Recommendations for Diagnostic and Prognostic Evaluation of Autosomal Dominant Polycystic Kidney Disease (ADPKD) with a Focus on Imaging

The Swiss Society of Radiology (SGR-SSR) and the Swiss Society of Nephrology Working Group of Inherited Kidney Disorders endorse the scientific content of this manuscript. The SGR-SSR agrees in particular with the suggested technique for image acquisition and measuring kidney volume. The society also agrees on the suggestion that treatment and imaging should be performed by the same institution, and imaging follow-up should, whenever possible, be performed by the same radiological institution which has performed the baseline study.

Empfehlungen zur diagnostischen und prognostischen Evaluation der autosomal-dominanten polyzystischen Nierenerkrankung (ADPKD) mit Fokus auf die Bildgebung

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease. Continuous growth of multiple cysts in both kidneys leads to progressive renal enlargement and ultimately to loss of kidney function. Treatment until recently has been largely symptomatic. The V2-receptor antagonist tolvaptan is the first specific treatment with proven efficacy to reduce cyst growth and to retard kidney function loss. Tolvaptan has become available for the treatment of ADPKD in Switzerland in 2016, but given its high costs and adverse effects on the one side and the considerable variability in progression and prognosis of ADPKD on the other, prescription of tolvaptan has been limited to patients with rapidly progressive disease. Criteria for rapid progression have been listed by the Federal Office of Public Health on the list of pharmaceutical specialties. This article gives recommendations on how to implement these criteria in the clinical routine, with a focus on imaging methods that are used to determine total kidney volume (TKV).

Background

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease which causes cyst proliferation and growth in the kidneys, leading to a progressive increase in kidney size and resulting in complications that include chronic and acute pain, hypertension, hematuria, cyst infections, and ultimately kidney failure, necessitating dialysis or renal transplantation.

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
CKD	Chronic kidney disease
CT	Computed tomography
FOPH	Federal Office of Public Health (German: BAG; Bundesamt für Gesundheit)
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
LS	List of pharmaceutical specialties (German: SL; Spezialitätenliste)
MRI	Magnetic resonance imaging
TKV	Total kidney volume
htTKV	Height-adjusted TKV

Praxis 2018; *107* (3): 158–164
https://doi.org/10.1024/1661-8157/a002890

A new medication, tolvaptan (Jinarc®), has received approval by European authorities as well as by Swissmedic and has been available in Switzerland since November 2016. It is the first approved pharmaceutical therapy available for patients with ADPKD that targets the underlying pathophysiology of the disease. However, treatment with tolvaptan has relevant side effects (the most important being polyuria and the potential for liver toxicity), is very expensive (ca. 25700 CHF per year) and does merely retard but not halt disease progression. Hence, tolvaptan treatment is merely recommended in ADPKD patients with rapidly progressive disease. Therefore, the prescription of tolvaptan in Switzerland is restricted by Swissmedic to ADPKD patients with typical imaging characteristics, CKD stages 1–3, and signs of rapidly progressing disease. Disease progression is very variable in ADPKD and difficult to predict. The Federal Office of Public Health (FOPH) has defined detailed criteria for insurance reimbursement on its list of pharmaceutical specialties (LS) [1] that are based on currently established risk factors for rapid progression (table 1). Diagnosis of ADPKD is usually established by imaging, and total kidney volume (TKV) is currently considered the best prognostic marker in ADPKD. As a consequence of the availability of tolvaptan we expect an increasing demand for imaging studies in the diagnostic and particularly prognostic evaluation for ADPKD.

While the criteria on the LS are useful to standardize reimbursement decisions by insurances, they leave several points open. (1) The prognostic accuracy of all currently established risk factors is limited, and adverse effects and risks of tolvaptan are not weighed equally by all patients. Therefore, treatment decisions must be made on an individual basis in a shared decision-making process with every patient, and there is no clear cut off as to whom to treat and whom not to treat. (2) The methods and time intervals to determine and follow TKV and glomerular filtration rate (GFR) are not specified on the LS. The latter raises the issue of reliable and comparable diagnostic evaluation and estimation of TKV, performed at different centers where these therapies will be initiated by the local nephrologists. Particularly, image acquisition should be standardized across centers to facilitate the comparison of serial kidney images acquired over time.

The aim of this newsletter is to provide a consensus recommendation on how to establish the diagnosis and predict prognosis of ADKPD and implement the criteria set by the FOPH to assess patients for eligibility for tolvaptan. Emphasis is put on total kidney volume (TKV) estimations based on minimal imaging requirements.

Diagnostic evaluation for ADPKD

First-line examination

In individuals at risk, *we recommend that the first-line diagnosis of ADPKD be based on ultrasound imaging following the criteria by Pei et al.* [2]: the detection of at least three (unilateral or bilateral) cysts in individuals aged 15–39 years and of at least two cysts in each kidney in individuals aged 40–59 years is sufficient for the diagnosis. In individuals aged ≥60 years, four or more cysts in each kidney would be re-

Table 1. Limitations for the prescription of tolvaptan as per the Swiss Specialty List (Spezialitätenliste)

Diagnostic criteria
proven ADPKD diagnosis by **either** imaging + family history (Pei-Ravine criteria [2]) **or** genetic testing AND typical imaging characteristics of ADPKD (bilateral and diffuse distribution of cysts, corresponding to class 1 according to the Mayo-classification [7])
Criteria relating to disease stage and prognosis
One of the following signs of rapid progression • proven eGFR loss of ≥5 ml/min/1.73m² over 1 year OR • TKV growth >5 % per year confirmed by at least 2 MRI- or CT-based measurements at least 6 months apart OR • ADPKD class 1C, 1D or 1E based on height-adjusted TKV and age according to the Mayo-classification OR • truncating PKD1-mutation AND PROPKD Score >6 [10] AND • TKV ≥750ml AND • eGFR ≥30 ml/min/1.73m²
Formal criteria for the prescription
• Tolvaptan can only be prescribed at a hospital with nephrology service by a specialist (FMH) in nephrology AND • The prescribing nephrologist must have received a special training by Otsuka Pharmaceutics (Switzerland GmbH) AND • Prior to prescription, a Kostengutsprache (refunding) must be requested from the patient's insurer

quired, but these patients will usually not qualify for treatment initiation with tolvaptan.

In patients without known family history for ADPKD but suggestive imaging results, we suggest screening of family members to establish family history. In patients with negative family history (presumed de-novo mutation), genetic analysis can be performed but is not considered mandatory if imaging results are highly suggestive of ADPKD (bilaterally enlarged kidneys with multiple cysts).

Second-line examination

Based on the criteria by Pei et al. [2], ADPKD cannot be excluded in individuals under age 40. However, patients under age 40 who do not fulfill these diagnostic criteria do not qualify for treatment with tolvaptan (because their TKV will be <750 ml), and ADPKD patients at risk for rapid progression will usually have unequivocal imaging results. If the disease needs to be excluded for other reasons (particularly in the evaluation for live kidney donation) in such an individual, we suggest that the following diagnostic modalities be chosen:

MRI imaging and application of diagnostic criteria as proposed by Pei et al. [3]. For this evaluation, use T2-weighted images with a slice thickness of 3 mm. The presence of >10 renal cysts in total is sufficient to rule in the diagnosis, and the finding of <5 cysts in total can be considered sufficient for disease exclusion.

Genetic analysis by direct sequencing of the PKD1 and 2 genes by the Sanger method or next generation sequencing. Be aware that a genetic mutation in PKD1 or PKD2 is not detectable in all individuals with ADPKD. Therefore, the exclusion of ADPKD in an individual at risk requires the detection of a mutation in an affected family member and the exclusion of the same mutation in the individual at risk.

Disease staging and prognostic evaluation of ADPKD

GFR-based criteria

Criterion: eGFR of ≥30 ml/min/1.73 m²

Tolvaptan is approved in Switzerland for ADPKD patients with stage 1–3 CKD (i.e. eGFR >30 ml/min/1.73 m2). Until recently, the use of tolvaptan in ADPKD patients with eGFR <45 ml/min/1.73 m2 was not recommended because of very limited data in this patient population, but a recently published study has now established safety and efficacy of tolvaptan also in ADKD patients with eGFR 25–60 ml/min/1.73 m2 at treatment initiation [4]. The creatinine-based CKD-EPI formula [5] is the best validated and most readily available method to determine eGFR in clinical practice. In special circumstances, such as extremes of body composition (muscle mass, obesity or low body mass index), alternative methods, such as the cystatin C-based CKD-EPI formula [6] or measured creatinine clearance should be used.

Criterion: Proven eGFR loss of ≥5 ml/min/1.73 m2 over 1 year

The method for determining eGFR, the number of measurements on which the eGFR loss needs to be based, and whether GFR slope should be calculated, has not been specified on the LS of the FOPH. As mentioned above, the creatinine-based CKD-EPI formula is the most feasible method to estimate GFR. Incorporating cystatin C-measurements into GFR estimation using a cystatin C- and creatinine-based formula only leads to a minor improvement of accuracy [5] but may be useful in select cases (such as patients with extremes of muscle mass). The criterion of GFR loss over time is insensitive for rapid progression in early disease stages since GFR decline is usually non-linear in ADPKD with a relatively stable GFR during early disease stages followed by an accelerated decline later during disease. It must be further noted that GFR estimates are relatively imprecise, particularly in the upper range, with several factors leading to variability: (1) measurement errors of serum creatinine; (2) limited accuracy of the CKD-EPI formula with a 95 %-CI of ca. +/–30 % [5]; (3) physiological short-term variability of true GFR based on hydration status, blood pressure and in particular dose adjustments of ACE-Inhibitors or angiotensin receptor blockers. For these reasons, *we suggest that this criterion should not be commonly used as the sole criterion for rapid progression.* Patients with such a rapid GFR-decline will almost always qualify for treatment also based on the Mayo-classification (see below) unless GFR decline is explained by other (non-ADPKD-related) factors. If treatment initiation is based on this criterion, (a) non-ADPKD-related causes for rapid GFR loss need to be excluded and (b) GFR loss must be based on several eGFR-determinations over time that show a continuous decline. We strongly suggest to extend the observation period beyond one year if feasible and to use at least 4 eGFR determinations based on the same method and the same laboratory (preferably the creatinine-based or the creatinine- and cystatin C-based CKD-EPI formula) to calculate eGFR slope by linear regression of eGFR over time.

TKV-based criteria

Several of the prescription criteria are based on the determination of TKV. Generally, a prognostic evaluation can either be based on TKV growth rate over time (calculated from serial TKV measurements over time) or on a single TKV measurement normalized to height and age (which reflects the result of cumulative kidney growth). For these different prognostic uses of TKV, it is imperative to be aware of the reliability / measurement error of the various methods to determine TKV. TKV can be de-

termined using one of three imaging modalities: ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI).

- Ultrasound: Ultrasound-based volume determinations are relatively imprecise [7–9] and both, systematic sonographic over- and underestimation of TKV have been reported (depending on local practice and examiners). However, ultrasound is cheap and usually performed as first-line imaging method for the diagnosis of ADPKD. Ultrasound-based kidney length determinations have been reported to be more precise than ultrasound-based TKV estimates based on the ellipsoid formula [7] and have been suggested as prognostic parameter [7]. However, the mentioned study did not relate kidney length to age, and kidney length is not used as a prognostic criterion by the FPPH on the LS criteria. Therefore, we recommend reporting the maximum diameter of the kidneys in all three dimensions (perpendicular to each other) and kidney volume estimation based on the ellipsoid formula (see below) whenever an ultrasound imaging is performed in patients with ADPKD. If the maximum longitudinal diameter does not fit a single ultrasound image, panoramic view mode is recommended where available. If the entire kidneys can be easily visualized by ultrasound and if the patient would belong to Mayo class 1A (see below) based on ultrasound-determined kidney volumes, we consider ultrasound imaging sufficient to classify her/him as low risk for progression. Considering the reported measurement errors for ultrasound-based TKV determinations [7–9], it would be extremely unlikely that such a patient would be reclassified by more than one class to fall into Mayo class 1C-E and qualify for treatment with tolvaptan. In all other cases, we recommend MRI-based volume determination for risk stratification.
- CT and MRI: We recommend that MRI is preferred over CT to reduce exposition to ionizing radiation. However, if CT-images have been acquired for other indications, a kidney volume determination can be performed based on these images. If there are contraindications for MRI (e.g. non-MRI-compatible pacemaker), low-dose CT or ultra-low dose CT techniques should be considered for total kidney volume estimations. Intravenous iodinated contrast agents for CT as well as gadolinium based contrast agents (GBCA) are usually not needed and should be reserved for special situations (e.g. suspected cancer). To facilitate comparability of MRI images across centers, we recommend the minimal MRI protocol shown in Box 1 (with additional sequences to be performed as needed in special circumstances or due to center preferences). Kidney volumes can then be calculated from CT or MR images using one of several methods: (a) manual or semi-automated contour tracing; (b) stereology; (c) the mid-slice method; or (d) the ellipsoid formula. In the first method, kidney volume is calculated by multiplying the area of every section with the section thickness and summing up the volume of each section. This method gives relatively precise measurements of kidney volume with a coefficient of variation for TKV 1.5 % [10] (which corresponds to a 95 %-CI for the measurement of +/–3 %), but the method is relatively time-consuming. Notably, the reported 95 %-CI was based on measurements performed from the same image dataset by two independent observers and hence does not include respiration artifacts and short-term volume variability (which further add to the measurement error). The second method, stereology, uses a similar approach to calculate kidney volumes (i.e. by summing up the area of each kidney section multiplied with section thickness), but instead of contour tracing, the cross section area of the kidneys is calculated from the number of intersections with a grid placed over the images. The coefficient of variation for stereology-based TKV measurements calculated based on two separate image acquisitions in the same subjects was ca. 3 % corresponding to a 95% Cl of +/- 6%[11]. A third, more simplified approach to calculate TKV relies on determining the kidney cross-section area on only one slice in the middle of the kidney (the mid-slice) and multiplying this area with section thickness, the number of sections spanning the entire kidney, and a correction factor (0.624 and 0.637 for the left and right kidney, respectively) [12]. As a fourth method, kidney volumes can be estimated based on maximal length, width and depth using the ellipsoid formula (box 2). Compared to stereologic volume de-

Box 1. Minimal suggested requirements for MRI.

T2-weighted single-shot fast spine echo images in respiratory triggered acquisition mode or breath hold (e.g. HASTE/SSFSE)

SSFSE/HASTE sequences without (or with) fat suppression are preferred
Obtain coronal, sagittal and axial planes
The whole kidneys must be within the field-of-view
Optimal slice thickness is 3–4 mm with 0 mm spacing

T1-weighted 3D gradient echo images in breath hold (e.g. 3D VIBE Dixon/3D Flash/3D SPGR)

Obtain coronal planes
Optimal slice thickness is 3–4 mm with 0 mm spacing

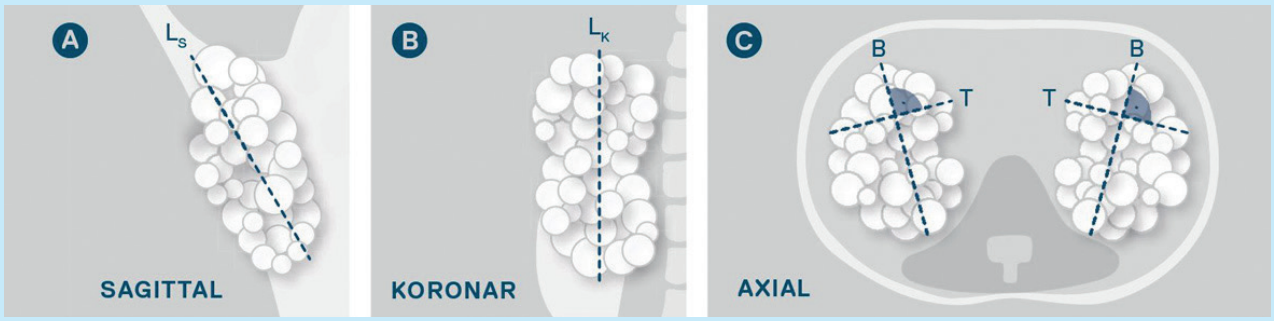
Intravenous Gadolinium-based contrast agents are not required for TKV determination and should be reserved for special situations (e.g. suspected malignoma).

Image documentation of the exact measurements should be stored in the hospital's picture archiving and communication system (PACS). If additional dedicated (non-PACS) software is used for contour tracing or stereology, measurements should be documented in a separated file for follow-up examinations.

Box 2. Calculation of TKV based on CT or MR images using the ellipsoid formula.

1. Measure kidney width and depth perpendicular to each other at the maximum transverse diameter on axial planes for each kidney.
2. Measure length from the maximum longitudinal diameter in both, sagittal and coronal planes for each kidney.
3. Calculate the volume of each kidney from the following formula:
   Volume = (length (sagittal) + length (coronal)) / 2 x width x depth x 0.524
4. Calculate TKV as the sum of the right and left kidney volume
   (alternatively, the values obtained in steps 1 and 2 can be entered into an online calculator available at http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754)

A = Maximum longitudinal diameter in sagittal planes
B = Maximum longitudinal diameter in coronal planes
C = Maximum transverse diameter (width and depth) on axial planes



terminations, the 95%-CI for ellipsoid volume determination was ca. +/–12% and +/–20% for the CRISP (a prospective study) and the Mayo (a retrospective cohort) datasets, respectively [13]. A recent study compared manual contour tracing, the mid-slice method and the ellipsoid method in a cohort of 178 ADPKD patients [14]. Precision was 3.2% for repeat contour tracing, 7.6% for the mid-slice method and 9.2% for the ellipsoid method, as compared to contour tracing (resulting in a 95%-confidence interval for these measurements of +/–6.4, 15.2 and 18.4%). Average analysis times were 55, 15 and 5 min, respectively. Thus, in particular the ellipsoid method allows to considerably save analysis time and has the additional advantage not to require special image analysis software, but results in somewhat lower precision. In select cases, where high precision is mandatory (see below), manual contour tracing is preferable over the ellipsoid method.

Table 2. PROPKD Score.
*Hemorrhagic events involving gross hematuria or cyst hemorrhages, cyst infections, or flank pain related to cysts

Criterion	Points
Male sex	1
Hypertension before 35 years of age	2
First urologic event* before 35 years of age	2
Mutation:	
PKD2	0
non-truncating PKD1	2
truncating PKD1	4
Risk category (median age of ESRD)	**Total points**
Low risk (70.6)	0–3
Intermediate risk (56.9)	4–6
High risk (49)	7–9

Criterion: single measurement of total kidney volume (TKV) >750 ml

As a criterion for the initiation of tolvaptan the limitation lists a total kidney volume (TKV) >750 ml in analogy to the inclusion criteria of the TEMPO 3:4 study [14]. It is not specified which imaging modality must be used for this evaluation. Based on the considerations outlined above, *we recommend MRI-based volume determination for this purpose and consider the ellipsoid formula as sufficiently precise.*

Criterion: class 1C-1E based on the Mayo classification system

The Mayo classification system allows prediction of progression of ADPKD based on a single TKV determination in relation to the age and height of a patient [13]. Patients are first classified as typical (class 1) or atypical (class 2) ADPKD with typical cases characterized by bilateral and diffuse distribution of cysts. Class-2 patients are uncommon, show unilateral, segmental or very asymmetric cyst distribution or relatively few but large cysts and generally have a better prognosis. Class-1 patients are

further divided into class 1A to 1E based on the height-adjusted TKV (htTKV) and age. The classification is available under http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754. The classification has been based on MRI or CT images, using the ellipsoid formula. As outlined above, *we prefer MRI over CT due to lower dose of ionizing radiation and we consider ultrasound-based kidney volume estimates sufficient for patients classified as 1A based on these estimates. In borderline cases (e.g. upper range of class 1B or lower range of class 1C), precise TKV determination based on contour tracing should be considered wherever available.*

Criterion: total kidney volume (TKV) increase of >5 % per year

This criterion is the most challenging regarding the precision of measurement. Therefore, the LS lists only CT and MRI as basis for total kidney volume (TKV) estimation. The required minimal interval of six months is very short, given the limited precision of TKV measurements. We therefore recommend the following:

- *If possible, use more than two MRI measurements (i.e. at least 3) and determine TKV change by regressing log-transformed TKV against time.*
- *Use the same volume measurement method based on the same MRI sequences preterably on the same MRI scanner performed at the same institute for all time points.* Ideally, the measurements are performed by the same observer at the same time but blinded to the time point of the MRI acquisition.
- *Be aware of the measurement error of the volumetric methods (see above). Therefore, TKV change from baseline to the last observation should be considerably more than the above-cited 95 %-CI for the measurement method.* Thus, the ellipsoid formula is usually suited for quantifying TKV change over time only if long (>5 years) follow-up times are used. For determining TKV changes over shorter periods of time, volumetry based on contour tracing or stereology is recommended.
- Most patients with >5 % TKV change per year will belong to Mayo class 1C, 1D or 1E. If a patient with Mayo class 1A or 1B exhibits a TKV progression of >5 % per year, the precision of the volumetry and the comparability of the serial measurements should be critically questioned.

Criterion: PROPKD Score

The PROPKD Score [16] includes both, clinical and genetic information (Table 2). Since genetic analysis is not routinely obtained in ADPKD patients, this criterion will probably rarely be applied.

Conclusion

This consensus recommendation shall form the basis for a standardized approach in Switzerland for the diagnostic and prognostic evaluation of ADPKD patient and the application of the LS criteria for treatment with tolvaptan. The suggested minimal MRI protocol is intended to facilitate longitudinal comparisons of images acquired at different institutions. The LS criteria leave many questions open, the detailed discussion of which is beyond the scope of this position paper. Treatment decisions always need to be made on an individualized basis, discussing potential benefits versus potential adverse effects, risks and costs and take into account individual patient factors, expectations, etc.

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Manuscript submitted: 01.06.2017
Revised Manuscript accepted: 30.10.2017
Conflicts of Interest: Prof. Dr. med. Gustav Andreisek and PD Dr. med. Andreas Kistler have been medical advisors for Otsuka Pharmaceutical Europe Ltd, Gallions, Wexhams Springs, Wexham, UK, and have received an honorarium. This has been officially disclosed and published by the company. The schematic drawing in Box 2 has been provided by Otsuka Pharmaceutical (Switzerland) GmbH, Sägereistrasse 20, 8152 Glattbrugg

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