COMPLEMENT 3 GLOMERULOPATHY (C3G):

A RARE KIDNEY DISEASE

C3G is a rare disease that can be difficult to distinguish from other more common types of GN that present with similar symptoms and histopathology. Unchecked activity of the complement system can result in C3 deposition in the glomerulus, which can cause inflammation and scarring. This can lead to chronic and irreversible kidney damage and significant burdens on patients' daily lives.

In this white paper, nephrologist **Dr Donald Molony** and renal pathologist **Dr Jose Torrealba** will review and share their perspectives about the following topics

1. C3G impact on patients
2. Clinical significance of the MPGN reclassification
3. Differential diagnosis of C3G from more common glomerulonephritides
4. Benefits of a nephrologist–pathologist partnership in C3G

C3, complement component 3; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.

The perspectives provided within this white paper by Dr Molony and Dr Torrealba are their own and not reflective of their affiliations.
The medical experts in this white paper have been paid by Novartis to provide their perspectives.

Donald Molony, MD

Nephrologist
The University Health Science Center at Houston
Houston, TX

Jose Torrealba, MD

Pathologist
UT Southwestern Medical Center
Dallas, TX

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C3G CAN PRESENT WITH SYMPTOMS OF GLOMERULONEPHRITIS (GN) AND CAN PROGRESS TO END-STAGE KIDNEY DISEASE (ESKD)

C3G can be heterogeneous in clinical presentation and prognosis: patients may present with low to heavy levels of proteinuria and hematuria. C3G can be acute, recurrent, or rapidly progressive. The 2 main patterns of disease are C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

Small cohort studies estimate the incidence of C3G to be between 1 and 3 cases per 1 million in the US. The incidence of C3G is similar between men and women and it affects individuals of all ages (median age at diagnosis: 23 years): Patients with DDD tend to present at a younger age than patients with C3GN. The age of diagnosis is approximately 30 years for C3GN and 19 for DDD.

C3G CAN PRESENT SIMILARLY TO OTHER MORE COMMON TYPES OF GN

CLINICAL PRESENTATION CAN INCLUDE:

- Hematuria
- Hypertension
- Renal insufficiency
- Proteinuria
- Nephritic syndrome
- Ocular complication (eg, drusen)
- Persistent hypocomplementemia

C3G can be stable for years, but rapid fluctuations in proteinuria can occur with acute renal deterioration without a clear triggering event.

C3G CAN PROGRESS TO ESKD AND ALLOGRAFT LOSS

APPROXIMATELY 50%
of patients with C3G progress to kidney failure within 10 years of diagnosis and require dialysis or transplant

STUDIES SHOW POST-TRANSPLANTATION RECURRENCE AND ALLOGRAFT LOSS ARE POSSIBLE IN BOTH DDD AND C3GN

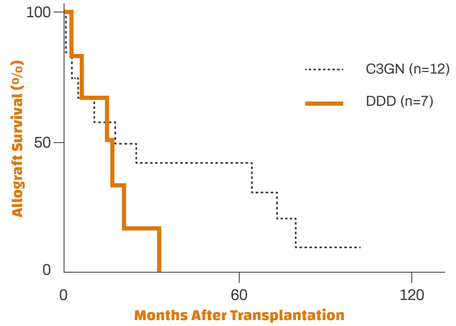
The estimated recurrence of C3G after transplantation pooled across existing studies is 72% (n=53/74).*

In a retrospective review of 70 patients with C3G in the UK and Ireland from 1992-2012, 20 patients reached end-stage renal disease (ESRD), where 6 patients with DDD and 7 patients with C3GN underwent renal transplantation. Of these patients, C3G recurrence in transplanted kidneys contributed to allograft loss in 50% of patients with DDD (n=3/6) and 75% of patients with C3GN (n=3/4).

C3, complement component 3; C3G, complement 3 glomerulopathy; GN, glomerulonephritis.

*Study location/center (disease), transplantation patients/total number of patients: France (C3GN), 6/10; France (DDD), 6/11; Columbia (C3GN), 10/12; Columbia (DDD), 6/7; Mayo Clinic (C3GN), 14/21; Netherlands (DDD)

A CASE SERIES REPORT OF RECURRENCE-FREE SURVIVAL IN C3GN AND DDD (N=19)†



A case series at Columbia University Medical Center (n=12 with C3GN, n=7 with DDD), median time to histological recurrence after transplantation for C3GN was 14 months vs 15 months for patients with DDD. Median time from transplantation to graft failure in 16 C3G patients was 42 months.†

† Recurrence-free survival in C3 glomerulonephritis (C3GN) and dense deposit disease (DDD; P = 0.2, Mantel-Cox log-rank test)

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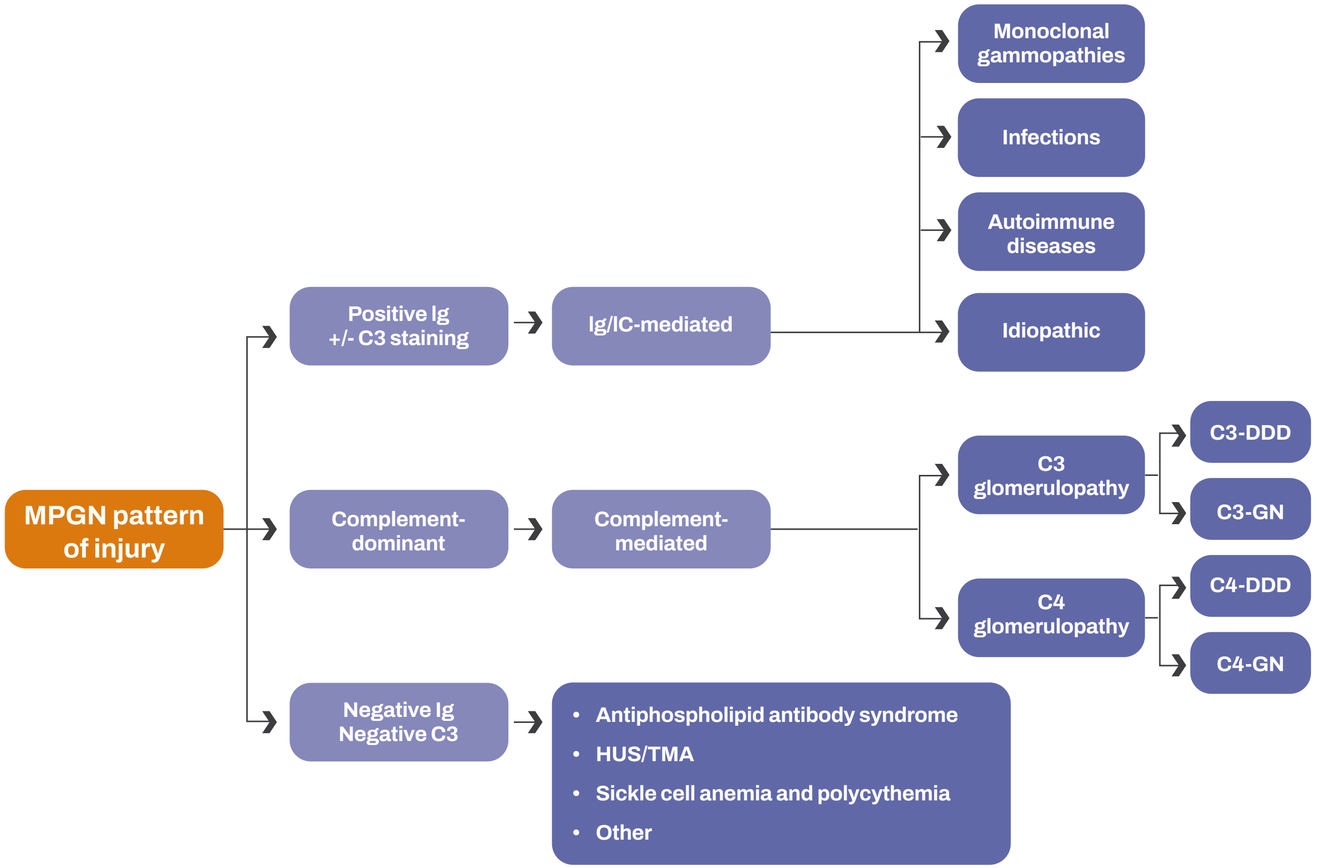
HOW MIGHT C3G AFFECT YOUR PATIENTS' QUALITY OF LIFE?

"In my experience, patients may be burdened by symptoms such as **edema and fatigue, both of which can interfere with the full expression of activities of daily living and with being comfortable**. In addition, **the notion that C3G can progress to renal failure**, which may require a transplant or dialysis, and the possibility of recurrence after a transplant, **can add to the psychological burden, in my experience**." **—Donald Molony, MD**

THE RECLASSIFICATION OF MPGN ALIGNS MORE CLOSELY WITH THE UNDERLYING DISEASE PATHOPHYSIOLOGY

Membranoproliferative glomerulonephritis (MPGN) was reclassified in 2012 based on the composition of immune deposits as revealed by immunofluorescence instead of appearance on light or electron microscopy. This more closely aligns with the underlying pathophysiology of disease.

PATHOPHYSIOLOGY OF MEMBRANOPROLIFERATIVE LESIONS



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C3, complement component 3; C4, complement component 4; C3G, complement 3 glomerulopathy; DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; IC, immune complex; Ig, immunoglobulin; KDIGO, Kidney Disease Improving Global Outcomes; TMA, thrombotic microangiopathy.

C3G IS CAUSED BY DYSREGULATION OF THE ALTERNATIVE COMPLEMENT PATHWAY

In C3G, uncontrolled activation of the alternative pathway results in the deposition of C3 fragments in the glomerular mesangium and along capillary walls. This can disrupt kidney function and can cause inflammation. Complement activation also contributes to the generation of the membrane attack complex and the release of inflammatory mediators. KDIGO guidelines recommend an in-depth study on the role of the complement system in C3G.

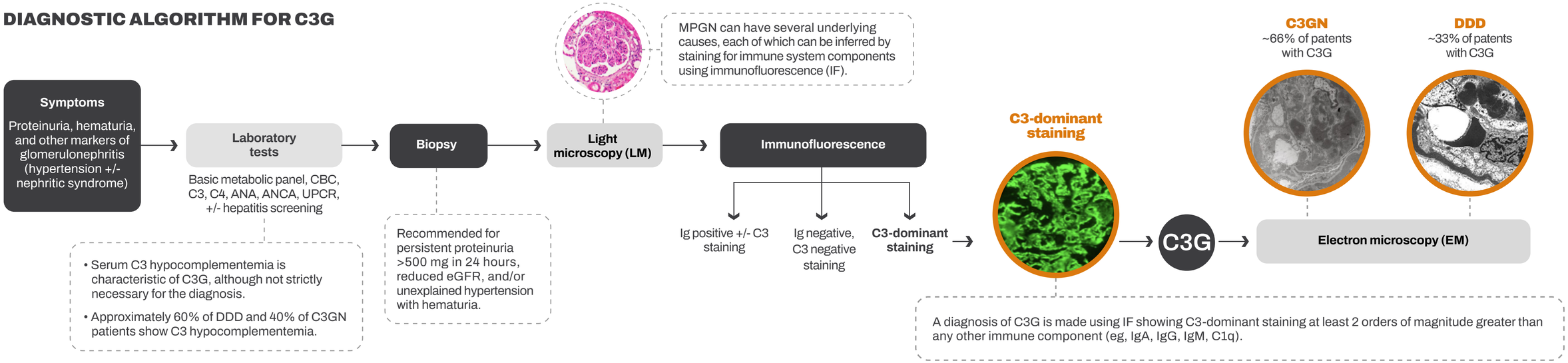
WHAT IS THE CLINICAL RELEVANCE OF THE RECLASSIFICATION OF MPGN I-III TO C3GN AND DDD?

"In my opinion, this reclassification provides a better understanding of the pathophysiology of the disease and gives us a better clinical-pathologic correlation. The group of diseases must be separated from those immunocomplex-related from those that are not. **Furthermore, distinguishing C3GN vs DDD is important for the prognosis of the patient, since it may lead to different approaches to management and they have different rates of recurrence of disease after transplant**, which is more likely in DDD."

—Jose Torrealba, MD

THE DIAGNOSTIC PATHWAY FOR C3G USUALLY BEGINS WITH A WORKUP FOR GLOMERULONEPHRITIS AND ENDS WITH A HISTOPATHOLOGIC DIAGNOSIS

DIAGNOSTIC ALGORITHM FOR C3G



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Smith RJH et al., C3 glomerulopathy—understanding a rare complement-driven renal disease, *Nat Rev Nephrol*, Vol 15, 132, 2019, Springer Nature

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ANA, antinuclear antibody;
ANCA, antineutrophilic cytoplasmic antibody;
C1q, complement component 1q;
C3, complement component 3;
C3G, complement 3 glomerulopathy;
C3GN, complement 3 glomerulonephritis;
C4, complement component 4;
CBC, complete blood count;
DDD, dense deposit disease;
eGFR, estimated glomerular filtration rate;
Ig, immunoglobulin; IgA, immunoglobulin A;
IgG, immunoglobulin G; IgM, immunoglobulin M;
MPGN, membranoproliferative glomerulonephritis;
UPCR, urine protein-creatinine ratio.

HOW CAN NEPHROLOGISTS, PATHOLOGISTS, AND INTERVENTIONAL RADIOLOGISTS BEST COLLABORATE WHEN DIAGNOSING C3G?

“**I make it a habit to provide my pathologists with the patient’s full clinical panel**, including antibody titers for autoimmune kidney disease and complement, and will discuss with them the complete clinical presentation and my suspected diagnosis. I find giving them this information up front is helpful, since staining isn’t the only criteria for a diagnosis.” **—Donald Molony, MD**

“**Specimen adequacy is a crucial step in the diagnostic process.** In our practice, the interventional radiologist does all the biopsies under the supervision of a trained physician to evaluate the tissue adequacy. It’s important to ensure that the need for special and proper handling of the tissue for EM and IF is considered so a successful biopsy is collected and preserved for analysis. At the same time, it is important for the renal pathologist to have a comprehensive clinical history and laboratory data provided by the nephrologist in order to facilitate and appropriate diagnosis.” **— Jose Torrealba, MD**

C3G CAN BE DIFFICULT TO DISTINGUISH FROM OTHER MORE COMMON TYPES OF GN THAT PRESENT WITH SIMILAR SYMPTOMS AND HISTOPATHOLOGY

MOST COMMON DIFFERENTIAL DIAGNOSES FOR C3G

IC-MPGN

Standard immunofluorescence protocols may fail to reveal staining for immunoglobulins due to antigenic masking and tissue preparation. Use of frozen tissue or pronase digestion on formalin-fixed tissue can reveal these deposits and help establish a diagnosis. C4d staining indicates classical or lectin pathway activation and can also be used to distinguish IC-MPGN from C3G.

A renal pathologist familiar with these nuances can facilitate a differential diagnosis.

MGRS

Patients >50 years old with GN should be evaluated for the presence of a monoclonal gammopathy; 30% to 50% of patients >50 years old with C3G have detectable monoclonal Ig (paraprotein) in serum or on kidney biopsy that is associated with renal disease. Monoclonal Ig can interact with complement proteins, thereby indirectly activating the alternative pathway.

Because the underlying driver of disease in MGRS is distinct from C3G, it is important to differentiate the type to inform approaches for management.

PIGN

Clinical manifestations of C3G can also be triggered by an infection. Post-infectious glomerulonephritis (PIGN) can be hard to distinguish from C3G on histopathology, since 30% of PIGN cases show C3-dominant staining.

Unlike C3G, nearly all patients with PIGN regain baseline kidney function and resolution of hematuria, proteinuria, and hypocomplementemia after 8 to 12 weeks. If PIGN is suspected, monitor serum C3 levels for normalization.

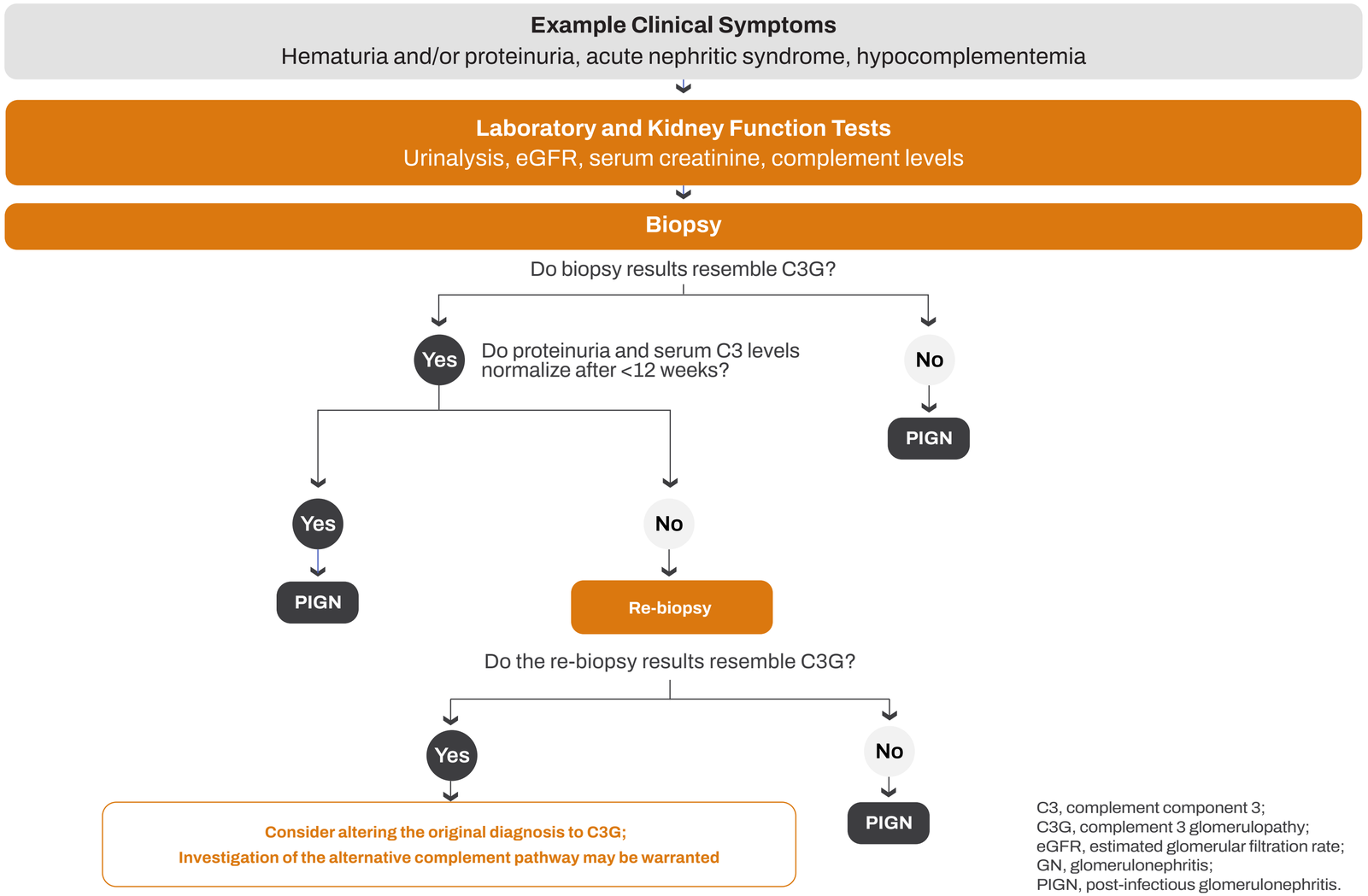
Correctly diagnosing C3G from PIGN is important given C3G risk of progression to ESKD.

See next page for PIGN diagnostic pathway

C3, complement component 3; C3G, complement 3 glomerulopathy; C4d, complement component 4d; ESKD, end-stage kidney disease; GN, glomerulonephritis; IC-MPGN, immune complex membranoproliferative glomerulonephritis; Ig, immunoglobulin; MGRS, monoclonal gammopathy of renal significance.

C3G CAN BE DIFFICULT TO DISTINGUISH FROM OTHER MORE COMMON TYPES OF GN THAT PRESENT WITH SIMILAR SYMPTOMS AND HISTOPATHOLOGY

PIGN DIAGNOSTIC PATHWAY



C3, complement component 3;
C3G, complement 3 glomerulopathy;
eGFR, estimated glomerular filtration rate;
GN, glomerulonephritis;
PIGN, post-infectious glomerulonephritis.

WITH THE SIMILARITIES OF C3G AND OTHER GLOMERULONEPHRITIDES, HOW DO CLINICIANS DISTINGUISH BETWEEN THEM?

"There is a lot of overlap in the clinical presentation of these diseases because the clinical measures are nonspecific: hematuria, proteinuria, and loss of kidney function. If a patient presents with hematuria, I aim to **exclude common causes of hematuria** like cystic lesions in the kidney, **rule out infection**, **determine whether hematuria is persistent or intermittent, and perform a biopsy** if hematuria is persistent."—**Donald Molony, MD**

NEW ICD-10-CM CODES WERE CREATED TO ALIGN WITH THE RECATEGORIZATION OF MPGNs

Atypical MPGN I and MPGN II are now renamed as C3G. Patients diagnosed with MPGN I-III may have been classified using obsolete codes. Correctly coding the 2 subtypes of C3G—DDD and C3GN—is critical for identifying appropriate disease etiology, patient segmentation, and care.

ICD-10-CM CODES FOR C3 GLOMERULOPATHY

Glomerulonephritis	
N00.A	Acute nephritic syndrome with C3 glomerulonephritis
N01.A	Rapidly progressive nephritic syndrome with C3 glomerulonephritis
N02.A	Recurrent and persistent hematuria with C3 glomerulonephritis
N03.A	Chronic nephritic syndrome with C3 glomerulonephritis
N04.A	Nephritic syndrome with C3 glomerulonephritis
N05.A	Unspecified nephritic syndrome with C3 glomerulonephritis
N06.A	Isolated proteinuria with C3 glomerulonephritis
N07.A	Hereditary nephropathy, not elsewhere classified with C3 glomerulonephritis

WHAT IS THE CLINICAL RELEVANCE OF DETERMINING C3G SEVERITY AS DESCRIBED IN THE NEW ICD-10-CM CODES?

“**The codes are used to identify patients and the specific disease**. For C3G, it is a key element for transplant referral, since it helps the nephrologist evaluate the patient’s potential for transplant and give an honest prognosis.” **—Donald Molony, MD**

FOR MORE INFORMATION ON C3G, PLEASE VISIT

www.GlomTalk.com

C3, complement component 3; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MPGN, membranoproliferative glomerulonephritis.

SUMMARY

“In my opinion, **patients can benefit from early identification of C3G, since prognosis for developing kidney failure is directly related to evidence of chronicity in the biopsy.** I think there’s a large number of individuals who may have mild, much more slowly progressive disease that is not being recognized early on or maybe even anywhere before they get to final kidney failure. Nephrologists should have a high index of suspicion for C3G even if patients present with asymptomatic proteinuria and/or hematuria.” **—Donald Molony, MD**

“Having a full clinical picture of a patient is helpful when I am trying to confirm my differential diagnosis. I often do not look at this information, beyond age or gender, before I start my analysis to avoid biasing my interpretation, but will always refer back to this information so that I can provide a clear diagnosis to the nephrologist. **Pathologists should always consider this full clinical picture when diagnosing C3G.**” **—Jose Torrealba, MD**

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C3G, complement 3 glomerulopathy.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080