



# Definition, diagnosis and clinical management of non-obstructive kidney dysplasia: a consensus statement by the ERKNet Working Group on Kidney Malformations

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## ABSTRACT

Kidney dysplasia is one of the most frequent causes of chronic kidney failure in children. While dysplasia is a histo-

logical diagnosis, the term 'kidney dysplasia' is frequently used in daily clinical life without histopathological confirmation. Clinical parameters of kidney dysplasia have not been clearly

defined, leading to imprecise communication amongst health-care professionals and patients. This lack of consensus hampers precise disease understanding and the development of specific therapies. Based on a structured literature search, we here suggest a common basis for clinical, imaging, genetic, pathological and basic science aspects of non-obstructive kidney dysplasia associated with functional kidney impairment. We propose to accept hallmark sonographic findings as surrogate parameters defining a clinical diagnosis of dysplastic kidneys. We suggest differentiated clinical follow-up plans for children with kidney dysplasia and summarize established monogenic causes for non-obstructive kidney dysplasia. Finally, we point out and discuss research gaps in the field.

**Keywords:** chronic renal failure, chronic renal insufficiency, guidelines, pediatrics, ultrasonography

## INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most frequent cause for chronic kidney failure (CKF) in children. Within the CAKUT spectrum, kidney dysplasia is the leading cause of CKF [1–3]. While ‘dysplasia’ *per se* is a histological term, the terms ‘kidney dysplasia’ or ‘renal dysplasia’ are commonly given as a diagnosis by clinicians based on sonography and clinical parameters in daily clinical practice. The additional common diagnosis, kidney hypoplasia, refers to small but otherwise normal-appearing kidneys [4], while the term ‘kidney hypodysplasia’ is used by some authors to describe dysplastic kidneys that are also small. Kidney aplasia and kidney agenesis represent the most severe form of this phenotypic spectrum.

Kidney dysplasia may present with or without obstruction of the urinary tract and with or without cysts in the kidney [5]. Independent but related conditions include (poly)cystic kidney diseases; for instance, autosomal recessive and autosomal dominant polycystic kidney disease (ARPKD, ADPKD) and multicystic dysplastic kidneys (MCDKs) [5, 6]. Polycystic kidney diseases and additional ciliopathies are a large group of defined monogenic conditions that should be considered as differential diagnoses in bilateral cystic kidney dysplasia. The MCDK is a common and well-recognizable example of unilateral kidney dysplasia. Affected children typically have good overall kidney function with contralateral compensatory kidney hypertrophy. In contrast, children with bilateral kidney dysplasia are at risk for severe chronic decline of kidney function, even though there is major clinical variability in the disease course.

Although kidney dysplasia is a very common diagnosis in pediatric nephrology, a recent survey revealed that there is a broad variability in the clinical findings attributed to kidney dysplasia [7]. First steps have been taken to standardize pediatric uro-radiological terms [4]. However, a specific consensus on clinical and sonographic surrogate markers for kidney dysplasia is missing.

Lack of a consensus clinical definition of kidney dysplasia based on non-histological findings has blurred clinical research in this field. Defining the condition more accurately will be essential to test the value of potential prognostic

parameters or therapeutic interventions in clinical studies and to transfer basic research findings to clinical application. The Working Group on Kidney Malformations and Ciliopathies in the European Reference Network on Rare Kidney Diseases (ERKNet) therefore conducted a systematic literature search on kidney dysplasia and elaborated consensus statements for different aspects of kidney dysplasia. In this consensus statement, we focus on kidney dysplasia without obstruction. Relevant aspects of obstructive nephropathy have been addressed by an independent ERKNet project [8]. We focus on the clinically most relevant cohort of patients with bilateral disease, which has the highest risk for CKF. Important aspects of MCDK with a single functional kidney are covered by independent initiatives [9]. We aim to propose a consensus approach to non-obstructive kidney dysplasia with a focus on pathological, clinical, imaging, genetic and basic science aspects for the management of children and adults, which may enable clinicians to communicate more accurately and researchers to use these more defined data for future clinical and basic research studies.

## METHODS

### Literature search

We conducted a systematic literature search on PubMed in early 2020 using the terms ‘renal dysplasia’, ‘kidney dysplasia’, ‘dysplastic kidney’, ‘dysplastic kidneys’, ‘renal hypodysplasia’, and ‘CAKUT’, which had to be present either in the study abstract or title. We thereby retrieved 1947 studies, which then were prescreened, filtered and evaluated by the authors (Supplementary data, Table S1). One thousand five hundred and seven studies were excluded based on the following six exclusion criteria: “case report” ( $n = 252$ ), “study focus other than kidney dysplasia” ( $n = 774$ ), “focus of study on lower urinary tract obstruction” ( $n = 114$ ), “no access to study through public libraries” ( $n = 8$ ), “language other than English” ( $n = 261$ ) and “review” ( $n = 98$ ). We retained 443 studies and assigned them based on the study focus to one of the following five thematic groups: “clinical” ( $n = 97$ ), “imaging” ( $n = 63$ ), “pathology” ( $n = 51$ ), “genetics” ( $n = 121$ ) and “basic research” ( $n = 111$ ).

### Elaboration and validation of key statements

We followed the Reporting Items for practice Guidelines in Healthcare (RIGHT) statement for practice guidelines and used the Delphi method [10]. A group of 23 experts on different aspects of kidney dysplasia was formed, including 11 pediatric nephrologists, a paediatrician with special training in genetics of CAKUT, a pediatric urologist, a neonatologist, a pediatric radiologist, a nuclear medicine physician, 3 pathologists, a kidney scientist and paediatrician in training, a kidney scientist/basic researcher, and 2 patient representatives. Most of the pediatric nephrologists had additional and complementing specialized training in genetics, fetal medicine or research on kidney development. Expert subgroups evaluated the results of the literature search to identify the most relevant publications. To counterbalance systematically missed studies

due to terminology issues, we encouraged participating experts to add highly relevant missing literature to the project. Forty-three additional potentially relevant studies were included this way. Working group members met at a hybrid ERKNet meeting held in Heidelberg in February 2020 to elaborate on key statements.

The proposed statements were then presented to all participating “experts” who served as a voting panel. Statements were graded in a Delphi process on a three-item scale (“I fully agree”; “I partially agree”; “I disagree”) with an option to add comments when no full agreement was scored. Eight of the 31 initial statements had a confirmation rate below 75% and were rephrased by the authors following the stated concerns. In a second step, statements were evaluated at an ERKNet online meeting of the working group. The rephrased statements now received an agreement rate above 90%. As an additional confirmation step, an independent expert panel of 25 members of the ESPN working group on CAKUT evaluated statements with an agreement rate >90%.

## RESULTS

### Pathology of kidney dysplasia

**Kidney dysplasia may be unilateral or bilateral. There may be segmental or diffuse involvement. Kidney dysplasia is often associated with additional features of CAKUT. Dysplastic kidneys are often cystic but unlike in typical presentations of polycystic kidney diseases, these kidneys are not massively enlarged but are about the size of normal for age kidneys or smaller.**

Kidney dysplasia is a severe phenotype within the CAKUT spectrum and is often associated with other CAKUT such as vesicoureteral reflux (VUR). Dysplastic kidneys are found with and without ureteral obstruction. In either case, hallmark findings are distinct from classic polycystic kidney disease (ARPKD, ADPKD).

**Histopathologically, there is a disorganized architecture of renal cortex and medulla with disrupted nephron differentiation (observed at low–medium-power magnification). At higher magnification, the most characteristic feature is primitive ducts (tubules) surrounded by collarettes of the mesenchymal tissue. Loose mesenchymal tissue and cartilage are common features. Cysts may be lined with cuboidal or columnar epithelium, or no epithelium at all. Glomerular pathology such as glomerulocystic changes is also described.**

Hallmark findings in dysplastic kidneys generally are a reduction of mature nephron mass and presence of non-functional and non-renal tissue, often in the form of mesenchymal cells and cartilage. Other types of non-renal tissue may also be present. Collarettes are characterized by densely packed cells. Cysts may be present but are not an obligatory finding.

### Basic science in kidney dysplasia

**Evidence from various rodent models suggests that defects of ureteric branching during early nephrogenesis result in a spectrum of phenotypes ranging from agenesis to kidney hypoplasia and kidney dysplasia. Ureteric branching is controlled through close signaling interactions between the cells of the ureteric bud and the metanephric mesenchyme.**

Nephrogenesis is a complex process that evolves around the interaction of the ureteric bud and the metanephric mesenchyme and their descendant structures including tightly controlled signaling cascades [11]. Variants in genes involved in these processes have been identified in multiple mouse models and patients with CAKUT. Genetic variants in patients with kidney dysplasia have been detected in genes whose targeted deletion, mutation or knockdown results in kidney dysplasia in model organisms including mice and zebrafish [12–14]. In our current pathogenic model, phenotypical variability in CAKUT is explained by subtle spatiotemporal differences of underlying nephrogenesis-disturbing events and affected cellular signaling and transcriptional programme [15].

**Evidence from human genetics and various model organisms suggest that dysregulation of multiple and tightly interacting signaling cascades during nephrogenesis results in kidney dysplasia.**

Signaling cascades involved in nephrogenesis are affected in several monogenic forms of CAKUT in humans and mouse models (for review see [16]).

**Tightly controlled cellular differentiation, mesenchymal to epithelial transition, and timed cell death of progenitor cells of the kidney are required for normal kidney development. In addition to genetic alterations, variations in epigenetic and environmental factors can result in kidney hypoplasia and kidney dysplasia.**

A stepwise switch from proliferation to differentiation of kidney progenitor cells is required for regular nephrogenesis [12, 17, 18]. Experimental evidence demonstrates that in addition to genetic variants, epigenetic regulators and environmental factors can affect nephrogenesis [19–21].

### Imaging and clinical management of kidney dysplasia

**Kidney hypoplasia and kidney dysplasia are two different entities and should ideally be separated because of potential prognostic relevance.**

The phenotype-group of kidney aplasia, dysplasia and hypoplasia is amongst the most frequent causes of CKF in children worldwide [1, 2]. The prognostic difference between kidney dysplasia and hypoplasia is currently unknown, as kidney dysplasia, hypoplasia or even aplasia are usually listed together in cohort studies [22]. The ESPN/ERA-EDTA Registry and NAPRTCS report patients with kidney dysplasia/hypoplasia/aplasia or even patients with any CAKUT as one disease group [1–3].

**Kidney ultrasound is the first-choice initial radiological modality to assess the clinical entity of kidney dysplasia, both before and after birth.**

The wide availability, absence of ionizing radiation and lack of need for sedation have made sonography the first-line imaging modality for investigation of the kidneys and urinary tract pre- and postnatally. Magnetic resonance imaging may be chosen on an individual basis but is currently not considered the standard of care for fetuses or pediatric patients with suspicion of kidney dysplasia.

**Dysplasia and hypoplasia are histological diagnoses. Nevertheless, we propose to accept ultrasound criteria to establish a classification as kidney dysplasia or hypoplasia for clinical differential diagnostic purposes, even without a histological confirmation.**

To strictly confirm dysplasia, a histological analysis of the kidneys would be required. The clinical diagnosis almost always lacks a pathological confirmation as dysplastic kidneys, in the absence of surgically treatable complications, remain *in situ* and therefore simply are not accessible for pathology evaluation. There is typically no indication to perform a biopsy due to the lack of therapeutic consequences. We therefore propose to accept sonographic parameters (see following statements) for routine “sonotyping” of kidneys. A defined kidney sonotype could serve as a basic dataset, enabling a more objective comparison of different “kidneys with anomalies”. Sonographic findings in dysplastic kidneys should be described using recently standardized terms [4]. Data correlating sonographic data to histology in kidney diseases are limited to biopsy specimens, mostly to adult patients or to children with lower urinary tract obstruction, and thus are of limited value here [23, 24].

**Kidney hypoplasia refers to a reduced kidney size [ $< -2$  standard deviation score (SDS) for length] with normal corticomedullary differentiation.**

In the healthy adult population, kidney size underlies a normal distribution and surprisingly does not necessarily correlate with the nephron numbers [25–27]. The sonographically determined kidney size in the pediatric population also has a normal distribution and is age-dependent [28, 29]. We propose to use the term kidney hypoplasia in a clinical context for small kidneys, as defined by variation in organ length by  $-2$  standard deviations from the mean, with intact corticomedullary differentiation and without additional parenchymal anomalies. For evaluation of the kidney length, we suggest using the age-dependent normative values by Obrycki *et al.* [30]. In daily clinical practice, 2.5th and 97.5th percentiles (Obrycki *et al.* Table 2) may be used as close approximations for 2 SDS. Alternatively, the age- and sex-independent parameter “body surface area-related renal volume” (BSARV) can be used without referring to normative tables [29]. Here, all kidneys with a BSARV below  $36 \text{ mL/m}^2$  and above  $96 \text{ mL/m}^2$  (mean BSARV  $\pm 2$  SDS) are considered hypotrophic or hypertrophic, respectively.

**We propose to accept the presence of reduced corticomedullary differentiation and/or diffuse cortical thinning in the absence of urinary tract dilatation, as sonographic equivalent of dysplasia, regardless of the size of the kidney, with or without cysts.**

A sonographic examination should be done by personnel experienced in the evaluation of pediatric kidneys and the urinary tract. Reduced corticomedullary differentiation is a generally accepted and plausible sonographic hallmark of kidney dysplasia [4]. It represents the only direct sonographic evidence of the disturbed kidney anatomical architecture. A secondary parameter that we consider useful in this context is diffuse cortical thinning [31]. Clinical experience suggests that the presence or absence of cysts also may be a relevant prognostic marker and should be reported, but we do not consider the presence of cysts an obligatory criterium of dysplastic kidneys.

**Prenatal ultrasonographic evaluation of the kidneys needs to encompass at least kidney length (expressed in SDS based on gestational age), kidney cortical thickness, corticomedullary differentiation, cysts, dilatation of the urinary tract (assessed at least by the anterior-posterior diameter of the pelvis of the kidney), bladder volume and documentation of amniotic fluid.**

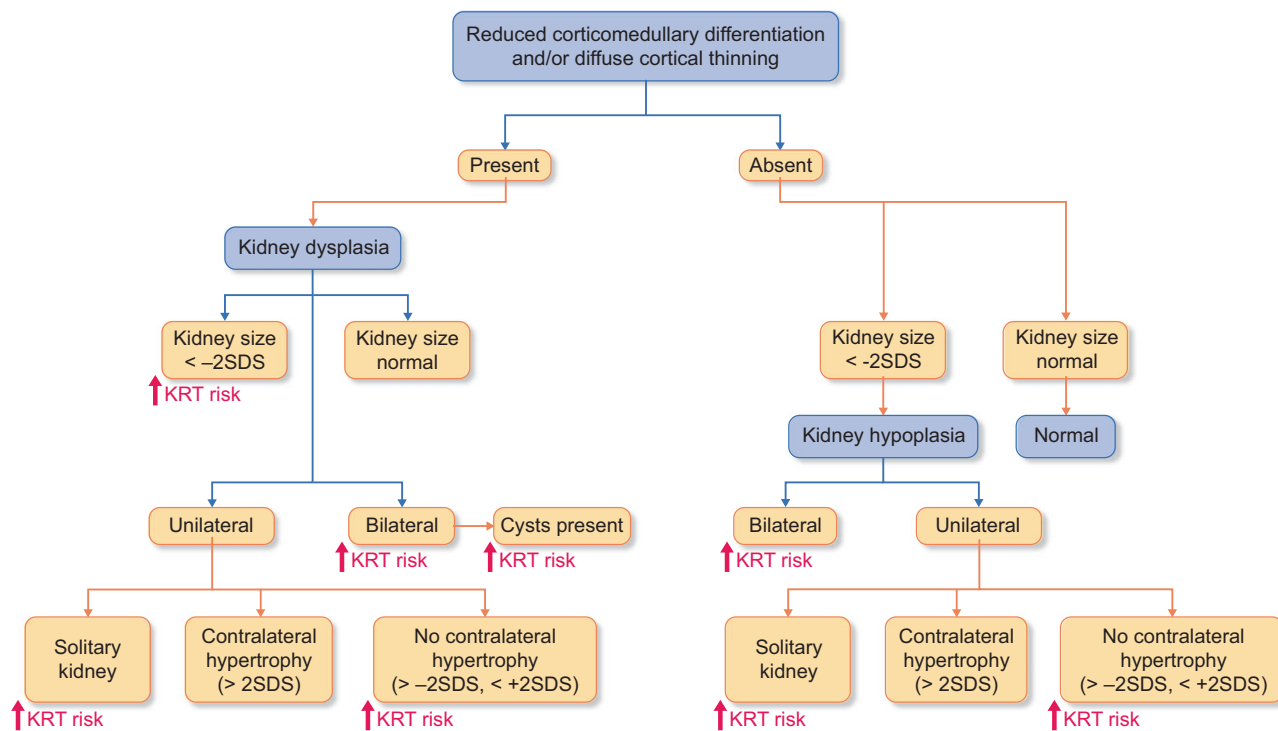
Assessment of these parameters facilitates the early detection of abnormal kidney development. Standardized reporting and interpretation of prenatal kidney ultrasound are challenged by the lack of established reference values for some parameters (e.g. cortical thickness) [32]. When kidney anomalies are detected in prenatal sonographic findings, we suggest considering a referral to a tertiary medical center for confirmation and providing families with available information on the detected pathology by multidisciplinary teams [33].

**Postnatal ultrasonic protocol needs to encompass at least kidney length (expressed in SDS based on the patient's length/height), kidney cortical thickness, corticomedullary differentiation, cysts, dilatation of the urinary tract and vascular patency using Doppler.**

Acknowledging that the quality of a sonogram is dependent on the observer's experience, overall diagnostic quality may be improved if minimally required parameters for a sonogram of the kidneys and urinary tract are defined. Standardized reporting of findings generates a reproducible sonographic phenotype or “sonotype” that communicates findings of potential prognostic relevance in a more objective dataset (Fig. 1).

#### Practice points: Diagnostic imaging in kidney dysplasia

- Definite diagnosis of kidney dysplasia per definition requires a histologic confirmation, which clinically and ethically is not indicated in most cases.
- The clinical diagnosis of kidney dysplasia is mainly based on ultrasound findings.



**FIGURE 1: A flowchart to assess “sonotypes” of dysplastic or hypoplastic kidneys and correlation of specific findings to an increased risk for CKD progression.** A flowchart for standardized ultrasound examination and reporting of kidneys in neonates, infants, and young children to help clinicians to come to a suspected diagnosis based on a specific “sonotype”. Risk-estimation for CKD progression to KRT is based on clinical expert experience. Additional sonographic findings of CAKUT should be assessed as they may influence clinical decision making. Additional examinations may be required based on the patient’s personal history. For evaluation of kidney length, we suggest using the age-dependent normative values published by Obrycki *et al.* [30]. In daily clinical practice, 2.5th and 97.5th percentiles (Obrycki *et al.* Table 2) may be used as close approximations for 2 SDS.

- Sonographic hallmark findings of kidney dysplasia are reduced corticomedullary differentiation and/or diffuse cortical thinning.
- Sonographic assessment of dysplastic kidneys (“sonotype”) should encompass: kidney length and volume; assessment of corticomedullary differentiation and cortical thinning; kidney echogenicity; and the presence, localization and size of cysts. In addition, assessment of kidney vascular patency, the kidney pelvis and the urinary tract is warranted.
- Kidney hypoplasia refers to small kidneys with normal corticomedullary differentiation. Hypoplasia should be separated from dysplasia in the description of sonographic findings when possible.
- Prenatal sonographic assessment in case of suspected kidney dysplasia should encompass assessment of amniotic fluid volume and bladder volume in addition to the above-mentioned evaluation of the kidneys and urinary tract.
- Voiding cystourethrography and kidney scintigraphy are not routinely required in children with kidney dysplasia without sonographic signs of urinary tract dilatation.

#### **Postnatal biochemical assessment of glomerular and tubular kidney function is required in all patients with bilateral dysplasia of the kidneys.**

Determination of kidney function in newborns by laboratory analyses of serum creatinine and/or cystatin C, electrolytes, acid–base balance, and urine biochemistry is warranted in patients with bilateral kidney dysplasia. The first postnatal biochemical assessment of kidney function should be performed at 24–96 h of age or depending on individual clinical situations because of fading biochemical influence of the placenta and maternal kidney function.

#### **Voiding cystourethrography is not routinely required in patients with kidney dysplasia without sonographic signs of urinary tract dilatation.**

The presence of kidney dysplasia may imply a higher risk for co-occurring VUR [34]. However, in our experience, high-grade VUR in the absence of urinary tract dilatation or subvesical stenosis is uncommon. Consequently, we do not recommend routine voiding cystourethrography (VCUG) in children with kidney dysplasia without febrile urinary tract infections and/or without dilatation of the urinary tract.

#### **Assessment of differential kidney function is not routinely required in bilateral kidney dysplasia without sonographic signs of urinary tract dilatation.**

Kidney (99mTc) scintigraphy implies an exposure to ionizing radiation, albeit very low (<1 mSv), and should be used

only if a change in patient management is considered. Routine determination of differential kidney function in bilateral kidney dysplasia in most cases has no consequence for clinical management.

**Kidney prognosis is worse in patients with bilateral kidney dysplasia compared with unilateral dysplasia.**

Children with unilateral kidney dysplasia, even if severe, generally have a good prognosis if the contralateral kidney is normal [35, 36]. Most of the patients with bilateral kidney dysplasia do not require kidney replacement therapy during infancy. In the NAPRTCS CKD registry cohort, about 50% progress to CKF within 5 years [37]. Typically, the estimated glomerular filtration rate (eGFR) improves within the first postnatal months to reach an individual baseline, which is considered to be linked to the individual nephron mass, and then declines slowly over years [38]. Individual courses during childhood are very heterogeneous and depend on accumulating individual factors like urinary tract infections, hypertension, proteinuria or developmental aspects.

**Other factors may be relevant as well, such as contralateral hypertrophy, dysplasia of a solitary kidney, presence of cysts, presence of VUR and a postobstructive state.**

In patients with unilateral kidney dysplasia, any pathology of the contralateral kidney may be relevant for a poorer prognosis, whereas the presence of hypertrophy improves prognosis [39]. In the KIMONO (KIDney of MONofunctional Origin) cohort, children with a single functioning kidney with additional ipsilateral CAKUT had a significantly shorter median time to develop symptoms of kidney injury than children without ipsilateral CAKUT [40].

**Follow-up of patients with unilateral kidney dysplasia should be performed at least yearly.**

Children with unilateral kidney dysplasia have a higher risk for progression of chronic kidney disease (CKD) than the normal population [35, 39, 40]. We therefore suggest at least annual follow-up visits up to the age of 18 years to identify early sequelae of CKD, such as hypertension or (micro)albuminuria. In young adults and in adulthood, we suggest regular follow-up visits depending on the clinical development and individual risk patterns of CKD, e.g. every other year. These follow-up visits should include a physical exam, blood pressure measurement, proteinuria/albuminuria screening and ideally a sonographic assessment of the contralateral “normal” kidney in preschool children.

**Follow-up of patients with bilateral kidney dysplasia should be performed into adulthood. Blood pressure and proteinuria should be assessed at least twice a year and eGFR at least every 6 months in the first year of life, after which the frequency should be tailored based on kidney function, ultrasound findings and other clinical factors. Ultrasonographic evaluation should be conducted yearly, although the frequency can be tailored based on kidney function, previous ultrasonic findings and other clinical factors.**

Assessment of blood pressure and screening for proteinuria/(micro)albuminuria in children and adults with bilateral kidney dysplasia needs to be performed regularly and lifelong [41]. Routine assessment of kidney function

in newborns with bilateral kidney dysplasia (creatinine and/or cystatin C, proteinuria) seems reasonable up to age 2 years because it helps to estimate the prognosis and to tailor individual follow-up plans. In children >2 years of age with a normal eGFR, routine assessment of eGFR should be considered in case of elevated blood pressure, proteinuria or albuminuria. Sonographic follow-up in children with bilateral kidney dysplasia becomes less important once concomitant urinary tract anomalies have been excluded because sonographic findings have likely no consequence for individual follow-up plans. The follow-up of known CKD risk factors like hypertension and proteinuria should follow overarching recommendations for CKD management, e.g. with yearly ambulant blood pressure measurement and strict blood pressure targets at or below the 50th percentile [42]. Treatment of hypertension in pediatric patients with kidney dysplasia should follow general principles according to the respective guidelines and recommendations. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have been recommended for children with CKD as first-line agents [43, 44]. In pregnancy, women with CKD are at increased risk for decompensation of CKD and adverse pregnancy outcomes and hence should be screened for hypertension, proteinuria, and urinary tract dilatation [45].

**Apparently, unaffected family members of individuals with unilateral or bilateral kidney dysplasia can be offered sonography of the kidneys and urinary tract.**

Sonography in family members (parents and siblings) of a patient with kidney dysplasia may identify hitherto unrecognized individuals with CAKUT, with potential therapeutic implications such as treatment of hypertension or early screening for diabetes mellitus in families with pathogenic variants in *HNF1B* [46]. In addition to imaging studies, screening for treatable but usually asymptomatic disease manifestations, such as hypertension and proteinuria, should be considered.

Practice points: Clinical management and follow-up in kidney dysplasia

- Patients with unilateral kidney dysplasia should be followed up yearly.
- Assessment of sequelae of CKD at least until adulthood to detect hypertension and/or (micro)albuminuria.
- Patients with bilateral kidney dysplasia should be followed up into adulthood tailored to individual circumstances.
- Assessment of blood pressure and urine twice a year to detect hypertension and/or (micro)albuminuria.
- Assessment of serum creatinine/cystatin C at least every 6 months in the first year of life to detect impairment of kidney function.
- Routine sonographic evaluation yearly after first year of life or tailored to individual circumstances.
- Chronic kidney disease should be treated in all patients with kidney dysplasia according to present guidelines.

### Genetic considerations in CAKUT and kidney dysplasia

In most children with CAKUT or kidney dysplasia, a monogenic cause cannot be identified [47–49]. Nevertheless, the occurrence of familial CAKUT and data from animal models provide evidence for genetic aetiologies for kidney dysplasia. In a minority of cases with isolated kidney dysplasia or syndromic cases, a monogenic cause or a pathogenic copy number variation (CNV) can be found [47, 49–52].

#### **Non-obstructive, isolated or oligosyndromic kidney dysplasia is caused by known monogenic causes or CNVs in 10%–15% of cases.**

Most children presenting with kidney dysplasia do not have other organ involvement, i.e. they have “isolated” CAKUT. However, kidney dysplasia may be part of many exceedingly rare multiorgan syndromes. The term “oligosyndromic” refers to patients with kidney dysplasia as the leading condition, who may exhibit other findings in other organs that might be missed, or only become recognizable later in life. Monogenic causes in these conditions can be identified in 10%–15% of cases [16, 53].

#### **Other cases of kidney dysplasia are suspected to be caused by not yet identified monogenic causes, oligogenic causes, genetic mosaicism, epigenetic factors and/or environmental factors.**

Newly identified monogenic causes of CAKUT are rare diseases, each accounting for only <0.1% of CAKUT cohorts. Thus, most CAKUT likely have an oligo/polygenic etiology and might be caused or modified by somatic variants and environmental factors [52, 54–57].

#### **Clinical manifestation of monogenic forms of kidney dysplasia are variable and may include other anomalies of the kidney and urinary tract (CAKUT) and extra-renal manifestations.**

Family members with identical pathogenic variants in a “CAKUT gene” may have different CAKUT phenotypes (variable expressivity) or even no phenotype at all (incomplete penetrance), a phenomenon that can also be seen in CAKUT mouse models [48]. Whether two conditions have a common underlying pathogenic sequence or arise independently remains unclear.

#### **Differentiation between kidney dysplasia and hypoplasia cannot be based on a molecular diagnosis.**

In families with multiple individuals with CAKUT, sonographic kidney dysplasia and hypoplasia may co-occur, making it impossible to distinguish the two conditions based on a genetic diagnosis [47]. Due to variable expressivity and incomplete penetrance, clear genotype–phenotype correlations currently cannot be defined.

#### **We recommend genetic testing for individuals diagnosed with familial kidney dysplasia or syndromic kidney dysplasia. We suggest genetic testing for individuals with bilateral kidney dysplasia.**

Identification of an underlying genetic variant in individuals with kidney dysplasia may be helpful for several reasons: (i) it can provide affected families with an unequivocal molecular diagnosis; (ii) in case of a *de novo* pathological variant, it reassures parents with the wish to have another child; (iii) it may enable personalized medical support including additional screening for subtle syndromic features; and (iv) it generates medical knowledge that might help to improve care in the future. Offering genetic counselling and testing according to the local legislation needs to respect and consider non-medical aspects relevant for patients and families, such as religious context, possible implications for health or disability insurance, or simply the wish to not know.

#### **Prenatal screening for pathogenic variants in genes that cause kidney dysplasia (see Table 1) should not generally be recommended, because the molecular diagnosis is not reliably predictive for kidney function. However, in fetuses with syndromic features and/or hyperechogenic kidneys with oligohydramnios, prenatal genetic testing for chromosomal imbalances (cGH/karyotype) or ciliopathies may be offered and discussed carefully with the parents if termination of pregnancy is considered.**

Prenatal genetic counselling and testing in fetuses with dysplastic kidneys may lead to termination of pregnancy and thus should be handled with the greatest caution. Prenatal sonography cannot reliably distinguish kidney dysplasia from other genetic kidney diseases such as ciliopathies. Hence, prenatal genetic testing should be focused on genetic conditions that, together with sonographic findings, correlate with a high degree of certainty with a dismal prognosis, e.g. syndromic diseases [58]. Prenatal counselling should address these aspects and should be detailed and respectful to non-medical aspects relevant for patients and families mentioned in the previous section. Prenatal testing should only be offered after consultation with experienced pediatric nephrologists and human geneticists in line with local legislation. To provide families of children with kidney dysplasia with the best counselling possible, we suggest implementing multidisciplinary clinics, including a human geneticist, a pediatric nephrologist, and, e.g. in case of oligo/anhydramnios, a neonatologist and gynaecologist [59].

#### **The causality of genetic variants in patients with kidney dysplasia should be interpreted with caution because many variants initially reported as causing CAKUT have not been confirmed in subsequent studies.**

The rapidly growing knowledge about human gene variations is extremely helpful in re-evaluating variants that in the past have been considered pathogenic. This corrective instrument seems particularly important in CAKUT and has repeatedly led to reclassification of variants formerly considered pathogenic to likely benign [48, 57]. The classification for genetic variants of the American College of Medical Genetics and Genomics should be applied [60].

Table 1. Genetic causes of a kidney dysplasia phenotype

	Kidney phenotype	Extrarenal phenotype	Mode of inheritance	Incomplete penetrance	Variable expressivity	Type of variant	Literature
<i>EYA1</i>	KHD, cystic dysplasia, unilateral/bilateral kidney agenesis, hydronephrosis, kidney malrotation, VUR	BOR syndrome 1, conductive/sensorineural deafness, preauricular pits, branchial anomalies, external ear anomalies, facial nerve palsy, arched palate, (congenital cataracts reported once)	AD	Yes	Yes	SNV, indel, CNV	Hwang, 2013, <i>Kidney Int</i> Heidet, 2017, <i>J Am Soc Nephrol</i> Unzaki, 2018, <i>J Hum Gen</i> Abdelhak, 1997, <i>Nat Genet</i>
<i>GATA3</i>	KHD, cysts, VUR, FSGS, single kidney	HDR syndrome, hypoparathyroidism with hypocalcemia, deafness, uterine anomalies	AD	Yes	Yes	SNV, CNV	Hwang, 2013, <i>Kidney Int</i> Heidet, 2017, <i>J Am Soc Nephrol</i> Belge, 2017, <i>NDT</i> Muroya, 2001, <i>J Med Genet</i> Van Esch, 2000, <i>Nature</i> De Tomasi, 2017, <i>AJHG</i> Sanna-Cherchi, 2017, <i>AJHG</i> Brophy, 2017, <i>Genetics</i>
<i>GREB1L</i>	KHD, unilateral/bilateral kidney agenesis, VUR, pelvic kidney, megaureter, duplex ureter	Uterine malformations	AD	Yes	Yes	SNV, indel	Hwang, 2013, <i>Kidney Int</i> Heidet, 2017, <i>J Am Soc Nephrol</i> Bekheirnia, 2017, <i>Genet Med</i> Bingham, 2002, <i>Genet Med</i> Edhill, 2008, <i>NDT</i> Ishiwa, 2019, <i>Pediatr Nephrol</i> Nakayama, 2010, <i>Pediatr Nephrol</i> Thomas, 2011, <i>Pediatr Nephrol</i> Ulinski, 2006, <i>J Am Soc Nephrol</i> Madariga, 2013, <i>CJASN</i> Horikawa, 1997, <i>Nat Genet</i>
<i>HNF1B</i>	KHD, multicystic dysplasia, single kidney, UPJO, hyperuricemia, hypomagnesemia, oligomeganephronia	Diabetes mellitus (MODY5), uterine malformations, pancreas hypoplasia/agenesia, elevation of liver transaminases, MRKHS	AD	Yes	Yes	SNV, indel, CNV	Hwang, 2013, <i>Kidney Int</i> Heidet, 2017, <i>J Am Soc Nephrol</i> Bekheirnia, 2017, <i>Genet Med</i> Bingham, 2002, <i>Genet Med</i> Edhill, 2008, <i>NDT</i> Ishiwa, 2019, <i>Pediatr Nephrol</i> Nakayama, 2010, <i>Pediatr Nephrol</i> Thomas, 2011, <i>Pediatr Nephrol</i> Ulinski, 2006, <i>J Am Soc Nephrol</i> Madariga, 2013, <i>CJASN</i> Horikawa, 1997, <i>Nat Genet</i>
<i>PAX2</i>	KHD, cystic dysplasia, oligomeganephronia, single kidney, VUR, horseshoe kidney	Optic nerve anomalies, retinal coloboma, morning glory syndrome, hearing loss	AD	Yes	Yes	SNV, indel, CNV	Hwang, 2013, <i>Kidney Int</i> Heidet, 2017, <i>J Am Soc Nephrol</i> Bekheirnia, 2017, <i>Genet Med</i> Ishiwa, 2019, <i>Pediatr Nephrol</i> Thomas, 2011, <i>Pediatr Nephrol</i> Madariga, 2013, <i>CJASN</i> Taranta, 2007, <i>Clin Nephrol</i> Sanyanusin, 1995, <i>Nat Genet</i>
<i>PBX1</i>	KHD, oligomeganephronia, horseshoe kidney, single kidney, duplex ureter, VUR	Developmental delay, hypotonia, ear malformations, deafness, heart defects, cryptorchidism, bone malformations, mild facial dysmorphism	AD	unknown	Yes	SNV, CNV	Heidet, 2017, <i>J Am Soc Nephrol</i> Le Tanno, 2017, <i>J Med Genet</i>



Table 1. Continued

	Kidney phenotype	Extrarenal phenotype	Mode of inheritance	Incomplete penetrance	Variable expressivity	Type of variant	Literature
<i>SALL1</i>	KHD, VUR, dystopic kidney	Townes-Brocks syndrome, dysplastic ears, bifid thumbs, triphalangeal thumbs, anorectal malformations, sensorineural hearing loss, facial nerve palsy, external ear anomalies, heart defects, microcephaly, developmental delay	AD	No	Yes	SNV, CNV	Hwang, 2013, <i>Kidney Int</i> Unzaki, 2018, <i>J Hum Gen</i> Kohlhase, 1998, <i>Nat Genet</i>
Large CNVs (e.g. 1q21, 4p16.1-p16.3, 16p11.2, 16p13.11, 17q12, and 22q11.2)	KHD, CAKUT	Diverse	n/a	unknown	unknown	CNV	Bekheirnia, 2017, <i>Genet Med</i> Sanna-Cherchi, 2012, <i>AJHG</i> Verbitsky, 2019, <i>Nat Genet</i> Haller, 2018, <i>PNAS</i> Lopez-Rivera, 2017, <i>NEJM</i>

Note: For detailed information on the cited references please refer to Supplementary data.

Abbreviations: AD, autosomal dominant; BOR, branchiootorenal syndrome (OMIM #113650); indel, short insertion/deletion; HDR, hypoparathyroidism, sensorineural deafness, and renal dysplasia (OMIM #146255); KHD, kidney hypodysplasia; MRKHS, Mayer-Rokitansky-Kuster-Hauser syndrome (OMIM #277000); SNV, single nucleotide variant; UPJO, ureteropelvic junction obstruction.

**For genetic testing, we suggest next-generation sequencing (NGS) as the primary screening tool. If negative, consider trio-whole-exome sequencing (WES)/whole genome sequencing (WGS) with subsequent evaluation of all genes implicated in monogenic hereditary kidney diseases.**

As a first-line genetic diagnostics for patients with CAKUT/kidney dysplasia, we recommend NGS as a panel analysis or WES with applied filters. In patients with CAKUT/kidney dysplasia, evaluation may prioritize genes in Table 1 as a first gene set to save resources and reduce incidental findings. However, if negative, the filter should be extended to genes that have been associated with kidney phenotypes in humans or animal models as phenocopies are common [61–63]. Patients with negative panel results and high suspicion for inherited kidney disease should be considered for trio-WES/WGS.

**In case of pregnancy after kidney dysplasia in a previous pregnancy, we suggest referral to a prenatal screening reference center at gestational week (16–) 18–20 to assess amniotic fluid volume and kidney morphology.**

The risk for recurrence of kidney dysplasia or other CAKUT with a negative genetic testing result is higher (up to 20%) than in the general population (<0.1%) [46, 64]. In case of a subsequent pregnancy, we recommend prenatal sonography in the gestational weeks 18–20. If prenatal vesicoamniotic shunting is an option, earlier gestational ages, e.g. at 16 weeks or even younger, should be considered as amniotic fluid volume at this time largely depends on fetal urine output and correlates with postnatal prognosis [65, 66].

#### Practice points: Genetic diagnostics and counselling in patients with kidney dysplasia

- In a minority of cases with isolated kidney dysplasia, monogenic variants or large copy number variants can be identified.
- Multiple genetic and non-genetic factors are likely to contribute to kidney dysplasia pathogenesis in most clinical cases.
- Extrarenal organs should be assessed as multiple syndromes with a kidney dysplasia phenotype are known.
- Genetic testing should be performed by experienced professionals after proper counselling with next generation sequencing-based approaches as a primary method.
- We recommend genetic testing in familial cases and for syndromic patients. We suggest genetic testing in bilateral kidney dysplasia.
- Variants in genes implicated in monogenic kidney dysplasia need to be interpreted with caution as a molecular genetic diagnosis cannot predict the phenotype in specific cases.

## DISCUSSION

The clinical diagnosis of kidney dysplasia is one of the most frequent causes of CKF in children [1–3]. In this consensus

statement, we propose key statements on the diagnosis and management of kidney dysplasia, primarily without obstruction. We have previously shown that the definition of kidney dysplasia varies greatly even amongst experts in pediatric nephrology and thus leads to inconsistent datasets that prevent recognition of relevant subtypes of kidney dysplasia [7]. Currently, most of the scientific evidence on courses of patients with dysplastic kidneys comes from either studies on general pediatric CKD or broader studies on CAKUT [1, 2]. For instance, the prognosis for a child with kidney dysplasia at the time of birth in many cases is unknown. Specific risk markers of patients with kidney dysplasia are not established. Acknowledging the fact that histopathological confirmation is an exception, we propose to accept sonographic findings as reasonably likely surrogate markers of kidney dysplasia sufficient for a clinical diagnosis. Our consensus statement may serve as a basis for future, more specific research studies on kidney dysplasia.

Several important clinical and scientific knowledge gaps remain to be addressed based on a standardized definition of kidney dysplasia. In a first step, the correlation of ultrasound findings with histopathology has not been validated systematically. We currently do not know whether there are histological subgroups among the cohorts we nowadays subsume as kidney dysplasia. It also remains unclear to what extent prenatal and postnatal sonographic findings in children with kidney dysplasia correlate, to what extent pre- and postnatal sonographic findings can be linked to kidney function, and whether there is a specific timepoint, a specific mode of imaging or a specific biochemical finding with prognostic value in kidney dysplasia patients. Ultrasound is the preferred method for daily clinical use in pediatrics, and potentially easy-to-obtain sonographic findings might be of prognostic value. As an example, clinicians tend to agree on the notion that children with dysplastic kidneys with or without cysts typically have a worse prognosis as compared with children with hypoplastic kidneys, but systematic evidence supporting this assumption is missing [22]. Beyond straightforward sonography, functional MRI studies have shown great potential in other kidney diseases or disorders of other organs [67]. Data on pediatric kidney disease remain scarce. A research initiative to link imaging findings with clinical and histopathologic data is needed for the CAKUT field. The field will need to bring together all these relevant items of information in an integrated dataset. Structured biobanking of kidney dysplasia samples for a standardized histological work-up and digital processing would have great potential to obtain novel and deep insights into the histopathology and potentially also the pathophysiology of kidney dysplasia [68]. Such samples could also be used for expression profiling, e.g. by multiomics methods to get deeper insights into dysregulated signaling patterns in dysplastic kidneys and as a basis for translational research between bedside and preclinical work with model organisms at the bench. In-depth genetic analyses of patients and tissue samples with a link to clinical findings will be needed to deepen our understanding of pathophysiological mechanisms. Yet, such studies are cumbersome and costly and require highly standardized collaboration in large international

consortia to generate comparable clinical data and high-quality biosampling. As biopsy samples will not be available for ethical reasons, nephrectomy samples or autopsies may partly be helpful for such studies, although they are also obviously subject to secondary changes related to CKF or changes associated with repetitive infections. Nephrectomy samples could, for example, be obtained within the frame of kidney transplantation.

In summary, we here provided consented statements based on an expert discussion and available evidence from the literature, covering different relevant aspects of kidney dysplasia. These statements may serve as a common ground for clinicians, patients and researchers. Furthermore, we identified research gaps and structural roadblocks in this field that led us to suggest a novel joint network for future studies on one of the most common causes of CKF in children and young adults.

#### Practice points: Open questions and research gaps in the field of “kidney dysplasia”

- Correlation of imaging findings with histopathologic findings:
  - What sonographic parameters correlate best with histologic dysplasia?
  - What is the difference between obstructive and non-obstructive dysplasia?
  - Which additional information on kidney dysplasia can be obtained by magnetic resonance imaging (MRI)?
- Correlation of imaging findings with clinical findings:
  - What sonographic parameters correlate best with clinical courses?
  - How well do pre- and postnatal findings correlate?
  - Are there subentities of kidney dysplasia that would benefit from specific management?
  - Can MRI application provide insights for clinical management?
- Biochemical markers and signatures for kidney dysplasia:
  - Can genetic, biochemical and/or clinical markers be identified that would help to diagnose dysplasia?
  - Can genetic, biochemical and/or clinical markers be identified that would differentiate between obstructive and non-obstructive dysplasia?
  - Can genetic, biochemical and/or clinical markers be identified that would help to predict clinical courses?
  - Can antenatal markers be identified to predict postnatal survival and kidney function?

#### SUPPLEMENTARY DATA

Supplementary data are available at [ndt](#) online.

## ACKNOWLEDGEMENTS

The authors thank the members of the working groups “Congenital malformations and Ciliopathies” (ERKNet) and “CAKUT” (ESPN) for their continuous support.

## FUNDING

This study has been supported by European Reference Network for Rare Kidney Disorders (ERKNet), which is partly co-funded by the European Union within the framework of the Third Health Programme “ERN-2016-Framework Partnership Agreement 2017–2021”. P.B. was supported by the German Research Foundation (DFG, Project-ID 454024652 and 445703531), the European Research Council (ERC; Consolidator Grant No 101001791) and the Federal Ministry of Education and Research (STOP-FSGS-01GM1901A). S.K. was supported by the Koeln Fortune program and Gusyk program, Faculty of Medicine, University of Cologne. A.W. acknowledges support from Medical Research Council Project grant MR/T016809/1. F.S. and M.C.L. were supported by the German Federal Ministry of Research and Education (BMBF grant 01GM1515 and 01GM1903).

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Received: 28.2.2022; Editorial decision: 15.6.2022