IgG4-Related Disease (IgG4-RD)

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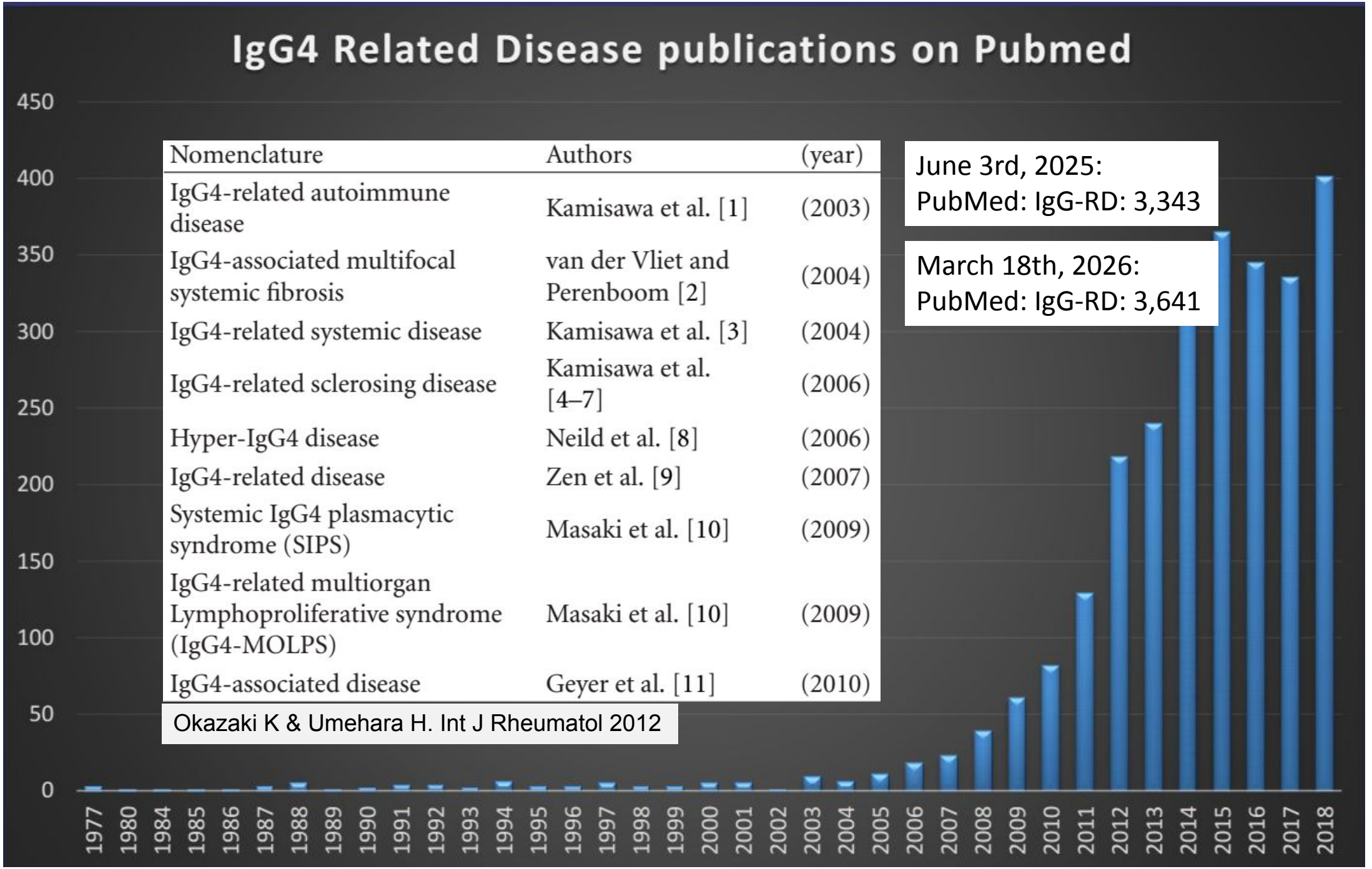
IgG4 Related Disease publications on Pubmed



Nomenclature	Authors	(year)
IgG4-related autoimmune disease	Kamisawa et al. [1]	(2003)
IgG4-associated multifocal systemic fibrosis	van der Vliet and Perenboom [2]	(2004)
IgG4-related systemic disease	Kamisawa et al. [3]	(2004)
IgG4-related sclerosing disease	Kamisawa et al. [4–7]	(2006)
Hyper-IgG4 disease	Neild et al. [8]	(2006)
IgG4-related disease	Zen et al. [9]	(2007)
Systemic IgG4 plasmacytic syndrome (SIPS)	Masaki et al. [10]	(2009)
IgG4-related multiorgan Lymphoproliferative syndrome (IgG4-MOLPS)	Masaki et al. [10]	(2009)
IgG4-associated disease	Geyer et al. [11]	(2010)

Okazaki K & Umehara H. Int J Rheumatol 2012

June 3rd, 2025:
PubMed: IgG-RD: 3,343

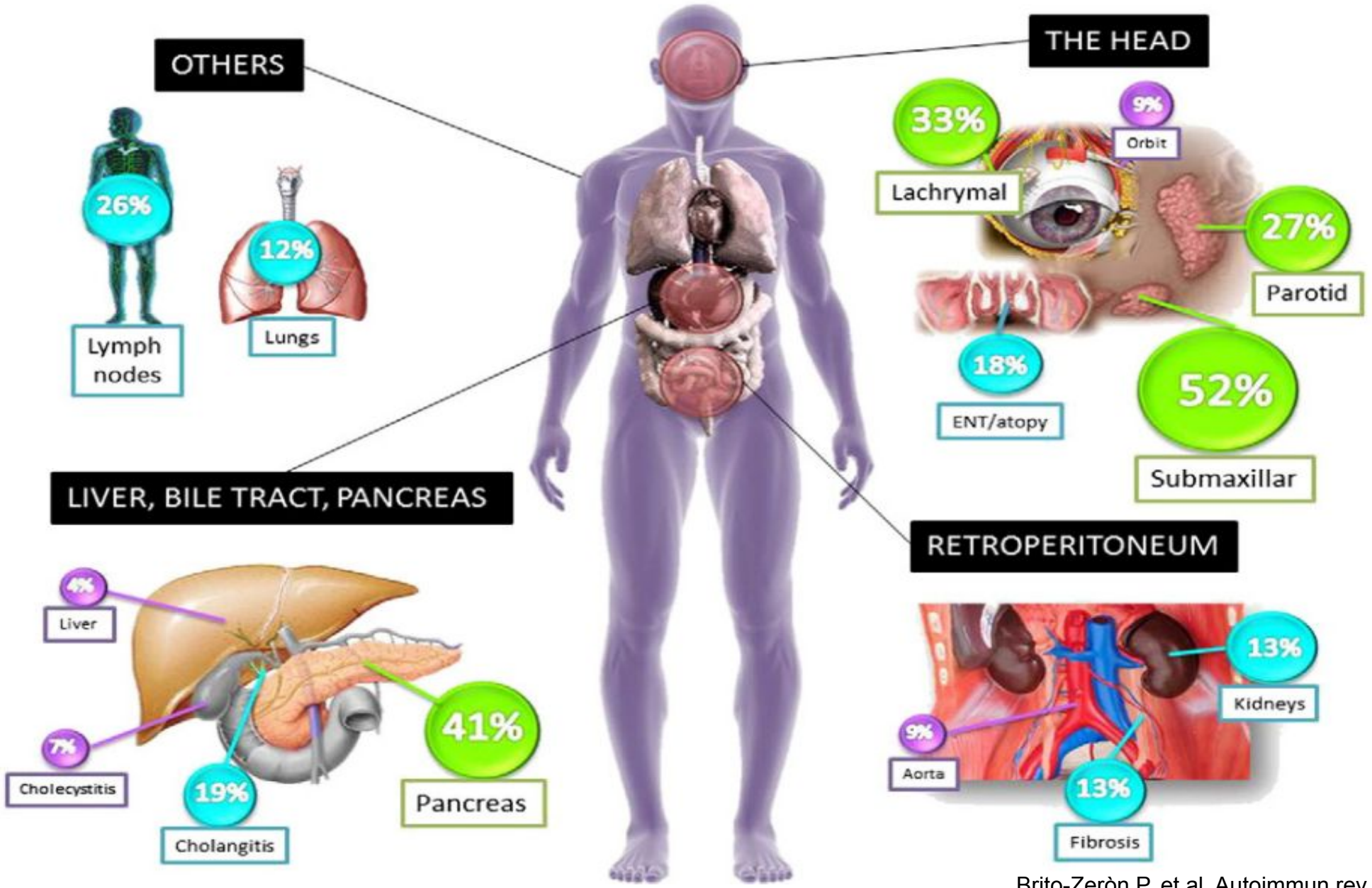
March 18th, 2026:
PubMed: IgG-RD: 3,641

Previously recognized conditions that are part of IgG4-related disease

Previous name	Affected organ	Reference
Mikulicz's disease	Salivary and lacrimal gland	Yamamoto et al.[28]
Küttner's tumour	Submandibular gland	Geyer et al.[29]
Riedel's thyroiditis	Thyroid	Dahlgren et al.[30]
Chronic sclerosing aortitis	Aorta	Stone et al.[31]
Morbus Ormond	Retroperitoneum	Hamano et al.[32]
Autoimmune pancreatitis	Pancreas	Hamano et al.[33]
Sclerosing cholangitis	Biliary system	Ghazale et al.[34]
Orbital pseudotumour	Orbita	Cheuk et al.[35]
Autoimmune hepatitis	Liver	Yada et al.[26]
Multifocal fibrosclerosis	Multiple organs	Kamisawa et al.[1]

Beyer et al, UEG journal 2014

Clinical presentation of IgG4-RD: up to 37 organ/systems involved



Brito-Zeròn P, et al. Autoimmun rev 2014;13:1203-1210.

Laboratory features

- Peripheral blood eosinophilia (27% of patients)
- ESR > CRP
- Hyperglobulinemia
- Serum IgE elevation (35% of patients)
- Serum IgG4 > 135 mg/dL (increased in only 60-70% of pts)

  Phenotype 4 □ 1 □ 3 □ 2
- Serum IgG1, IgG2, IgG3 elevation
- Low C3 - C4 complement levels
- ANA and RF +/-
- ANCA / SSa / SSb -

Review

Blood biomarkers recommended for diagnosing and monitoring IgG4-related disease. Considerations from the ERN ReCONNET and collaborating partners

L. Iaccarino[1], R. Talarico[2], E. Bozzalla-Cassione[3], G.R. Burmester[4], E.L. Culver[5], A. Doria[1], M. Ebbo[6], P.M. van Hagen[7], E. Hachulla[8], J.A.M. van Laar[7], M. Lanzillotta[9,10], F. Martinez-Valle[11], C. Montecucco[3], S. Monti[3], C. Nalli[12], N. Schleinitz[6], A. Tincani[12], E. Della-Torre[9,10], T. Alexander[4,13]

European Reference Network
for rare or low prevalence complex diseases

Network Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

Table II. Proposed blood biomarkers recommended for diagnosing and monitoring IgG4-RD according to clinical relevance.

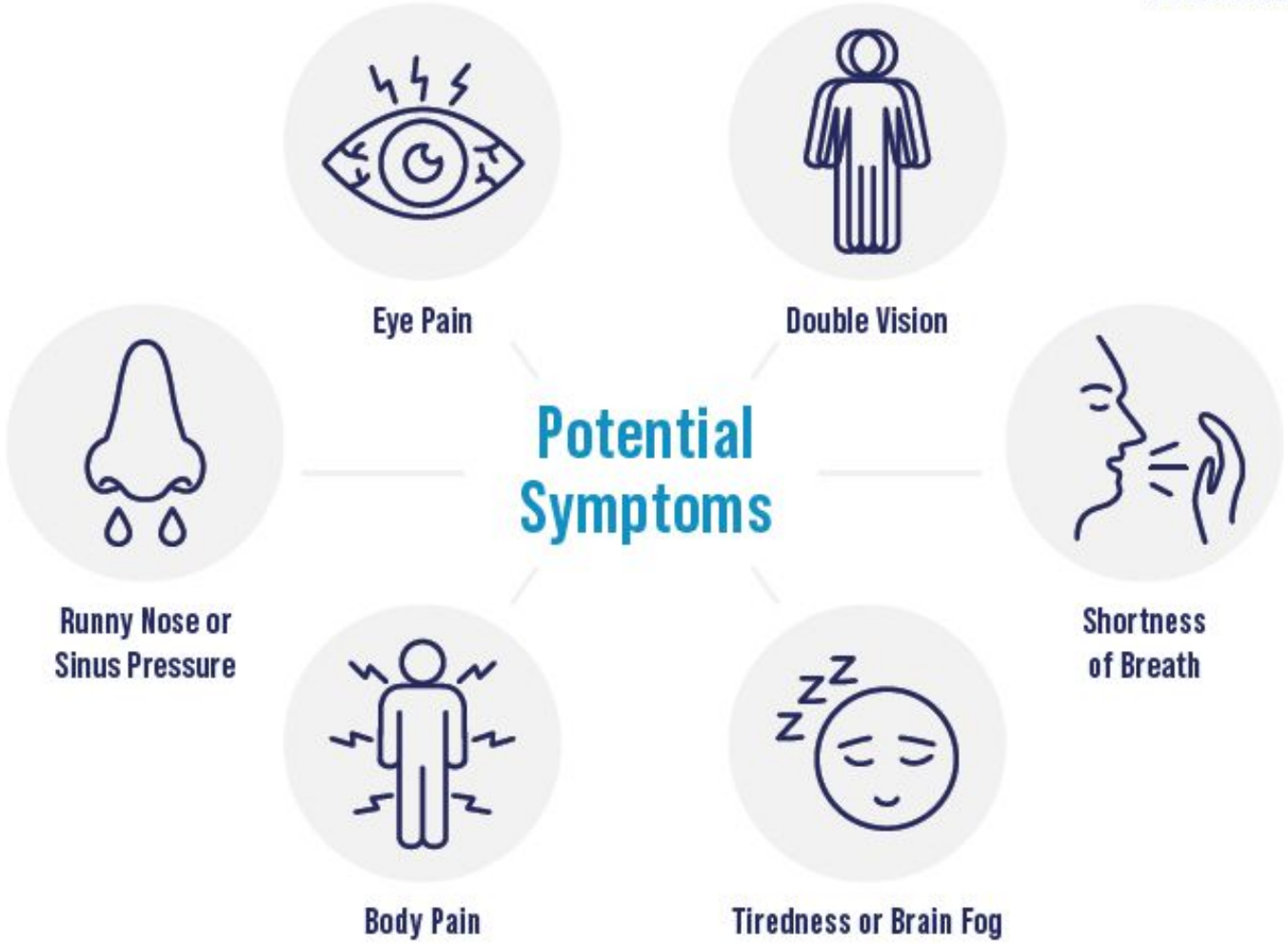
Clinical relevance	Biomarkers recommended in clinical routine	Biomarkers to be considered
Diagnosis	IgG4, IgG2, IgE, C3/C4, sIL-2R, Eosinophils, CRP/ESR	Plasmablasts
Disease activity	IgG4, C3/C4, sIL-2R, CRP/ESR	Plasmablasts
Prognosis	IgG4, IgE, sIL-2R, Eosinophils, CRP/ESR	Plasmablasts, memory B-cells, IgA, TNF-α
Clinical phenotype and organ specific markers	IgG4, IgE, C3/C4, Eosinophils, CRP/ESR	IgG2 (orbital disease), sFLC (renal), IFNα (AIP)
Degree of fibrosis		CCL18, GDF-15, ELF

CCL18: C-C motif chemokine ligand 18; CrP: C-reactive Protein; ELF: enhanced liver fibrosis; ESR: erythrocyte sedimentation rate; GDF-15: growth differentiation factor 15; sIL-2R: soluble interleukin-2 receptor; sFLC: serum free light chains.

Clin Exp Rheumatol 2022; 40 (Suppl. 134): S71-S80.

"I was called a hypochondriac countless times."

"When I would lean down to tie my shoes, it felt like I was running a marathon. Turned out, my heart was enlarged and the size of a 300-pound man's."



Several patients noted that, even when they did find a specialist or rheumatologist who would see them, providers often lacked the specific knowledge to treat IgG4-RD. One patient recalled her provider telling her, "I do not know how to care for you."

"I wonder where I would be if I had gotten the infusion in the first place."

"My ability to complete daily activities is nonexistent."

ERN Reconnet webpage

How Patients Describe IgG4-RD

Sequelae of IgG4-RD

- **Aortitis Inflammatory ->** aortic aneurysms can continue to enlarge and are at risk for dissection.
- **Retroperitoneal Fibrosis** -> Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.
- **Proximal biliary strictures** -> Untreated disease can lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.
- **Tubulointerstitial Nephritis** -> Untreated disease may lead to irreversible chronic kidney disease.
- **Pachymeningitis** -> Untreated disease puts the patient at risk for neurologic deficits and/or seizures.
- **Pancreatic enlargement** -> Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.
- **Pericarditis** ->Untreated disease may lead to tamponade or constrictive pericarditis

How to manage patients with IgG4-RD?

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

IgG4-related diseases: state of the art on clinical practice guidelines

Luca Iaccarino,[1] Rosaria Talarico,[2] Carlo Alberto Scirè,[3] Zahir Amoura,[4] Gerd Burmester,[5] Andrea Doria,[1] Karim Faiz,[6] Charissa Frank,[7] Eric Hachulla,[8] Miguel Hie,[4] David Launay,[8] Carlomaurizio Montecucco,[9] Sara Monti,[9] Luc Mouthon,[10] Angela Tincani,[11] Paola Toniati,[11] Pieter Martin Van Hagen,[6] Ronald F Van Vollenhoven,[12] Stefano Bombardieri,[13] Ulf Mueller-Ladner,[14] Matthias Schneider,[15] Vanessa Smith,[16,17] Maurizio Cutolo,[18] Marta Mosca,[2,19] Tobias Alexander[5]

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Author and year	Description
Khosroshahi *et al*, 2015	Systematic review, multiple specialists, guidelines for diagnostic and treatment, so far first real guidelines; very helpful for the physician in clinical practice
Deshpande *et al*, 2013	Review on existing data for terminology, pathology and immunopathology, no real guidelines, no systematic review; recommendations are lacking, so the usefulness of this paper is limited
Deshpande *et al*, 2012	Consensus statement on pathology, only expert opinion, no clear systematic review; no systematic methods for formulating recommendations key histopathological features and IgG4 assessment are clearly defined
Stone *et al*, 2012	Review on terminology based on expert opinion. Although experts from different specialties were present, this is rather expert consensus than a clear recommendation; no systematic guidelines are reported and key messages are not easily identifiable

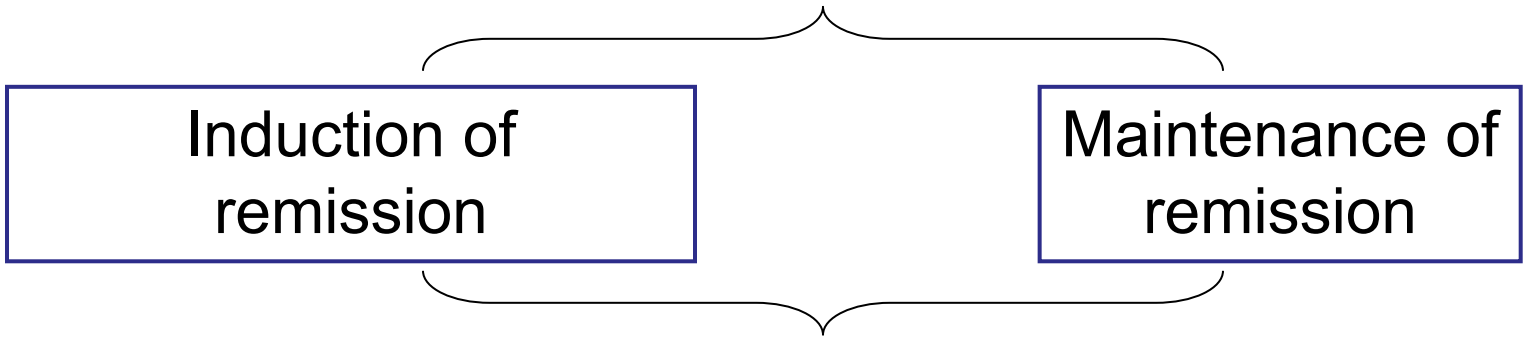
Iaccarino L, *et al*. *RMD Open* 2019;**4**:e000787.

Treatment guidelines – medical therapy

General considerations

- Symptomatic / asymptomatic / urgent cases
- Limited window of time: “reversible vs not-reversible fibrosis”
- Relapsing remitting course

Objectives

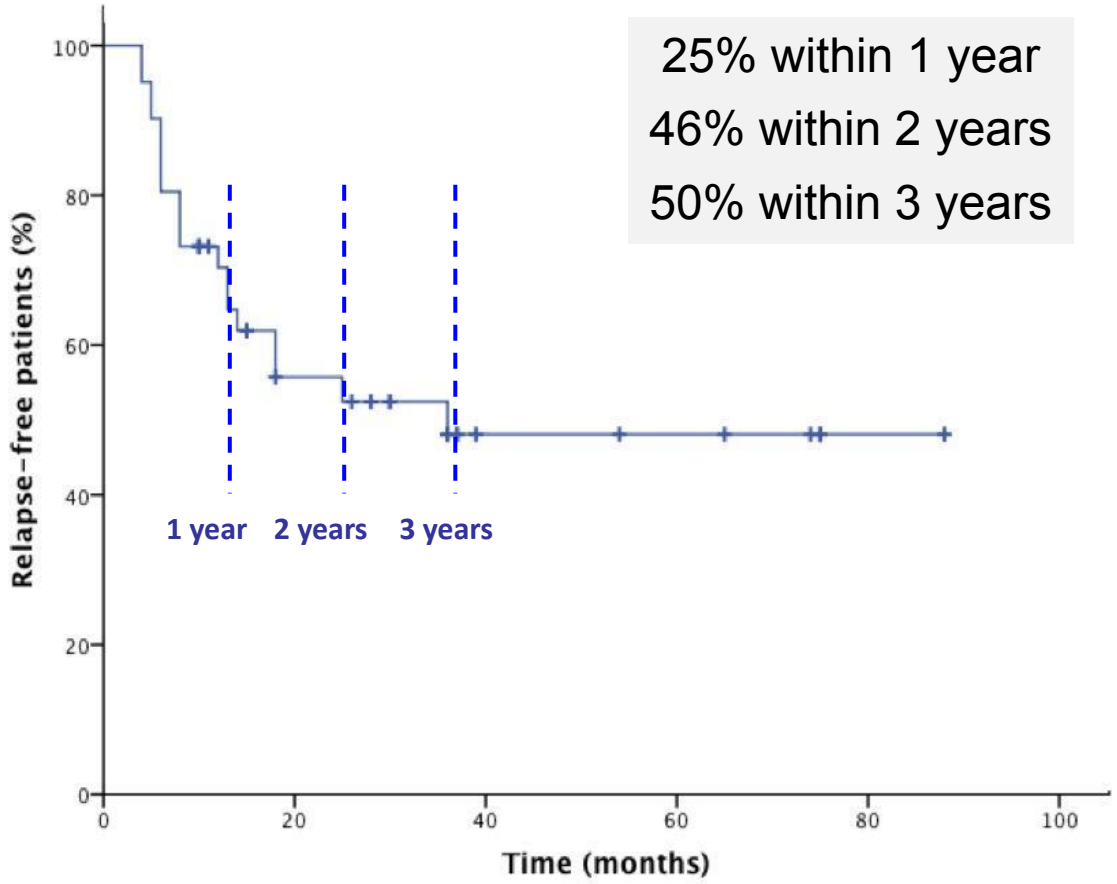


Clinical Biochemical/Serologic
Radiological

Koshroshahi, Arthritis Rheumatol, 2015
Della Torre, J Clin Immunol, 2016

Treatment guidelines

Disease relapse



25% within 1 year
46% within 2 years
50% within 3 years

<u>Predictors of relapse</u>

- multiorgan disease
- high serum IgG4
- high serum IgE

Kamisawa, Gut, 2008
Della Torre, Scand J Rheumatol, 2015
Wallace, Rheumatology, 2016