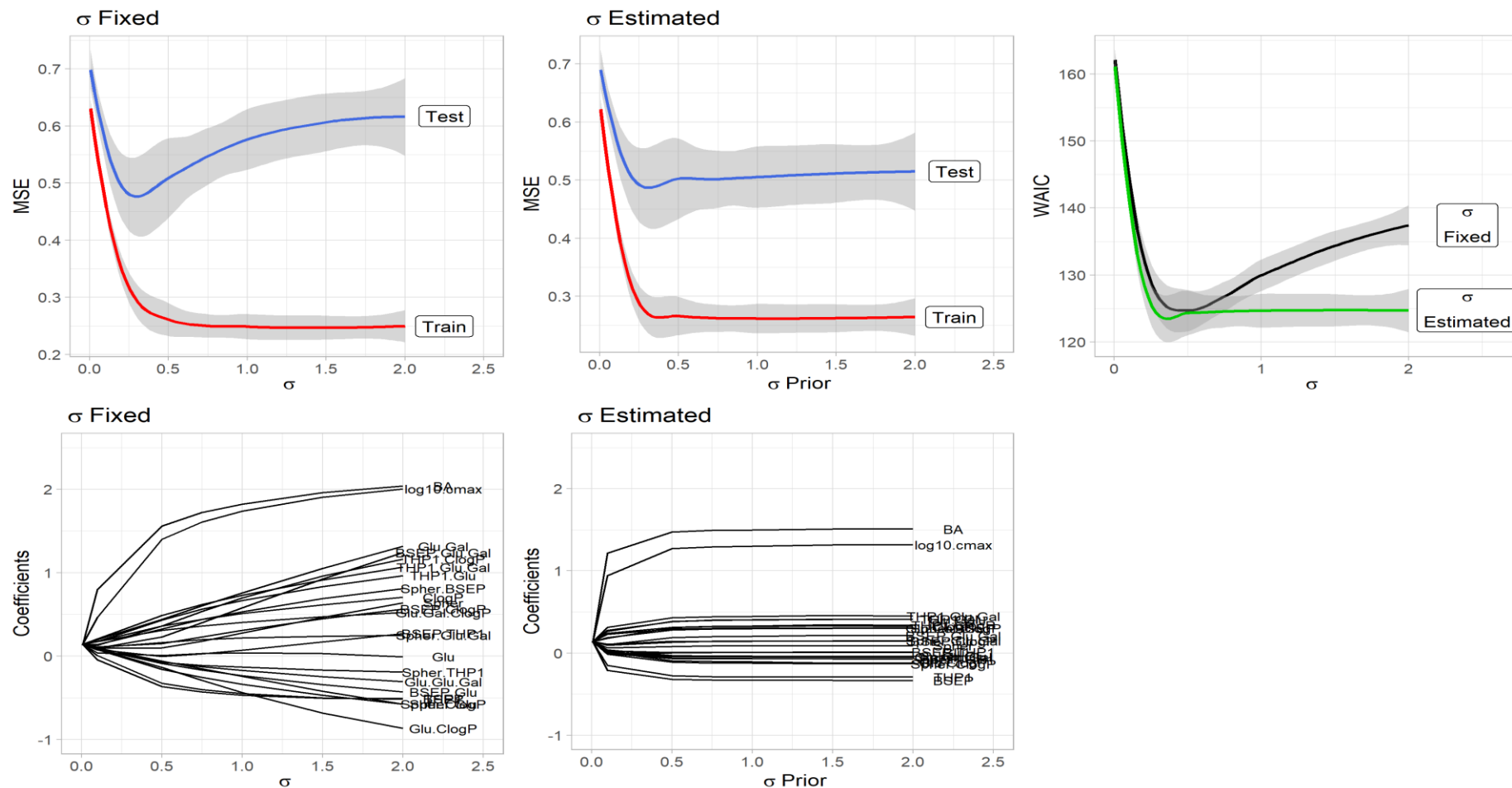
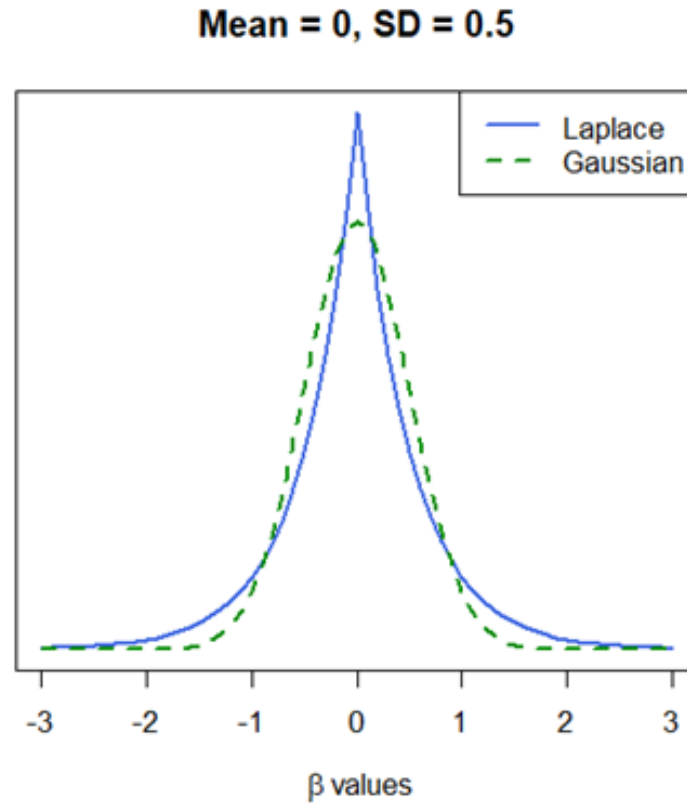


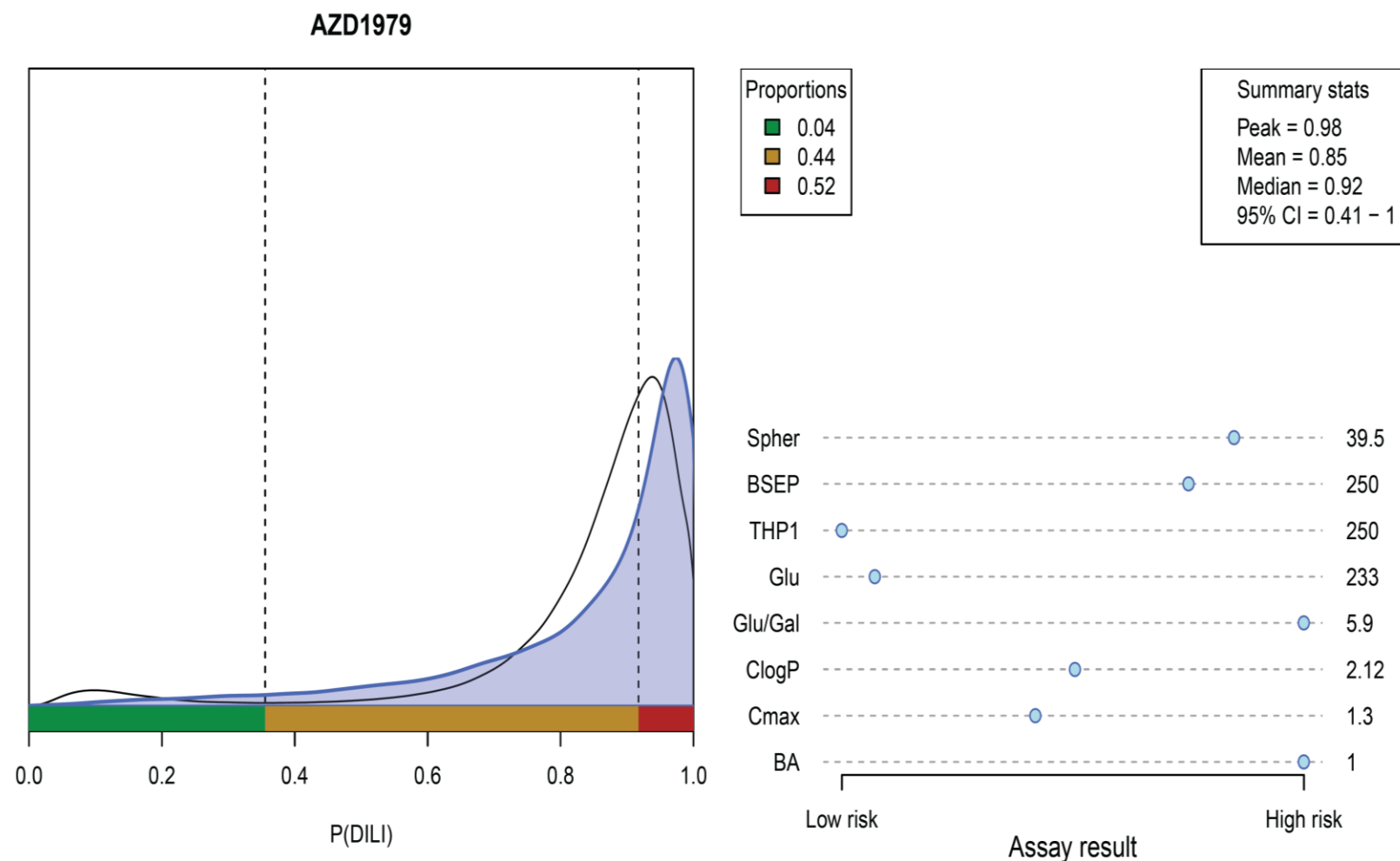
Supplementary Figure 1. Distribution of variables. Variables that are IC50 values have a spike at high values, which represent the maximum concentration tested and correspond to no concentration-response relationship.



Supplementary Figure 2. Bayesian hyperparameter tuning. Five-fold cross-validation was done five times for different values of the hyperparameter σ , which controls the flexibility of the model. As σ gets larger, the fixed- σ model starts to overfit, which can be seen as an increase in the mean-squared error of the test data (MSE; top-left) and an increase in the Watanabe-Akaike information criterion (WAIC; top right). However, when σ is estimated from the data, both the test MSE (top middle) and WAIC (top right) remain constant as σ increases, indicating that overfitting is not occurring. This can also be seen in the bottom two plots where the coefficients continue to get larger in the fixed- σ model (bottom left) until they reach the maximum likelihood value, but the coefficients level off to smaller values when σ is estimated (bottom right).



Supplementary Figure 3. The Laplace distribution. A Gaussian distribution is shown for comparison, and both distributions have the same mean and standard deviation. The Laplace distribution has more mass at zero and heavier tails, which allows some β values to be large, if supported by the data.

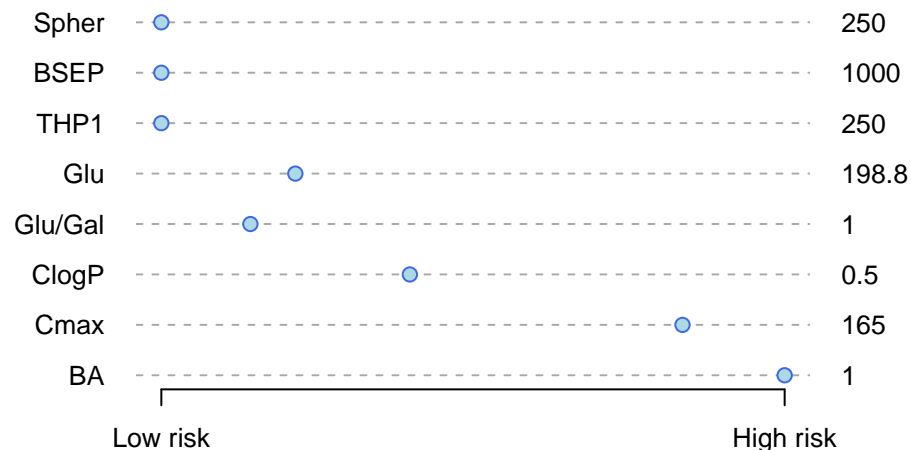
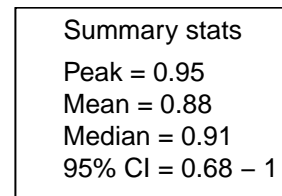
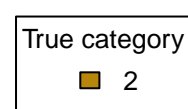
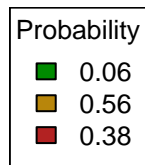
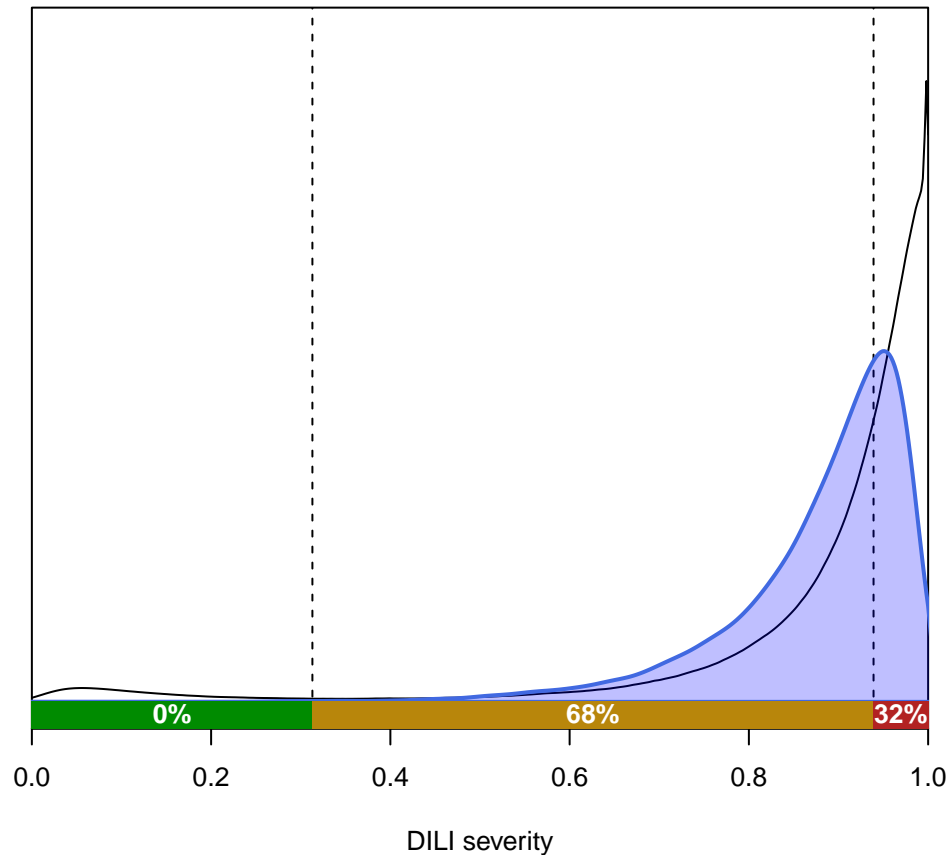


Supplementary Figure 4. The predicted hepatotoxicity risk for the melanin-concentrating hormone receptor 1 antagonist, AZD1979.

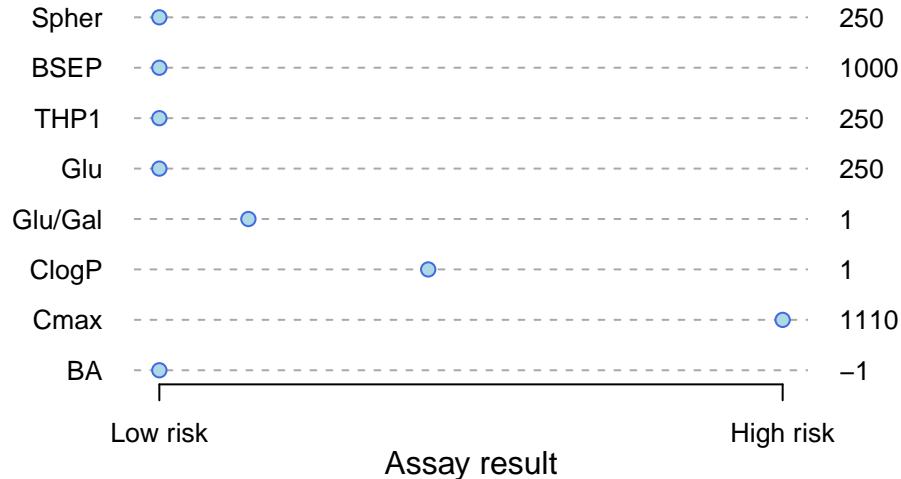
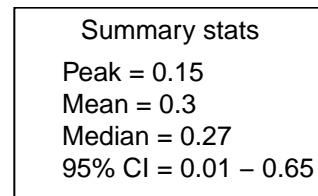
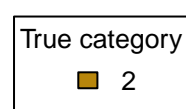
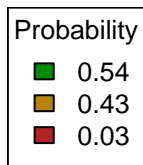
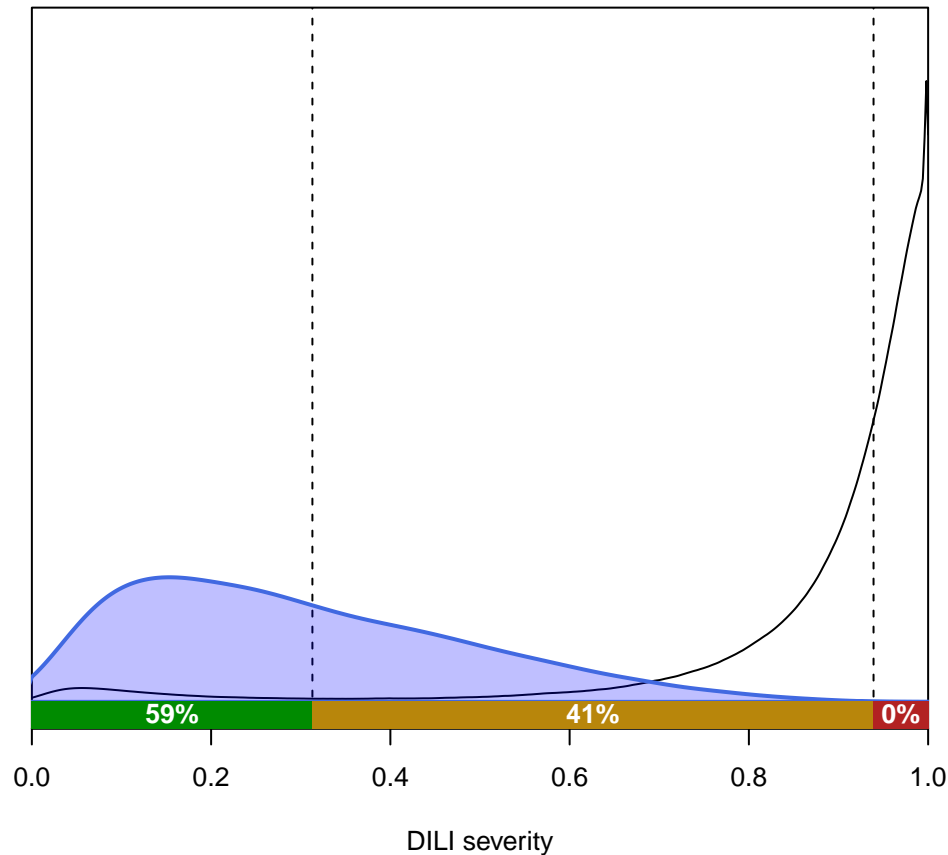
Supplementary Table 2. Improvements in DILI risk assessment in AstraZeneca

	ARMSIII model	DILI Bayesian model	Improvement
Validation compounds	36	96	Includes more diverse compounds
Assays	THLE, MRP2, Mitotox, BSEP, CVB	3D Spheroid, THP1, BSEP, mitotoxicity + combinations (HCA)	Addition of more physiologically relevant assays
Predicted exposure	dose	Cmax	Systemic concentration
Incorporates bioactivation	Covalent binding	GSH-, CN-adduct formation, in vivo evidence (defined by FDA)	Aligns with FDA recommendations (Chen et al,. 2016)
Data integration	Assays given equal weight & combined - “bin & sum” calculation (above threshold in x assays)	Uses a statistical model and cross validation to optimally combine assay data	Flexible framework for addition/removal of assays based on emerging science
Prediction output	Prediction is a number from 0-4	Prediction is a continuous probability of DILI risk with uncertainty	More quantitative and includes uncertainty
Visualisation	Visualisation is a point in a quadrant	Visualisation is full probability distribution of DILI risk + comparisons with other compounds	Know when predictions are uncertain

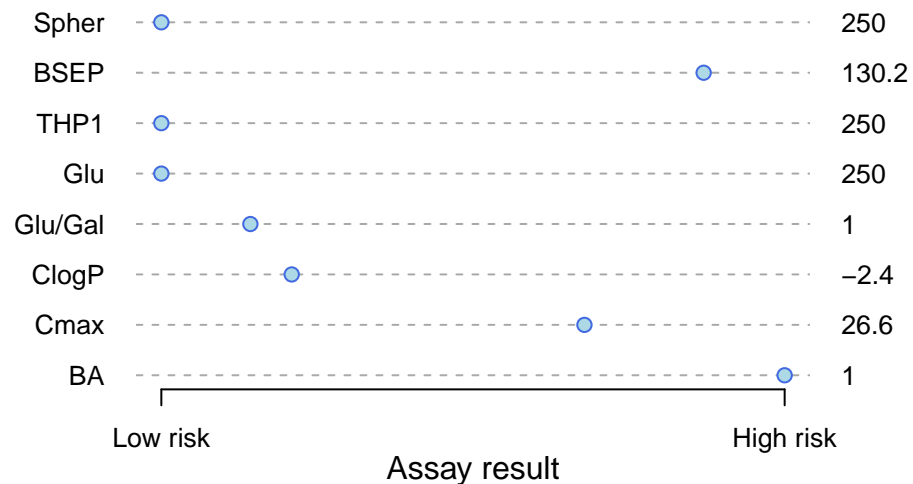
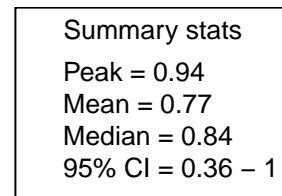
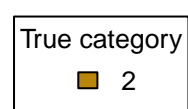
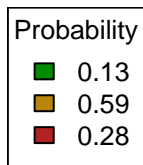
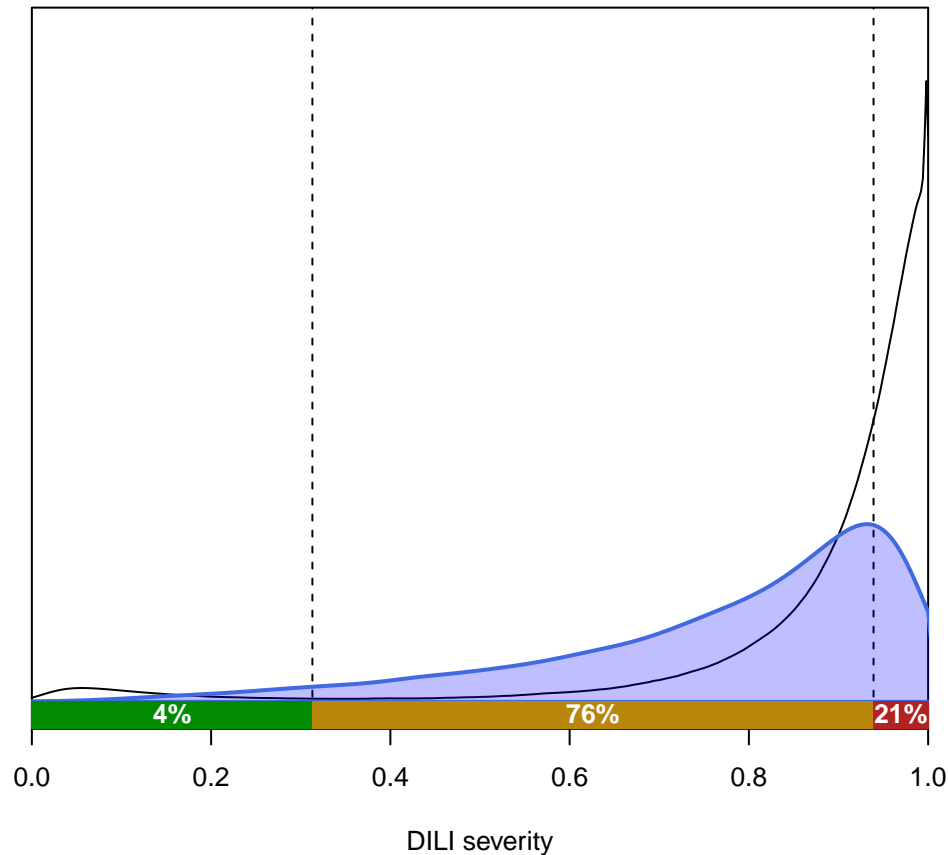
Acetaminophen



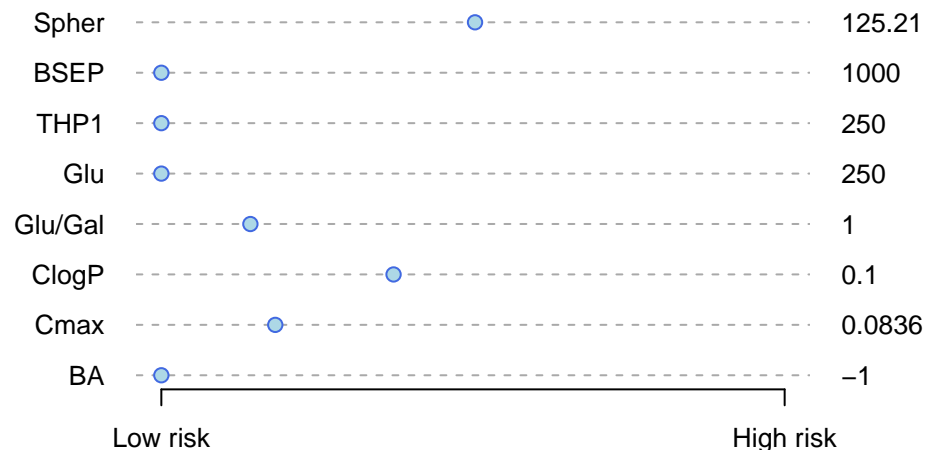
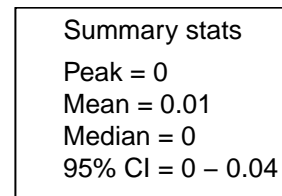
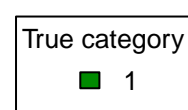
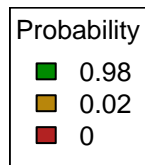
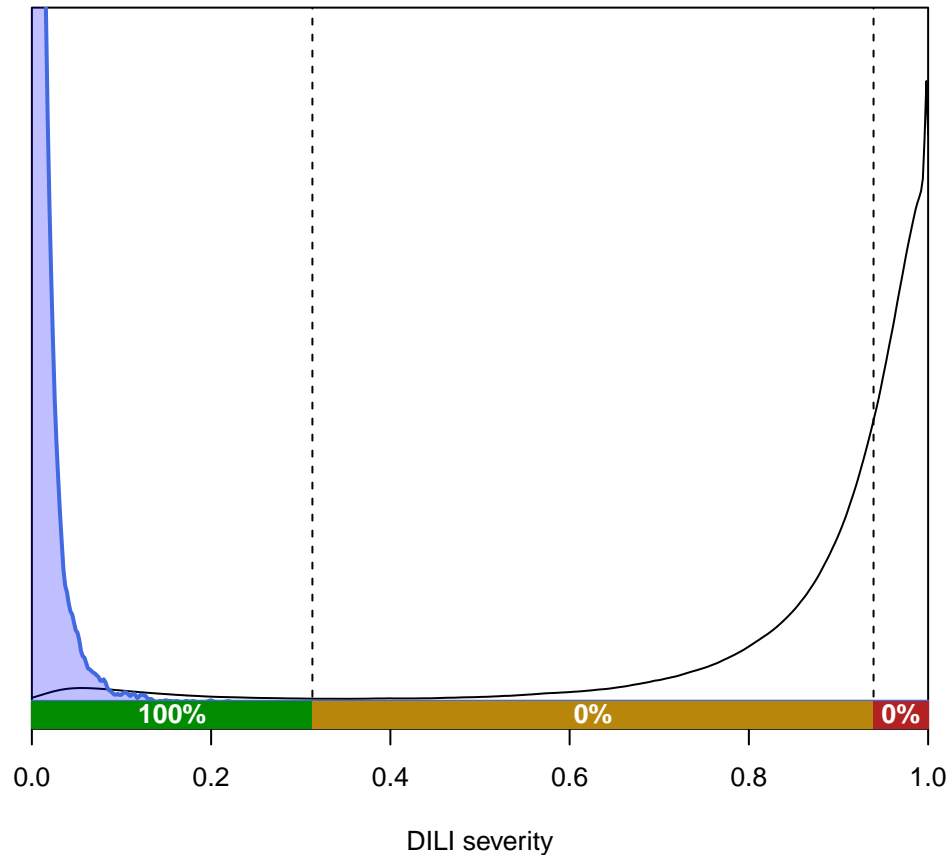
Acetylsalicylic acid



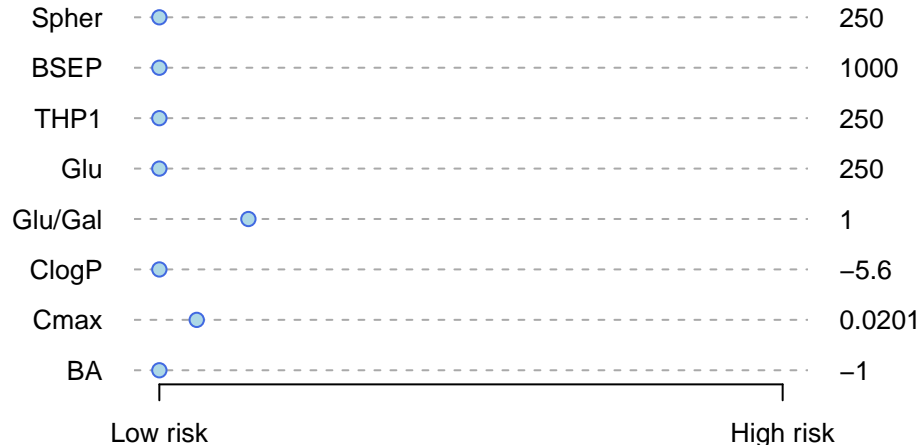
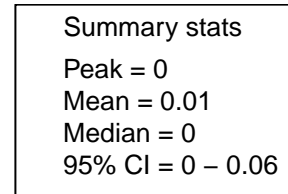
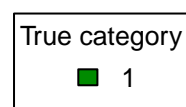
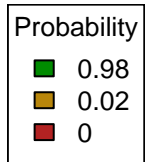
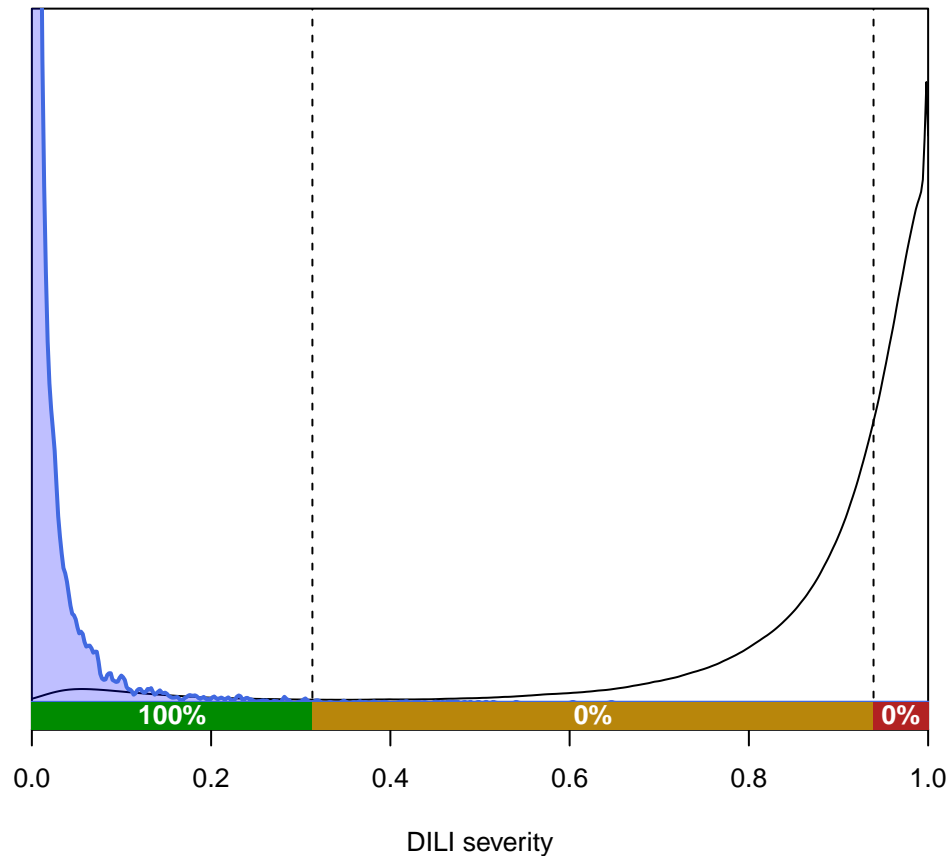
Acyclovir



Albuterol

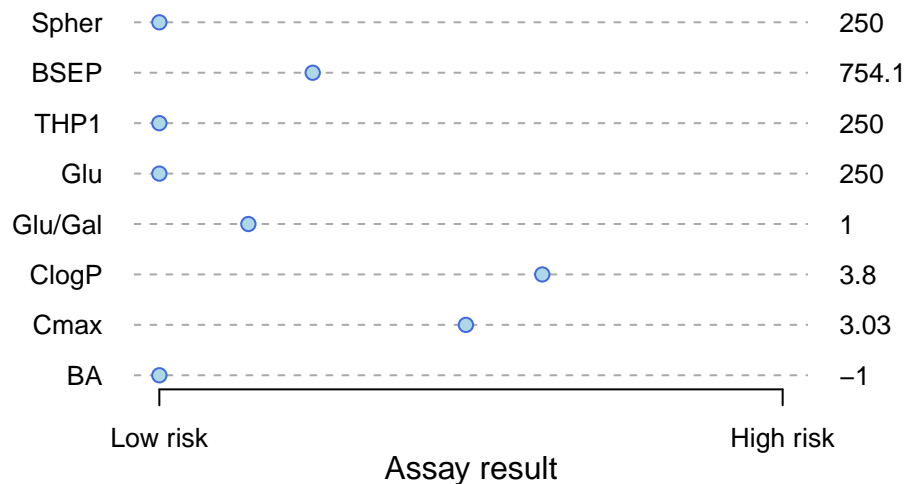
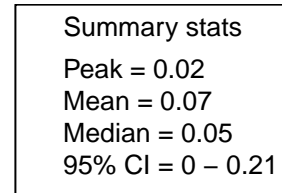
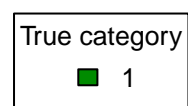
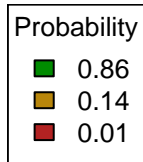
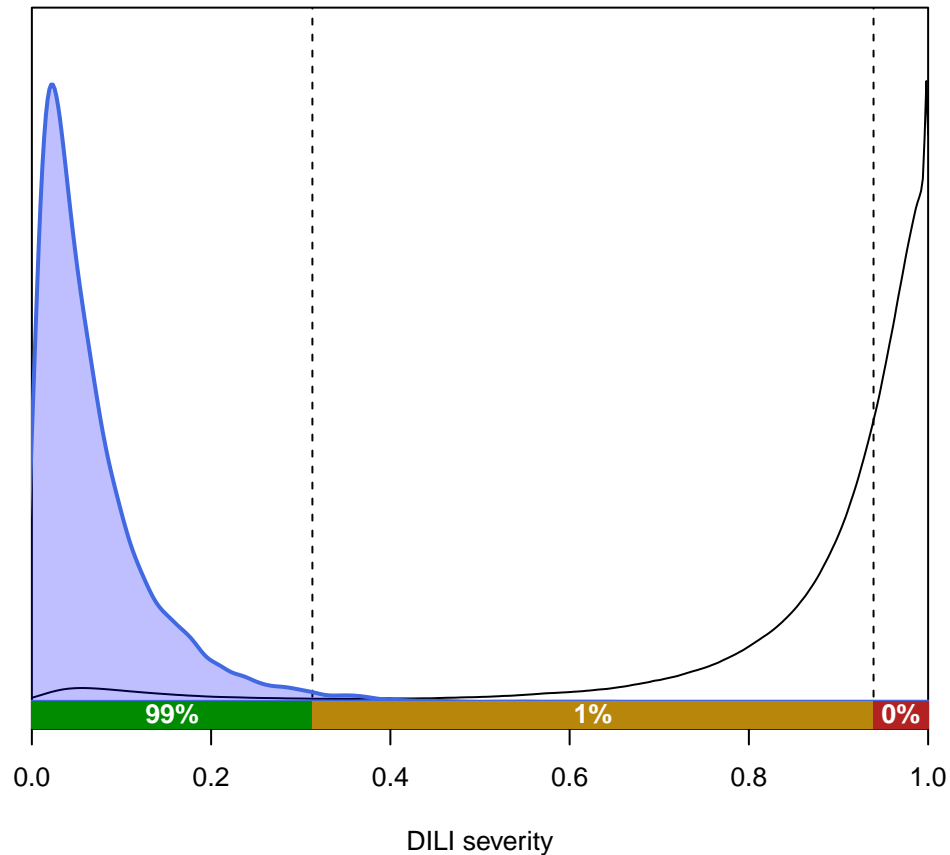


Alendronate

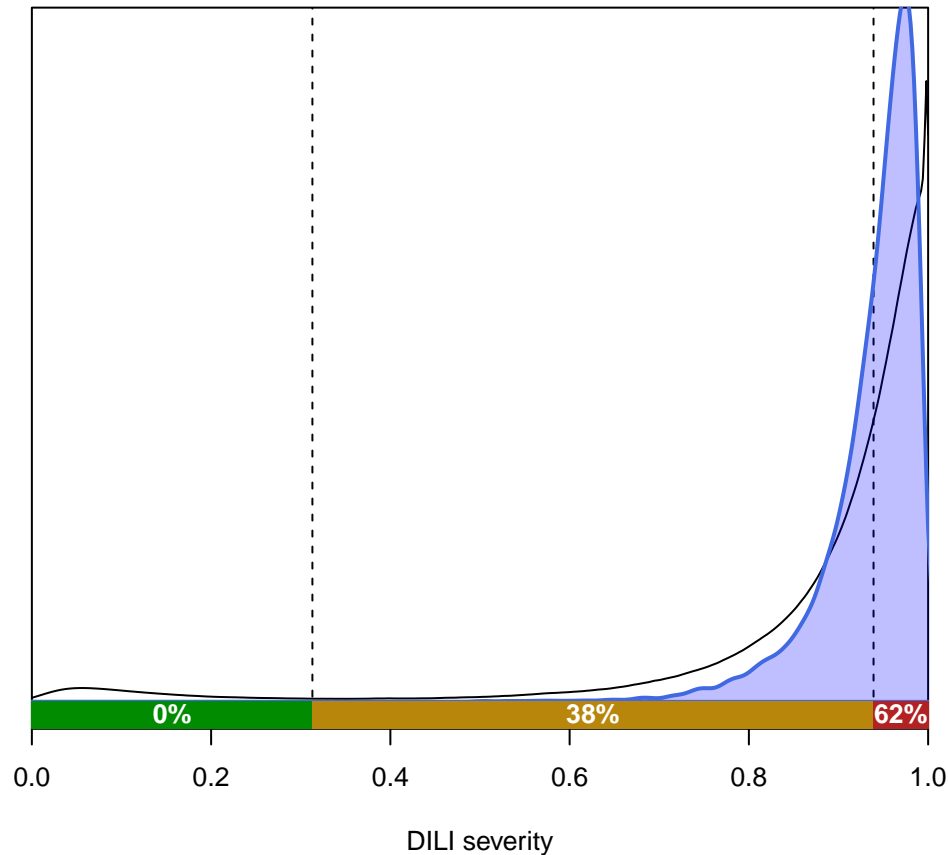


Assay result

Ambrisentan



Aminopyrine



Probability

- 0.03
- 0.44
- 0.53

True category

2

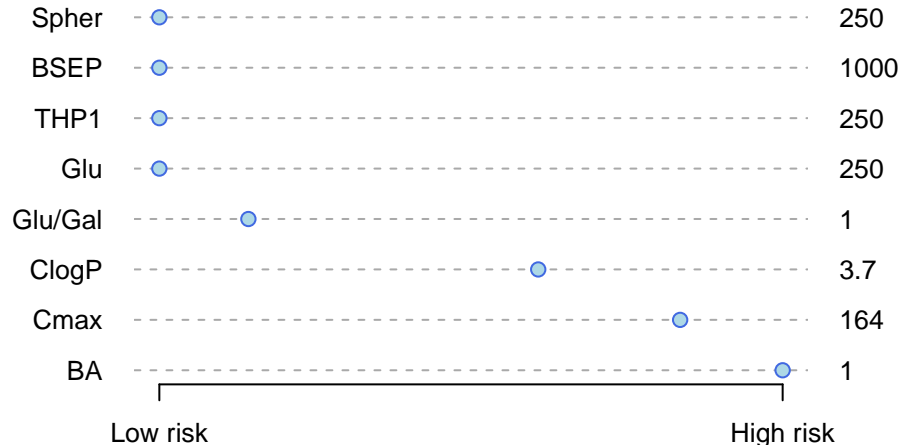
Summary stats

Peak = 0.98

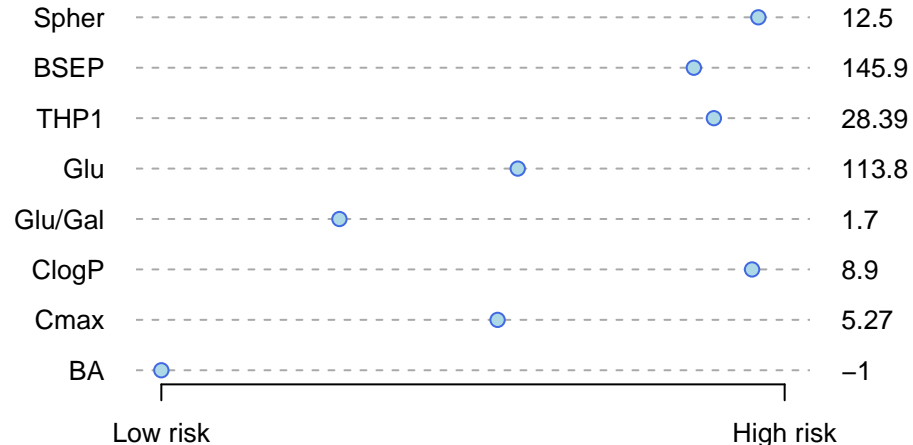
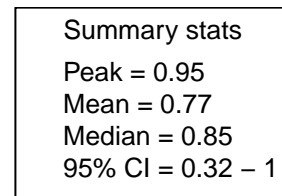
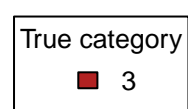
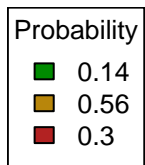
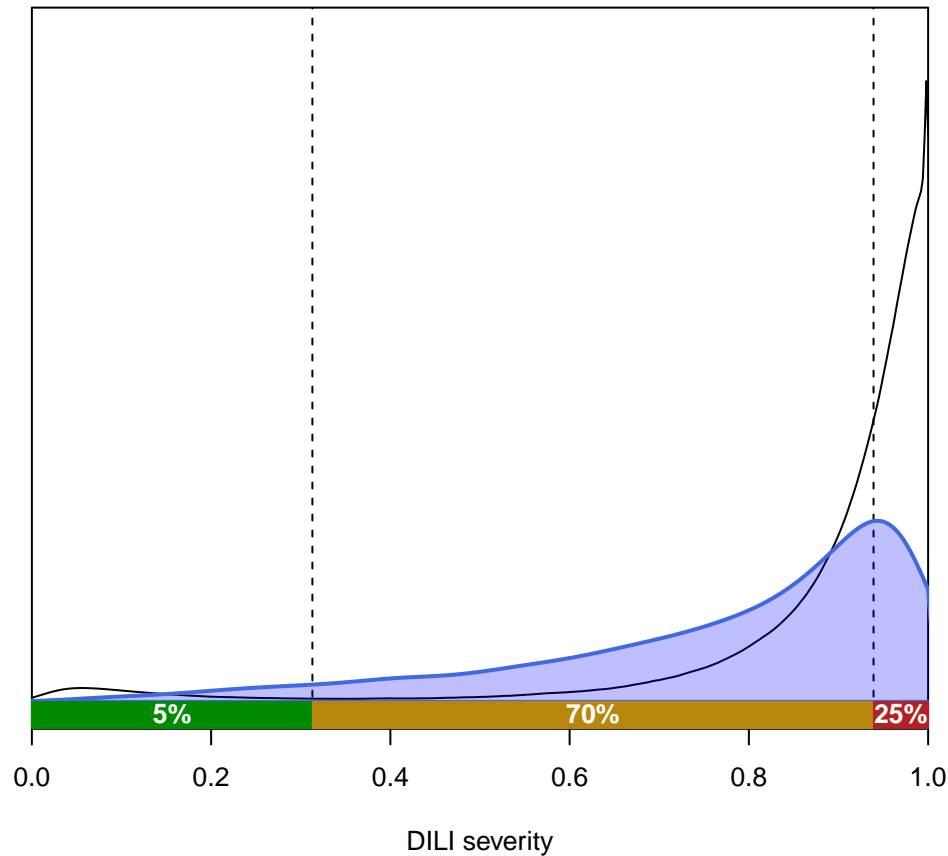
Mean = 0.94

Median = 0.95

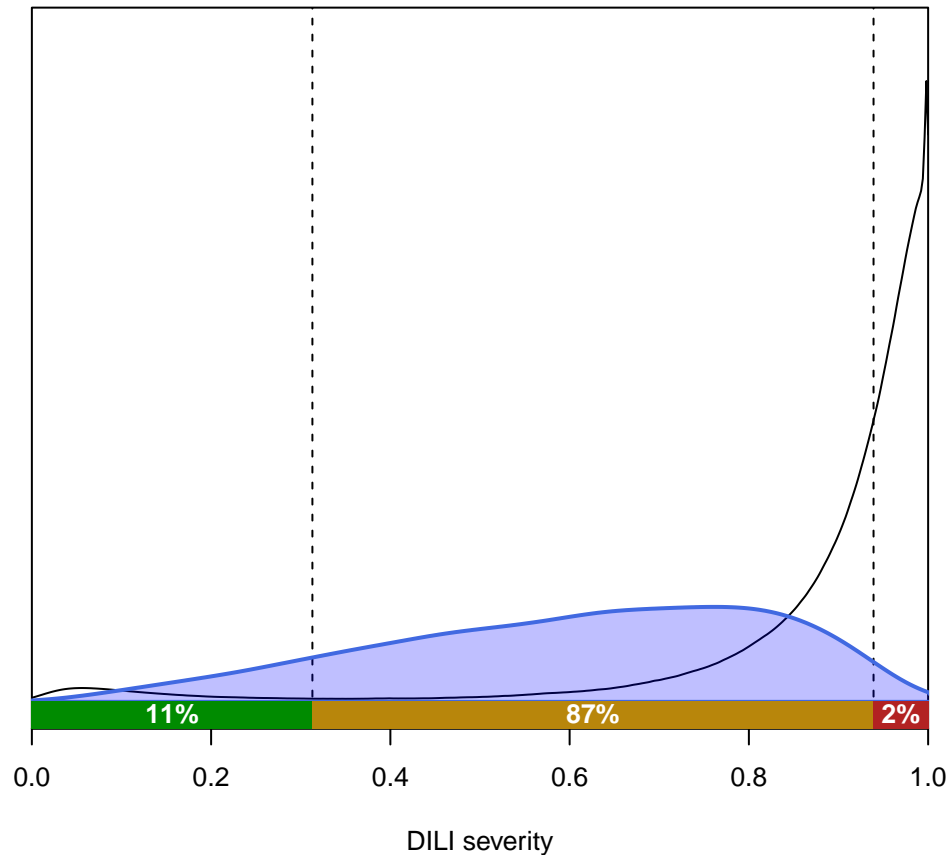
95% CI = 0.83 – 1



Amiodarone



Amlodipine



Probability

- 0.24
- 0.63
- 0.13

True category

2

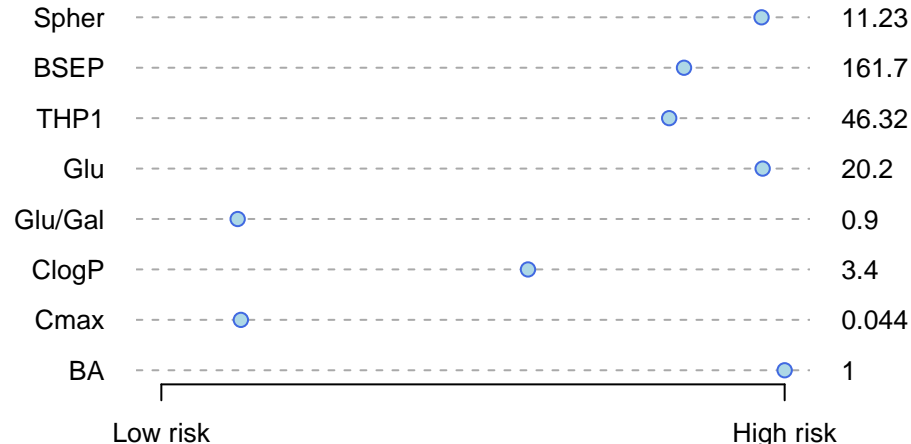
Summary stats

Peak = 0.77

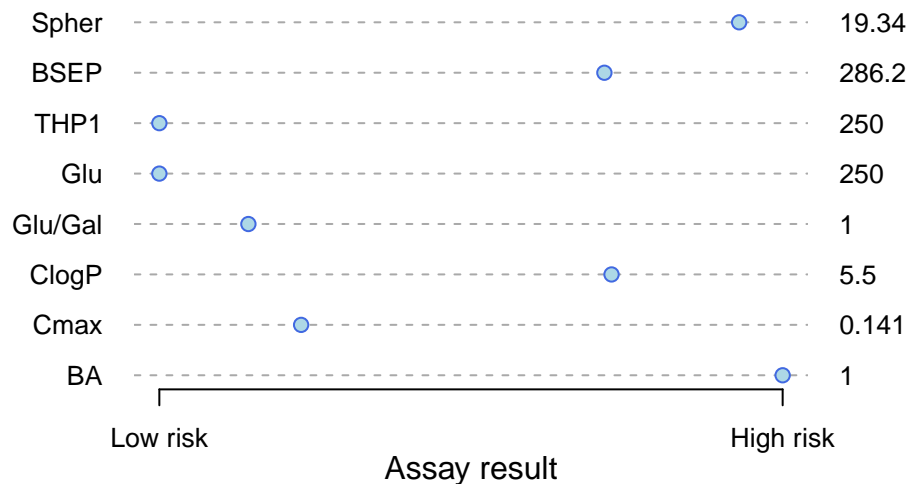
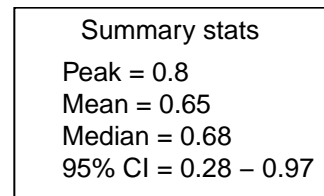
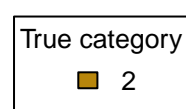
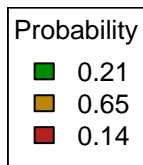
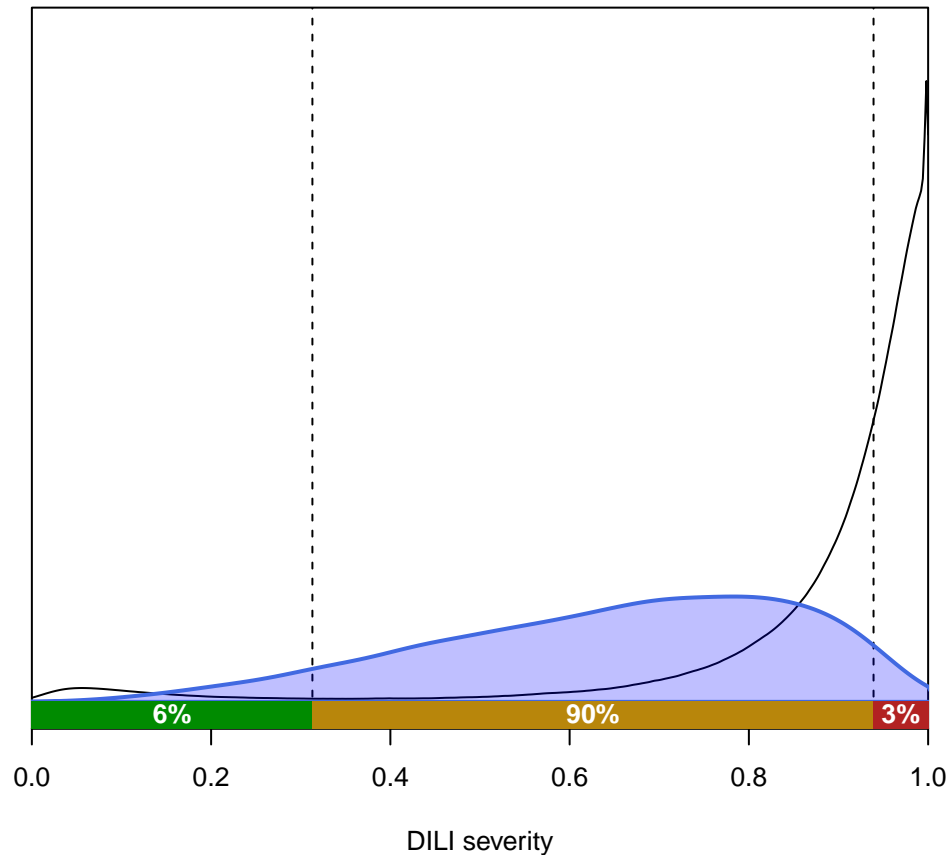
Mean = 0.6

Median = 0.63

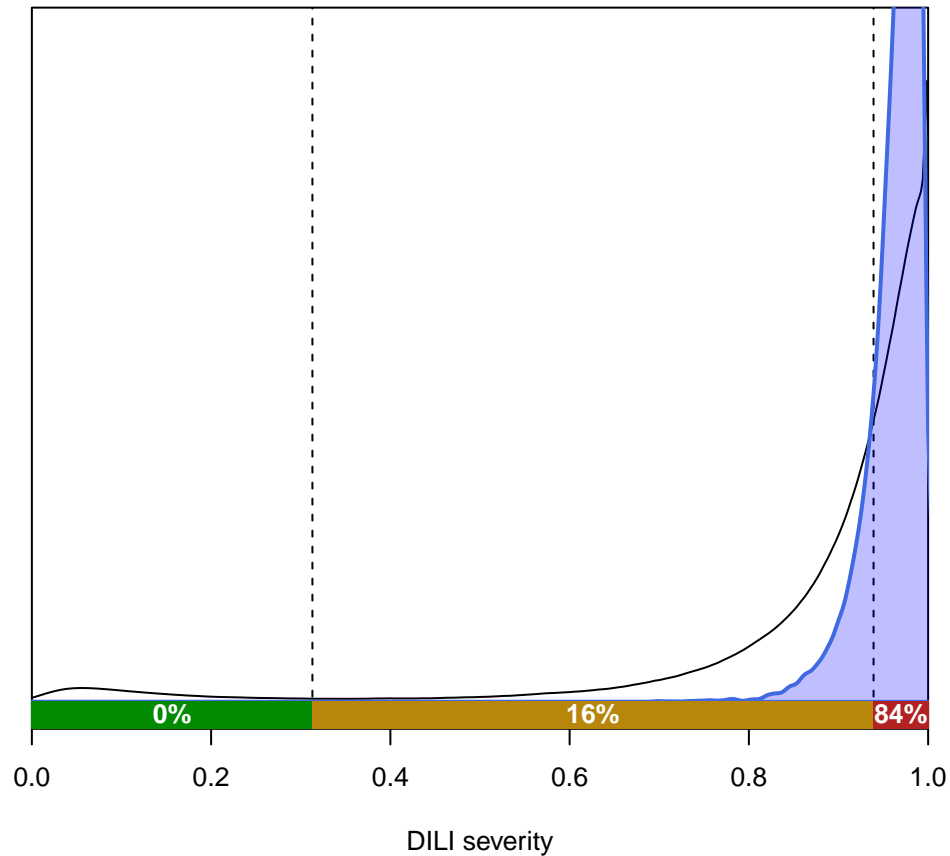
95% CI = 0.2 – 0.96



Amodiaquine



Benoxaprofen



Probability

- 0.02
- 0.33
- 0.66

True category

3

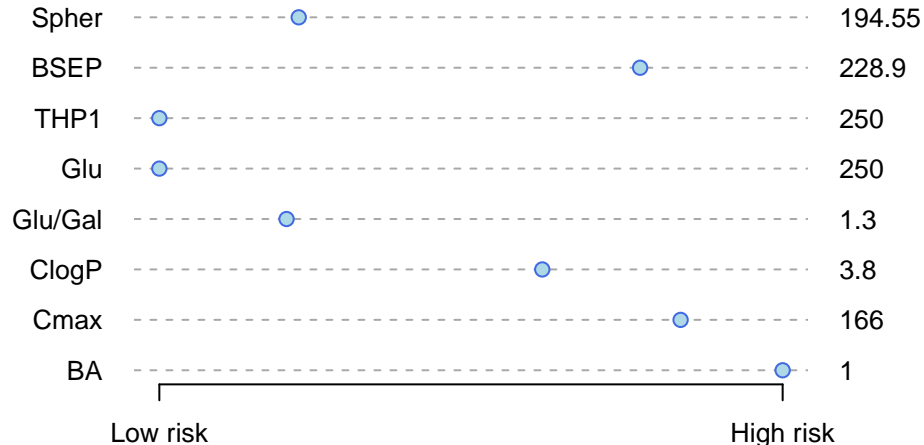
Summary stats

Peak = 0.98

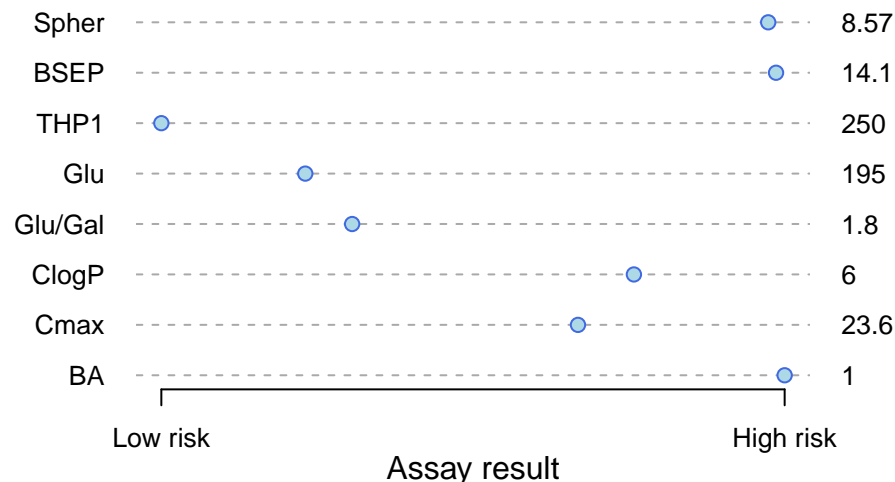
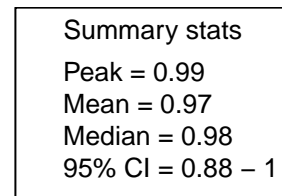
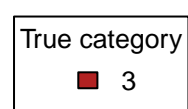
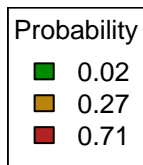
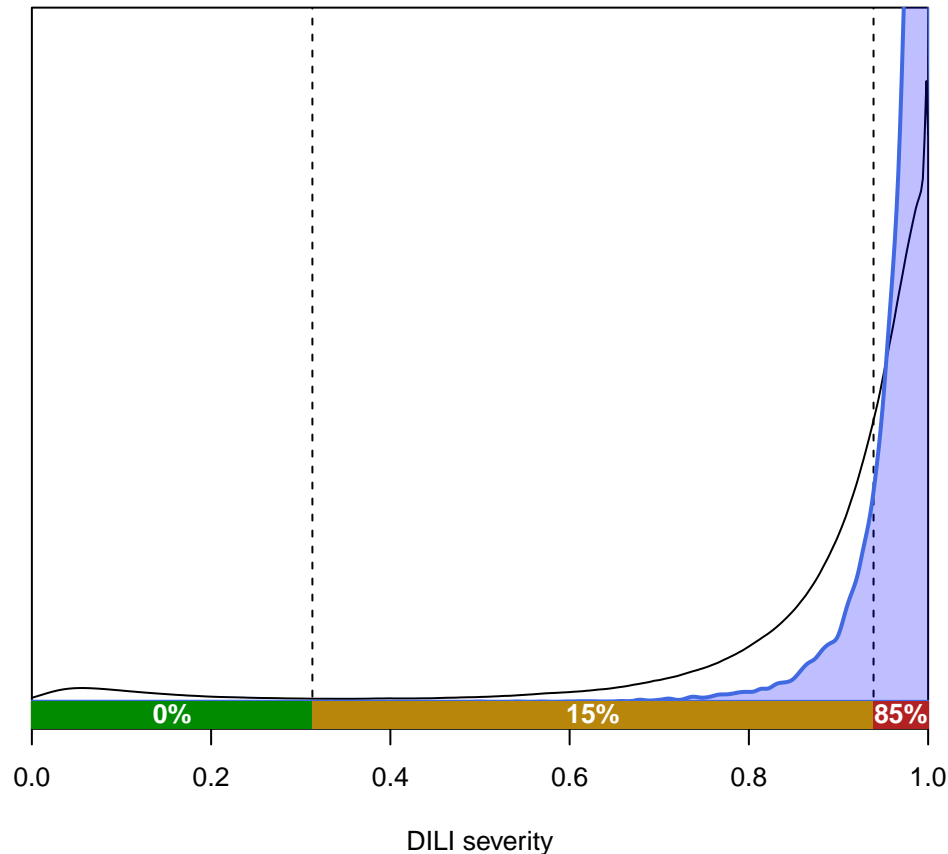
Mean = 0.96

Median = 0.97

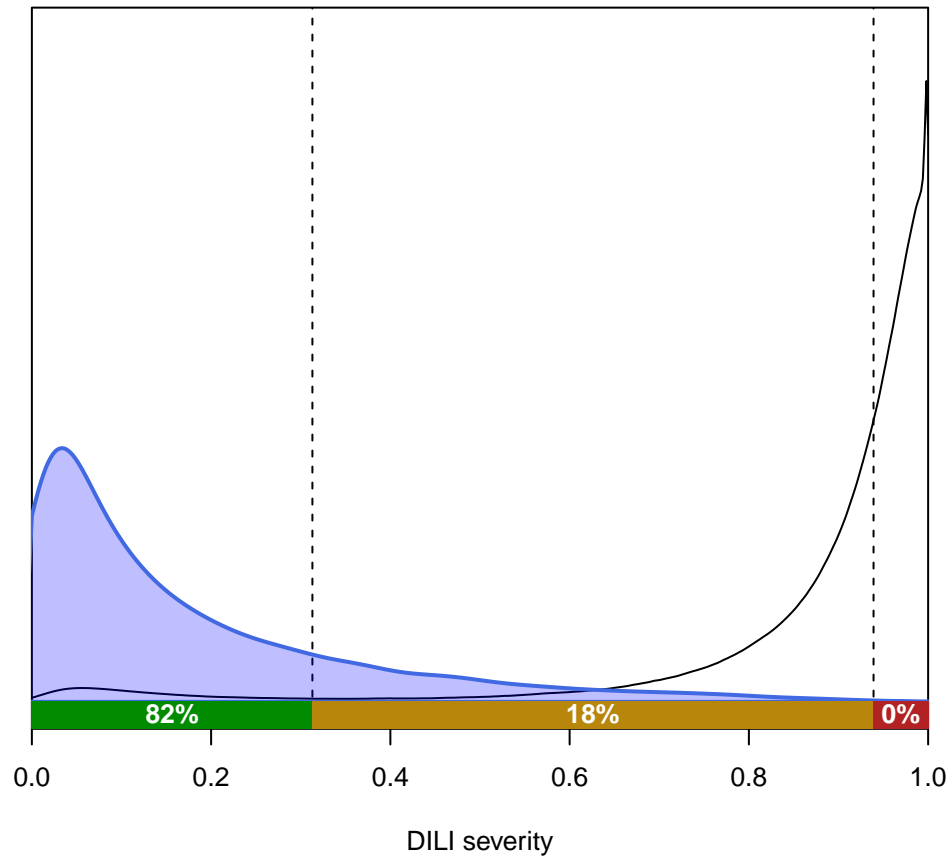
95% CI = 0.9 - 1



Benzbromarone



Benzotropine



Probability

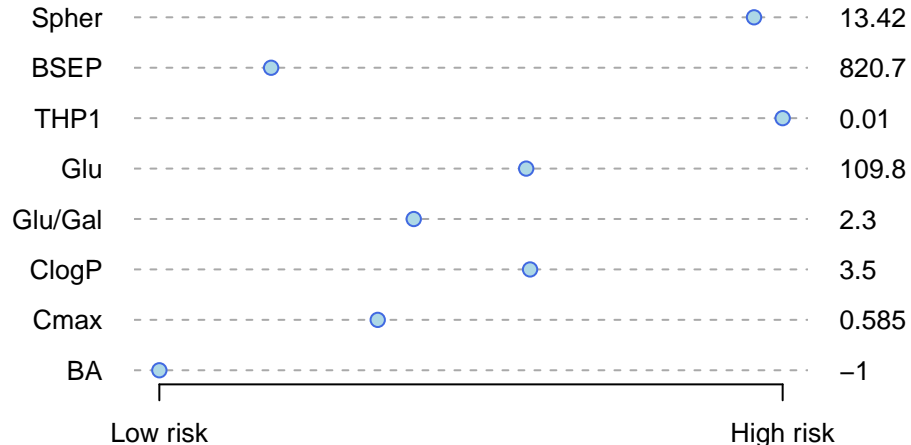


True category

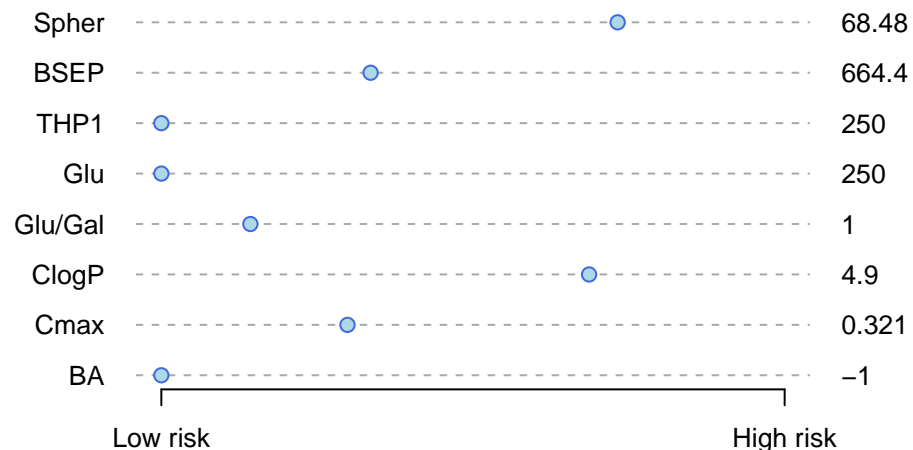
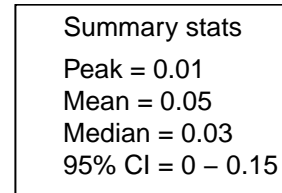
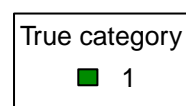
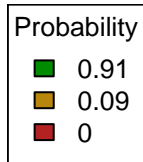
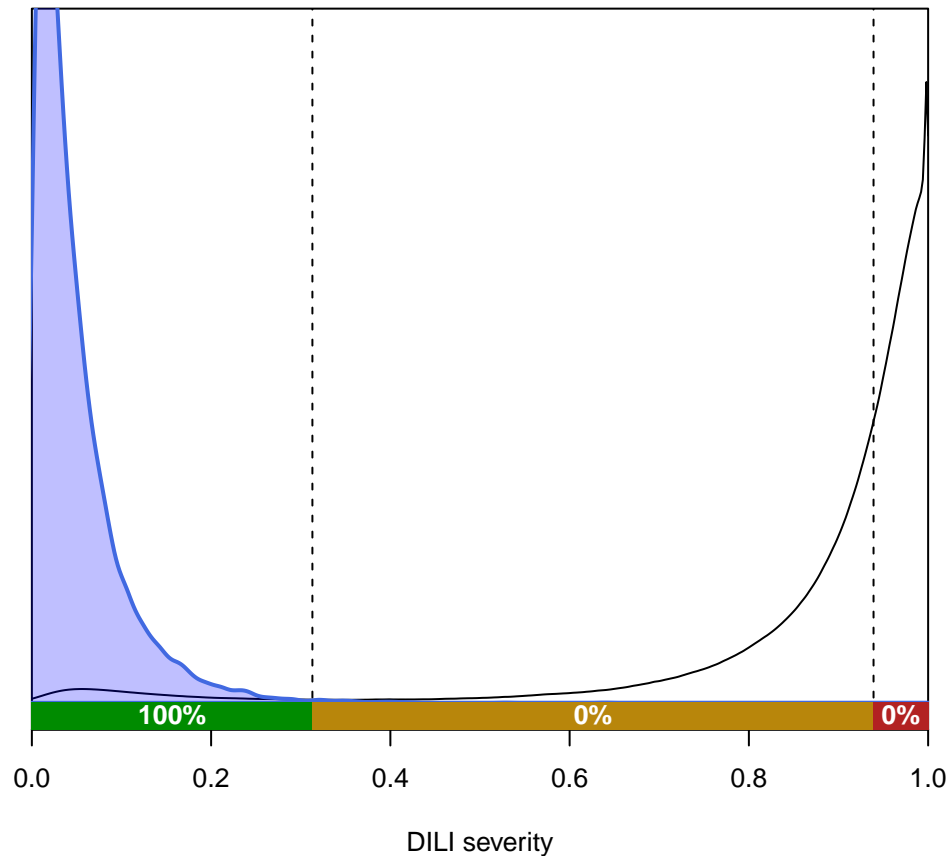


Summary stats

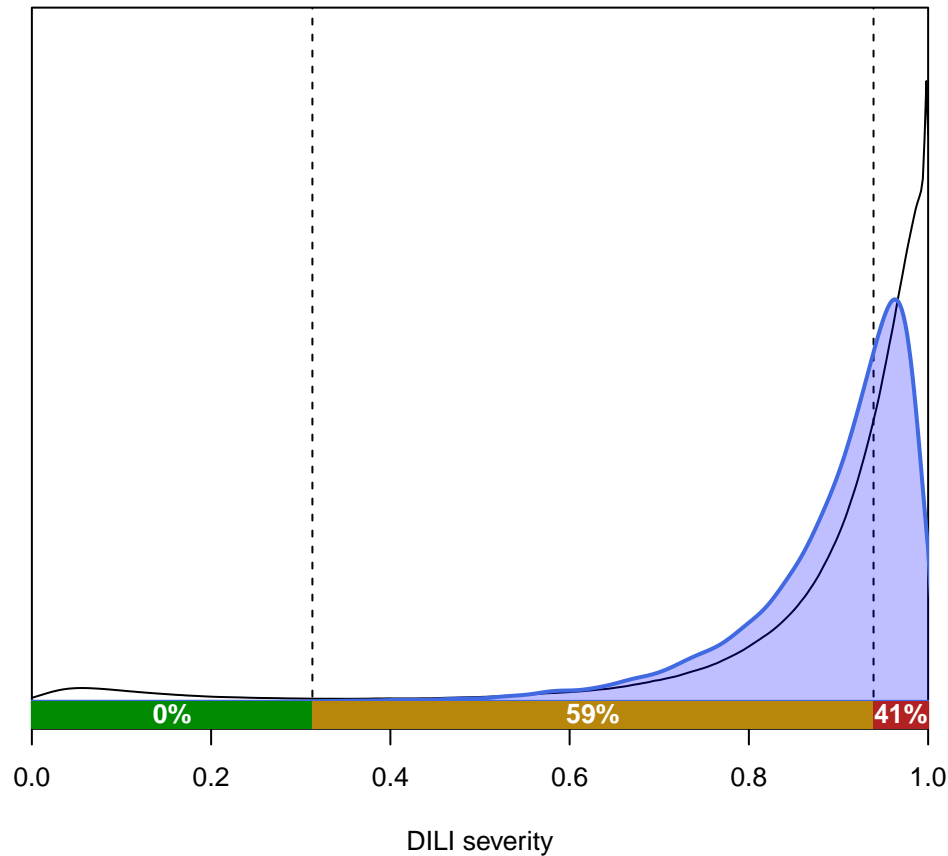
Peak = 0.03
Mean = 0.17
Median = 0.1
95% CI = 0 – 0.58



Biperiden



Bosentan



Probability

- 0.06
- 0.52
- 0.42

True category

3

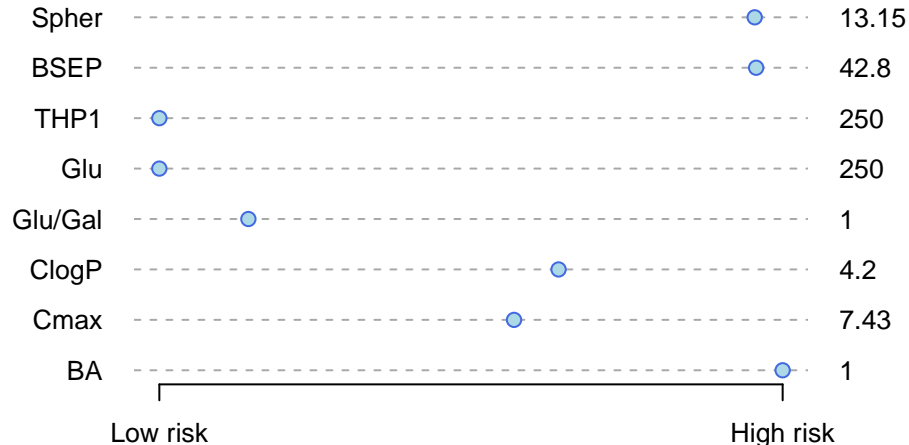
Summary stats

Peak = 0.97

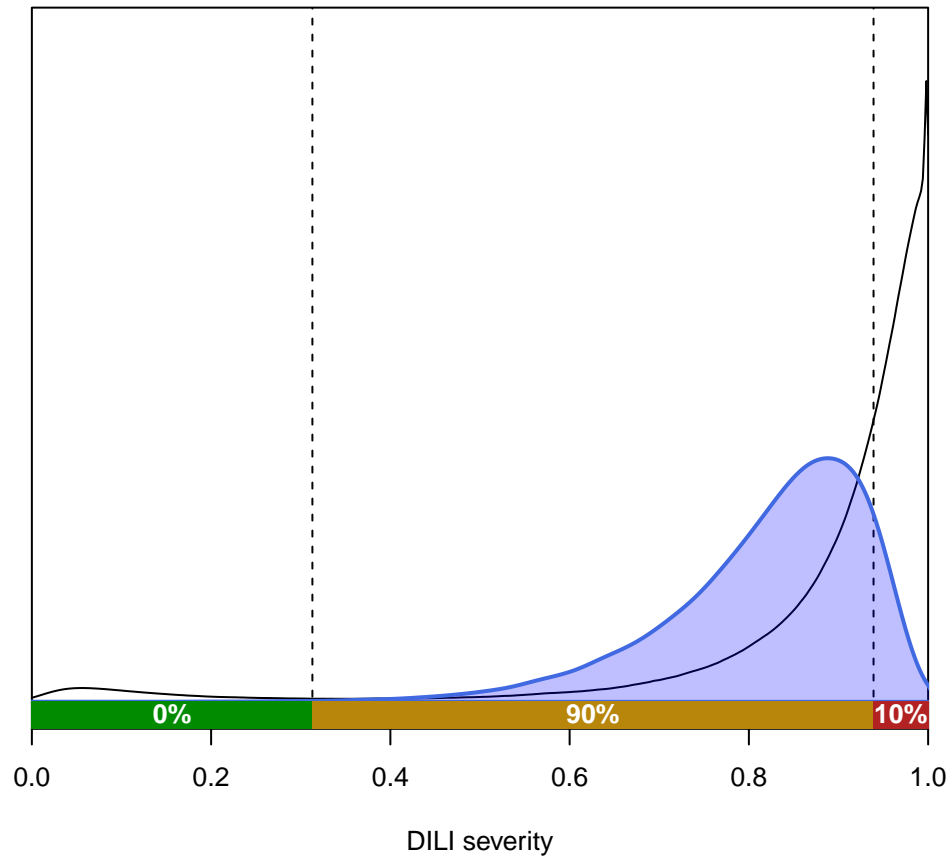
Mean = 0.89

Median = 0.92

95% CI = 0.69 – 1



Bromfenac



Probability



True category

3

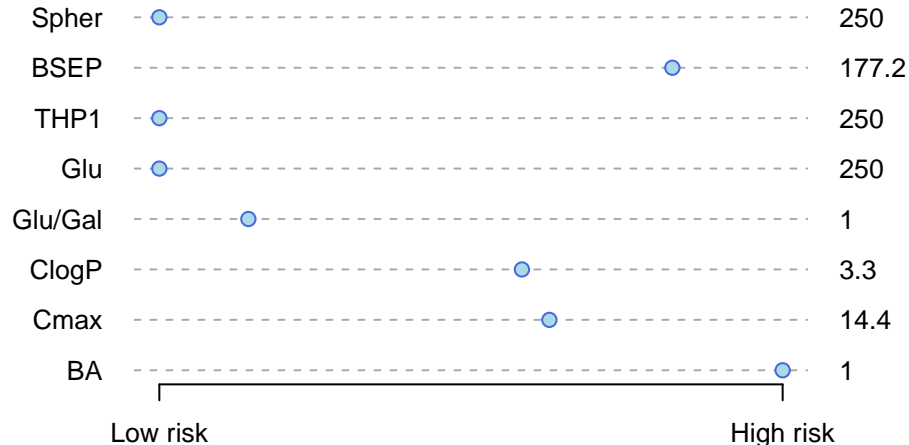
Summary stats

Peak = 0.89

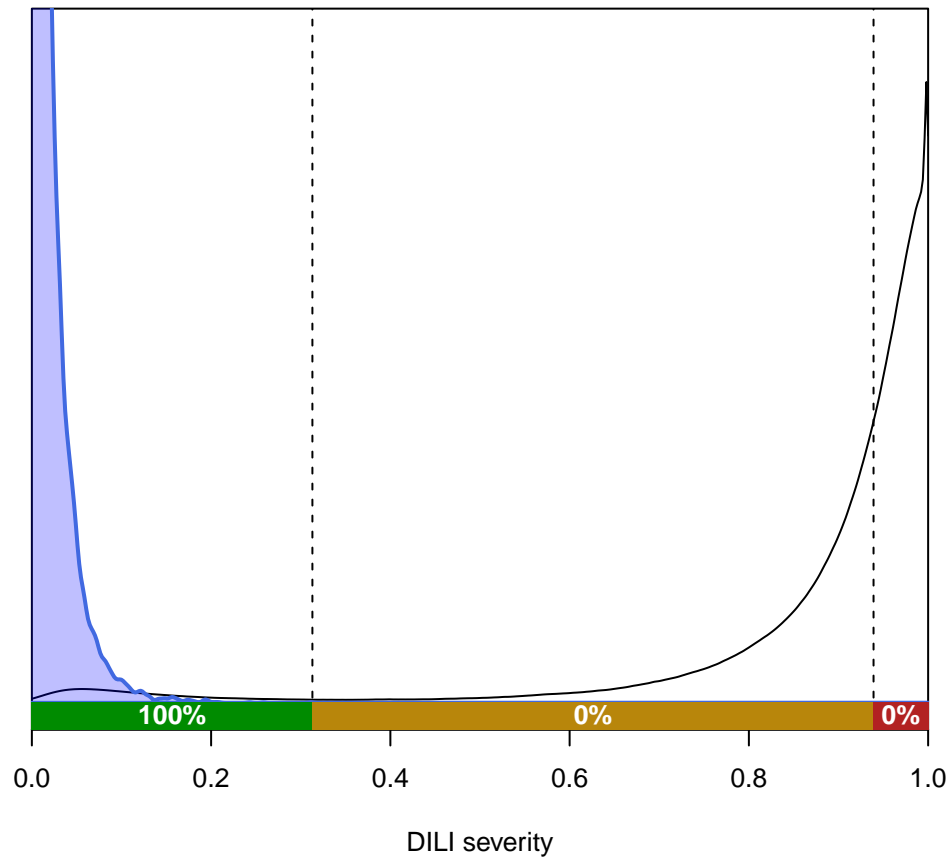
Mean = 0.82

Median = 0.85

95% CI = 0.6 – 0.98



Bumetanide



Probability

- 0.96
- 0.04
- 0

True category

1

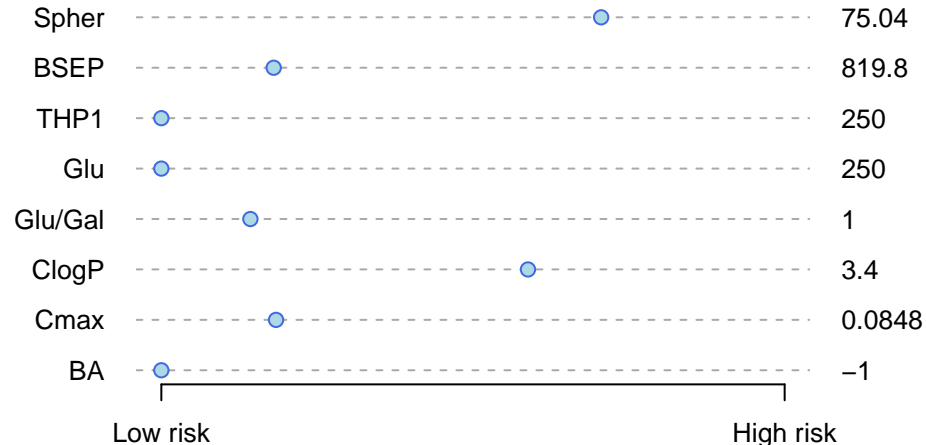
Summary stats

Peak = 0

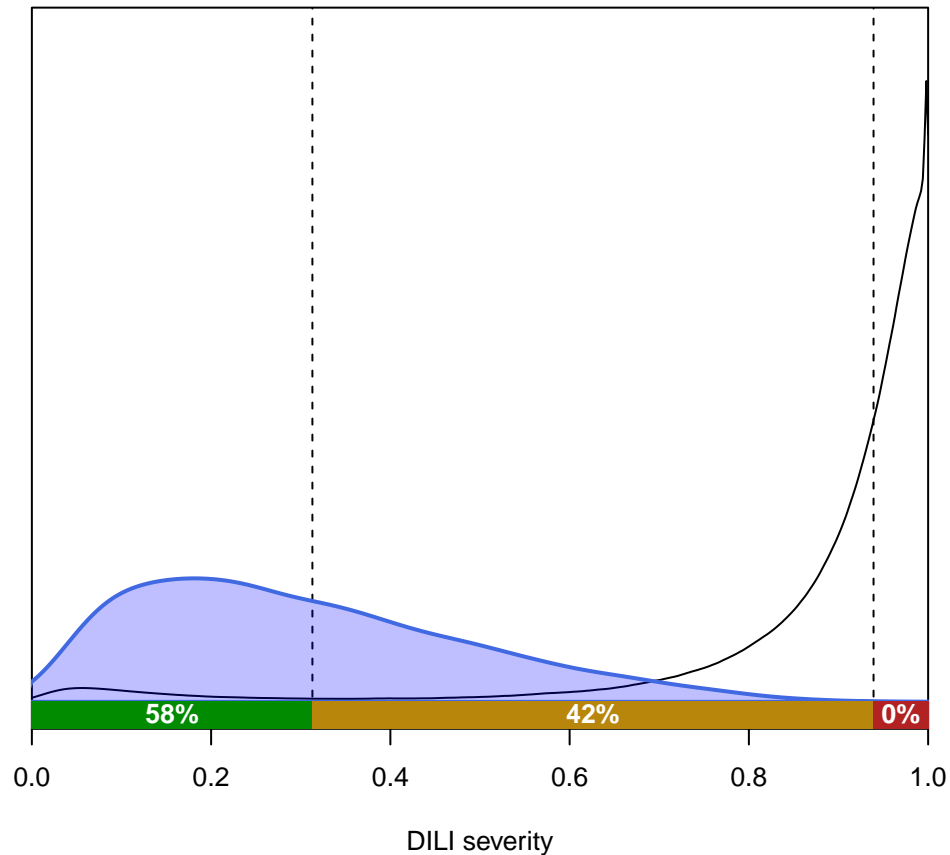
Mean = 0.02

Median = 0.01

95% CI = 0 – 0.06



Buspirone



Probability

- 0.54
- 0.43
- 0.03

True category

1

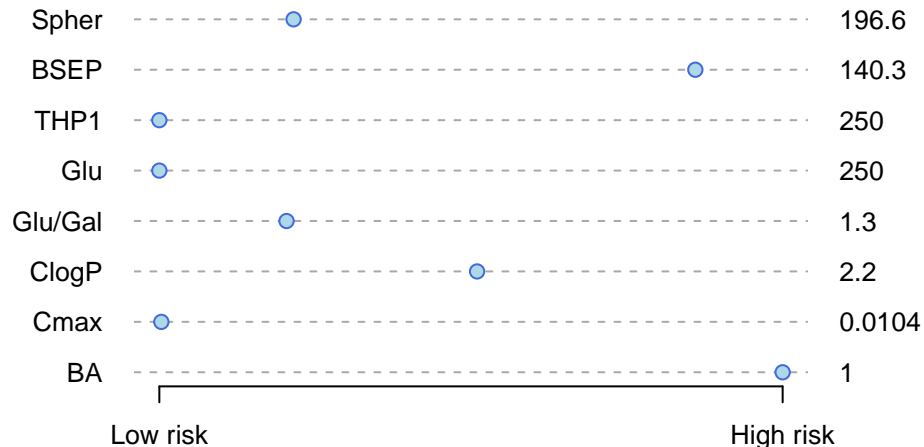
Summary stats

Peak = 0.18

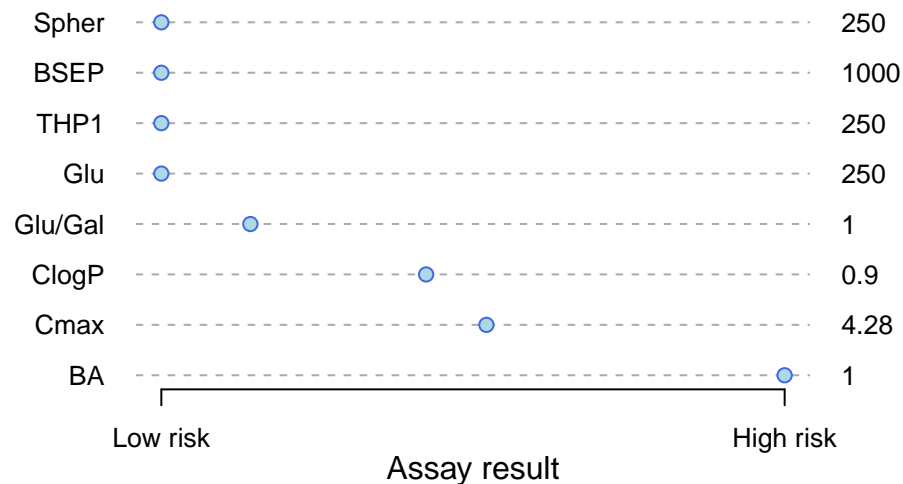
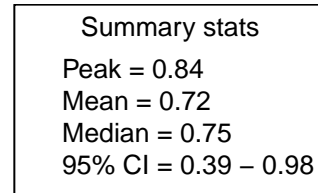
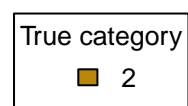
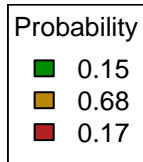
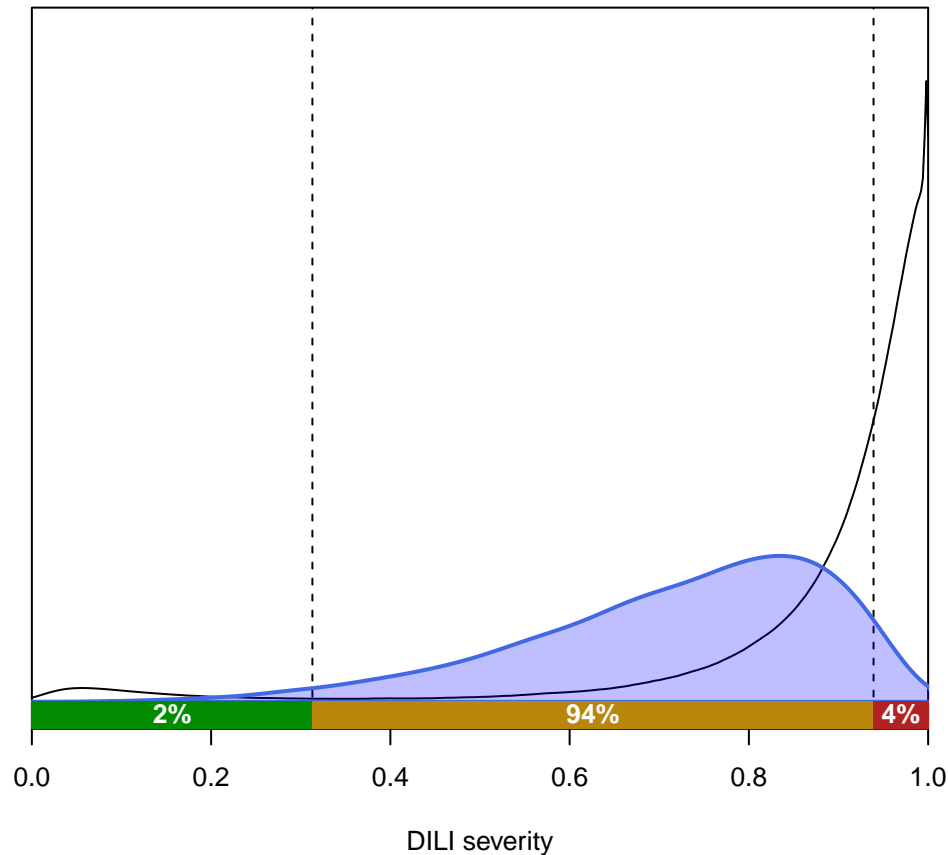
Mean = 0.3

Median = 0.27

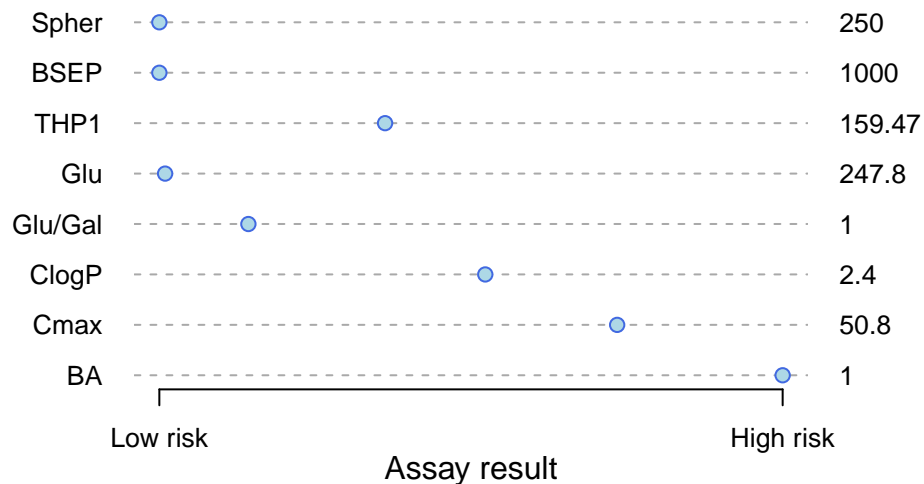
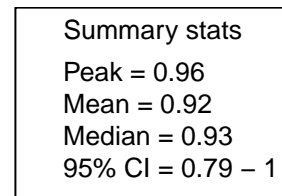
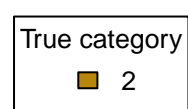
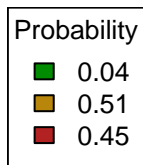
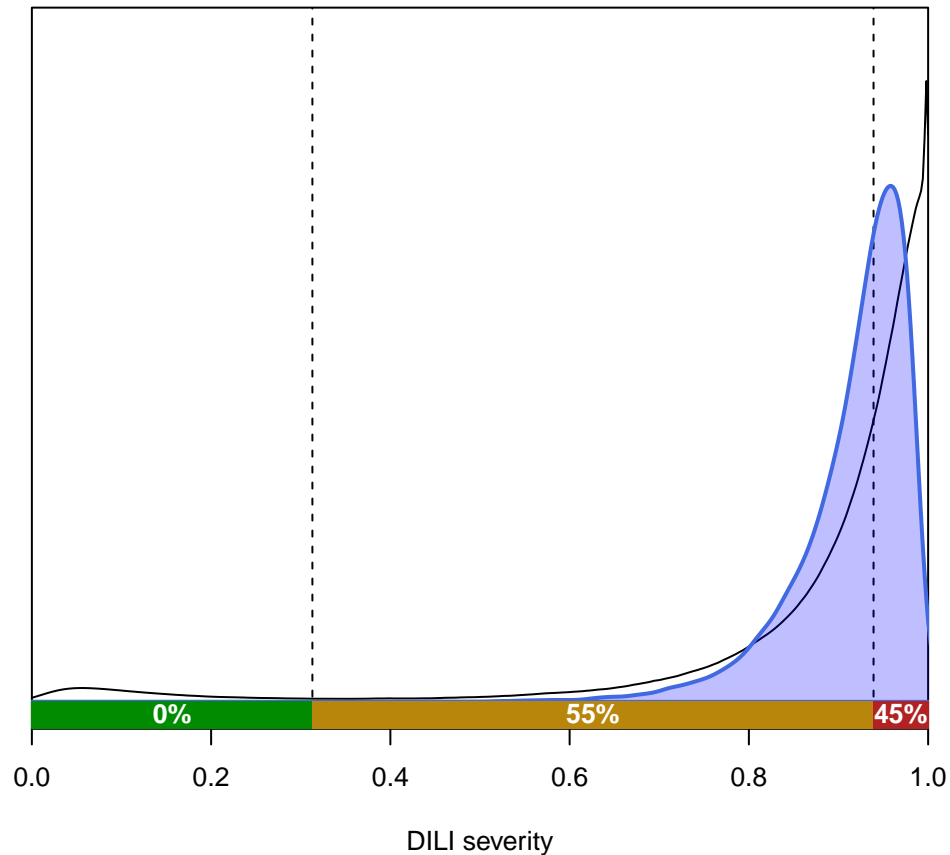
95% CI = 0.02 – 0.66



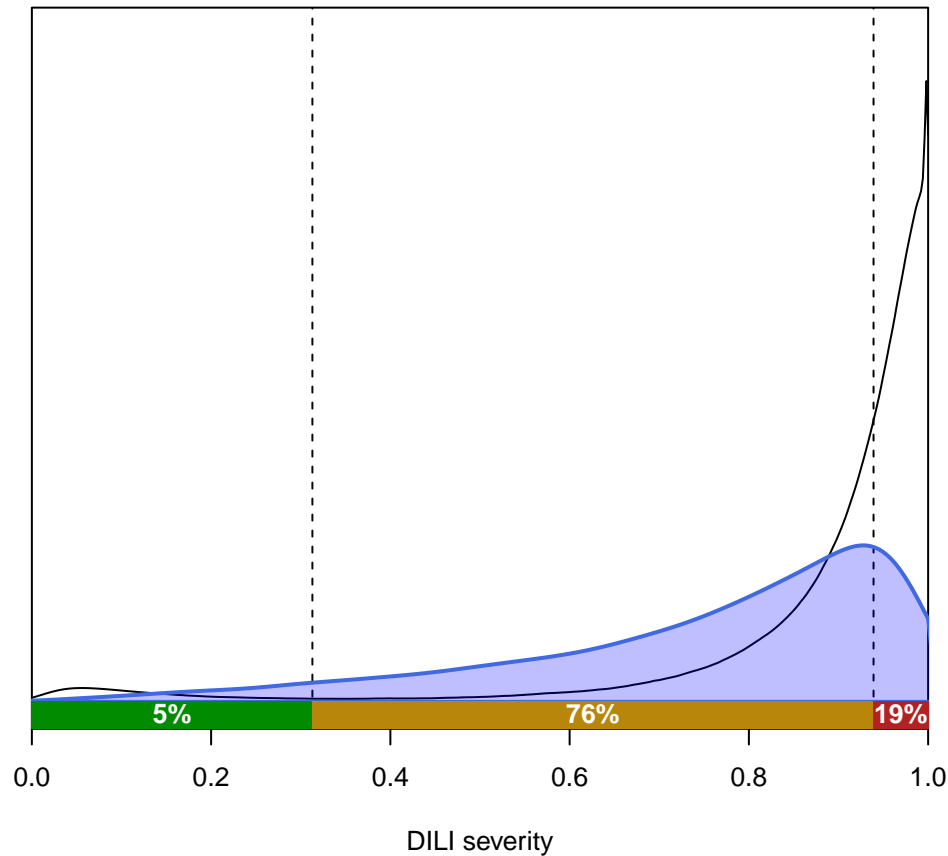
Captopril



Carbamazepine



Celecoxib



Probability

- 0.14
- 0.6
- 0.26

True category

2

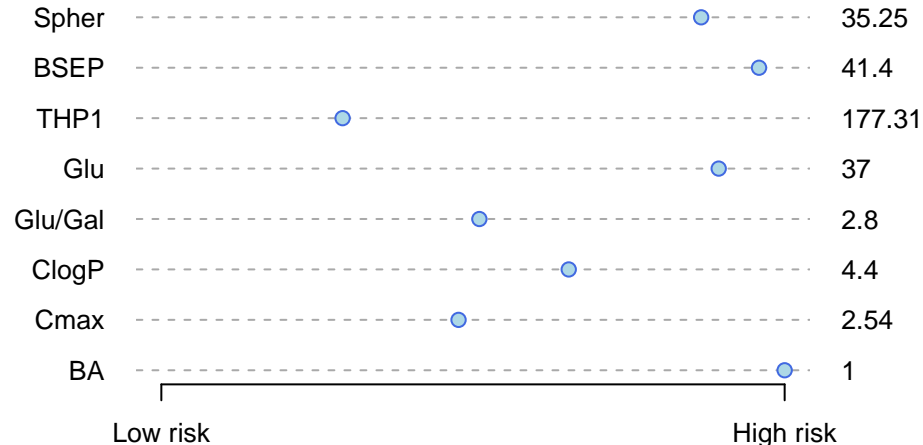
Summary stats

Peak = 0.94

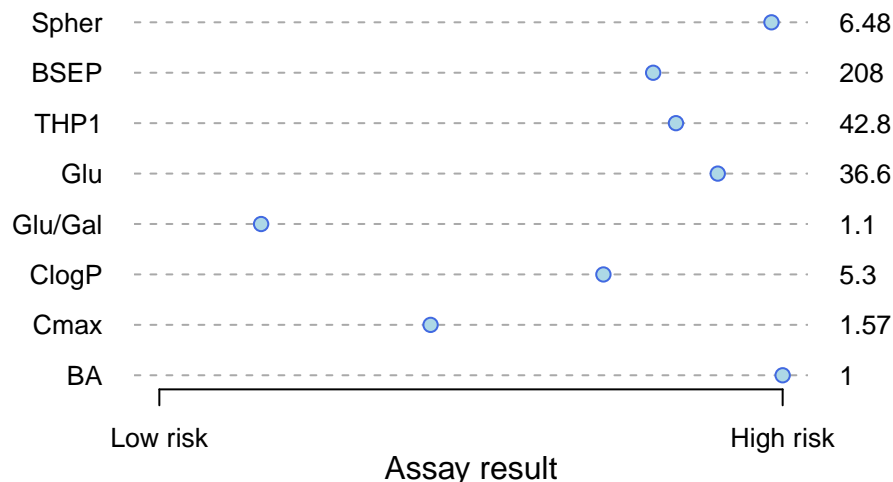
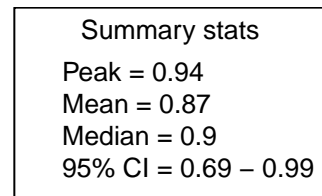
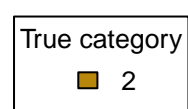
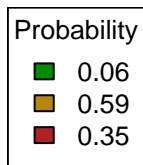
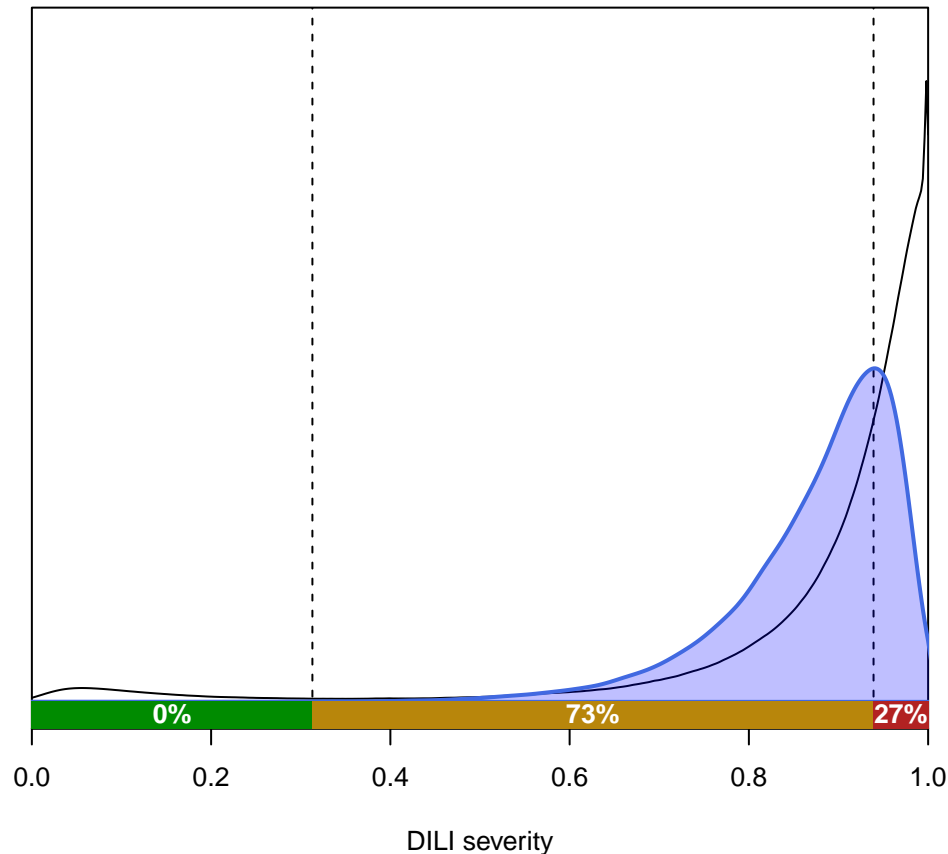
Mean = 0.75

Median = 0.81

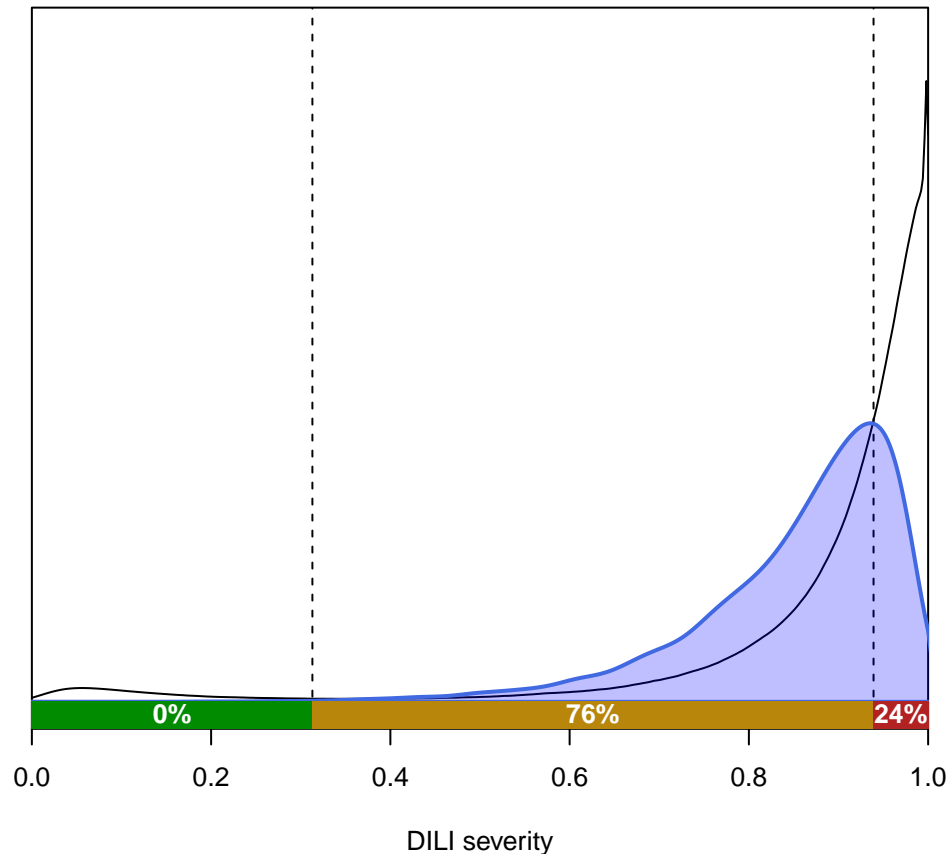
95% CI = 0.31 – 1



Chlorpromazine



Clomipramine



Probability

- 0.07
- 0.61
- 0.32

True category

2

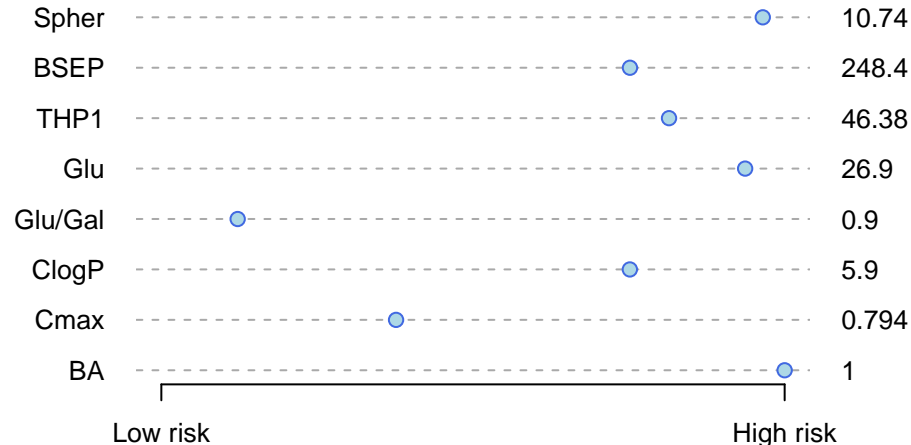
Summary stats

Peak = 0.94

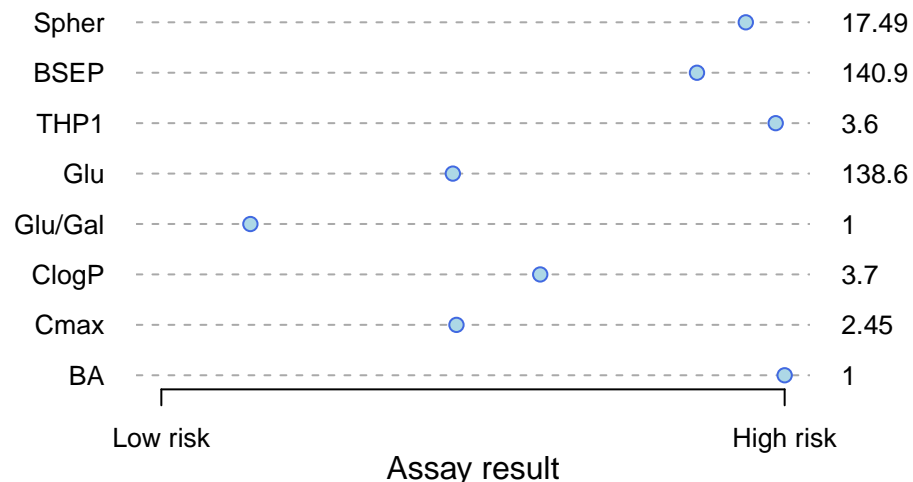
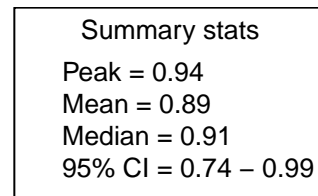
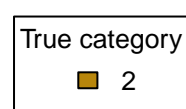
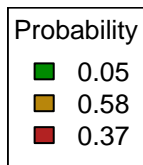
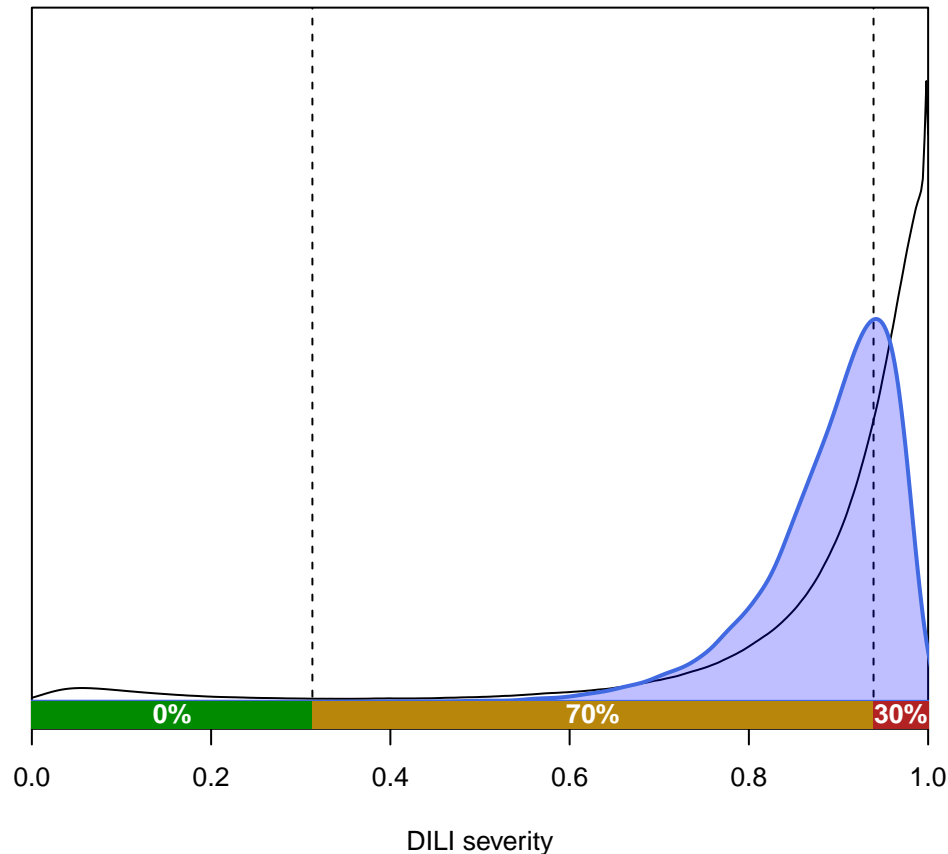
Mean = 0.85

Median = 0.88

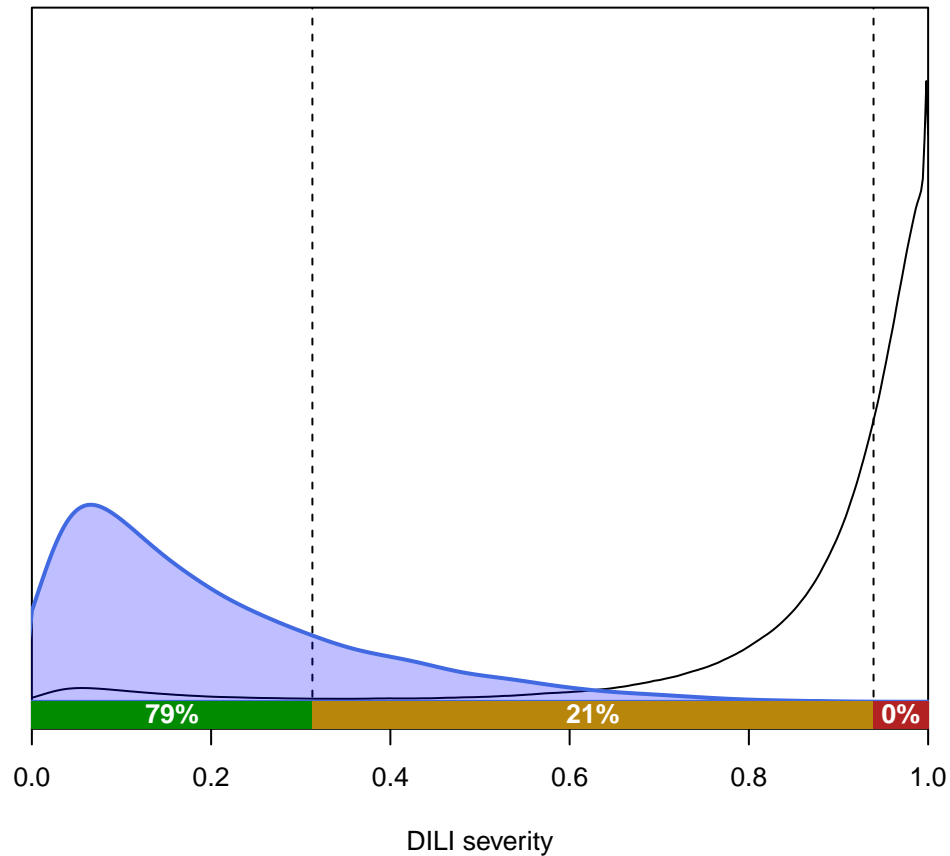
95% CI = 0.62 – 1



Clozapine



Cycloserine



Probability

- 0.68
- 0.3
- 0.02

True category

1

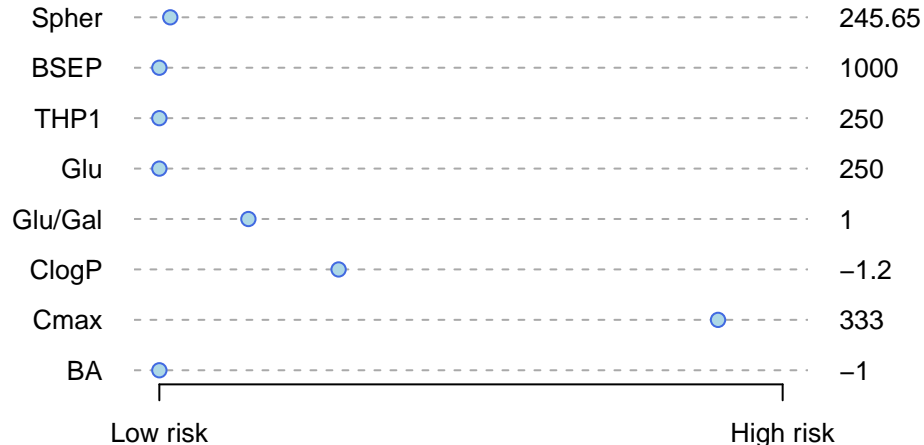
Summary stats

Peak = 0.06

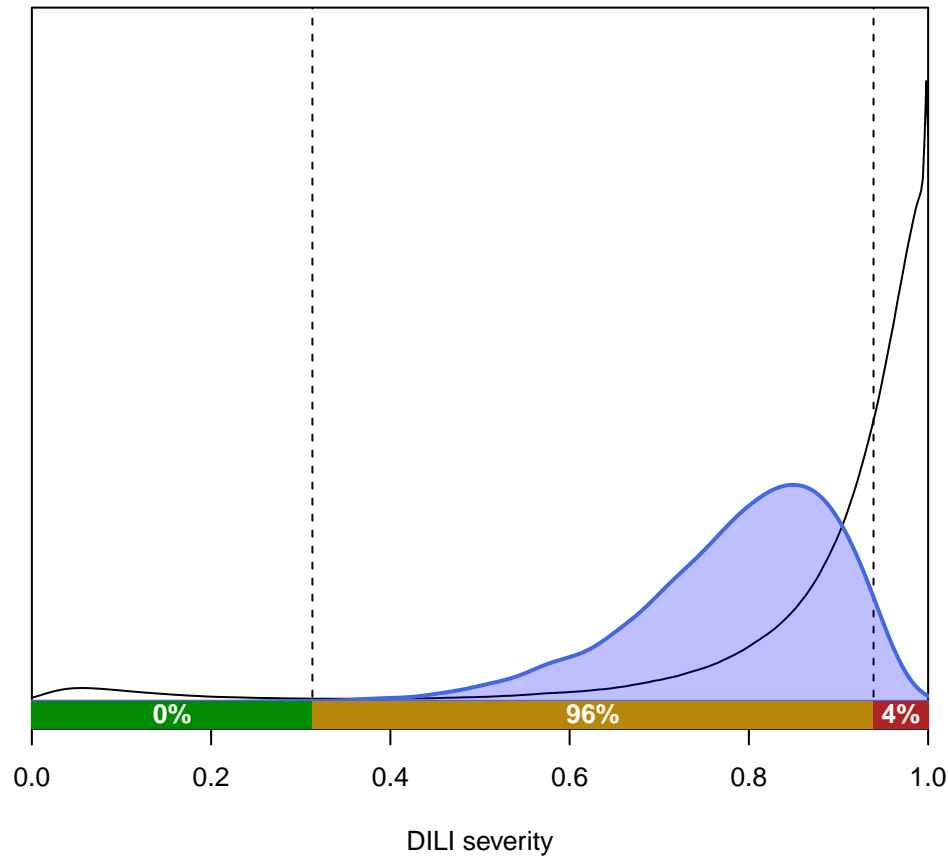
Mean = 0.2

Median = 0.15

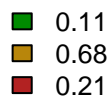
95% CI = 0 - 0.53



Dantrolene



Probability



True category

3

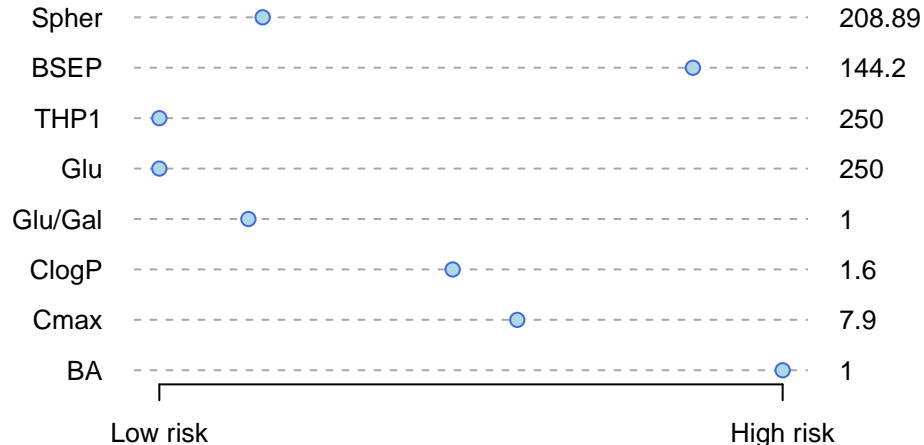
Summary stats

Peak = 0.85

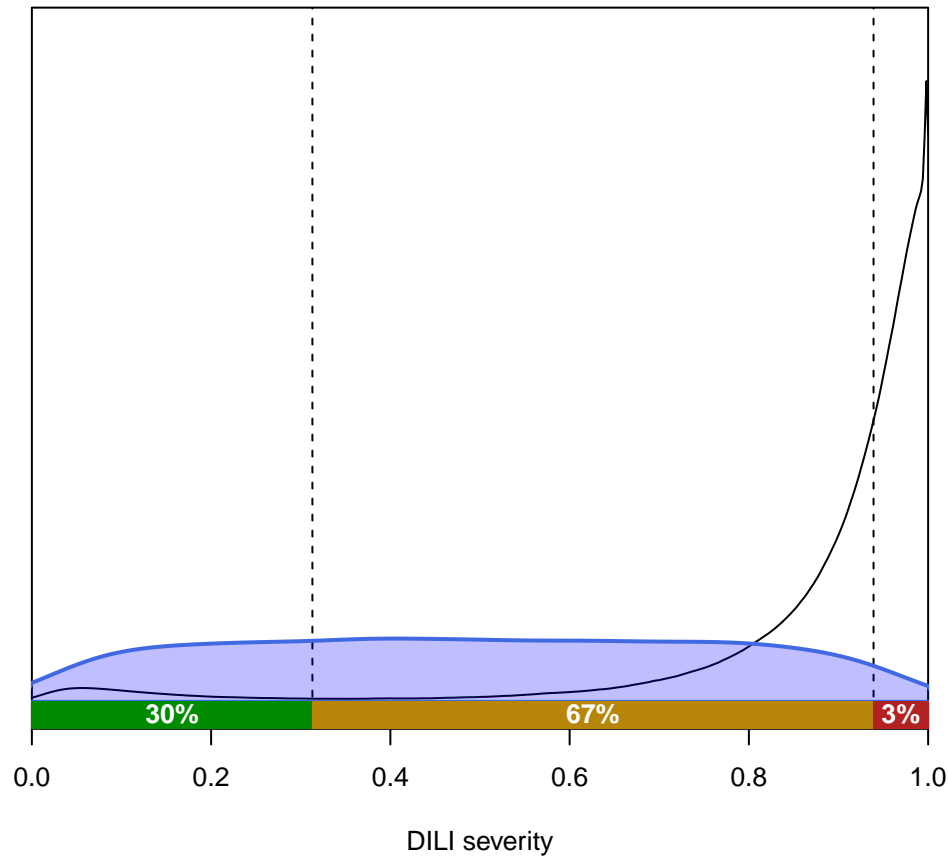
Mean = 0.79

Median = 0.81

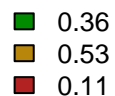
95% CI = 0.57 – 0.97



Desipramine



Probability

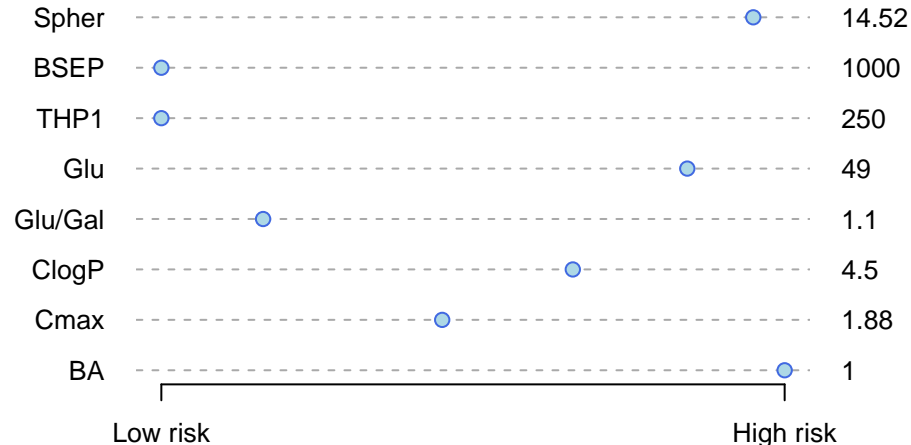


True category

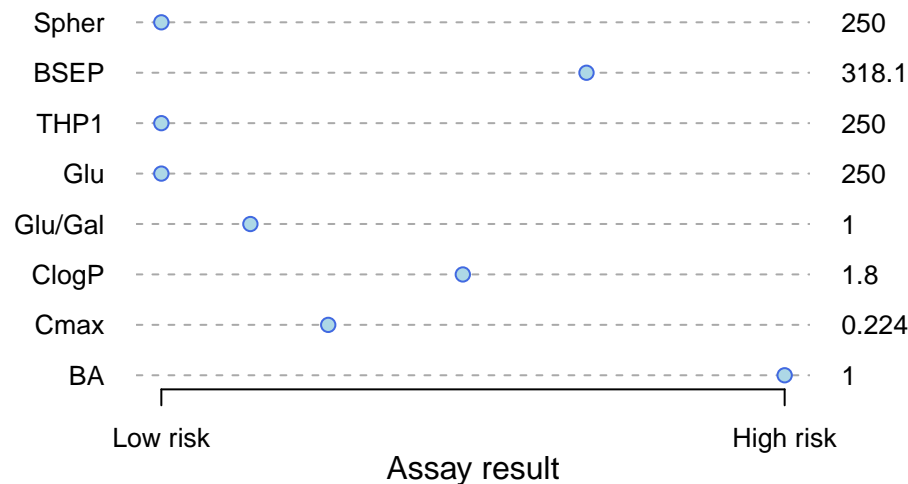
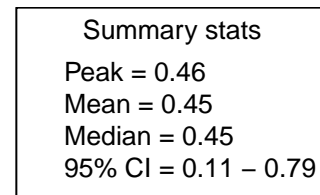
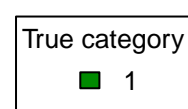
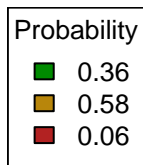
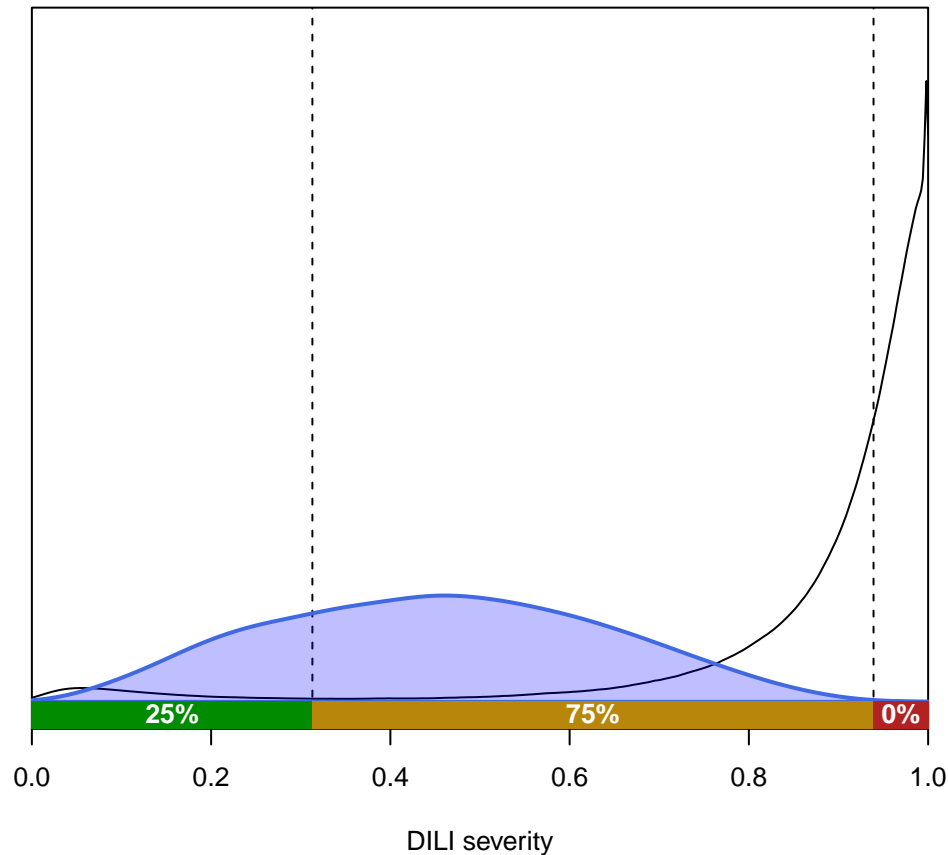


Summary stats

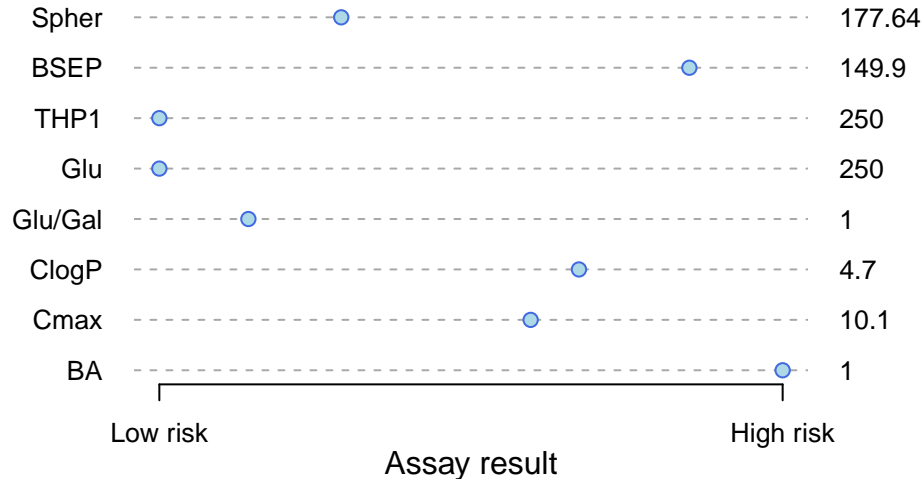
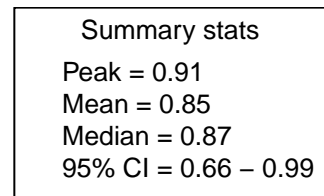
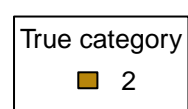
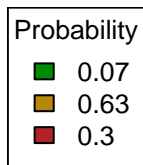
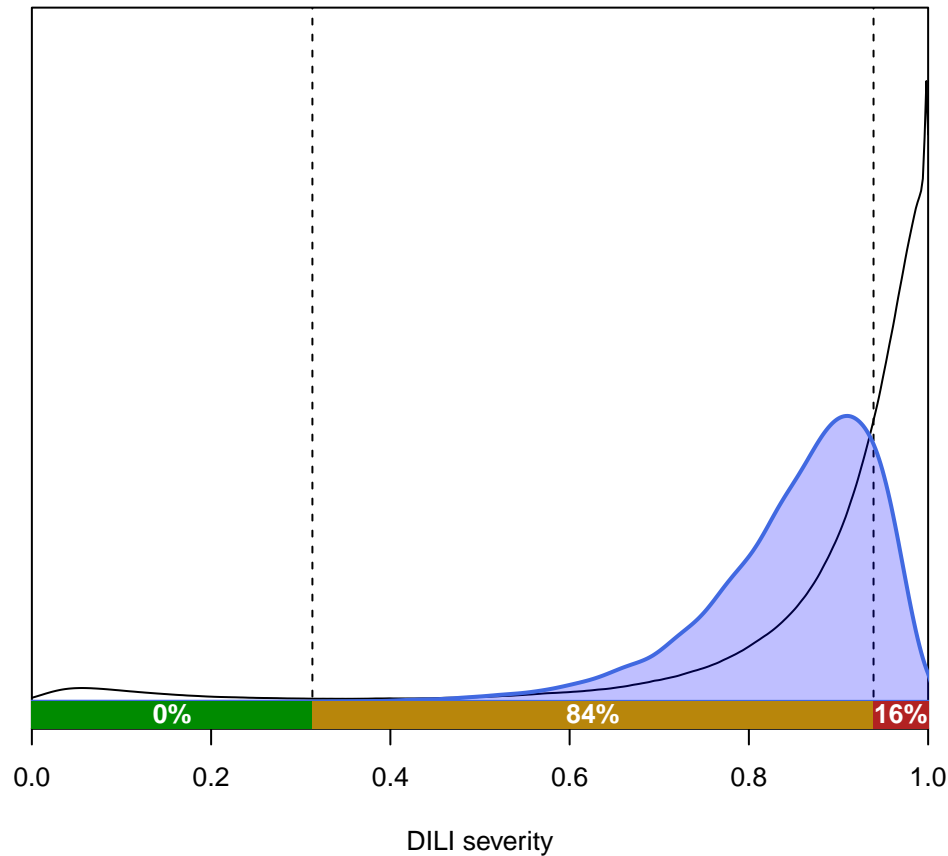
Peak = 0.39
Mean = 0.49
Median = 0.49
95% CI = 0.03 – 0.93



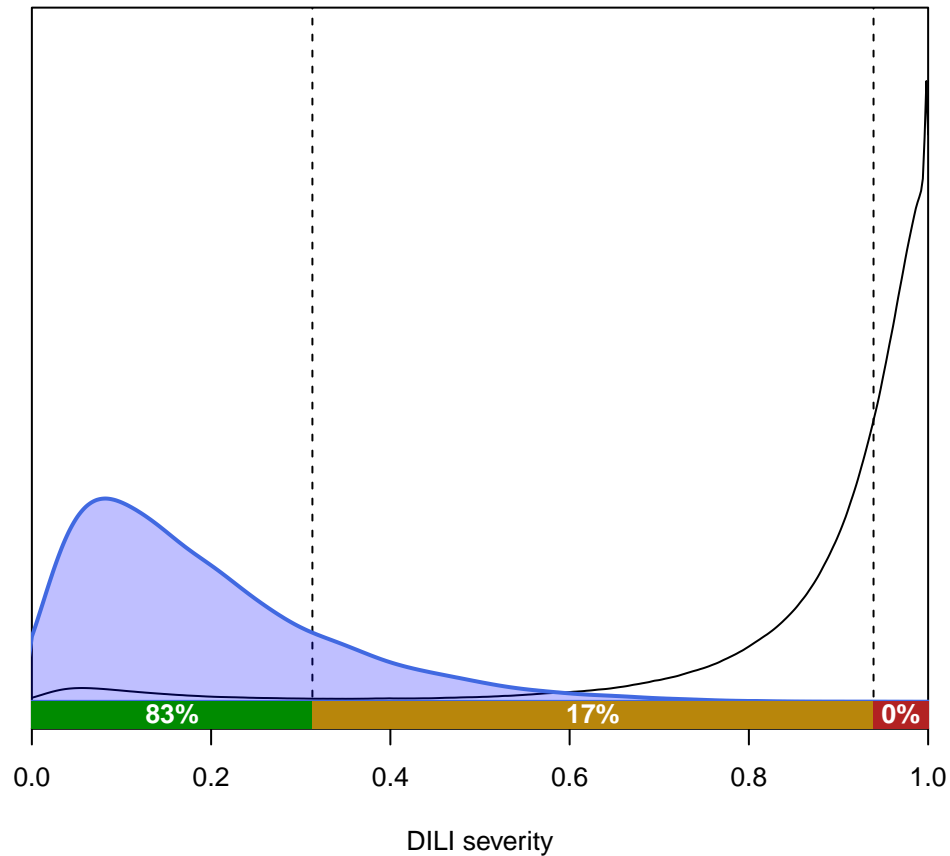
Dexamethasone



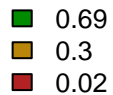
Diclofenac



Entacapone



Probability

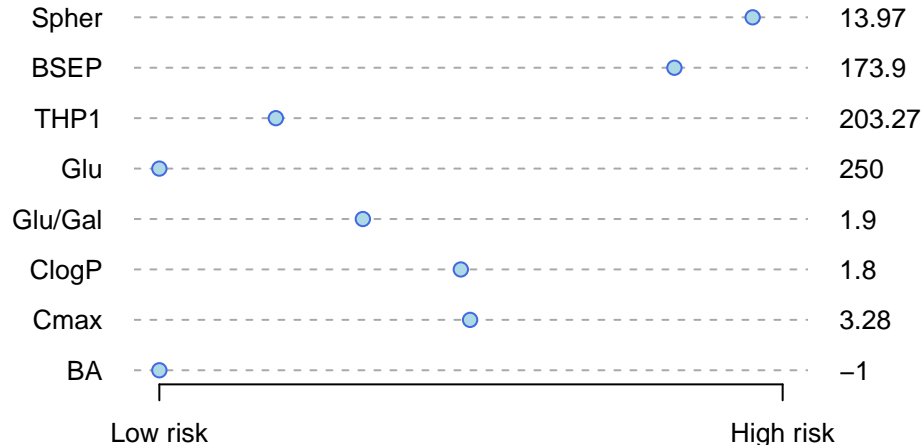


True category

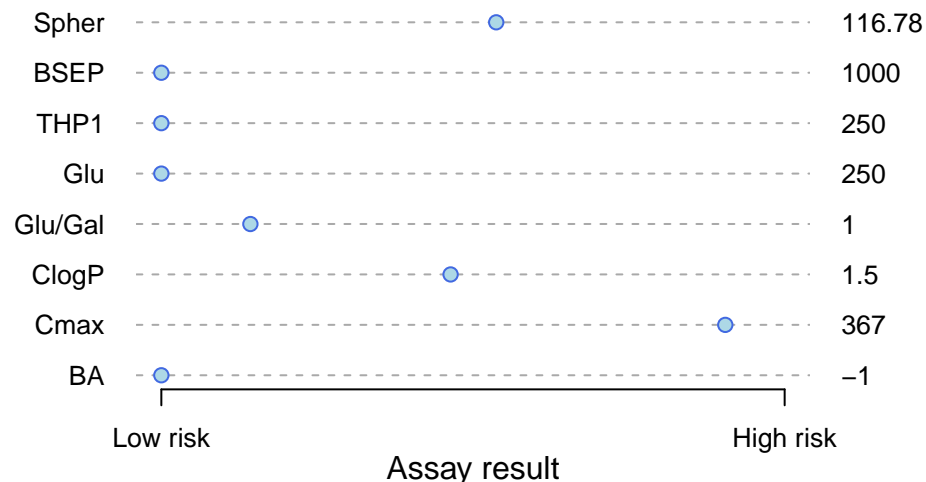
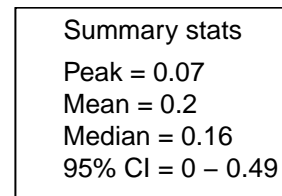
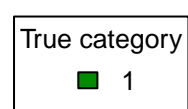
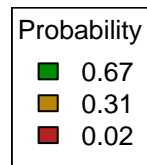
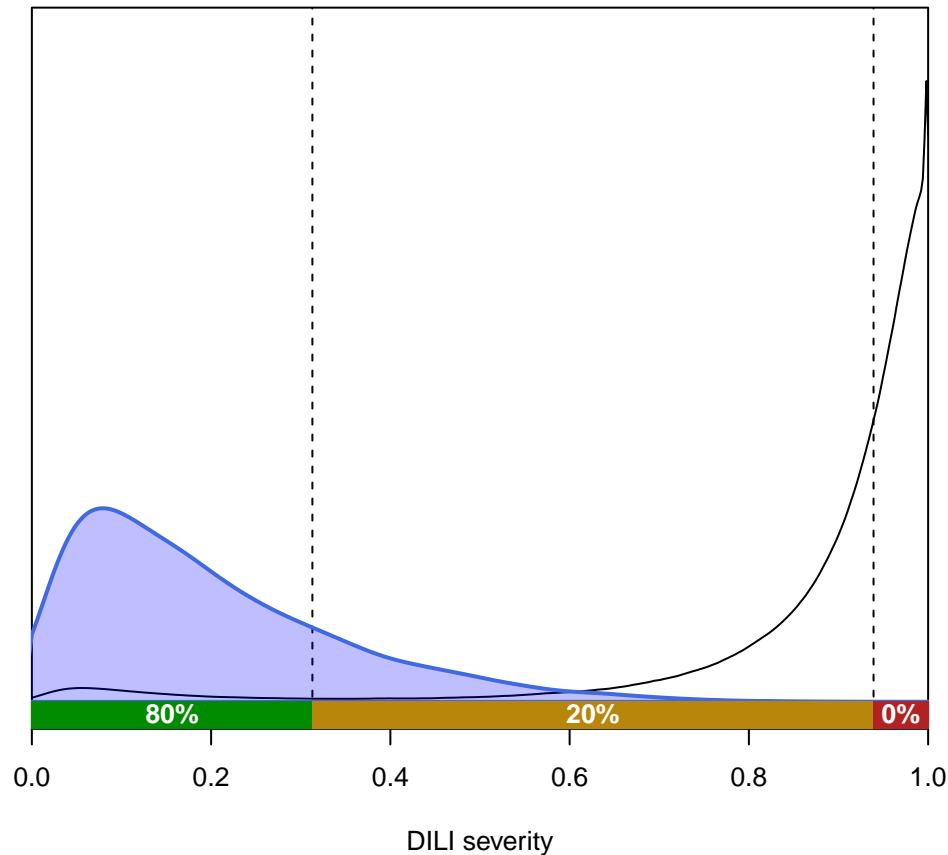


Summary stats

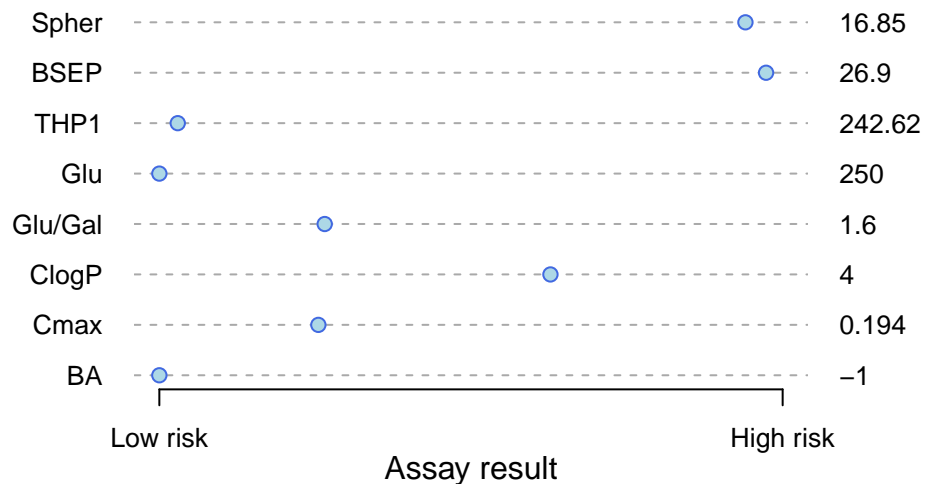
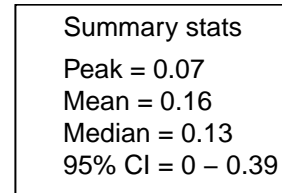
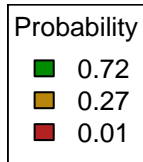
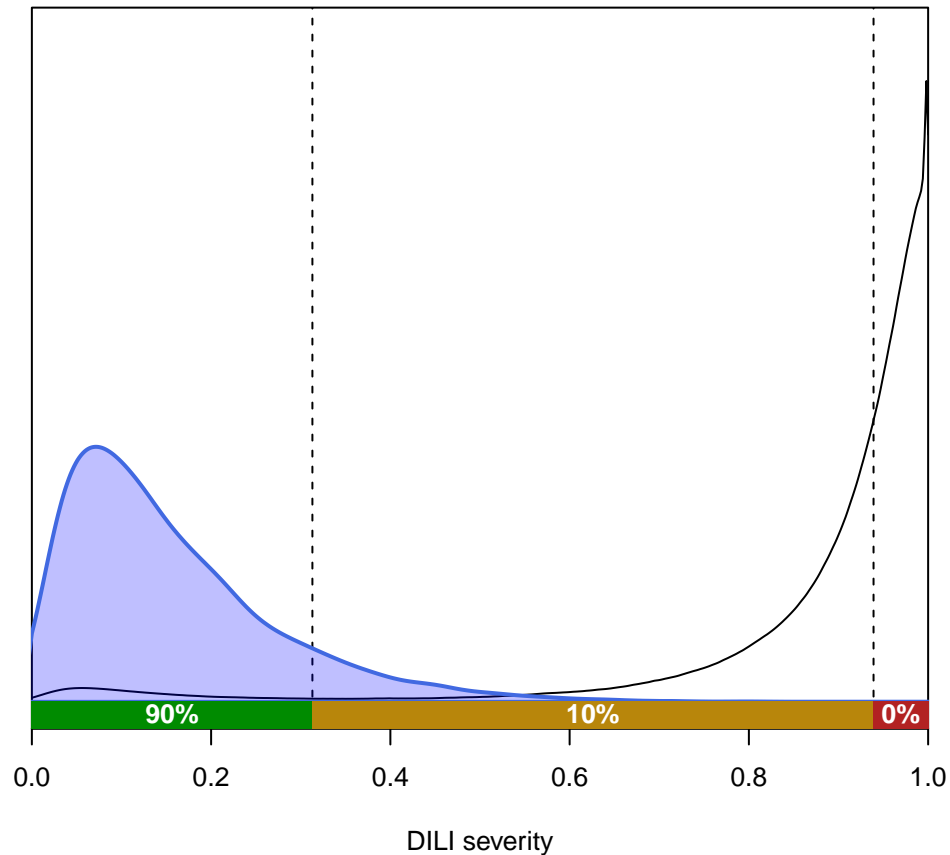
Peak = 0.08
Mean = 0.19
Median = 0.15
95% CI = 0 – 0.47



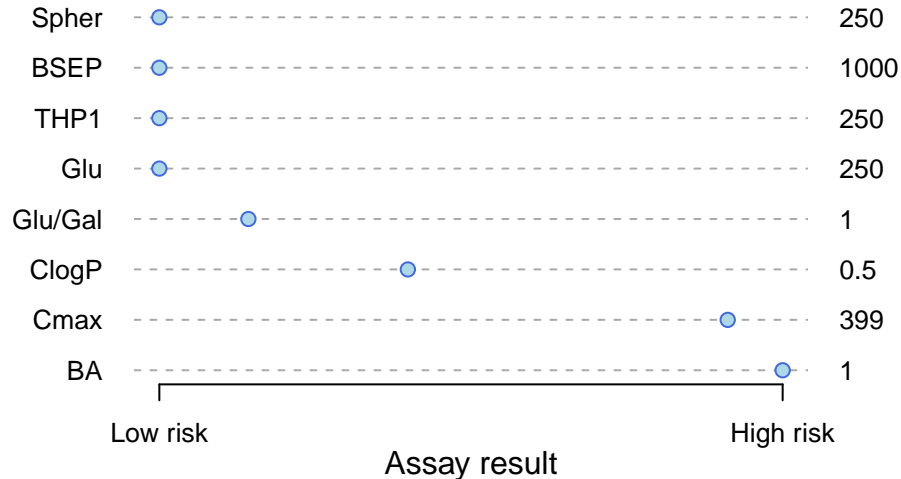
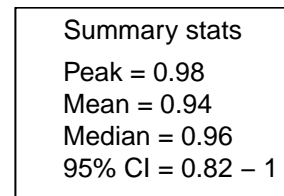
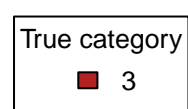
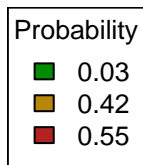
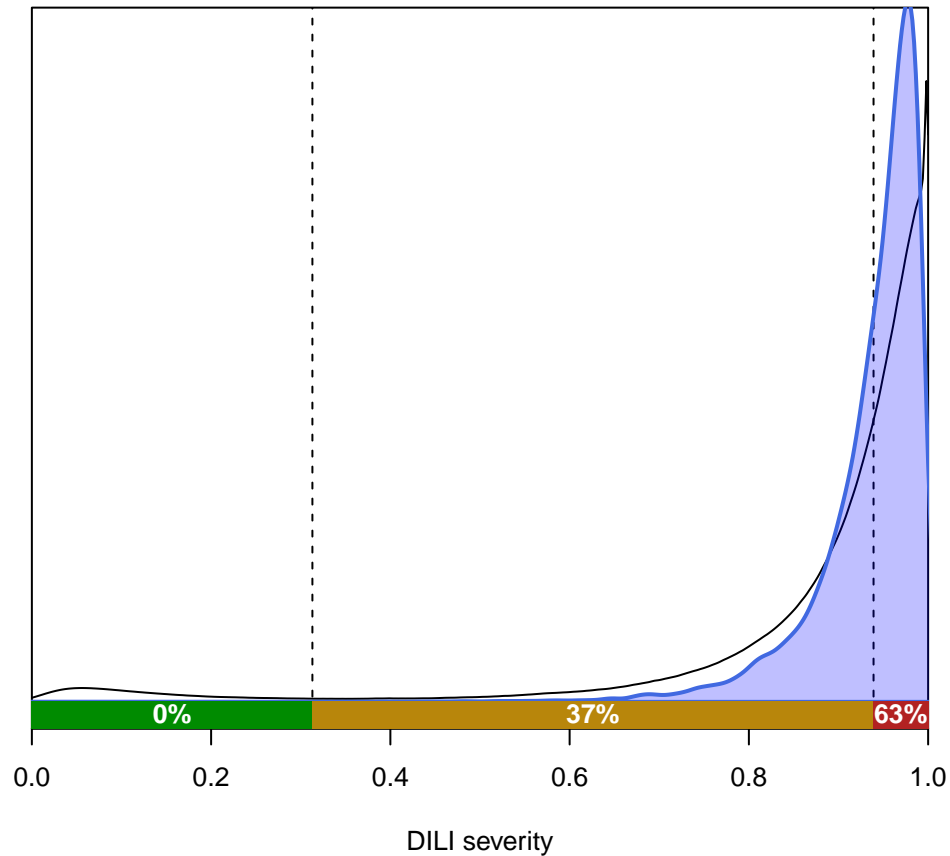
Ethotoin



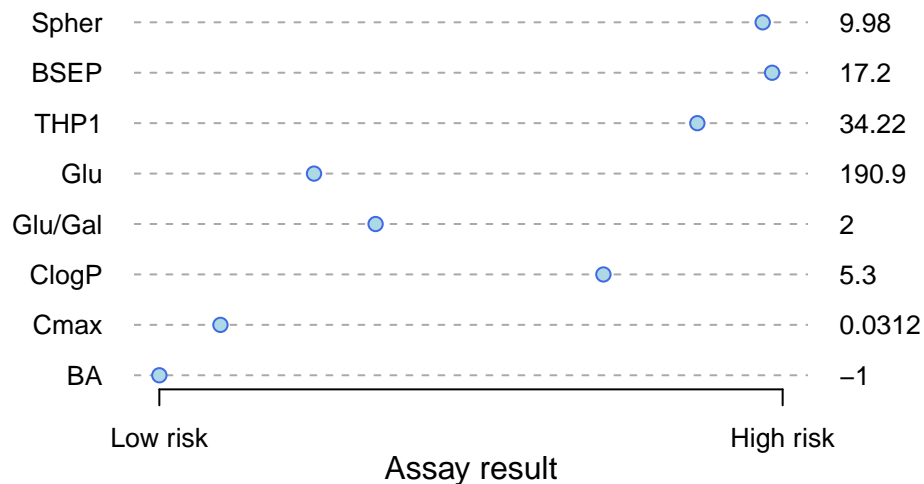
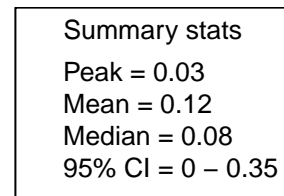
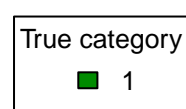
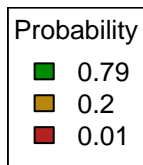
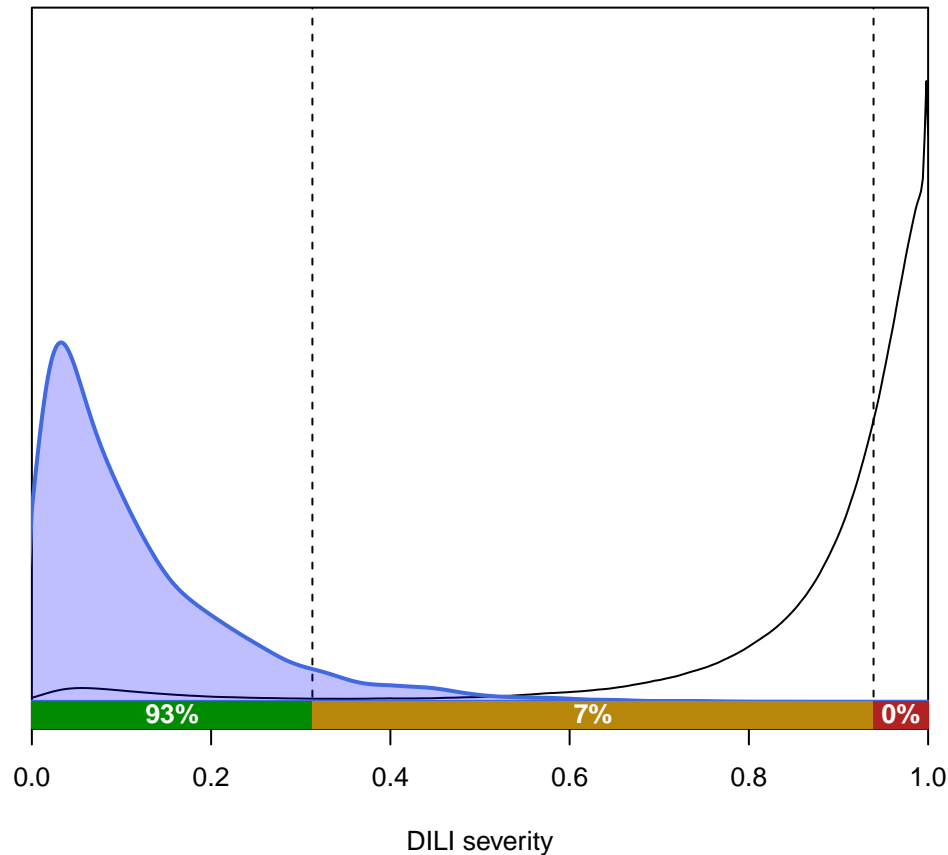
Ezetimibe



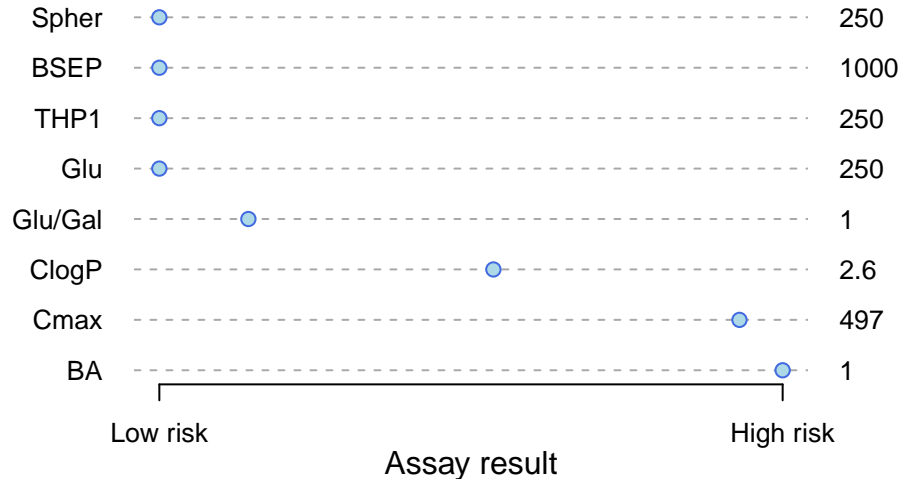
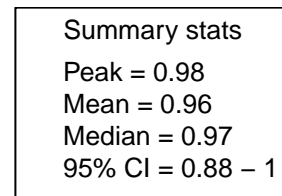
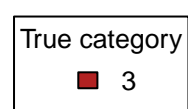
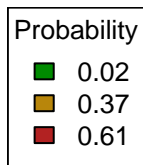
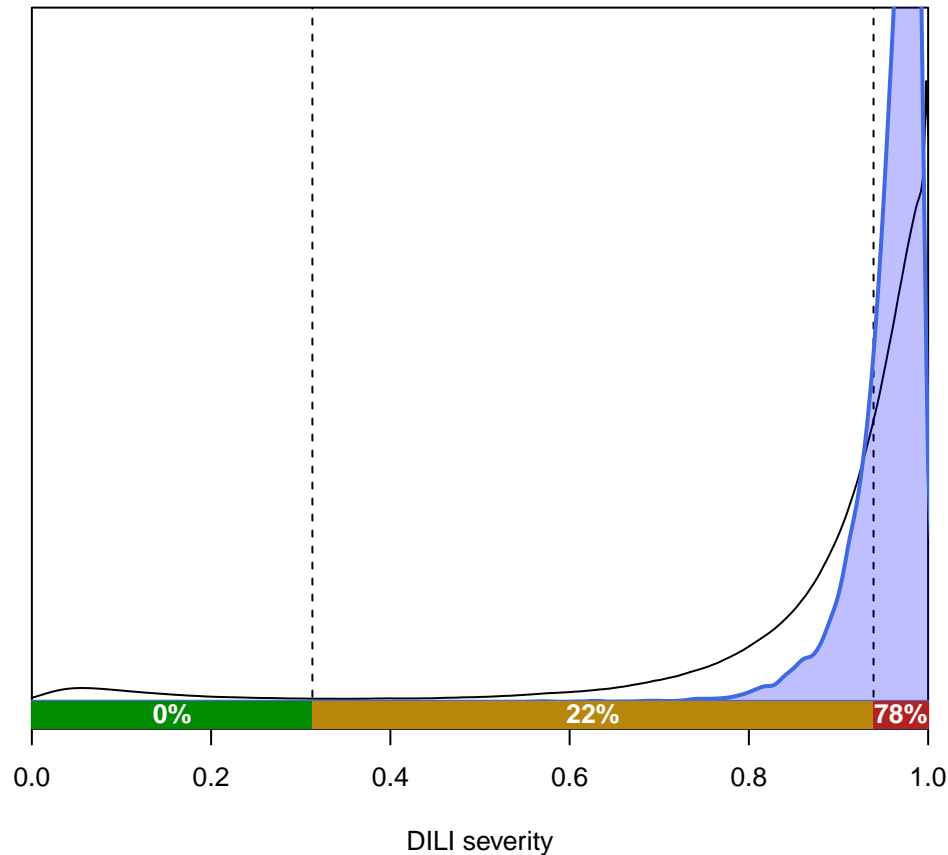
Felbamate



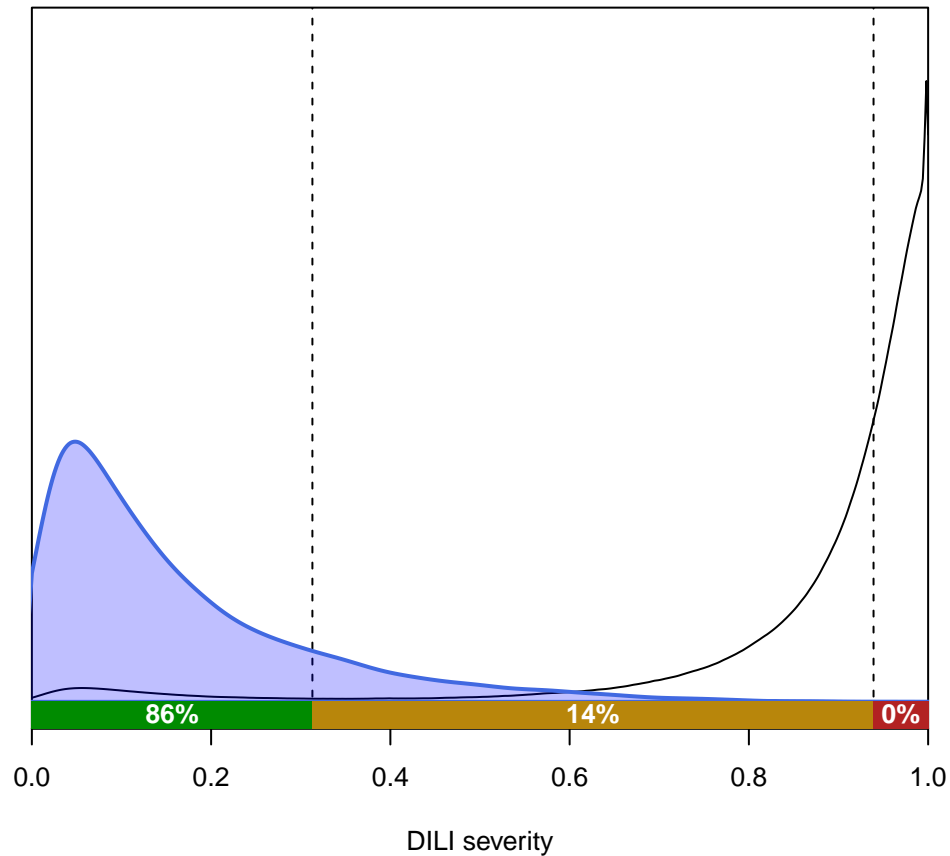
Felodipine



Fenclozic Acid



Flavoxate



Probability

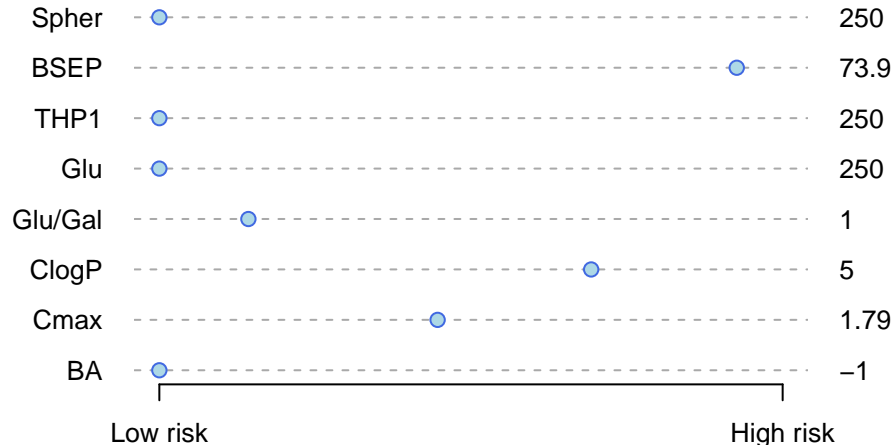


True category

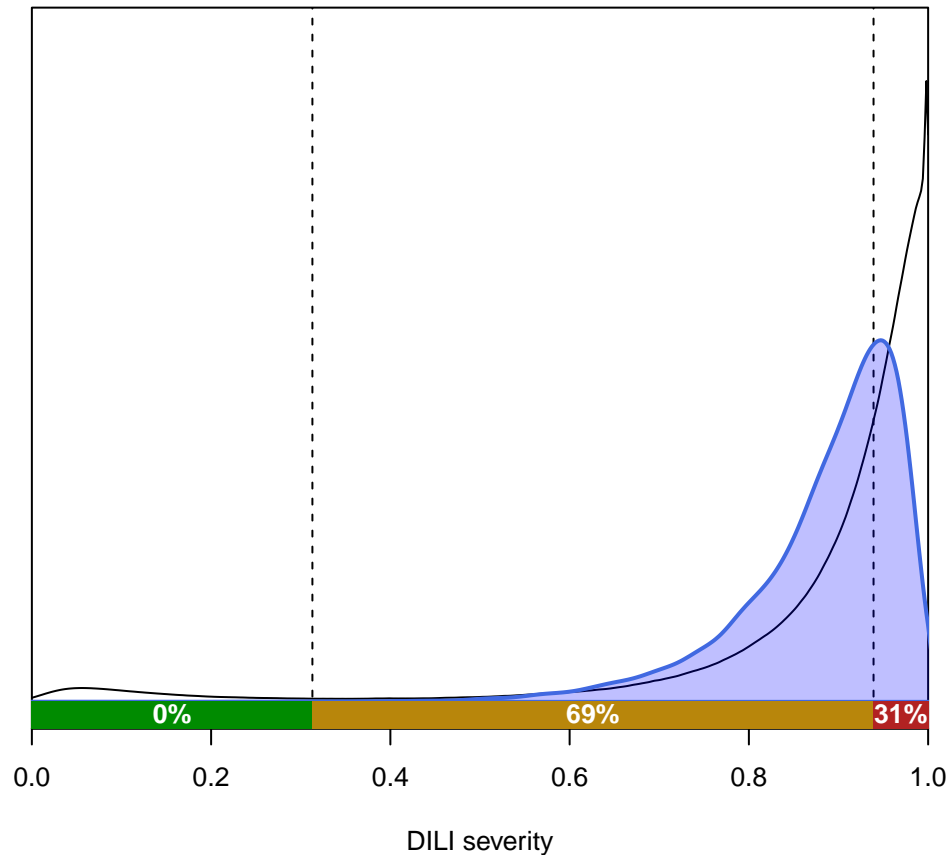


Summary stats

Peak = 0.04
Mean = 0.16
Median = 0.11
95% CI = 0 - 0.48



Flucloxacillin



Probability

- 0.05
- 0.57
- 0.37

True category

2

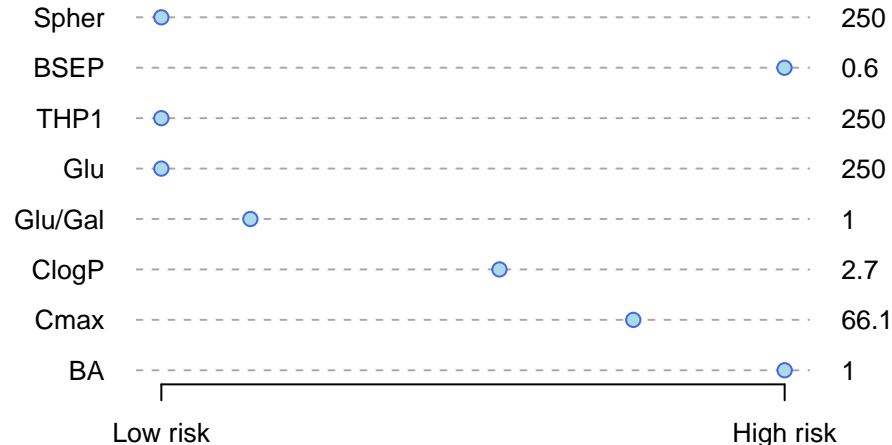
Summary stats

Peak = 0.95

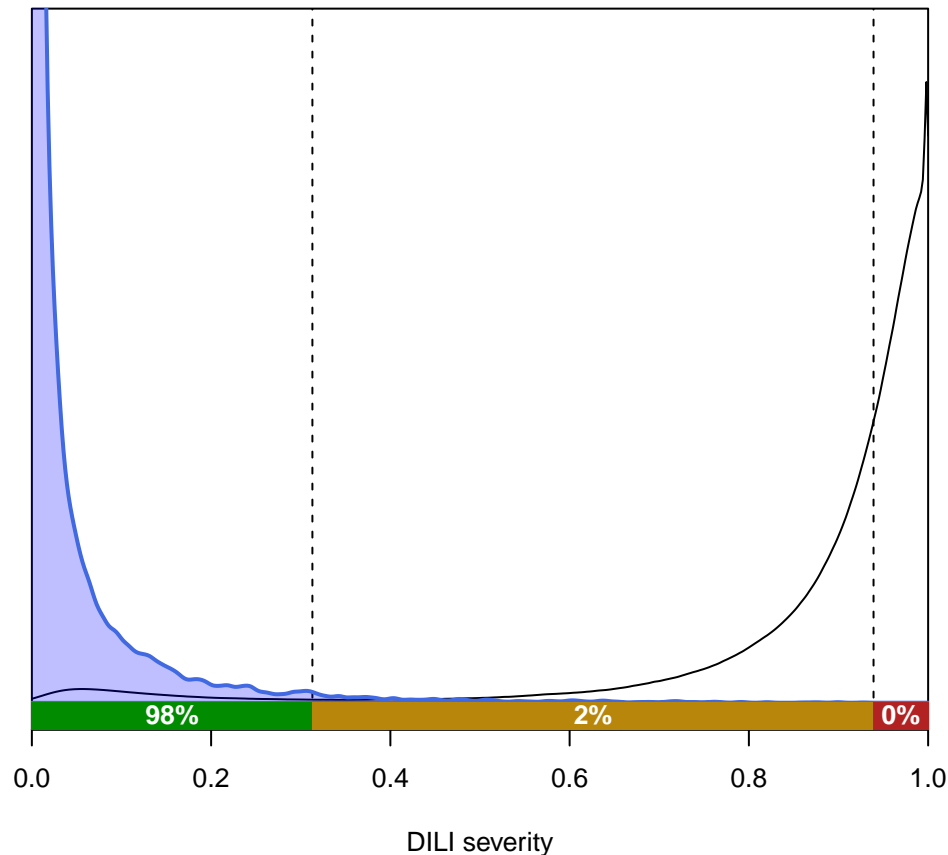
Mean = 0.88

Median = 0.91

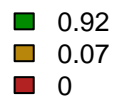
95% CI = 0.7 – 1



Fludarabine



Probability

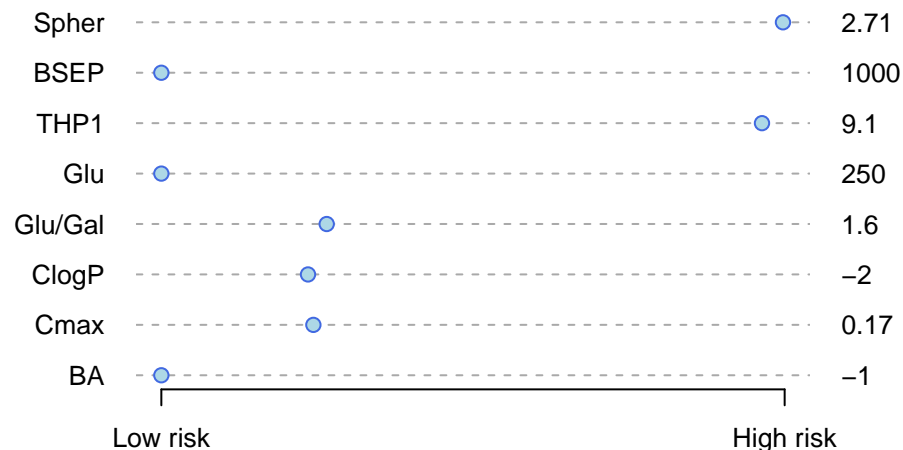


True category

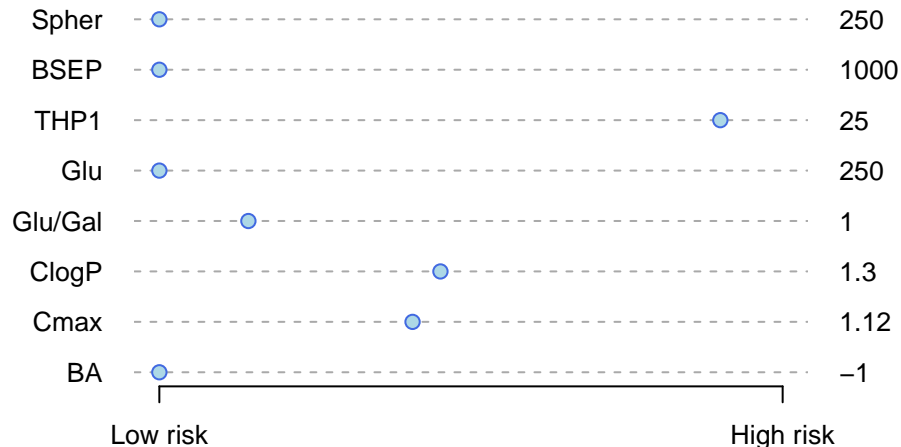
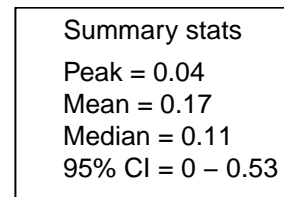
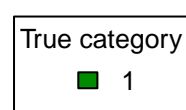
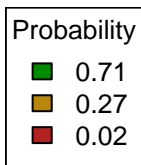
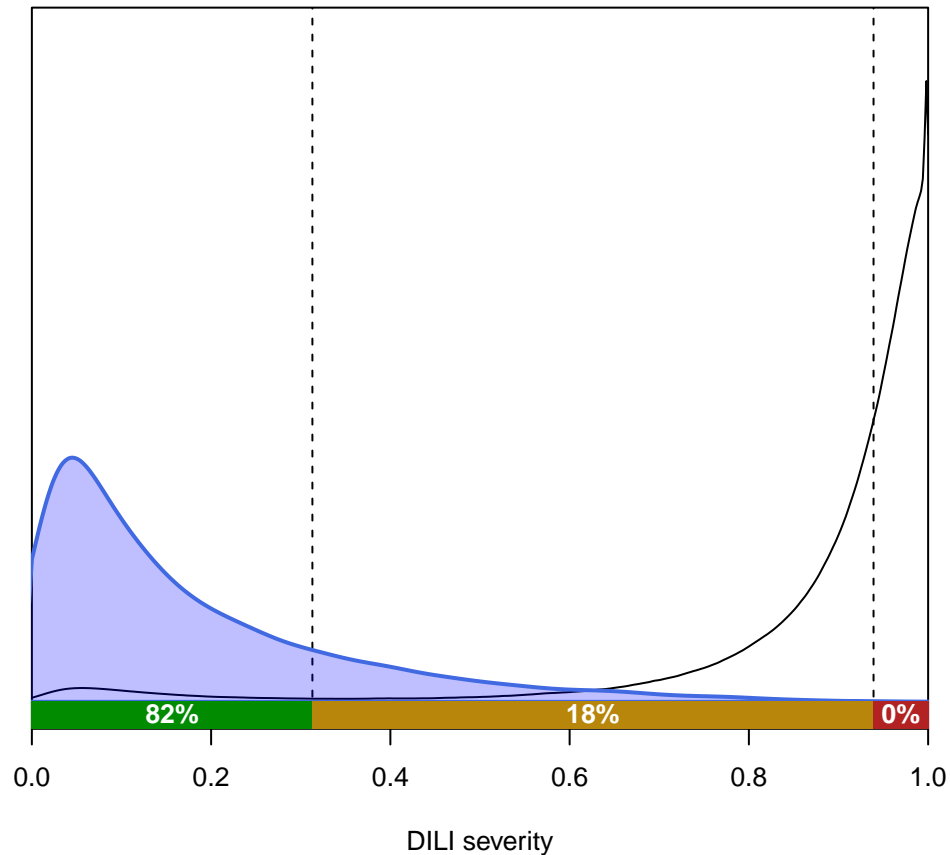


Summary stats

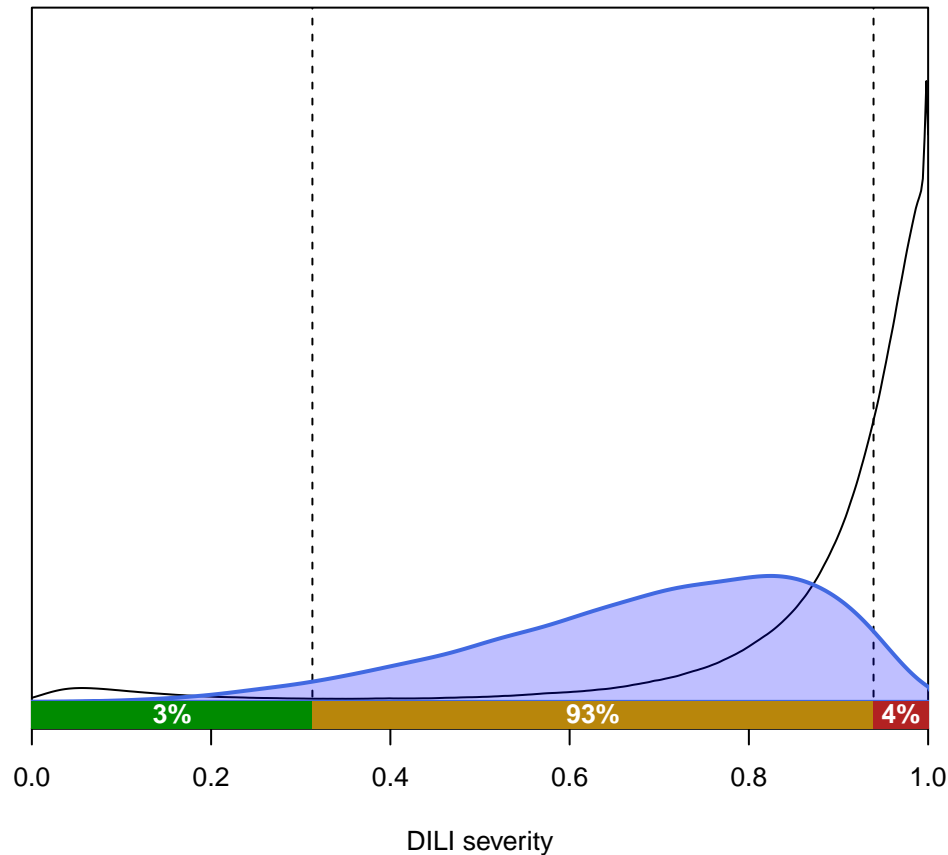
Peak = 0
Mean = 0.04
Median = 0.01
95% CI = 0 – 0.2



Flumazenil



Fluoxetine



Probability

- 0.17
- 0.67
- 0.16

True category

2

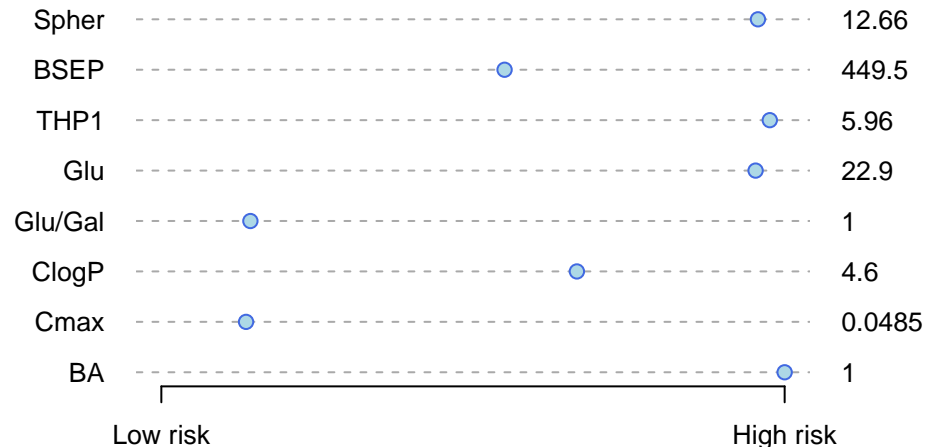
Summary stats

Peak = 0.83

Mean = 0.69

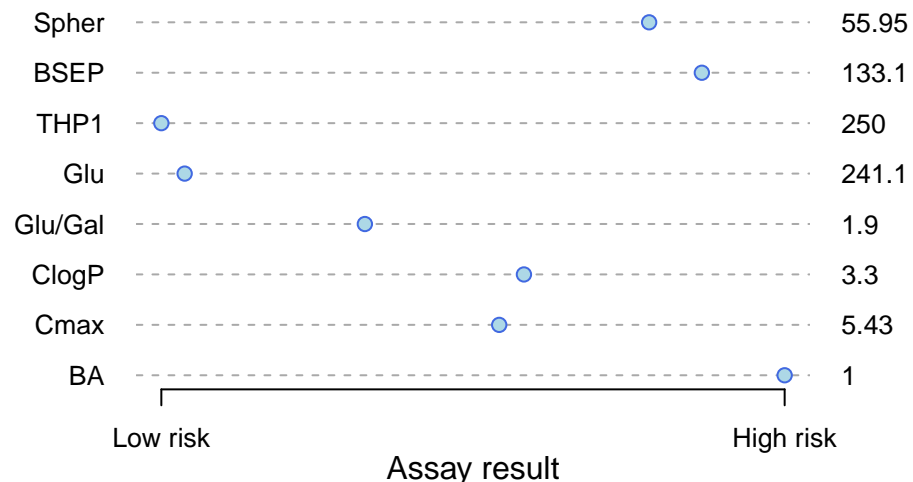
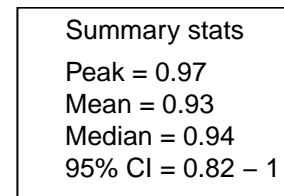
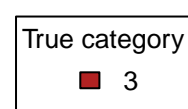
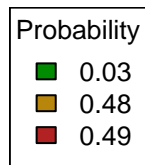
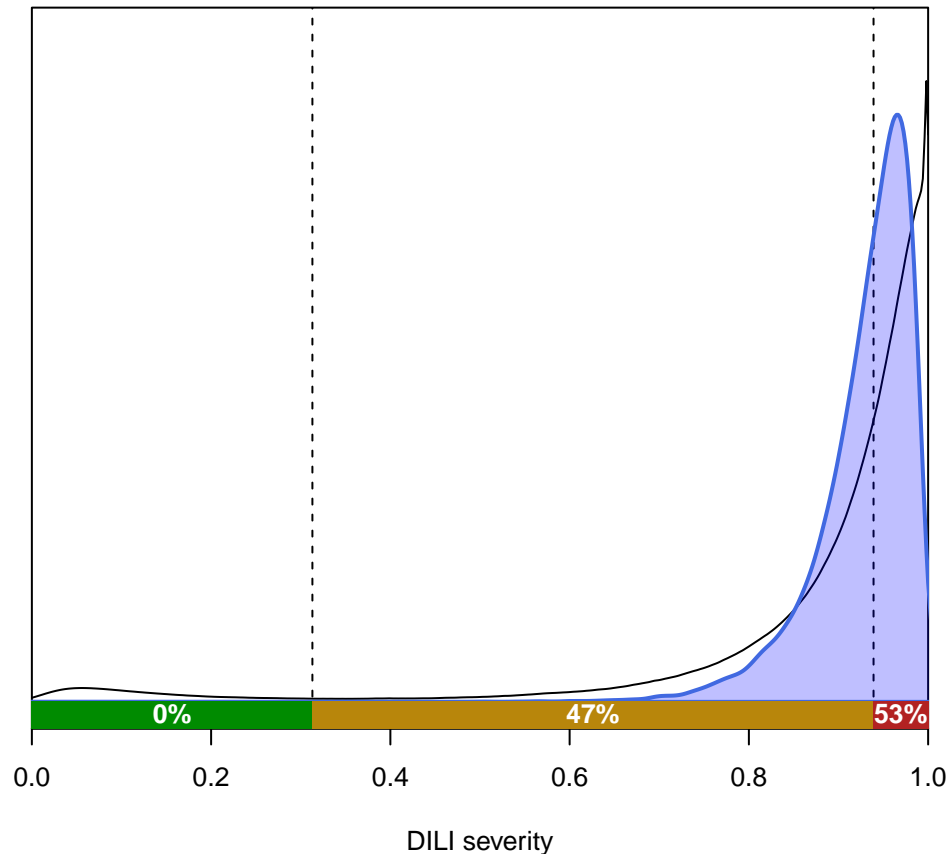
Median = 0.72

95% CI = 0.35 – 0.98

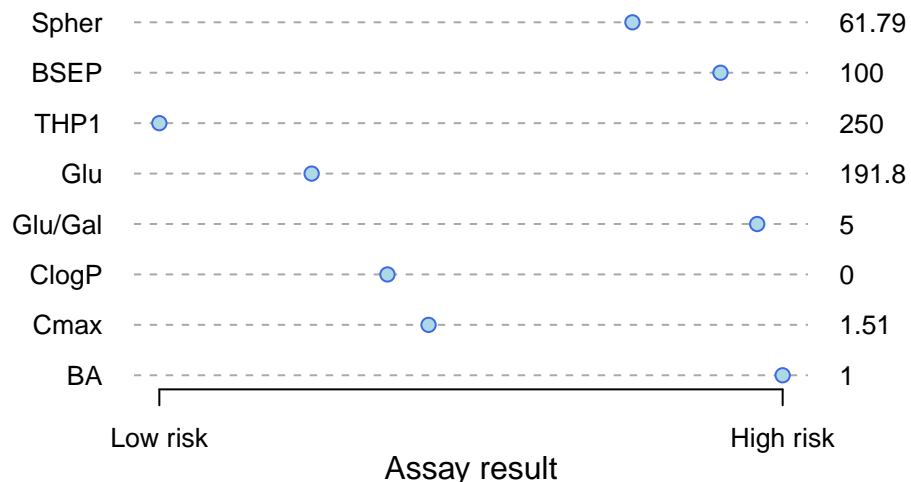
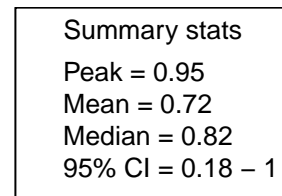
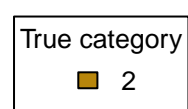
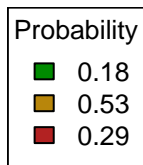
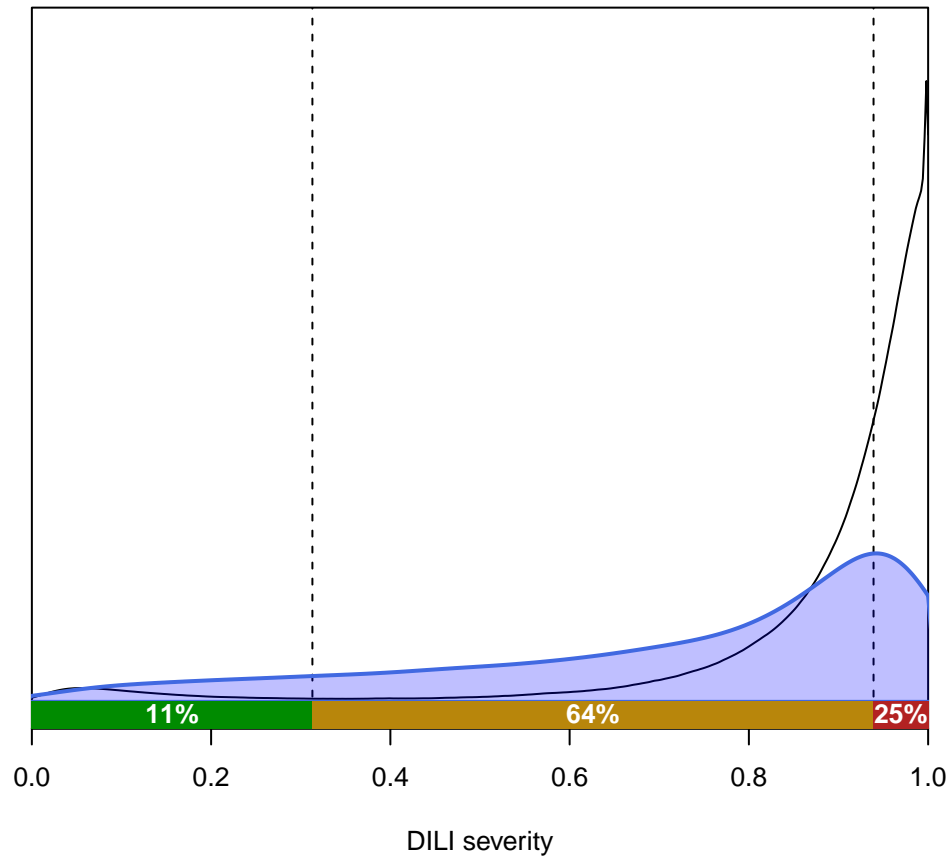


Assay result

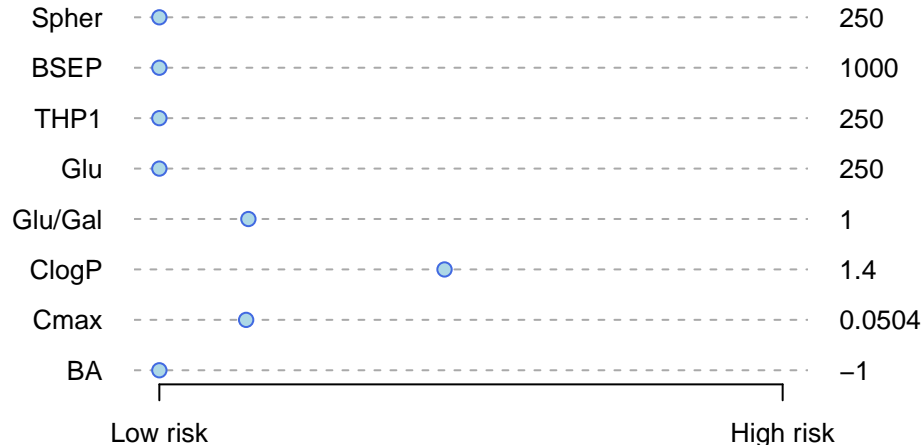
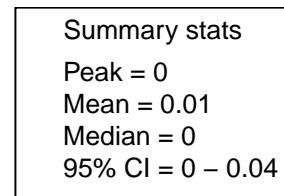
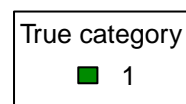
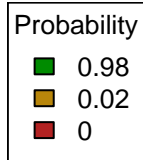
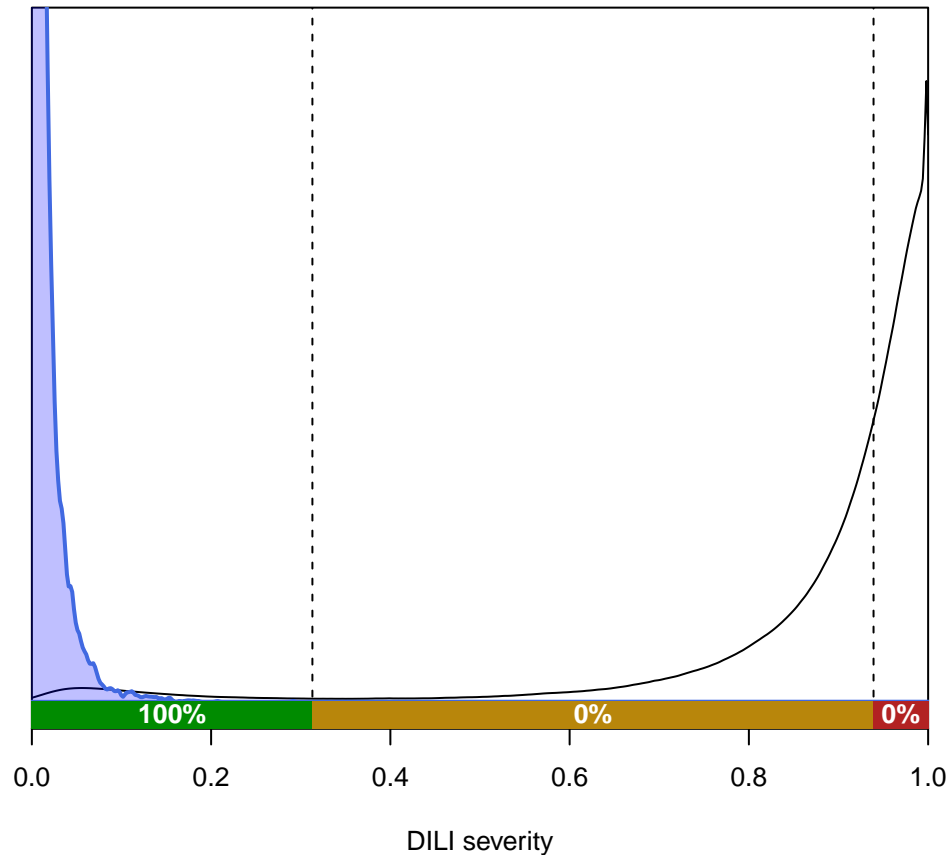
Flutamide



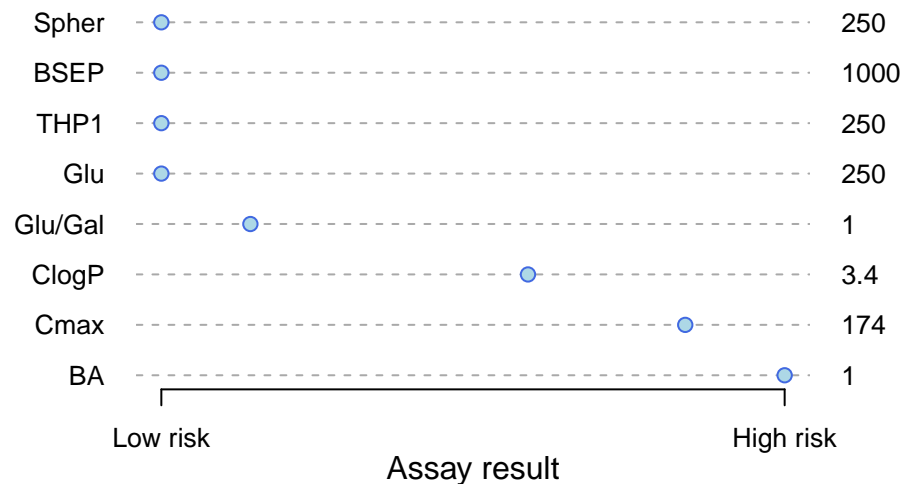
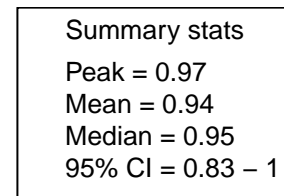
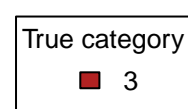
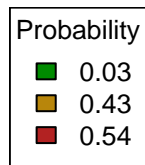
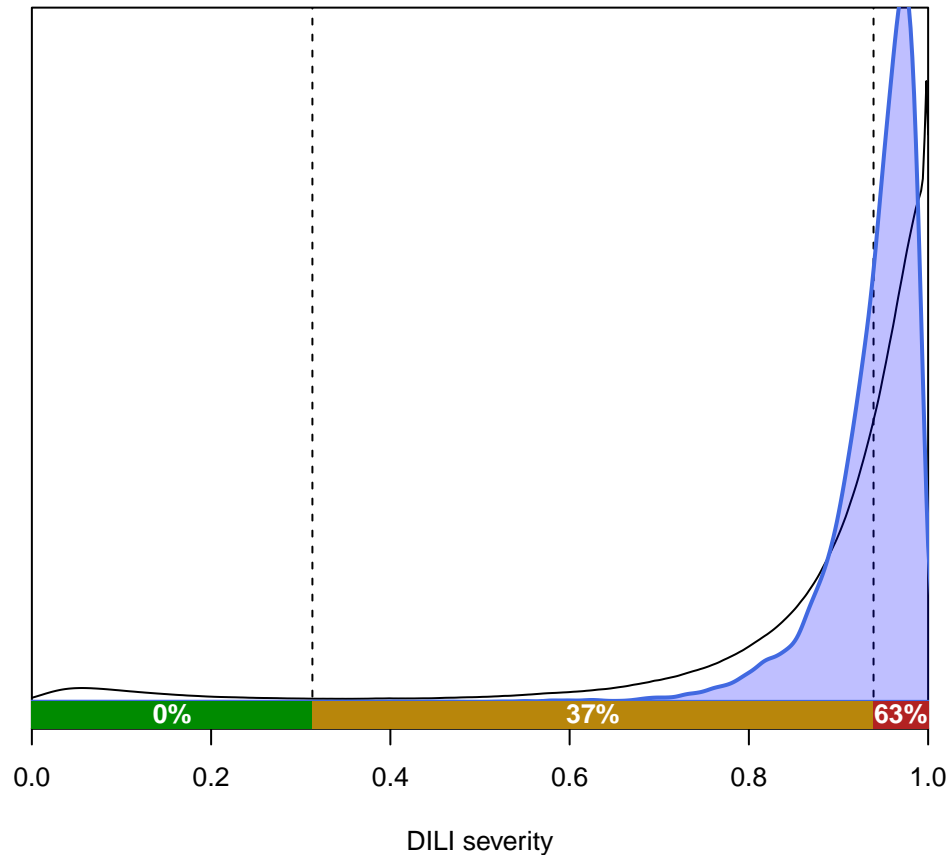
Furazolidone



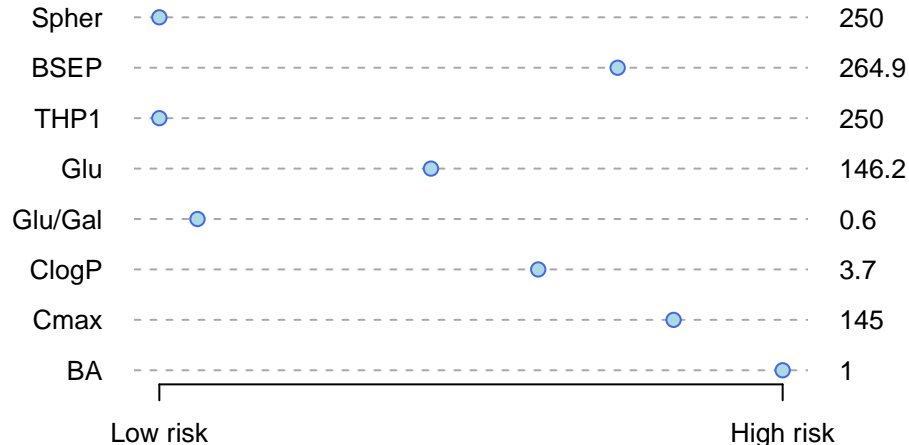
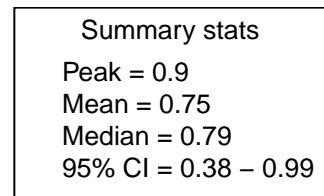
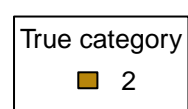
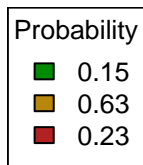
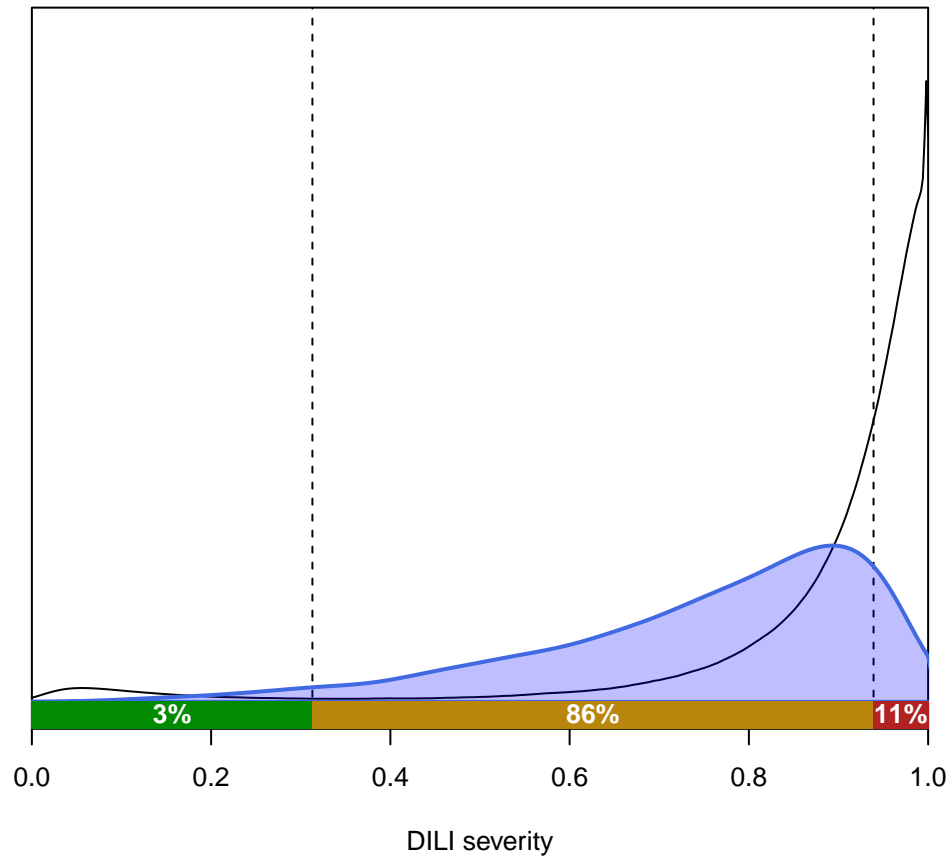
Guanethidine



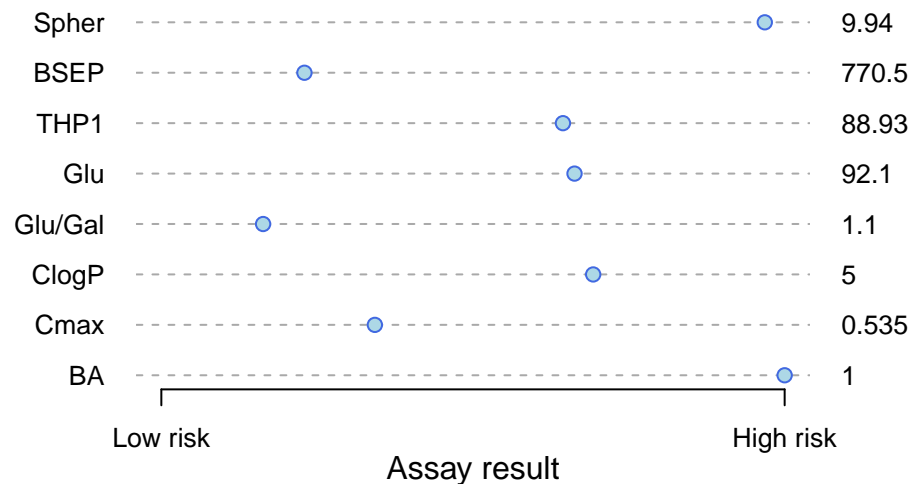
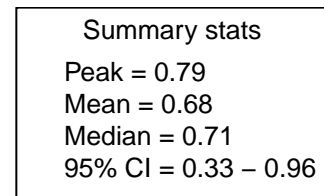
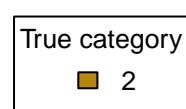
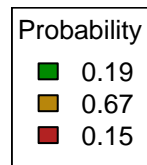
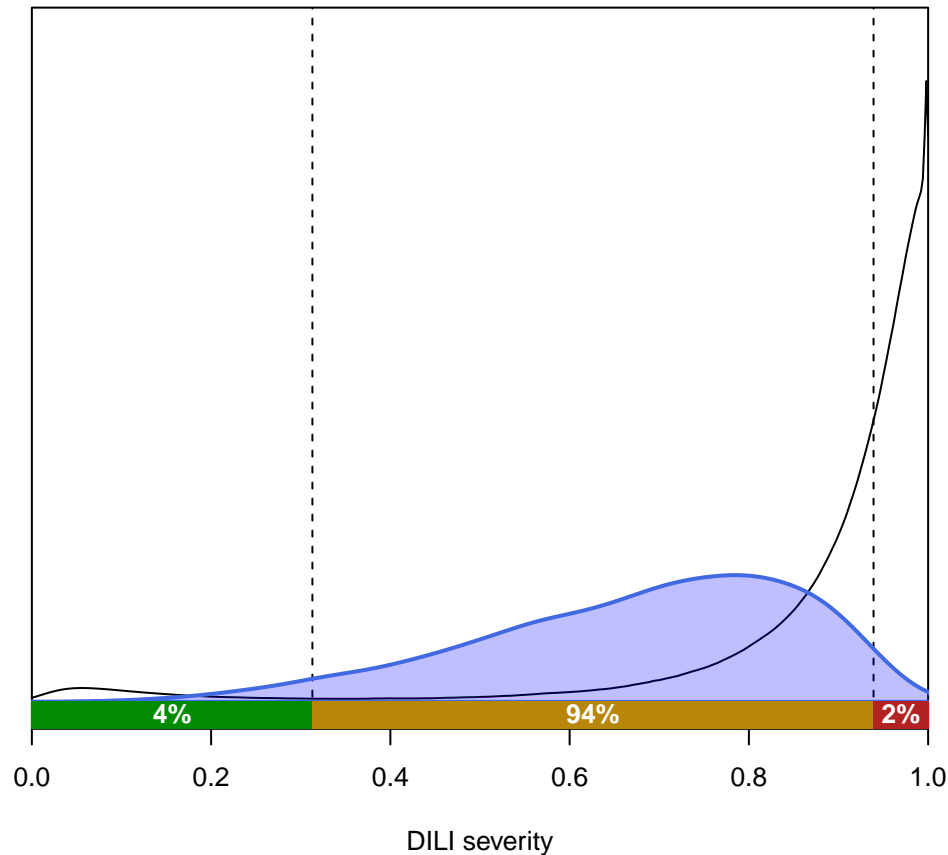
Ibuprofen



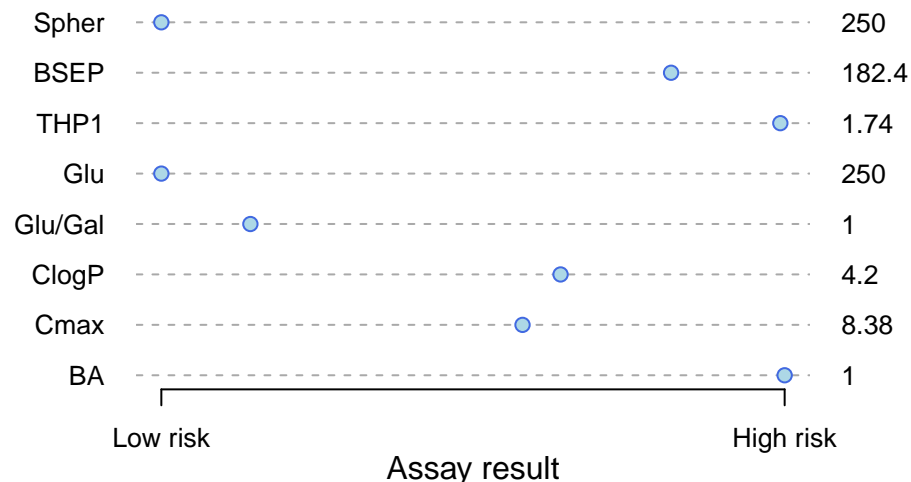
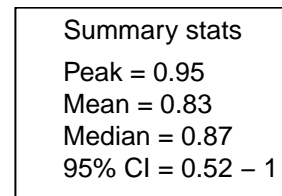
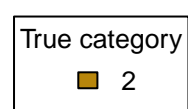
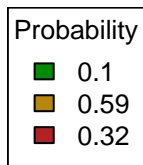
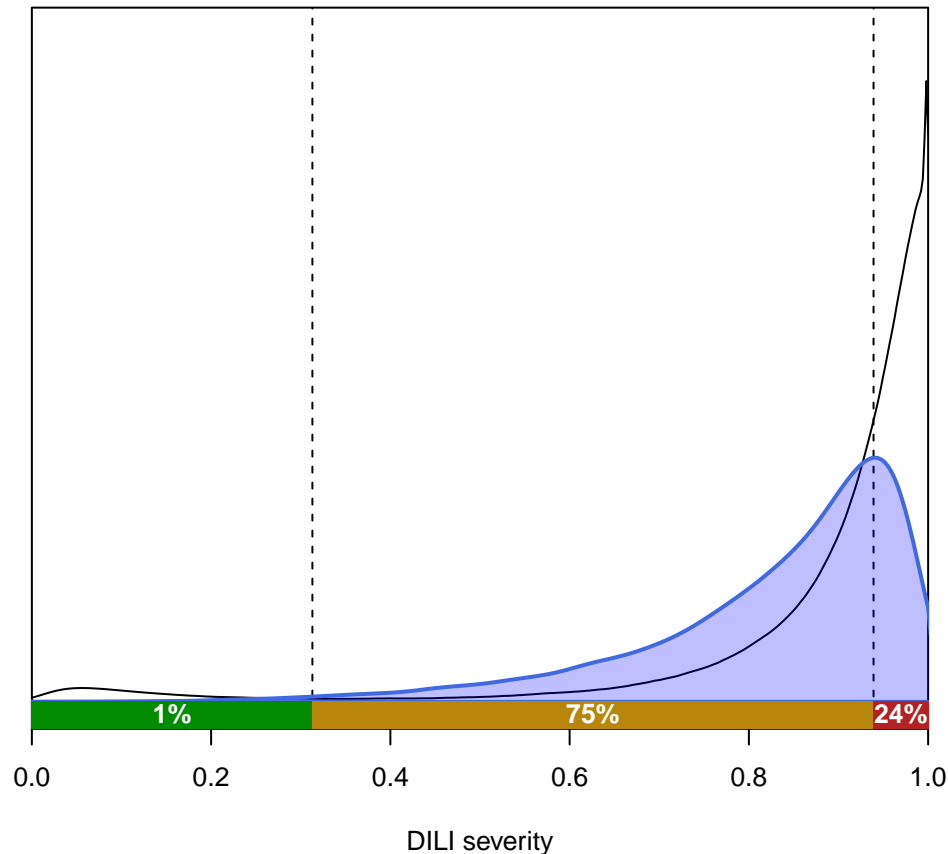
Ibuprofen



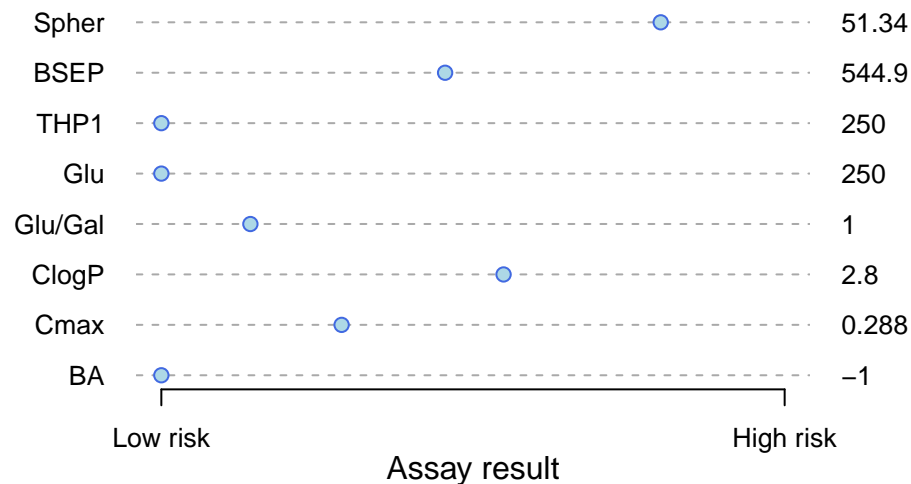
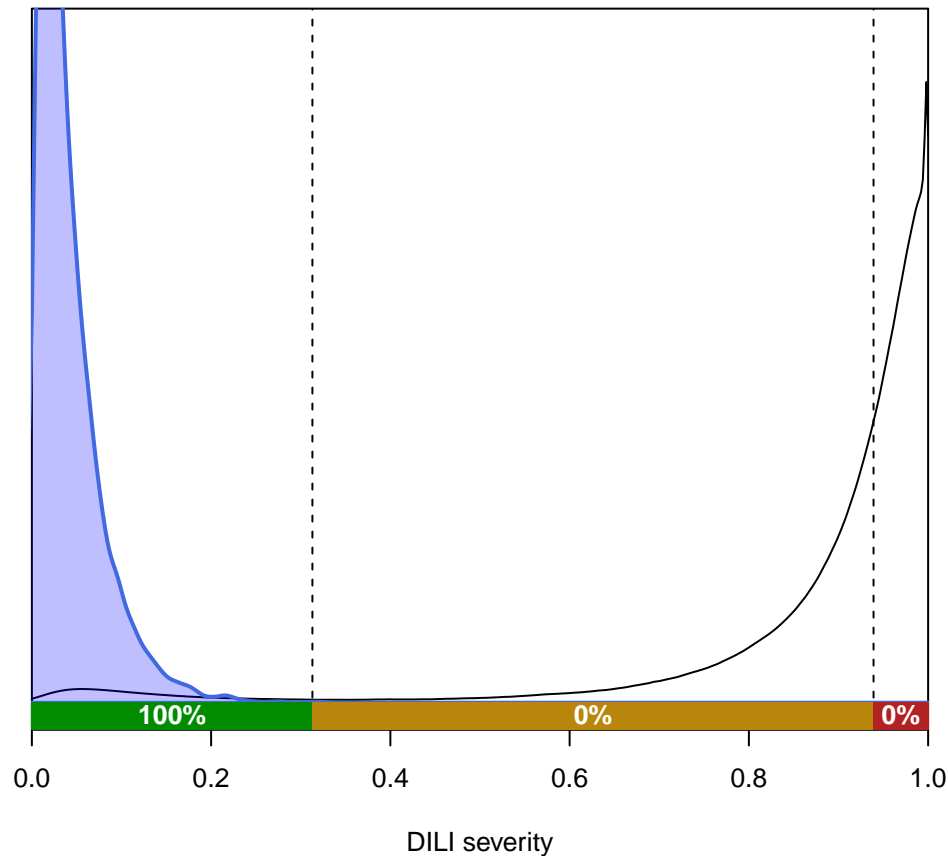
Imipramine



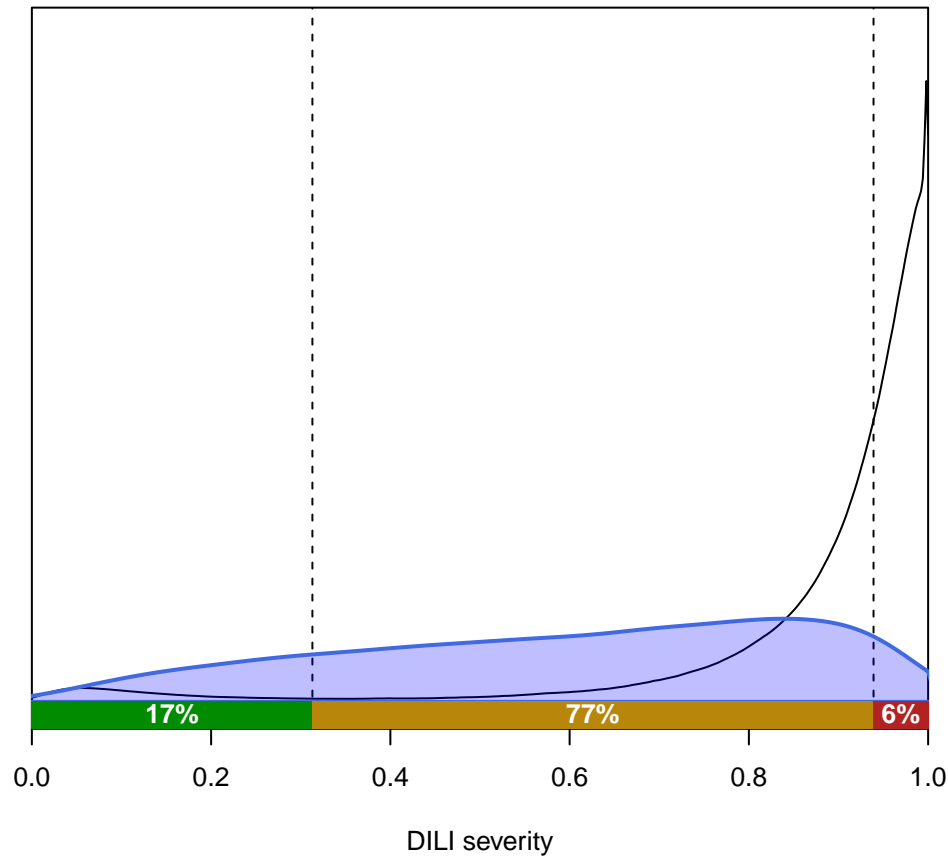
Indomethacin



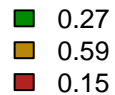
Indoramin



Itraconazole



Probability

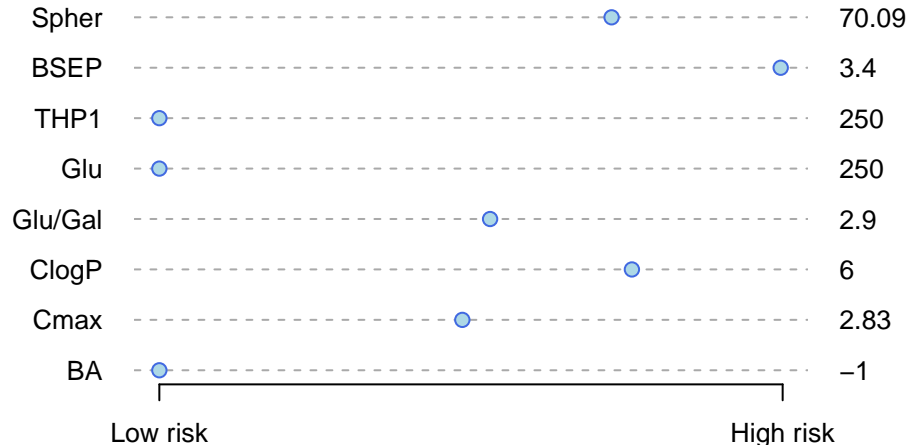


True category

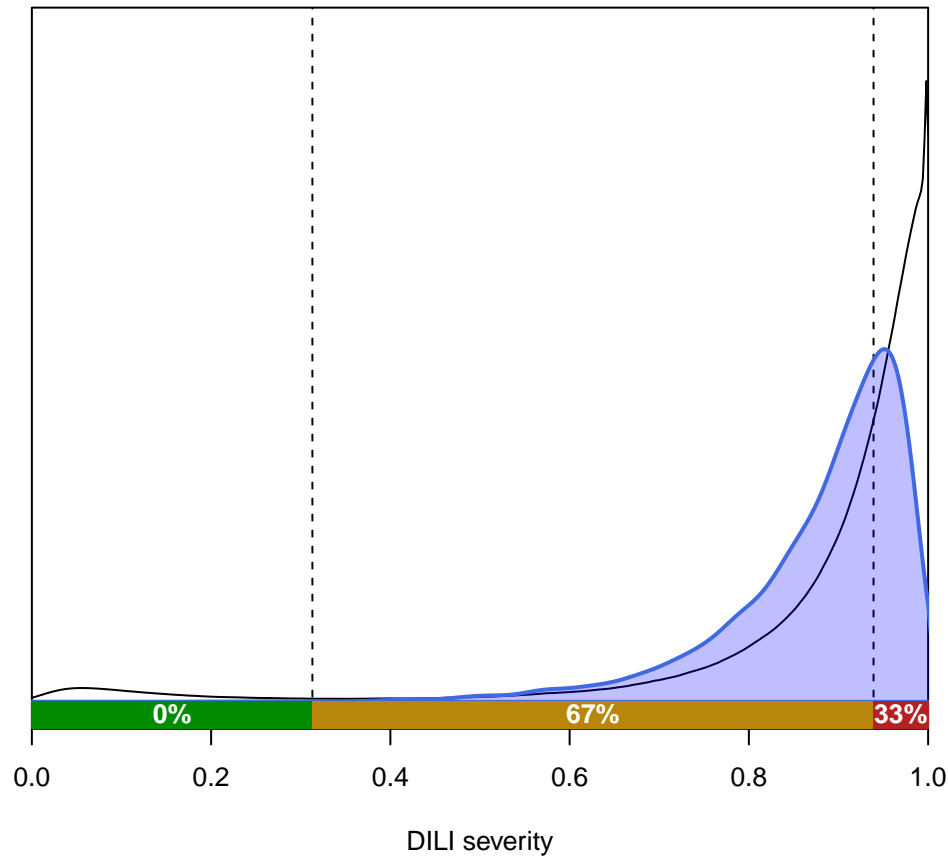


Summary stats

Peak = 0.84
Mean = 0.6
Median = 0.63
95% CI = 0.15 – 0.99



Ketoconazole



Probability

- 0.06
- 0.57
- 0.37

True category

3

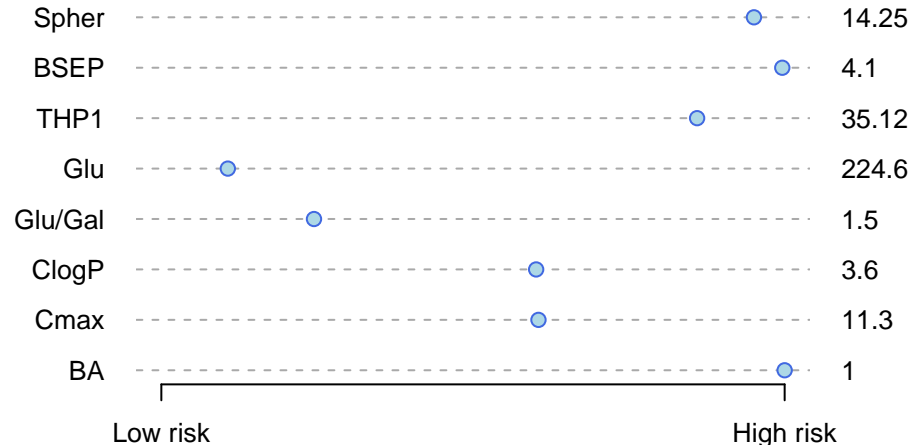
Summary stats

Peak = 0.95

Mean = 0.88

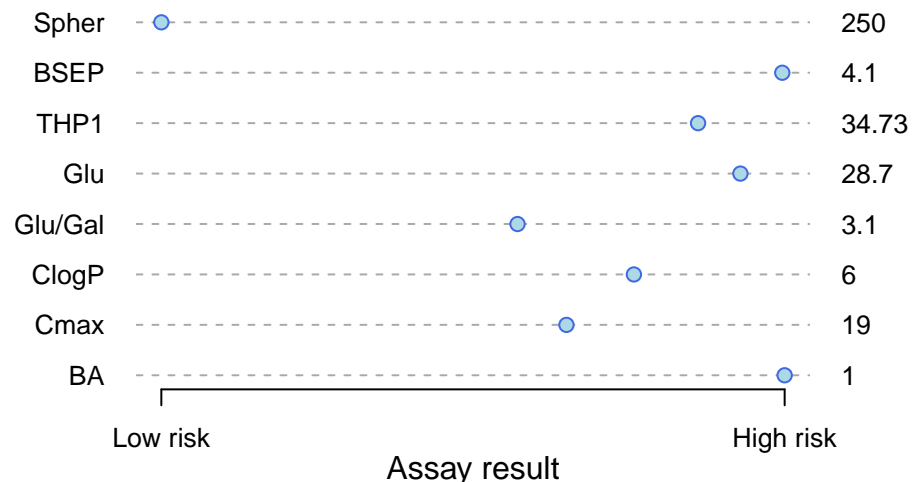
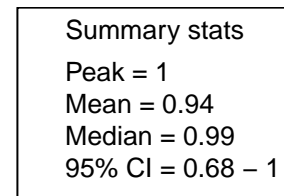
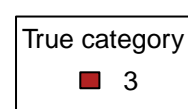
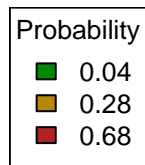
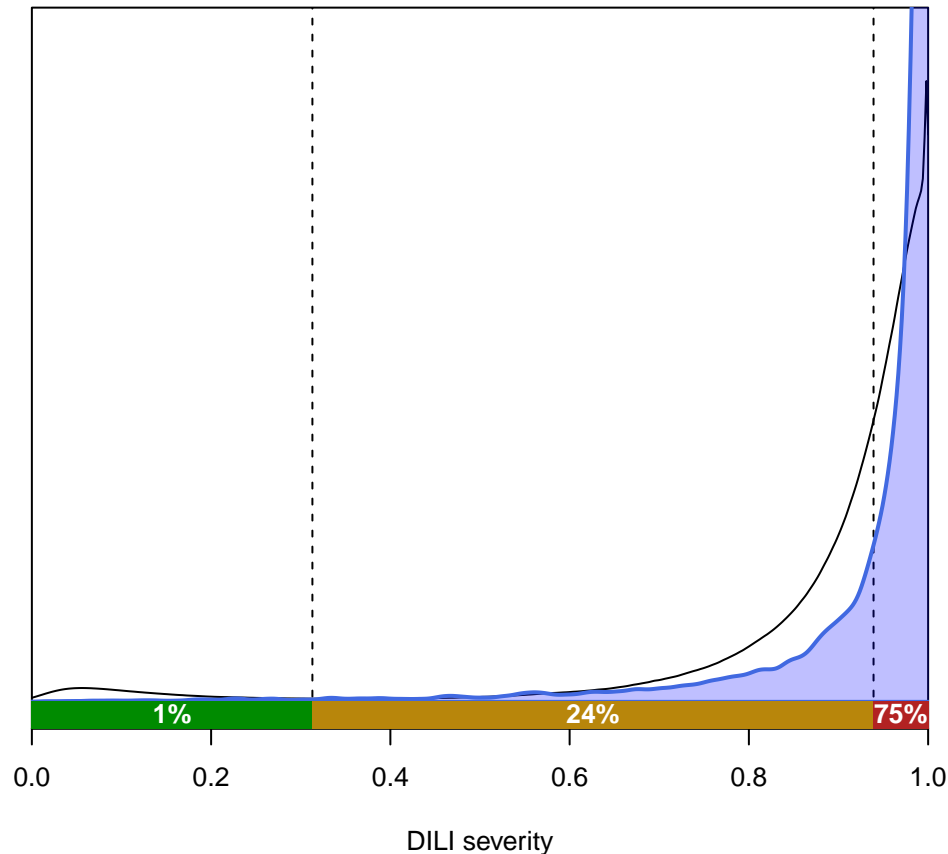
Median = 0.91

95% CI = 0.67 - 1

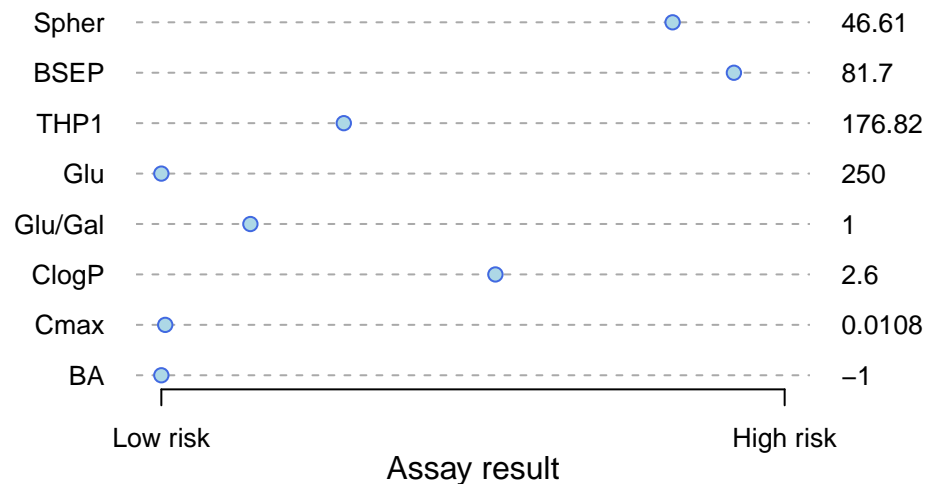
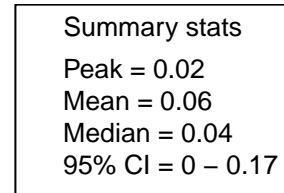
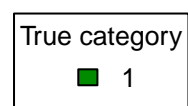
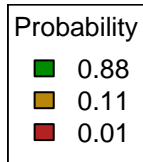
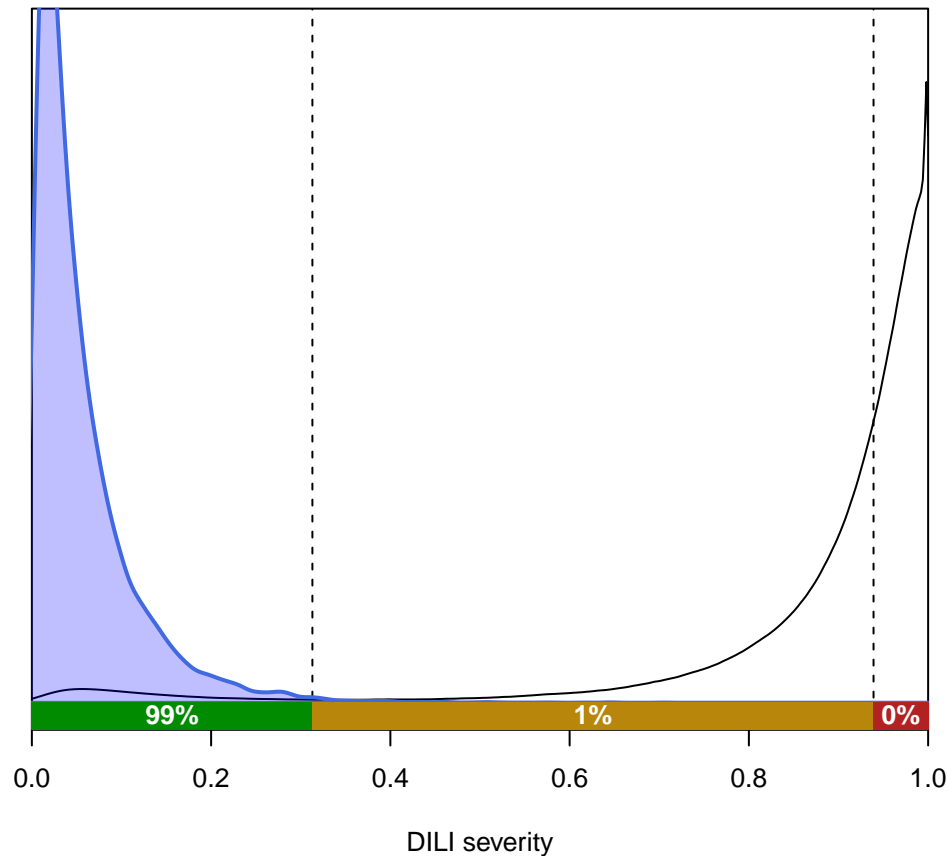


Assay result

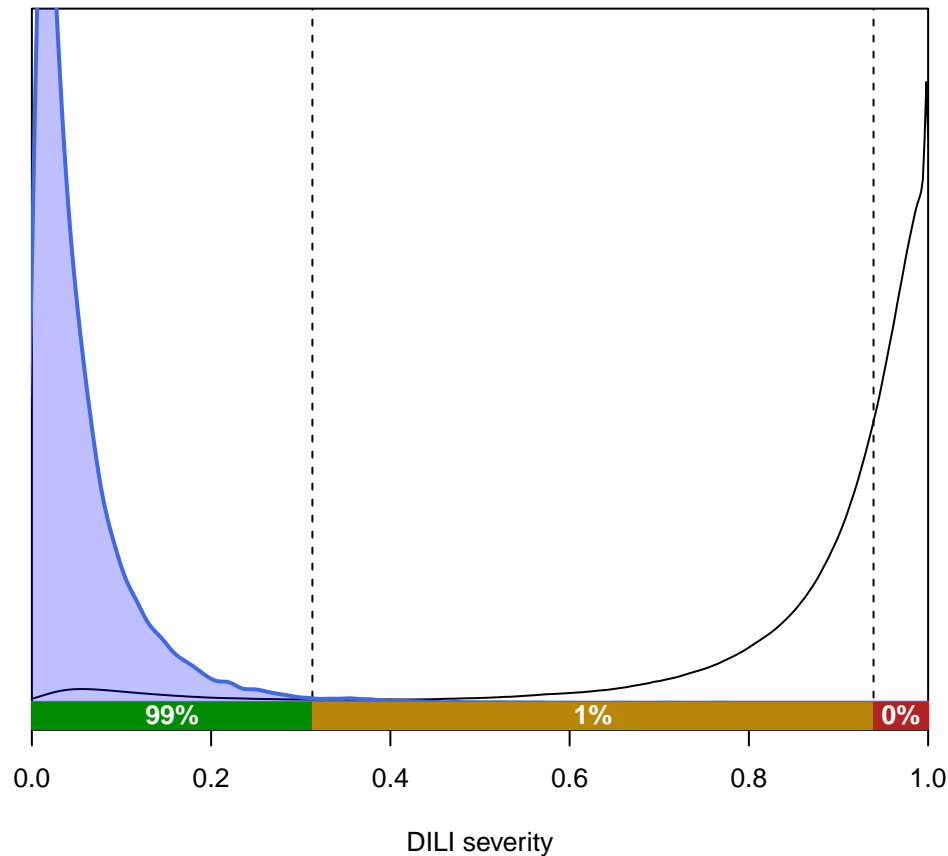
Lapatinib



Liothyronine



Mecamylamine



Probability

- 0.89
- 0.1
- 0

True category

1

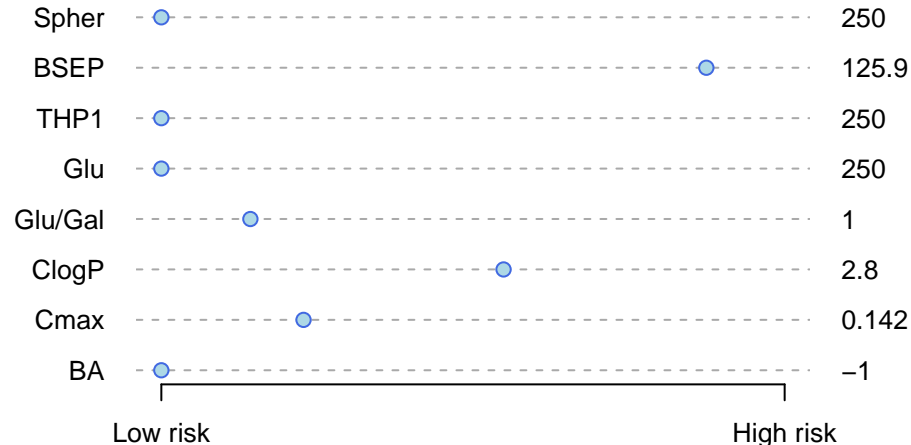
Summary stats

Peak = 0.01

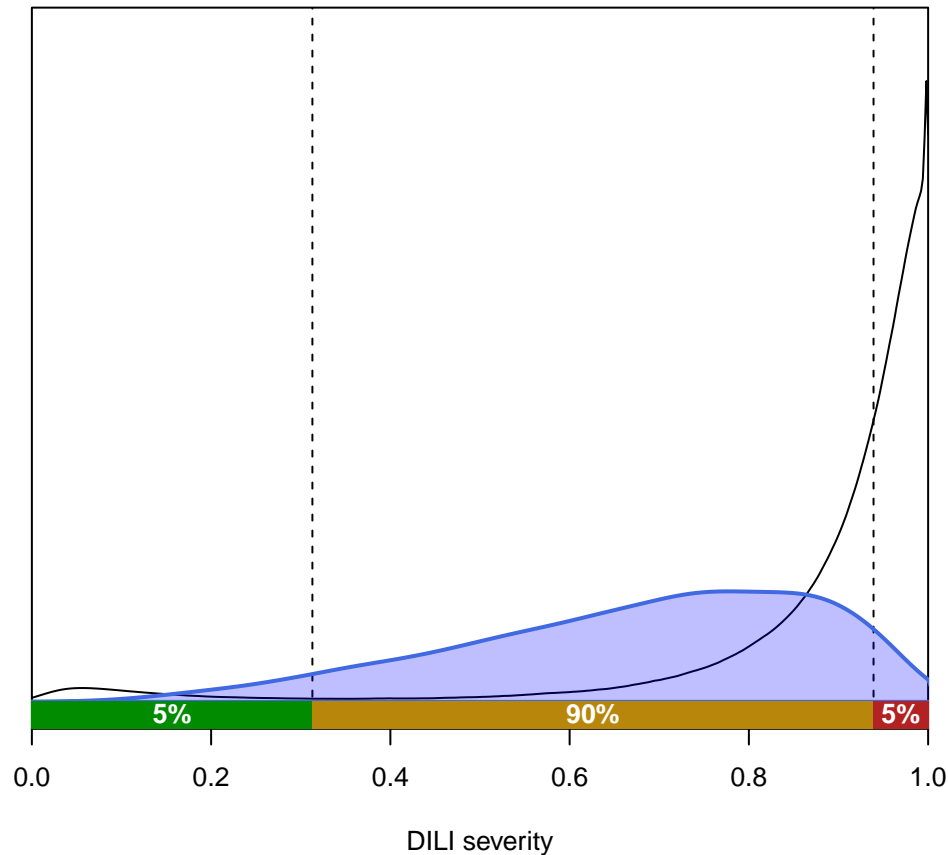
Mean = 0.05

Median = 0.03

95% CI = 0 – 0.17



Meclofenamate



Probability

- 0.2
- 0.64
- 0.16

True category

1

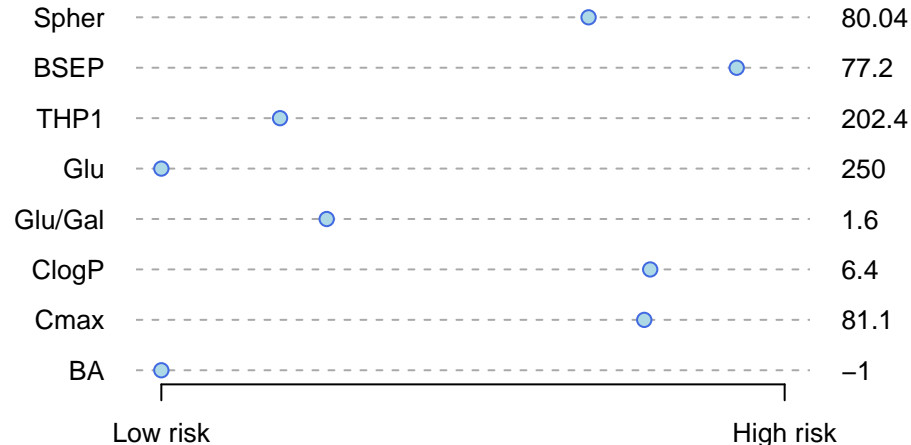
Summary stats

Peak = 0.76

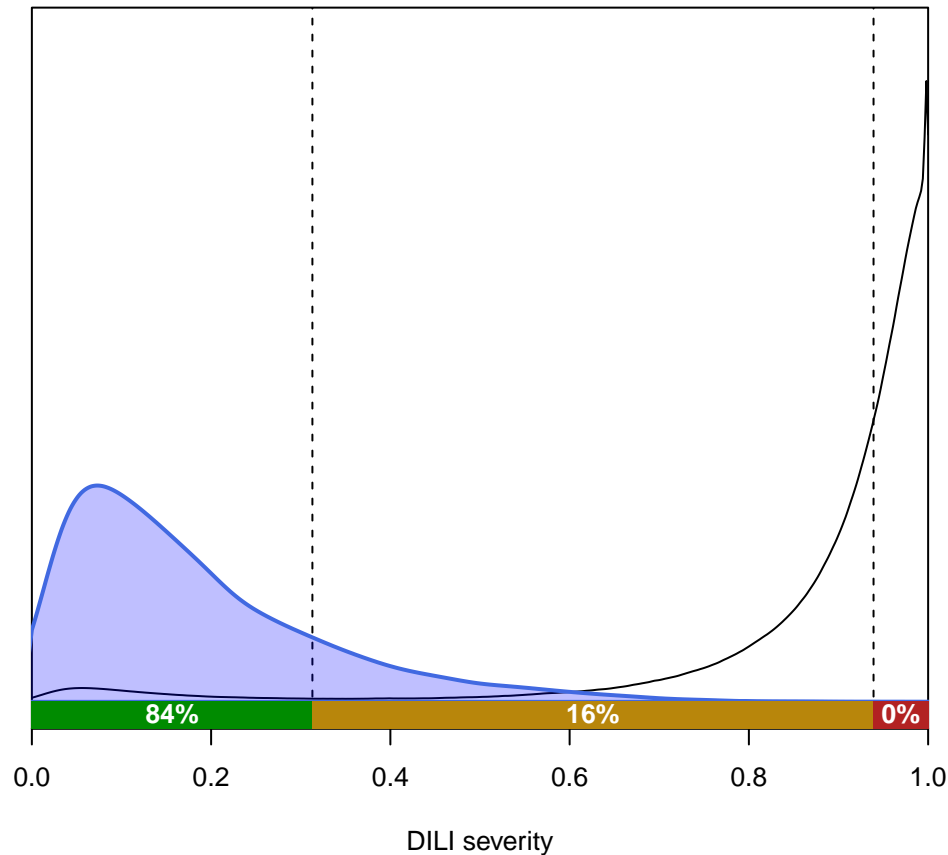
Mean = 0.68

Median = 0.71

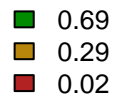
95% CI = 0.3 – 0.98



Metergoline



Probability



True category



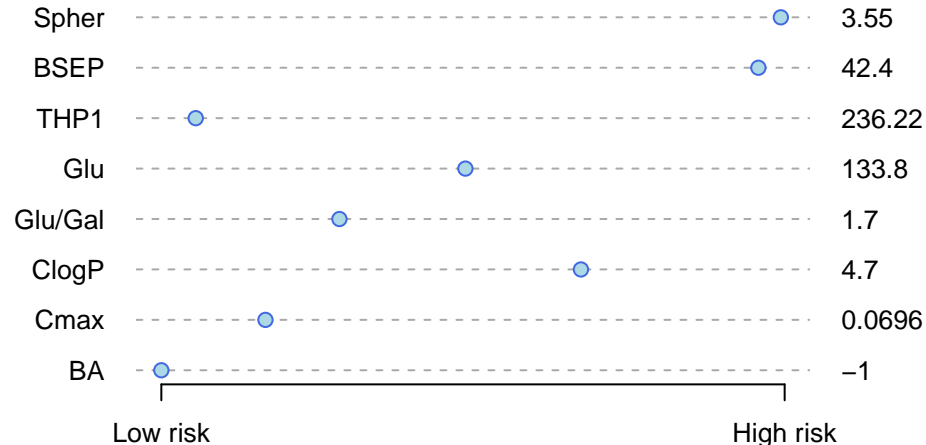
Summary stats

Peak = 0.07

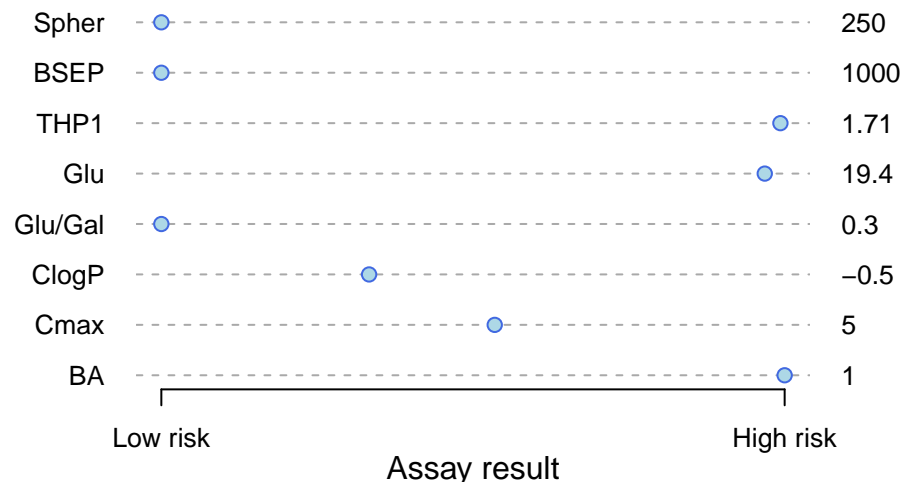
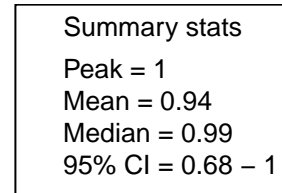
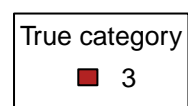
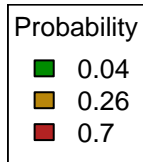
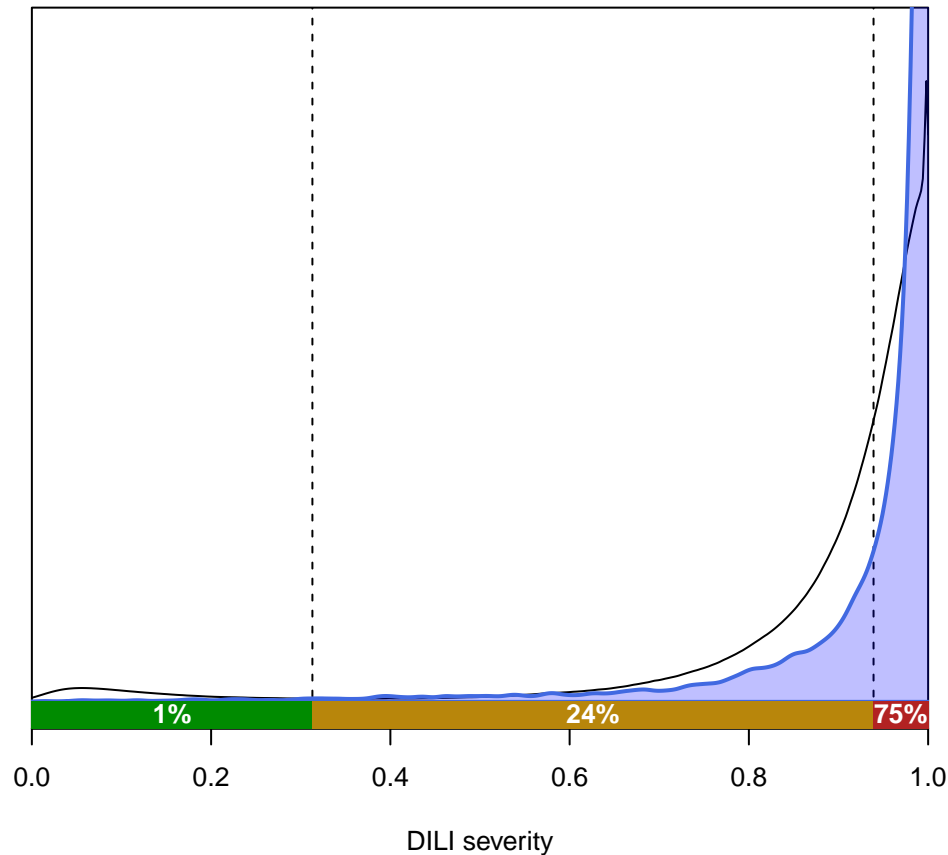
Mean = 0.18

Median = 0.14

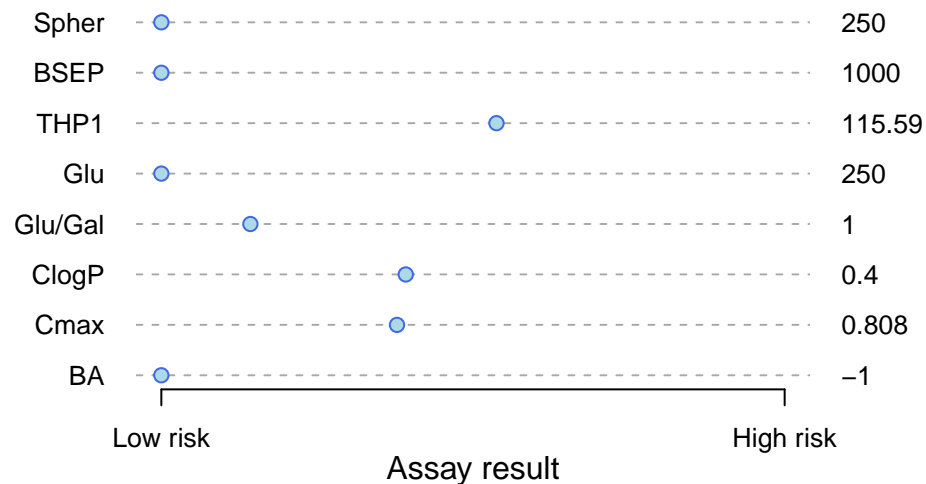
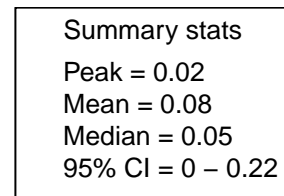
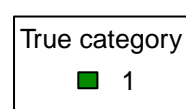
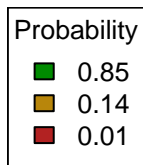
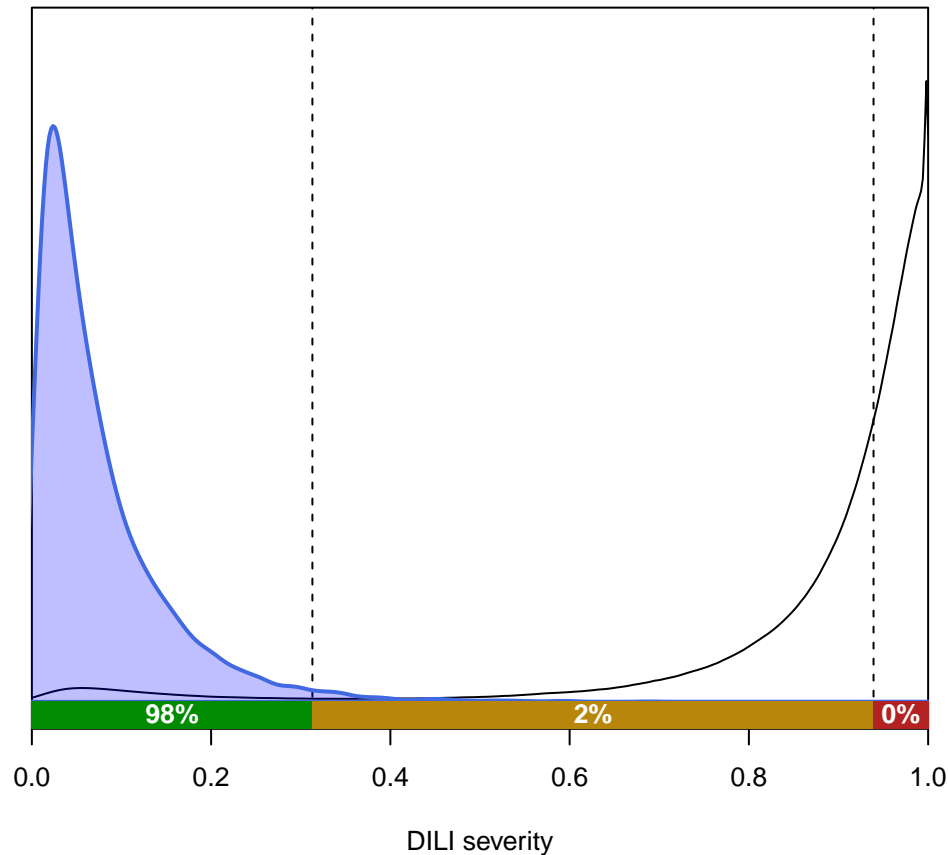
95% CI = 0 – 0.47



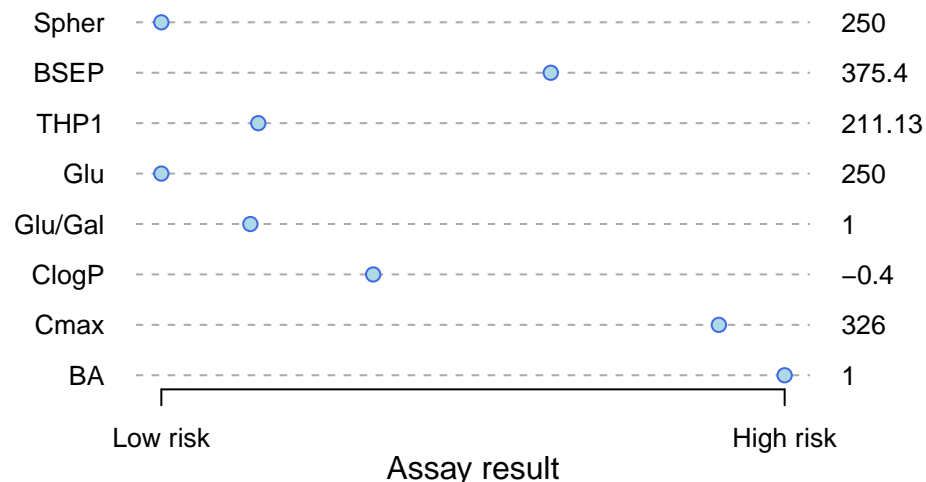
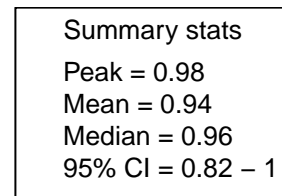
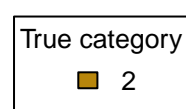
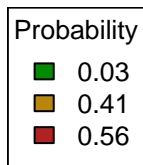
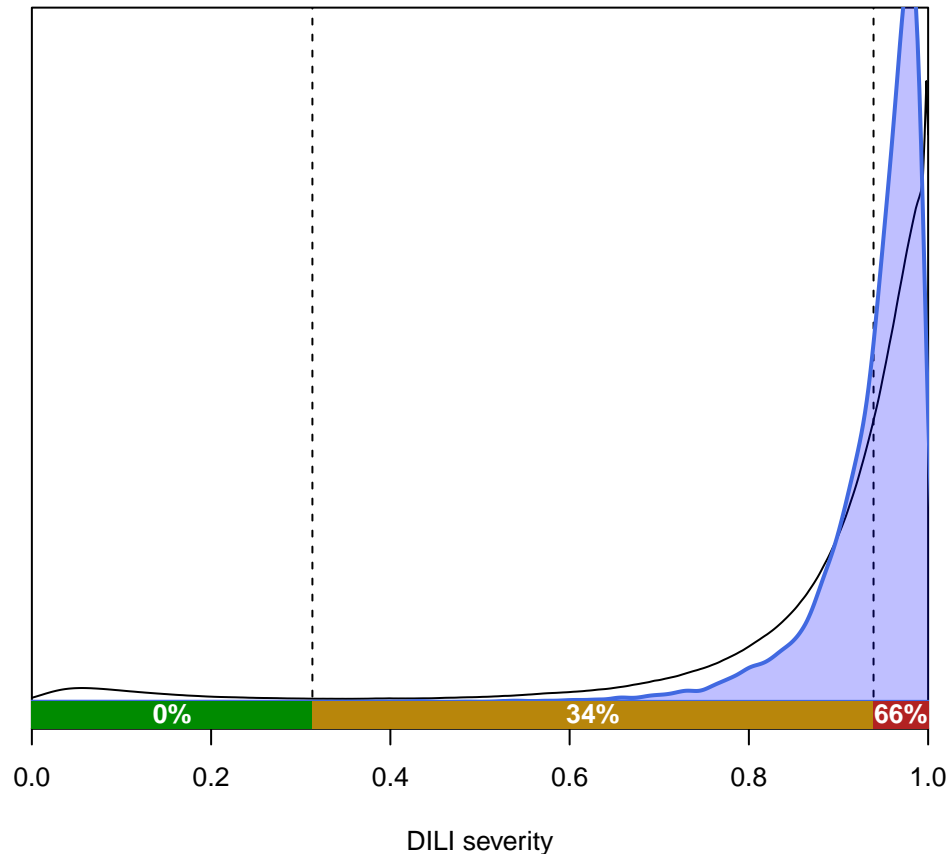
Methotrexate



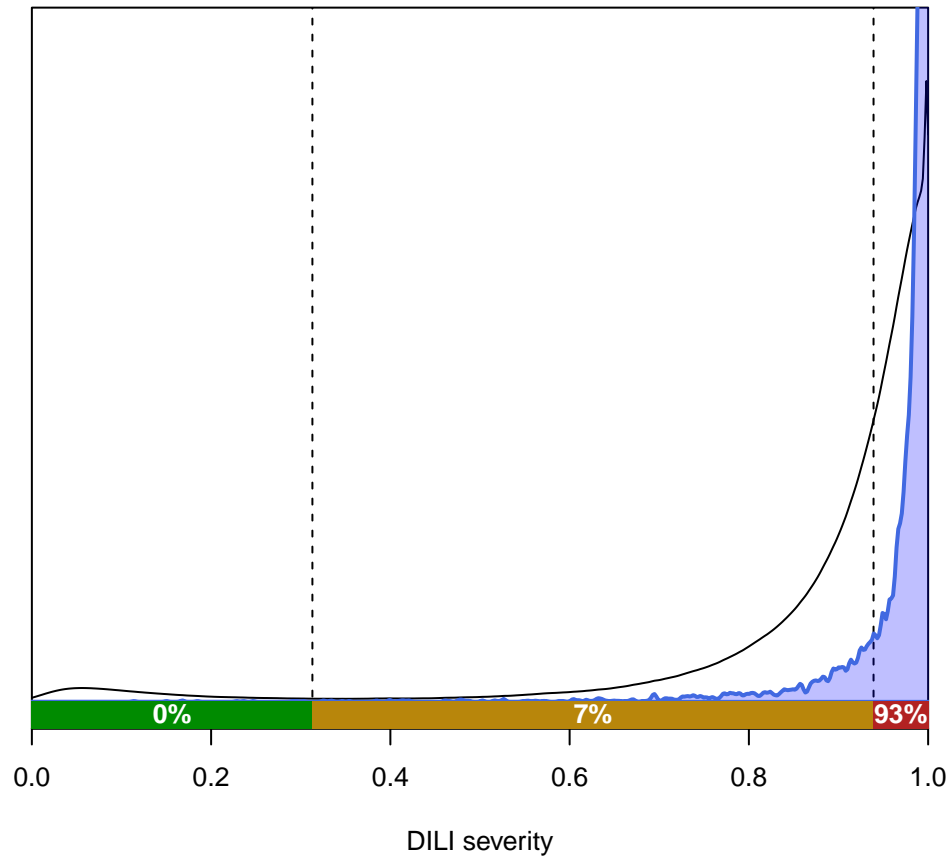
Nadolol



Naproxen



Nefazodone



Probability

- 0.01
- 0.12
- 0.87

True category

3

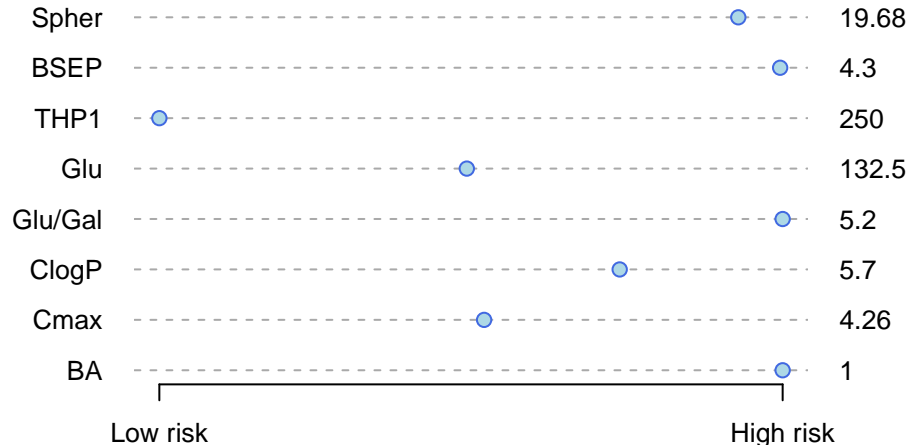
Summary stats

Peak = 1

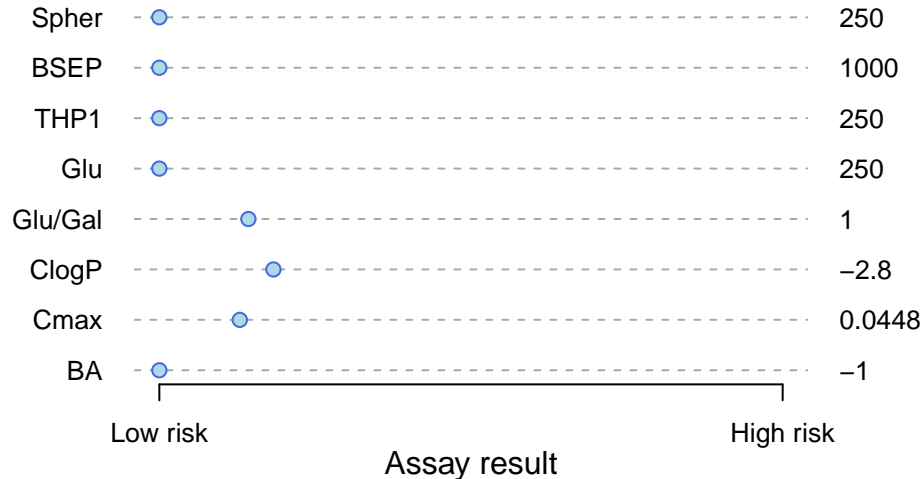
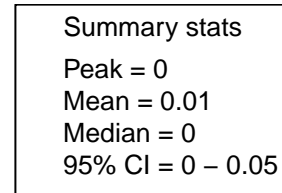
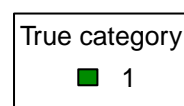
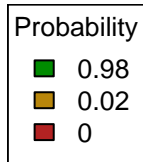
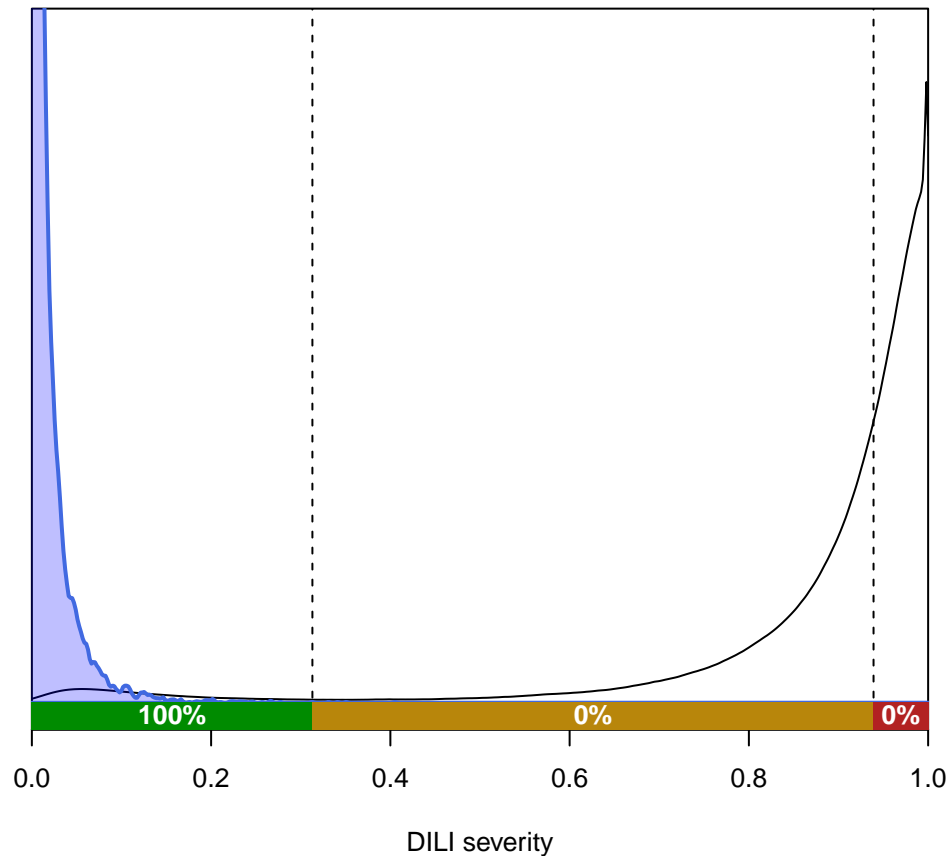
Mean = 0.98

Median = 1

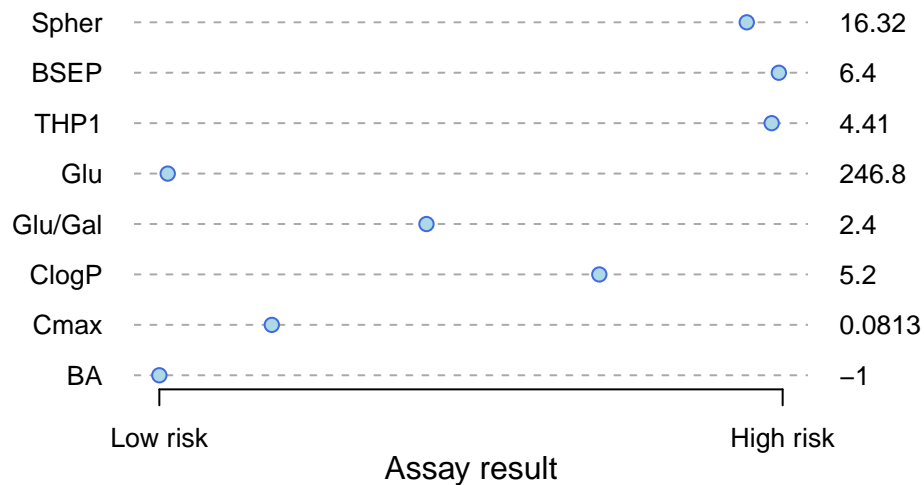
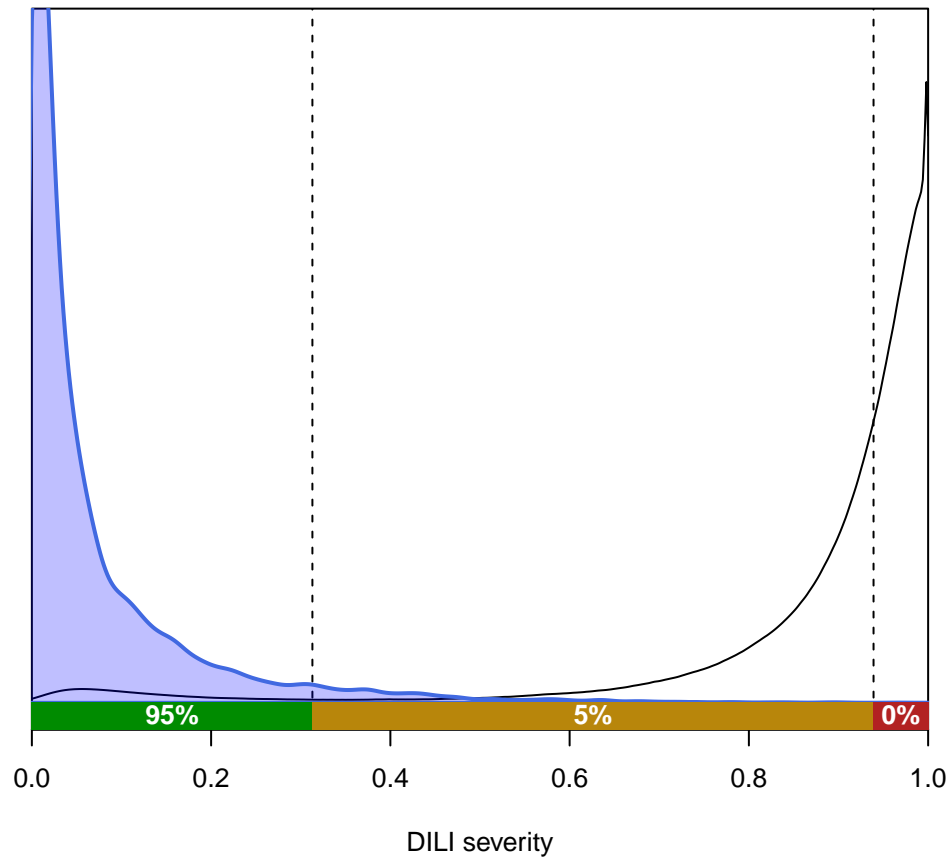
95% CI = 0.91 – 1



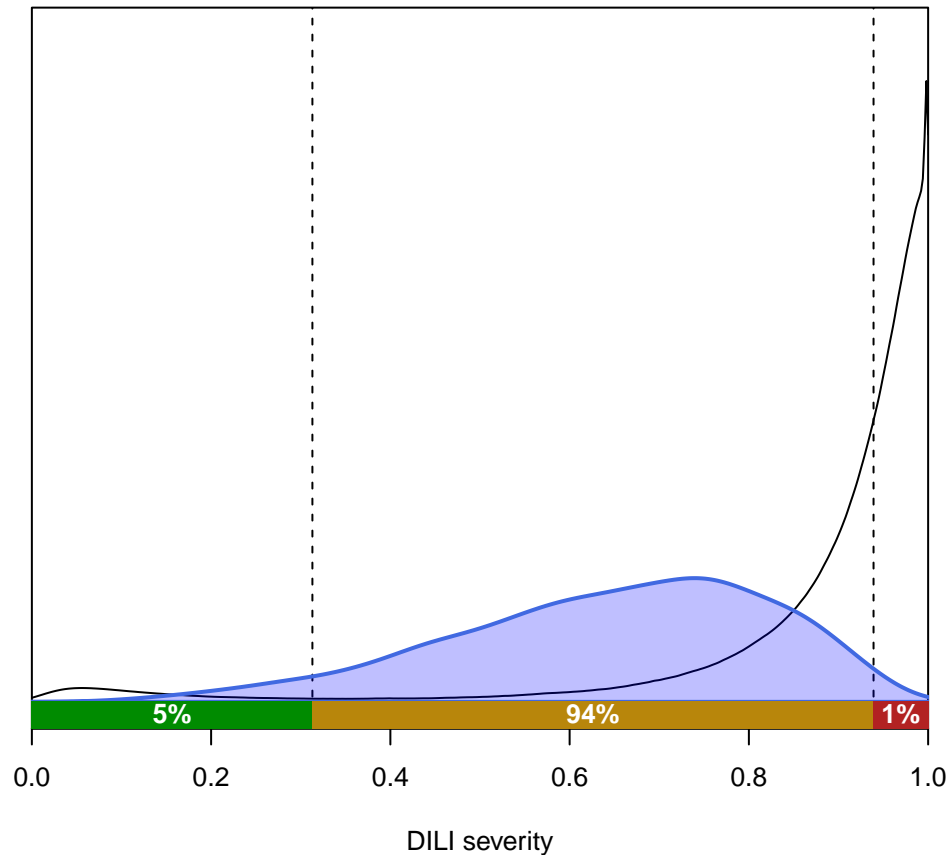
Neostigmine



Nicardipine



Nifedipine



Probability

- 0.21
- 0.66
- 0.13

True category

2

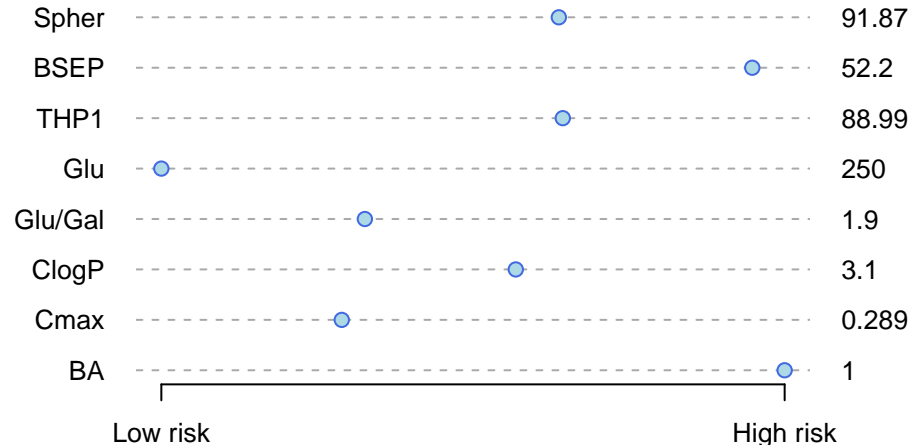
Summary stats

Peak = 0.74

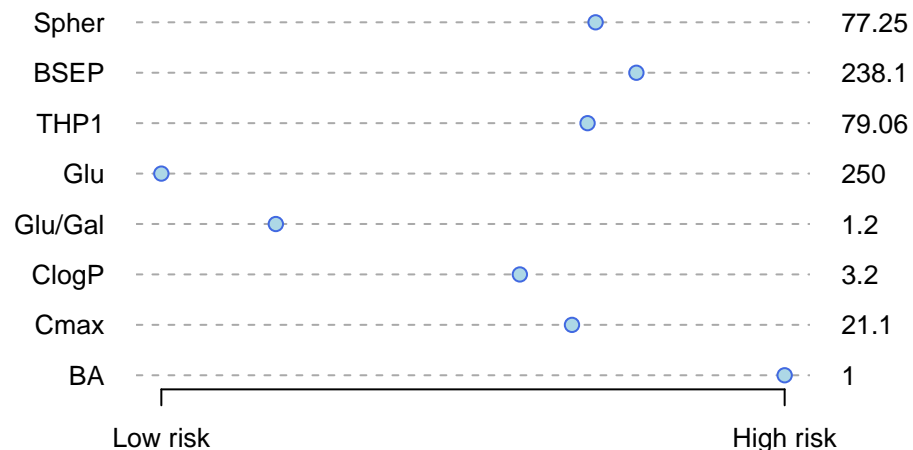
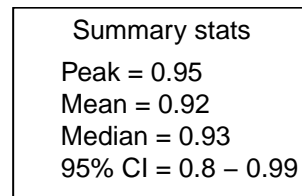
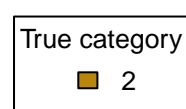
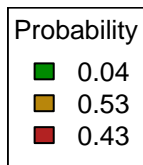
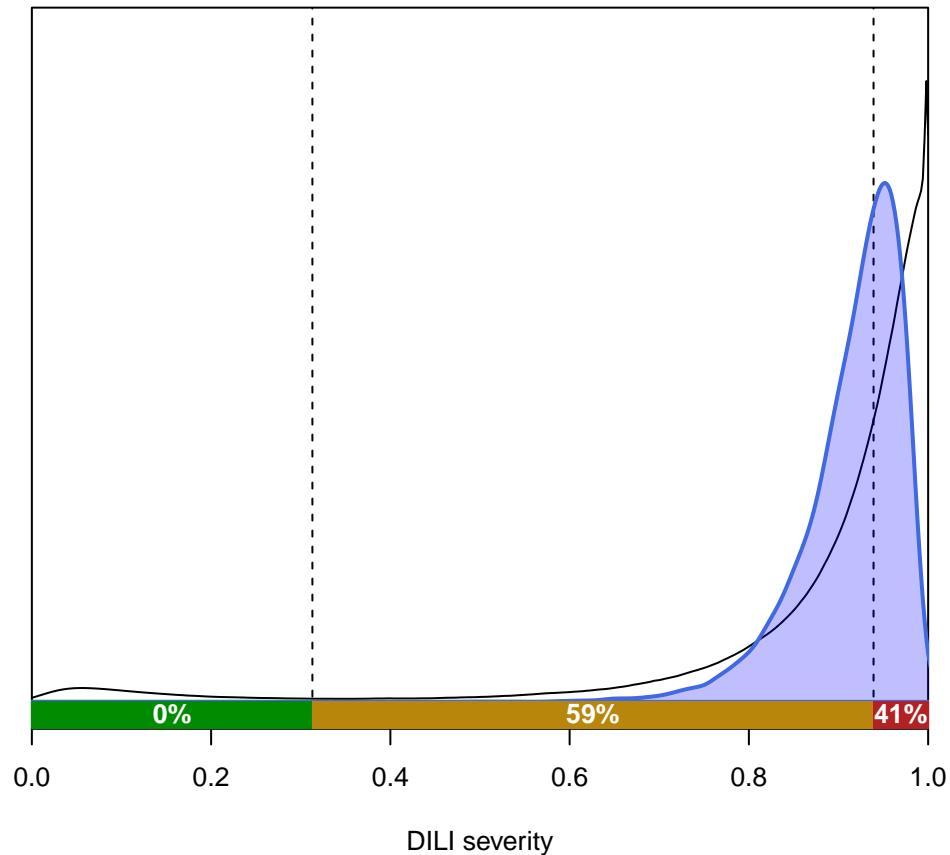
Mean = 0.65

Median = 0.67

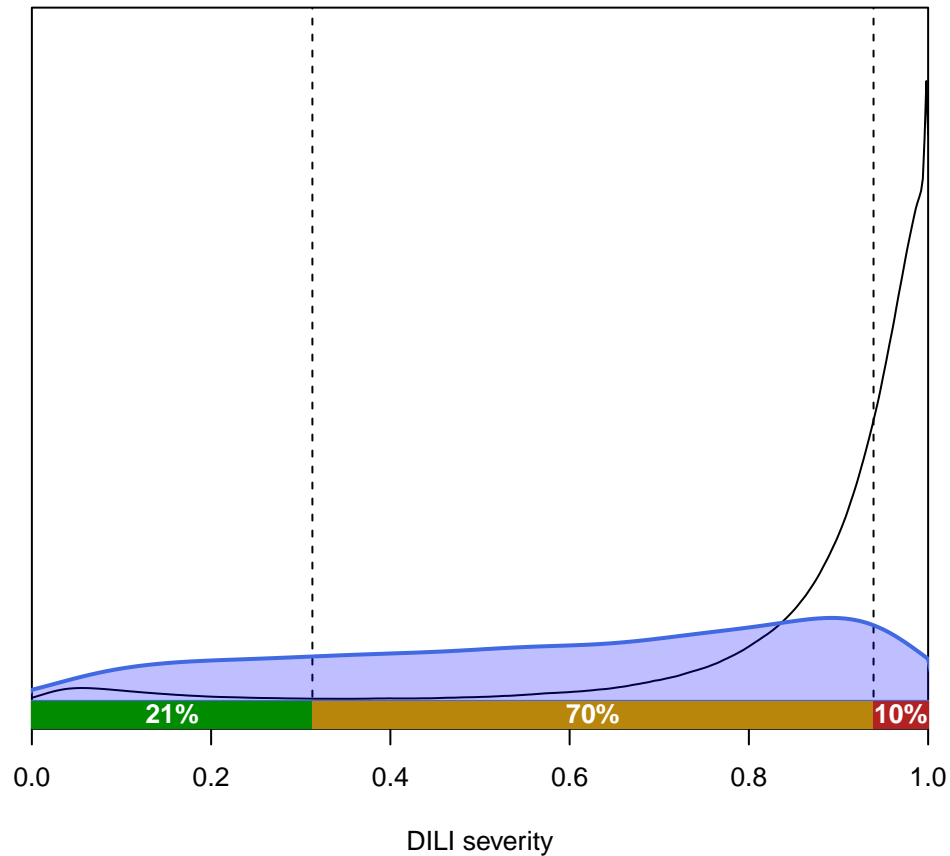
95% CI = 0.3 – 0.95



Nimesulide



Nitrofurantoin



Probability

- 0.28
- 0.56
- 0.17

True category

2

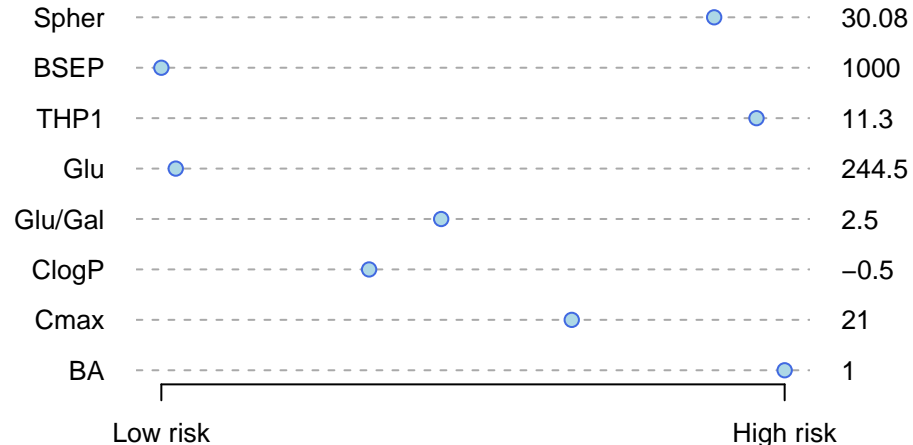
Summary stats

Peak = 0.9

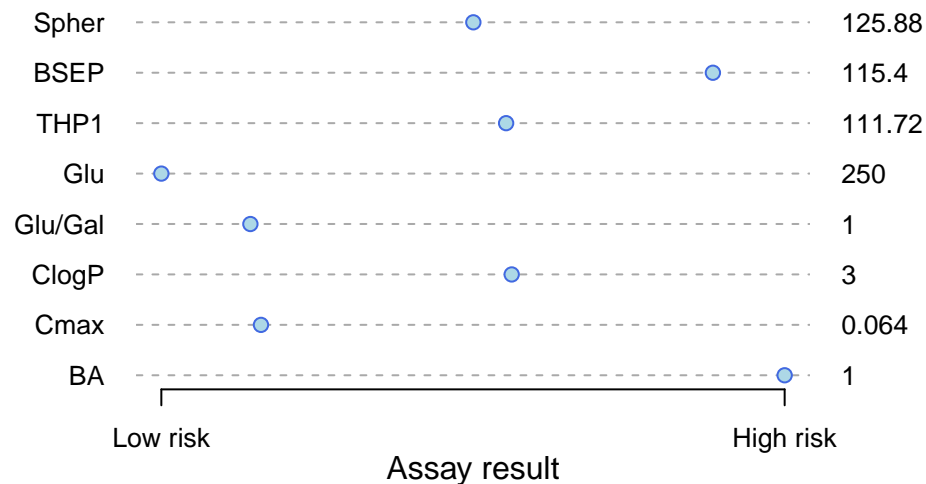
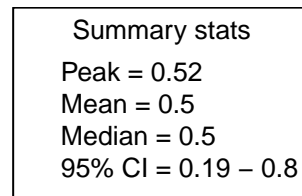
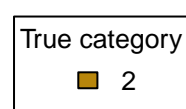
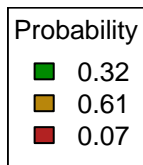
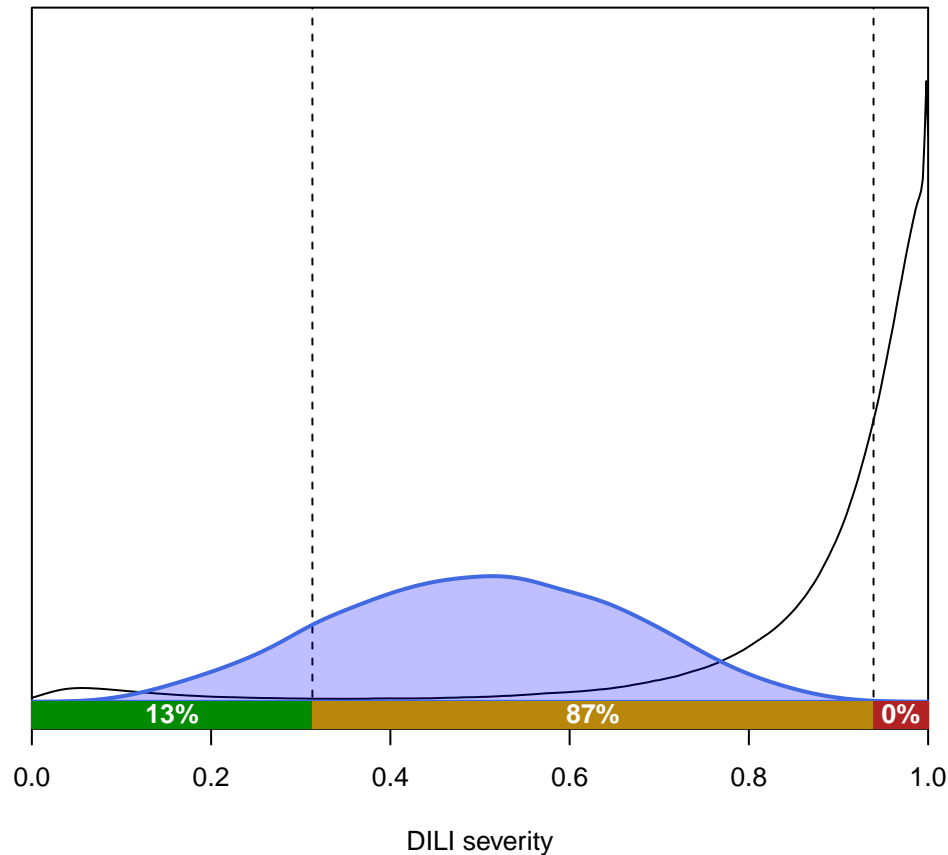
Mean = 0.59

Median = 0.63

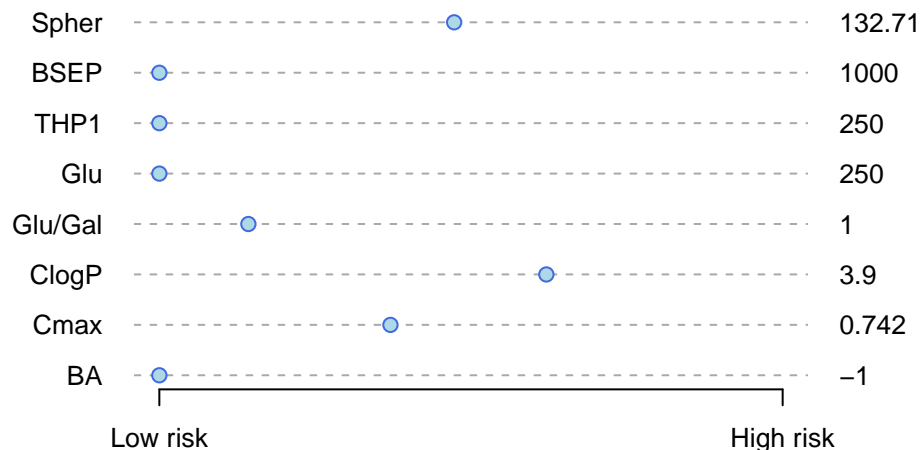
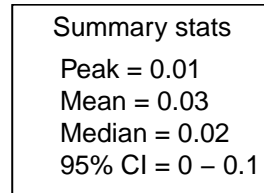
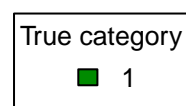
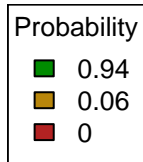
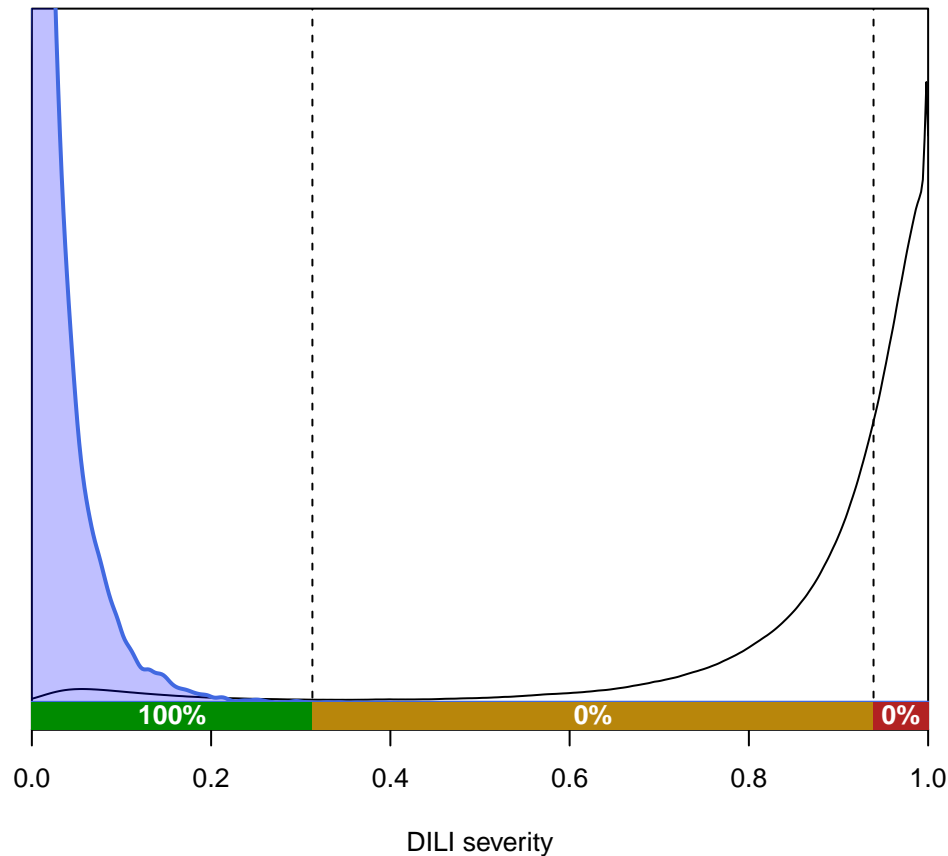
95% CI = 0.1 – 1



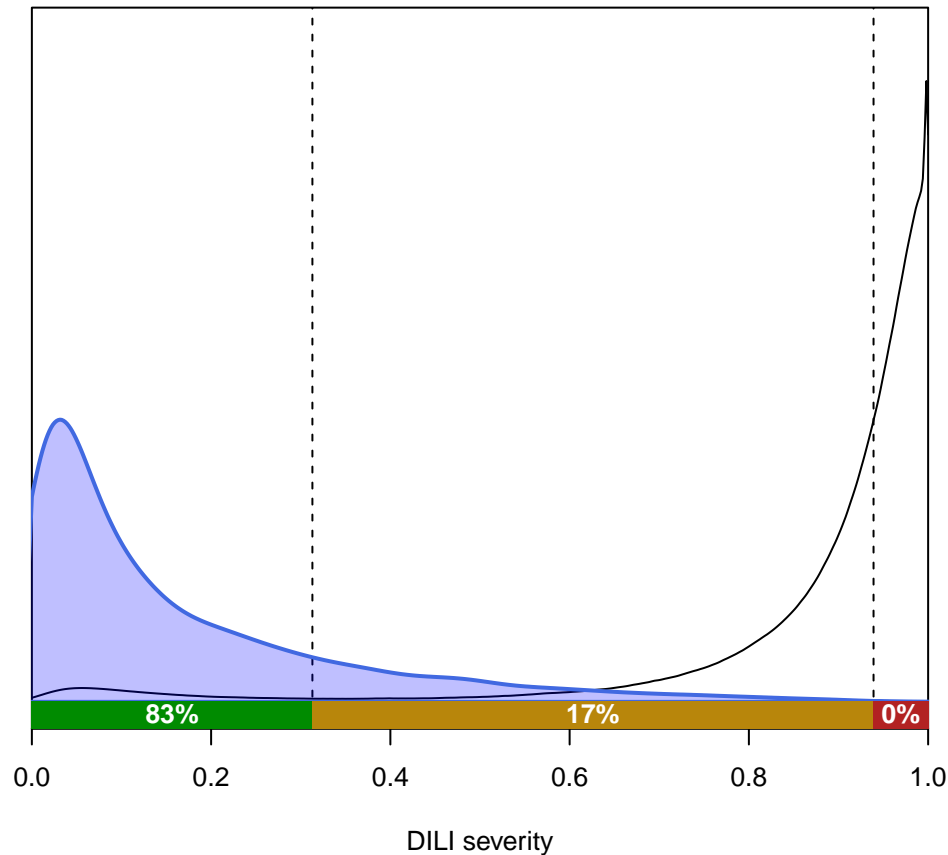
Olanzapine



Orphenadrine



Oxybutynin



Probability

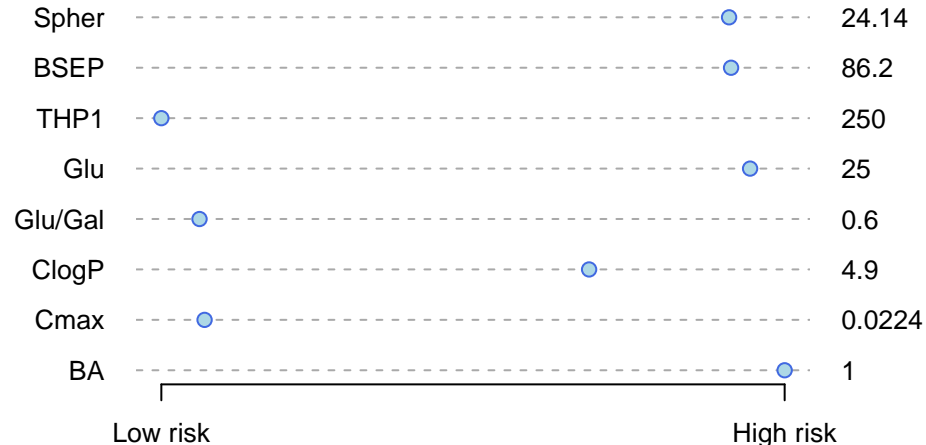


True category

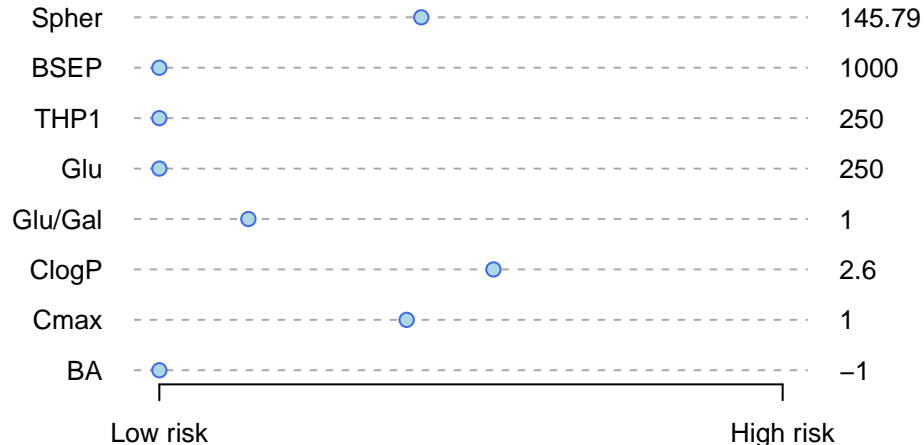
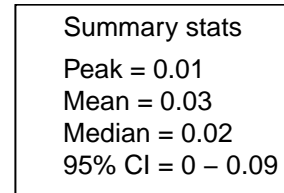
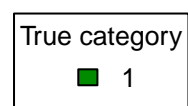
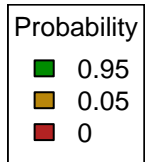
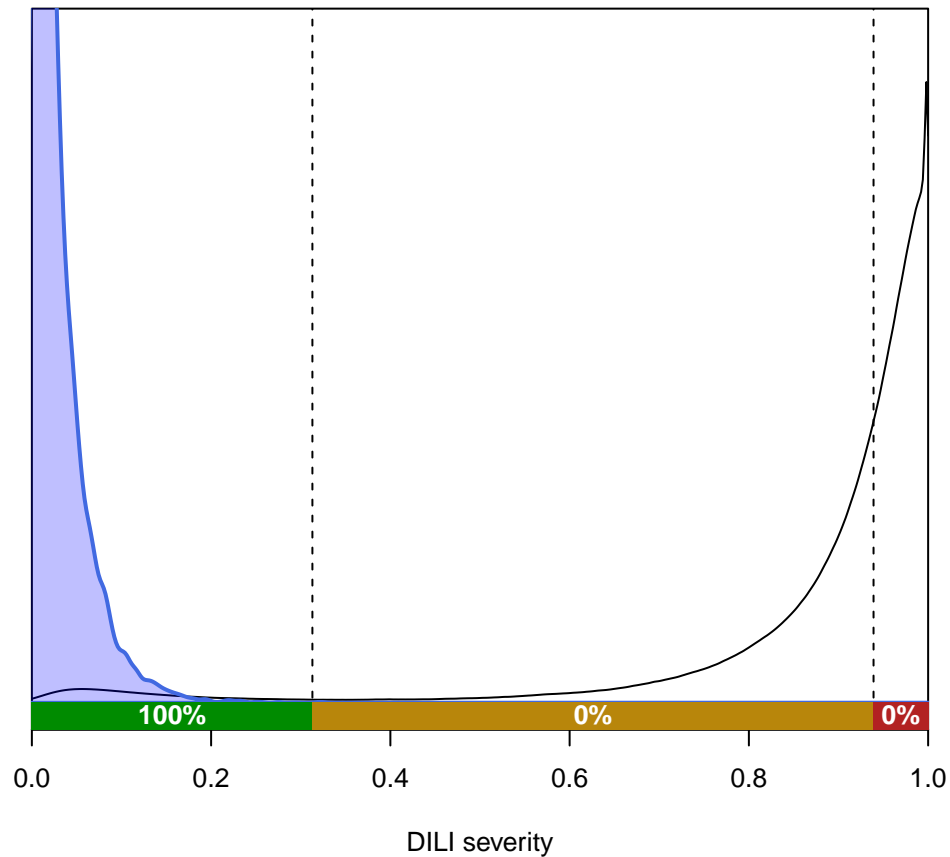


Summary stats

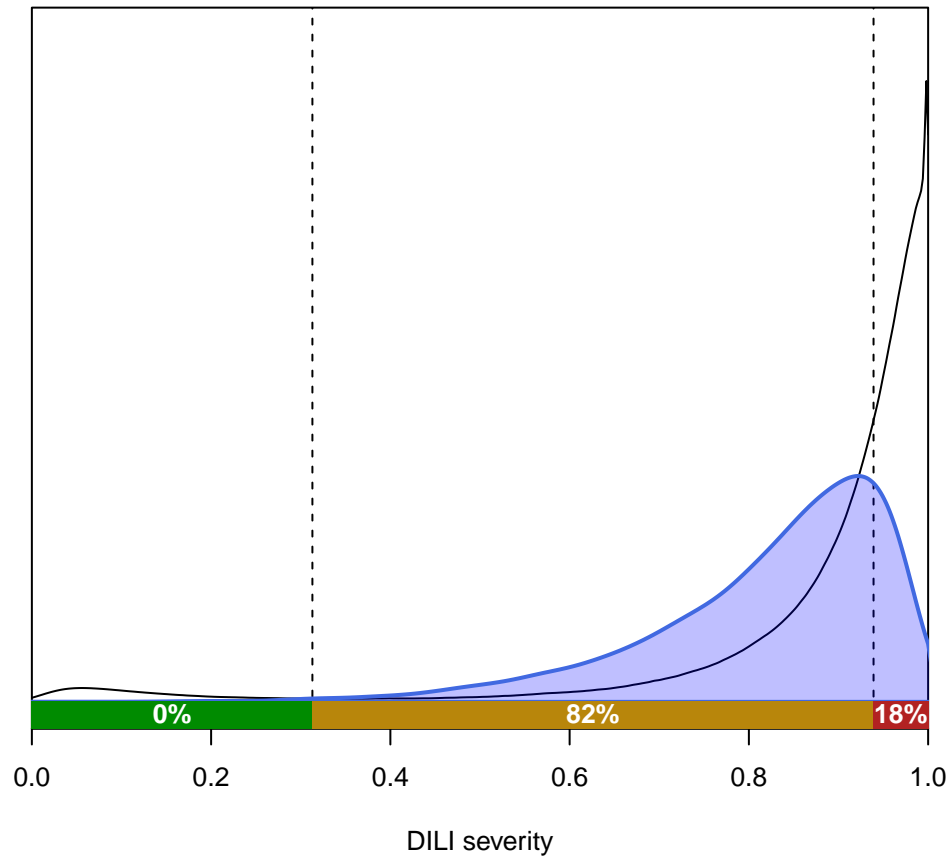
Peak = 0.03
Mean = 0.16
Median = 0.09
95% CI = 0 – 0.55



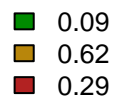
Pargyline



Paroxetine



Probability



True category

2

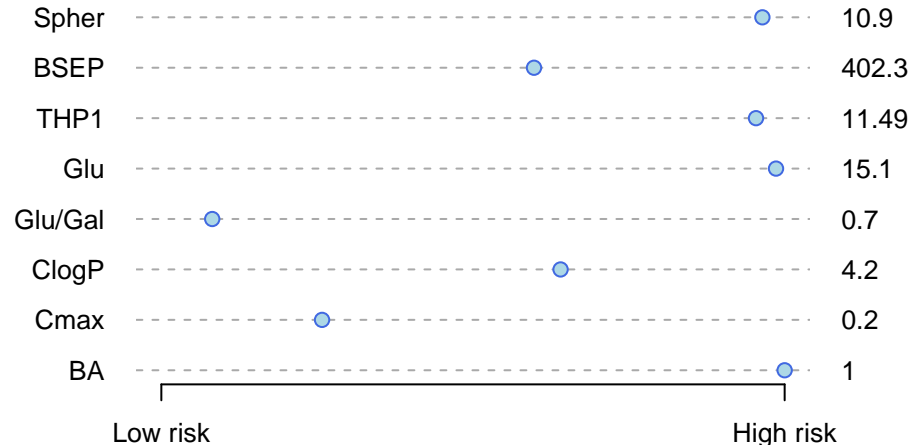
Summary stats

Peak = 0.93

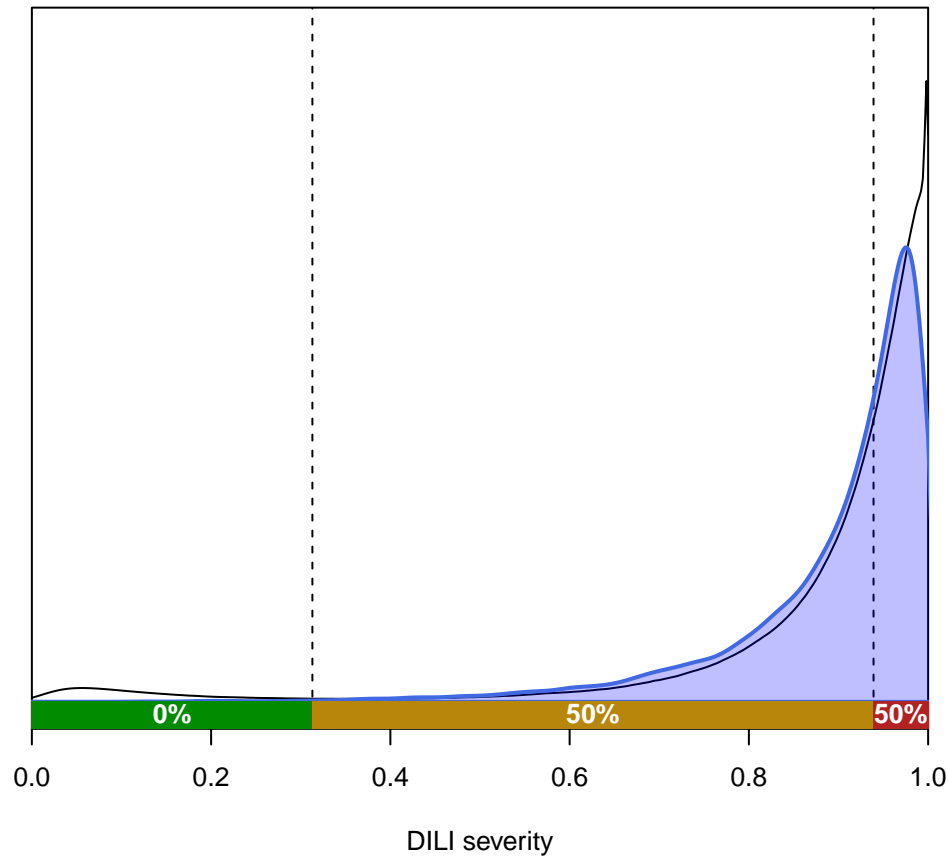
Mean = 0.82

Median = 0.86

95% CI = 0.55 – 0.99



Perhexiline



Probability

- 0.05
- 0.48
- 0.47

True category

3

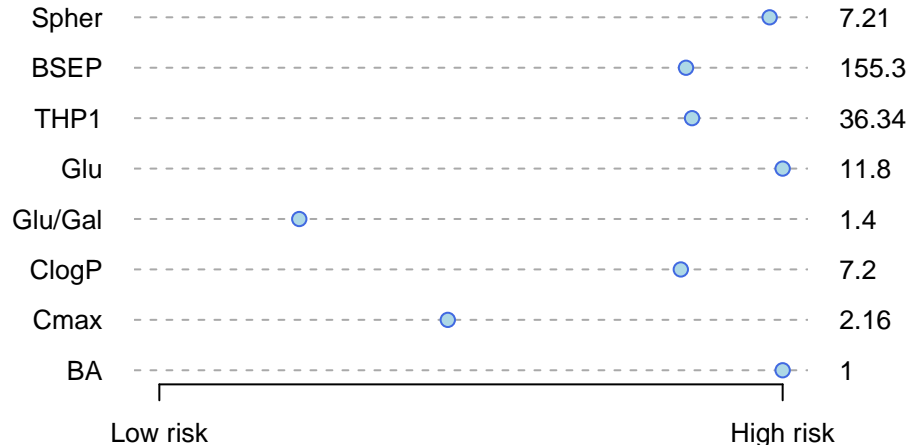
Summary stats

Peak = 0.98

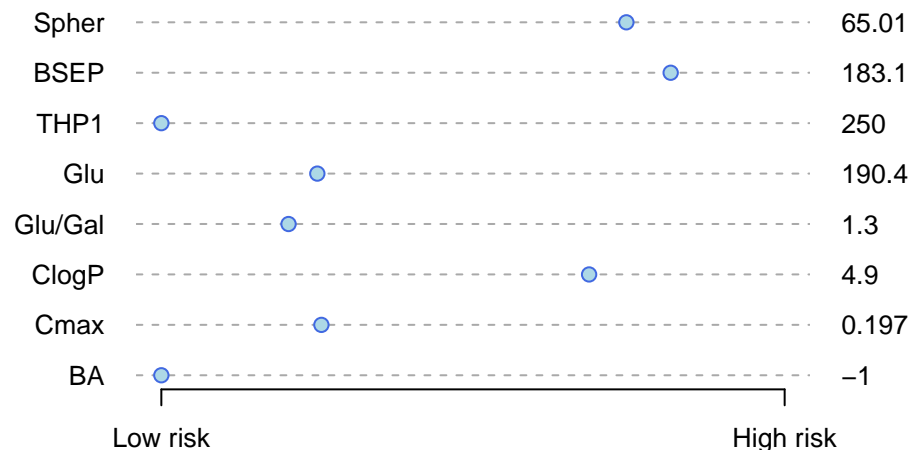
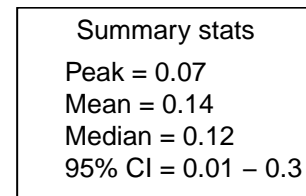
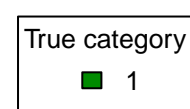
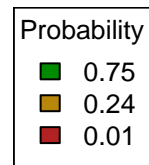
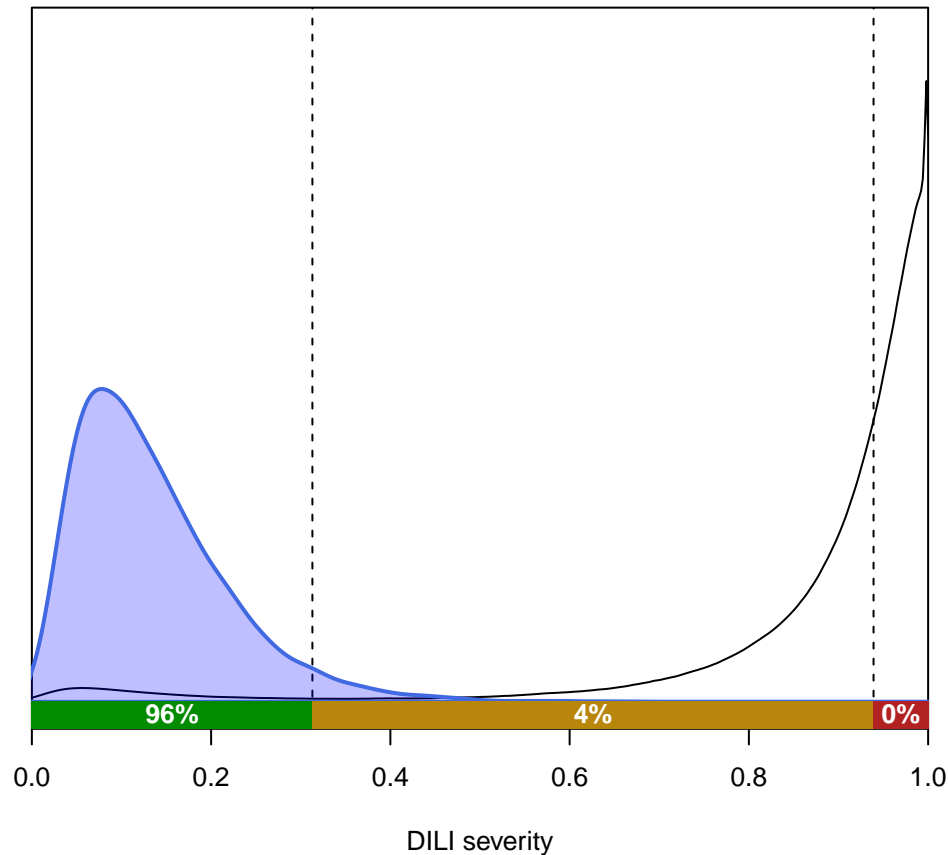
Mean = 0.9

Median = 0.94

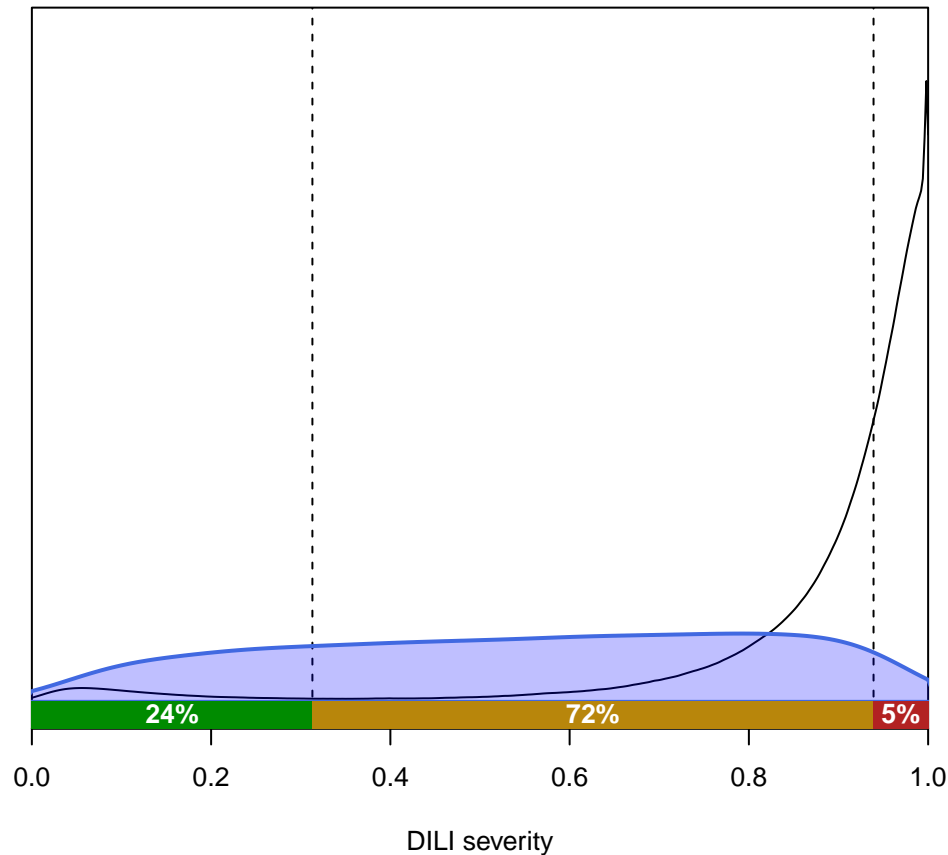
95% CI = 0.66 – 1



Phenoxybenzamine



Pimozide



Probability

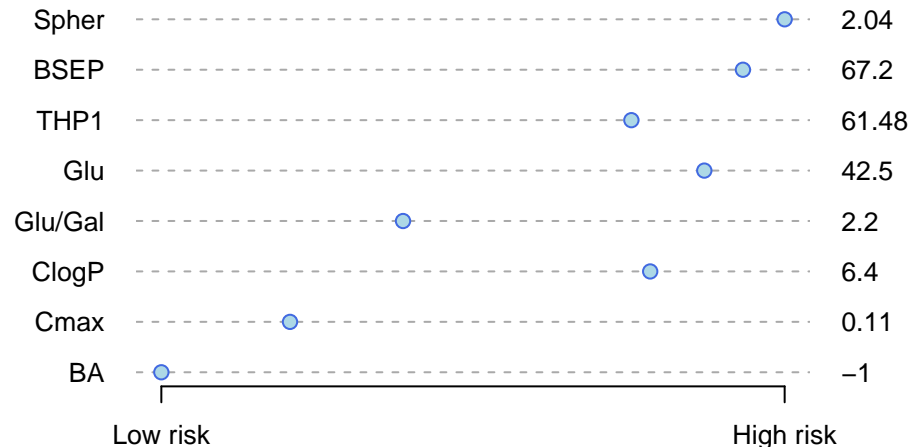


True category



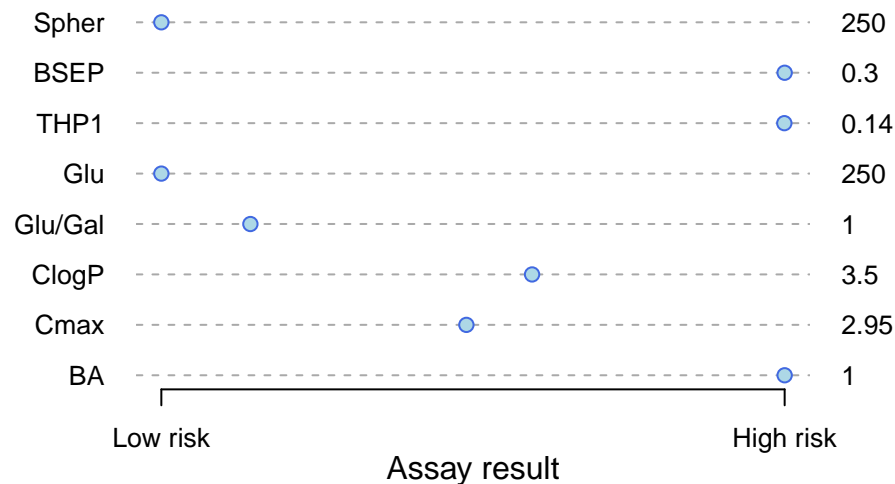
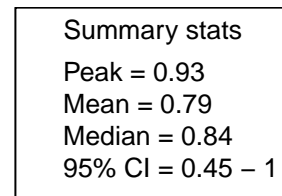
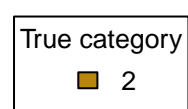
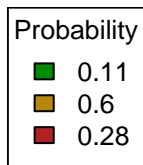
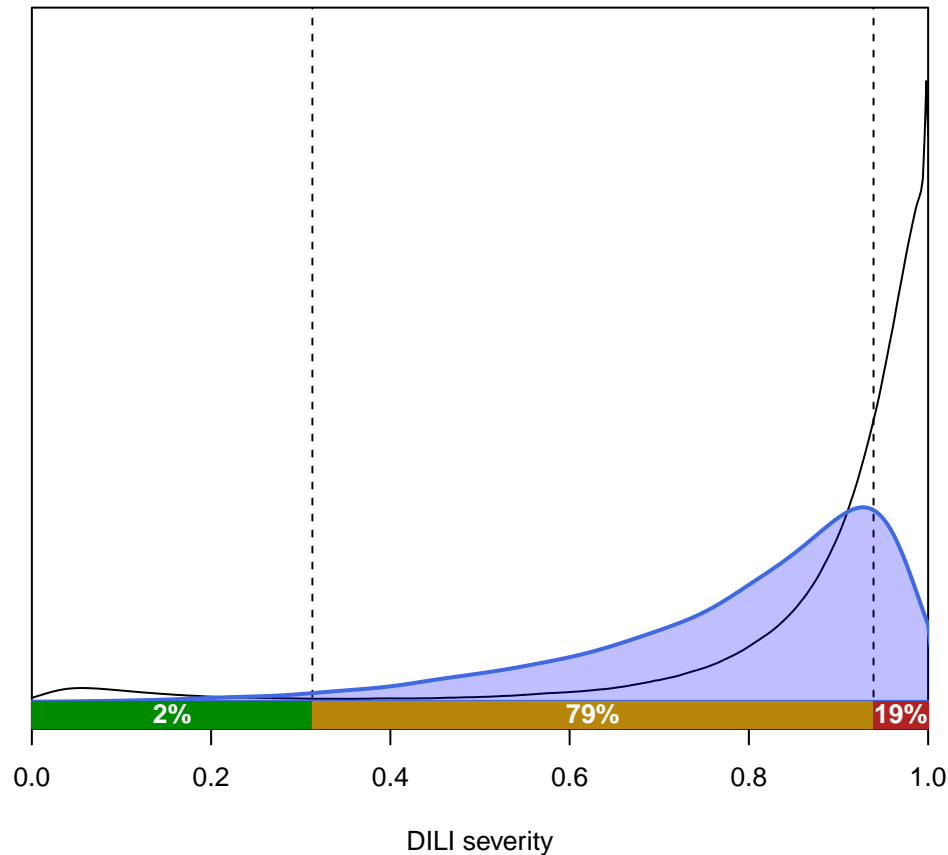
Summary stats

Peak = 0.8
Mean = 0.54
Median = 0.56
95% CI = 0.1 – 0.98

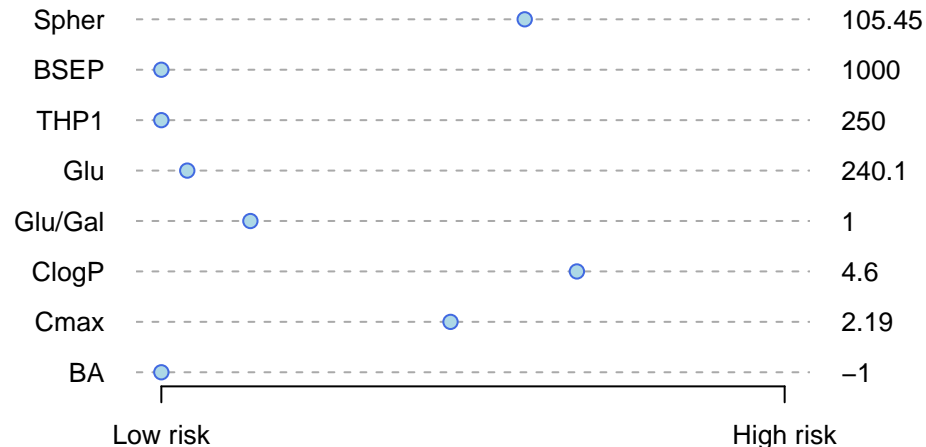
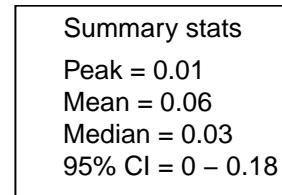
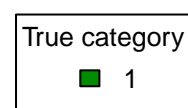
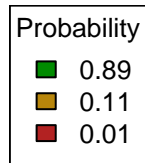
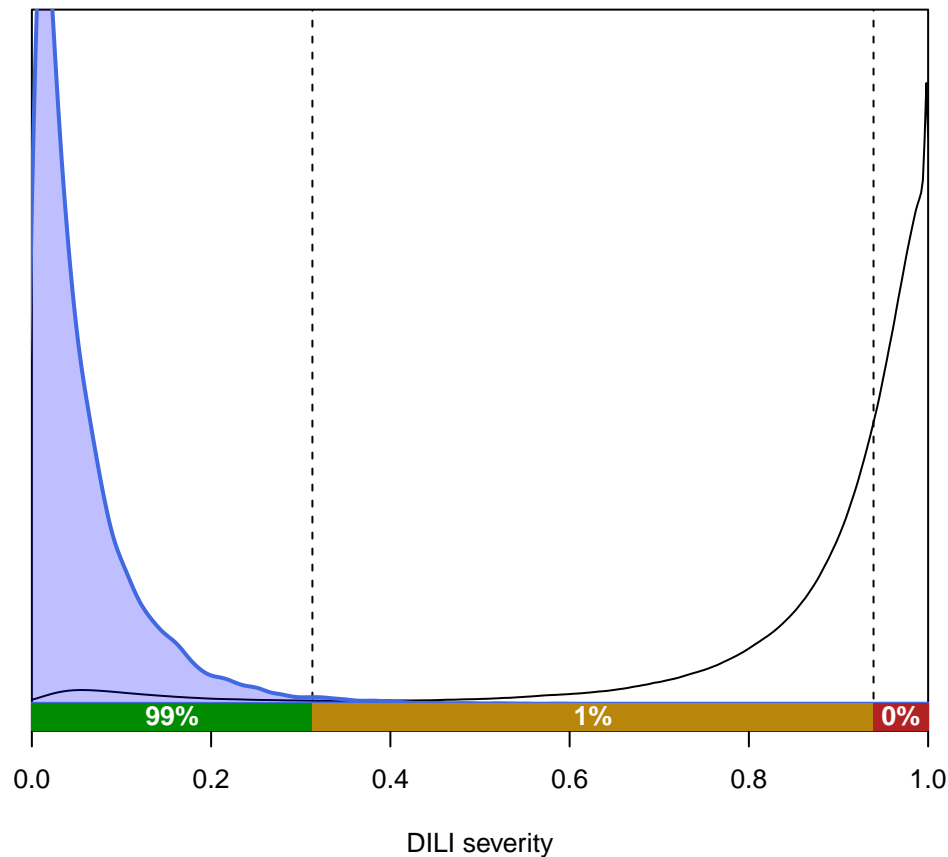


Assay result

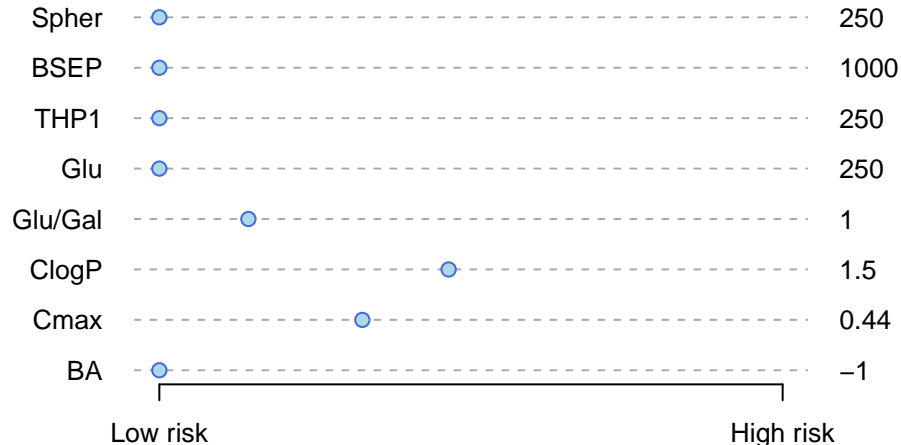
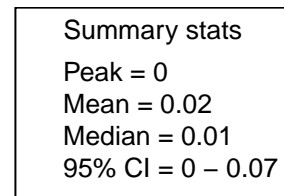
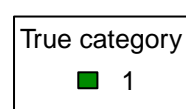
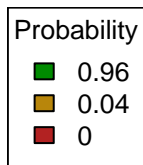
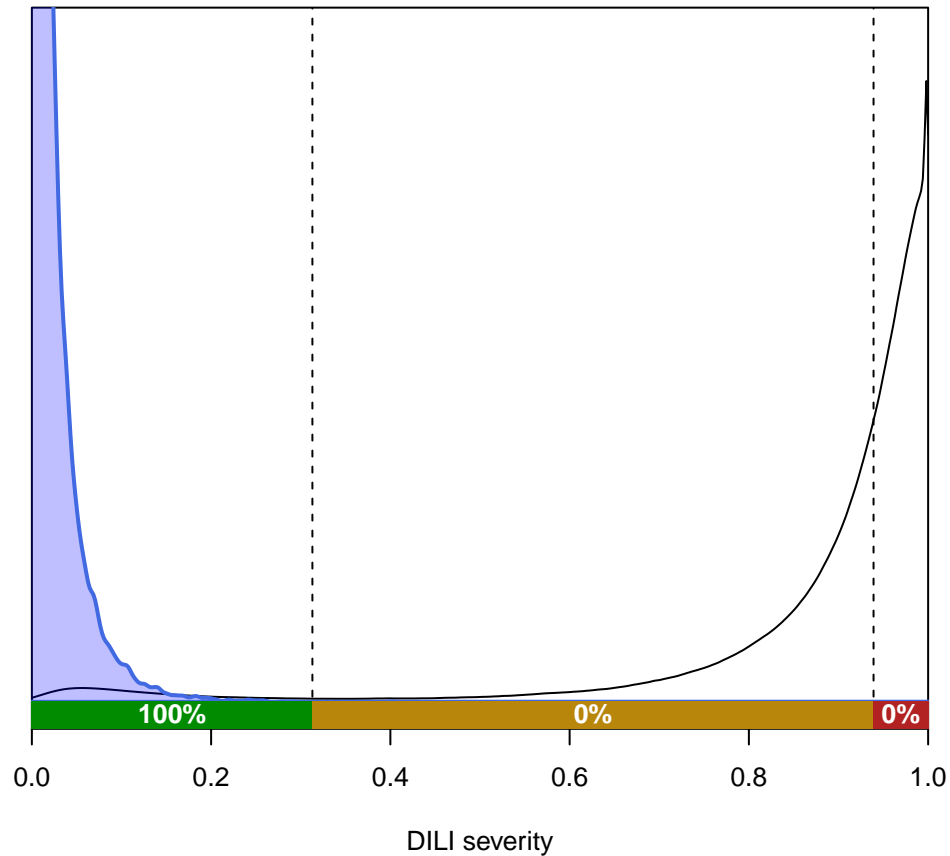
Pioglitazone



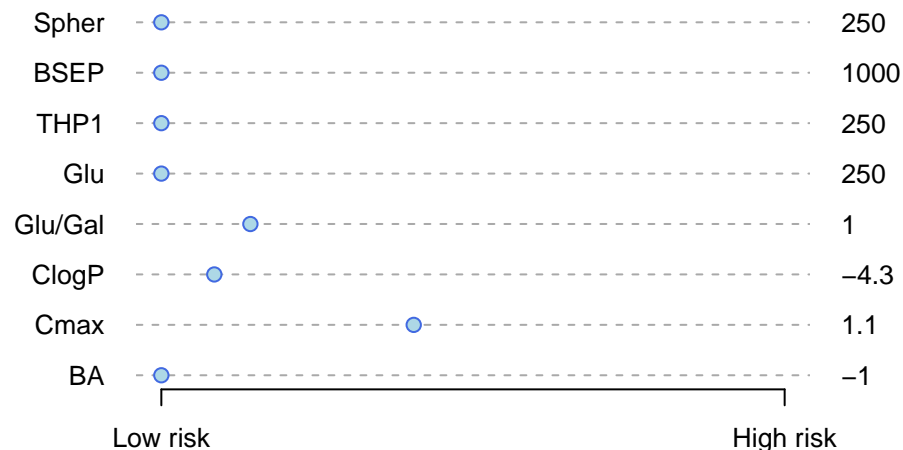
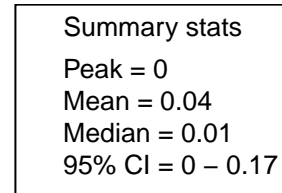
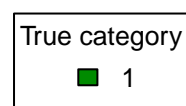
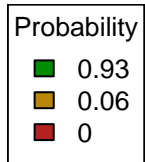
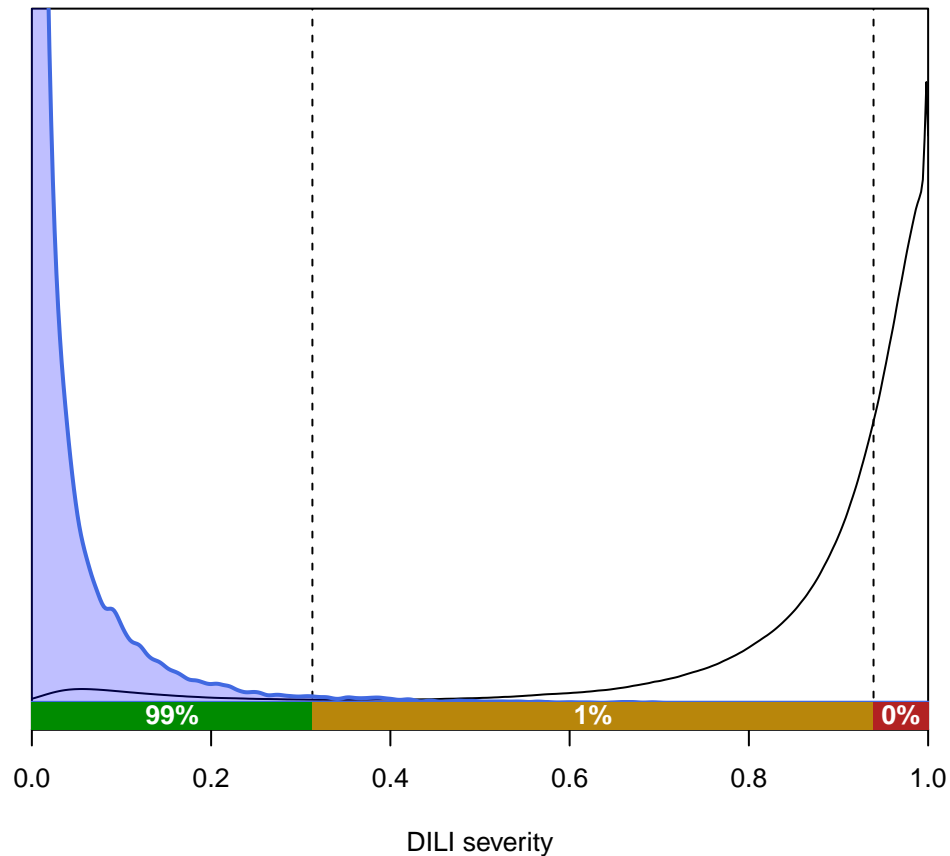
Procyclidine



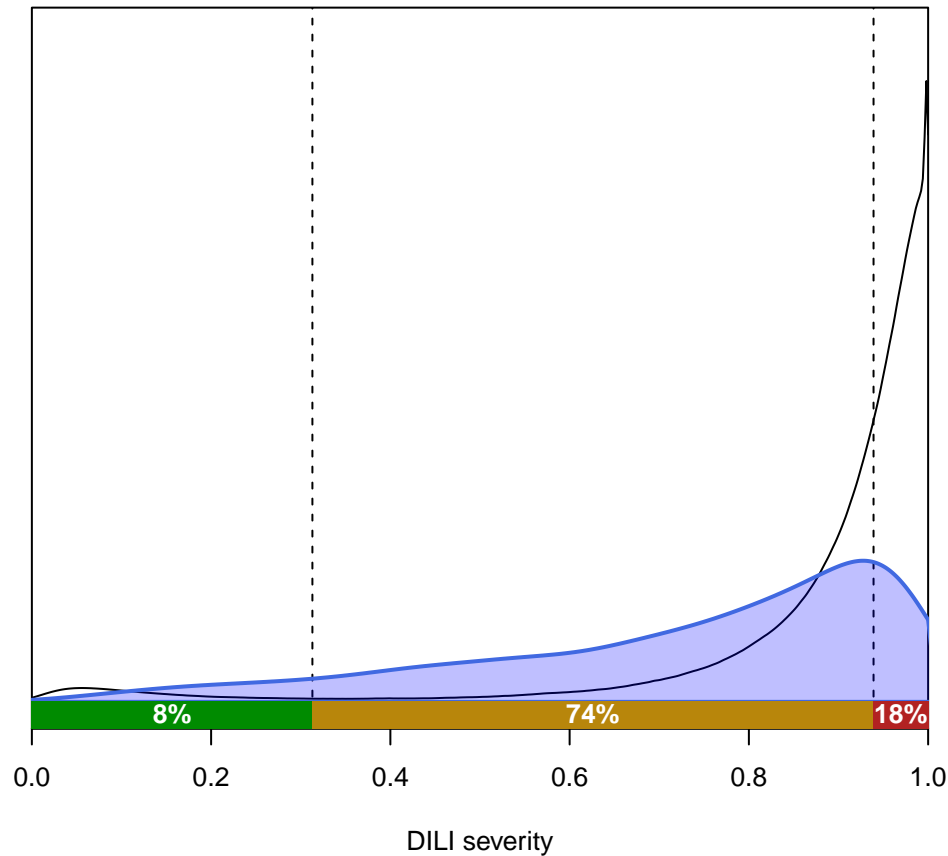
Propantheline



Pyridostigmine



Rimonabant



Probability

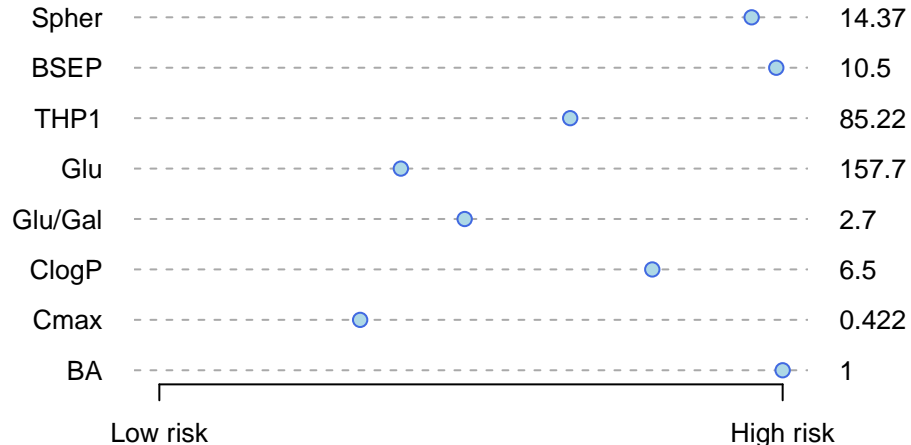


True category

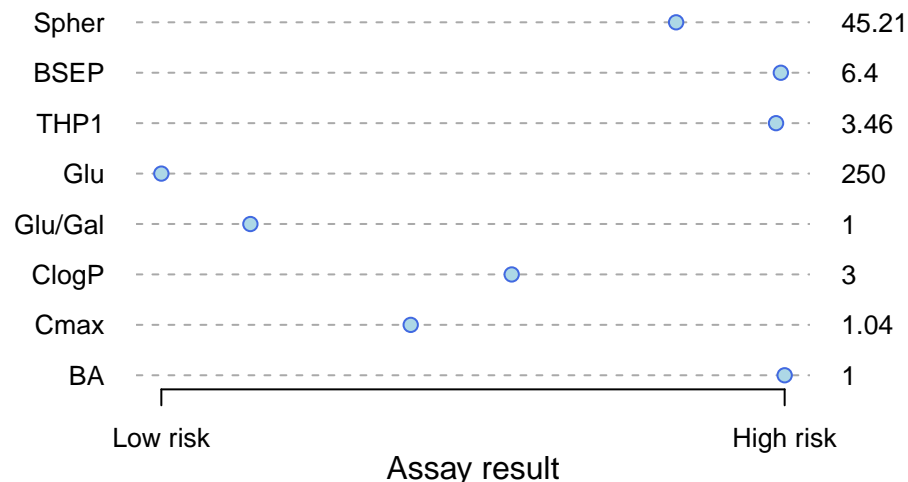
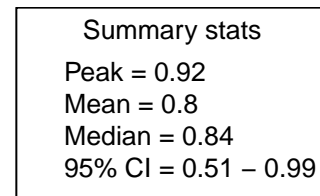
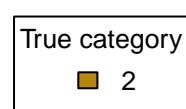
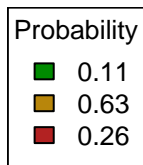
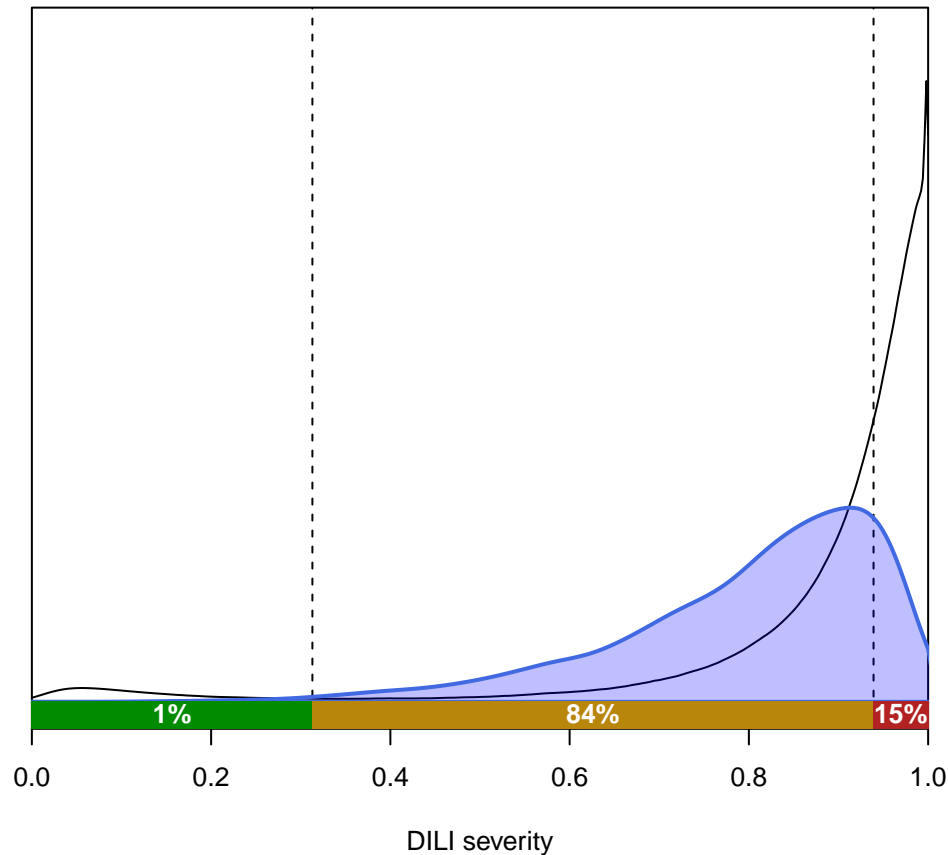


Summary stats

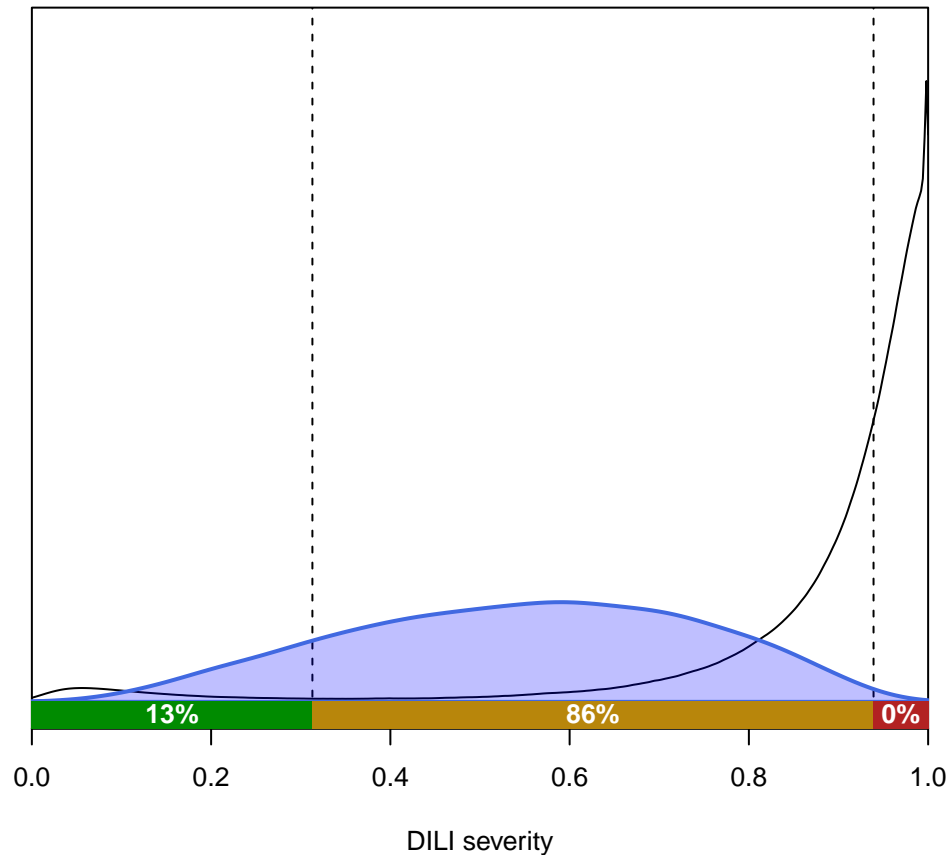
Peak = 0.94
Mean = 0.73
Median = 0.8
95% CI = 0.25 – 1



Rosiglitazone



Simvastatin



Probability

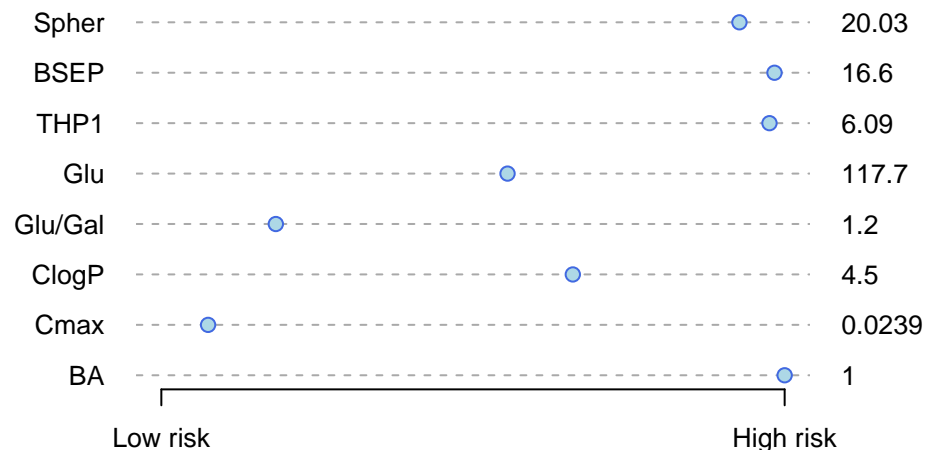


True category

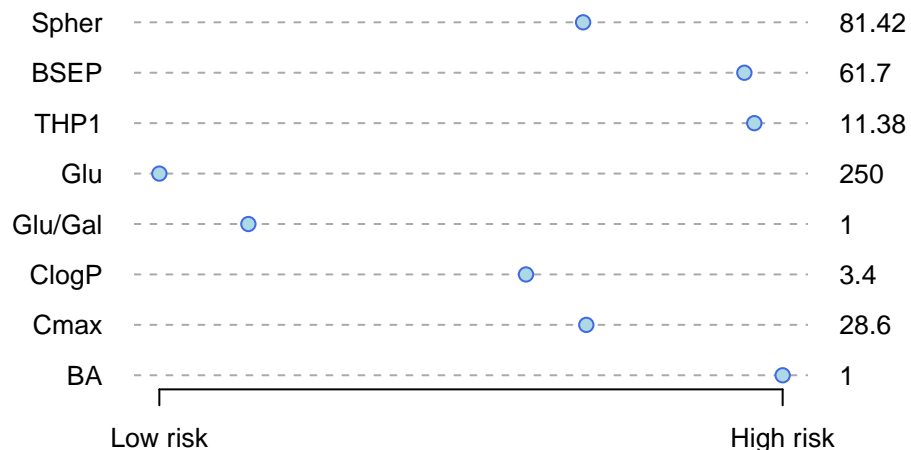
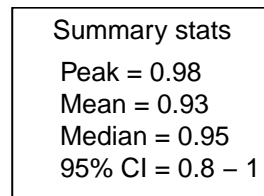
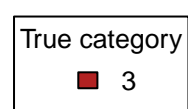
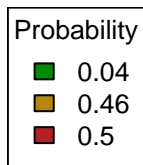
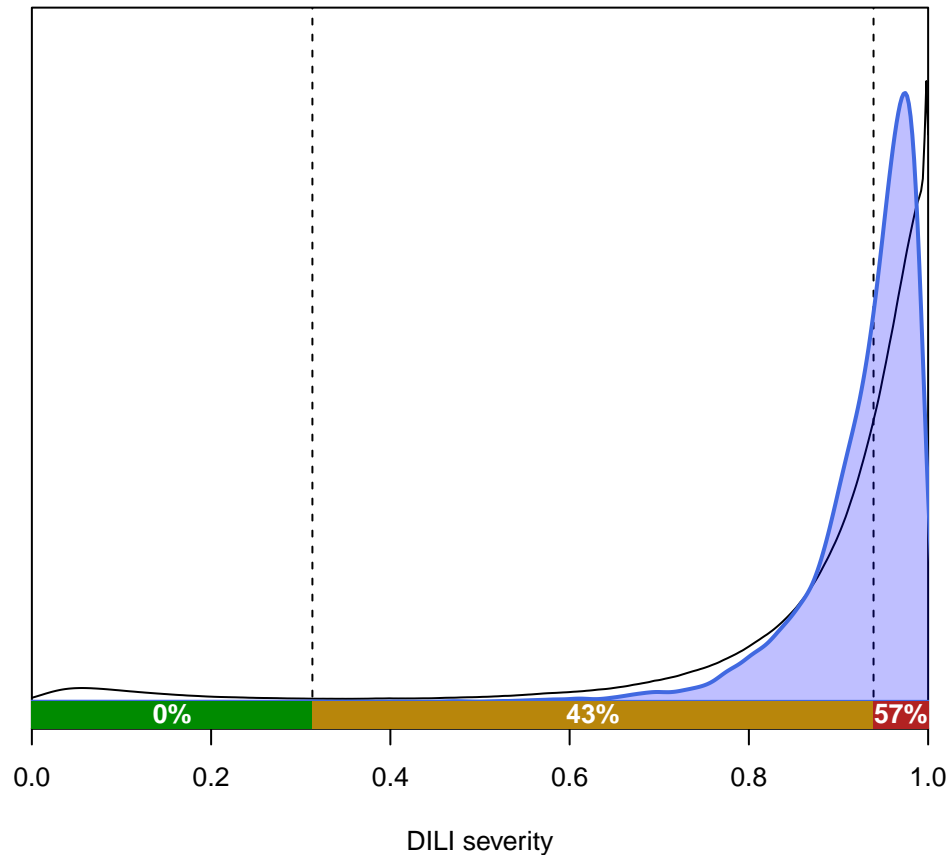


Summary stats

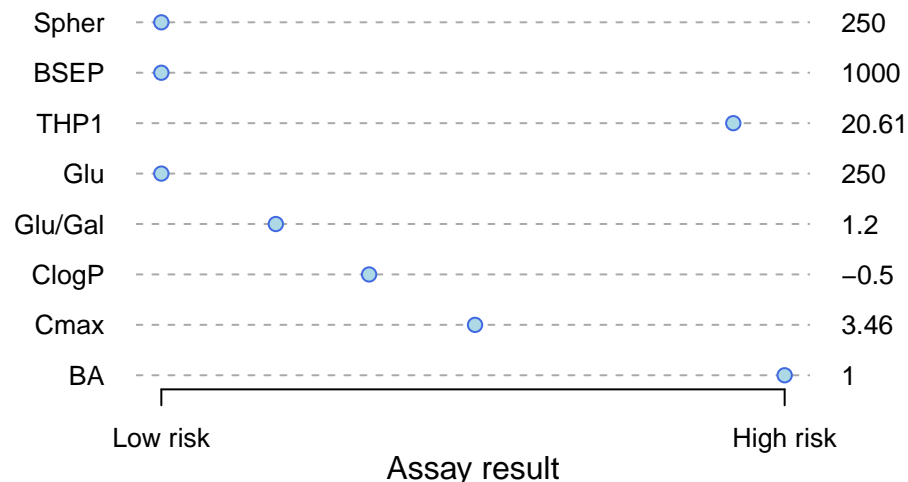
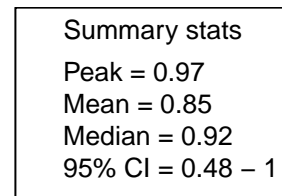
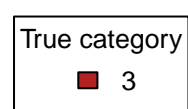
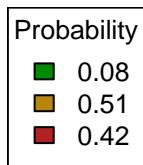
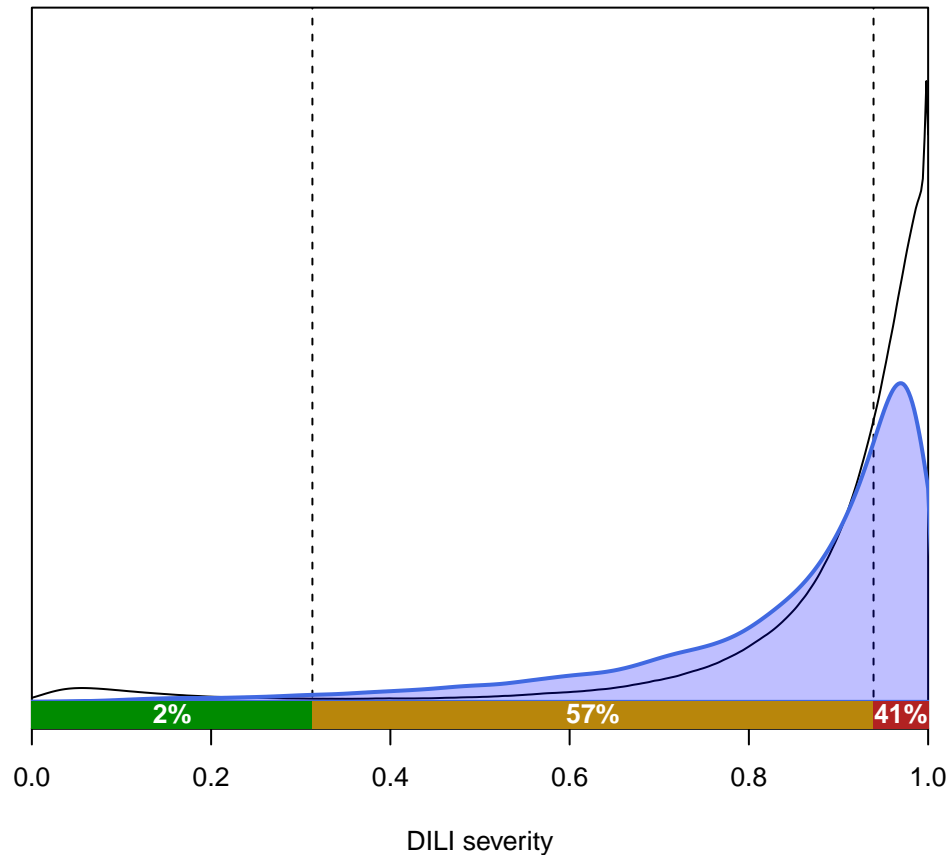
Peak = 0.59
Mean = 0.55
Median = 0.56
95% CI = 0.2 – 0.9



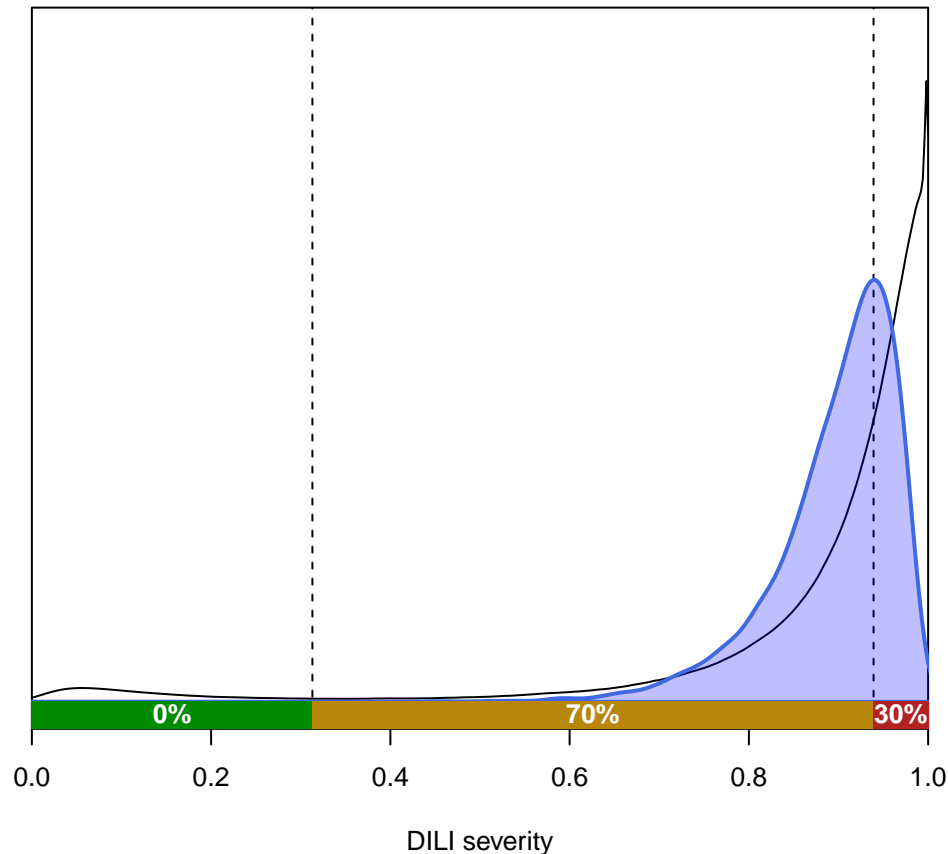
Sitaxsentan



Stavudine



Sudoxicam



Probability

- 0.05
- 0.58
- 0.37

True category

3

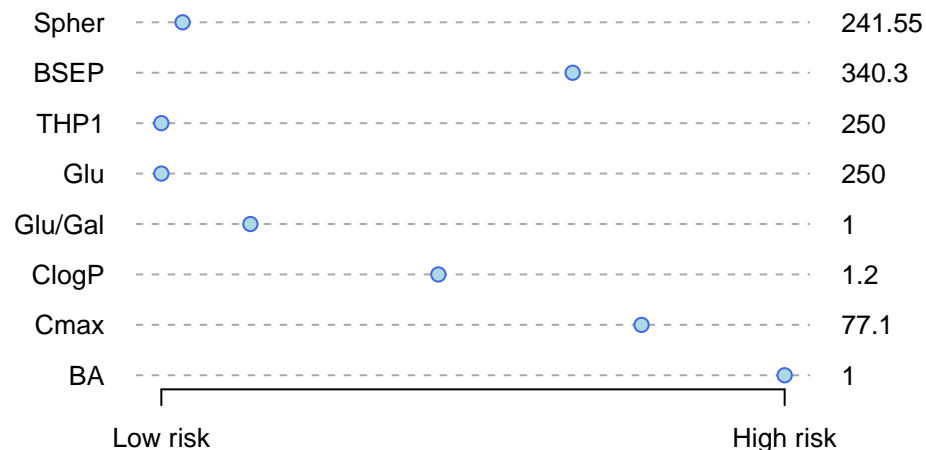
Summary stats

Peak = 0.94

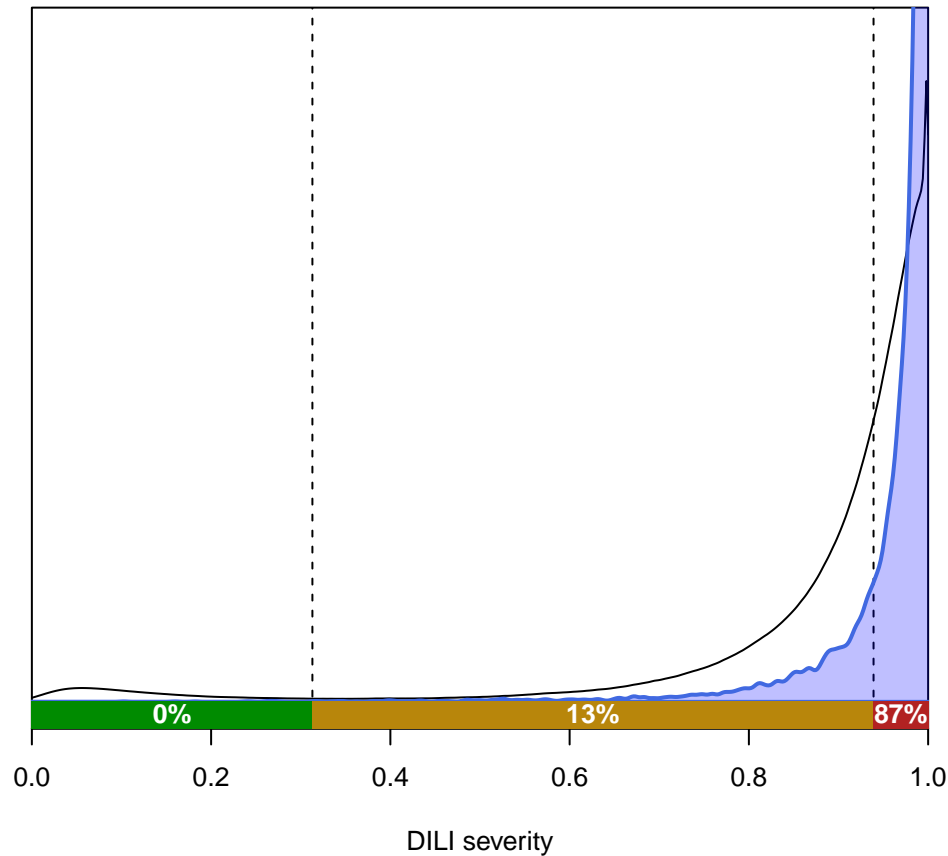
Mean = 0.9

Median = 0.91

95% CI = 0.75 – 0.99



Sunitinib



Probability

- 0.02
- 0.2
- 0.78

True category

3

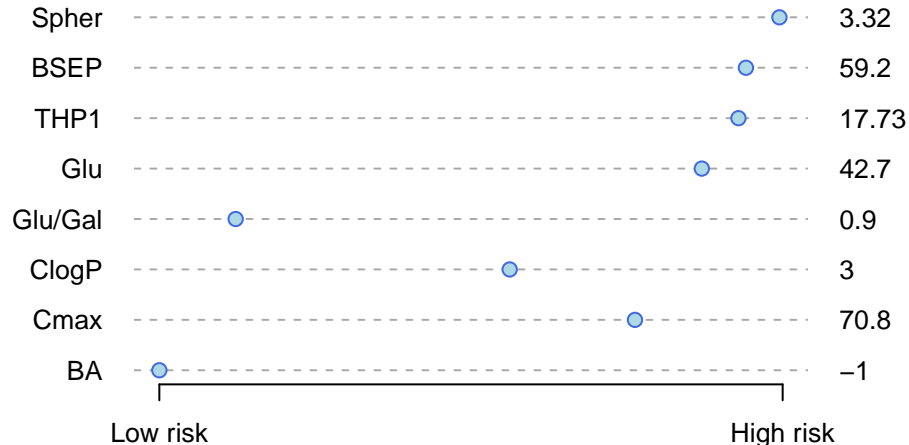
Summary stats

Peak = 1

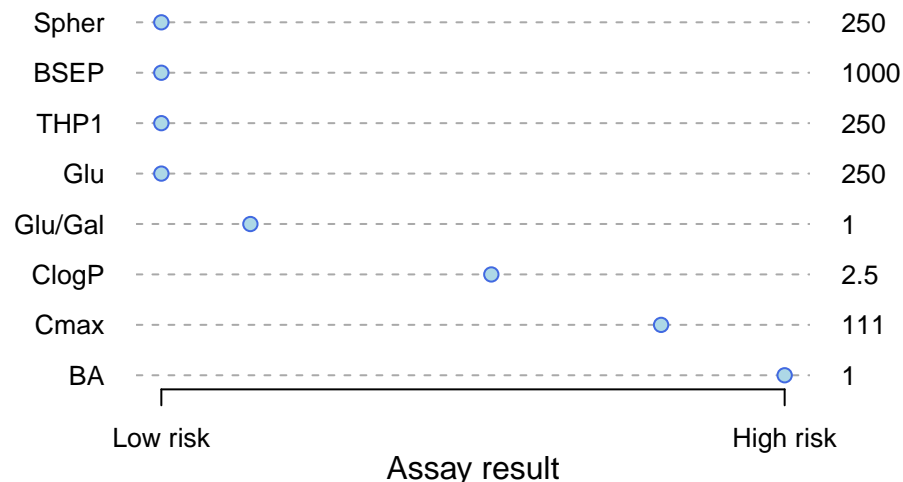
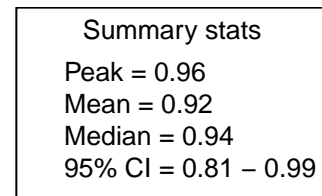
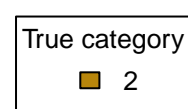
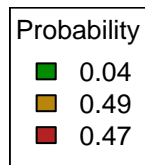
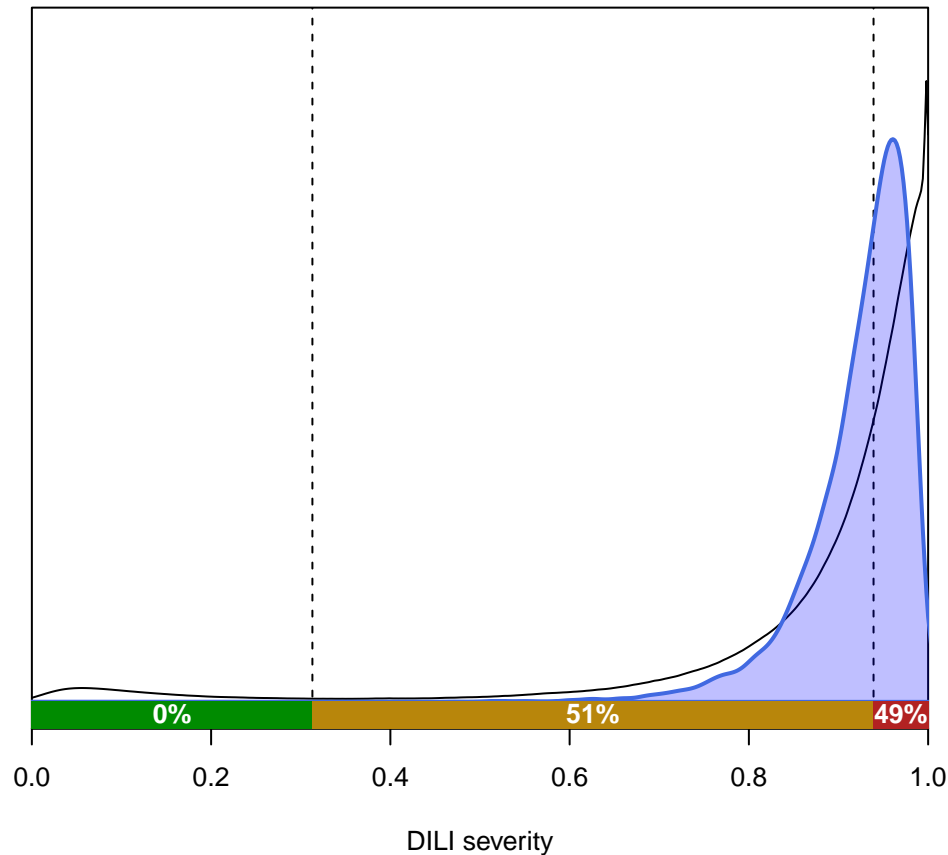
Mean = 0.97

Median = 0.99

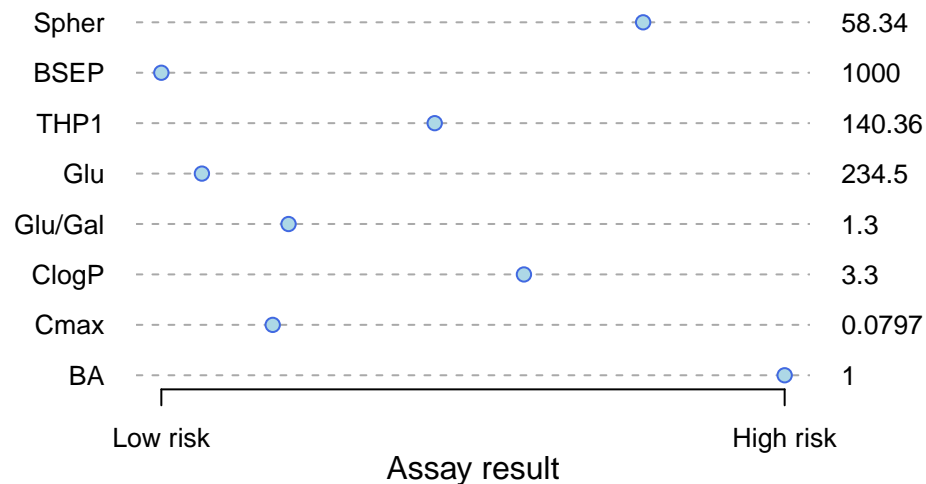
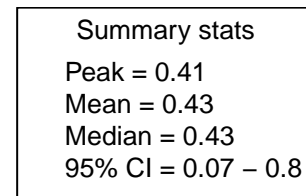
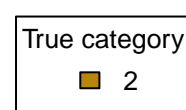
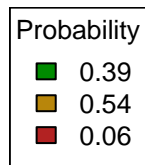
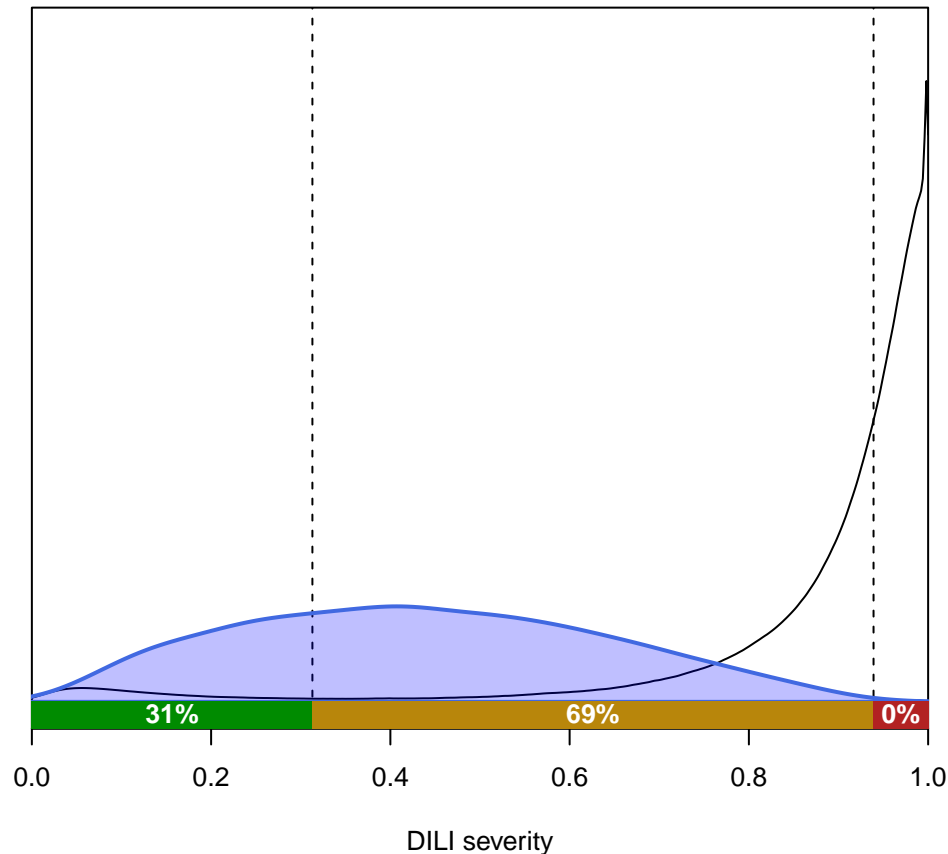
95% CI = 0.86 - 1



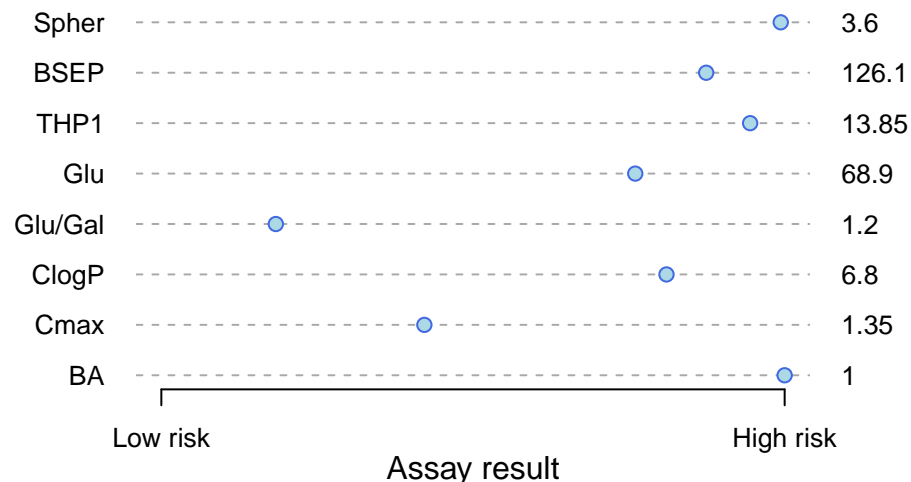
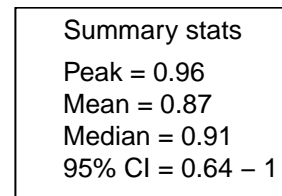
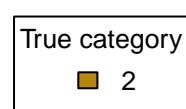
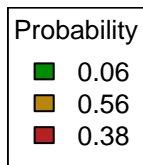
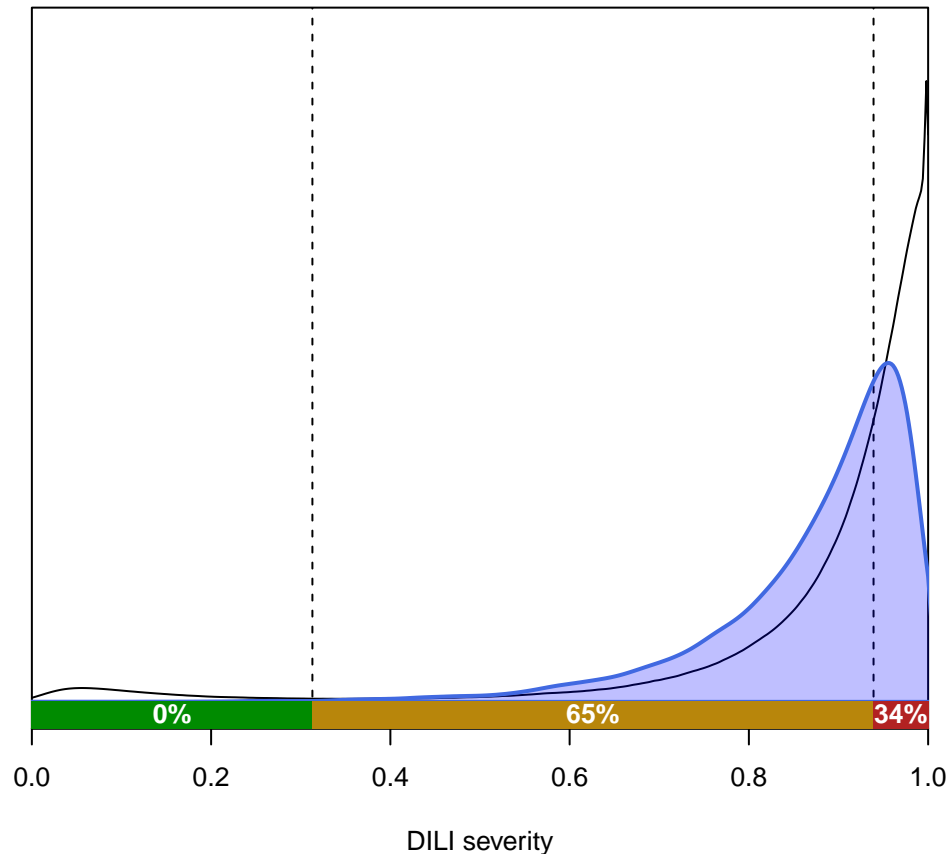
Suprofen



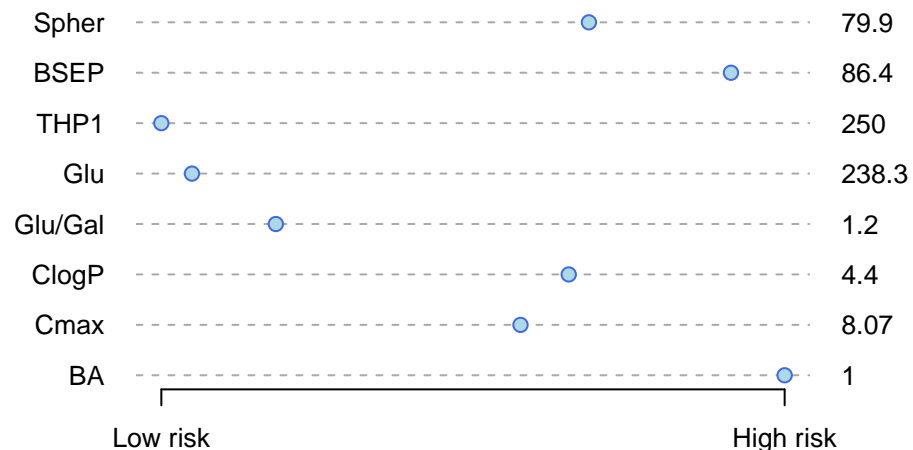
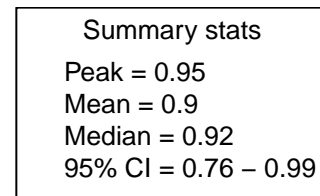
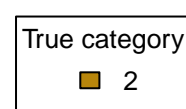
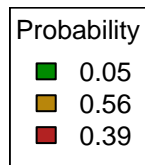
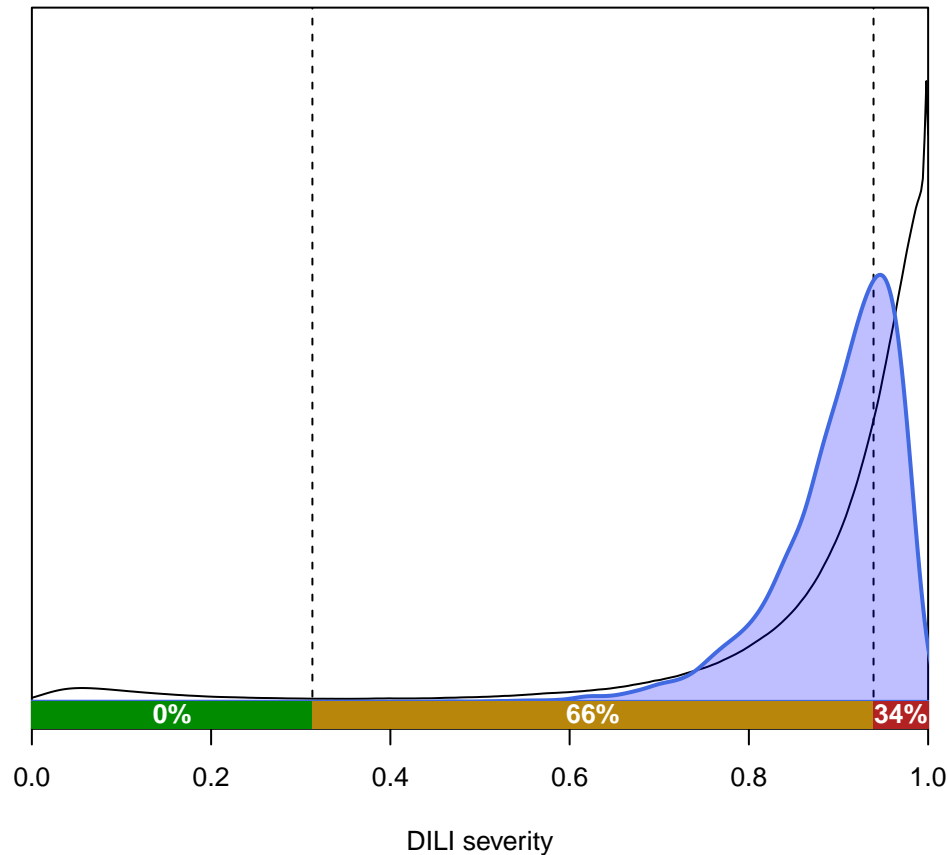
Tacrine



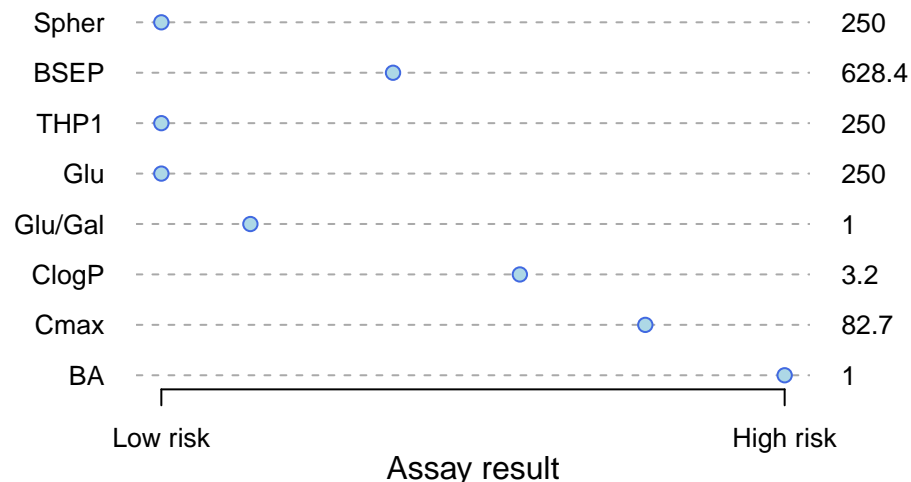
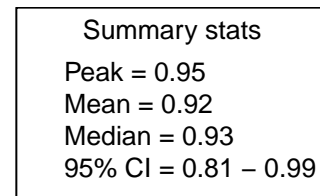
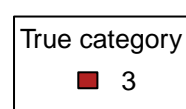
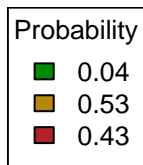
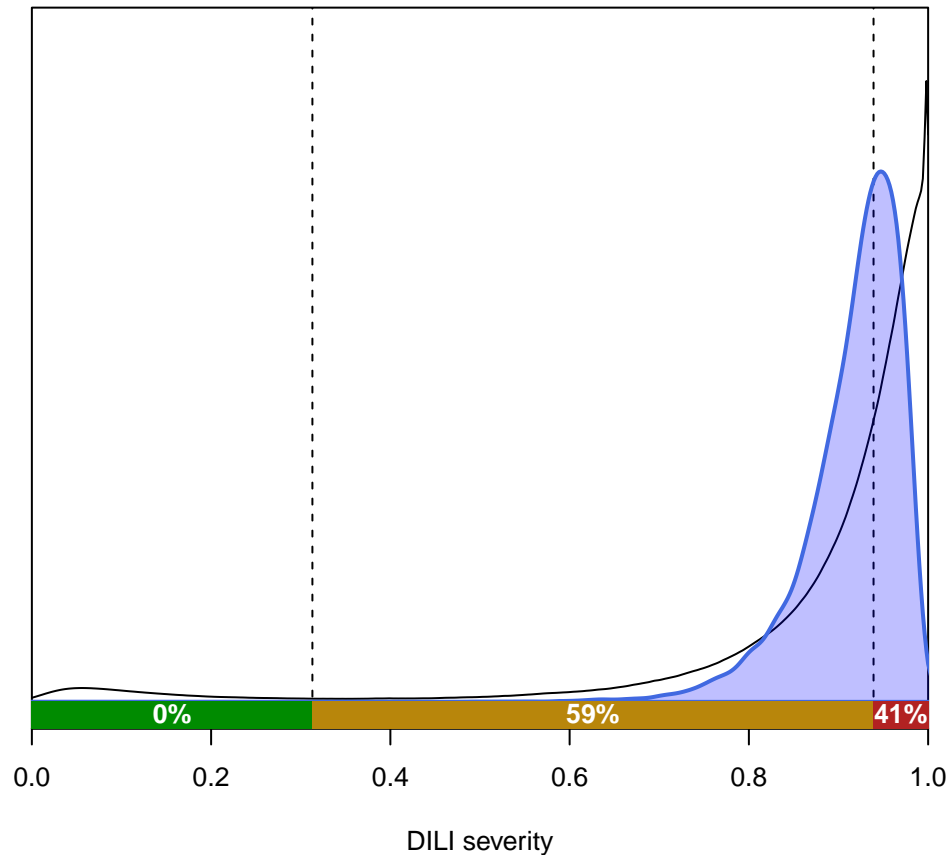
Tamoxifen



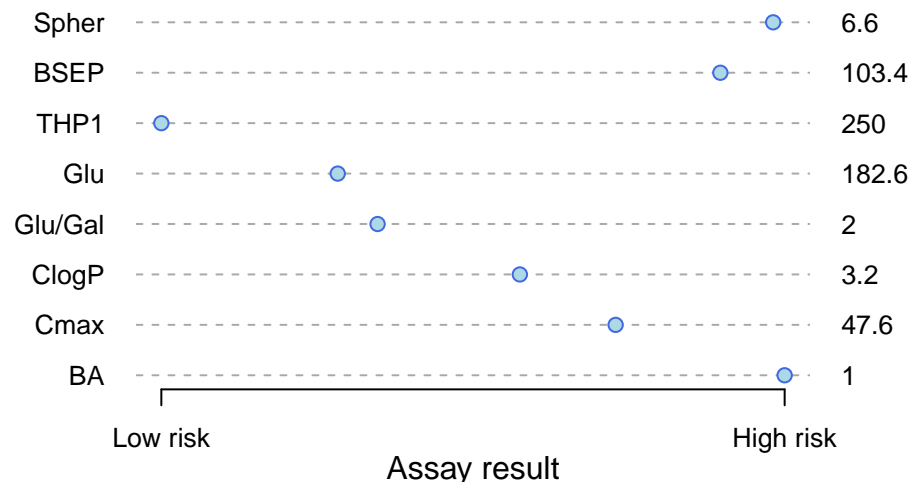
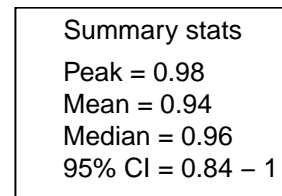
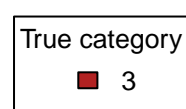
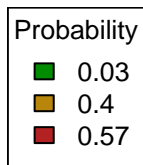
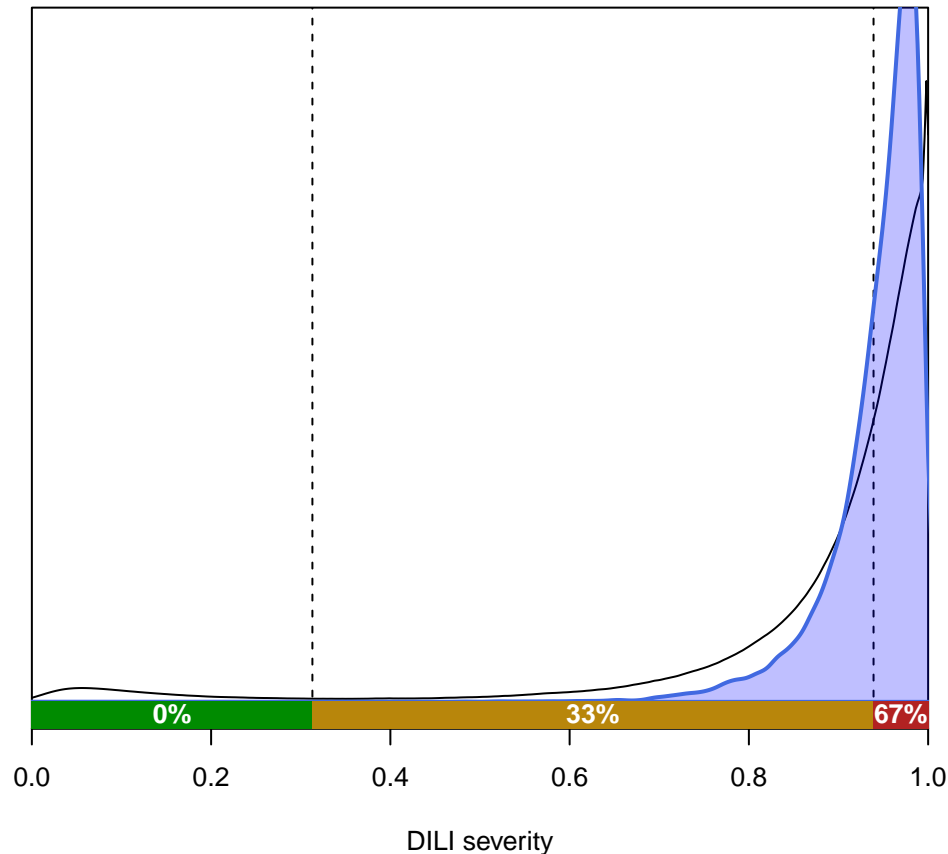
Ticlopidine



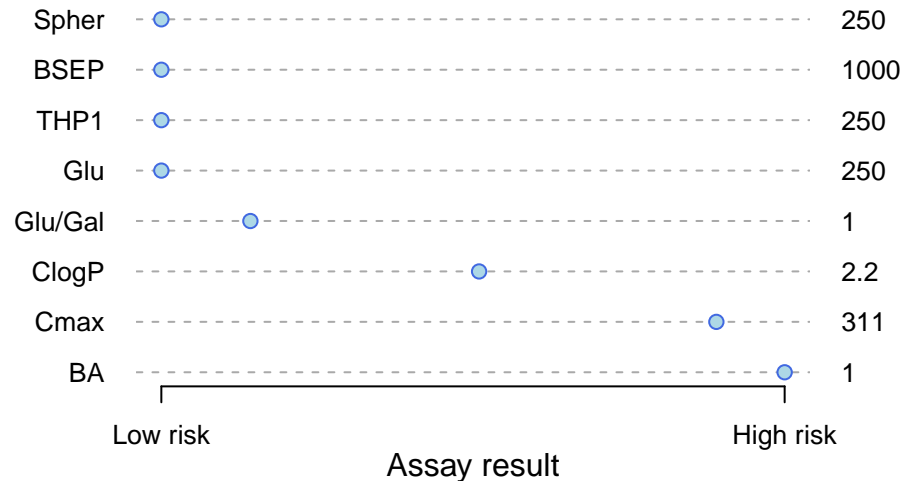
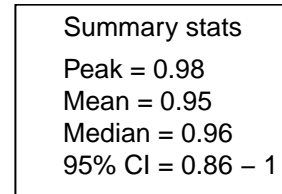
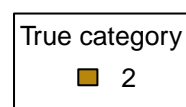
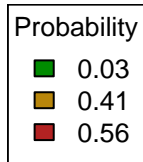
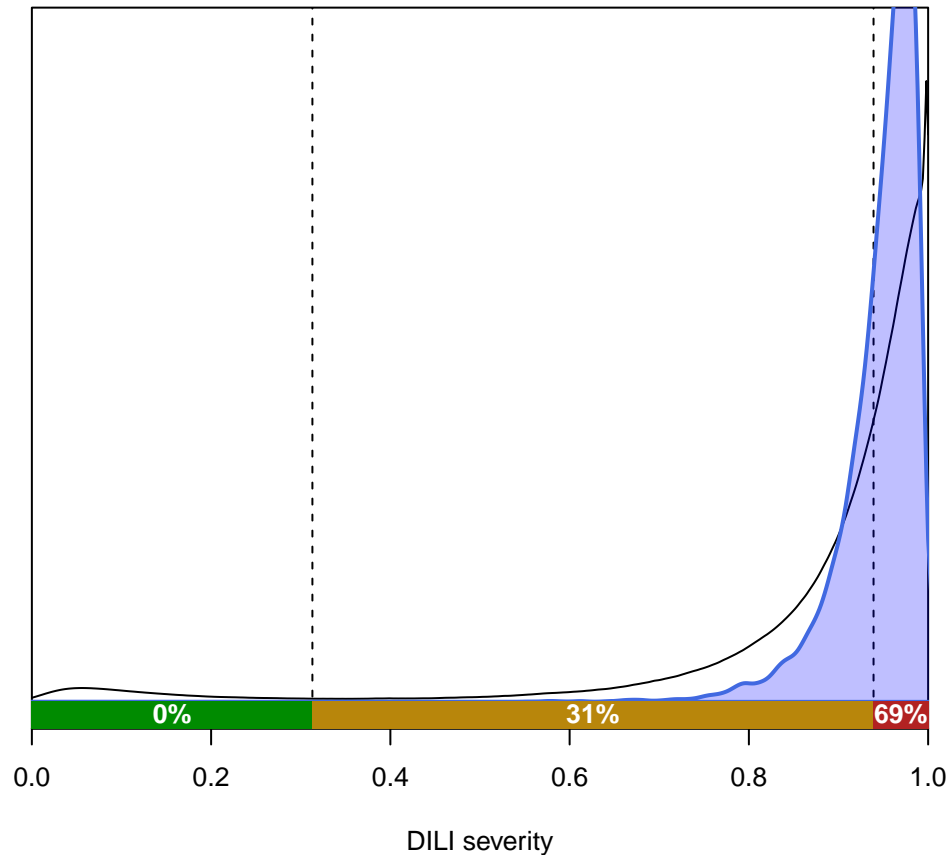
Tienilic acid



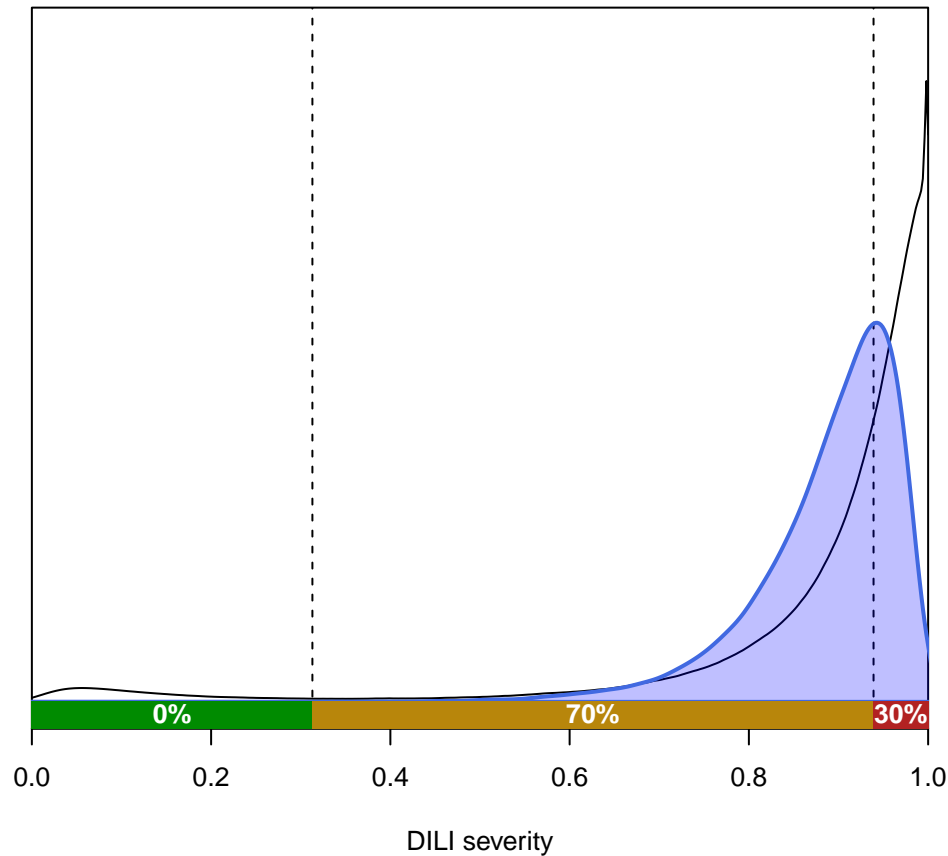
Tolcapone



Tolmetin



Troglitazone



Probability



True category

3

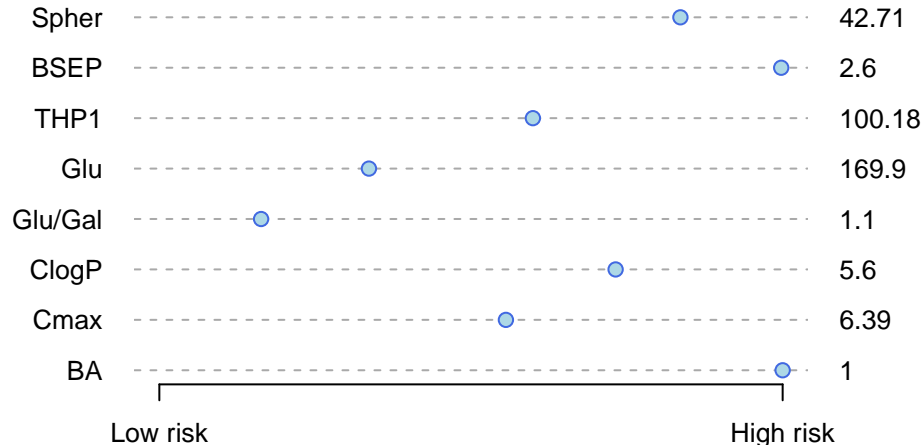
Summary stats

Peak = 0.94

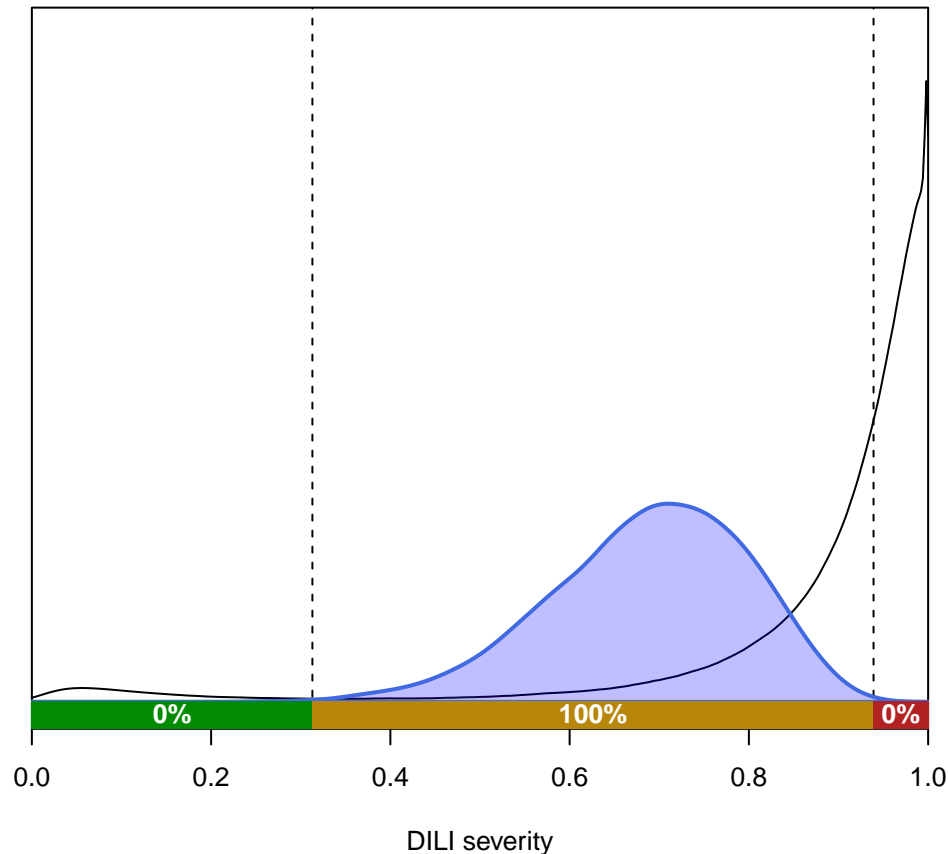
Mean = 0.89

Median = 0.91

95% CI = 0.73 – 0.99



Verapamil



Probability

- 0.17
- 0.7
- 0.13

True category

2

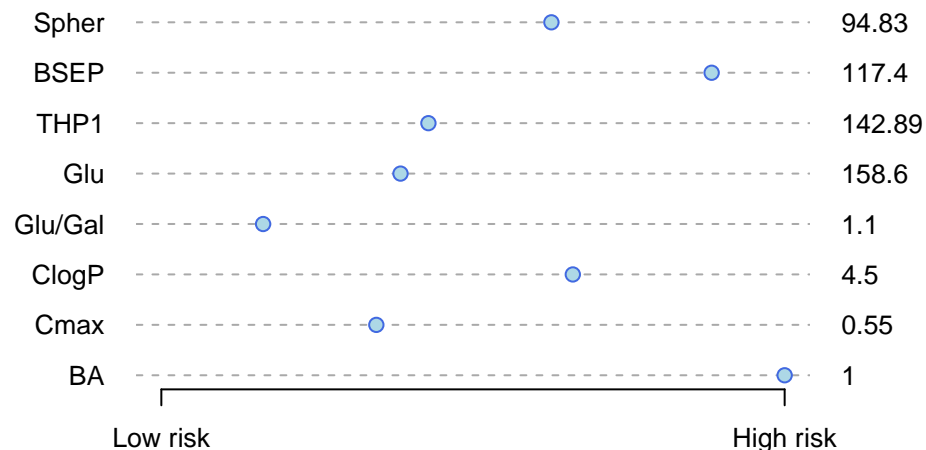
Summary stats

Peak = 0.71

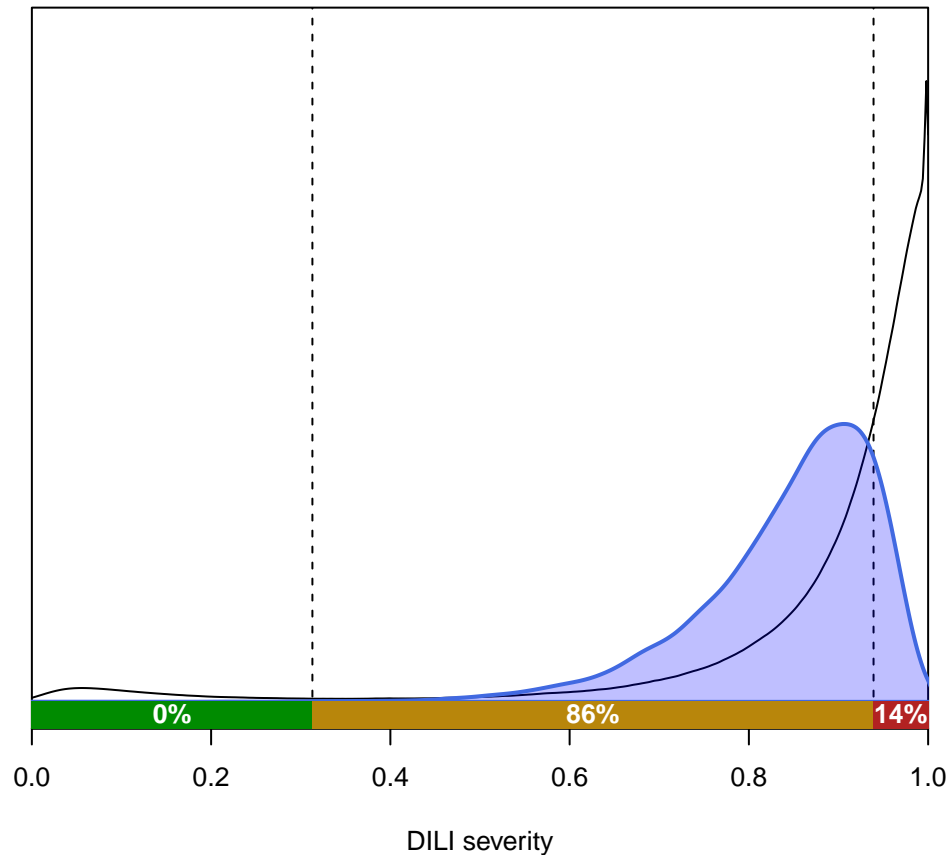
Mean = 0.69

Median = 0.7

95% CI = 0.48 – 0.89



Warfarin



Probability

- 0.08
- 0.64
- 0.29

True category

2

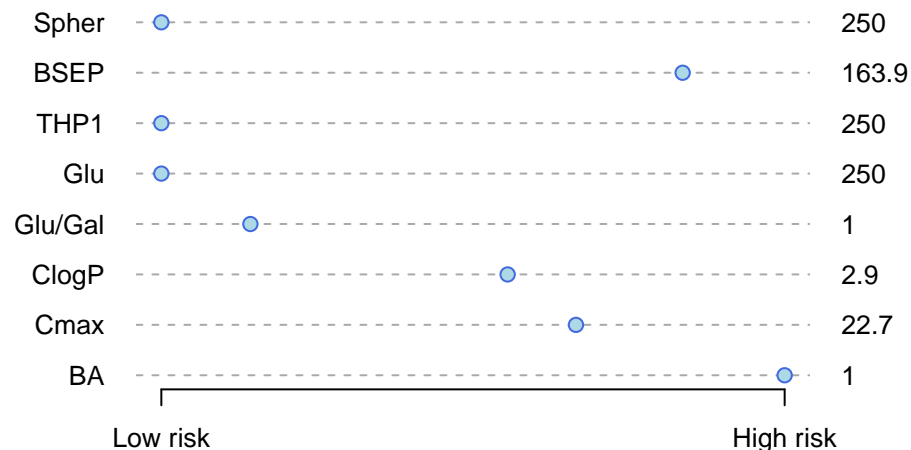
Summary stats

Peak = 0.91

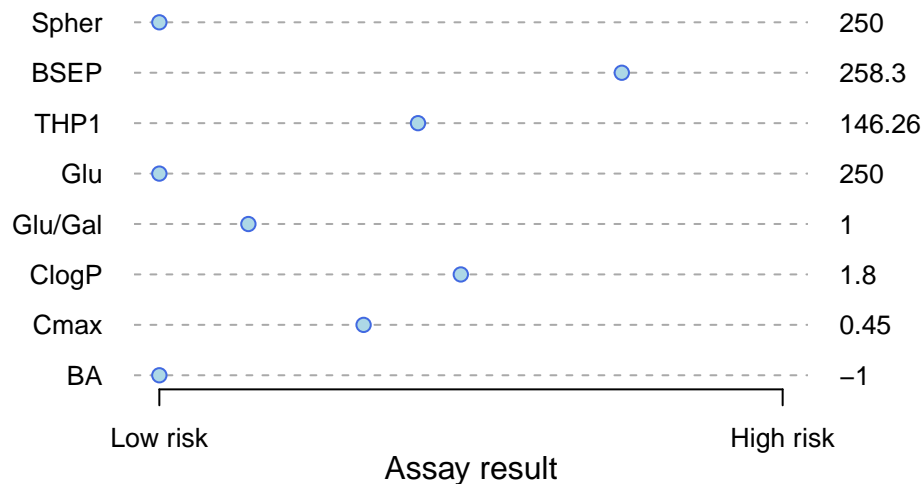
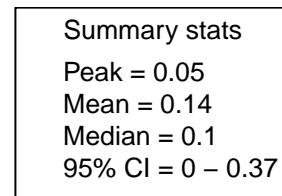
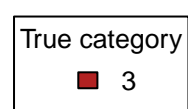
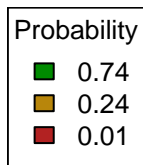
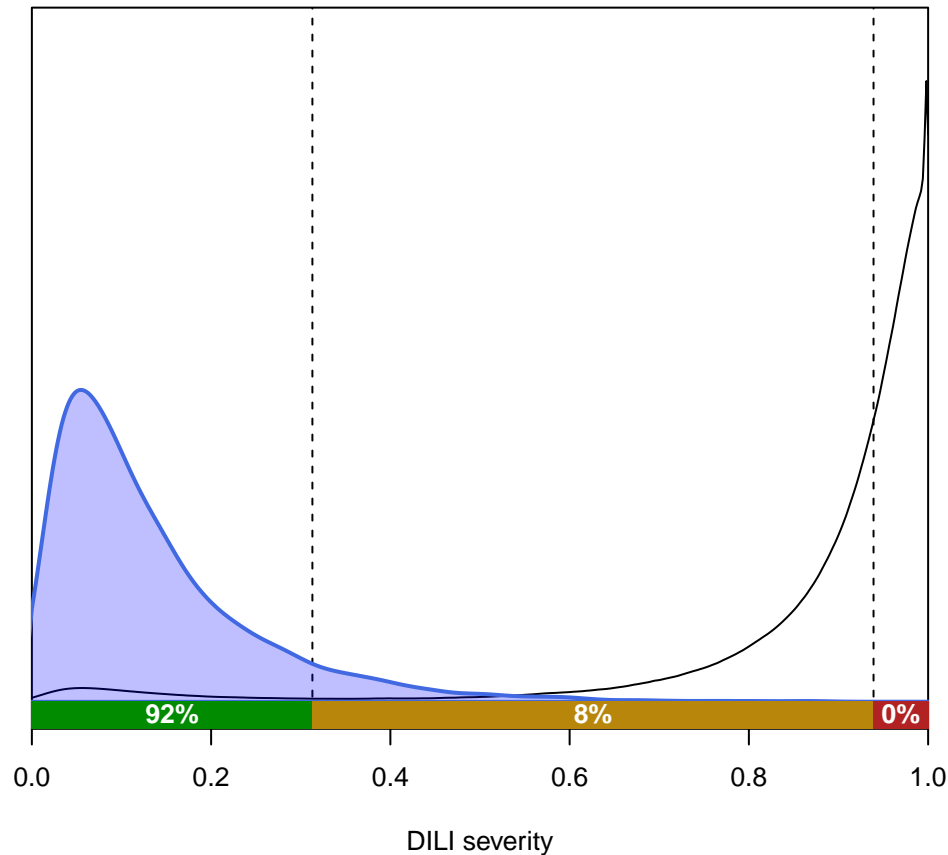
Mean = 0.84

Median = 0.87

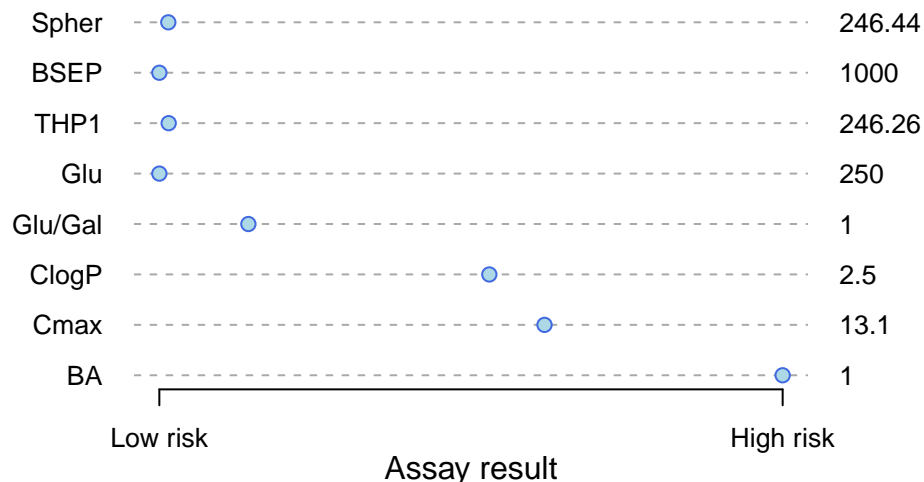
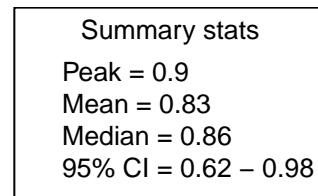
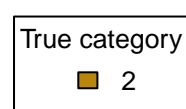
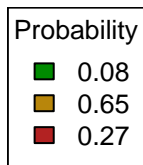
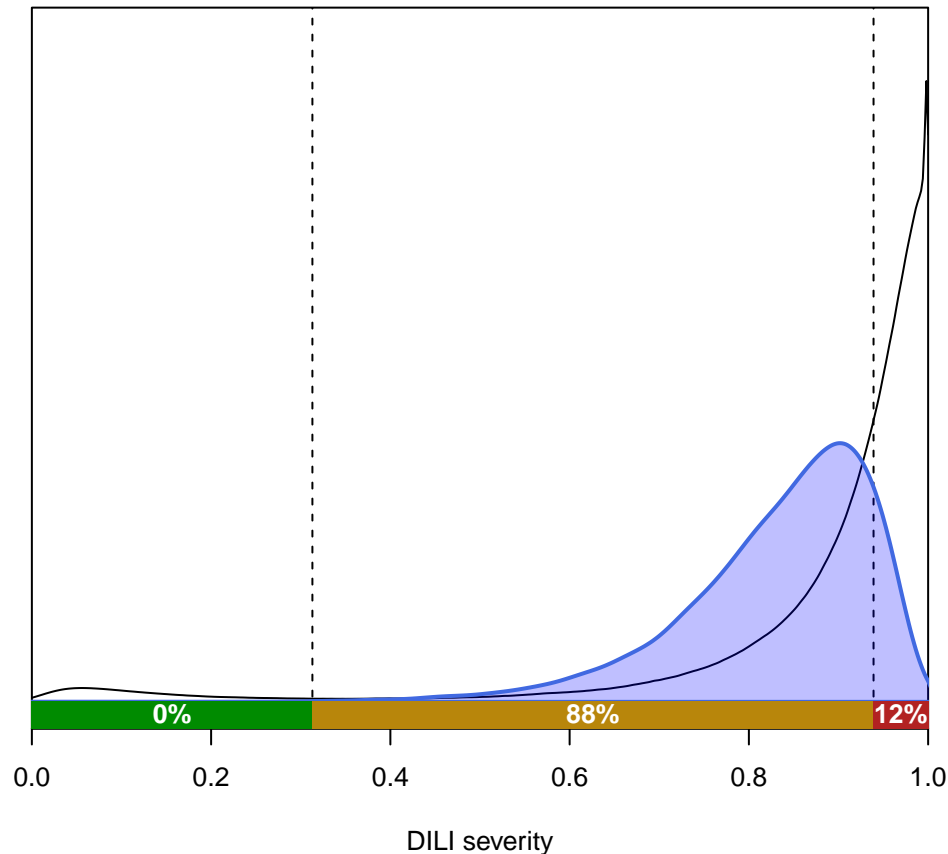
95% CI = 0.65 – 0.98



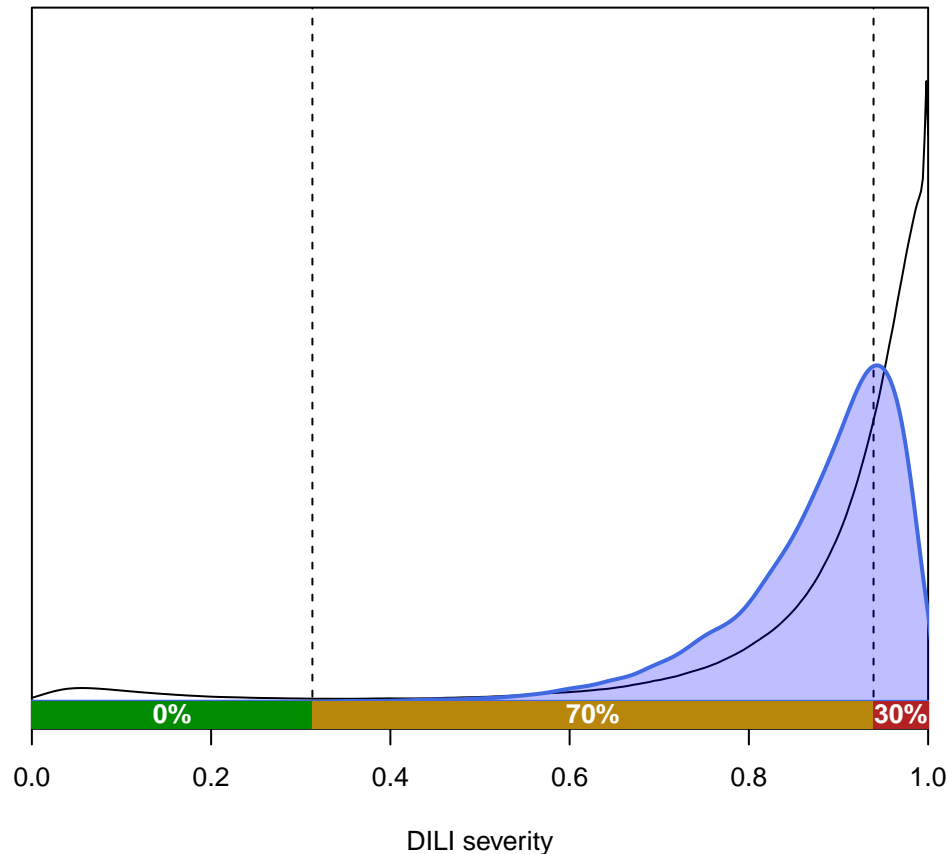
Ximelagatran



Zileuton



Zomepirac



Probability

- 0.06
- 0.56
- 0.38

True category

1

Summary stats

Peak = 0.94

Mean = 0.88

Median = 0.9

95% CI = 0.69 – 1

