# DIAGNOSTICO EN ENFERMEDADES RELACIONADAS CON LA IgG4

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XII CONGRESO DE AADEA

**Conflictos de Interés:**

Participación en Advisory remunerados a cargo de Horizon Therapeutics

IP en ensayo clínico MITIGATE

Miembro del Adjudication Committee del ensayo clínico MITIGATE

Participación en ensayo clínico INDIGO en IgG4RD

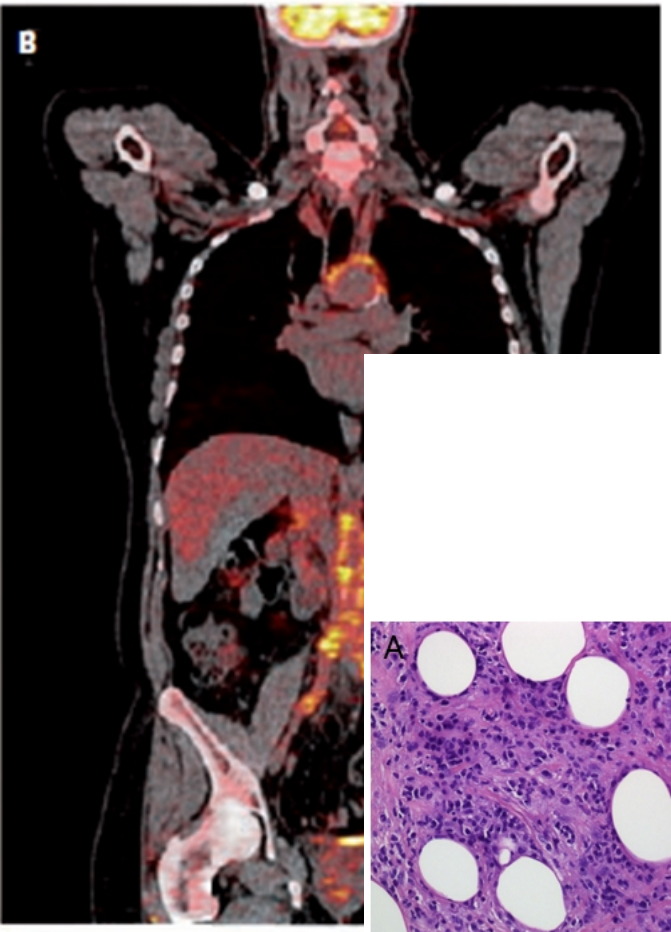
Participación en charlas renumeradas y Advisory boards por Pfizer, Alnylam y Akcea.

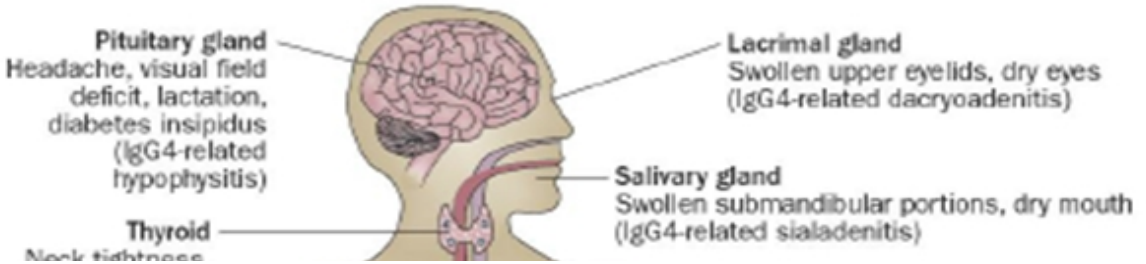
Participación en Ensayo clínicos HELIOS A y B.

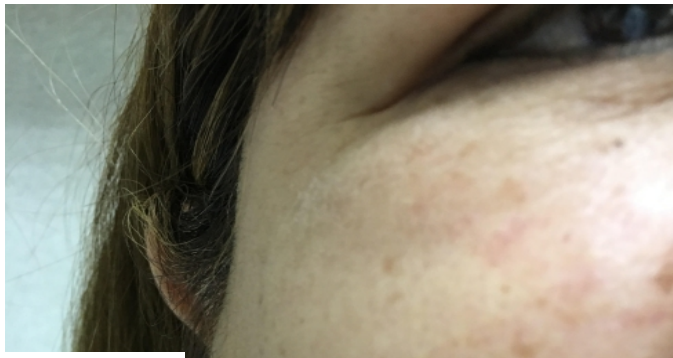
# tement on the pathology of

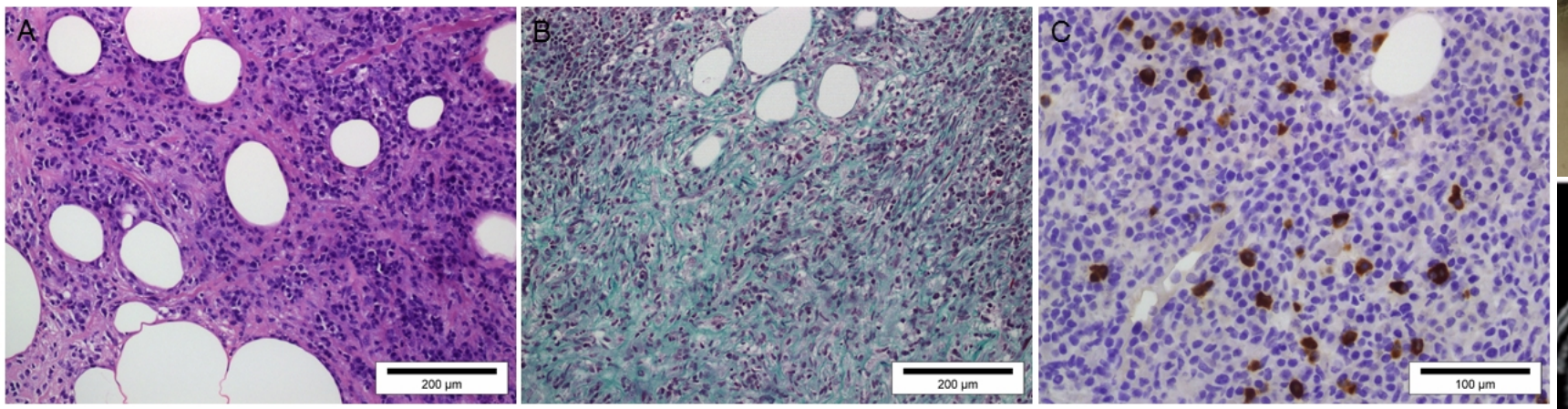
IgG4-related disease is a newly recognized fibro-inflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4$^+$ plasma cells; storiform fibrosis; and—often but not always—elevated serum IgG4 concentrations.[1,2] The disease was initially recognized in the pancreas, disease now known as autoimmune pancreatitis. Autoimmune pancreatitis was linked with the presence of elevated levels of serum IgG4 in 2001.[1]

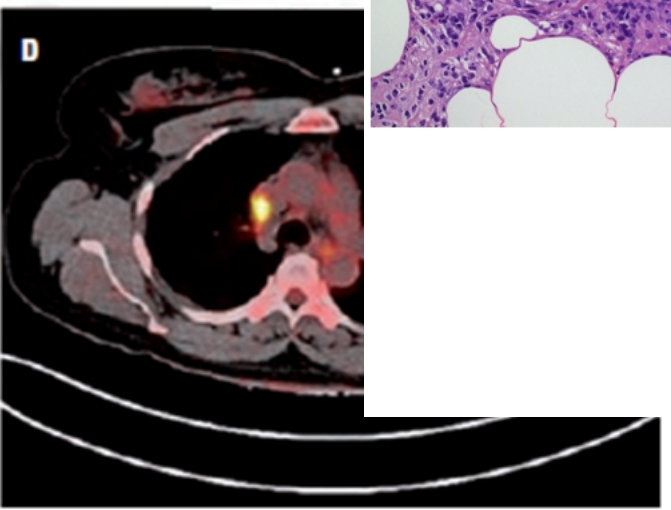
MODERN PATHOLOGY (2012) 25, 1181–1192

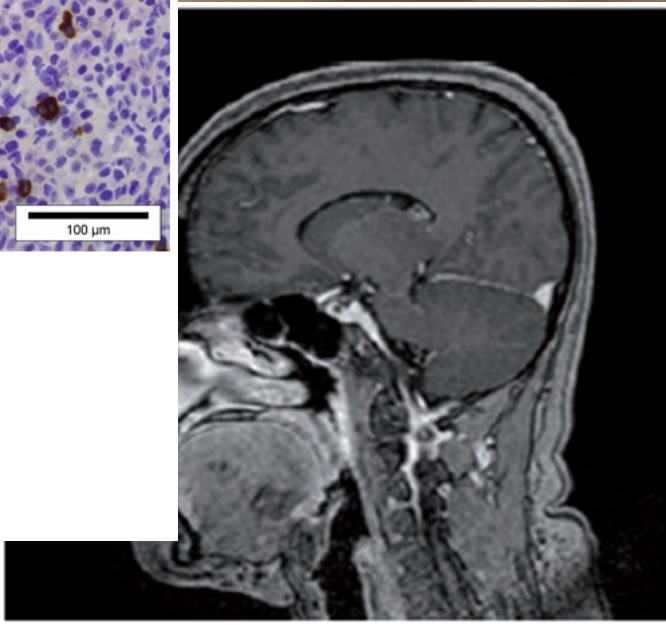

B


Pituitary gland
Headache, visual field deficit, lactation, diabetes insipidus (IgG4-related hypophysitis)
Thyroid
Lacrimal gland
Swollen upper eyelids, dry eyes (IgG4-related dacryoadenitis)
Salivary gland
Swollen submandibular portions, dry mouth (IgG4-related sialadenitis)

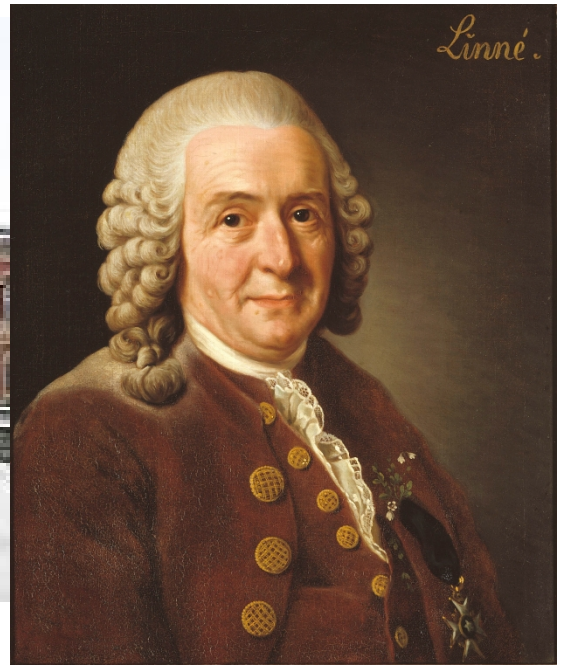



A
200 µm
B
200 µm
C
100 µm


D



# TAXONOMIA: ciencia de la clasificación



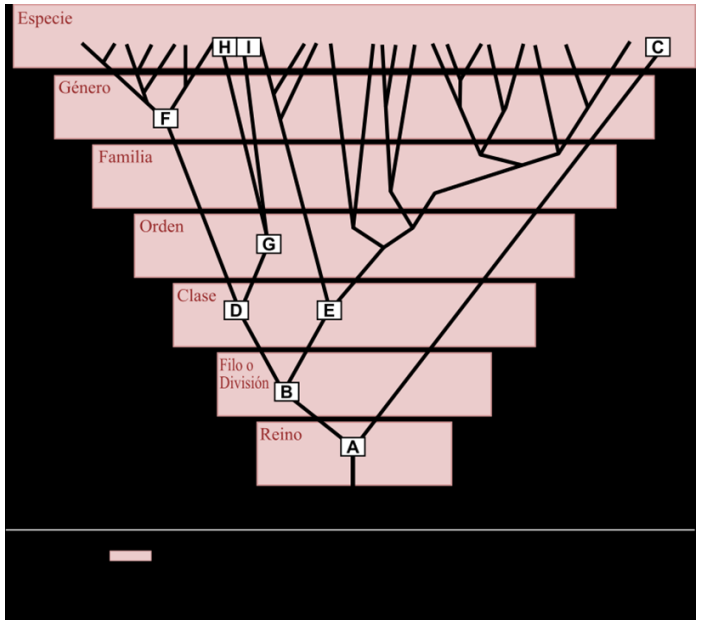

*Carl Nilsson Linnaeus*
***Carolus Linneo***

*Rashult 23 mayo 1707- Uppsala 10 de mayo 1778*

***Creador de la clasificación de los seres vivos o taxonomía***

Sistema de nomenclatura binomial

Primer término nombre del Género
Segundo término nombre de la especie



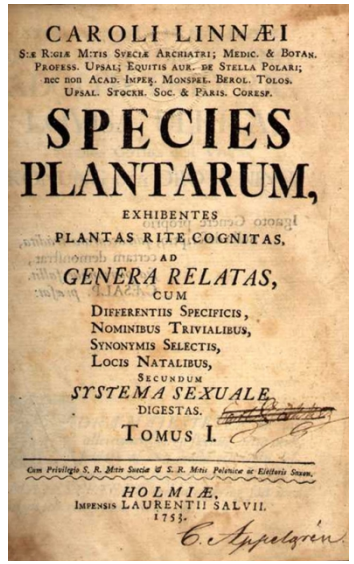

Reino

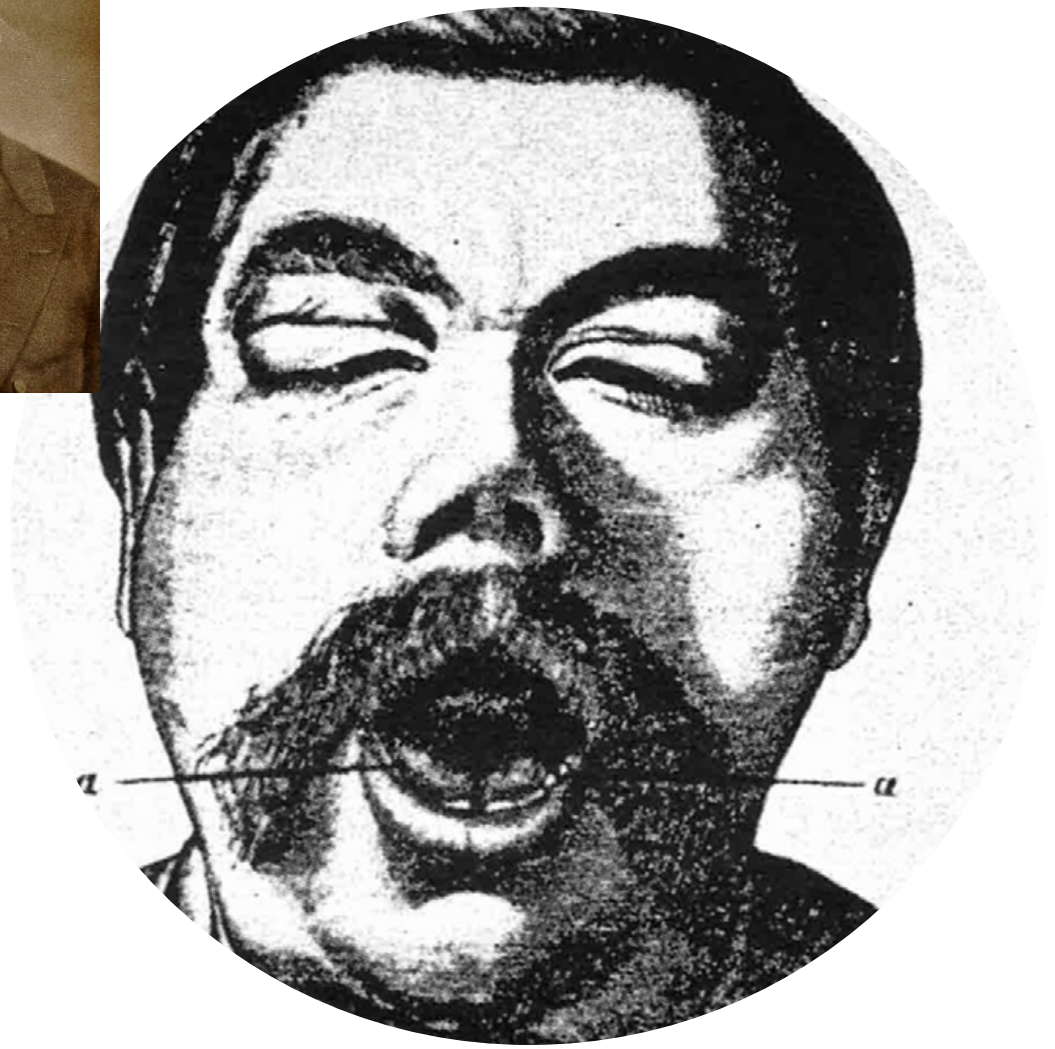
Tipos

Clases

Familias

Géneros


CAROLI LINNÆI
SPECIES PLANTARUM,
EXHIBENTES PLANTAS RITE COGNITAS, AD GENERA RELATAS, CUM DIFFERENTIIS SPECIFICIS, NOMINIBUS TRIVIALIBUS, SYNONYMIS SELECTIS, LOCIS NATALIBUS, SECUNDUM SYSTEMA SEXUALE DIGESTAS.
TOMUS I.
HOLMIÆ, IMPENSIS LAURENTII SALVII.
1753.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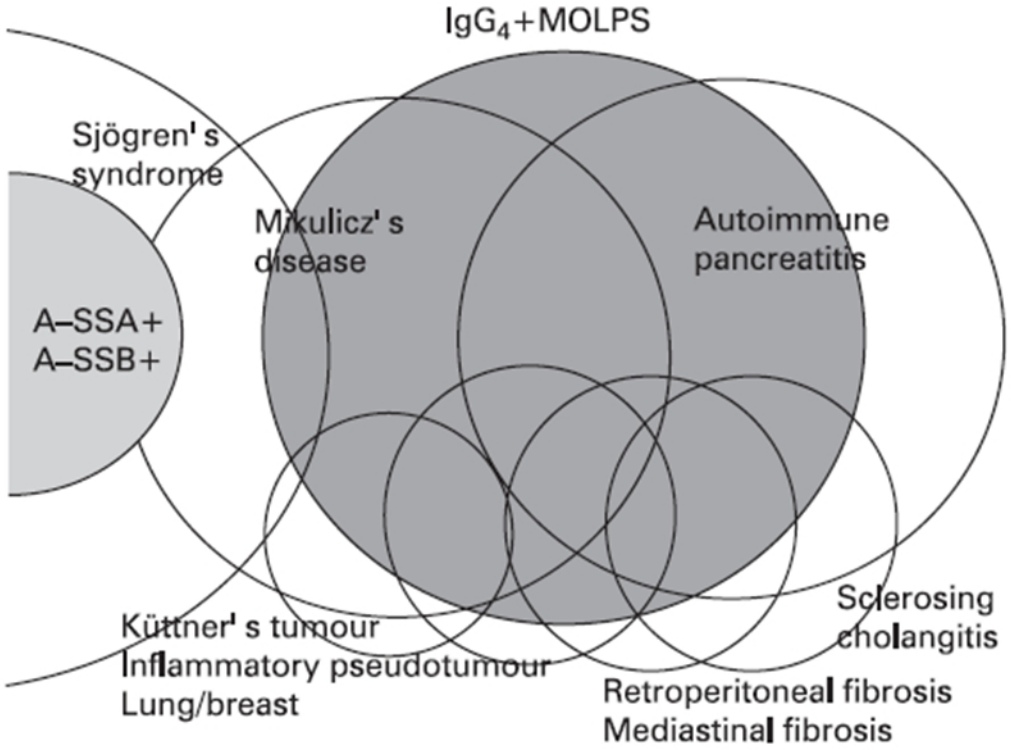



**¿PARA QUÉ UN DIAGNÓSTICO?**

PRONÓSTICO
TRATAMIENTO
INVESTIGACIÓN (registros)

*Herramientas diagnósticas de la IgG4RD*

Carruthers MN, *et al. Ann Rheum Dis* 2015;**74**:14–18.

Clínica

IgG4

Sensibilidad 90%
Especificidad 60%
VPN 96%
VPP 34%

Laboratorio

Plasmablastos circulantes

IgG4+ BCR

Pruebas de Imagen

TAC

RM

18 FDG-PET/TC

Anatomía Patológica

Respuesta a Tratamiento

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



**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.

# Perspectiva histórica del diagnóstico de la IgG4RD


Consensus statement on the pathology of IgG4-related disease

## Consensus statement for IgG4-RD: International Team

**Biopsia es imprescindible**

definitive diagnosis. Thus, when referring to conclusions that can be made from the interpretation of pathology results alone, we avoid terms such as 'definite', preferring instead 'histologically suggestive of IgG4-related disease'.

*Histológicamente muy sugestiva*
*probable*
*insuficiente*

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

Cases with ≥ 2 pathology features

Cases with 1 pathology feature

| | Numbers of IgG4+ plasma cells (/hpf) | | Ref |
|---|---|---|---|
| Meningus | >10 | >10 | 55 |
| Lacrimal gland | >100 | >100 | 28 |
| Salivary gland | >100 | >100 | 17,34 |
| Lymph node | >100 | >50 | 27 |
| Lung (surgical specimen) | >50 | >50 | 10,35 |
| Lung (biopsy) | >20 | >20 | 10,35 |
| Pleura | >50 | >50 | 6 |
| Pancreas (surgical specimen) | >50 | >50 | 30,32 |
| Pancreas (biopsy) | >10 | >10 | 56,57 |
| Bile duct (surgical specimen) | >50 | >50 | 49 |
| Bile duct (biopsy) | >10 | >10 | 58,59 |
| Liver (surgical specimen) | >50 | >50 | 49 |
| Liver (biopsy) | >10 | >10 | 12,60 |
| Kidney (surgical specimen) | >30 | >30 | 15 |
| Kidney (biopsy) | >10 | >10 | 61 |
| Aorta | >50 | >50 | 16,51,52 |
| Retroperitoneum | >30 | >30 | 8 |
| Skin | >200 | >200 | 62,63 |

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

Orange boxes = Probable histological features of IgG4-RD

*Deshpande V, et al. Mod Pathol. 2012;25(9):1181–92*

# Comprehensive Diagnostic Criteria for IgG4-RD: Japanese Team

REVIEW ARTICLE

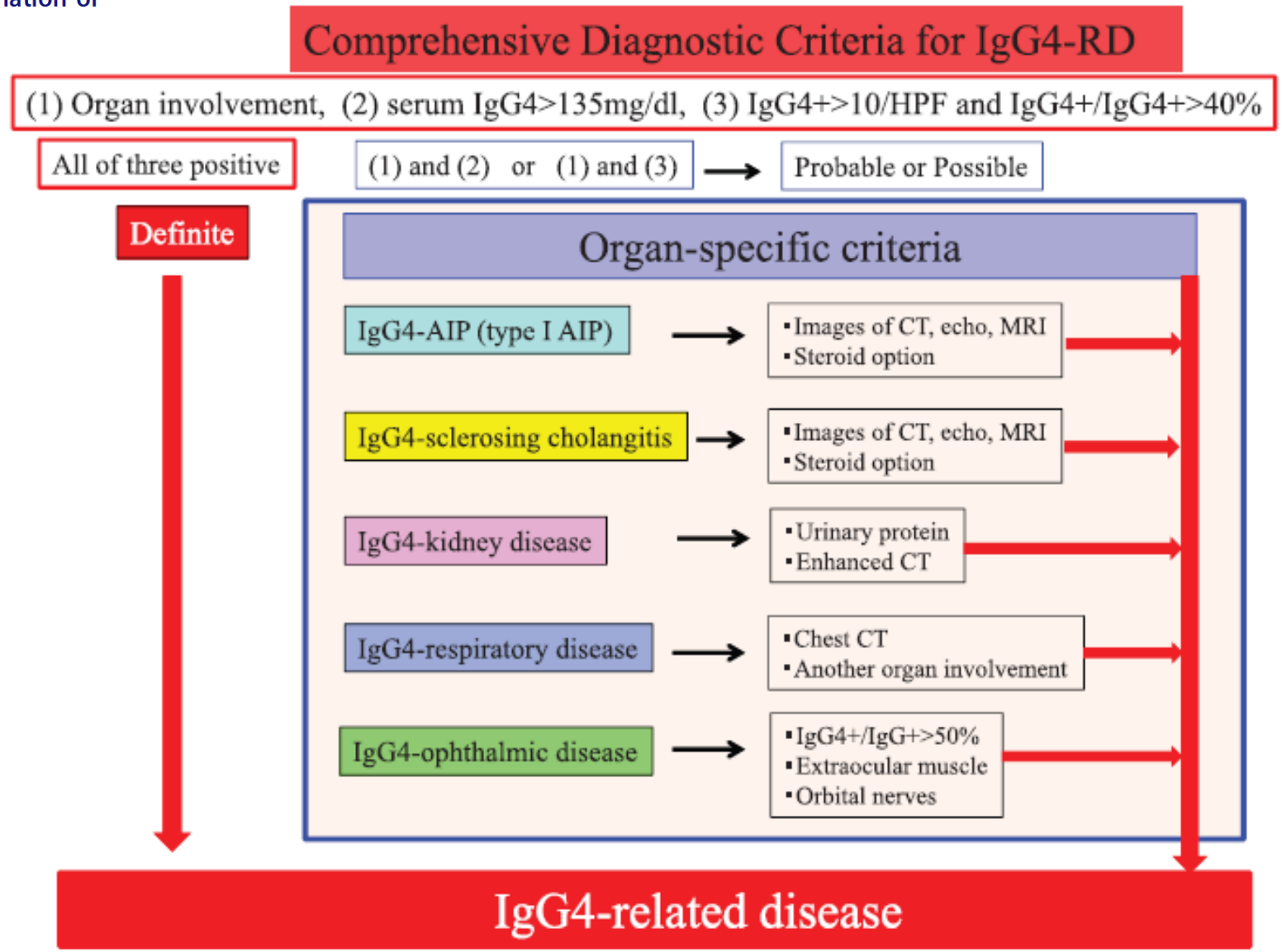
Current approach to the diagnosis of IgG4-related disease – Combination of comprehensive diagnostic and organ-specific criteria

MODERN RHEUMATOLOGY, 2017
VOL. 27, NO. 3, 381–391
http://dx.doi.org/10.1080/14397595.2017.1290911

***Definitivo***

***Probable***

***Posible***



# The 2019 American College of Rheumatology/ European League Against Rheumatism classification criteria for $IgG_4$-related disease

| Step | Categorical assessment or numerical weight |
|---|---|
| Step 1. Entry criteria | |
| Characteristic* clinical or radiological involvement of a typical organ (eg, pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland (Riedel's thyroiditis)) OR pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs | **Yes**† or No |

| *Step 2. Exclusion criteria: domains and items*‡ | Yes or **No**§ |
|---|---|
| Clinical | |
| Fever | |
| No objective response to glucocorticoids | |
| Serological | |
| Leucopenia and thrombocytopenia with no explanation | |
| Peripheral eosinophilia | |
| Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase) | |
| Positive SSA/Ro or SSB/La antibody | |
| Positive double-stranded DNA, RNP or Sm antibody | |
| Other disease-specific autoantibody | |
| Cryoglobulinemia | |
| Radiological | |
| Known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated | |
| Rapid radiological progression | |
| Long bone abnormalities consistent with Erdheim-Chester disease | |
| Splenomegaly | |
| Pathological | |
| Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated | |
| Markers consistent with inflammatory myofibroblastic tumour | |
| Prominent neutrophilic inflammation | |
| Necrotizing vasculitis | |
| Prominent necrosis | |
| Primarily granulomatous inflammation | |
| Pathologic features of macrophage/histiocytic disorder | |
| Known diagnosis of the following: | |
| Multicentric Castleman's disease | |
| Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present) | |
| Hashimoto thyroiditis (if only the thyroid is affected) | |

Wallace ZS, *et al*. *Ann Rheum Dis* 2019;**0**:1–11. doi:10.1136/annrheumdis-2019-216561

Turk J Med Sci
(2020) 50: 1616-1631

| If case meets entry criteria and does not meet any exclusion criteriaproceed to Step 3 ¶ | | Step 4: Total inclusion points |
|---|---|---|
| **Step 3. Inclusion criteria: domains and items** | Numerical weight | |
| Serum IgG4 concentration | | |
| · Normal or not checked | 0 | |
| · >Normal but <2x upper limit of normal | +4 | |
| · 2-5x upper limit of normal | +6 | |
| · ≥5x upper limit of normal | +11 | |
| Bilateral lacrimal, parotid, sublingual and submandibular glands | | |
| · Not set of glands involved | 0 | |
| · One set of glands involved | +6 | |
| · Two or more sets of glands involved | +14 | |
| Chest | | |
| · Not checked or neither of the items listed is present | 0 | |
| · Peribronchovascular and septal thickening | +4 | |
| · Paravertebral band-like soft tissue in the thorax | +10 | |
| Pancreas and biliary tree | | |
| · Not checked or neither of the items listed is present | 0 | |
| · Diffuse pancreas englargement (loss of lobulations) | +8 | |
| · Diffuse pancreas englargement and capsule-like rim with decreased enhancement | +11 | |
| · Pancreas (either of above) and biliary tree involvement | +19 | |
| Kidney | | |
| · Not checked or neither of the items listed is present | 0 | A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20. |
| · Hypocomplementemia | +6 | |
| · Renal pelvis thickening/soft tissue | +8 | |
| · Bilateral renal cortex low-density areas | +10 | |
| Retroperitoneum | | |
| · Not checked or neither of the items listed is present | 0 | |
| · Diffuse thickening of the abdominal aortic wall | +4 | |
| · Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries | +8 | |
| Histopathology | | |
| · Uninformative biopsy | 0 | |
| · Dense lymphocytic infiltrate | +4 | |
| · Dense lymphocytic infiltrate and obliterative phlebitis | +6 | |
| · Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis | +13 | |
| Immunostaining ** | | |
| 0–16, as follows: | | |
| · Assigned weight is 0 if: the IgG4+/IgG+ratio is 0%–40% or indeterminate and the number of IgG4+cells/hpf is 0–9 *** | | |
| · Assigned weight is 7 if: (1) the IgG4+/IgG+ ratio is ≥41% and the number of IgG4+cells/hpf is 0–9 or indeterminate or (2) the IgG4+/IgG+ ratio is 0%–40% or indeterminate and the number of | | · Assigned weight is 14 if: (1) the IgG4+/IgG+ ratio is 41%–70% and the number of IgG4+cells/hpf is ≥10 or (2) the IgG4+/IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50. Assigned weight is 16 if: the IgG4+/IgG+ratio is ≥71% and the number of IgG4+cells/hpf is ≥51. |

*Criterios de Inclusión (Dominios):*

**Niveles séricos IgG4**

**Histología**

**Inmunohistoquímica**

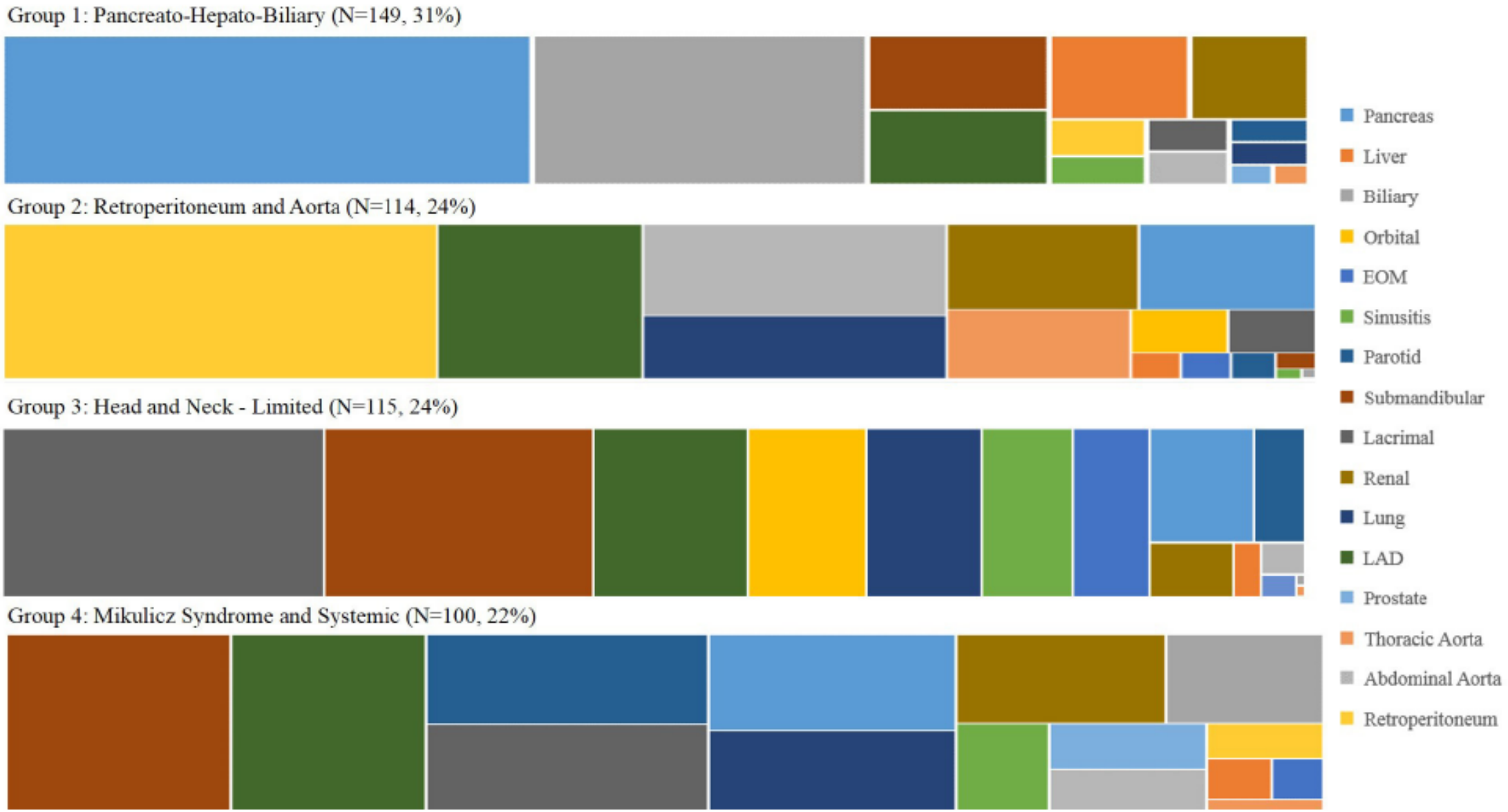
**Clínica**

# Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts

Zachary S Wallace,[1,2,3] Yuqing Zhang,[1,2,3] Cory A Perugino,[1,3] Ray Naden,[4] Hyon K Choi,[1,2,3] John H Stone,[1,3] for the ACR/EULAR IgG4-RD Classification Criteria Committee

| Covariate | Group 1 'Pancreato-Hepato-Biliary' | Group 2 'Retroperitoneum and Aorta' | Group 3 'Head and Neck-Limited' | Group 4 'Mikulicz and Systemic' |
|---|---|---|---|---|
| Female (%) | 21% | 25% | 76% | 22% |
| Asian (%) | 37% | 25% | 67% | 52% |
| Age at diagnosis (year, mean, SD) | 63 (13) | 58 (16) | 55 (13) | 63 (13) |
| Time to diagnosis (year, mean, SD) | 0.9 (1.8) | 1.8 (4.0) | 2.3 (3.4) | 2.0 (3.6) |
| Serum IgG4 concentration (mg/dL, median, IQR) | 316 (147–622) | 178 (63–322) | 445 (183–888) | 1170 (520–2178) |

*Wallace ZS, Ann Rheum Dis, 2019*




**igure 1** Distribution of organ involvement in each group (% of overall cohort). EOM, extraocular muscle; Lad, lymphadenopathy.

*Wallace ZS, Ann Rheum Dis, 2019*

**Table 2** Phenotypic groups of IgG4-RD (derivation cohort)*

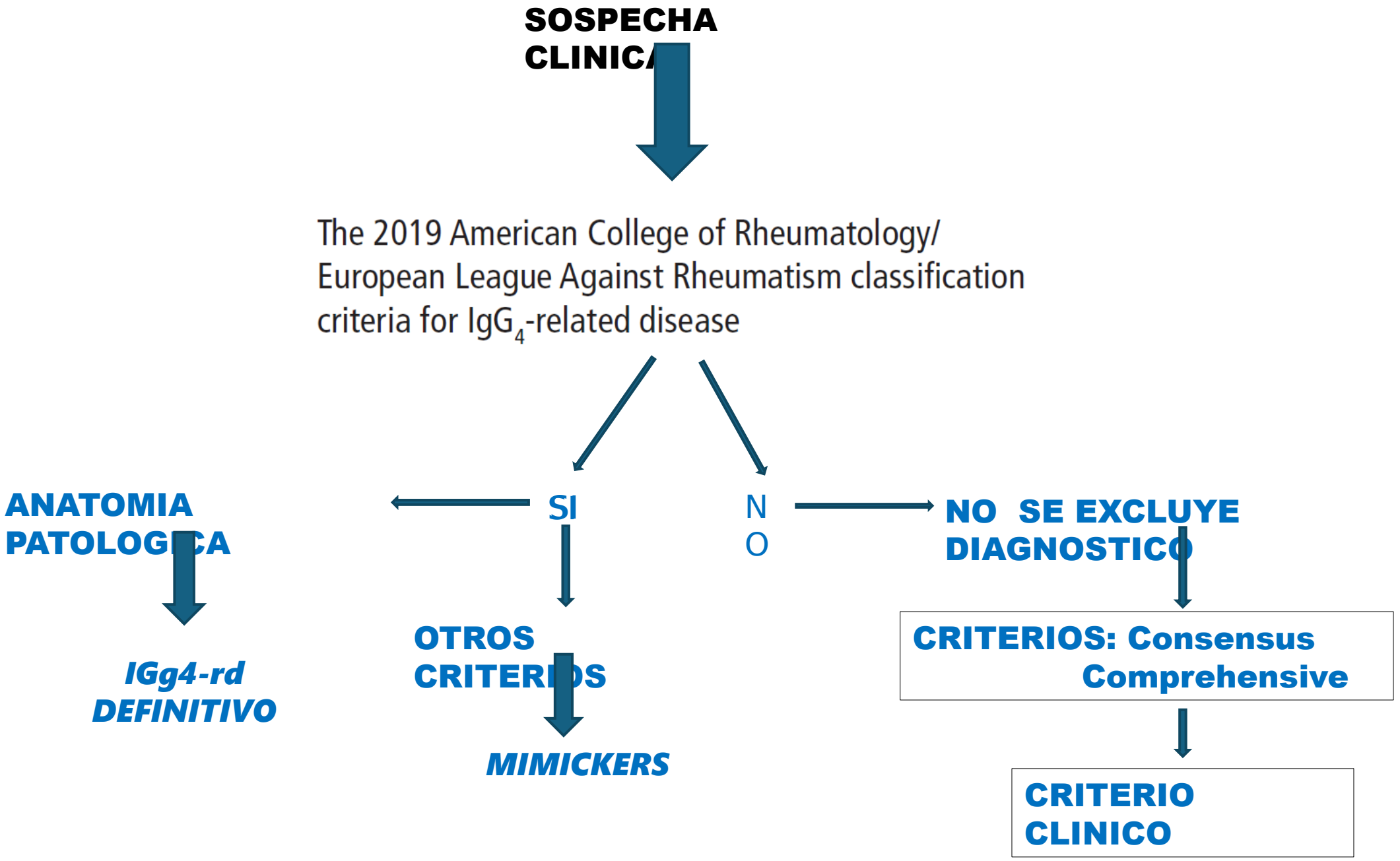
| Variables used to identify groups† | Group 1 'Pancreato-Hepato-Biliary' (%) | Group 2 'Retroperitoneum and Aorta' (%) | Group 3 'Head and Neck-Limited' (%) | Group 4 'Mikulicz and Systemic' (%) | P value |
|---|---|---|---|---|---|
| Pancreas | 87 | 12 | 15 | 46 | <0.001 |
| Liver | 13 | 1 | 2 | 5 | <0.001 |
| Biliary | 55 | <1 | <1 | 27 | <0.001 |
| Orbital | <1 | 3 | 22 | <1 | <0.001 |
| Extraocular muscle | <1 | 1 | 13 | 4 | <0.001 |
| Sinusitis | 3 | <1 | 17 | 16 | <0.001 |
| Parotid gland | 2 | 1 | 22 | 49 | <0.001 |
| Submandibular gland | 15 | 5 | 50 | 77 | <0.001 |
| Lacrimal gland | 3 | 3 | 60 | 48 | <0.001 |
| Renal | 11 | 13 | 5 | 36 | <0.001 |
| Lung | 2 | 15 | 7 | 39 | <0.001 |
| Lymph node | 15 | 25 | 29 | 67 | <0.001 |
| Prostate | 1 | <1 | <1 | 14 | <0.001 |
| Thoracic aorta | 1 | 10 | 1 | 3 | <0.001 |
| Abdominal aorta | 3 | 22 | <1 | 13 | <0.001 |
| Retroperitoneum | 4 | 53 | 2 | 8 | <0.001 |
| Proportion of cohort | 31 | 24 | 24 | 22 | |
| Average probability (Mean) | 93 | 92 | 90 | 90 | |

*Only cases (n=478) with complete covariate data are included in the latent class analysis with covariates.
†All percentages are probabilities that the manifestation occurs in that group, conditional on latent class membership (eg, totals will not equal 100%).
IgG4-RD, IgG4-related disease.

*Wallace ZS, Ann Rheum Dis, 2019*

**Table 2.** Differential diagnosis of IgG4-related disease.

| | |
|---|---|
| ***Autoimmune disorders*** | |
| ***-Rheumatic conditions*** | |
| Sarcoidosis | ***Infections*** |
| Sjogren's syndrome | Bacterial |
| ANCA-associated vasculitis | Viral |
| -Granulomatosis with polyangiitis | Mycobacterial |
| -Eosinophilic granulomatosis with polyangiitis | Spirochetal |
| -Microscopic polyangiitis | Fungi |
| Takayasu's arteritis-giant cell arteritis | ***Lymphoproliferative disorders*** |
| Behçet disease | MALT lymphoma with plasmocytic differentiation |
| ***-Nonrheumatic conditions*** | Plasma cell neoplasia |
| Primary biliary cirrhosis-primary sclerosing cholangitis | Follicular lymphomas |
| Autoimmune hepatitis | |
| Hashimoto's thyroiditis | |
| Castleman's disease | |
| Lymhomatoid granulomatosis | |
| ***Systemic inflammatory disorders*** | ***Tumors*** |
| Rosai-Dorfman disease | Inflammatory myofibroblastic tumor |
| Multicentric Castleman disease | Adenocarcinoma and squamous cell carcinoma |
| Chronic sialadenitis | |
| Type 2 AIP | ***Eosinophilic disorders*** |
| Inflammatory bowel disease | Eosinophilic angiocentric fibrosisKimura |
| Erdheim-Chester disease | diseaseAnjiolymphoid hyperplasia with eosinophilia |


SOSPECHA CLINICA
The 2019 American College of Rheumatology/ European League Against Rheumatism classification criteria for IgG4-related disease
ANATOMIA PATOLOGICA
IGg4-rd DEFINITIVO
SI
OTROS CRITERIOS
MIMICKERS
NO
NO SE EXCLUYE DIAGNOSTICO
CRITERIOS: Consensus Comprehensive
CRITERIO CLINICO

# gracias

*Fernando.Martinez@vallhebron.cat*