



Immunoglobulin G4- Related Disease (IgG4-RD)

ICD-10 Coordination and Maintenance Meeting
March 8-9, 2022

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Presentation Outline

- Immunoglobulin G4-Related Disease (IgG4-RD) Overview
 - Background
 - Manifestations/ Clinical Presentation
 - Epidemiology
 - Diagnosing IgG4-RD
 - Standard of Care
 - Clinical Programs
 - Burden of Illness
- Rationale For New ICD-10-CM Code
 - Improved time to diagnosis
 - Improving understanding of disease and its manifestations
 - Improved care access

Background

- Immunoglobulin G4-Related Disease (IgG4-RD) is an orphan disease characterized only in this century. It is a multifocal inflammatory condition that may have its roots in autoimmunity, but its etiology at this time remains unknown.
- IgG4-RD is considered a chronic, relapsing-remitting, immune-mediated fibroinflammatory disorder.
 - If undiagnosed or treated incorrectly, organ failure and death can ensue.
- IgG4-RD is not associated with pain and may be asymptomatic, which can lead to advanced stage disease and late identification by specialty physicians
- Lymphocytes such as regulatory T and B cells have been shown to exhibit altered behavior in IgG4-RD and may play a role in disease manifestation.
 - Because the pathophysiology of IgG4-RD is well understood, novel therapeutics may be beneficial for patients with this disease.

1. Khalili OM. IgG-4 Related Disease: An Introduction. *Mo Med* 2018; 115: 253-256 ([Link](#))
2. Uchida K, Okazaki K. Roles of Regulatory T and B Cells in IgG4-Related Disease. *Curr Top Microbiol Immunol* 2017;401:93-114 ([Link](#))

Manifestations And Clinical Presentation of IgG4-RD

- Mass lesions (swelling of involved organs, mimicking malignancy)
- Atopic features (asthma, allergic rhinitis, eczema)
- Dense lymphoplasmacytic infiltrate
- IgG4-positive plasma cells present in large numbers in tissues
- Storiform fibrosis (distinctive histopathological feature)
- Elevated serum IgG4 concentrations

1 Wallace ZS et al. The 2019 American College of Rheumatology/European League against Rheumatism Classification Criteria for IgG4-Related Disease. *ACR* 2020; 72: 7-19. ([Link](#))

Epidemiology of IgG4-RD

- Underappreciation, coupled with mis- or under-diagnosis, has hindered accurate estimates of the incidence and prevalence of IgG4-RD
- No studies have assessed the prevalence of IgG4-RD in the US
 - Extrapolation from studies outside the US highlights that individuals in their 50's may be most likely to develop the disease.
 - Physician experience shows that the disease occurs across a range of age groups, races, and ethnicities, with no significant predilections for population subgroups.
- As many as 85% of patients with IgG4-RD have active disease at the time of diagnosis
- Pancreatic involvement is the most common manifestation, which is present in around 20-25% of IgG4-RD cases
- There are currently no diagnostic biomarkers for IgG4-RD
 - Elevated serum IgG4 occurs in most, but not all patients

1. IgG4-Related Disease Epidemiology Report 2019: Total Diagnosed Prevalent Cases were 204,818 in 2017 in the 7MM - Forecast to 2028. *Businesswire* 2019 ([Link](#))
2. Wallace ZS et al. The 2019 American College of Rheumatology/European League against Rheumatism Classification Criteria for IgG4-Related Disease. *ACR* 2020; 72: 7-19. ([Link](#))
3. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan. *Int J Rheumatol* 2012; 2012: 35871 ([Link](#))
4. Salvadori M, Tsalouchos A. Immunoglobulin G4-related kidney diseases: An updated review. *World J Nephrol* 2018; 7:29-40. ([Link](#))

Diagnosing IgG4-RD

- There is no single diagnostic test for IgG4-RD
- Diagnosis is established through consideration of:
 - Clinical features
 - Serologic findings
 - Radiologic evidence
 - Pathological data
- The diagnosis of IgG4-RD is made by many specialists including but not limited to neurologists, gastroenterologists, pulmonologists, and rheumatologists who recognize various characteristics of the disease

1. Della-Torre E, Stone JH. "How I Manage" IgG4-Related Disease. *J Clin Immunology* 2016; 36: 754-763 ([Link](#))
2. Wallace ZS et al. IgG4 Related Disease Clinical and Laboratory Features in One Hundred Twenty-Five Patients. *Arthritis Rheum* 2015; 67: 2466-2475 ([Link](#))
3. Khosroshahi A et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 67(7): 1688-1699. ([Link](#))

Standard of Care

- Classification criteria for IgG4-RD were first published in 2020
- Despite guidelines and established clinical nomenclature, the ability of clinicians in practice to diagnosis and treat IgG4-RD remains suboptimal
- An IgG4-RD responder index has been developed and validated to guide physicians through disease activity across a range of domains, providing a correlate for the level of response that treatment has on patients
- Many patients use daily glucocorticoids to manage their disease; however,
 - IgG4-RD patients on steroids often relapse
 - Despite efficacy of steroids, co-morbidities in the patient population may complicate candidacy for treatment with these drugs
- Few clinical studies are underway that examine the use of targeted therapies to treat IgG4-RD

1. Wallace ZS et al. The 2019 American College of Rheumatology/European League against Rheumatism Classification Criteria for IgG4-Related Disease. *ACR* 2020; 72: 7-19. ([Link](#))
2. Wallace ZS et al. IgG4 Related Disease Clinical and Laboratory Features in One Hundred Twenty-Five Patients. *Arthritis Rheum* 2015; 67: 2466-2475 ([Link](#))
3. Perugino CA, Stone JH. Current and Future Approaches to the Treatment of IgG4-Related Disease. *Z Rheumatol* 2016; 75:681-86. ([Link](#))
4. Wallace ZS et al. An International Multispecialty Validation Study of the IgG4-Related Disease Responder Index. *Arthritis Care Res* 2018;70(11): 1671-1678 ([Link](#))
5. Carruthers MN, Stone JH, Deshpande V, Khosroshahi A. Development of an IgG4-RD Responder Index. *Int J Rheumatol* 2012; 2012:259408 ([Link](#))

Burden of Illness

- The inability to quickly rule out critical organ involvement contributes to poorer patient outcomes.
 - Patients not able to receive the proper diagnosis and treatment face the loss of function of critical organs such as the pancreas, kidney, and liver. The downstream effects of organ loss are widespread for this patient population.
- Patients with IgG4-RD disease tend to experience emotional distress linked to the lack of unity within the healthcare community in understanding this disease.
- Numerous consultations may be needed, putting burden on the healthcare system that includes:
 - Prolonged diagnostic timelines due to limited access to early screening and testing procedures
 - Misdiagnosis and associated patient emotional burden
 - Misdiagnosis and associated healthcare spend
 - Unnecessary procedures associated with diagnosis
 - Heightened visit frequency for diagnosis
 - Heightened visit frequency due to treatment relapse
 - Limited centers of excellence
 - Addition of organ transplant candidates

Implications of New ICD-10-CM For IgG4-RD

- More research and disease awareness is needed to understand incidence and prevalence of this population and those efforts are currently hampered by disease-tracking limitations.
 - Creation of an ICD-10-CM code for IgG4-RD will improve tracking and benefit both clinical and research efforts.
- An ICD-10-CM code specific to IgG4-RD will differentiate IgG4-RD from other diseases and will ultimately lead to:
 - Unification in understanding patient manifestations, leading to more nuanced provider understanding and enhanced patient outcomes.
- IgG4-RD is a unique disease, and assignment of its own ICD-10-CM code will facilitate the understanding of this condition, and this will also enable epidemiological and provider understanding of the disease to advance.



Appendix

Clinical Programs

There are currently 2 studies with published data on clinicaltrials.gov

Study Number, Phase	Type of therapy	Enrollment, results date, study design	Outcome Assessment
NCT02725476 Phase I-II	Monoclonal antibody	N=20 Results posted Dec 7, 2018 Single arm, open label	Met primary outcome of improvement in IgG4-RD activity (responder index) . 80% responded at follow up day 169
NCT01584388 Phase I-II	Monoclonal antibody	N=30 Results posted Jul 2, 2017 Single arm, open label	Met primary outcome of improvement in IgG4-RD activity based on responder index at 6 months . 96.7% exhibited decline in RI by 2 points or more and maintained at 6 months

Overview of All Clinical studies /

(N = 29)	Targeted therapies	Recruiting	Interventional	Completed	Unknown Status ⁱ	Early/Phase I	Phase II	Phase III
Number of Studies	5	10	20	8	8	3	8	2

- NCT02725476. Study to Evaluate the Effect of XmAb@5871 on Disease Activity in Patients With IgG4-Related Disease (RD). ([Link](#))
- NCT01584388. Rituximab in IgG4-RD: A Phase 1-2 Trial. ([Link](#))

i. Unknown status indicates that a study has passed its completion date and status has not been verified in more than two years
RI: responder index