Isolated and persistent glomerular hematuria in adults

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INTRODUCTION

Hematuria is a common finding in glomerular diseases. In the patient with persistent microscopic hematuria, dysmorphic red blood cells (RBCs) and RBC casts suggest the presence of a glomerular disease, as does the presence of albuminuria:

- (See "Etiology and evaluation of hematuria in adults", section on 'Glomerular versus nonglomerular bleeding'.)
- (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults", section on 'Types of proteinuria'.)

Patients with glomerular hematuria often have other abnormalities, including proteinuria, edema, hypertension, and impaired glomerular filtration rate. However, in some patients the only manifestation of glomerular disease is persistent microscopic hematuria, similar to that seen with extraglomerular causes of bleeding such as prostatic disease and kidney stones.

The evaluation and diagnosis of isolated and persistent glomerular hematuria in adults are discussed in this topic. The overall etiology and evaluation of hematuria in adults and the differential diagnosis of glomerular disease in adults are presented separately:

- (See "Etiology and evaluation of hematuria in adults".)
- (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

The evaluation of hematuria in children is also discussed elsewhere:

- (See "Evaluation of gross hematuria in children".)

- (See "Evaluation of microscopic hematuria in children".)

DEFINITION

Microscopic hematuria is **isolated** when it occurs in an asymptomatic patient who has a normal rate of albumin excretion, a normal glomerular filtration rate, and normal blood pressure.

Patients presenting with isolated microscopic hematuria should initially be reexamined over a period of one to four weeks to ascertain if the hematuria is **persistent**. Transient hematuria is a relatively common finding over time in adults and may be induced by factors such as exercise or infection. (See "Etiology and evaluation of hematuria in adults" and "Exercise-induced hematuria".)

Signs of glomerular bleeding (best identified by a nephrologist or other experienced examiner) include a dysmorphic appearance of some red blood cells (RBCs) or RBC casts on microscopic examination of the urine sediment and, in patients with gross hematuria, a brown, cola-colored urine (table 1 and picture 1A-C). (See "Etiology and evaluation of hematuria in adults", section on 'Glomerular versus nonglomerular bleeding'.)

CAUSES

Most adult cases of persistent isolated hematuria due to glomerular disease are attributable to immunoglobulin A (IgA) nephropathy, Alport syndrome, or thin basement membrane nephropathy (TBMN) [1-6].

- (See "IgA nephropathy: Clinical features and diagnosis".)
- (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)".)
- (See "Thin basement membrane nephropathy (benign familial hematuria)".)

IgA nephropathy — IgA nephropathy is a form of glomerulonephritis in which poorly galactosylated IgA antibodies deposit in the mesangium along with an immunoglobulin G (IgG) autoantibody and complement factor 3 (C3). Patients may present with persistent microscopic hematuria or intermittent gross hematuria during an upper respiratory infection, termed "synpharyngitic" to differentiate it from the timing of postinfectious glomerulonephritis that is commonly associated with streptococcal infections. IgA nephropathy can be associated with preserved kidney function, proteinuria, progressive chronic kidney disease, or crescentic glomerulonephritis. If associated with systemic symptoms such as a vasculitic rash involving IgA

deposits, arthralgias, or abdominal pain, it is termed IgA vasculitis (Henoch-Schönlein purpura). IgA nephropathy is not usually associated with a family history of kidney disease. (See "IgA nephropathy: Pathogenesis and etiology" and "IgA nephropathy: Clinical features and diagnosis".)

Alport syndrome — Alport syndrome (also referred to as hereditary nephritis) is an inherited progressive form of glomerular disease that is often associated with sensorineural hearing loss and ocular abnormalities [1-4]. Alport syndrome is a primary basement membrane disorder arising from variants in genes encoding several members of the collagen IV protein family. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)" and "Genetics, pathogenesis, and pathology of Alport syndrome (hereditary nephritis)".)

The classical presentation of Alport syndrome is based upon clinical manifestations of affected males with X-linked disease. These features include glomerular disease that progresses to end-stage kidney disease (ESKD), ocular abnormalities (eg, anterior lenticonus), sensorineural hearing loss, and a positive family history of kidney failure and hearing loss. However, it is not unusual for male patients with Alport syndrome, including adults, to present with isolated hematuria. Although patients with autosomal recessive disease presenting in adulthood will often exhibit chronic kidney disease and extrarenal features, they may also present with isolated hematuria. Females with X-linked disease and patients with autosomal dominant disease have a more varied course, ranging from isolated microscopic hematuria to progressive kidney failure, and hearing loss and ocular abnormalities may also be present [7].

Thin basement membrane nephropathy — TBMN (also called thin basement membrane disease) is considered a relatively common disorder. In most patients, the only abnormal finding on kidney biopsy is diffuse thinning of the glomerular basement membranes (GBMs) requiring electron microscopy (EM) for the diagnosis. Historically, these patients were often described as having benign familial hematuria; however, because of the increased risk of developing kidney failure, this terminology is not favored and should no longer be used. Some patients given a diagnosis of TBMN also exhibit a focal segmental glomerulosclerosis (FSGS) lesion on the kidney biopsy.

TBMN is often familial, with a family history of hematuria being noted in 30 to 50 percent of cases. TBMN seems to account for most cases of what has been called benign familial hematuria. Numerous heterozygous variants in the collagen IV genes *COL4A3* and *COL4A4*, as well as hemizygous and heterozygous variants in *COL4A5,* have been identified in patients with so-called TBMN. Although variants in these genes are not identified in all patients given a diagnosis of TBMN, no other loci for this condition have been identified. Some clinicians, including the authors of this topic, consider hematuria and thin GBM associated with

COL4A3/*COL4A4* variants to be autosomal dominant Alport syndrome and use the term "hematuria with thin glomerular basement membranes" for patients in whom mutations in collagen IV genes cannot be identified. (See "Thin basement membrane nephropathy (benign familial hematuria)".)

Less common causes — Although mild postinfectious glomerulonephritis can also lead to isolated glomerular hematuria, there is usually rapid resolution of the urinary abnormalities within three to six months in this setting. In addition, C3 glomerulopathy occasionally produces isolated hematuria although decreased glomerular filtration rate or proteinuria is usually present and C3 levels may be normal or low. (See "Poststreptococcal glomerulonephritis" and "C3 glomerulopathies: Dense deposit disease and C3 glomerulonephritis".)

CONFIRMATION OF ISOLATED AND PERSISTENT GLOMERULAR HEMATURIA

Exclusion of nonglomerular hematuria — In patients with persistent isolated microscopic hematuria, it is important to exclude nonglomerular causes of hematuria as part of the evaluation. Such workup may include imaging of the upper and lower urinary tract and cystoscopy. Patients with evidence of glomerular hematuria by urine microscopy (eg, red blood cell [RBC] casts, dysmorphic appearance of some RBCs) may **not** need to be evaluated for potentially serious urologic disease unless the patient has clinical risk factors for a urologic cause of microscopic hematuria [8,9]. In patients with normomorphic RBCs in the urinary sediment or for whom reliable examination of the urinary sediment (ie, by a nephrologist or other experienced examiner) is not available, urologic causes of hematuria must be considered. (See "Etiology and evaluation of hematuria in adults", section on 'Glomerular versus nonglomerular bleeding' and "Etiology and evaluation of hematuria in adults", section on 'Risk factors for malignancy' and "Etiology and evaluation of hematuria in adults", section on 'Overall approach to the evaluation'.)

Exclusion of proteinuria and/or abnormal kidney function — Most patients with isolated and persistent glomerular hematuria will have already had a urinalysis with examination of the urinary sediment, serum chemistries with blood urea nitrogen (BUN) and creatinine, and quantification of urinary protein excretion (spot urine protein-to-creatinine ratio or 24-hour urine collection for protein). If such tests have not yet been performed or if the results are not available, we obtain these tests to confirm that the patient has isolated hematuria. Patients with a urine albumin excretion above 30 mg/day and/or an elevated serum creatinine level should not be considered to have isolated hematuria and should be evaluated for glomerular disease. (See 'Definition' above and "Etiology and evaluation of hematuria in adults", section on 'Glomerular versus nonglomerular bleeding' and "Glomerular disease: Evaluation and

differential diagnosis in adults", section on 'Glomerulonephritis (hematuria with proteinuria, kidney function impairment, or other manifestations)'.)

DIAGNOSIS

The most common causes of isolated and persistent glomerular hematuria in adults (IgA nephropathy, Alport syndrome, and thin basement membrane nephropathy [TBMN]) can often be distinguished by the features in the patient's history [3-5,10]. The definitive diagnosis can be established by molecular genetic testing and/or kidney biopsy (or, in some instances, skin biopsy) (algorithm 1) [11].

Initial evaluation — In adult patients with confirmed isolated and persistent glomerular hematuria (see 'Confirmation of isolated and persistent glomerular hematuria' above), we perform the following initial evaluation:

- History and physical examination, looking for the following features:
  - History of gross (visible) hematuria, especially during an acute upper respiratory tract infection, which is relatively common in IgA nephropathy but is unusual (occurring in less than 10 percent of cases) in patients given a diagnosis of TBMN or Alport syndrome [3,12]. Such patients also commonly have microscopic hematuria.
  - Family history of hematuria, which is common in patients diagnosed with TBMN or Alport syndrome but occurs in only isolated cases of IgA nephropathy [13].
  - Family history of kidney failure of unclear etiology, which suggests a diagnosis of Alport syndrome.
  - Personal and/or family history of sensorineural hearing loss, which is suggestive of Alport syndrome. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Hearing loss'.)
  - History of flank pain during an acute upper respiratory tract infection, which may be associated with IgA nephropathy. (See "IgA nephropathy: Clinical features and diagnosis", section on 'Clinical features'.)
  - History of acute kidney injury, which can be seen in patients with IgA nephropathy. (See "IgA nephropathy: Clinical features and diagnosis", section on 'Clinical features'.)

- Adult onset of hematuria, which suggests a diagnosis of IgA nephropathy. The presence of hematuria since childhood is more suggestive of a diagnosis of Alport syndrome or TBMN.

- Ocular findings characteristic of Alport syndrome, such as anterior lenticonus, dot and fleck retinopathy, and corneal changes (posterior polymorphous dystrophy and recurrent corneal erosion). Referral to an ophthalmologist may be required to properly evaluate these ocular features. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Ocular manifestations'.)

- Serum complement factor 3 (C3) and C4 complement levels

- Antinuclear antibody (ANA)

Establishing the diagnosis

Patients with positive serologic testing — In adult patients who are found to have a low serum C3 and/or C4 complement level and/or a positive ANA titer, a diagnosis of complement-mediated (eg, C3 glomerulopathy) or immune-mediated (eg, lupus nephritis) glomerulonephritis should be suspected. Such patients should undergo a kidney biopsy to establish a tissue diagnosis as well as a serological evaluation for complement-mediated or autoimmune disorders. (See "C3 glomerulopathies: Dense deposit disease and C3 glomerulonephritis" and "Lupus nephritis: Diagnosis and classification" and "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Laboratory testing'.)

Patients with negative serologic testing — In adult patients who are found to have normal serum C3 and C4 complement levels and a negative ANA titer, our subsequent approach depends upon the presence or absence of a family history or physical features consistent with Alport syndrome.

Family history or physical features of Alport syndrome — Patients who have an established family history of Alport syndrome **or** who have sensorineural hearing loss and/or ocular findings (such as lenticonus or fleck retinopathy) consistent with Alport syndrome should undergo molecular genetic testing for variants in *COL4A3*, *COL4A4*, and *COL4A5*, if possible, to determine if they have Alport syndrome. Such patients have a high probability of having a diagnosis of Alport syndrome, and genetic testing can confirm the diagnosis and provide information that is valuable for predicting prognosis and genetic counseling. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on

'Molecular genetic testing' and "Genetics, pathogenesis, and pathology of Alport syndrome (hereditary nephritis)".)

- If genetic testing is available, the preferred method of genetic testing depends upon whether a diagnosis of Alport syndrome has been previously confirmed in the patient's family by genetic testing. (See 'Molecular genetic testing' below.)

  - If genetic testing has **not** previously been performed in any of the patient's family members (ie, in patients with a family history of Alport syndrome, the diagnosis of Alport syndrome was established based upon clinical and/or pathologic features and family history alone), we typically perform next-generation sequencing (NGS) for variants in *COL4A3*, *COL4A4*, and *COL4A5*.

  - If genetic testing has previously confirmed the diagnosis of Alport syndrome in any of the patient's family members, we perform targeted mutational analysis, rather than complete NGS, to determine if the patient has the same mutation identified in the patient's family member(s) with Alport syndrome.

  If molecular genetic testing reveals a *COL4* variant (ie, NGS reveals a *COL4* mutation or targeted mutational analysis reveals that the patient has the same genetic mutation as that identified in the patient's family member[s] with Alport syndrome), a diagnosis of Alport syndrome can be established in the patient. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Diagnosis'.)

  If molecular genetic testing does **not** reveal a *COL4* variant, a diagnosis of Alport syndrome may still be possible, since NGS does not identify all *COL4* variants that cause Alport syndrome and rare patients with negative targeted analysis may have a different mutation than the one in other family members (eg, in families with digenic inheritance) [14,15]. In this setting, a kidney biopsy can help to distinguish the diagnosis of Alport syndrome from other possible kidney parenchymal disorders (such as IgA nephropathy). However, the risks of kidney biopsy should be weighed against the potential benefits of establishing a diagnosis (eg, predicting prognosis and genetic counseling in patients found to have Alport syndrome) and potential therapies.

  Since evidence supporting the use of renin-angiotensin system (RAS) blockade for patients with Alport syndrome, TBMN, or IgA nephropathy with isolated hematuria is not yet definitive, patients should be informed that conservative monitoring (ie, urinalysis and measurement of serum creatinine and urine protein excretion on an annual basis) is also an option, and a kidney biopsy can be deferred until the patient develops signs of progressive kidney disease (eg, increasing serum creatinine or urine albumin excretion >30

mg/day). However, a kidney biopsy is indicated if the patient is being actively evaluated as a potential living donor for kidney transplantation or if the patient and provider agree that treatment would be initiated once a diagnosis is established. It is our opinion that such patients should undergo a biopsy since the initiation of RAS blockade prior to the development of proteinuria has been shown to be safe. This decision should be individualized after a discussion of the risks and benefits with the patient. (See 'Kidney biopsy' below and "Kidney transplantation in adults: Evaluation of the living kidney donor candidate", section on 'Hematuria'.)

If a kidney biopsy cannot be performed (ie, not available or contraindicated), an alternative test to confirm the diagnosis of X-linked Alport syndrome is to perform a skin biopsy with immunostaining for the alpha-5 chain of collagen IV. (See 'Skin biopsy' below.)

- If genetic testing is not available or prohibited by cost, we discuss the options of performing a kidney biopsy to establish a diagnosis versus conservative monitoring for progressive kidney disease. The risks of kidney biopsy should be weighed against the potential benefits of establishing a diagnosis and potential therapies. If a kidney biopsy cannot be performed (ie, not available or contraindicated), an alternative test to confirm the diagnosis of X-linked Alport syndrome is to perform a skin biopsy with immunostaining for the alpha-5 chain of type IV collagen. (See 'Kidney biopsy' below and 'Skin biopsy' below.)

No family history and no physical features of Alport syndrome — In patients who do not have a family history of Alport syndrome **and** who do not have sensorineural hearing loss and/or ocular findings characteristic of Alport syndrome, subsequent testing depends upon whether the patient has a family history of hematuria and/or end-stage kidney disease (ESKD) of unclear etiology:

- If the patient has a family history of hematuria and/or ESKD of unclear etiology, we perform molecular genetic testing for variants in *COL4A3*, *COL4A4*, and *COL4A5* by NGS. Such patients have a high probability of having kidney disease due to a *COL4* mutation (ie, Alport syndrome or TBMN). Direct sequencing of these genes can confirm the diagnosis of Alport syndrome or TBMN and provide information that is valuable for predicting prognosis and genetic counseling. Our diagnostic approach is similar to that discussed above for patients with a family history or physical features of Alport syndrome. (See 'Family history or physical features of Alport syndrome' above.)

- If the patient does **not** have a family history of hematuria or ESKD of unclear etiology, the options of performing molecular genetic testing for variants in *COL4A3*, *COL4A4*, and

COL4A5 by NGS; conservative monitoring for progressive disease (ie, urinalysis and measurement of serum creatinine and urine protein excretion on an annual basis); or performing a kidney biopsy to establish a diagnosis should be discussed with the patient. The risks of kidney biopsy should be weighed against the potential benefits of establishing a diagnosis and potential therapies. The same considerations for performing a kidney biopsy should be made as in patients with a family history or physical features of Alport syndrome. A kidney biopsy is often **not** performed in this setting, since the likelihood of finding a treatable disease in isolated glomerular hematuria is very low. However, if the patient develops signs of progressive kidney disease (eg, increasing serum creatinine or urine albumin excretion >30 mg/day), a kidney biopsy is indicated. (See "IgA nephropathy: Treatment and prognosis", section on 'Risk factors for disease progression'.)

Tests used to establish the diagnosis

Molecular genetic testing — Molecular genetic testing for variants in *COL4A3*, *COL4A4*, and *COL4A5* is the diagnostic procedure of choice to confirm that a patient's hematuria is associated with a *COL4* mutation. Genetic testing for *COL4* mutations can be performed by NGS, which enables simultaneous analysis of the *COL4A3, COL4A4,* and *COL4A5* genes, or by targeted mutational analysis, which focuses on a specific variant in one of the *COL4* genes. Both types of genetic testing are commercially available in the United States and Europe. A more detailed discussion of molecular genetic testing for *COL4* mutations is presented elsewhere. (See "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Molecular genetic testing'.)

Kidney biopsy — A kidney biopsy can help to distinguish between the most common causes of isolated and persistent glomerular hematuria. While there is evolving evidence that treatment of patients with Alport syndrome with isolated hematuria may be beneficial, it is not yet definitive (see "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Management'). Thus, clinicians should clearly discuss the benefits and risks of kidney biopsy with their patients and provide patients with the option of conservative management and pursuing kidney biopsy only if they show signs of progressive kidney disease (eg, proteinuria, hypertension, deterioration in kidney function). However, as mentioned above, a kidney biopsy is indicated if the patient is being actively evaluated as a potential living donor for kidney transplantation. (See 'Establishing the diagnosis' above.)

If a kidney biopsy is performed, the biopsy specimen should be analyzed by light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). IF is required to establish a diagnosis of IgA nephropathy, C3 glomerulopathy, or lupus nephritis. EM is required to evaluate abnormalities of the glomerular basement membrane (GBM), such as thinning or longitudinal

splitting (lamellation), that are characteristic of TBMN or Alport syndrome. If EM is not available, the utility of the kidney biopsy in establishing a diagnosis for isolated and persistent glomerular hematuria is limited. In such cases, immunostaining for the alpha-3, alpha-4, and alpha-5 chains of collagen IV may be informative; however, the sensitivity of collagen IV staining for the diagnosis of Alport syndrome varies depending upon the age at diagnosis, sex, and mode of inheritance (table 2) [16-19]. When tools to fully evaluate kidney biopsy samples are not available, the clinician may decide to closely monitor the patient for signs of progressive kidney disease rather than proceeding with biopsy. (See "Thin basement membrane nephropathy (benign familial hematuria)", section on 'Indications for kidney biopsy' and "IgA nephropathy: Clinical features and diagnosis", section on 'Pathology'.)

In patients who undergo kidney biopsy for the evaluation of isolated and persistent glomerular hematuria, we approach the kidney biopsy as follows:

- If the patient is found on kidney biopsy to have thin and/or lamellated GBMs by EM, the diagnoses of Alport syndrome and TBMN should be suspected, although thin GBMs can also be seen as an incidental finding in patients with other glomerular diseases [20,21]. Immunostaining for the alpha-3, alpha-4, and alpha-5 chains of type IV collagen should be then performed to help distinguish between these diagnoses (table 2). (See "Genetics, pathogenesis, and pathology of Alport syndrome (hereditary nephritis)", section on 'Kidney' and "Thin basement membrane nephropathy (benign familial hematuria)", section on 'Distinction from Alport syndrome'.)

    - If immunostaining reveals an abnormal staining pattern for the alpha-3, alpha-4, and alpha-5 chains of type IV collagen, a diagnosis of Alport syndrome can be established in the patient.

    - If immunostaining reveals a normal staining pattern for the alpha-3, alpha-4, and alpha-5 chains of type IV collagen, a diagnosis of Alport syndrome or TBMN is possible since collagen IV staining can be seen in patients with TBMN as well as those with Alport syndrome who have hemizygous and heterozygous variants in *COL4A5*, heterozygous variants in *COL4A3* and *COL4A4*, or variants in both alleles of *COL4A3* and *COL4A4* (table 2). Thus, in this setting, normal collagen IV staining cannot distinguish between patients with Alport syndrome and TBMN. We consider such patients with normal collagen IV staining to have "hematuria with abnormal glomerular basement membranes" and monitor them closely for signs of progressive kidney disease.

    All patients with a possible diagnosis of Alport syndrome or TBMN based on kidney biopsy findings should undergo genetic testing, which can give vital information on the mode of

inheritance and risk of progression to kidney failure.

- If the patient does not have thin and/or lamellated GBMs by EM, a diagnosis of Alport syndrome or TBMN is unlikely. Immunostaining for the alpha-3, alpha-4, and alpha-5 chains of type IV collagen may still be informative. If the patient is found to have histologic findings consistent with other renal parenchymal disease (eg, IgA nephropathy), further evaluation and management should be guided by the patient's specific pathologic diagnosis. If the findings on kidney biopsy are not consistent with any other renal parenchymal disease, the patient should be reevaluated for nonglomerular causes of hematuria. (See "Etiology and evaluation of hematuria in adults".)

Skin biopsy — A skin biopsy with immunostaining for the alpha-5 chain of type IV collagen is an alternative test that can be used to confirm the diagnosis of X-linked Alport syndrome. We do **not** routinely perform skin biopsies as part of the evaluation of isolated and persistent glomerular hematuria, given their limited utility in diagnosing autosomal forms of Alport syndrome and their inability to exclude other renal parenchymal disorders as a cause of hematuria.

A skin biopsy may be helpful if molecular genetic testing and/or kidney biopsy cannot be performed in a patient who is suspected of having a diagnosis of X-linked Alport syndrome. The absence of epidermal basement membrane staining for the alpha-5 chain of collagen IV is diagnostic of X-linked Alport syndrome. However, approximately 20 percent of males with X-linked Alport syndrome and 30 to 40 percent of heterozygous females will have normal immunostaining for the alpha-5 chain. In addition, all patients with autosomal recessive and autosomal dominant Alport syndrome have normal skin reactivity for the alpha-5 chain. Thus, the presence of epidermal basement membrane staining for the alpha-5 chain of collagen IV does not exclude a diagnosis of X-linked or autosomal Alport syndrome. (See "Genetics, pathogenesis, and pathology of Alport syndrome (hereditary nephritis)", section on 'Skin' and "Clinical manifestations, diagnosis, and treatment of Alport syndrome (hereditary nephritis)", section on 'Kidney and skin biopsy'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Glomerular disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Blood in the urine (hematuria) in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Blood in the urine (hematuria) in adults (Beyond the Basics)" and "Patient education: Glomerular disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition** – Microscopic hematuria is **isolated** when it occurs in an asymptomatic patient who has a normal rate of albumin excretion, a normal serum creatinine concentration, and normal blood pressure. Patients presenting with isolated microscopic hematuria should initially be reexamined over a period of one to four weeks to ascertain that the hematuria is **persistent**. Transient hematuria is a relatively common finding over time in adults and may be induced by factors such as exercise or infection. Signs of glomerular bleeding (best identified by a nephrologist or other experienced examiner) include a dysmorphic appearance of some red blood cells (RBCs), RBC casts, and, in patients with gross hematuria, a brown, cola-colored urine (table 1 and picture 1A-C). (See 'Definition' above.)
- **Causes** – Most adult cases of persistent isolated hematuria due to glomerular disease are attributable to immunoglobulin A (IgA) nephropathy, Alport syndrome, or thin basement membrane nephropathy (TBMN). (See 'Causes' above.)
- **Evaluation and diagnosis**

- In patients with persistent isolated microscopic hematuria, it is important to exclude nonglomerular causes of hematuria as part of the evaluation. Such workup may include imaging of the upper and lower urinary tract and cystoscopy. (See 'Confirmation of isolated and persistent glomerular hematuria' above.)

- The most common causes of isolated and persistent glomerular hematuria (IgA nephropathy, Alport syndrome, and TBMN) can often be distinguished by the features in the patient's history. The definitive diagnosis can be established by molecular genetic testing and/or kidney biopsy (or, in some cases, skin biopsy) (algorithm 1). (See 'Diagnosis' above.)

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Topic 3053 Version 29.0

GRAPHICS

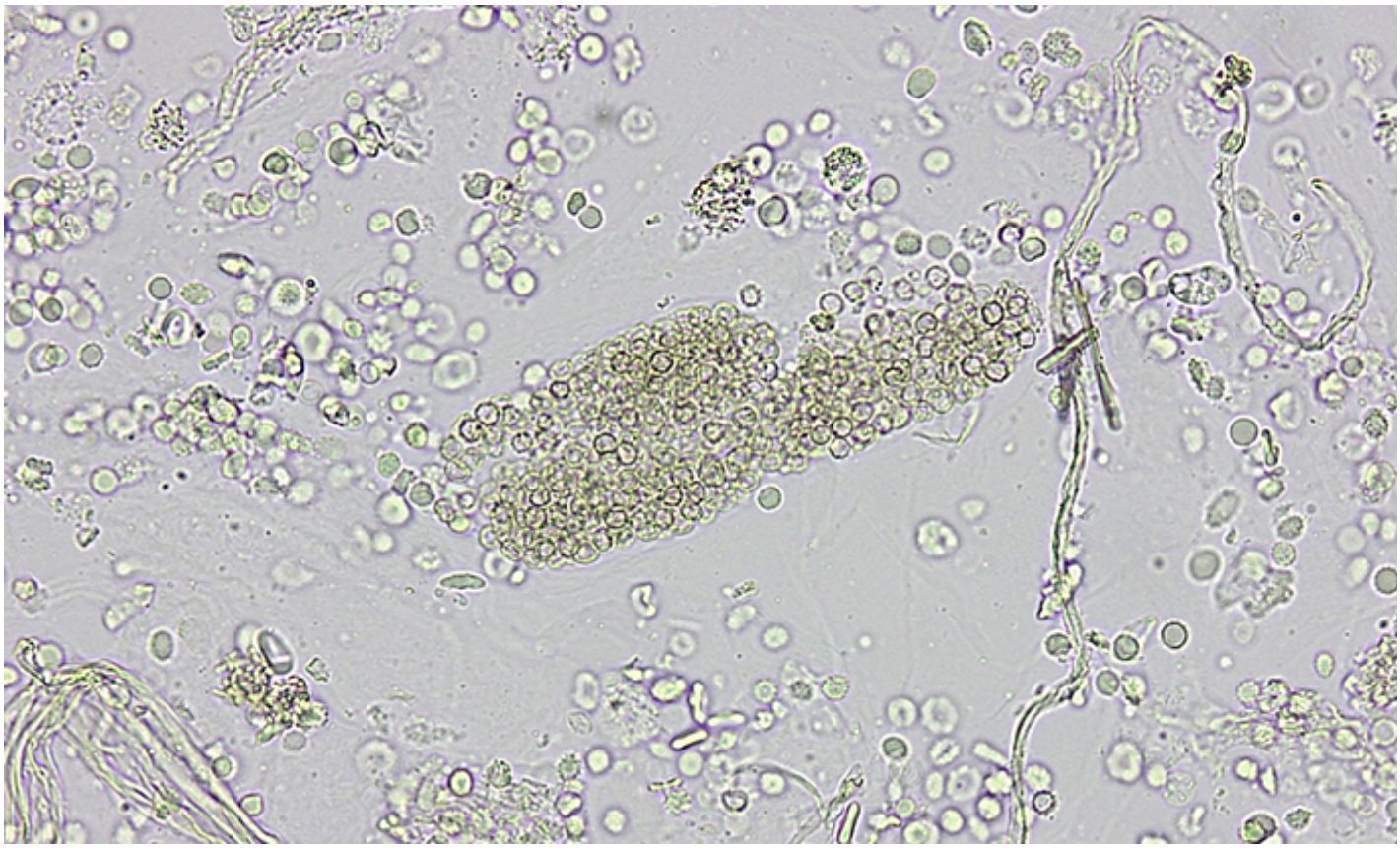
Distinguishing extraglomerular from glomerular hematuria

	Extraglomerular	Glomerular
Color (if macroscopic)	Red or pink	Red, smoky brown, or "Coca-Cola"
Clots	May be present	Absent
Proteinuria	Usually absent	May be present
RBC morphology	Normal	Dysmorphic
RBC casts	Absent	May be present

RBC: red blood cell.

Graphic 65786 Version 5.0

Photomicrograph of urine sediment with a red cell cast

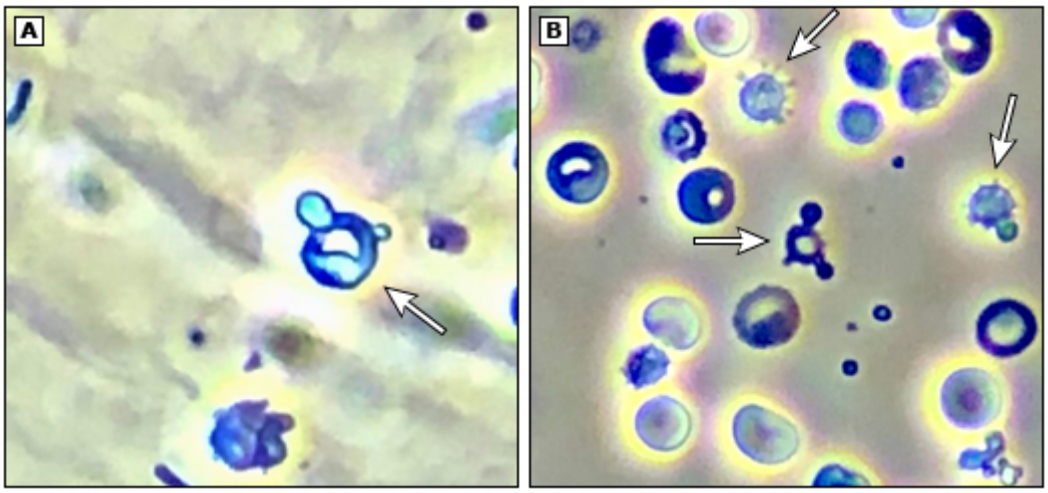


Urine sediment showing free red cells and a red cell cast that is tightly packed with red cells. It is more comr for red cell casts to have fewer red cells trapped within a hyaline or granular cast. Red cell casts are virtually diagnostic of glomerulonephritis or vasculitis.

Courtesy of James F Simon, MD.

Graphic 55778 Version 4.0

Phase-contrast micrograph showing dysmorphic RBCs in urine sediment

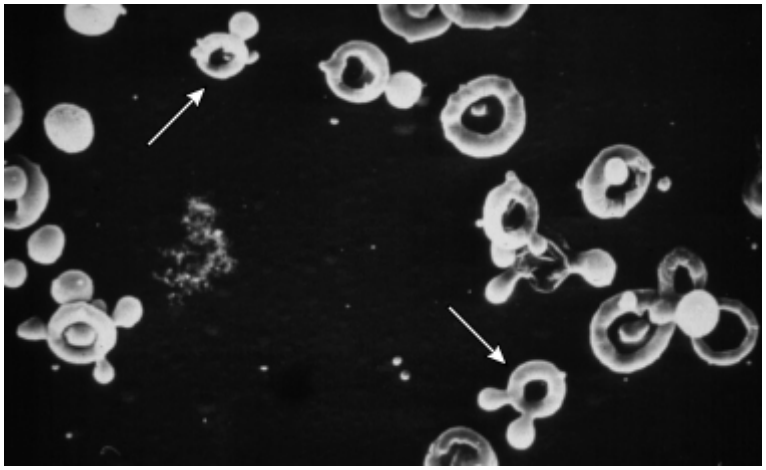


Phase-contrast microscopy showing dysmorphic red blood cells (RBCs) and acanthocytes in the urinary sediment of a patient with glomerular hematuria. Acanthocytes (arrows) can be recognized as ring forms with vesicle-shaped protrusions.

Courtesy of Juan Carlos Q Velez, MD.

Graphic 130438 Version 1.0

Scanning electron micrograph showing dysmorphic red cells in urine sediment

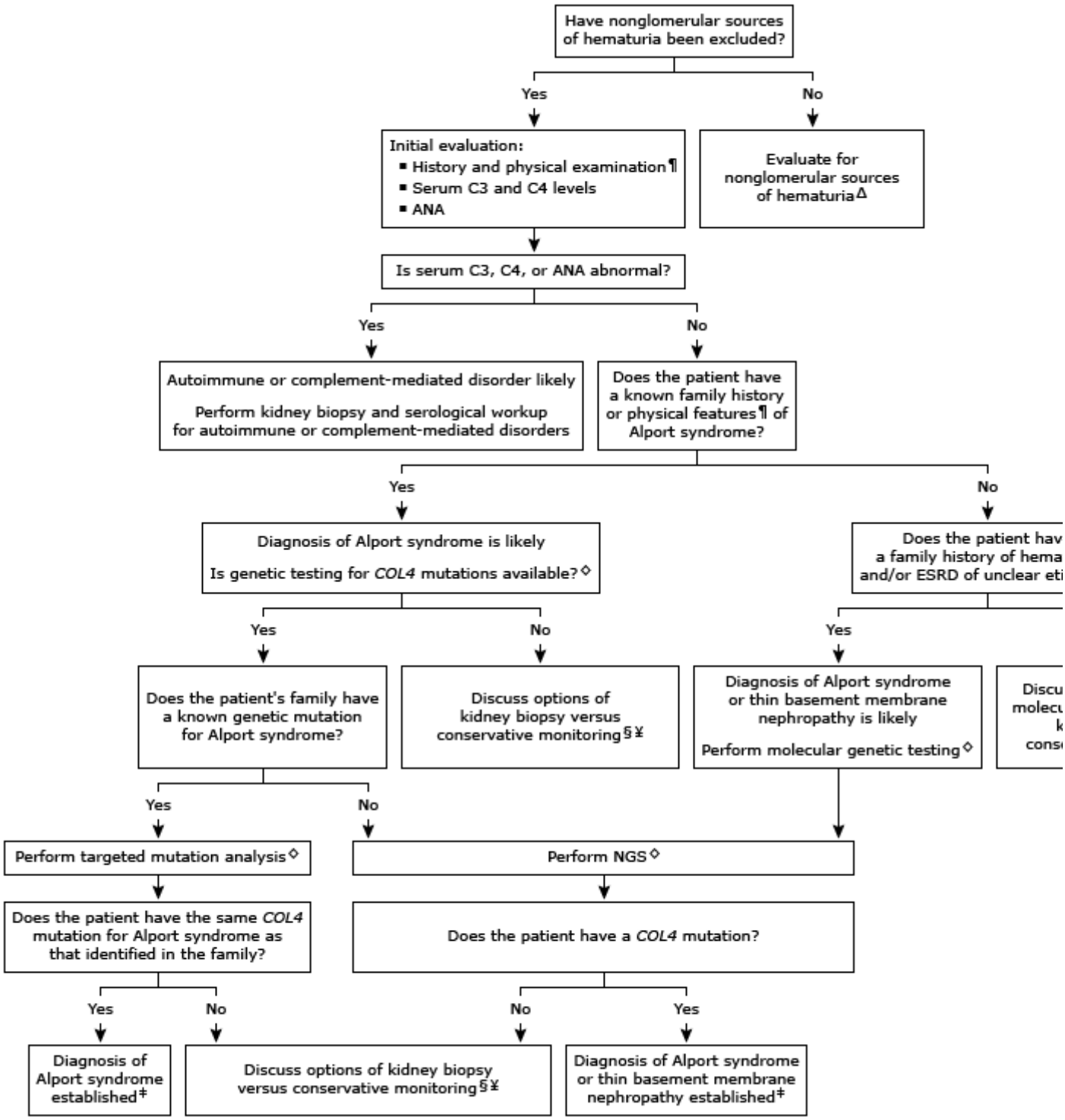


Scanning microscopy showing dysmorphic red cells in a patient with glomerular bleeding. Acanthocytes can be recognized as ring forms with vesicle-shaped protrusions (arrows).

Courtesy of Hans Köhler, MD.

Graphic 62064 Version 3.0

Evaluation of the adult patient with isolated and persistent glomerular hematu



ANA: antinuclear antibody; NGS: next-generation sequencing; ESRD: end-stage renal disease; RBCs: red bloc
immunoglobulin A.

* Isolated hematuria is defined as hematuria that occurs in an asymptomatic patient who has a normal rate
excretion, a normal serum creatinine concentration, and normal blood pressure. Persistent hematuria is her
present on repeat urinalyses over a period of 1 to 4 weeks. Signs of glomerular hematuria include a dysmor
some RBCs, RBC casts, and, in patients with gross hematuria, a brown, cola-colored urine.

¶ Patients should be evaluated for a personal history of gross hematuria, acute kidney injury, sensorineural
pain during an acute respiratory infection, or kidney stones. In addition, patients should be assessed for a fa
Alport syndrome, hematuria, and/or renal failure of unclear etiology. Physical exam should include an evalu
findings characteristic of Alport syndrome (eg, lenticonus, fleck retinopathy). Referral to an ophthalmologist
properly evaluate these ocular features.

Δ Refer to UpToDate topics on the evaluation of hematuria in adults. Patients with evidence of glomerular he
microscopy (eg, RBC casts, dysmorphic appearance of some RBCs) may not need to be evaluated for potenti
disease unless the patient has clinical risk factors for a urologic cause of microscopic hematuria.

◇ Molecular genetic testing for mutations in *COL4A3*, *COL4A4*, and *COL4A5* is the diagnostic procedure of cho
patient's hematuria is associated with a *COL4* mutation. Genetic testing for *COL4* mutations can be performe
enables simultaneous analysis of the *COL4A3*, *COL4A4*, and *COL4A5* genes, or by targeted mutational analysis
specific variant or mutation in one of the *COL4* genes.

§ A kidney biopsy can help to distinguish between the most common causes of isolated and persistent glom
However, the risks of kidney biopsy should be weighed against the potential benefits of establishing a diagn
prognosis and genetic counseling in patients found to have Alport syndrome) and potential therapies. Since
specific therapies for patients with Alport syndrome, thin basement membrane nephropathy, or IgA nephro
hematuria, patients should be informed that conservative monitoring (ie, urinalysis and measurement of se
urine protein excretion on an annual basis) is also an option, and a kidney biopsy can be deferred until the p
signs of progressive renal disease (eg, increasing serum creatinine or urine albumin excretion >30 mg/day).
biopsy is indicated if the patient is being actively evaluated as a potential living donor for kidney transplanta

¥ If a kidney biopsy cannot be performed (ie, not available or contraindicated), an alternative test to confirm
linked Alport syndrome is to perform a skin biopsy with immunostaining for the alpha-5 chain of type IV coll
expression of the alpha-5(IV) chain does not, however, exclude a diagnosis of Alport syndrome.

‡ Hemizygous or heterozygous mutations in *COL4A5* are consistent with X-linked Alport syndrome. Mutation
COL4A3 or *COL4A4* are consistent with autosomal recessive Alport syndrome. Heterozygous mutations in *COL*
consistent with autosomal dominant Alport syndrome or thin basement membrane nephropathy.

Graphic 118662 Version 2.0

Type IV collagen immunostaining patterns in Alport syndrome and thin basement membrane nephropathy

Disease	Alpha-3 chain	Alpha-4 chain	Alpha-5 chain
Alport syndrome			
X-linked inheritance – males	Absent*	Absent*	Absent*
X-linked inheritance – females	Patchy*	Patchy*	Patchy*
Autosomal recessive inheritance	Absent*	Absent*	Absent in GBM, present in basement membranes of Bowman's capsule and the distal tubule*
Autosomal dominant inheritance	Present	Present	Present
Thin basement membrane nephropathy¶	Present	Present	Present

Type IV collagen immunostaining is a useful adjunct to routine evaluation of kidney biopsy samples from patients with isolated glomerular hematuria, particularly when a specific diagnosis is not provided by routine immunofluorescence and electron microscopy. Abnormal type IV collagen immunostaining is highly suggestive of Alport syndrome. It is important to note that thin GBMs and normal type IV collagen immunostaining may be observed in patients with hemizygous and heterozygous mutations in *COL4A5*, heterozygous mutations in *COL4A3* and *COL4A4*, and mutations in both alleles of *COL4A3* and *COL4A4* and may be associated with progressive renal disease. Except as noted, the present/absent designation in the table refers to GBM staining only.

GBM: glomerular basement membrane.

* Up to 20% of male patients and 30 to 40% of female patients with X-linked Alport syndrome may exhibit positive staining for the alpha-3, alpha-4, and alpha-5 chains of type IV collagen. Some patients with autosomal recessive Alport syndrome have normal type IV collagen immunostaining.

¶ Some clinicians (including the authors of the associated topic) consider patients who have thin GBMs and a *COL4A3* or *COL4A4* mutation to have autosomal dominant Alport syndrome.

Graphic 118692 Version 1.0

Contributor Disclosures

Clifford E Kashtan, MD Grant/Research/Clinical Trial Support: Reata Pharmaceuticals [Chronic kidney disease];Sanofi Genzyme [Alport syndrome];Travere Therapeutics[Alport Syndrome]. Consultant/Advisory Boards: Acceleron[Alport syndrome];BridgeBio[Alport Syndrome];Daiichi Sankyo [Alport syndrome];METiS Pharmaceuticals[Alport syndrome];ONO Pharmaceuticals [Alport syndrome]. All of the relevant financial relationships listed have been mitigated. **James F Simon, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Richard J Glassock, MD, MACP** Employment: Karger Publishers [Associate Editor of Nephrology Viewpoints blog for American Journal of Nephrology]. Equity Ownership/Stock Options: Reata [Alport syndrome, pulmonary hypertension, diabetic nephropathy]. Consultant/Advisory Boards: Alexion [Pharmaceutical development]; Arrowhead [Complement-mediated GN]; Aurinia [Voclosporin, lupus nephritis]; BioCryst [IgA nephropathy and C3GN]; Calliditas [IgA nephropathy]; Chinook [Pharmaceutical development]; Equillium Bio [IgA nephropathy, lupus nephritis]; Horizon Pharma [IgA nephropathy]; Ionis [IgA N and anti-PLA2R antibody-associated MN]; National Institutes of Health [NEPTUNE study chair]; Nephro-Sys [Novel agent for GN]; Novartis [IgA nephropathy]; Omeros [IgA nephropathy]; Otsuka Pharmaceuticals [IgA nephropathy]; Renasight [Genetics in kidney disease]; River Renal [R3RE-01 in primary FSGS]; Therini Bio [Novel agent for GN]; Travere [Focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy]; Vera pharamaceuticals [Pharmaceutical development]; Vertex Inc [Novel drug compound for treatment of APOL1-related FSGS]. Speaker's Bureau: Aurinia [Lupus nephritis]. Other Financial Interest: American Association of Kidney Patients [Board member; non-profit voluntary health organization]; Oxford Medical Publishers [Primary glomerular disease]; University Kidney Research Organization [Nephrology]. All of the relevant financial relationships listed have been mitigated. **Fernando C Fervenza, MD, PhD** Grant/Research/Clinical Trial Support: Achillion Pharmaceuticals [C3 glomerulonephritis]; Alnylam Pharmaceuticals [IgA nephropathy]; Genentech [Membranous nephropathy, fibrillary GN]; Janssen Pharmaceutical [Monoclonal protein-mediated kidney diseases, lupus nephritis]; Morphosys AG [IgA nephropathy]. Consultant/Advisory Boards: Alexion [C3 glomerulopathy, IgA nephropathy]; Alnylam Pharmaceuticals [IgA nephropathy]; BioCrystal Pharmaceuticals [C3 glomerulopathy]; Equilium, Inc [Lupus nephritis]; Galapagos [Focal segmental glomerulosclerosis]; GlaxoSmithKline [Lupus nephritis]; Novartis [IgA Nephropathy]; Otsuka [IgA nephropathy]; Takeda [IgA nephropathy]. All of the relevant financial relationships listed have been mitigated. **Albert Q Lam, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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