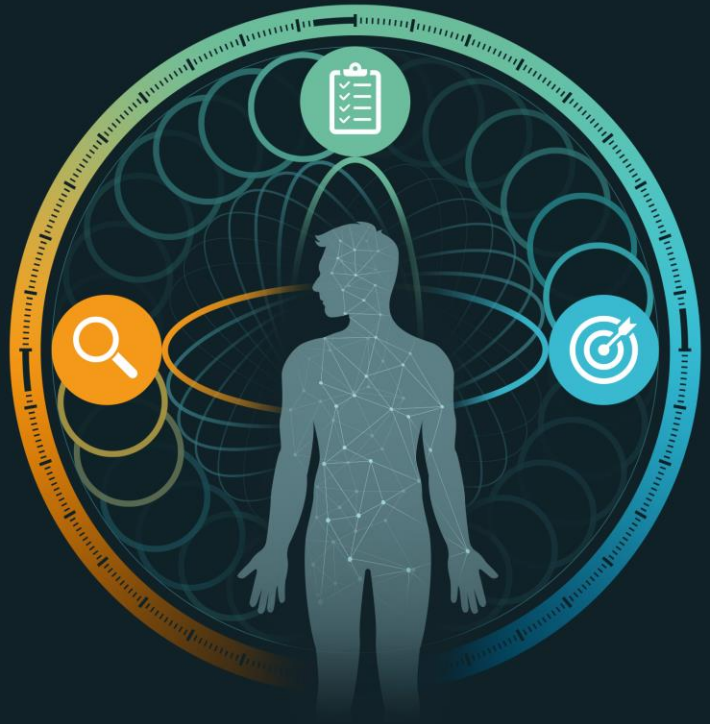
SYMPOSIUM

# IgG4-related disease:

## How to identify, diagnose and treat



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# Agenda

- **Introduction and welcome**
  *Prof. John Stone*
- **The many faces of IgG4-related disease**
  *Prof. John Stone*
- **From suspicion to confirmation of IgG4-related disease**
  *Dr Emanuel Della Torre*
- **A new era for treating IgG4-related disease**
  *Dr Arezou Khosroshahi*
- **Panel discussion**
  *All faculty*
- **Meeting summary and close**
  *Prof. John Stone*

***Each session will include interactive audience polling and audience Q&As. The panel discussion will include a patient case.***

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# Learning objectives

1. Describe the complex pathophysiology and clinical manifestations of IgG4-related disease
2. Outline the diagnostic and classification criteria for IgG4-related disease
3. Discuss current treatments for IgG4-related disease as well as novel, emerging targeted treatment options

# Expert panel

**Prof. John Stone (Chair)**
Harvard Medical School and
Massachusetts General Hospital
Boston, MA, USA

**Dr Emanuel Della Torre**
Vita-Salute San Raffaele University
and San Raffaele Hospital
Milan, Italy

**Dr Arezou Khosroshahi**
Emory University School of Medicine
Atlanta, GA, USA

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# The many faces of IgG4-related disease

**Prof. John Stone**
Harvard Medical School and
Massachusetts General Hospital
Boston, MA, USA

# IgG4-RD was first identified in 2003[1]

True **prevalence** is unknown[2]

Average age at diagnosis is **50–70 years old**[2]

**Male** predominance[2]

**Immune-mediated progressive** condition[1–3]

**Relapsing–remitting** disease course[2]

**Smoking** is the only established modifiable risk factor[2]

IgG4-RD, immunoglobulin G4-related disease.

1. Tanaka Y, Stone JH. *Modern Rheumatol.* 2023;33:229–36; 2. Katz G, Stone JH. *Ann Rev Med.* 2022;73;545–62; 3. Perguino CA, Stone JH. *Nat Rev Rheumatol.* 2020;16:702–14.

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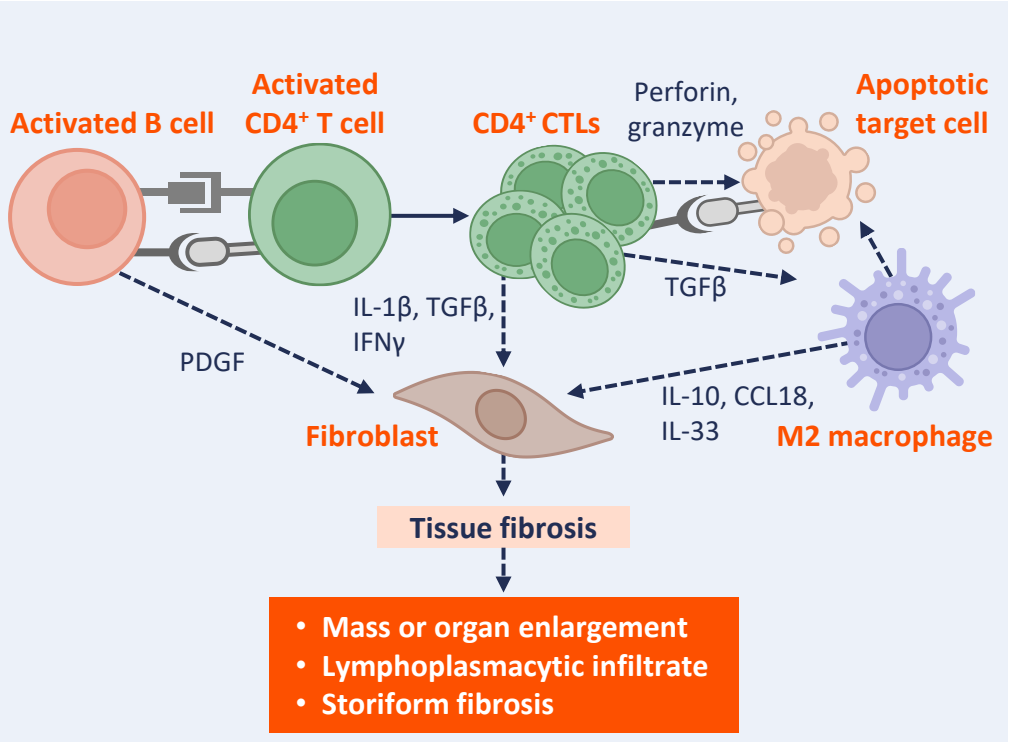
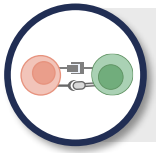
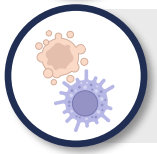
# Pathogenesis of IgG4-RD leads to tissue fibrosis



**Activated B cells** migrate to inflamed tissues and **promote T-cell expansion and differentiation** into CD4⁺ CTLs

**CD4⁺ CTLs induce apoptosis** by releasing perforin and granzyme



**Activated M2 macrophages clear apoptotic cells**

**Activated immune cells promote activation of fibroblasts**

**Fibroblasts secrete ECM proteins, resulting in tissue remodelling and fibrosis**

CCL18, CC-chemokine 18; CD, cluster of differentiation; CTLs, cytotoxic T lymphocytes; ECM, extracellular matrix; IFNγ, interferon-γ; IgG4-RD, immunoglobulin G4-related disease; IL, interleukin; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor-β.

Perugino CA, Stone JH. *Nat Rev Rheumatol*. 2020;16:702–14.

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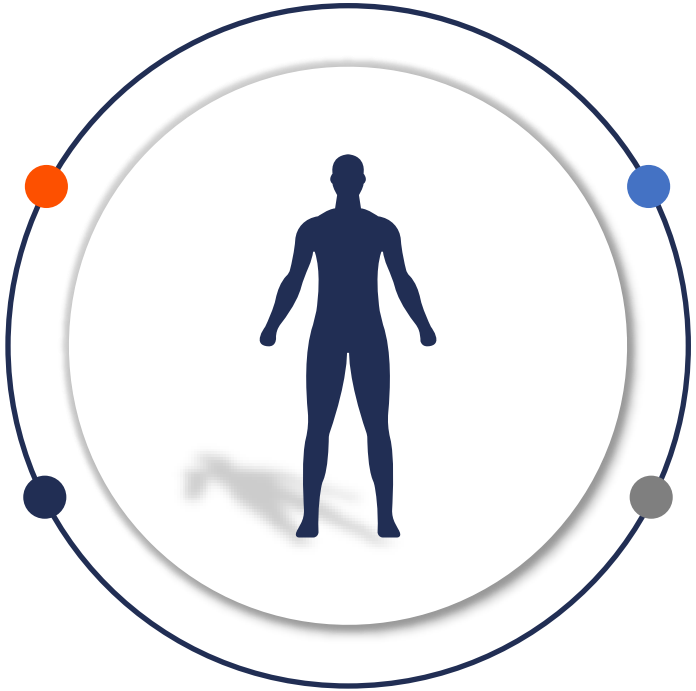
# Clinical presentation of IgG4-RD is heterogeneous[1]

Typically presents in an indolent fashion[1]

Most common presentation is a mass lesion or organ enlargement[2]



Mass lesions are frequently mistaken for malignancy[1]

Symptoms are typically attributable to tumefactive or inflammatory lesion(s)[3]

IgG4-RD, immunoglobulin G4-related disease.

1. Katz G, Stone JH. *Annu Rev Med.* 2022;73:545–62; 2. Al-Khalili O, et al. *Mo Med.* 2018;115:253–56; 3. Wallace ZS, et al. *Clin Chest Med.* 2019;40:583–97.

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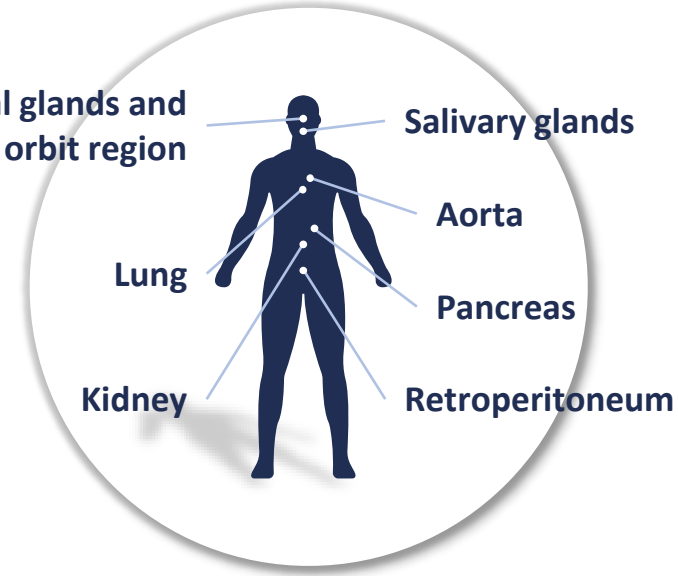
# IgG4-RD can affect nearly any organ[1]

## Typical organs involved in IgG4-RD[2]





**of patients have multiple organs affected[3]**

**Symptoms vary depending on organs or tissues involved[4]**

IgG4-RD, immunoglobulin G4-related disease.

1. Tanaka Y, Stone JH. *Mode Rheumatol.* 2023;33:229–36; 2. Chen Y, et al. *Chin Med J (Engl).* 2022;135:381–92; 3. Bhardwaj S, et al. *J Postgrad Med*. 2018;64:119–22; 4. Al-Khalili O, et al. *Mo Med.* 2018;115:253–56.

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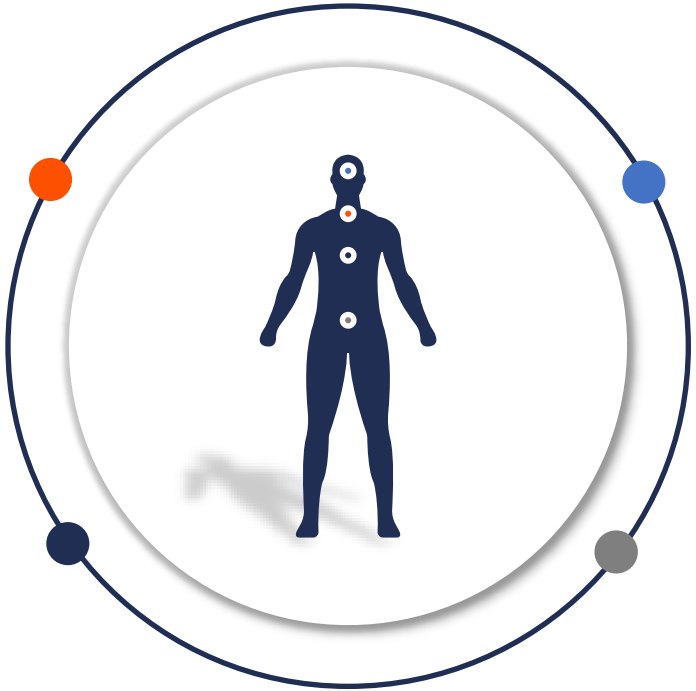
# Clinical manifestations vary by organ(s) involved

## Head and neck

Dacryoadenitis, dacryocystitis, orbital myositis, orbital pseudotumour, uveitis, scleritis| sialoadenitis | chronic nasorhinosinusitis | Riedel thyroiditis | vocal cord lesions, supraglottic stenosis

## Chest

Parenchymal lung disease, pleural disease, lymphadenopathy | pericarditis, coronary arteritis, pseudotumour | fibrosing mediastinitis, paravertebral mass | aortitis, periaortitis



## Pituitary and nervous system

Hypophysitis | hypertrophic pachymeningitis | vague dysesthesias over the cheek | asymptomatic

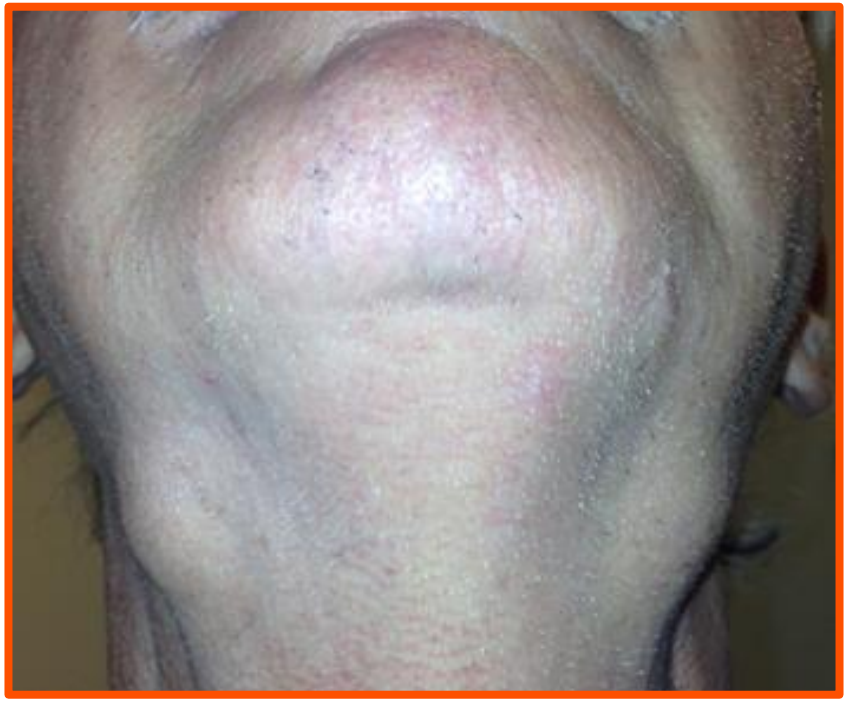
## Abdomen and pelvis

AIP type I, pseudotumour | sclerosing cholangitis, sclerosing cholecystitis, pseudotumour | sclerosing mesenteritis | aortitis and periaortitis, retroperitoneal fibrosis | tubulointerstitial nephritis, membranous GN | prostatitis

AIP, autoimmune pancreatitis; GN, glomerulonephropathy.

Katz G, Stone JH. *Annu Rev Med*. 2022;73;545–62.

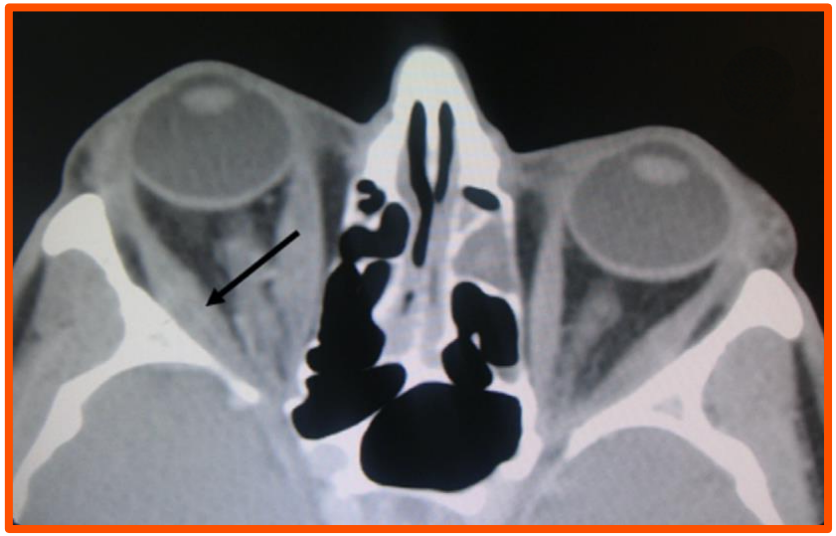
# Submandibular gland disease



Images courtesy of Stone J. Personal communication 2023.

# ‘Idiopathic orbital inflammation’

## Extra-ocular muscle involvement



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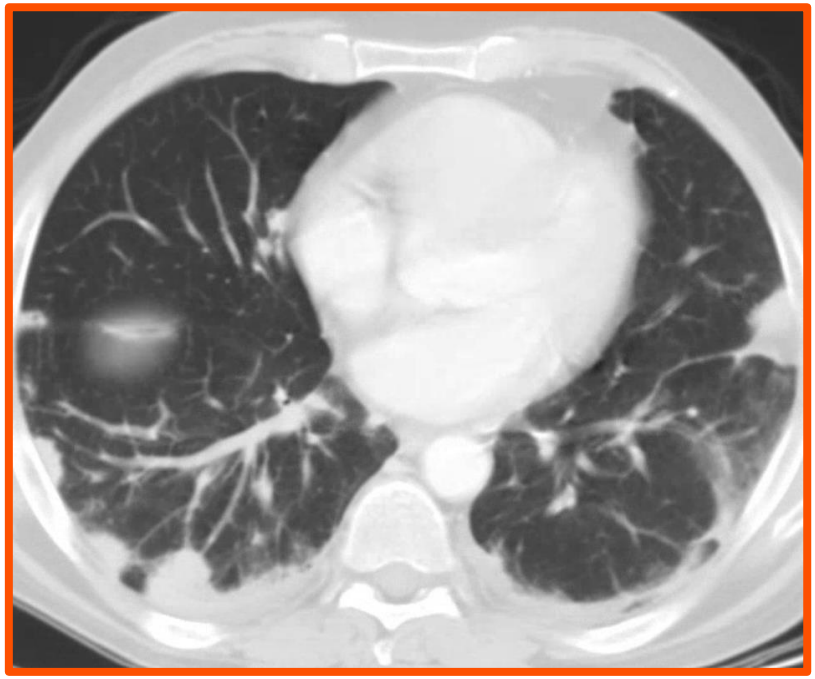
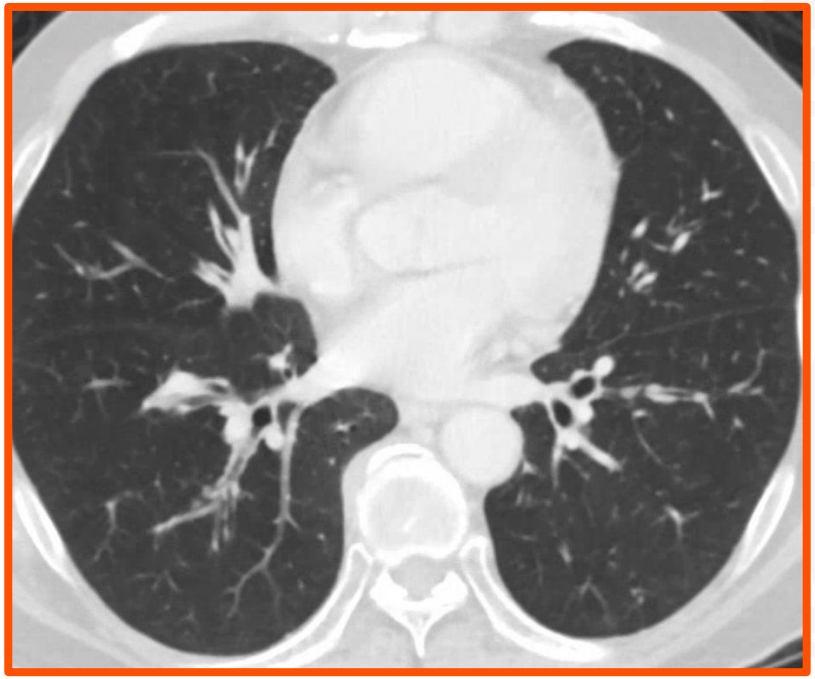
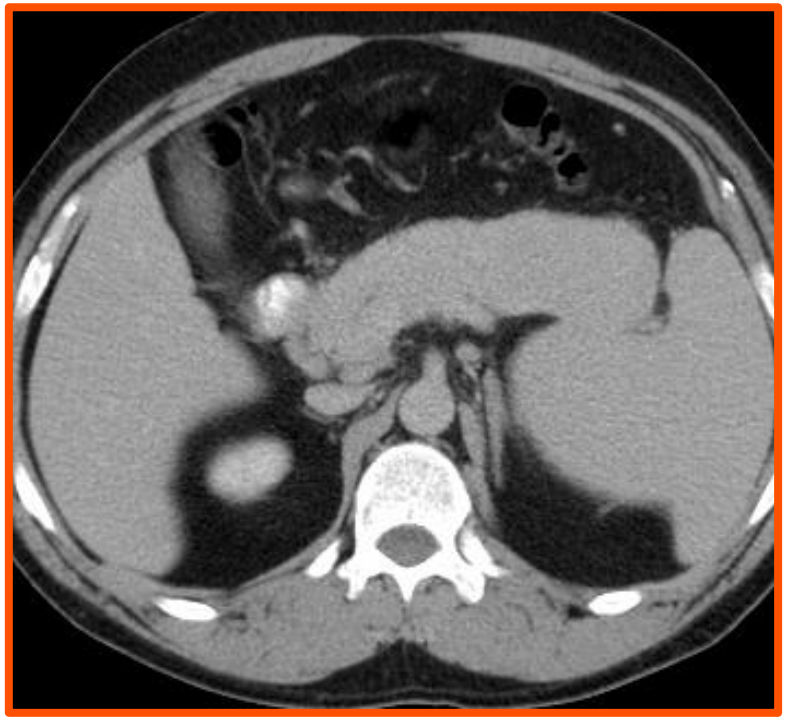
# Pulmonary nodules, pleural effusions, airway thickening

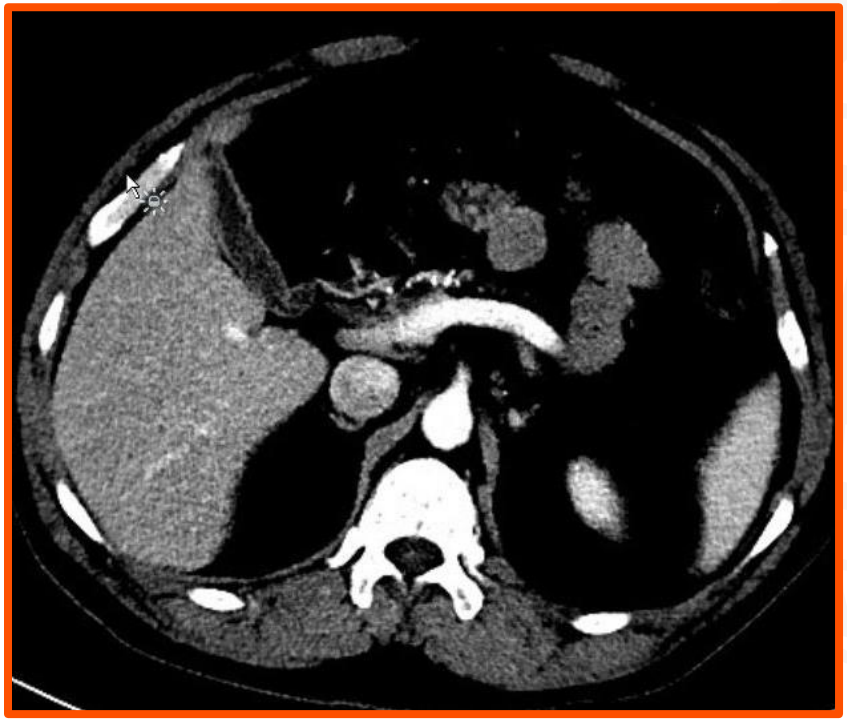




Images courtesy of Stone J. Personal communication 2023.

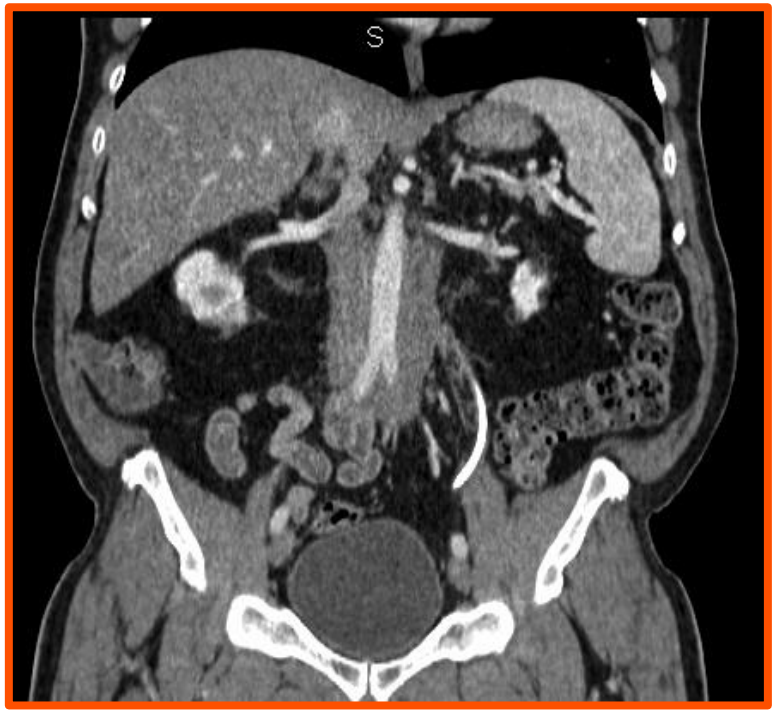
# Autoimmune pancreatitis

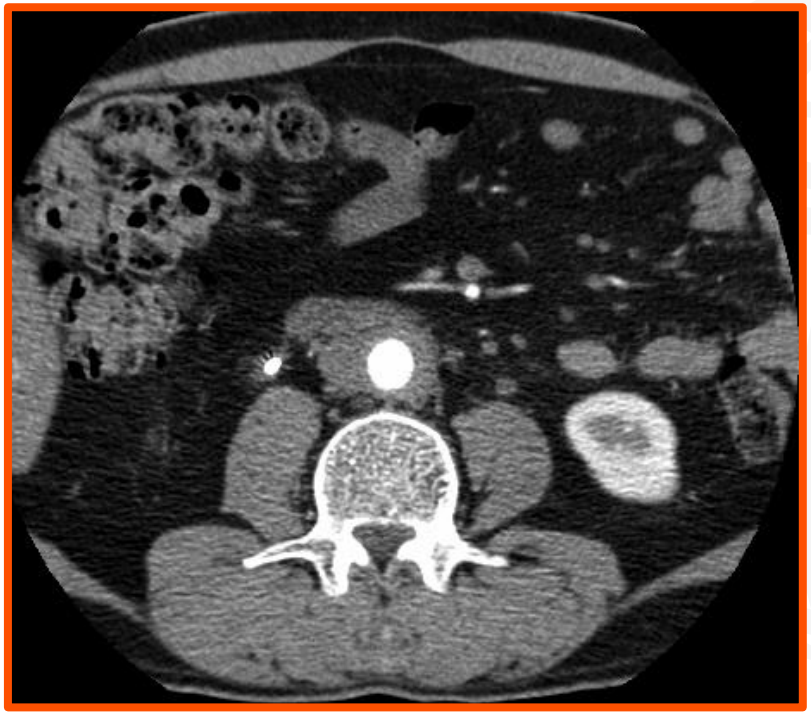




Images courtesy of Stone J. Personal communication 2023.

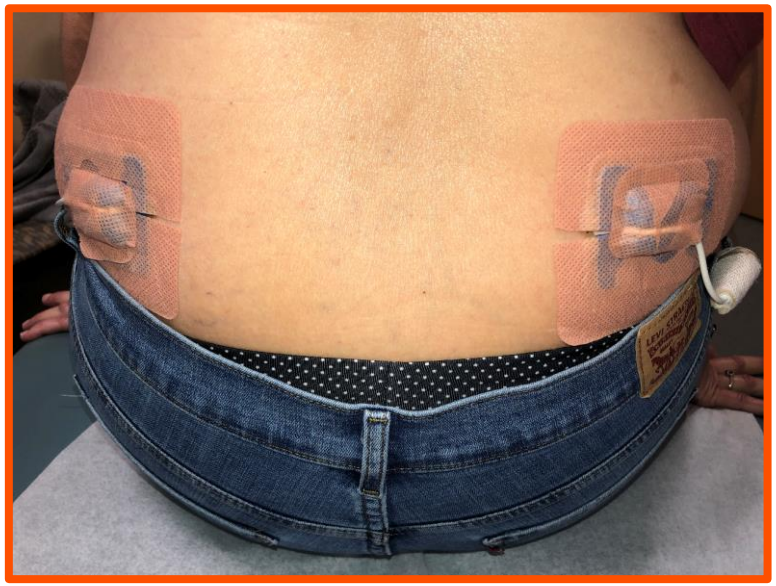
# Retroperitoneal fibrosis and periaortitis



Images courtesy of Stone J. Personal communication 2023.

# Hydronephrosis, stents, nephrostomy tubes



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# IgG4-RD has noticeable patterns of involvement[1]

## Atopy

**Allergic symptoms common in those with head and neck involvement[1]**

**Elevated serum IgE levels and eosinophilia[1]**

**Role of allergies in IgG4-RD is unclear[2]**


## Constitutional symptoms[1]

**Prominent constitutional symptoms are atypical**

**Fever is a highly atypical symptom**

**Substantial weight loss may occur in AIP type 1**

AIP, autoimmune pancreatitis; Ig, immunoglobulin; IgG4-RD, IgG4-related disease.

1. Katz G, Stone JH. *Annu Rev Med*. 2022;73;545–62; 2. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75.

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# Two subtypes of IgG4-RD have been described

## Proliferative subtype[1]

**Multiorgan involvement**
Glandular tissues, pancreas, bile ducts, kidneys, lungs, sinuses and lymph nodes

**IgG4:** ↑
**IgE:** ↑
**IgG1:** ↑
**Eosinophils:** ↑
**Complement levels:** ↓

**Treatment responsive**

## Fibrotic subtype[1]

**Single or multiorgan involvement**
Retroperitoneum, mesentery, mediastinum, pachymeninges and thyroid

**IgG4:** Normal
**IgE:** Normal
**IgG1:** Normal
**Eosinophils:** Not characteristic
**Hypocomplementemia:** Not characteristic

**Limited treatment response**

**Biological differences between these subtypes remains uncertain[2]**

↑, elevated; Ig, immunoglobulin; IgG4-RD, IgG4-related disease.
1. Katz G, Stone JH. *Annu Rev Med*. 2022;73;545–62; 2. Tanaka Y, Stone JH. *Modern Rheumatology*. 2023;33:229–36.

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# Summary


**IgG4-RD was recognized** as a distinct autoimmune disease **two decades ago**[1,2]

**IgG4-RD is an insidiously progressive disease** typified by tumour-like mass formation in many organs[2]

**Typical organs affected by IgG4-RD** are the lacrimal glands, major salivary glands, orbits, lungs, paravertebral soft tissue, pancreas, biliary tree, kidneys, retroperitoneum, aorta, meninges and thyroid gland[1]

**Expanding knowledge of the pathophysiology of IgG4-RD** offers the possibility of **novel therapeutic approaches**[2]

IgG4-RD, immunoglobulin G4-related disease.

1. Katz G, Stone JH. *Annu Rev Med*. 2022;73;545–62; 2. Perugino CA, Stone JH. *Nat Rev Rheumatol*. 2020;16:702–14.

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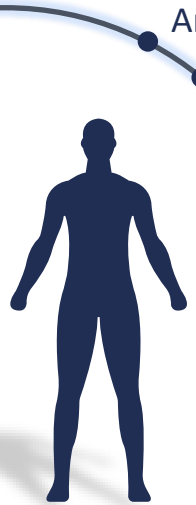
# From suspicion to confirmation of IgG4-related disease

**Dr Emanuel Della Torre**
Vita-Salute San Raffaele University and
San Raffaele Hospital
Milan, Italy

# IgG4-RD represents a diagnostic challenge

## Some differential diagnoses of IgG4-RD[1]



- Amyloidosis
- Atherosclerosis
- Cholangiocarcinoma
- Erdheim–Chester disease
- Giant cell arteritis
- Graves' disease
- ILD
- Lymphoma
- Pancreatic malignancy
- Renal cell carcinoma
- Sarcoidosis
- Sjögren syndrome

**Elevated serum IgG4 levels are not essential for diagnosis[2–4]**

**No specific single marker or clinical feature for a definitive diagnosis[5]**

Ig, immunoglobulin; IgG4-RD, IgG4-related disease; ILD, interstitial lung disease.

1. Katz G, Stone JH. *Annu Rev Med*. 2022;73;545–62; 2. Löhr J-M, et al. *United European Gastroenterol J.* 2020;8:637–66; 3. Wallace ZS, et al. *Arthritis Rheumatol.* 2020;72:7–19; 4. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75; 5. Olmos RD, et al. *Autops Case Rep.* 2021;11:e2021312.

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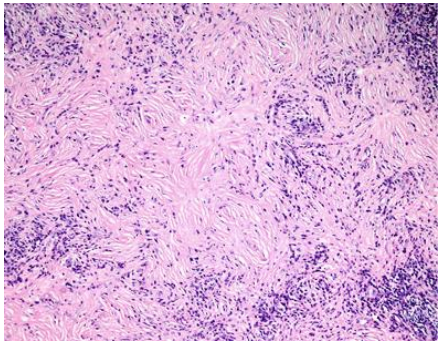
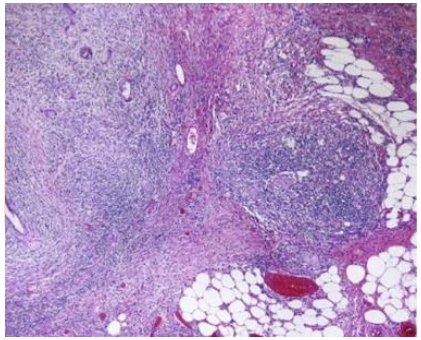
# Definitive diagnosis requires histological confirmation

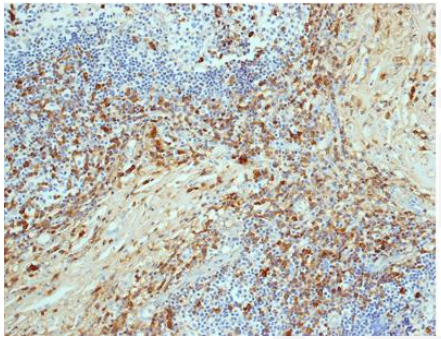
- Storiform fibrosis
- Lymphoplasmacytic infiltrate
- IgG4-positive plasma cells
- Obliterative phlebitis
- Eosinophilic infiltrate
- IgG4/IgG plasma cells >40%

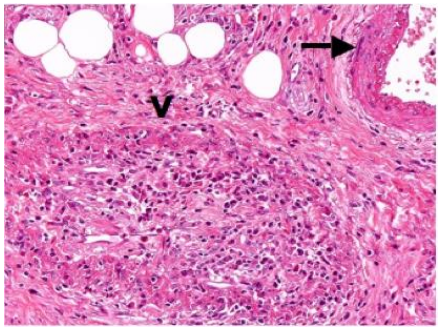
Ig, immunoglobulin.

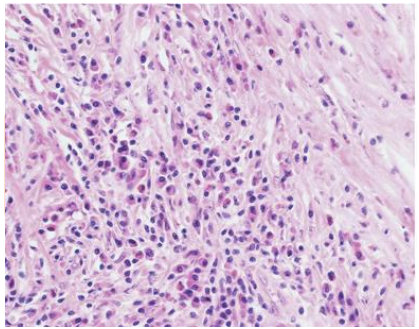
# Definitive diagnosis requires histological confirmation

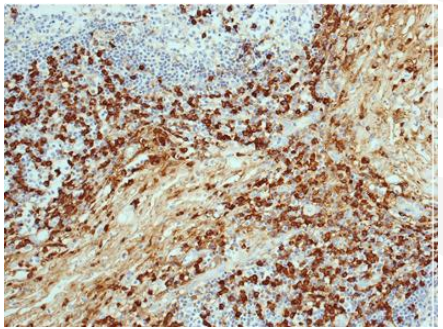






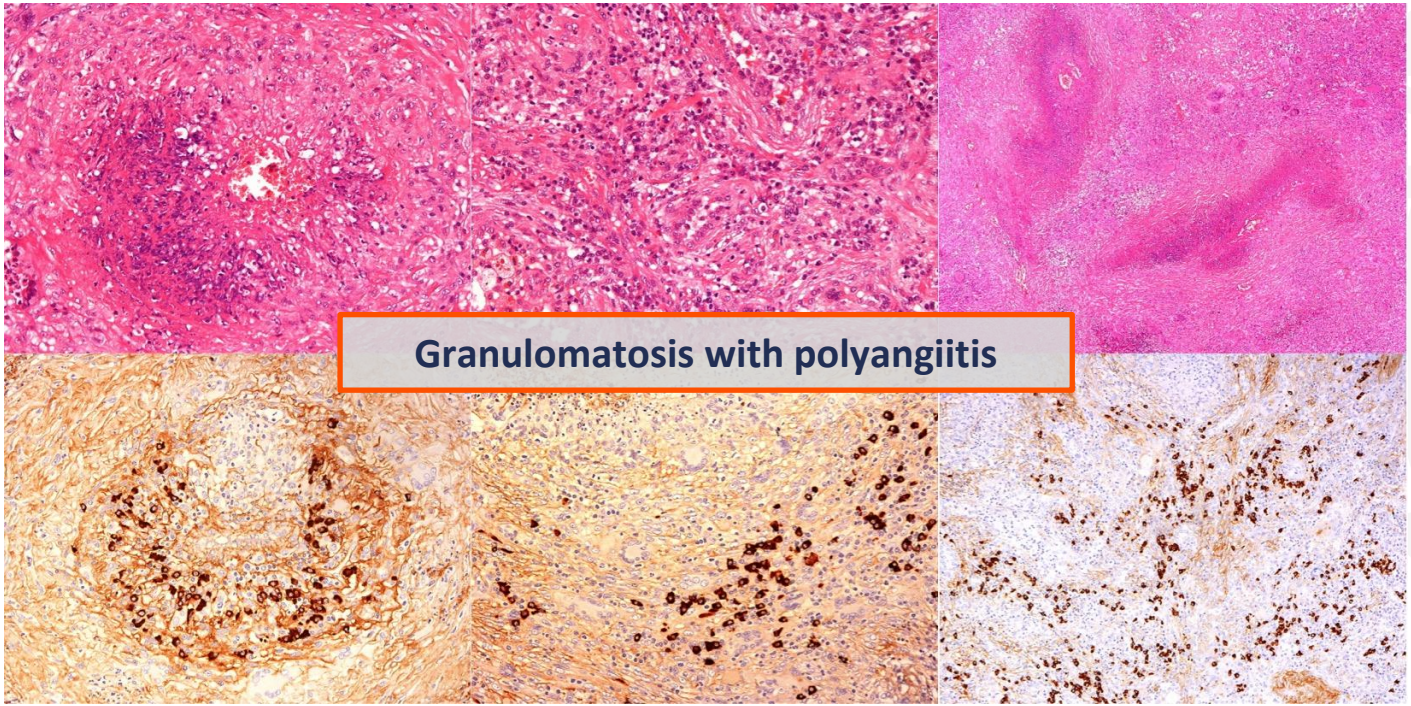




# Definitive diagnosis requires histological confirmation

## Histological analysis of a pulmonary lesion

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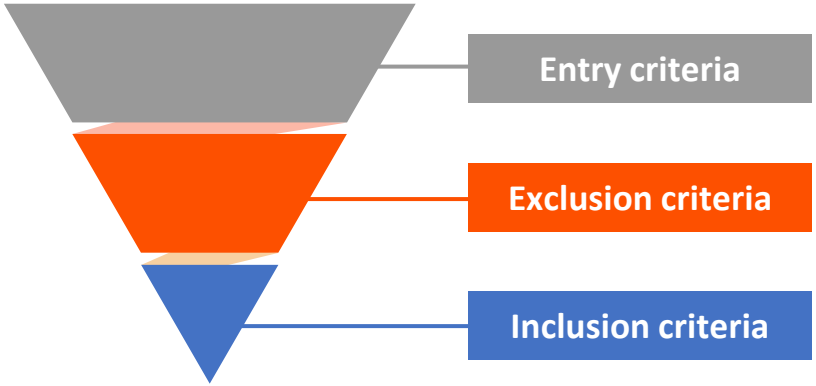
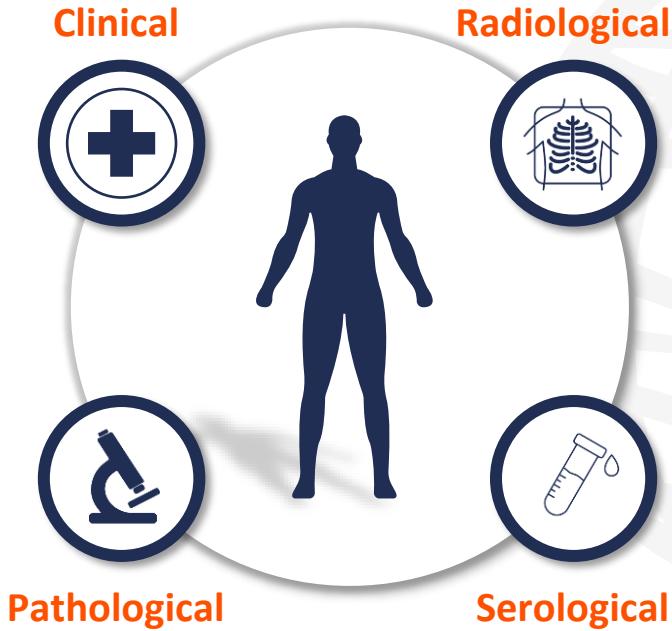
# Three-step classification criteria based on four domains

## The 2019 ACR and EULAR classification criteria




ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.
Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19.

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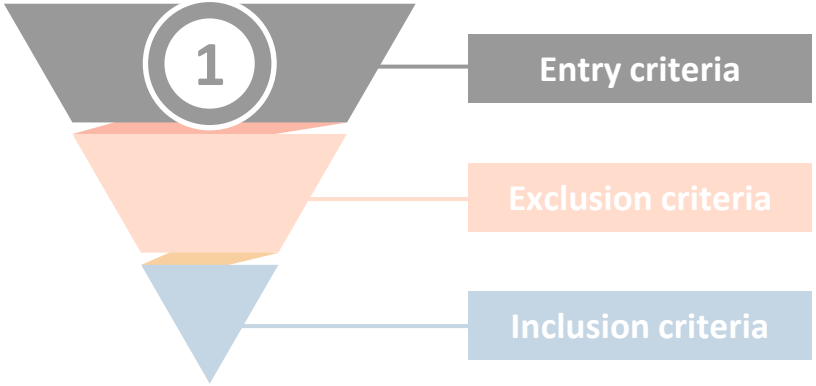
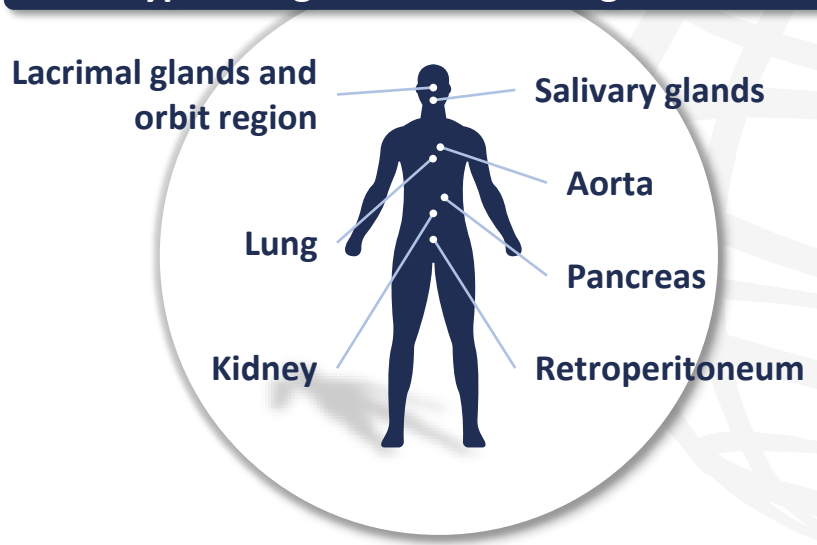
# Three-step classification criteria for IgG4-RD: Entry

## The 2019 ACR and EULAR classification criteria[1]




**Typical organs involved in IgG4-RD[2]**




ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; IgG4-RD, immunoglobulin G4-related disease.

1.Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19; 2. Chen Y, et al. *Chin Med J (Engl).* 2022;135:381–92.

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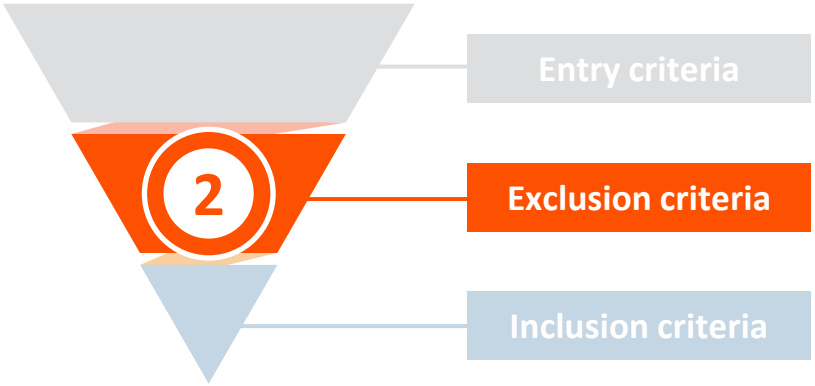
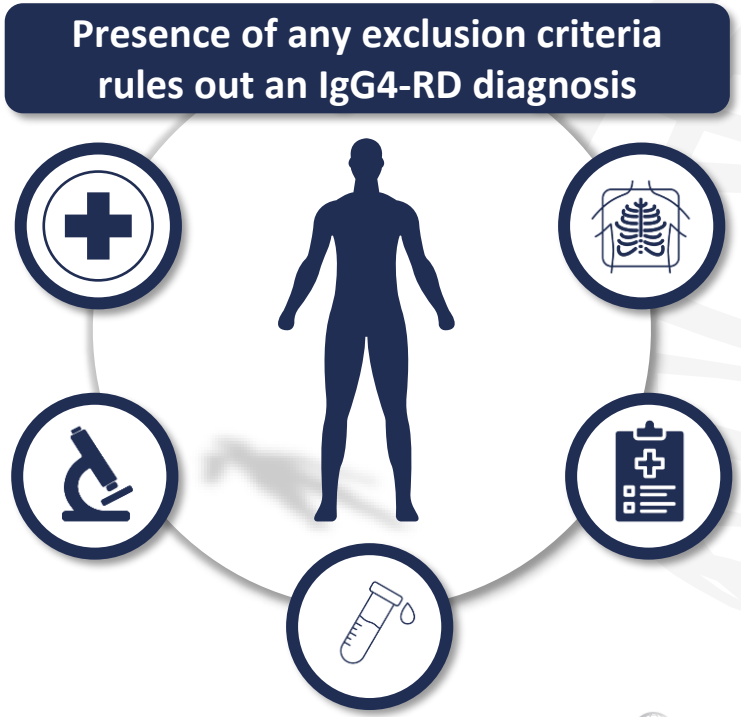
# Three-step classification criteria for IgG4-RD: Exclusion

## The 2019 ACR and EULAR classification criteria




ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; IgG4-RD, immunoglobulin G4-related disease.
Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19.

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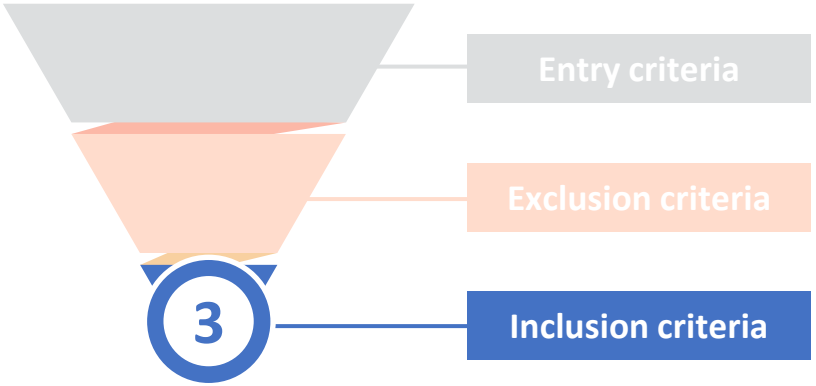
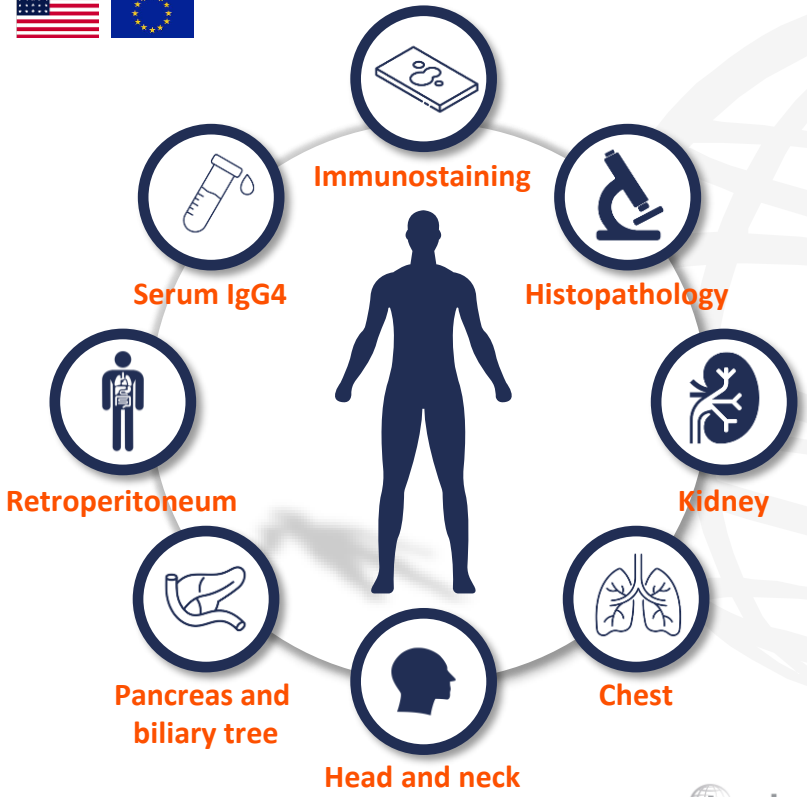
# Three-step classification criteria for IgG4-RD: Inclusion

## The 2019 ACR and EULAR classification criteria




**A weighted score of ≥20 points across 8 domains fulfils classification criteria**




ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; Ig, immunoglobulin; IgG4-RD, IgG4-related disease.

Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19.

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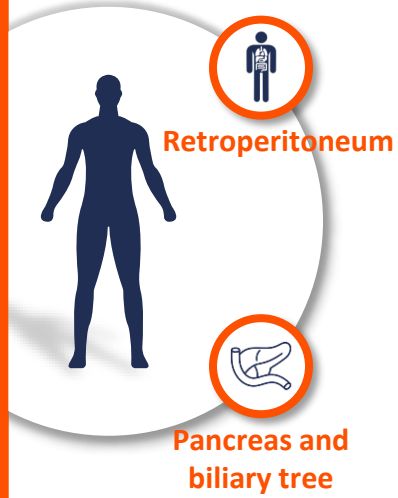
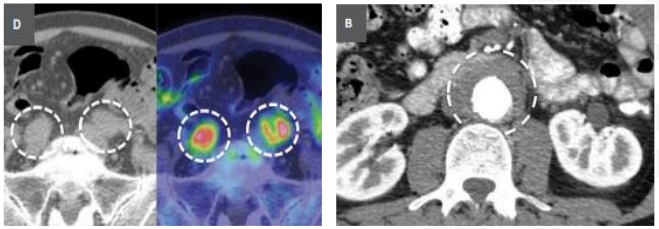
# Inclusion criteria: Organ involvement

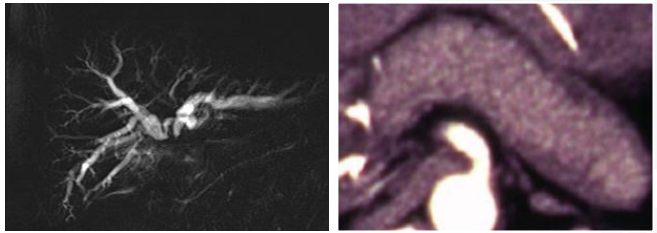
## The 2019 ACR and EULAR classification criteria




| Retroperitoneum | Score |
|---|---|
| Diffuse thickening of abdominal aortic wall | +4 |
| Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries | +8 |

| Pancreas and biliary tree | Score |
|---|---|
| Diffuse pancreas enlargement | +8 |
| Diffuse pancreas enlargement AND capsule-like rim with decreased enhancement | +11 |
| Pancreas (either of above) and biliary tree involvement | +19 |



ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.
Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19. Images courtesy of Della Torre E. Personal communication 2023.

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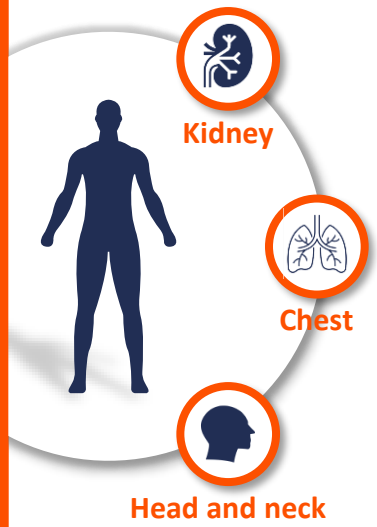
# Inclusion criteria: Organ involvement

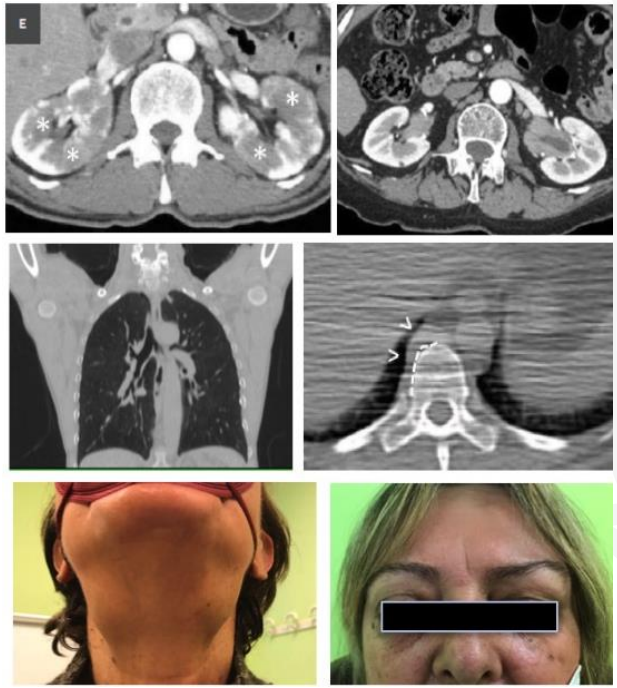
## The 2019 ACR and EULAR classification criteria




| Kidney | Score |
|---|---|
| Hypocomplementemia | +6 |
| Renal pelvis thickening/soft tissue | +8 |
| Bilateral renal cortex low-density areas | +10 |

| Chest | Score |
|---|---|
| Peribronchovascular and septal thickening | +4 |
| Paravertebral band-like soft tissue in the thorax | +8 |

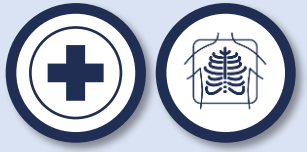
| Head and neck: Glands involved | Score |
|---|---|
| 1 set | +6 |
| ≥2 sets | +14 |



ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.
Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19. Images courtesy of Della Torre E. Personal communication 2023.

# The 2020 RCD criteria for IgG4-RD

## Developed by a Japanese IgG4 multidisciplinary team organized by the MHLW of Japan

| | |
|---|---|
| **Clinical and radiological**  | **One or more organs with characteristics of IgG4-RD:**<br>• **Diffuse/localized swelling** or **a mass** or **nodule**<br>In single organ involvement, lymph node swelling is omitted |
| **Serological**  | **Serum IgG4 levels >135 mg/dL** |
| **Pathological**  | **Positive for two criteria:**<br>1. **Dense lymphocyte and plasma cell infiltration with fibrosis**<br>2. **IgG4+ plasma cells/IgG+ cells >40%** AND **IgG4+ plasma cells >10/hpf**<br>3. **Typical tissue fibrosis,** particularly storiform fibrosis, or obliterative phlebitis |

hpf, high-power field; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; RCD, revised comprehensive diagnostic; MHLW, Ministry of Health, Labour and Welfare.

Umehara H, et al. *Mod Rheumatol*. 2021;3:529–33.

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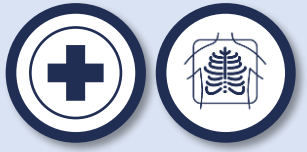
# The 2020 RCD criteria for IgG4-RD: Possible

## Developed by a Japanese IgG4 multidisciplinary team organized by the MHLW of Japan

**Clinical and radiological**



**One or more organs with characteristics of IgG4-RD:**

- **Diffuse/localized swelling** or **a mass** or **nodule**

In single organ involvement, lymph node swelling is omitted

**Serological**

**Serum IgG4 levels >135 mg/dL**

**Pathological**

**Positive for two criteria:**

1. **Dense lymphocyte and plasma cell infiltration with fibrosis**
2. **IgG4+ plasma cells/IgG+ cells >40%** AND **IgG4+ plasma cells >10/hpf**
3. **Typical tissue fibrosis,** particularly storiform fibrosis, or obliterative phlebitis

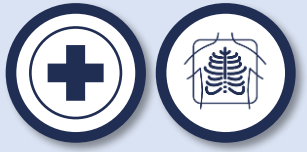
hpf, high-power field; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; RCD, revised comprehensive diagnostic; MHLW, Ministry of Health, Labour and Welfare.

Umehara H, et al. *Mod Rheumatol*. 2021;3:529–33.

# The 2020 RCD criteria for IgG4-RD: Probable

## Developed by a Japanese IgG4 multidisciplinary team organized by the MHLW of Japan

**Clinical and radiological**



**One or more organs with characteristics of IgG4-RD:**

- **Diffuse/localized swelling** or **a mass** or **nodule**

In single organ involvement, lymph node swelling is omitted

**Serological**

**Serum IgG4 levels >135 mg/dL**

**Pathological**

**Positive for two criteria:**

1. **Dense lymphocyte and plasma cell infiltration with fibrosis**
2. **IgG4+ plasma cells/IgG+ cells >40%** AND **IgG4+ plasma cells >10/hpf**
3. **Typical tissue fibrosis,** particularly storiform fibrosis, or obliterative phlebitis

hpf, high-power field; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; RCD, revised comprehensive diagnostic; MHLW, Ministry of Health, Labour and Welfare.

Umehara H, et al. *Mod Rheumatol*. 2021;3:529–33.

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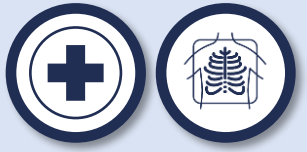
# The 2020 RCD criteria for IgG4-RD: Definite

## Developed by a Japanese IgG4 multidisciplinary team organized by the MHLW of Japan

**Clinical and radiological**



**One or more organs with characteristics of IgG4-RD:**

- **Diffuse/localized swelling** or **a mass** or **nodule**

In single organ involvement, lymph node swelling is omitted

**Serological**

**Serum IgG4 levels >135 mg/dL**

**Pathological**

**Positive for two criteria:**

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hpf, high-power field; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; RCD, revised comprehensive diagnostic; MHLW, Ministry of Health, Labour and Welfare.

Umehara H, et al. *Mod Rheumatol*. 2021;3:529–33.

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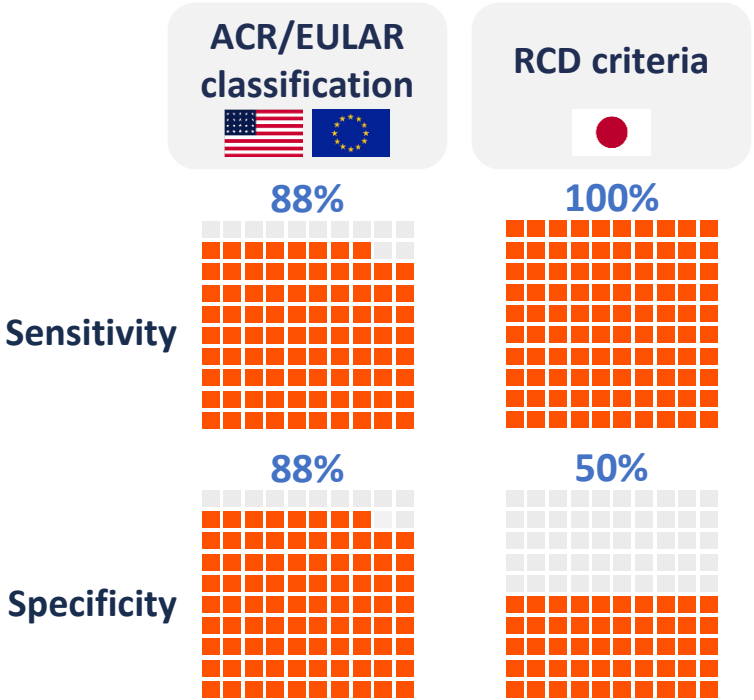
# Diagnostic criteria in practice: Japanese experience

## Retrospective, single-centre study (N=50) of patients with suspected IgG4-RD




**42/50 suspected cases diagnosed with IgG4-RD**

**Patients with IgG4-RD had significantly more affected organs (p=0.002)**

**Patients with a single affected organ and IgG4-RD had significantly higher serum IgG4/IgG ratios (p=0.044)**

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; RCD, revised comprehensive diagnostic.

Kogami M, et al. *Sci Rep.* 2023;13:2509.

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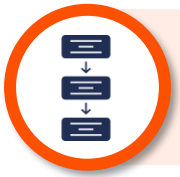
# Summary

Even with a high level of clinical suspicion, **diagnosing IgG4-RD can be challenging**[1,2]

**Definitive diagnosis** of IgG4-RD requires **histological confirmation**[2]



**The three-step ACR/EULAR classification criteria for** IgG4-RD includes entry, exclusion and inclusion criteria[3]

**Japanese revised IgG4-RD diagnostic criteria consists of three domains:** Clinical and radiological features; serological diagnosis; and pathological diagnosis[4]

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; IgG4-RD, immunoglobulin G4-related disease.

1. Díaz Olmos R, et al. *Autops Case Rep*. 2021;11:e2021312; 2. Iaccarino L, et al. *RMD Open*. 2019;4:e000787; 3. Wallace ZS, et al. *Arthritis & Rheumatol.* 2020;72:7–19; 4. Umehara H, et al. *Mod Rheumatol*. 2021;3:529–33.

# A new era for treating IgG4-related disease

**Dr Arezou Khosroshahi**
Emory University School of Medicine
Atlanta, GA, USA

# Effective management of IgG4-RD

**Induction**
with GCs[1,2]

**Maintenance**
with low-dose GCs, immunosuppression, rituximab (under investigation)[1,2]

**Monitor**
biomarkers of IgG4-RD activity e.g. serum IgG4 levels[3]

## Management should factor in the natural history of IgG4-RD

- Occasional spontaneous remission[4]
- Indolent, progressive organ involvement[5,6]
- Additional organ involvement over time[6]
- Irreversible damage of vital organs[6,7]

GC, glucocorticoid; Ig, immunoglobulin; IgG4-RD, IgG4-related disease.

1. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75; 2. Lanzillotta M, et al. *Expert Rev Clin Immunol*. 2021;17:471–83; 3. Iaccarino L, et al. *Clin Exp Rheumatol*. 2022;40 Suppl 134:71–80; 4. Brito-Zerón P, et al. *Medicine.* 2016;95:e4002; 5. Al-Khalili O, et al. *Mo Med.* 2018;115:253–56; 6. Katz G, Stone JH. *Ann Rev Med*. 2022;73;545–62; 7. Karim F, et al. *Pediatr Rheumatol Online J*. 2016;14:18.

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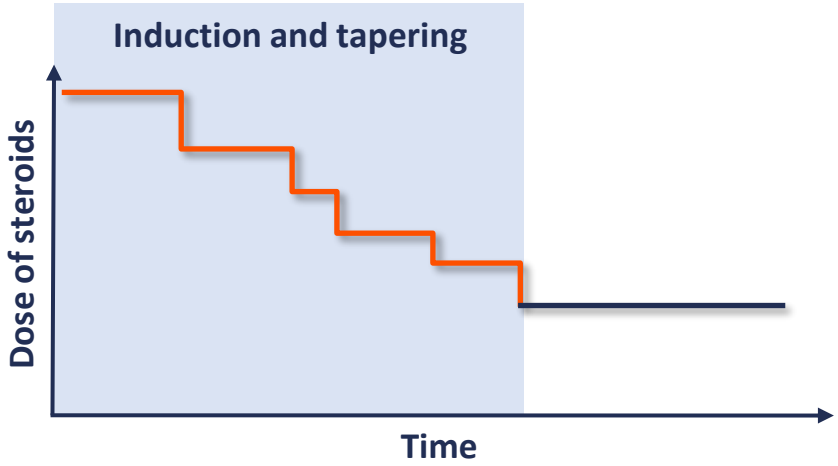
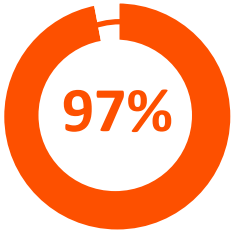
# GCs are the cornerstone of IgG4-RD treatment




**Induction:** 30–40 mg/day prednisone, maintained for 4 weeks[1]

**Tapering:** GC dose is then gradually tapered over 8–12 weeks[2]

**Treatment goals: Reduce inflammation and preserve organ function[1]**




**of patients have a therapeutic response to GC monotherapy[3]**

GC, glucocorticoid; IgG4-RD, immunoglobulin G4-related disease.

1. Tanaka Y, Stone JH. *Mod Rheumatol*. 2023;33:229–36; 2. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75;
3. Brito-Zerón P, et al. *Medicine*. 2016;95:e4002.

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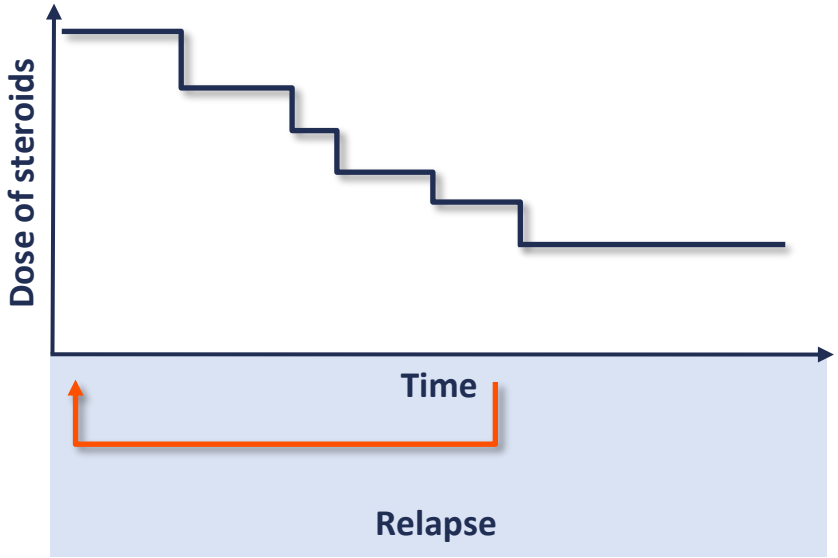
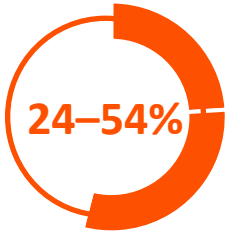
# Relapses are common following steroid tapering




**Treatment:** GC dose, as per the induction regimen[1]

**Patient presentation:**
Organomegaly and organ dysfunction[2]




**of patients relapse after reduction of GC dose[2]**

GC, glucocorticoid.

1. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75; 2. Zongfei J, et al. *Arthritis Res Ther*. 2022;24:106.

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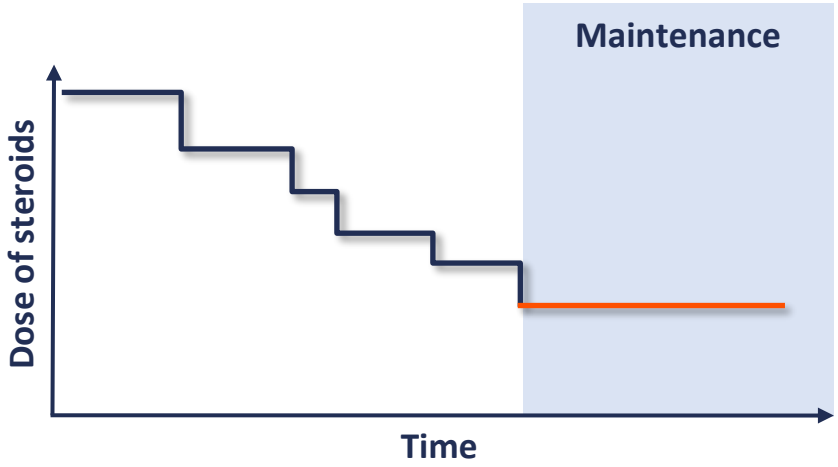
# Maintenance therapy with low-dose GCs[1]




**Treatment goal: Maintain remission[3]**

**Long-term GC treatment** is associated with adverse effects[2]

**Maintenance:** GCs + immunosuppressants; but evidence for their efficacy remains slim[3]

**Maintenance:** Use targeted therapy; B cell depletion (off-label)[4]

GC, glucocorticoid.

1. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75; 2. Nakaymada S, Tanaka Y. *Modern Rheumatol.* 2023;33:266–70; 3. Tanaka Y, Stone JH. *Modern Rheumatology.* 2023;33:229–36; 4. Lanzillotta M, et al. *Mod Rheumatol*. 2023;33:258–65.

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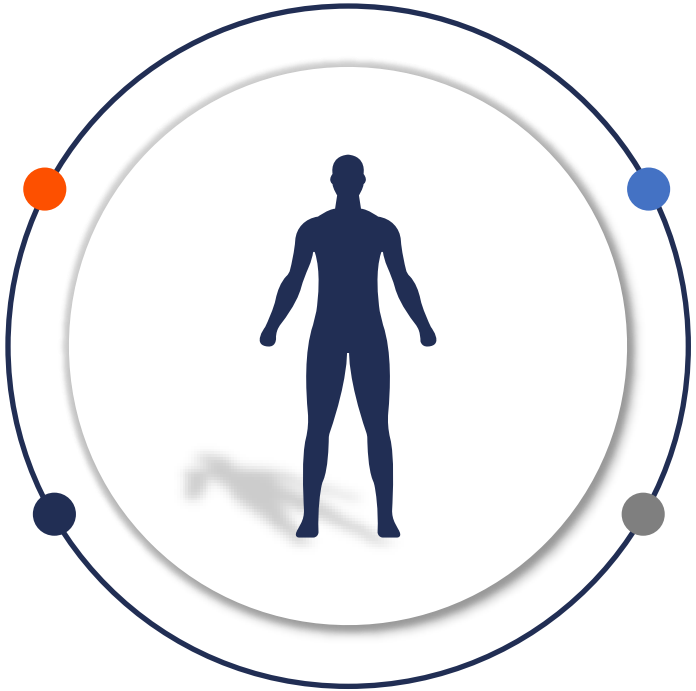
# Treatment decisions are multifactorial

## Disease-related factors

**Disease subtype**
e.g. inflammatory or fibrotic[1]

**Clinical disease phenotype**
e.g. isolated organ vs multisystemic[2,3]



**Urgency of presentation**
e.g. biliary stricture vs lymphadenopathy[2,4]

**Predictors of relapse**
e.g. multi-organ disease, prior flare, serum IgG4 levels >2 x ULN, ↑ serum IgE, peripheral eosinophilia[5–7]

↑, elevated; Ig, immunoglobulin; IgG4-RD, IgG4-related disease; ULN, upper limit of normal.

1. Tanaka Y, Stone JH. *Mod Rheumatol.* 2023;33:229–36; 2. Lee C, Hung To C, et al. *J Clin Rheumatol.* 2023;23:25–34; 3. Chen Y, et al. *Chin Med J (Engl).* 2022;135:381–92; 4. Goodchild G, et al. *Clinical Medicine.* 2020;20:e32–9; 5. Zongfei J, et al. *Arthritis Res Ther*. 2022;24:106; 6. Wallace ZS, et al. *Rheumatology (Oxford).* 2016;55:1000–8; 7. Perugino C, et al. *Rheumatol Ther.* 2023.10:1795–808.

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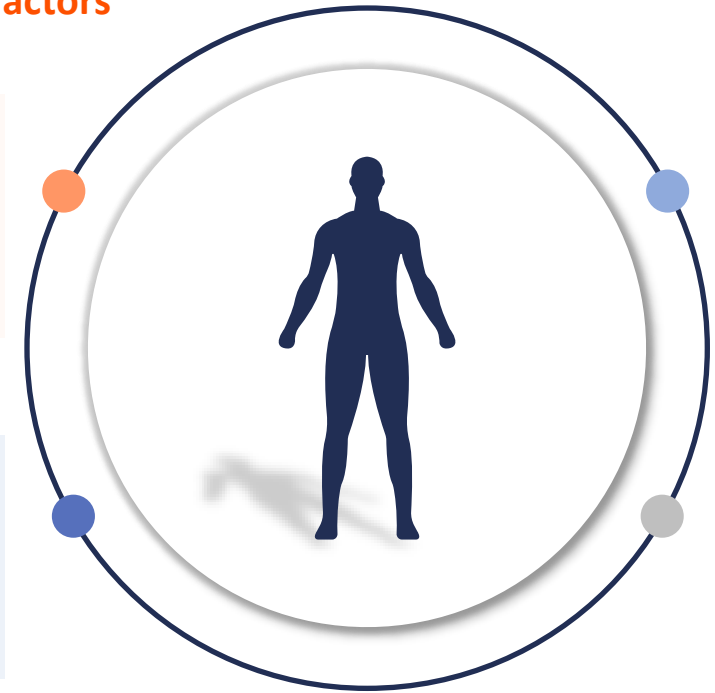
# Treatment decisions are multifactorial

## Patient- and social-related factors

### Age
e.g. IgG4-RD affects middle aged and elderly individuals, but can also affect children[1]

### Comorbidities
e.g. diabetes[2]



### Public health factors
e.g. pandemic[3]

### Insurance coverage
e.g. whether treatment is covered in full[4]

IgG4-RD, immunoglobulin G4-related disease.

1. Chen C, et al. *Exp Ther Med*. 2018;15:2739–48; 2. Regev K, et al. *JAMA Neurol*. 2014;71:767–70; 3. Chen Y, et al. *Semin Arthritis Rheum*. 2020;50:559–63; 4. Dawkins B, et al. *Trop Med Int Health*. 2021;26:1177–88.

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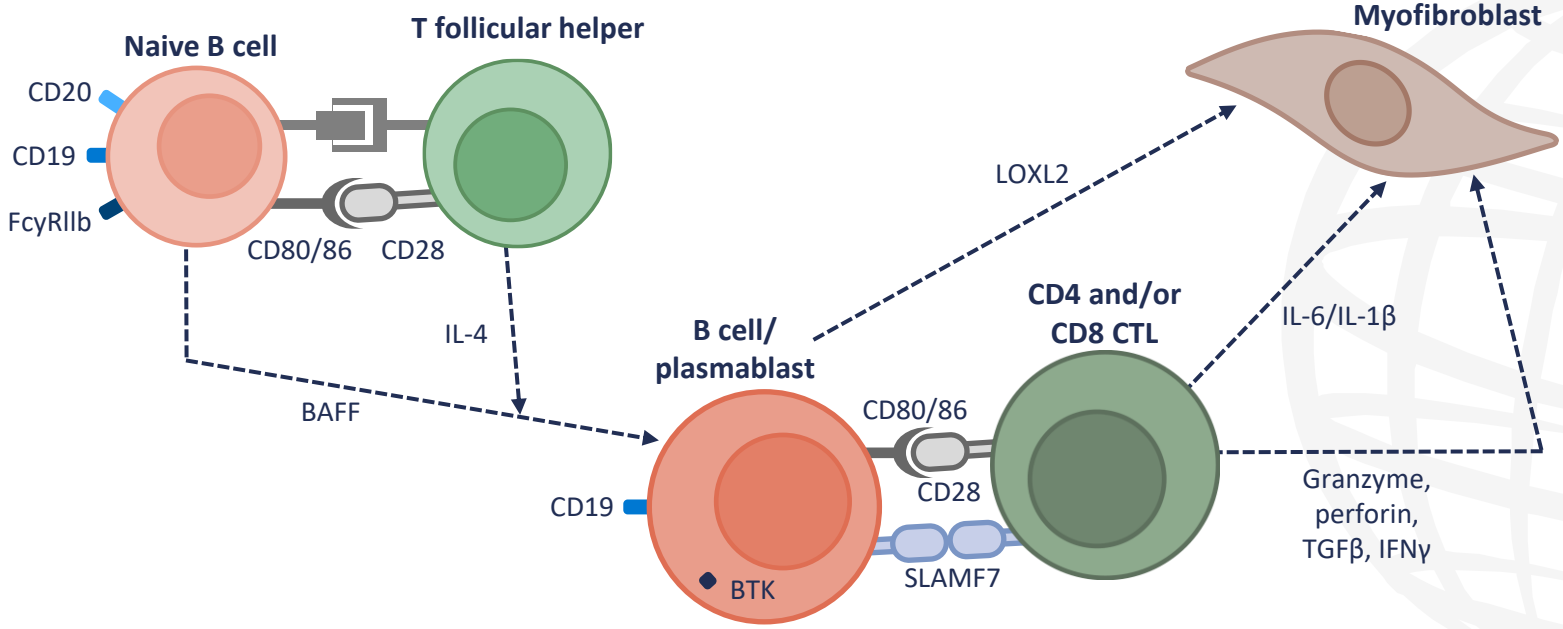
# New treatments target IgG4-RD pathophysiology[1–3]




BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CTL, cytotoxic T lymphocytes; IgG4-RD, immunoglobulin G4-related disease; IFNγ, interferon-γ; IL, interleukin; LOXL2, lysyl oxidase homolog 2; SLAMF7, surface antigen CD319; TGFβ, transforming growth factor-β.

1. Lanzillotta M, et al. *Br Med J*. 2020;369:m1067; 2. Lanzillotta M, et al. *Expert Rev Clin Immunol.* 2021;17:471–83; 3. Lanzillotta M, et al. *Mod Rheumatol*. 2023;33:258–65.

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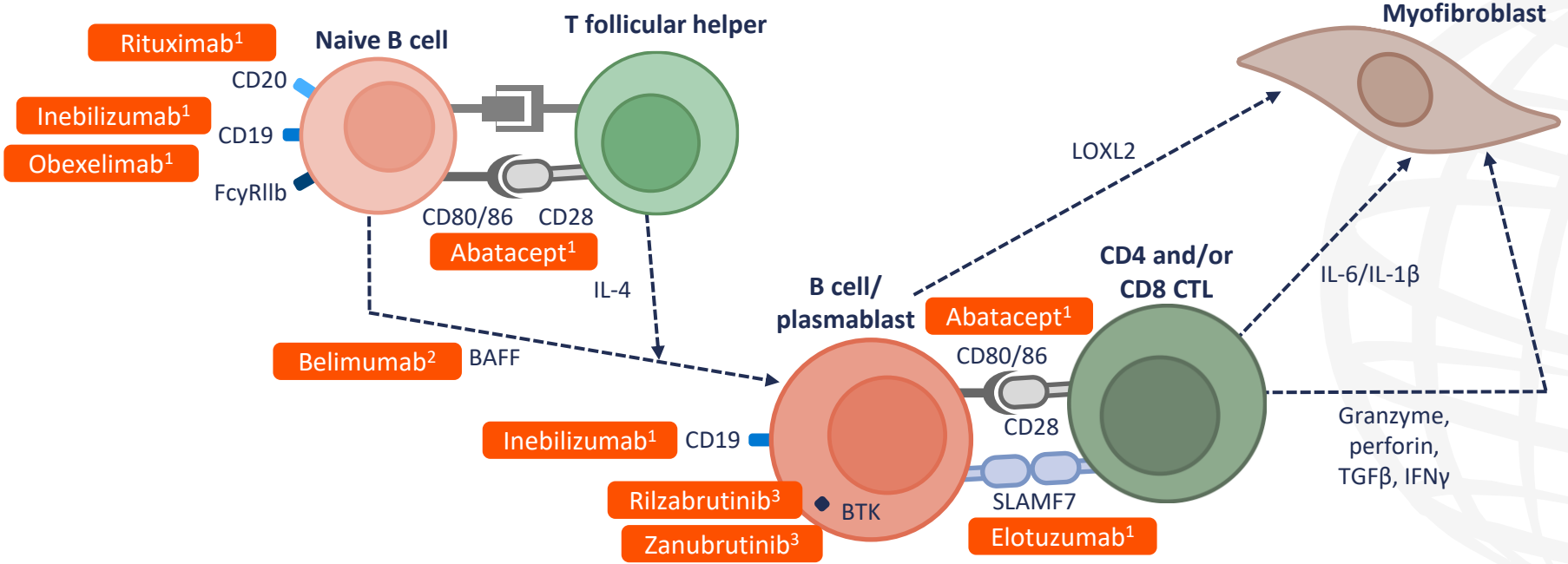
# New treatments target IgG4-RD pathophysiology[1–3]




BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CTL, cytotoxic T lymphocytes; IgG4-RD, immunoglobulin G4-related disease; IFNγ, interferon-γ; IL, interleukin; LOXL2, lysyl oxidase homolog 2; SLAMF7, surface antigen CD319; TGFβ, transforming growth factor-β.

1. Lanzillotta M, et al. *Br Med J*. 2020;369:m1067; 2. Lanzillotta M, et al. *Expert Rev Clin Immunol.* 2021;17:471–83; 3. Lanzillotta M, et al. *Mod Rheumatol*. 2023;33:258–65.

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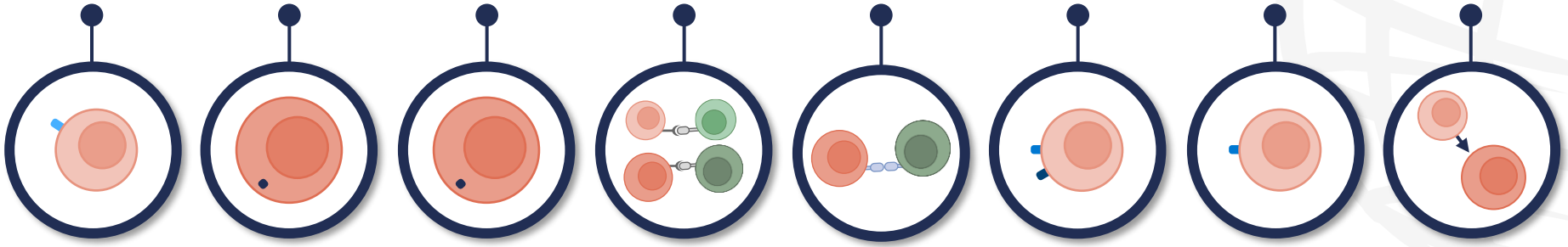
# Novel targeted agents are in clinical development[1–3]

| Phase I/II | Phase II | | | | Phase III | | Phase IV |
|---|---|---|---|---|---|---|---|
| Rituximab | Rilzabrutinib | Zanubrutinib | Abatacept | Elotuzumab | Obexelimab | Inebilizumab | Belimumab |
| NCT01584388 **Completed** | NCT04520451 **Active** | NCT04602598 **Recruiting** | NCT03669861 **Completed** | NCT04918147 **Recruiting** | NCT05662241 **Recruiting** | NCT04540497 **Active** | NCT04660565 **Recruiting** |



1. Nakaymada S, Tanaka Y. *Mod Rheumatol.* 2023;33:266–70; 2. Lanzillotta M, et al. *Mod Rheumatol.* 2023;33:258–65; 3. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ searchable by NCT number (accessed November 2023).

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# Summary

**Treatment decisions should be individualized** based on the natural history of IgG4-RD, as well as patient- and disease-specific factors[1–3]

**GCs remain the cornerstone for inducing disease remission**[4]

Advances in understanding the pathogenesis of IgG4-RD has prompted the **development of novel targeted agents** that may provide steroid-sparing options in the future[4,5]

**Life-long follow-up of patients** with IgG4-RD is advisable[6]

GC, glucocorticoid; IgG4-RD, immunoglobulin G4-related disease.

1. Weiss MA, et al. *Am J Case Rep*. 2018;19:1232–36; 2. Goodchild G, et al. *Clinical Medicine.* 2020;20:e32–9; 3. Wallace ZS, et al. *Clin Chest Med*. 2019;40: 583–97;
4. Perguino CA, Stone JH. Z *Rheumatol*. 2016;75:681–6; 5. Abraham M, Khosroshahi A. *Expert Rev Clin Immunol*. 2017;13:867–75;
6. Löhr J-M, et al. *United European Gastroenterol J.* 2020;8:637–66.

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# Panel discussion

**Prof. John Stone (Chair)**
Harvard Medical School and
Massachusetts General Hospital
Boston, MA, USA

**Dr Emanuel Della Torre**
Vita-Salute San Raffaele University
and San Raffaele Hospital
Milan, Italy

**Dr Arezou Khosroshahi**
Emory University School of Medicine
Atlanta, GA, USA

# Patient case: Presentation

## George

**Age:** 60 years

**Sex:** Male

**Presentation:** *Sudden onset of abdominal pain, jaundice and weight loss. Has a medical history of multiple allergies*

# Patient case: Diagnostic tests

## George

**Age:** 60 years

**Sex:** Male

**Serology:** *Laboratory assessment showed abnormal liver function tests and elevated CA 19-9.*

**Radiology:** *Abdominal ultrasound demonstrated extensive biliary ductal dilatation. CT/MRI/MRCP revealed a 4.6 cm pancreatic head mass.*

CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

# Patient case: Diagnostic tests

## George

**Age:** 60 years **Sex:** Male

**Serology:** *Laboratory assessment showed abnormal liver function tests and elevated CA 19-9.*

**Radiology:** *Abdominal ultrasound demonstrated extensive biliary ductal dilatation. CT/MRI/MRCP revealed a 4.6 cm pancreatic head mass.*

**What additional tests would you perform?**

a. **Biopsy to detect malignant cells; immunostain for IgG4**
b. **Measure response to high-dose prednisone**
c. **Measure serum IgG4 levels**
d. **PET-CT to detect pancreatic and extra-pancreatic lesions**

CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; Ig, immunoglobulin; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PET, positron emission tomography.