A Drug Development Tool for Trial Enrichment in Patients With Autosomal Dominant Polycystic Kidney Disease

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Introduction: Total kidney volume (TKV) is a promising imaging biomarker for tracking and predicting the natural history of patients with autosomal dominant polycystic kidney disease.

Methods: A drug development tool was developed by linking longitudinal TKV measurements to the probability of a 30% decline of estimated glomerular filtration rate (eGFR) or end-stage renal disease. Drug development tools were developed based on observational data collected over multiple decades for an eGFR decline and end-stage renal disease in 641 and 866 patients with autosomal dominant polycystic kidney disease, respectively.

Results: The statistical association between predicted TKV at the time of a 30% decline of eGFR and that at the time of end-stage renal disease were both highly significant (P < 0.0001). The drug development tool was applied to demonstrate the utility of trial enrichment according to prespecified baseline TKV, age, and eGFR as enrollment criteria in hypothetical clinical trials. Patients with larger TKV (>1000 ml) displayed steeper slopes of hazard, which translated into a higher risk of a 30% decline of eGFR within each baseline age (< or ≥40 years) or baseline eGFR (< or ≥50 ml/min per 1.73 m²) subgroups.

Discussion: These results suggest that, when eGFR is preserved, patients with larger TKV are more likely to progress to a 30% decline of eGFR within the course of a clinical trial, whereas eGFR and age displayed limited predictive value of disease progression in early disease. Pharmaceutical sponsors and academic investigators are encouraged to prospectively employ the above drug development tool to optimize trial designs in patients with autosomal dominant polycystic kidney disease.

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KEYWORDS: end-stage renal disease; renal function decline; total kidney volume; trial enrichment

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Guidance for Industry on the Qualification of Drug Development Tools (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf) acknowledges that biomarkers may assess many different types of biological characteristics or parameters including radiographic or other imaging-based measurements. The Polycystic Kidney Disease Outcomes Consortium (PKDOC) has identified TKV as an imaging biomarker that is most relevant for tracking and predicting the natural history of ADPKD. The PKDOC has developed the first-ever Clinical Data Interchange Standards Consortium therapeutic-area-specific data standards for ADPKD to allow for the mapping and integration of observational data from both patient registries and Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort studies into a common dataset. This rich and robust dataset has allowed the PKDOC to develop a statistical model linking longitudinal TKV measurements in concert with age and estimated glomerular filtration rate (eGFR) to the probability of a 30% decline of eGFR or end-stage renal disease (ESRD) and ultimately leverage the model as a drug development tool (DDT) for trial enrichment in patients with ADPKD.

**METHODS**

The PKDOC has developed the first-ever Clinical Data Interchange Standards Consortium data standards for ADPKD to allow for the mapping and pooling of available data into a common dataset that has been used to support the regulatory qualification of TKV by the FDA and European Medicines Agency. This common dataset is one of the largest ever datasets of patients with ADPKD, with a total of 2355 patients. The PKDOC dataset includes 1182 subjects who have at least 2 images for the measurement of TKV taken at least 6 months apart. Observational, prospectively obtained data from 5 sources were aggregated into a common database in a standard Clinical Data Interchange Standards Consortium structure: (i) University of Colorado – Denver, (ii) Mayo Clinic, (iii) Emory University, (iv) CRISP1, and (v) CRISP2. The content of these databases is described elsewhere and in Supplementary Table S1.

**Construction of DDT**

Joint models linking longitudinal TKV measurements, in combination with other prognostic factors, were constructed for the probability of a 30% decline of eGFR as well as ESRD. In a first step, linear mixed-effect models with a random intercept were used to fit ln-transformed TKV values for all datasets. Patients with at least 2 TKV measurements separated by at least 6 months were included in the analysis. Baseline TKV was defined as the first TKV measurement for a subject, irrespective of modality including computerized tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), whereas baseline age was the age associated with the first TKV measurement. The population for the assessment of a 30% decline of eGFR included 1182 patients with at least 2 images of TKV.

For the time-to-event model of a 30% decline of eGFR, the association parameter between predicted TKV at the time of a 30% decline of eGFR was modeled using a piecewise linear model (12 knots). Baseline eGFR was calculated from the first valid serum creatinine measurement on or within 365 days of the baseline TKV. Because many of the creatinine measurements were made using older colorimetric methods, eGFR was derived using the original Modification of Diet in Renal Disease equation for creatinine methods that are not calibrated to an isotope dilution mass spectrometry reference method. For creatinine methods calibrated to an isotope dilution mass spectrometry reference method, the isotope dilution mass spectrometry–traceable Modification of Diet in Renal Disease study equation was used to derive eGFR. Because the goal of this project was to determine whether TKV, along with other prognostic factors such as baseline age and eGFR, can accurately predict the risk of a decline of eGFR, only endpoint measurements that occurred after the first baseline TKV measurement were considered. A subsequent (confirmatory) measurement within any timeframe was required to confirm that the original 30% decline was not transient. Data rules are summarized in Supplementary Table S2. Of the 1182 patients with at least 2 images of TKV, a total of 541 patients did not have eGFR at baseline or a confirmatory eGFR (Supplementary Figure S1). As a result, a total of 641 patients were used in the joint analysis of TKV and the probability of a 30% decline of eGFR. Baseline eGFR and baseline age were statistically significant parameters for joint modeling of TKV and the probability of a 30% decline of eGFR.

For the ESRD model, the association parameter between predicted TKV at the time of ESRD was modeled using a Weibull model. ESRD was defined as a patient with either dialysis or transplant. Of the 1182 patients with at least 2 images of TKV, a total of 316 patients did not have eGFR at baseline or a missing date of ESRD. Data rules are summarized in Supplementary Table S2 and data flow is displayed in Supplementary Figure S1. As a result, a total of 866 patients were used in the joint analysis of TKV and the probability of ESRD. Baseline age, baseline eGFR, and interaction terms were found statistically significant for the ESRD model.
Data utilized for analysis came from registries as opposed to clinical trials and patients were seen on an irregular basis. For example, the endpoint of an eGFR decline could only be defined after a minimum of 2 measurements of TKV. There is a slight possibility of bias due to missing data, but this is thought to be unlikely because data missingness was due to the randomness of the available registry data.

Data Splitting and Interval Validation
Cross-validation was performed using a 5-fold or 10-fold cross-validation approach. Data were split into 5 parts with roughly equal number of subjects. Splitting was stratified to maintain a similar proportion of patients from the CRISP and registry datasets in the reference and test datasets. Each fold served as a test dataset in the following steps, whereas the rest of the data consisted of the training dataset (i.e., the 4 other folds). The joint model (including prognostic factors) was fitted to the training dataset (4/5 of the folds). Prediction of disease outcomes for the test dataset was performed by simulating from the joint model using each individual prognostic factor (longitudinal TKV data, baseline age, and baseline eGFR) from the test dataset. Model-based predicted probabilities in the test dataset were compared with observed disease outcomes in the test dataset. Predictive performance of the joint model was assessed by computing descriptive statistics of observed versus predicted probability of disease outcomes (precision and accuracy). The above steps were repeated for each fold.

Software
Joint modeling and cross-validation was performed using the JM package in R 3.0.2 (64-bit).

RESULTS
Baseline Characteristics
A total of 1182 patients with ADPKD and at least 2 TKV data collected over 30 years of follow-up were available in the database. Figure 1 provides a high-level visual perspective of the mix of imaging modalities for subjects with at least 2 TKV measurements from 5 clinical sites. Several imaging modalities have been utilized to determine TKV in patients with ADPKD. These included US as determined using the ellipsoid method, MRI, and CT scan.

Figure 1. Time span and modalities of images for subjects with 2 or more images (n = 1182). CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; CT, computerized tomography; MRI, magnetic resonance imaging; TKV, total kidney volume; US, ultrasound.
Baseline characteristics of subjects with ADPKD included in the joint model analysis are presented in Table 1. A total of 541 patients were excluded for the 30% decline of eGFR endpoint because of missing baseline eGFR or if the endpoint was observed between the first and second TKV measurement. For the 30% decline of the eGFR model, a total of 641 patients with at least 2 TKV measurements separated by at least 6 months were included in the analysis of a 30% decline of eGFR (30.0%). The populations used in modeling the probability of a 30% decline of eGFR consisted of 1140 subjects with mean baseline TKV, age, and eGFR of 1141 ml, 33.2 years, and 84.3 ml/min per 1.73 m², respectively. For ESRD, a total of 316 patients were excluded because of missing baseline eGFR or a missing date of ESRD. For the ESRD model, a total of 866 patients with at least 2 TKV measurements separated by at least 6 months were included in the joint model analysis are presented in Table 1. A total of 541 patients were excluded for the 30% decline of eGFR endpoint because of missing baseline eGFR or if the endpoint was observed between the first and second TKV measurement. For the 30% decline of the eGFR model, a total of 641 patients with at least 2 TKV measurements separated by at least 6 months were included in the analysis of a 30% decline of eGFR (30.0%). The populations used in modeling the probability of a 30% decline of eGFR consisted of 1140 subjects with mean baseline TKV, age, and eGFR of 1141 ml, 33.2 years, and 84.3 ml/min per 1.73 m², respectively. For ESRD, a total of 316 patients were excluded because of missing baseline eGFR or a missing date of ESRD. For the ESRD model, a total of 866 patients with at least 2 TKV measurements separated by at least 6 months were included in the joint model analysis are presented in Table 1.

### Table 1. Baseline characteristics of subjects with ADPKD included in the joint model analysis

| Baseline characteristics | Population for the analysis of 30% decline of eGFR (N = 641) | Population for the analysis of ESRD (N = 866) |
|--------------------------|---------------------------------------------------------------|--------------------------------------------------|
| TKV (ml)                 | 1141 (1186.1)                                                | 1214 (1249.4)                                    |
| Age (yr)                 | 33.2 (15.64)                                                 | 34.7 (15.91)                                     |
| Genotype                 |                                                               |                                                  |
| PKD1                     | 386 (60.2)                                                   | 470 (54.3)                                       |
| PKD2                     | 45 (7.0)                                                     | 51 (5.9)                                         |
| Missing                  | 196 (30.6)                                                   | 328 (37.9)                                       |
| No mutation detected     | 14 (2.2)                                                     | 17 (2.0)                                         |
| Sex                      |                                                               |                                                  |
| Male                     | 245 (38.2)                                                   | 333 (38.5)                                       |
| Female                   | 396 (61.8)                                                   | 533 (61.5)                                       |
| Race                     |                                                               |                                                  |
| White                    | 595 (92.8)                                                   | 798 (92.1)                                       |
| Black                    | 29 (4.5)                                                     | 37 (4.3)                                         |
| Other                    | 17 (2.7)                                                     | 31 (3.6)                                         |
| Genotype                 |                                                               |                                                  |
| PKD1                     | 386 (60.2)                                                   | 470 (54.3)                                       |
| PKD2                     | 45 (7.0)                                                     | 51 (5.9)                                         |
| Missing                  | 196 (30.6)                                                   | 328 (37.9)                                       |
| No mutation detected     | 14 (2.2)                                                     | 17 (2.0)                                         |

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PKD, polycystic kidney disease; TKV, total kidney volume.

### Table 2. Final parameters of the joint model for the probability of avoiding a 30% decline of eGFR and ESRD

| Endpoints | Parameters | Coefficient (SE) | z value | P value |
|-----------|------------|------------------|---------|---------|
| 30% decline of eGFR | TKV model Intercept | 6.6884 (0.0348) | 191.9 | <0.0001 |
|            | Rate of growth model | 0.0516 (0.0024) | 21.8 | <0.0001 |
|            | Association (TKV→event) | 0.8457 (0.1204) | 7.02 | <0.0001 |
|            | Baseline eGFR Intercept | 0.0101 (0.0032) | 3.19 | 0.0014 |
|            | Baseline age | 0.0004 (0.0077) | 0.0519 | 0.9586 |
| ESRD      | TKV model Intercept | 6.712 (0.0301) | 223.0 | <0.0001 |
|            | Rate of growth model | 0.0560 (0.0020) | 28.4 | <0.0001 |
|            | Association (TKV→event) | 1.2365 (0.1631) | 7.58 | <0.0001 |
|            | Baseline eGFR | -0.0391 (0.0135) | -2.90 | 0.0037 |
|            | Baseline age | 0.0355 (0.0169) | 2.10 | 0.0357 |

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; TKV, total kidney volume.
enrichment strategies according to this baseline characteristic.

For the ESRD model, the rate of growth of TKV was 0.056 (corresponding to 5.60% per year). The association between the predicted TKV value at the time of ESRD (Weibull function) was highly statistically significant ($P < 0.0001$). Baseline eGFR ($P = 0.0037$) and baseline age ($P = 0.0357$) were also statistically significant in addition to a statistically significant interaction between baseline eGFR and age.

Adequacies of TKV models for the 30% decline of eGFR and ESRD endpoints are presented in Figure 2. Overall, subject-level model-predicted versus observed log-transformed TKV and standardized residuals were very well fitted with the model (Figure 2a). This was demonstrated by the locally weighted scatter-plot smoother (LOESS, red dashed line) between subject-level prediction and observed values which were very close to the identity curve (i.e., black line). Furthermore, the distribution of standardized subject-level residuals was homogeneously distributed around 0, suggesting no residual effect (Figure 2b). Adequacies of event models, linking individual subject level TKV data to a 30% decline of eGFR and ESRD endpoints over follow-up time, are presented in Figure 3. Time to a 30% decline of eGFR and ESRD endpoints were well fitted with the joint model as demonstrated by the model-predicted value (red line) relative to observed probabilities (black lines) and 95% confidence intervals. A 5-fold data splitting method was used to evaluate the predictive performance of the final joint models. The predictive performance of the model was assessed by deriving mean prediction error and root-mean-square error values of individual observed versus predicted values for a 30% decline of eGFR and ESRD endpoints. Results of the cross-validation are presented in Supplementary Tables S3 and S4.

**Figure 2.** Subject-level model-predicted versus (a) observed log transformed TKV and (b) standardized residuals for a 30% decline of eGFR and ESRD endpoints. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

**Figure 3.** Model-predicted versus observed probabilities for avoiding a 30% decline of eGFR and ESRD over time. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

**Application of DDT for Trial Enrichment**

The DDT was applied to demonstrate the utility of trial enrichment according to prespecified baseline TKV, age, and eGFR as enrollment criteria. The joint model was used to perform trial simulations to ultimately derive the predicted probabilities of a 30% decline of eGFR according to specific inclusion criteria of baseline TKV ($\geq 1000$ ml), baseline age ($< 40$ years), and baseline eGFR ($< 50$ ml/min per $1.73$ m$^2$). The predicted probabilities of avoiding a 30% decline of eGFR according to baseline TKV are presented in Figure 4. Patients with larger TKV ($\geq 1000$ ml) displayed steeper slopes of hazard, which translated into a higher risk of a 30% decline of eGFR within each
baseline age (< or ≥40 years) or baseline eGFR (< or ≥50 ml/min per 1.73 m²) subgroups. Patients with TKV ≥ 1000 ml, eGFR < 50 ml/min per 1.73 m², and age ≥ 40 years displayed the highest risk of a 30% decline in eGFR. These results suggest that patients with larger TKV are more likely to progress to a 30% decline in eGFR.

Figure 4. Trial enrichment example—mean (95%) predicted probabilities for avoiding a 30% decline of eGFR as a function of baseline TKV categories. eGFR, estimated glomerular filtration rate; TKV, total kidney volume.

Figure 5. Trial enrichment example—mean (95%) predicted probabilities for avoiding a 30% decline of estimated glomerular filtration rate (eGFR) as a function of baseline eGFR categories.
decline of eGFR, independent of other baseline characteristics.

In Figure 5, the predicted probabilities of avoiding a 30% decline of eGFR in patients with baseline eGFR \(< 50\) ml/min per 1.73 m\(^2\) were similar to those in patients with baseline eGFR \(\geq 50\) ml/min per 1.73 m\(^2\) in all subgroups, with the exception of patients \(\geq 40\) years of age and baseline TKV \(\geq 1\) liter (lower-right panel). The predicted probabilities of avoiding a 30% decline of eGFR according to baseline age are presented in Figure 6. Overall, predicted probabilities of avoiding a 30% decline of eGFR in patients \(< 40\) years were similar to those in patient \(\geq 40\) years of age.

Numerical values of predicted probabilities of a 30% decline of eGFR over time as a function of TKV, eGFR, or age are presented in Table 3. At year 3, median predicted probabilities of a 30% decline in eGFR in patients with TKV \(\geq 1000\) and \(< 1000\) ml were 9.88% and 5.09%, respectively. At year 5, median predicted probabilities of a 30% decline in eGFR in patients with TKV \(\geq 1000\) and \(< 1000\) ml were 20.8% and 11.3%, respectively. Finally, median predicted probabilities of a 30% decline in eGFR at year 10 in patients with TKV \(\geq 1000\) and \(< 1000\) ml were 53.1% and 34.3%, respectively. Conversely, baseline eGFR and age did not provide a discrimination in probabilities of a 30% decline in eGFR. Numerical values of predicted probabilities of a 30% decline of eGFR by TKV within each category of eGFR and age are presented in Table 4. Patients with larger TKV \((\geq 1000\) ml) displayed steeper slopes of hazard, which translated into a higher risk of a 30% decline of eGFR within each baseline age \(<\) or \(\geq 40\) years) or baseline eGFR \((<\) or \(\geq 50\) ml/min per 1.73 m\(^2\)) subgroups. These results suggest that, when eGFR is preserved, patients with larger TKV are more likely to progress to a 30% decline of eGFR within the course of a clinical trial, whereas eGFR and age displayed limited predictive value of disease progression in early disease.

**DISCUSSION**

The current work presents evidence that supported the regulatory qualification of TKV as a prognostic biomarker according to its Context of Use, based on definitions set forth by the FDA’s Guidance on the Qualification Process for Drug Development Tools (Guidance Compliance Regulatory Information), and the European Medicines Agency’s “Qualification of novel methodologies for drug development.”17,18 The DDT consists of a joint model linking the probability of a 30% decline of eGFR and ESRD as a function of longitudinal TKV. Joint modeling is considered as the gold standard method for assessing the effect of longitudinal time-varying covariates (e.g., TKV) in a

![Figure 6. Trial enrichment example—mean (95%) predicted probabilities for avoiding a 30% decline of estimated glomerular filtration rate (eGFR) as a function of baseline age categories.](image-url)
The measured GFR was not available for the vast majority of patients. Although the measured GFR has frequently been thought of as a “gold standard” for clinical trial outcomes, recent analyses indicate that eGFR is comparable to mGFR for association with adverse outcomes such as ESRD and cardiovascular events.\textsuperscript{21}

Data utilized for analysis came from registries as opposed to clinical trials and patients were seen on an irregular basis. There is a slight possibility of bias due to missing data, but this is thought to be unlikely because data missingness was due to the randomness of the available registry data.

Overall, the qualification of TKV as an imaging biomarker for tracking and predicting the natural history of ADPKD represents a significant, innovative step forward to establishing the commitment of health authorities, clinicians, and patients to address the unmet needs for this debilitating condition, thereby encouraging researchers and the pharmaceutical industry to develop promising new therapies for these patients. When used to assess the effect of interventional therapy, TKV will need to be assessed in the context of the investigational agent’s mechanism of action and its potential for nephrotoxicity or other side effects that could impact renal function. The DDT tools (model codes) are available at https://c-path.org/. Pharmaceutical sponsors and academic investigators are encouraged to prospectively employ the above joint model to optimize trial designs in patients with ADPKD.

Table 4. Trial enrichment example—tabulation of mean predicted probabilities of a 30% decline of eGFR as a function of baseline TKV, eGFR, and age categories

| Time (yr) | eGFR < 50 (ml/min per 1.73 m$^2$) | eGFR ≥ 50 (ml/min per 1.73 m$^2$) | eGFR < 50 (ml/min per 1.73 m$^2$) | eGFR ≥ 50 (ml/min per 1.73 m$^2$) |
|-----------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| TKV ≤ 1000 ml | | | | |
| 1 | 2.10% | 1.80% | 1.60% | 1.50% |
| 2 | 4.70% | 4.10% | 3.70% | 3.40% |
| 3 | 11.6% | 10.1% | 9.30% | 8.50% |
| 4 | 18.5% | 16.1% | 14.8% | 13.7% |
| 5 | 24.3% | 21.1% | 19.5% | 18.2% |
| 6 | 29.2% | 25.6% | 23.6% | 22.3% |
| 7 | 40.0% | 35.2% | 32.9% | 31.0% |
| 8 | 48.4% | 43.6% | 41.0% | 38.7% |
| 9 | 53.7% | 48.7% | 46.0% | 43.6% |
| 10 | 59.0% | 53.8% | 51.0% | 48.5% |

| Time (yr) | eGFR < 50 (ml/min per 1.73 m$^2$) | eGFR ≥ 50 (ml/min per 1.73 m$^2$) | eGFR < 50 (ml/min per 1.73 m$^2$) | eGFR ≥ 50 (ml/min per 1.73 m$^2$) |
|-----------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| TKV < 1000 ml | | | | |
| 1 | 0.90% | 0.80% | 0.83% | 0.85% |
| 2 | 2.10% | 2.00% | 1.91% | 1.96% |
| 3 | 5.30% | 5.10% | 4.93% | 5.01% |
| 4 | 8.70% | 8.40% | 8.24% | 8.31% |
| 5 | 11.6% | 11.2% | 11.1% | 11.3% |
| 6 | 14.5% | 13.9% | 13.8% | 14.0% |
| 7 | 20.9% | 19.9% | 20.1% | 20.4% |
| 8 | 26.9% | 25.6% | 25.9% | 26.2% |
| 9 | 31.0% | 29.4% | 29.8% | 30.3% |
| 10 | 35.2% | 33.4% | 33.9% | 34.6% |

eGFR, estimated glomerular filtration rate; TKV, total kidney volume.
similar to other models that have been made publicly available by the FDA. 22–24

DISCLOSURE
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SUPPLEMENTARY MATERIAL
Table S1. Description of timeframe of enrollment, number of subjects enrolled, and process of each study/registry.  

Table S2. Data rules.  
Table S3. Cross-validation of the joint model—predicted probabilities for avoiding a 30% worsening of eGFR.  
Table S4. Cross-validation of the joint model—predicted probabilities of avoiding eSRD.  
Figure S1. Flowchart for data flow. Supplementary material is linked to the online version of the paper at http://www.kireports.org/.

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