natera™ | Renasight™ Kidney gene panel

Insights from RenaCARE: Genetics Driving Precision Medicine in Kidney Disease

How Renasight™ comprehensive genetic testing addresses key gaps in the diagnosis of kidney disease to enable tailored treatment and management options

Introduction

Chronic kidney disease (CKD) is the fastest-growing non-communicable disease in the U.S., affecting more than 37 million people (~1 in 7 adults).[1] In addition to the morbidity and mortality of the disease, CKD represents a significant economic burden on the healthcare system, costing more than $85 billion (23.5%) of Medicare spending alone in 2020.[2]

CKD has a vast spectrum of underlying causes, and the current standard of care often relies on basic measurements of kidney function, imaging, and histology to inform diagnosis.[3] This limited approach has left significant gaps in the accuracy, completeness, and specificity of clinical diagnoses largely within five main categories, each with their own challenges:

1. **Non-specific CKD diagnoses**
   Diagnoses based on comorbidities and clinical presentations (e.g., diabetes, hypertension, hematuria, and proteinuric disease suggestive of glomerulopathy) that mask the true cause of a patient's kidney disease prevent tailored treatment based on a more specific and accurate underlying cause.
2. **Defining the subtype of a CKD diagnosis**
   Clinical diagnoses are often comprised of different subtypes, each with a distinct genetic origin. Not knowing the definitive subtype of many diseases prevents specific treatment pathways and obscures prognosis (e.g., *PKD1* vs *PKD2* in cystic nephropathy).
3. **Unknown cause of CKD**
   CKD symptoms are present but lack clinical presentations/features that enable a causative diagnosis, ultimately limiting specific treatment options.
4. **Utilization of targeted therapies**
   Diagnoses based solely on clinical symptoms without detailed genetic information limit opportunities to identify targeted therapies and clinical trial opportunities.
5. **Use of unnecessary and invasive diagnostic biopsies**
   In many cases, genetic testing can clarify a diagnosis and obviate the need for invasive procedures that often still require subsequent clarification.

Genetic testing is an underutilized tool in the evaluation of CKD patients, despite recent studies[4,7] demonstrating meaningful diagnostic and clinical utility for genetic testing in this setting. 1 in 5 patients with CKD has a genetic cause,[4] identification of which can enable physicians to properly diagnose and stratify CKD patients to solve many of the aforementioned limitations of the current standard of care diagnostic techniques. Renasight™ Clinical Application, Review, and Evaluation (RenaCARE) is an ongoing prospective study that was designed to assess the diagnostic and clinical utility of the 385-gene Renasight™ test across 1623 CKD patients enrolled from 31 U.S. community and academic medical institutions. Physicians provided the primary clinical disease characterization in one of thirteen categories prior to genetic testing for each patient. Results from an initial analysis of the study were published in the *Journal of the American Society of Nephrology* in October 2023[5] (these results hereinafter referred to as the "RenaCARE" study). Results showed 20.8% of CKD patients had positive genetic findings, 48.8% of patients with positive results received a new or reclassified diagnosis, and an additional 17.2% received a positive genetic finding that did not explain their reported clinical presentation and therefore remained at-risk for development for features of the genetic condition (hereinafter referred to as an "at risk" diagnosis). Further, 34.0% of patients with positive results received a defined subtype of disease and confirmed the clinical presentation. Providers reported a change in management plan for 90.7% of positive results, including a change in treatment for 32.9% of positive cases.

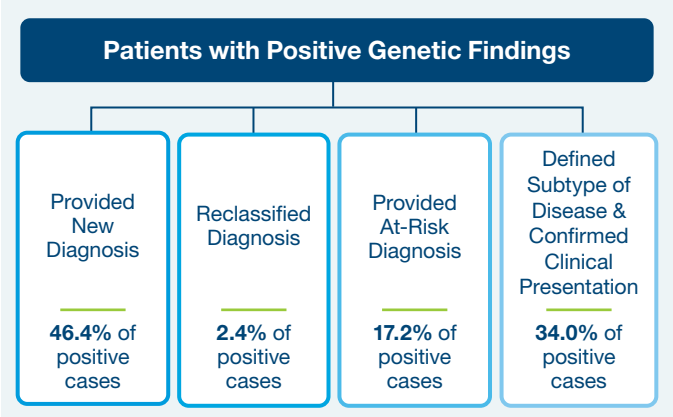

Diagram 1. Cases with positive results in the RenaCARE study were stratified into these categories of impact on the original clinical diagnosis/characterization.

1. Non-Specific CKD Diagnoses

Data from RenaCARE showed that 46.0% of patients enrolled in the study had CKD attributed to nephropathy associated with diabetes or hypertension, hematuria, or proteinuric disease suggestive of a glomerulopathy. These are often non-specific and symptom-based presentations, and, in many cases, are found to be comorbidities and not the main cause of disease. Failing to further investigate the primary cause limits the opportunity for the patient to be appropriately treated. Patients with these clinical presentations comprised 32.5% (n=110) of positive cases identified in this study. When screening positive, 70.0% of these patients (77/110) received a new or reclassified diagnosis:

a) Diabetes

8.7% (18/206) of patients clinically characterized within the *nephropathy associated with diabetes* category received a positive result (i.e., diagnostic yield). Of these, 5.6% defined a subtype of disease and confirmed the clinical presentation, 44.4% received a new or reclassified diagnosis, and 50.0% received an at-risk diagnosis. Further, 25.0% of cases with positive results reported a change in treatment plan related to the test result.

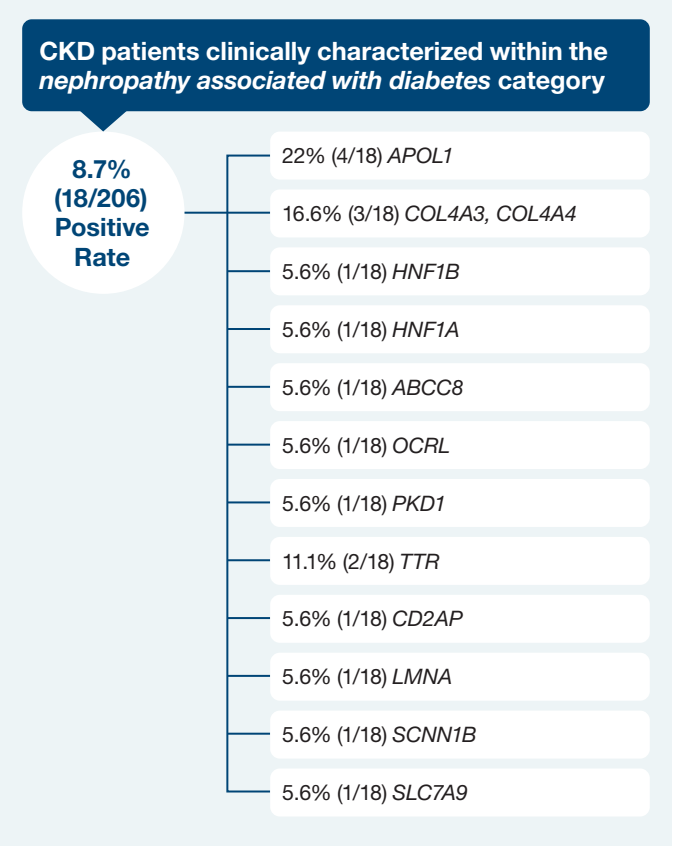

Figure 1a. Breakdown of positive genetic findings from all patients clinically characterized within the *nephropathy associated with diabetes* category from the RenaCARE study.

i) APOL1 (Susceptibility to End-Stage Kidney Disease [ESKD] & Focal Segmental Glomerulosclerosis [FSGS])

22.2% (4/18) of positive cases within the *nephropathy associated with diabetes* category.

Clinical Utility Implications

Multiple targeted therapies for patients with *APOL1* high-risk genotypes are expected to come to market soon. Today, patients are eligible for clinical trials, such as the Vertex Pharmaceuticals phase II/III trial *"VX-147 in Adult and Pediatric Participants With APOL1- Mediated Proteinuric Kidney Disease."* Results of Vertex's phase II trial, recently published in the *New England Journal of Medicine*, demonstrated that treatment with of inaxaplin (VX-147) led to a 48% reduction in proteinuria, stating "targeted inhibition of *APOL1* channel function with inaxaplin reduced proteinuria in participants with two *APOL1* variants and focal segmental glomerulosclerosis."[6]

ii) COL4A3, COL4A4 (Alport Syndrome; Autosomal Dominant [AD] / Autosomal Recessive [AR])

16.6% (3/18) of positive cases within the *nephropathy associated with diabetes* category.

Clinical Utility Implications

- Studies have shown up to 62% of Alport Syndrome patients are misdiagnosed or not diagnosed, thereby limiting the opportunities to leverage the specific management recommendations for Alport Syndrome, which are different than those of a non-specific CKD diagnosis.[7]
- Treating patients with Alport Syndrome with protein in their urine (microalbuminuria) at a very early stage with RAAS blockade (e.g. ACEi/ARB therapies),[8] or with an SGLT2 blocker, has a protective effect, and can slow the decline of eGFR and disease progression.[9] These therapies may not be prescribed for an undiagnosed patient unless the patient has significant levels of protein in their urine, therefore missing the opportunity to treat early and slow disease progression.
- Use of immunosuppressive therapies, which reduce the strength of the immune system, can put patients at risk of serious side effects such as infection, increased risk of malignancy, and developing diabetes. While commonly used for CKD patients with persistent proteinuria without a genetic etiology, immunosuppressive therapy should be avoided in individuals with biopsy-proven FSGS with COL4-related Alport Syndrome as they would be ineffective and potentially harmful.[10]
- Knowing the genetic type of Alport Syndrome can provide further clarity on disease progression and patient prognosis. Risk of progression to ESKD is dependent on the form of Alport Syndrome (AD, AR or XL) and onset of treatment is dependent on the form, patient's sex, and degree of disease progression. For example, guidelines recommend initiation of RAAS blockade at the time of diagnosis in males with X-linked (XL) Alport Syndrome *(COL4A5)* and males and females with autosomal recessive Alport Syndrome *(COL4A3, COL4A4)* given their high risk of progression to kidney failure, whereas those with the dominant form and a lower risk of renal insufficiency should present with microalbuminuria, hypertension or proteinuria before initiating therapies.[11] If genetic testing is not done and the diagnosis is not clinically recognized, irreversible kidney damage may occur.

iii) **Additional genes** of note within the *nephropathy associated with diabetes* category:

- ***HNF1B* (1/18).** Associated with autosomal dominant tubulointerstitial disease, renal cysts, diabetes, electrolyte abnormalities, and genitourinary structural abnormalities, however, the disorder is highly variable and presents differently across patients. Unlike disease types associated with variants in *HNF1A,* insulin therapy is often required for individuals with *HNF1B*-mediated disease.[12] Given the importance of properly diagnosing this condition and the association of hypomagnesemia, even when a patient presents solely with a magnesium deficiency, genetic testing should be considered.[13]
- ***HNF1A* (1/18).** *See clinical utility implications in Section 2.b.iv*

b) Hypertension

There was a 14.2% (37/260) diagnostic yield among patients clinically characterized within the *nephropathy associated with hypertension* category. Of these, 2.7% defined a subtype of disease and confirmed the clinical presentation, 64.9% received a new or reclassified diagnosis, and 32.4% received an at-risk diagnosis. Further, 8.6% of cases with positive results reported a change in treatment plan related to the test result.

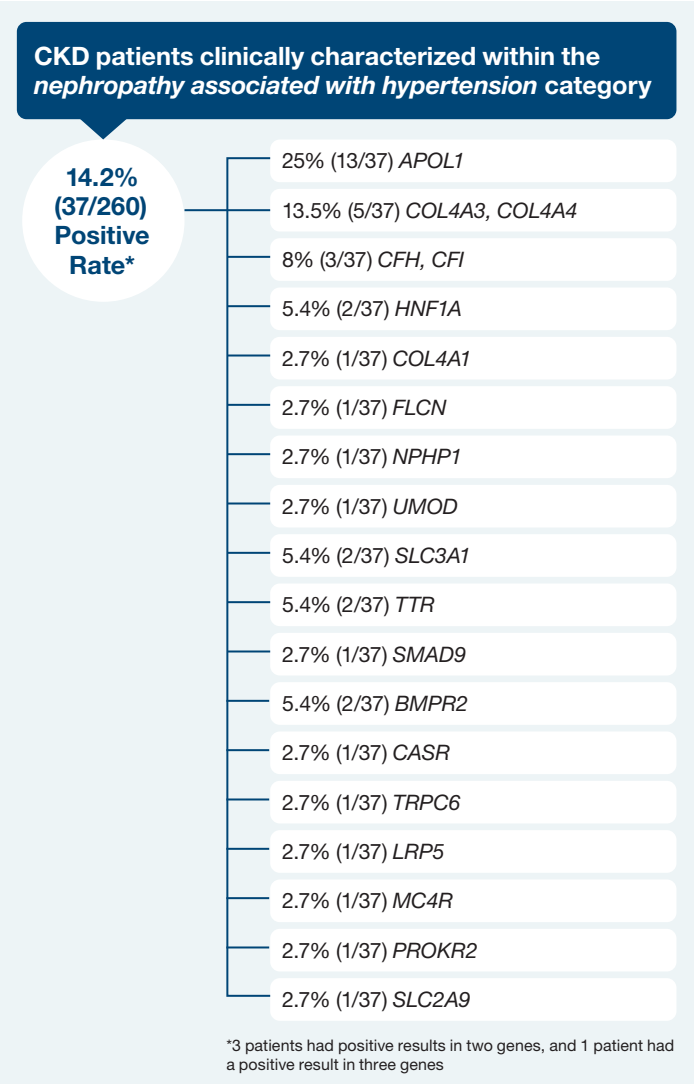

Figure 1b. Breakdown of positive genetic findings from all patients clinically characterized within the *nephropathy associated with hypertension* category from the RenaCARE study.

i) APOL1 (susceptibility to ESKD and FSGS)

35.1% (13/37) of positive cases within the *nephropathy associated with hypertension* category.

Clinical Utility Implications

- Individuals with *APOL1* high-risk genotypes are ~7-10 times more likely to develop hypertension-associated ESKD compared to individuals without *APOL1* high-risk genotypes. Controlling hypertension shows only a modest effect on slowing the development or progression of *APOL1* nephropathy. This suggests that hypertension may be the consequence, rather than the cause, of CKD in individuals with *APOL1* high-risk genotypes.[14]
- *See targeted therapy considerations in Section 1.a.i*

ii) COL4A3, COL4A4 (Alport Syndrome; AD/AR)

13.5% (5/37) of positive cases within the *nephropathy associated with hypertension* category (*COL4A3:* n=2; *COL4A4*: n=3). Reduced penetrance for Complement Factor H Deficiency (AR); Hemolytic Uremic Syndrome, Atypical (aHUS; AD/AR); C3 Glomerulopathy (AD).

Clinical Utility Implications

- *See clinical utility implications in Section 1.a.ii*

iii) CFH, CFI (Complement disorders)

8.1% (3/37) of positive cases within the *nephropathy associated with hypertension* category (*CFH:* n=2; *CFI:* n=1).

Clinical Utility Implications

- The genetic contributions to each of these disorders are important for treatment and understanding the risk for recurrence after transplant. For individuals with *CFH*/*CFI*-related aHUS, the risk of graft failure due to recurrence of disease ranges from 30–100%. Treatment with eculizumab, a drug that inhibits this complement pathway, can improve outcomes for patients and may be used to help maintain kidney function after transplant.[15]

iv) HNF1A (Maturity Onset Diabetes of the Young "MODY")

5.4% (2/37) of positive cases within the *nephropathy associated with hypertension* category. In both cases, the patient's diagnosis was reclassified after genetic testing.

Clinical Utility Implications

- A genetic diagnosis of *HNF1A*-MODY should be managed via prescription of low dose sulfonylureas as a first-line therapy, in contrast to Type 1 Diabetes, which is generally treated with insulin. Sulfonylureas act downstream of the genetic defect to increase insulin secretion via a glucose-independent mechanism. Patients with *HNF1A*-MODY who were previously misdiagnosed with type 1 diabetes and treated with insulin may be able to discontinue insulin therapy and start treatment with sulfonylureas without the risk of ketoacidosis. Individuals may have an increased risk to develop certain types of tumors or cancer affecting the kidney (renal cell carcinoma), liver (hepatic adenomas or hepatic carcinoma), and possibly the pancreas.[16]

v) **Additional genes** of note within the nephropathy associated with hypertension category:

- ***COL4A1* (1/37) *(Hereditary Angiopathy with Nephropathy, Aneurysms And Muscle Cramps [HANAC]; AD).*** Characterized by thin or damaged blood vessels in the kidneys and kidney cysts that can result in bilateral retinal arteriolar tortuosity with transient visual loss after retinal hemorrhage, often with a favorable visual prognosis. Most individuals with HANAC will have muscle cramps. Cardiac symptoms, including irregular heartbeat (arrhythmia), have also been reported.
  - Without a genetic diagnosis of HANAC, referral to cardiology may not occur until an episode of arrhythmia occurs, which has been associated with sudden death.
  - Patients with HANAC should avoid anticoagulant use and minimize high-risk behaviors associated with hypertension, stroke, and head trauma/ pressure.[17]
- ***FLCN* (1/37) *(Birt-Hogg-Dube Syndrome; AD).*** Individuals with Birt-Hogg-Dube (BHD) syndrome have a fifty-fold greater risk of developing spontaneous pneumothorax and a seven-fold increased risk for developing renal tumors that can be cancerous. Once diagnosed, an active surveillance program may be initiated based on the individualized presentation. While ablation therapy is often utilized for treating small renal tumors, due to the rate of recurrence in BHD, ablation is generally not recommended.[18,19]
- ***NPHP1* (1/37) *(Nephronophthisis; AR).*** Individuals with this disease can have inflammation and scarring of the kidneys and cyst formation in the medulla of the kidney. Presentation of the disease can be highly variable, can affect multiple organ systems, and often leads to ESKD in the first two decades of life. Nephronophthisis does not recur in a transplanted kidney.[20]
- ***UMOD* (1/37).** *See clinical utility implications in Section 3.c*

c) Hematuria

There was a 33.3% (15/45) diagnostic yield among patients clinically characterized within the *hematuria* category. Of these, 100.0% received a new diagnosis. Further, 60.0% of cases with positive results reported a change in treatment plan related to the test result.

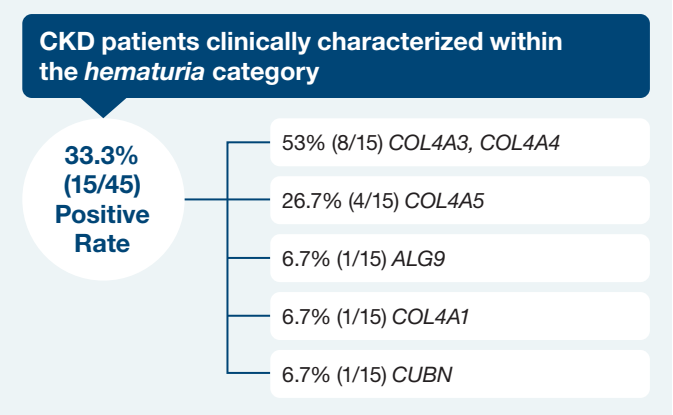

Figure 1c. Breakdown of positive genetic findings from all patients clinically characterized within the *hematuria* category from the RenaCARE study.

i) ***COL4A3, COL4A4 (Alport Syndrome; AD/AR)***
53% (8/15) of positive cases within the *hematuria* category.

COL4A5 (Alport Syndrome; XL)
26.7% (4/15) of positive cases within the *hematuria* category.

Clinical Utility Implications

- *See clinical utility implications in Section 1.a.ii*

ii) **Additional genes** of note within the *hematuria* category:

- ***ALG9* (1/15) *(Polycystic Kidney and Liver Disease; AD).*** PKD associated with variants in this gene is typically mild-to-moderate with evidence of reduced penetrance, liver cysts, and discordance of kidney size with function. Tolvaptan is not recommended for treatment as it would be with more progressive forms associated with *PKD1.*[21]
- ***COL4A1* (1/15).** *See clinical utility implications in Section 1.b.v*
- ***CUBN* (1/15) *(Proteinuria, chronic benign; AR).*** Individuals may have a favorable prognosis of no risk for reduced kidney function.[22] Patients often go through diagnostic workup including biopsy that would have been unnecessary if initial genetic testing had been performed.

d) Proteinuric disease suggestive of a primary glomerulopathy (proteinuric glomerulopathy)

There was a 16.9% (40/236) diagnostic yield among patients clinically characterized within the *proteinuric glomerulopathy* category. Of these, 2.5% defined a subtype of disease and confirmed the clinical presentation, 75.0% received a new diagnosis, and 22.5% received an at-risk diagnosis. Further, 19.4% of cases with positive results reported a change in treatment plan related to the test result.

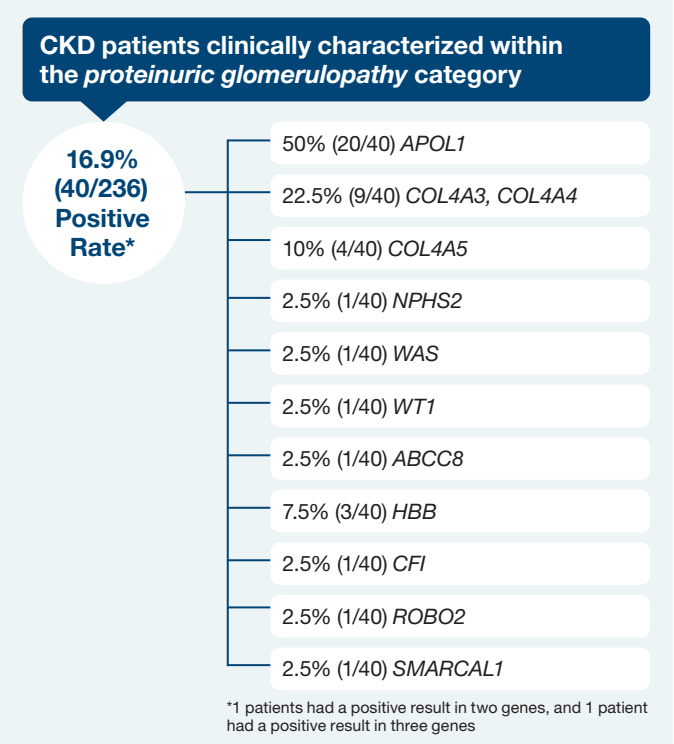

Figure 1d. Breakdown of positive genetic findings from all patients clinically characterized within the *proteinuric glomerulopathy* category from the RenaCARE study.

i) APOL1 (susceptibility to ESKD and FSGS)

50.0% (20/40) of positive cases in the *proteinuric glomerulopathy* category.

Clinical Utility Implications

- *See targeted therapy considerations in Section 1.a.i*

ii) COL4A3, COL4A4 (Alport Syndrome; AD/AR)

22.5% (9/40) of positive cases in the *proteinuric glomerulopathy* category (*COL4A3:* n=2; *COL4A4:* n=6, *COL4A3+COL4A4:* n=1).

COL4A5 (Alport Syndrome; XL)

10% (4/40) of positive cases in the *proteinuric glomerulopathy* category.

Clinical Utility Implications

- *See clinical utility implications in Section 1.a.ii*

iii) Additional genes of note within the *proteinuric glomerulopathy* category:

- ***NPHS2* (1/40) *(Nephrotic Syndrome type 2; AR).*** Characterized by severe and rapidly progressive that typically progresses to ESKD early in life. Focal segmental glomerulosclerosis (FSGS) and steroid resistant nephrotic syndrome (SRNS) can vary significantly.[23]
- ***WAS* (1/40) *(Wiskott-Aldrich syndrome Immune deficiency; XL).*** Characterized by eczema and a poor ability to clot blood properly. Some individuals have renal findings including inflammation of the kidneys (nephritis), renal insufficiency and ESKD.[24]
- ***WT1* (1/40) *(Progressive SRNS/FSGS +/- sexual differentiation disorder; AD).***[25]

2. Defining the Subtype of a CKD Diagnosis

Subtyping a CKD diagnosis through diagnostic genetic testing can provide information on targeted treatment pathways, important information on disease progression, and the need to monitor for extrarenal features. In cystic disease, genetic testing can help distinguish between typical autosomal dominant polycystic kidney disease (ADPKD) and atypical ADPKD. In addition, testing can definitively subtype typical ADPKD, determining if the patient has *PKD1* or *PKD2*, which provides information about treatment pathways and disease progression.

Variants in PKD1 and PKD2 comprise the majority of positive findings among cystic disease cases, however, they do not account for more atypical/mild forms that may be indistinguishable on imaging (ultrasound, CT, MRI) and carry very different prognoses and extrarenal disease burden if not recognized. Atypical forms may be more common than previously published; in fact, experience from Renasight™ commercial testing has shown a diverse genetic spectrum that underlies autosomal dominant cystic disease, and more than 25% of genetic diagnoses encompass non-classical cystic disease *(IFT140, HNF1B, UMOD, ALG9, GANAB, SEC63, PRKCSH).*[26]

a) Cystic Nephropathy

The RenaCARE study showed substantial utility in diagnosing and managing patients presenting with cystic nephropathy. There was a 49.6% (130/262) diagnostic yield among patients clinically characterized within the *cystic nephropathy* category. Of these, 79.2% defined a subtype of disease and confirmed the clinical presentation, 15.4% received a new or reclassified diagnosis, and 5.4% received an at-risk diagnosis. Further, 49.2% of cases with positive results reported a change in treatment plan related to the test result.

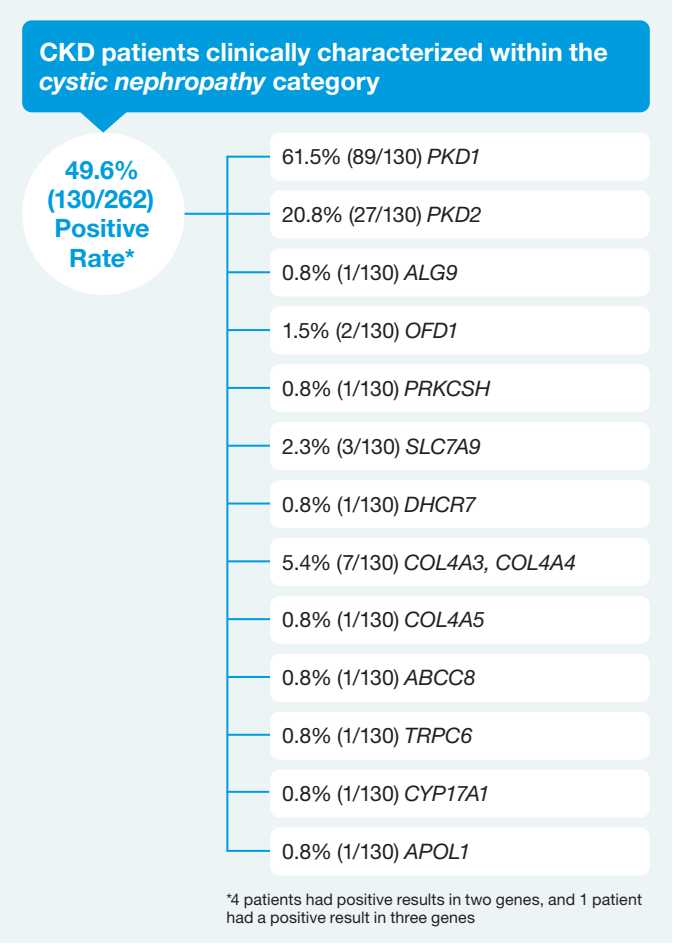

Figure 2. Breakdown of positive genetic findings from all patients clinically characterized within the *cystic nephropathy* category from the RenaCARE study.

i) PKD1, PKD2 (ADPKD)

89.2% (116/130) of cases with a positive result in the *cystic nephropathy* category received a molecular diagnosis with a *PKD1* (76.7%, 89/116) or *PKD2* (23.3%, 27/116) variant.

Clinical Utility Implications

- Prognosis of progression to ESKD is gene/variant dependent, with common variants including *PKD1* truncating, *PKD1* non-truncating and *PKD2* variants.[27]
  - *PKD1* truncating variants (complete loss of function of one copy of the *PKD1* gene): these patients progress to kidney failure, on average, in their 50s.

  - *PKD1* non-truncating variants (potential for partial residual function of *PKD1* protein): the average age of onset of kidney failure for these patients is in their 60s.
  - *PKD2* variants (any type of variant in the *PKD2* gene): these patients typically exhibit kidney survival until approximately 80 years of age.
- This genetic delineation provides prognostic information that has significant implications for patient management, including determinations for use of tolvaptan, the only FDA-approved drug for the treatment of ADPKD.[28] The greatest effect of treatment with tolvaptan is in individuals with rapidly progressing disease, which involves a risk assessment (PROPKD score) and ideally integrates the patient's specific gene and variant type.[29]
- Without genetic data, risk assessment relies on family history data which is unreliable given intrafamilial variability.

ii) Additional genes of note within the *cystic nephropathy* category:

Atypical forms of polycystic kidney disease (PKD) made up 3.1% (4/130) of the positive cases within the *cystic nephropathy* category, but of note, other data sets have shown a higher proportion of atypical forms of PKD.[26] Positive gene findings allow for better interpretation of imaging results as these forms of disease cannot be differentiated by imaging alone.

- ***ALG9* (1/130).** These patients have a less severe form of disease than predicted for *PKD1* or *PKD2,* and rapid progression is not predicted for patients with variants in this gene. As such, tolvaptan would not be recommended.[21]
- ***OFD1* (2/130).** 15%–50% cases progress to ESKD following development of polycystic kidney disease. Variability in presentation of extrarenal features affecting the face/mouth, digits, and brain, which, when mild, may not warrant referrals to subspecialties without genetic confirmation.[30]
- ***PRKCSH* (1/130) *(AD Polycystic Liver Disease; ADPLD).*** Liver cysts can be present in ADPKD and can be indistinguishable from those associated with ADPLD. However, the small numbers of renal cysts associated with ADPLD do not typically lead to renal expansion, increased total kidney volume, or kidney dysfunction. Therefore, appropriate therapy depends on distinguishing between ADPKD and ADPLD, which, in ADPLD, is reserved for symptomatic patients due to the increasing size of liver cysts.[31]

iii) Positive cases identified with cystic gene without original characterization of cystic nephropathy

7.2% (15/208) of positive cases within the RenaCARE study were not enrolled with a clinical disease category of cystic disease, yet were then diagnosed during the study as having a genetic finding associated with cystic disease. Across a diverse spectrum of clinical presentations, these cases underscore the heterogeneity of kidney disease and how patients can easily be misclassified—further emphasizing the need for genetic testing in specifying the diagnosis.

3. Unknown Cause of CKD

Up to 15% of CKD patients are not clinically diagnosed with a cause for their disease.[32] Without a specific diagnosis, patients may not receive the appropriate tailored treatments and post-transplant management considerations. Often, the only option for patients with an unknown cause is managing the symptoms of their condition as disease worsens. In the RenaCARE study, 8.1% of patients were clinically characterized with CKD of unknown etiology. There was a 18.2% (24/132) diagnostic yield among patients in this category. Of these, 87.5% received a new diagnosis, accounting for 15.9% of all unknown etiology cases. Additionally, 12.5% of cases with positive results received an at-risk diagnosis.

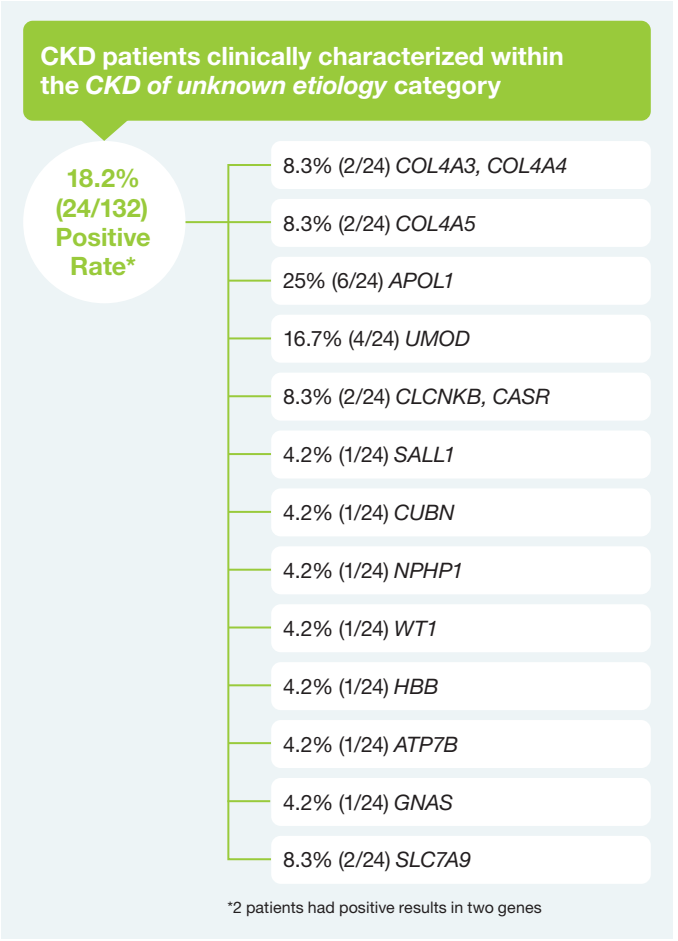

Figure 3. Breakdown of positive genetic findings from all patients clinically characterized within the *CKD of unknown etiology* category from the RenaCARE study.

These new diagnoses include:

a) *COL4A3, COL4A4 (Alport Syndrome; AD/AR)*

8.3% (2/24) of cases with a positive result within the *unknown cause* category.

COL4A5 (Alport Syndrome; XL)

8.3% (2/24) of cases with a positive result within the *unknown cause* category.

Clinical Utility Implications

- *See clinical utility implications in Section 1.a.ii*

b) *APOL1 (susceptibility to ESKD and FSGS)*

25% (6/24) of cases with a positive result within the *unknown cause* category.

- *See targeted therapy considerations in Section 1.a.i*

c) *UMOD (Autosomal dominant tubulointerstitial kidney disease; ADTKD)*

16.7% (4/24) of cases with a positive result within the unknown cause category.

Clinical Utility Implications

The prognosis of *UMOD*-related ADTKD typically includes slow, progressive renal disease with the risk of hyperuricemia and gout, a phenotype that is not specific to a single underlying etiology. An estimated 25% of patients have kidney cysts. In addition, pathological findings in ADTKD are often non-specific, limiting the diagnostic utility of biopsy. For these reasons, ADTKD is difficult to diagnose without genetic testing. Once *UMOD*-related disease is identified, ESKD is inevitable and has no specific renal treatments but knowing the risk for gout, initiation of allopurinol, a urate-lowering therapy, and a low purine diet can prevent gout attacks and should be continued through life.[33]

d) *CLCNKB (Bartter syndrome type 3), CASR (Familial Hypocalciuric Hypercalcemia type 1)*

8% (2/24) of cases with a positive result within the *unknown cause* category *(CLCNKB: n=1; CASR: n=1)*.

Clinical Utility Implications

Diseases associated with variants in either *CLCNKB* or *CASR* are electrolyte disorders, which can be difficult to characterize on clinical features alone. An accurate diagnosis of an electrolyte disorder helps guide the physician to use specific therapies indicated in each of these diseases to not only restore the electrolyte imbalance but also avoid further events.

- ***CLCNKB*** Bartter syndrome type 3 is characterized by salt wasting with potassium and calcium imbalances and can be difficult to distinguish clinically from Gitelman syndrome. Genetic testing is recommended to confirm disease type and determine effective therapies. Patients with Bartter syndrome may have growth retardation that can improve with treatment and renal insufficiencies that require sodium and potassium supplementation, while patients with Gitelman syndrome are managed by using potassium sparing diuretics, often at higher than normal doses.[34]
- ***CASR*** Familial Hypocalciuric Hypercalcemia type 1 causes high calcium levels that can lead to kidney stones.[35] Familial hypocalciuric hypercalcemia (FHH) and another condition, primary hyperparathyroidism (PHPT), have overlapping clinical and biochemical findings but differentiation is critical due to significantly different treatment approaches.[36]

e) Additional genes of note within the *CKD of unknown cause* category:

16.7% (4/24) the of positive results within the *CKD of unknown cause* category had individual gene findings, each with their own prognosis and management path that is highly targeted compared to the "unknown" status before genetic testing:

- ***SALL1* (1/24) *(Townes-Brock syndrome; AD).*** A multisystem developmental syndrome classically characterized by anal, hand, and ear anomalies that can be highly variable. Functional and structural renal findings with renal cysts can lead to ESKD.[37]
- ***CUBN* (1/24).** *See clinical utility implications in Section 1.c.ii*
- ***NPHP1* (1/24) *(Nephronophthisis; AR).*** *See clinical utility implications in Section 1.b.v*
- ***WT1* (1/24) *(AD progressive SRNS/FSGS +/- sexual differentiation disorder).*** Renal manifestations can be variable and include persistent proteinuria and SRNS that would not respond to steroid therapies. SNRS is irreversible and progressively leads to ESKD. FSGS is a common histologic finding but does not correlate with clinical findings and can be highly variable, so it is no longer considered a first-tier diagnostic measure.[38] Genotype-phenotype correlations are well described, further lending to the utility of genetic testing and the corresponding anticipated progression of the glomerulopathy and expected sexual variations.

4. Utilization of Targeted Therapies

The evolution and adoption of genetic testing has enabled the design of new drugs and therapies targeting specific genetic conditions. The use of these personalized approaches has transformed care in many specialties, and nephrology is no exception. Currently, there are already 24 therapeutics available for conditions identified by Renasight™ testing. In the RenaCARE study, 120 patients with positive results (35.5% of positive results, and 7.4% of all patients enrolled) received a diagnosis that could make them eligible for currently available therapeutics (listed in Table 1).

In addition, there is a continuously expanding pipeline of development of novel therapeutics that target kidney and rare diseases that previously had no therapy. There are currently 271 drugs in Phase I-III clinical trials for clinical areas addressed by Renasight™ testing (listed in Table 2). Natera has ongoing efforts to connect patients and their providers with clinical trial sites for eligibility screening.

Genetic testing is the key prerequisite to identifying potential personalized therapies, and when patients are not provided with comprehensive genetic testing, many will miss out on the opportunities for novel treatments and potential clinical trials.

Table 1: Therapies Currently Available

Gene	Condition	# of Therapies Available	Generic Name	Therapy — Manufacturer
PKD1	Polycystic Kidney Disease	1	Tolvaptan	Jynarqu™ — Otsuka
GLA	Fabry Disease	4	Enzyme Replacement Therapy Chaperone Therapy	Elfabrio™ — Chiesi Fabrazyme™ — Sanofi Genzyme Replagal™ — Takeda Galafold™ — Amicus
JAG1, NOTCH2	Alagille Syndrome	2	Odevixibat Maralixibat chloride	Bylvay™ — Albiero Livmarli™ — Mirum
TTR	Hereditary Amyloidosis	4	Vutrisiran Patisiran Inotersen Tafamidis meglumine	Amvuttra™ — Alnylam Onpattro™ — Alnylam Tegsedi™ — Akcea Vyndaqel™ — Pfizer
ARL6, BBS1, BBS10, BBS12, BBS2, BBS4,BBS5, BBS7, BBS9, C8orf37, LZTFL1, MKKS, SDCCAG8, TTC8, WDPCP	Bardet-Biedl syndrome	1	Setmelanotide	Imcivree™ — Rhythm Pharmaceuticals
CTNS	Cystinosis	2	Cysteamine bitartrate	Procysbi™ — Horizon Therapeutics Cystagon™ — Mylan Pharmaceuticals Inc.
SLC3A1, SLC7A9	Cystinuria	1	Tiopronin	Thiola™ — Travere
MEFV	Familial Mediterranean Fever	2	Anakinra Colchicine	Kineret™ — Sobi Colcrys™ — Takeda
C3, CFH, CFHR5, CFI, DGKE, THBD	Atypical Hemolytic Uremic Syndrome (aHUS)	3	Avacopan Eculizumab Ravulizumab	Tavneos™ — Amgen Solaris™ — AstraZeneca Ultomiris™ — AstraZeneca
AGXT	Primary hyperoxaluria, Type 1	1	Lumasiran	Oxlumo™ — Alnylam
ALPL	Hypophosphatasia	1	Asfotase alfa	Strensiq™ — AstraZeneca
DLC1, LAMB2, MAGI2, PLCE1, PTPRO, TNS2	Nephrotic Syndrome	1	Ciclosporin	Neoral™ — Novartis
KRAS, PTPN11	Noonan Syndrome	1	Somatropin	Norditropin™ — Novo Nordisk

Table 2: Global Clinical Trials for Renal Disease

Conditions	Trial Phase	# of Trials
Alport Syndrome Atypical Hemolytic Uremic Syndrome C3 Glomerulopathy Cystinuria Fabry Disease Alagille Syndrome Cystinosis Polycystic Kidney Disease Renal Disease	Phase I	55
	Phase I/II	14
	Phase II	92
	Phase II/III	17
	Phase III	92

5. Use of Unnecessary and Invasive Diagnostic Biopsies

During the initial evaluation of CKD, many patients, especially those with suspicion of glomerular disease with proteinuria, will require a biopsy to gain insight into a diagnosis. In addition to the psychological and economic burden of diagnostic biopsies, the invasive nature of kidney biopsy carries the risk of many complications. One study of 345 patients assessed the inherent risk of kidney biopsy, finding that 6% of patients developed a complication.[39] Further, progressive kidney disease may result in small fibrotic kidneys where biopsy is not an option, leaving only clinical determinants to elucidate a cause in the absence of genetic testing.

In the RenaCARE study, 19.4% (38/196) of patients with a biopsy prior to genetic testing had a positive genetic finding. Of the positive cases, 71.1% (27/38) received a new diagnosis based on findings from the Renasight™ test, suggesting that diagnostic biopsies for some of these patients may have been avoided if they had received the Renasight™ test first. In fact, providers reported that positive results from Renasight™ testing allowed avoidance of biopsy for 10 patients in the study.

Application to End Stage Kidney Disease (ESKD)

The diagnostic yield among the ESKD cohort was 14.7% (28/190). Of these, 60.7% received a new diagnosis and 28.6% received an at-risk diagnosis.

Roughly 808,000 individuals in the US have ESKD.[40] Many of these patients have the same issues described above with unknown or nonspecific diagnoses, but are in late stages of disease necessitating dialysis or transplant. The utility of a genetic diagnosis gains even more importance when post-transplant prognosis and recurrence risks are in question. In these patients, treatment protocols differ, especially for those who are at high risk for recurrence and premature graft loss as compared to patients at low risk for recurrence. These recurrence risks are often based on understanding the mechanism of disease, which may best be recognized through genetic testing. Patients at low risk can avoid unnecessary preconditioning therapies and would not be expected to benefit from prophylactic or therapeutic plasmapheresis following a kidney transplant.

One example is primary FSGS, which is associated with a high risk of recurrence in a graft after kidney transplantation, reaching 30% after a first transplant and 80–100% after a second kidney transplant.[41] In contrast, the recurrence of genetic FSGS is rare.[42] Exceptions to this rule have been documented in specific forms of genetic FSGS that can often only be revealed through a molecular result.

Another example is Atypical Hemolytic Uremic Syndrome (aHUS), which has a high risk of recurrence after transplant, and if not treated properly, will cause graft failure and a return to dialysis.[43] With an accurate diagnosis prior to transplant, the physician can monitor for recurrence and treat with a targeted therapy (eculizumab) which has a high success rate.[44] Also, in many cases, it provides valuable information in personalizing the immunosuppression in post-transplant care.

Example genes

- **Complement disorders: *CFH, CFI (aHUS, Complement Factor H/Factor I Deficiency, and C3 Glomerulopathy).*** Genetic knowledge of this class of disorders is important for the treatment and assessment of recurrence risk after transplant. The risk of graft failure due to recurrence of disease stemming from complement disorders ranges from 30-100%. Molecular genetic testing can help to define graft prognosis; thus, all affected individuals should undergo such testing prior to transplantation.[45] Prophylactic treatment with eculizumab, a drug that inhibits this complement pathway, can improve outcomes for patients and may be used to help maintain kidney function after transplant.
- **Genetic FSGS and SRNS: *NPHS2* and *WT1* *(Nephrotic Syndrome type 2; progressive SRNS/ FSGS +/- sexual differentiation disorder).*** The timing of disease recurrence following kidney transplant can vary dramatically in patients with monogenic forms of SRNS/FSGS. Normally, recurrence in patients with non-monogenic forms of SRNS/FSGSR occurs early on, whereas patients with monogenic forms have been found to experience recurrence much later than would be expected. In these cases, patients responded quickly to plasmapheresis and/or immunosuppression and had good graft function. This evidence suggests that in cases of monogenic SRNS/FSGS, recurrence is a different entity to that of other forms of SRNS/FSGS, with a potentially better clinical course and outcome. By identifying genetic etiologies of SRNS/FSGS and discerning their clinical course following transplant, patients may benefit from better graft outcomes.[46]
- ***HNF1B (MODY).*** To minimize the risk for new-onset diabetes after kidney transplantation (NODAT), minimizing immunosuppressive therapies that are associated with hyperglycemia, specifically calcineurin inhibitors (CNIs) and corticosteroids, should be considered in patients with *HNF1B*-associated disease.[47]

Given that 14.7% of ESKD cases had positive genetic findings, genetic testing in the transplant setting is uniquely important when a donor candidate is related to the recipient. A definitive genetic test to screen biological donors will identify those who may be asymptomatic carriers due to their younger age and/or variability in presentation. Donation from an individual with an underlying risk of genetic kidney disease (regardless of their presentation) could place the recipient at risk for adverse long-term renal problems and jeopardize the outcome of the transplanted kidney.

Conclusions

Addressing the prominent and growing epidemic of CKD starts with improving diagnostic tools and enabling personalized insight into the cause of disease for individual patients. Comprehensive genetic testing with the Renasight™ test provides critical clarity for the nephrology field, which until now, has been burdened by traditional narrow diagnostic techniques. Improving the accuracy of CKD diagnosis augments providers' ability to inform and guide treatment and management decisions that can help improve patient outcomes.

The 20.8% diagnostic yield for kidney genetics in RenaCARE exceeds clinical precedents for implementation of routine testing within an at-risk population. For comparison, studies of hereditary cancer testing in breast cancer patients have shown a 6%[48] positive rate for the *BRCA1* and *BRCA2* genes and a 8.65%[49] positive rate for a multi-cancer genetic panel. Other studies of patients diagnosed with a variety of cancers have reported 13.3%[50] and 16.7%[51] positive rates with a broad panel of cancer predisposition genes. These cohorts, with a diagnostic yield of between 6.0% and 16.7% have received Medicare or commercial insurance coverage in most cases. In a separate study of routine screening of unaffected women in community obstetrics and gynecology practices that meet the National Comprehensive Cancer Network (NCCN) criteria for being "high-risk", 5.5%[52] of women tested positive for genes associated with hereditary cancer. Based on their personal and family history, these patients are generally covered by commercial insurance companies. Finally, 16.1%[53] of adults 50 years or older screen positive with Cologuard™, the FDA approved, stool-based DNA test for colorectal cancer screening.

Furthermore, the RenaCARE study highlights how improved diagnosies from the Renasight™ test can drive changes in patient care. By improving the accuracy of and correcting diagnoses, patients with positive genetic results received defined subtype of disease and confirmed the clinical presentation in 34.0% of cases, while 48.8% received a new or reclassified diagnosis, and 17.2% received an at-risk diagnosis. More importantly, results from Renasight™ testing drove tangible adjustments to the treatment of disease in 32.9% of patients with positive results. Given the clear, demonstrated utility of genetic testing in nephrology, this study adds to the literature supporting the incorporation of comprehensive genetic testing into the standard care for kidney patients.

		Positive Cases			
		Impact on kidney disease diagnosis			
Clinical disease category	Diagnostic Yield %, N	Defined subtype of disease & confirmed presentation, %	Provided new or reclassified diagnosis, %	At-risk diagnosis, %	Positives leading to change in treatment %, N*
All categories	20.8% (338/1623)	34.0%	48.8%	17.2%	32.9% (103/313)
Nephropathy associated with diabetes mellitus	8.7% (18/206)	5.6%	44.4%	50.0%	25.0% (4/16)
Nephropathy associated with hypertension	14.2% (37/260)	2.7%	64.9%	32.4%	8.6% (3/25)
Hematuria	33.3% (15/45)	0.0%	100.0%	0.0%	60.0% (9/15)
Proteinuric disease suggestive of a primary glomerulopathy	16.9% (40/236)	2.5%	75.0%	22.5%	19.4% (7/36)
Cystic nephropathy	49.6% (130/262)	79.2%	15.4%	5.4%	49.2% (63/128)
CKD of unknown etiology	18.2% (24/132)	0.0%	87.5%	12.5%	23.8% (5/21)
ESKD	14.7% (28/190)	10.7%	60.7%	28.6%	11.1% (3/27)
Other	*15.8% (46/292)*	*13.0%*	*65.2%*	*21.7%*	*40.9% (9/22)*

Non-Specific CKD Diagnoses Defining the Subtype of a CKD Diagnosis Unknown Cause of CKD

*Only includes cases when treatment question was answered

Table 3. Positive genetic findings, diagnostic yield, diagnostic utility implications, and clinical utility implications according to clinical characterization in the RenaCARE study.

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