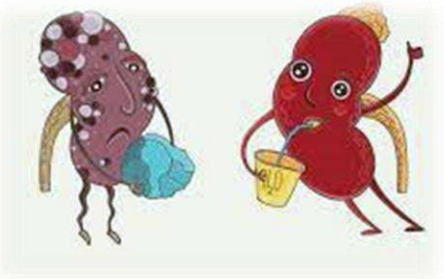
Evaluation of Cystic Kidney Diseases
What is new?



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Overview

- Introduction
- Classification
- Approach to Renal Cystic Disease
- Evaluation of Cystic Kidney Disease
  - Clinical
  - Radiological
  - Genetic Evaluation
- What is new?
  - Emerging concepts
  - Role of Biomarkers
  - ADPKD –Changing Guidelines
- Conclusion

Renal cystic diseases - Background

- Broad group of disorders ,heterogeneous in origin and pathogenesis
- Renal cysts arising from the nephrons and collecting system
- Varable phenotypic expression and outcome.
- Manifest during foetal life, infancy, childhood, or adulthood.

What is the Challenge?

- Cysts in the Kidney represents a spectrum rather than a specific Disease
- Cysts can arise in a large variety of illnesses
- Imaging patterns evolve over time
- Extrarenal features of systemic diseases may not manifest in the young

Radiology 2019; 290:769–782

Renal Cystic Disease- Classification

- Developmental cystic renal disease - Non hereditary
  - Cystic dysplasia, Multi-cystic Dysplastic Kidney(MCDK)
  - Cystic dysplasia with obstruction
- Inherited cystic Kidney disease (iCKD) –Hereditary Ciliopathies
  - **Single-gene disorders**
    - Autosomal recessive polycystic kidney disease (ARPKD)
    - Autosomal dominant polycystic kidney disease (ADPKD)
    - Juvenile nephronophthisis (JNPHP)
    - Medullary cystic kidney disease
- Systemic disease with associated renal cysts
  - Tuberous sclerosis complex
  - VHL
- Unilateral renal cystic disease
  - Non genetic forms - simple kidney cysts (Size ,contrast enhancement, Wall irregularities,septae, and calcification)
- Acquired cystic renal disease
  - CKD
  - Cortical micro cysts in TIN
  - Post Liver Transplantation

Kurschat et al . An approach to cystic kidney diseases: the clinician's view. Nat Rev Nephrol. 2014

What is special in Kids ?

- A larger proportion of genetic diseases unlike adults
  - Inherited cystic kidney disease (iCKD) - Genetic Ciliopathies
  - Renal Cystic disease associated with Syndromes-Tuberous sclerosis, VHL Disease
- Solitary kidney cysts may be completely benign if develop during adulthood but may represent early PCKD in a child
- Cystic Renal Dysplasia
- Only few
  - Simple cysts
  - Acquired cystic kidney disease.

Prenatal Suspicion of Cystic Kidney Disease

Routine prenatal US and advanced US technology- Earlier and earlier diagnosis

In Utero- Imaging findings that portend poor prognosis

- Enlarged Kidneys
- Hyper-echogenicity
- Oligohydramnios
- Extrarenal features, such as congenital malformations
- Reduced lung volume

Regular Monitoring

Multidisciplinary care

Evaluation of Cystic Kidney Diseases

Clinical

Imaging

Genetic

Biomarkers in Cystic Kidney Diseases

Clinical Assessment in Cystic Kidney Disease

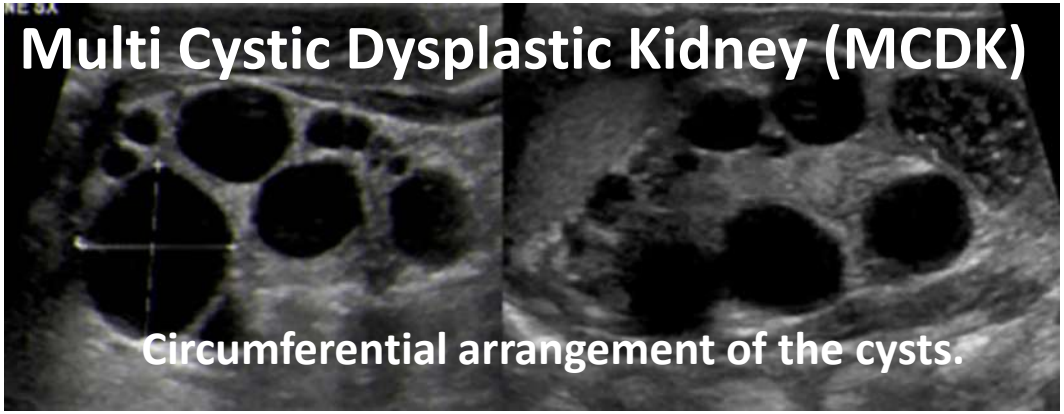
Some General Rules

- Manifestation of Cysts
  - Focal disease (simple and complex kidney cysts)
  - Affecting a whole kidney(multicystic dysplastic kidney or cystic dysplasia)
  - Bilateral cystic disease (ARPKD or ADPKD).
- Clinical Presentation often (but not always) helps in diagnosis
  - Age at presentation
  - Laterality
  - Renal imaging characteristics, including renal size, distribution & number of cysts
  - The presence/distribution of extra renal manifestations.

It is important to take the clinical context into consideration when assessing renal cystic disease in children

Cystic renal dysplasia

(Non hereditary renal Malformations)



MCDK : Incidence of 0.3 to 1 per 1000 live births.

Alteration in parenchymal differentiation-Non functioning kidney with multiple cysts

Detected by routine Prenatal screening ultrasound

Most infants with unilateral MCDK are asymptomatic.

Conservative Management – Clinical assessment & Serial renal ultrasounds

- Assess contra lateral kidney growth
- Involution of the affected kidney.

Assess for hypertension ,Proteinuria & eGFR.

Cystic dysplasia with obstruction-eg. PUV,PUJO

Inherited Cystic Kidney Diseases(iCKD)

Disease	AD/ AR	Gene	Typical decade of diagnosis; ESRD	Characteristics	Prevalence
Autosomal dominant polycystic kidney disease (ADPKD), type 1	AD	*PKD1*	Childhood–30s; 50s	• Early age of cyst onset, hypertension, ESRD, innumerable small renal cortical cysts	• ~78% of ADPKD • ~1 in 2,000
Autosomal dominant polycystic kidney disease, type 2	AD	*PKD2, GANAB*	30s; 70s	• Late age of cyst onset, hypertension, ESRD, fewer, larger renal cysts and liver cysts very common	• ~13% of ADPKD • ~1 in 7,000
Autosomal recessive polycystic kidney disease	AR	*PKHD1*	Birth; early childhood	• Neonatal death in 30% of patients, Potter phenotype, oligohydramnios • Renal symptoms include early renal failure and severe polycystic kidneys • Biliary symptoms include dysgenesis, portal hypertension and cholangitis	~1 in 20,000

Inherited Cystic Kidney Diseases(iCKD)

Renal cysts and diabetes syndrome	AD	*HNF1B*, *TCF2*	Teens; 15% ESRD in teens	• Renal cysts, diabetes, hypomagnesaemia, hyperuricaemia and genital tract malformations; also known as mature-onset diabetes of youth 5 (MODY5)	Unknown
Polycystic liver disease	AD	*PRKCSH*, *SEC63*, *LRP5*, *GANAB*, *ALG8*, *SEC61B*	30s; NA	• Massive liver volume expansion with numerous cysts, liver cysts were traditionally considered entirely isolated from polycystic kidneys, but phenotypic overlap with ADPKD now recognized	• Isolated: ~1 in 100,000 • Liver cysts in up to 90% of patients with ADPKD
Autosomal dominant tubulointerstitial kidney disease	AD	*UMOD*, *MUC1*, *REN*	Teens–20s; 40s–60s	• Slowly progressive kidney disease, medullary cysts, hyperuricaemia and gout in ADTKD–*MUC1*; also known as medullary cystic kidney disease	Unknown
Medullary sponge kidney	NA	Unknown; familial clustering	30s; NA	• Medullary nephrocalcinosis, nephrolithiasis	~1 in 5,000
Nephronophthisis	AR	>90 genes	Childhood; teenage years	• Paediatric-onset tubulointerstitial nephritis, large range of rare monogenic multisystem conditions (including Joubert, Senior–Loken, Bardet–Biedl and Meckel–Gruber syndromes)	Rare

Inherited Cystic Kidney Diseases(iCKD)

Tuberous sclerosis	AD	*TSC1*, *TSC2*	Childhood; 40s	• Dermatomal symptoms include facial angiofibroma, shagreen patch and hypomelanotic macules • Cerebral symptoms include cortical tubers, subependymal giant cell astrocytoma, seizures and developmental delay • Renal symptoms include polycystic kidneys and angiomyolipoma • Pulmonary symptoms include lymphangioleiomyomatosis • Ophthalmic symptoms include retinal hamartomas	~1 in 10,000
TSC2–PKD1 contiguous deletion syndrome	AD	*TSC2–PKD1*	Childhood; 20s	• Similar presentation to that of tuberous sclerosis with more severe renal phenotype	Rare
Von Hippel–Lindau disease	AD	*VHL*	20s; NA	• Neuroendocrine tumours of the pancreas, pheochromocytoma, renal cell carcinoma, serous cystadenomas, cerebellar and spinal haemangioblastoma, retinal angioma	~1 in 36,000

To Recapitulate the clinical profile

CKD stages 4-5, small kidneys	Acquired renal cystic disease
PLD with no or few renal cysts	ADPLD
Congenital hepatic fibrosis	ARPKD
Facial angiofibroma, cortical tubers, subependymal nodules, renal angiomyolipomas, retinal hamartomas	Tuberous sclerosis complex (TSC)†
Hemangioblastoma, retinal angioma, pheochromocytoma, RCC	Von Hippel-Lindau syndrome
Oral/facial/digital abnormalities	X-linked dominant OFD1
Corticomedullary cysts, progressive CKD, small kidneys, gout	ADTKD-*MUC1*, ADTKD-*UMOD*
Renal cysts, diabetes mellitus, hypomagnesaemia, genital malformation, gout	ADTKD-*HNF1B*

Role of Radiology in Cystic Kidney Disease

Accurate diagnosis

Prognosis

Rational Management

Radiology in Cystic Kidney Diseases

Ultrasound
Primary technique
For diagnosis & follow up

- Conventional Ultrasound
- High Resolution Ultrasound

MRI

- Specific Indications
- Preferred over CT
- No ionizing Radiation

CT Scan

CT or MRI is not recommended for routine assessment of kidney cysts

USS most important diagnostic imaging technique for the first diagnosis and follow-up.

Radiology in Evaluation

An International Working Group Consensus Statement

Main recommendations :

US is the method of choice when assessing pediatric kidney cysts

- Renal US yields essential diagnostic information In ARPKD or other ciliopathies
- Abdominal US is needed for diagnosis and screening of portal hypertension.
- US is usually sufficient for follow-up in kidney imaging

Selected indications for MRI and contrast-enhanced US.

- MRI can be valuable for clinical trials in patients with ADPKD or in older children with tuberous sclerosis complex to evaluate both kidney cysts and angiomyolipomas
- MRI for assessment of TKV (Total Kidney Volume)

CT should be avoided whenever possible because of ionizing radiation.

Gimpel et al Imaging of Kidney Cysts and Cystic Kidney Diseases in Children : An International Working Group Consensus Statement .Radiology 2019; 290:769–782

Ultrasonography in Cystic Kidney Diseases

Steps in Assessment

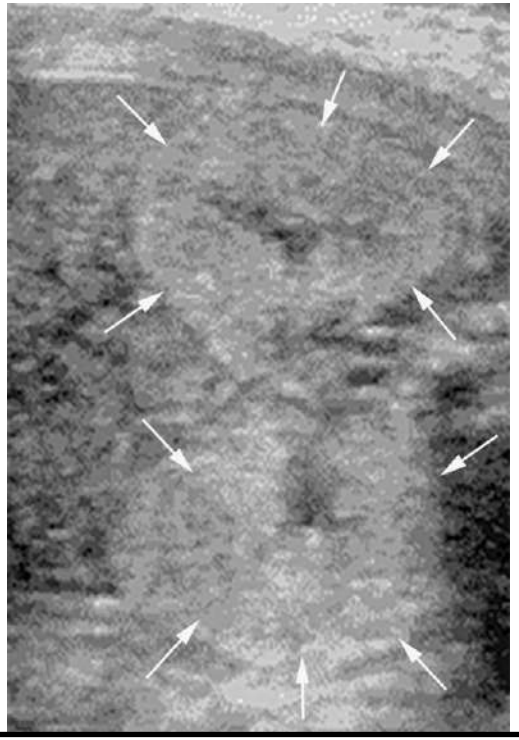
- **Assess general appearance of kidneys- morphology, size, and echo graphic structure**
  - Size(regular, reduced, and increased) according to the age, weight & height
  - Kidney Volume
  - Echogenicity of the cortex
  - Corticomedullary differentiation -regular, increased, reduced, absent or even reversed due to hyper echogenicity of the medulla with respect to the cortex
- **Assess the character of Cysts- number, size, location**
  - Location (subcapsular/cortical ,medullary, corticomedullary border, diffusely or segmentally spread
  - Laterality (uni- or bilateral
  - Number of Cysts (one, two to five, six to 10, or more than 10)
  - Size (maximum diameter of the largest cyst) .
- **Extrarenal assessment** –Liver & Pancreas affected in syndromes like VHL, TS, ARPKD.
- **Assessment of first degree relatives** - to confirm or exclude hereditary forms (ADPKD, NPHP) .

Caveats in sonography

Single & multiple cysts ranging from several cms to a few mms up to sub-millimetric cysts not detectable as they are smaller than the resolution of standard US probes

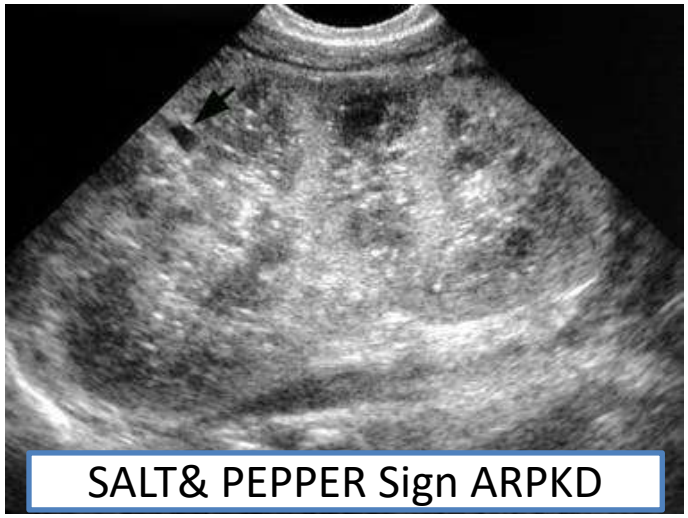
(medullary sponge kidney, neonatal ADPKD or ARPKD).

Multiple very small cysts generate abnormal parenchymal echogenicity (salt-and-pepper sign-ARPKD) or even solely increased echogenicity without visible cysts.

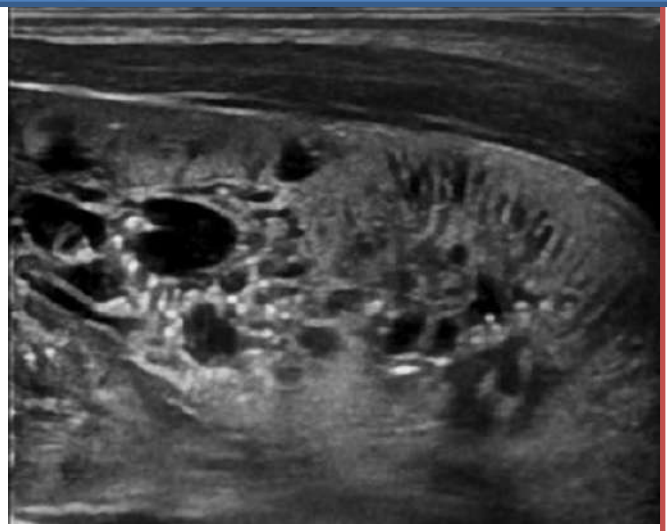


ARPKD : Fetal US shows bilateral enlarged kidneys with increased echogenicity and loss of CMD caused by increased acoustic interfaces produced by tiny innumerable cysts.

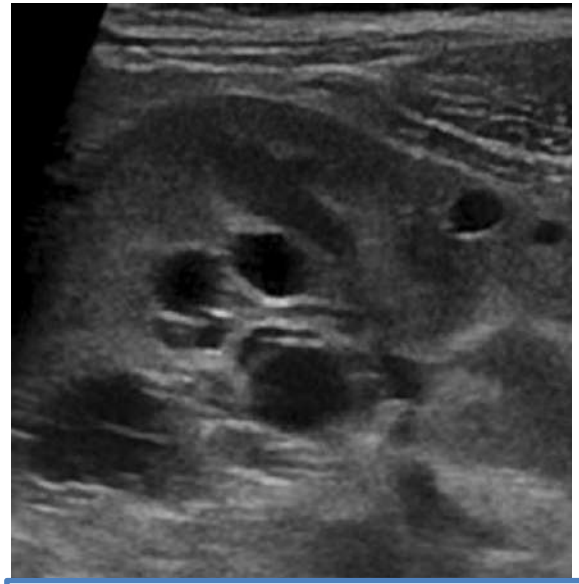
Let us brush through some of these findings



SALT& PEPPER Sign ARPKD



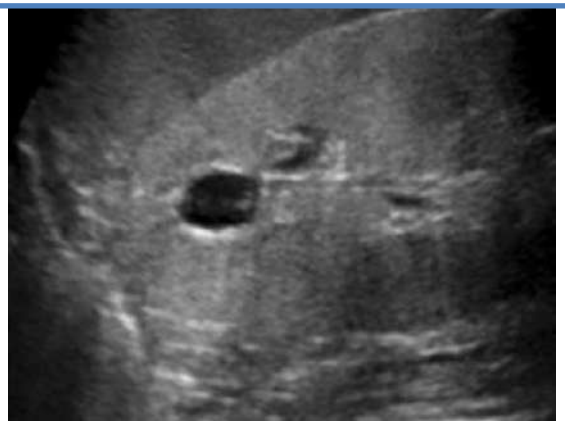
High-frequency US in ARPKD: *multiple hyperechogenic dots with "comet-tail" reverb and some macroscopic cysts between countless tiny microcysts in a radial distribution representing dilated tubules*



Ultrasound Diagnostic Criteria for PKD1 (Ravine/Pei)

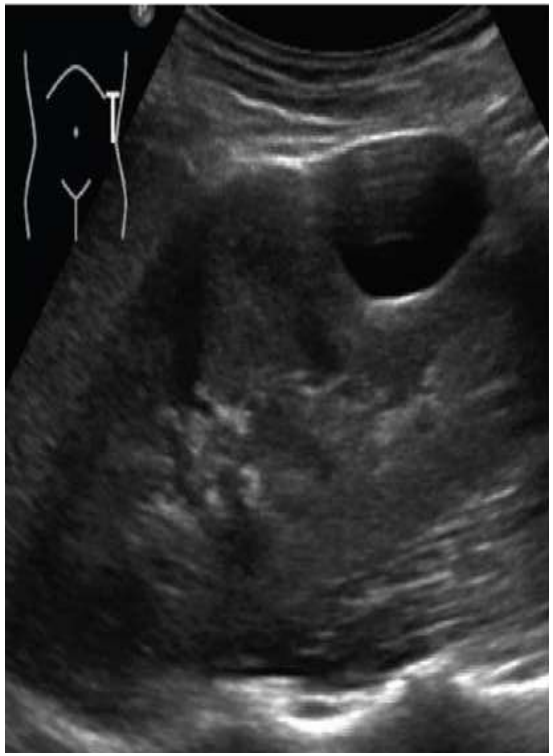
Age (years)	Criteria	Sensitivity	Specificity
< 30	Total of 2 cysts in one or both kidneys	84	100
30 – 60	Total of 4 or more cysts	96	95
> 60	4 or more cysts in each kidney	100	83

NPHP- Di*ffuse increase in parenchymal echoes with loss/poor CMD.Cysts affect the medulla as well as CM junction*



Cortical & Medullary Cysts with intervening normal Parenchyma -ADPKD

Simple Cyst



USS criteria simple cyst:

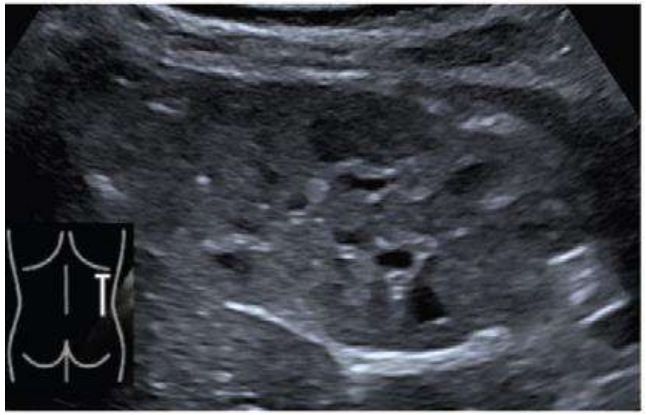
1. Spherical or ovoid
2. Single
3. Sharply defined with thin wall
4. Absence of internal echoes –Anechoic
5. Good transmission of sound waves with acoustic enhancement
6. Nonseptated
7. Separate from collecting System
8. No doppler flow
9. Normal parenchyma

Clinical work-up and at least one follow-up US to rule out development of another cystic kidney disease.

No need for contrast-enhanced US, MRI or CT.

B. Kim et al.: Inherited renal cystic diseases Abdom Radiol (2016)

Juvenile Nephronophthisis



Hepatic Fibrosis &
Portal Hypertension

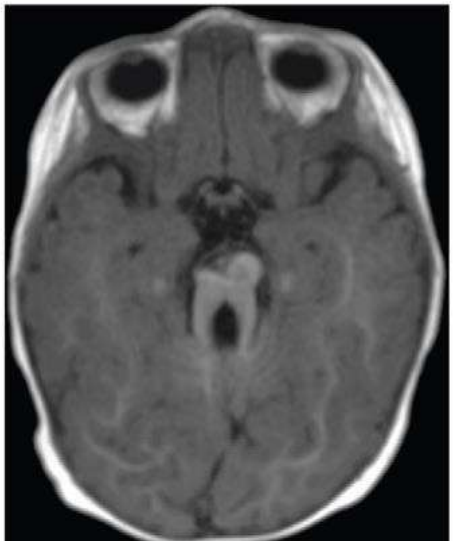
Normal-sized or small kidneys and bilaterally increased echogenicity. Cysts not universally present, not mandatory for diagnosis.

Cysts at the CM junction suggests nephronophthisis - associated renal phenotype.

Infantile nephronophthisis usually manifests as enlarged kidneys and cortical microcysts prenatally or in neonates. Can Be part of a number of syndromes

In children suspected of having nephronophthisis and disability, developmental delay, or cerebral dysfunction, cranial MRI is suggested to look for cerebellar vermis hypoplasia.—

Abnormally deep interpeduncular fossa; elongated, thick, and mal-oriented superior cerebellar peduncles; and absent or hypoplastic cerebellar vermis that together give the appearance of a "molar tooth.

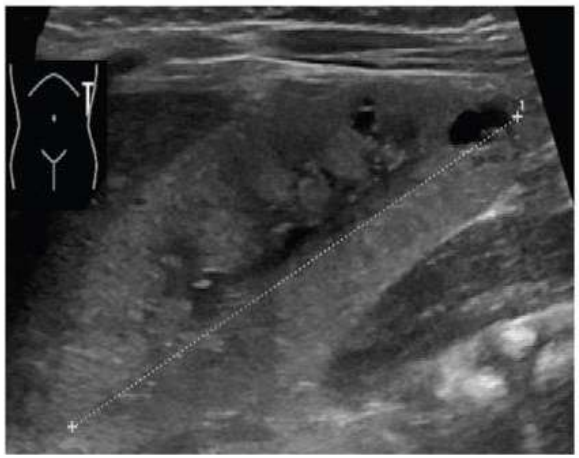


HNF1 B Disease

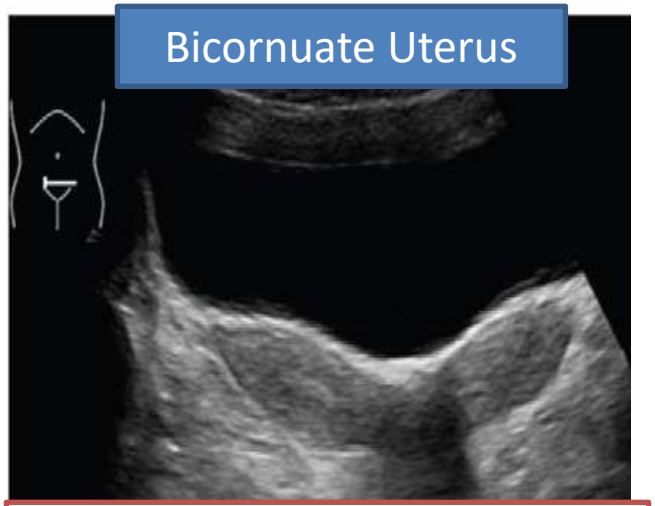
HNF1B deletions - part of chromosome 17q12 deletion syndrome.

HNF1B nephropathy -most common cause of kidney hyper echogenicity at prenatal US and kidney cysts in older children

Mutations of the gene (*TCF2*) for HNF-1-beta. *L*ocation chromosome 17q12
Inheritance- AD 50% de novo mutations with a negative family history.
A family history of maturity-onset diabetes of the young type 5 (RCAD syndrome) gestational diabetes, hyperuricemia, or concurrent hypomagnesemia.



Ultrasound Kidneys
Hypodysplasia,
Uni or bilateral Cysts
Agenesis or normal kidney



Mullerian Duct Abnormalities
Pancreatic Anomalies
Diabetes,Hyperuricemia,Hypo magnesemia

MRI

MRI preferred to CT- Avoid ionizing radiation in children.

Specific Indications

- Detection of AML in TSC
- Total kidney volume (TKV) measurements (Clinical trials of ADPKD).
- Rule out malignancy in complex cysts.

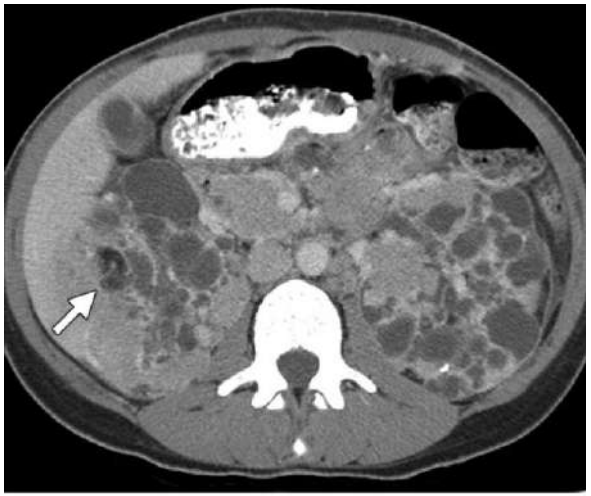
Gadolinium CI

- eGFR < 30ml/m/m^2 NSF
- H/o allergic reactions to Gadolinium

Gadolinium Caution

- Infancy, eGFR <60ml/mt/m^2
- Should not be used twice within 7 days

MRI Sequences in Evaluation



T1- or T2-weighted sequences - to delineate kidney outline and TKV.

T2-weighted sequences- cyst volume measurement in ADPKD

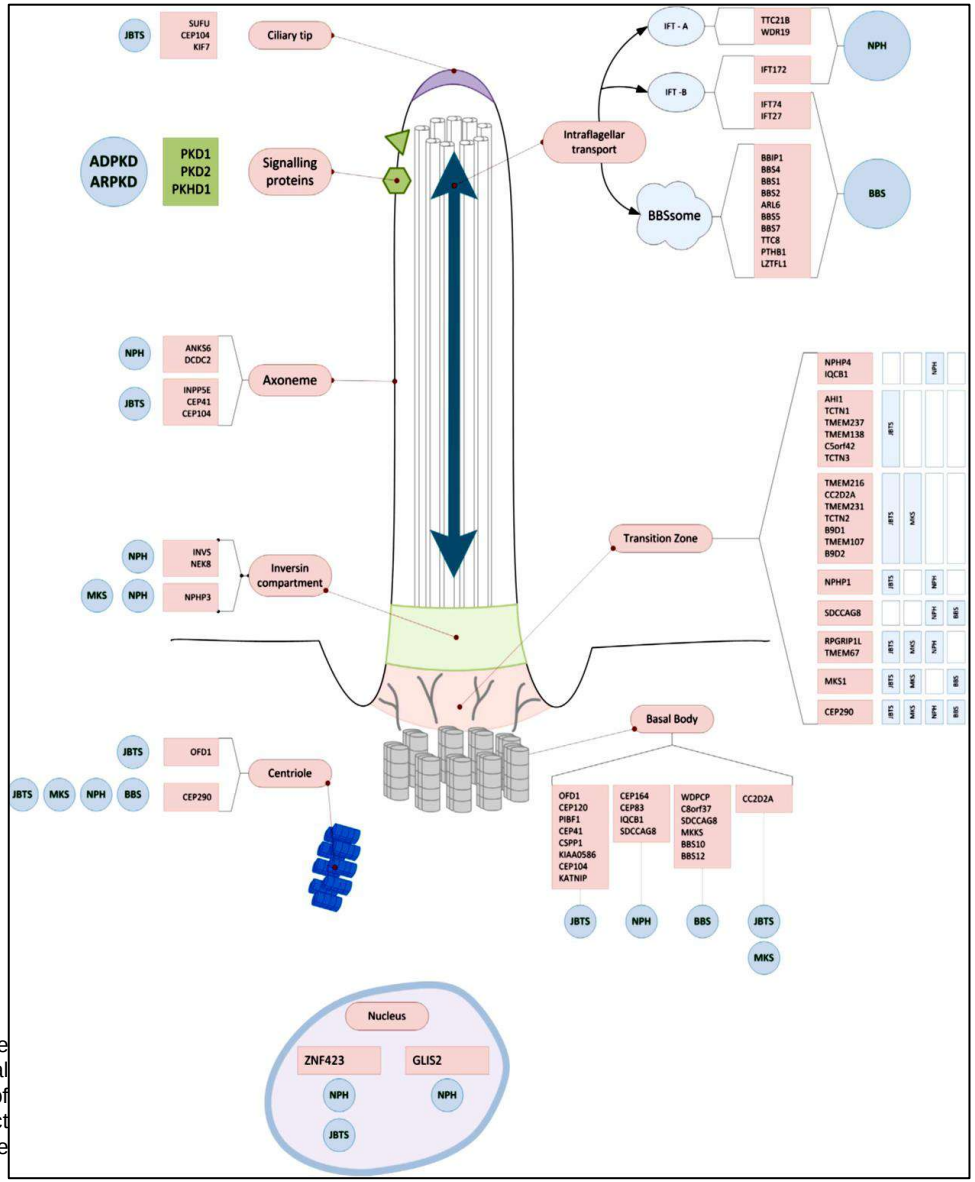
Contrast enhanced T1-weighted sequences- hemorrhage and tumors

Diffusion-weighted MRI- Assessing suspected tumors.

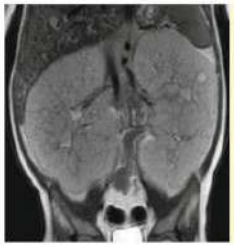
Fat-suppression techniques- Angiomyolipoma.

Cystic Kidney Diseases- A Ciliopathy

- The genetic discoveries revolutionized our molecular understanding of iCKDs.
- Given the enormous genetic complexity of cystic kidney diseases, they are unified by a single pathophysiological concept
- **Ciliary hypothesis -** Most genes that have been identified so far encode proteins that co-localize in primary cilia and even interact as functional ciliary clusters suggested the existence of a common pathophysiological pathway
- Nearly all protein products of disease-causing genes identified so far have been linked to the generation or function of the primary cilium.

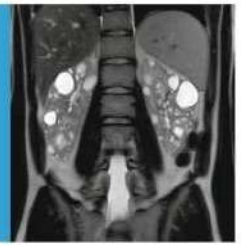


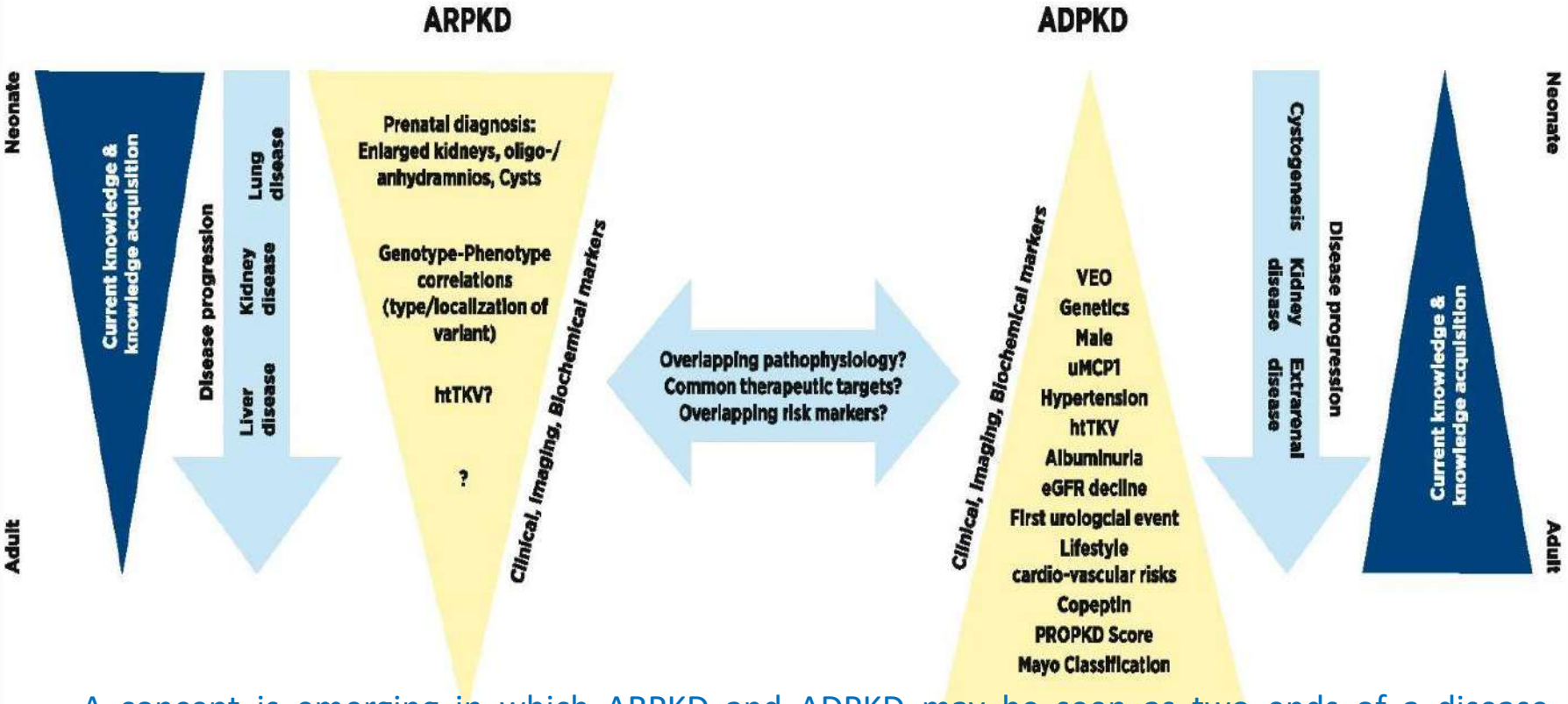
Almost all gene products mutated in hereditary cystic kidney diseases are located at the primary cilium, the ciliary base, or the basal body. Some of the proteins form functional units (Polycystin1/2; BBSom; Nephrocystin-4,5) and are found at characteristic parts of the cilium (e.g., ciliary base). While for some of the gene mutations there is a clear impact on regular ciliary function (e.g., disrupting intraflagellar transport), for most others the exact pathophysiological mechanisms still remain to be unraveled.



PKD Disease spectrum Influenced by

Genetics · Epigenetics · Environmental factors



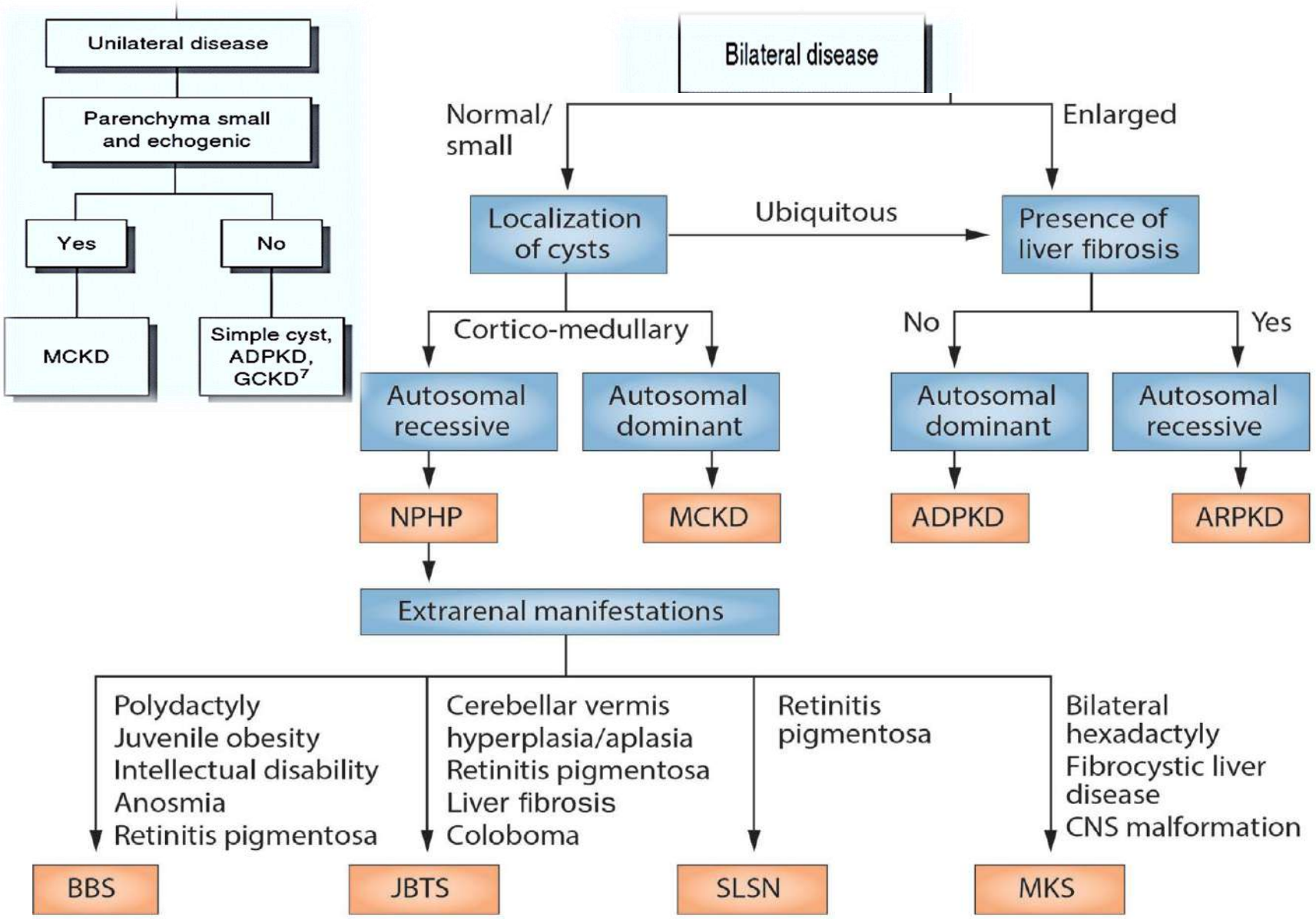


A concept is emerging in which ARPKD and ADPKD may be seen as two ends of a disease spectrum with overlapping genetic and clinical features . Cell biological and clinical research approaches expanded our knowledge of the pathogenesis of ADPKD & ARPKD and revealed some mechanistic overlap between them.

*Liebau, M.C., Mekahli, D. Translational research approaches to study pediatric polycystic kidney disease. Mol Cell Pediatr **8**, 20 (2021).*

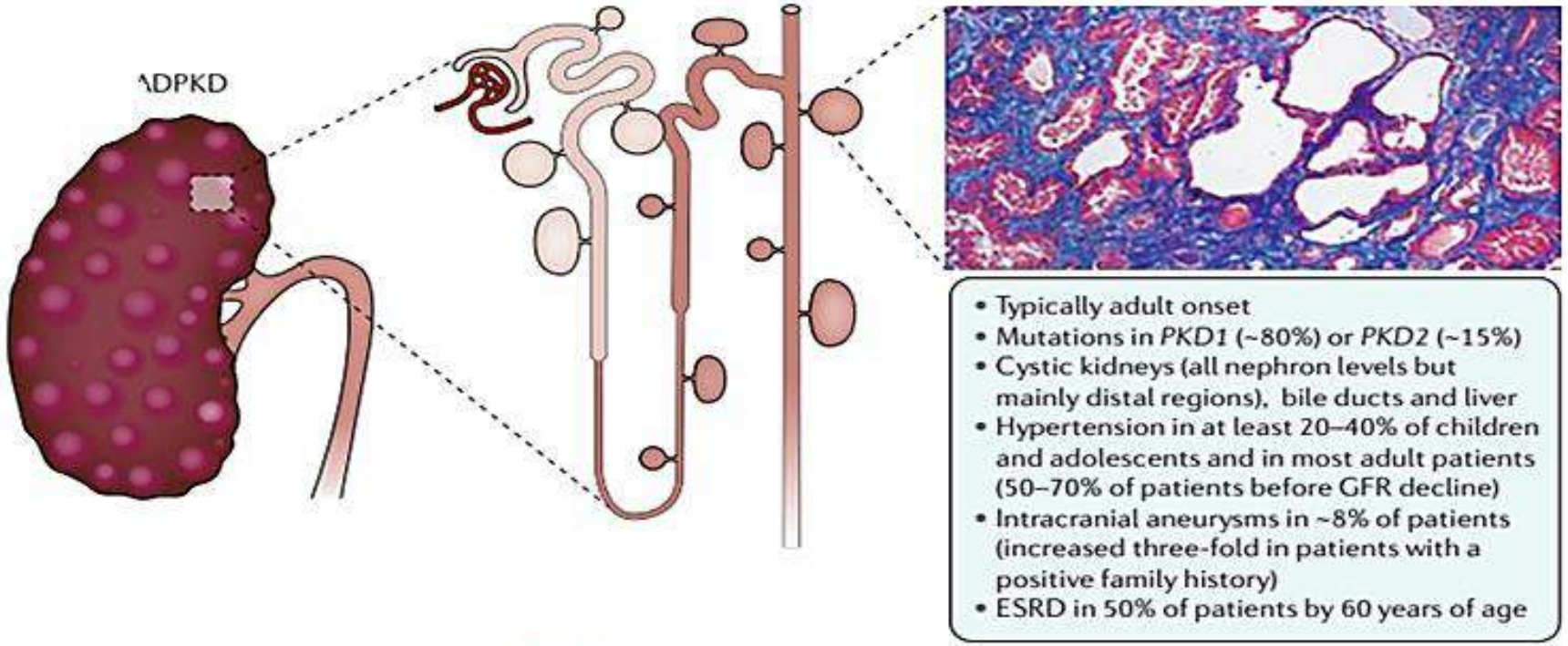
Nature Reviews | Disease Primers 2018

Diagnostic algorithm for Cystic kidney diseases combining clinical judgment with imaging modalities and molecular genetics.

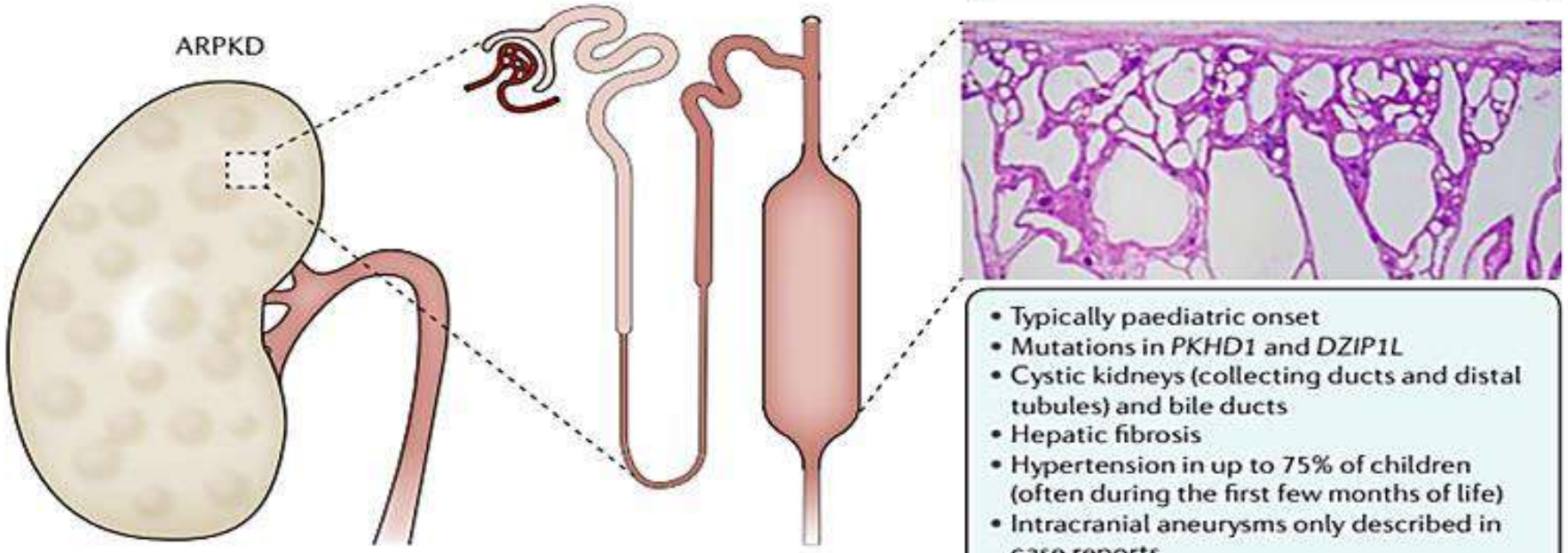


Müller R-U et al 2018 Front. Pediatr. 6:65.

Few specific Conditions
&
Recent Developments in Evaluation

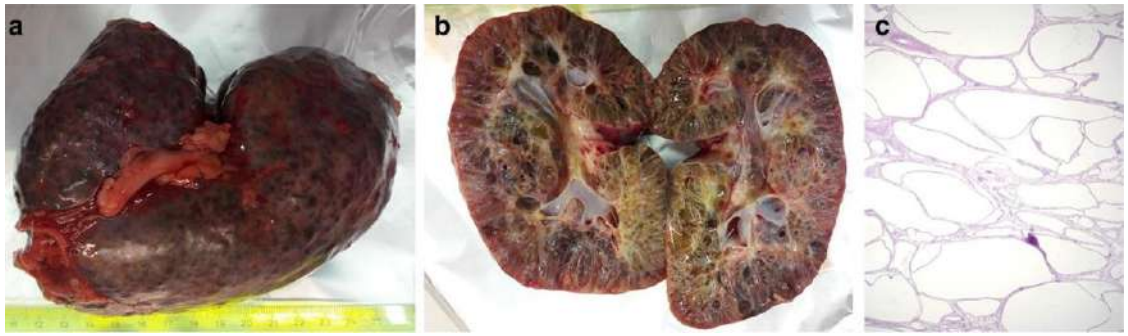


- Typically adult onset
- Mutations in *PKD1* (~80%) or *PKD2* (~15%)
- Cystic kidneys (all nephron levels but mainly distal regions), bile ducts and liver
- Hypertension in at least 20–40% of children and adolescents and in most adult patients (50–70% of patients before GFR decline)
- Intracranial aneurysms in ~8% of patients (increased three-fold in patients with a positive family history)
- ESRD in 50% of patients by 60 years of age



- Typically paediatric onset
- Mutations in *PKHD1* and *DZIP1L*
- Cystic kidneys (collecting ducts and distal tubules) and bile ducts
- Hepatic fibrosis
- Hypertension in up to 75% of children (often during the first few months of life)
- Intracranial aneurysms only described in case reports
- ESRD in 60% of patients by 20 years of age

Autosomal recessive polycystic kidney disease (ARPKD)



Characterized by **multiple non obstructive microscopic renal cysts**

Bilateral, symmetrical dilatation and elongation of 10-90% of collecting ducts

Cystic structures –radially oriented cylindrical or fusiform ectatic spaces, with poor CMD due to the extension of the elongated and dilated collecting ducts from the medulla to the cortex.

Reniform shape maintained as collecting duct cysts usually minute (< 3 mm).

Congenital Hepatic Fibrosis :Malformation of developing ductal plate in Liver.

Liver biopsy findings: enlarged, fibrotic portal tracts and hyperplastic, dilated, and dysgenetic biliary ducts with normal hepatocytes.

Portal Hypertension with splenomegaly, varices, and GI hemorrhage.

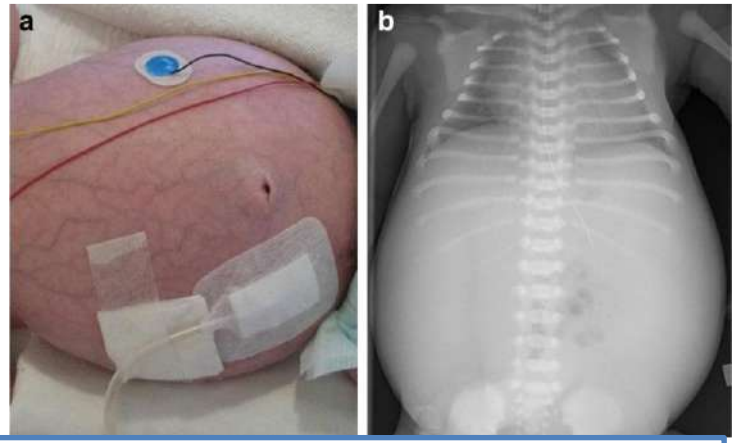
Mutation in the *PKHD1* gene, coding for fibrocystin.

DAZ interacting Protein 1 –like protein (DZIP1L) as a new cause for early onset cystic kidney diseases. *DZIP1L* encodes a protein located at the ciliary- transition-zone leading to a phenotype mimicking ARPKD when mutated

Evaluation of ARPKD

Clinical

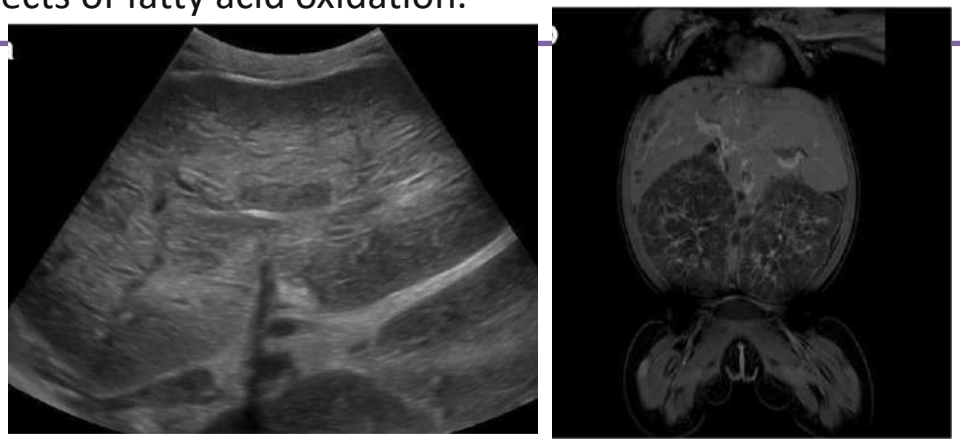
Oligohydramnios
Potters Sequence
Bilateral massively enlarged kidneys
Pulmonary Hypoplasia



The clinical spectrum is highly variable, ranging from late-onset milder forms, to severe perinatal manifestations (more often associated with truncating PKHD1 changes)

Clinical differentiation between ARPKD and very-early-onset forms of ADPKD (VEO ADPKD) difficult. Broad differential diagnoses- Bardet-Biedl syndrome (BBS), HNF1B-nephropathy, Cystic kidney dysplasia,infantile nephronophthisis and defects of fatty acid oxidation.

Radiological



Max Christoph Liebau.Early clinical management of autosomal recessive polycystic kidney disease.Pediatric Nephrology (2021) 36:3561–3570

ARPKD - Radiology

Ultrasound :

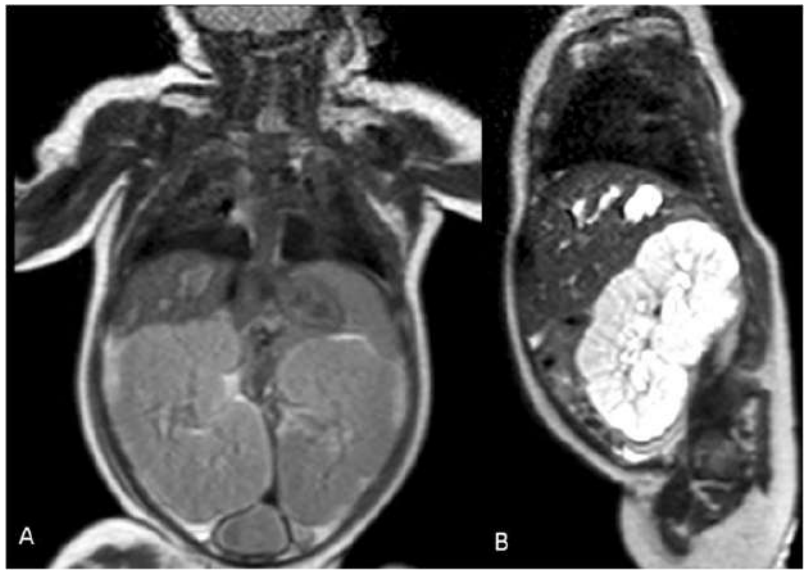
- Echogenic and large Kidneys with lost CMD
- Echogenicity of the kidneys in older children similar to that of ADPKD.
- Macrocysts more typical of ADPKD sometimes present.
- Older children & adolescents: Hepatic abnormalities prominent presenting feature.

MRI :

Enlarged kidneys with hyperintense T2-weighted signals.

- **RARE-MR Urography:** Characteristic hyperintense, linear radial pattern in the cortex and medulla representing microcystic dilatation

Radionuclide studies: DMSA and liver HIDA imaging



MRI T1 sequence, in coronal plane, shows enlargement of both kidneys, with altered structure and bulged margins, and hepatomegaly with at least two cystic lesions in segments VII and VIII. **b**. T2 sequence delayed enhanced image shows enlarged kidney with inverted structure, and at least two cystic focal lesions in segments VII and VIII of the liver

Prenatal diagnosis -ARPKD

- **Prenatal ultrasound:** May present in the second trimester but usually not apparent until after 30 weeks' gestation
  - **O**ligohydramnios
  - Large renal masses
  - Absence of foetal bladder filling.
- **Potential markers for ARPKD:**
  - Increased maternal alpha fetoprotein
  - Amniotic fluid trehalase activity (not specific or sensitive for detection in utero)
- **Genetic testing** available only for families having an affected child.
- **Future**

  With the recent cloning and ongoing characterization of PKHD1, direct mutation analysis may become available.

Preimplantation genetic diagnosis in ARPKD

Possible in ARPKD especially for expecting parents with a previous child with severe disease course or couples with a high risk of recurrence.

If the PKHD1 variants have been identified in the parents, an embryo can be biopsied for genetic testing after in vitro fertilization

Cystic Index in ARPKD

Evolving Concept

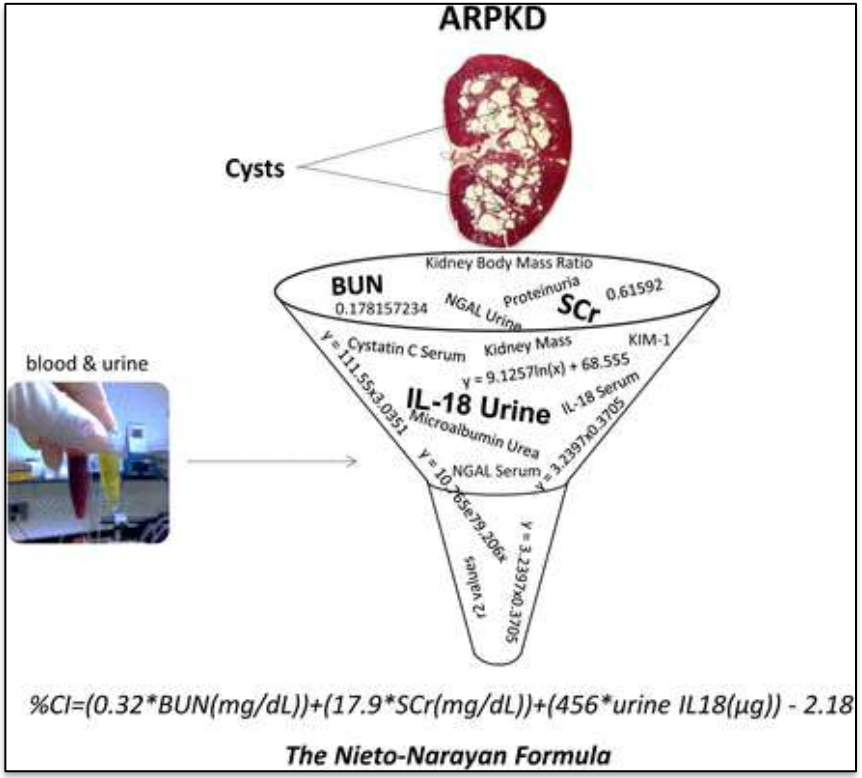
- Progressive enlargement of the kidneys due to formation and expansion of fluid-filled cysts.
- Congenital and progression leads to ESKD ---require nephrectomy + KRT.
- Compute the Cystic Index i.e. Percent of Kidney occupied by cysts
- Increasing cystic index drives both renal expansion and organ dysfunction
- Serial determination of CI helps in decisions on elective nephrectomy and prioritization on the transplant waitlist
- Clinical trials in ARPKD evaluating the efficacy of novel drug candidates could benefit from serial determination of CI.

  - Utilization of ultrasound for assessing disease progression is highly limited.
  - MRI or CT more reliable for determination of CI. But expensive, time-consuming and impractical in children

Huang B, Paka P, McCormack S, Zhou P, Paka L, Yamin M,et al. A Biomarker Cluster for Polycystic Kidney Disease: Correlation with Cystic Index. Recent Patents on Biomarkers. 2015; 5: 35–43.

Cystic Index & Biomarkers in ARPKD

Rodent model of ARPKD.



Male PCK (PCK/CrljCrl-Pkhd1pck/Crl) rats carrying the *PKHD1* mutation for ARPKD, had 1 kidney removed at ~10.5 weeks of age to accelerate renal dysfunction.

Animals were sacrificed at age 13.5 weeks. Immediately prior to sacrifice, 24 hr urine was collected in metabolic cages and animals weighed.

Blood was drawn at sacrifice and the kidney retrieved for analysis.

Levels of a panel of kidney-relevant biomarkers were analyzed using either enzyme-linked immunoabsorbent assay (*ELISA*)

Linear correlation between BUN, SCr and 24 hr urine IL-18 and CI

Nieto JA, Yamin MA, Goldberg ID, Narayan P. An Empirical Biomarker-Based Calculator for Cystic Index in a Model of Autosomal Recessive Polycystic Kidney Disease-The Nieto-Narayan Formula. PLoS One. 2016 Oct 3;11(10)

ADPKD

- Most common inherited human kidney disease -Incidence - 1 in 1000.
- Adult PKD- a misnomer- ADPKD in the fetus, newborn, and older child and adolescent
- Mutations in either *PKD1* (85 percent of patients) or *PKD2* genes (15 percent)
  - Proteins encoded polycystin 1 and polycystin 2 are localized to the primary cilia of renal epithelial cells.
  - PKD1 has been mapped to chromosome 16p13.3 &PKD2 linked to chromosome 4q13-q23
- Systemic disease :Progressive cystic enlargement of the kidneys with variable extra renal manifestations in the GIT,CVS, reproductive organs and brain.
- Early onset of disease (in utero or in the first year of life) with symptoms similar to those with ARPKD.
- Gross or microscopic hematuria, hypertension, proteinuria, cyst infection, and renal insufficiency.

Clinical spectrum of ADPKD in Children

- In utero diagnosis by ultrasound
- Potter's phenotype indistinguishable from ARPKD.
- Large hyper-echoic kidneys with or without macro cysts and variable degrees of renal insufficiency in infancy
- Hypertension in newborn or infant and even in children with normal renal function
- Renal cysts noted on ultrasound in asymptomatic children
- Abdominal pain, palpable masses, gross or microscopic hematuria, UTIs, abdominal or inguinal hernias and hypertension in older children.
- Concentrating defect may be present, leading to polyuria and polydipsia
- Complications :Rare in Children
    - Gross hematuria
    - UTI in particular cyst infection
    - Hemorrhage into cysts
    - Flank pain
    - Renal calculi.
    - Perinephric abscess
    - Chronic pyelonephritis
    - Sepsis.

ADPKD- The Wind of Change ---Why?

To date consensus has dictated deferring investigations in asymptomatic children who are at risk, driven by both the belief that it is an adult disease and the absence of treatments to modify the disease course.
Recommendation till now was against pre-symptomatic screening of children

- Up to one third of children with ADPKD are now known to have overt hypertension.
- LVH occurs both in hypertensive children (defined as blood pressure above the 95th percentile for age, sex, and height) and normotensive children with blood pressure between the 75th and 95th centile.
- Regulating the blood pressure of normotensive children to the 50th percentile using angiotensin converting enzyme inhibitors halts the progression of LVH and fall in renal function.
- Addition of pravastatin substantially reduced the progression of structural kidney disease.
- Normotensive young patients with ADPKD also have biventricular diastolic dysfunction, endothelial dysfunction, increased carotid intima-media thickness, and impaired coronary flow velocity reserve.

Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int 2015;88:17-27. doi:10.1038/ki.2015.59 pmid: 25786098.

ADPKD –Wind of Change

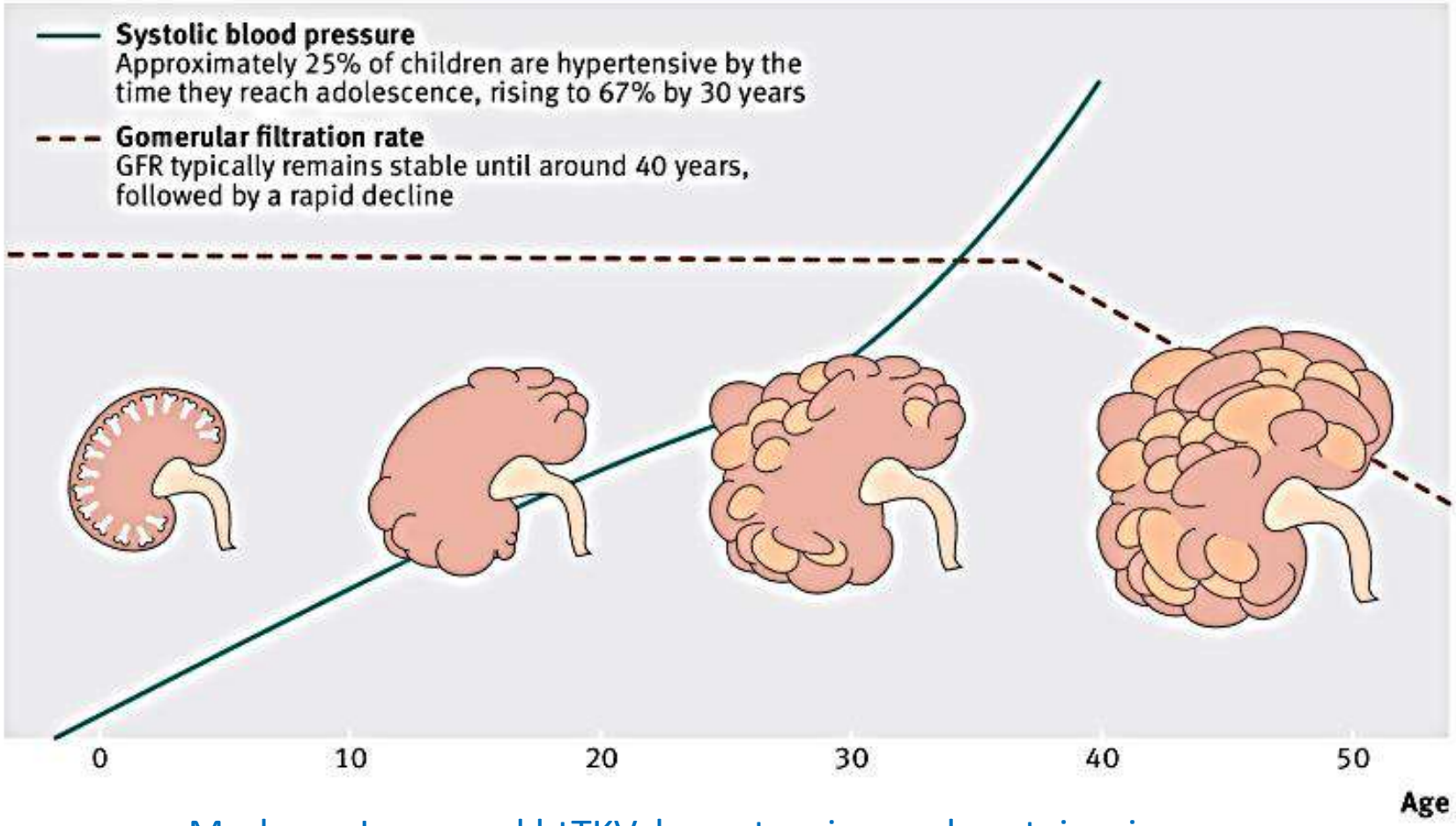
- While ADPKD typically becomes clinically symptomatic in adulthood, cystogenesis starts in childhood or even antenatally.
- It was for a long time believed that children of patients with ADPKD should not be examined
- A “wind of change” has recently been noted in this field
- More attention has been given to a concept of prevention of disease progression by early modification of ADPKD risk factors.
- Initiate treatment of modifiable risk factors already in children.
- The challenges for treating ADPKD in childhood and adolescence have recently been summarized and first specific recommendations on the diagnosis and management of ADPKD in children and young people have been published

Chapman et al.Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a KDIGO controversies conference.Kidney Int 2015;88:17-27.

De Rechter S, Bammens B, Schaefer F et al (2018) Unmet needs and challenges for follow-up and treatment of autosomal dominant polycystic kidney disease: the paediatric perspective. Clin Kidney J 2018.11:i14–i26.

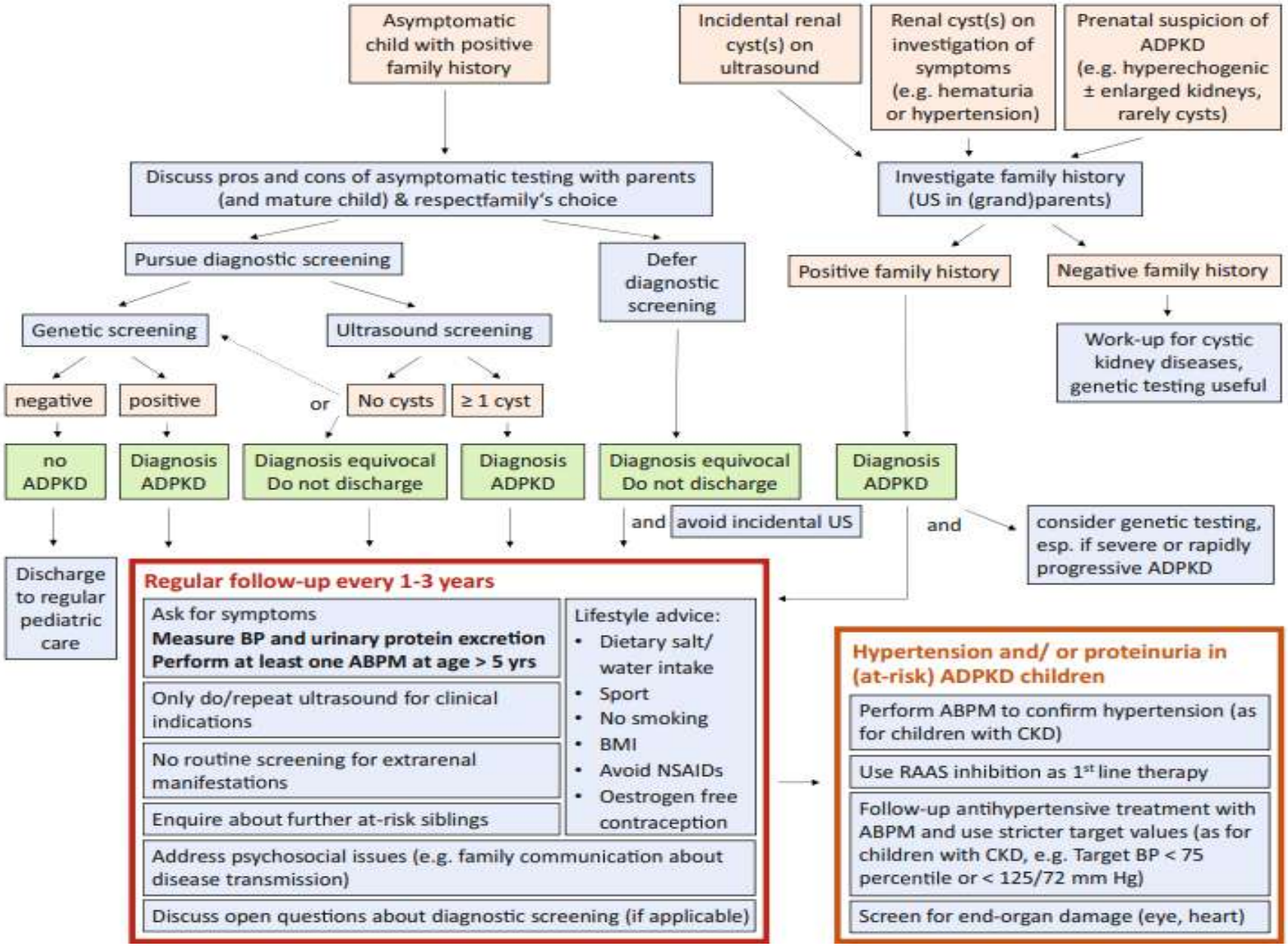
Gimpel C, Bergmann C, Bockenhauer D et al (2019) International consensus statement on the diagnosis and management of ADPKD in children and young people. Nat Rev Nephrol 2019.

ADPKD -Screen now to save later?



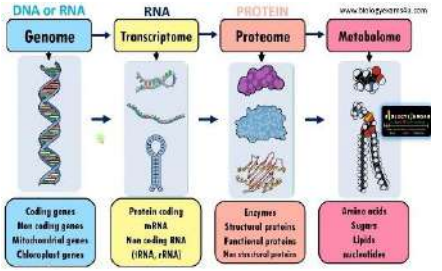
Markers : Increased htTKV, hypertension and proteinuria

Polubothu et al.Autosomal dominant polycystic kidney disease in children. BMJ, 2016
Chapman et al.Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a KDIGO controversies conference.Kidney Int 2015;88:17-27.



Chapman et al.Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a KDIGO controversies conference.Kidney Int 2015;88:17-27.

Serum and Urinary biomarkers, metabolomics



- Biomarkers should not only associate with eGFR or TKV cross-sectionally, but should also be predictive of longitudinal changes in TKV and/or decline in eGFR.
- Severity of ADPKD is associated with an increasingly impaired urine-concentrating ability and lower urinary osmolality; therefore, maximum urine-concentrating ability after water deprivation has been used to assess disease severity
- Plasma copeptin, urinary epidermal growth factor (EGF) and urinary MCP-1 as potential early markers as prognostic indicators for the severity and progression of ADPKD has been evaluated
- Copeptin, which is the stable portion of the precursor of AVP, is an easily measured surrogate indicator of AVP production that can be measured in urine or serum.
- Higher AVP levels are associated with a worse renal prognosis in ADPKD
- Urinary MCP-1 - an easily obtainable marker of disease severity for subgroups of pediatric ADPKD patients . It may in the future be complemented by radiological findings obtained by both novel MR techniques or 3D-ultrasound

De Rechter S, Bammens B, Schaefer F et al (2018) Unmet needs and challenges for follow-up and treatment of autosomal dominant polycystic kidney disease: the paediatric perspective. Clin Kidney J 11:i14–i26.

ADPKD –Mass spectroscopic Analysis- Proteomics and Exosomes

Buccal saliva sample
DNA studies including whole-genome, whole-exome or gene panel-targeted resequencing

Blood sample
Genomic, epigenomic, transcriptomic and metabolomic analysis

Cyst fluid sample
Genomic, transcriptomic, proteomic, metabolomic and microRNA analysis of single cells, the cell-free fraction and exosomes

Urine sample
Genomic, transcriptomic, proteomic, peptidomic, metabolomic and microRNA analysis of single cells, the cell-free fraction and exosomes

Exosomes

Vesicles released from plasma membrane of cells

Present in all bodily fluids

Contain cellular proteins, RNA and metabolites

Thought to have a role in cell-to-cell communication and transport

Apolipoprotein A1
Antithrombin III
Fibrinogen
α1 antitrypsin

Reduced levels of PC1 and PC2 have been detected in urinary exosomes
Overabundance of desmosome components (periplakin and envoplakin), villin 1 and complement proteins in the urinary exosomes

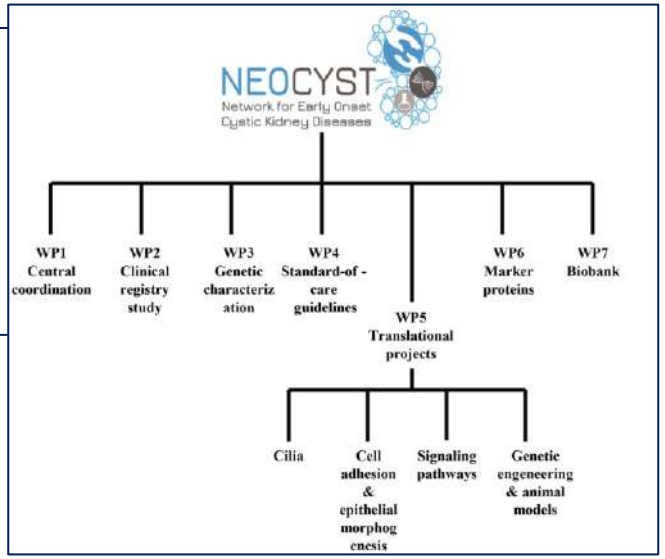
Promising Therapy in Future

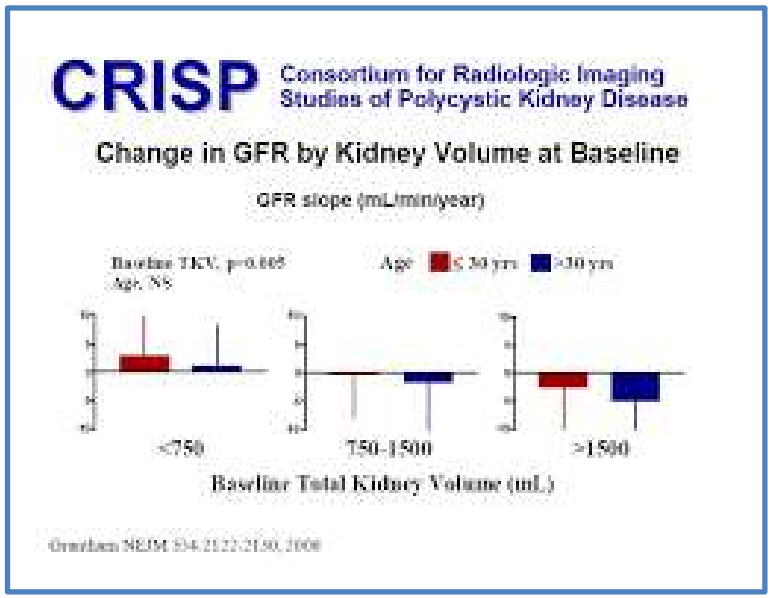
- Successful therapy will require knowledge of the extent of the disease, when therapy begins and the rate of progression, will require multiple agents or a single agent that hits multiple targets, and the choice of targets will be stage specific and change as disease progresses.
- In the near future, the most promising therapies will target key signaling intermediates that integrate multiple pathways- multi-kinase inhibitors such as tesevatinib (TSV) -currently under Phase 2 clinical trial for ADPKD (NCT02616055) and recently received FDA approval for a Phase 1 trial in young kids with ARPKD.

Sweeney WE Jr and Avner ED (2017) Emerging Therapies for Childhood Polycystic Kidney Disease. Front. Pediatr. 5:77. doi: 10.3389/fped.2017.00077

Consortium in Cystic Kidney Diseases

- **NEOCYST**- Network for Early Onset Cystic Kidney Disease- a consortium of clinical, genetic, and translational researchers devoted to the study of early-onset cystic kidney diseases with a work package devoted to the development of guidelines and position papers





Toronto Genetic Epidemiology Study of Polycystic kidney disease (TGESP)

Conclusion

- Cystic Kidney Disease remains a challenge in Pediatric Nephrology.
- Renal cysts occur in a variety of diseases in children.
- Cysts may be due to genetic disorders, nonhereditary fetal malformations (ie, cystic renal dysplasia) , or rarely may be acquired.
- As simple cysts are extremely rare in childhood , the finding of even one renal cyst should alert the clinician to the possibility of ADPKD.
- Genetic Evaluation helps in definitive diagnosis, prognostication & targeted therapy
- A lot has been learned over the past two decades, but multiple open questions still remain - whether cystic diseases comprise a spectrum with common basic pathophysiology?
- An urgent need exists to improve our understanding of the disease course and to identify additional specific, early, and precise prognostic risk markers for kidney and liver disease, as well as for prenatal prediction of the postnatal outcome.


Hope


Thank
you