

Focal Segmental Glomerulosclerosis

Avi Z. Rosenberg*† and Jeffrey B. Kopp*†

Abstract

Focal segmental glomerulosclerosis (FSGS) is a leading cause of kidney disease worldwide. The presumed etiology of primary FSGS is a plasma factor with responsiveness to immunosuppressive therapy and a risk of recurrence after kidney transplant—important disease characteristics. In contrast, adaptive FSGS is associated with excessive nephron workload due to increased body size, reduced nephron capacity, or single glomerular hyperfiltration associated with certain diseases. Additional etiologies are now recognized as drivers of FSGS: high-penetrance genetic FSGS due to mutations in one of nearly 40 genes, virus-associated FSGS, and medication-associated FSGS. Emerging data support the identification of a sixth category: APOL1 risk allele-associated FSGS in individuals with sub-Saharan ancestry. The classification of a particular patient with FSGS relies on integration of findings from clinical history, laboratory testing, kidney biopsy, and in some patients, genetic testing. The kidney biopsy can be helpful, with clues provided by features on light microscopy (e.g., glomerular size, histologic variant of FSGS, microcystic tubular changes, and tubular hypertrophy), immunofluorescence (e.g., to rule out other primary glomerulopathies), and electron microscopy (e.g., extent of podocyte foot process effacement, podocyte microvillous transformation, and tubuloreticular inclusions). A complete assessment of renal histology is important for establishing the parenchymal setting of segmental glomerulosclerosis, distinguishing FSGS associated with one of many other glomerular diseases from the clinical-pathologic syndrome of FSGS. Genetic testing is beneficial in particular clinical settings. Identifying the etiology of FSGS guides selection of therapy and provides prognostic insight. Much progress has been made in our understanding of FSGS, but important outstanding issues remain, including the identity of the plasma factor believed to be responsible for primary FSGS, the value of routine implementation of genetic testing, and the identification of more effective and less toxic therapeutic interventions for FSGS.

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*Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland; and †Kidney Disease Section, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Correspondence: Dr. Jeffrey B. Kopp, Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, 10 Center Drive, Bethesda, MD 20892-1268. Email: jbkopp@nih.gov

Introduction

Focal segmental glomerulosclerosis (FSGS) is the leading glomerular cause of ESRD in the United States. FSGS refers to a histologic pattern that is a characteristic of perhaps six distinct underlying etiologies sharing a common theme of podocyte injury and depletion. The diagnosis and evaluation of FSGS rely on integration of the clinical history (family history, birth history, peak weight and body mass, and medication use), clinical laboratory findings (serum albumin, urine protein, and viral serologies), and renal histopathology. Proteinuria may be in the nephrotic or subnephrotic range. Critical is the elimination of other systemic diseases or primary renal diseases that may result in a similar presentation. Many reviews cover various aspects of FSGS and include comprehensive reviews (1–4), disease mechanisms (5–8), pediatric disease (9), immunologic aspects (10), treatment in children (11), and treatment in adults (12–14). We focus here on a practical approach to FSGS assessment on clinical and histopathologic grounds in the context of our current understanding of disease mechanisms and genetics.

difficult to ascertain given the large global variations in the indications, accessibility, and pathology support for kidney biopsy. McGrogan *et al.* (15) reviewed published literature from around the world and reported that annual incidence rates ranged from 0.2 to 1.8/100,000 population per year. Australia, with a liberal biopsy policy, had among the highest incidence of FSGS (15,16). A population-based study in the southwestern United States examined 2501 adult kidney biopsies performed between the years 2000 and 2011 (17). Over the 12 years studied, FSGS was the most common diagnosis (39% of biopsies), with an increasing incidence rate (from 1.6 to 5.3 patients per million). Although the average incidence rate was 2.7 patients per million, there was a significant racial/ethnic predilection. FSGS incidence rates are generally higher in men, being approximately 1.5-fold higher than in women.

In 2004, Kityakara *et al.* (18) noted a two-decade-long trend of increasing ESRD attributed to FSGS in the United States. Incident rates, expressed as patients per million, were 6.8 in blacks, 3.7 in Hispanics, and 1.9 in whites. The rise in FSGS prevalence has been observed in other populations as well. In Nigeria, the leading cause of nephrotic syndrome has shifted from quartan malaria (ca. 1960s) to membranoproliferative GN (ca. 1980s) to FSGS (present) (19). The factors responsible for the increasing incidence and prevalence of FSGS are largely unknown. Some of the increase is likely attributable to improved recognition

Epidemiology and Global Burden

The prevalence of FSGS, relative to other glomerular disease diagnoses, seems to be increasing worldwide, and it is a major contributor to ESRD. However, the absolute incidence and prevalence of FSGS are

(particularly where indications for kidney biopsy are broadening and the procedure is more available). There may well be an absolute rise in incidence of adaptive FSGS compounded by obesity and chronic inflammation, but epidemiologic data are lacking.

Among the primary nephrotic diseases, FSGS is most likely to progress to ESRD. Within FSGS categories, emerging data indicate that an association with APOL1 defines a group most likely to progress to ESRD. Histologic variants portend outcome with variable rates of progression (collapsing variant greater than not otherwise specified [NOS] greater than tip lesion).

Classification

Classification of FSGS is multifaceted and includes pathophysiologic, histologic, and genetic considerations. D'Agati *et al.* (20) initially proposed that FSGS be divided into primary (idiopathic) and secondary forms. The latter might be considered to include familial/genetic forms, virus-associated forms, drug-induced forms, and forms mediated by adaptive structural-functional responses (*i.e.*, in the setting of congenital or acquired reduction of renal mass/nephron complement). Clinical response and prognosis may relate to the histologic variant, most notably the glucocorticoid responsiveness of the tip lesion and the aggressive, unrelenting nature of the collapsing variants (21,22). It is with this in mind that the variants are included in standard pathology reports. More recently, efforts to identify genetic drivers of FSGS in at-risk populations have gained momentum, with the most recent addition including the *APOL1* genetic variant as a major association with FSGS in individuals of sub-Saharan African descent with FSGS (23).

Putting together the genetic susceptibility, pathophysiologic drivers, clinical history, and response to therapy (summarized in Table 1), we believe that it is useful to cluster FSGS into six clinical forms (Figure 1, Table 2). These include two common forms (primary FSGS and adaptive FSGS) and three less common forms (high-penetrance genetic FSGS, viral-mediated FSGS, and medication-associated FSGS) (24). Evidence is mounting to consider another form—APOL1-associated FSGS (discussed below). With regard to primary FSGS, some would prefer the term idiopathic FSGS; both are defined as a disease that arises spontaneously or is of unknown cause, and we would view these terms as interchangeable.

Histopathology

Historically, degenerative glomerular lesions of FSGS were those seen in the progression of minimal change disease (MCD; formerly lipoid nephrosis), and it was subsequently noted that these patients had an accelerated clinical course (25,26). In contrast to MCD, FSGS glomeruli show segmental solidification of the glomerular tuft. Tubulointerstitial scarring indicative of glomerular disease may also be observed. It is not uncommon that a biopsy with minimal glomerular changes may have tubulointerstitial damage, suggesting that FSGS might have been present on unsampled glomeruli.

The distinction between MCD and FSGS is critical, because both present with proteinuria, podocyte injury, and minimal immune deposits. For the biopsy to exclude FSGS as a cause of nephrotic syndrome and assess the degree of cortical involvement, adequate renal cortical sampling is required. The involvement of glomeruli in focal glomerular processes follows a binomial distribution, and thus, for focal disease, more glomeruli are necessary to

Table 1. Data relevant in evaluating a patient with the histologic diagnosis of FSGS

Relevant Clinical History	Laboratory Data	Renal Biopsy Findings
Family history of kidney disease Birth weight, gestational age at birth, congenital cyanotic heart disease Sickle cell disease	Serum albumin before therapy Urine protein-to-creatinine ratio	FSGS histologic variant Glomerular size (glomerulomegaly)
History consistent with reflux nephropathy or reduced renal mass	Change in urine protein-to-creatinine ratio after maximal renin-angiotensin-aldosterone therapy and dietary sodium restriction	Electron microscopy: extent of foot process effacement; podocyte microvillus transformation
Peak and present body mass index: obesity, extreme muscular development Viral infection: HIV, cytomegalovirus Medication, past or present: IFN, lithium, bisphosphonate, androgen abuse, chronic use of nephrotoxic drugs	Change in urine protein-to-creatinine ratio after immunosuppressive therapy	Electron microscopy: tubuloreticular inclusions in glomerular endothelial cells (IFN effect)

Modified from Kopp (24), with permission.

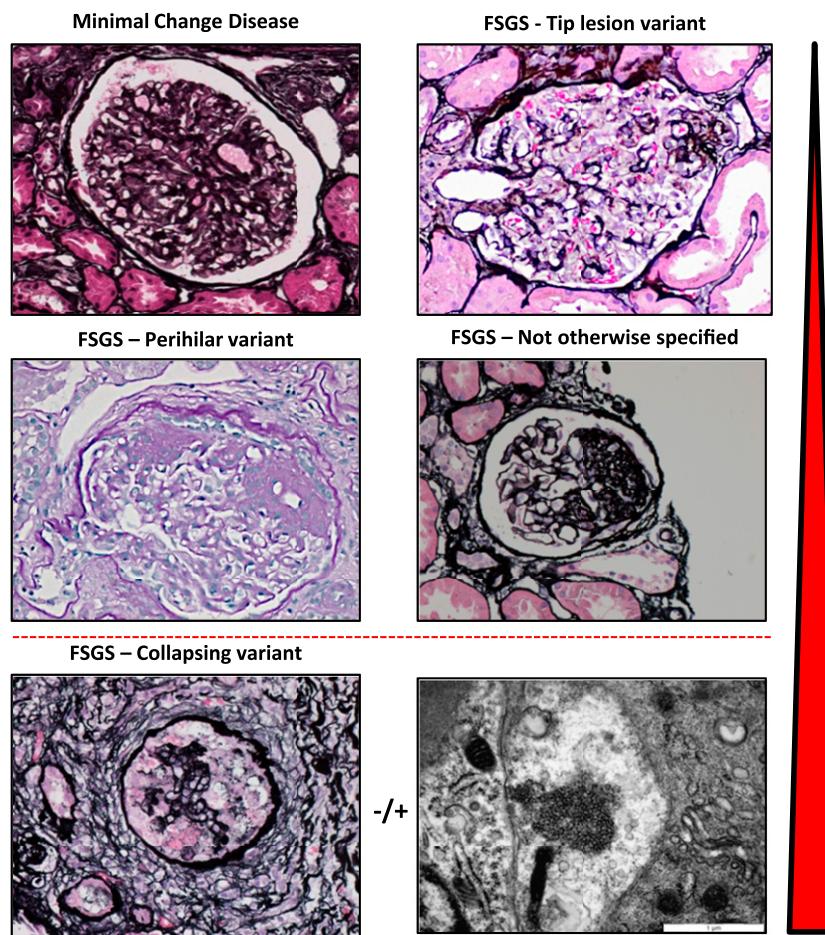


Figure 1. | Histopathology of minimal change disease and focal segmental glomerulosclerosis. Minimal change disease shows patent glomeruli in the absence of tubulointerstitial scarring (silver stain, $\times 40$). The tip lesion represents a focal adhesion of the glomerular tuft to Bowman's capsule near the proximal tubule takeoff (silver stain, $\times 400$). The most common forms of FSGS seen in adaptive FSGS and across all etiologies of FSGS are the perihilar variant (periodic acid–Schiff stain, $\times 40$) and not otherwise specified pattern (silver stain, $\times 400$). The most distinctive variant is the collapsing variant (collapsing glomerulopathy; silver stain, $\times 40$). A specific instance of collapsing variant can be appreciated in the setting of endothelial tubuloreticular inclusions seen on ultrastructural analysis. These may be observed in high IFN states, including viral infection and exogenous IFN. The red arrowhead indicates the relative response to therapy and propensity of progression of these various forms, with minimal change disease and tip lesion being most responsive and least progressive and collapsing glomerulopathy being most therapy resistant and rapidly progressing.

observe an affected glomerulus (27,28). There is also zonal proclivity for FSGS, such that juxamedullary/inner cortex glomeruli are the first affected progressing to involve the outer cortex at a later stage of disease (24). Fogo *et al.* (29) further show that the focality of sclerotic lesions is greater in children than in adults, suggesting a need for more comprehensive sampling. Differential staining patterns for synaptopodin (30) and dystroglycan (31) may distinguish steroid-sensitive MCD versus steroid-resistant MCD (likely unsampled FSGS) and FSGS.

A simulation study has highlighted two issues with respect to diagnostic yield of renal biopsies in FSGS (28). (1) If glomerular scars are uniformly distributed in a biopsy with 10–30 glomeruli, the diagnostic accuracy for the detection of at least one scarred glomerulus will be 80% when at least 10% of juxamedullary glomeruli or 20% of other cortical glomeruli are scarred. (2) With an average of 20 glomeruli with 20%–60% glomerular sclerosis, the predicted error rate is $\pm 50\%$ for extent of glomerular

involvement. This suggests caution when making treatment recommendations on the basis of the extent of involved glomeruli (Supplemental Figure 1).

The Columbia classification of FSGS recognized five morphologic patterns, all of which involve obliteration of the capillary lumens and for the most part, have good reproducibility across independent observers (20,32) (Figure 2). Two distinctive forms are the tip lesion and the collapsing variant. Tip lesions affect the portion of the glomerular tuft juxtaposed to the tubular pole. Abnormalities include adhesion to Bowman's capsule at the tip, hypercellularity, presence of foam cells, and/or sclerosis. By contrast, the collapsing variant shows segmental or global mesangial consolidation and loss of endocapillary patency in association with extracapillary epithelial hypertrophy and/or proliferation. Microcystic tubular dilation is frequently present. The perihilar and NOS variants are determined by whether the segmental sclerosis/segmental obliteration of capillary loops with matrix increase (with or

Table 2. Characteristic clinical and pathology features of the six forms of FSGS

Characteristic Features	Primary FSGS	Adaptive FSGS	APOL1 FSGS	Genetic FSGS	Infection/Inflammation Associated	Medication-Associated FSGS
Mechanism of Podocyte Injury	Circulating factor, possibly a cytokine	Mismatch between metabolic load and glomerular capacity	APOL1 variant-initiated inflammation	High-penetrance genetic variants (Mendelian or mitochondrial inheritance)	Postulated role of IFN and possible other cytokines	Presumed direct effect on podocytes
History	Acute onset of edema	Reduced renal mass: low birth weight, oligomeganephronia, ureteral reflux, morbid obesity; increased single-nephron GFR; cyanotic congenital heart disease, sickle cell anemia	Family history, may be unremarkable	Family history, may be unremarkable with recessive inheritance genes	HIV, CMV, possible: parvovirus B19, Still disease, natural killer cell leukemia	Bisphosphonate, lithium
Laboratory tests	Many have high-grade proteinuria and nephrotic syndrome	Any level of proteinuria, serum albumin may be normal	Any level of proteinuria	Any level of proteinuria	Any level of proteinuria	Any level of proteinuria
Renal pathology	Widespread foot process effacement	Large glomeruli, perihilar sclerosis variant most typical, partial foot process effacement	May resemble primary or adaptive forms	Variable	Variable	Variable
Treatment and response	May respond to IST	Responds well to RAAS antagonism, often with >50% proteinuria reduction	May respond to therapies used for primary and adaptive forms	High-penetrance genetic mutations; usually does not respond to IST	Treat the virus	Stop the medication
Recurrence after renal transplant	Possible	Unlikely	Possible	Unlikely	Possible if infection/inflammation persists	Unlikely

CMV, cytomegalovirus; IST, immunosuppressive therapy; RAAS, renin-angiotensin-aldosterone system; CG, collapsing glomerulopathy. Modified from Kopp (24), with permission.

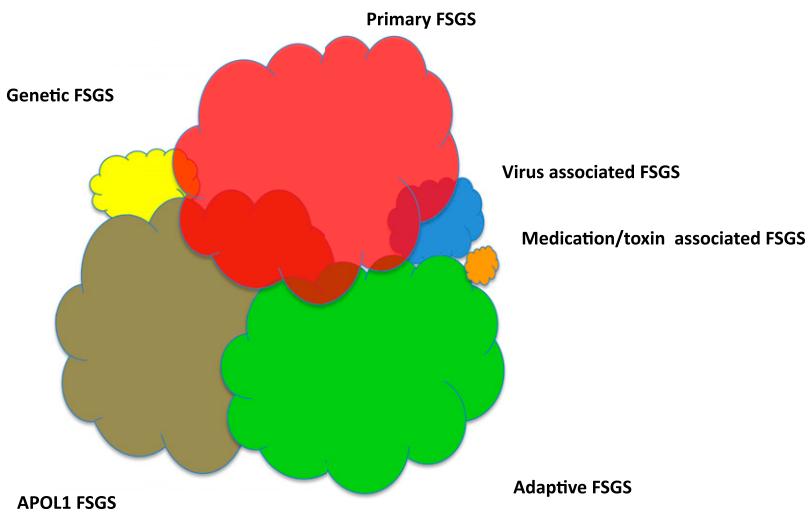


Figure 2. | The six forms of FSGS. These syndromes include three forms that are most common, including primary FSGS, adaptive FSGS, and APOL1 FSGS. These forms are probably of approximately equal prevalence in the United States adult population. Three forms are less common, including genetic FSGS (by which is meant high-penetrance genetic causes), medication-associated FSGS, and viral FSGS. The approximate relative distribution of these variants in the United States population at present is shown by the size each cloud, although firm data on prevalence are lacking. The absolute frequency of these FSGS forms is influenced by race/ethnicity (particularly in the frequency of APOL1 risk variants), age (children are less likely to have adaptive FSGS), and the frequency of exposures to toxins (e.g., heroin) and medications and having viruses (e.g., HIV).

without hyalinosis) involves the segment near the hilum or the specific segment cannot be determined, respectively. The cellular lesion is perhaps the most difficult lesion to identify reproducibly and shows segmental endocapillary hypercellularity occluding lumens with or without foam cells and karyorrhexis (32). Some biopsies will show multiple morphologic lesions (33,34), and the Columbia classification suggests a hierarchy for diagnosis, such that the presence of the higher-ranking lesion determines the clinical course: collapsing variant, tip lesion, cellular variant, perihilar variant, and lastly, NOS (reviewed in Stokes and D'Agati [35]). Including the pattern of FSGS has standardized the reporting of FSGS lesions and provides prognostic information. Nonetheless, this classification system was designed to rely solely on pathologic criteria and does not integrate these findings with clinical and genetic information.

Complete renal pathologic evaluation includes immunofluorescence analysis and electron microscopy, which help to exclude focal and segmental glomerular scarring as an injury pattern that can be seen as an element of any chronic progressive renal diseases, including lupus nephritis, IgA nephropathy, and diabetic nephropathy (36). As such, to avoid confusion, it is probably best to avoid using the term FSGS in this setting. Low or moderate amounts of IgM are frequently present in the mesangium of patients with FSGS. Thurman and colleagues (37) have proposed

that IgM may bind neopeptides in the mesangium that are exposed after nonimmune injury, resulting in complement deposition and glomerular injury.

Ultrastructural examination adds to the assessment in three ways. First, it can exclude the presence of immune complexes and abnormal deposits, such as amyloid. Second, it can exclude basement membrane abnormalities seen in genetic disorders of collagen; the appearance of COL4 mutations among the list of genes associated with FSGS suggests that the alterations in basement membrane at the ultrastructural level may be subtle or undetectable. Third, it can provide an estimate of the severity of podocyte injury (fractional foot process effacement) and injury pattern (microvillus transformation). Mean foot process width is greater in primary FSGS compared with adaptive FSGS and may serve as a helpful, although subtle, clue (38).

The use of all three renal pathology modalities (light microscopy, electron microscopy, and staining for Ig and complement) is critical in making the distinction between MCD and FSGS. Extensive podocyte injury at the ultrastructural level with adequate numbers of normal-appearing glomeruli and nonscarred tubulointerstitium by light microscopy suggests MCD. Nevertheless, individuals with a diagnosis of MCD who are resistant to glucocorticoid therapy or manifest deterioration in renal function

may have FSGS that was not sampled on the first biopsy and is shown on a subsequent renal biopsy.

Mechanisms of Disease

FSGS is a diverse syndrome that arises after podocyte injury from diverse causes: some known and others unknown (39). The sources of podocyte injury are varied (circulating factors [primary FSGS], genetic abnormalities, viral infection, and medication), although the effect on podocytes is similar. For the most part, the interplay among these drivers is unclear and likely complex. For instance, adaptive FSGS involves both podocyte stress (a mismatch between glomerular load and glomerular capacity) and a genetic susceptibility. Wiggins and colleagues (40) have elegantly shown this in a rat model that combines genetic susceptibility, renal mass reduction (uninephrectomy), and obesity (increased glomerular load).

Importantly, podocyte injury from any of the forms of FSGS (or from other glomerular diseases) will initiate a similar process, resulting in the pathologic features of adaptive FSGS.

It is thought that there is progressive loss of injured podocytes into the urinary space. Podocyte depletion arising from an inability to replicate (although nuclear division may occur, at least in animals) and results in podocyte catastrophe (41). To balance this deficit, podocytes compensate by hypertrophy to cover more of the glomerular capillary surface. In a recent insightful and provocative review, Kriz and Lemley (42) proposed that shear stress forces on podocytes are a critical factor driving podocyte injury. In adaptive FSGS, glomerular hypertrophy occurs early in the disease process; in other forms of FSGS and other glomerular diseases, glomerular hypertrophy occurs with progressive nephron loss, leading to increased pressures and flows in the remaining patent glomeruli.

The following sections address pathologic mechanisms, therapy, and treatment for each of the FSGS syndromes. The typical onset ages and approximate relative incidence rates are shown schematically in Supplemental Figure 1.

Primary FSGS

Primary FSGS is a distinct entity, and paradoxically, it is best defined, at this time, as what it is not (*i.e.*, not one of the other forms of FSGS). As a practical matter, this means assessing the likelihood of other forms. This includes ruling out adaptive FSGS (by medical history, peak or current body weight, renal biopsy features, serum albumin, or proteinuria response to renin-angiotensin-aldosterone system [RAAS] antagonism), genetic FSGS (*via* genetic test panels on the basis of family history and age of onset), viral FSGS (by appropriate virologic testing), and medication-associated FSGS (by medication history). Emerging data support that APOL1-associated FSGS may make up yet another form of primary FSGS.

The mechanism of podocyte injury in at least some patients with primary FSGS likely involves a circulating factor, possibly a cytokine that makes particular subjects susceptible. The best evidence for a circulating factor comes from the experience with recurrent FSGS immediately (on a scale of hours to several weeks) after kidney transplant. The cytokine or cytokines responsible for recurrent FSGS after kidney transplant remain to be defined. In an unusual and

striking case that supports the cytokine hypothesis, a kidney was transplanted into a recipient with FSGS; proteinuria developed, and the transplanted kidney showed podocyte foot process effacement. Subsequently, the kidney was removed and transplanted into a patient with ESRD due to diabetes, and in the new host, the kidney functioned well without proteinuria (43). Current candidates for the recurrent FSGS factor, reviewed recently (44), include cardiotrophin-like cytokine factor 1 (45), apoA1b (an isoform of ApoA1) (46), anti-CD40 antibody (47), and serum urine-type plasminogen activator receptor (suPAR) (48). The role of suPAR remains controversial (49). suPAR levels were reported in FSGS and other primary glomerular diseases (50). In primary and adaptive FSGS (51), elevated levels may (52) or may not (53) predict glucocorticoid sensitivity, and a role for different forms of suPAR has been suggested as reviewed recently (54). Recurrent FSGS plasma affects the cytoskeleton of cultured podocytes, including promoting cell mobility by phosphorylating vasodilator-stimulated phosphoprotein (55) and disassembling focal adhesion complexes (56). The lack of suitable animal models has hindered progress in this area.

It is quite likely that other patients with what is now diagnosed as primary FSGS will be reassigned to alternative etiologies, including new genes, environmental factors, and/or microorganisms.

Primary FSGS has several prototypical characteristics. It is probably the most common form in adolescents and young adults, although it may occur at any age. It is commonly associated with nephrotic-range proteinuria (sometimes massive), reduced plasma albumin levels, and hyperlipidemia. Histologically, it may manifest as the tip variant, collapsing variant, or NOS variant.

Current therapy for primary FSGS is on the basis of immunosuppressive agents; it is now apparent that a number of these, including glucocorticoids and calcineurin inhibitors, directly modulate the podocyte phenotype (57). Recently, it has been shown that the effects of glucocorticoids may be mediated by Krüppel factor 15, a zinc finger transcription factor (57,58). In a recent retrospective case series involving 476 subjects, the use of glucocorticoids and/or cyclosporin was associated with improved outcomes compared to no immunosuppression, with a hazard ratio of 0.49 (95% CI, 0.28 to 0.86) for ESRD whereas the use of cyclosporine with or without glucocorticoids was not associated with benefit HR 0.42 (95% CI, 0.15 to 1.18) (59). Despite the limitations of a retrospective study design, this provides new evidence to support therapy.

Recurrent FSGS remains a vexing clinical problem. The histologic variant in the native kidney does not predict recurrence, although it is notable that only one of 77 initial kidney biopsies from subjects who subsequently had recurrent FSGS showed the perihilar variant (60). Therapy with plasma exchange may induce a remission, typically temporary. Canaud *et al.* (61) reported favorable results from a small series of adult subjects ($n=10$) with a regimen that included glucocorticoids and cyclosporin initially administered intravenously.

Adaptive FSGS

Adaptive FSGS, which has also been called, perhaps more accurately, postadaptive FSGS (62), arises after a period of nephron-level glomerular hyperfiltration and glomerular hypertension after pathophysiology as identified

by Brenner and Mackenzie (63). Total GFR may be elevated, normal, or decreased at the outset.

Conditions that are associated with an increase in total kidney GFR include congenital cyanotic heart disease (64), sickle cell anemia (65), obesity (66), androgen abuse (67), sleep apnea (68), and high-protein diet. The duration of single-nephron glomerular hyperfiltration is typically measured in decades before progressive glomerulosclerosis eventually reduces total GFR. Conditions associated with reduced renal mass include prematurity and/or small for gestation age (69), renal anomalies, reflux nephropathy, and AKI. Any chronic glomerular or tubular disease may reduce the total nephron function and result in adaptive FSGS that is superimposed on the primary disorder.

Adaptive FSGS arises from the processes described above involving increased single-nephron GFR (often with intraglomerular hypertension), leading to progressive cycles of glomerular hypertrophy; podocyte hypertrophy, stress, and depletion; and synechia formation and excess extracellular matrix deposition within the glomerulus as described so well by Kriz and Lemley (70).

Renal biopsy features that support the diagnosis of adaptive FSGS include large glomeruli, a preponderance of perihilar scars among glomeruli showing sclerotic changes, and only partial foot process effacement. Clinical features include a normal serum albumin, which is unusual in primary FSGS. A complete response to RAAS antagonism, particularly when combined with sodium restriction and a rise or normalization of serum albumin, supports the diagnosis of adaptive FSGS, although it does not exclude other forms of FSGS.

Genetic FSGS

Genetic FSGS takes two forms. First, some patients are associated with variants in susceptibility genes (*i.e.*, some individuals with a particular variant will develop FSGS, and other individuals will not). By far, the most common example of this is the newly identified association with *APOL1* as discussed below. Other genetic risk loci include *PDSS1* (71) and numerous others (72,73). More are likely to be discovered in the near future. Second, other patients are associated with high-penetrance mutations that manifest either Mendelian inheritance (for nuclear genes) or maternal inheritance (for genes encoded by mitochondrial DNA). The number of genes associated with FSGS rises every year, in large part because of the dissemination of whole-exome sequencing. To date, at least 38 genes have been identified as shown in Table 3. (For simplicity, genes such as *CFH* and *C3*, which represent distinct syndromes that could be mistaken for FSGS when ultrastructure examination is not performed, have not been listed in Table 3. Other genes that have provisionally been associated with FSGS but lack the robust data needed to firmly establish causality are not shown [*e.g.*, *ACLS4*, *ALG1*, *NEIL1*, *PMM2*, *PODLX*, *SYNPO*, and *ZEB1*].)

Some genes are associated with a syndrome that includes extrarenal manifestations, and this can provide a clinical clue that a patient might have a mutation in a particular gene. Some genes are associated with characteristic changes in basement membrane morphology (*e.g.*, *LXMB1* and *COL4A3–5*) or mitochondrial morphology (*e.g.*, the genes associated with mitochondrial encephalopathy, lactic acidosis, stroke-like episode syndrome) that may provide such

clues. Other genes are associated with therapeutic response. (Table 5 does not include genes associated with steroid-sensitive nephrotic syndrome, for which renal biopsies have not been done. Some genetic variants shown in Table 5 are associated with glucocorticoid sensitivity; *e.g.*, *PTPRO* [74].)

Should patients with FSGS undergo genetic testing? The answer to this question remains unclear. With regard to pediatric patients, Hildebrandt and coworkers (75) have suggested that every family with a child who has FSGS deserves to be offered an opportunity to have a genetic diagnosis (RE). Benefits of this approach may include a guide to appropriate therapy (*e.g.*, avoidance of glucocorticoids except for in genetic forms that may be responsive and coenzyme Q10 therapy for particular mitochondrial mutations), prognosis (typical native kidney outcomes and likelihood of transplant recurrence), and family issues (identification of disease in other family members and prenatal testing). To be sure, caution is warranted, in that systematic studies of the response of genetic forms of FSGS to various therapies have not been carried out. High-penetrance genetic causes are more likely to be identified in childhood nephrotic syndrome (approximately 60%) than in that in older children and adolescents (approximately 5%), with lower rates in adults (75,76). Genetic testing in adults with FSGS is indicated where there is a family history, because some genes have mutations associated with autosomal dominant mutations (*IFN2* and *ATCN4*).

What is the most appropriate and cost-effective way to carry out genetic testing? When a family has not had gene testing previously that identified a specific gene, the most effective approach is to use panels that focus on early-onset FSGS (infant and early childhood) or adult-onset FSGS. Genetic test resources around the world are available at the Genetic Test Registry, National Center for Biotechnology Information, National Institutes of Health (<http://www.ncbi.nlm.nih.gov/gtr>).

A more comprehensive approach is a whole-exome scan, which provides DNA sequence for the approximately 180,000 exons that make up the approximately 22,000 human genes; this may, in the near future, replace the use of selected gene panels. Genetic testing may identify known mutations that prior experience has shown are associated with FSGS, but it may also identify protein-altering mutations (*e.g.*, missense mutations that change an amino acid or introduce a stop codon) of unknown significance. With comprehensive genetic exploration, there is also the possibility of unexpected identification of genetic variants that have significance for the individual and family. An advisory group from the American College of Human Genetics has provided a recommended list of 56 genes for which variants that are likely to be disease associated should be reported to the individual or family; this list will likely expand over time (77). Therapy for genetic FSGS is generally conservative and on the basis of RAAS antagonism. Calcineurin inhibitors may have an effect in a minority of patients (78). As noted above, coenzyme Q10 may benefit individuals with mutations in certain mitochondrial defects.

Virus-Associated FSGS

Among infections, viruses are predominantly implicated in causing FSGS. HIV-1 is strongly associated with FSGS,

Table 3. Genetic FSGS: Genetic variants with syndromes with Mendelian and mitochondrial inheritance

Genetic FSGS can be categorized as susceptibility genes (not shown; *e.g.*, *APOL1*) and genes with Mendelian and mitochondrial inheritance (38 genes shown above); genes for which casual evidence is not yet entirely convincing or associations are with unbiopsied nephrotic syndrome are omitted. These gene products are located in various podocyte cell compartments, although some proteins are present in more than one location (the number of genes in each compartment are tabulated in the last row). Nonsense genes are those in which mutations are associated with manifestations only in the kidney; syndromic genes are those in which mutations are also associated with extrarenal manifestations, in some cases with variable penetrance (some individuals with certain mutations may have a purely renal phenotype). For some diseases, eponyms or syndromic names are provided in parentheses. Most genes affecting mitochondrial function are encoded by

nuclear genes. MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes. ^aThe two MELAS genes are encoded by mitochondrial DNA and show mitochondrial inheritance.

particularly the collapsing glomerulopathy variant, although other variants are also seen (79). The mechanisms likely involve direct infection of podocytes (80). A similar renal syndrome can be reproduced in transgenic mice bearing HIV-1 Nef (81) or Vpr (82) accessory proteins, suggesting possible mechanisms.

Interestingly, the effect of HIV on podocytes is strongest in individuals with two *APOL1* risk alleles, with an odds ratio of 29 in the United States (83) and an odds ratio of 89 in South Africa (84). Most individuals with HIV-associated nephropathy (HIVAN) have one or two *APOL1* risk alleles.

Other viruses that have been implicated in causing FSGS include cytomegalovirus, parvovirus B19, and Epstein-Barr virus, with the evidence perhaps stronger for cytomegalovirus compared with the others (reviewed in Chandra and Kopp [85]).

Certain parasites have also been associated with FSGS, presumably by stimulating innate immune pathways in ways that injure podocytes. These include *Plasmodium* (malaria) (86), *Schistosoma mansoni* (87), and filariasis (88), although these seem to be rare events given the frequency of these infections.

Medication-Associated FSGS

There is a relatively short list of medications that cause FSGS. IFN- α , - β , or - γ therapy has been associated with the development of collapsing glomerulopathy in a case series of 11 subjects (89).

Several other medications have been associated with FSGS; a genetic predisposition is plausible but has not been shown. Bisphosphonates are associated with podocyte injury, including MCD, FSGS, and particularly, collapsing FSGS (collapsing glomerulopathy) as first reported by Markowitz *et al.* (89). As in HIVAN, the abundant cells in Bowman's space are derived from the parietal epithelium (90). The mechanism by which bisphosphonates act remains obscure. Lithium therapy has been associated with MCD, which typically reverses within weeks after stopping the medication, and FSGS, which may also be reversible (91). The mechanism of podocyte injury, if that is the mechanism, remains to be determined. Sirolimus, particularly when the plasma levels are high, has been associated with FSGS (92) as well as exacerbating preexisting FSGS (93). Anthracycline medications, including doxorubicin (Adriamycin) and daunomycin, have been associated with FSGS (94), and doxorubicin, a podocyte toxin, has been widely used to generate a mouse model of FSGS (95).

Emerging Pathologic Mechanisms: *APOL1*-Associated FSGS

The identification of genetic variants in *APOL1* in patients with FSGS has been an important discovery for FSGS and related diseases. Unlike certain genes that have not shown firm causality to FSGS, data are mounting for the role of *APOL1*. Although confirmatory data are required, the strength and consistency of the genetic association, the exclusion of other genetic variants in this genomic region, and the demonstration that the expression of the renal risk variants (but not the common allele) causes FSGS in transgenic mice (96) are highly supportive of the role of *APOL1* genetic variants as causal for FSGS.

APOL1-associated FSGS is a major form of FSGS in countries with individuals of sub-Saharan African descent. The effect is largely recessive, requiring two risk alleles, although in certain situations (e.g., HIV-positive South Africans), a single copy of a risk allele G1 has a significant association with HIVAN (84). In the United States, approximately 40% of ESRD attributed to FSGS occurs in blacks, and of this, 72% is associated with *APOL1* genetic variants (83); thus, approximately one third of FSGS in the United States is associated with *APOL1* variants.

APOL1-associated FSGS can present in various ways: it may present as a primary FSGS, with severe nephrotic syndrome, or as recurrence after kidney transplant, or it manifest as adaptive FSGS with preserved serum albumin and minimal edema. One setting in which the adaptive processes drive *APOL1* FSGS is perhaps the report that *APOL1* variants are associated with proteinuric sickle cell nephropathy (97), although a systematic study of kidney histology in *APOL1*-associated sickle nephropathy is still lacking. *APOL1* high-risk alleles are strongly associated with collapsing glomerulopathy in several settings: (1) HIVAN, in which 72% have two *APOL1* high-risk alleles (83), and (2) the use of exogenous IFN (98) and in lupus (99).

Emerging data support defining *APOL1* FSGS as a separate category of FSGS. First, the *APOL1* risk alleles represented confer susceptibility, but most subjects with two risk alleles will not develop kidney disease; thus, *APOL1* differs from the high-penetrance genetic variants in most other forms of genetic FSGS. Second, *APOL1* FSGS is by far the most common form of genetic FSGS in countries with substantial African descent populations. Third, the diagnosis of *APOL1* FSGS may have implications for prognosis, with more rapid progression to ESRD, and it may have implications for the selection of living donors. Fourth, novel therapeutics may become available that target *APOL1* variant-driven molecular pathways.

Therapeutic Approaches

Therapy should be individualized on the basis of the particular form of FSGS as well as factors particular to the patient, such as age and comorbidities. Therapy for primary FSGS and in rare instances, genetic FSGS, particularly when nephrotic proteinuria is present, involves the use of medications that are immunosuppressive but also have direct effects on podocytes. These therapies are summarized in Tables 4 and 5 and discussed below. A comprehensive analysis of approaches to steroid-sensitive and -resistant FSGS is available from the Kidney Diseases Improving Global Outcomes initiative, and the reader is referred to this initiative for a detailed and thoughtful discussion (100) as well as recent reviews (13). FSGS may be responsive to therapy with glucocorticoids, although relapses are typical. Randomized, controlled trials are few. Interestingly, functional polymorphisms in the glucocorticoid receptor encoded by *NR3C1* have been associated with both relapse and frequent relapse (101). Cyclosporin plus low-dose prednisone was shown in a randomized, controlled trial to be superior to prednisone alone in preserving renal function assessed as creatinine clearance (102). Mycophenolate mofetil has not been tested as monotherapy for FSGS, but it has been tested in combination with glucocorticoids in

Table 4. Treatment recommendations for children with FSGS

Setting	Therapy	Comment
On presentation	Prednisone: initially daily and then alternate days	
Frequently relapsing or steroid dependent	Prednisone: initially daily and then alternate days at lowest dose to prevent relapse	
Same, with steroid-related adverse events	Alkylating agent (cyclophosphamide or chlorambucil), calcineurin inhibitor, levamisole, mycophenolate mofetil	No RCT comparing one agent with another; listed in alphabetical order
Steroid resistant	Calcineurin inhibitor	Also ACE inhibitor and angiotensin receptor blocker; sodium restriction
	If no remission, mycophenolate mofetil, corticosteroids, or both	

Recommendations from the Kidney Disease Improving Outcomes Global initiatives. Doses and durations of therapy are provided in Lopez-Hellin *et al.* (46). In the nosology presented here, these recommendations would apply to nephrotic forms of primary FSGS, APOL1 FSGS, and certain rare forms of genetic FSGS. RCT, randomized, controlled trial; ACE, angiotensin-converting enzyme.

three trials against active comparators that were either glucocorticoids or cyclosporin (reviewed in Senthil Nayagam *et al.* [103]). None of the trials showed significant differences between groups, and although sample sizes were small, particularly for noninferiority trials, these data suggest efficacy.

Several Cochrane reviews are available covering treatment of FSGS in adults (104) and children using not only glucocorticoids (105) but also, other therapies, including cyclophosphamide, azathioprine, levamisole, mizoribine, and rituximab (106,107). Many other agents have been tested in small trials or reported as case series, and they have been the subject of recent reviews (13,108–111). These agents include the following: adalimumab, an anti-TNF mAb (112); pirfenidone, an antifibrotic agent that suppresses TGF- β signaling (113); fresolimumab, an anti-TGF- β mAb (114); pulse steroids plus cyclophosphamide (115);

and saquinavir (116). Achtar gel is unusual in that it was approved in the 1950s by the US Food and Drug Administration for nephrotic syndrome under criteria that were less stringent than required today. Small case series suggest limited efficacy of Acthar in some individuals with FSGS (117,118) as has been reviewed (119); a randomized, controlled trial is in progress. Galactose, proposed as therapy for recurrent FSGS, has been shown to lack efficacy in steroid-resistant primary FSGS in children (120). Sirolimus may accelerate progression of FSGS and should be avoided (93). Ongoing and recently completed phase 3 trials have shown some efficacy with sparsentan, an irbesartan-like molecule that also antagonizes endothelin receptor, and abatacept, a CD80 antagonist (121).

There is considerable incentive for the pharmaceutical and biotechnology industry to develop novel therapies for

Table 5. Treatment recommendations for adults with FSGS

Setting	Therapy	Comment
Nephrotic forms of primary FSGS, ^a APOL1 FSGS, certain steroid-sensitive genetic forms of FSGS	Prednisone, initially daily or alternate days ^a	Alternate for patients at high risk for steroid complications: calcineurin inhibitors ^a
Steroid-resistant FSGS with nephrotic syndrome ^a	Calcineurin inhibitor ^a (cyclosporin and possibly, tacrolimus)	
Refractory FSGS with nephrotic syndrome ^a	Mycophenolate mofetil plus high-dose dexamethasone ^a	
All forms of FSGS with subnephrotic proteinuria	ACE inhibitor and angiotensin receptor blocker; dietary sodium restriction	Thiazide diuretic may potentiate the antiproteinuric of RAAS antagonism

Therapy doses are in ref. 46. Cyclosporin has been shown effective in randomized, controlled trials, whereas tacrolimus has not. In the nosology presented here, these recommendations would apply, when nephrotic syndrome is present, to primary FSGS, APOL1 FSGS, and certain rare forms of genetic FSGS that may be steroid sensitive. ACE, angiotensin-converting enzyme; RAAS, renin-angiotensin-aldosterone system.

^aRecommendations from the Kidney Disease Improving Outcomes Global initiatives for idiopathic FSGS with nephrotic syndrome are extended here to other forms of FSGS as shown.

FSGS, a rare disease as defined by the US Food and Drug Administration that lacks therapies that are both safe and effective. Gipson and colleagues (122) have proposed a new paradigm for therapeutics development that involves a deep understanding of disease mechanisms in patient subsets, enriching study populations for subjects most likely to respond on the basis of those biologic insights, and adaptive trial designs to improve efficiency (122,123).

Medication-associated FSGS can generally be managed by stopping the offending medication, and virus-associated FSGS can be best addressed by initiating antiviral therapy with additional adjunctive therapies as indicated. Currently, therapy for APOL1 FSGS is directed toward addressing the other FSGS classes (*e.g.*, primary, adaptive, virus associated, or medication associated) that may coexist with APOL1 FSGS. Future therapies for cell injury pathways initiated by APOL1 variant expression are likely to be developed.

The customary definition of response is similar to that of other nephrotic diseases and assumes baseline proteinuria in the nephrotic range (*i.e.*, urine protein-to-creatinine ratio [uPCR] ≥ 2 g/g). First void urine is preferred, because that uPCR most closely correlates with the 24-hour uPCR. Complete remission (CR) is defined as uPCR < 0.2 g/g, and partial remission (PR) is defined as having 50% reduction from baseline proteinuria and uPCR < 2 g/g.

RAAS antagonism therapy is central to all progressive CKD, and it is the treatment that directly addresses the hemodynamic alterations in adaptive FSGS. RAAS antagonist therapy also has a role in genetic FSGS (evidence limited to case reports [124]) and APOL1 FSGS (no published data), particularly when adaptive hemodynamic mechanisms are likely at work (*e.g.*, an individual who was born prematurely is now obese and has a normal serum albumin, despite substantial proteinuria), and may reduce proteinuria in primary FSGS adjunctive to immunosuppressive therapies. RAAS antagonist monotherapy was shown in a retrospective study to be superior to immunotherapy in a pediatric FSGS cohort in Philadelphia (with 55% black subjects) (125). As with all progressive CKD, attention to BP control, smoking, obesity, and serum bicarbonate and urate are indicated, and consideration should be given to statin therapy.

The effects of RAAS antagonist therapy are potentiated by dietary sodium restriction and low-dose thiazide diuretic (126). Although hydrochlorothiazide is the most widely used thiazide diuretic, an alternative is chlorthalidone, which has certain features to recommend its more widespread use: it has longer duration of action, it is more kaliuretic (particularly helpful when low GFR compromises potassium excretion), and it has been shown to improve cardiovascular outcomes, which other thiazides have not been shown to do.

The issue of combining an angiotensin-converting enzyme inhibitor (ACEi) and an angiotensin receptor blocker (ARB) is fraught with uncertainty. A meta-analysis of this combination therapy in IgA nephropathy suggested proteinuria reduction compared with single therapy, but only one study involved subjects with nephrotic-range proteinuria (127). The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial Study showed that this combination is associated with adverse cardiovascular outcomes in an older population with a high prevalence of cardiovascular disease (128); similarly, the VA

Diabetes in Nephropathy Study of diabetic nephropathy (median age of 64 years old) showed a trend toward benefit but was stopped early due to safety concerns (129). These studies may have limited relevance to younger patients with FSGS, particularly those with preserved GFR, who may tolerate this combination better. RAAS antagonism and particularly, the combination of ACEi and ARB will lower GFR by reducing efferent arteriolar vascular tone and thus, reducing intraglomerular capillary pressure, the driving force for glomerular filtration. Thus, a modest decrease in GFR may be tolerated, providing evidence that RAAS antagonism has been achieved. Nevertheless, there are no trials of suitable size to justify this approach from an efficacy or safety standpoint.

An alternate approach to RAAS antagonism is to combine an ACEi or ARB with an aldosterone antagonist (130). This approach may have less effect on reducing glomerular capillary pressure, but aldosterone antagonists are potent antifibrotic agents. Recent data have shown that aldosterone is positioned upstream of multiple profibrotic pathways and that angiotensin 2 is only one of many stimuli to aldosterone production (131). This combination confers a risk for hyperkalemia, particularly with reduced GFR; this may be controlled with dietary restriction and diuretics, although close monitoring may be required.

Glucocorticoids have some efficacy in primary FSGS, although they have not been tested against placebo in a randomized, controlled trial. Response rates, defined as CR plus PR, tend to be higher in children (often approximately 50%) compared with adults. For APOL1 FSGS, response rates to glucocorticoids are probably similar to those seen in primary FSGS, although the data are limited (83). The mechanism by which glucocorticoids affect podocytes are poorly understood; these agents are known to have direct effects on cultured podocytes (132). Recently, it has been suggested that these agents can expand the population of myeloid-derived suppressor cells that downregulate T cell function (133). Reliable and validated biomarkers of steroid responsiveness would be valuable. There are few data on which to base a determination of the appropriate dose and duration of glucocorticoid therapy. Biomarkers for responsiveness to glucocorticoid therapy would be valuable to reduce or avoid the need to expose patients to drugs to which they will not respond. Preliminary studies that await validation in larger cohorts include the ratio of podocin mRNA to synaptopodin mRNA, particularly when the diagnostic uncertainty with regard to MCD versus FSGS exists (134). Immunohistochemical detection of reduced expression of synaptopodin and receptor-type tyrosine-protein phosphatase O (PTPRO or GLEPP1) may be useful in identifying steroid-resistant patients (135). Conversely, reduced eGFR at presentation does not predict nonresponsiveness to glucocorticoids (136).

Calcineurin inhibitors, including cyclosporin and tacrolimus, are mainstays of FSGS therapy for both steroid-sensitive individuals who cannot tolerate continued steroid therapy and steroid-resistant FSGS. Cyclosporin was shown superior to placebo in the North American collaborative trial of steroid-resistant FSGS, with the primary outcome of CR or PR occurring in 70% with cyclosporin and 4% with placebo (102). Similarly, an open label study of cyclosporin in steroid-resistant nephrotic syndrome in

China showed a 75% response rate (137). The FSGS Clinical Trial, which enrolled mostly children, showed that response rates are similar for cyclosporin and mycophenolate mofetil in blacks with and without high-risk *APOL1* genotypes, although group sizes were small (138). Although patients may relapse when calcineurin inhibitors are discontinued, many subjects remain in remission.

A number of novel therapies have been explored in small trials. Some of these therapies have some promise, including pirfenidone (113) and saquinavir (116). Other therapies that have been shown to be ineffective or even harmful include sirolimus (93), galactose (139), and adalimumab (mAb directed against TNF) (139). Other immunosuppressive agents that have been used include azathioprine and mizoribine, although limited data for their success are available.

Recently, there has been a surge of interest in developing new therapies for FSGS and other primary glomerular diseases, all of which are defined as rare by the US Food and Drug Administration, and therefore, new therapies have certain commercial benefits. This is an exciting time for researchers of FSGS, and this is a time that patients with FSGS and their families have reason for cautious optimism. Ongoing or recently completed trials within the United States include a phase 1 study of *N*-acetyl mannosamine (metabolic precursor of sialic acid) and phase 2/3 studies of sparsentan (a modified form of irbesartan that also antagonizes endothelin-1), abatacept (a fusion protein that targets CD80), Acthar (pituitary extract), fresolimumab (mAb directed against TGF- β), isotretinoin (retinoic acid derivative), and losmapimod (an mitogen-activated protein kinase inhibitor). Trials in other countries are studying dapagliflozin (Canada), lipoprotein removal (Japan), and mesenchymal stem cell therapy (Iran). Given the diverse forms of FSGS and the multiple molecular pathways involved in the pathogenesis of each form, it is critical that these trials and future trials characterize subjects with sufficient depth to determine the characteristics of responders and nonresponders.

FSGS comprises a complex set of syndromes, most with multiple causes, and hence, FSGS represents a diagnostic challenge that requires close and thoughtful collaboration between patient, family, nephrologist, pathologist, and geneticist to gather the necessary data. Information from clinical history, laboratory testing, renal biopsy, and in some patients, genetic testing can be used to identify which syndrome is present, guide therapy, and provide prognostic information. Many forms of FSGS tend to progress to ESRD, but new therapies are being tested that may improve the prognosis.

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