Top 10 Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for the Management of Focal Segmental Glomerulosclerosis

1 Primary FSGS

Primary FSGS will be used to denote the disease entity presumably caused by an as yet unidentified podocyte-toxic factor that is often amenable to immunosuppression. It is a clinical-pathologic syndrome characterized by FSGS lesions on histopathology with diffuse foot process effacement on electron microscopy, presence of nephrotic syndrome as defined by proteinuria >3.5 g/day plus hypoalbuminemia of <30 g/l, without the presence of a genetic or secondary cause. (Figure 1 & 2)

2 FSGS of Undetermined Cause (FSGS-UC)

FSGS can occur in the absence of a genetic or identifiable secondary cause, without nephrotic syndrome nor meeting the criteria for diffuse foot process effacement on electron microscopy and will be ascribed the term FSGS-UC. These individuals should be given supportive therapy and not be started on immunosuppression, with close monitoring of proteinuria and serum albumin. (Figure 1)

3 Genetic testing for FSGS

Genetic testing in adults with FSGS lesions should not be done routinely but may be considered in certain clinical situations, especially when there is a strong family history or resistance to immunosuppression. These individuals should be referred to specialized centers with expertise in genetic counselling and testing. (Figure 3)

4 Secondary FSGS

Adults with FSGS who do not have nephrotic syndrome should be evaluated for a secondary cause. Individuals with secondary forms of FSGS should not be given immunosuppressive treatment.

5 Initial treatment for primary FSGS

High-dose oral glucocorticoids are recommended as the first-line immunosuppressive treatment for primary FSGS. However, in adults with relative contraindications or intolerance to glucocorticoids, calcineurin inhibitors may be considered as an alternative first-line initial therapy in patients with primary FSGS.

6 Duration of high dose glucocorticoid treatment

Initial high-dose glucocorticoids should be continued until complete remission is achieved or as tolerated by patients up to a maximum of 16 weeks, which is used as the definition for steroid resistance. Patients who are likely to respond to therapy will demonstrate some degree of proteinuria reduction before 16 weeks and there is no need to persist with high dose glucocorticoid treatment if the proteinuria shows no signs of reduction, especially when the patient is experiencing side effects.

7 Glucocorticoid-resistant primary FSGS

Cyclosporine or tacrolimus treatment is recommended for adults with steroid-resistant primary FSGS, and should be dosed for at least 6 months before considered resistant.

8 Duration of calcineurin inhibitor therapy

Adults with steroid-resistant primary FSGS who respond to calcineurin inhibitor treatment should receive the drug for a minimum of 12 months, so as to minimize the risk of relapses.

9 Treatment beyond glucocorticoid and calcineurin inhibitors

Adults who have steroid-resistant primary FSGS with resistance or intolerance to calcineurin inhibitors should be referred to specialized centers for consideration of rebiopsy, alternative treatment, or enrollment in a clinical trial.

10 Treatment of relapsing primary FSGS

Adults with previous steroid-sensitive primary FSGS who experience a relapse can be treated using the same approach as that for adults with relapsing minimal change disease.

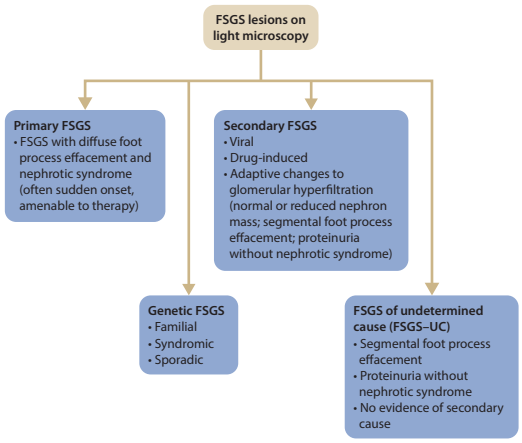

Figure 1

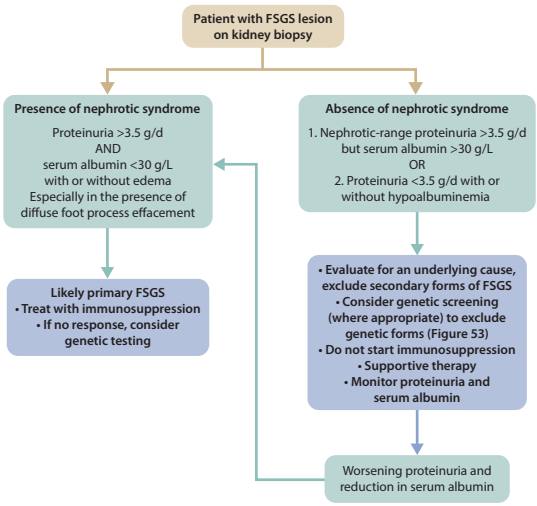

Figure 2

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic

Considerations for genetic testing in adults with FSGS

- When there is a strong family history and/or clinical features suggestive of a syndromal disease
- Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype
- Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment
- Determining the risk of recurrent disease in kidney transplantation
- Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants
- Aiding in prenatal diagnosis

Figure 3