Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder of the kidneys with an estimated prevalence of less than 5 patients per 10,000 population in the EU. It is a systemic disorder characterised by the progressive development of renal cysts resulting in impaired renal function, which in many cases leads ultimately to end-stage renal disease (ESRD). ADPKD is associated with a high degree of inter-patient heterogeneity both in terms of likelihood of, and rate of progression towards, ESRD. The optimal methods to predict and measure ADPKD disease progression, especially in the early stage of the disease when renal function is well preserved, remain to be determined. Consolation of the clinical and scientific data in this disease area is necessary to define appropriate indicators of risk and endpoints that can be used to effectively predict disease progression and assess the efficacy of treatments in development.

Based on this, the objective of this study was to develop a bespoke and validated model for predicting disease progression and estimating long-term outcomes in ADPKD, using measurable/observable baseline patient and/or clinical characteristics.

### METHODS

#### Systematic review

A systematic literature review was conducted of clinical trials, observational studies and reviews to identify the key prognostic indicators for ADPKD progression. Total kidney volume (TKV), in combination with eGFR, were used as the key indicators for ADPKD. Total kidney volume (TKV), in combination with eGFR, were used as the key indicators for ADPKD progression.

#### ADPKD Outcomes Model

An individual patient simulation was developed in Microsoft Excel in conjunction with clinical experts. Patients are defined at baseline by age, gender, estimated glomerular filtration rate (eGFR) and TKV. The model simulates the TKV and eGFR progression of a cohort of subjects (up to 10,000) with ADPKD for a specific time horizon (Figure 2).

Two regression equations were fitted to the patient-level data, one for prediction of TKV and one for prediction of eGFR, the latter of which was dependent on the former. TKV and eGFR trajectories can be estimated on a continuous scale, with values updated in annual increments. The simulation continues until the patient enters ESRD or death. Outputs include the incidence and time to ESRD, and time spent in each chronic kidney disease (CKD) stage.

#### Equations

Equations were also developed using aggregated slope coefficients published from the CRISP study for the purposes of validation and predictions have been validated with a group of clinical experts.

#### Results

**Outputs**

Differences in TKV can lead to significant variation in outputs (Figure 3 and Table 1) demonstrating the importance of TKV as a prognostic indicator. To illustrate this, patients with mean age 40 years and eGFR 80 ml/min/1.73 m² who progress, show a variation in the mean time to ESRD when baseline TKV is varied:

- **Baseline TKV 1,000 ml:** 17 years
- **Baseline TKV 1,500 ml:** 14 years
- **Baseline TKV 2,000 ml:** 12 years

**Table 1.** Time spent in CKD stage 2, 3, 4, and in ESRD varied by TKV across all patients with mean age 40 years and eGFR 80 ml/min/1.73 m²

<table>
<thead>
<tr>
<th>TKV (ml)</th>
<th>CKD stage 2</th>
<th>CKD stage 3</th>
<th>CKD stage 4</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>7.1 (0.6)</td>
<td>6.7 (0.7)</td>
<td>2.9 (0.4)</td>
<td>2.00</td>
</tr>
<tr>
<td>1,500</td>
<td>5.2 (0.4)</td>
<td>5.0 (0.4)</td>
<td>2.6 (0.3)</td>
<td>2.00</td>
</tr>
<tr>
<td>2,000</td>
<td>4.0 (0.5)</td>
<td>5.1 (0.4)</td>
<td>2.3 (0.3)</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*Mean time (a standard deviation), years.*

**Validation**

TKV and eGFR trajectories predicted using the TEMPO 3.4 equations were validated against predictions from the CRISP equations and show a good fit to these real-world data (Figure 4). The age at ESRD simulated by the model is similar to that reported by recent studies including patients with similar baseline characteristics. In addition, the model structure, inputs and outputs have been co-developed with and validated by a steering group of ADPKD clinical experts (authors ACGM, BD, KS, FVC and GW).

### CONCLUSIONS

The importance of TKV as a prognostic indicator is supported by a systematic literature review, real-world outcomes, clinical management guidelines and expert opinion. The validated outputs of a model developed around this principle in a placebo arm of a large clinical trial are an important step forward in the understanding of ADPKD progression. The model has demonstrated both face and predictive validity and can be used to identify the risk and rate of progression towards ESRD for different ADPKD patient subgroups, particularly in the early stages of ADPKD where there is greatest uncertainty. It has the potential to provide the foundation for greater understanding of patient risk stratification and the clinical and economic evaluations of future therapies.

### REFERENCES


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