Understanding the Individual Contributions to Multivariate Outliers in Assessments of Data Quality

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Introduction

- Two aspects to data quality
  - Identifying anomalous data or observations
  - Investigating why the unusual data may have occurred
- Identification
  - Exceed a statistically-relevant threshold
  - Meaningful Δ, though not significant
  - In general, when results do not align with our expectations
- Investigation
  - Natural differences among patients or technique
  - Carelessness
  - Misconduct

Mahalanobis Distance

- Mahalanobis distance[1] is often recommended to identify unusual observations from many variables
- Considers the pairwise correlation among variables
- Distance is often calculated from the centroid, or the multivariate mean
- Two considerations
  - Outliers: Patients extreme in one or more covariates that cause them to be far away from the centroid
  - Inliers [2]: Patients close to the centroid that could be considered too good to be true

Challenge

- Efficiently identify inliers and outliers
- Potentially create thresholds of varying severity to triage numerous signals
- Investigate what contributes to the outlier by partitioning the distance among the covariates
- Quickly and easily…
- … and without a lot of statistics or numbers

Data

- Phase II clinical trial to examine the safety and efficacy of the xanomeline transdermal therapeutic
- Patients with mild to moderate Alzheimer's disease
- 254 patients randomized 1:1:1 to either high or low dose xanomeline or placebo
- 17 clinical sites
- 44 covariates measured at baseline: age, vital signs, laboratory measurements and a subset of items from questionnaires
- Data available from CDISC[3]

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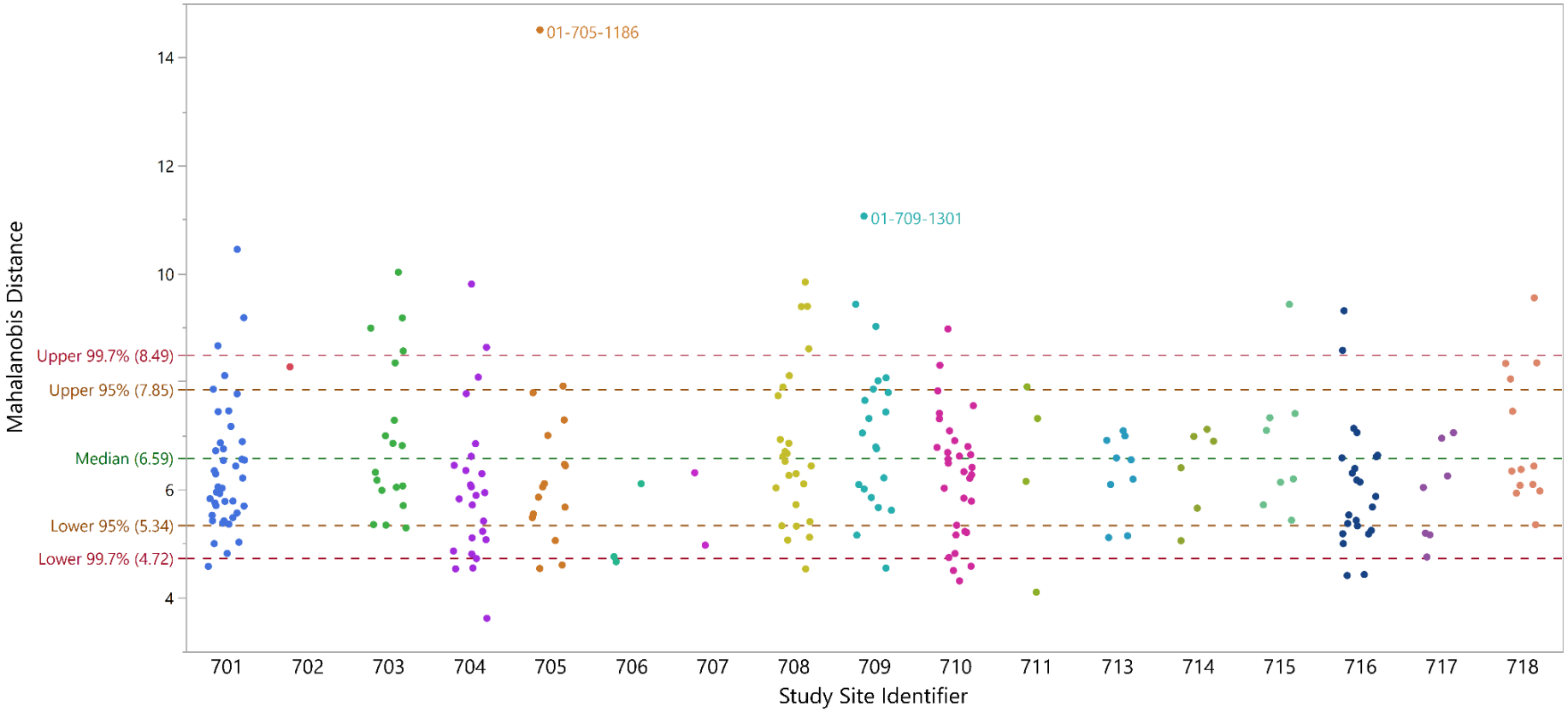
Mahalanobis Distance



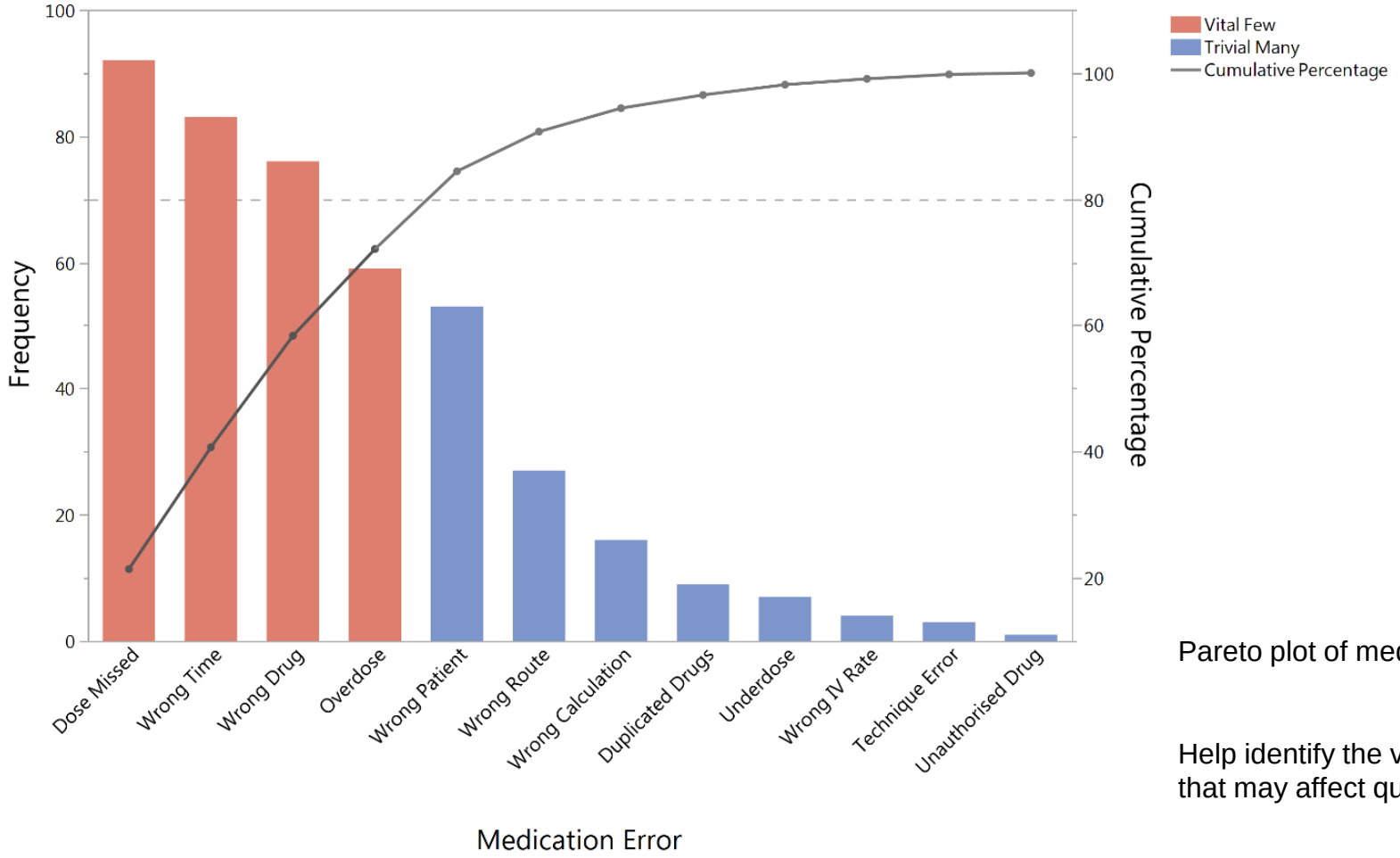
Investigation

- Identified the outliers and inliers
- Question that we constantly received
  - What covariates caused outliers to be unusual?
- Partition the squared-distance into components that reflect the degree to which each covariate contributes
- Call these components c_{ij}, ith person, jth covariate
- Values aren't particularly meaningful
- Compute proportions p_{ij} of the squared-distance attributable to a covariate

Investigation

- Some math:
  - $C = (Y_{cs}E)D_{\sqrt{\lambda}}^{-1}E^T$ defines contributions, though no straightforward interpretation
  - $t_i^2 = \sum_{j=1}^{p} c_{ij}^2$
  - Define contribution proportions $p_{ij} = \frac{c_{ij}^2}{t_i^2}$, the proportion of the squared Mahalanobis distance of observation i that is attributable to covariate j
- Contribution proportions have more straightforward interpretation and can leverage Pareto plots for summary

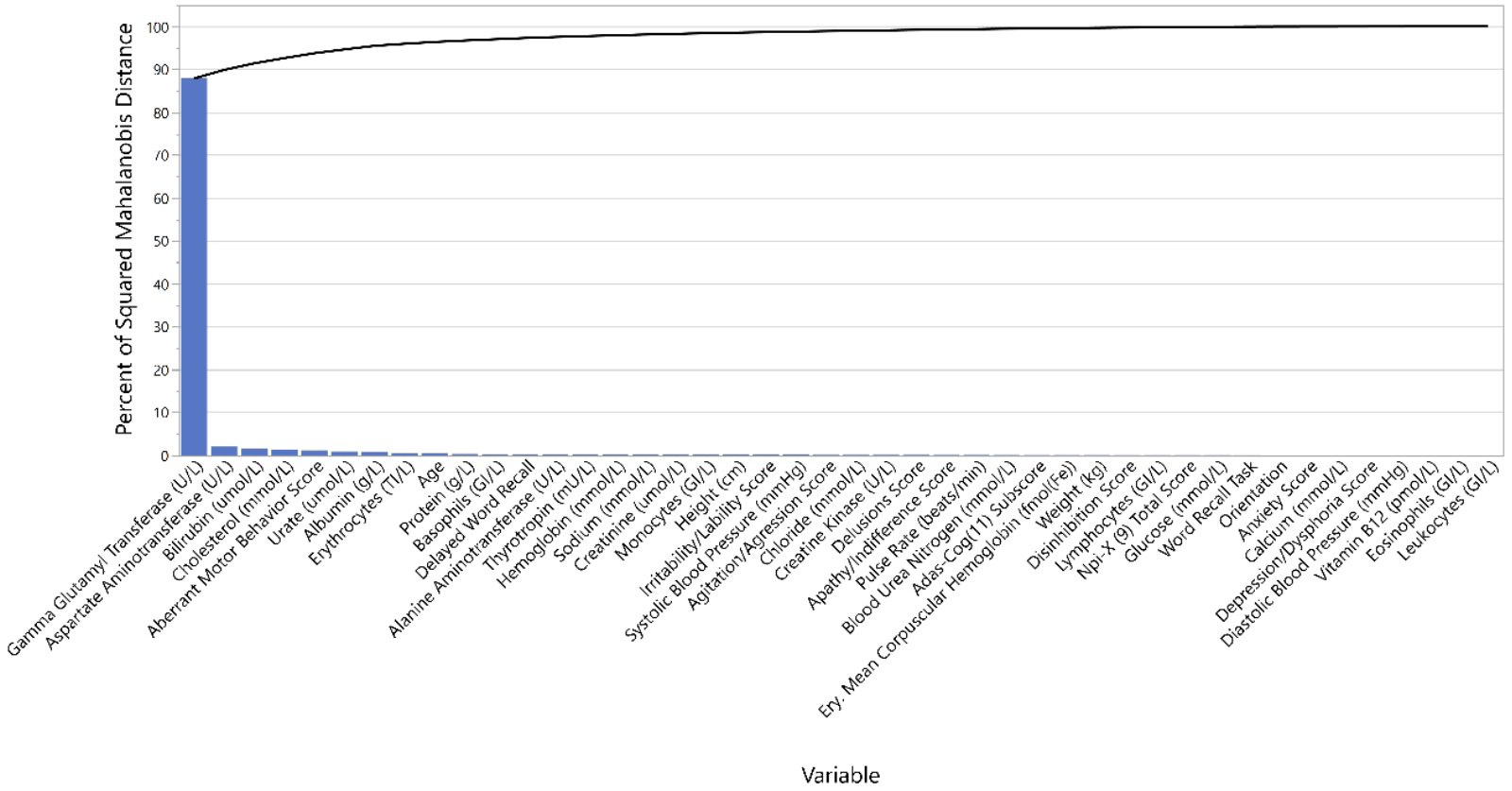
Pareto Plot - Medication Errors



Pareto plot of medication errors

Help identify the vital few issues that may affect quality.

Investigation



Pareto plots per person – 01-705-1186
Black line reflects cumulative proportion of error
Covariates ordered according to contribution

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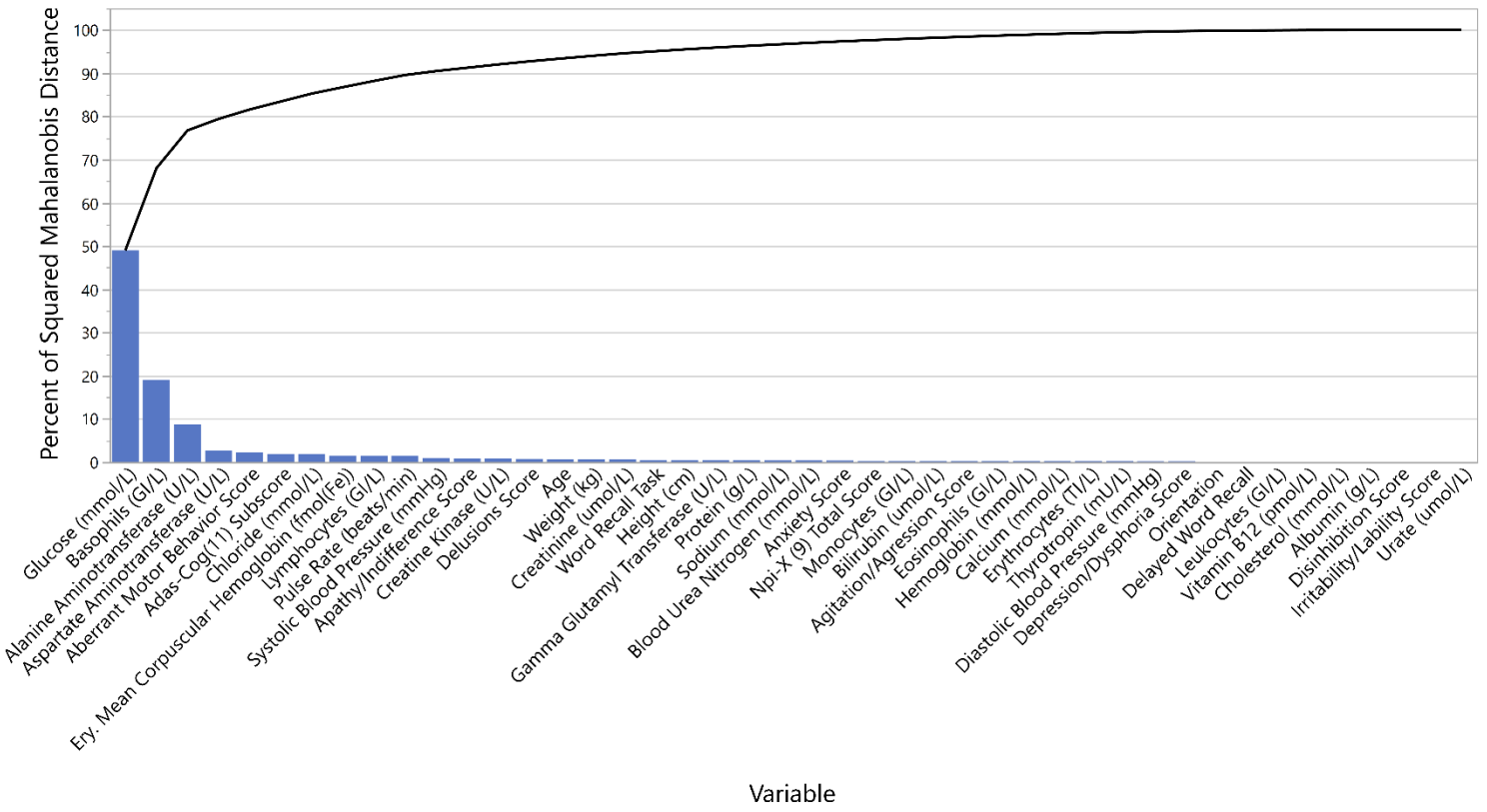
Investigation



Pareto plots per person – 01-709-1301
Black line reflects cumulative proportion of error
Covariates ordered according to contribution

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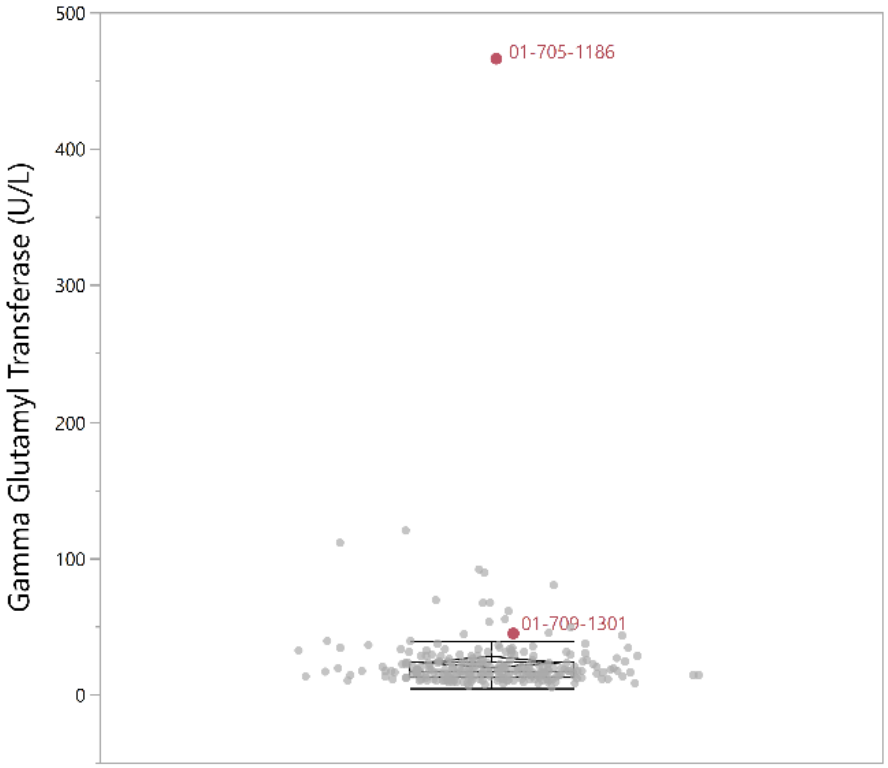
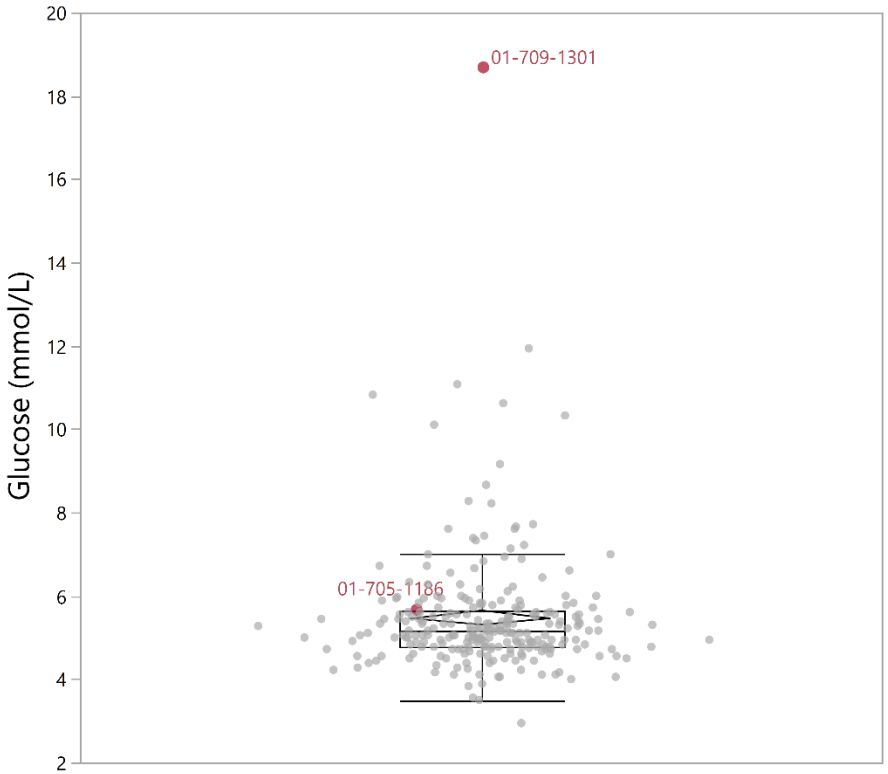
Mahalanobis Distance





Box plots to assess meaningful covariates in context of entire population.

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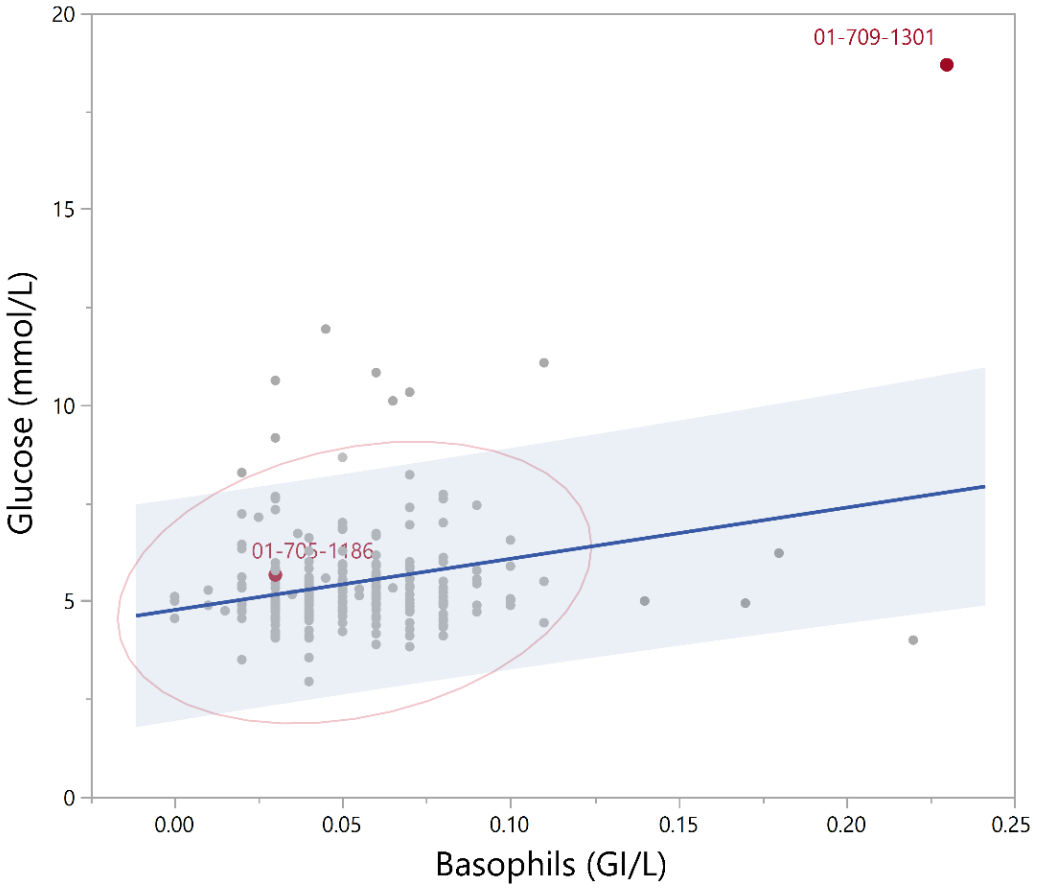
Mahalanobis Distance



Scatter plot with regression line and confidence interval and density ellipse

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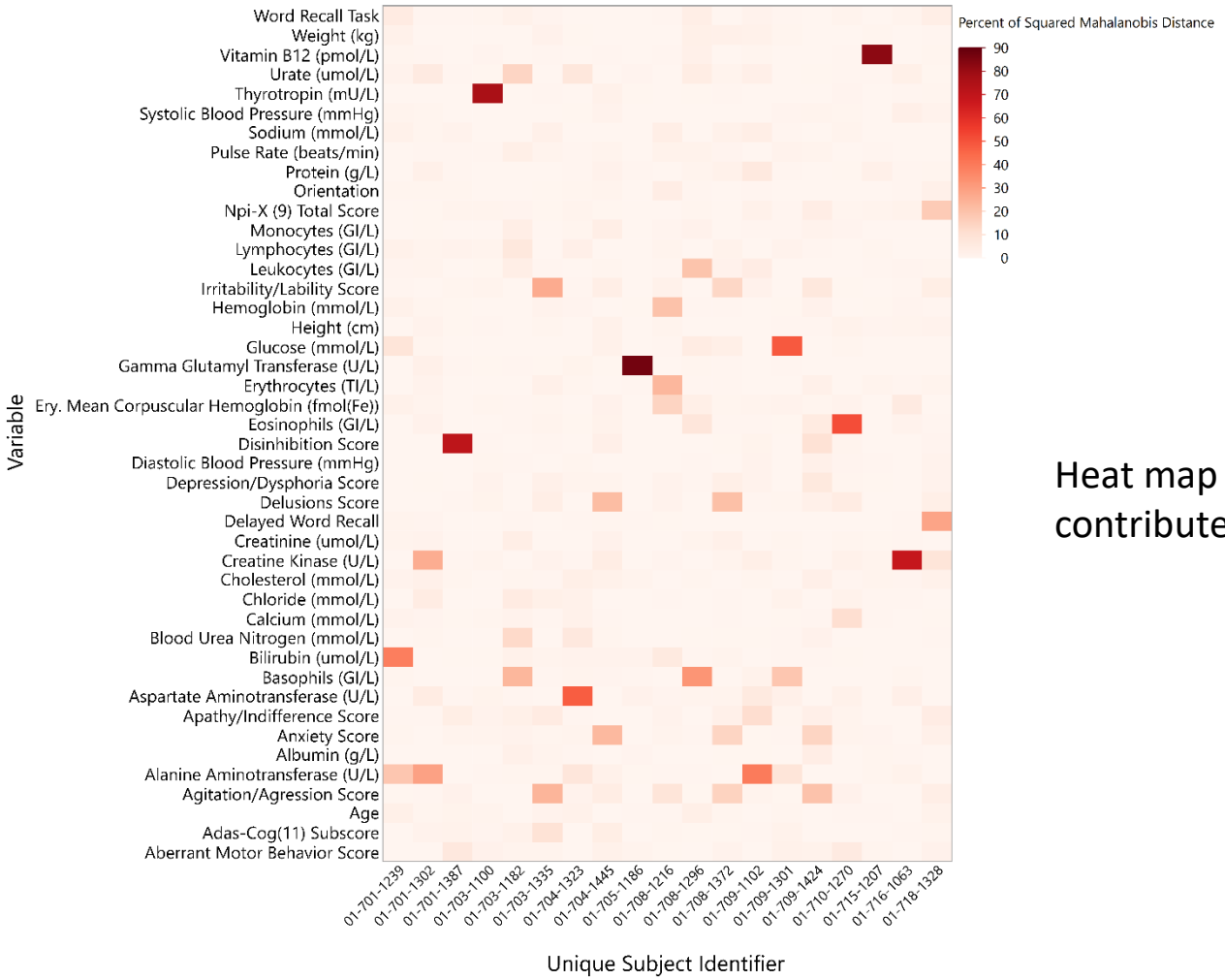
Mahalanobis Distance



Heat map to assess which covariates contribute to outlier status.

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Conclusions

- Assessed unusual observations
- Described thresholds of varying severity
- Proposed contribution proportions as a straightforward way to identify influential covariates
- Visualize contribution proportions with Pareto plots
- Use additional graphics to assess outliers in the context of the population
- Limitations
  - Requires normality of original covariates
  - Not useful for inliers

References

1. Mahalanobis PC (1936). On the generalised distance in statistics. *Proceedings of the National Institute of Sciences of India* 2: 49–55.
2. Evans S. (2001). Statistical aspects of the detection of fraud. In: Lock S & Wells F, eds. *Fraud and Misconduct in Biomedical Research, Third Edition*. London: BMJ Books.
3. CDISC SDTM / ADaM Pilot Project. (2012). Data Package.
4. Zink RC, Castro-Schilo L & Ding J. Understanding the influence of individual variables contributing to multivariate outliers in assessments of data quality. *Pharmaceutical Statistics* (in print).