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Mallinckrodt Pharmaceuticals
Autoimmune and Rare Diseases

FSGS and Nephrotic Syndrome

Kirk Campbell, M.D.

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Autoimmune and Rare Diseases

Thanks to our speaker!

Kirk Campbell, M.D.

- Associate Professor of Medicine, Vice Chair for Diversity and Inclusion and Director of the Nephrology Fellowship Program at Icahn School of Medicine at Mount Sinai
- In addition to treating patients with renal disease, Dr. Campbell leads an NIH-funded research program focused on understanding the mechanism of podocyte injury in the progression of proteinuric kidney diseases.
- He actively participates in clinical trials testing novel agents for primary glomerular disease.
- Prior Nephcure Foundation Young Investigator Awardee

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Objectives

- Explain proteinuria (protein in urine)
- Define nephrotic syndrome
- Describe the features and development of FSGS
- Discuss current and upcoming treatment options

Why is this topic important?

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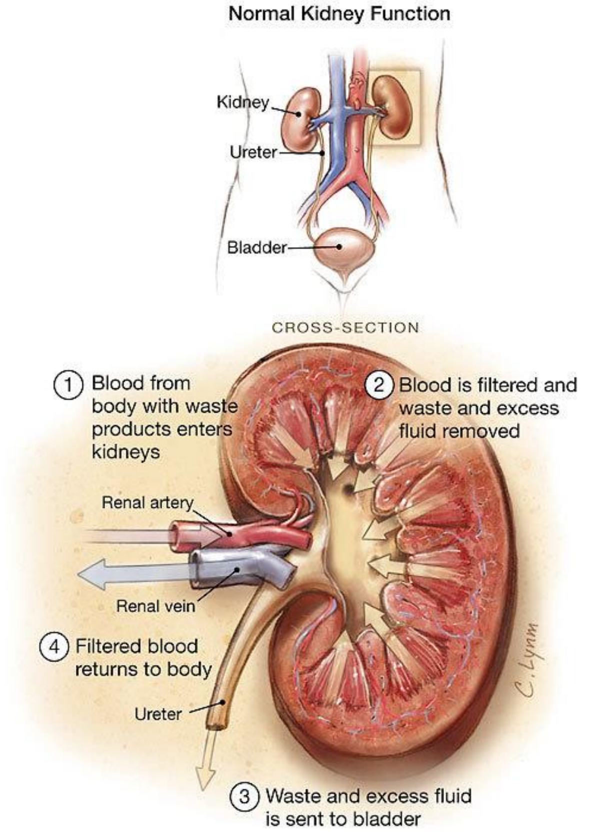
Kidneys remove waste and fluid in urine



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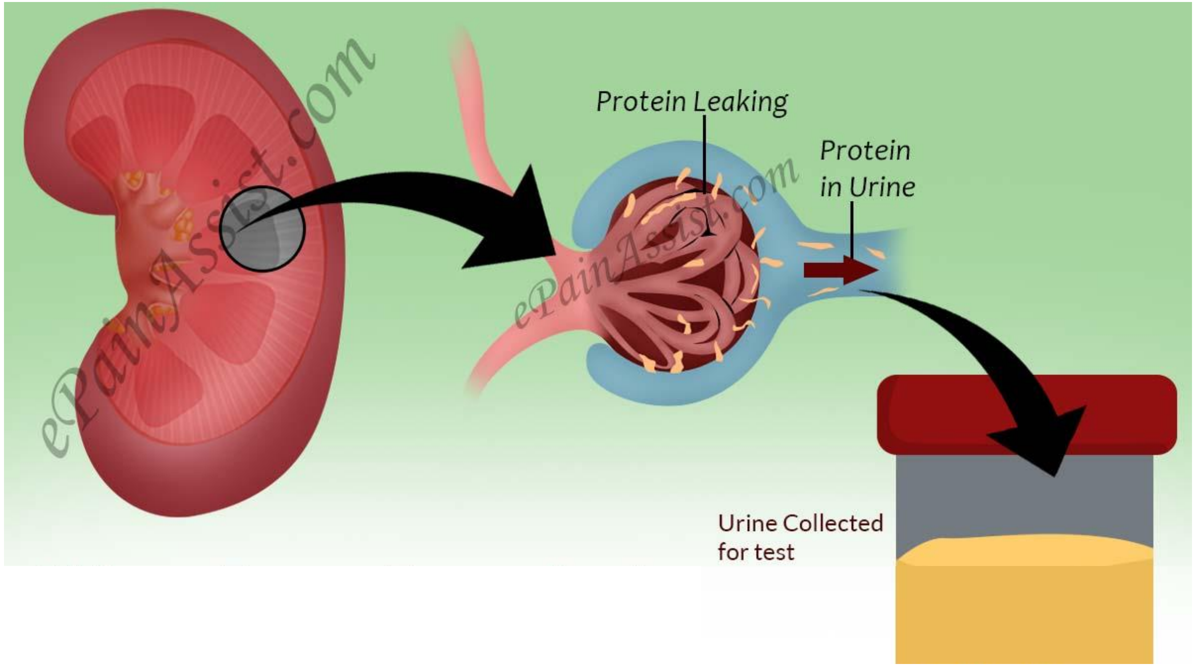
Proteinuria = protein in the urine



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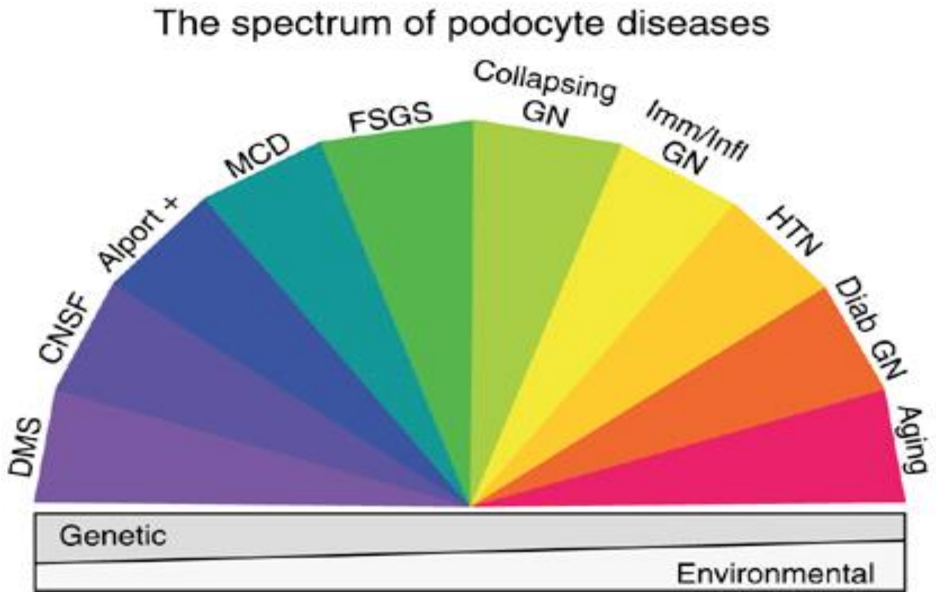
Burden of proteinuric kidney disease



~ 90% of ESKD

~$20 billion/year expenditure

Wiggins, Kidney Int 2007

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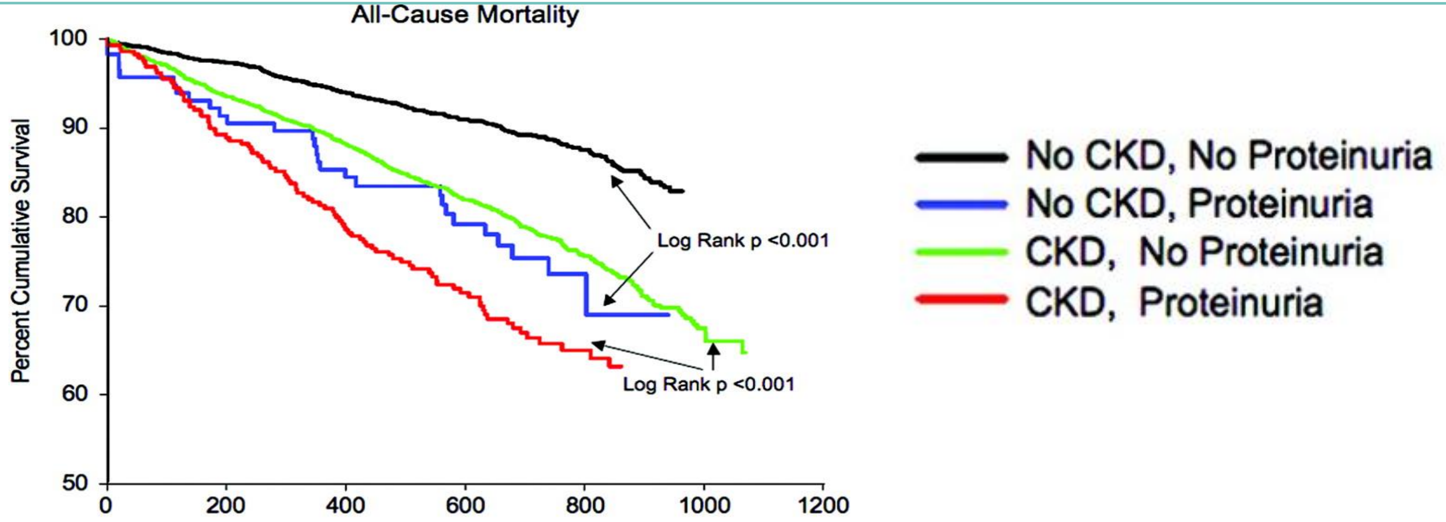
Proteinuric kidney disease as a cause of death in the US

Table B. Deaths and death rates for 2010, and age-adjusted death rates and percent changes from 2009 to 2010, for the 15 leading causes of death: United States, final 2009 and preliminary 2010

Rank[1]	Cause of death (based on the *International Classification of Diseases, Tenth Revision*, Second Edition, 2004)	Number	Death rate	Age-adjusted death rate 2010	Age-adjusted death rate 2009[2]	Age-adjusted death rate Percent change
...	All causes	2,465,932	798.7	746.2	749.6	–0.5
1	Diseases of heart (I00–I09,I11,I13,I20–I51)	595,444	192.9	178.5	182.8	–2.4
2	Malignant neoplasms (C00–C97)	573,855	185.9	172.5	173.5	–0.6
3	Chronic lower respiratory diseases (J40–J47)	137,789	44.6	42.1	42.7	–1.4
4	Cerebrovascular diseases (I60–I69)	129,180	41.8	39.0	39.6	–1.5
5	Accidents (unintentional injuries) (V01–X59,Y85–Y86)[3]	118,043	38.2	37.1	37.5	–1.1
6	Alzheimer's disease (G30)	83,308	27.0	25.0	24.2	3.3
7	Diabetes mellitus (E10–E14)	68,905	22.3	20.8	21.0	–1.0
8	Nephritis, nephrotic syndrome and nephrosis (N00–N07,N17–N19,N25–N27)	50,472	16.3	15.3	15.1	1.3
9	Influenza and pneumonia (J09–J18)[4]	50,003	16.2	15.1	16.5	–8.5
10	Intentional self-harm (suicide) (X60–X84,Y87.0)[3]	37,793	12.2	11.9	11.8	0.8
11	Septicemia (A40–A41)	34,843	11.3	10.6	11.0	–3.6
12	Chronic liver disease and cirrhosis (K70,K73–K74)	31,802	10.3	9.4	9.1	3.3
13	Essential hypertension and hypertensive renal disease (I10,I12,I15)	26,577	8.6	7.9	7.8	1.3
14	Parkinson's disease (G20–G21)	21,963	7.1	6.8	6.5	4.6
15	Pneumonitis due to solids and liquids (J69)	17,001	5.5	5.1	4.9	4.1
...	All other causes (residual)	488,954	158.5	...	...	...

CDC National Vital Statistics Report 2012

Regardless of CKD status, proteinuria increases chances of death



Inder S. Anand et al. Circulation. 2009;120:1577-1584

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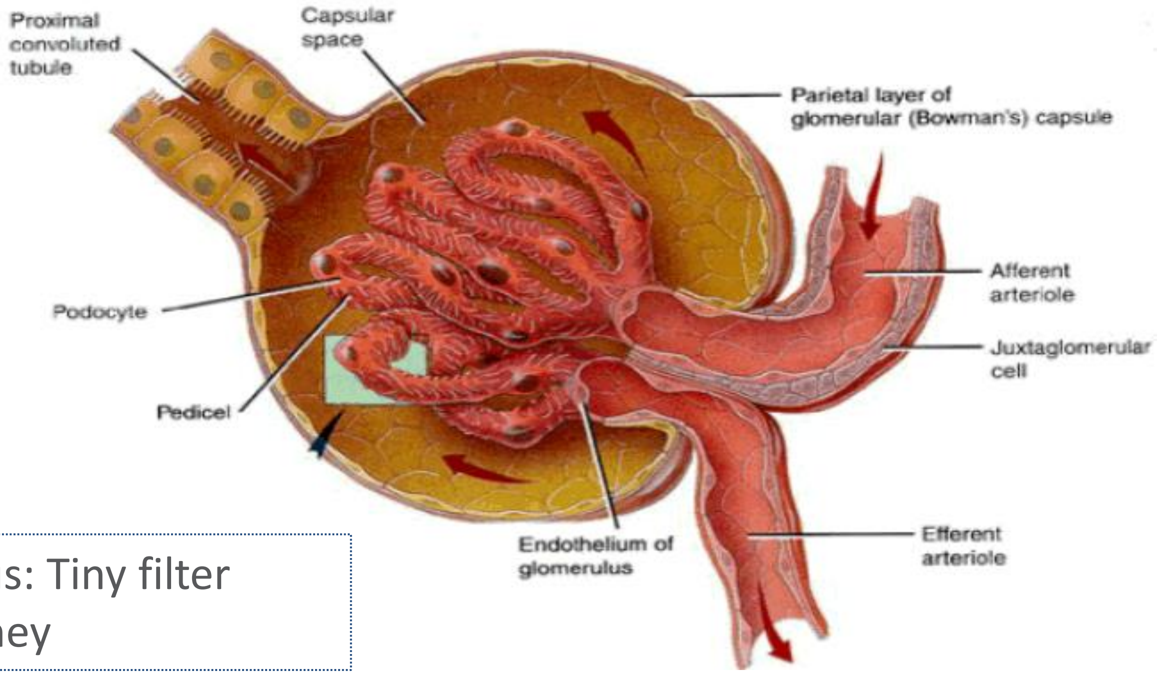
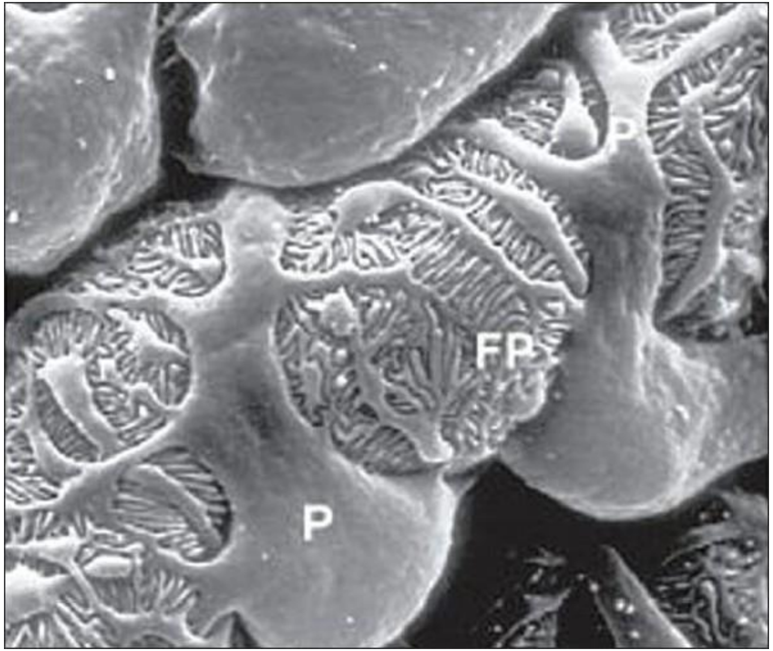
Anatomy of the glomerulus



Glomerulus: Tiny filter inside kidney

Podocytes = key target cells for injury



Nephrotic Syndrome

- Proteinuria greater than 3.5 grams/day
  - Too much protein leaving through the urine as a result of broken kidney filters
- Hypoalbuminemia (low albumin in blood)
- Hyperlipidemia (too much fat, such as cholesterol, in blood)
- Edema (swelling)

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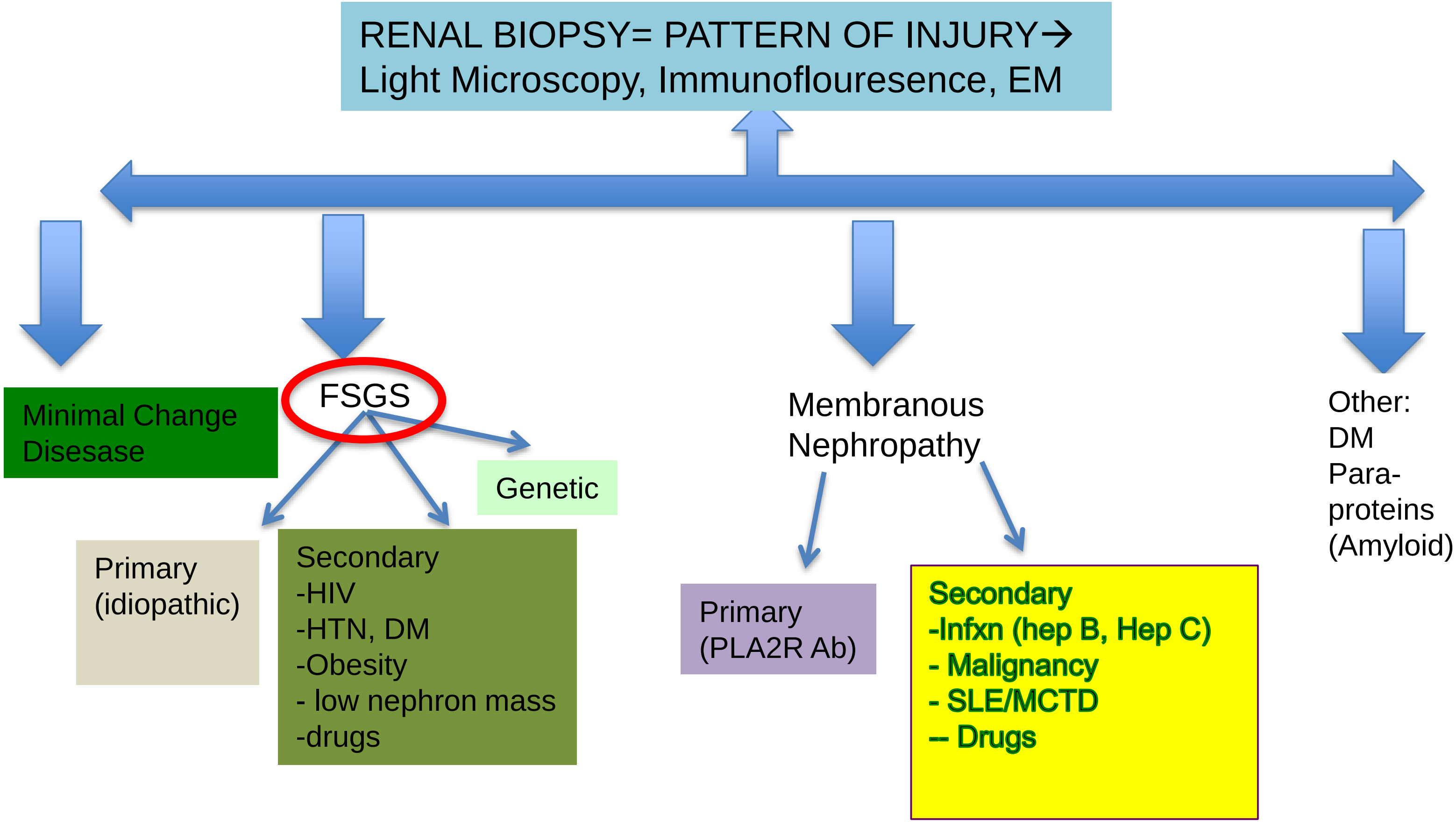
Nephrotic Processes



What is FSGS?

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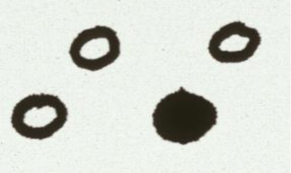
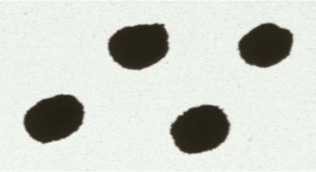
Focal segmental glomerulosclerosis FSGS

- Focal segmental glomerulosclerosis (FSGS) involves scars on some of your kidneys' filters. The scarring makes it hard for your kidneys to filter out wastes from your body and can lead to kidney failure.

- FSGS: A histologic pattern of injury (**not a "disease"**)
  - Focal: Some (less than 50% or half) of glomeruli affected
  - Segmental: Only portion of affected glomerulus is sclerosed or hardened

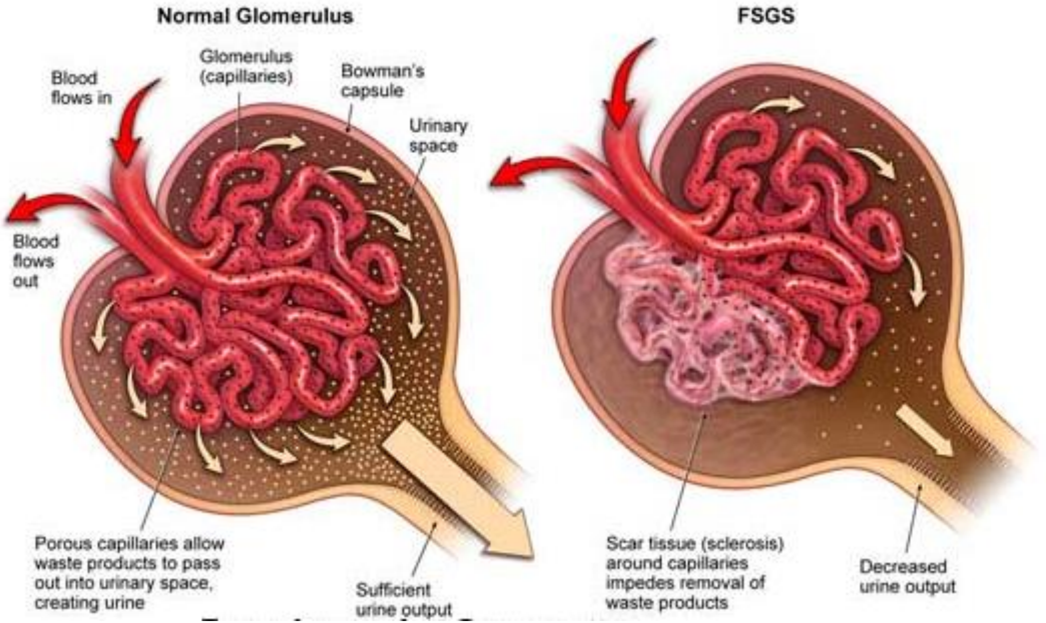
1. Focal Vs Diffuse





2. Segmental Vs Global

FSGS


Normal Glomerulus
FSGS
Blood flows in
Glomerulus (capillaries)
Bowman's capsule
Urinary space
Blood flows out
Porous capillaries allow waste products to pass out into urinary space, creating urine
Sufficient urine output
Scar tissue (sclerosis) around capillaries impedes removal of waste products
Decreased urine output

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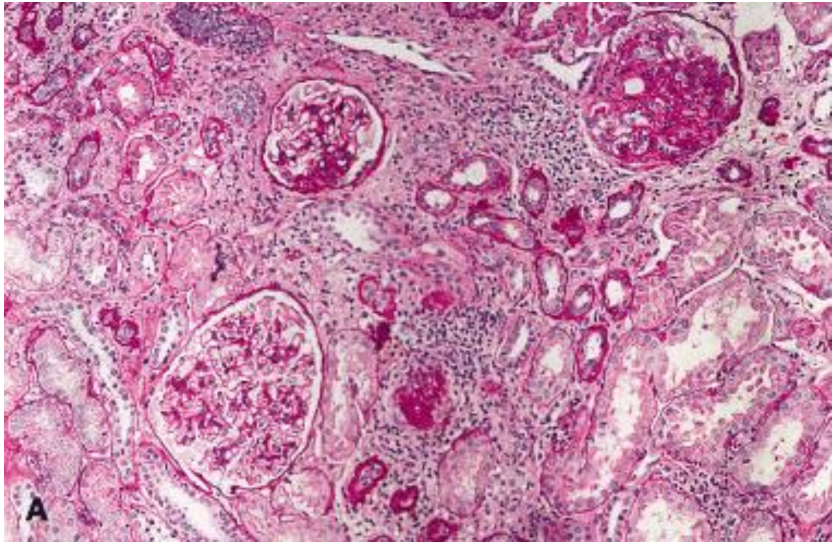
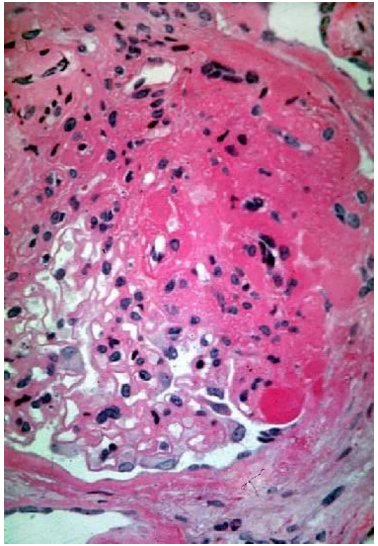
FSGS





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Causes of FSGS

Mechanical stretch

- Unilateral renal agenesis or hypoplasia
- Renal ablation—remnant kidney
- Obesity
- Reflux interstitial nephropathy
- Extensive nephron loss secondary to various
- renal diseases, including glomerulopathies
- Oligomeganephronia

Viral infections

- HIV-associated nephropathy
- Parvovirus B19
- Simian virus 40
- Hepatitis C virus
- Cytomegalovirus
- Epstein–Barr virus

Hereditary conditions

- Gene defects in the slit diaphragm (nephrin,
- podocin, CD2-associated protein, α-actinin 4)
- *WT1* mutation (Frasier syndrome)
- Mitochondrial cytopathies
- *SMARCA1* gene mutations (Schimke syndrome

Toxic agents

- Heroin
- Pamidronate
- Lithium
- Interferon-α

Ischemia (reduced blood flow)

- Cholesterol crystal embolism
- Renal artery stenosis
- Malignant hypertension
- Hypertensive nephrosclerosis (especially in
- blacks)
- Calcineurin-inhibitor toxicity
- Renal-transplant rejection

Aging

Congenital cyanotic heart disease

Epidemiology

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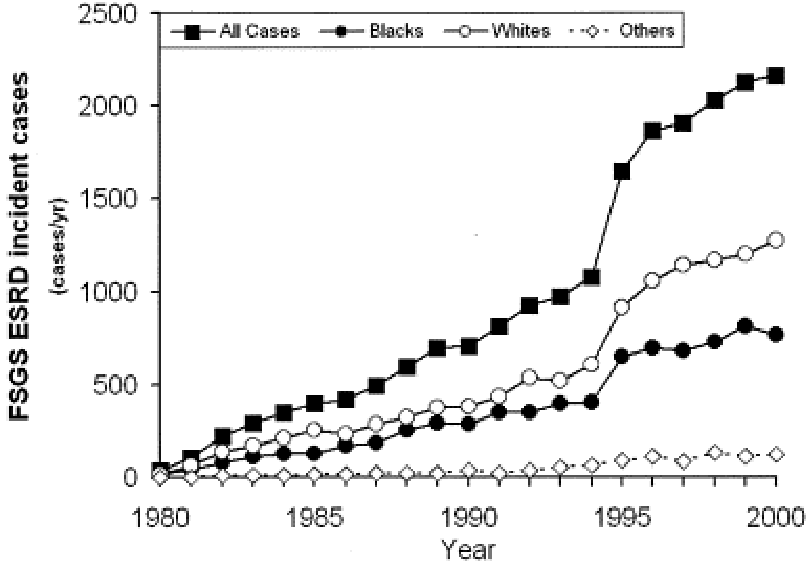
Kidney failure due to FSGS



Incidence data from USRDS

Kopp et al. Am J Kid Dis 2004

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Increase in FSGS incidence

- New York: 1974-1993
  - Frequency of all forms of FSGS among renal biopsies increased 7-fold

Barisoni et al. J Am Soc Nephrol 1994

- Chicago/Midwest: 1974-1993
  - Idiopathic (unknown cause) FSGS increased from 4% to 12% in adult biopsies

Haas et al. Am J Kidney Dis 1995

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USRDS Stat

- FSGS is currently the most common primary *glomerular disease* causing kidney failure in the United States

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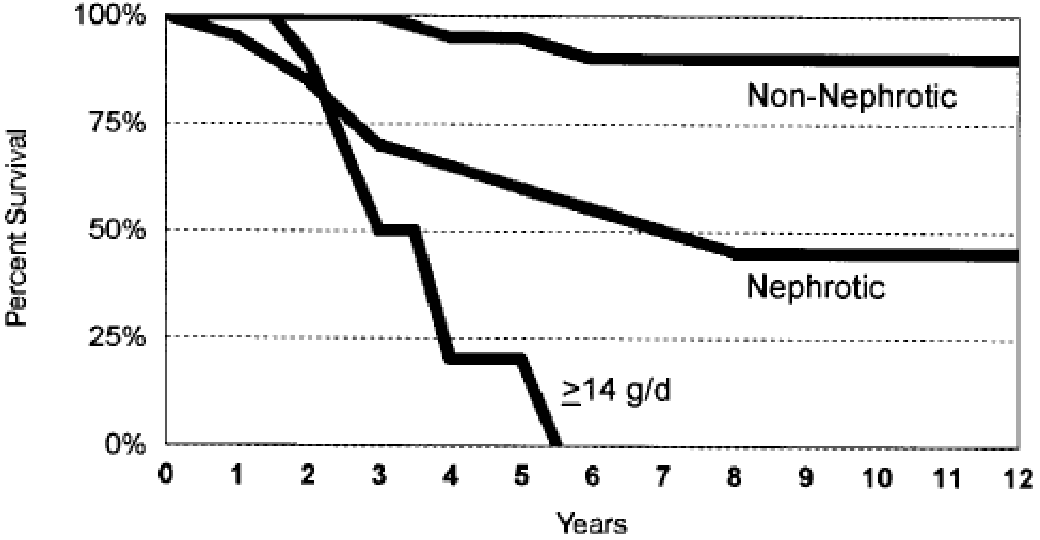
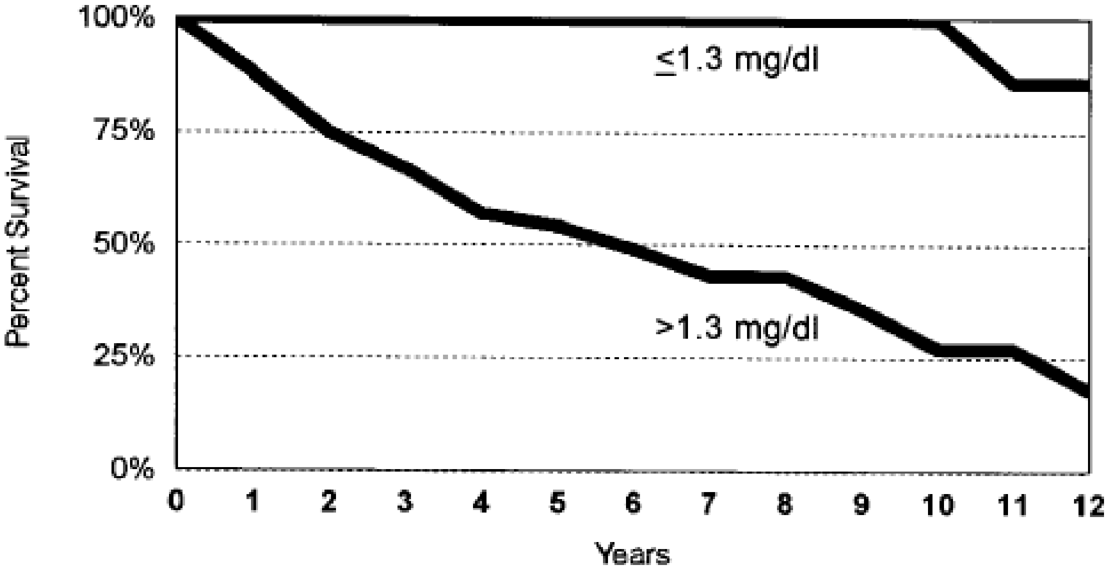
What factors impact prognosis/outcome?

Prognosis/outcomes of Proteinuria



Korbet, Neph Dial Transpl 1999

Prognosis/outcomes – Renal function



Korbet, Neph Dial Transpl 1999

Genetics of FSGS

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Familial or Genetic FSGS

- NPHS1 (nephrin) - **AR**
  Kestila et al. , Mol Cell 1998
- NPHS2 (podocin) -**AR**
  Boute et al, Nat Genetics 2000
- PLCE -**AR**
  Hinske et al. Nat Genetics 2006

- ACTN4 (alpha-actinin-4) - **AD**
  Kaplan et al, Nat Genetics 2000
- TRP6 (transient receptor potential cation channel 6) - **AD**
  Winn et al., Science 2005
  Reiser et al., Nat Genetics 2005
- INF2 (Formin)
  Pollak et al Nat Gen 2009 – **AD**
- ANLN (Anillin)
  Winn et al J Am Soc Neph, 2014 -**AD**

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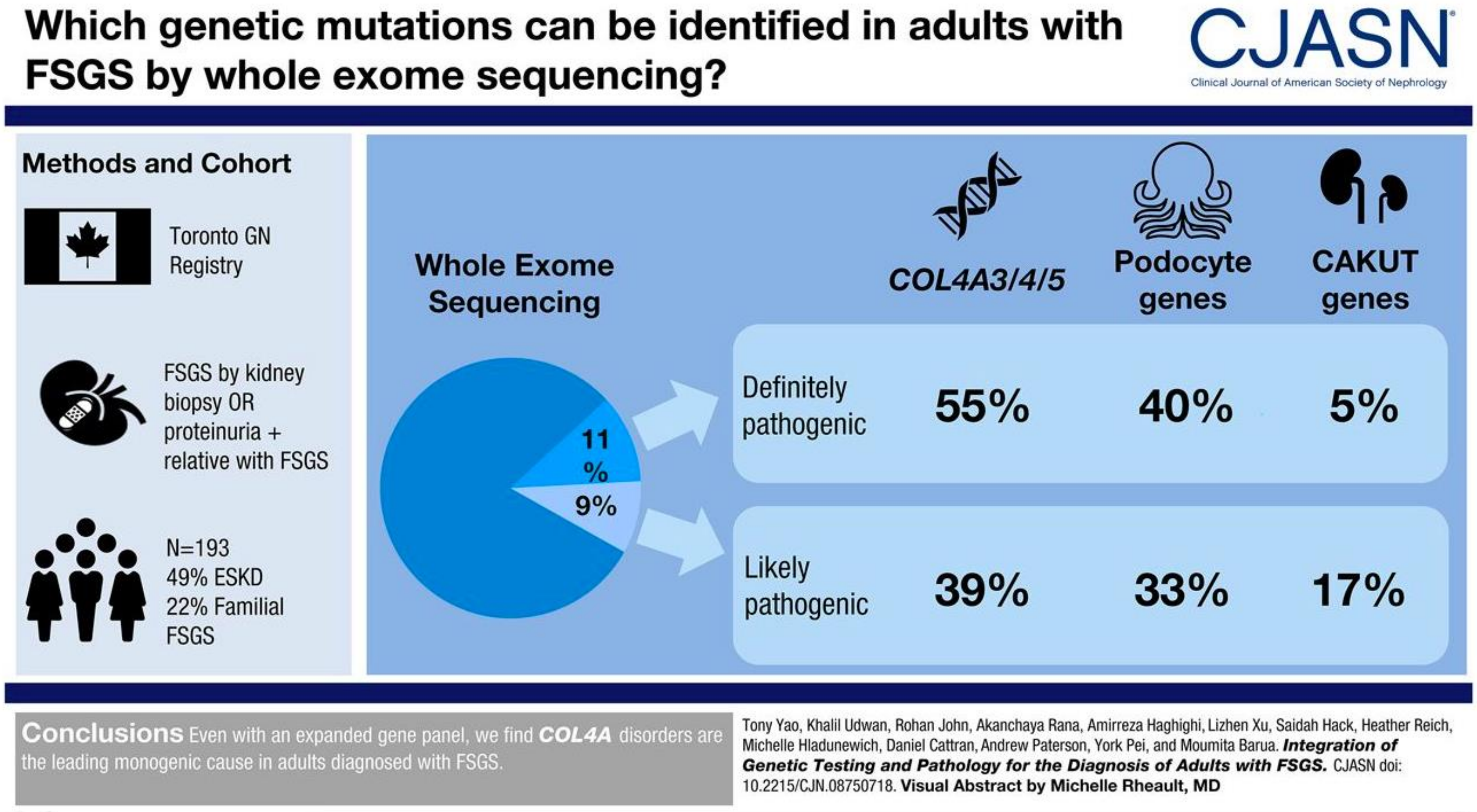
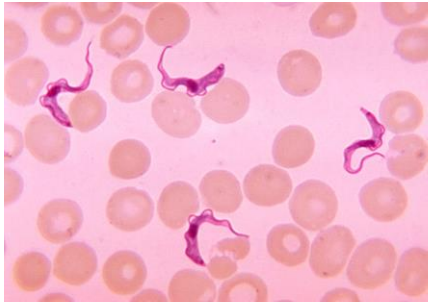
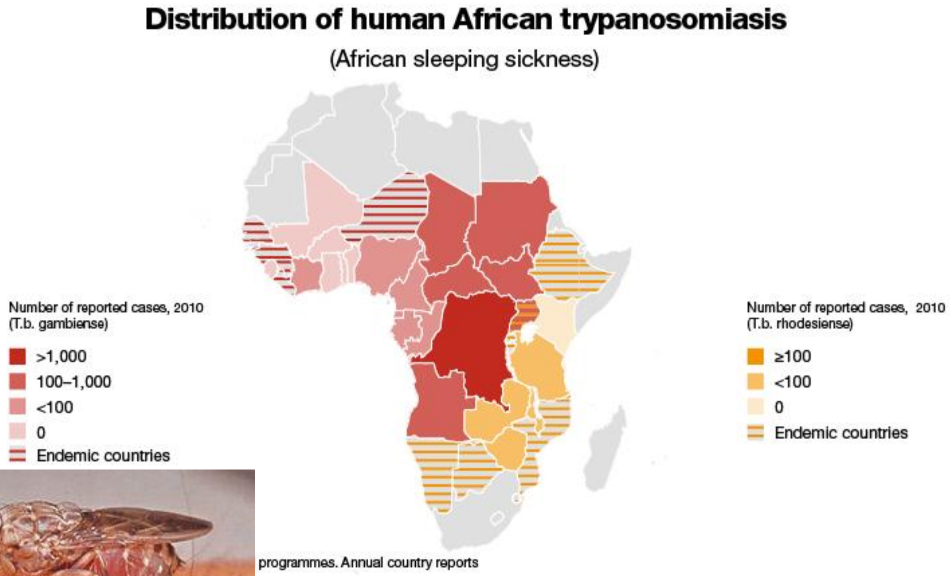


Yao et al. Clin J Am Soc Neph 2019

Fly-borne parasitic infection





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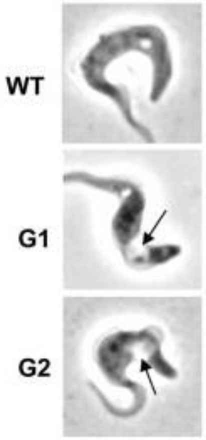
Apol1 G1 and G2 variants

Increased risk of non-diabetic kidney disease

- Especially FSGS and hypertensive disease

Resistance to Trypanosomes parasite



Kidney Transplant in FSGS

Steroid-Resistant Nephrotic Syndrome: Recurrence After Transplantation

LEOPOLDO RAIJ, M.D., JOHN R. HOYER, M.D., and ALFRED F. MICHAEL, M.D.,
Minneapolis, Minnesota

Raij et al. Ann Int Med 1972

RECURRENCE OF IDIOPATHIC NEPHROTIC SYNDROME AFTER RENAL TRANSPLANTATION

JOHN R. HOYER LEOPOLDO RAIJ
ROBERT L. VERNIER RICHARD L. SIMMONS
JOHN S. NAJARIAN ALFRED F. MICHAEL

Departments of Pediatrics, Internal Medicine, and Surgery, University of Minnesota Medical School, Minneapolis, Minnesota 55455, U.S.A.

[redacted] An appealing hypothesis is that a circulating humoral substance in these patients injures glomerular membranes, causing increased permeability to protein. The nature of such a factor(s) is not known. Careful clinical studies of patients with the idiopathic nephrotic syndrome after renal transplantation may throw light on the pathogenesis of this disorder.

The Lancet · Saturday 19 August 1972

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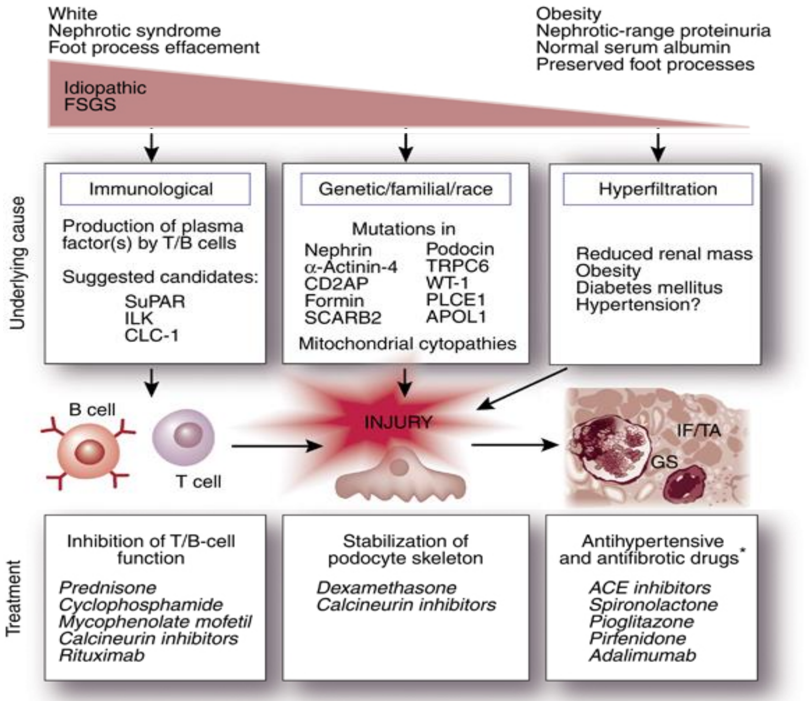
Evidence for circulating factor in FSGS

- Transplant patients
  - Up to 30-40% recurrence post-transplant
  - Risk higher with subsequent transplants
  - Blood plasma from patients with recurrent FSGS can cause proteinuria in rats

Linking the understanding of the pathogenesis to treatment



Deegens et al. Kidney Int 2011

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Existing validated targets?

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NEPHROTIC SYNDROME CLINICAL TRIALS ARE HAPPENING.

TRIAL NAME (sponsor)	PATIENT DIAGNOSIS	AGE RANGE	DRUG/ COMPOUND	EGFR
AURONA (Aurinia Pharmaceuticals, Inc.)	FSGS	18 - 75	Voclosporin	>30
CCX140-B IN SUBJECTS WITH FSGS (ChemoCentryx, Inc.)	FSGS	18 - 75	CCX140-B	>30
DUPLEX (Retrophin, Inc.)	FSGS	8 – 75	Sparsentan	>30
FIRSTx (Complexa, Inc.)	FSGS	18+	CXA-10	>45
PODOCYTE CLINICAL TRIAL (Mallinckrodt Pharmaceuticals)	FSGS	18+	Acthar	>30
TRIAL TO EVALUATE PF-06730512 IN ADULTS WITH FSGS (Pfizer Inc.)	FSGS	18 - 70	PF- 06730512	>45
ABATACEPT TO REDUCE PROTEINURIA (Bristol-Myers Squibb Company)	Treatment Resistant FSGS or MCD	6 – 75	Abatacept	>45
EFFICACY & SAFETY OF BLESELUMAB TO PREVENT RECURRENCE (Astellas Pharma US, Inc.)	De novo transplant due to FSGS	18+	Bleselumab (added to SOC)	N/A

Conclusions

- It has been found that FSGS is a common underlying cause of renal disease
  - FSGS is the most common cause of idiopathic (unknown cause) nephrotic syndrome in USA
  - Most common primary glomerular disease underlying kidney failure in USA
  - Increasing in incidence for unclear reasons

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Conclusions

- Apol1 mutations are highly associated with FSGS
- Genetics of podocytopathies becoming increasingly clinically relevant
- Evidence supports a central role for a circulating factor in FSGS
- Targeted therapy for podocyte dysfunction being pursued

Live Q&A

Write in your questions now!

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Living Kidney Donation: Everything you Need to Know

Friday, April 12, 2019 from 1:00 – 2:00 p.m. EST

Keith Melancon, MD

Join us to hear more about:

- An overview of the living kidney donation process
- Common concerns held by people who are considering donating a kidney (for example, whether women who donate can have children after surgery)
- How kidney donation affects the health of the donor
- Financial considerations for living donors

Go to www.KidneyFund.org/webinars to learn more and register!