About the Authors

Sinthiha Krishnan, MD

Dr. Sinthiha Krishnan is an Internal Medicine resident at Western University's Windsor Campus (Windsor, ON,Canada) with clinical and academic interests in rheumatology, dermatology, an immunology. Her work focuses on immunologic mechanisms underlying inflammatory disease and improving clinically relevant approaches to diagnosis and care.

Affiliations: Division of Rheumatology, Department of Medicine, Western University, London, ON, Canada
Division of General Internal Medicine-Windsor Campus, Western University, London, ON, Canada

Andreu Fernández-Codina, MD

Dr. Andreu Fernández-Codina is a rheumatologist and Associate Professor of Medicine at Western University, Canada. He completed a PhD on IgG4-related disease and conducts clinical and translational research in vasculitis, connective tissue diseases, and other systemic autoimmune rheumatic diseases. He is a member of the Canadian Vasculitis Network (CanVasc) and serves as an IgG4-related disease representative within the European Reference Network ReCONNET.

Affiliations: Division of Rheumatology, Department of Medicine, Western University, London, ON, Canada
Division of General Internal Medicine-Windsor Campus, Western University, London, ON, Canada
Division of Rheumatology, Rheumatology Research Group, Hospital Universitari Vall d'Hebron, Barcelona, Spain

.

doi.org/10.58931/crt.2026.3171

The Emerging Role of IgG4 in Rheumatology

Sinthiha Krishnan, MD
Andreu Fernández-Codina, MD

Immunoglobulin G4 (IgG4) is the least abundant IgG subclass and possesses unique structural and functional properties, including Fab-arm exchange, weak complement activation, and reduced Fc receptor binding. These features confer a predominantly immunomodulatory profile that distinguishes IgG4 from other IgG subclasses. Historically associated with allergic responses and immune tolerance, IgG4 has gained increasing attention following the recognition of IgG4-related disease (IgG4-RD), a systemic fibroinflammatory condition characterized by tumefactive lesions, IgG4-positive plasma cell infiltration, and storiform fibrosis.

Beyond IgG4-RD, IgG4 responses have also been described in several rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, anti-neutrophil cytoplasmic autoantibody-associated vasculitis, and Sjögren disease. In these diseases, IgG4 may function as a marker of chronic immune activation, an immunomodulatory adaptation, or contribute to disease pathogenesis; however, its precise role remains poorly understood. Elevated serum IgG4 levels or tissue infiltration by IgG4+ plasma cells lacks disease specificity and should be interpreted within an appropriate clinical and histopathologic context.

This review summarizes the biological features of IgG4, its established association with IgG4-RD, and its emerging significance across rheumatic diseases. Understanding the context-dependent role of IgG4 may improve diagnostic interpretation and advance our understanding of immune-mediated disease in rheumatology.

Introduction

Immunoglobulin G (IgG) antibodies are divided into four subclasses: IgG1, IgG2, IgG3, and IgG4, each with distinct structural and immunologic functions. Among these subclasses, IgG4 is the least abundant, accounting for approximately 3–6% of total serum IgG.[1] Historically, IgG4 was considered a benign and anti-inflammatory immunoglobulin due to its poor ability to activate complement, weak Fc receptor binding, and limited ability to form stable immune complexes.

Interest in IgG4 was initially focused on allergic conditions and parasitic infections. Over the last two decades, however, evidence has shifted attention toward systemic autoimmune disorders following the recognition of IgG4-related disease (IgG4-RD).[2,3] Beyond IgG4-RD, accumulating evidence suggests that IgG4 responses are also present in a range of other conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody-related vasculitis (AAV), and Sjögren disease (SjD).[4] Nevertheless, the precise role of IgG4 in these entities remains unclear—whether as a pathogenic driver, biomarker of chronic immune stimulation, or immunologic epiphenomenon. This review explores the biology of IgG4 and its expanding significance across rheumatology.

Biology of IgG4: Why Is It Different?

Structural and Functional Features

IgG4 is structurally and functionally distinct from other IgG subclasses due to its ability to undergo Fab-arm exchange, a dynamic process in which half-molecules are exchanged between antibodies, generating bispecific, functionally monovalent molecules.[1,5] This structural feature reduces effective cross-linking of antigens and limits immune complex formation. As a result, IgG4 demonstrates weak binding to activating Fc receptors and a limited ability to activate complement via C1q. Collectively, these properties

render IgG4 as the least pro-inflammatory IgG subclass.

Compared with IgG1 and IgG3, IgG4 has a limited capacity to mediate antibody-dependent cellular cytotoxicity or activate the classical complement pathway, further contributing to its "non-inflammatory" profile.[1] Functionally, IgG4 antibodies are considered "blocking antibodies" that are capable of competitively inhibiting antigen–antibody interactions and dampening effector immune responses rather than amplifying inflammation.

Immunological Context

IgG4 class switching is driven by T helper 2 (Th2) and T follicular helper (Tfh2) cells, with key mediators including interleukin (IL)-4, IL-10, and IL-21.[4] IL-4 and IL-13 promote class-switch recombination toward IgG4, while IL-10 and IL-21 further support plasma cell differentiation and IgG4 production. Regulatory T cells may also promote IgG4 production during chronic antigen exposure, supporting immune tolerance and limiting tissue injury.

A prevailing hypothesis proposes that IgG4 develops as an adaptive response to persistent antigen stimulation, such as chronic allergen exposure or infection, in which immune dampening may be beneficial.[6] In this model, the immune system gradually shifts toward a less inflammatory phenotype to limit tissue damage associated with persistent immune activation.

However, in IgG4-RD, the activation of Tfh cells and plasmablast populations suggest a dysregulated immune activation rather than a simple protective immune tolerance. This highlights the dual nature of IgG4: an antibody adapted to suppress inflammation that is also paradoxically associated with fibroinflammatory disease. Within rheumatology contexts, IgG4 is interpreted as a marker of chronic immune activation and immune dysregulation rather than a direct driver of inflammation.

IgG4-Related Disease: The Prototype

Clinical Overview

IgG4-RD is a systemic fibroinflammatory disorder characterized by immune activation, tumefactive lesions, and progressive organ damage. It is a rare condition typically affecting patients in the sixth decade of life, with male predominance. The incidence is 1.2 per 100,000 persons-year.[7] Commonly involved organs include pancreas and the biliary tree (48%), salivary glands (38%), lacrimal glands (26%), orbits (7%), kidneys (16%), lungs (14%), retroperitoneum (16%), lymph nodes (28%), and aorta (10%).[8] Multiorgan involvement is common, affecting two or more organ systems simultaneously in two thirds of the cases.[9]

Patients often present with subacute, painless swelling or enlargement of affected organs. Four clinical phenotypes have been described to encompass the usual presentations: **1)** pancreato-hepato-biliary, **2)** retroperitoneum and aorta, **3)** head and neck—limited, and **4)** Mikulicz syndrome and systemic.[8] Patients with IgG4-RD have a two-fold increase in mortality compared to the general population and remain at risk for chronic organ damage including pancreatic insufficiency, renal dysfunction, or development of arteria aneurysms.[7]

IgG4-RD frequently mimics infections, malignancy, or other inflammatory or infiltrative conditions, making diagnosis particularly challenging.

Histopathology and Diagnosis

Histopathologically, IgG4-RD is defined by a triad of dense lymphoplasmacytic infiltrates, storiform fibrosis ('cartwheel-shaped'), and obliterative phlebitis. Eosinophilic infiltration might also be present. Immunostaining demonstrates IgG4+ plasma cells, although different threshold counts apply depending on the specific tissue. An IgG4+/IgG plasma cell ratio ≥0.4 further supports the diagnosis.[10]

Importantly, neither the presence of IgG4-positive plasma cells in the tissue nor elevated serum IgG4 levels is specific for IgG4-RD. Similar infiltrates may occur in malignancy, vasculitis, infection, and other immune-mediated diseases. In addition, up to 30–40% of patients with biopsy-confirmed IgG4-RD may have normal serum IgG4 concentrations.[8] Elevated serum IgG4 levels may also be observed in allergic, infectious, and other autoimmune diseases. Therefore, serum IgG4 should be viewed as a supportive finding rather than a diagnostic marker.

Circulating plasmablasts can serve as biomarkers for disease activity and treatment response in IgG4-RD. Unfortunately, access to this test remains outside of routine clinical practice. Among patients with elevated baseline serum IgG4, changes in levels may help predict treatment response or disease flares, although less

consistently than plasmablast counts. Ultimately, diagnosis relies on histopathological confirmation in an appropriate clinical and radiologic context.[10] Although originally designed for research purposes, the 2019 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria offer a good framework to exclude other mimicking conditions.[11]

Immunopathogenesis

The pathogenesis of IgG4-RD involves complex interactions among B cells, plasmablasts, T cells, and macrophages.[12] Antigen presentation in the germinal centres by Tfh lymphocytes and follicular dendritic cells initiates the immune response. However, only a limited number of these antigens have been identified. Subsequent B cell activation promotes plasma cell differentiation and immunoglobulin class switching toward IgG4 and Immunoglobulin E (IgE) production. Oligoclonal expansion of plasmablasts and CD4+ cytotoxic T lymphocytes (CTLs) is observed in peripheral blood and tissues.

Tissue injury and fibrosis arise by different mechanisms. CD4+ CTLs may contribute directly to tissue damage through cytotoxic pathways. CD4+ CTLs, macrophages, and plasma cells promote fibroblast activation and extracellular matrix deposition through profibrotic cytokine signalling.

The Role of IgG4: Marker or Mediator?

Despite its central role in the IgG-RD nomenclature, the exact pathogenic contribution of IgG4 remains unclear. Limited *in vitro* data support a direct pathogenic role for IgG4 itself. B cell depletion therapy has shown clinical improvement and marked plasmablast population reductions, yet serum IgG4 levels may remain elevated.[11] This temporal dissociation favours the possibility that IgG4 reflects ongoing immune activation as an epiphenomenon, rather than serving as the main driver of the disease.

From a clinical perspective, acknowledging the limitations of serum IgG4 is essential. Both tissue and serum IgG4 findings must be interpreted cautiously within the appropriate clinical, radiographic, and histologic context.

IgG4 in Other Rheumatic Diseases

Although IgG4 is strongly associated with IgG4-RD, increasing evidence suggests that IgG4 responses also occur across a broader spectrum of rheumatic diseases (**Table 1**).

Rheumatoid Arthritis

RA is a chronic autoimmune disease characterized by synovial inflammation, autoantibody production, and progressive joint destruction. Anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) are RA's immunological hallmarks. While IgG1 is the most abundant form of ACPAs and RF, a significant portion of these autoantibodies belongs to the IgG4 subclass.[1] The role of IgG4 in RA remains controversial, as conflicting evidence supports both pathogenic and immunomodulatory effects.

On one hand, elevated IgG4-ACPA levels have been associated with higher disease activity, increased inflammatory markers, and more severe radiographic progression.[13] Furthermore, serum IgG4 levels in RA correlate with interleukin 6 levels.[14] These findings suggest that IgG4 may reflect persistent immune stimulation within chronic RA, potentially having a pathogenic role. On the other hand, persistent exposure to citrullinated antigens may promote Th2- and regulatory T cell-mediated cytokine signalling, thereby favouring IgG4 class switching. IgG4-ACPAs demonstrate a limited ability to activate complement because of weak C1q binding and reduced Fc receptor affinity compared to IgG1-ACPAs. Subclass switching to IgG4 in RA may represent an adaptive or compensatory immunoregulatory response that develops during chronic immune dysregulation and prolonged antigenic stimulation.[13] Consequently, the precise pathogenic role of IgG4-ACPAs remains uncertain.

Systemic Lupus Erythematosus

SLE is characterized by autoantibody production, immune complex deposition, and complement-mediated tissue injury.[15] In contrast to IgG1 and IgG3 autoantibodies, which strongly activate complement, IgG4 autoantibodies exhibit limited pro-inflammatory effector functions.

IgG4 anti-double-stranded DNA (anti-dsDNA) antibodies have been identified in patients with SLE, especially among those with lupus nephritis. Some studies suggest that, because IgG4 binds

Disease	IgG4 Findings	Clinical Relevance
IgG4-Related Disease	Elevated serum IgG4 levels; abundant IgG4+ plasma cells in affected tissues	Hallmark disease feature, although IgG4 likely reflects underlying immune dysregulation more than pathogenicity
Rheumatoid Arthritis	IgG4-ACPAs, IgG4-RF, and elevated serum IgG4 levels reported in some patients	Associated with chronic antigenic stimulation; may correlate with greater disease activity and structural damage
Systemic Lupus Erythematosus	IgG4 anti-dsDNA antibodies, particularly in lupus nephritis	May have a protective role because of limited complement activation, overall clinical significance remains uncertain
ANCA-Associated Vasculitis	IgG4 MPO-ANCA, PR3-ANCA, and occasional IgG4-rich tissue infiltrates	May contribute to disease activity; important source of diagnostic overlap with IgG4-RD
Sjögren Disease	Occasional IgG4+ plasma cells in salivary glands; serum IgG4 levels are usually normal	Major diagnostic mimic of IgG4-RD; clinicopathologic correlation is therefore essential
Other Rheumatic Diseases (*systemic sclerosis, inflammatory myopathies*)	Sporadic reports of elevated serum IgG4 levels and tissue infiltration	Likely reflects chronic inflammation and fibrosis rather than a disease-specific mechanism

Table 1. Clinical Relevance of IgG4 Across Rheumatic Diseases; *courtesy of Sinthiha Krishnan, MD and Andreu Fernández-Codina, MD.*

Abbreviations: ACPA: Anti-Neutrophil Cytoplasmic Antibody; **ANCA:** anti-neutrophil cytoplasmic antibodies; **dsDNA:** double-stranded deoxyribonucleic acid; **IgG4:** Immunoglobulin G 4; **IgG4-RD:** IgG4-related disease; **MPO:** Myeloperoxidase; **PR3:** Proteinase 3; **RF:** Rheumatoid factor

poorly to C1q, IgG4-containing immune complexes may generate less tissue inflammation within the skin, kidneys, and vasculature.[16] These observations have led to the hypothesis that IgG4 anti-dsDNA may represent an adaptive response to mitigate chronic immune activation in SLE. However, it remains to be established whether IgG4 contributes to disease modulation or merely simply reflects ongoing immune dysregulation.

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

AAV encompasses a group of necrotizing small vessel vasculitides characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) in the serum. A subset of both anti-myeloperoxidase and anti-proteinase-3 ANCA belong to the IgG4 subclass. AAV includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis.[17]

Experimental studies have shown that IgG4-ANCA can activate neutrophils and contribute to oxidative burst responses, suggesting a potential role in vasculitic injury.[18] However, the specific pathogenic contribution of IgG4-ANCA compared with other ANCA subclasses remains incompletely understood. In EGPA, elevated serum IgG4 concentrations may also reflect the underlying Th2-predominant immune response associated with asthma, eosinophilia, and allergic disease.[19] Thus, while the classical biologic properties of IgG4 suggest predominantly immunomodulatory functions, some observations support a potential pro-inflammatory role in selected settings.

The possibility of an overlap between AAV and IgG4-RD deserves particular consideration. Both diseases share similar anatomical sites, including the sinuses, orbits, lungs, or retroperitoneum.[20] Some patients with GPA exhibit increased IgG4-positive plasma cell infiltration in sinus and periorbital biopsy specimens, creating diagnostic challenges. Shared organ involvement and histopathologic findings must therefore be interpreted alongside distinguishing features such as necrotizing vasculitis and granulomatous inflammation, which are characteristic of AAV but not of IgG4-RD. Interestingly, both groups of diseases respond well to glucocorticoids and B cell depletion. True overlap syndromes have been reported, although their exact nature remains debated.

Importantly, the ACR/EULAR classification criteria explicitly exclude patients with AAV features.[11] Consequently, the presence of elevated serum IgG4 levels or tissue IgG4-positive plasma cells should not be considered sufficient evidence for IgG4-RD in the absence of compatible clinical and pathologic findings.

Sjögren Disease

SjD and IgG4-RD share several overlapping features, particularly involving the salivary and lacrimal glands. Both disorders may present with gland enlargement, and less often, interstitial nephritis. In contrast to IgG4-RD, patients with SjD will typically present with sicca symptoms, vasculitic manifestations, positive TROVE2/Ro60 and/or La autoantibodies, and normal or decreased serum IgG4 levels.[21] Furthermore, IgG4-RD lesions might affect other organs, such as the pancreas or retroperitoneum, which are not typically affected in SjD.

Histopathologic overlap may also occur. Salivary gland biopsies may occasionally demonstrate some IgG4+ plasma cells along with lymphocytic infiltrates in SjD. In IgG4-RD, however, IgG4+ plasma cells are usually more abundant, although storiform fibrosis and obliterative phlebitis might be absent in lacrimal and salivary glands specimens.[22] This reinforces the concept that IgG4+ plasma cell infiltration is not disease-specific. Instead, IgG4 responses may emerge across multiple chronic inflammatory states involving persistent immune activation and tissue remodelling.

Other Rheumatic Conditions

Elevated serum IgG4 levels and increased IgG4-positive plasma cell infiltrates have also been described in systemic sclerosis and inflammatory myopathies.[23] These findings are generally thought to reflect chronic inflammation and fibrosis rather than a specific pathogenic role for IgG4. However, the available evidence remains limited and does not allow definitive conclusions.

Future Directions

Future research on IgG4 should focus on the contexts in which it acts as an immunomodulatory molecule versus those in which it may contribute to disease pathogenesis across different rheumatic conditions. Advanced molecular techniques and a better understanding of B cell responses might help address this question. Additionally, reproducible and accessible biomarkers are needed to diagnose and monitor IgG4-RD. The emergence of B-cell targeted therapies such as inebilizumab and obeleximab will likely reshape the management of IgG4-RD while providing new insights into disease-pathogenesis.[24,25]

Conclusion

IgG4 emerges as an immunological adaptation during chronic antigen exposure and immune activation. Although IgG4 is closely associated with IgG4-RD, IgG4 responses have also been observed across a range of other rheumatic diseases. In most contexts, this response remains regulatory, whereas in others it might trigger inflammation and tissue damage. Understanding this duality remains key to interpreting the role of IgG4 across rheumatology.

Correspondence

Andreu Fernández Codina, MD
Email: Andreu.fernandezcodina@lhsc.on.ca

Financial Disclosures

S.K.: None declared.
A.F-C.: Honorarium: Amgen, Sanofi

References

1. Rispens T, Huijbers MG. The unique properties of IgG4 and its roles in health and disease. Nat Rev Immunol. 2023;23(11):763-778. doi:10.1038/s41577-023-00871-z
2. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38(10):982-984. doi:10.1007/s00535-003-1175-y
3. Stone JH. IgG4-related disease: lessons from the first 20 years. Rheumatology (Oxford). 2025;64(Supplement_1):i24-i27. doi:10.1093/rheumatology/keaf008
4. Akiyama M, Alshehri W, Ishigaki S, Saito K, Kaneko Y. The immunological pathogenesis of IgG4-related disease categorized by clinical characteristics. Immunol Med. 2025;48(1):11-23. doi:10.1080/25785826.2024.2407224
5. Aalberse RC, Schuurman J. IgG4 breaking the rules. Immunology. 2002;105(1):9-19. doi:10.1046/J.0019-2805.2001.01341.X
6. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. Clin Exp Immunol. 2015;181(2):191-206. doi:10.1111/cei.12641
7. Wallace ZS, Miles G, Smolkina E, et al. Incidence, prevalence and mortality of IgG4-related disease in the USA: a claims-based analysis of commercially insured adults. Ann Rheum Dis. 2023;82(7):957-962. doi:10.1136/ard-2023-223950
8. Wallace ZS, Zhang Y, Perugino CA, et al. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. Ann Rheum Dis. 2019;78(3):406-412. doi:10.1136/annrheumdis-2018-214603
9. Martínez-Valle F, Fernández-Codina A, Pinal-Fernández I, Orozco-Gálvez O, Vilardell-Tarrés M. IgG4-related disease: Evidence from six recent cohorts. Autoimmun Rev. 2017;16(2):168-172. doi:10.1016/j.autrev.2016.12.008
10. Umehara H, Okazaki K, Kawa S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol. 2021;31(3):529-533. doi:10.1080/14397595.2020.1859710
11. Wallace ZS, Naden RP, Chari S, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Ann Rheum Dis. 2020;79(1):77-87. doi:10.1136/annrheumdis-2019-216561
12. Peyronel F, Della-Torre E, Maritati F, et al. IgG4-related disease and other fibro-inflammatory conditions. Nat Rev Rheumatol. 2025;21(5):275-290. doi:10.1038/s41584-025-01240-x
13. Lin G, Li J. Elevation of serum IgG subclass concentration in patients with rheumatoid arthritis. Rheumatol Int. 2010;30(6):837-840. doi:10.1007/s00296-009-1330-8
14. Sakthiswary R, Shaharir S, Abdul Wahab A, Uma Rajeswaran V. Comparison of IgG4 with inflammatory cytokines (IL-1, IL-6 and TNFα) in rheumatoid arthritis. Front Immunol. 2025;16(July):1607074. doi:10.3389/fimmu.2025.1607074
15. Hoi A, Igel T, Mok CC, Arnaud L. Systemic lupus erythematosus. Lancet. 2024;403(10441):2326-2338. doi:10.1016/S0140-6736(24)00398-2
16. Zeng Y, Zhang Y, Chen Q, et al. Distribution of IgG subclass anti-nuclear antibodies (ANAs) in systemic lupus erythematosus. Lupus. 2021;30(6):901-912. doi:10.1177/0961203321995242
17. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11. doi:10.1002/art.37715
18. Holland M, Hewins P, Goodall M, Adu D, Jefferis R, Savage COS. Anti-neutrophil cytoplasm antibody IgG subclasses in Wegener's granulomatosis: A possible pathogenic role for the IgG4 subclass. Clin Exp Immunol. 2004;138(1):183-192. doi:10.1111/j.1365-2249.2004.02566.x
19. Wilson-Morkeh H, Seluk L, Bosch P, et al. Targeting Immunologic Pathways in Eosinophilic Granulomatosis With Polyangiitis: Translating Emerging Evidence Into Clinical Practice. Allergy. January 2026:1-17. doi:10.1111/all.70215
20. Wang C, He R, Bai X, et al. Immune cell crosstalk between ANCA-associated vasculitis and IgG4-related disease: an unresolved pathogenic link. Front Immunol. 2025;16(October):1-12. doi:10.3389/fimmu.2025.1660956
21. Liu Y, Li J. Preferentially immunoglobulin (IgG) subclasses production in primary Sjögren's syndrome patients. Clin Chem Lab Med. 2011;50(2):345-349. doi:10.1515/CCLM.2011.771
22. Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. Nat Rev Rheumatol. 2024;20(8):473-491. doi:10.1038/s41584-024-01135-3
23. Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020;16(12):702-714. doi:10.1038/s41584-020-0500-7
24. Stone JH, Khosroshahi A, Zhang W, et al. Inebilizumab for Treatment of IgG4-Related Disease. N Engl J Med. 2025;392(12):1168-1177. doi:10.1056/NEJMoa2409712
25. Della-Torre E, Baker MC, Zhang W, et al. Obexelimab for the Treatment of IgG4-Related Disease. N Engl J Med. June 2026. doi:10.1056/NEJMoa2601337