MCKD has an autosomal dominant pattern of inheritance, and the median age of onset of renal disease is 28.5 years. Nephronophthisis is more common than MCKD and is the most common cause of ESRD in first 3 decades of life.

Several genes are associated with the nephronophthisis and MCKD phenotypes. Mutations in at least two genes *(MUC1, Uromodulin)* can lead to MCKD. Nephronophthisis is caused by mutations in at least 18 genes: *NPHP1, NPHP2* (now called *INVS*), *NPHP3, NPHP4, NPHP5* (now *IQCB1*), *NPHP6* (now *CEP290*), *NPHP7* (now *GLIS2*), *NPHP8* (now *RPGRIP1L*), *NPHP9* (now *NEK8*), *NPHP10* (now *SDCCAG8*), *NPHP11* (now *TMEM67*), *NPHP12* (now *TTC21B*), *NPHP13* (now *WDR1*), and *NPHP14-18*. Functional defects of any of the proteins associated with these genes can lead to ciliary dysfunction and development of multiple cysts.

The three clinical forms of nephronophthisis are based on the onset of ESRD: an infantile form with a median onset at 1 year of age, a juvenile form with a median onset at 13 years of age, and an adolescent form with a median onset at 19 years of age. In patients with MCKD, ESRD develops between the ages of 50 and 70 years.

The diagnosis of nephronophthisis or MCKD is based mainly on clinical features. Medullary cysts, a low urinary specific gravity, and absence of significant proteinuria may suggest either disease. Genetic testing is available for several gene mutations and can be applied based on the age at presentation. Siblings can be screened by renal ultrasound and urine concentration test results. Renal biopsy is usually not indicated because the findings of interstitial fibrosis and tubular atrophy are nonspecific.

No specific treatment is available for nephronophthisis or MCKD, and treatment is mainly supportive. Sodium supplementation for salt wasting, allopurinol for gout, and dialysis or renal transplantation for ESRD are part of supportive care. The time of onset of ESRD varies between 30 and 60 years, depending on the type of mutation. Nephronophthisis or MCKD does not recur after renal transplantation.

## MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK), also known as Lenarduzzi-Cacchi-Ricci disease, is a relatively uncommon congenital disorder. It usually occurs sporadically, but familial cases have been reported. MSK is characterized by ectasia and cystic dilation of medullary and papillary collecting ducts, resulting in a spongy appearance of the kidney on imaging. MSK is associated with urinary acidification and concentration defects, a high risk of nephrocalcinosis and renal stones, and a moderate risk of urinary infections and renal failure. The prevalence of MSK is 1 case in 5000 persons in the general population, and 15% to 20% of patients with nephrolithiasis have MSK.

No clear genetic basis for MSK has been established. MSK is usually detected between the ages of 30 and 50 years. Most patients with MSK are asymptomatic and may have incidental finding on imaging. The clinical course is benign and is not associated with ESRD.

When suspected, CT urography has replaced intravenous urography as the imaging study of choice for the diagnosis of MSK. There is retention of contrast media in renal pyramids and cystic collecting ducts, giving the appearance of blush or diffused linear striations. Nephrocalcinosis is common in patients with MSK but is not required to make the diagnosis of MSK. CT imaging may help in excluding papillary necrosis, ADPKD, obstruction, or pyelonephritis.

## RENAL TUMORS

Each year, approximately 65,000 new cases of renal cancer are diagnosed, and 14,000 deaths from renal cell carcinoma (RCC) are reported in the United States. Most cases are sporadic, but there is an association between RCC and VHLD and tuberous sclerosis that has helped to explain the cellular mechanisms involved.

RCC originates from renal epithelial cells and accounts for 85% of renal cancers. Based on histology, the five subtypes are clear cell, papillary (chromophilic), oncocytoma, collecting duct (Bellini's duct), and chromophobe RCC. Clear cell carcinoma is the most common subtype and accounts for about 75% to 80% of all cases.

The classic triad of symptoms of flank pain, hematuria, and a palpable flank mass is uncommon (10%). About 50% of cases are identified as a result of an incidental finding on radiographic imaging. Other clinical symptoms are nonspecific and include fatigue, anemia, and weight loss. Paraneoplastic syndromes associated with RCC include erythrocytosis (i.e., overproduction of erythropoietin), hypercalcemia (i.e., excess parathyroid hormone–related peptide), hepatic dysfunction (i.e., Stauffer's syndrome), and cachexia.

The initial diagnosis of RCC is usually made by imaging. Unlike simple cysts, which are anechoic, round, and smooth walled, RCC is more likely to be a septate, irregular, thick-walled mass. When RCC is suspected, additional evaluation by CT urography or magnetic resonance imaging (MRI) is usually required, along with complete staging and evaluation for metastases (Table 29-6).

When possible, the primary treatment of localized RCC is surgical resection, which usually includes complete or partial nephrectomy. Locally advanced or metastatic RCC is treated medically with chemotherapy and immunomodulatory therapy with interleukin-2. Newer therapies based on molecular targeting of the mammalian target of rapamycin (mTOR), which regulates vascular endothelial growth factor (VEGF), and several tyrosine kinases are promising.

The prognosis for RCC depends primarily on the clinical stage at the time of presentation as assessed by the tumor-node-metastasis (TNM) criteria. TNM stages I through III have a better prognosis than TNM stage IV (metastatic) RCC. With documented metastases, the 1-year survival rate is 12% to 71%, and the 3-year survival rate is 0% to 31%. Other poor prognostic factors include a lower Karnofsky performance status, elevated lactate dehydrogenase level, low hemoglobin level, and hypercalcemia.

## ACQUIRED CYSTIC KIDNEY DISEASE IN RENAL FAILURE

Acquired cystic kidney disease (ACKD) is not associated with hereditary causes of cyst formation but occurs in the setting of chronic kidney disease of many causes. It is defined by three or more cysts per kidney in a patient with chronic kidney disease or