Enhancing Visual Analytics Approaches in Safety Monitoring

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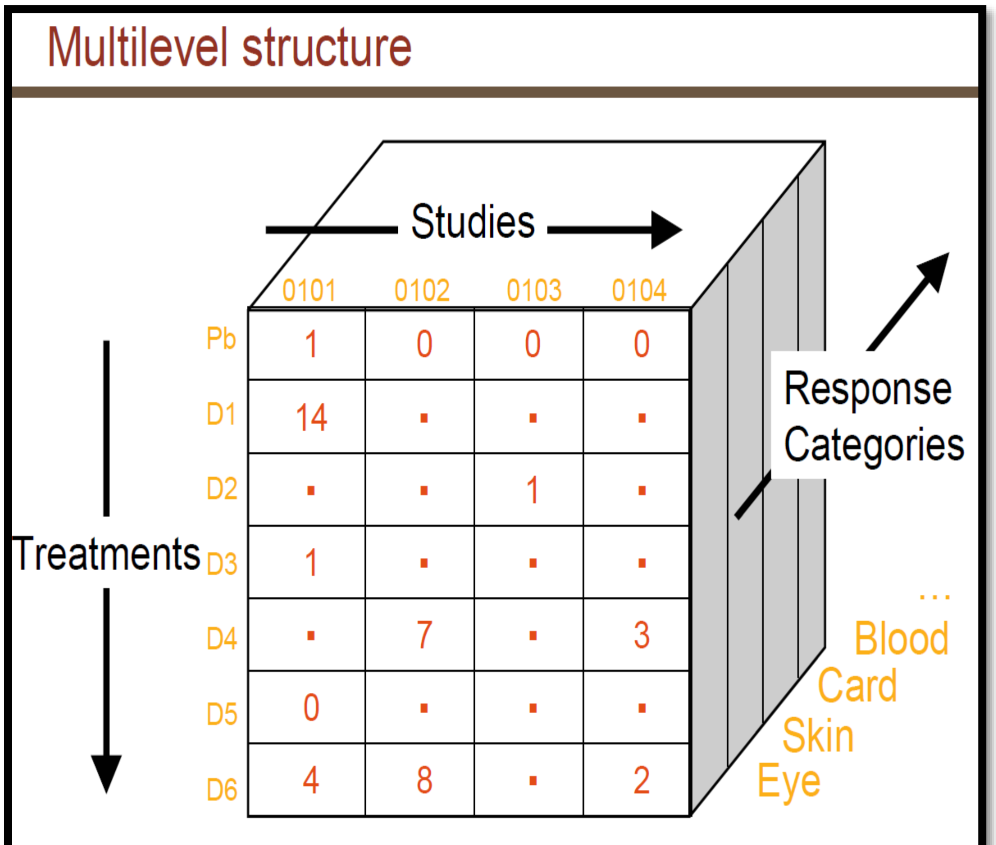
Outline

- Overview
- Asking the Right Question
- Enhancing Visual Analytics and Safety Monitoring
- Bayesian Analytic Graph with Example
- Choosing the Right Tools
- Concluding Remarks

Complexity of Safety Data



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D2	.	.	1	.
D3	1	.	.	.
D4	.	7	.	3
D5	0	.	.	.
D6	4	8	.	2

+

Other Safety Data

- Lab data
- Vital Signs
- ECG
- Etc

Characterize safety profile of drug…this may evolve over time

Source: http://www.meduniwien.ac.at/ROeS/ROeS_Seminar_Bern_2007/talks/ROeS2007_Kerman.pdf

Need for Graphs

- Safety data present many challenges with regard to analysis and interpretation:
  - Clinical trials generally not sufficient to detect safety signals
  - Safety data are multidimensional and interrelated in nature and some key safety concerns may not be unknown prior to trial
  - Pathological features of diseases lead to heterogeneous subpopulations and data with non-normal distributions
- Using tabular formats for safety data results in large volumes of output
  - Descriptive summary tabular outputs and individual patient data are rarely analytical
- There is great benefit to use visual methods to accompany or use with tabular formats or replace tabular formats altogether

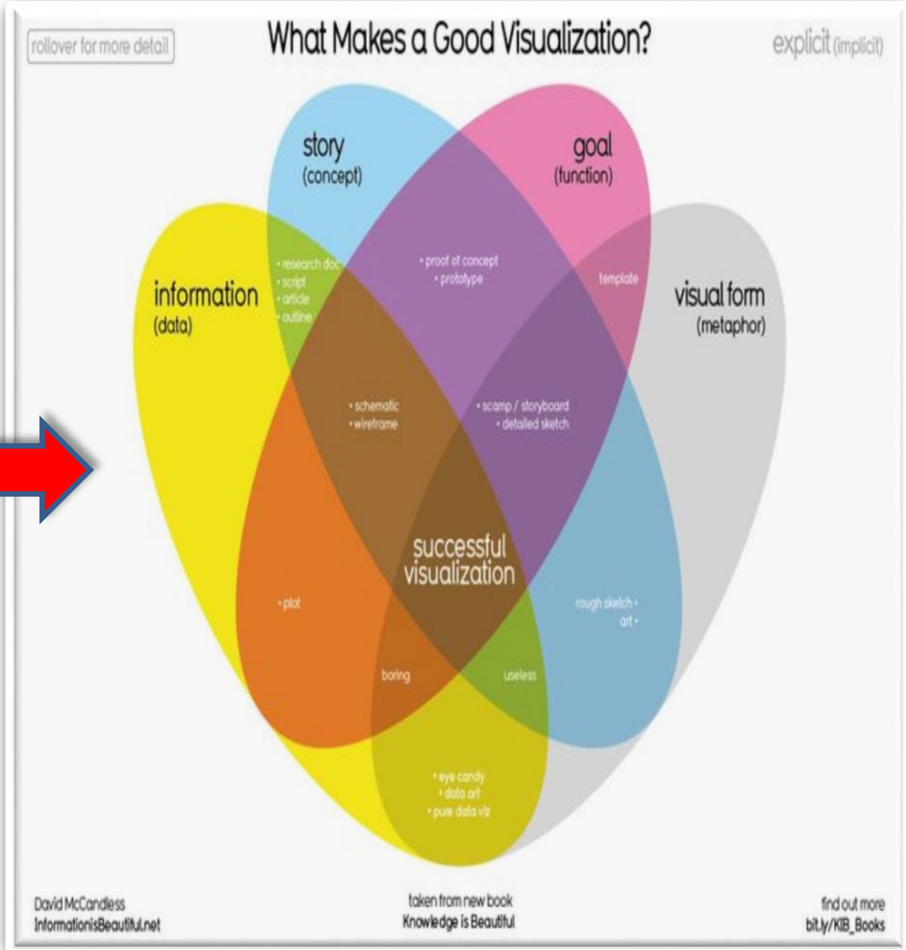
Need for Graphs

Harrell (2005)	• *Graphs, Not Tables!*
	  • *Have pity on statistical and medical reviewers*
	  • *Difficult to see patterns in tables*
	  • *Substituting graphs for tables increases efficiency of review*

Wittes (1996)	*A plethora of tables and graphs that describe safety may bury some true signal in a cacophony of numbers*
Vlachos (2015)	*Graphics are an underutilized resource in safety*
McKain et al (2015)	*Traditional case reviews and TLs not sufficient for safety surveillance principles – use graphs*
Regulatory Guidance	*ICH-E3, FDA Safety Review Guidance - recommendations for using visuals*

Graphs Principles

- *Duke (2014), Duke et al (2015) - Good graphing principles and good graphic design*
  - Graphs for safety data must also adhere to good graphing principles and good design for graph construction
  - There must be a goal, a story, information to be delivered and a visual form to make visualization successful
  - These aspects are especially in the context of safety monitoring in order to help identify safety signals early using visual forms



Source: http://www.informationisbeautiful.net/2015/workshops-are-beautiful-learn-our-dataviz-process/

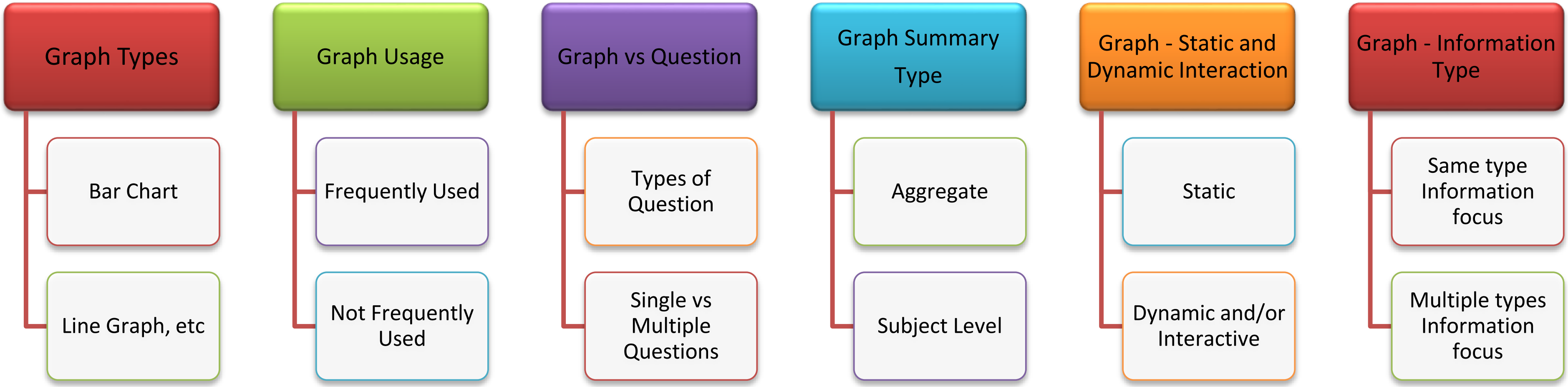
Asking the Right Question

- In order to effectively use visual analytics in safety monitoring, it is a good idea to begin with some questions with regards to safety data under consideration

Asking the Right Question

- Examples of some questions one may ask:
  - Which AEs are elevated in treatment versus control?
  - What is the constellation of AEs that come with the drug?
  - Is there any evidence of a dose-response-relationship?
  - Is the potential AE of interest increasing over time?
  - Is there a difference in the time to the first event across treatment groups?
  - Which AEs are elevated in patient subgroups?
  - What are the risk factors of the AE?
  - …

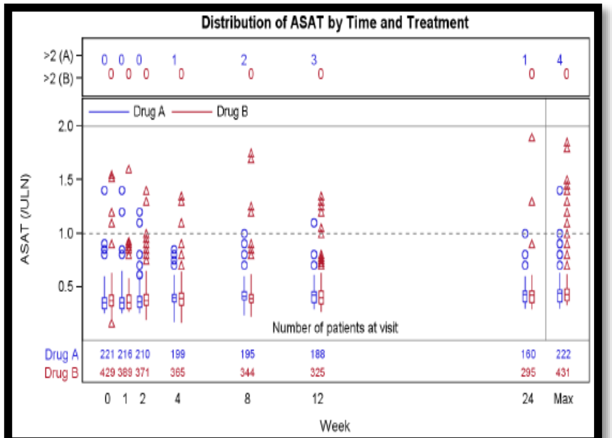
Graph Complexity

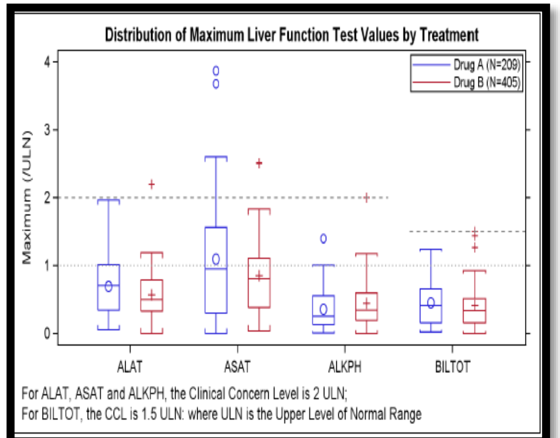


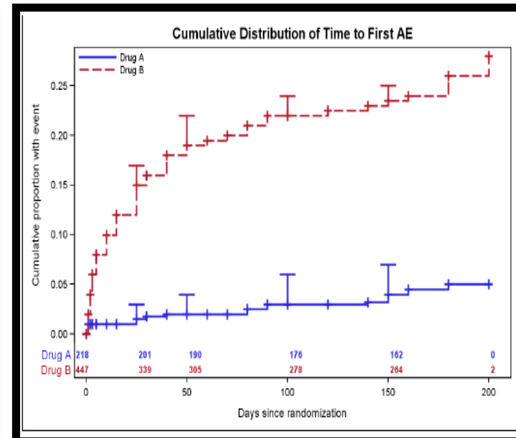
The most appropriate graph type depends on the clinical question and data available

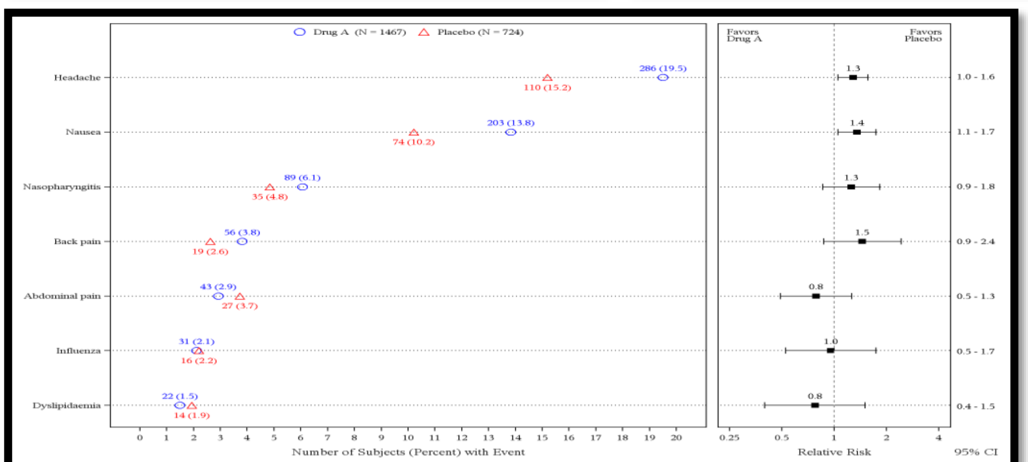
Some Considerations and Graph Choices

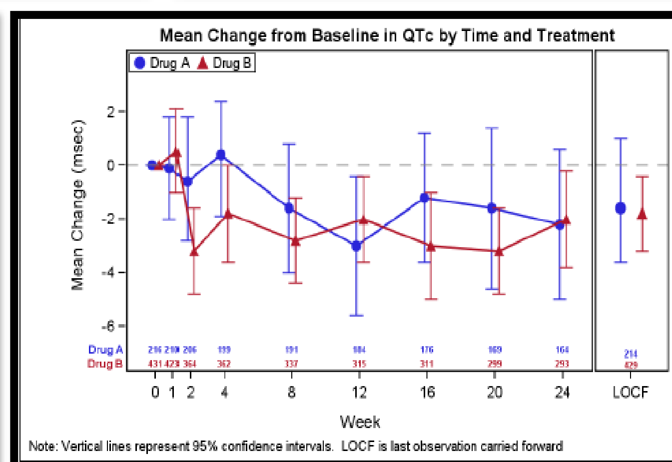
Main stream graphs in the analysis of safety data





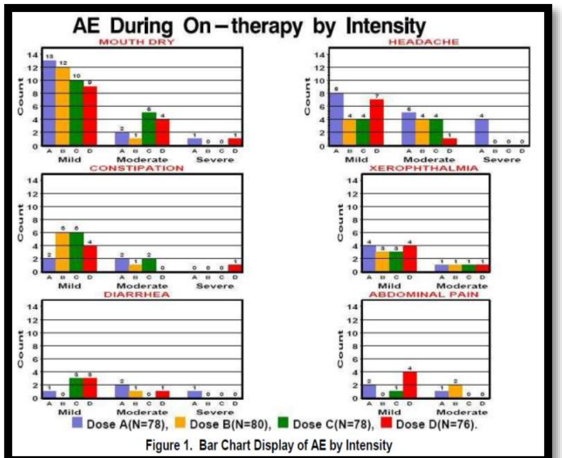


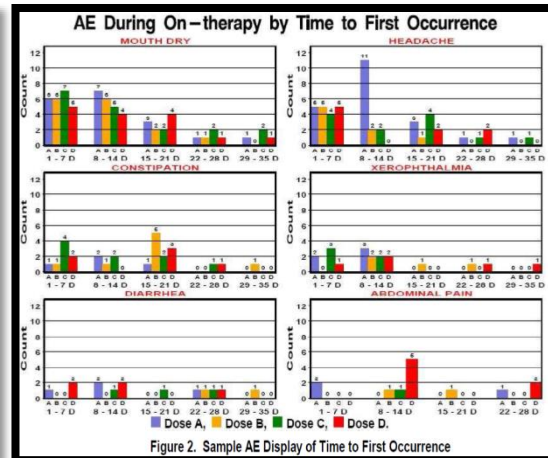


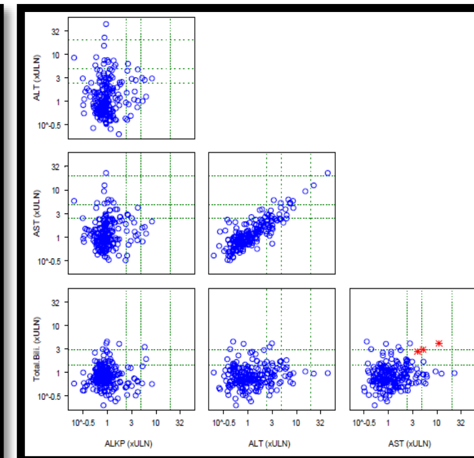


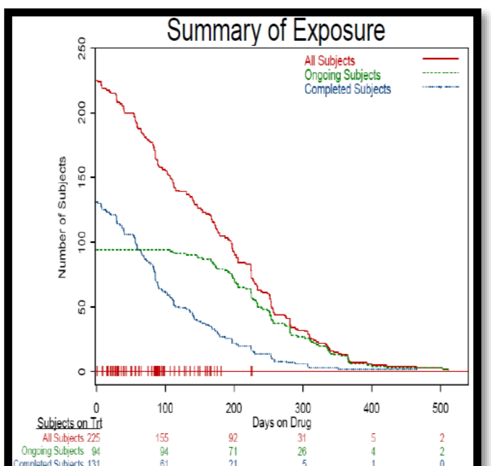
Some Considerations and Graph Choices

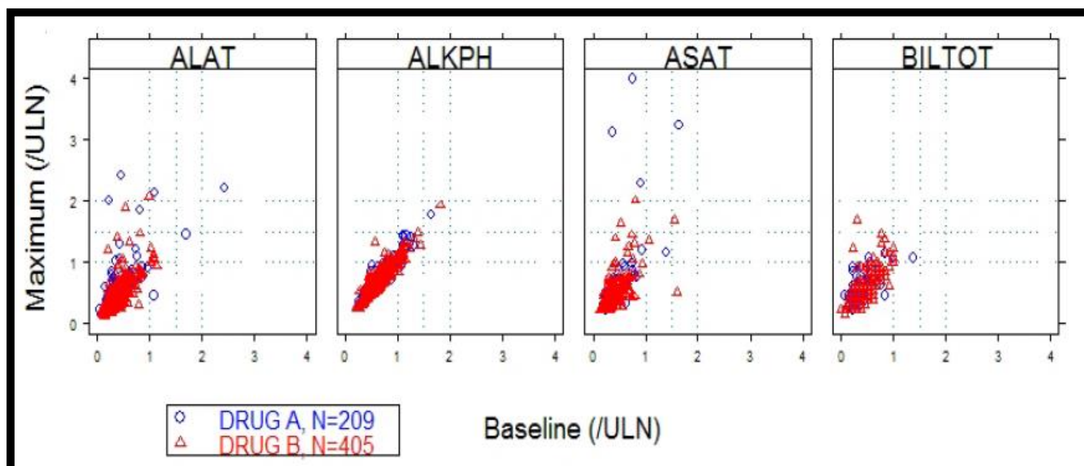
Main stream graphs in the analysis of safety data





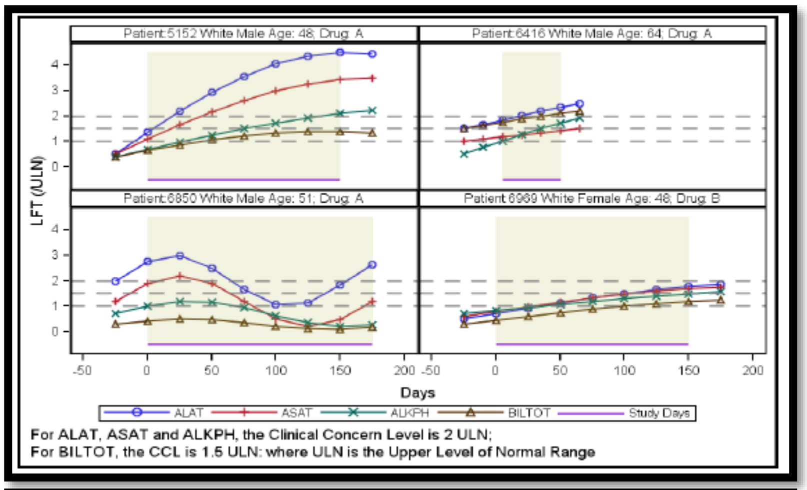


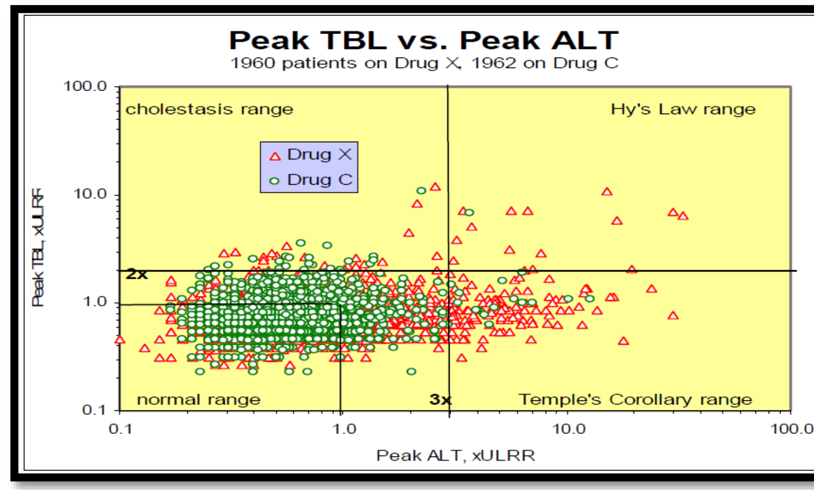


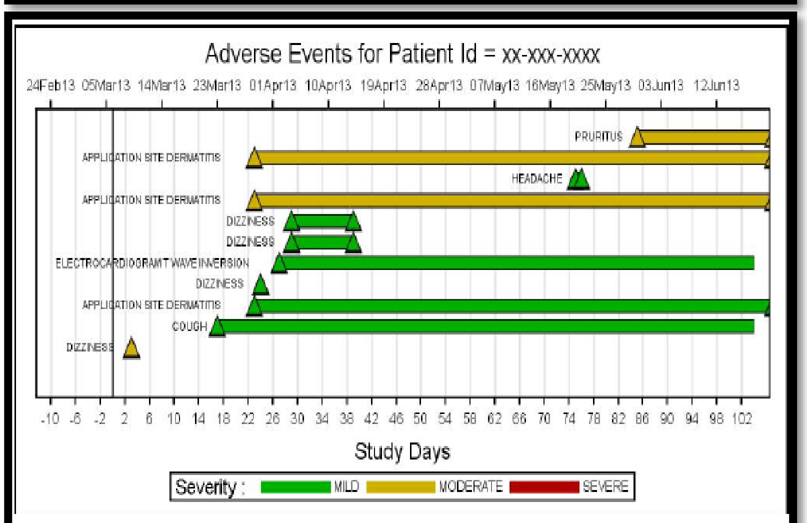


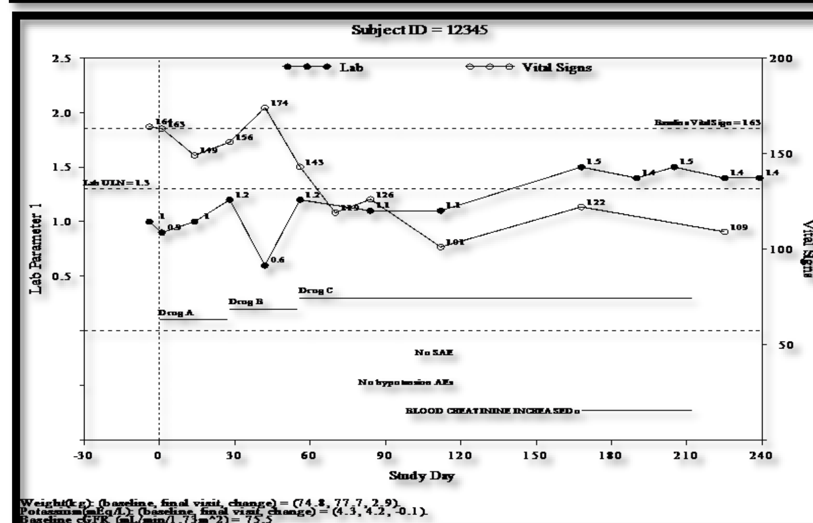
Some Considerations and Graph Choices

Main Stream Graphs in the Analysis of Safety Data









Some Considerations and Graph Choices

- Not so main stream graphs in the analysis of safety data

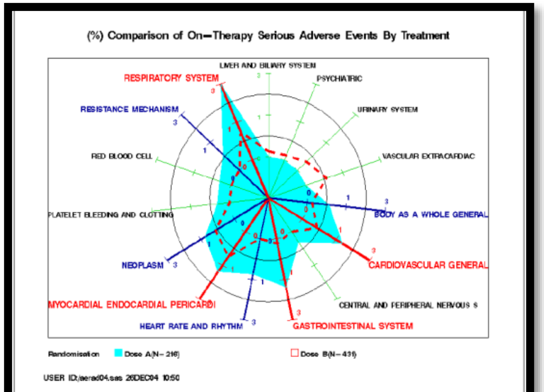


Figure 3. Wedge Type of Serious AE Display

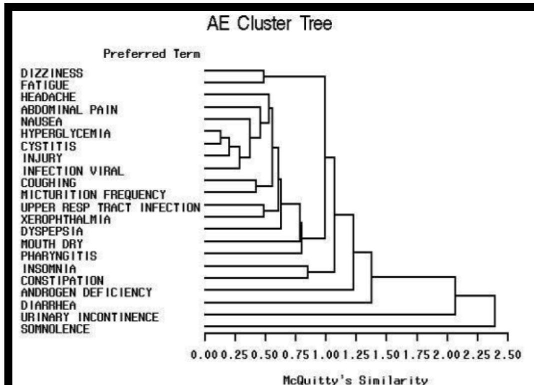


Figure 5. Sample AE Cluster Plot

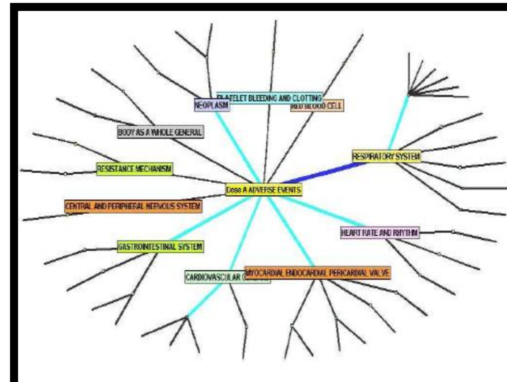


Figure 9. A Treeview of Serious AEs

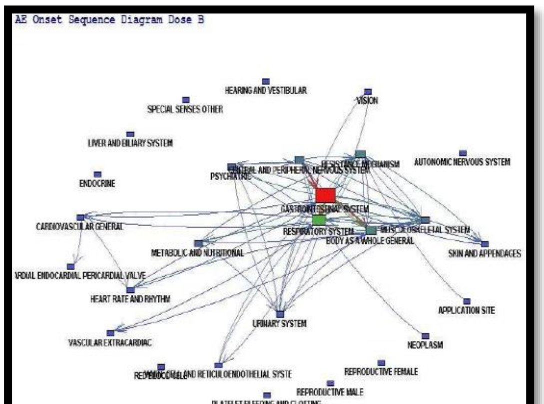


Figure 13. Constellation Display of AE Onset Sequence

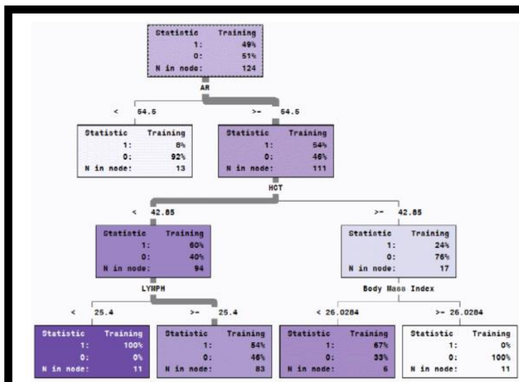
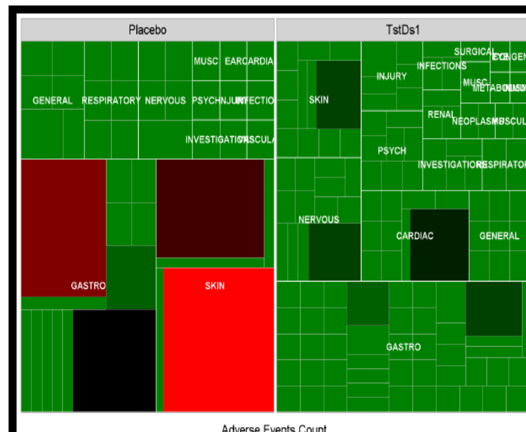


Figure 10. A Recursive Partition Tree for AE Occurrence Prediction

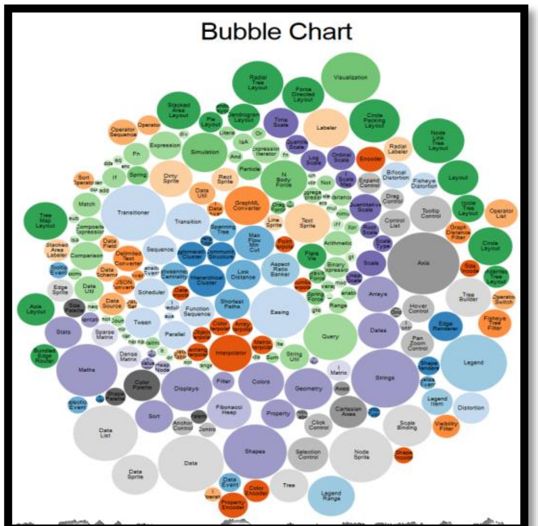
V. RADAR CHART

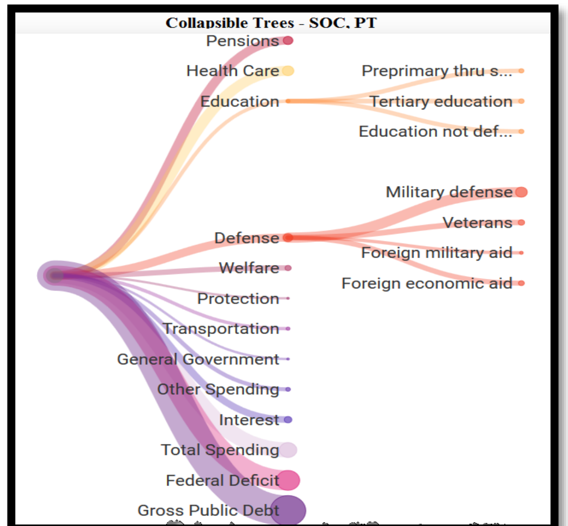


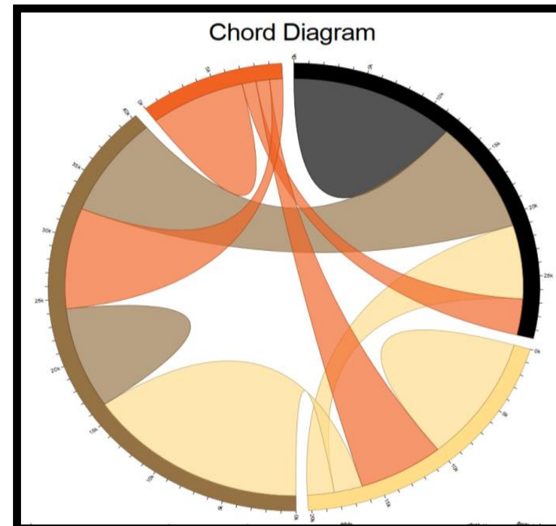
Graph enhancement? Interactivity, dynamic, animation, drill down, connectivity, etc

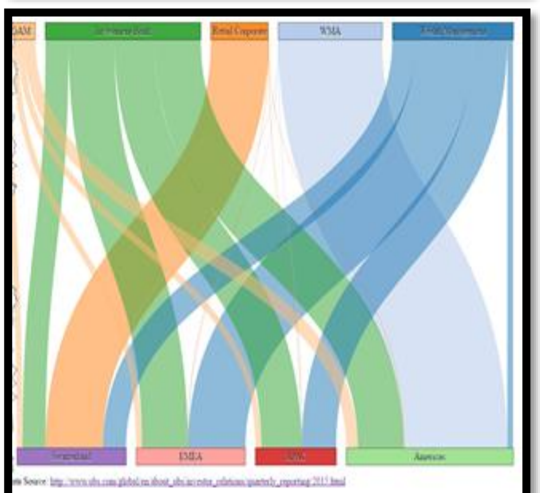
Some Considerations and Graph Choices

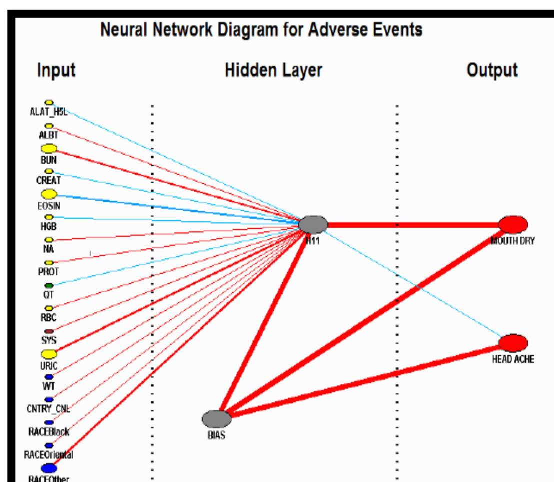
- *Borrow ideas from other areas*

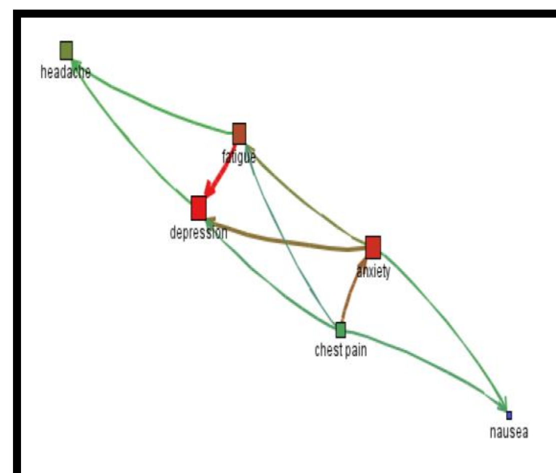








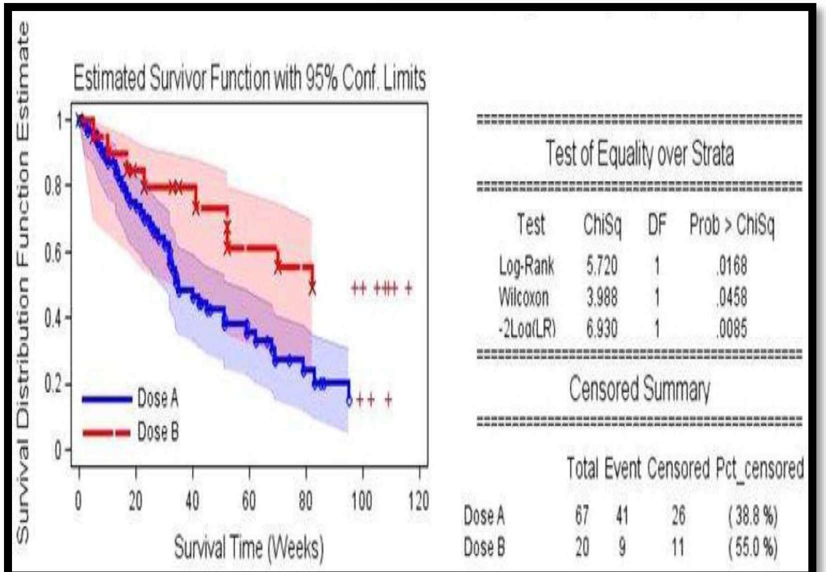




Enhancing Visual Analytics and Safety Monitoring

- Example: KM Plot – highlight details

Paper PO10
Clinical Adverse Events Data Analysis and Visualization
Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.



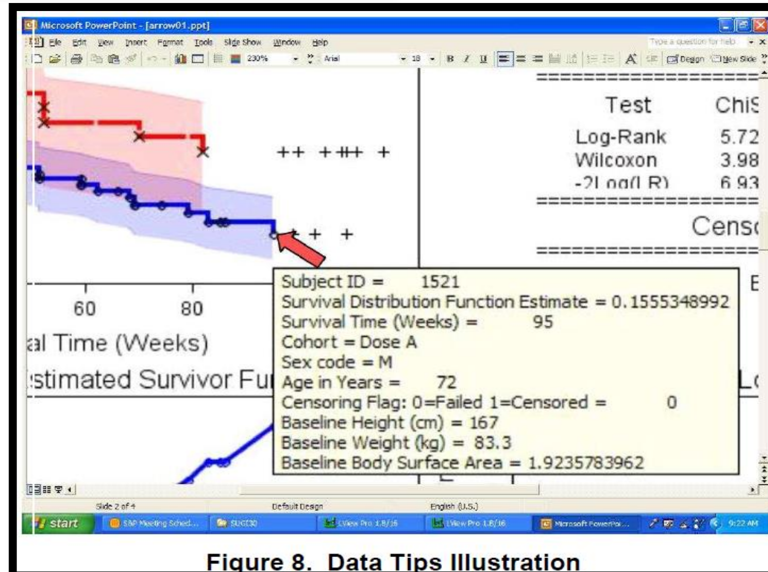


Figure 8. Data Tips Illustration

Static → **Enhancement** → **Package/App**

Adobe Acrobat Document

1_KM_Plot.html 2_KM_Plot.html

https://sachsmc.github.io/interactive-KM/

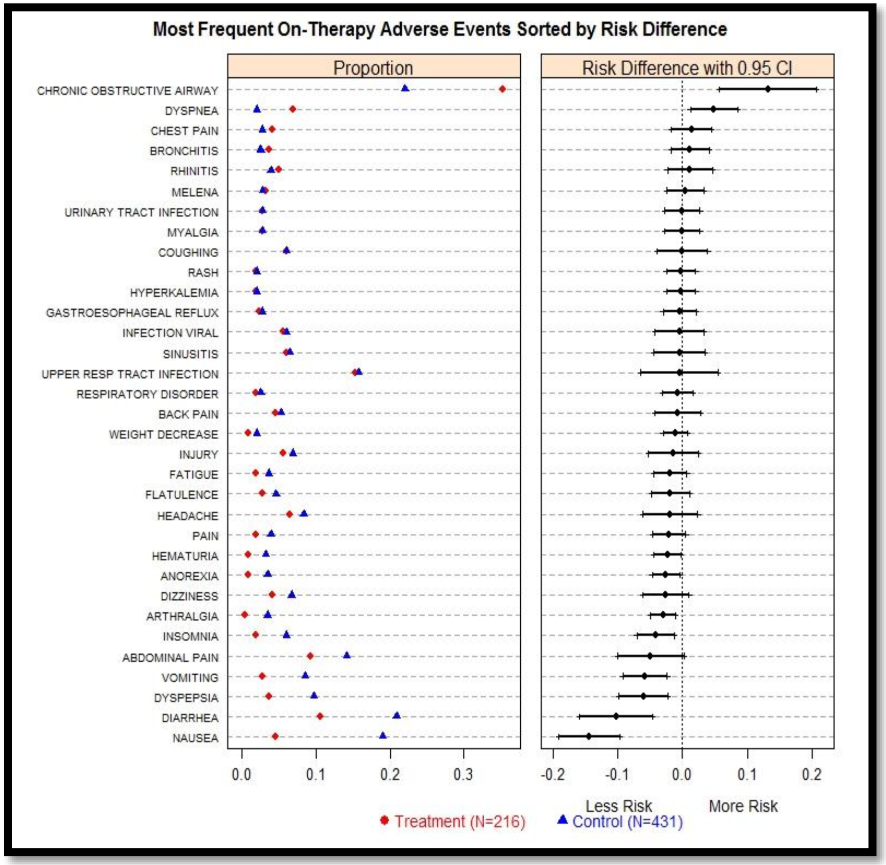
https://github.com/selcukorkmaz/geneSurv

Enhancing Visual Analytics and Safety Monitoring

- Enhance - make the graphs more useful in some way
  - Using other graphics outputs by borrowing new and informative visualization and tools, e.g., from visual analytics of big data, e.g., D3.js: https://github.com/d3/d3/wiki/Gallery
  - Incorporating Bayesian ideas in graphs, where applicable
  - Using readily available open source resources that are freely available

Enhancing Visual Analytics and Safety Monitoring

- Interactivity – Allow user to interact with the graphic - Examples



Enhancements

- https://www.rdocumentation.org/packages/HH/versions/3.1-34/topics/AEdotplot
- https://becca-krouse.shinyapps.io/aetableapp/
- https://rhoinc.github.io/viz-library/examples/0008-safetyExplorer-default/ae-table/

Incorporating Bayesian Thought

- Bayesian approaches
  - Provides a single, coherent framework in which diverse elements of the data can be modeled
  - Can handle multiplicity issue
  - Can be used in the modeling and prediction
  - Incorporates prior information
  - Does not rely on asymptotic properties in dealing with rare events

"Safety assessment is one area where frequentist strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise." (Pharmaceutical Report, 2002) – G.Chi, H.M. Hung, R. O‟Neill

Incorporating Bayesian Thought

- Example: Confidence Interval vs. Credible Interval
  - Confidence interval is a frequentist term meaning that with a large number of repeated samples, N% of times, the true value of the parameter will fall within the range of LCL – UCL
  - Credible Interval is a Bayesian term, can also be called 'Bayesian Posterior Interval'.
    - A Bayesian credible interval incorporates information from the prior distribution into the estimate, while confidence intervals are based solely on the data.
    - A N% credible interval for the parameter t is LCL – UCL means that the posterior probability that it lies in the interval from LCL – UCL is 0.N.

Incorporating Bayesian Thought

- Example – Rare events setting
  - Meta-Analysis setting for an AE of special interest – Bayesian approach to the rescue!

Table 1. CV Rare Adverse Events: Conventional Approach

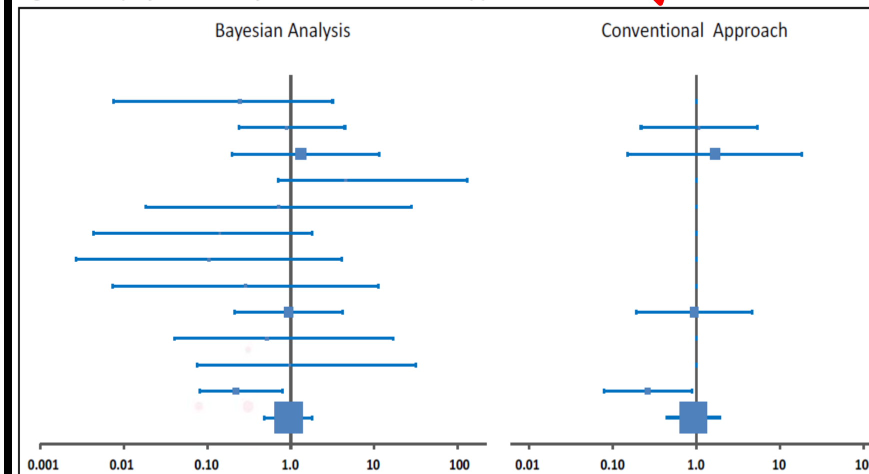
	Events		Exposure pt-years		Event rates				Relative Risk	
Study	Drug	placebo	Drug	placebo	Drug	95% CL	placebo	95% CL	RR	95% CL
1	0	1	59.5	35.3	0.0	(,)	28.3	(4.0 , 201.1)		(,)
2	6	2	100.9	36.1	59.5	(26.7 , 132.4)	55.4	(13.9 , 221.5)	1.07	(0.22 , 5.32)
3	2	1	31.1	25.7	64.3	(16.1 , 257.1)	38.9	(5.5 , 276.2)	1.65	(0.15 , 18.23)
4	7	0	118.1	48.6	59.3	(28.3 , 124.3)	0.0	(,)		(,)
5	0	0	102.8	73.4	0.0	(,)	0.0	(,)		(,)
6	0	1	53.0	18.1	0.0	(,)	55.2	(7.8 , 392.2)		(,)
7	0	0	47.8	5.0	0.0	(,)	0.0	(,)		(,)
8	0	0	121.3	34.7	0.0	(,)	0.0	(,)		(,)
9	3	3	128.9	120.9	23.3	(7.5 , 72.2)	24.8	(8.0 , 76.9)	0.94	(0.19 , 4.65)
10	1	0	90.9	19.5	11.0	(1.5 , 78.1)	0.0	(,)		(,)
11	1	0	52.4	20.9	19.1	(2.7 , 135.5)	0.0	(,)		(,)
12	20	3	948.6	37.2	21.1	(13.6 , 32.7)	80.6	(26.0 , 250.1)	0.26	(0.08 , 0.88)
Total	40	11	1855.3	475.4					0.92	(0.44 , 1.92)

Overall relative risk estimated by the MH approach

Table 2. CV Rare Adverse Events: Bayesian Approach

Events		Exposure pt-years		Event rates				Bayes Relative Risk	
Drug	placebo	Drug	placebo	Bayes rate	95% CI	Bayes rate	95% CI	RR	95% CI
0	1	59.5	35.3	11.6	(0.43 , 62.0)	47.5	(6.86 , 157.8)	0.25	(0.008 , 3.16)
6	2	100.9	36.1	66.1	(27.89 , 129.4)	74.1	(17.14 , 200.1)	0.89	(0.238 , 4.42)
2	1	31.1	25.7	86.0	(19.89 , 232.3)	65.3	(9.42 , 216.8)	1.32	(0.199 , 11.40)
7	0	118.1	48.6	64.9	(29.24 , 122.1)	14.3	(0.52 , 75.9)	4.55	(0.702 , 129.83)
0	0	102.8	73.4	6.7	(0.25 , 35.9)	9.4	(0.34 , 50.3)	0.71	(0.018 , 27.85)
0	1	53.0	18.1	13.1	(0.48 , 69.6)	92.7	(13.38 , 307.8)	0.14	(0.004 , 1.82)
0	0	47.8	5.0	14.5	(0.53 , 77.2)	138.6	(5.06 , 737.8)	0.10	(0.003 , 4.08)
0	0	121.3	34.7	5.7	(0.21 , 30.4)	20.0	(0.73 , 106.3)	0.29	(0.007 , 11.16)
3	3	128.9	120.9	28.5	(8.46 , 68.0)	30.4	(9.01 , 72.5)	0.94	(0.212 , 4.16)
1	0	90.9	19.5	18.5	(2.66 , 61.3)	35.5	(1.30 , 189.2)	0.52	(0.040 , 16.84)
1	0	52.4	20.9	32.0	(4.62 , 106.3)	33.2	(1.21 , 176.5)	0.96	(0.075 , 31.31)
20	3	948.6	37.2	21.8	(13.70 , 32.6)	98.7	(29.30 , 235.7)	0.22	(0.082 , 0.79)
40	11	1855.3	475.4					0.94	(0.480 , 1.81)

Figure 1. Display of Data: Bayesian vs Conventional Approaches



Case Study: Meta-Analysis of Rare Adverse Events

Source: https://www.kjcstatistics.com/wp-content/uploads/2016/07/KJC_Meta-Analysis-for-Rare-Adverse-Events.pdf

Incorporating Bayesian Thought

- Bayesian modeling is a natural choice to incorporate the complex hierarchical structure of the AE data
- Hierarchical mixture models by Berry & Berry(2004)
  - Three-level hierarchical mixed model
    - The most basic level is type of AE.
    - The second level is body system, each of which contains a number of types of possibly related Aes
    - The highest level is the collection of all body systems.
    - Our analysis allows for borrowing across body systems, but there is greater potential-depending on the actual data-for borrowing within each body system.

  - Current traditional approach of flagging routinely collected AEs based on unadjusted p-values or CIs can result in excessive false positive signals
  - Simulation showed that the FWERs/FDRs for Bayes model results are much lower

Incorporating Bayesian Thoughts

- Example – Volcano Plot using P-value (frequentist) versus use of OR (Bayesian) (Xia, Ma, Carlin 2011)
  - Bayesian inference on volcano plot
  - AE_{bj} is flagged if
    - $Pr(\theta_{bj} > d^* \mid Data) > p$, where θ_{bj} is log-OR in Binomial models and log-RR in Poisson models
    - d^* and p are pre-specified constants

Frequentist Using Fishers Exact test

Bayesian Version Using P(OR > 1)

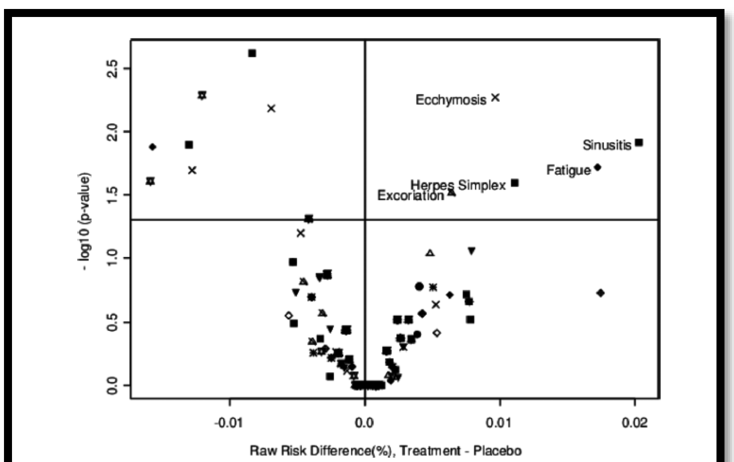


Figure 1 Volcano plot of risk differences versus unadjusted Fisher's exact test *p*-values.

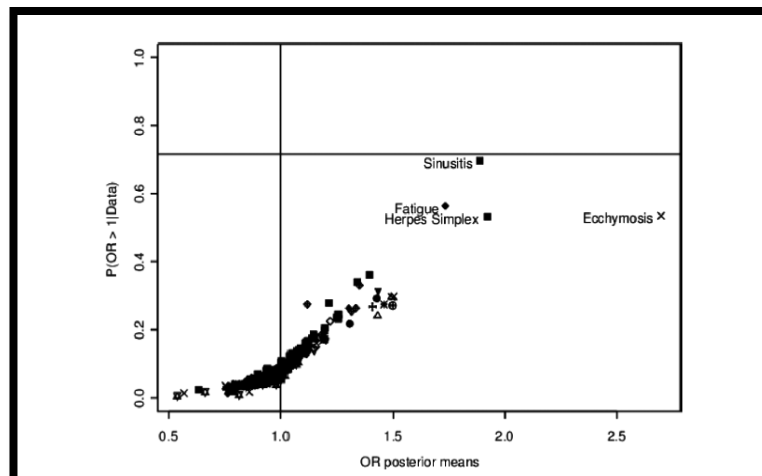


Figure 2 Volcano plot of posterior estimates from binomial hierarchical model with mixture prior.

Visual Tool Selection

- There are many tools (commercial and free) available that can be used in visual analytics in safety monitoring

Older Tools

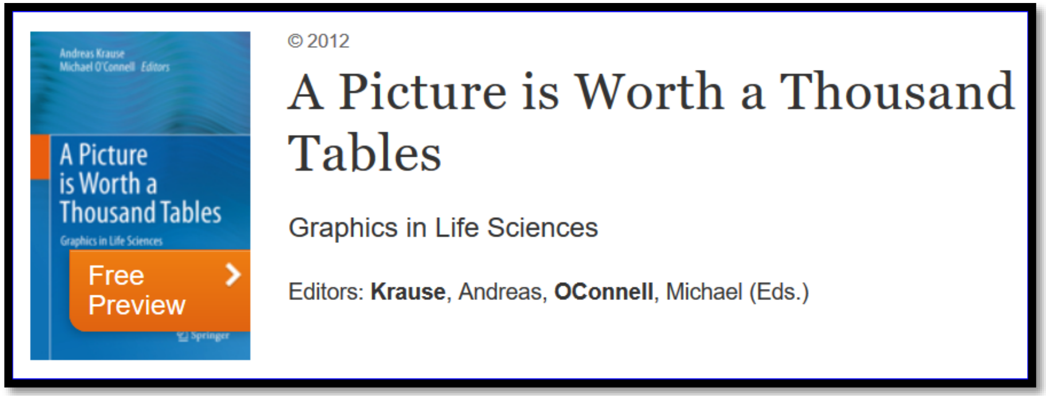
- SAS, SAS JMP,
- JReview
- Splus, Spotfire
- SAS, JMP
- J-Review

Newer Tools

- R, R Shiny, R html widgets, Numerous R Packages
- SAS JMP Clinical
- Python, Jypiter Notes, Rodeo
- Tableau, QlikView
- Java, D3.js

Visual Analytics and Safety Monitoring Efforts

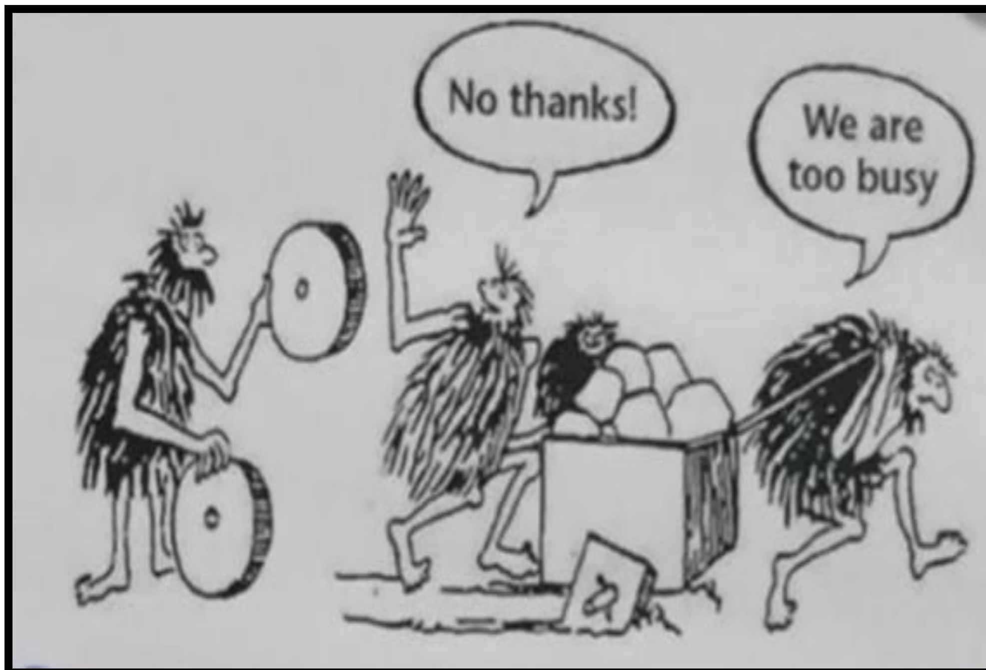
– Some collaborative commendable efforts, e.g.,
  - CTSPedia
    - http://www.ctspedia.org/do/view/CTSpedia/AllGraphicalEntries
  - A Picture is Worth a Thousand Tables
    - http://www.elmo.ch/doc/life-science-graphics/



Concluding Remarks

- Visual analytics can help in safety monitoring and safety data analysis
- Utilizing visualization tools can help exploration and substantially improve information gain for safety monitoring activities
- Consider the important principles of graph construction in safety monitoring
- The visual type and tool used depend on the questions under consideration in the safety monitoring activity
- Various visual enhancements tools available for the end-user allowing for efficient safety monitoring
- Bayesian modeling is a natural choice to incorporate the complex hierarchical structure of the AE data
- Embrace new ideas

Time to Embrace New Ideas!



It's easy to get stuck in your ways.. Don't be too busy to try new ideas.
buffer-media-uploads.s3.amazonaws.com

Acknowledgement

- Rebecca Krouse, Jeremy Wildfire, Ryan Bailey – Rho Inc.
  – SafetyExplorer Tool
- Junfang Chen – Takeda
  – Visual analytics implementation
- Collaborators in WS 2
  – Karolyn Kracht - AbbVie


Q&A

Reference