Therapeutic Approach To Podocytopathic Diseases

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- Proteinuric kidney diseases can be divided into glomerular or non-glomerular forms, depending on whether protein loss occurs across the glomerular filtration barrier or results from insufficient reabsorption of filtered protein by the proximal tubule

- Glomerular proteinuria is defined by a predominance of albumin whereas, in non-glomerular forms, albumin is only a minor component

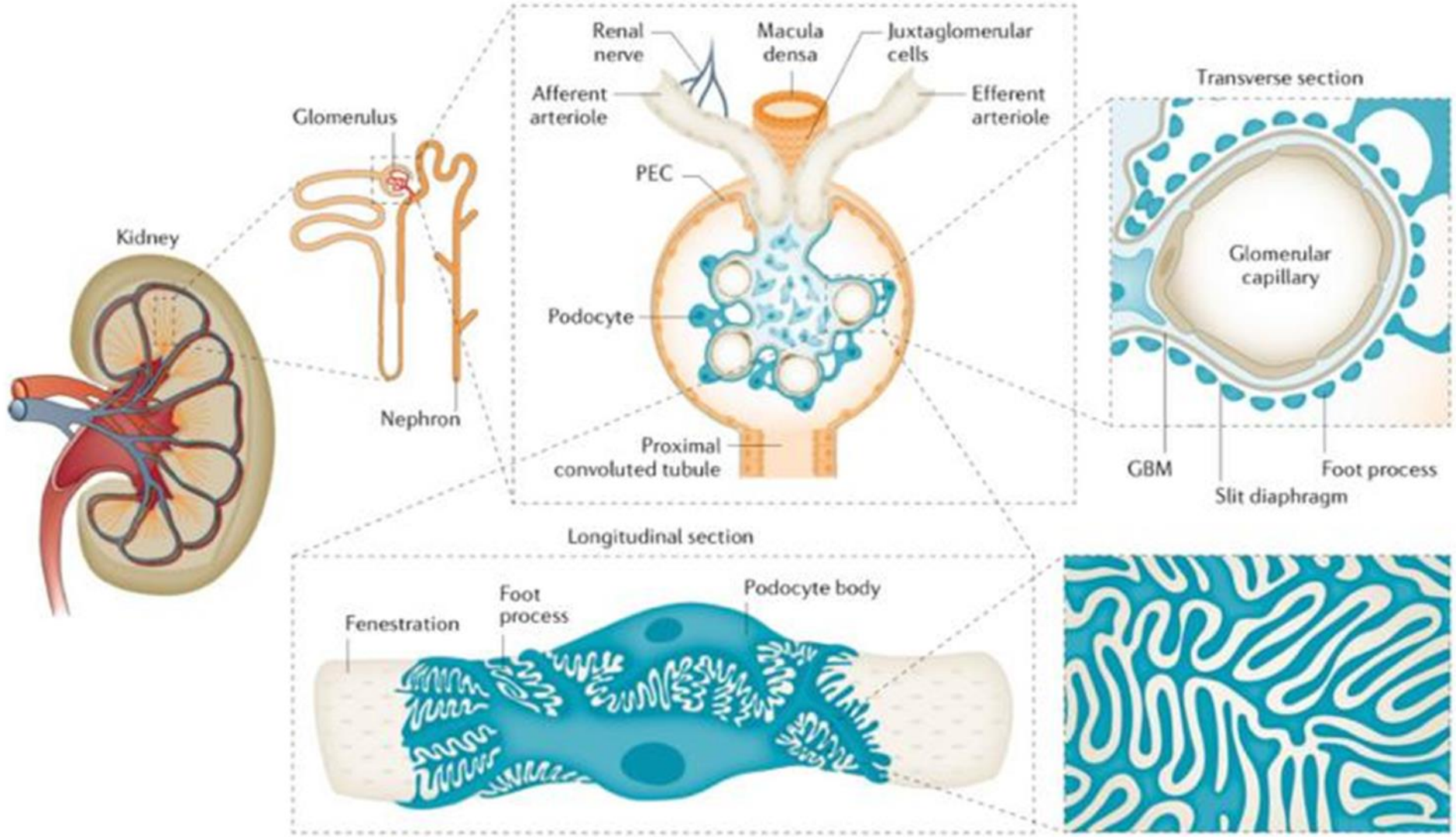


Fig. 2 | **Structure of the nephron, the glomerulus and the filtration barrier.** The kidney is comprised of functional units, nephrons, each of which is made of a glomerulus and a tubule. In healthy humans, the average number of nephrons is ~1 million (range 250,000 to <2.5 million). The glomerulus is composed of a tuft of capillaries covered by visceral epithelial cells — the podocytes — and surrounded by a capsule lined on the inner surface by parietal epithelial cells (PECs). The latter cell population contains podocyte progenitors, which are motile and progressively differentiate into podocytes in the region near the vascular pole of the glomerulus. The vascular pole of the glomerulus includes both the afferent and efferent arterioles (transverse section). The outermost layer is composed of podocytes adhering to the glomerular basement membrane (GBM) and interdigitating (longitudinal section), with the slit diaphragm spanning each gap between pairs of foot processes. The innermost layer is constituted by fenestrated endothelial cells.

- podocyte injuries without immune complex deposits produce different histopathological lesion patterns evident on biopsy, of which four types can be distinguished;

- Diffuse mesangial sclerosis (DMS)
- Minimal change disease
- focal segmental glomerulosclerosis (FSGS)
- Collapsing glomerulopathy

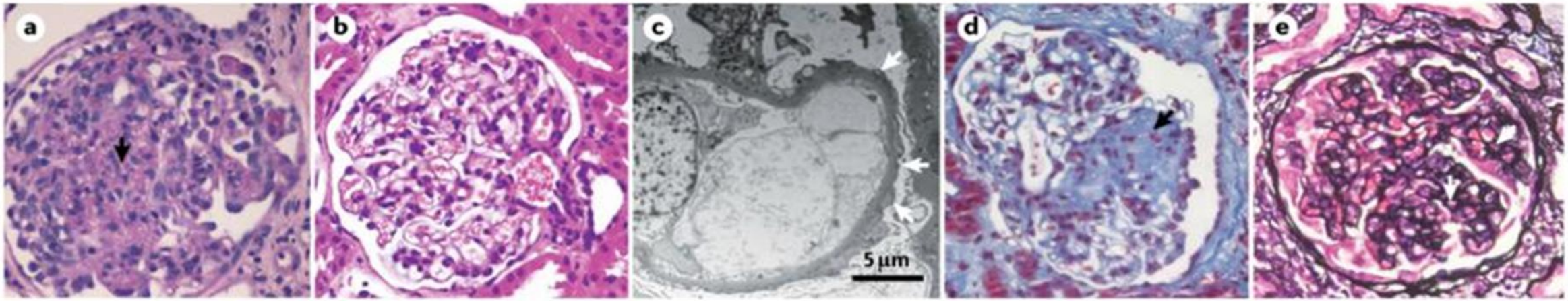


Fig. 7 | **Pathology of podocytopathies. a** | The lesion pattern of diffuse mesangial sclerosis occurs only in young children and is usually associated with severe nephrotic syndrome. The glomerulus shows diffuse mesangial sclerosis (arrow) with prominent mesangial consolidation, closure of the capillary loops and overlying prominent immature podocytes. Periodic acid–Schiff staining; magnification ×400. **b** | The lesion pattern of minimal changes on light microscopy shows a normal glomerulus. Haematoxylin and eosin staining; magnification ×200. **c** | On electron microscopy, minimal change disease foot process effacement (arrows) is visible. Minimal change lesions are usually associated with steroid-sensitive nephrotic syndrome but can also be associated with isolated proteinuria or, rarely, with steroid-resistant nephrotic syndrome, particularly in the early phases of the disease. **d** | The lesion pattern of focal segmental glomerulosclerosis (FSGS) is associated with diverse clinical presentations but most frequently with isolated proteinuria or steroid-resistant nephrotic syndrome. FSGS lesions (arrow) have been distinguished into five subtypes but the lack of accuracy to predict a specific cause of disease or outcome limits their clinical relevance[264]. In addition, particularly in maladaptive FSGS, lesions typically start in juxtamedullary nephrons, which are sensitive to haemodynamic injury and harbour fewer podocyte progenitors, which explains why FSGS starts and is more frequently observed in juxtamedullary glomeruli[53]. Perihilar and cellular variants share an intermediate prognosis and the former is associated with maladaptive (secondary) causes[265]. Coarse segmental staining for IgM and C3 can occur with minimal or FSGS lesions. At electron microscopy, limited effacement with narrow foot processes is frequent in maladaptive podocytopathy with secondary FSGS lesions[197], whereas diffuse foot process effacement is typical of primary podocytopathies and virus-related or drug-related podocytopathy[266–268]. Masson's trichrome staining; magnification ×200. **e** | The lesion pattern of collapsing glomerulopathy is less common and usually associated with severe steroid-resistant nephrotic syndrome. Traditionally, collapsing glomerulopathy has been associated with people of African descent and a fast rate of progression to end-stage kidney disease, whereas tip lesions (which are the result of proliferation of parietal epithelial cells at the urinary pole) are associated with white ethnicity, a low histological score at presentation and a better response to therapy. The collapse of the tuft is evident by the circular black lines (capillaries) and loss of the urinary space (arrows). Jones methenamine silver staining; magnification ×200.

- The histomorphological lesions are unspecific lesions and represent different patterns of podocyte injury rather than defining a unique disease cause or diagnosis that would imply a specific therapy

- The prognosis of patients with genetic podocytopathy is generally poor, with >50% of patients developing ESKD within 5 years of the diagnosis; patients who lack a genetic cause of the disease have a better prognosis, particularly when they are responsive to immunosuppressive treatmen

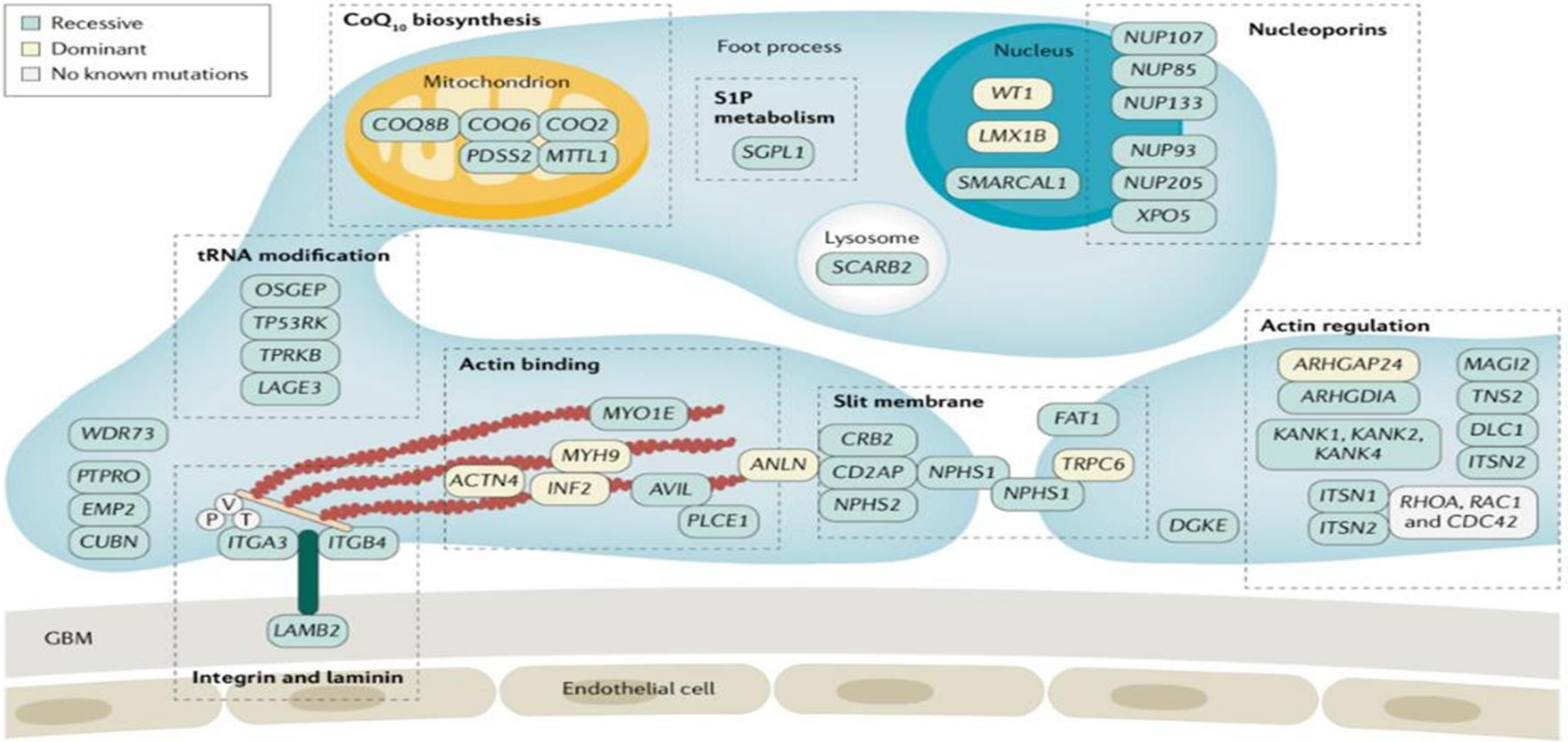


Fig. 5 | **Monogenetic diseases and SRNS.** Identification of single-gene causes of steroid-resistant nephrotic syndrome (SRNS) placed the podocyte at the centre of SRNS pathogenesis because most of the implicated genes are expressed in podocytes. Foot processes interdigitate with those from neighbouring podocytes, forming the glomerular slit membrane, which is critical for filtering and retention of protein in the bloodstream. Its integrity is lost in nephrotic syndrome. Proteins encoded by genes that, if mutated, cause monogenic SRNS localize to specific subcellular sites of podocytes depicted here. CoQ_{10}, coenzyme Q_{10}; GBM, glomerular basement membrane; P, paxillin; T, talin; V, vilin. Adapted with permission from REF.[263], Oxford University Press.

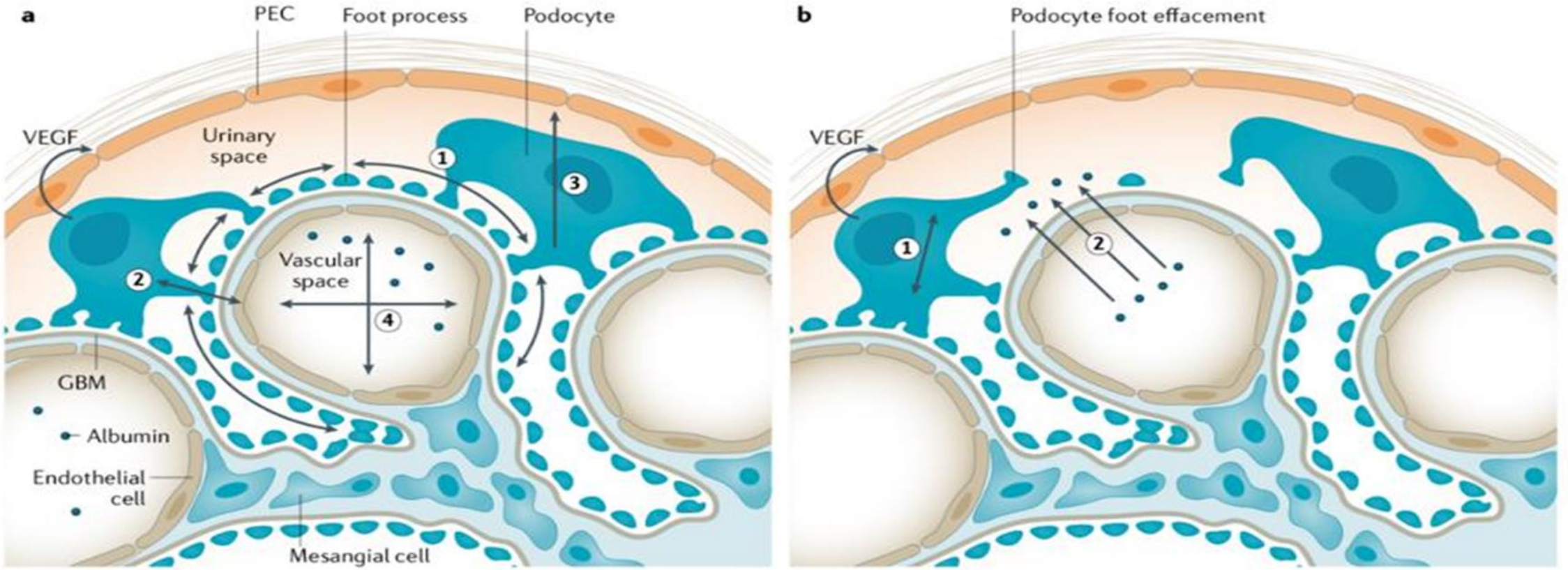


Fig. 3 | **Mechanical podocyte stress. a** | Under normal conditions, several kinds of physical stress are present in the glomerulus[46,47]. The hydrostatic pressure gradient across the glomerular capillary and the Bowman (urinary) space outside the capillary creates circumferential stress on the podocyte foot processes (**1**). Fluid filtration across the glomerulus generates shear stress on the lateral aspects of the foot processes (**2**). Filtrate flow laterally across the podocyte cell body in the Bowman space confers shear stress (**3**). Podocyte-derived vascular endothelial growth factor (VEGF) acts on intravascular endothelial cells and is needed for maintaining the glomerular filtration barrier and keeping serum proteins such as albumin inside the vasculature (**4**). **b** | Numerous medical conditions increase the filtration load to the kidneys, which translates into increasing filtration pressure at the level of individual glomeruli. As a trade-off, horizontal podocyte stress (**1**) increases as the number of podocytes remains constant. Such podocyte stretching ultimately leads to compromise of the filtration barrier, podocyte detachment and loss, and proteinuria. Proteinuria also increases oncotic pressure acting on podocytes (**2**), as protein in the Bowman space further increases the amount of fluid passing the filtration barrier, which defines single-nephron filtration. This mechanism is common to most forms of progressive chronic kidney disease, as the total effective glomerular filtration surface declines. Hyperfiltration is present early in some forms of chronic glomerular disease, including diabetes mellitus. GBM, glomerular basement membrane; PEC, parietal epithelial cell.

drive focal scarring. Indeed, the proliferation, migration — or persistent NOTCH expression[61], activated parietal

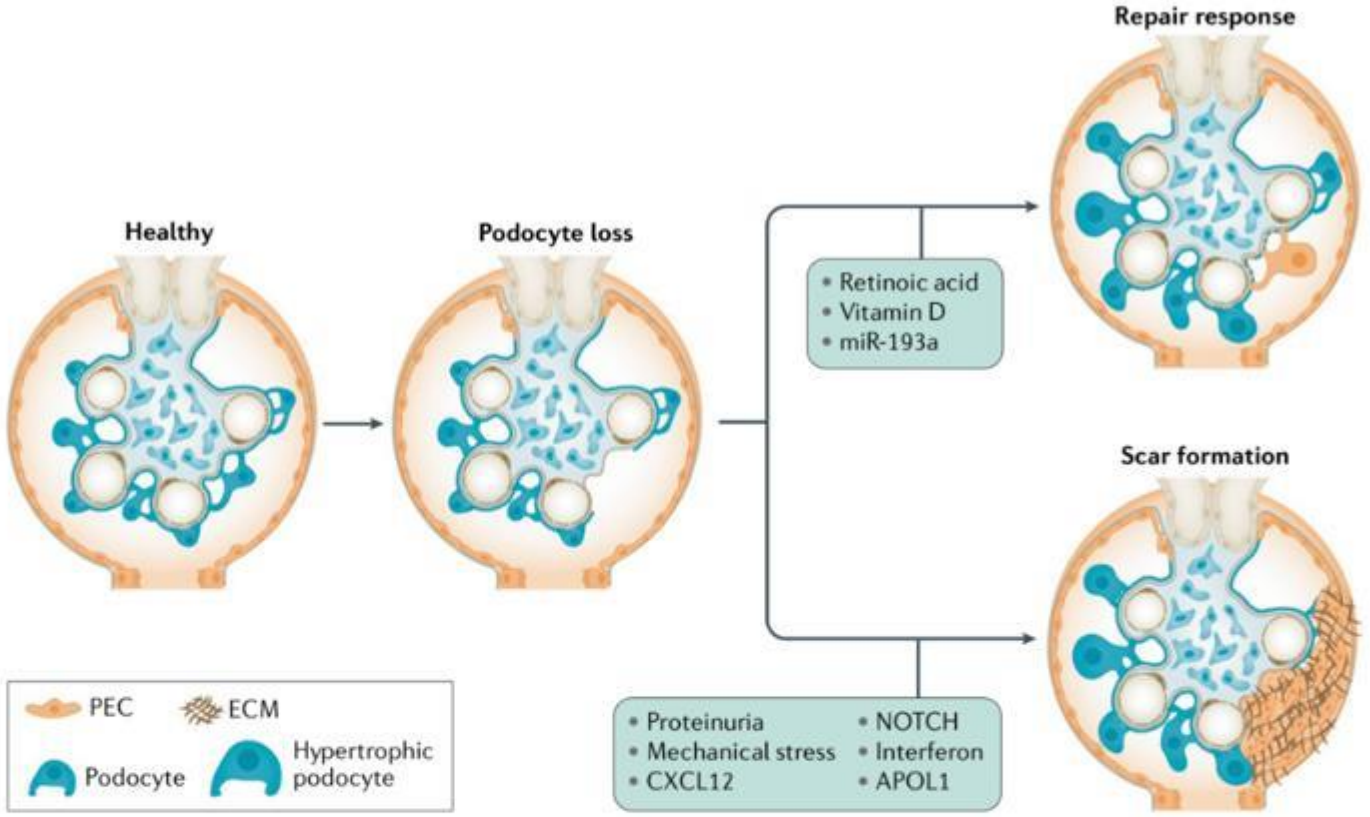
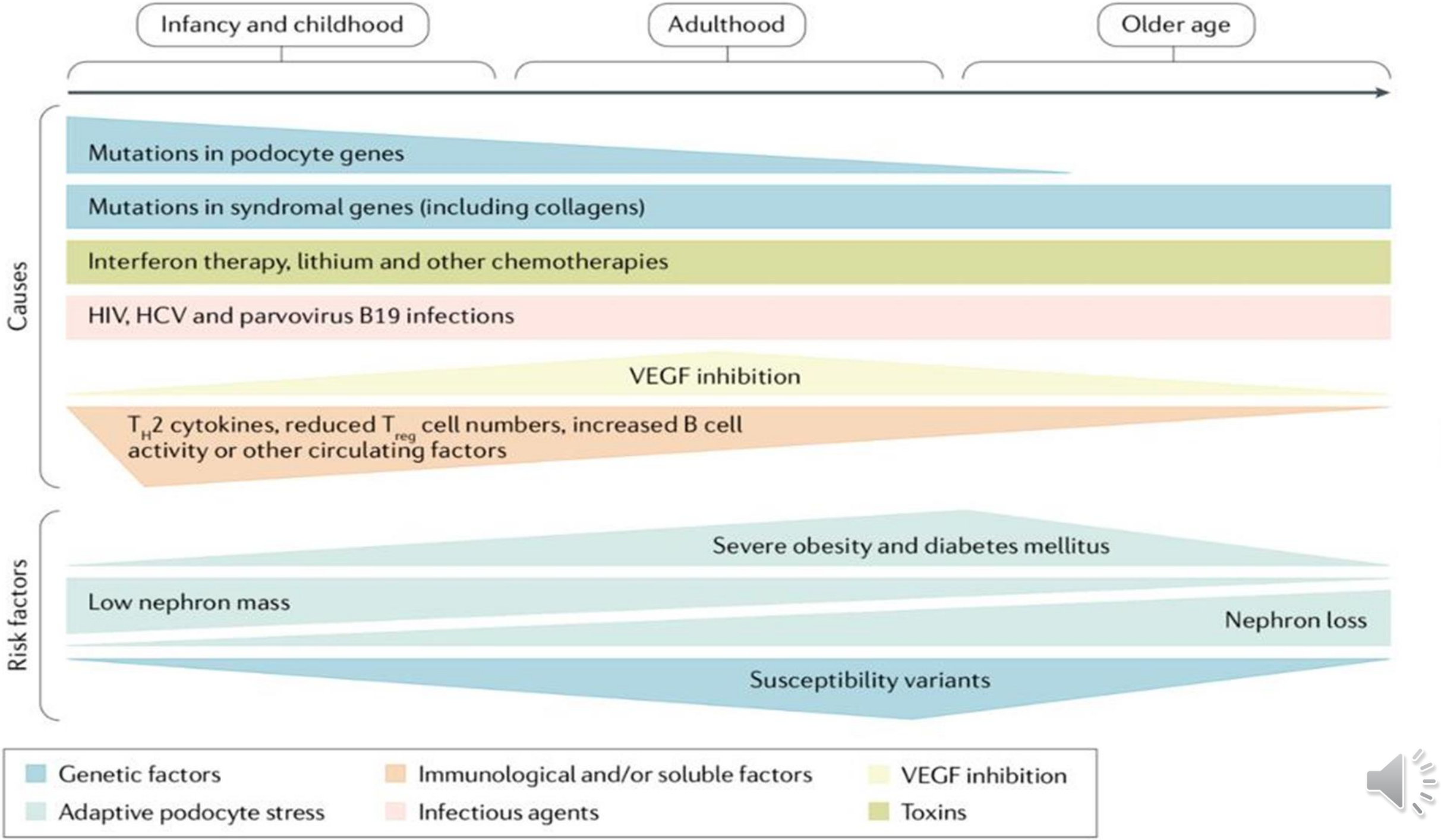


Fig. 4 | **Consequences of podocyte loss.** Following injury, podocyte loss can occur that can trigger two responses. First, the remaining podocytes adapt by increasing their size to cover the newly denuded glomerular basement membrane (podocyte hypertrophy). Second, parietal epithelial cells (PECs) along the Bowman capsule, which include a population of resident podocyte progenitors, supply new podocytes after injury and loss. These mechanisms contribute to podocyte functional recovery and reduce proteinuria following injury but can be inefficient or become maladaptive. Indeed, hypertrophic podocytes may be unable to maintain a normal foot process structure, leading to a further increase in local shear stress that triggers further podocyte detachment. In addition, differentiation of PECs into podocytes can be hampered by mechanical stress and proteinuria, leading to inefficient podocyte regeneration and scar formation. ECM, extracellular matrix.

- Risk factors Podocytopathies can have a single cause, as frequently in the many monogenetic forms manifesting early in life or in the forms arising from a single environmental risk factor

- Podocytopathies can have a combination of multiple genetic and/or environmental risk factors causing podocyte injury, acting in concert to reach a threshold effect for the development of proteinuria


Infancy and childhood
Adulthood
Older age
Causes
Mutations in podocyte genes
Mutations in syndromal genes (including collagens)
Interferon therapy, lithium and other chemotherapies
HIV, HCV and parvovirus B19 infections
VEGF inhibition
T_H2 cytokines, reduced T_{reg} cell numbers, increased B cell activity or other circulating factors
Risk factors
Severe obesity and diabetes mellitus
Low nephron mass
Nephron loss
Susceptibility variants
Genetic factors
Adaptive podocyte stress
Immunological and/or soluble factors
Infectious agents
VEGF inhibition
Toxins

❖ New-onset nephrotic syndrome

- Oral steroid therapy for at least 2–3 months is typically initiated with new-onset nephrotic syndrome without histological confirmation by kidney biopsy in children and adolescents

- Hypertension
- Gross haematuria
- Marked elevation in serum creatinine
- Abnormal complement levels
- Extrarenal symptoms

- Approximately 80–90% of patients will experience complete remission within the 4 weeks of initiating therapy but some centres also administer three intravenous pulses of methylprednisolone every other day at this point.

- Patients who do not undergo complete remission and perhaps those with only a modest partial remission are categorized as having SRNS and require prompt kidney biopsy and genetic testing

- Only 30% of children with SSNS maintain remission, 10–20% will have fewer than four relapses and the remaining will have frequent relapses (FRNS) or will relapse while on a steroid taper (SDNS)

- Response to therapy is typically slower in adults than in children, justifying prolonged steroid courses before defining treatment failure is needed

- Mycophenolate mofetil combined with low-dose steroids may induce disease remission in adult podocytopathies at rates comparable with standard therapy, possibly alleviating the risk of steroid-related adverse effects such as diabetes and hypertension in high-risk patients.

- Slow tapering of immunosuppressive drugs over 6 months is a widely accepted measure to reduce the risk of relapse

- Almost all children with FRNS experience a progressive decrease in the number of relapses over time and many ultimately go into sustained or even permanent remission.
- Limited long-term outcome data in adults suggests that patients who have frequent relapses or SDNS during childhood are at risk of experiencing relapses during adulthood and adverse drug effects
- Kidney function remains normal in adulthood as long as patients remain responsive to treatment and long-term sequelae are generally related to medication adverse effects
- Various glucocorticoid regimens have been used to treat FRNS and SDNS. Frequent relapses usually require steroid dose adjustment above the individual threshold

- Alternate-day steroid dosing (in children) and steroid-sparing agents are commonly used to avoid long-term steroid toxicity

- Calcineurin inhibitors are frequently chosen as steroid-sparing agents based on evidence from small trials despite relapse rates as high as 75% upon discontinuation.

- These events often lead to prolonged treatment courses, which pose a considerable risk of calcineurin inhibitor-induced nephrotoxicity

Table 2 | **Potential adverse events associated with immunosuppressive treatment**

Treatment	Possible adverse effects	Measures to reduce toxicity
Steroids	Cataracts[233]; excessive weight gain, obesity or Cushingoid features[243]; suppression of the hypothalamic–pituitary–adrenal axis[244]; behaviour disturbances (such as hyperactivity or depression); hypertension[243]; osteopenia[243]; statural growth impairment (in children)[232]	Alternate-day therapy or low dose (<1 mg) whenever possible[234]
Ciclosporin	Nephrotoxicity[229,230,245,246]; hyperlipidaemia; hypertrichosis; gum hypertrophy	Blood trough level should not exceed 200 ng/ml (REF.[247]); once remission is achieved, decrease the dose to <5 mg/kg (REF.[248])
Tacrolimus	Nephrotoxicity[249]; glucose intolerance; headache; seizures	If possible, target lower trough concentrations (3–5 ng/ml)[250]
Mycophenolate mofetil	Gastrointestinal disturbances (abdominal pain and diarrhoea); haematological abnormalities and infections; teratogenic effects	Monitoring to target area under the curve (>45 μg·h·ml)[251]; recommend contraception in women with child-bearing potential[252]
Rituximab	Infusion-related reactions; leukopenia and/or hypogammaglobulinaemia; neutropenia; hepatitis induced by hepatitis B virus reactivation; progressive multifocal leukoencephalopathy; pulmonary fibrosis	If anaphylaxis is suspected, discontinue treatment; regular monitoring of complete blood count; recommend G-CSF and antibiotics administration if severe neutropenia with infection occurs; discontinue treatment
Levamisole	Neutropenia; vasculitis; flu-like symptoms	Regular monitoring of complete blood count; discontinue treatment if neutropenia or vasculitis occur
Cyclophosphamide	Neutropenia and infection[253]; gonadal toxicity; malignancy; alopecia; haemorrhagic cystitis	Discontinue treatment if the WBC count falls <3,000/mm^3 (until the count rises); maximum daily dose and cumulative dose should not exceed 2.5 mg/kg and 300 mg/kg, respectively

- In paediatric patients, mycophenolate mofetil seems equally as effective as levamisole but not as effective as ciclosporin in achieving remission although the evidence is still limited

- In addition, higher doses of mycophenolate mofetil than those used in kidney-transplanted recipients seem to be necessary in children with nephrotic syndrome to achieve remission

- Adrenocorticotropic hormone has been used but its efficacy is controversial because studies yielded conflicting results

- In a very small number of cases, patients who were initially steroid sensitive become steroid resistant but can be usually successfully treated with alternative immunosuppressive therapies. these patients are at increased risk for ESKD

- SRNS Steroid resistance is defined as the lack of complete remission despite full-dose steroids for an adequate period of time

- Screening for genetic mutations should be performed in all children as well as in adults with SRNS before considering additional immunosuppressive therapies as these are rarely effective in podocytopathies with a genetic cause

- Genetic testing results take at least 4–6 weeks to become available, it may be appropriate to start a second-line therapy in selected patients in the interim

- In patients in whom a genetic mutation is identified, immunosuppressive treatments can usually be discontinued and anti-proteinuric regimens with a RASi become the mainstay of therapy to attenuate CKD progression

- Approximately 60% of steroid-resistant patients may respond to ciclosporin or tacrolimus at moderate doses with reduced proteinuria and slower or halted CKD progression

- As relapse is frequent after the withdrawal of these drugs, prolonging treatment for 1–3 years after remission is achieved is advisable.

- Mycophenolate mofetil alone achieves remission in fewer than half of patients but its use as maintenance treatment might reduce the calcineurin inhibitor dose and limit nephrotoxicity.

- Mycophenolate mofetil in combination with calcineurin inhibitors may be a rescue approach.

- Given the value of rituximab as a treatment in SSNS and immune-mediated podocytopathies, other CD20-targeting or B cell-targeting drugs are being considered

- **Ofatumumab** is a more potent CD20+ B cell depleter and may replace rituximab in patients with drug hypersensitivity

- **Belimumab** (which targets B cell-activating factor), is an established maintenance therapy in SLE & other forms of nephrotic syndrome

- Many attempts to find new treatments for podocytopathies beyond the traditional immunosuppressive drugs have been unsuccessful

- In secondary podocytopathies, management is focused on treating the underlying disorder.

- Genetic testing identifies the diagnosis underlying SRNS in up to 30–60% of children and young adults, and some of these patients may benefit from avoiding unnecessary immunosuppressant therapies and from receiving specific treatments

- For example, patients with pathogenetic mutations in coenzyme Q10 biosynthesis (COQ2, COQ6 and ADCK4) may respond to oral coenzyme Q10 supplementation.

Complications

- Nephrotic syndrome requires additional treatment for symptoms and to prevent complications

❖ Edema

- Patients are initially treated with loop diuretics and dietary sodium restriction to ~2 g per day and are monitored closely for clinical signs of hypovolaemia

- Amiloride ,Thiazide diuretics or, alternatively, triamterene or acetazolamide can be combined with loop diuretics in patients with refractory oedema

- Hyperlipidaemia is problematic in patients with nephrotic proteinuria as it increases the risk for progressive loss of renal function and cardiovascular disease

- Statins are the treatment of choice if hyperlipidaemia persists after treatment of the underlying kidney disorder with immunosuppressive therapy and/or a RASi.

- Cytochrome P3A4 inhibitors such as cyclosporin, increase plasma levels of statins and require dose adaptations of the statins

❖ Thromboembolism

- Adults with nephrotic syndrome have a high incidence (10–40%) of arterial and venous thrombosis, particularly deep vein and renal vein thrombosis, in some cases leading to pulmonary embolism

- Venous and arterial thromboses are reported in only 2–3% of children with nephrotic syndrome, although this may be an underestimate because many episodes are asymptomatic.

- Adults and infants with congenital nephrotic syndrome are at increased risk for renal vein thrombosis but this complication is rare in children

- Pulmonary embolism should be suspected in patients with pulmonary or cardiovascular symptoms and can be confirmed by radioisotope scanning

- Prophylactic anticoagulation with oral anticoagulants is recommended only

- After the first thromboembolic episode
- Albumin concentration is <2 g/dl
- Fibrinogen is >6 g/l
- Anti thrombin III is <70% of normal

- Prophylactic anticoagulation is continued for as long as these alterations persist

❖ Infections

- To prevent pneumococcal infections, children and adult with nephrotic syndrome should receive 1–2 doses of conjugate 13-valent pneumococcal vaccine (PCV13) preceding the 23-valent polysaccharide (PPSV23) (if not previously immunized)

- Varicella can also cause major morbidity and mortality in these patients

- Centre-specific guidelines on influenza vaccination should be followed

- In general, vaccinations pose a minimal risk for relapse of nephrotic syndrome; further, the protection gained greatly outweighs this risk

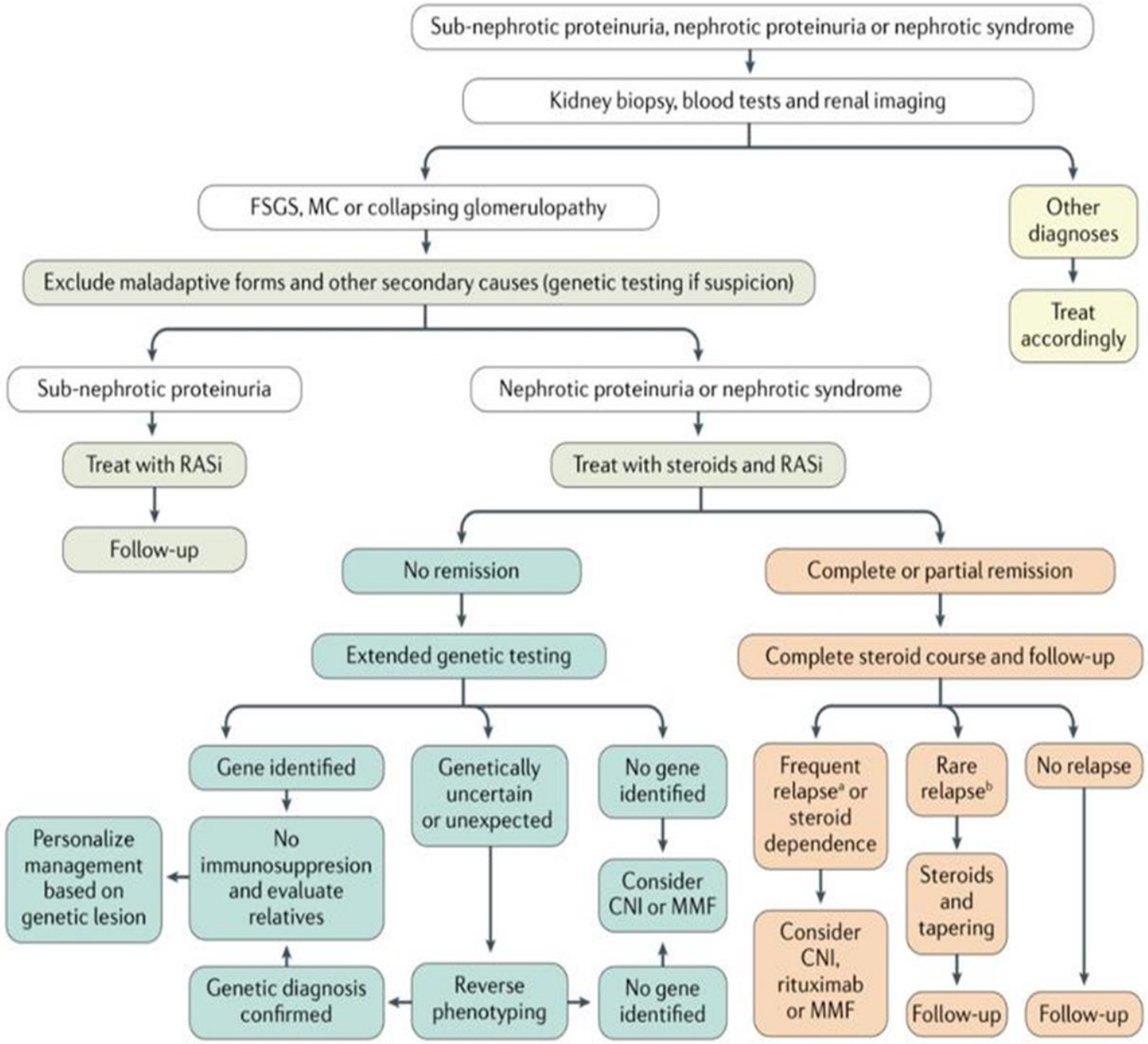
- A genetic diagnosis may generate new questions for families

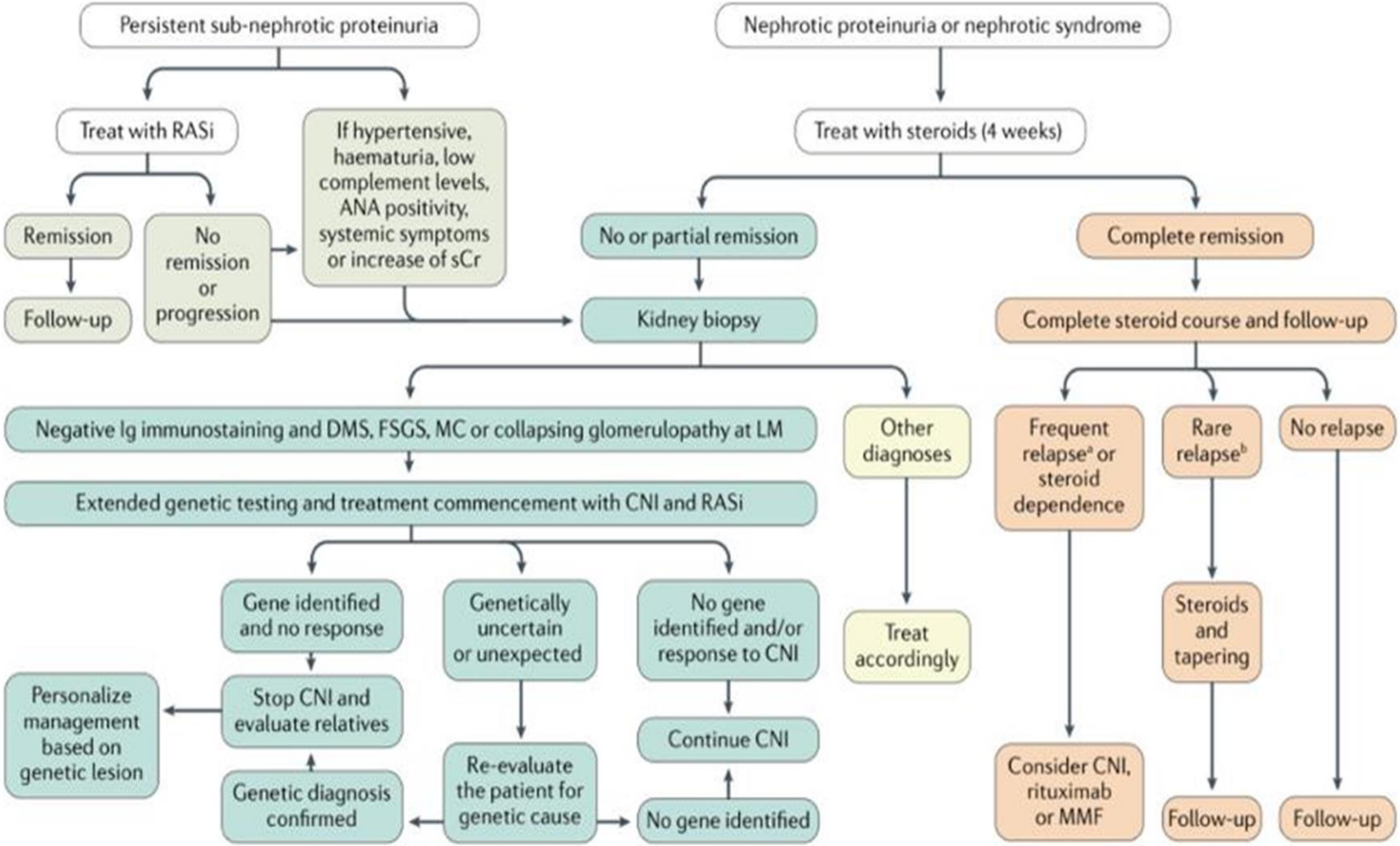
- Whether or not to test other family members ?

- Benefits of genetic testing include the opportunity for early diagnosis through screening and for selecting the optimal therapy

- Risks include anxiety about test results, access to health insurance in some countries and the possibility of unexpected information about biological relationships among family members

- The universal right to not know, especially for clinically unaffected family members, should be respected


Sub-nephrotic proteinuria, nephrotic proteinuria or nephrotic syndrome
Kidney biopsy, blood tests and renal imaging
FSGS, MC or collapsing glomerulopathy
Other diagnoses
Exclude maladaptive forms and other secondary causes (genetic testing if suspicion)
Treat accordingly
Sub-nephrotic proteinuria
Nephrotic proteinuria or nephrotic syndrome
Treat with RASi
Treat with steroids and RASi
Follow-up
No remission
Complete or partial remission
Extended genetic testing
Complete steroid course and follow-up
Gene identified
Genetically uncertain or unexpected
No gene identified
Frequent relapse[a] or steroid dependence
Rare relapse[b]
No relapse
Personalize management based on genetic lesion
No immunosuppresion and evaluate relatives
Consider CNI or MMF
Steroids and tapering
Consider CNI, rituximab or MMF
Genetic diagnosis confirmed
Reverse phenotyping
No gene identified
Follow-up
Follow-up


Persistent sub-nephrotic proteinuria
Treat with RASi
Remission
Follow-up
No remission or progression
If hypertensive, haematuria, low complement levels, ANA positivity, systemic symptoms or increase of sCr
Nephrotic proteinuria or nephrotic syndrome
Treat with steroids (4 weeks)
No or partial remission
Kidney biopsy
Negative Ig immunostaining and DMS, FSGS, MC or collapsing glomerulopathy at LM
Extended genetic testing and treatment commencement with CNI and RASi
Gene identified and no response
Stop CNI and evaluate relatives
Genetic diagnosis confirmed
Personalize management based on genetic lesion
Genetically uncertain or unexpected
Re-evaluate the patient for genetic cause
No gene identified and/or response to CNI
Continue CNI
No gene identified
Other diagnoses
Treat accordingly
Complete remission
Complete steroid course and follow-up
Frequent relapse[a] or steroid dependence
Consider CNI, rituximab or MMF
Rare relapse[b]
Steroids and tapering
Follow-up
No relapse
Follow-up

❖ OUTLOOK

- **Specific molecular pathways** (altered in the underlying podocytopathy)
- **Protect podocytes** (injury, detachment and loss)
- **Stem cell therapy** (pluripotent stem cells)
- **Genetic modified cells**
- **Small interfering RNA therapeutics**
- **Cell regeneration**

THANK YOU FOR ATTENTION