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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 m^2) 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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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. There is an increasing body of evidence demonstrating that the kidneys of patients with ADPKD progressively increase in size from birth throughout life, and the clinical symptoms and signs of ADPKD including hypertension, gross hematuria, flank and abdominal pain, and declining glomerular filtration rate (GFR) are associated with increased kidney volume.[1,2] The clinical course of ADPKD is marked by a decades-long period of stable kidney function, as measured by GFR, despite the relentless expansion of total kidney volume (TKV) due to growth of cysts. There is evidence in the literature from both animal and human studies to support TKV as a prognostic endpoint for use in clinical trials for ADPKD.[1,3–5]

Medical imaging is gaining an important role in clinical trials. This has been driven by significant improvements in medical imaging technology and quality and the increasing need to leverage these technologies to reduce drug development time. The US Food and Drug Administration's (FDA's) Critical Path Initiative acknowledges the potential value of imaging as a research tool in drug development. In addition, the recent FDA

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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.[6] 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.[6] 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.[6]

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.[7–9] In a first step, linear mixed-effect models with a random intercept were used to fit ln-transformed TKV values for all datasets.[9] 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.[10] 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.[11] 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.[12,13] 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.