

The **cg** package for comparison of groups

useR! 2010 conference

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Non-Clinical Statistics group

21 July 2010



Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.



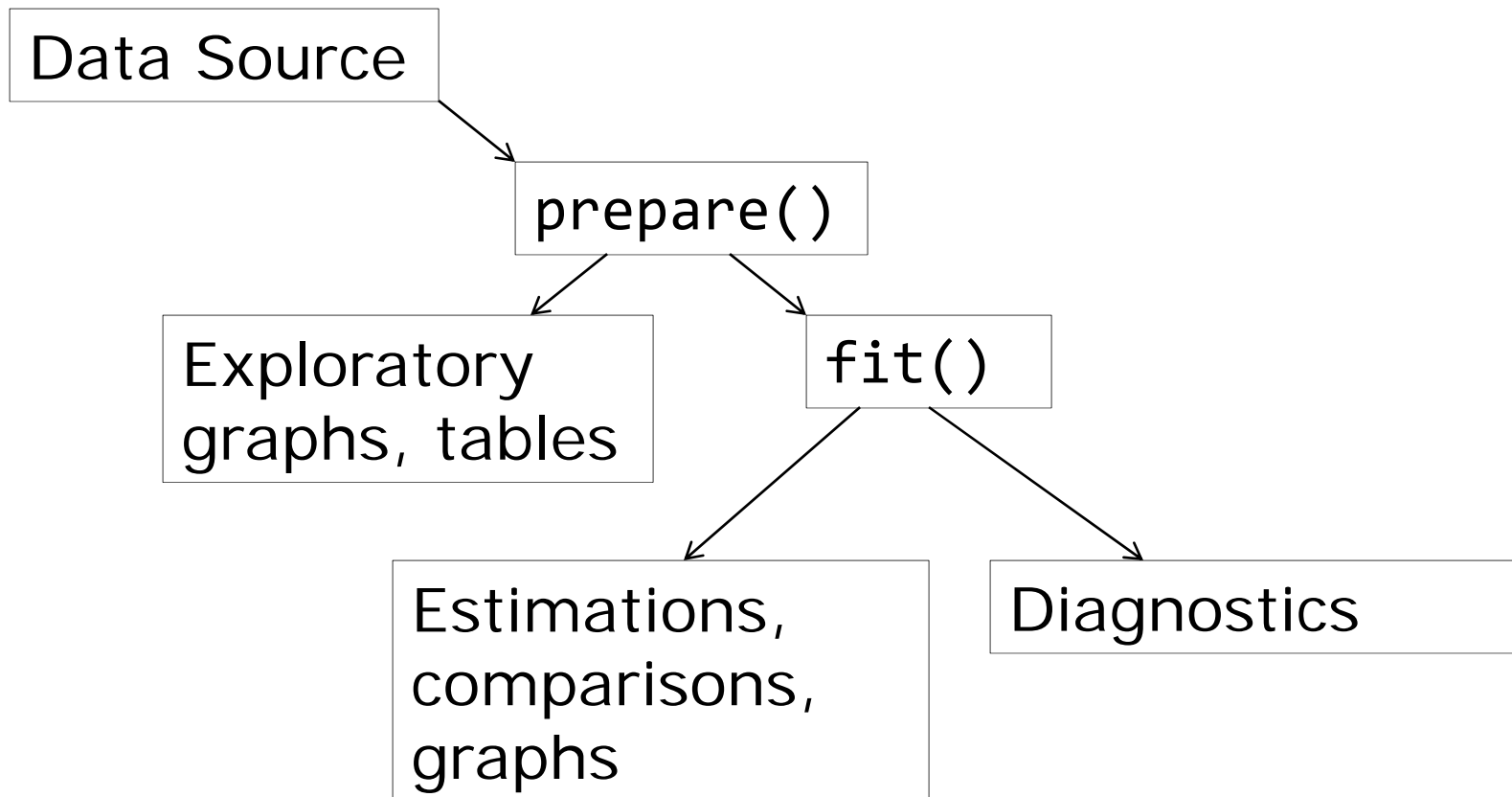
Non-Clinical Statistics collaborations with Johnson & Johnson pharmaceutical research

- Portion of Studies focused on Comparisons
- In-vivo, In-vitro
- Not Clinical, so do-it-yourself perspectives

Issues, even for one-factor linear model / unpaired samples

- Data Graphs
- Percent Differences
- Logarithmic Scaling
- Multiple Comparisons
- Outliers
- Censoring
- Error Bars
- Magnitudes of Effects and Differences
- Sample Size
- Digit Display

Strategy of **cg** Evaluation



Data Set # 1: canine

Rhodes, L., Ding, V.D.H., Kemp, R.K., Khan, M.S., Nakhla, A.M., Pikounis, B., Rosner, W., Saunders, H.M. and Feeney, W.P. (2000). "Estradiol causes a dose dependent stimulation of prostate growth in castrate beagle dogs." *The Prostate*, Volume 44, 8-18.

Endpoint Measure of
Prostate Volume (cc³)

AE	E1	E2	CC	NC
9.132	10.356	37.2	1.975	9.301
10.07	6.313	12.639	3.125	13.531
20.077	21.708	16.791	4.433	12.84
14.691	12.651	36.996	6.154	14.336
23.698	15.464	22.808	4.175	25.102

One Factor, 5 levels (groups)

AE: castration plus estradiol and androstanediol

E1: castration plus low dose estradiol,

E2: castration plus high estradiol

CC: castration alone,

NC: No treatment (normal controls).

Data Set # 2: gmcsfcens

Shealy, D. et al. (2010). "Characterization of Golimumab (CNTO148), a human monoclonal antibody specific for human tumor necrosis factor α ", *mAbs*, Volume 2, Issue 4, 428-439.

One Factor,
6 levels (groups)

	PBS/Tg 197	1mg/kg/Tg 197	3mg/kg/Tg 197	10 mg/kg/Tg 197	30 mg/kg/Tg 197	PBS/WT
1	143.535	116.515	<82.5	97.31	<74.94	<74.94
2	108.51	207.785	<82.5	<82.5	75.53	76.68
3	124.575	109.94	102.525	<82.5	88.94	78.86
4	91.6	168.595	<82.5	<82.5	<74.94	99.63
5	161.575	166.99	<82.5	<82.5	102.805	<74.94
6	<82.5	<82.5	<82.5	<82.5	95.71	77.8
7	<82.5	135.34	<82.5	<82.5	80.91	
8	106.4	<82.5	<82.5		<74.94	

Endpoint Measure of GM-CSF (pg/ml):
Granulocyte macrophage colony-stimulating factor

Tg197: Transgenic mouse model for TNF α expression

PBS: Phosphate buffered saline control

WT: Wild Type

Data Set Preparations

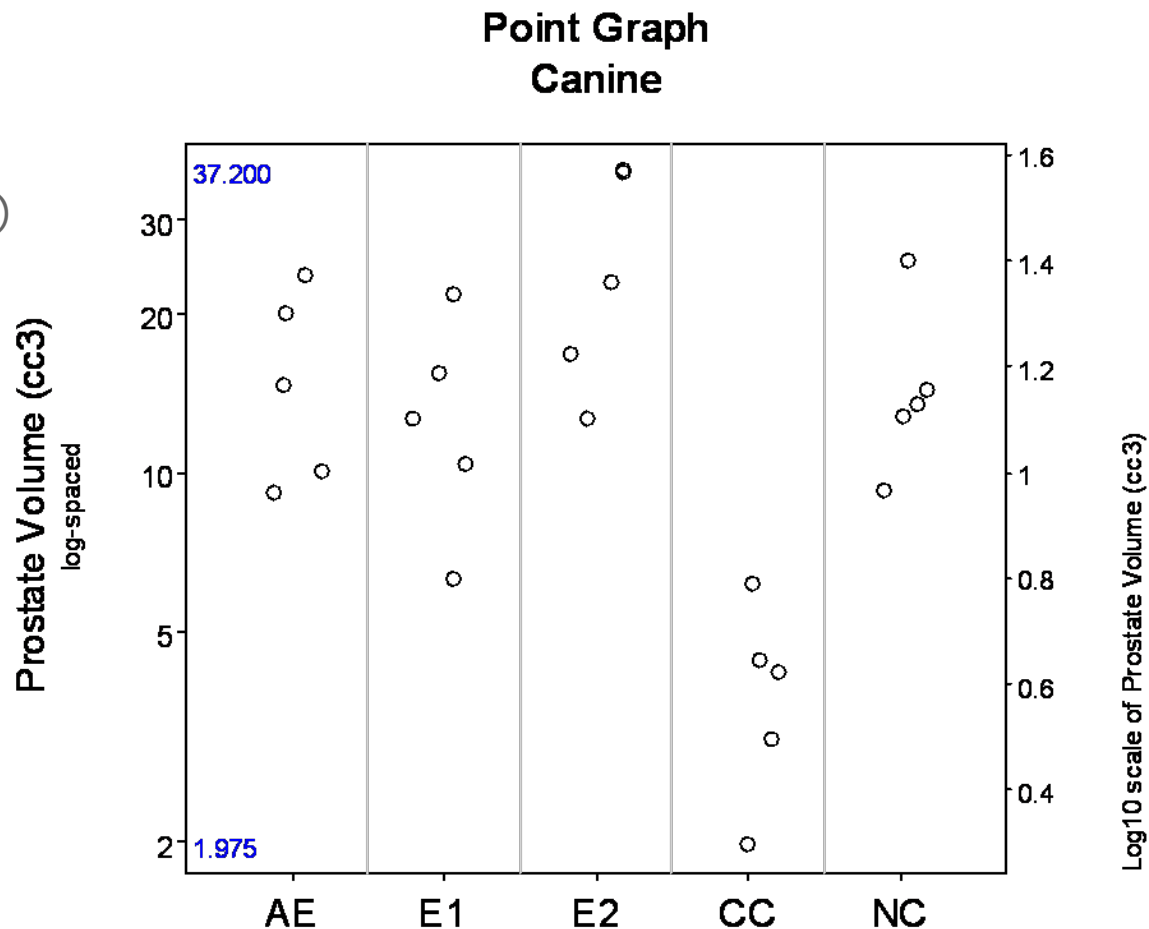
```
> canine.data <- prepareCGOneFactorData(canine.dfr, format="groupcolumns",  
                                         analysisname="Canine",  
                                         endptname="Prostate Volume (cc3)",  
                                         logscale=TRUE,  
                                         stamps=FALSE, refgrp="CC")
```

OR something similar

```
> prepare(type="onefactor",  
          dfr=canine.dfrlisted,  
          format="listed",  
          analysisname="Canine",  
          endptname=expression(  
            paste("Prostate Volume (", plain(cc)^3, ")", sep="")),  
          logscale=TRUE,  
          stamps=FALSE, refgrp="CC")
```

Exploratory

- > pointGraph(canine.data)
- > # boxplot(canine.data)
- > descriptiveTable(canine.data)



Exploratory

```
> descriptiveTable(canine.data)
```

Descriptive Table of Canine

Endpoint: Prostate Volume (cc3)

	n	Min	25%ile	Median	75%ile	Max	Mean	StdDev	StdErr	GeoMean	SEGeoMean
1	5	9.132	10.070	14.691	20.077	23.698	15.534	6.302	2.818	14.508	2.703
2	5	6.313	10.356	12.651	15.464	21.708	13.298	5.772	2.582	12.266	2.529
3	5	12.639	16.791	22.808	36.996	37.200	25.287	11.372	5.086	23.159	4.952
4	5	1.975	3.125	4.175	4.433	6.154	3.972	1.559	0.697	3.710	0.708
5	5	9.301	12.840	13.531	14.336	25.102	15.022	5.954	2.663	14.220	2.284

Fit & Evaluations

```
> canine.fit <- fit(canine.data)
```

```
> ## Comparisons Tables
```

```
> canine.comps0 <- comparisonsTable(canine.fit)
```

```
> canine.comps1 <- comparisonsTable(canine.fit, mcadjust=TRUE,  
                                     type="allgroupstocontrol", refgrp="CC")
```

```
## Comparisons Graphs
```

```
> comparisonsGraph(canine.comps0)
```

```
> comparisonsGraph(canine.comps1, ticklabels=list(mod="add", marks=300))
```

```
## Error Bar Graphs
```

```
errorBarGraph(canine.fit)
```

```
errorBarGraph(canine.fit, mcadjust=TRUE, model="olonly")
```

```
## Group Summary Table
```

```
grpSummaryTable(canine.fit)
```

Fit & Evaluations

```
> canine.comps1 <- comparisonsTable(canine.fit, mcadjust=TRUE,  
                                     type="allgroupstocontrol", refgrp="CC")
```

Comparisons Table of Canine

Endpoint: Prostate Volume (cc3)

Percent Differences (A vs. B)

Least Squares Model Fit

95% Confidence (alpha of 0.05), Multiplicity Adjusted

	estimate	se	lowerci	upperci	pval	meanA	seA	meanB	seB
AE vs. CC	291	106	90	705	<0.001	14.508	2.792	3.710	0.714
E1 vs. CC	231	90	61	580	0.001	12.266	2.361	3.710	0.714
E2 vs. CC	524	170	203	1185	<0.001	23.159	4.457	3.710	0.714
NC vs. CC	283	104	86	689	<0.001	14.220	2.737	3.710	0.714

Resistant & Robust Model Fit

95% Confidence (alpha of 0.05), Multiplicity Adjusted

	estimate	se	lowerci	upperci	pval	meanA	seA	meanB	seB
AE vs. CC	288	112	81	732	<0.001	14.504	2.953	3.740	0.762
E1 vs. CC	230	95	54	610	0.002	12.350	2.526	3.740	0.762
E2 vs. CC	521	180	189	1237	<0.001	23.233	4.763	3.740	0.762
NC vs. CC	278	108	76	709	0.001	14.121	2.859	3.740	0.762

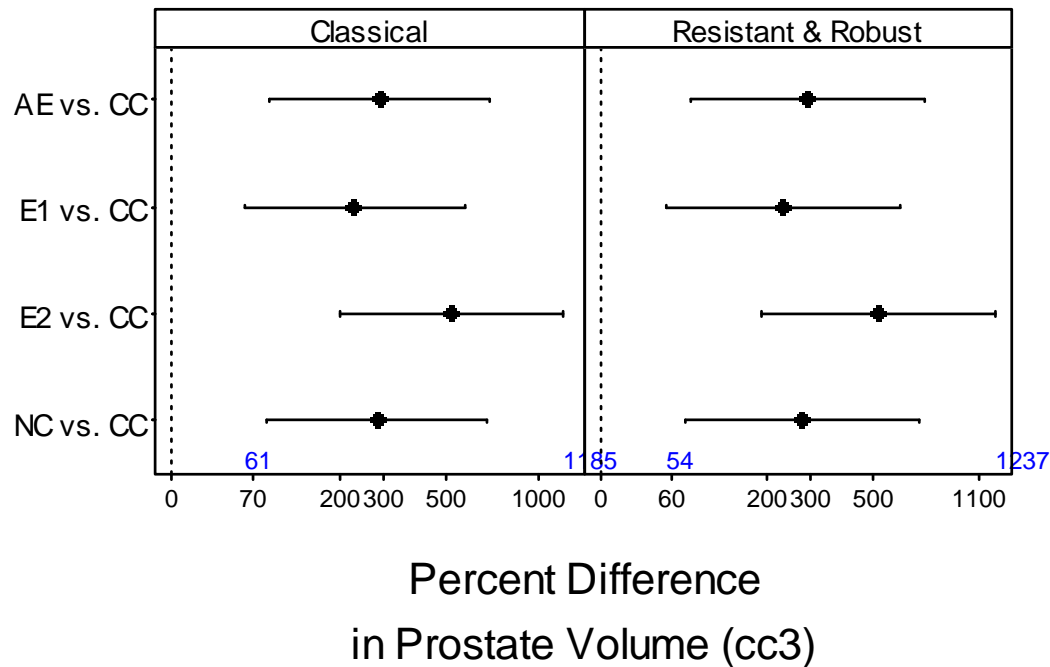
Fit & Evaluations

```
> comparisonsGraph(canine.comps1, ticklabels=list(mod="add", marks=300))
```

Comparisons Graphs Canine

Error bars that do not cross the zero line indicate statistically significant difference(s) at 5% significance level (Multiplicity adjusted)

All Groups versus Control



Fit & Evaluations

```
> errorBarGraph(canine.fit, mcadjust=TRUE, model="olonly")
```

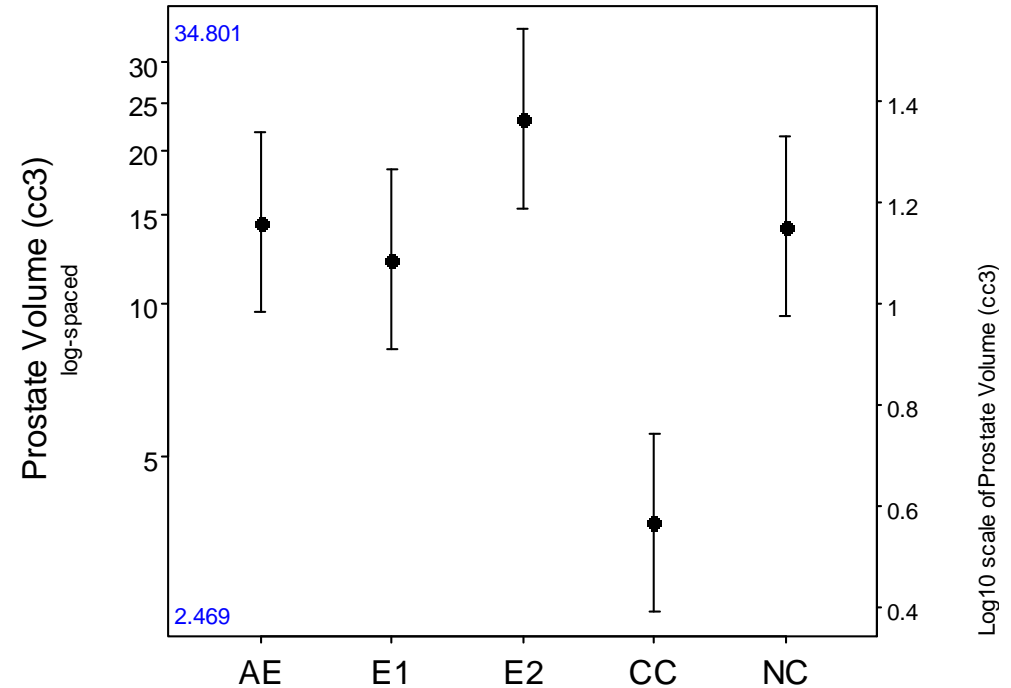
Some time may be needed as the critical point from the `multcomp::summary.glht` function call is calculated. Please wait...

... Done. Critical point from Least Squares fit is calculated.

Error Bar Graph, Classical analysis

Canine

Non-overlapping error bars indicate statistically significant difference(s) at 5% significance level (Multiplicity adjusted)



Statistical Notes

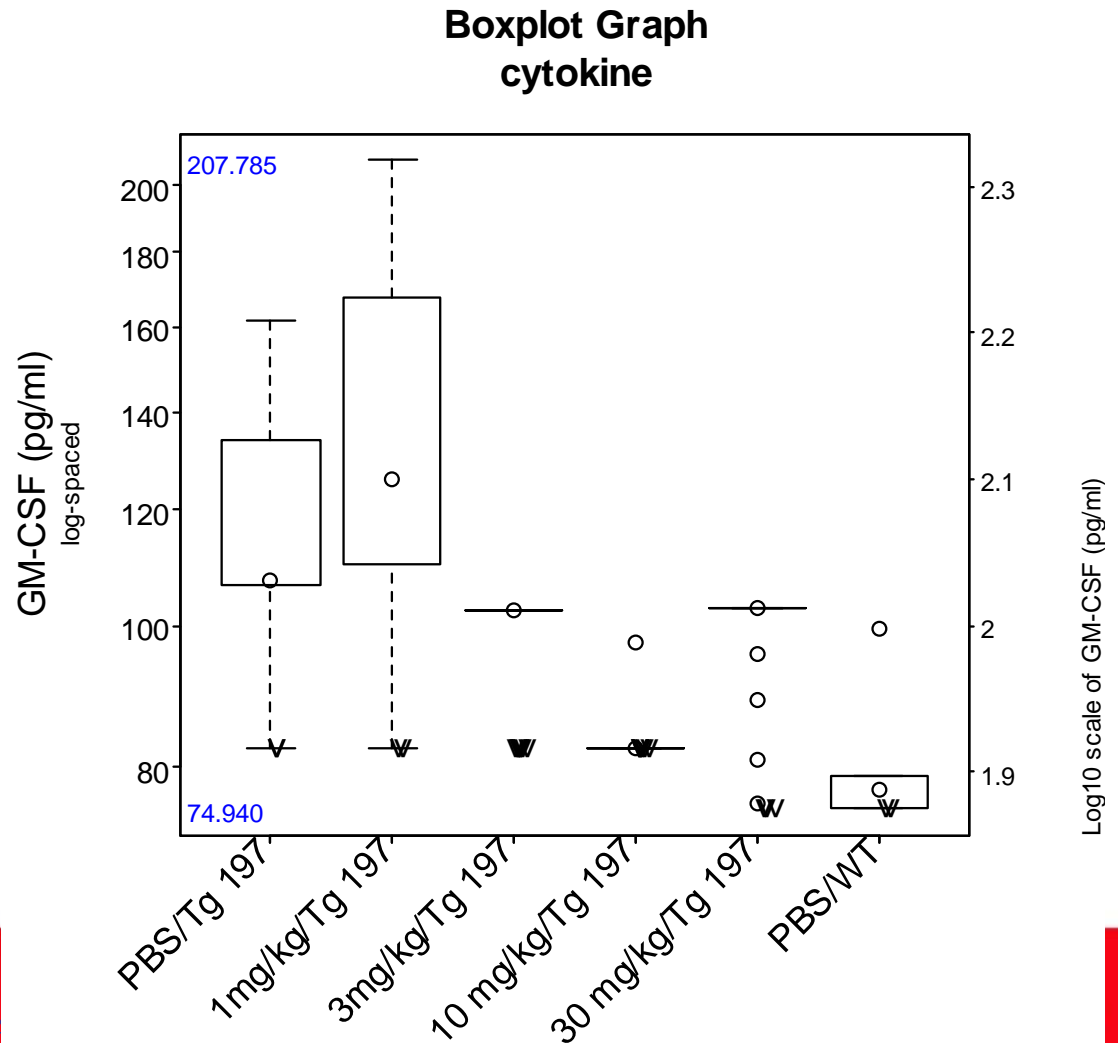
- Andrews, Sarner and Snee (1980) method used in Error Bar Graphs
- Purposeful Avoidance of Skyscraper/Antennae/Dynamite Error Bar Chart Depiction
- **MASS::rlm()** with method="MM" used for resistant / robust
- **multcomp** package used for multiple comparisons to avoid slot machine of procedure choices

Censoring to Handle Limits of Detection

- Accelerated Failure Time (AFT) model, lognormal / Gaussian distribution assumed
- Accommodate Left, Right, and Interval Censoring, courtesy of `survival::survreg()`.
- Once the AFT model is fit, proceed as before for comparison evaluations.

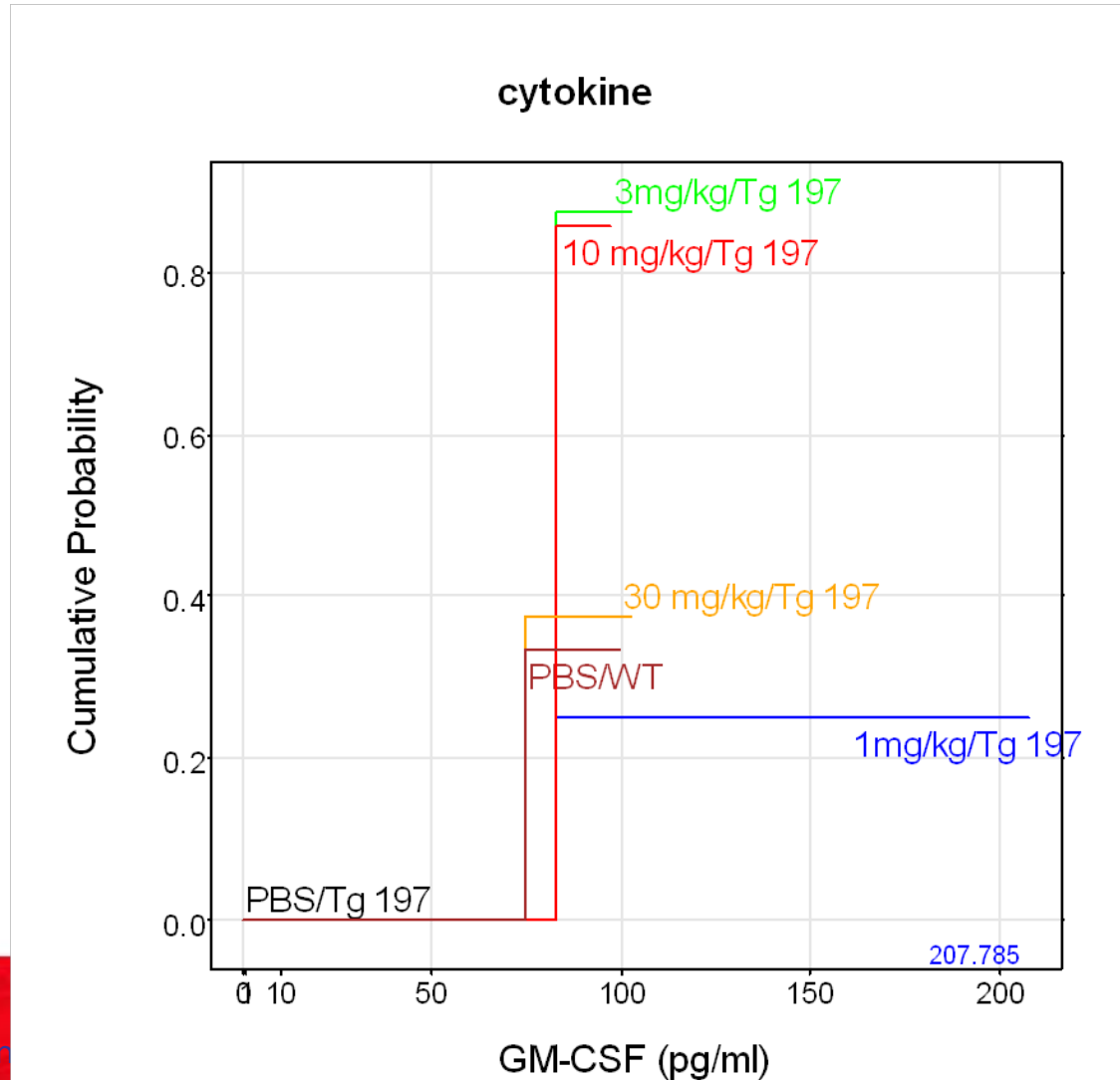
Exploration

```
> boxplot(gmcsfcens.data)
```



Exploration

```
> kmGraph(gmcsfcens.data, title="",  
          distfcn="cumulative")
```



Exploration

```
> descriptiveTable(gmcsfcens.data)
```

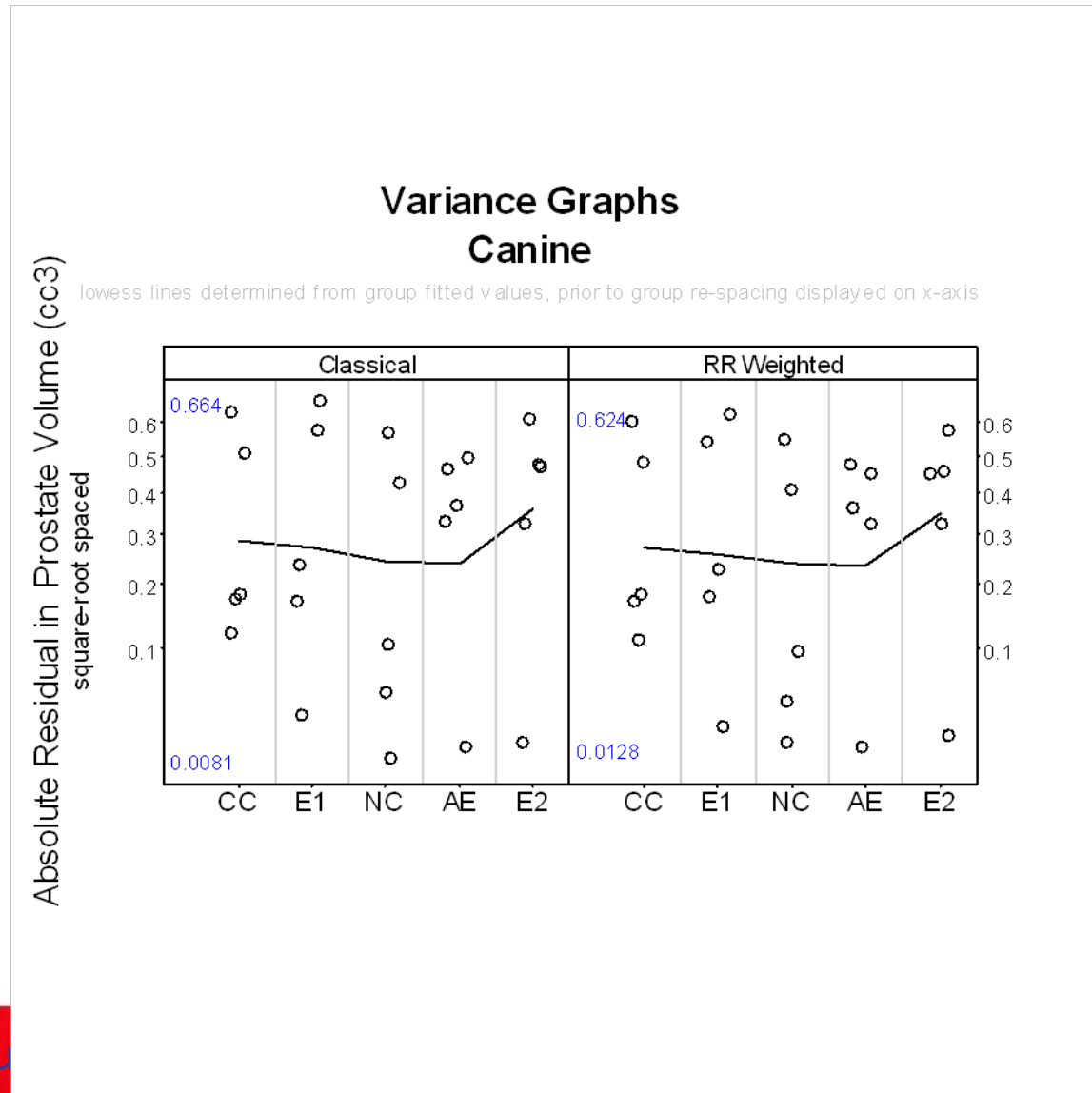
Descriptive Table of cytokine

Endpoint: GM-CSF (pg/ml)

	n	ncensored	ncomplete	Min	25%ile	Median	75%ile	Max	Mean	StdDev	StdErr	GeoMean	SEGeoMean
1	8		2	6	<82.500	106.400	107.455	134.055	161.575	<NA>	<NA>	<NA>	<NA>
2	8		2	6	<82.500	109.940	125.927	167.792	207.785	<NA>	<NA>	<NA>	<NA>
3	8		7	1	<82.500	102.525	102.525	102.525	102.525	<NA>	<NA>	<NA>	<NA>
4	7		6	1	<82.500	82.500	82.500	82.500	97.310	<NA>	<NA>	<NA>	<NA>
5	8		3	5	<74.940	102.805	102.805	102.805	102.805	<NA>	<NA>	<NA>	<NA>
6	6		2	4	<74.940	74.940	77.240	78.860	99.630	<NA>	<NA>	<NA>	<NA>

Diagnostics

- > # qqGraph(canine.fit)
- > varianceGraph(canine.fit)



Sample Size

```
canine.samp <- samplesizeTable (canine.fit, direction = "increasing",  
                                model = "olonly",  
                                mmdvec = c (5, 10, 25, 50, 75, 100) )
```

The nmax threshold specified at 1000 was reached for at least one of the specified differences.

Sample Size Table for Canine

Endpoint: `paste(plain("Prostate Volume (cc3)"))`

Percent Differences

80% Power and 5% Significance Level

Variability Estimate (Log scale) of 0.4303

2 Groups

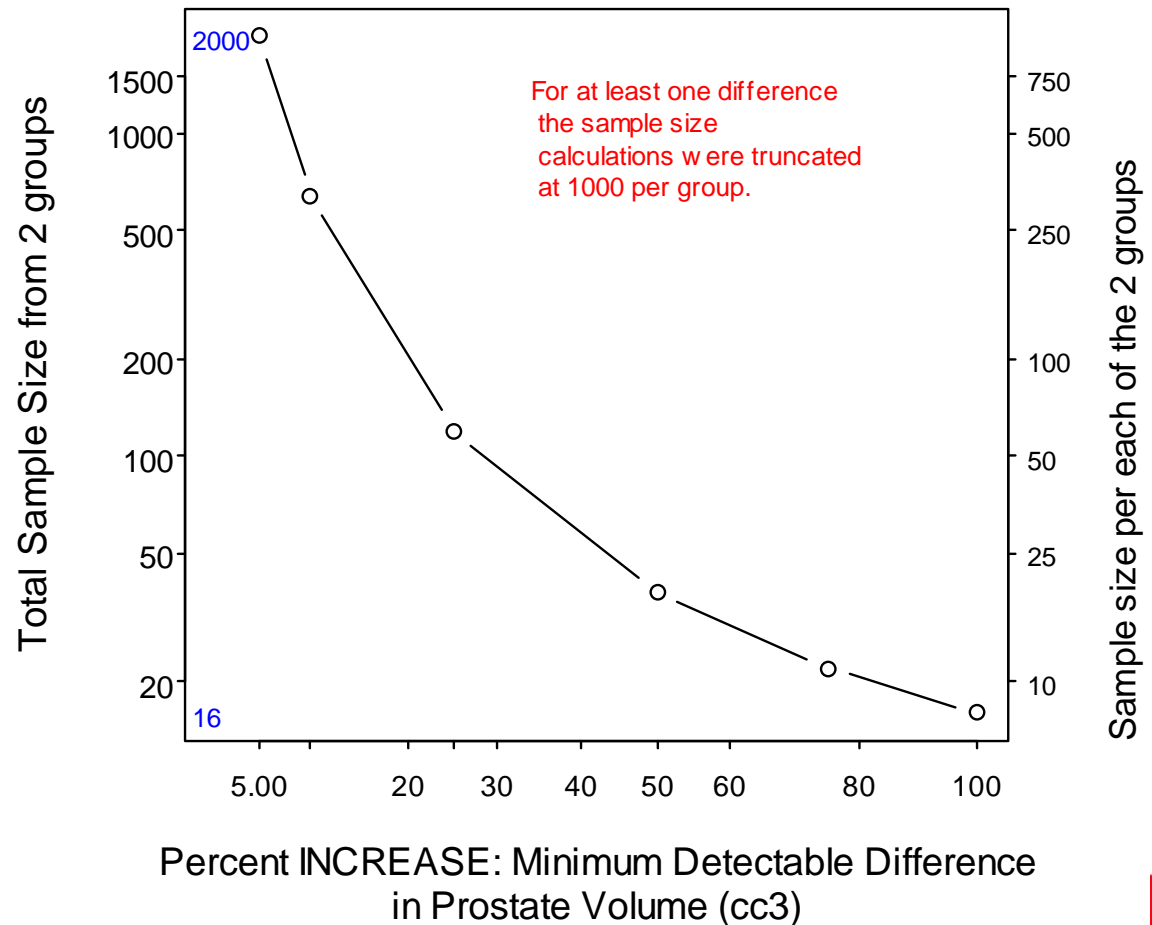
n per group	N	Total
5	>1000	>2000
10	321	642
25	60	120
50	19	38
75	11	22
100	8	16

Sample Size

> samplesizeGraph (canine.samp)

Sample Size Graph Canine

80 % Power ; 5 % Significance Level ; Classical Variability Estimate (Log scale) of 0.4303



Summary

- Package **cg** “almost there” for CRAN publishing later this year
- Flow of wrapper functions to guide the full analysis and interpretation of the data.
- Motivated to address common “in practice” issues

Acknowledgments

- Authors of MASS, survival, multcomp, lattice, grid, rms, ...
- R core packages and the team
- R community
- Conference organizers