

# Advanced Statistical Graphics – a smart and intuitive approach

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# Agenda

- **Statistical Graphics for Clinical Trials**
- **Generation of Reporting Graphics**
  - Creation of a graph template via Point&Click
  - Apply template to different data set
  - Use template in production – via SAS
- **Statistical Graphics and Analysis used interactively**
  - Introduction to interactive analysis
  - How to integrate statistical analysis and graphics
    - Assessing treatment effects on AE using Bagging
    - Time-to-Event Analysis
    - Bivariate Analysis

# Clinical (Statistical) Graphics – Areas of Usage

*Many domains, functions benefit from statistical graphics*

- Trial Design
- Safety Data Analysis
  - Laboratory Measurements
  - Vitals Signs Measurements
  - Adverse Events
- Efficacy Data Analysis
- Patient Profiles
- Demographics
- Trial Metrics

*O'Connell and Pietzko (2009), Statistical Graphics for Exploration  
Presentation, Publication and Submission in Clinical Development  
TIBCO Whitepaper ([available here](#))*

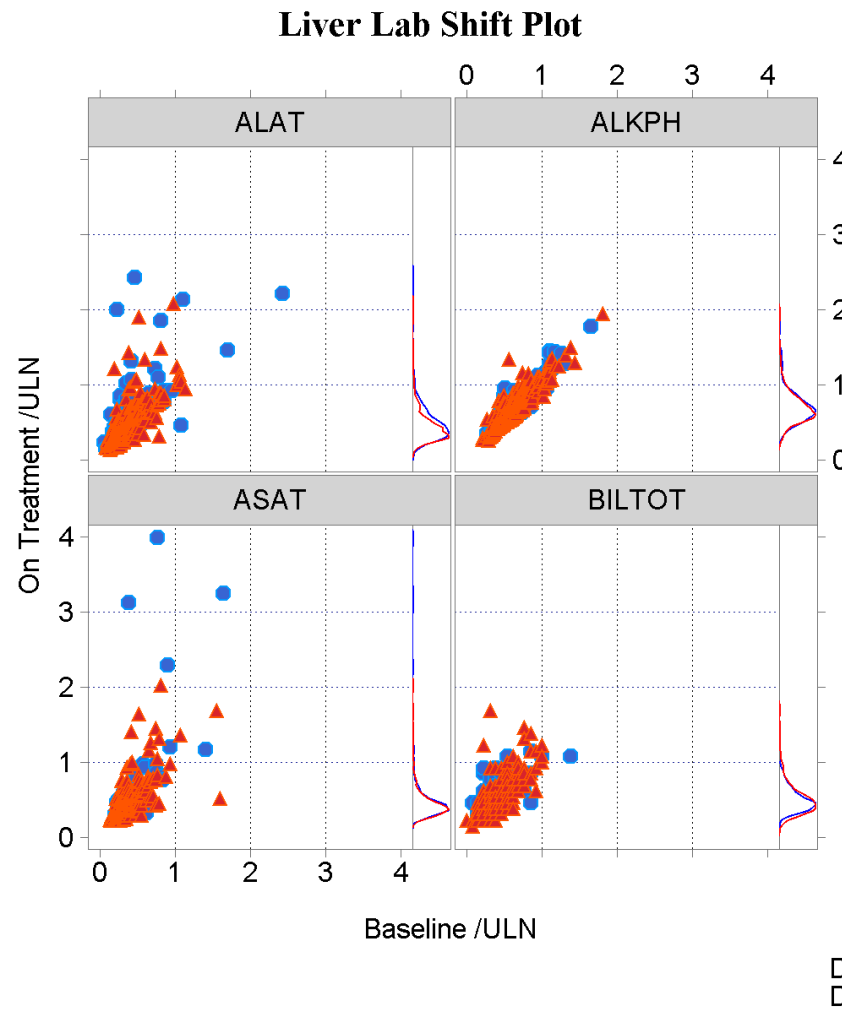
# Reporting: TIBCO Spotfire Clinical Graphics - Usage

1. **Best Practice Graphics Catalogue –**
  - Inbuilt Palette
  - Customization
2. **Point & Click Interface to all Graphs in the “Catalogue”**
3. **SAS Macros for all Graphs in the “Catalogue”**

**Example: Lab Shift Plot**

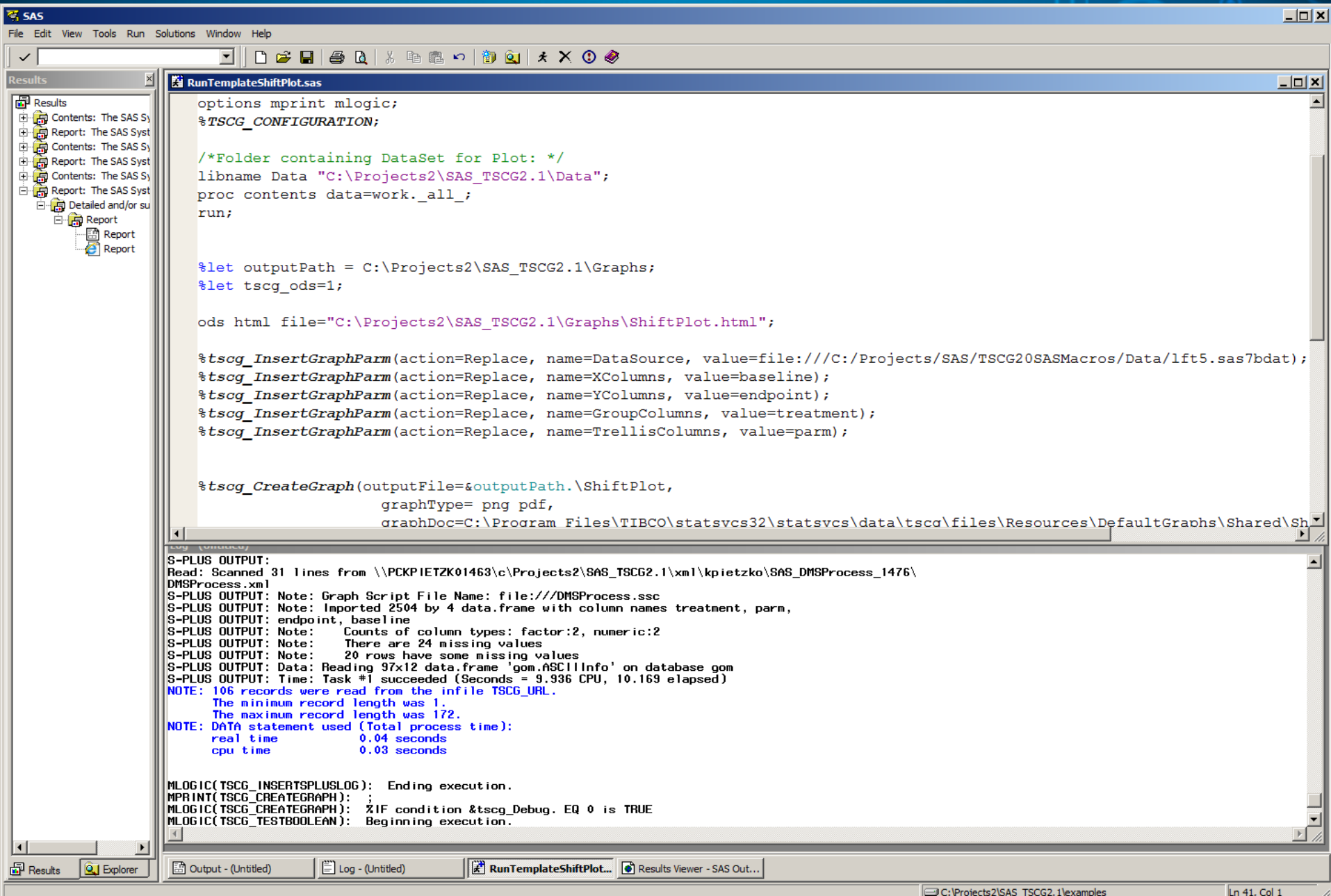
Standardization - best practices and efficiencies

# Shift Plot



Data: <http://PCKPIETZKO01197:8080/SplusServer/webdav/tscg/files/DataSources/Users/kpietzk0/ltf5.sas7bdat>  
Author: kpietzk0  
Last Modified: 2009-08-24T11:44:42.6250000+02:00  
Version: 2.0.1; Validation: Not Validated

# SAS Macros - Calling a Template from inside SAS



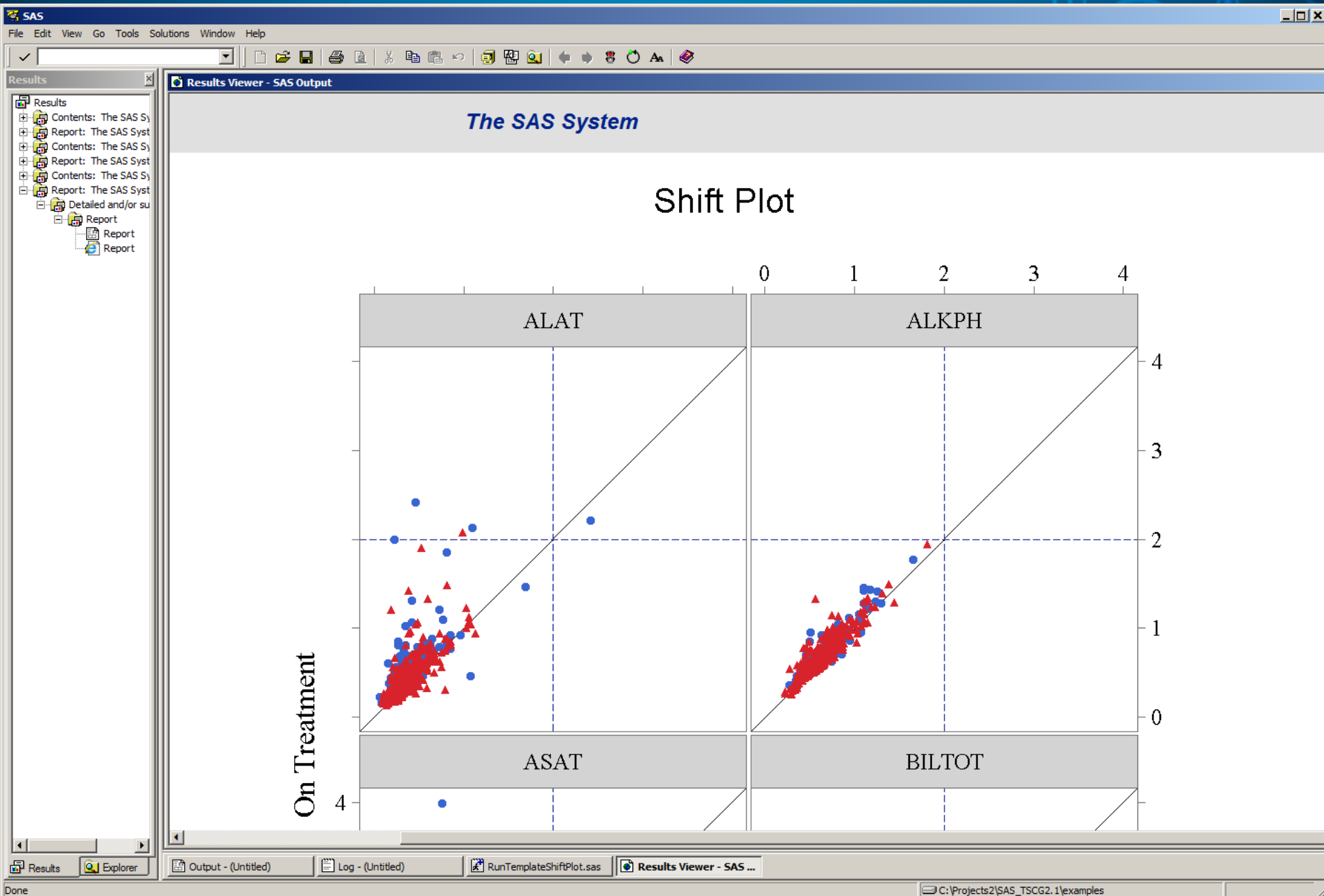
The screenshot displays the SAS IDE interface. The main editor window shows the macro code for `RunTemplateShiftPlot.sas`. The macro includes options for printing and logging, sets a library path to `C:\Projects2\SAS_TSCG2.1\Data`, and defines the output path as `C:\Projects2\SAS_TSCG2.1\Graphs`. It uses the `%tscg_InsertGraphParm` macro to configure the graph parameters and the `%tscg_CreateGraph` macro to generate the plot.

The Results pane shows the output of the macro execution, including the following log messages:

```
S-PLUS OUTPUT:  
Read: Scanned 31 lines from \\PCKPIETZK01463\c\Projects2\SAS_TSCG2.1\xml\kpietzk\SAS_DMSProcess_1476\  
DMSProcess.xml  
S-PLUS OUTPUT: Note: Graph Script File Name: file:///DMSProcess.ssc  
S-PLUS OUTPUT: Note: Imported 2504 by 4 data.frame with column names treatment, parm,  
S-PLUS OUTPUT: endpoint, baseline  
S-PLUS OUTPUT: Note: Counts of column types: factor:2, numeric:2  
S-PLUS OUTPUT: Note: There are 24 missing values  
S-PLUS OUTPUT: Note: 20 rows have some missing values  
S-PLUS OUTPUT: Data: Reading 97x12 data.frame 'gom.ASCIIInfo' on database gom  
S-PLUS OUTPUT: Time: Task #1 succeeded (Seconds = 9.936 CPU, 10.169 elapsed)  
NOTE: 106 records were read from the infile TSCG_URL.  
The minimum record length was 1.  
The maximum record length was 172.  
NOTE: DATA statement used (Total process time):  
real time 0.04 seconds  
cpu time 0.03 seconds  
  
MLOGIC(TSCG_INSERTSPUSLOG): Ending execution.  
MPRINT(TSCG_CREATEGRAPH): ;  
MLOGIC(TSCG_CREATEGRAPH): %IF condition &tscg_Debug. EQ 0 is TRUE  
MLOGIC(TSCG_TESTBOOLEAN): Beginning execution.
```

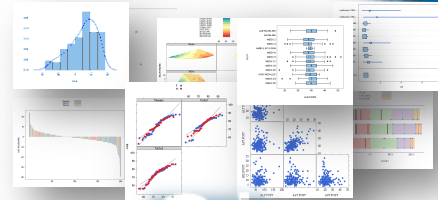
The bottom status bar indicates the current file is `C:\Projects2\SAS_TSCG2.1\examples` and the cursor is at line 41, column 1.

# SAS Macros - Calling a Template from inside SAS



# Clinical Graphics Concept

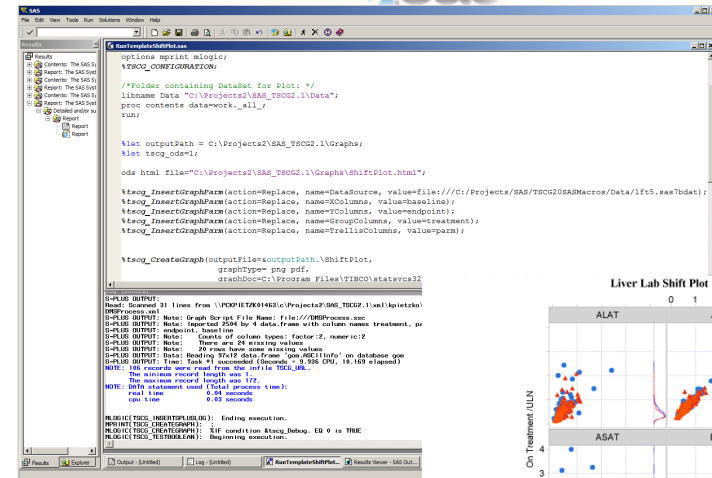
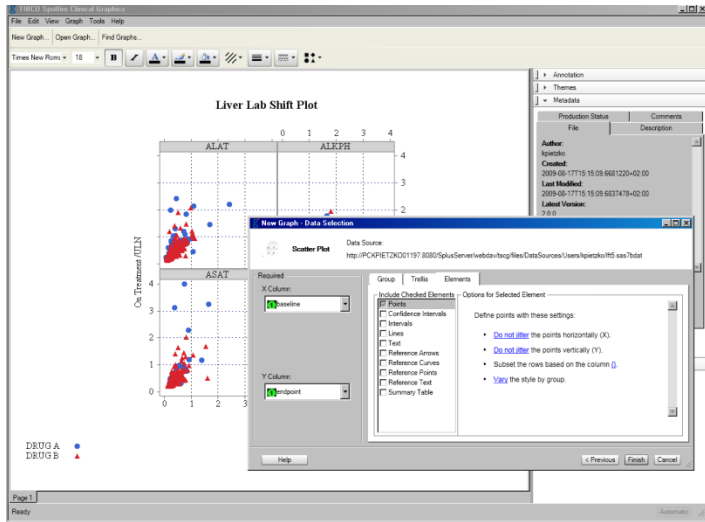
## S+ Clinical Graphics Server Central Graph Catalogue



S+

sas

S+ TIBCO Spotfire® Clinical Graphics



Point & Click  
Create Templates  
Ad Hoc Reporting

SAS Macros  
Batch Production

Date: http://PCP/ETZK001197/8080/SpotfireServer/webdav/tug/has/DataSources/Users/spotfire05.sas?url=tbl  
Author: spotfire  
Last Modified: 2009-08-24T11:44:02+0200+0200  
Version: 2.0.1, Validation: Not Validated

# Clinical Trials - Safety Data Analysis

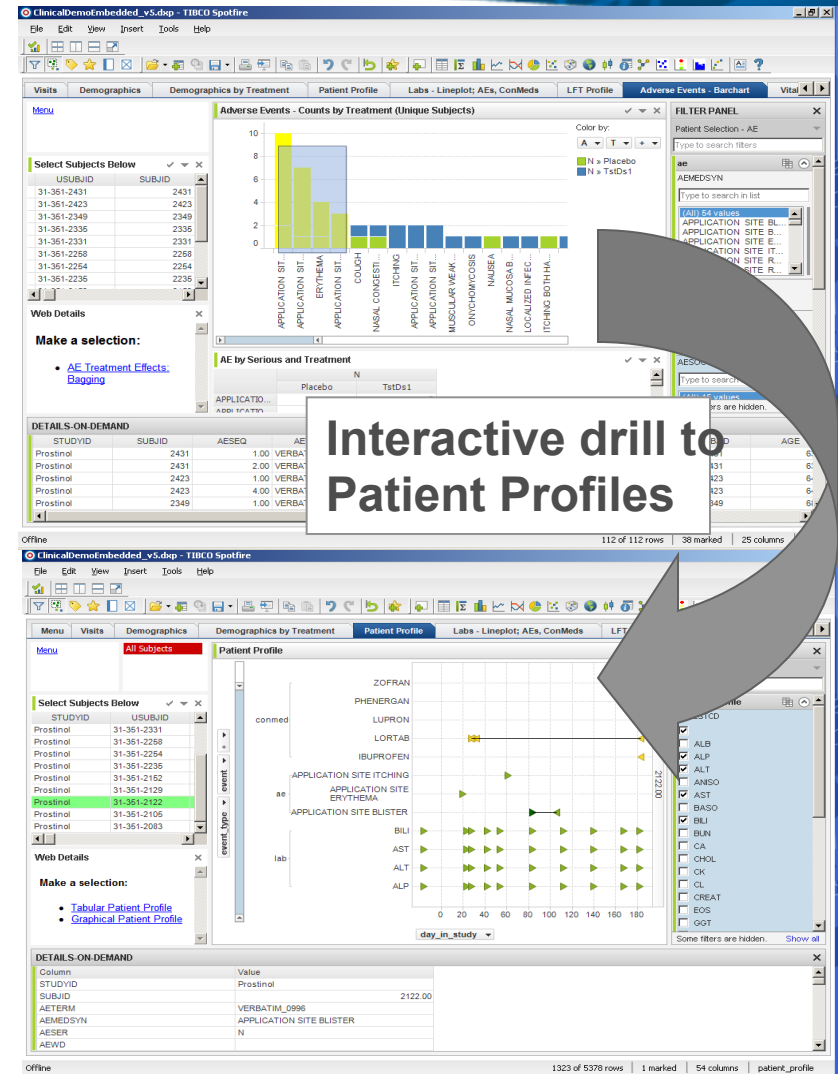
- **Lots of data**
- **Analysis of data – early and often**
  - Data Visibility is needed
- **Statistics / Analytics are required**
  - Statistics: analyze data at population level
  - Analyze data at subject level
- **Graphics – the key to success**
  - Targeted statistical graphics: AE' s, labs, vitals
  - Interactive data review – drill down to patient level
  - **Graphical Review – early and often !!**



# Safety Data Analysis – using Spotfire and S-Plus

- Identify relationships in data
  - Safety vs dosing, exposure, conmeds, AEs...
- Fast medical review of clinical data
  - Explore the crucial data – AEs, labs, demog, drug exposure, drug response, conmeds etc.
  - Decrease manual listings, processes
- Rapid data quality assessment

**+ Add statistical value to it**



# Safety Data Analysis– Assessing Treatment Effect on AE

|                | <b>X variables</b> (explanatory variables) |             |            |             | <b>Y variable</b> |
|----------------|--------------------------------------------|-------------|------------|-------------|-------------------|
| <b>Subject</b> | <b>AE-1</b>                                | <b>AE-2</b> | <b>...</b> | <b>AE-n</b> | <b>Treatment</b>  |
| 1001           | ...                                        | ...         | ...        | ...         | Placebo           |
| 1002           | ...                                        | ...         | ...        | ...         | Treated           |
| ...            | ...                                        | ...         | ...        | ...         | ...               |
| 1200           | ...                                        | ...         | ...        | ...         | Placebo           |

One Model in Southworth and O' Connell (2009) is

$$Y = f(X, b) + e$$

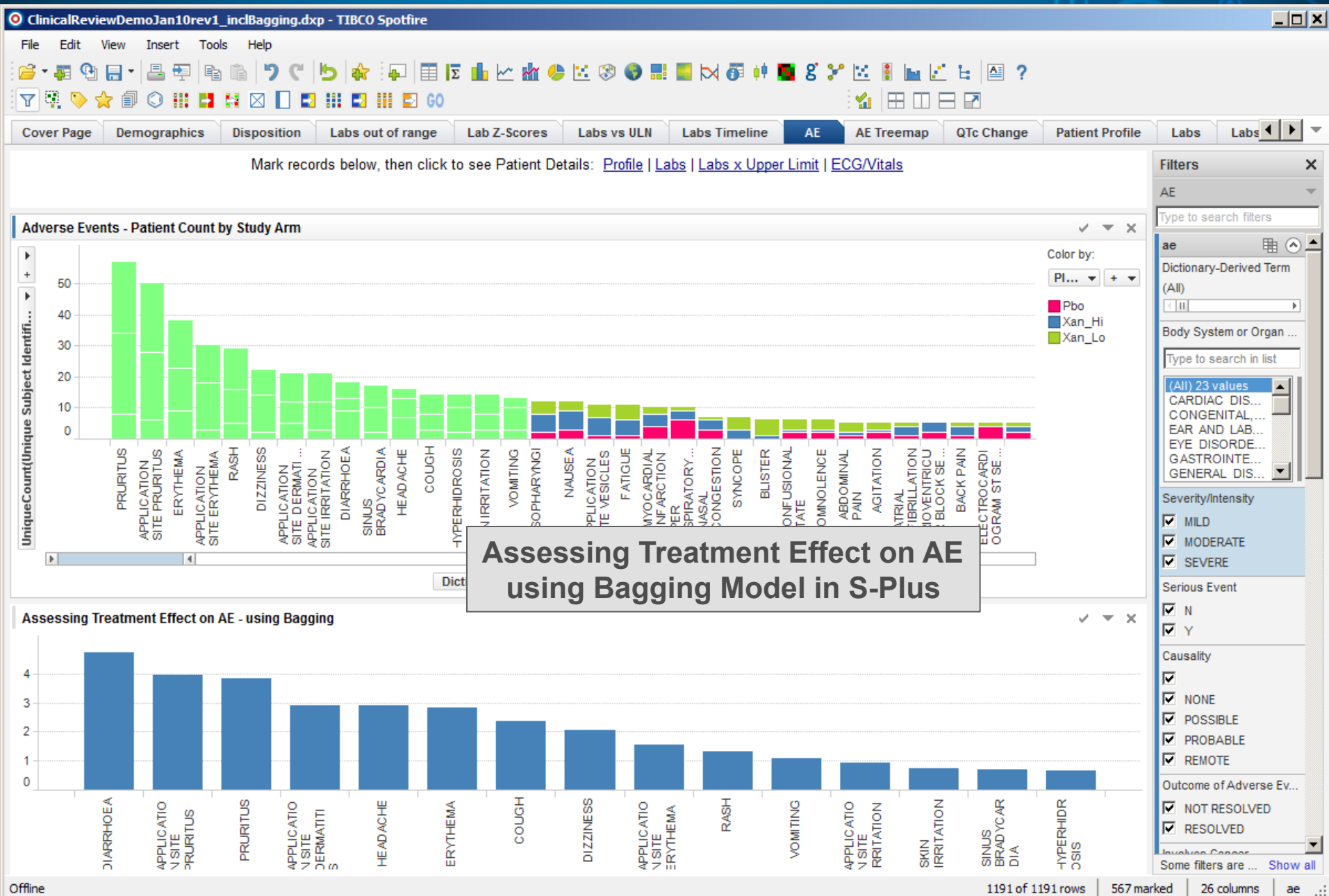
**f** is forest of classification trees (bagging)

- Resample data matrix (bootstrap, with replacement)
- Fit tree to each sample; average (vote) over all trees

Calculate **Variable Importance** for each **AE** from forest

- High Variable Importance => potential treatment-emergence

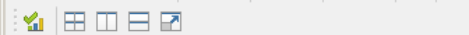
# Safety Data Analysis - interactive



# Survival Analysis - interactive

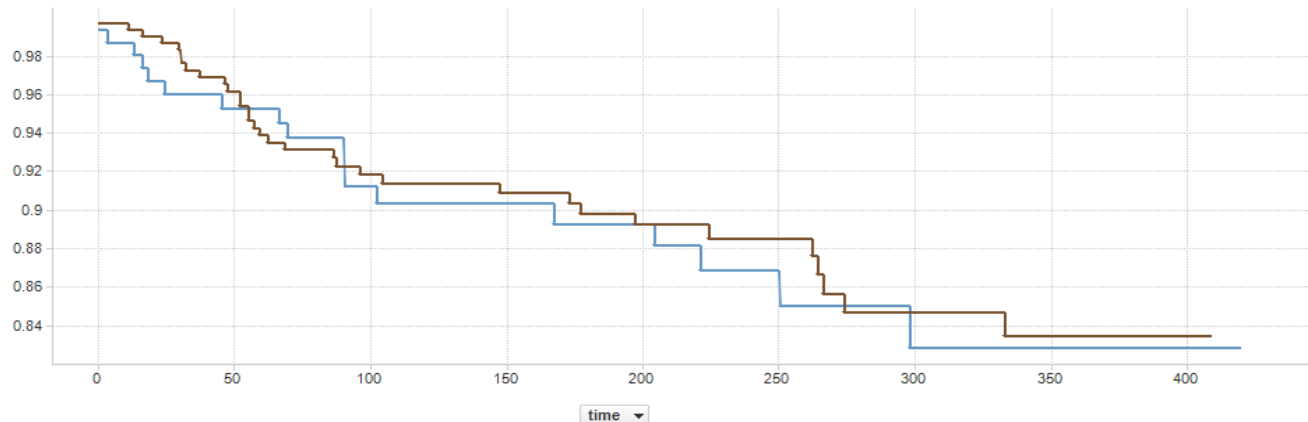
KaplanMeier-Example.dxp - TIBCO Spotfire

File Edit View Insert Tools Help



Cover Page Bar Chart and KM Table View

Kaplan-Meier - Time to Event



Data table:

TTE Kapl...

Color by:

strata +

group=2

group=4

Filters

adtte

Study Identifier

☒ SF

Sex

☒ F

☒ M

Description of Planned Arm

☒ Treat2

☒ Treat4

Parameter Description

☐ (All)

☒ Time to bacterial related events

☐ Time to blood-related events

☐ Time to gastro events

☐ Time to hepatic related events

☐ Time to TEAE

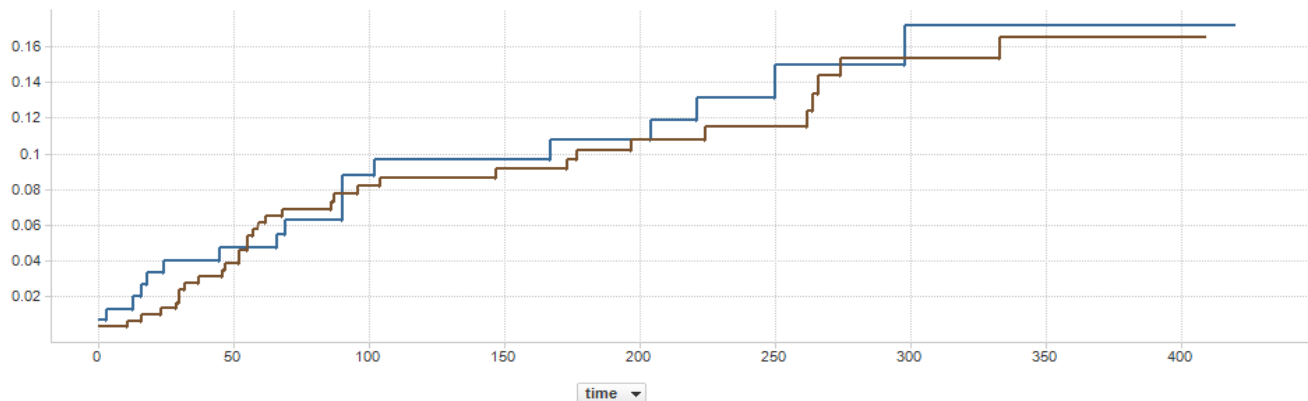
☐ Time to urin related events

☐ (None)

Number at Risk

| strata  | 0.00 | 50.00 | 100.00 | 150.00 | 200.00 | 250.00 | 300.00 | 350.00 | 400.00 |
|---------|------|-------|--------|--------|--------|--------|--------|--------|--------|
| group=2 | 152  | 129   | 104    | 88     | 82     | 48     | 39     | 34     | 1      |
| group=4 | 308  | 257   | 208    | 178    | 155    | 101    | 78     | 67     | 2      |

Cumulative Incidences - censored Data



Data table:

TTE Kapl...

Color by:

strata +

group=2

group=4

Some filters are hidden. [Show all](#)

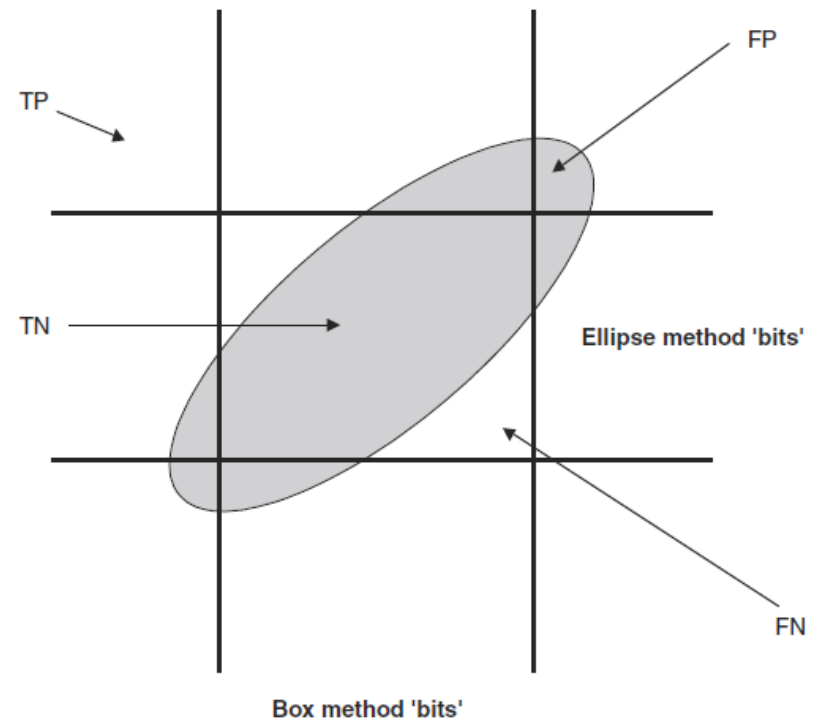
# Bivariate Analysis of Lab Data – illustrated in Spotfire

## □ Standard approach:

- Univariate normal ranges (Box – method)

## □ Graphical approach:

- Multivariate normal ranges
- Box vs Ellipse

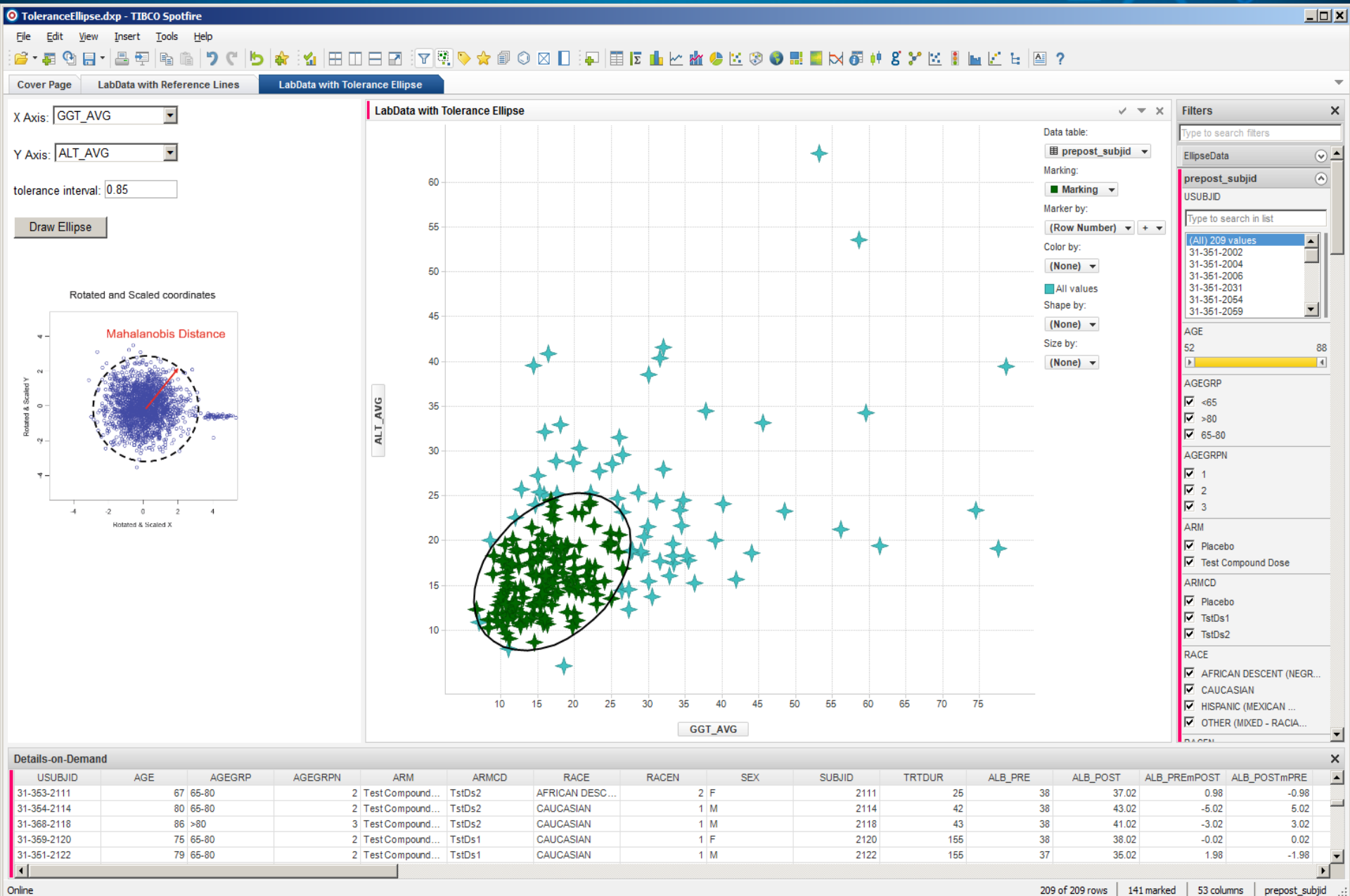


**Source:** Donald C. Trost

*Multivariate prob based detection of DILI signals\_Trost 2006.pdf*

*Mathematical Medicine, Pfizer Global Research and Development, Groton, Connecticut, USA*

# Tolerance Ellipse - interactive



# Summary

## □ Reporting Graphics

- Statistical graphics for use in clinical study reports, submission documents, presentations, and journal articles
  - Graphs are defined once on a single platform with a point and click user interface
  - Shared graphs for reuse in exploratory, production and presentation environments

## □ Interactive Analysis

- In-stream monitoring of complex clinical and operational data – combining statistical analysis with interactive capabilities, like marking, filtering and drill-down.
  - Interactive data review analysis
  - Enhanced by using statistical methods

# Thank you !!

## Questions ?????

Contact us:

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<http://spotfire.tibco.com/spotfire-for-you/by-industry/life-sciences/life-sciences-analytics.aspx>

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