

Drug-Induced Liver Injury (DILI) Classification using US Food and Drug Administration (FDA)-Approved Drug Labeling and FDA Adverse Event Reporting System (FAERS) data

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Research Questions

Why does defining
DILI positive and
negative valuable?

Do we ultimately
labeling properly to
save lives?

What do we get from
assessing hepatotoxicity?

Research Problems

- Defining DILI positive & negative is **challenging** as it requires considering:
 - causality, incidence, and severity of the liver injury events caused by each drug.
- Biomarkers and methodologies are being developed to assess hepatotoxicity **but**:
 - require a list of drugs with well-annotated DILI potential



Research Problems, cont.

- A drug classification scheme is essential to evaluate the performance of existing DILI biomarkers and discover novel DILI biomarkers **but**:
 - **no** adopted practice can classify a drug's DILI potential in humans.



Research Problems, cont.

- Drug labels used to develop a systematic and objective classification scheme[Rule-of-two (RO2)]. **However:**
 - highly context specific
 - rarity of DILI in the premarket experience
 - the complex phenotypes of DILI.
 - drugs are often used in combination with other medications.



Research Solution

Integrating

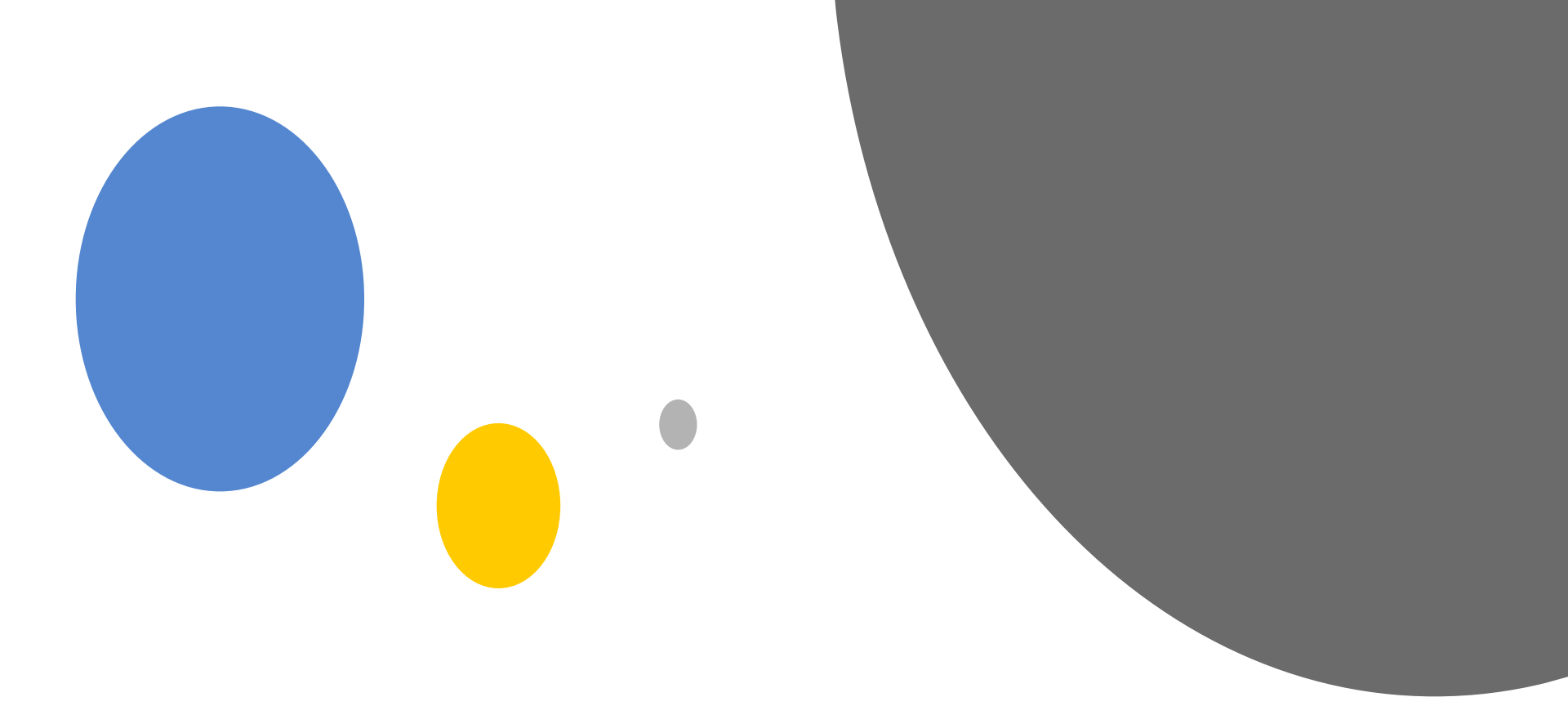
the post-marketing data into the drug-label based approach.

- the FDA FAERS database to improve the DILI classification.

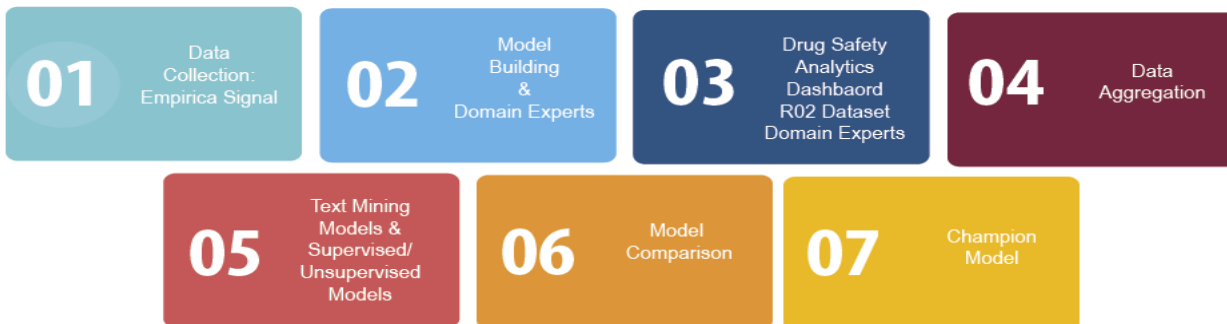
Developing

a statistical prediction models for better predicting DILI.

- the unstructured & unstructured data (premarket and post market DILI narrative reports).



Methodology



DATA EXTRACTION/PREPROCESSING/VISUALIZATION



DATA EXTRACTION/PREPROCESSING/VISUALIZATION

1

Empirica
Signal

2

Drug Safety
Analytics
Dashboards

3

Rule-of-two
dataset

DATA EXTRACTION/PREPROCESSING/VISUALIZATION

Empirica Signal

Empirica Signal
served as the
source of data
retrieval based on
(PT) or (SMQ)

SMQ equals to
'Drug related
hepatic disorders
- severe events
only (SMQ)
[narrow]'

171,890 cases
have been
retrieved with
several data
mining statistics

(PRR)
(EBGM)
(EB05)
(ROR)
(RR)

DATA EXTRACTION/PREPROCESSING/VISUALIZATION

Empirica Signal

01

Prioritizing investigations might be based on scores for **statistical significance**, rather than for **association**.

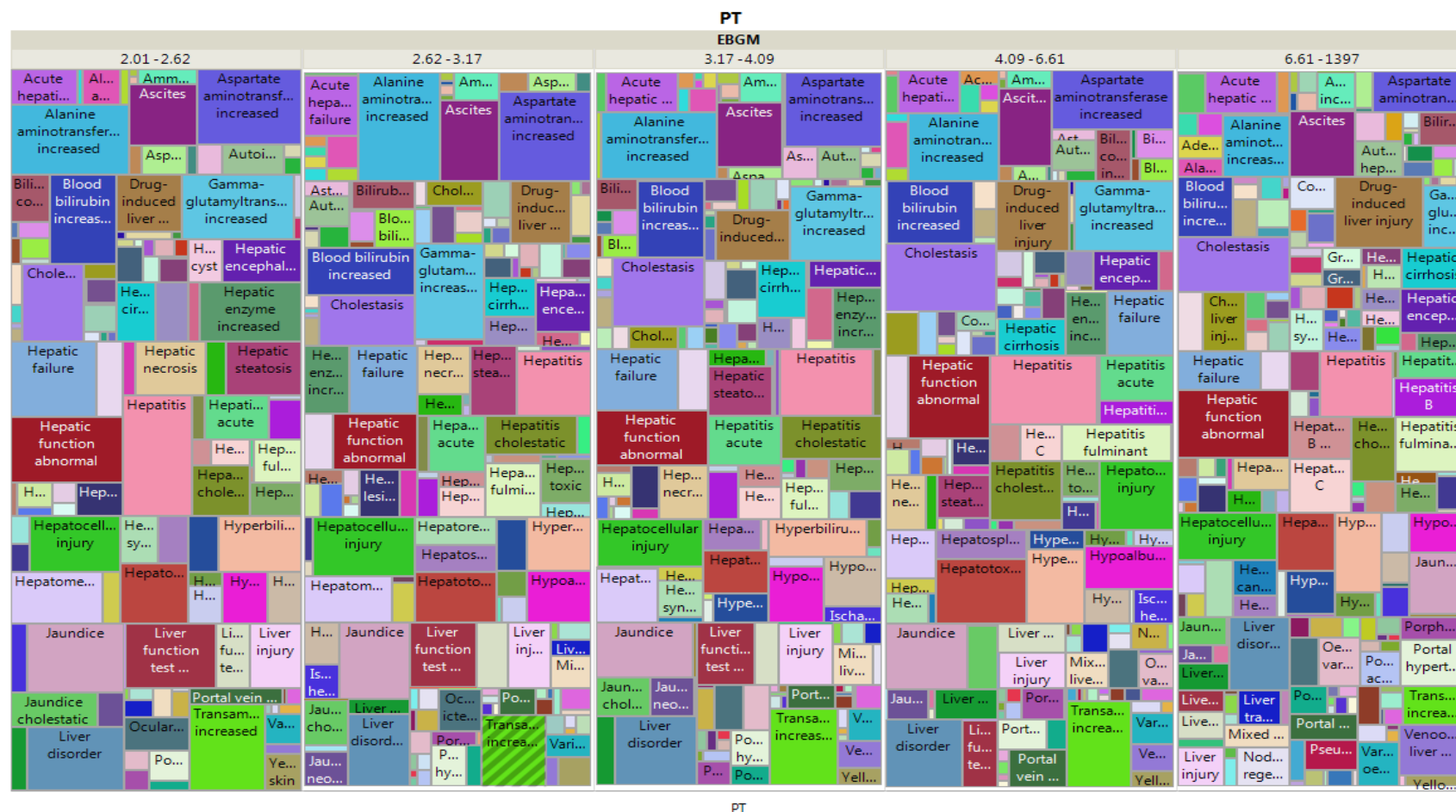
- using a PRR or ROR p-value to rank associations causes **unnecessary focus** on drugs and events.

02

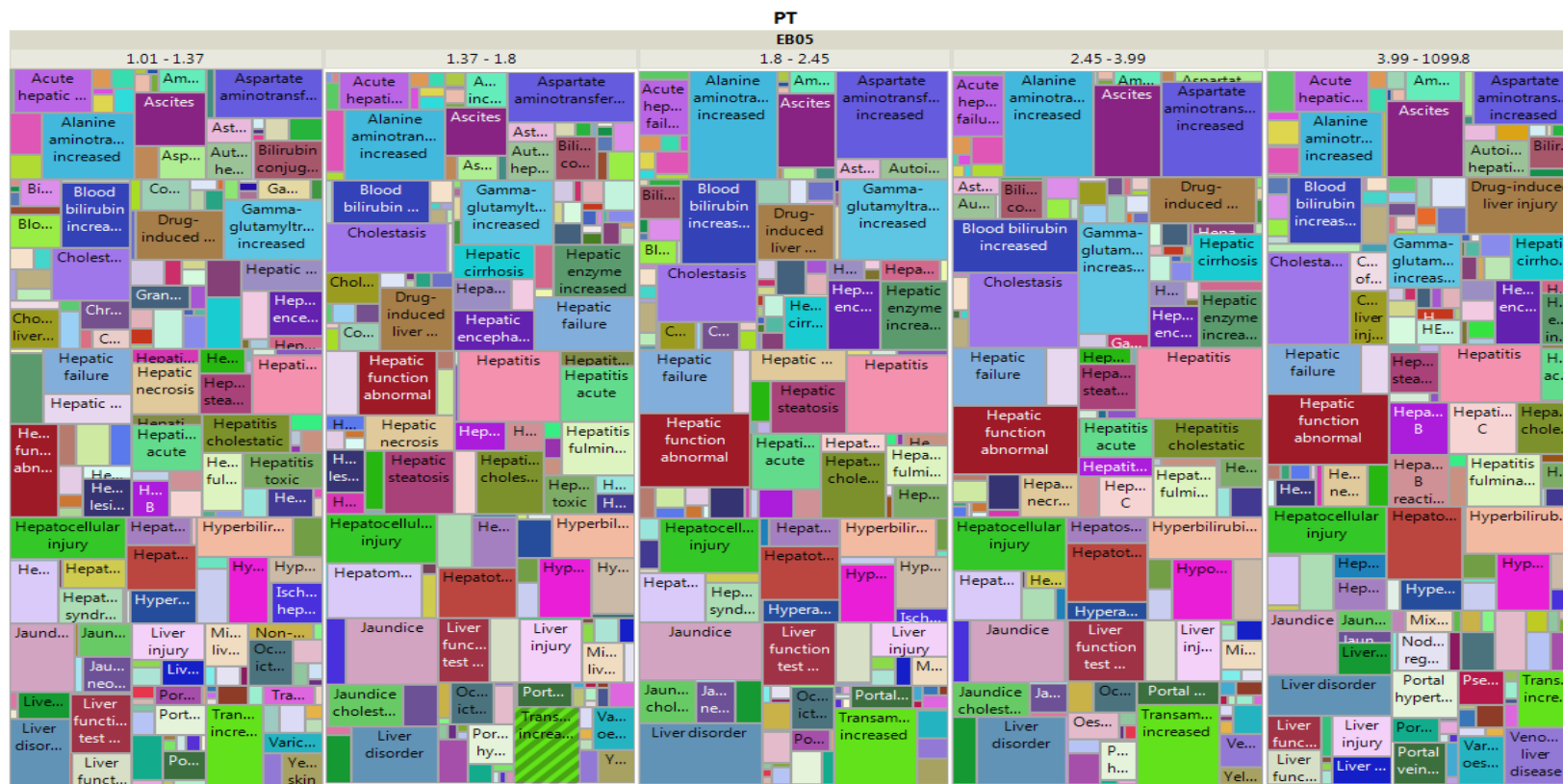
Prioritizing investigations, **in this research**, are based on **both** significance and association scores (**EB05 &EBGM**).

DATA EXTRACTION/PREPROCESSING/VISUALIZATION

Empirica Signal_EBGM



Empirica Signal_ EB05



DATA EXTRACTION/PREPROCESSING/VISUALIZATION DRUG SAFETY ANALYTICS DASHBOARDS

- Retrieving FAERS hepatic failure data (Nov.1997- March 2018).
- Events are customized using SMQ:
 - select drug related hepatic disorders-severe events only.
 - groupings of terms from one or more SOC's related to:
 1. defined medical condition
 2. area of interest
 3. terms related to signs, symptoms, diagnoses, syndromes, physical findings, laboratory test data related to DILI.



DATA EXTRACTION/PREPROCESSING/VISUALIZATION DRUG SAFETY ANALYTICS DASHBOARDS



304,000 cases are retrieved and data was prepared for both the unsupervised and supervised learning.



class variables and text are transferred to interval ones using some techniques such as text clustering, text rule builder, and text profile.

DATA EXTRACTION/PREPROCESSING/VISUALIZATION DRUG SAFETY ANALYTICS DASHBOARDS



Data is dominated by cases with serious outcome value of Yes ($Y=1$).

model with such dominate outcome will be biased.

To compensate for the rare proportion of No ($No=0$) in the raw data, over-sampling is performed

produce a more balanced data set

keep the patterns that appear in the data traceable in the sample.

DATA EXTRACTION/PREPROCESSING/VISUALIZATION

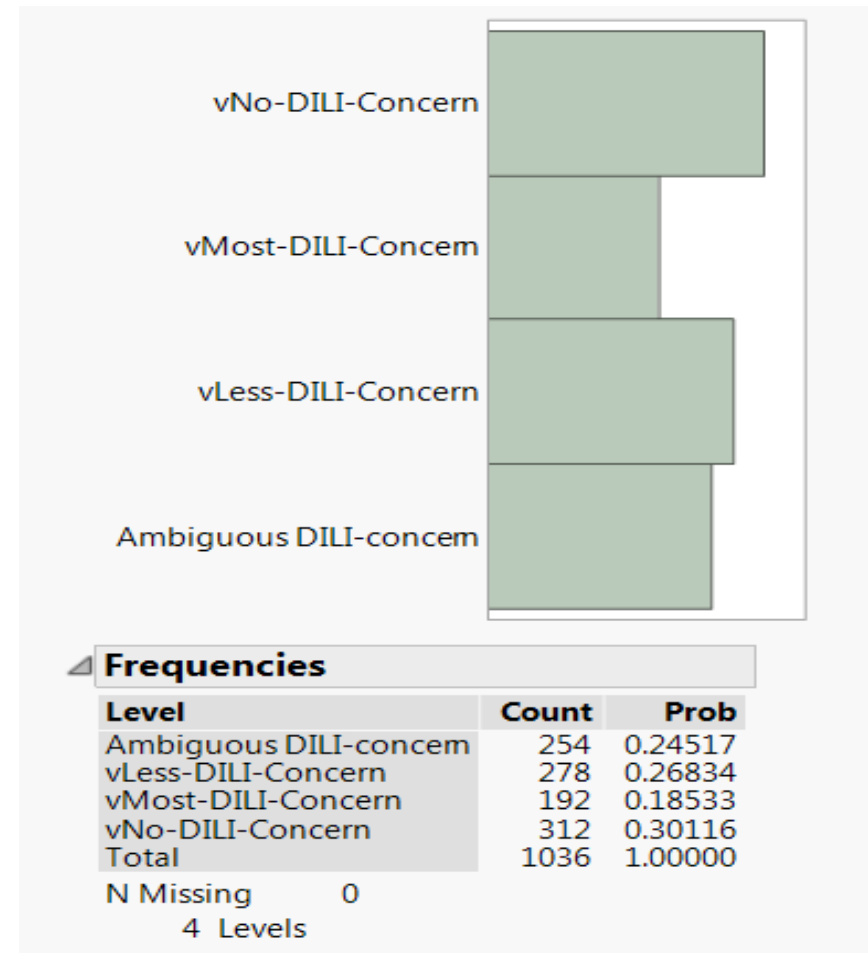
RULE-of-TWO (RO2) DATASET

- FDA-**approved** label
- **Human** use only
- A **single** active molecule in the dosage form
- Administered through oral or parenteral route
- Approved for **five years**
- Commercially available and affordable for future study.

DATA EXTRACTION/PREPROCESSING/VISUALIZATION

RULE-of-TWO (RO2) DATASET

- 1036 FDA- approved drugs were classified into:
 - 192 vMost-DILI concern,
 - 278 vLess-DILI concern,
 - 312 vNo-DILI concern
 - 254 Ambiguous DILI concern drugs.



ANALYTICS APPLICATIONS

Association Analysis



ANALYTICS APPLICATIONS

Association Analysis



- **Association analysis** is used to identify and visualize relationships (association) between different objects.
- Query could be nontrivial to be answered manually with big dataset.

For example:

- What linkage of DILI preferred terms can be observed from post-market data?
- Association analysis can address such relationship by:
 - defining **association rules**
 - calculating the **support** for the combination of the PTs

ANALYTICS APPLICATIONS Association Analysis



- Three scenarios are developed for the subset data from Empirica Signal (14,436 cases).
- Association models are built based on different settings for *minimum support, minimum confidence, minimum lift, maximum antecedents, and maximum rule size*.
- The enumeration of these values allow us to:
 - **cover** more association rules.
 - understand the **optimal setting**.

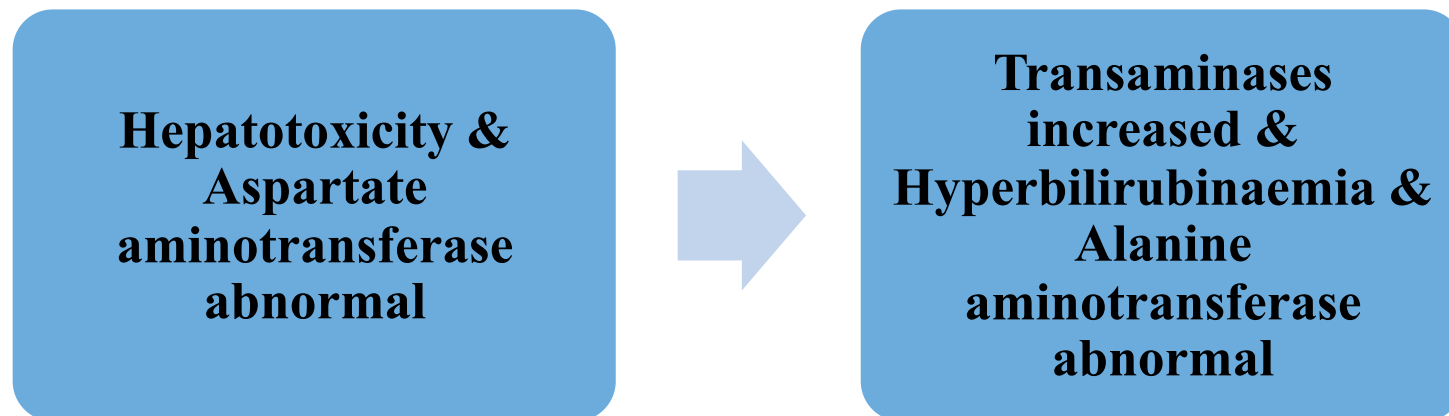
ANALYTICS APPLICATIONS

Association Analysis_Rules Table



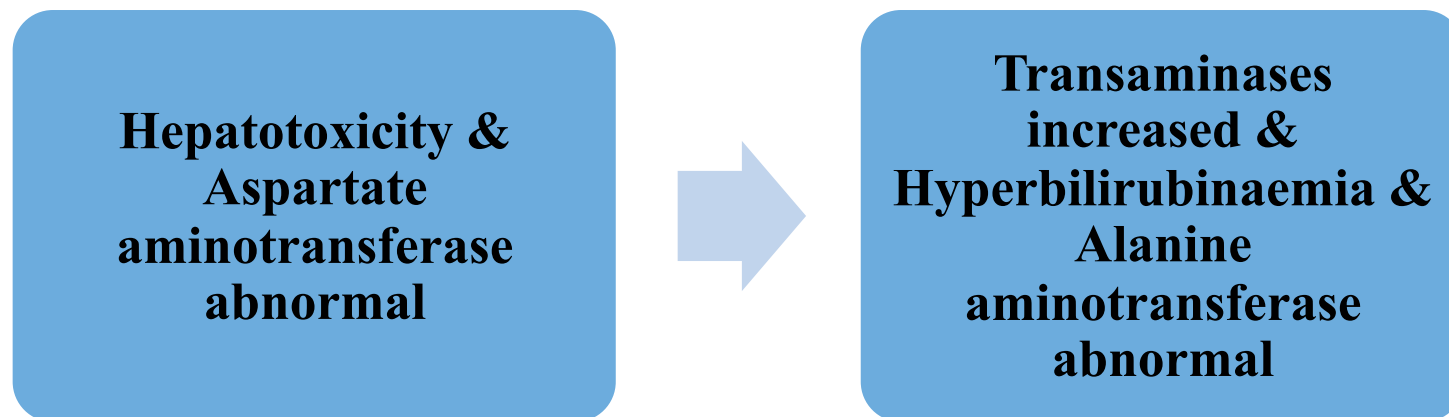
Expected Confidence(%)	Confidence(%)	Support(%)	Lift	Transaction Count	Rule ▲
1.89	62.50	1.44	32.99	25.00	Hepatotoxicity & Aspartate aminotransferase abnormal ==> Transaminases increased & Hyperbilirubinaemia & Alanine aminotransferase abnormal
2.64	88.89	1.38	33.66	24.00	Oesophageal varices haemorrhage & Cholestasis & Ascites ==> Varices oesophageal & Portal vein thrombosis
2.64	88.89	1.38	33.66	24.00	Oesophageal varices haemorrhage & Cholestasis & Blood bilirubin increased ==> Varices oesophageal & Portal vein thrombosis
2.01	75.00	1.38	37.33	24.00	Oesophageal varices haemorrhage & Cholestasis ==> Varices oesophageal & Hyperbilirubinaemia & Hepatotoxicity
2.24	75.00	1.38	33.50	24.00	Oesophageal varices haemorrhage & Cholestasis ==> Varices oesophageal & Portal hypertension & Hepatotoxicity
2.41	88.89	1.38	36.87	24.00	Oesophageal varices haemorrhage & Hepatitis C & Blood bilirubin increased ==> Portal vein thrombosis & Hepatic cirrhosis
2.41	85.71	1.38	35.55	24.00	Oesophageal varices haemorrhage & Hepatitis C & Hepatic failure ==> Portal vein thrombosis & Hepatic cirrhosis
1.78	68.57	1.38	38.53	24.00	Oesophageal varices haemorrhage & Hepatitis C ==> Portal vein thrombosis & Hepatic cirrhosis & Blood bilirubin increased
1.89	68.57	1.38	36.20	24.00	Oesophageal varices haemorrhage & Hepatitis C ==> Portal vein thrombosis & Hepatic failure & Hepatic cirrhosis
1.95	71.43	1.44	36.60	25.00	Oesophageal varices haemorrhage & Hepatitis C ==> Portal vein thrombosis & Hyperbilirubinaemia & Hepatic cirrhosis
1.95	68.57	1.38	35.13	24.00	Oesophageal varices haemorrhage & Hepatitis C ==> Varices oesophageal & Portal vein thrombosis & Hepatic cirrhosis
2.18	71.43	1.44	32.74	25.00	Oesophageal varices haemorrhage & Hepatitis C ==> Varices oesophageal & Portal vein thrombosis & Hyperbilirubinaemia
3.04	100.00	1.49	32.87	26.00	Oesophageal varices haemorrhage & Hepatotoxicity & Blood bilirubin increased ==> Varices oesophageal & Hyperbilirubinaemia
2.58	96.00	1.38	37.16	24.00	Oesophageal varices haemorrhage & Hepatotoxicity & Hepatic cirrhosis ==> Varices oesophageal & Transaminases increased
3.04	100.00	1.44	32.87	25.00	Oesophageal varices haemorrhage & Hepatotoxicity & Hepatic failure ==> Varices oesophageal & Hyperbilirubinaemia
2.07	77.42	1.38	37.46	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Hyperbilirubinaemia & Cholestasis
2.35	77.42	1.38	32.89	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Portal hypertension & Cholestasis
2.53	87.10	1.55	34.48	27.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Portal hypertension & Hyperbilirubinaemia
2.18	77.42	1.38	35.49	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Portal vein thrombosis & Hyperbilirubinaemia
2.35	77.42	1.38	32.89	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Portal vein thrombosis & Portal hypertension
2.30	77.42	1.38	33.72	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Transaminases increased & Hepatic cirrhosis
1.89	77.42	1.38	40.87	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Transaminases increased & Hyperbilirubinaemia
2.18	77.42	1.38	35.49	24.00	Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Transaminases increased & Portal hypertension
2.58	92.31	1.38	35.73	24.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Cholestasis ==> Varices oesophageal & Hepatotoxicity
2.12	73.53	1.44	34.62	25.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Hepatic cirrhosis ==> Portal vein thrombosis & Hepatitis C
2.12	76.47	1.49	36.00	26.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Hepatic cirrhosis ==> Varices oesophageal & Hepatitis C
2.12	72.73	1.38	34.24	24.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Hepatic encephalopathy ==> Varices oesophageal & Hepatitis C
2.41	83.33	1.44	34.56	25.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Hepatitis C ==> Portal vein thrombosis & Hepatic cirrhosis
2.58	85.71	1.38	33.18	24.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia & Hepatotoxicity ==> Varices oesophageal & Transaminases increased
1.78	61.36	1.55	34.48	27.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Portal vein thrombosis & Hepatic cirrhosis & Blood bilirubin increased
1.66	56.82	1.44	34.13	25.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Portal vein thrombosis & Hepatitis C & Hepatic cirrhosis
1.61	56.82	1.44	35.35	25.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Hepatitis C & Blood bilirubin increased
1.66	54.55	1.38	32.76	24.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal hypertensive gastropathy & Portal hypertension
1.89	63.64	1.61	33.59	28.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal vein thrombosis & Hepatic encephalopathy
2.07	68.18	1.72	32.99	30.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal vein thrombosis & Hepatic failure
1.66	56.82	1.44	34.13	25.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal vein thrombosis & Hepatitis C
1.55	54.55	1.38	35.19	24.00	Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal vein thrombosis & Hepatotoxicity
1.78	64.86	1.38	36.45	24.00	Oesophageal varices haemorrhage & Jaundice ==> Portal vein thrombosis & Hepatic cirrhosis & Blood bilirubin increased
1.95	64.86	1.38	33.23	24.00	Oesophageal varices haemorrhage & Jaundice ==> Portal vein thrombosis & Hyperbilirubinaemia & Hepatic cirrhosis
1.95	64.86	1.38	33.23	24.00	Oesophageal varices haemorrhage & Jaundice ==> Varices oesophageal & Portal vein thrombosis & Hepatic cirrhosis
1.78	63.16	1.38	35.49	24.00	Portal hypertension & Hepatitis C ==> Portal vein thrombosis & Hepatic cirrhosis & Blood bilirubin increased
1.89	65.79	1.44	34.73	25.00	Portal hypertension & Hepatitis C ==> Portal vein thrombosis & Hepatic failure & Hepatic cirrhosis
1.95	68.42	1.49	35.06	26.00	Portal hypertension & Hepatitis C ==> Portal vein thrombosis & Hyperbilirubinaemia & Hepatic cirrhosis
1.95	71.05	1.55	36.40	27.00	Portal hypertension & Hepatitis C ==> Varices oesophageal & Portal vein thrombosis & Hepatic cirrhosis
2.64	88.89	1.84	33.66	32.00	Portal hypertension & Oesophageal varices haemorrhage & Blood bilirubin increased ==> Varices oesophageal & Portal vein thrombosis
2.58	85.71	1.38	33.18	24.00	Portal hypertension & Oesophageal varices haemorrhage & Cholestasis ==> Varices oesophageal & Hepatotoxicity
2.64	89.29	1.44	33.81	25.00	Portal hypertension & Oesophageal varices haemorrhage & Hepatomegaly ==> Varices oesophageal & Portal vein thrombosis
2.58	85.71	1.38	33.18	24.00	Portal hypertension & Oesophageal varices haemorrhage & Hepatotoxicity ==> Varices oesophageal & Transaminases increased
2.12	70.59	1.38	33.23	24.00	Portal hypertension & Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Hepatitis C
1.89	70.59	1.38	37.26	24.00	Portal hypertension & Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal hypertensive gastropathy
2.64	91.18	1.78	34.53	31.00	Portal hypertension & Oesophageal varices haemorrhage & Hyperbilirubinaemia ==> Varices oesophageal & Portal vein thrombosis
1.55	51.06	1.38	32.95	24.00	Portal hypertension & Oesophageal varices haemorrhage ==> Portal vein thrombosis & Portal hypertensive gastropathy
1.55	51.06	1.38	32.95	24.00	Portal hypertension & Oesophageal varices haemorrhage ==> Varices oesophageal & Portal hypertensive gastropathy & Ascites
1.49	51.06	1.38	34.21	24.00	Portal hypertension & Oesophageal varices haemorrhage ==> Varices oesophageal & Portal hypertensive gastropathy & Hyperbilirubinaemia

Association Analysis_Rule Example



- A confidence of 62.5% of the events where the *condition PTs* *Hepatotoxicity & Aspartate aminotransferase abnormal* appear in DILI cases, *the consequent PTs* *Transaminases increased & Hyperbilirubinaemia & Alanine aminotransferase abnormal* will also appears.

Association Analysis_Rule Example



- A lift is **32.99**, indicating a likely dependency.
- A lift ratio >1 indicates that the consequent PTs
Transaminases increased & Hyperbilirubinaemia & Alanine aminotransferase abnormal

have an affinity for the condition PTs

Hepatotoxicity & Aspartate aminotransferase abnormal”.

ANALYTICS APPLICATIONS

Association Analysis

Rules generated might be **sufficient** for understanding the association.

Additional analysis was performed so that similar PTs are grouped together using a matrix reducing methodology.

Topics (grouped PTs) are created by rotating the SVD on the transaction item matrix.

The grouped PTs are then presented to domain experts to assign informative names.

Experts independently provided their assigned topic names and majority consistent in topic naming are employed to assign name(s) for the generated topics.

Item	Topic Name
Bacillary angiomatosis	Various hepatic disorders, particularly vascular, Hepatic Infection/vascular, Hepatic vascular disorders, complications of liver transplantation, nonspecific clinical finding, infectious hepatitis, liver injury clinical finding
Hepatic cyst infection	
Hepatic artery stenosis	
Perihepatic abscess	
Hepatic artery aneurysm	
Portal vein stenosis	
Splenorenal shunt	
Hepatitis infectious mononucleosis	
Hepatic vein stenosis	
Portal vein occlusion	
Portal vein phlebitis	
Chronic graft versus host disease in liver	
Hepatic artery occlusion	

DATA SETS AGGREGATION

**04**Data
Aggregation

This research data has two different domains (i.e., pre-marketing and post-marketing).

RO2 dataset mainly based on drug labeling and incorporating information to verify the drugs causality of DILI in humans..

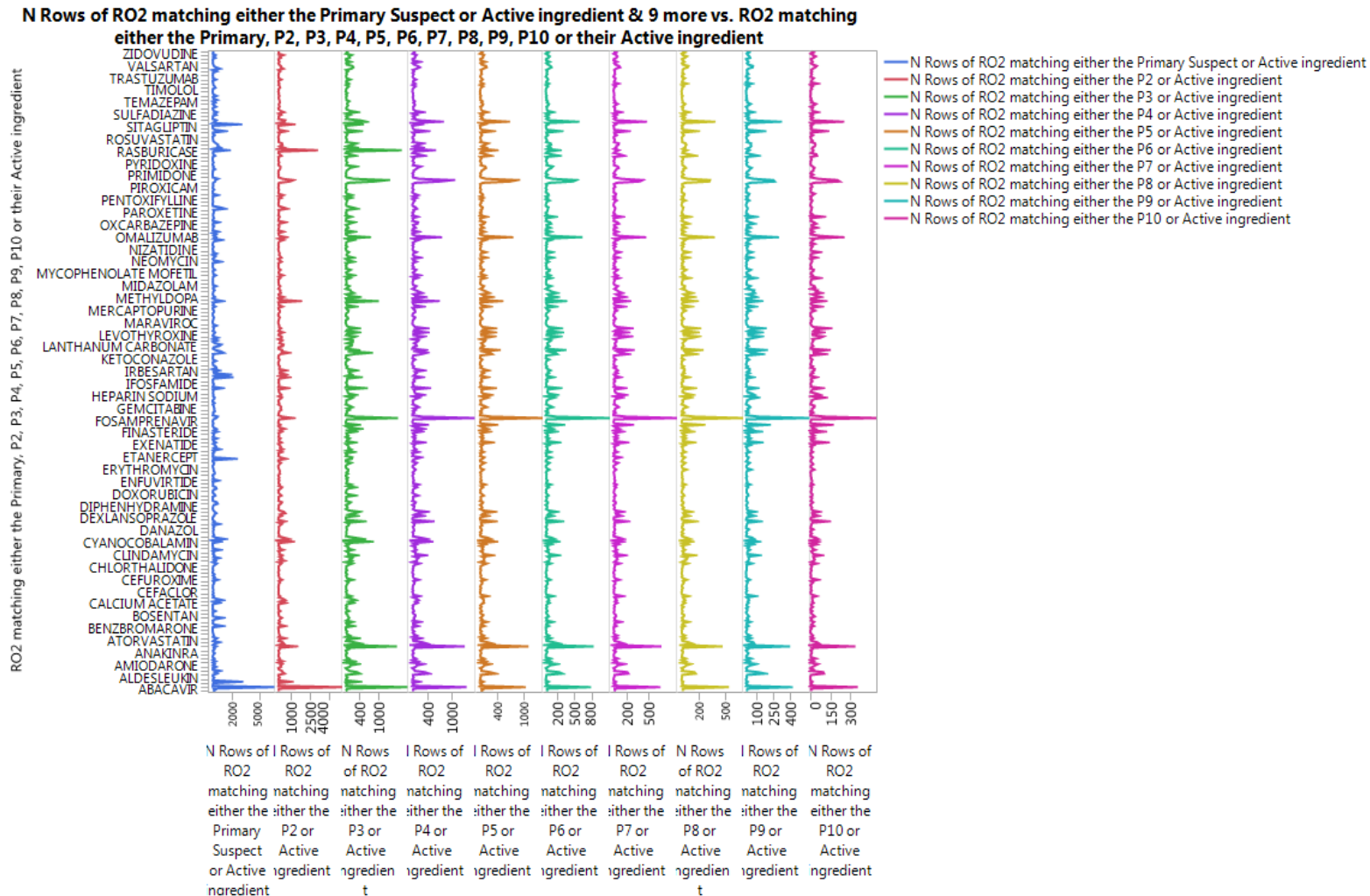
Empirica Signal and Drug Safety Analytics Dashboards are based on FAERS data which is post-marketing data.

Numerous customized SQL were developed to match the RO2 compound names (1036 unique drugs) with 182474 DILI cases from FAERS.

DATA SETS AGGREGATION

DATA SETS AGGREGATION

Number of cases that RO2 list matching FAERS data for DILI.



PREDICTIVE ANALYSIS

Text Analytics



05

Text Mining
Models &
Supervised/
Unsupervised
Models

PREDICTIVE ANALYSIS

Text Analytics

“The term **text analytics** describes a set of linguistic, statistical, and machine learning techniques that model and structure the information content of textual sources for business intelligence, exploratory data analysis, research, or investigation.”*

Or, put more simply...

*“Using technology to **scale** the human acts of **reading, organizing, and quantifying** freeform text in meaningful ways.”*



- Capture information embedded in text that is critical to risk assessments
 - Signs
 - Symptoms
 - Disease status/severity
 - Medical history

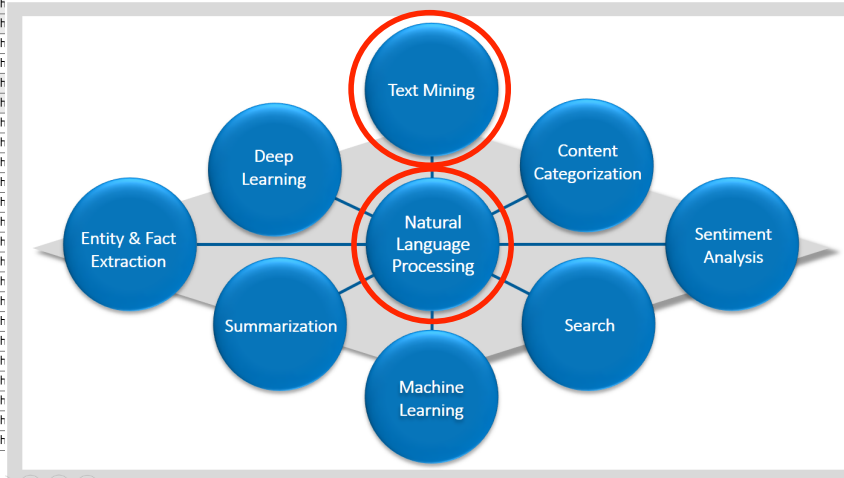
Text Analytics-Text Parsing and Text Filtering

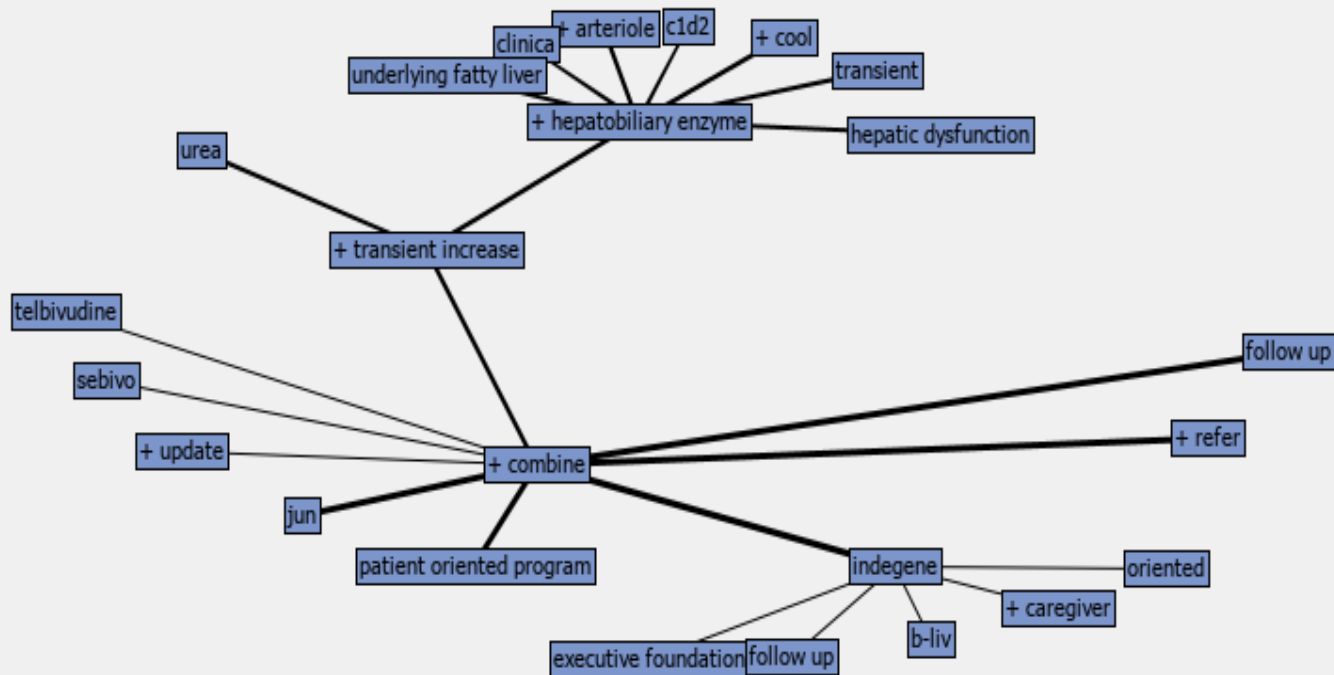


- Stemming
- Misspellings
- Synonyms
- Noun groups
- Parts-of-Speech
- Term filtering
- Term Mapping
- Native Language Models

Documents				
NARRATIVE	TEXTFILTER_SNIPPET	TEXTFILTER_RELEVANCE		
Carol's disease [Dilatation intrahepatic duct congenital] (Ascites), [Hepatosplenomegaly],	... [L, alkaline phosphatase 73	0.401		
This case was reported in a literature article and described the occurrence of liver failure in a	...), abnormal alkaline	0.401		
This case was reported in a literature article and described the occurrence of liver failure in a	...), abnormal alkaline	0.401		
This case was reported in a literature article and described the occurrence of liver failure in a	...), abnormal alkaline	0.401		
Serious, Related, Unlisted.	... pyruvic transaminase and alkaline	0.401		
EVENTS: Hepatic cirrhosis, Anemia, Portal hypertension, Hepatobiliary insufficiency,	... hepatic function. Alkaline	0.429		
This 65-year-old female subject was enrolled in a blinded study for the treatment of diabetes	... laboratory results (alkaline	0.401		
A healthcare professional reported on 27JAN98 that a 68 year old Caucasian female,	... ALP (alkaline	0.401		
A health care professional reported on 20FEB98 that a 56 year old female patient, CAK,	... and elevated alkaline	0.457		
A health care professional reported on 20MAY98 a 70 year old male patient who experienced	... albumin 6.7, alkaline	0.457		
Patient is a female with type II diabetes. Between March and June 1997, while taking Rezulin	... normal), alkaline phosphatase	0.429		
THE PREVIOUS NARRATIVE SENT ON 07FEB00 HAS BEEN SEPARATED TO REFLECT WHICH	... RESULTS REVEALED AN ALKALINE	0.401		
A consumer's mother, who is a nurse, reported on 13APR00 that her son developed an	...), and alkaline phosphatase	0.401		
Information was received initially on 13-OCT-00 from a healthcare professional describing a	... [L, alkaline phosphatase 301	0.485		
Additional information was received which included the recovery date for the event of	... aminotransferase 78, alkaline	0.401		
Additional information received: test results: Cytosol dosing, medical history, confirmation of	...); blood alkaline phosphatase	0.401		
Additional information was received from a healthcare professional which added the events of	... except for his alkaline	0.541		
A 66-YEAR-OLD FEMALE PATIENT WAS HOSPITALIZED DUE TO JAUNDICE, WEIGHT LOSS,	... 1.65, and ALKALINE	0.513		
Tasmar Regulatory Authority Report (Canada) (ID #120085)	... LDH INCREASED, ALKALINE	0.429		
Subject ID: G5001DIAZ This 47-year-old male subject was enrolled in the Promacta REMS	... 2010, peak alkaline	0.457		
Subject ID: G5001DIAZ This 47-year-old male subject was enrolled in the	... 1.31 and alkaline phosphatase	0.401		

Terms						
TERM	FREQ	# DOCS	KEEP	WEIGHT	ROLE	ATTRIBUTE
alkaline	2327	1102	☒	0.001	Adj	Alpha
phosphatase	2240	1084	☒	0.008	Noun	Alpha
phosphatases	13	10			Noun	Alph
phosphatase	2227	1078			Noun	Alph
patient	10328	1046	☒	0.003	Noun	Alph
alkaline phosphatase	2012	1016	☒	0.003	Noun Group	Alph
alkaline phosphatases	11	10			Noun Group	Alph
alkaline phosphatase	2001	1010			Noun Group	Alph
liver	5183	975	☒	0.047	Noun	Alph
information	2758	881	☒	0.033	Noun	Alph
history	1676	873	☒	0.019	Noun	Alph
bilirubin	3094	854	☒	0.001	Noun	Alph
event	2531	774	☒	0.052	Noun	Alph
medical	1433	758	☒	0.01	Adj	Alph
case	1571	756	☒	0.004	Noun	Alph
discontinue	1252	742	☒	0.008	Verb	Alph
start	1362	736	☒	0.001	Verb	Alph
medication	1327	706	☒	0.005	Noun	Alph
mg	3150	700	☒	0.055	Noun	Alph
physician	2450	695	☒	0.004	Noun	Alph
hepatitis	2500	685	☒	0.004	Noun	Alph
year	917	682	☒	0.008	Noun	Alph
include	1278	673	☒	0.001	Verb	Alph
concomitant	1004	672	☒	0.0	Adj	Alph
reveal	1928	653	☒	0.064	Verb	Alph





Supervised & Unsupervised Models

**05**

Text Mining
Models &
Supervised/
Unsupervised
Models

PREDICTIVE ANALYSIS

Supervised & Unsupervised Models

MBR

Decision
Tree

Text Rule
Builder

Text Topic

Neural
Network

Text
Cluster

Regression

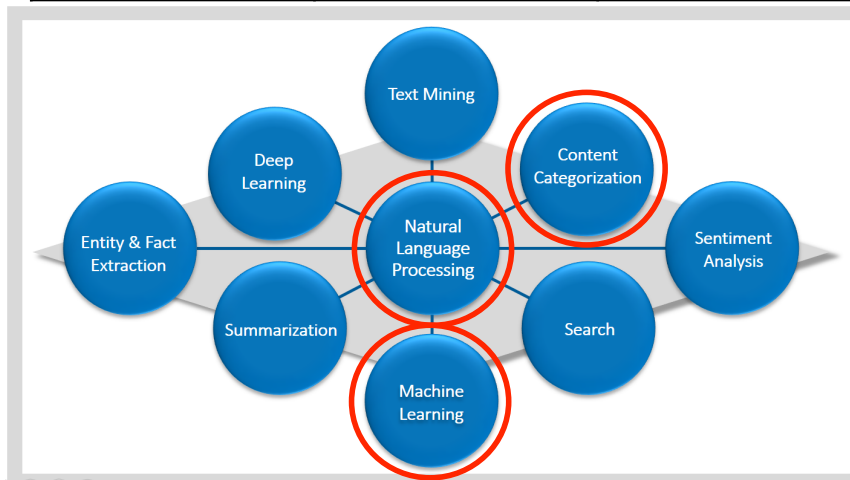
PREDICTIVE ANALYSIS

Supervised Model-Decision Tree



- Decision Tree is developed to perform:
 - Predict new cases
 - Select useful inputs
 - Optimize complexity.

Predictive Modeling Task	General Principle	Decision Trees
Predict new cases	Decide, rank, or estimate	Prediction Rules
Select useful inputs	Eradicate redundancies and irrelevancies	Split Search
Optimize complexity	Tune models with validation data	Pruning



Text
Cluster

PREDICTIVE ANALYSIS Supervised Model-Decision Tree

- To utilize **unstructured data** in building the **decision tree**, a **text cluster** is built prior to the decision tree.
- FAERS cases are assigned to mutually exclusive clusters.
- **Clustering** is achieved by deriving a **numeric representation** for each document.
- Producing the numeric representation for each cluster is implemented through **SVD** to organize terms and documents into a common semantic space based upon **term co-occurrence**.

PREDICTIVE ANALYSIS

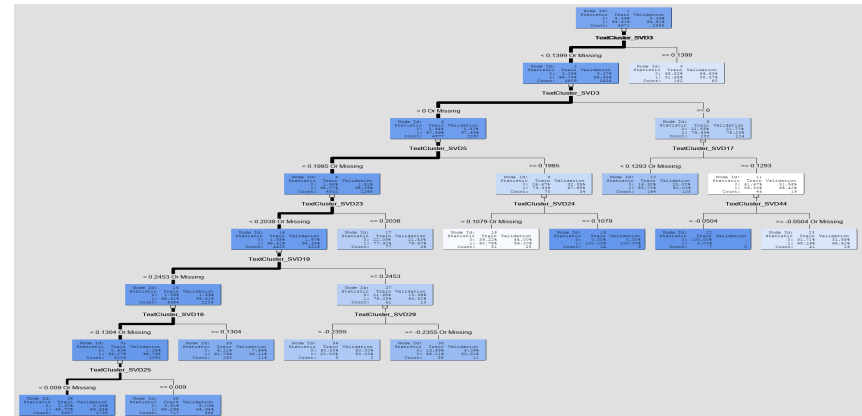


Supervised Model-Decision Tree

- The **output** from the cluster analysis is the **input** to the decision tree modeling.

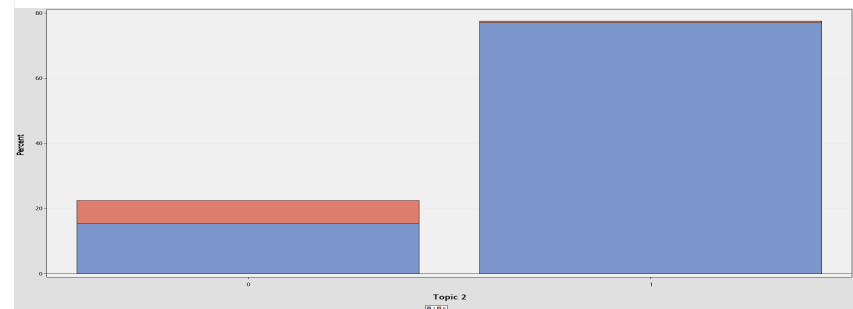
Cluster ID	Descriptive Terms
1	...
2	+grade clofarabine +leukemia cytarabine myeloid transplantation +regimen 'acute myeloid leukemia' aml +group median +study acute iv +cell +investigator +action kg +enrol +dose +age +die +platelet +total +count
3	+lesion +mri 'multiple sclerosis' sclerosis +age multiple +feature literature +author prior +neurologist left +suspect +refer +diagnose 'drug indication' +symptom +condition +level hepatic +sample +dose spontaneous +case +indication
4	cirrhosis troglitazone rezulin portal +esophageal varix +bleed fibrosis chronic +biopsy gastrointestinal +type elevated significant +liver biopsy' hypertension medically additional mellitus 'diabetes mellitus' +physician diabetes +request ascites +relate unknown
5	liver jaundice +failure +pain ascites unspecified abdominal +injury heart +liver failure' +problem +abdominal pain' +unspecified injury' troglitazone +disease rezulin +request hepatitis +encephalopathy +die elevated diabetes autopsy +total bilirubin' +laboratory
6	+patient troglitazone medical +increase +physician +discontinue +outcome daily +value experienced +recover serious unspecified +damage +transaminase sgpt sgot health diabetes iu mellitus 'diabetes mellitus' +concomitant medication' +condition follow-up
7	+bleed gastrointestinal +failure +state +severe heart +die +liver damage' +cause +note +blood dilin +set rezulin autopsy +develop +encephalopathy jaundice +unit +death +sample march +period acute +continue
8	+death +die +cause +failure autopsy +liver failure' rezulin troglitazone heart +perform +hospital +late +develop +request +level unknown +encephalopathy hepatic diabetes +problem +physician +patient +condition additional +laboratory
9	portal +vein fibrosis +liver biopsy' +biopsy +cell cirrhosis chronic hypertension +lesion +show +note +mri hla +severe splenectomy +etiology +grade +score negative ascites gaucher +encephalopathy +disease +associate
10	gemtuzumab +result ozogamicin mylotarg acute myeloid 'gemtuzumab ozogamicin' aml ascites +concomitant therapy' +investigator +leukemia 'acute myeloid leukemia' +study cytarabine +assessment relatedness +injection +product +enrol 'blood bilirubin' +medical history' +cell 'alanine ...
11	+count +cell +platelet white +blood dl +decrease iu +find abnormal +control +hospitalize 'diabetes mellitus' +injection mellitus follow-up negative binding 'alanine aminotransferase' alanine +total bilirubin' ap +old mg +year
12	rosiglitazone max 'rosiglitazone maleate' maleate +liver injury' march 'unknown time' +period hepatotoxicity 'drug indication' 'severe hepatotoxicity' withrosiglitazone +accompany +article +author +define +determine +encephalopathy +subject transplantation +etiology +exclude +liver failure' ...
13	+pain left +abdominal pain' heart abdominal +present +etiology +type +note +effect +replacement +hospital +show +symptom opinion elevated +request review +site prior +accompany quality +late chronic +mri
14	cerezyme gaucher 'gaucher disease' transplantation +replacement 'enzyme replacement therapy' 'gaucher patient' +gaucher cell' splenectomy +genotype +esophageal varix' opinion unrelated kg +enzyme +bleed +begin fibrosis +regimen march +cell +type +age +severe +determine ...

- Two decision tree models have been developed.
- 1st tree: the SVD numeric values have been **rejected** only the nominal values of cluster numbers will **input** the decision tree modeling with other FAERS input variables.
- 2nd tree: the SVDs is **utilized** as input to the decision tree with other FAERS variables and cluster number variable has been **rejected**.



Variable Importance

Variable Name	Label	Number of	Importance	Validation	Ratio of
		Splitting Rules		Importance	Validation to Training Importance
TextCluster_SVD3		2	1.0000	1.0000	1.0000
TextCluster_SVD5		1	0.2455	0.2964	1.2074
TextCluster_SVD23		1	0.2061	0.1778	0.8629
TextCluster_SVD44		1	0.1930	0.0753	0.3904
TextCluster_SVD24		1	0.1831	0.1979	1.0809
TextCluster_SVD17		1	0.1808	0.0000	0.0000
TextCluster_SVD29		1	0.1601	0.0627	0.3917
TextCluster_SVD19		1	0.1518	0.0733	0.4484
TextCluster_SVD16		1	0.1364	0.1168	0.8563
TextCluster_SVD25		1	0.1015	0.1319	1.3000



Predictive Analysis

Supervised & Unsupervised Models



Discussion and Conclusion

Model Comparison

Visualization of results in
interactive reporting tool

Model improvement

Application to other
adverse event scenarios

Thank you



Q&A

