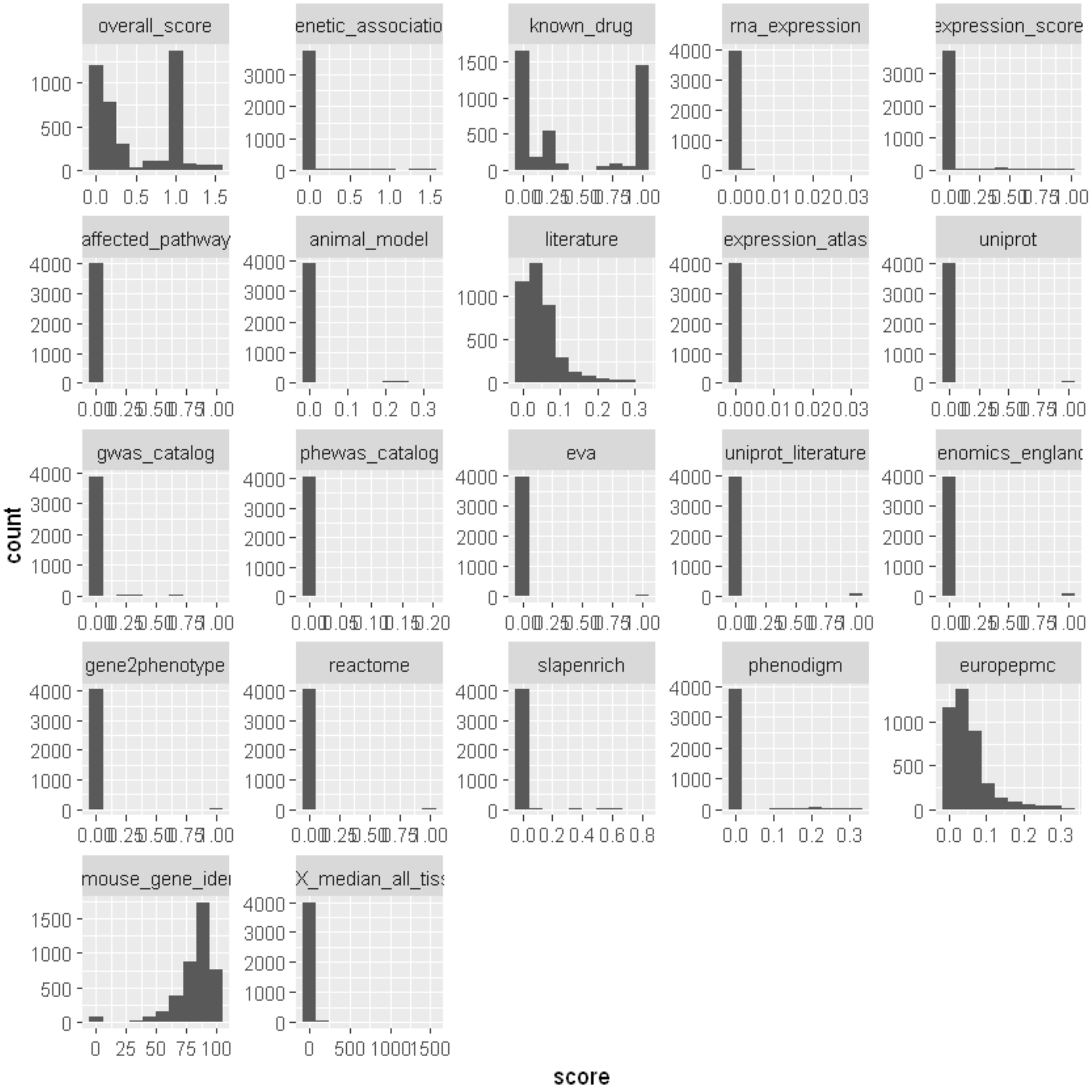
```
In [147]: all.long = gather(all.data[, c(id.vars, outcome.vars, ot.scores,
                                         otsrc.scores, gene.qvars)],
                            datasource, score,
                            overall_score:GTEX_median_all_tissues,
                            factor_key = TRUE)
          ot.long = gather(all.data[, c(id.vars, outcome.vars, ot.scores,
                                        otsrc.scores)],
                           datasource, score,
                           overall_score:europepmc,
                           factor_key = TRUE)
```

```
In [148]: dim(ot.long)
          summary(ot.long)
```

1. 81280 2. 9

```
     key               symbol                            disease_label
 Length:81280       Length:81280       rheumatoid arthritis     : 2600
 Class :character   Class :character   psoriasis                : 2280
 Mode  :character   Mode  :character   asthma                   : 2080
                                       pain                     : 2040
                                       Alzheimers disease       : 1460
                                       type II diabetes mellitus: 1460
                                       (Other)                  :69360
            Clinical.Label_PP            Furthest.Phase
 Clinical Failure    :55440   Clinical Phase I  :15540
 In Progress Clinical:    0   Clinical Phase II :30120
 Succeeded           :25840   Clinical Phase III: 9100
                              Succeeded         :25840
                              Withdrawn         :   680


     Therapeutic.Direction clinical.outcome               datasource
 Activator       :16940     Failure:55440    overall_score      : 4064
 Inhibitor       :44940     Success:25840    genetic_association: 4064
 Mixed or Unknown:19400                      known_drug         : 4064
                                             rna_expression     : 4064
                                             expression_score   : 4064
                                             affected_pathway   : 4064
                                             (Other)            :56896
     score
 Min.   :0.00000
 1st Qu.:0.00000
 Median :0.00000
 Mean   :0.06529
 3rd Qu.:0.00000
 Max.   :1.51246
```

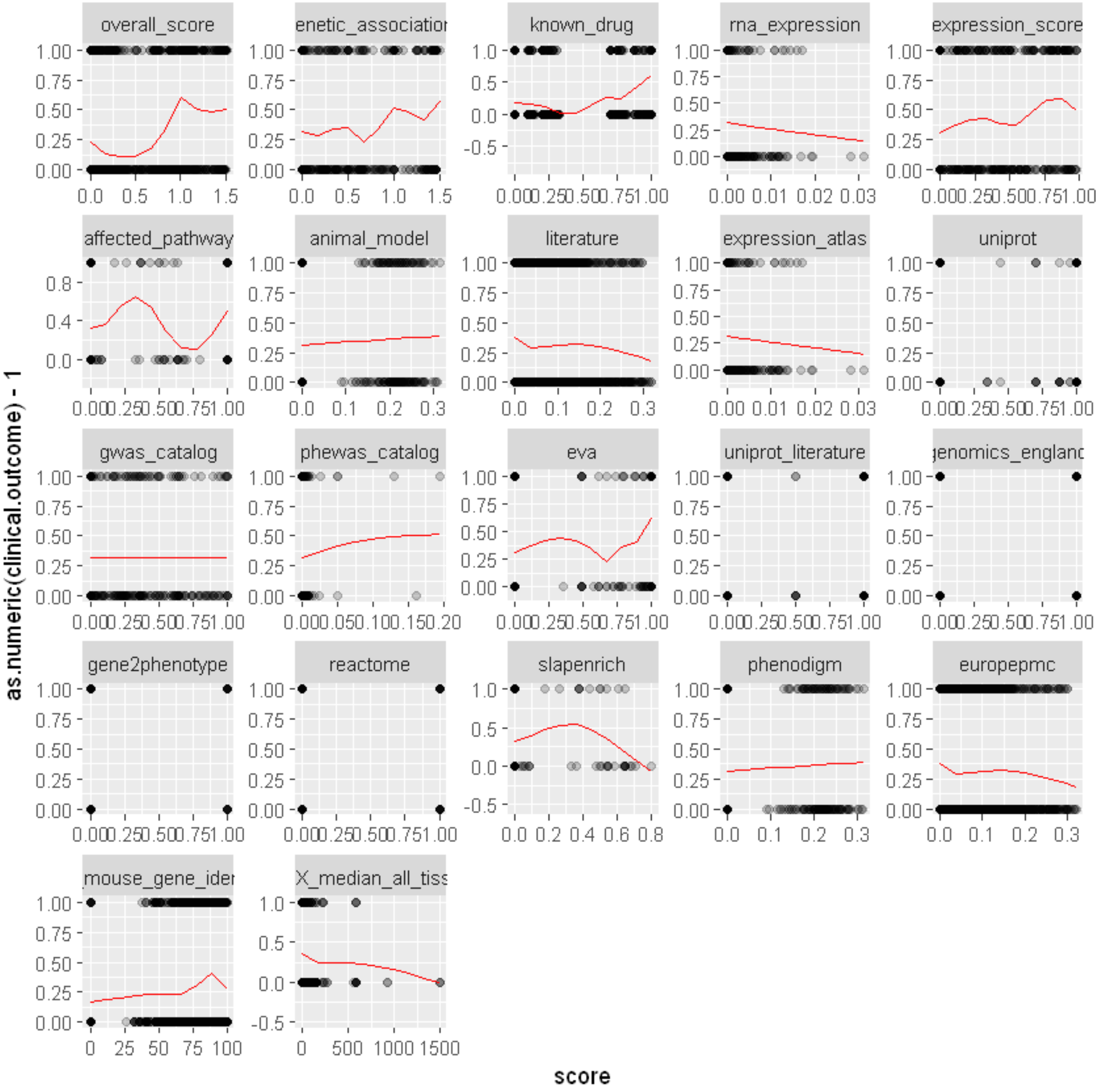
```
In [149]: g = ggplot(all.long, aes(score)) +
            geom_histogram(bins = 10) +
            facet_wrap(~datasource, scales = "free")
          print(g)
```



```
In [150]: g = ggplot(all.long, aes(score, as.numeric(clinical.outcome) - 1)) +
              geom_point(alpha = 0.2) +
              stat_smooth(geom = "line", n = 10, color = "red") +
              facet_wrap(~datasource, scales = "free")
          print(g)
```

```
`geom_smooth()` using method = 'gam'
Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
```

```
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."
```



1.3.2 Converting scores into binary measures of positive and negative evidence

Looking at the relationship between the various Open Targets scores and T-I success, it appears that score values below 0.25 are generally associated with lower success rates, though this varies for many score types. Let's set a threshold value of 0.1 and call everything that exceeds that as having positive evidence.

```
In [151]: pos.score.vars = paste(c(ot.scores, otsrc.scores), ".pos", sep = "")
          names(pos.score.vars) = c(ot.scores, otsrc.scores)
          for(i in names(pos.score.vars)) {
              all.data[, pos.score.vars[i]] = cut(all.data[, i], c(0, 0.1, 100),
                                                  labels = c("Negative", "Positive"),
                                                  include.lowest = TRUE)
          }
          do.call("rbind", apply(all.data[, pos.score.vars], 2, table))
```

	Negative	Positive
overall_score.pos	1328	2736
genetic_association.pos	3762	302
known_drug.pos	1768	2296
rna_expression.pos	4064	4064
expression_score.pos	3707	357
affected_pathway.pos	4003	61
animal_model.pos	3895	169
literature.pos	3543	521
expression_atlas.pos	4064	4064
uniprot.pos	3982	82
gwas_catalog.pos	3880	184
phewas_catalog.pos	4061	3
eva.pos	3965	99
uniprot_literature.pos	3965	99
genomics_england.pos	3965	99
gene2phenotype.pos	4038	26
reactome.pos	4036	28
slapenrich.pos	4031	33
phenodigm.pos	3895	169
europepmc.pos	3543	521

```
In [152]: or.mat = matrix(NA, ncol = 3, nrow = length(pos.score.vars),
                         dimnames = list(pos.score.vars,
                                         c("OR", "Lower", "Upper")))
          or.list = list()
          for(i in pos.score.vars) {
              or.list[[i]][["Table"]] = table(all.data[, "clinical.outcome"],
                                             all.data[, i])
              or.list[[i]][["Test"]] = fisher.test(or.list[[i]][["Table"]])
              or.mat[i,] = unlist(or.list[[i]][["Test"]][c("estimate", "conf.int")])
          }
          or.mat
```

	OR	Lower	Upper
overall_score.pos	3.4077847	2.8823575	4.041107
genetic_association.pos	1.3713346	1.0667681	1.757202
known_drug.pos	3.7213146	3.1993641	4.335960
rna_expression.pos	0.0000000	0.0000000	Inf
expression_score.pos	1.9182899	1.5296043	2.403548
affected_pathway.pos	1.6058173	0.9239383	2.758392
animal_model.pos	1.3948836	1.0004791	1.933610
literature.pos	0.9537654	0.7766443	1.167726
expression_atlas.pos	0.0000000	0.0000000	Inf
uniprot.pos	1.7862454	1.1180972	2.838363
gwas_catalog.pos	0.9612435	0.6854023	1.334392
phewas_catalog.pos	4.2943947	0.2233737	253.147237
eva.pos	1.8161668	1.1877704	2.765425
uniprot_literature.pos	2.0582880	1.3501468	3.133274
genomics_england.pos	2.2367178	1.4687687	3.407862
gene2phenotype.pos	2.5189388	1.0779164	5.980811
reactome.pos	2.1576534	0.9503662	4.899130
slapenrich.pos	1.2280304	0.5490118	2.622947
phenodigm.pos	1.3948836	1.0004791	1.933610
europepmc.pos	0.9537654	0.7766443	1.167726

Repeat categorization for human-mouse protein sequence identity and GTEx median tissue (not currently in Open Targets).

```
In [153]: pos.gene.qvars = paste(gene.qvars, ".pos", sep = "")
          all.data = all.data %>%
              mutate(pc_mouse_gene_identity.pos =
                     ifelse(pc_mouse_gene_identity > 70, "Positive", "Negative")) %>%
              mutate(GTEX_median_all_tissues.pos =
                     ifelse(GTEX_median_all_tissues < 0.5, "Positive", "Negative"))
          apply(all.data[, pos.gene.qvars], 2, table)
```

	pc_mouse_gene_identity.pos	GTEX_median_all_tissues.pos
Negative	597	2328
Positive	3467	1736

```
In [154]: or.mat = matrix(NA, ncol = 3, nrow = length(pos.gene.qvars),
                          dimnames = list(pos.gene.qvars, c("OR", "Lower", "Upper")))
          or.list = list()
          for(i in pos.gene.qvars) {
              or.list[[i]][["Table"]] = table(all.data[, "clinical.outcome"],
                                              all.data[, i])
              or.list[[i]][["Test"]] = fisher.test(or.list[[i]][["Table"]])
              or.mat[i,] = unlist(or.list[[i]][["Test"]][c("estimate", "conf.int")])
          }
          or.mat
```

	OR	Lower	Upper
pc_mouse_gene_identity.pos	1.713860	1.392942	2.118962
GTEX_median_all_tissues.pos	1.289462	1.126355	1.476164

1.3.3 Categorical gene features

```
In [155]: summary((all.data[, gene.cvars]))
```

```
            protein_class                 target_class     topology_type
 Secreted protein  : 239   7TM_Group1          : 998   Membrane  : 358
 Oxidoreductase    : 229   Enzyme_all_others   : 545   MultiTM   :1751
 Membrane receptor : 220   Receptor_all_others : 444   Secreted  : 593
 Enzyme            : 188   Ion Channel         : 385   SingleTM  : 612
 Serotonin receptor: 147   Extracellular Ligand: 306   Unattached: 750
 (Other)           :2753   Kinase_Protein      : 247
 NA's              : 288   (Other)             :1139
      target_location              ExAC_LoF
 Cytoplasm    : 210   Intolerant to LoF:1175
 Exposed      :2186   Missing          :  96
 Free         : 593   Tolerant to LoF  : 702
 Mitochondrion: 152   Unclassified     :2091
 Nucleus      : 432
 Organelle    : 491
 Unknown      :   0
```

```
In [156]: protein.classes = table(all.data$protein_class)
          common.protein.classes = names(protein.classes[protein.classes >= 50])
          all.data$pcred = as.character(all.data$protein_class)
          all.data$pcred[!(all.data$pcred %in% common.protein.classes)] = "Other"
          g = glm(clinical.outcome ~ pcred, all.data, family = binomial(link = "logit"))
          summary(g)
          anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ pcred, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.6651  -0.6923  -0.6923   1.1149   2.7971

Coefficients:
                                                          Estimate Std. Error
(Intercept)                                                 0.8842     0.2727
pcredAdrenergic receptor                                   -0.4268     0.3272
pcredCC chemokine receptor                                 -4.7760     1.0463
pcredDopamine receptor                                     -1.1355     0.3416
pcredEnzyme                                                -2.7591     0.3471
pcredGABA-A receptor                                       -0.7431     0.3619
pcredHistamine receptor                                    -1.0993     0.3829
pcredHydrolase                                             -0.8465     0.3871
```

```
pcredMembrane receptor                                      -1.3468     0.3058
pcredNuclear hormone receptor subfamily 3 group C member 1   0.2144     0.3971
pcredOpioid receptor                                        -0.8543     0.3662
pcredOther                                                  -2.1907     0.2782
pcredOxidoreductase                                         -0.7355     0.3032
pcredProstanoid receptor                                    -2.4482     0.4569
pcredSecreted protein                                       -1.7859     0.3078
pcredSerine protease S1A subfamily                          -0.4622     0.3402
pcredSerotonin receptor                                     -1.3410     0.3210
pcredSLC06 neurotransmitter transporter family              -0.9795     0.3494
pcredUnclassified protein                                   -2.0127     0.3668
pcredVoltage-gated sodium channel                           -0.8568     0.3594
                                                           z value Pr(>|z|)    
(Intercept)                                                  3.242 0.001186 ** 
pcredAdrenergic receptor                                    -1.305 0.192056    
pcredCC chemokine receptor                                  -4.565 5.00e-06 ***
pcredDopamine receptor                                      -3.324 0.000887 ***
pcredEnzyme                                                 -7.948 1.89e-15 ***
pcredGABA-A receptor                                        -2.053 0.040048 *  
pcredHistamine receptor                                     -2.871 0.004094 ** 
pcredHydrolase                                              -2.187 0.028778 *  
pcredMembrane receptor                                      -4.404 1.06e-05 ***
pcredNuclear hormone receptor subfamily 3 group C member 1   0.540 0.589257    
pcredOpioid receptor                                        -2.333 0.019640 *  
pcredOther                                                  -7.876 3.38e-15 ***
pcredOxidoreductase                                         -2.426 0.015283 *  
pcredProstanoid receptor                                    -5.358 8.39e-08 ***
pcredSecreted protein                                       -5.802 6.55e-09 ***
pcredSerine protease S1A subfamily                          -1.358 0.174314    
pcredSerotonin receptor                                     -4.178 2.94e-05 ***
pcredSLC06 neurotransmitter transporter family              -2.803 0.005060 ** 
pcredUnclassified protein                                   -5.487 4.08e-08 ***
pcredVoltage-gated sodium channel                           -2.384 0.017129 *  
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5082.3  on 4063  degrees of freedom
Residual deviance: 4608.9  on 4044  degrees of freedom
AIC: 4648.9

Number of Fisher Scoring iterations: 6
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4063	5082.330	NA
pcred	19	473.3949	4044	4608.935	2.105904e-88

```
In [157]: g = glm(clinical.outcome ~ target_class, all.data,
                  family = binomial(link = "logit"))
          summary(g)
          anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ target_class, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.1486  -0.9563  -0.7664   1.4068   2.0867

Coefficients:
                                             Estimate Std. Error z value
(Intercept)                                   -1.3106     0.2300  -5.698
target_class7TM_Group1                         0.7858     0.2392   3.286
target_classEnzyme_all_others                  0.7654     0.2466   3.104
target_classEnzyme_Esterase                    0.3649     0.2871   1.271
target_classEnzyme_Transferase                 0.1066     0.5192   0.205
target_classExtracellular Ligand              -0.1424     0.2724  -0.523
target_classExtracellular_all_others          -0.1935     0.3744  -0.517
target_classIon Channel                        0.7284     0.2534   2.875
target_classKinase_Protein                    -0.7463     0.3053  -2.445
target_classNuclear Receptor                   1.1745     0.2691   4.365
target_classOther                              0.5634     0.3063   1.839
target_classProtease                           0.7022     0.2687   2.613
target_classReceptor_all_others                0.2359     0.2545   0.927
target_classTranscriptional_Factor_all_others -0.3571     0.4145  -0.862
target_classTransporter                        1.2425     0.2831   4.389
                                             Pr(>|z|)
(Intercept)                                  1.21e-08 ***
target_class7TM_Group1                        0.00102 **
target_classEnzyme_all_others                 0.00191 **
target_classEnzyme_Esterase                   0.20373
target_classEnzyme_Transferase                0.83731
target_classExtracellular Ligand              0.60107
target_classExtracellular_all_others          0.60532
target_classIon Channel                       0.00404 **
target_classKinase_Protein                    0.01449 *
target_classNuclear Receptor                 1.27e-05 ***
target_classOther                             0.06590 .
target_classProtease                          0.00897 **
```

```
target_classReceptor_all_others                0.35408
target_classTranscriptional_Factor_all_others  0.38886
target_classTransporter                       1.14e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5082.3  on 4063  degrees of freedom
Residual deviance: 4907.3  on 4049  degrees of freedom
AIC: 4937.3

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4063	5082.330	NA
target_class	14	175.033	4049	4907.297	6.572631e-30

```
In [158]: g = glm(clinical.outcome ~ topology_type, all.data,
                  family = binomial(link = "logit"))
          summary(g)
          anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ topology_type, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0467  -0.9520  -0.7557   1.4210   1.6699

Coefficients:
                        Estimate Std. Error z value Pr(>|z|)
(Intercept)              -0.3154     0.1070  -2.947   0.0032 **
topology_typeMultiTM     -0.2410     0.1180  -2.043   0.0410 *
topology_typeSecreted    -0.6377     0.1409  -4.526 6.00e-06 ***
topology_typeSingleTM    -0.7919     0.1421  -5.571 2.53e-08 ***
topology_typeUnattached  -0.7939     0.1364  -5.820 5.87e-09 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5082.3  on 4063  degrees of freedom
Residual deviance: 5012.0  on 4059  degrees of freedom
AIC: 5022
```

```
Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4063	5082.330	NA
topology_type	4	70.36218	4059	5011.967	1.903393e-14

```
In [159]: g = glm(clinical.outcome ~ target_location, all.data,
                  family = binomial(link = "logit"))
          summary(g)
          anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ target_location, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0782  -0.8878  -0.8075   1.4978   1.7427

Coefficients:
                             Estimate Std. Error z value Pr(>|z|)
(Intercept)                   -1.2712     0.1668  -7.619 2.55e-14 ***
target_locationExposed         0.5436     0.1730   3.143  0.00168 **
target_locationFree            0.3180     0.1904   1.671  0.09475 .
target_locationMitochondrion   1.0333     0.2335   4.425 9.65e-06 ***
target_locationNucleus         0.1226     0.2012   0.609  0.54239
target_locationOrganelle       0.8793     0.1905   4.615 3.93e-06 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5082.3  on 4063  degrees of freedom
Residual deviance: 5028.8  on 4058  degrees of freedom
AIC: 5040.8

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4063	5082.330	NA
target_location	5	53.48264	4058	5028.847	2.677045e-10

```
In [160]: g = glm(clinical.outcome ~ ExAC_LoF, all.data,
                  family = binomial(link = "logit"))
```

```
        summary(g)
        anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ ExAC_LoF, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0383  -0.8965  -0.8854   1.4871   1.6532

Coefficients:
                        Estimate Std. Error z value Pr(>|z|)
(Intercept)             -0.73428    0.06232 -11.782  < 2e-16 ***
ExAC_LoFMissing          0.39781    0.21620   1.840  0.06576 .
ExAC_LoFTolerant to LoF -0.33791    0.10669  -3.167  0.00154 **
ExAC_LoFUnclassified     0.03036    0.07774   0.390  0.69618
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5082.3  on 4063  degrees of freedom
Residual deviance: 5063.0  on 4060  degrees of freedom
AIC: 5071

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4063	5082.330	NA
ExAC_LoF	3	19.30799	4060	5063.022	0.0002360979

1.4 Save the main analysis dataset as an RData file

```
In [161]: save(all.data, file = "datathon_OTdata.RData", compress = TRUE)
```

1.5 Example prediction model

1.5.1 Backwards stepwise regression

```
In [162]: set.seed(6475250)
          train.select = sample(1:nrow(all.data), size = nrow(all.data) * 0.8,
                                replace = FALSE)
          train.data = all.data[train.select,]
          test.data = subset(all.data, !(key %in% train.data$key))
```

```
In [163]: indep.vars = c(pos.score.vars, pos.gene.qvars,
                         "pcred", "target_class", "topology_type",
                         "target_location", "ExAC_LoF")
          ## Eliminate those that are too rare to be robust and the known drug (chembl) informa
          indep.vars = indep.vars[!(indep.vars %in%
                                    c("overall_score.pos", "known_drug.pos", "affected_pathway
                                     "uniprot.pos", "eva.pos", "rna_expression.pos", "expressio
                                     "phewas_catalog.pos"))]
          full.glm = glm(clinical.outcome ~ ., train.data[, c("clinical.outcome", indep.vars)]
                         family = binomial)
          anova(full.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3250	4058.658	NA
genetic_association.pos	1	2.787913e+00	3249	4055.870	9.497785e-02
expression_score.pos	1	2.587386e+01	3248	4029.997	3.644709e-07
animal_model.pos	1	4.634689e-01	3247	4029.533	4.960072e-01
literature.pos	1	1.212461e+00	3246	4028.321	2.708452e-01
gwas_catalog.pos	1	9.557707e+00	3245	4018.763	1.991116e-03
uniprot_literature.pos	1	2.892674e-03	3244	4018.760	9.571076e-01
genomics_england.pos	1	1.417754e+00	3243	4017.342	2.337734e-01
gene2phenotype.pos	1	3.976117e-01	3242	4016.945	5.283253e-01
reactome.pos	1	9.262695e-01	3241	4016.018	3.358342e-01
slapenrich.pos	1	1.025964e+00	3240	4014.992	3.111085e-01
phenodigm.pos	0	0.000000e+00	3240	4014.992	NA
europepmc.pos	0	0.000000e+00	3240	4014.992	NA
pc_mouse_gene_identity.pos	1	2.264431e+01	3239	3992.348	1.949367e-06
GTEX_median_all_tissues.pos	1	7.932390e+00	3238	3984.416	4.855761e-03
pcred	19	3.453882e+02	3219	3639.028	9.160902e-62
target_class	14	5.637783e+01	3205	3582.650	5.012276e-07
topology_type	4	2.786617e+01	3201	3554.784	1.327662e-05
target_location	4	2.321013e+00	3197	3552.463	6.769459e-01
ExAC_LoF	3	1.239957e+00	3194	3551.223	7.434378e-01

```
In [164]: back.glm = step(full.glm, trace = 0)
          anova(back.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3250	4058.658	NA
genetic_association.pos	1	2.787913	3249	4055.870	9.497785e-02
expression_score.pos	1	25.873863	3248	4029.997	3.644709e-07
gwas_catalog.pos	1	9.697834	3247	4020.299	1.844853e-03
pcred	19	372.635128	3228	3647.664	2.108716e-67
target_class	14	63.213543	3214	3584.450	3.180536e-08
topology_type	4	26.850235	3210	3557.600	2.131400e-05

For comparison, here's the result of the forward stepwise selection. It does not retain any of the Target-indication information.

```
In [165]: null.glm = glm(clinical.outcome ~ 1, train.data, family = binomial)
          forward.glm = step(null.glm,
                          scope = list(lower = formula(null.glm),
                                      upper = formula(full.glm)),
                          direction = "forward", trace = 0)
          anova(forward.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3250	4058.658	NA
pcred	19	362.08369	3231	3696.575	3.234423e-65
target_class	14	71.65409	3217	3624.921	9.667941e-10
topology_type	4	28.08843	3213	3596.832	1.196862e-05
expression_score.pos	1	18.59139	3212	3578.241	1.619507e-05
genomics_england.pos	1	15.26273	3211	3562.978	9.354418e-05

Let's take a look at the estimates of the probabilities of success for the failed and successful target-indication pairs for the training and testing data sets.

```
In [166]: test.data$pred.prob = predict(back.glm, newdata = test.data,
                                      type = "response")
          train.data$pred.prob = predict(back.glm, newdata = train.data,
                                        type = "response")
```

```
In [167]: by(train.data[, "pred.prob"], list(train.data$clinical.outcome), summary)
```

```
: Failure
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.01055 0.14633 0.22336 0.26958 0.36068 0.79590
------------------------------------------------------------
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.05106 0.23989 0.41994 0.41788 0.57511 0.80216
```

```
In [168]: by(test.data[, "pred.prob"], list(test.data$clinical.outcome), summary)
```

```
: Failure
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.01055 0.15404 0.22444 0.27318 0.36068 0.80888
------------------------------------------------------------
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.06506 0.28071 0.43494 0.43507 0.58749 0.85248
```

There are several indications approved for many of the targets (drugs). Let's check how these compare when we limit the results just to the first approved indication for a given target.

```
In [169]: lVec = test.data$Indication.with.First.Clinical.Outcome.for.Target %in% "Y"
          by(test.data[lVec, "pred.prob"], list(test.data$clinical.outcome[lVec]), summary)
```

```
: Failure
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max. 
0.01055 0.14633 0.22336 0.23923 0.25208 0.76777 
------------------------------------------------------------ 
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max. 
 0.1371  0.2741  0.4431  0.4420  0.5885  0.7786 
```

```
In [170]: train.data = train.data %>%
              mutate(pred.outcome = ifelse(pred.prob >= 0.5, "Success", "Failure"))
          test.data = test.data %>%
              mutate(pred.outcome = ifelse(pred.prob >= 0.5, "Success", "Failure"))
```

Confusion matrices if we set a threshold of 0.5 to categorize the results as a success.

```
In [171]: cat("train.data\n")
          xtabs(~ clinical.outcome + pred.outcome, train.data)
          cat("test.data\n")
          xtabs(~ clinical.outcome + pred.outcome, test.data)
```

```
train.data
```

```
                pred.outcome
clinical.outcome Failure Success
         Failure    1992     230
         Success     671     358
```

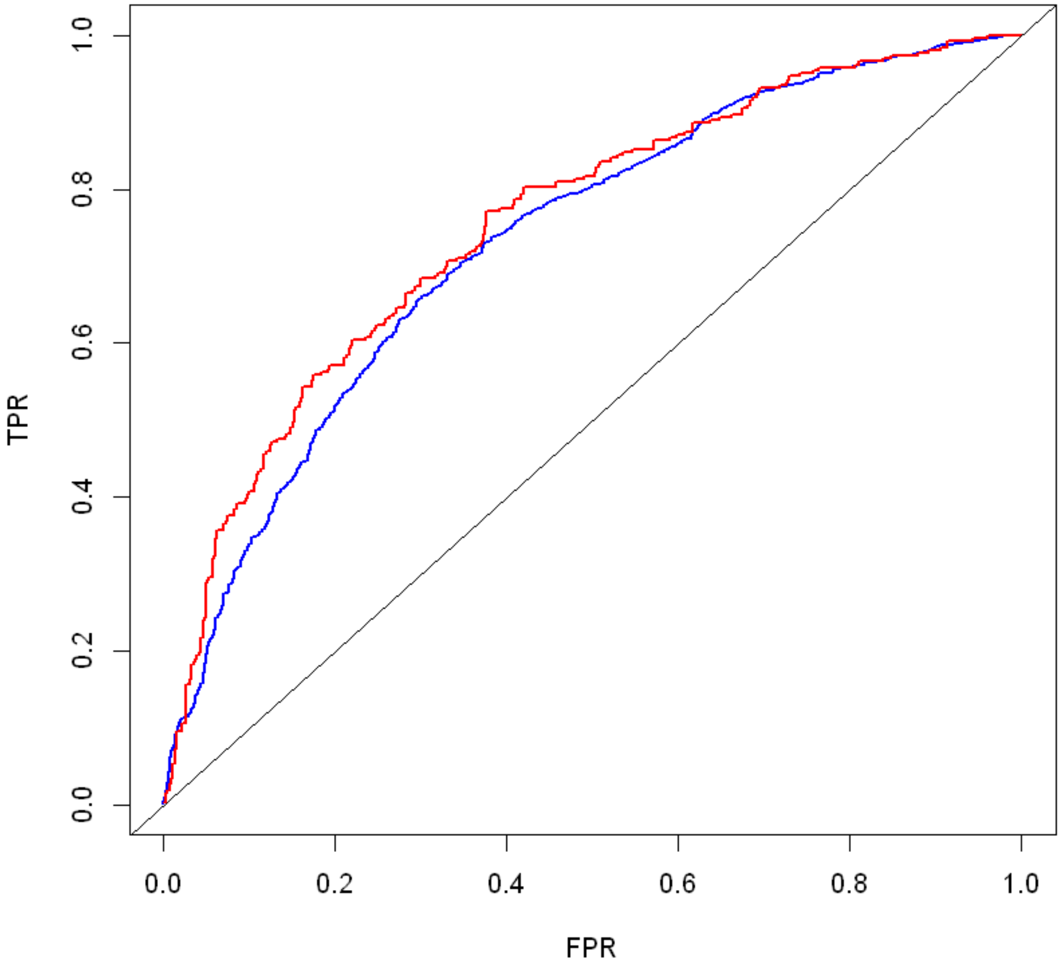
```
test.data
```

```
                pred.outcome
clinical.outcome Failure Success
         Failure     497      53
         Success     159     104
```

```
In [172]: ## I just stole this code from Revolutions at
          ## http://blog.revolutionanalytics.com/2016/11/calculating-auc.html
          simple_roc <- function(labels, scores){
            labels <- labels[order(scores, decreasing=TRUE)]
            data.frame(TPR=cumsum(labels)/sum(labels), FPR=cumsum(!labels)/sum(!labels), label
          }

          simple_auc <- function(TPR, FPR){
            # inputs already sorted, best scores first
            dFPR <- c(diff(FPR), 0)
```

```r
  dTPR <- c(diff(TPR), 0)
  sum(TPR * dFPR) + sum(dTPR * dFPR)/2
}

roc.train = simple_roc(train.data$clinical.outcome %in% "Success",
                      train.data$pred.prob)
roc.test = simple_roc(test.data$clinical.outcome %in% "Success",
                      test.data$pred.prob)
plot(TPR ~ 1 - FPR, roc.train, type = "l", lwd = 2, col = "blue")
lines(TPR ~ 1 - FPR, roc.test, lwd = 2, col = "red")
abline(0, 1)

auc.train = simple_auc(roc.train$TPR, roc.train$FPR)
auc.test = simple_auc(roc.test$TPR, roc.test$FPR)
round(c(auc.train = auc.train, auc.test = auc.test), 3)
```

auc.train	0.733	**auc.test**	0.755



1.6 Some cautionary notes

While the strategy of using the historical drug development record to fit models of target--indication success has many advantages, we also need to be aware of limitations in the data. For example: * Less than 5% of protein--coding genes have ever been explored in the clinic * The proteins that have been explored in the clinic represent a very biased subset of the coding genes as a whole

```
In [173]: n_distinct(all.data$entrez_id)
          all.data  %>%
              group_by(clinical.outcome) %>%
              summarise(unique = n_distinct(entrez_id))
```

798

clinical.outcome	unique
Failure	744
Success	329

- A modest number of diseases have been explored, and for a highly biased subset of corresponding targets

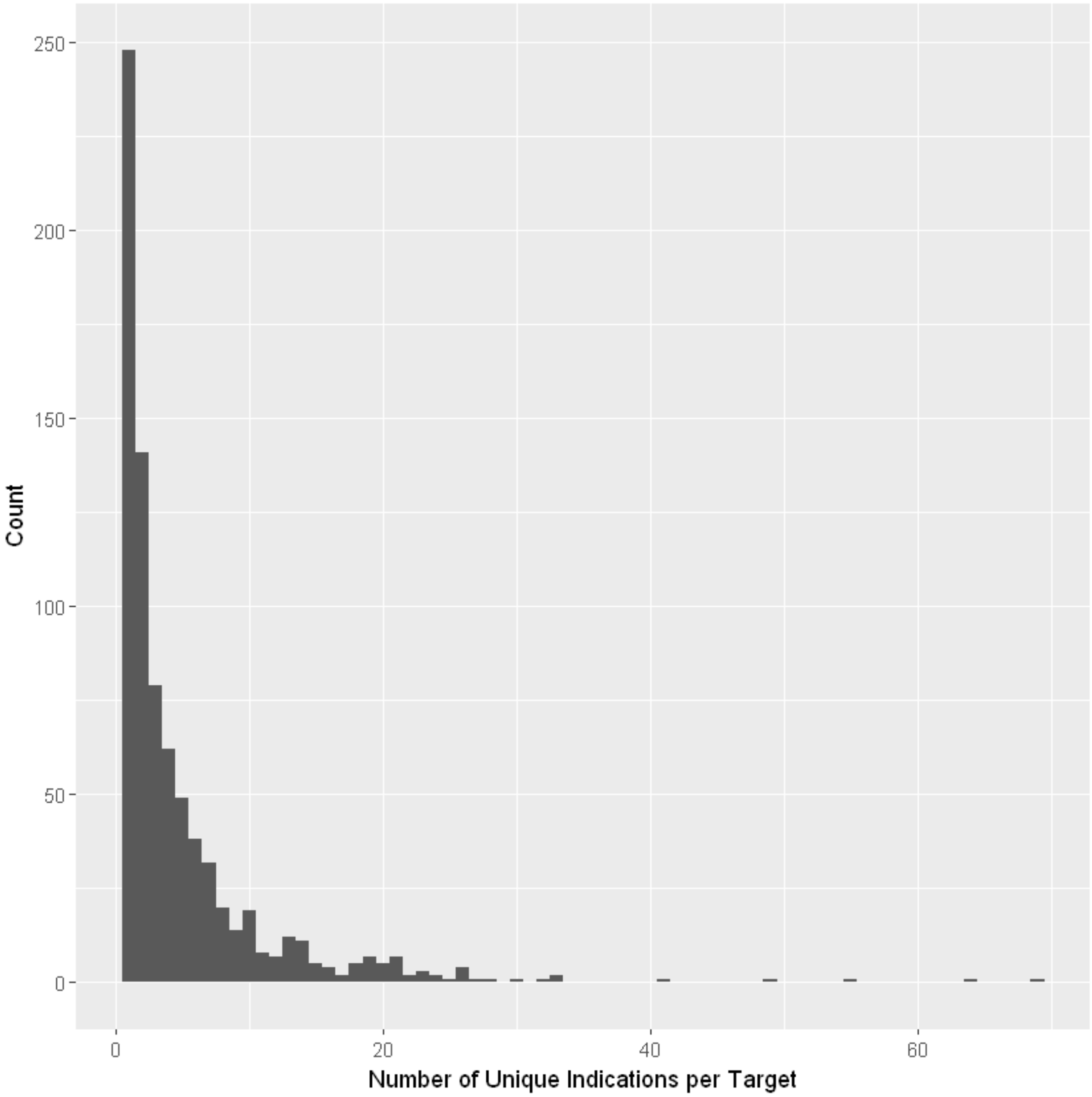
```
In [174]: n_distinct(all.data$MeSH_ID)
          all.data  %>%
              group_by(clinical.outcome) %>%
              summarise(unique = n_distinct(MeSH_ID))
```

403

clinical.outcome	unique
Failure	312
Success	298

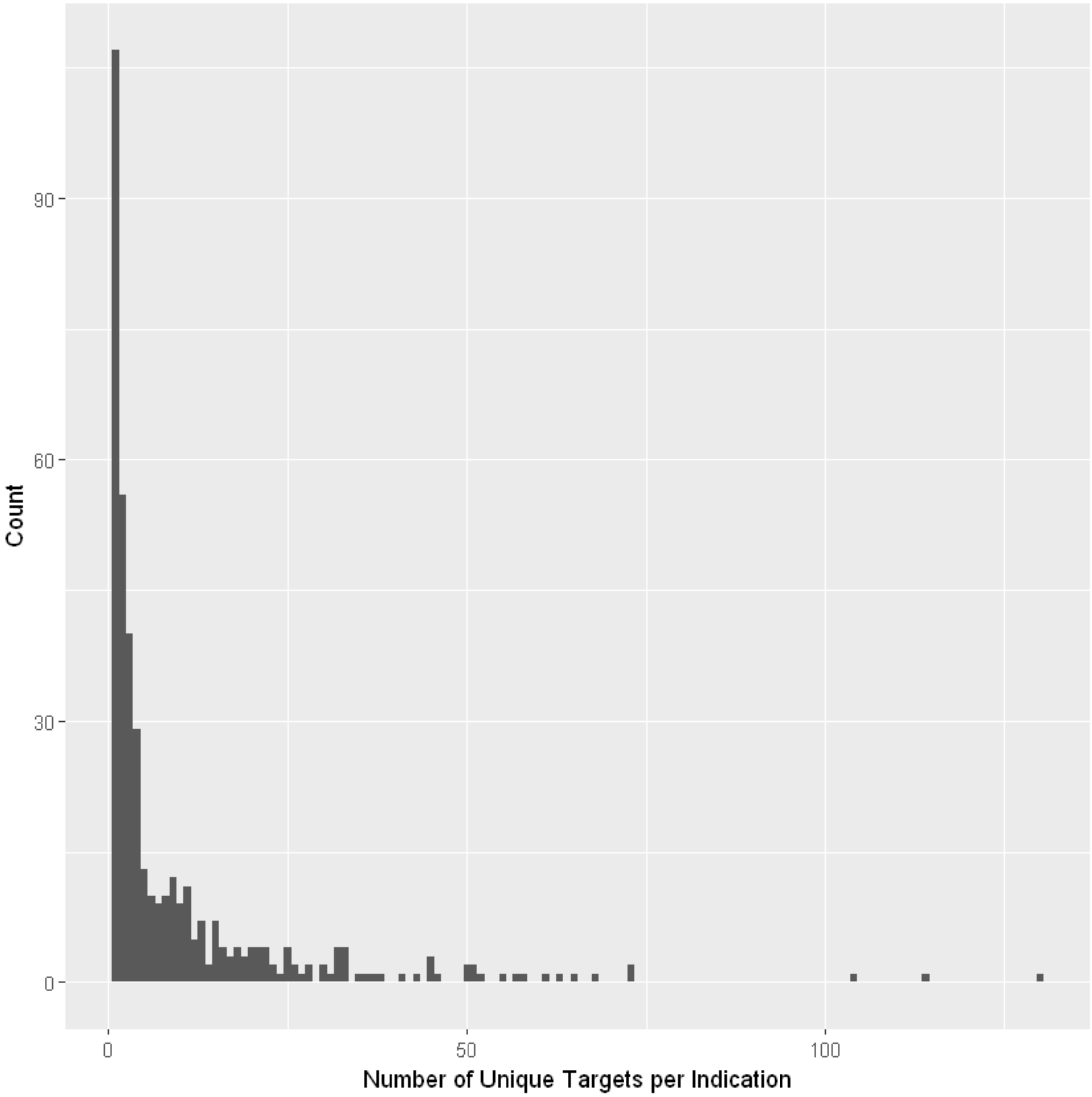
- Some indications have been pursued by a lot of targets

```
In [175]: x <- table(as.character(all.data$entrez_id))
          g <- ggplot(data.frame(Ind = x), aes(Ind.Freq)) + geom_histogram(binwidth = 1) +
              labs(x = "Number of Unique Indications per Target", y = "Count")
          print(g)
```



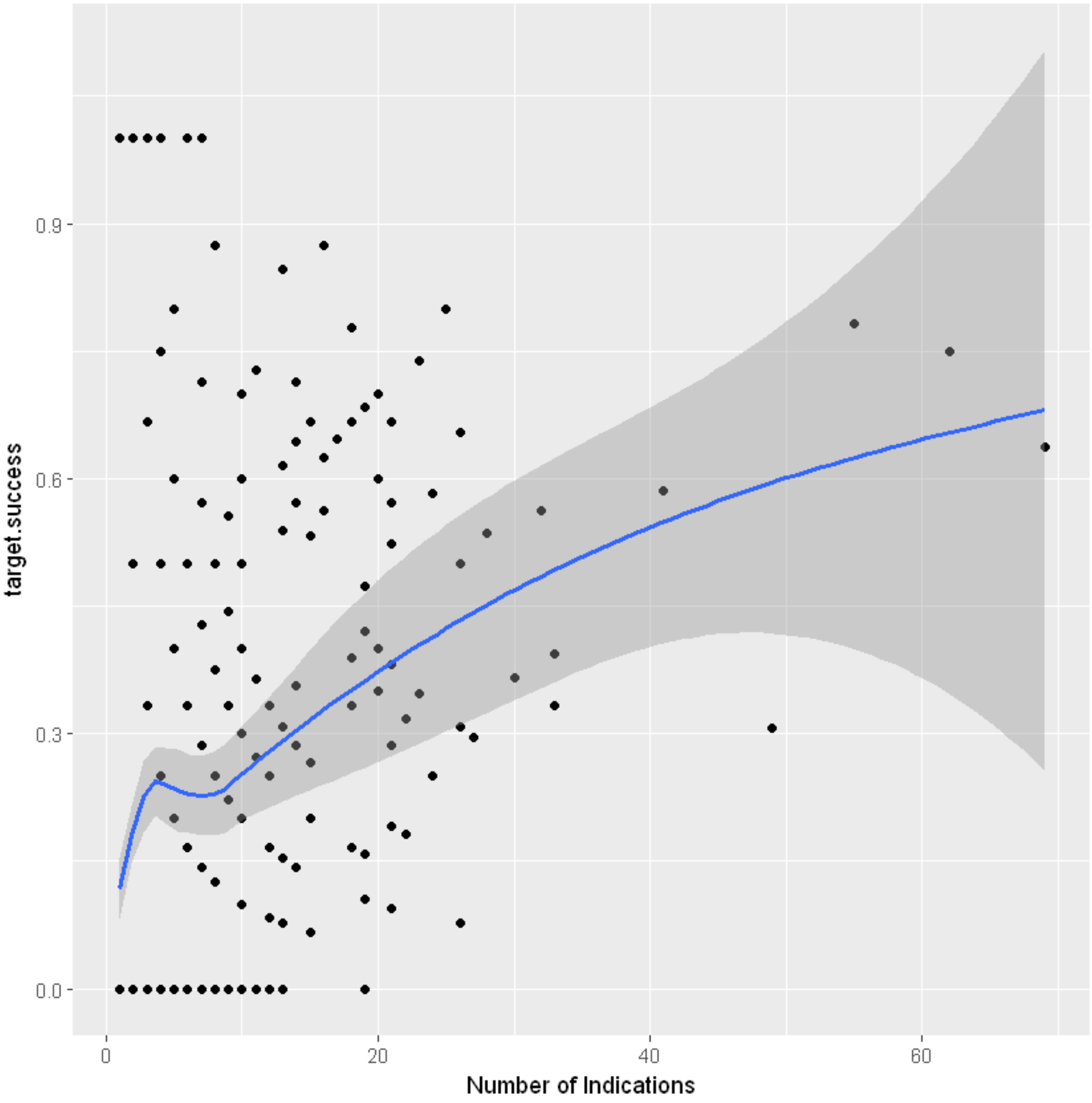
- Some targets have been studied for lots of indications

```
In [176]: x <- table(as.character(all.data$MeSH_ID))
          g <- ggplot(data.frame(Ind = x), aes(Ind.Freq)) + geom_histogram(binwidth = 1) +
              labs(x = "Number of Unique Targets per Indication", y = "Count")
          print(g)
```



- Targets that have been tried for a larger number of indications show a higher proportion of success, with a strong preference for indication adjacencies. These could be considered as duplicates of one another

```
In [177]: success.fxn = function(x) { sum(x %in% "Success")/length(x) }
          target.success = all.data %>%
              group_by(entrez_id) %>%
              summarise(ind.count = n_distinct(MeSH_ID),
                        target.success = success.fxn(clinical.outcome))
          g <- ggplot(target.success, aes(ind.count, target.success)) + geom_point() +
              geom_smooth(method = "loess") + xlab("Number of Indications")
          print(g)
```



1.7 Repeating simple logistic model without duplicate targets

We can assess the robustness of our prediction model by repeating the logistic regression model selection on a subset of the data that retains only a single, randomly selected indication for each target.

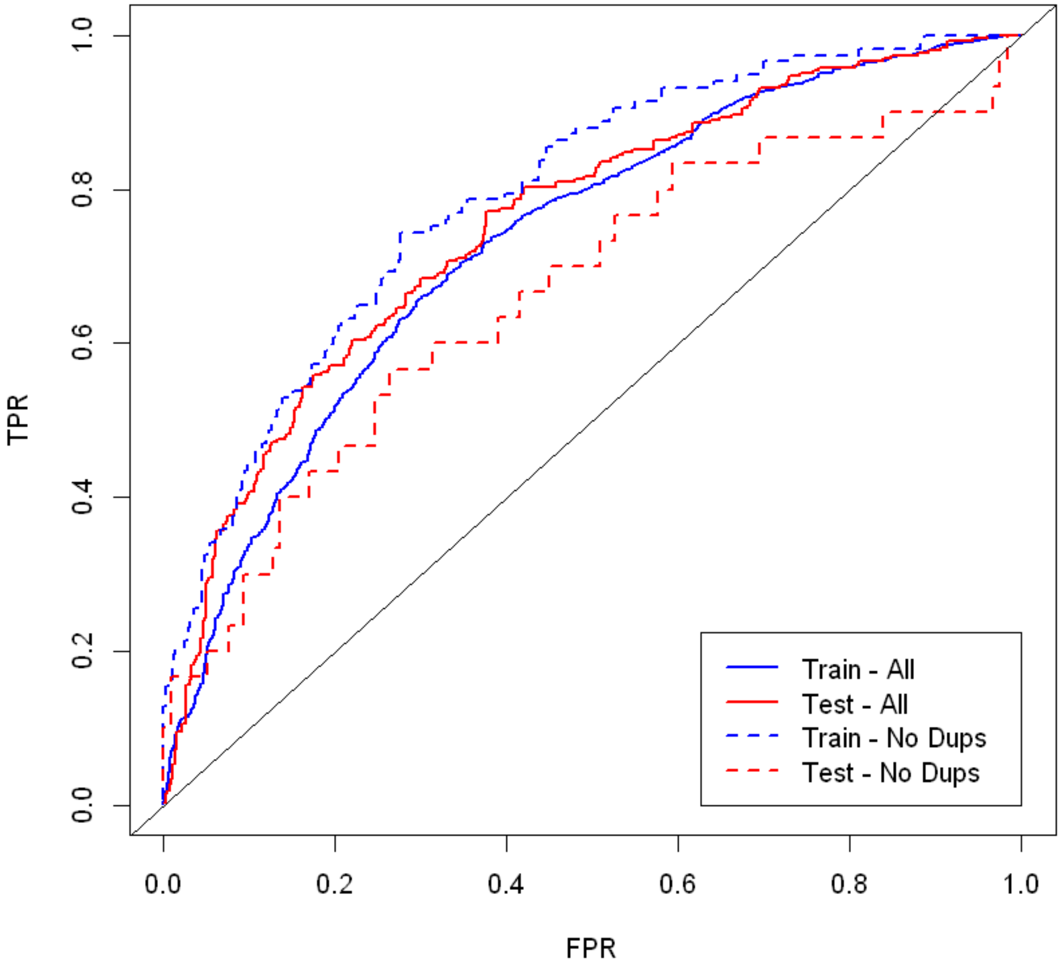
```
In [178]: ## Create subset of all.data, randomly selecting one indication per target
          u.all.data = subset(all.data[sample(1:nrow(all.data)),],
                              !duplicated(entrez_id))
          ## Randomly select training and test set
          u.all.data$Train = sample(c(TRUE, FALSE), size = nrow(u.all.data),
                                     replace = TRUE, prob = c(0.8, 0.2))
          summary(u.all.data[, c("clinical.outcome", "entrez_id", "MeSH_ID", "Train")])
```

```
 clinical.outcome   entrez_id            MeSH_ID       Train        
 Failure:651      Min.   :        2   D001172: 33   Mode :logical  
 Success:147      1st Qu.:     1820   D009190: 31   FALSE:148      
                  Median :     3716   D011565: 27   TRUE :650      
                  Mean   :   136739   D001249: 21                  
                  3rd Qu.:     6366   D003924: 18                  
                  Max.   :100133941   D000544: 17                  
                                      (Other):651                  
```

```
In [179]: u.train.data = subset(u.all.data, Train)
          u.test.data = subset(u.all.data, !Train)
          u.indep.vars = indep.vars[!(indep.vars %in% "phenodigm.pos")]

          u.full.glm = glm(clinical.outcome ~ .,
                          u.train.data[, c("clinical.outcome", u.indep.vars)],
                        family = binomial)
          u.backward.glm = step(u.full.glm, trace = 0)
          anova(u.backward.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	649	612.8115	NA
expression_score.pos	1	7.801133	648	605.0104	5.221349e-03
uniprot_literature.pos	1	15.874205	647	589.1362	6.769512e-05
reactome.pos	1	5.045345	646	584.0908	2.469219e-02
pc_mouse_gene_identity.pos	1	3.796741	645	580.2941	5.135244e-02
pcred	19	59.663736	626	520.6304	4.373491e-06
target_location	5	25.435363	621	495.1950	1.147920e-04

```
In [180]: u.test.data$pred.prob = predict(u.backward.glm, newdata = u.test.data,
                                       type = "response")
          u.train.data$pred.prob = predict(u.backward.glm, newdata = u.train.data,
                                        type = "response")

In [181]: u.roc.train = simple_roc(u.train.data$clinical.outcome %in% "Success",
                                u.train.data$pred.prob)
          u.roc.test = simple_roc(u.test.data$clinical.outcome %in% "Success",
                                u.test.data$pred.prob)
          plot(TPR ~ 1 - FPR, roc.train, type = "l", lwd = 2, col = "blue")
          lines(TPR ~ 1 - FPR, roc.test, lwd = 2, col = "red")
          lines(TPR ~ 1 - FPR, u.roc.train, lwd = 2, col = "blue", lty = 2)
          lines(TPR ~ 1 - FPR, u.roc.test, lwd = 2, col = "red", lty = 2)
          abline(0, 1)
          legend(1, 0, c("Train - All", "Test - All", "Train - No Dups", "Test - No Dups"),
                 lty = c(1, 1, 2, 2), lwd = 2, col = rep(c("blue", "red"), 2), xjust = 1, yjus
```



1.8 Assessment of first indication versus random indications for targets

```
In [182]: x = xtabs(~ Indication.with.First.Clinical.Outcome.for.Target + clinical.outcome, al
          print(x)
```

```
                                                clinical.outcome
Indication.with.First.Clinical.Outcome.for.Target Failure Success
                                                N    2424    1118
                                                Y     348     174
```

```
In [183]: fisher.test(x)
```

```
Fisher's Exact Test for Count Data

data:  x
p-value = 0.4208
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.8862145 1.3227013
sample estimates:
odds ratio
  1.084055
```

```
In [184]: all.data$Train = all.data$key %in% train.data$key
          x2 = xtabs(~ Train + clinical.outcome, all.data)
          print(x2)
```

```
       clinical.outcome
Train   Failure Success
  FALSE     550     263
  TRUE     2222    1029
```

```
In [185]: fisher.test(x2)
```

```
Fisher's Exact Test for Count Data

data:  x2
p-value = 0.7049
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.8193584 1.1464610
sample estimates:
odds ratio
 0.9684309
```