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National Organization for Rare Disorders

Rare Disease Cures Accelerator-Data and Analytics Platform
Virtual Workshop 2020

Up Next: *Case Study 3: RDCA-DAP drug development tool prototypes- examples of the use of integrated rare disease data to accelerate drug development*

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RDCA-DAP drug development tool prototypes:

Examples of the use of integrated rare disease data to accelerate drug development

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Background

Contains Nonbinding Recommendations

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

FDA qualification decision:

- Baseline TKV is a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient's eGFR), for inclusion in interventional clinical trials.

Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

What is the purpose of the Surrogate Endpoint Table?

FDA reasonably likely surrogate designation:

- TKV could be used as a surrogate endpoint in an FDA accelerated approval process, with an acceptable plan for a post-marketing confirmatory trial would be required
- TKV could potentially be accepted as an endpoint in and of itself (girth or size), but the bar for safety would be high, and the treatment effect would likely need to be large
- Under a “Stratified Trial Design”, eGFR could be used as an endpoint when eGFR is declining more rapidly, while TKV could be used as an endpoint when eGFR is declining very slowly, and if there was an effect in both groups, a drug could receive approval for both populations
- If the drug effect were significant enough to virtually halt cyst growth, TKV could be used as the endpoint in such a trial

Quantitative solutions for PKD (beyond a surrogate)

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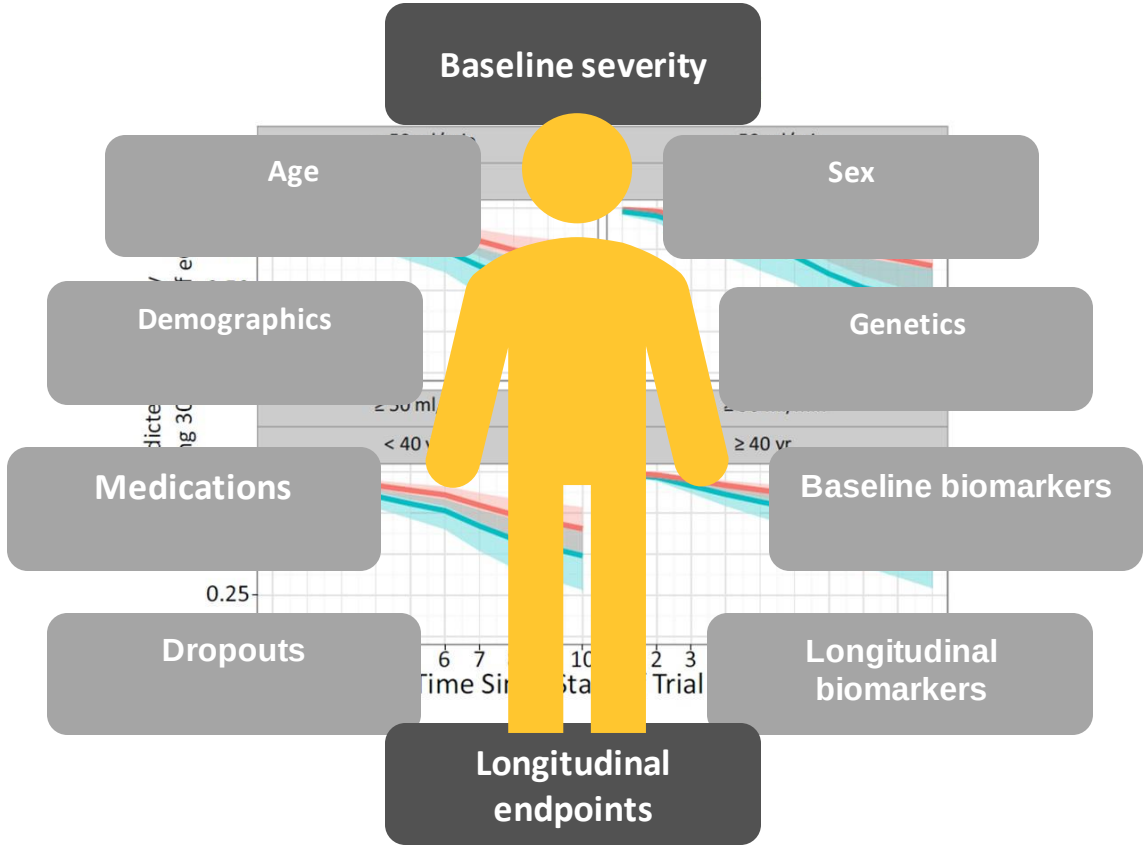
Input

Clinical Data

Transformation

Disease Modeling

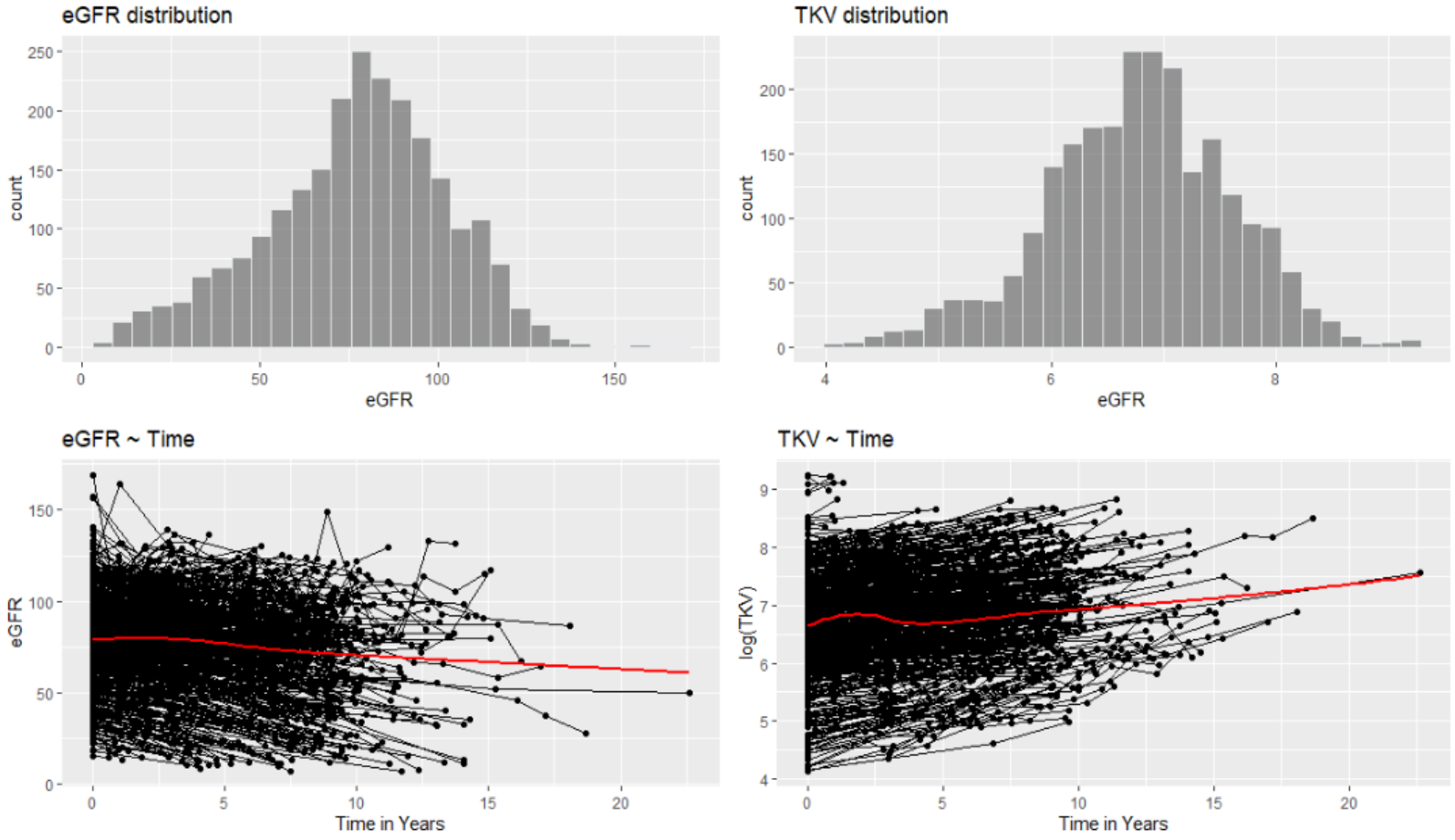


Output

Actionable Knowledge

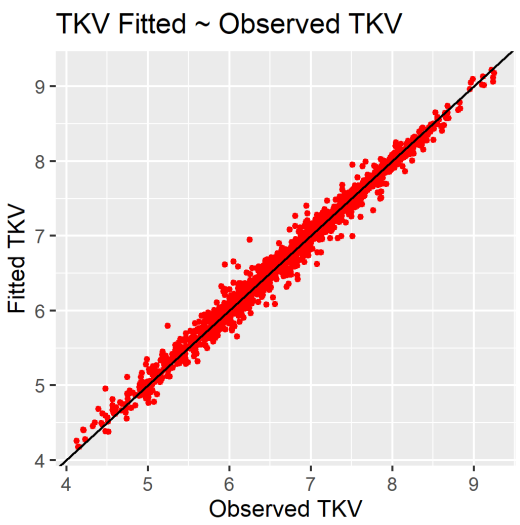
- Joint understanding of TKV+eGFR dynamics, and time-varying probability of eSRD
- Trajectory Rate Predictors
- Web Clinical Trial Simulator

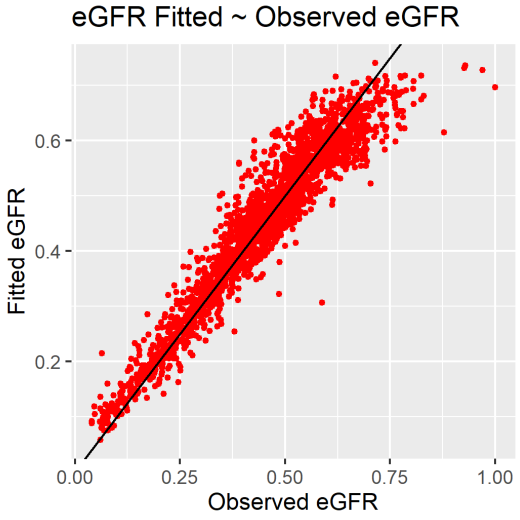
Understanding TKV and eGFR dynamics in PKD



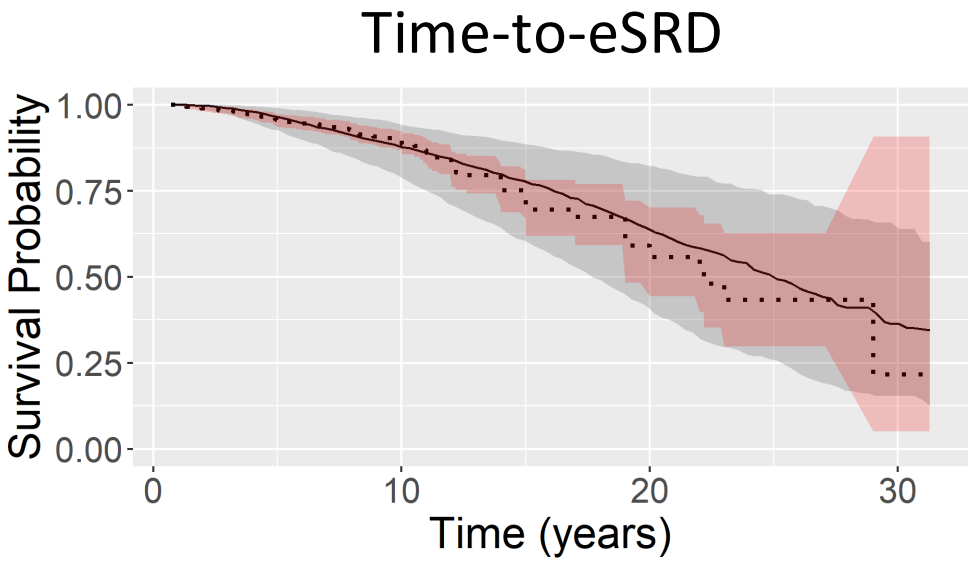
- The underlying patient-level data are very rich
- Patient-level data with high variability requires sophisticated quantitative approaches
- This allows the identification and quantification of sources of variability (genetics, demographics, baseline severity, comorbidities, concomitant drug use, etc.)

Clinical trial simulator for PKD





The multivariate model properly describes the data

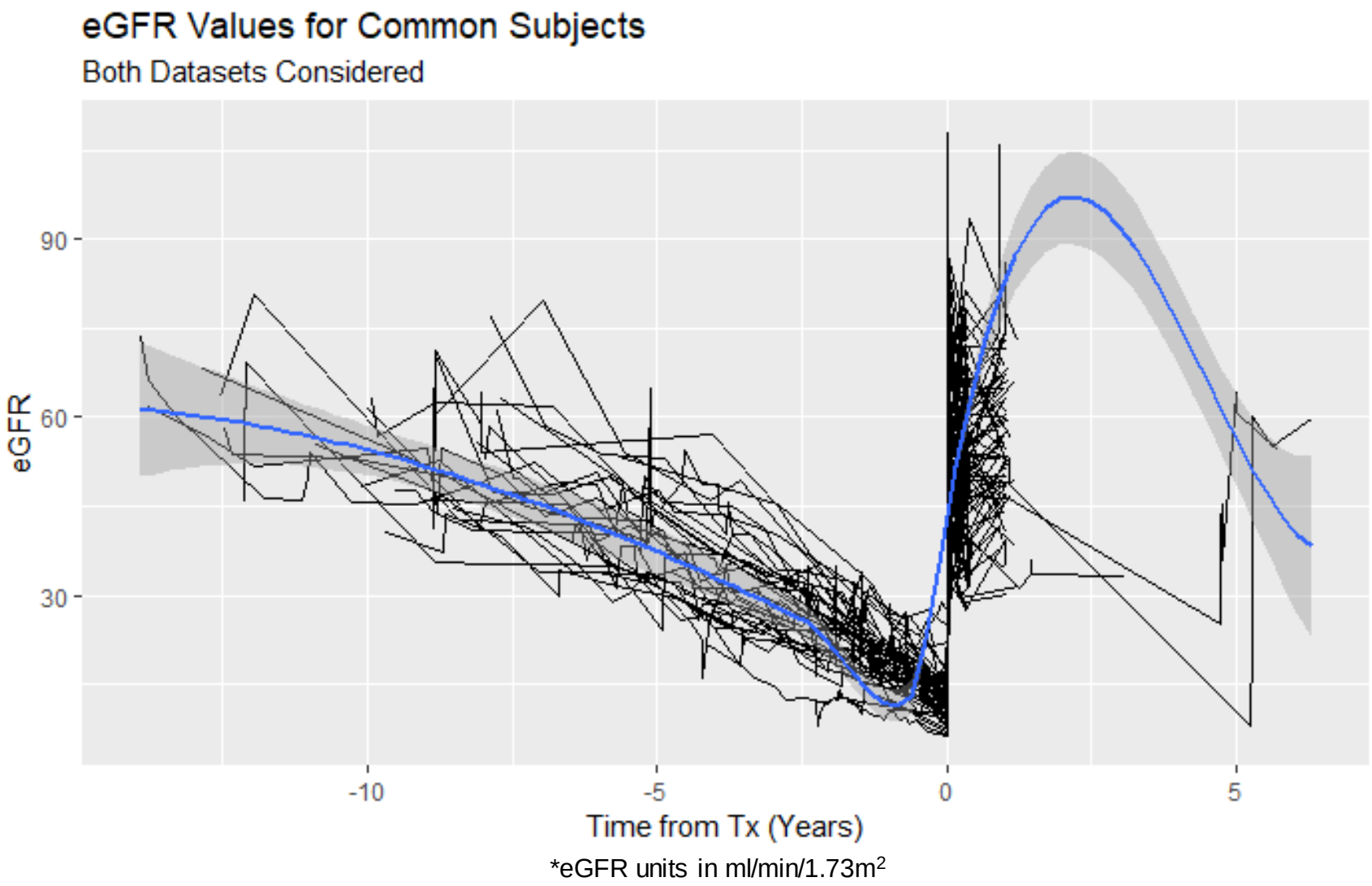


Joint modeling properly describes the relationship between TKV+eGFR dynamics and the time-varying probability of eSRD

Next steps

- Continuous expansion of the PKD patient-level data sources in RDCA-DAP
- Continuous collaboration between RDCA-DAP and PKD-OC
- Complete a clinical trial simulator for PKD
- Submit for regulatory review and potential endorsement

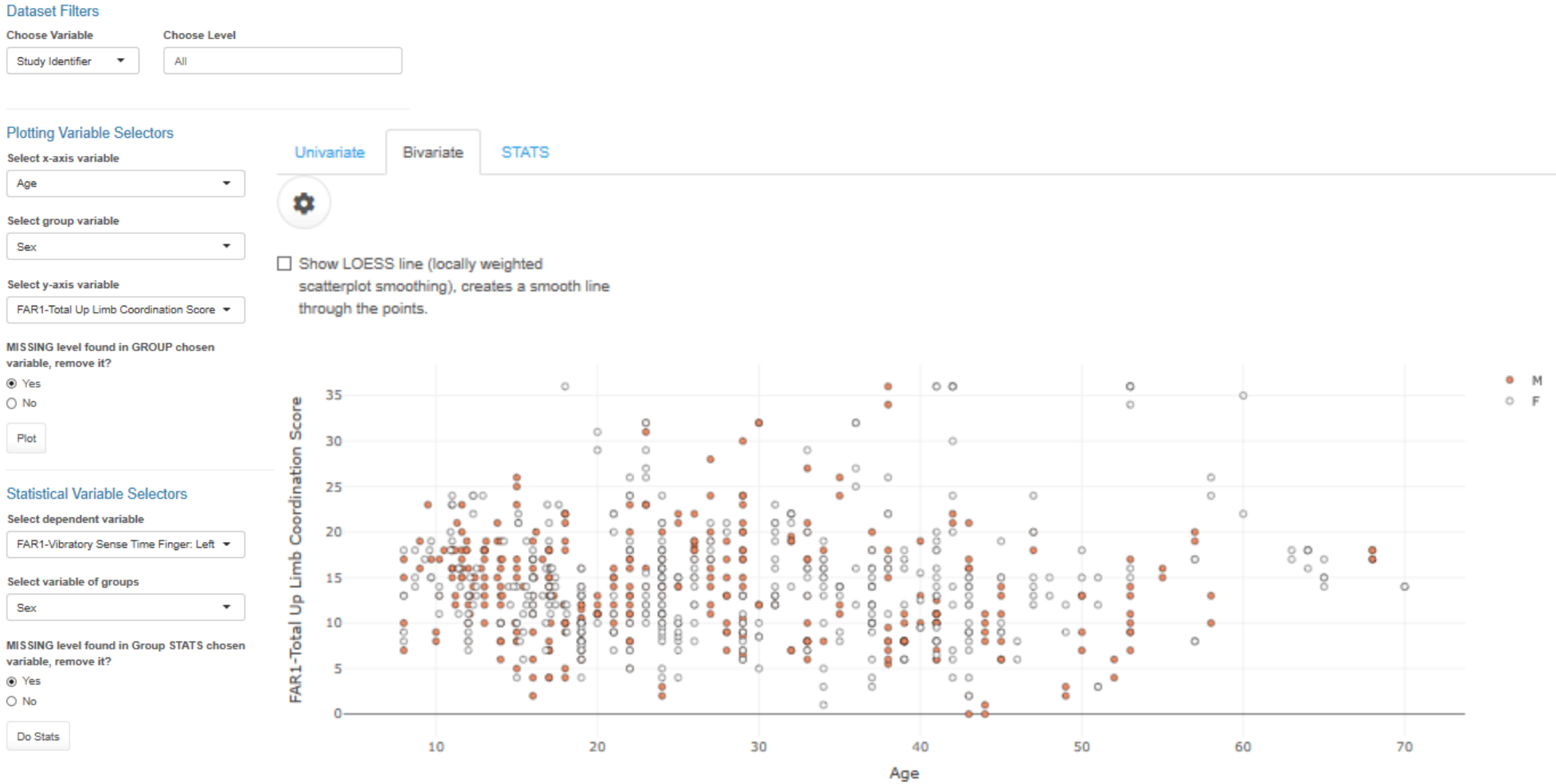
Data Interoperability solutions: PKD and kidney transplant – eGFR profiles



*eGFR units in ml/min/1.73m^2

- Understanding data across indications
- Provides valuable learnings for other efforts
- Can inform solutions for drug development in PKD and kidney transplant therapeutics

Meaningfully exploring patient-level data in Friedreich's ataxia



- User friendly interfaces democratize the ability of researchers to interact with data
- Provides valuable learnings across RDCA-DAP
- Can form the basis for the generation of comprehensive plans to develop tangible drug development solutions

Meaningfully exploring patient-level data in Friedreich's ataxia

Number of groups: 2

The suggested test (and default) is: 'Wilcoxon Rank Sum Test or Mann-Whitney Test', but careful statistical and clinical interpretation is recommended.

If the tests aren't correct choose one of the three mean difference hypothesis tests:

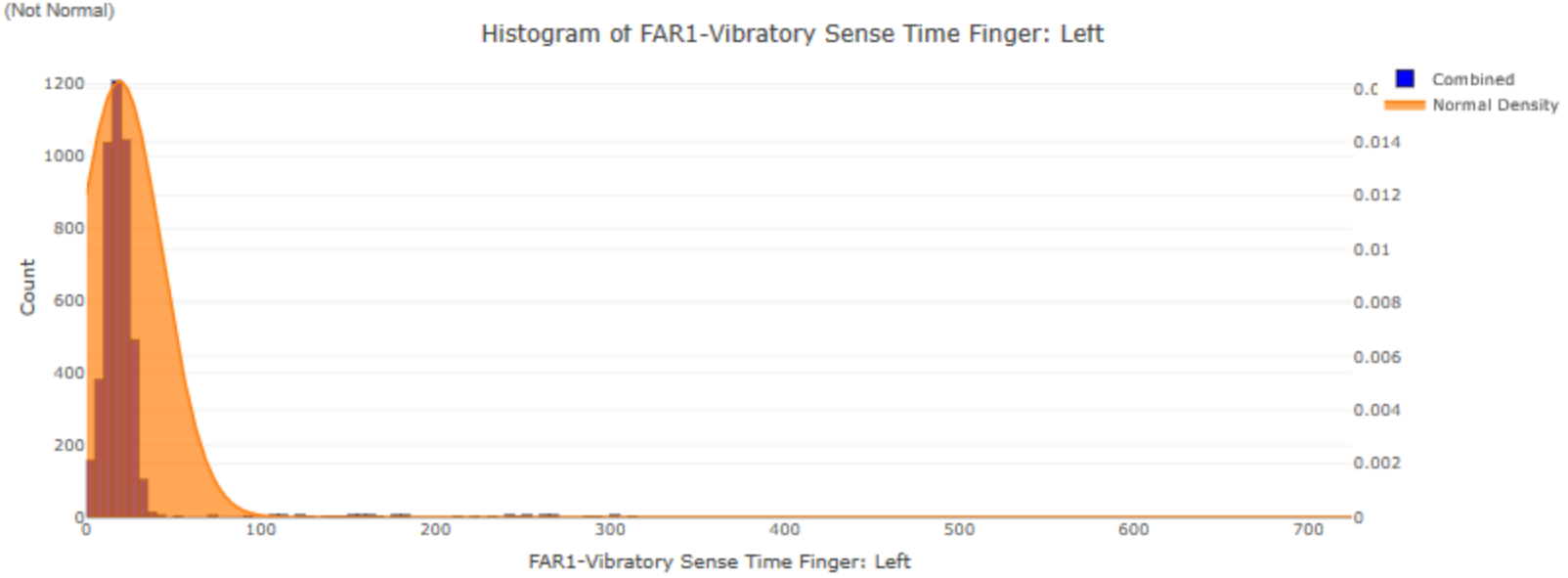
Mean Difference test for 2 samples:

- (●) Wilcoxon Rank Sum Test or Mann-Whitney Test (Not normal)
- ( ) Students t-Test (Normal Unequal Variances)
- ( ) Students t-Test (Normal Equal Variances)

p-value of test: 0.00063

Shapiro-Wilk Normality Test p-value

p-value = 0.00000
Using a p-value at less than 0.05 to determine significance:
(Not Normal)



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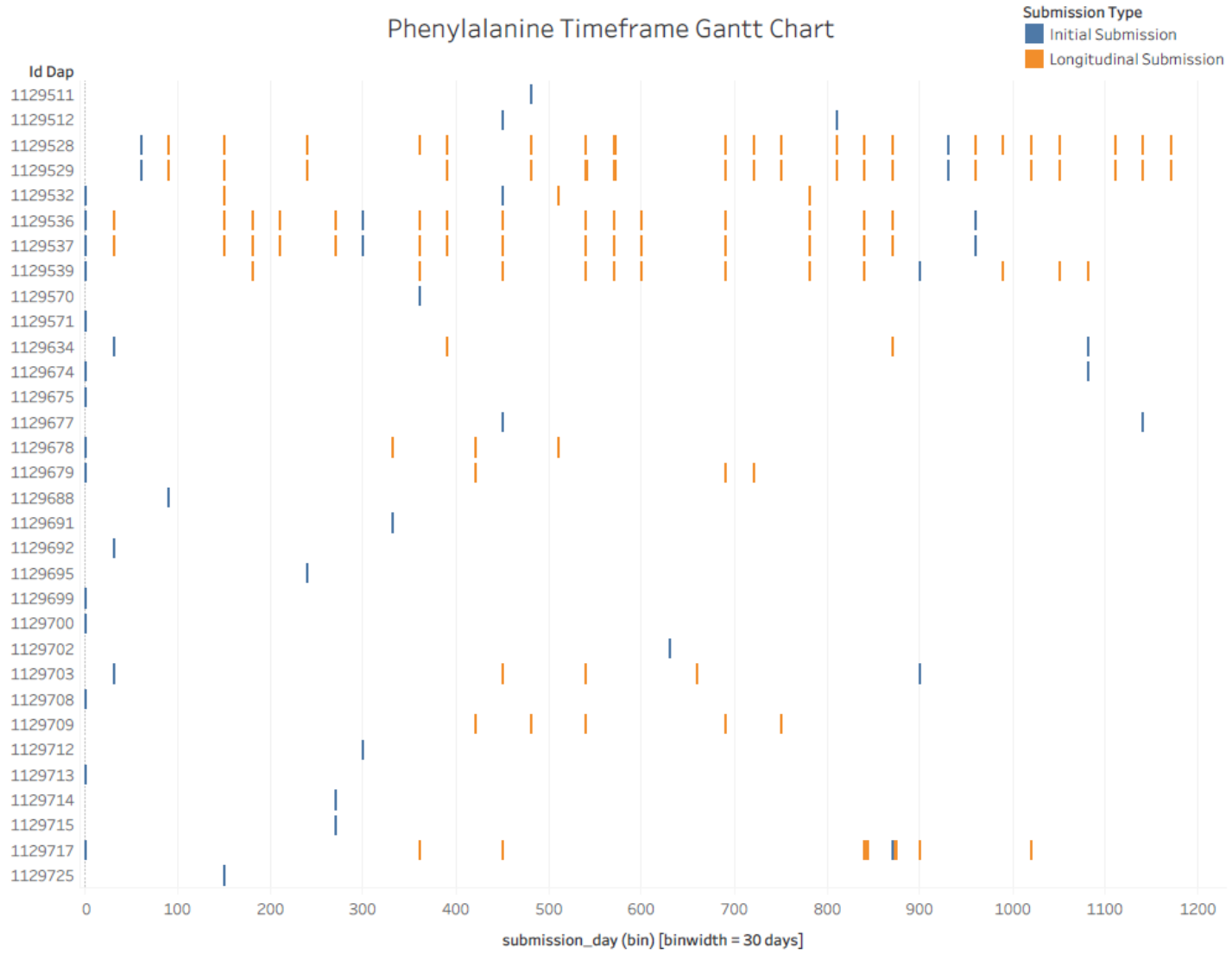
Meaningfully exploring patient-level data in PKU



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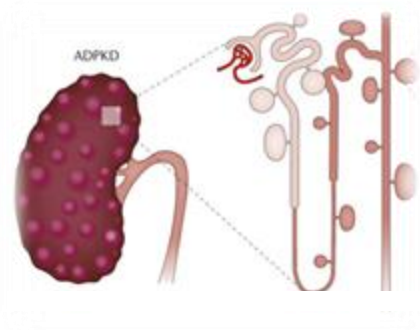
IMPACT



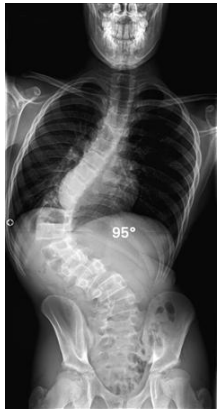
Polycystic kidney disease:

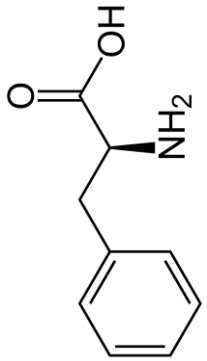
Biomarker dynamics model coupled with disease progression model that facilitated the approval of the first-ever treatment to slow disease progression, also solidifying a pipeline of over ten novel drugs under development.

Now taking the next step to expand the set of quantitative solutions, to accelerate medical product development in PKD even more.

Kidney transplantation:

Data interoperability maximizes the information value of the patient-level data across indications. Gained insights provide the potential for optimized medical product development beyond a single indication





Friedreich's ataxia and phenylketonuria:

A patient-level data foundation has been laid, on top of which quantitative insights can be gained, aiming to accelerate medical product development for individuals in need

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THANK YOU!

Don't forget to answer survey questions.

For more information, email rdcadap@c-path.org

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