Sjögren's Disease: Diagnostic Pitfalls

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Disclosures

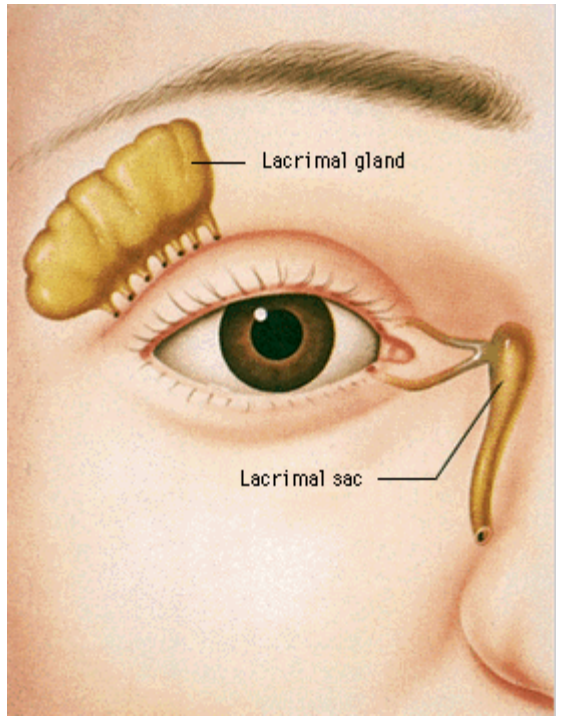
- Consultant: BMS, Novartis, Otsuka/Visterra, Amgen, Kiniksa, Target RWE, iCell
- Patents filed: Sara McCoy, Miriam Shelef, Michael Newton, Zihao Zheng. Novel Auto-Antibodies And Method To Detect Sjögren's Disease. PCT patent application PCT/US2023/071892 filed 8/9/2023

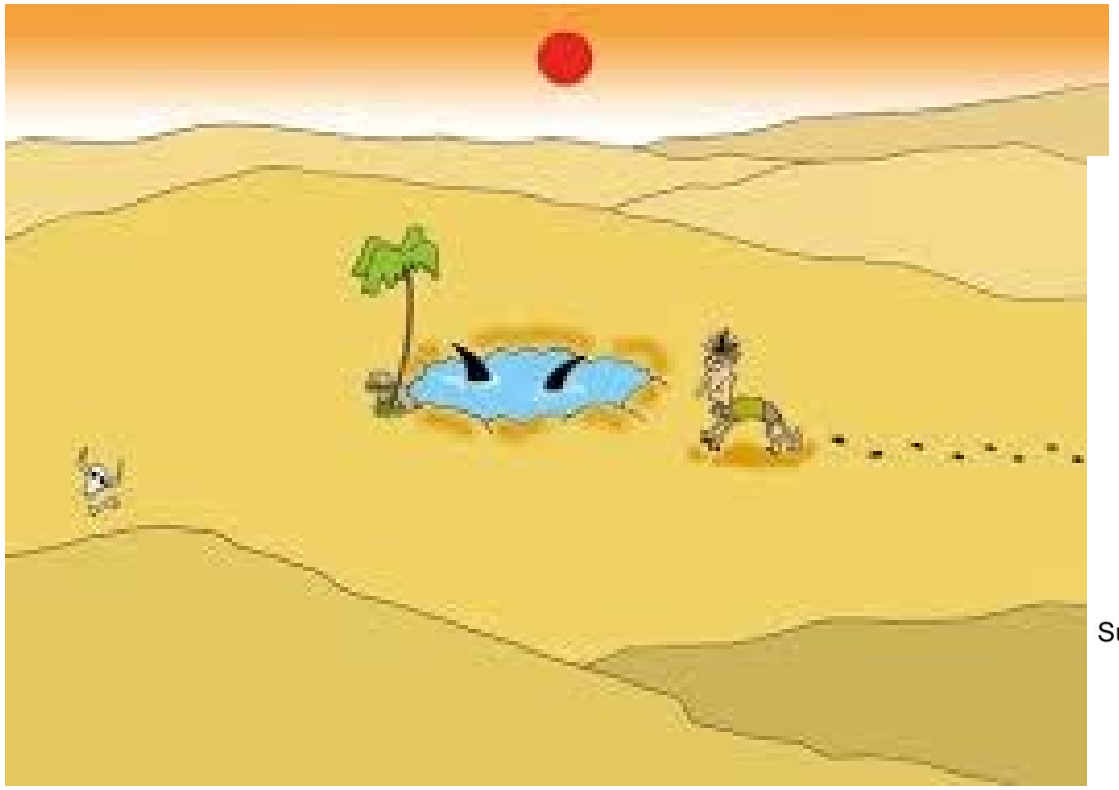
Outline

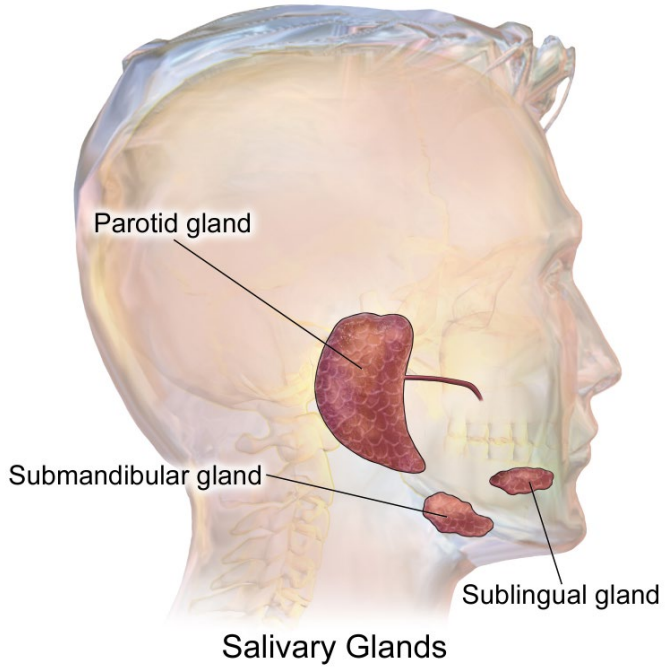
- Background
- Pathogenesis
- Diagnosis-past, present, and future
- Why diagnosis matters-inflection point is now

Sjögren's Disease: Overview

Chronic inflammation of the lacrimal & salivary glands→ eye & mouth dryness







Salivary Glands

Primary vs. Secondary

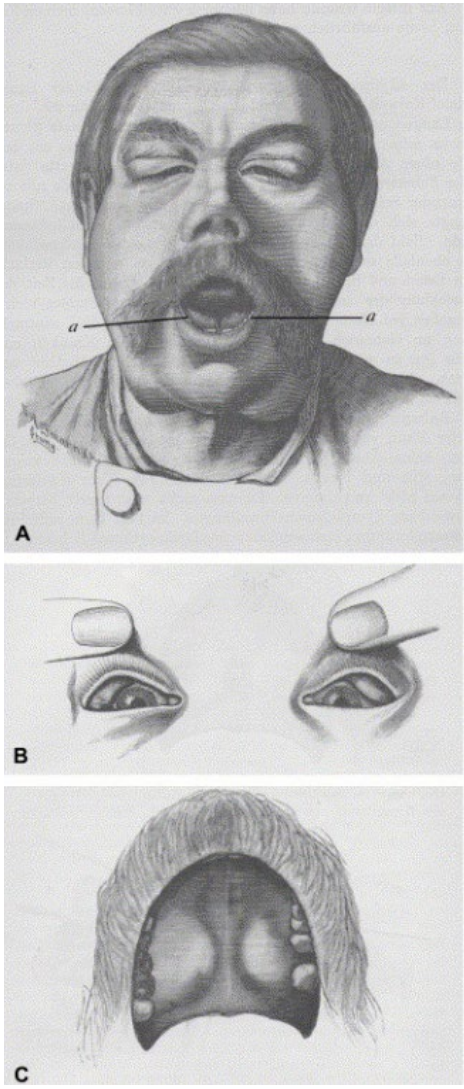
- Sjögren's disease
  - alone without another coexistent autoimmune disease

- ~~**Secondary**~~ **Overlap or Associated** Sjögren's disease
  - In presence of another autoimmune disease
  - Example: Rheumatoid arthritis, systemic lupus erythematosus

- Symptoms/diagnosis otherwise the same

History

- 1888: Dr. W.B. Hadden-London
  - 65 year old female with severe dry mouth
    - Tongue red "…dry and cracked in all directions like crocodile skin"
    - Unable to swallow
    - No tears to cry
    - Treated with pilocarpine
    - Coined "xerostomia"
- 1888:Dr. J Mukulicz-Koenigsberg
  - 42 year old farmer with painless symmetric swelling of lacrimal and salivary glands
    - Oral and ocular dryness
    - 1 year later died and autopsy showed swollen major salivary glands with inflammatory cell infiltrate
    - "Mukulicz syndrome"



Sarmiento-Monroy et al. 2013; Ihrler et al. 2005

History

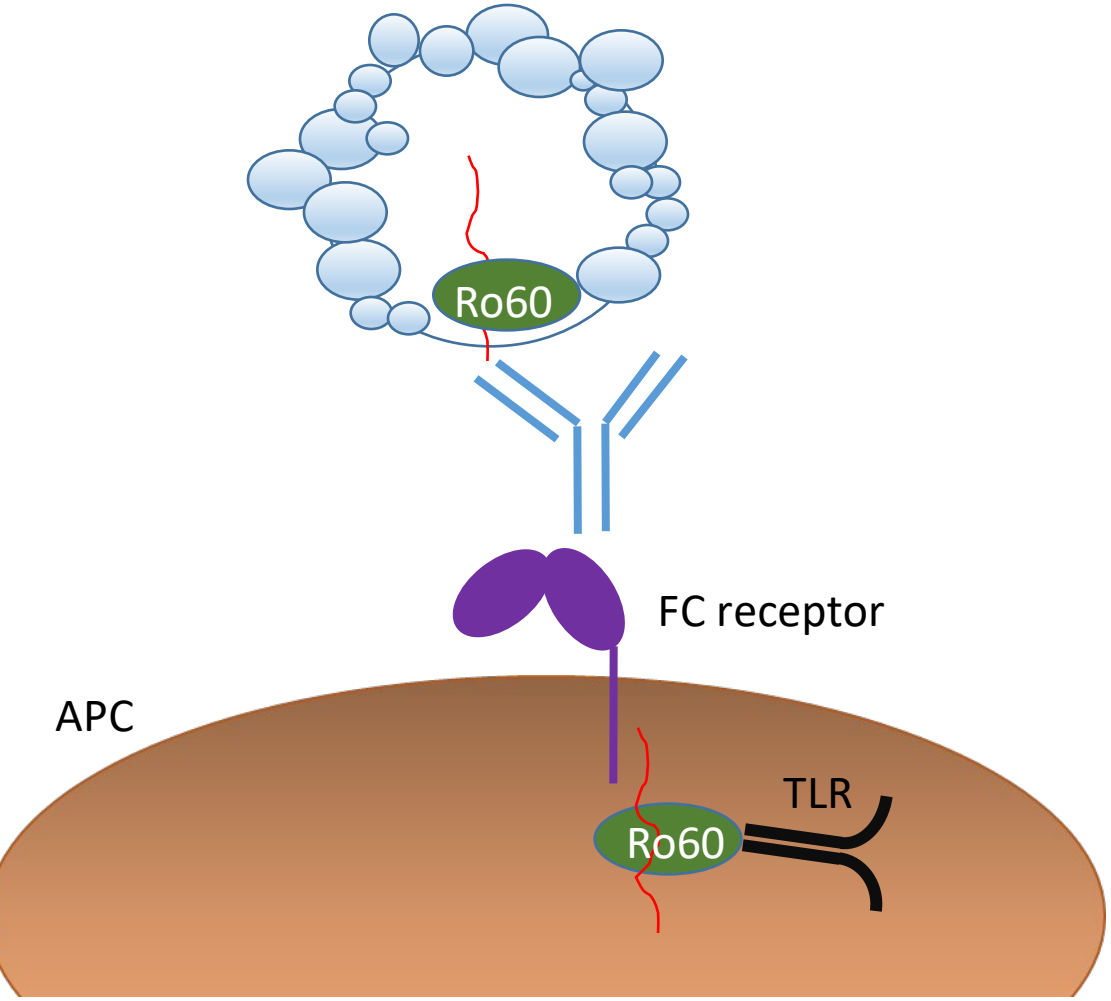
- 1933 Henrik Sjögren-Stockholm
- Described 19 women with dryness-13 had RA
- Dr. Marie Sjögren, ophthalmologist, worked as collaborator

Who Gets Sjögren's Disease?

- Women greater than men (9:1)
- Average onset 56
- Variable estimates of how prevalent: 0.04%→2%?
- Prevalence in older ~5-14%

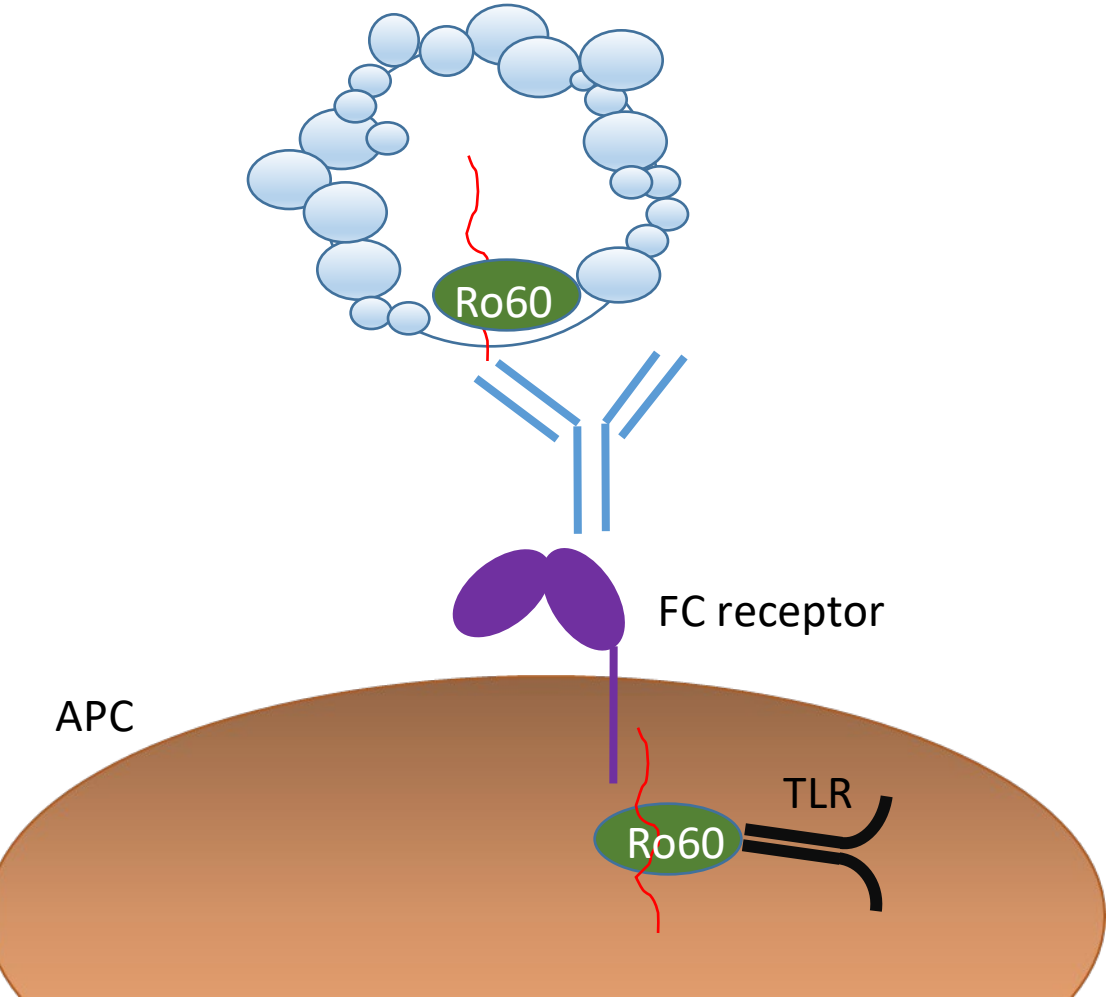
Qin B et al. 2015; Patel R et all.2014

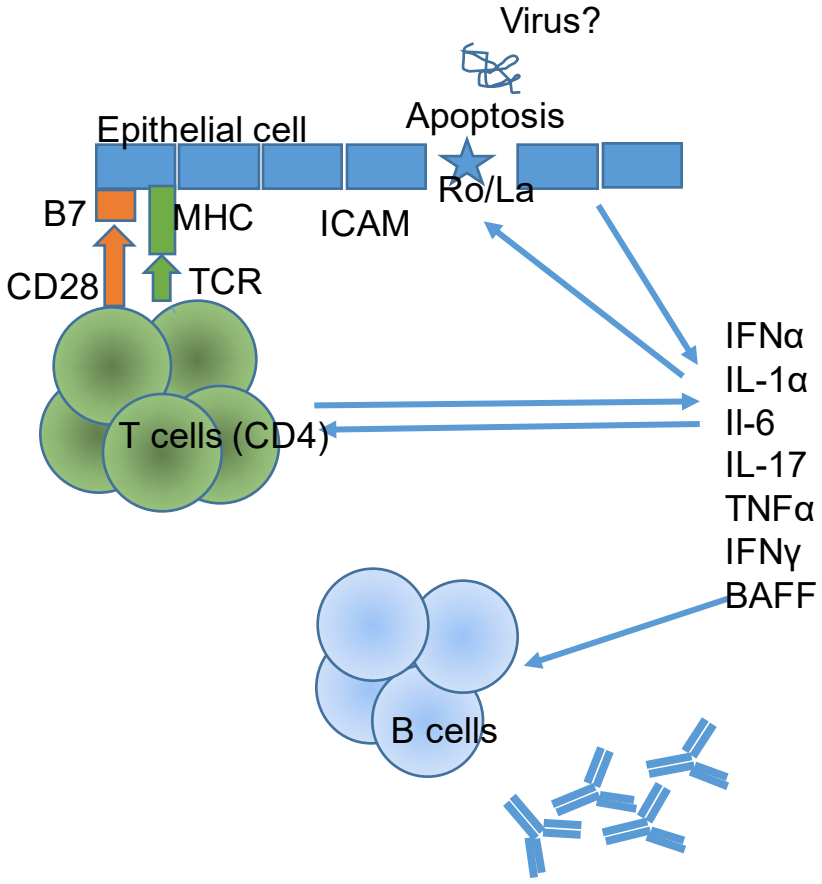
Pathogenesis of SjD



Anderson. Lancet. 1961; Yoshimi. Clinical and Developmental Immunology. 2012

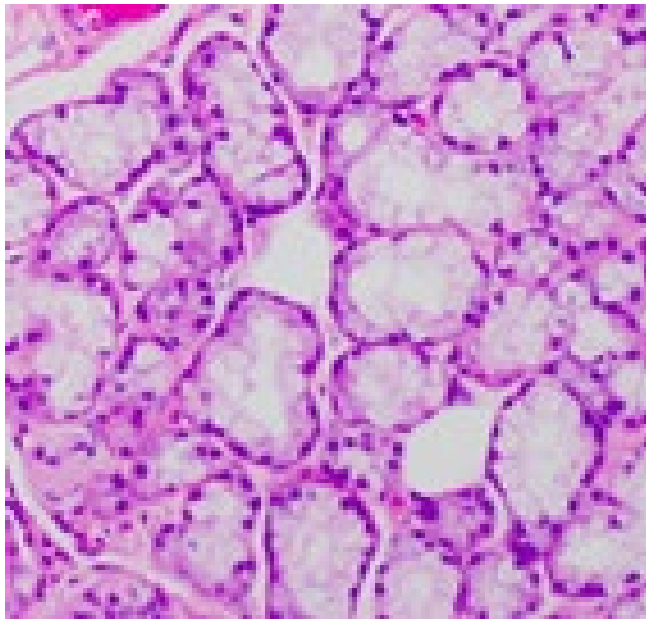
Pathogenesis of SjD

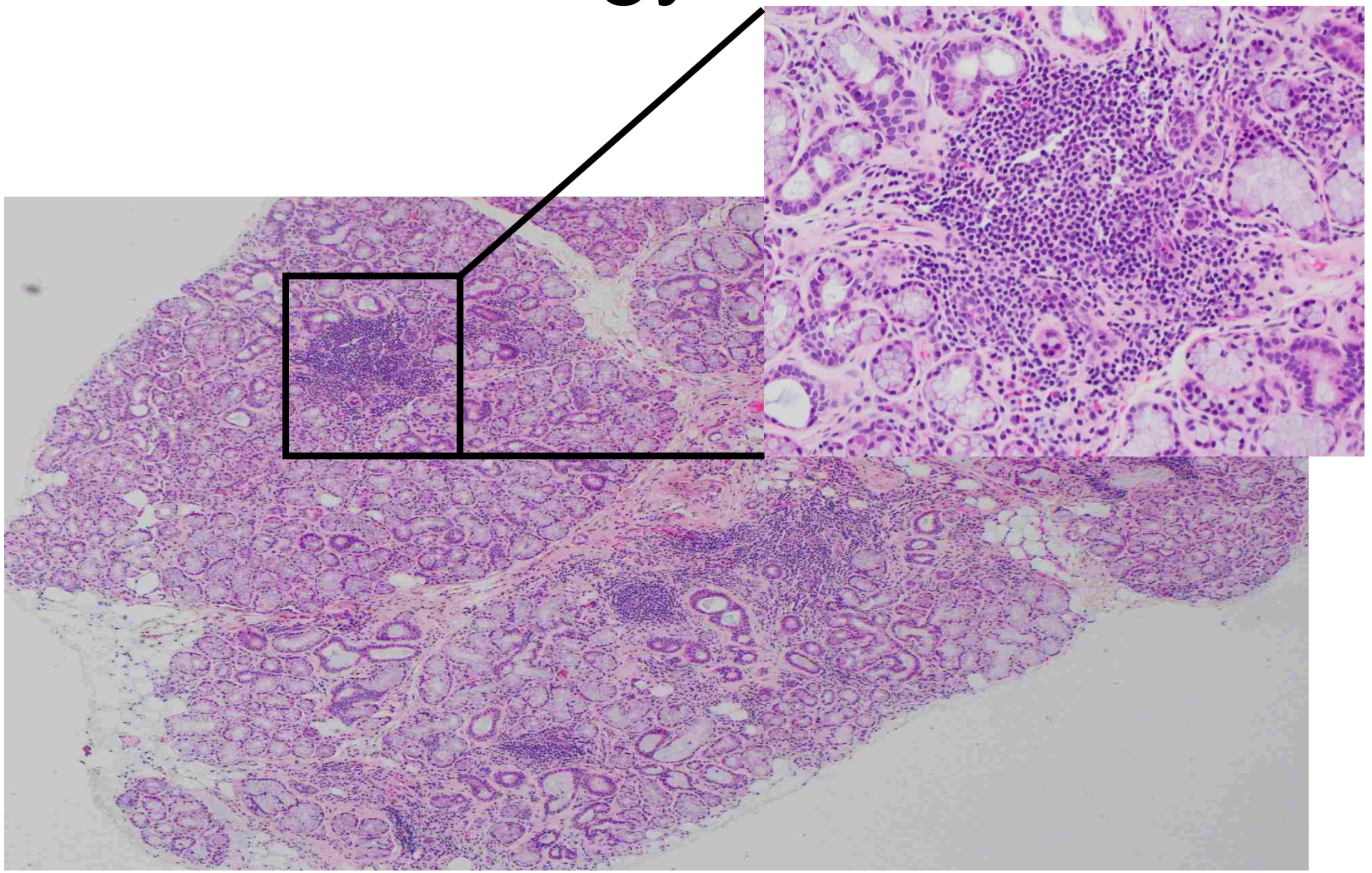




Anderson. Lancet. 1961; Yoshimi. Clinical and Developmental Immunology. 2012

Sjögren's Disease Histology





Normal Gland

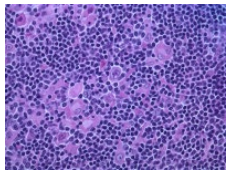
Sjögren's Gland

What are the end results?

Severe sicca symptoms/signs

- Dry mouth, eye, nasal, skin and vaginal dryness
- Salivary gland swelling
- Cavities
- Thrush
- Trouble eating, speaking, swallowing pills

Extraglandular Involvement (~1/2)

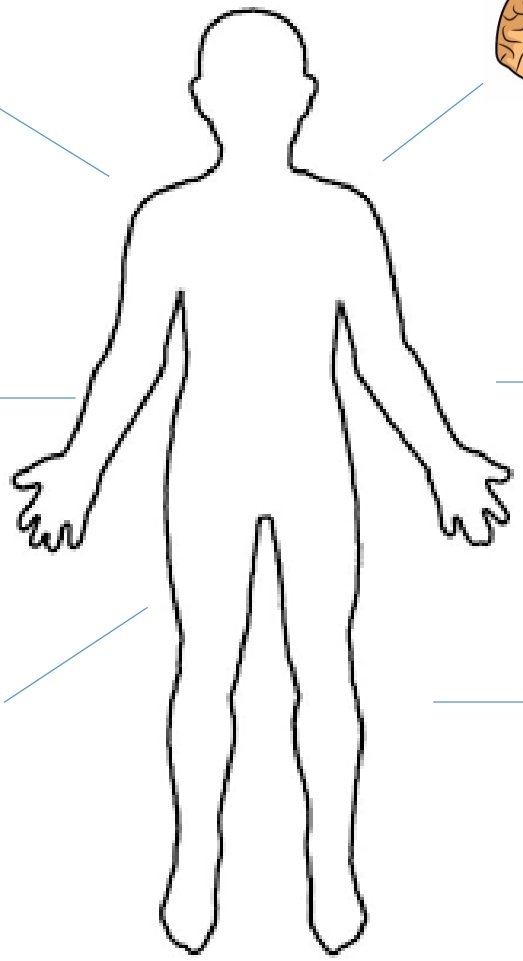


Blood counts/Cancer

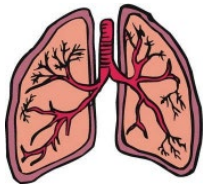
- Lymphoma ~ 15 fold increase

Gastrointestinal

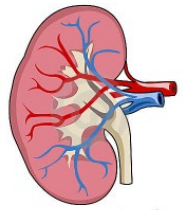
Joints



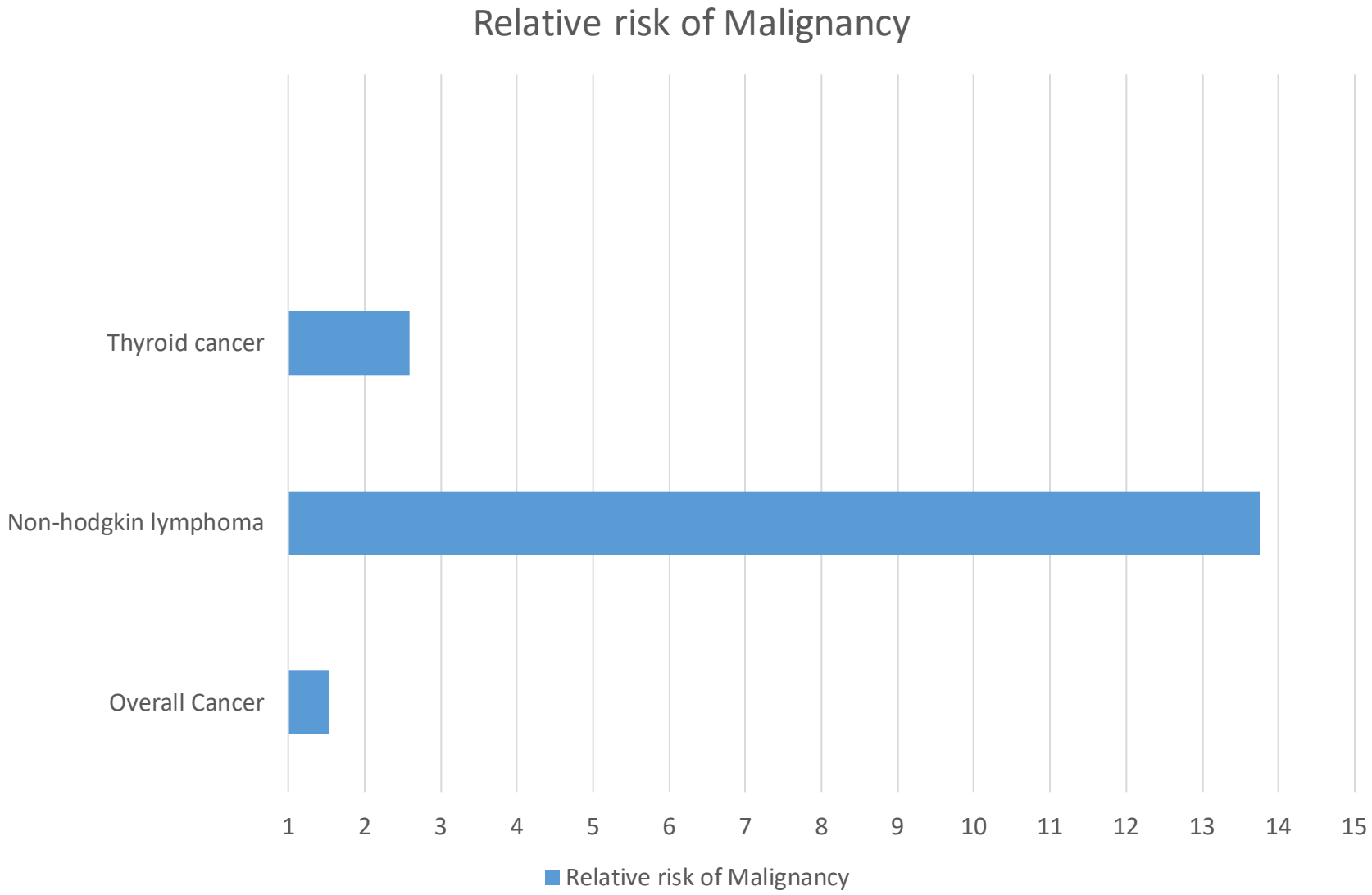
Nervous system



Lungs



Kidney



Ann Rheum Dis 2014;**73**:1151-1156. Rheumatology(Oxford) 2015

Although no overall increased risk in mortality…

Risk Factor	Relative Risk Mortality
Age	1.09
Male	2.18
Parotid Enlargement	1.81
Extraglandular involvement	1.77
Vasculitis	7.27
Anti SSB	1.45
Low C3	2.14
Low C4	3.08
Cryoglobulinemia	2.62

Singh et al. Rheumatology (Oxford). 2015

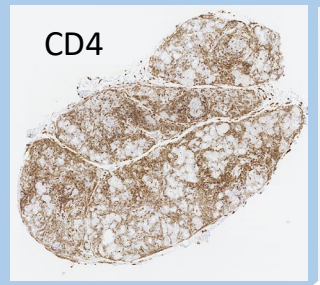
Diagnosis

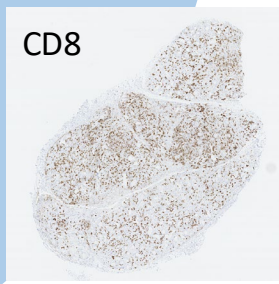
Causes of Dry Eye & Mouth

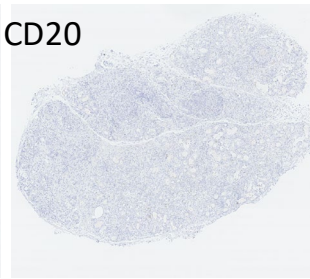
Dry Eye
- Blepharitis
- Allergic conjunctivitis
- Poor lid closure
- Lasik
- Contact lenses
- Ocular sensory loss/hyposecretion

- Age
- Smoking
- Medications
- Radiation
- Vitamin Def.
- DM2
- Sarcoidosis
- GVHD
- HIV/HCV
- **ICI**

Dry Mouth
- Mouth breathing
- Dental prostheses
- Parkinsons or Alzheimer's



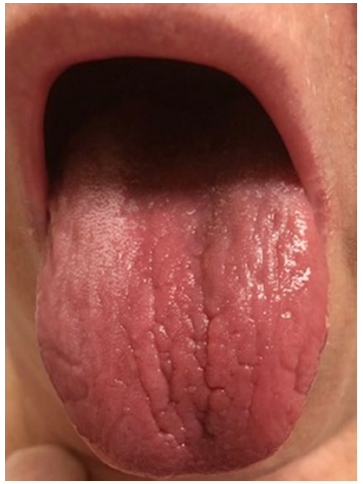




Cornec D et al., Clinic Rev Allerg Immunol. 2015; Baer AN et al. Rheum Dis Clin North Am. 2018; Tanasiewecz M et al., Adv Clin Exp Med. 2016; Warner et al. Oncologist. 2019. Images adapted from Dr. Alan Baer

History

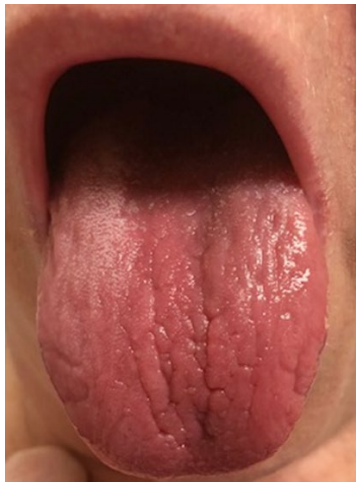
- **Recurrent** sensation of sand or gravel in the eyes
- **Daily**, persistent, troublesome dry eyes **> 3 months**
- Tear substitutes > **3 times a day**
- Dry mouth > **3 months**
- **Frequently** drink liquids to swallow dry food
- Recurrent/persistently swollen salivary glands
  - 98% specificity (sensitivity 36%)



Vitali C et al. Ann Rheum Dis 1994; Fox P J. Am Dent Assoc 1987

Oral Exam

- Rule out other causes
- Salivary pooling
- Dentition
- Glandular exam

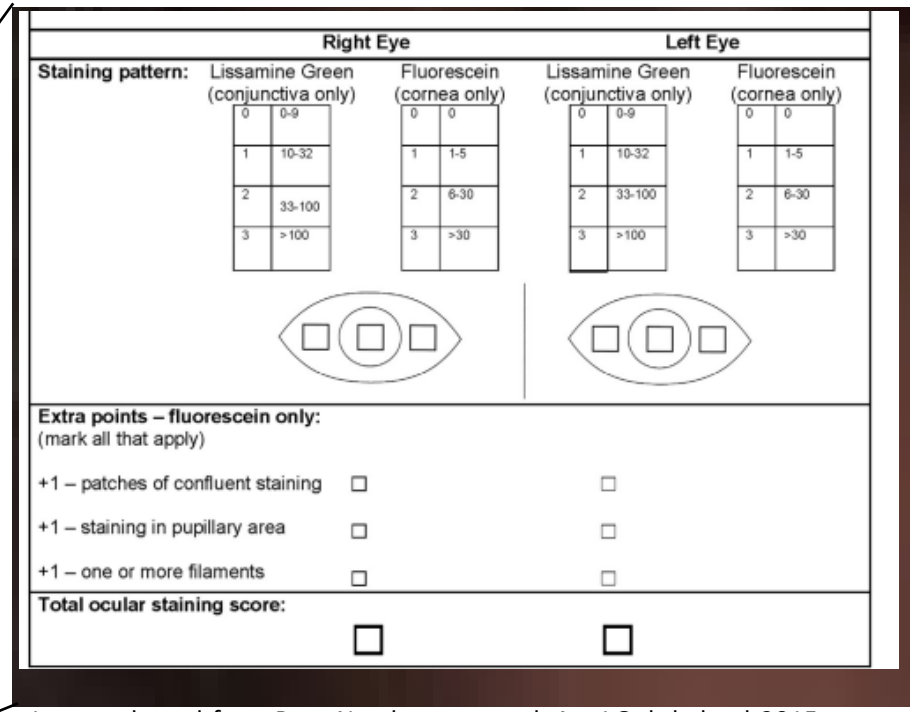



Oral Exam

- Unstimulated salivary flow
  - Weigh collection receptacle
  - Position/prepare patient
  - Collect in receptacle x 5 minutes
  - Weigh collection receptacle
  - 1 g = 1mL

Ocular Exam

- Rule out other causes
- Dry eyes
  - Schirmer's test
    - ≤5 mm/5 minutes
  - Ocular Staining Score
    - ≥ 5 in at least one eye



	Right Eye		Left Eye	
Staining pattern:	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)	Lissamine Green (conjunctiva only)	Fluorescein (cornea only)
	0 0-9 1 10-32 2 33-100 3 >100	0 0 1 1-5 2 6-30 3 >30	0 0-9 1 10-32 2 33-100 3 >100	0 0 1 1-5 2 6-30 3 >30
Extra points – fluorescein only: (mark all that apply)				
+1 – patches of confluent staining	☐		☐	
+1 – staining in pupillary area	☐		☐	
+1 – one or more filaments	☐		☐	
Total ocular staining score:	☐		☐	

Image adapted from Rose-Nussbaumer et al. Am J Ophthalmol 2015.

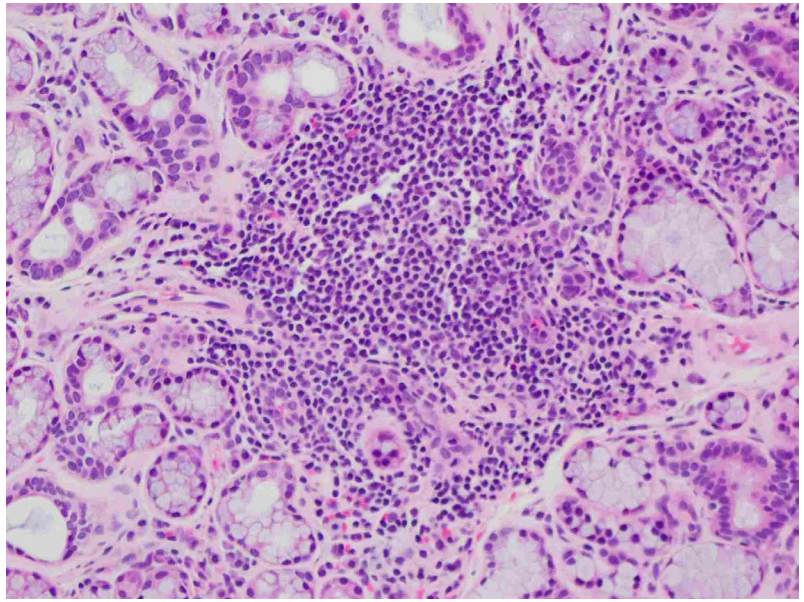
Diagnostic Tools-Labs

Lab	Prevalence
Anti-SSA Ab	60-80%
ANA*	60-85%
Rheumatoid Factor	50%
Anti-centromere	4-27%
Anti-CCP	7%
Anti-RNP	5%

*Anti-nuclear mitotic apparatus

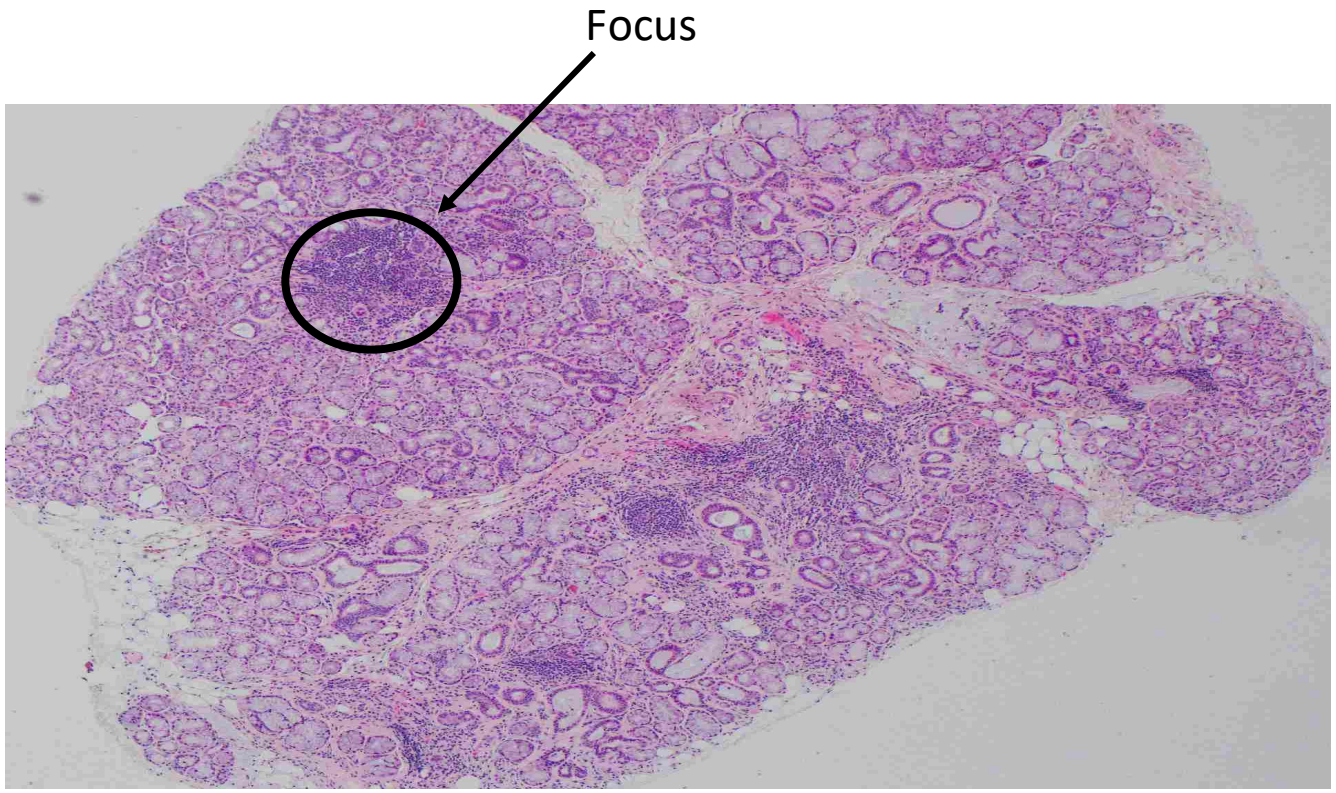
Mariette X et al. NEJM. 2018; Patel R et al. Clin Epidemiol. 2014; Kitagawa et al. 2012; Barcelos et al. Acta Rheumatol Port. 2009; Abbara RMD Open 2019; Arcani et al. Rheumatology (oxford). 2021

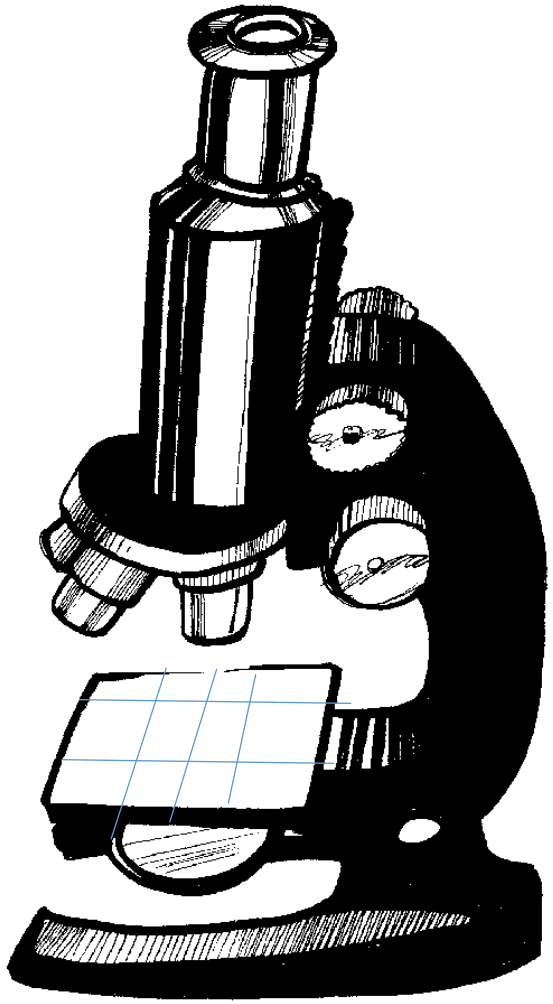
Diagnostic Tools-Biopsy



Focus Score

- Number of foci (50 lymphocytes) per 4 mm^2



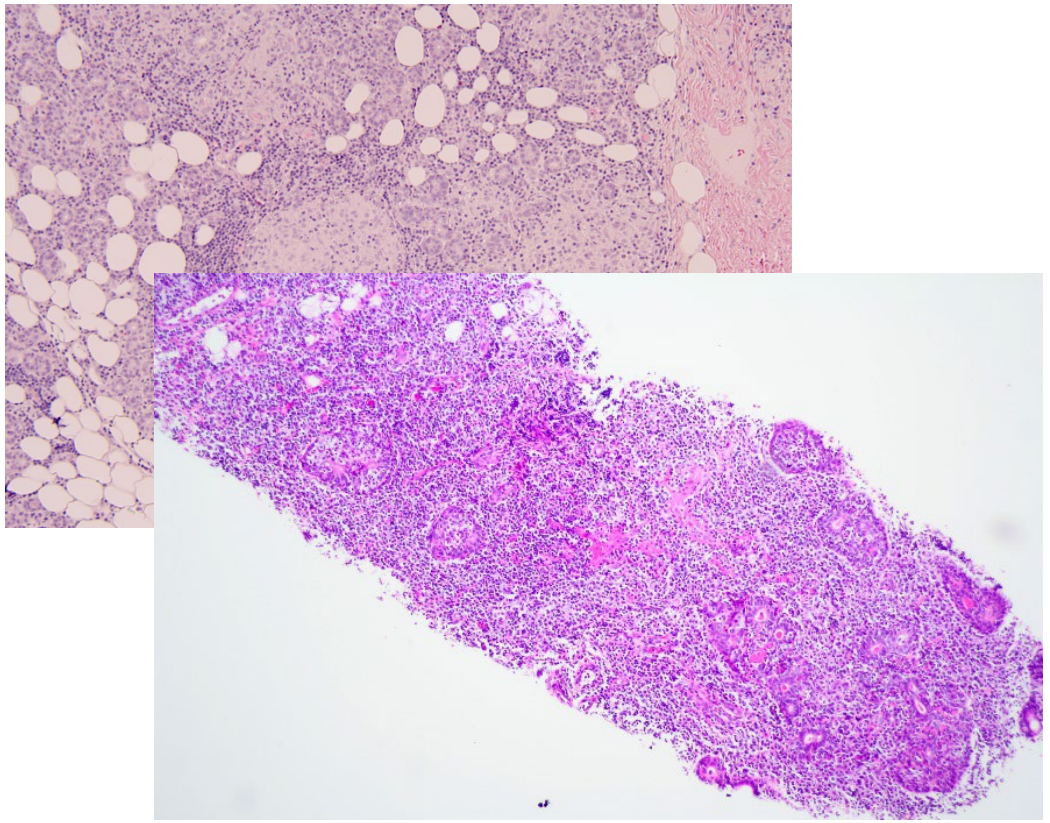


Focus score ≥ 1 foci/4mm^2 supports diagnosis

Diagnostic Tools-Biopsy

- Sarcoid
- Amyloid
- Hemochromatosis
- IgG4-related disease
- Lymphoma
- Benign lymphoepithelial lesion
    - MALT
    - CTD
    - Idiopathic

Prognostic value

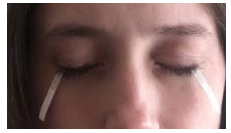


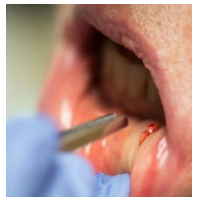
Hachulla et al. Arthritis Rheum 1993. Nessan et al., N Engl J Med 1979; Ward-Booth et al., Oral Surg Oral Med Oral Pathol 1981; Janin A et al., Clin Exp Rheumatol. 1992; Baer AN et al., Oral Surg Oral Med Oral Pathol 2013; Risselada AP et al., Ann Rheum Dis. 2014.

ACR/EULAR Classification Criteria

- Exclude head/neck radiation, Hep C, HIV/AIDS, sarcoid, amyloid, graft vs. host disease, IgG4
- Total score ≥ 4

Category	Score
Schirmer's test ≤5 mm/5 minutes	1
Ocular Staining Score ≥ 5 in at least one eye	1
Unstimulated whole salivary flow ≤0.1 ml/minute	1
Focus score ≥ 1	3
Ant-SSA (Ro) antibody	3



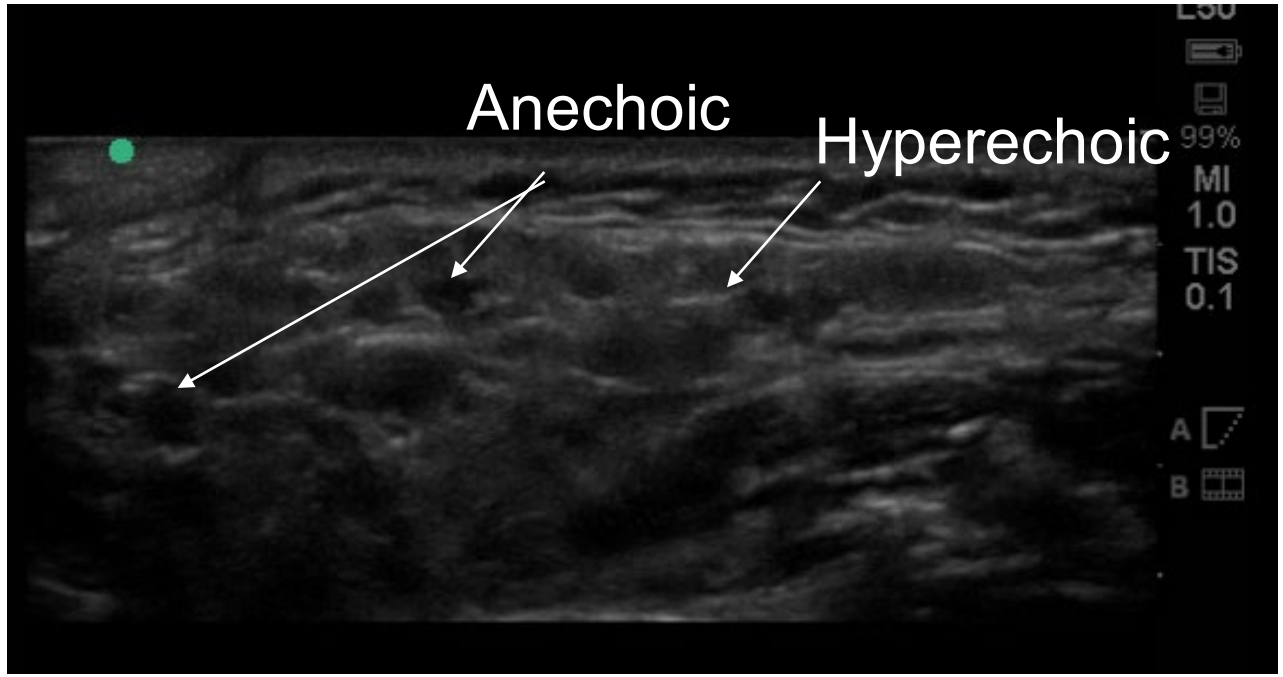


Criteria does not = diagnosis

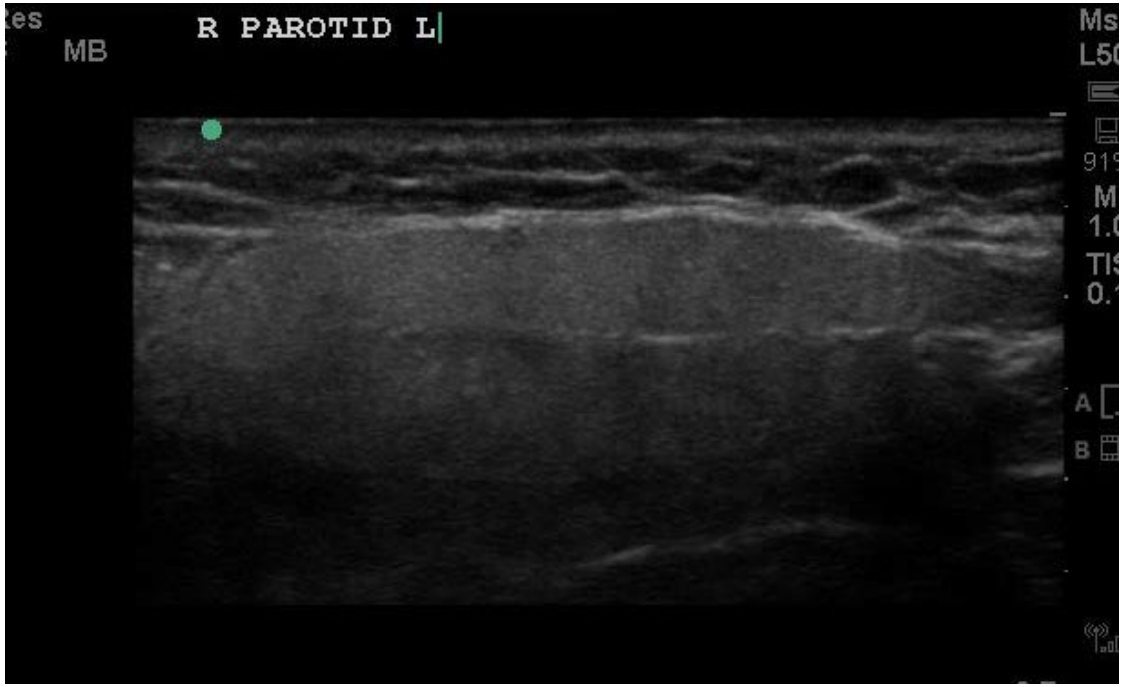
Shiboski C et al. Arthritis Rheumatol. 2017

What about new tools for diagnosis?

Diagnostic Tools-SGUS



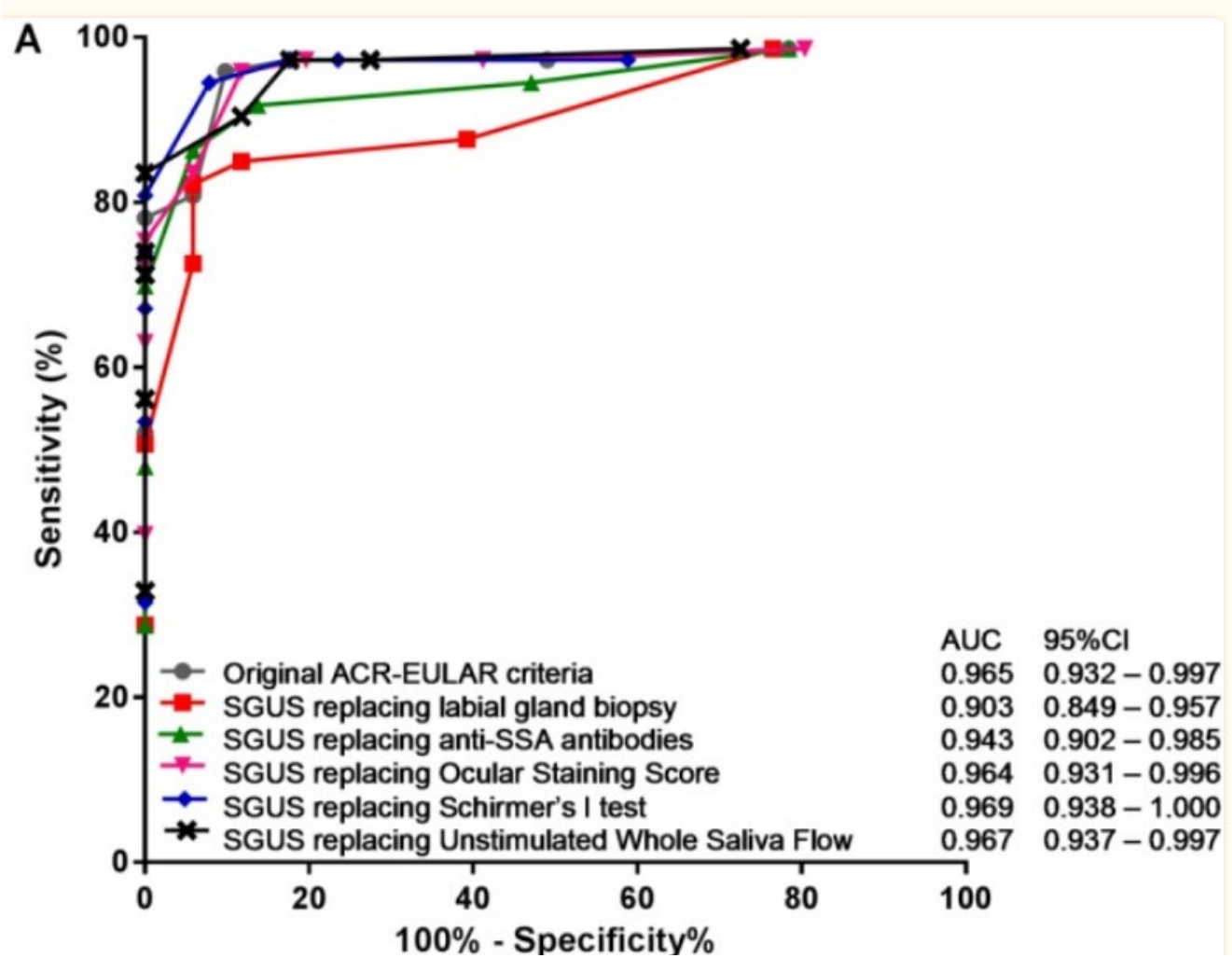
Sjögren's Disease parotid gland



Normal parotid gland

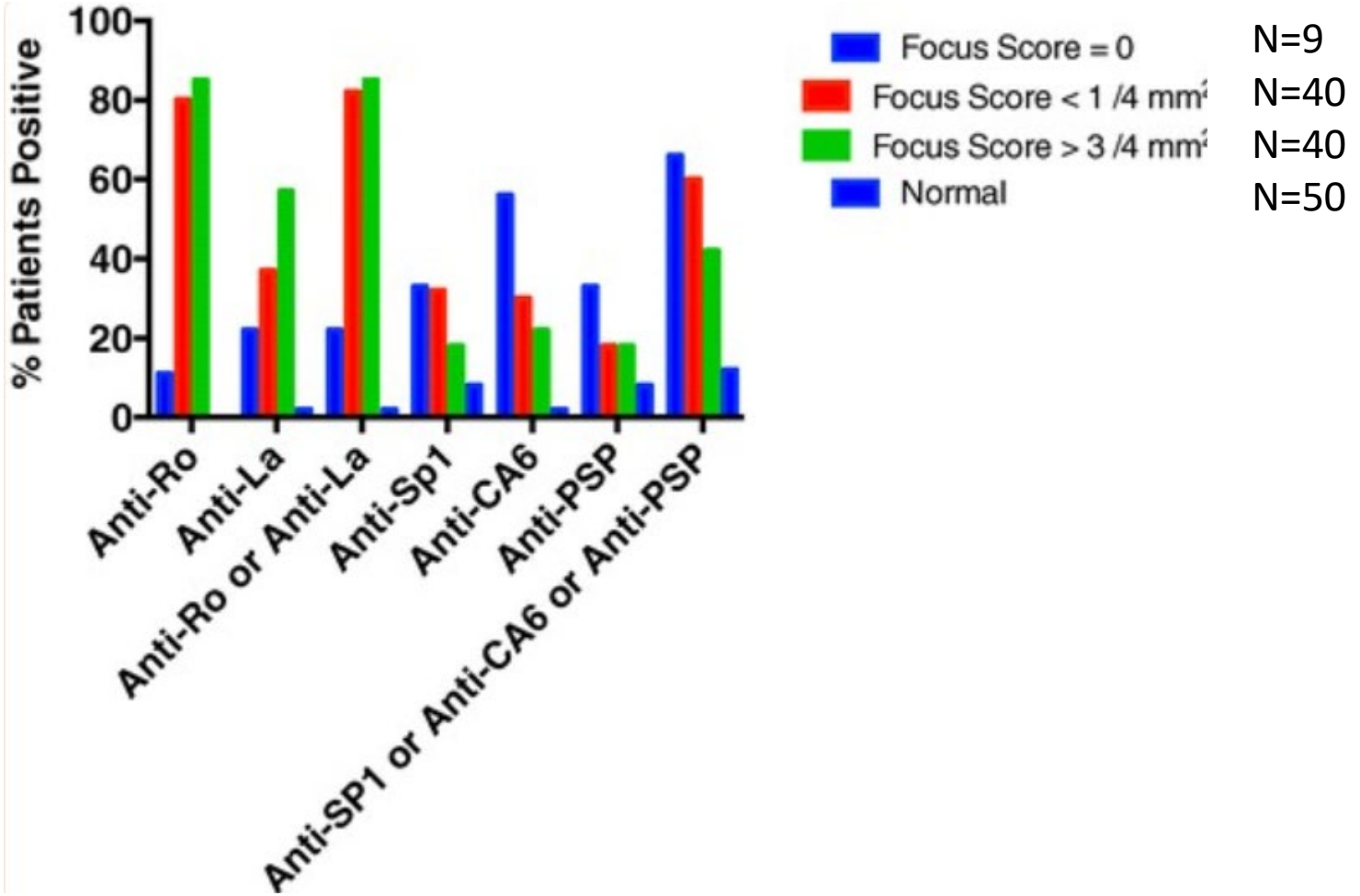
Cornec D et al. Arthritis Rheum 2013; Takagi Y et al. Plos One 2018, Mossel E Ann Rheum Dis. 2017; Nimwegen et al. Arthritis Care Res. 2020

Can SGUS replace parts of ACR-EULAR criteria?



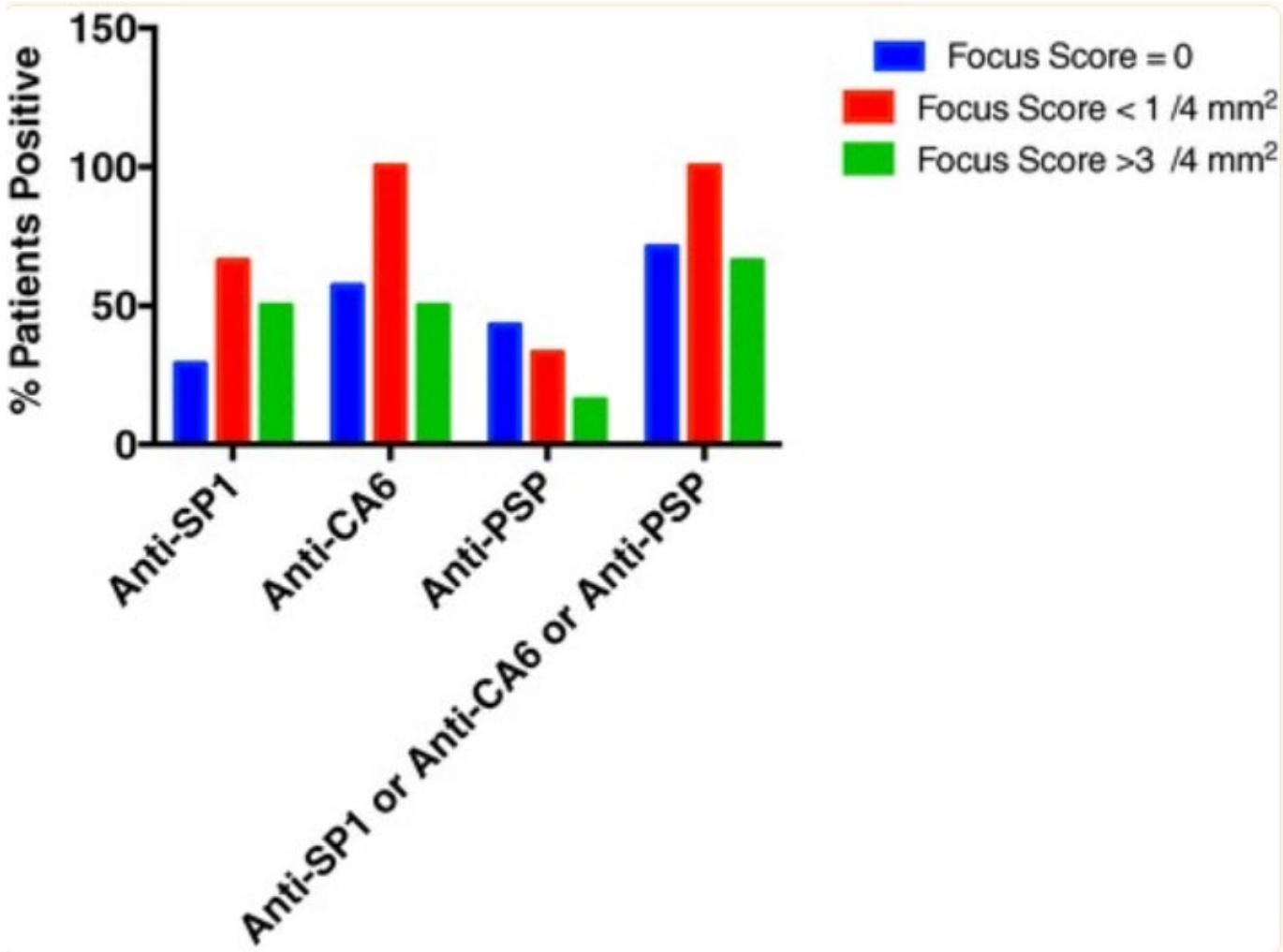
Van Nimwegen et al. Arthritis Care Res (Hoboken). 2020 Apr

SjD panel Sp1, CA6, & PSP: Caution



Suresh BMC Ophthalmol. 2015

Sp1, CA6, & PS no difference between bx+/-



N=7
N=3
N=6

Sp1, CA6, & PSP do not predict SjD among dry patients

N=9 SSA- SjD

	SS Dry Eye (n = 46)	Non-SS Dry Eye (n = 14)	Controls (n = 25)	*P* (SS vs. Non-SS Dry Eye)	*P* (Among 3 Groups)
Traditional antibodies*	37 (80.4%)	0	0	**<0.001**	**<0.001**
Anti-SSA	37 (80.4%)	0	0	**<0.001**	**<0.001**
Anti-SSB	23 (50.0%)	0	0	**0.001**	**<0.001**
RF and ANA ≥1:320	25 (54.3%)	0	0	**<0.001**	**<0.001**
Novel antibodies†	28 (60.9%)	7 (50.0%)	4 (16.0%)	0.47	**0.001**
Anti-SP1	6 (13.0%)	2 (14.3%)	2 (8.0%)	0.91	0.78
Anti-CA6	24 (52.2%)	6 (42.9%)	2 (8.0%)	0.54	**0.001**
Anti-PSP	5 (10.9%)	2 (14.3%)	0	0.73	0.19

Results are represented as the number of patients who tested positive (percentage). The χ^2 test was used for comparison between groups.
Bolded values represent $P < 0.05$.
*Anti-SSA and/or anti-SSB and/or combination of RF and ANA ≥1:320.
†Anti-SP1 and/or anti-CA6 and/or anti-PSP.

Comparison of Serologic Profile of Subjects According to Study Groups

Karakus et al. Cornea. 2018

Sp1, CA6, & PSP: no association between positive biopsy & antibodies

N=9 SSA- SjD

	Biopsy Positive (n = 17)	Biopsy Negative (n = 19)	*P*
Traditional antibodies*	9 (52.9%)	5 (26.3%)	0.1
Anti-SSA	9 (52.9%)	5 (26.3%)	0.1
Anti-SSB	8 (47.1%)	2 (10.5%)	**0.02**
RF	9 (52.9%)	5 (26.3%)	0.1
ANA ≥1:320	12 (70.6%)	3 (15.8%)	**0.001**
RF and ANA ≥1:320	8 (47.1%)	1 (5.3%)	**0.006**
Novel antibodies†	12 (70.6%)	8 (42.1%)	0.09
Anti-SP1	3 (17.6%)	2 (10.5%)	0.65
Anti-CA6	9 (52.9%)	7 (36.8%)	0.33
Anti-PSP	4 (23.5%)	2 (10.5%)	0.39

Results are represented as the number of patients who tested positive (percentage). The χ^2 test was used for comparison between groups.
Bolded values represent $P < 0.05$.
*Anti-SSA and/or anti-SSB and/or combination of RF and ANA ≥1:320.
†Anti-SP1 and/or anti-CA6 and/or anti-PSP.

parison of Serologic Profile of Dry Eye Patients with Positive Minor Salivary Gland Biopsy versus Dry Eye Patients Negative Biopsy

Karakus et al. Cornea. 2018;

Sp1, CA6, & PSP shouldn't be used for SSA-SjD diagnosis

Antibody Test	No Sjögren's syndrome* (Non-SS) (N=129)	Sjögren's syndrome** (SS) (N=81)	Fisher's exact P-value
Novel autoantibodies:			
Salivary protein 1 (SP-1)			
IgG (≥20 EU/ml)	6 (4.7%)	6 (7.4%)	0.54
IgA (≥20 EU/ml)	4 (3.1%)	3 (3.7%)	1.00
IgM (≥20 EU/ml)	6 (5%)	11 (14%)	0.03
Any positive	16 (12.4%)	17 (21.0%)	0.12
Carbonic Anhydrase 6 (CA-6)			
IgG (≥20 EU/ml)	8 (6.2%)	5 (6.2%)	1.00
IgA (≥20 EU/ml)	9 (7.0%)	1 (1.2%)	0.09
IgM (≥20 EU/ml)	12 (9.3%)	7 (8.6%)	1.00
Any positive	26 (20%)	12 (15%)	0.36
Parotid specific protein (PSP)			
IgG (≥20 EU/ml)	6 (4.7%)	5 (6.2%)	0.75
IgA (≥20 EU/ml)	14 (10.9%)	17 (21.0%)	0.048
IgM (≥20 EU/ml)	11 (8.5%)	9 (11.1%)	0.63
Any positive	27 (21%)	28 (35%)	0.04

N=6 seronegative

Bunya et al. Cornea. 2018

We should not use these antibodies…

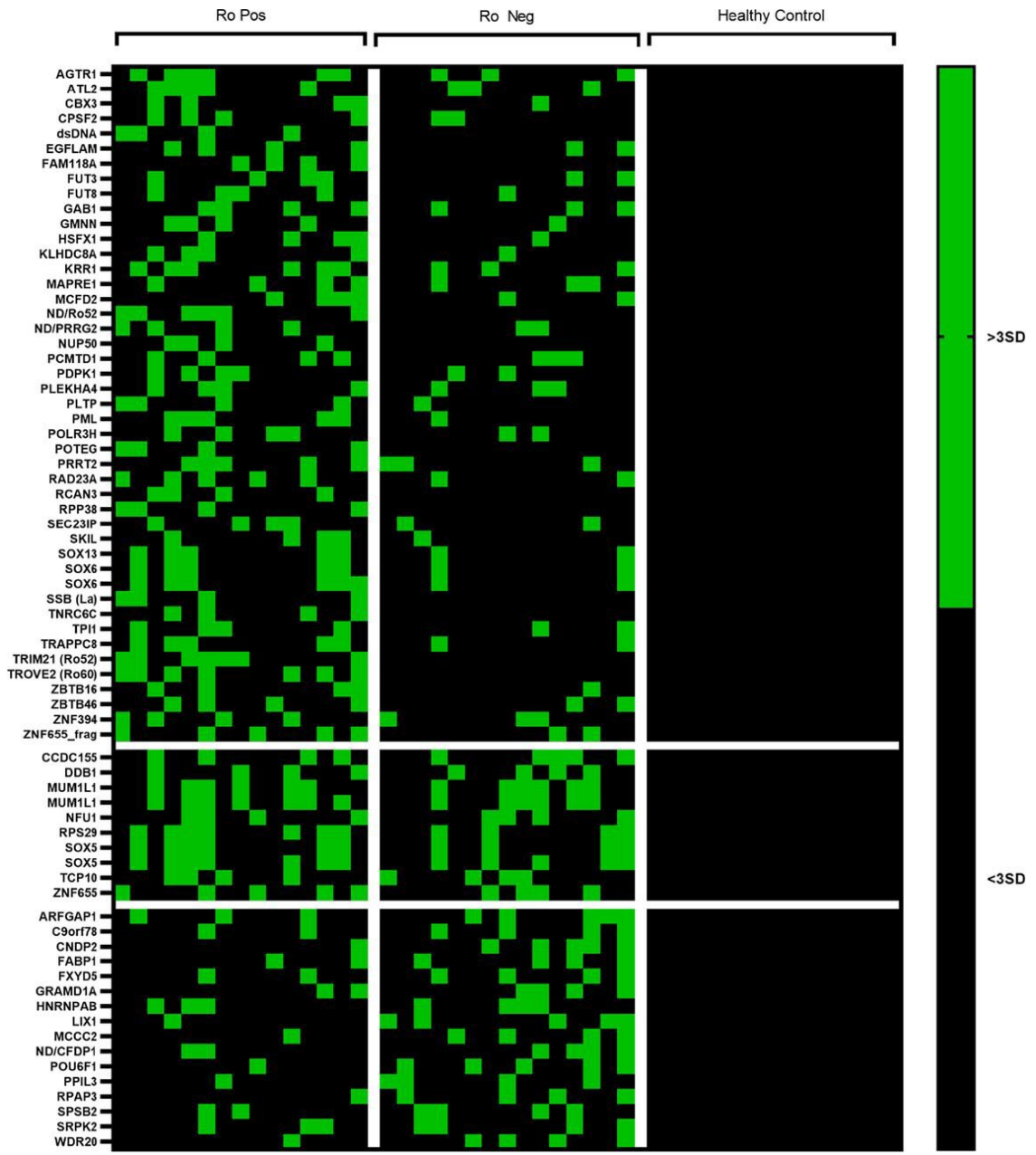
Work continues to address the clinical need

New autoantibodies-Proteome

- case-control study of SjD, healthy (HC) and other disease (OD) controls.
- A discovery dataset of plasma samples (n=30 SjD, n=15 HC) on human proteome of19 500 proteins.
- Validation dataset of from additional SjD cases (n=46 anti-Ro^{+}, n=50 anti-Ro^{-})

Longobardi et al. Ann Rheum Dis. 2023

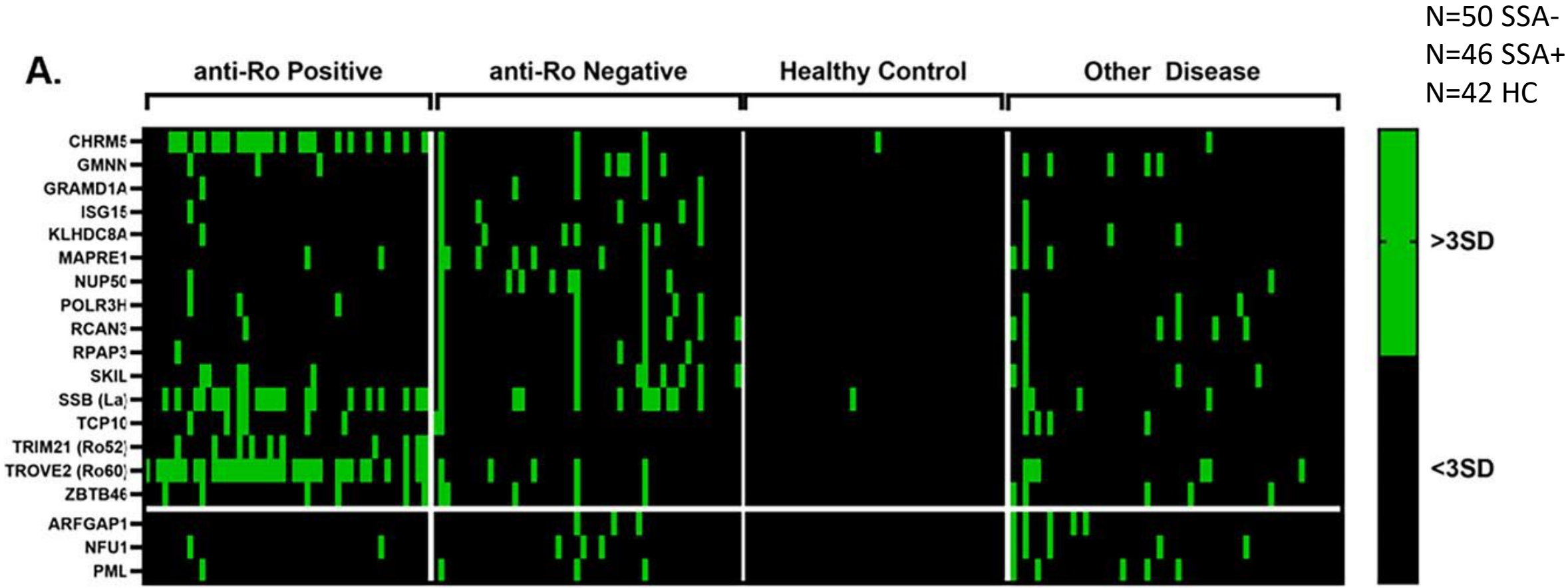
Whole human proteome: New antibodies in Ro positive & Ro negative



N=15 SSA-
N=15 SSA+

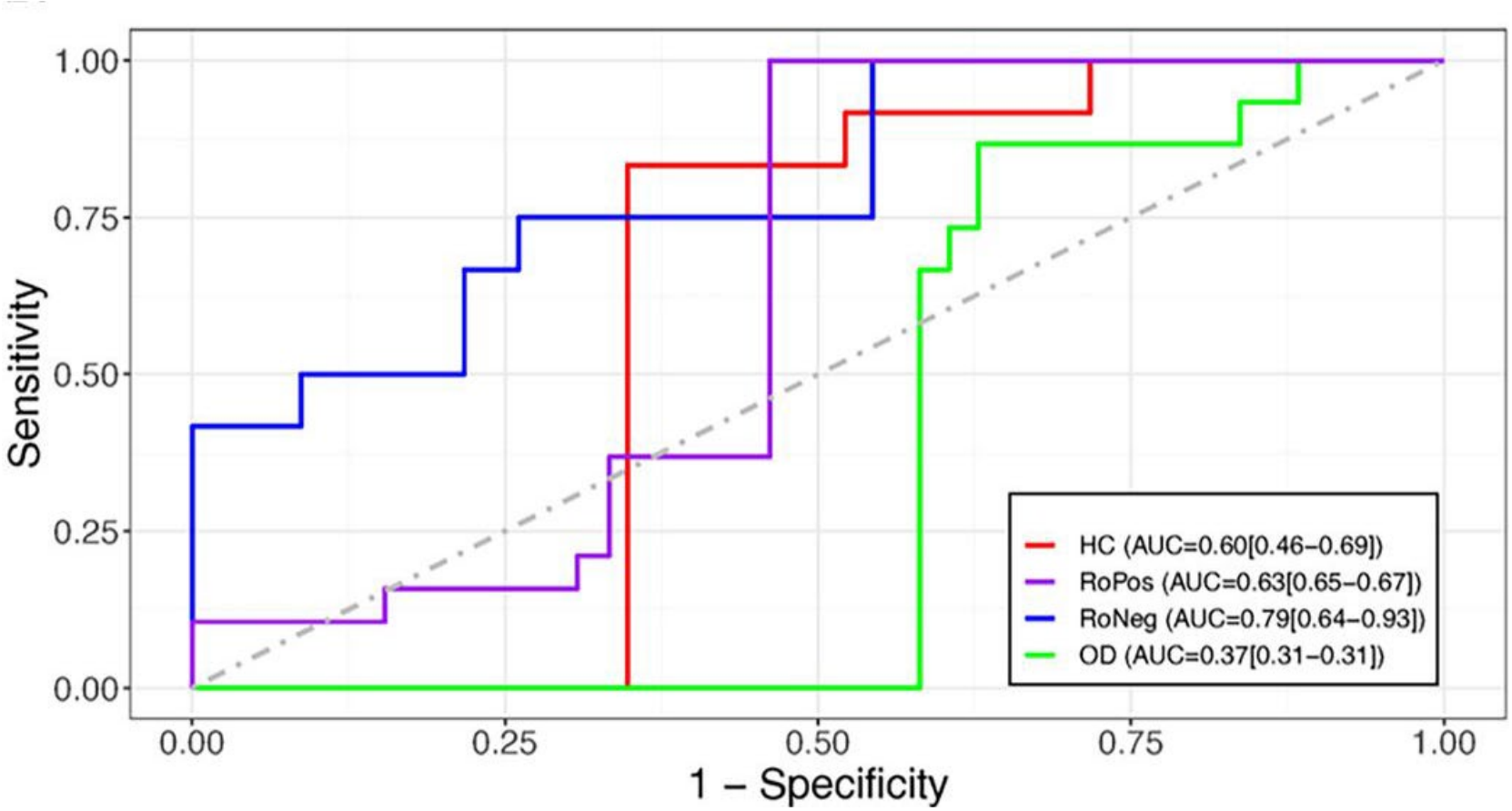
Longobardi et al. Ann Rheum Dis. 2023

Validation set identifies 16 new specificities

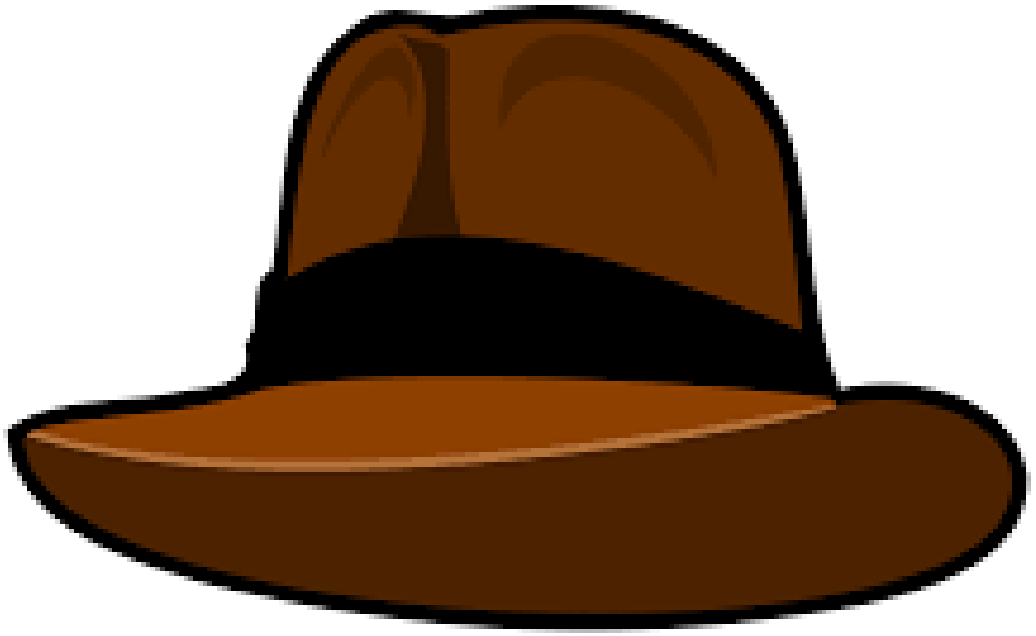


Longobardi et al. Ann Rheum Dis. 2023

A model of a 12-antigen panel has good predictive ability for SSA- SjD



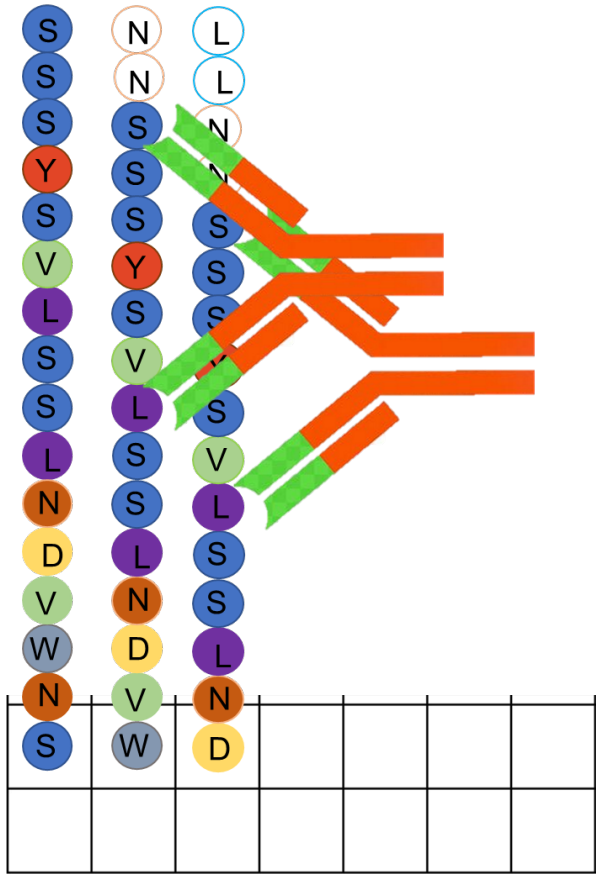
Longobardi et al. Ann Rheum Dis. 2023



Methods

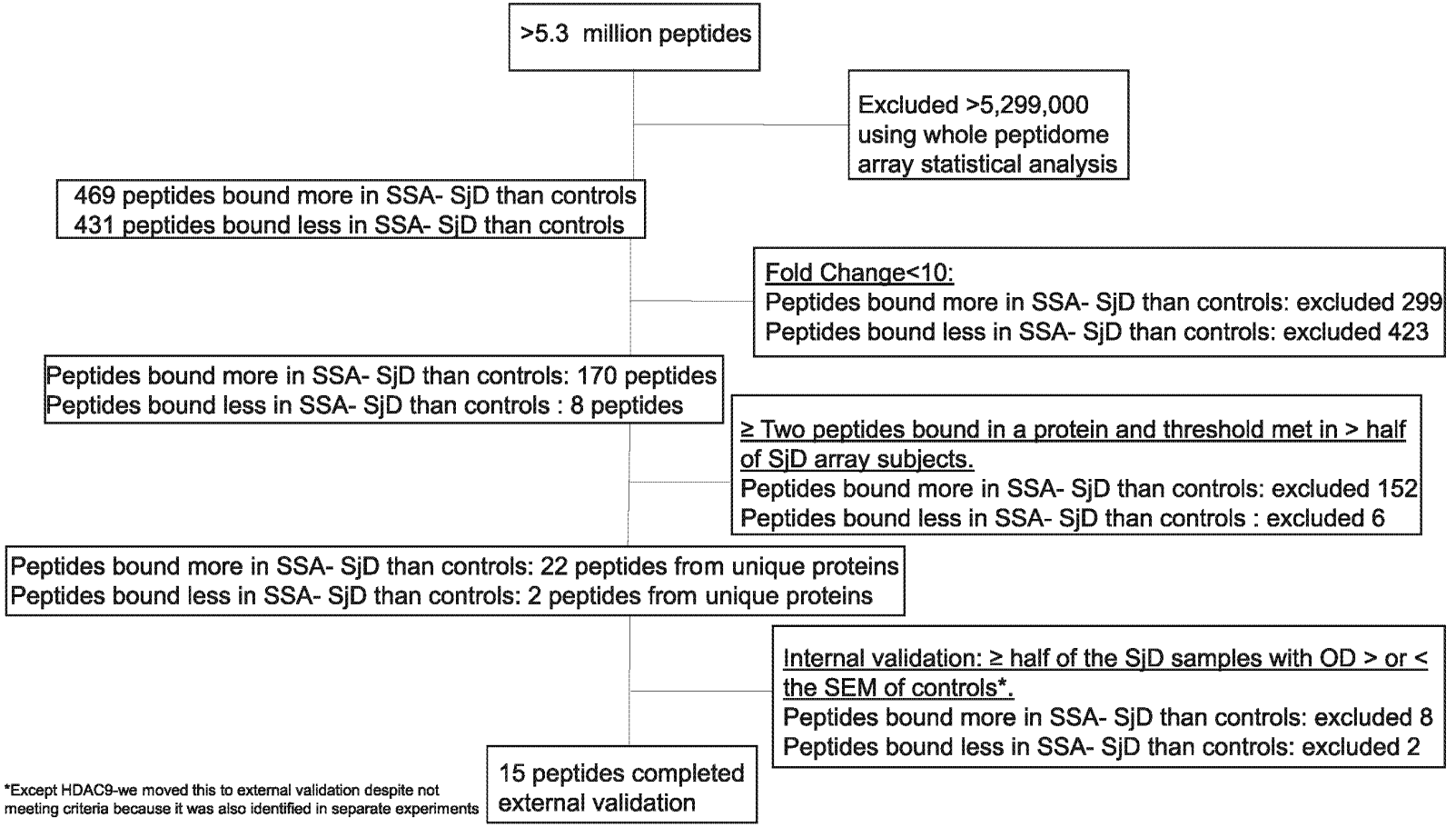
- Initial identification
  - Whole peptidome array
  - MixTwice analysis
- Confirmation
  - ELISA
    - N=76 SSA- SjD
    - N=76 SSA+ SjD
    - N=75 Sicca controls
    - N=38 Autoimmoimmune controls

Combined controls

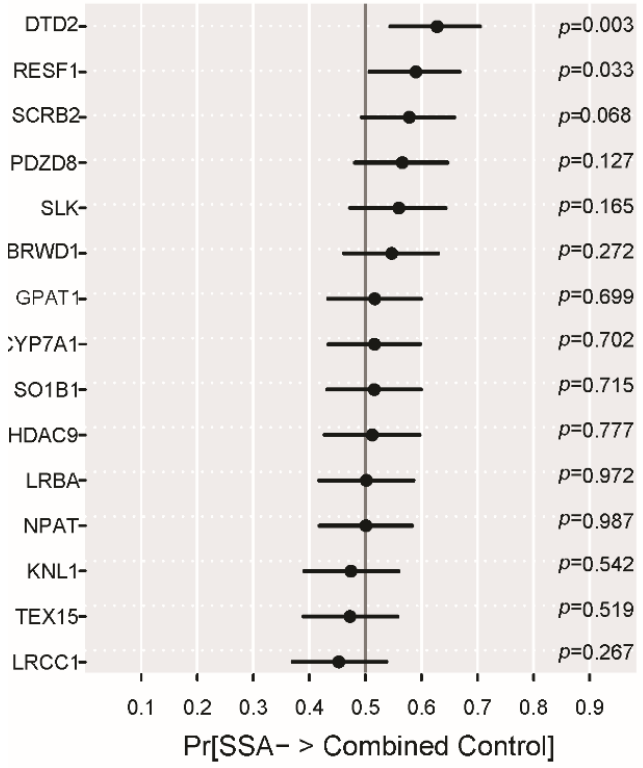


Zheng et al. Bioinformatics 2021.

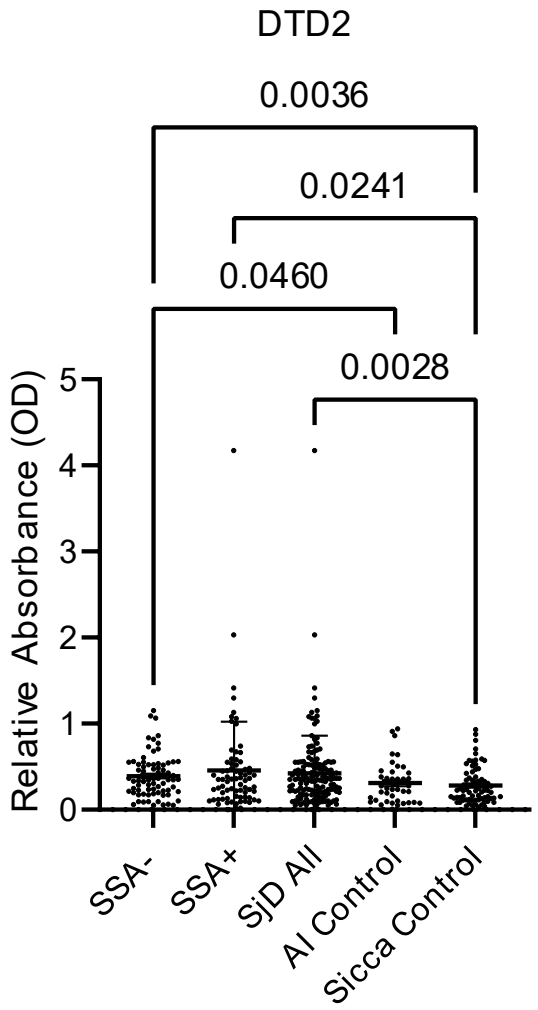
Consort Flow For Peptide Selection-15 peptides selected for external validation



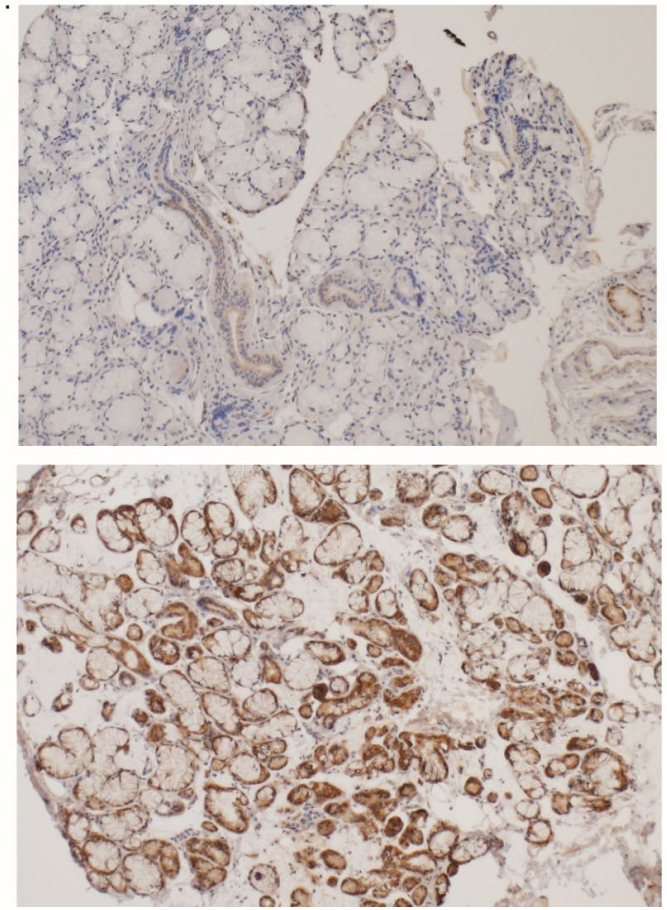
Antibodies to D-aminoacyl-tRNA deacylase 2 higher in SSA- SjD than controls

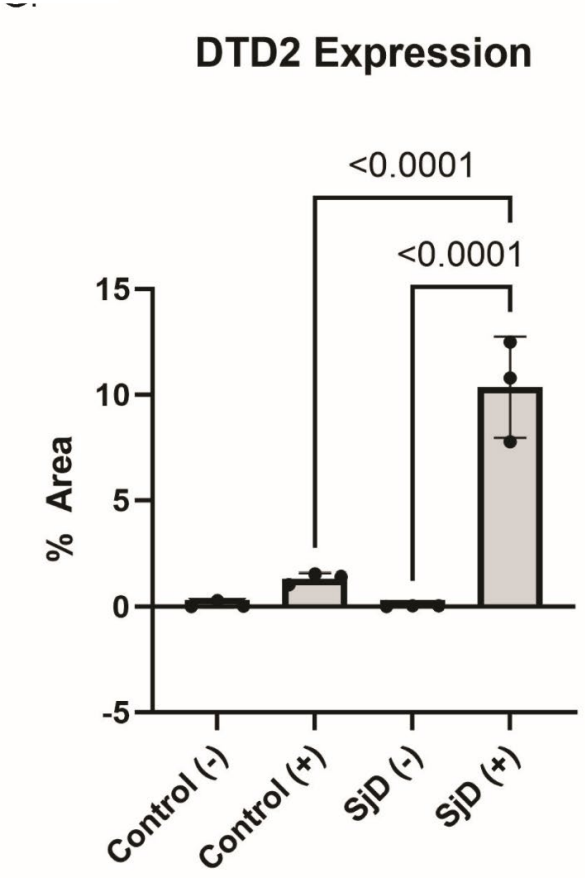


FDR SjD vs. Combined Controls		
Protein	1-sided p	1-sided q
DTD2	0.001	0.021
RESF1	0.017	0.124
SCRB2	0.034	0.172
PDZD8	0.063	0.238
SLK	0.083	0.248
BRWD1	0.136	0.341
CYP7A1	0.352	0.584
SO1B1	0.358	0.584
HDAC9	0.389	0.584
GPAT1	0.35	0.584
LRBA	0.486	0.618
NPAT	0.494	0.618
KNL1	0.73	0.794
TEX15	0.741	0.794
LRCC1	0.867	0.867



DTD2 is increased in SSA- SjD SG tissue





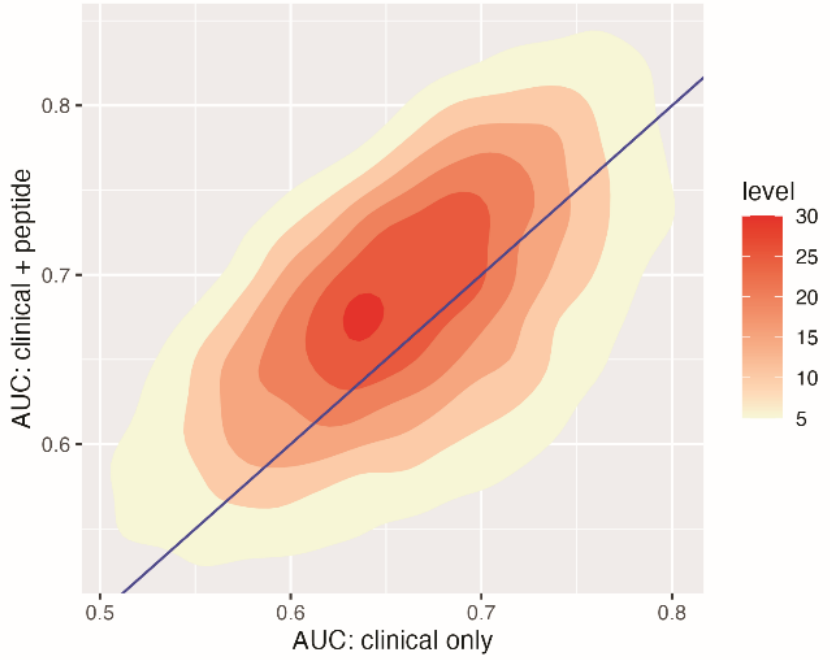
A predictive model w clinical variables shows good discrimination between SSA-

SjD & controls

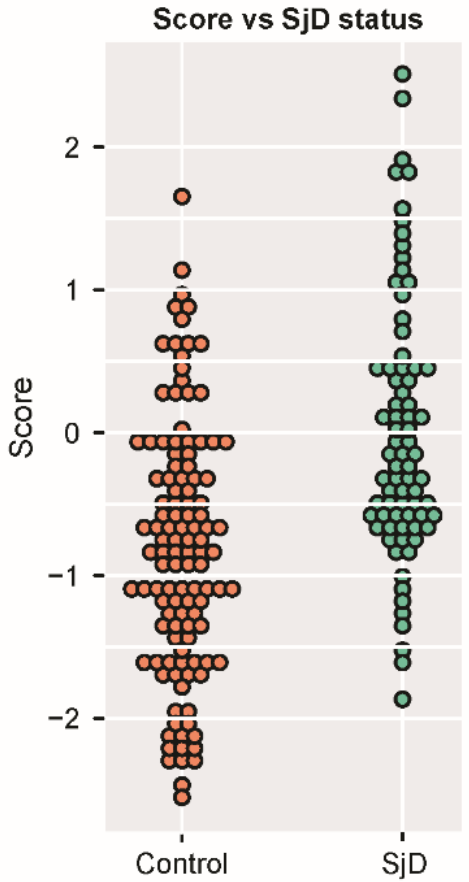
A.

Term	Estimate	p-value	Single term deletion ΔAUC	Single term deletion ΔR^2_N
$\sqrt{\text{DTD2}}$	$2.68_{0.847}$	0.002	-3.65%	-4.84%
$\sqrt{\text{UWS}}$	$-1.39_{0.400}$	<0.001	-5.53%	-6.02%
High ANA (≥320)	$1.18_{0.430}$	0.006	-2.19%	-3.51%
Constant	$-1.16_{0.551}$	—		

C.



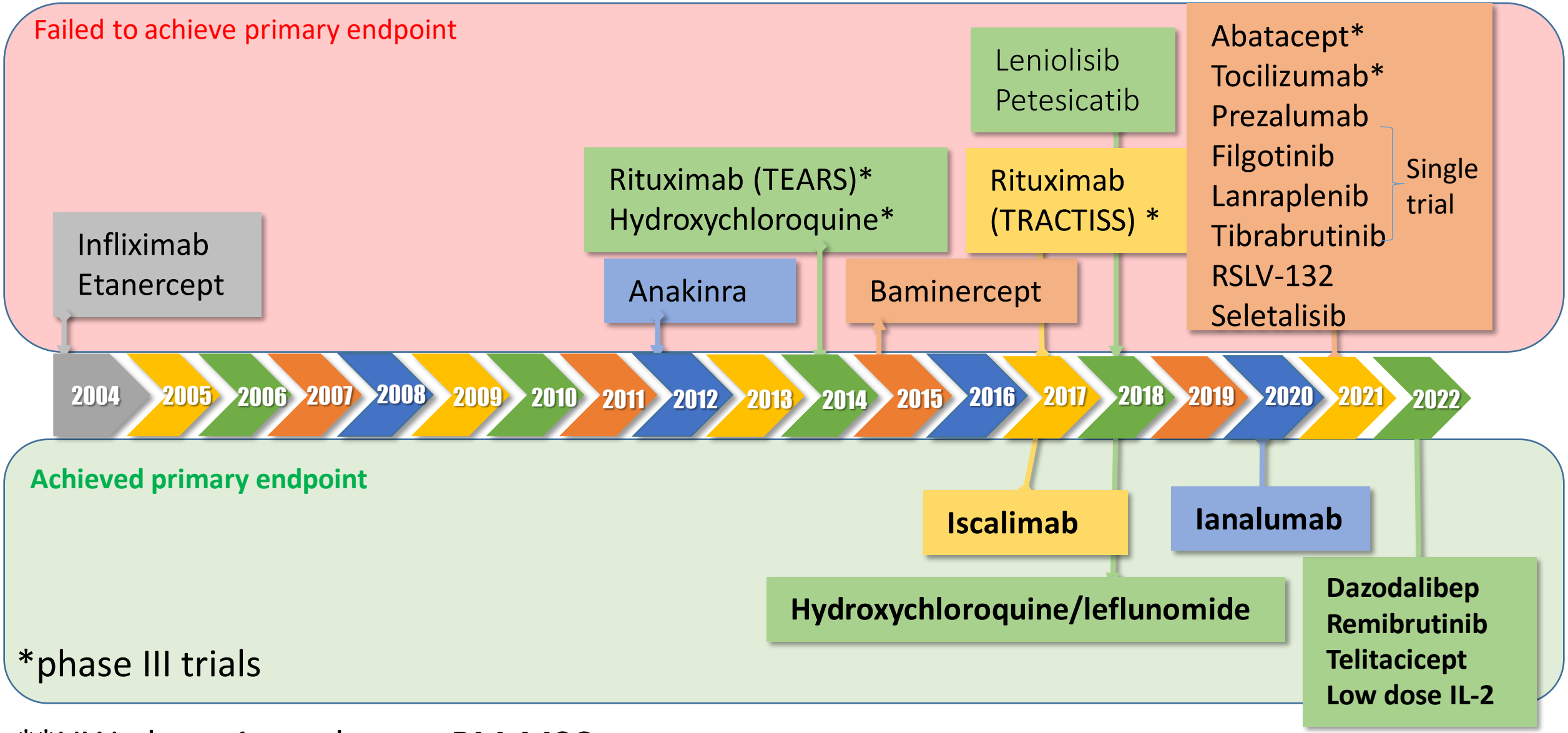
B.



No FDA approved systemic treatment

- Symptomatic therapy remains mainstay

Placebo-controlled drug trials in Sjögren's



*phase III trials

**UW phase 1 autologous BM-MSC

Slide adapted from Dr. Alan Baer

Conclusions

- Appropriate diagnostic evaluation worthwhile
- New diagnostic tests actively being developed/validated
- Treatment horizons opening

“Medicine is a science of uncertainty and an art of probability”

-William Osler