



ERICA ERN Research Conference

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ERN ReCONNET Red Flags for primary care: An approach to promote early diagnosis in rare and complex conditions

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The common challenges of RDs

**Scattered
knowledge**

**Low
expertise**

Knowledge

**RCT in small
populations**

**Low
evidence**

Research

**Phenotypic
variability**

**Different
organ
involvement**

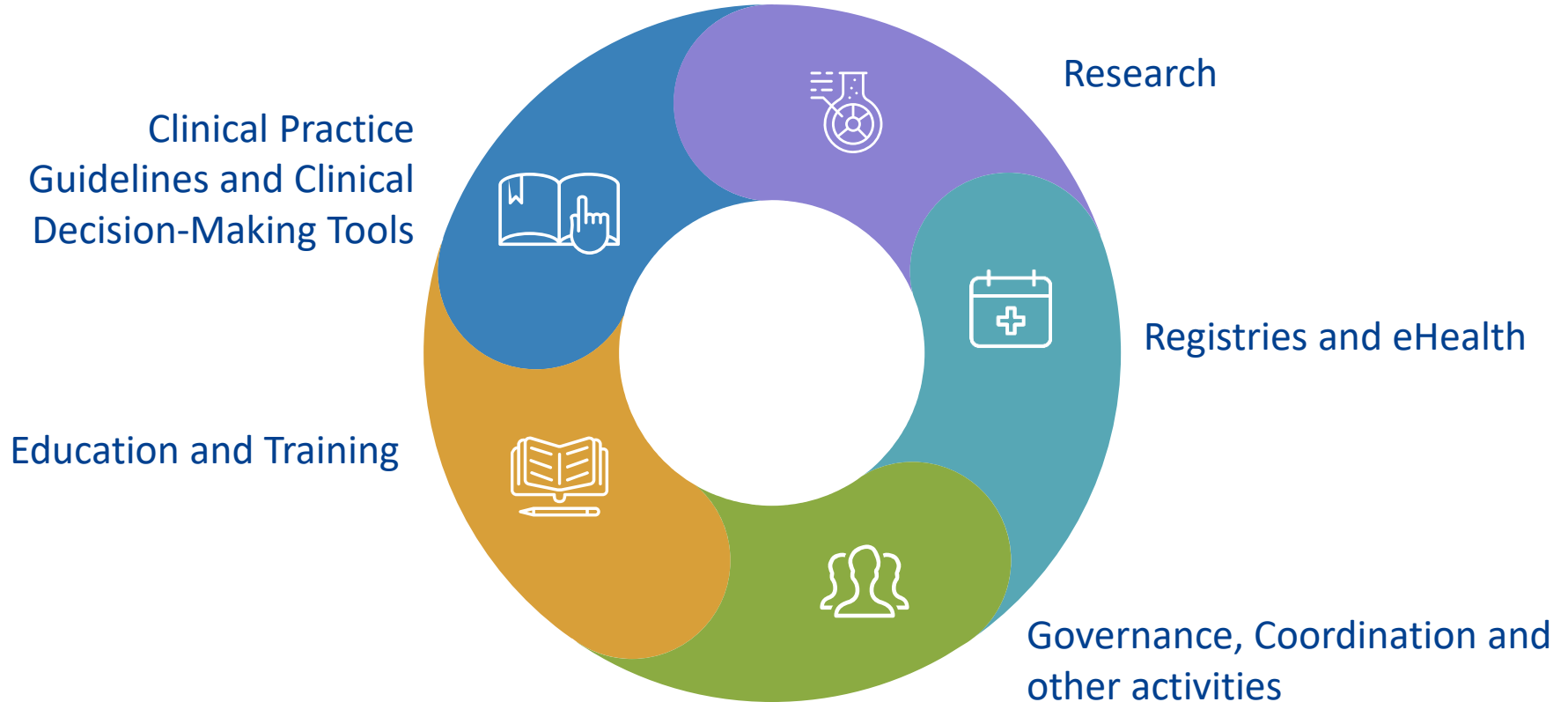
Complexity

**Delay in
recognition**

**Long
patients'
journey**

Diagnosis

ERN ReCONNET core activities



Clinical Practice
Guidelines and Clinical
Decision-Making Tools

Research

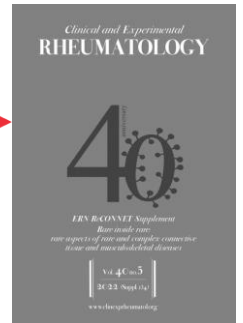
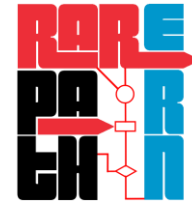
Registries and eHealth

Governance, Coordination and
other activities

Education and Training

Research and Quality of Care

- ❁ Patient's care pathways and organisation of care (RarERN Path methodology™)
- ❁ ERN ReCONNET Supplement “Rare inside Rare” (14 papers)
- ❁ VACCINATE Study, COVID-related initiatives
- ❁ Economic burden of disease
- ❁ Study on cross-border procedures in ERN centres
- ❁ Transition of Care
- ❁ ERN ReCONNET Good Practice Sharing Initiative



ERN ReCONNET COVID-19 Webinars

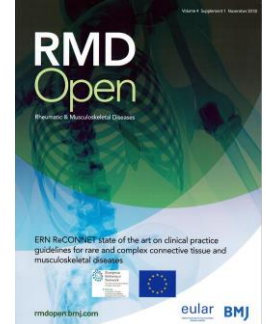


ERN ReCONNET Workshops on vaccination and management



Clinical Practice Guidelines and Clinical Decision-Making Tools

- ERIN ReCONNET Supplement on the State of the Art of CPGs in rCTDs (12 papers)
- ERIN ReCONNET points to consider for treating patients living with autoimmune rheumatic diseases with antiviral therapies and anti-SARS-CoV-2 antibody products (endorsed x7 MS)
- Adherence to CPGs and awareness
- Adaptation of existing CPGs
- Lay versions
- Expert Panel CPGs and CDMTs
- Webinar “What you need to know on CPGs”



Recommendations

ERIN ReCONNET points to consider for treating patients living with autoimmune rheumatic diseases with antiviral therapies and anti-SARS-CoV-2 antibody products

R. Talarico¹, G.A. Ramirez², S.C. Barreira³, C. Cardamone⁴, P. Triggianese⁵, S. Aguilera⁶, J. Andersen⁷, T. Arvin⁸, E. Benistan⁹, G. Bertias¹⁰, A. Bortoluzzi¹¹, C. Bouillon¹², I. Bullas¹³, G.R. Burnstein¹⁴, S. Calles¹⁵, P.E. Carneiro¹⁶, R. Cervara¹⁷, M. Cutolo¹⁸, L. Dazian¹⁹, E. Della-Torre²⁰, R. Faria²¹, J.E. Fonseca²², I. Galetti²³, E. Hachulla²⁴, L. Inacciarino²⁵, S. Jacobsen²⁶, N. Khmelinskii²⁷, M. Lampert²⁸, D. Martinello²⁹, A. Meyer³⁰, G. Moroncini³¹, G. Nag³², M. Okesaka³³, C. Pantili³⁴, M. Pilecky³⁵, M. Piatek³⁶, S. Rodan³⁷, C. Richaoui³⁸, V.C. Romão³⁹, M. Schneider⁴⁰, S. Sokolova⁴¹, G.A. Szefer⁴², G. Szomoru⁴³, V. Szust⁴⁴, A. Sull⁴⁵, C. Tsai⁴⁶, S.W. Tai⁴⁷, A. Tinazzi⁴⁸, M.C. Vonk⁴⁹, M. Trakoudou⁵⁰, M. Moses⁵¹

Red Flags for RDs

Why?	To reduce the delay in diagnosis of RDs
Who?	Different stakeholders, including clinicians, ePAG, GP (President of the European Society of GPs)
What?	Signs and symptoms for early diagnosis

ERN ReCONNECT Red Flags Project

- Early referral
- Contractor: **Aragon Health Sciences Institute (IACS, Spain)**
- The Expert Panel on CPGs agreed to prioritise IgG4-RD as the first disease that will be addressed for the development of Red Flags.

ERN ReCONNET

Red Flags Workflow



01

SLR



02

Expert Opinion



03

Proposal of RF



04

Agreement



05

Publication on RF

The Case of IgG4

Primary review question

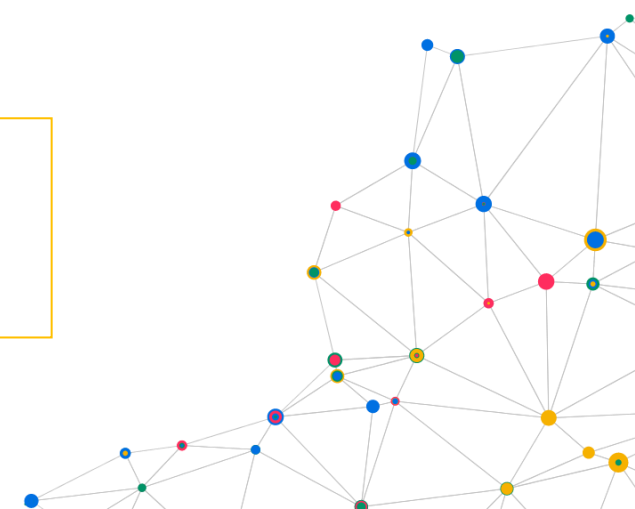
In patients presenting in a primary care setting, which signs and symptoms should arouse suspicion of immunoglobulin G4-related disease?



SLR results

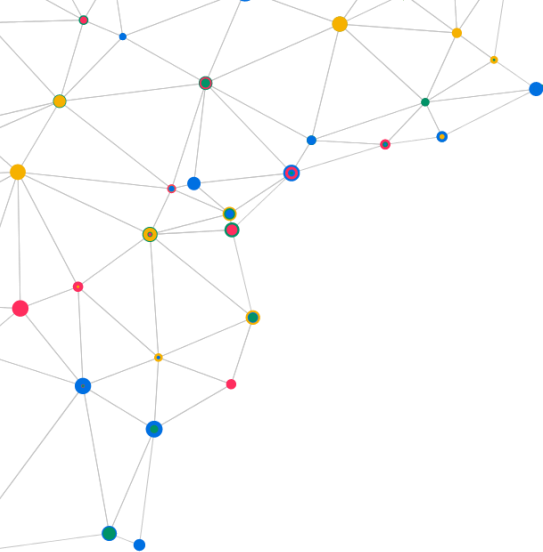
Expert opinion

Red Flags for IgG4



PICO

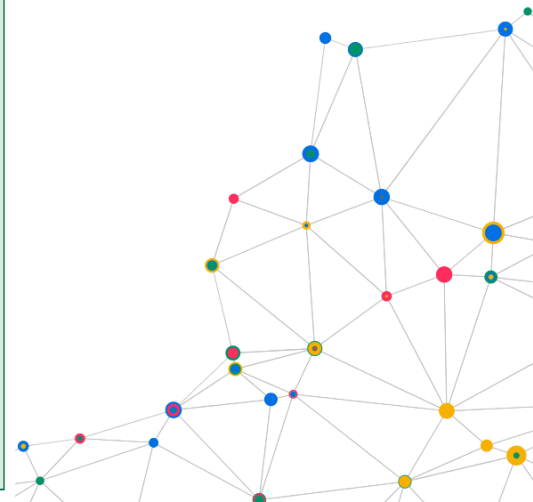
Population	Intervention	Comparison	Outcome
Patients with IgG4-related disease. IgG4-related disease is an immune-mediated condition that can affect multiple organ systems	Differential diagnosis of a healthcare professional through signs and symptoms identification	None	Signs and symptoms' diagnostic accuracy for IgG4-related disease: <ul style="list-style-type: none">· Sensitivity· Specificity· Predictive values· Likelihood ratios· Area under the curve Signs and symptoms' prevalence



	Type of study	Study quality
Clinical history, signs, and symptoms		
Male sex	One diagnostic precision; ²¹ two cohort studies ^{17,18}	One high risk of bias; ²¹ one fair quality; ²¹ and one high quality ¹⁷
Age ≥ 60 years	Two diagnostic precision; ^{10,11} two cohort studies ^{12,14}	One high risk of bias; ¹⁰ two fair quality; ^{10,17} and one high quality ¹⁴
Swelling in one or more organ system*	Three diagnostic precision; ^{13,15} one cohort study ¹⁶	Three high risk of bias; ^{13,15} one high quality ¹⁶
Swelling in two or more organ systems*	One diagnostic precision; ⁸ one cohort study ⁷	One high risk of bias; ⁸ one fair quality ⁷
Pancreas and biliary tree involvement	One diagnostic precision; ²⁰ one cohort study ⁷	One high risk of bias; ²⁰ one fair quality ⁷
History of allergy or atopy	One diagnostic precision ⁶	One high risk of bias ⁶
Occupational exposures	One diagnostic precision ⁶	One high risk of bias ⁶
History of autoimmune diseases	One diagnostic precision ⁶	One high risk of bias ⁶
Response to steroids	One diagnostic precision; ²³ one cohort study ¹⁴	One high risk of bias ²³ and one high quality ¹⁴
Spontaneous improvement or resolution of masses	One diagnostic precision ⁶	One high risk of bias ⁶
Common laboratory findings and basic imaging techniques		
Laboratory		
Increased serum IgE concentrations	Two diagnostic precision ^{11,14}	One high risk of bias; ¹¹ one fair quality ¹⁴
Peripheral eosinophilia	Three diagnostic precision ^{14,15}	Two high risk of bias; ^{10,11} one fair quality ¹⁴
Increased serum IgG concentrations	One diagnostic precision ⁶	One high risk of bias ⁶
Hypergammaglobulinaemia	One diagnostic precision ⁶	One high risk of bias ⁶
Hypocomplementemia	One diagnostic precision ⁸	One high risk of bias ⁸
Radiology imaging		
Solitary mass	One diagnostic precision ⁶	One high risk of bias ⁶
Diffuse enlargement of organs	Two diagnostic precision ^{11,14}	Two high risk of bias; ^{10,11}
Fibrotic thickening of organs	One diagnostic precision ⁶ ; one cohort study ¹⁴	One high risk of bias; ⁶ one high quality ¹⁴
Specific laboratory findings, advanced imaging techniques, histology, and immunohistochemistry		
Laboratory		
Increased serum IgG4 concentration*	Four diagnostic precision; ^{11,12} two cohort studies ^{17,18}	Three high risk of bias; ^{11,12,14} two fair quality; ^{10,17} and one high quality ¹⁸
Serum IgG4 concentration ≥ 2 times the upper limit of normal*	Two diagnostic precision; ^{14,18} one cohort studies ⁷	Two high risk of bias; ^{14,18} one fair quality ⁷
Serum IgG4 concentration ≥ 5 times the upper limit of normal*	One diagnostic precision; ²⁰ one cohort study ⁷	One high risk of bias; ¹⁴ one fair quality ⁷
Radiology imaging		
Band-like soft tissue (in the thorax, renal pelvis, aorta, or iliac arteries)	One diagnostic precision ⁸	One high risk of bias ⁸
Capsule-like rim surrounding the pancreas	One diagnostic precision ⁸	One high risk of bias ⁸
Histology and immunohistochemistry		
Tissue eosinophilia	One diagnostic precision ⁶	One high risk of bias ⁶
IgE ⁺ mast cells	One diagnostic precision ⁶	One high risk of bias ⁶
IgG4 ⁺ plasma cells*	One diagnostic precision ⁶	One high risk of bias ⁶
IgG4 ⁺ IgG ⁺ plasma cells ratio > 40%*	One diagnostic precision ⁶	One high risk of bias ⁶
Lymphoplasmacytic infiltration*	Two diagnostic precision ^{11,17}	Two high risk of bias; ^{11,17}
Dense lymphocytic infiltration*	One diagnostic precision ⁸	One high risk of bias ⁸
Obliterative phlebitis	Two diagnostic precision; ^{10,11} one cohort study ⁷	Two high risk of bias; ^{10,11} one fair quality ⁷
Fibrosis*	One diagnostic precision ⁷	One high risk of bias ⁷
Steriiform fibrosis*	Two diagnostic precision; ^{11,12} one cohort study ¹⁷	Two high risk of bias; ^{11,12} one fair quality ¹⁷

*Potential red flags referring to the same concept

Table 1: Potential red flags for IgG4-related disease



Agreement

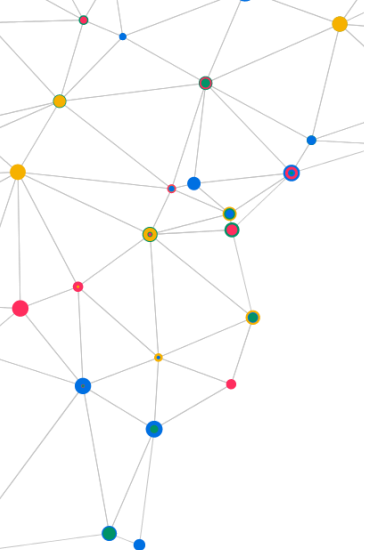
The identification of the final Red Flags will be performed by means of an agreement process.

The members of the Task Force will be asked :

- to indicate their agreement with each item with “yes” o “no” and
- to vote on their level of agreement (LoA), using a scale of 0–10 (0 indicating no agreement at all and 10 indicating full agreement).

A consensus is accepted if $>75\%$ (threshold pre-agreed) of the members voted in favour of each item.

The mean and SD of the LoA, as well as the percentage of the Task Force members with an agreement ≥ 8 will be reported.



Identification of red flags for IgG4-related disease: an international European Reference Network for Rare Connective Tissue Diseases framework

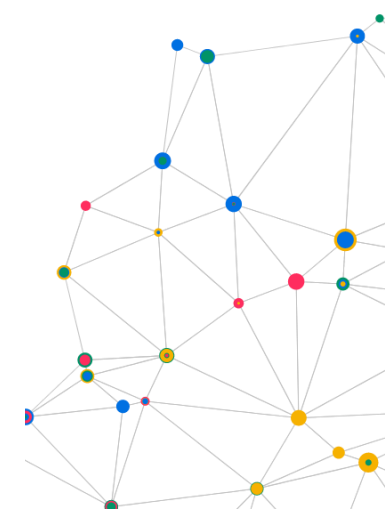
Emanuel Della-Torre ¹, Rosaria Talarico ², Jose Ballarin ³, Emanuele Bozzalla-Cassione ⁴, Chiara Cardamone ⁵, Cosimo Cigolini ⁶, Francesco Ferro ⁶, Tomas Fonseca ⁷, George E Fragoulis ⁸, Ilaria Galetti ⁹, Maria Gerosa ¹⁰, José Hernández-Rodríguez ¹¹, Marco Lanzillotta ¹², Diana Marinello ², Thierry Martin ¹³, Fernando Martinez-Valle ¹⁴, Maria Maślińska ¹⁵, Michele Moretti ², Marta Mosca ², Ulf Müller-Ladner ¹⁶, Cecilia Nalli ¹⁷, Giovanni Orsolini ¹⁸, Cristina Pamfil ¹⁹, Guillermo Perez-García ²⁰, Roberta Priori ²¹, Giacomo Quattrocchio ²², Andreas Ramming ²³, Francesca Regola ¹⁷, Vasco C Romão ²⁴, Augusto Silva ²⁵, Jan A M van Laar ²⁶, Maria Jose Vicente-Edo ²⁰, Shlomo Vinker ²⁷, Tobias Alexander ²⁸

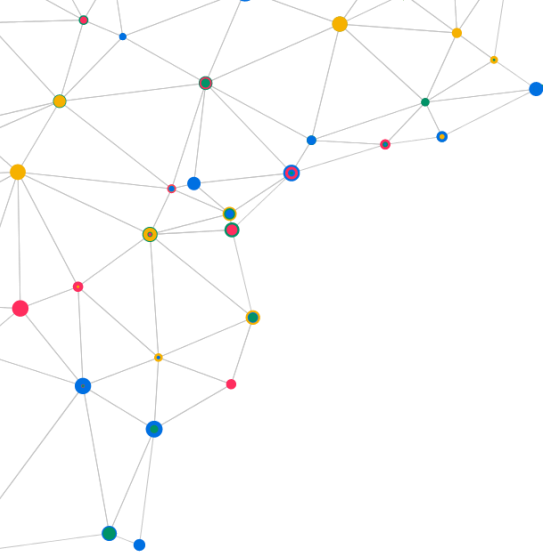
Affiliations + expand

PMID: 39486422 DOI: [10.1016/S2665-9913\(24\)00192-9](https://doi.org/10.1016/S2665-9913(24)00192-9)

Abstract

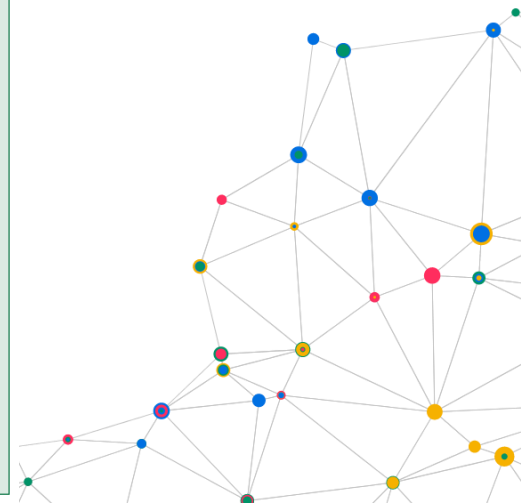
IgG4-related disease is a rare fibroinflammatory condition. Prompt recognition is fundamental to initiate treatment and to prevent organ damage. Diagnostic and classification criteria are primarily intended for use by clinicians with established expertise in IgG4-related disease. Absence of disease awareness among primary care physicians and specialists without expertise in IgG4-related disease remains the main cause of diagnostic delay. We aimed to identify red flags that might increase the suspicion of IgG4-related disease in primary and secondary care settings. A task force of experts in IgG4-related disease from the European Reference Network for Rare Connective Tissue Diseases (ERN-ReCONNET), patient representatives, and primary care physicians derived potential red flags for IgG4-related disease through a systematic literature search and a level of agreement exercise. Five red flags reached 100% agreement among experts: swelling in one or more organ system; pancreatic and





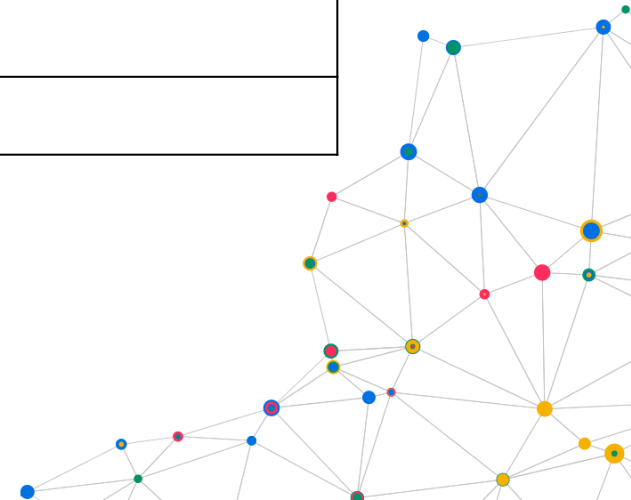
	Agreement on consideration as red flag*	Level of agreement†
Clinical history, signs, and symptoms		
Swelling in one or more organ system‡	100%	9-26
Pancreas and biliary tree involvement§	100%	8-78
Response to steroids	95-7%	8-13
Spontaneous improvement or resolution of masses	56-5%	6-24
Aged 60 years or older	52-2%	5-40
History of allergy or atopy	52-2%	4-59
Occupational exposure	0%	NA
History of autoimmune diseases	0%	NA
Male sex	0%	NA
Laboratory findings		
Increased serum IgG4 concentration	100%	9-14
Hypergammaglobulinemia	73-9%	6-55
Peripheral eosinophilia	65-2%	5-90
Hypocomplementemia	60-9%	6-11
Increased serum IgE concentration	52-2%	5-61
Increased serum IgG concentration	69-6%	6-19
Imaging findings		
Capsule-like rim surrounding the pancreas	95-7%	9-14
Band-like soft tissue (intrathoracic, perirenal, intrapelvic, periaortic, or periiliacal)	95-7%	8-45
Fibrotic thickening of organs	91-3%	7-82
Diffuse enlargement of organs	82-6%	8-15
Solitary mass	69-6%	6-14
Histopathological features		
IgG4+ plasma cell tissue infiltration	100%	9-30
Obliterative phlebitis	100%	8-74
Lymphoplasmocytic infiltration	95-7%	8-55
Fibrosis	91-3%	8-39
Tissue eosinophilia	82-6%	6-70
IgE+ mast cells	52-2%	5-88
*Agreement on consideration as red flag is expressed as mean percentage of positive answers. †Level of agreement is expressed as mean value of expert evaluation on a 0-10-point scale. ‡Consider typical organs, in which swelling should raise suspicion for IgG4-related disease: submandibular glands, parotid glands, thyroid, and lacrimal glands; the orbital and periorbital region; the pancreas and the biliary tract; the retroperitoneum and the kidneys. §Consider global or focal tumefaction of the pancreatic gland, thickening, stenosis, and dilatation of the biliary tract.		

Table 2: Red flags of IgG4-related disease

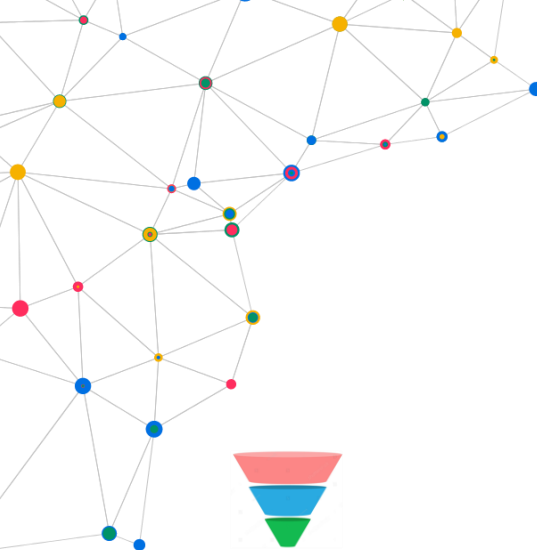


ERN ReCONNECT Red Flags ongoing

Disease	Status
IgG4-RD	Published
Idiopathic inflammatory myopathies	Almost completed
Antiphospholipid syndrome	Ongoing
Systemic sclerosis	Ongoing



ERN ReCONNET Red Flags Workflow



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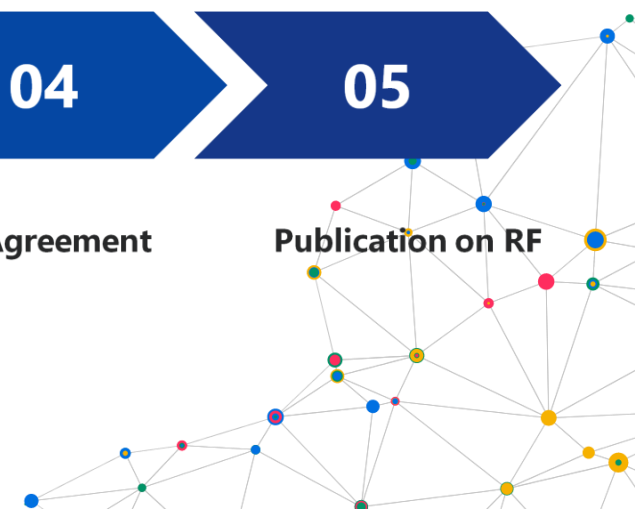
SLR

Expert Opinion

Proposal of RF

Agreement

Publication on RF



General considerations on Red Flags for RDs

- Early recognition is always important in RDs
- GPs are fundamental in the patients' care pathways of several RDs
- ERNs can make the difference in promoting early diagnosis and access to care



‘An impossibility is only a possibility you don't understand yet’

A boy called Christmas

