Questions to be addressed

1. Defining and naming the syndrome

Unifying features:
- Autosomal dominant inheritance (or de novo mutation)
- Tubulointerstitial pathology
  (tubular atrophy, interstitial fibrosis, TBM abnormalities (?), absence of gross glomerular pathology)
- Slowly progressive CKD with ESRD usually after 30-40 yrs.
- Small kidney size
- Mild proteinuria at most
- Not regularly hypertensive
- Few if any extrarenal manifestations (cave: HNF1B)

Previous terminology:
- UAKD
- FJHN
- TIN
- MCKD I and II
- (Glomerulocystic kidney disease)

Proposal for new terminology
- Requirements:
  o Simple
  o Applicable prior (w/o) genetic testing
  o With possibility to stratify on the basis of genetic testing
  o With optional extension as additional defects may become identified
  o Not misleading (as MCKD, FJHN,...)

- Options:
  o Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD), Type ..... Advantage: analogous to ADPKD (could also lead to mix-up)

2. Diagnostic criteria and work-up
- Which signs and symptoms should raise the suspicion of the entity:
  Familial CKD with normal or small kidney size (in contrast to ADPKD), no signs of glomerular disease
  or
CKD of unclear origin in a single individual in the absence of signs of glomerular disease

- Which work-up is reasonable in cases with suspected diagnosis?
  e.g. Glucose tolerance test, liver function tests, uric acid (in relation to GFR), uric acid fractional excretion, abdominal ultrasound?

- Which signs and symptoms are needed to make the diagnosis:
  
  Familial CKD with normal/small kidneys (in contrast to ADPKD), no signs of glomerular disease  
  or  
  CKD of unclear origin in a single individual in the absence of signs of glomerular disease  
  and  
  Biopsy in at least one family member with tubulointerstitial pattern  
  (NOTE: genetic testing not required for diagnosis)

3. Do biopsies require special work-up?
   - Staining for UMOD, MUC, TBM aspect and constituents?
   - EM?

4. Is urine analysis helpful to raise the suspicion or to make the diagnosis?
   - UMOD?
   - MUC1?
   - Spot or collection?

5. Who should receive genetic testing?
   - Patients who request certainty about diagnosis, prognosis and possible inheritance
   - Special considerations for minors

6. How should genetic testing be performed?
   - Genetic testing for the underlying disorders can be done sequentially or in parallel  
   - Clinical signs can guide the sequence of testing:  
     hyperuricemia / early gout \( \rightarrow \) UMOD  
     anemia \( \rightarrow \) REN  
     Extrarenal pathology \( \rightarrow \) HNF1B  
     Glomerulocystic disease and proteinuria \( \rightarrow \) UMOD and HNF1B
   - Technical approach:  
     .... (confirmation?)  
   - How is a pathogenic variant defined (i.e. how are irrelevant variants excluded?)

7. What is the optimal management?
   - ACE-I or ARBs in the absence or presence of hypertension
   - Uric acid lowering therapy; if yes, which agent?
   - Diet and lifestyle?
   - Avoidance of nephrotoxic agents

8. What is the optimal follow-up?
   - Which tests should be performed and at which intervals?
     S-crea, eGFR, spot-urine

9. Future research directions?
   - What is the prevalence of the syndrome and of the respective gene defects?
   - What is the link between UMOD hyperuricemia and gout?
   - Is uromodulin involved in non-UMOD disorders?
   - Common pathway HNF1B - UMOD - REN - MUC1?
   - Genotype - phenotype correlations?
   - Value of urinary uromodulin and MUC1?