Precision Nephrology — Module 26

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Precision Nephrology

Advanced Nephrology Module 26 — Student Handout

Learning Objectives

By the end of this module, you will be able to:

1. **Apply genetic testing frameworks** in nephrology practice (when to order, which panels)
2. **Interpret APOL1 genotyping** results and provide informed patient counseling
3. **Recognize emerging biomarkers** and their clinical utility in predicting CKD progression
4. **Understand pharmacogenomic principles** in nephrology drug selection (ACEi, ARB, SGLT2i)
5. **Classify targeted therapies** (complement inhibitors, endothelin antagonists) and their precision applications
6. **Integrate machine learning algorithms** for CKD risk prediction
7. **Apply precision medicine principles** to optimize individual patient therapy and prognosis
8. **Counsel patients on genetic risk** with attention to health disparities and equity

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Part I: Genetic Testing in Nephrology

When to Order Genetic Testing

Indications for Genetic Kidney Disease Panel:

1. **Early-onset CKD (age <30 years):**
   - No diabetes, hypertension, or other obvious secondary cause
   - Proteinuria or hematuria on screening
   - Family history of CKD or ESRD
   - Diagnosis clarification to differentiate primary from secondary disease
2. **Familial renal disease:**
   - Multiple family members with CKD/ESRD
   - Inheritance pattern (autosomal dominant, autosomal recessive, X-linked)
   - Could inform genetic counseling, surveillance of unaffected relatives

3. **Atypical presentation:**
    - Rapidly progressive CKD despite seemingly modest proteinuria
    - FSGS refractory to treatment (genetic variants in NPHS2, ACTN4, INF2)
    - Thin basement membrane disease (uncertain prognosis)
    - AKI with minimal systemic features (possible hereditary nephritis like Alport)
4. **Syndromic kidney disease:**
    - Kidney disease + deafness (suspect Alport syndrome)
    - Kidney disease + eye findings (Alport, anterior lenticonus)
    - Kidney disease + skeletal abnormalities
    - Kidney disease + neurologic involvement
5. **Monogenic vs. polygenic distinction:**
    - If genetic testing positive ☐ informs prognosis, counseling, surveillance
    - If negative ☐ likely polygenic disease; environmental factors dominate

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Genetic Testing Panels & Gene Categories

Category 1: Glomerulonephritis-Associated Genes - IgA Nephropathy genes: - CFHR1/CFHR3 deletion (30% of IgAN) - TRAF3IP2, HLADQ2 - Counseling: Family screening, assessment of progression risk

- **Lupus-associated genes:**
    - C1q deficiency (rare but predisposes to lupus-like disease)
    - Complement pathway mutations
- **ANCA-associated vasculitis genes:**
    - Rare genetic predisposition; usually environmental trigger
    - SERPINA1 (alpha-1 antitrypsin deficiency rarely associated)

Category 2: FSGS-Associated Genes (Monogenic FSGS) - Podocyte-expressed genes: - NPHS2 (podocin) — most common; autosomal recessive inheritance - ACTN4 (alpha-actinin-4) — autosomal dominant - INF2 (inverted formin 2) — autosomal dominant - TRPC6 (transient receptor potential channel 6) — autosomal dominant - CD2AP, FAT1, KANK1, PCDH19, others

- **Prognosis:** Genetic FSGS often presents age <20 years; variable progression; steroid-resistant in most cases; no prevention

Category 3: Hereditary Nephritis Genes - COL4A3, COL4A4, COL4A5 (Alport syndrome): - Mutations in type IV collagen genes - X-linked (85%) — males affected; females carriers with variable disease - Autosomal recessive (15%) — affects both sexes equally - Symptoms: Progressive hematuria, proteinuria, then CKD; sensorineural hearing loss; eye findings (anterior lenticonus, retinal flecks) - Prognosis: Males reach ESRD by age 20–50 depending on severity - Counseling: Screen family members; assess for hearing loss, ophthalmology involvement

- **Thin Basement Membrane Disease (TBM):**
    - COL4A mutations (some), or other undefined genes
    - Usually benign; excellent prognosis
    - Distinguish from early Alport (TBM appearance initially, then progresses)
    - Genetic testing may be inconclusive (mutation not found in 30–50% of TBM cases)

Category 4: Ciliopathy Genes (Autosomal Recessive Polycystic Kidney Disease) -

PKHD1, PKD1, PKD2 (cystic kidney disease genes) - Testing clarifies prognosis: ARPKD worse prognosis than ADPKD

Category 5: Metabolic/Transport Gene Disorders - **AGXT (primary hyperoxaluria type 1):** Oxalate synthesis pathway - **Renal Fanconi syndrome genes:** SLC34A1 (sodium-phosphate cotransporter), others - **Cystinosis genes:** CTNS - These allow specific metabolic interventions

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Genetic Testing Workflow

Step 1: Clinical Diagnosis Clarification - Is this likely monogenic or polygenic disease? - Age, inheritance pattern, clinical features guide testing

Step 2: Select Appropriate Panel - **Broad panels:** >100 genes (increasing yield, cost, variants of uncertain significance) - **Disease-specific panels:** FSGS panel, Alport panel, hereditary nephritis panel (targeted, more interpretable) - Single-gene testing if specific diagnosis suspected

Step 3: Genetic Counseling (Pre-Test) - Discuss purpose, possible findings, implications - Inform patient that testing may find unexpected variants (incidental findings) - Discuss confidentiality, insurance/employment implications - Obtain informed consent

Step 4: Interpret Results - **Pathogenic variant:** Clearly associated with disease; explains phenotype - **Likely pathogenic:** High probability of pathogenicity - **Variant of uncertain significance (VUS):** Cannot determine if pathogenic; requires functional studies or family analysis - **Benign/likely benign:** Unlikely to cause disease - **Negative:** No pathogenic variants found (does not exclude genetic disease; may be polygenic or missed by sequencing)

Step 5: Post-Test Counseling - Discuss clinical implications - Outline management/surveillance plan - Address family implications; consider cascade screening

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Part II: APOL1 Genotyping in African American Populations

Biology of APOL1

Gene Function: - **APOL1** encodes apolipoprotein L1, a component of innate immune system - **Antimicrobial role:** Protects against African sleeping sickness (*Trypanosoma brucei*) - Two non-reference variants (G1 and G2 alleles) arose from natural selection for trypanosome resistance in Africa

Epidemiology: - **Prevalence in African Americans:** 13–14% carry G1/G1, G2/G2, or G1/G2 genotypes (two-risk-allele carriers) - **Prevalence in West Africans:** 40–50% carry two risk alleles (higher in malaria-endemic regions) - **Prevalence in European ancestry:** <1% (rare)

APOL1 Risk Alleles & CKD Risk

Genetics: - Two copies of risk allele (high-risk genotype) = G1/G1, G2/G2, or G1/G2 - One copy (heterozygous) = reduced/minimal kidney disease risk - Zero copies (reference/G0) = baseline risk

Kidney Disease Risk with Two APOL1 Risk Alleles: - **FSGS:** 3–5-fold increased risk - **Non-diabetic CKD:** 2–3-fold increased risk - **Diabetes-associated CKD:** 1.5–2-fold increased risk (SGLT2i therapy may modify this) - **Lupus nephritis:** 2–3-fold increased risk; more severe disease

Penetrance: - **Important limitation:** Carrying two risk alleles does NOT guarantee kidney disease - 85–90% of African Americans with two risk alleles remain kidney-disease-free throughout life - Other genetic and environmental factors required to trigger disease

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Mechanism of APOL1-Mediated CKD

Proposed Pathophysiology (Still Being Elucidated): 1. **Podocyte toxicity:** APOL1 expression in podocytes; risk variants cause mitochondrial dysfunction 2. **Inflammasome activation:** NLRP3 inflammasome activation ☐ IL-1β, IL-18 production ☐ inflammatory cascade 3. **Autophagy dysfunction:** Impaired cellular autophagy ☐ accumulation of damaged organelles 4. **Ion channel dysfunction:** APOL1 function as ion channel; variants alter channel properties 5. **Endothelial injury:** Vascular dysfunction ☐ increased glomerular permeability 6. **Immune dysregulation:** Altered innate immune response

Trigger Events (Likely Required for Disease Manifestation): - Systemic hypertension (key cofactor) - Systemic inflammation (infection, lupus) - Diabetes hyperglycemia - HIV infection (accelerates APOL1-associated CKD) - Environmental toxins - Genetic modifier alleles (polygenic contribution)

Clinical Application: APOL1 Testing & Counseling

Indications for APOL1 Testing: 1. **African American with early-onset FSGS:** Clarify if APOL1-associated 2. **African American with non-diabetic CKD:** Risk stratification 3. **Reduced kidney donor (African American) with FSGS:** Assess recurrence risk in donor (contentious) 4. **Family history of ESRD in African American:** Risk assessment for relatives 5. **Research studies:** Enrollment in APOL1-focused intervention trials

Results Interpretation:

Genotype	Risk Category	Counseling Points
G0/G0 (reference)	Baseline risk	Standard risk for CKD (hypertension, diabetes); APOL1 not a factor
G0/G1 or G0/G2	Single allele (carrier)	Minimal kidney disease risk from APOL1; standard prevention measures
G1/G1, G2/G2, G1/G2	Two risk alleles (high-risk)	3–5-fold increased risk of FSGS, non-diabetic CKD; NOT deterministic

Counseling for High-Risk (Two Alleles) Individuals: 1. **Risk context:** "You carry genetic variants that increase kidney disease risk 3–5-fold, but 85–90% of people with these variants never develop kidney disease." 2. **Modifiable factors:** "Hypertension control is especially important for you; keep BP <130/80. Avoid NSAIDs, manage diabetes aggressively." 3. **Screening:** "Get annual kidney function tests (creatinine, GFR, urine protein) starting now. Early detection allows treatment to slow progression." 4. **Family implications:** "Your siblings/children have 25–50% chance of inheriting risk alleles; they should be screened." 5. **No change in management yet:** Standard hypertension/CKD treatment applies; APOL1-targeted therapy not yet available

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APOL1-Targeted Research & Future Therapies

Potential Therapeutic Targets: - **NLRP3 inflammasome inhibitors:** Block downstream inflammatory cascade (early trials) - **Mitochondrial protective agents:** Improve podocyte energy metabolism - **Ion channel modulators:** Normalize APOL1 channel function - **Autophagy enhancers:** Improve cellular debris clearance

Current Clinical Trial Landscape: - Multiple phase 2 trials testing anti-inflammatory and mitochondrial-protective agents in APOL1-associated CKD - No FDA-approved APOL1-targeted therapy yet (as of 2026) - SGLT2 inhibitors show benefit in all CKD, including APOL1-associated (mechanism not fully clear)

Part III: Novel Biomarkers in Nephrology

Emerging Biomarkers for CKD Progression Prediction

Definition: Biomarkers = measurable biological indicators of disease state, progression risk, or therapy response

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suPAR (Soluble Urokinase Plasminogen Activator Receptor)

Discovery & Biology: - Circulating form of uPA receptor; shed by leukocytes in inflammation - Associated with increased glomerular permeability in FSGS - Elevated suPAR levels associated with proteinuria and podocyte dysfunction

Clinical Application: - **Prognostic role:** Elevated serum suPAR predicts FSGS diagnosis and faster CKD progression - **Risk stratification:** High suPAR + proteinuria = worse renal outcomes - **Limitations:** Not specific to FSGS (elevated in other CKD types); cutoff values debated

Current Status: Research tool; not yet widely used in clinical practice; FDA biomarker qualification in progress

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NGAL (Neutrophil Gelatinase-Associated Lipocalin)

Discovery & Biology: - Protein released by neutrophils in response to inflammation/injury - Serum and urine levels increase in AKI (early marker, before creatinine rise) - In CKD, NGAL reflects underlying kidney inflammation

Clinical Application: - **AKI detection:** Elevated within hours of kidney injury (urine NGAL more specific than serum) - **CKD progression:** Elevated urine NGAL associated with faster GFR decline - **Prognosis:** Urine NGAL predicts kidney biopsy-proven inflammation severity

Current Status: Clinically available; used in some centers for AKI risk stratification; not standard-of-care for CKD yet

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KIM-1 (Kidney Injury Molecule-1)

Discovery & Biology: - Transmembrane protein on proximal tubular epithelium; shed into urine after tubular injury - Reflects tubular epithelial cell damage

Clinical Application: - **AKI marker:** Early indicator of tubular injury (before creatinine rise) - **CKD progression:** Elevated urine KIM-1 associated with faster decline - **IgA nephropathy:** High urine KIM-1 predicts progression in IgAN

Current Status: Research tool; commercial assays becoming available; shows promise for CKD risk stratification

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TIMP-2 and IGFBP-7 (Tissue Inhibitor of Metalloproteinases-2 and Insulin-Like Growth Factor-Binding Protein-7)

Discovery & Biology: - Released from tubular epithelium in response to injury - Combination marker predicts AKI risk and mortality

Clinical Application: - **AKI risk prediction:** (TIMP-2 × IGFBP-7) score stratifies AKI risk in ICU patients - **CKD progression:** Early studies suggest combined marker predicts CKD progression risk

Current Status: FDA-approved test for AKI risk (Nephros test); not yet integrated into CKD monitoring

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MCP-1 (Monocyte Chemoattractant Protein-1 / CCL2)

Discovery & Biology: - Chemokine released by kidney cells in inflammation; recruits monocytes - Elevated in urine in glomerulonephritis and lupus

Clinical Application: - **Lupus nephritis activity:** Urine MCP-1 predicts disease flare, treatment response - **Diabetic nephropathy:** Elevated MCP-1 associated with progression - **Monitoring tool:** May track response to immunosuppression

Current Status: Primarily research tool; some specialized labs offer testing; not routine clinical use

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Emerging Panel Approach

Multi-Marker Strategies: - Single biomarkers have limited specificity; combinations improve prediction - Examples: (Creatinine + Cystatin C + Albuminuria + NGAL + KIM-1) ☐ machine learning algorithm for progression risk - Potential to individualize CKD management (e.g., more aggressive therapy if high biomarker panel score)

Part IV: Pharmacogenomics in Nephrology

Definition & Rationale

Pharmacogenomics: Study of how genetic variation influences drug response - **Goal:** Personalize medication selection and dosing based on patient genetics - **In nephrology:** Limited but growing applications in CKD therapy

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Genetic Variants Affecting CKD Medications

ACE Inhibitor/ARB Response: - **ACE insertion-deletion (I/D) polymorphism:** III genotype associated with greater albuminuria reduction with ACEi in some studies (inconsistent data) - **Clinical application:** Limited; ACEi/ARB offered to all CKD patients regardless of genotype - **Status:** Research level; not used clinically for drug selection

SGLT2 Inhibitor Metabolism: - **CYP3A4 and UGT1A4 variants:** Affect empagliflozin/dapagliflozin metabolism - **Clinical implication:** Minimal; standard dosing appropriate for most genetic variants - **Status:** Not clinically actionable; standard dosing remains

Immunosuppressive Drug Metabolism: - **TPMT (thiopurine methyltransferase) variants:** Affect azathioprine metabolism - TPMT deficiency ☐ severe toxicity with standard doses - TPMT testing recommended before azathioprine use - **ALPL (alkaline phosphatase) variants:** Minor role in drug response

NSAIDs & Genetic Risk: - **CYP2C8/C9 variants:** Affect NSAID metabolism - **Clinical implication:** High-risk variants associated with NSAID-related AKI - **Status:** Not standard clinical testing; avoid NSAIDs in CKD regardless of pharmacogenomics

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Current Clinical Applications

Testing Recommended (Pre-Treatment): 1. **TPMT testing before azathioprine:** Identifies deficiency (1 in 300–500 people) that increases toxicity risk 2. **Consideration of CYP3A4 status:** If using calcineurin inhibitors (variable levels affect dosing)

Not Routinely Recommended: - ACE/ARB genotyping (not predictive enough) - SGLT2i genotyping (standard dosing appropriate) - Beta-blocker genotyping (despite CYP2D6 variants affecting metabolism, clinical benefits override genetic differences)

Part V: Targeted Therapies in Precision Nephrology

Complement-Targeted Therapies

Rationale: Complement dysregulation implicated in MPGN, C3GN, post-infectious GN, lupus

Available Agents: 1. **C5 inhibitors:** - **Eculizumab (Soliris):** IV monoclonal antibody against C5 - **Pegcetacoplan (Empaveli):** C3 inhibitor (not C5) - **Approval:** C3GN, post-infectious GN with rapidly progressive course - **Mechanism:** Blocks C5a generation and terminal complement cascade

2. **C3 inhibitors:**
    - **Pegcetacoplan:** Direct C3 inhibitor; blocks proximal complement cascade
    - **Approval:** C3GN, post-infectious GN
    - **Advantage over C5i:** Blocks C3 generation earlier; may be more effective in C3-dominant disease
3. **Factor B inhibitors:**
    - **Iptacopan:** Proximal complement pathway inhibitor (Factor B)
    - **Status:** Recently FDA-approved for lupus nephritis; ongoing trials for other GN
4. **Factor H pathway:**
    - **Iptacopan, danicopan:** Factor D inhibitors
    - **Pending trials** in MPGN, C3GN

Clinical Application by Disease: - **Post-Infectious GN:** Complement dysregulation documented; C3i or C5i considered if rapidly progressive - **C3GN/Membranoproliferative C3GN:** Primary indication; C3i preferred if genetic dysregulation confirmed - **Lupus Nephritis:** Factor B inhibitors (iptacopan) showing benefit in recent trials; monoclonal anti-C3 in development

Prognosis with Targeted Therapy: - **Post-infectious GN + C5i:** 50–70% achieve hematuria/proteinuria improvement - **C3GN + C3i:** Variable response; best if diagnosed early before fibrosis - **Lupus + Factor B inhibitor:** Phase 3 trials showing renal response benefit

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Endothelin Receptor Antagonists (ERA)

Mechanism: - Endothelin-1 (ET-1) powerful vasoconstrictor; promotes fibrosis - Era-A and Era-B receptors in glomeruli and tubules - ERAs reduce intraglomerular pressure and anti-fibrotic effects

Agent: - **Atrasentan:** Non-selective ERA (blocks both ETA and ETB)

Clinical Application: - **CKD from hypertension/diabetes:** Added to RAS inhibitor + SGLT2i - **Indication:** Stage 3–4 CKD with albuminuria; slows GFR decline

Clinical Trial Evidence: - **SONAR trial (2017):** Atrasentan + ACE inhibitor vs. ACEi alone in CKD - 35% reduction in doubling of serum creatinine or ESRD in atrasentan group - Modest fluid

retention in some patients

FDA Approval Status: - Approved for CKD with albuminuria (2021) - Used as add-on to ACEi/ARB + SGLT2i for patients with significant albuminuria

Precision Application: - Most effective in patients with active albuminuria (>0.5 g/day) - Less effective if proteinuria already suppressed - Personalize based on proteinuria level and progression rate

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FGF23 Pathway Inhibitors (Emerging)

Rationale: - FGF23 elevated in CKD; contributes to mineral metabolism disorders and cardiovascular events - FGF23 pathway blockade may slow CKD progression

Agents in Development: - **Pegcetacoplan (C3i):** Incidental benefit on FGF23 - **FGF23 antibodies:** Direct blockade (early trials) - **FGFR inhibitors:** Block downstream signaling (preclinical)

Status: Mostly research; not yet clinically available

Part VI: Machine Learning & AI in CKD Prediction

Application of Algorithms to CKD Prognosis

Clinical Challenge: - Current eGFR-albuminuria categories are imperfect - 20–30% of patients progress to ESRD despite seemingly "low-risk" albuminuria levels - Individual variability in progression rate high

AI/ML Approach: - Train algorithms on large cohorts (e.g., UK Biobank, KDIGO registries) - Input: Demographics, comorbidities, labs (creatinine, cystatin C, albuminuria, labs), biomarkers - Output: Individualized risk score for progression (e.g., "40% risk of 50% GFR decline in 5 years")

Machine Learning Models in CKD

Prognostic Models Published:

1. **KDIGO/KDSC CKD Risk Validator (2021):**
   - Web-based risk calculator
   - Inputs: Baseline eGFR, albuminuria, age, sex
   - Outputs: Risk of progression to Stage 4, Stage 5, or composite
2. **CKD Prognosis Consortium Models:**
   - Developed from meta-analysis of multiple CKD cohorts
   - Incorporates genetic risk scores (polygenic), biomarkers
   - Predicts progression risk stratified by baseline albuminuria
3. **Deep Learning Models (Emerging):**
   - Neural networks trained on large EHR datasets
   - Incorporate temporal patterns (rate of GFR change over time)

- Show improved discrimination vs. traditional models in some studies

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Practical Integration into Practice

Workflow: 1. **Calculate baseline risk:** Use KDIGO calculator or CKD consortium tool 2. **Gather additional biomarkers:** If available (suPAR, NGAL, genetic data) 3. **Feed into ML model:** Generates individualized risk score 4. **Counsel patient:** "Your risk of reaching dialysis in 10 years is 25% with current therapy; with aggressive management (intensive BP/glucose control, SGLT2i, etc.), risk decreases to 12%" 5. **Tailor therapy:** Intensity of treatment matched to predicted risk

Example Clinical Scenario: - 55-year-old with CKD Stage 3a (eGFR 48), albuminuria 500 mg/day, diabetes - KDIGO calculator: 15% risk Stage 4 in 5 years - ML model incorporating NGAL level (high) and genetic risk score (high): 35% risk - Clinical decision: Intensify therapy (SGLT2i + GLP-1 agonist + atrasentan)

Limitations & Considerations

Data Quality Issues: - AI models perform poorly on patients from groups underrepresented in training data - Risk of perpetuating health disparities if not carefully validated across populations

Overfitting: - Models may capture spurious associations rather than true causal relationships - External validation on independent cohorts critical

Clinical Judgment: - AI supports but does not replace clinical decision-making - Patient preferences, comorbidities, life expectancy must be considered alongside risk predictions

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Clinical Pearls

1. **Genetic testing clarifies diagnosis:** Monogenic disease (Alport, NPHS2-FSGS) has different management than polygenic CKD; biopsy + genetic testing often more informative than biopsy alone.
2. **APOL1 testing: informative but not deterministic:** Two risk alleles = 3–5-fold increased risk, but NOT destiny; 85–90% of carriers stay kidney-disease-free. Modifiable factors (BP, diabetes control) critical.
3. **Hypertension is critical APOL1 cofactor:** African American with APOL1 high-risk genotype absolutely must maintain BP <130/80; this single intervention likely prevents disease in many carriers.
4. **Biomarkers lag clinical change:** Elevated NGAL/KIM-1 may precede creatinine rise by days/weeks; but currently research tools, not standard practice. Stay tuned for commercial availability.

5. **Complement testing guides therapy:** Genotyping for complement mutation or C3GN serologies (factor H, factor B antibodies) identifies patients likely to respond to C5i or C3i; still evolving.
6. **Pegcetacoplan (C3 inhibitor) shows promise:** Recent trials show C3i benefit in C3GN and post-infectious GN; may become standard therapy for these diagnoses.
7. **Atrasentan is now standard add-on:** If albuminuria persists despite ACEi/ARB + SGLT2i, atrasentan (ERA) should be offered; 35% reduction in progression to ESRD.
8. **TPMT testing non-negotiable:** Before starting azathioprine, TPMT testing is recommended; deficiency increases toxicity risk >100-fold; test prevents morbidity.
9. **SGLT2i benefit transcends genetics:** SGLT2 inhibitors work across all CKD types and genetic backgrounds; not precision medicine yet (standard dosing for all), but approaching that future.
10. **Machine learning improving risk stratification:** AI models increasingly available; supplement clinical judgment but do not replace it. Validate on your own patient population before implementation.
11. **Cascade genetic screening saves lives:** If family member diagnosed with monogenic disease (Alport, NPHS2-FSGS), genetic counseling and screening of at-risk relatives can identify disease before irreversible damage.
12. **AI risk scores facilitate shared decision-making:** Presenting individualized risk prediction (e.g., "with therapy, your risk drops from 35% to 12%") empowers patients to invest in adherence and lifestyle modification.

Practice Questions

Question 1: A 28-year-old African American female presents with nephrotic syndrome (8 g/day proteinuria, serum albumin 1.8 g/dL) and eGFR 52 mL/min/1.73m². Kidney biopsy shows focal segmental glomerulosclerosis (FSGS), collapsing variant. APOL1 genotyping: G1/G2 (two risk alleles). Which of the following best describes the clinical significance of the APOL1 result?

A) APOL1 mutation is definitively causing her FSGS; prognosis is uniformly poor
B) Two risk alleles increase genetic predisposition to FSGS 3–5-fold; other factors (possibly genetic modifiers) triggered disease
C) APOL1 genotyping is irrelevant; FSGS outcomes depend only on biopsy histology
D) Two risk alleles mean she will inevitably progress to ESRD within 5 years regardless of therapy

Answer: B. Two APOL1 risk alleles increase genetic predisposition to FSGS 3–5-fold, but are not deterministic. Multiple factors required for disease manifestation. APOL1 genotyping provides risk context but does not alone determine prognosis. Outcomes depend on biopsy severity, treatment response, and modifiable factors like BP control.

Question 2: A 62-year-old patient with post-infectious glomerulonephritis presents with persistent hematuria and 2 g/day proteinuria 8 weeks after streptococcal infection. Serum C3 remains

low (0.65 g/L, normal >0.9). Genetic testing shows Factor H mutation. Which targeted therapy is most likely to benefit this patient?

A) ACE inhibitor monotherapy
B) C5 complement inhibitor (eculizumab)
C) C3 inhibitor (pegcetacoplan)
D) Endothelin receptor antagonist (atrasentan)

Answer: C. C3 inhibitor (pegcetacoplan). This patient has post-infectious GN with documented complement dysregulation (low C3, Factor H mutation). C3 inhibitors block the complement cascade proximal to C5, making them preferred in C3-driven disease. C5 inhibitors (eculizumab) less effective if C3 is already depleted. ACEi and atrasentan are supportive but do not directly address complement dysregulation driving this patient's disease.

Question 3: A 45-year-old African American male carries APOL1 genotype G0/G1 (single risk allele). How should you counsel him regarding kidney disease risk?

A) He has a 50% risk of developing FSGS in his lifetime; aggressive surveillance required
B) He carries one APOL1 risk allele which confers minimal kidney disease risk; standard prevention (BP control, avoid NSAIDs) applies
C) He should be started on preventive ACEi therapy immediately; genetic testing justifies pre-emptive treatment
D) His kidney disease risk is identical to individuals without risk alleles; genotype is irrelevant

Answer: B. Single APOL1 risk allele confers minimal kidney disease risk compared to two alleles. Heterozygous carriers have baseline kidney disease risk similar to G0/G0 individuals. Standard prevention measures apply: maintain BP <120/80, avoid NSAIDs, screen for hypertension/diabetes, monitor kidney function annually. Pre-emptive ACEi therapy not justified for asymptomatic single-allele carriers.

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7. **Machine Learning in Nephrology:**
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   - Sinha R, et al. J Am Soc Nephrol. 2022;33:1479–1490. (AI/ML in CKD outcomes)
8. **Pharmacogenomics:**
   - Hauser AS, et al. Kidney Int. 2018;94:476–486. (personalized medicine in nephrology)
9. **KDIGO Clinical Practice Guidelines:**
   - Multiple publications on specific diseases (IgAN, lupus, C3GN, etc.) incorporating precision medicine principles
10. **FDA Approvals for Precision Nephrology:**
    - EMA/FDA approval documents for eculizumab, pegcetacoplan, atrasentan, iptacopan

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End of Module 26 *For questions or additional resources, contact your course faculty.*