CAKUT in the 21st Century

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IPNA – AfSPN Junior Master Class

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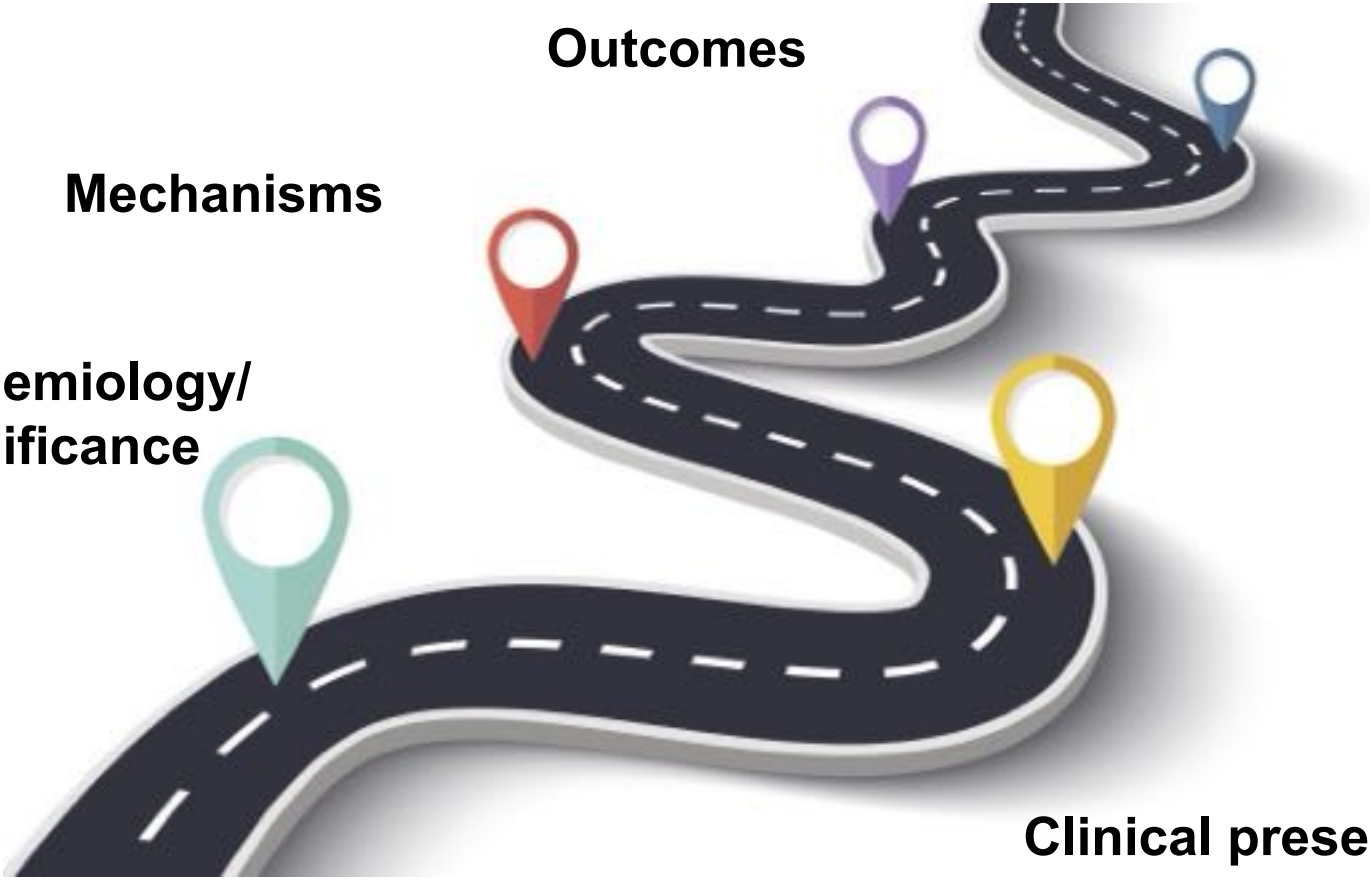
CAKUT Roadmap



Objectives

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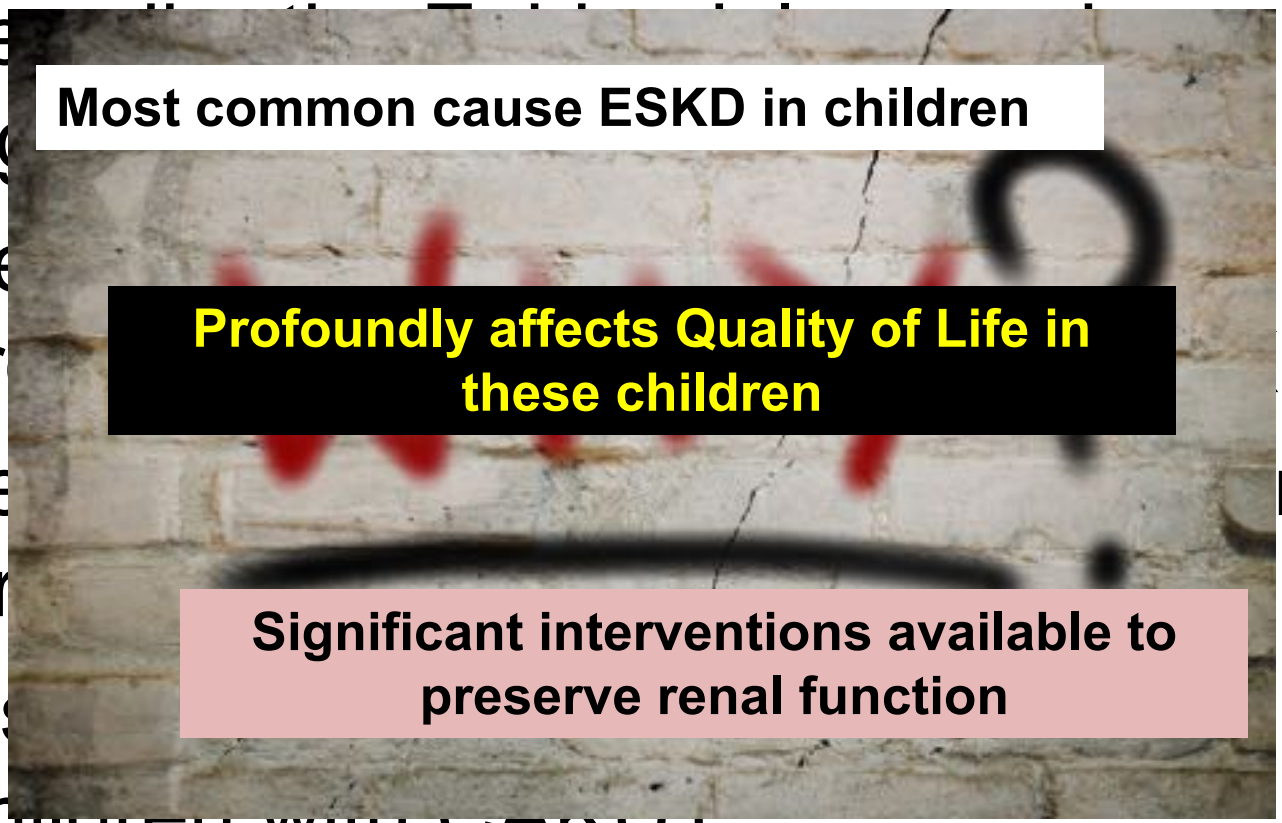
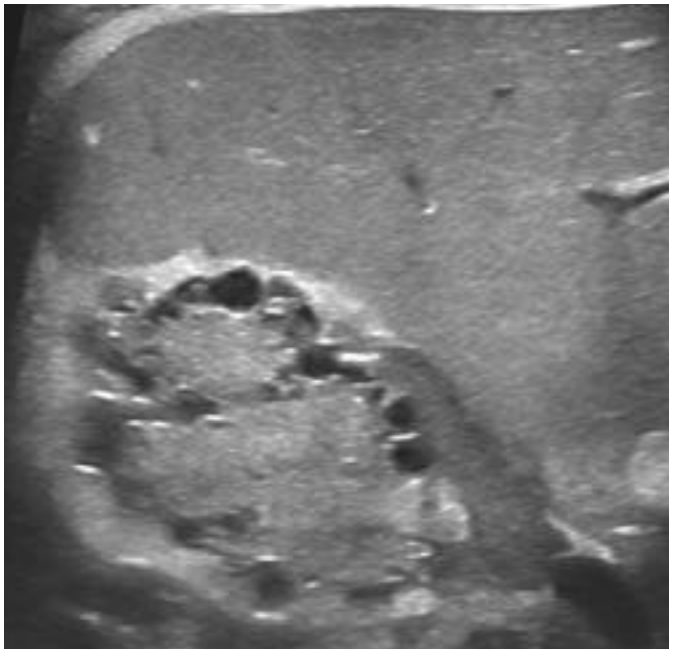
   Children with CAKUT

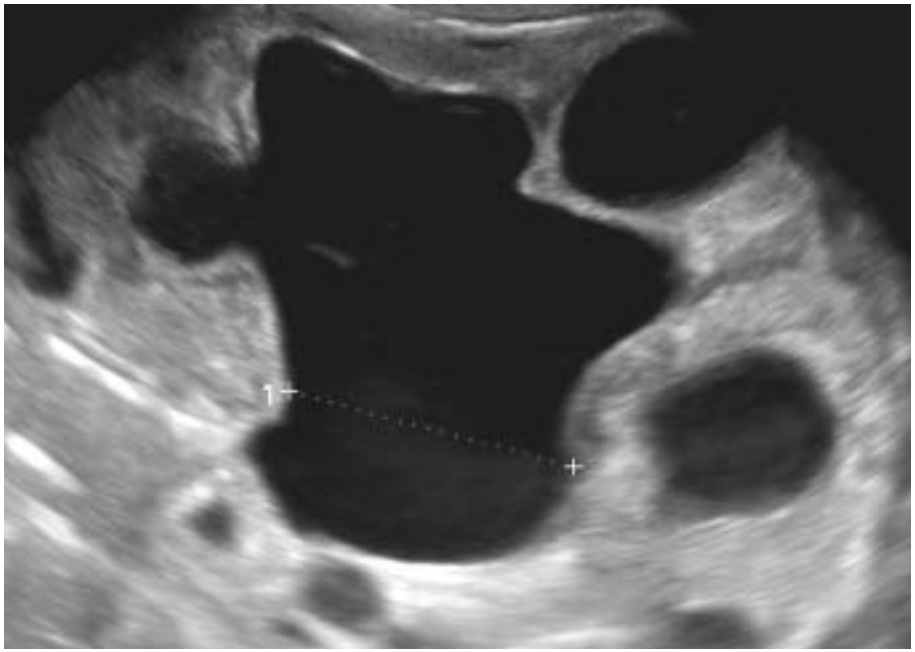


1-day old female

- 2.1 kg, 31 weeks gestation, history of amnioinfusions, suspected L MCDK and R hyperechoic kidney. Anuric. Transferred for urgent nephrology & urology consultation

R cystic dysplasia, L hydronephrosis (?UPJO) with urinoma





No urine in bladder. L nephrostomy tube with urine output. Tunneled PD catheter DOL#2. Dialysis DOL#6-15. Pyeloplasty. Renal recovery

9 yo: GFR 74 ml/min/1.73 M2; normal intelligence, good QOL

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Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

- Common (3-6 per 1000 live births);
- 23% of overall birth defects
- Congenital Defects
  - can be bilateral or unilateral
  - different ones often coexist in an individual
  - most common is VUR

CAKUT and Pediatric ESKD

Distributions by diagnosis	Number
Obstructive uropathy	1,385
Aplastic/hypoplastic/dysplastic kidney	1,125
Other	913
FSGS	557
Reflux nephropathy	536
Polycystic disease	257
Prune belly	185

40-50% of Pediatric ESKD

NAPRTCS, 2008

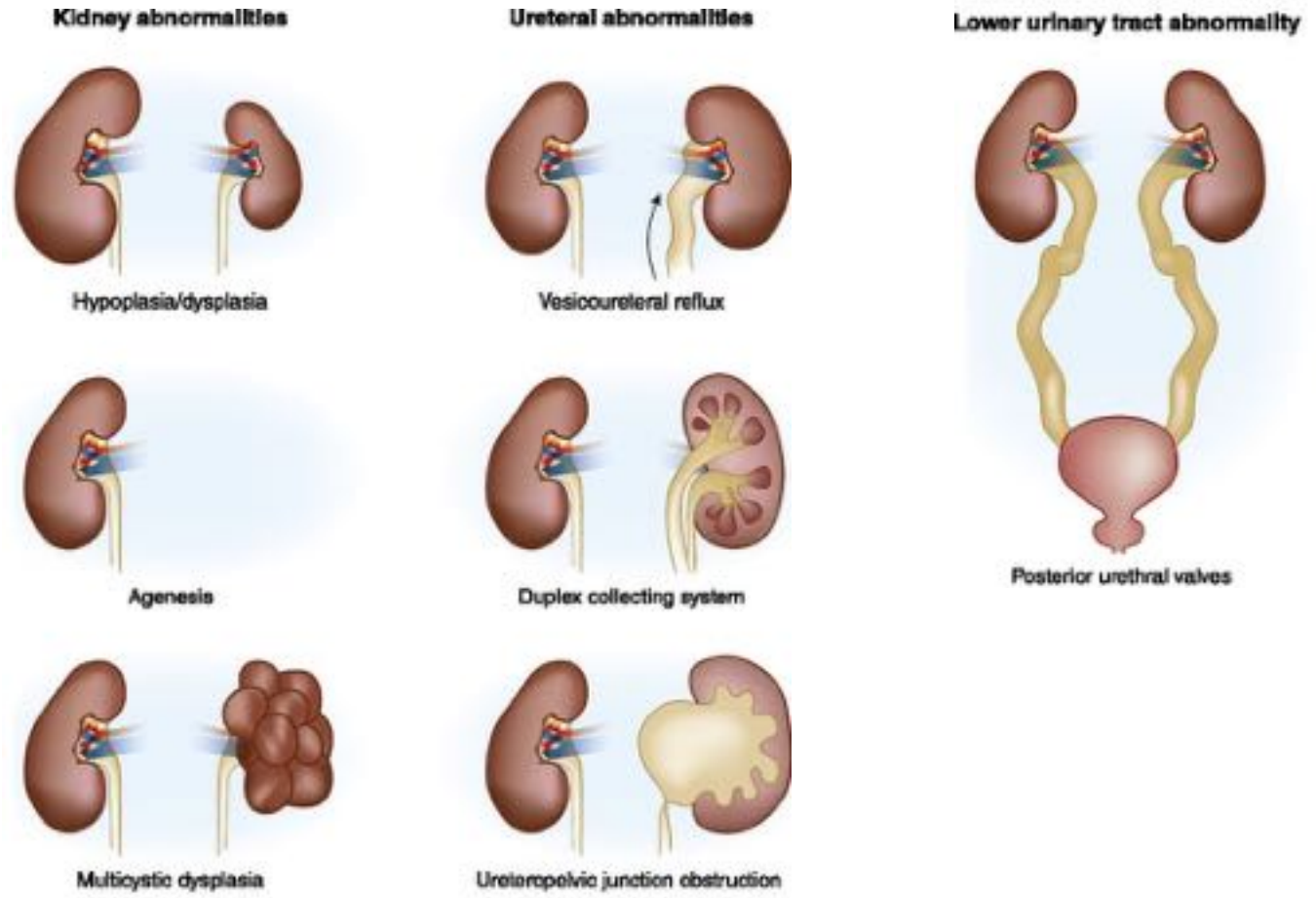
CAKUT Causes and Clinical Presentations

- 25% of cases have a **genetic** basis
- Also can be due to *environmental* factors
  - Micronutrients (e.g., folate, vitamin A deficiency)
  - Maternal diabetes
  - ACEi
  - *In vitro* fertilization
- Isolated vs. syndromic

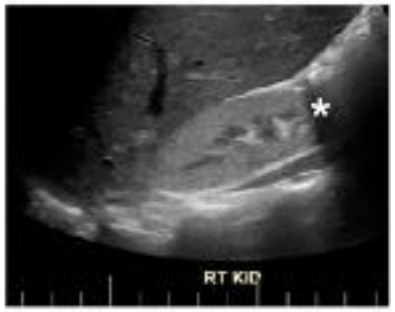
Clinical presentations:

- Abnormal pre or postnatal imaging
- UTI
- Renal insufficiency/poor growth
- Abnormal bladder function
- Abdominal mass/pain

The anatomic spectrum of CAKUT



Kidney Hypoplasia



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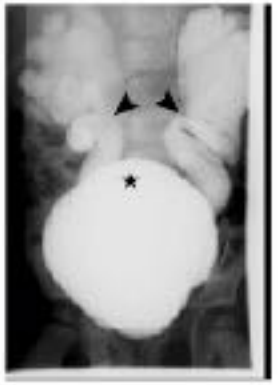
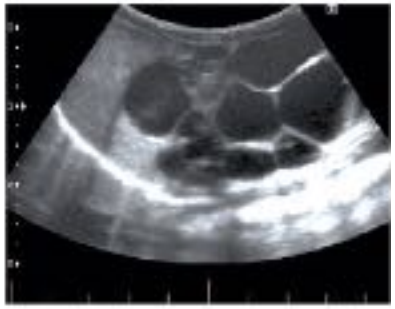
Vesico-Ureteric Reflux



Multicystic Dysplastic Kidney



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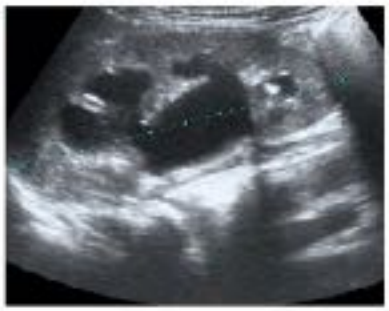
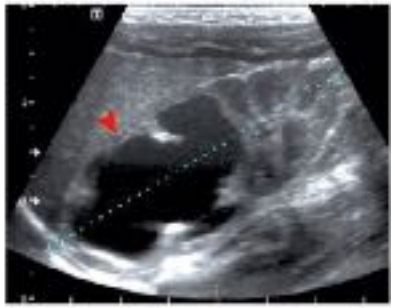
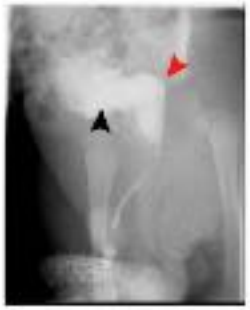
Uretero-Pelvic Junction Obstruction



Duplex Kidney



Posterior Urethral Valves



Gupta and Murugupoopathy (2020) *CJASN*

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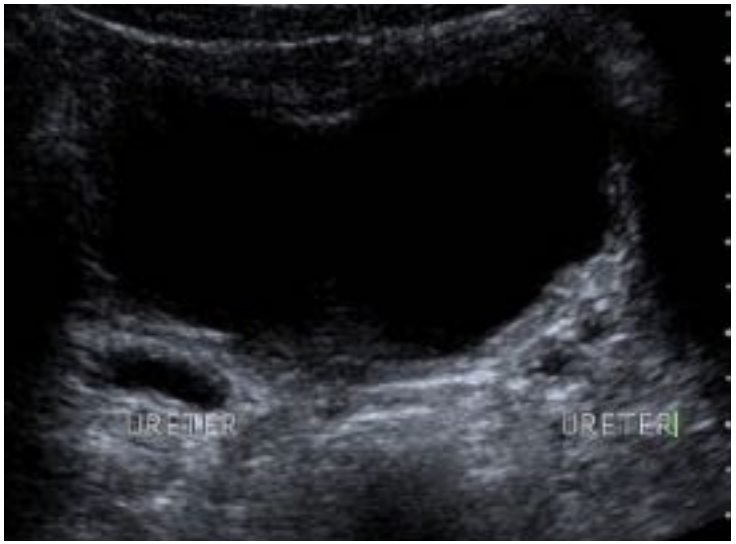
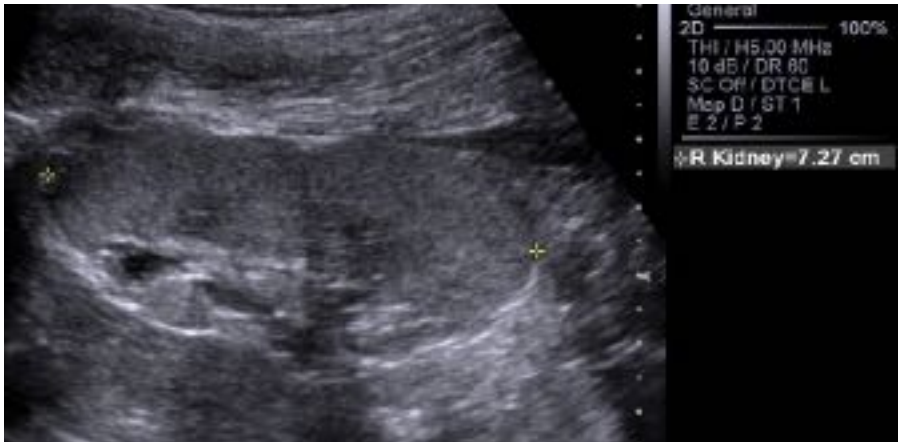
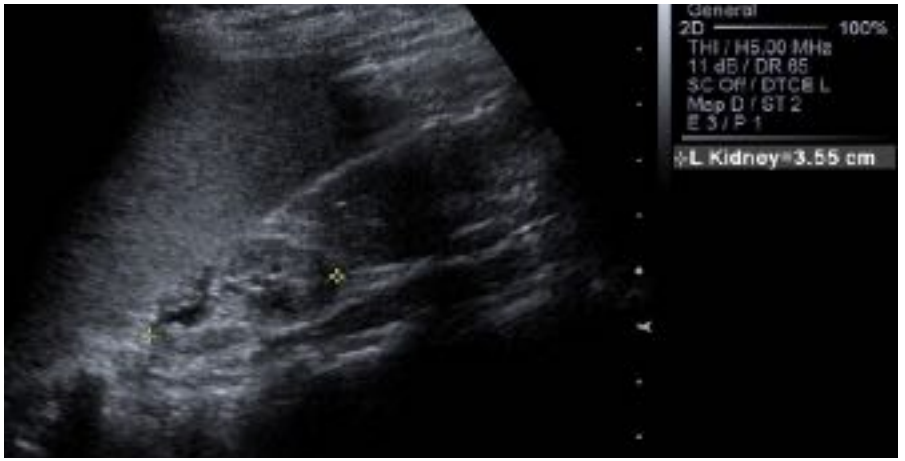
8 year old Nepali boy with *E. coli* urosepsis, history of bowel and bladder dysfunction







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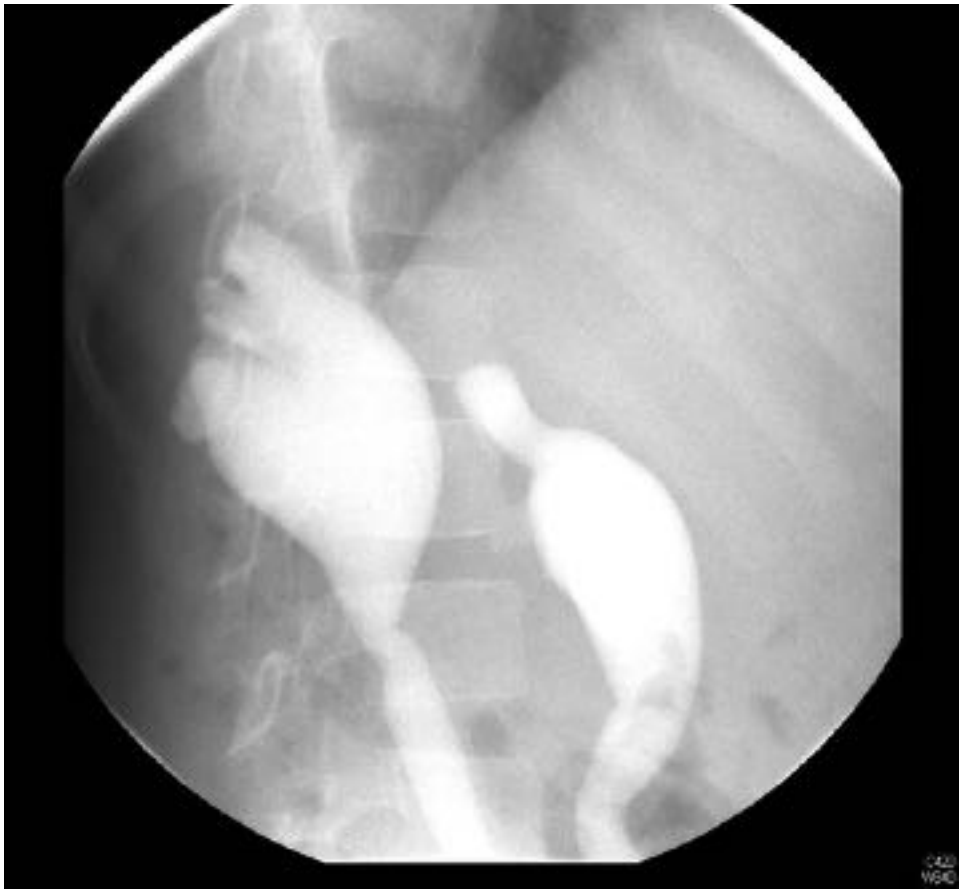
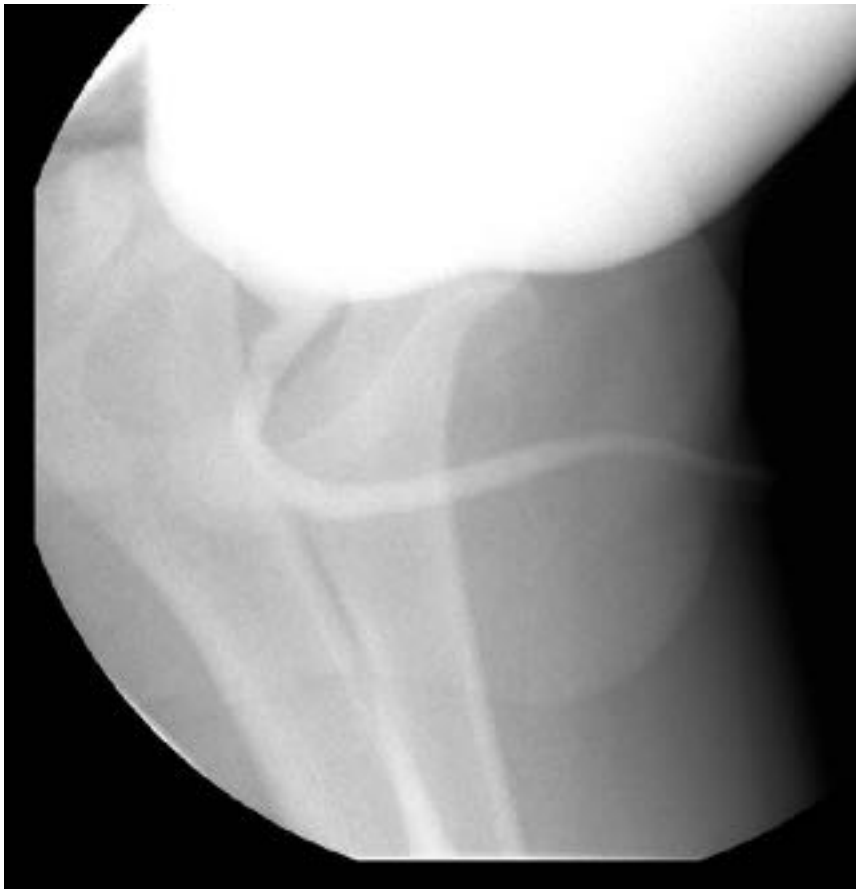
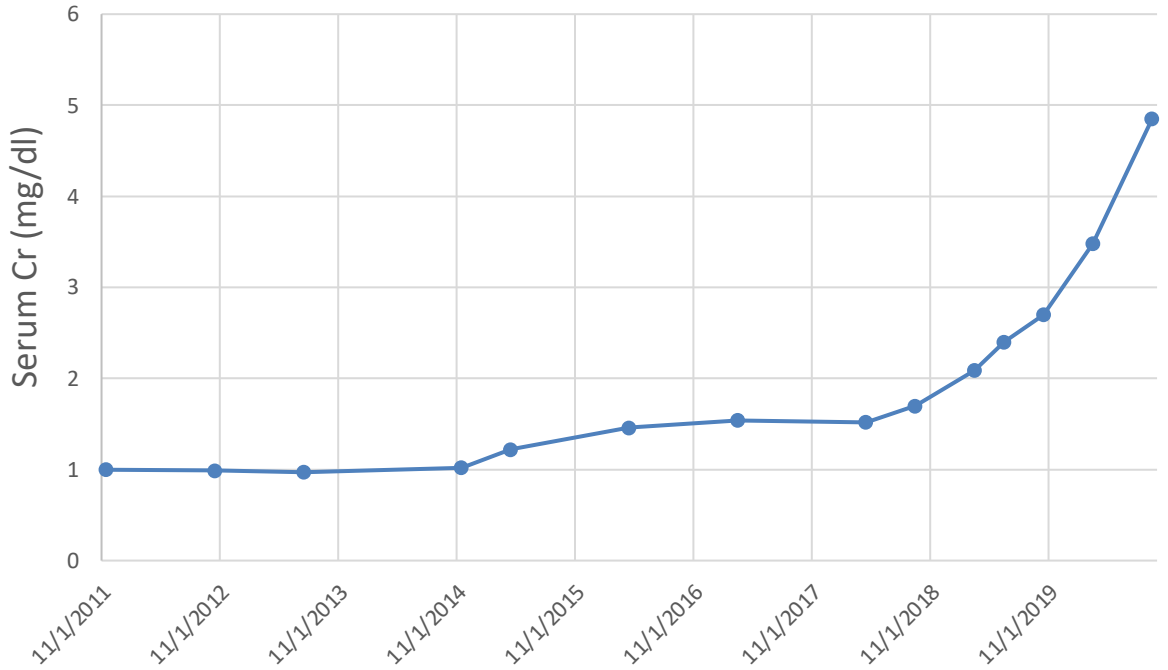
VCUG

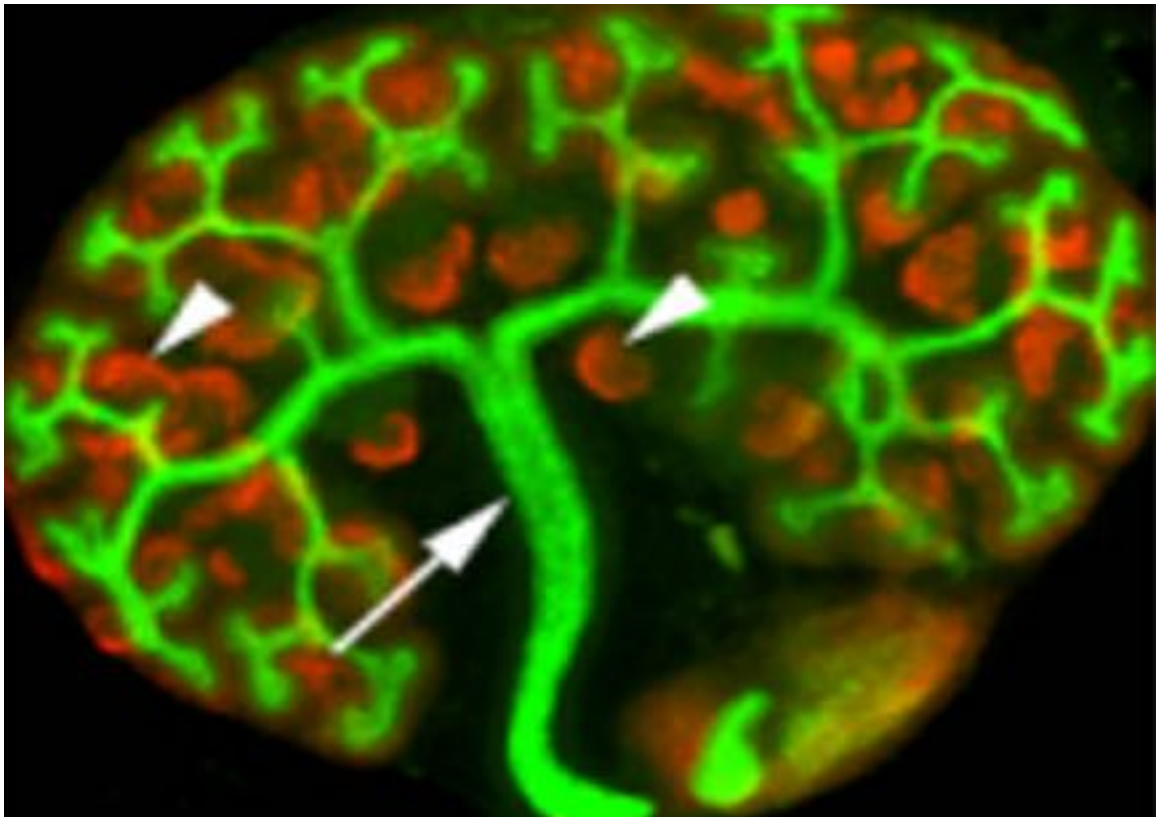




Fast forward to 2020



Mechanisms of CAKUT



CAKUT typically arises from combination of genetic & environmental factors but monogenic disorders explain some CAKUT cases.

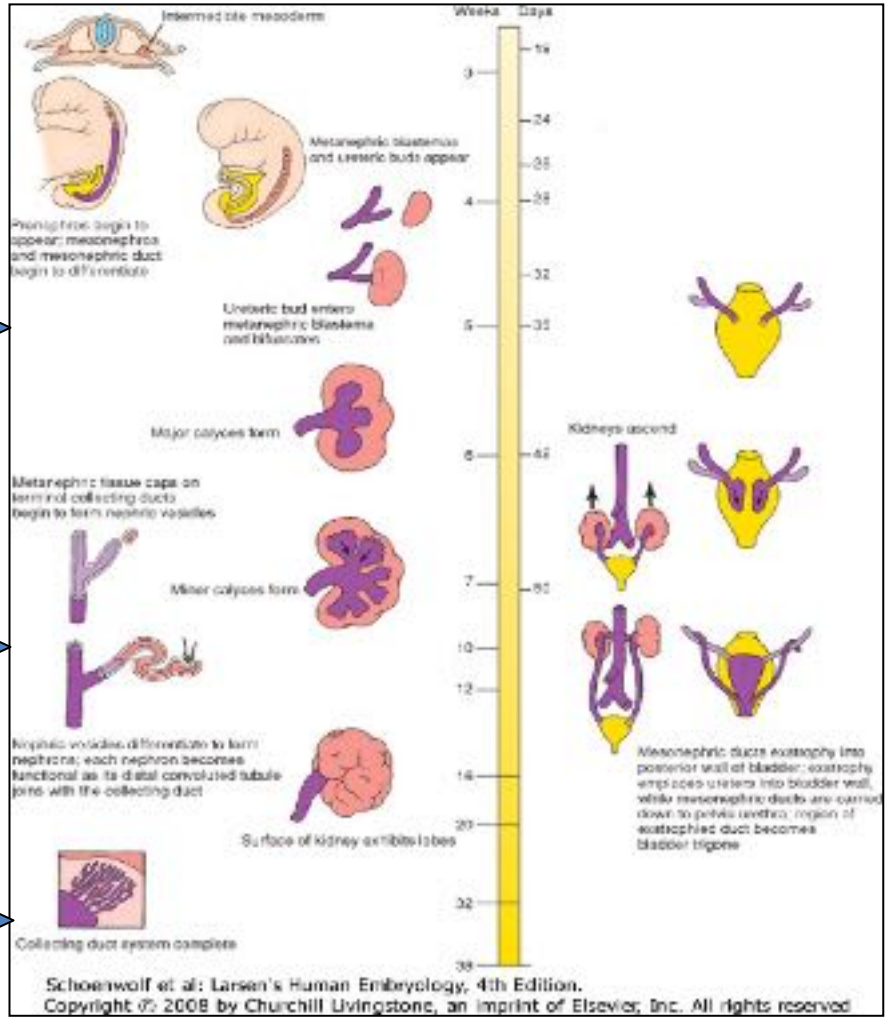
15% of all CAKUT explained by Heterozygous dominant gene mutations in 2 transcription factors: *HNF1B* and *PAX2*

Urinary Tract Development

Onset of Metanephric Kidney Development

Onset of Urine Production

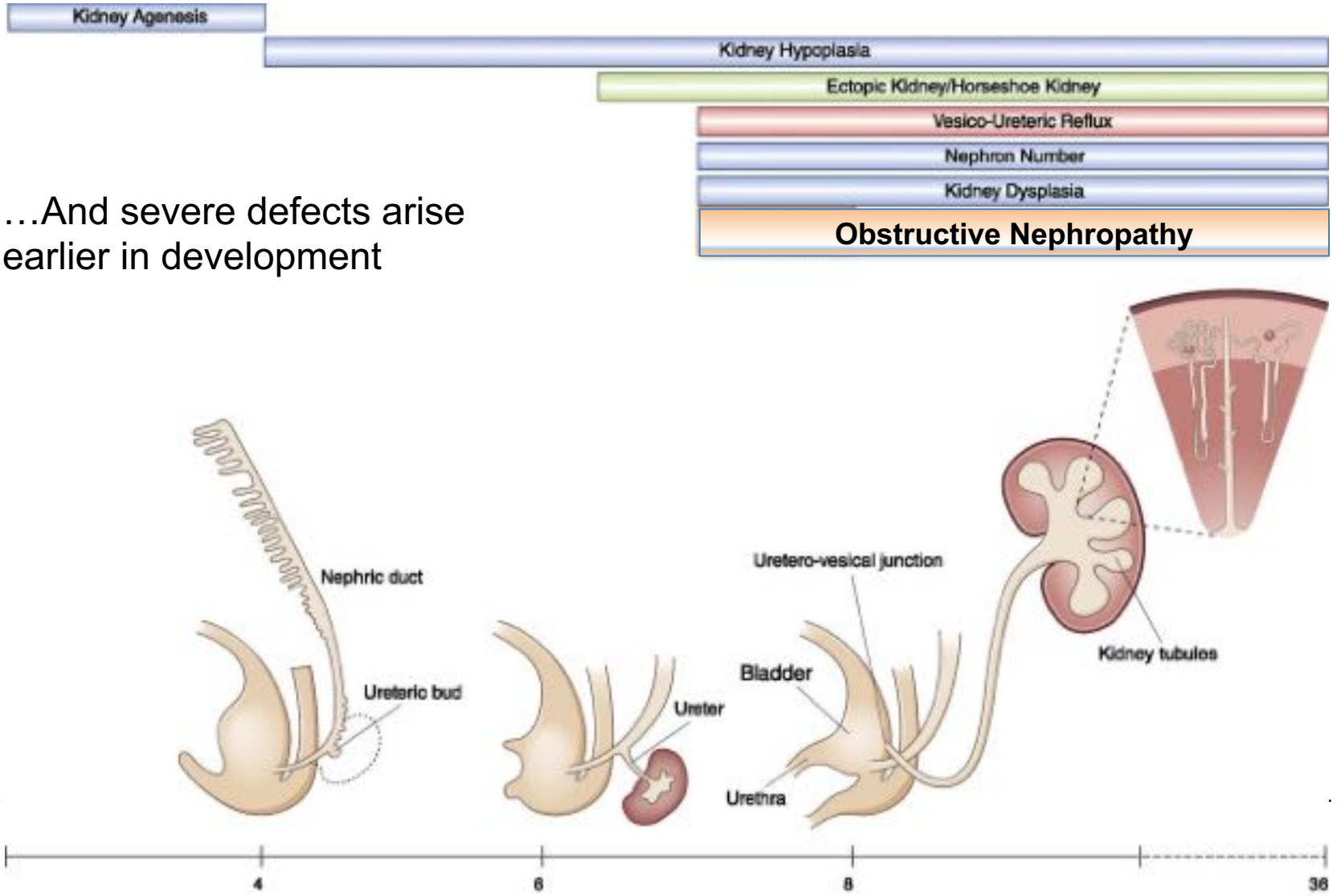
Glomerulogenesis Is Complete



Nephrogenesis occurs between wks 6-36 of gestation – final outcome = 200,000 – 2,000,000 nephrons/kidney – tremendous variability

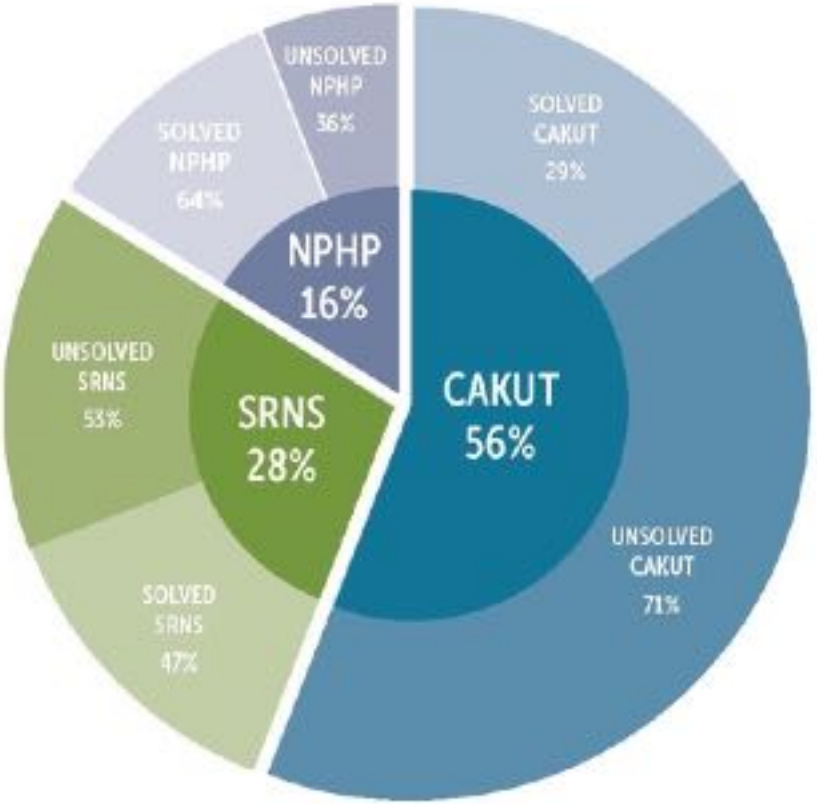
As Always - Timing is Everything!

…And severe defects arise earlier in development



Gupta and Murugupoopathy (2020) *CJASN*

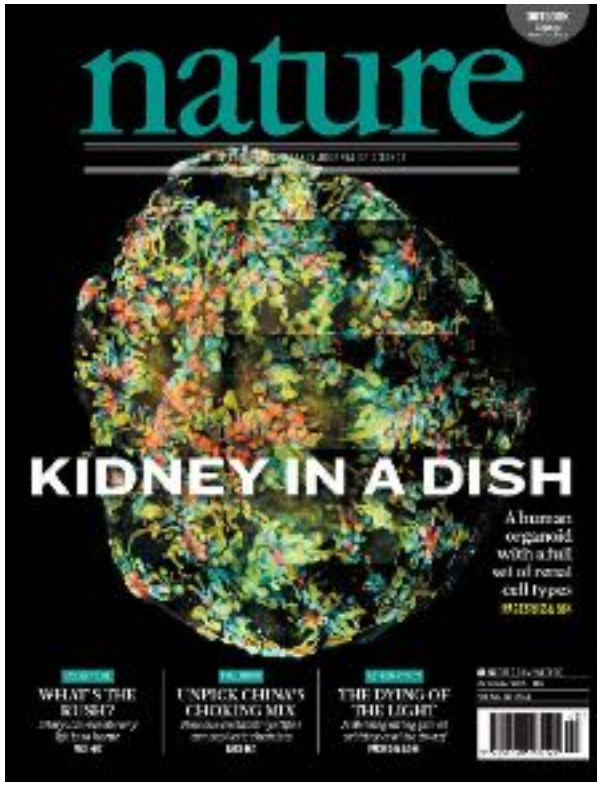
“Solved” vs. Unsolved Causes of ESRD

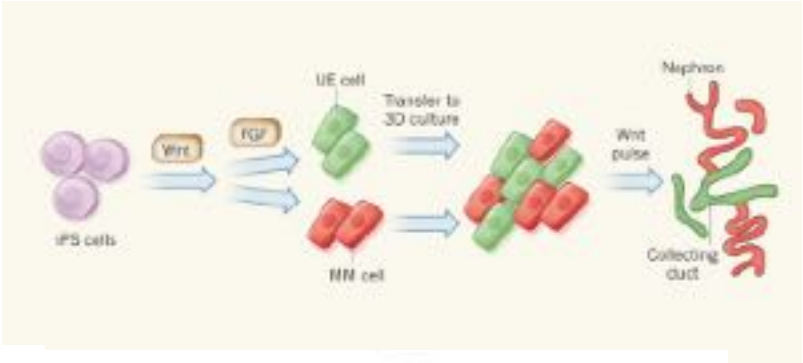


- 68 patients with ESRD underwent WES
- 40% had causative mutation
- CAKUT accounted for 56% patients with ESRD
- Of these, 29% had causative mutation

Mann *et al*. (2019) *JASN*

Utilizing Human Organoids to Study Development and CAKUT





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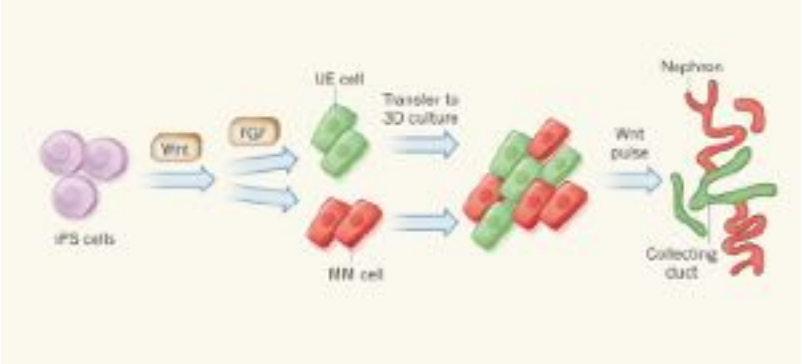
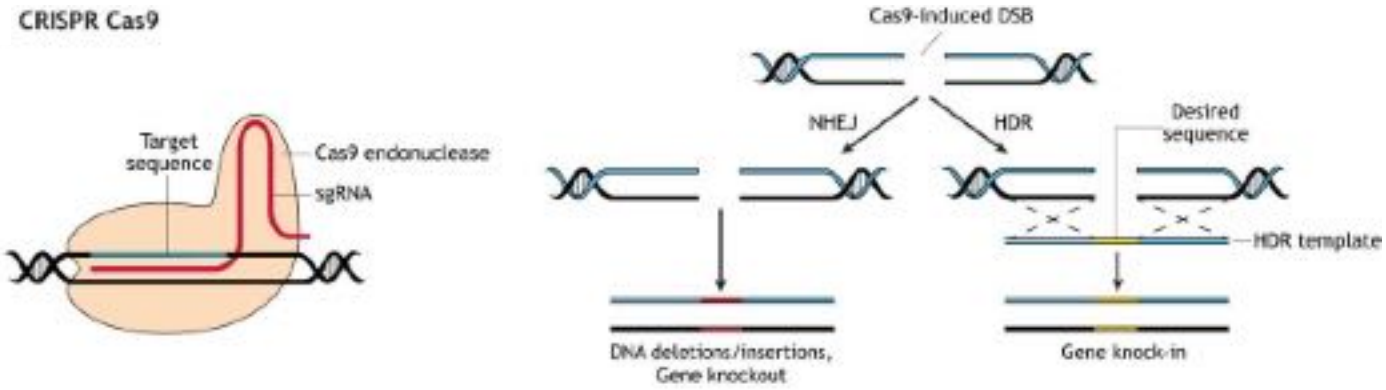
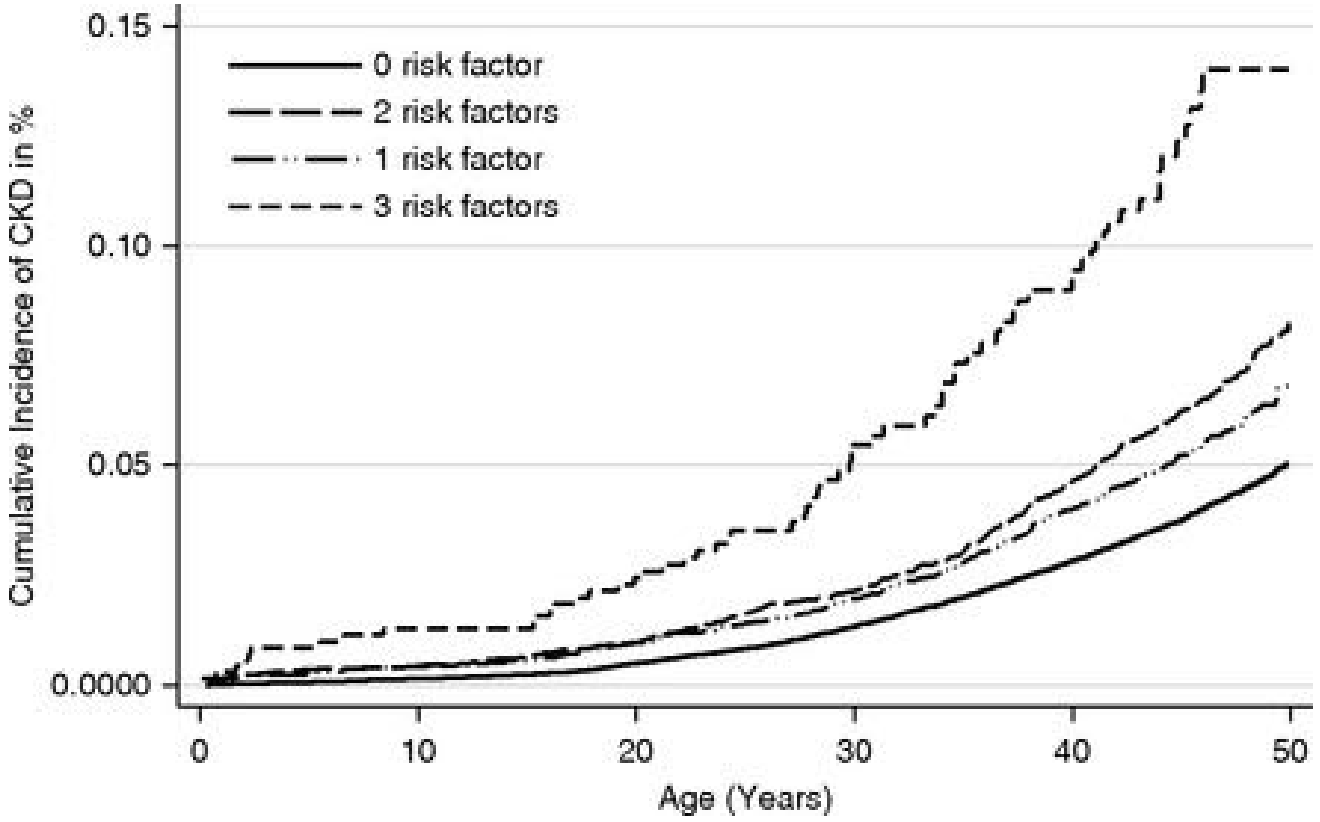
Genome Editing: Confer/Correct CAKUT in Organoids



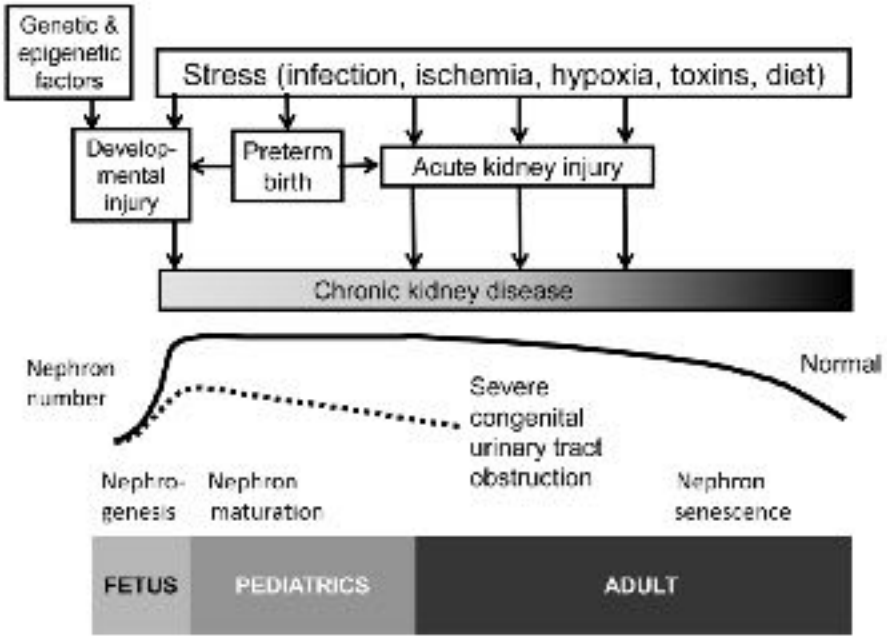


Additive effect of LBW, SGA, prematurity on CKD incidence



Gjerde (2020) *CJASN*

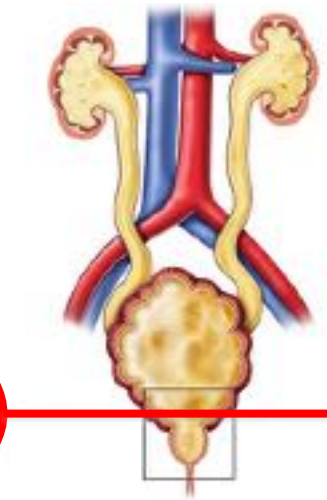
CAKUT Outcomes



Chevalier (2015) *Adv Chronic Kidney Dis*.

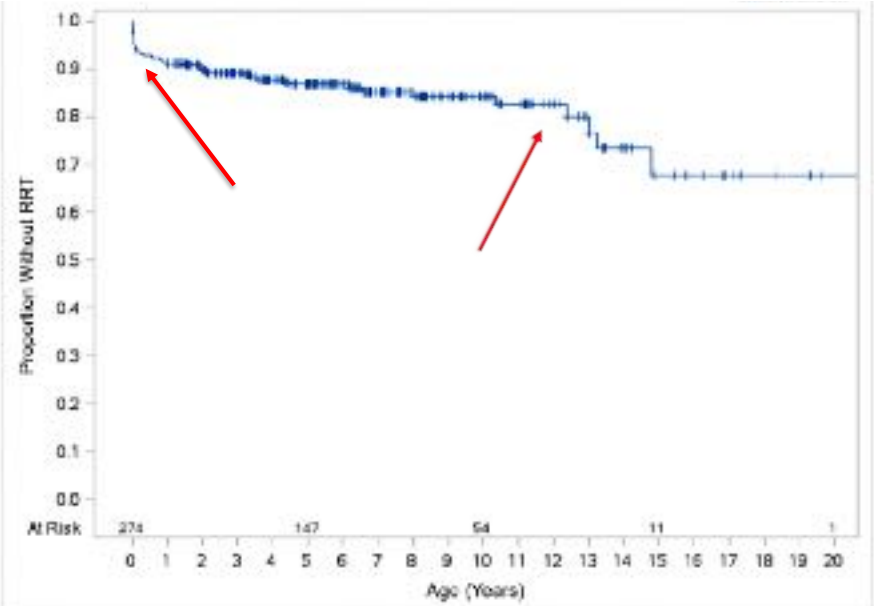
CAKUT Outcomes - PUV

- 1/5000-1/8000 male births
- Partial bladder outlet obstruction
- 15-20% will progress to ESKD during childhood



Who will need renal replacement therapy?

RRT in a Birth Cohort of Boys with PUV



- 273 cases
- 5 institutions
- 1995-2004

McLeod et al (2018) *Pediatrics*

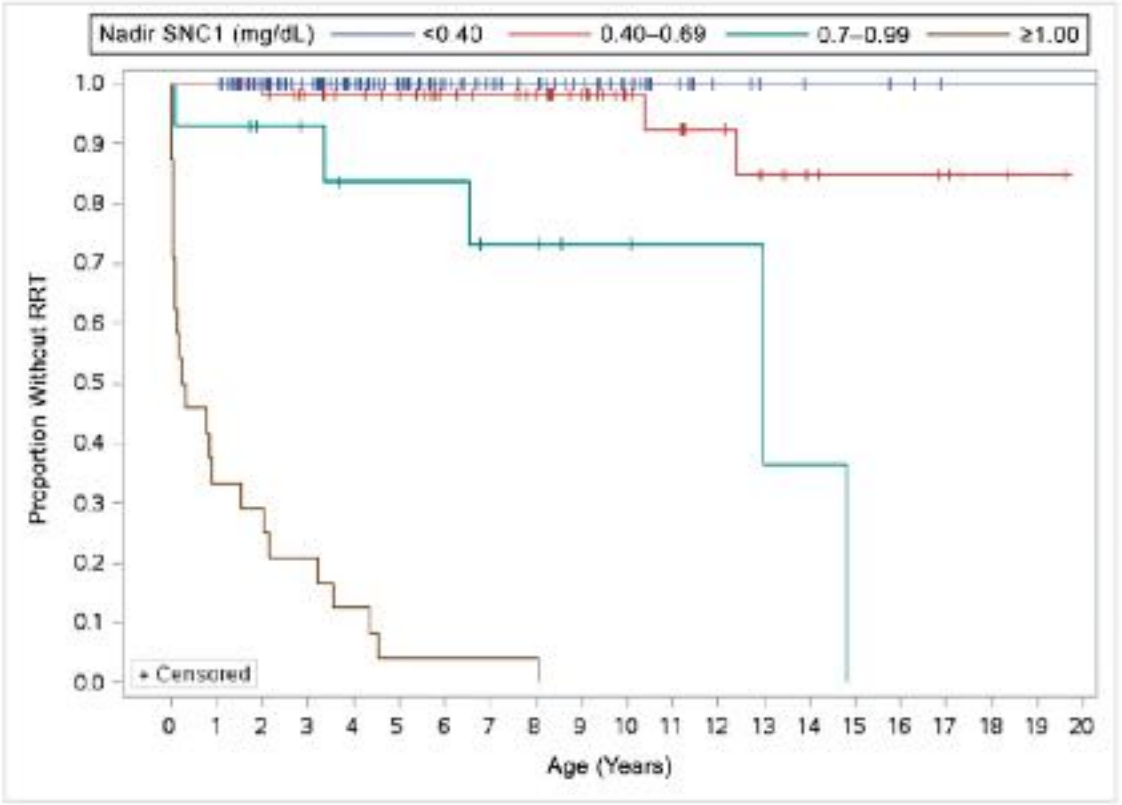
CKD progression continues into adulthood

Predictors of ESKD in Childhood PUV

- Dysplasia
- Prenatal markers
  - echogenic, cystic kidneys; severe oligohydramnios, urine electrolytes?
- Postnatal markers – renal parenchymal size
  - Serum Cr nadir, especially in first yr of life
  - Persistent proteinuria

Serum Nadir Cr during the first year of life (SNC1)

- Retrospective cohort study
- 274 consecutive male infants with confirmed PUV
- Underwent intervention for PUV within 90 days of life
- 15% required RRT



McLeod *et al*. (2019) *Pediatrics*.

Conclusions

- Congenital anomalies remain the major cause of CKD and ESKD in children.
- Increasing evidence CAKUTs have a genetic basis, although combinations of genetic and environmental insults likely account for most CAKUT
- Radiologic features, laboratory markers of renal dysfunction, and urinary markers help predict ESKD.
- **Plenty of work left to do!**

A Highly Recommended Reference

A Primer on Congenital Anomalies of the Kidneys and Urinary Tracts (CAKUT)

Vasikar Murugapoopathy[1] and Indra R. Gupta[1,2]

- *Clin J Am Soc Nephrol*. (2020)15(5):723-731. PMID: 32188635.

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Thanks

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Question #1

- Which of the following mechanisms can cause CAKUT?
  - (A) Genes
  - (B) Environmental exposures
  - (C) Syndromes
  - (D) None of the above
  - (E) A, B, and C

Answer #1

- Which of the following mechanisms can cause CAKUT?

  (A) Genes (*HNF1B*, *PAX2*)

  (B) Environmental exposures (ACEi, maternal DM)

  (C) Syndromes (BOR, renal coloboma)

  (D) None of the above

  (E) A, B, and C

Question #2

- Which of the following best predicts need for renal replacement therapy in boys with PUV?

(A) Echogenic, cystic kidneys with poor corticomedullary differentiation
(B) Serum nadir creatinine of >/= 1.0 mg/dL at one year of life
(C) Oligohydramnios
(D) Prematurity / IUGR
(E) None of the above

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Question #3

- Which of the following CAKUTs can occur in the same patient?

(A) Multicystic dysplastic kidney and UPJ obstruction
(B) Duplex kidney and upper pole ureterocele
(C) Renal dysplasia and high-grade VUR
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