Virtual control groups in animal toxicology studies

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PointCross

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Background

- Building virtual control arm using historical data is widely applied in clinical research, offering the possibility to increase efficiency and reduce costs.
- Using virtual control groups (VCG) in animal toxicology studies is offering similar perspectives while contributing to the principles of the 3R (Replacement, Reduction and Refinement)
- The work presented here is part of the IMI eTRANSAFE project devoted to the creation of in silico tools for data mining and the prediction of potential toxicity.

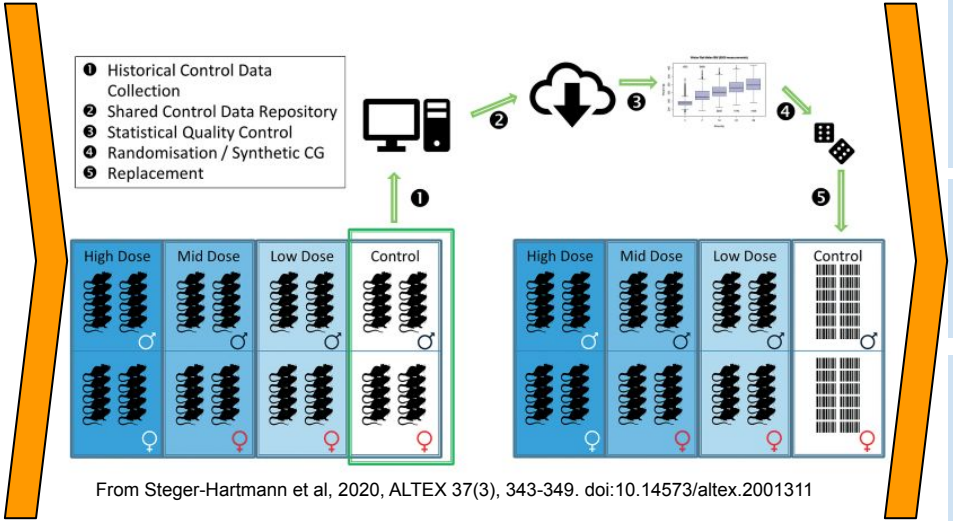
Virtual Control Group (VCG) Project

AIM & Expected Impact

AIM

Assess feasibility of
* using historical control data of non-clinical in-vivo toxicology studies **to build virtual control groups and reduce control animals** and
* sharing control animals data amongst pharmaceutical companies (IMI eTRANSAFE consortium)

Method & Results



From Steger-Hartmann et al, 2020, ALTEX 37(3), 343-349. doi:10.14573/altex.2001311

Expected IMPACT

Understanding of sources of variability in animals and opportunity to put unexpected & unusual project findings into historical context.

Reduce 4-weeks GLP Tox **control groups by 30-60%**, cost reduction by ~10-15%

Create a VCG repository with several harmonized Pharma datasets & new exploration tools (shiny apps)

VCG Repository Content

Study parameter

- Study Year
- Breeding
  - Animal strain
  - Facility / animal supplier
- Vehicle info
  - Vehicle type
  - Route of administration
- Animals handling
  - Housing type
  - Housing group
- Assay platform

Animal parameters

- Age, sex
- Body weight (BW), body weight gain, organ weights
- Food consumption
- Haematology (17 parameters)
  - RBC, HGB, HCT, MCV, MCH, MCHC, PLT, RET, WBC, NEU, LYM, EOS, BASO, MONO, LUC, PT R, APTT R
- Clinical chemistry (19 parameters)
  - NA, K, CA, CL, IP, GLUC, UREA, CREA, TBIL, CHOL, TRIG, BA, TP, ALB, A/G ratio, ALAT, ASAT, AP, GLDH
- Urinalysis (9 parameters)
  - pH, PRO, GLU, BIL, BLO, KET, SED, SG, UWG
- Gross Pathology/Histopathology
  - 48 organs selected

Parameters in green are used in the PoC study presented here

Proof of Concept Study

Summary

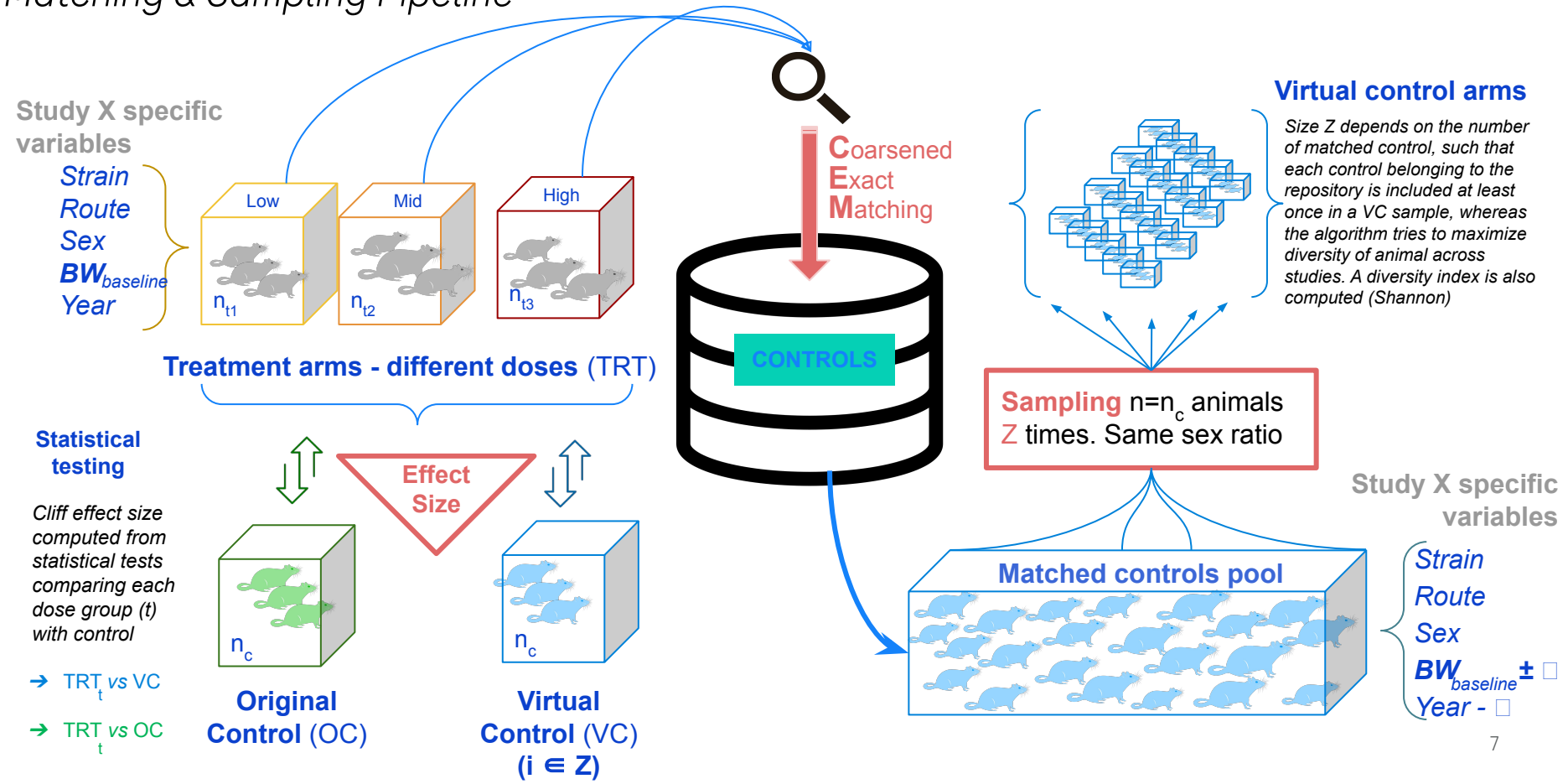
Objective: Replace original control rats by historical controls in a set of **67 toxicology Roche four-week studies** and compare treatment effects on a set of 19 clinical chemistry parameters using original controls and historical controls.

Method:

- Select **161 studies** in the Roche database to build a repository of control rats (**12 198 animals**)
  - With rats from 3 strains (Wistar, Wistar Han, SD)
  - Using only oral route of administration
  - With body weight data available at study start, for each rat
  - With clinical chemistry data available at week 4 +/-7 days, for each rat
- For each study of the 67 studies, groups of historical controls (coming from Roche repository) were built using matching methods

Proof of Concept Study

Matching & Sampling Pipeline



Groups Comparison

Statistical Method

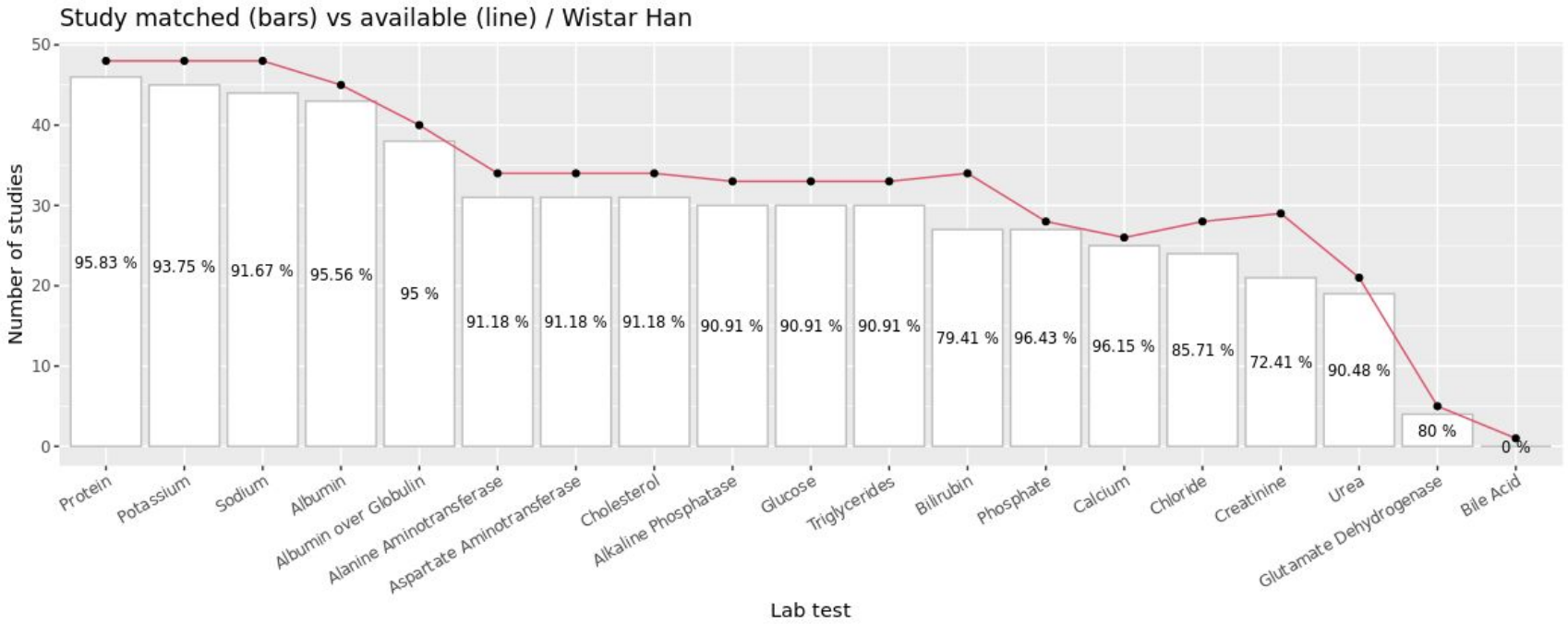
- Typical statistical analysis performed in toxicology studies rely on a statistical decision-tree approach checking the normality of the data then testing the homogeneity of variance followed by a test comparing group means (e.g. ANOVA or Kruskall-Wallis) and a test comparing treated to control (e.g. Dunnett, Dunn). These analysis are performed separately in males and females.

- For each laboratory test, we reproduced the original analysis performed in each of the selected 67 studies, on the original dataset, and on the additional ~100 datasets(Z) built by substituting control arm data with historical data. Pvalues and effect size (Cliff's Delta) were computed for each comparison
  - Other statistical approaches, not using statistical decision trees could be used such as robust tests (Kluxen, Hothorn. Arch Toxicol. 2019) and models including covariates such as gender and body weight.

Results

Matching Results - by Chemical Parameter

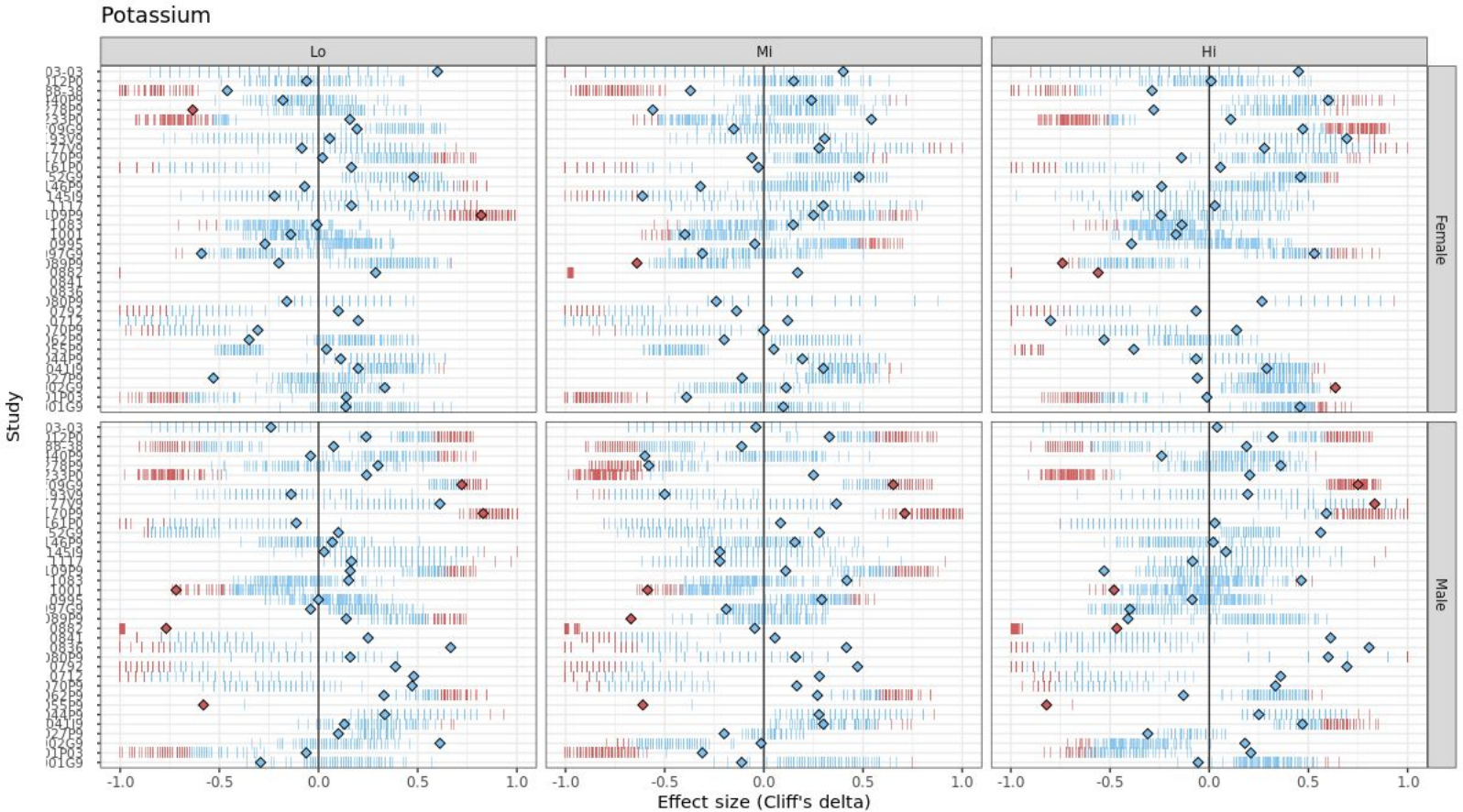
Wistar-Han Strain only



For all analytes (but bile acid, creatinine and bilirubin) we successfully built historical control groups for 80 % or more of the studies.

Group comparisons - Effect sizes and Significance

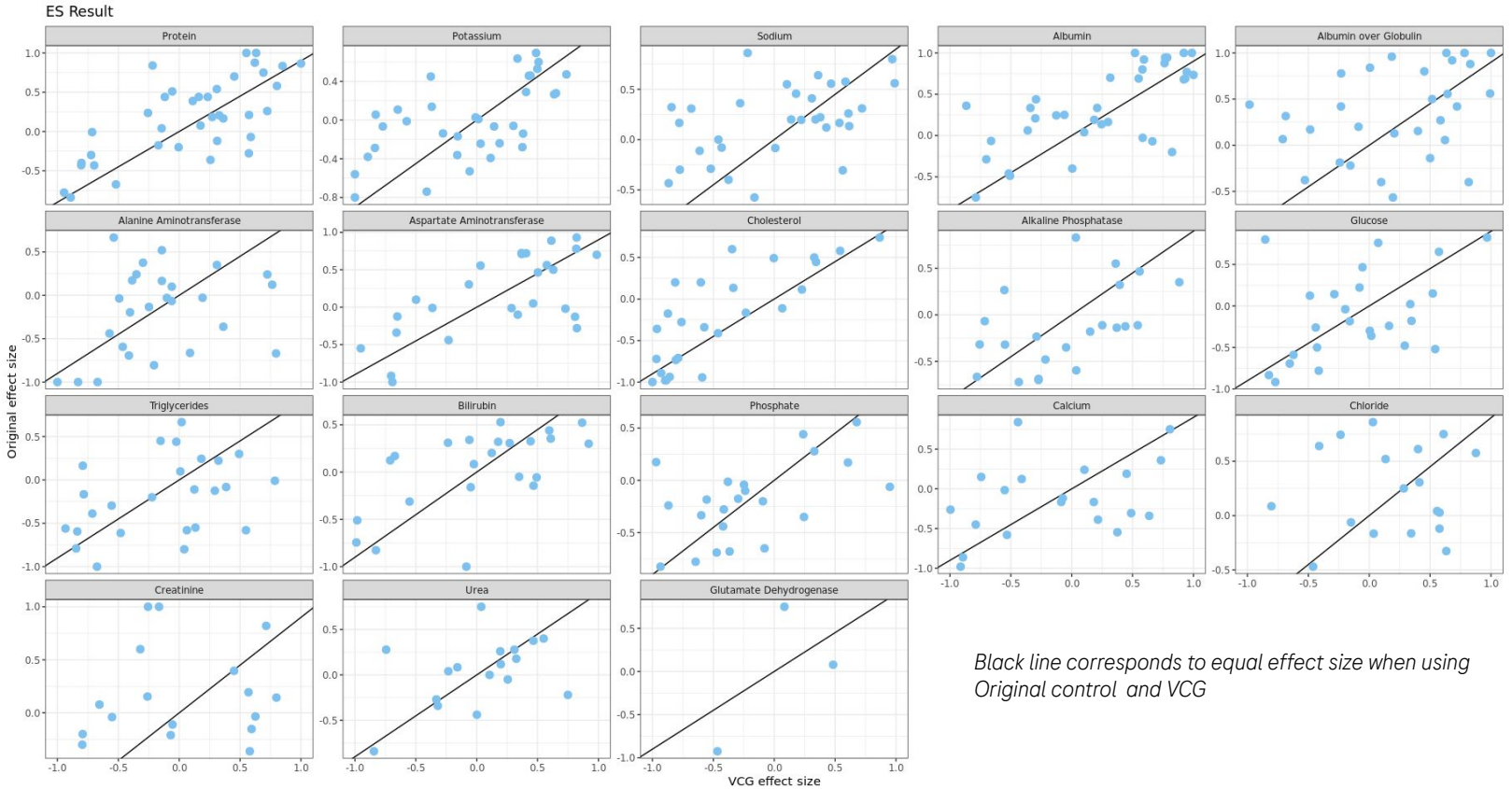
Control versus treated groups (low, medium and high doses) in females and males



Overall good agreement between tests using original & historical controls (VCG)

Results for the 19 parameters studied

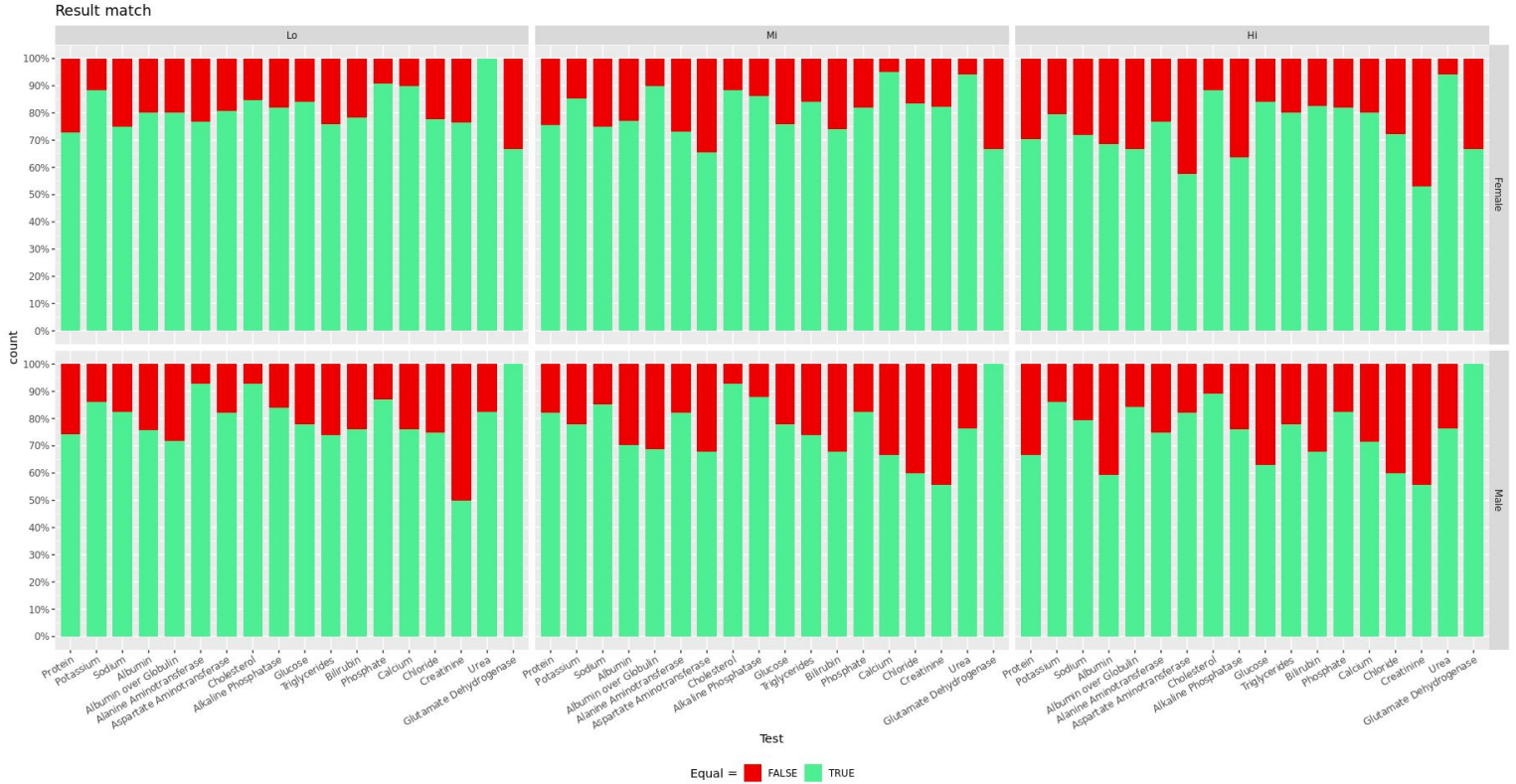
Effect Size - High dose vs Control in females



Black line corresponds to equal effect size when using Original control and VCG

Results from statistical comparisons with original or historical controls

P values - Control versus treated groups (low, medium and high doses) in females and males



Summary

- It is possible to use a repository of control animals data to build virtual control groups and reproduce results obtained with original controls

Next Steps

- Complete the curation and harmonization of data.
- Understand the endpoints variability in control animals and the role of experimental factors
- Analyze the additional confounding factors and study specific settings to understand root causes of non equality of treatment effects when using historical controls.
- Use robust statistical tests instead of statistical decision trees
- Run the same analysis using controls from the eTRANSAFE VCG repository and assess the risk associated with VCG use in future toxicology studies (partial replacement of concurrent controls)
- Discuss possible implementation of VCG in GLP rat studies (on-going discussions with regulatory agencies)

Thank you

Doing now what patients need next