

## Supplementary Appendix

### **RANDOM FOREST MODEL**

For the random forest regression models, we employed the implementation of random forest regressors (`sklearn.ensemble.RandomForestRegressor`) packaged with the Python `scikit-learn` package (v1.1.2). For building trees in the random forest model, subjects were selected from the treatment arm of the trial. Data from all sampled time points was used (n=1802). We selected the input/ predictor features of total testosterone, SHBG, estradiol, and dihydrotestosterone concentrations; the regressed output value was the percent free testosterone fraction. Prior to training, we randomly segregated the data into training and testing sets. To assess robustness of the findings, data were randomly split into training (80%, n=1441) and test sets (20%, n=361) and cross-validation and random search procedures were used to select appropriate parameters for the random forest model. We also used graphical and quantitative methods to assess goodness-of-fit between empirical free testosterone values and predicted levels derived from random forest model. The values derived from the random forest model exhibited high level of concordance with the laboratory-measured values of percent free testosterone ( $R^2$  0.78,  $p= 2.2 \times 10^{-74}$ ), confirming the robustness of the analytical model (Figure 1).

To investigate the effect of random forest hyperparameters, we performed a randomized search over the number of trees, maximum features and minimum data points considered for each decision boundary, the minimum samples permitted in leaf nodes, and whether to use bootstrap resampling. The split criterion was set to squared-error. Within this randomized search space, we performed five-fold cross-validation. The

results indicated a relative lack of susceptibility to many of the model hyperparameters except for bootstrap resampling. We selected a final model featuring incorporating the suggested hyperparameters from this procedure.

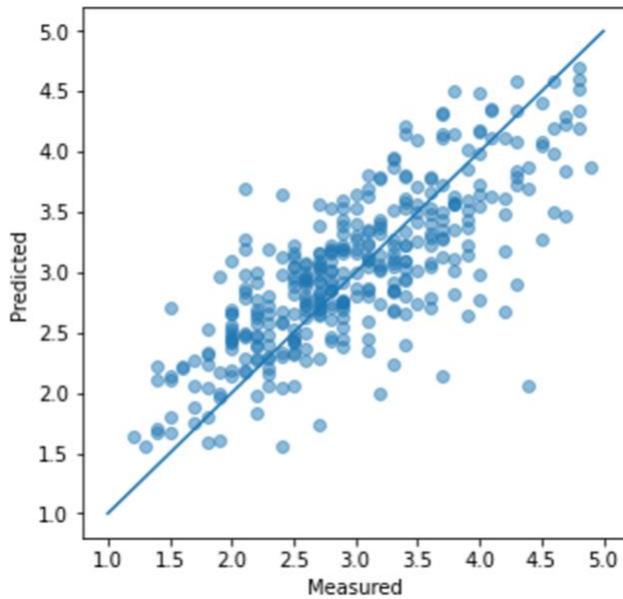


Figure 1. The concordance between the free testosterone measured using the equilibrium dialysis method and the values derived from the Random Forest model. The solid line represents the line of identity.