

Sjögren's Disease: Then and Now

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Disclosures

BMS: Consultant

Novartis: Consultant

Boehringer Ingelheim: Consultant

Objectives

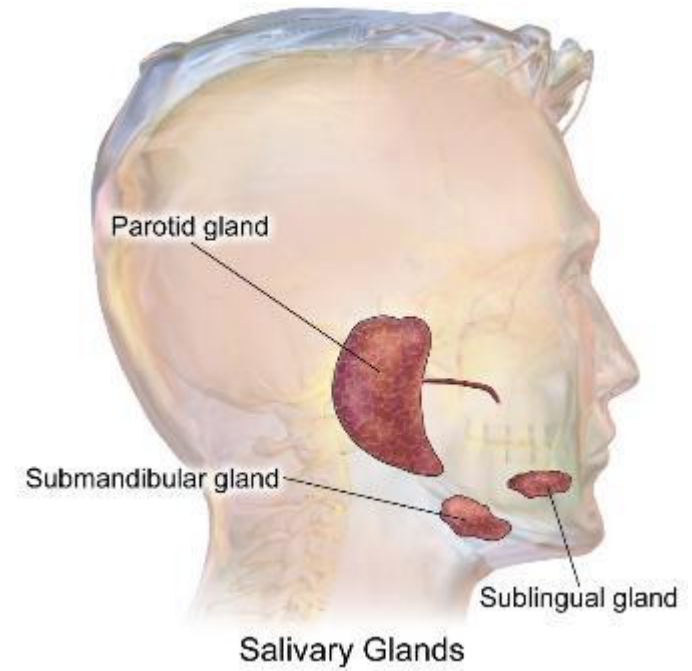
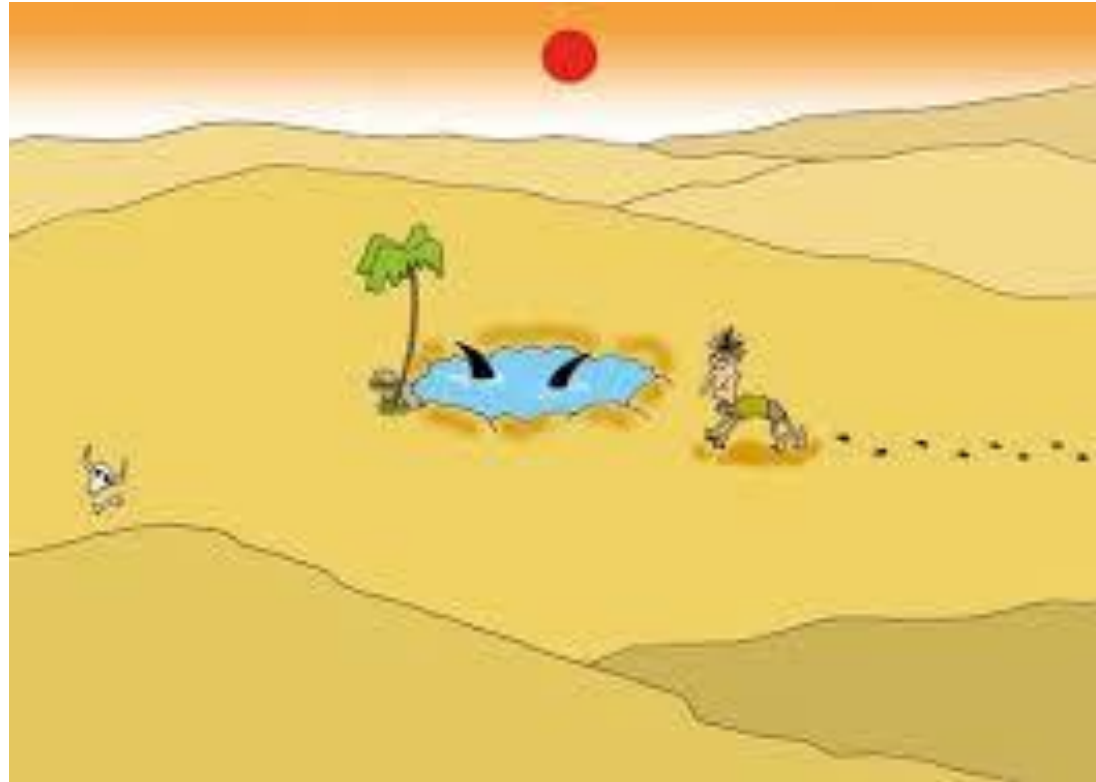
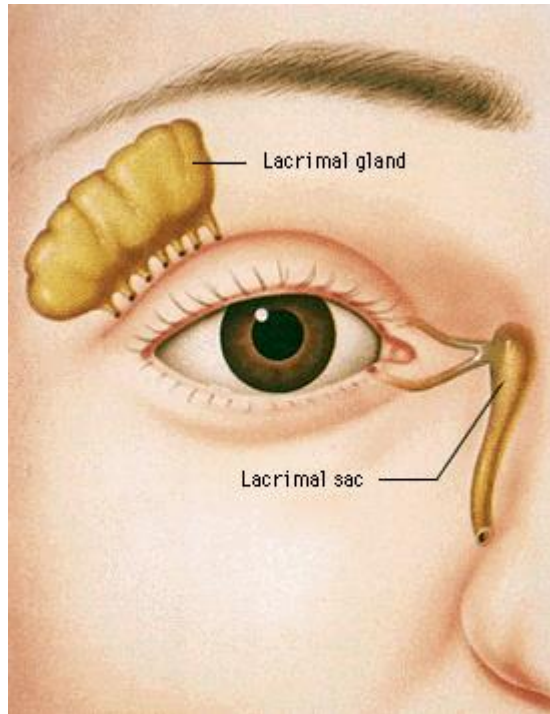
1. Detail how SjD endotypes provide insight to and management of SjD
2. Be familiar with how to diagnose SjD and how this might change in the future
3. Acknowledge new pulmonary screening guidelines
4. Determine how disease activity metrics might affect future therapeutics selection

Outline

- History
- Etiopathogenesis
- Diagnosis
- Evaluation/management

Sjögren's Disease

Oral/ocular sicca due to chronic inflammation of exocrine glands



Primary vs. Overlap

Primary Sjögren's

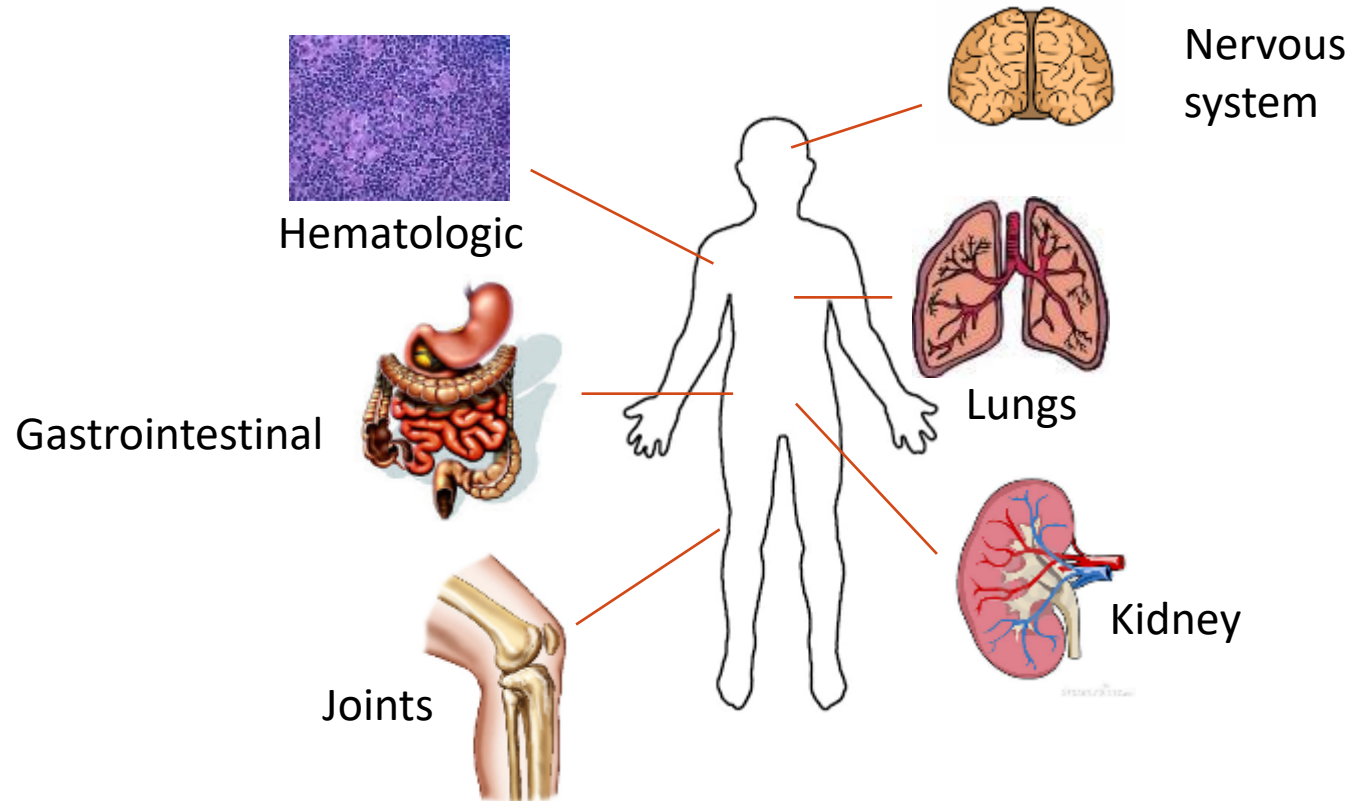
- alone without another coexistent autoimmune disease

Overlap Sjögren's

- In presence of another autoimmune disease
- Example: Rheumatoid arthritis, systemic lupus erythematosus

Symptoms/diagnosis otherwise the same

Extraglandular Involvement



Polling Question 1

What year did we first introduce pilocarpine for treatment of Sjögren's disease?

- A. 1992
- B. 1888
- C. 2003
- D. 1975

History

1888: Dr. W.B. Hadden

- 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 jaborandi (pilocarpine)
 - Coined “xerostomia”

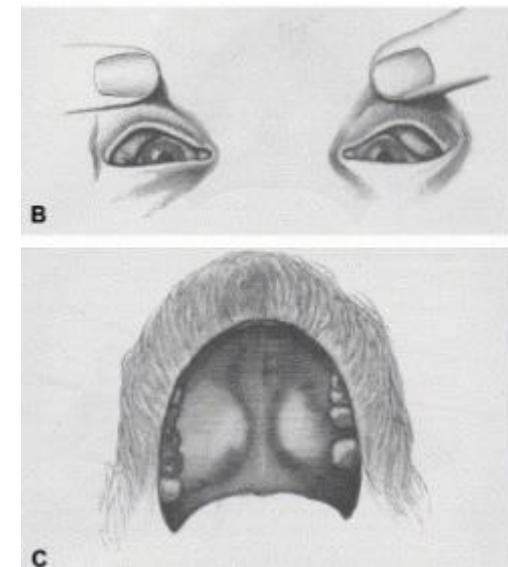
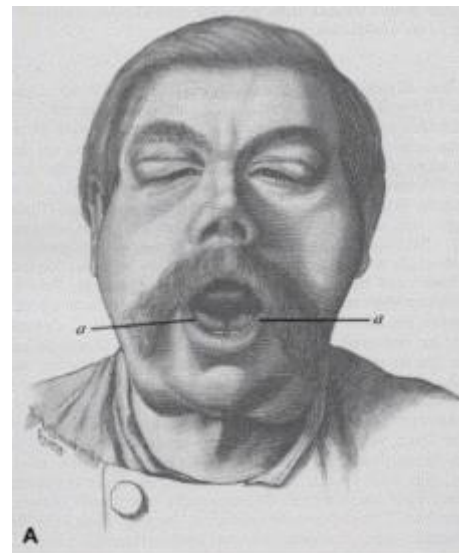


Jaborandi plant

History

1888: Dr. J Mukulicz

- 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”



History

1933 Henrik Sjögren

Described 19 women with dryness-13 had RA

Dr. Marie Sjögren, ophthalmologist, worked as collaborator



1. Etiopathogenesis

Epidemiology

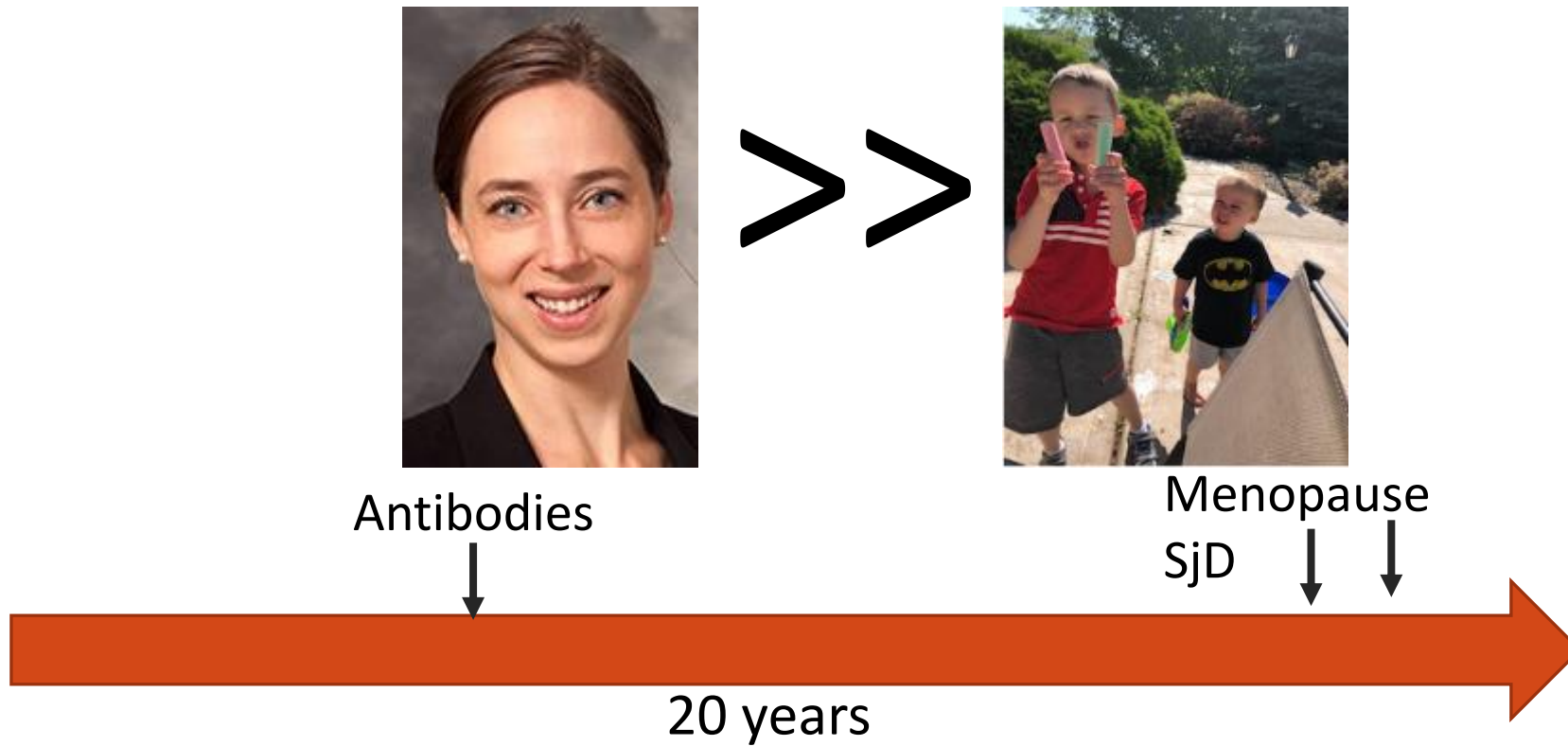
Women greater than men: 9:1 -20:1

Average onset: 56

Variable estimates of how prevalent: ~1%

Prevalence in older patients (>55): ~5%

Epidemiology

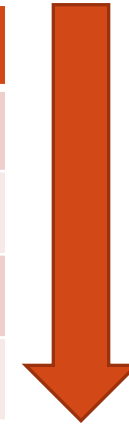


Sex hormones protect against SjD vs. sicca controls

Composite estrogen score (CES): 0-5

- early menarche (≤ 10 years)
- high parity (≥ 3)
- hysterectomy
- use of hormone therapy
- late menopause (≥ 53 years)

	OR	95% CI
CES 0	REF	REF
CES 1	0.81	0.67-0.99
CES 2	0.74	0.57-0.97
CES ≥ 3	0.5	0.30-0.86



- **Increased** estrogen = **lower** SjD
- Dose response relationship

Hormone exposure → increased risk vs. healthy controls

Risk Ratio of Sjögren's Associated with Endogenous and Exogenous Sex-Hormone Exposure			
			Multivariable*
Variable	SjD (n=546)	Control (n=1637)	RR (95% CI)
Endogenous Hormone Exposures			
Endometriosis	220 (40)	541 (33)	1.26 (1.05-1.52)
Hysterectomy, no bilat oophorectomy	52 (10)	85 (5)	1.51 (1.13-2.03)
Fibroids	285 (52)	673 (41)	1.44 (1.19-1.73)
Menstrual Irregularity	112 (21)	229 (14)	1.34 (1.07-1.67)
Menorrhagia	113 (21)	234 (14)	1.36 (1.09-1.68)
PCOS/hirsutism/cysts	77 (14)	127 (8)	1.65 (1.28-2.12)
Post-menopausal	360 (66)	898 (55)	1.46 (1.20-1.77)
Exogenous Hormone Exposures			
Combined HRT ever	48 (9)	98 (6)	1.36 (1.00-1.86)
ERT (any)	208 (38)	386 (24)	1.78 (1.47-2.14)
OCP ever	114 (21)	242 (15)	1.40 (1.09-1.79)
OCP dose (mcg)	11.9 (16)	8.5 (12)	1.01 (1.00-1.02)

BMI → decreased risk vs. healthy controls

Risk Ratio of Sjögren's Associated with Endogenous and Exogenous Sex-Hormone Exposure			
			Multivariable*
Variable	SjD (n=546)	Control (n=1637)	RR (95% CI)
BMI (continuous)	28.8 (10)	30.3 (8)	0.98 (0.97-0.99)

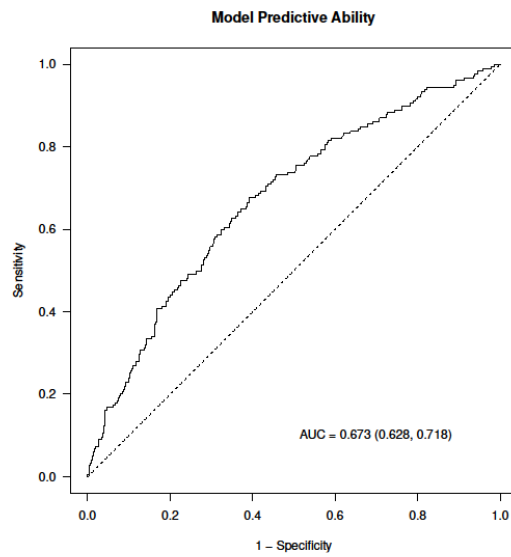
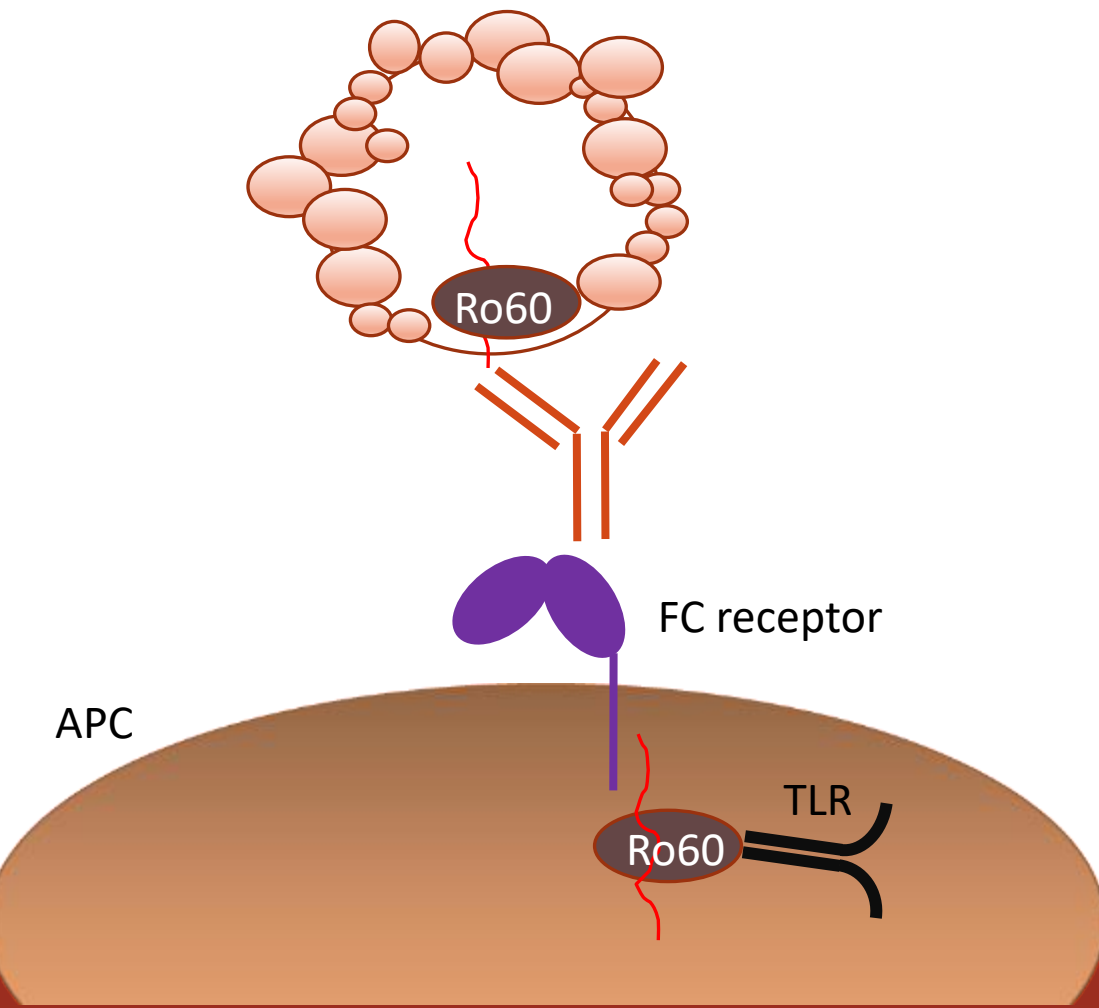


Table 6. Optimized Multivariable Model Association with Sjögren's

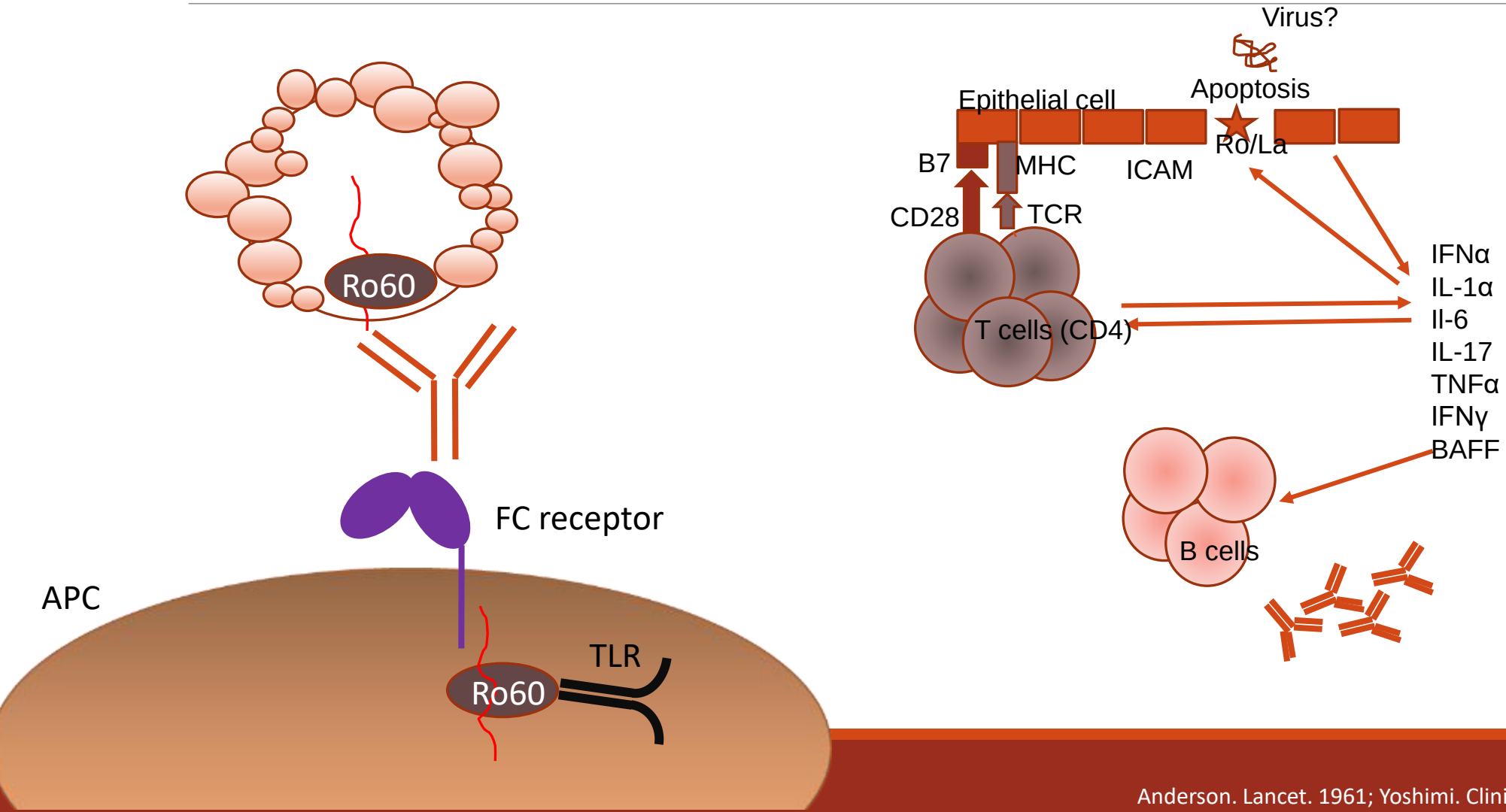
	Coefficient	OR (95% CI)	p-value
Intercept	-0.783		
Fibromyalgia	0.917	2.50 (1.93 – 3.25)	< 0.001
Diabetes	-1.303	0.27 (0.13 – 0.50)	< 0.001
Osteoporosis	0.612	1.84 (1.27 – 2.66)	0.001
BMI	-0.027	0.97 (0.95 – 0.99)	0.005
HRT Ever	0.0475	1.61 (1.22 – 2.12)	0.001

BMI=body mass index; HRT=estrogen-only hormone replacement therapy; n=96 subjects excluded for missing data.

Pathogenesis



Pathogenesis



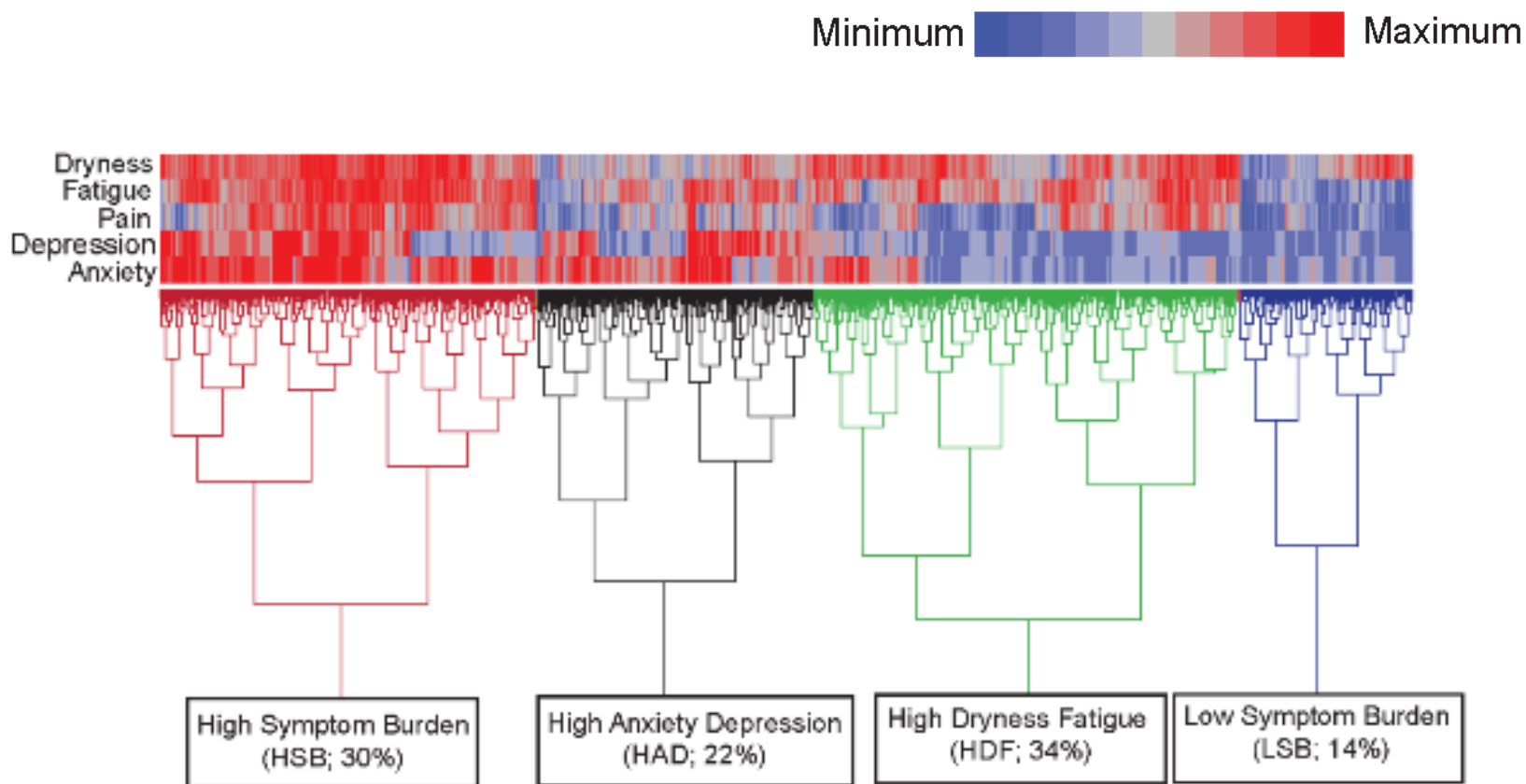
Stratification for Pathogenic Insights

Heterogeneity

Stratification→

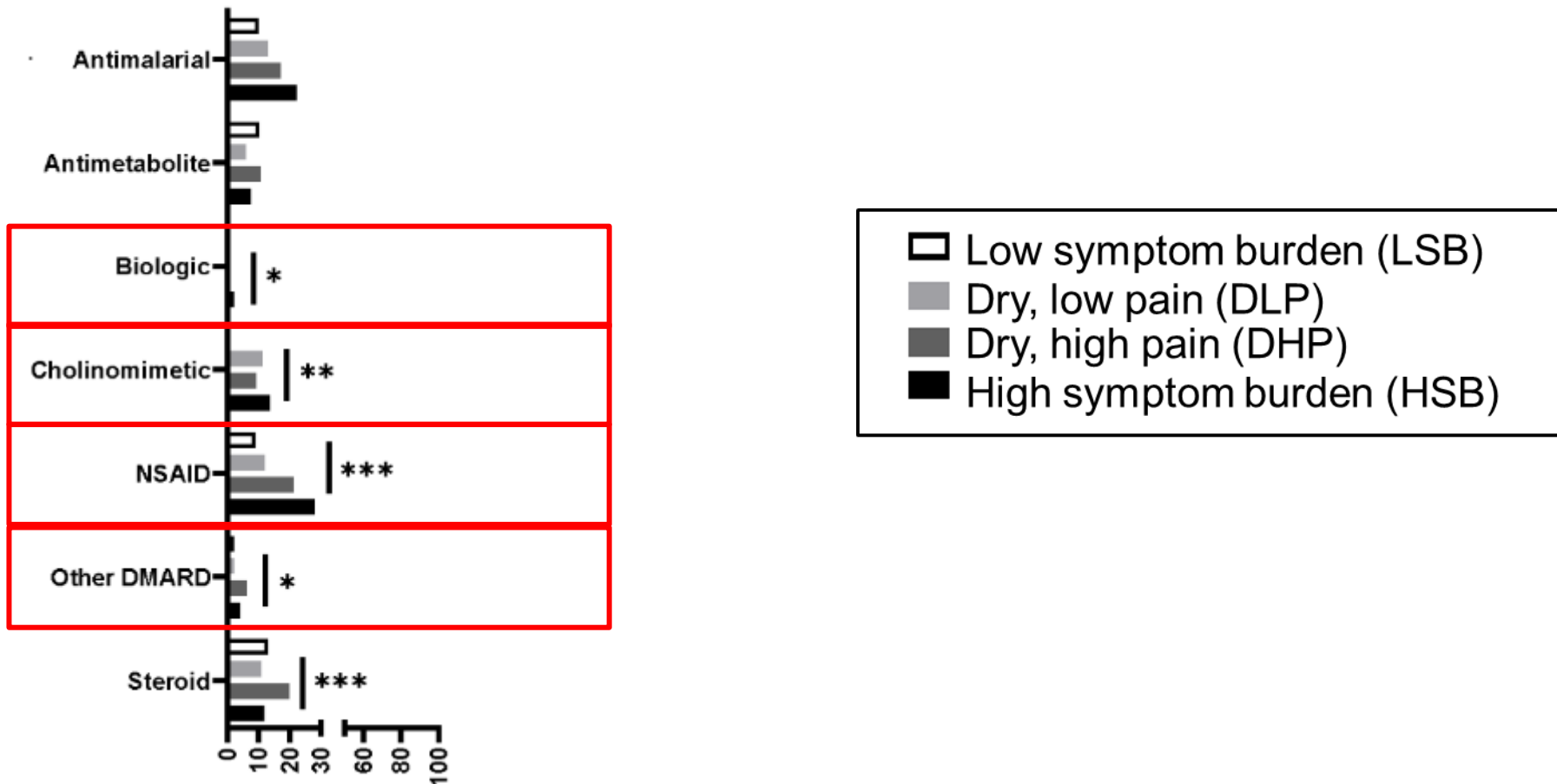
- Increased pathogenic insight into subgroups
- Promotes therapy tailored to subgroup
- Improves patient-provider relationships

Four symptom-based clusters



Cluster	Patients
High Symptom Burden	540
High Anxiety Depression	336
High Dryness Fatigue	432
Low Symptom Burden	146
Total	1,454

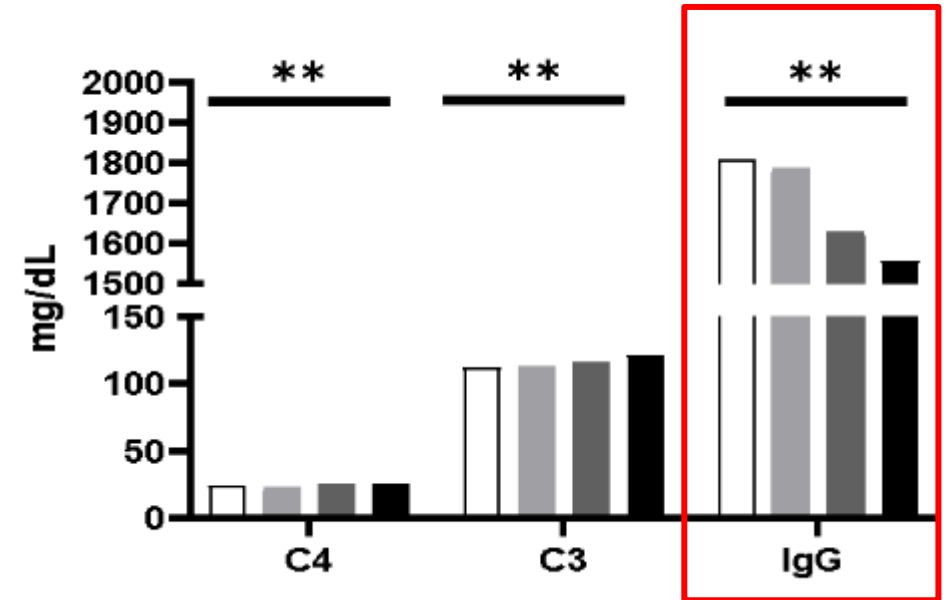
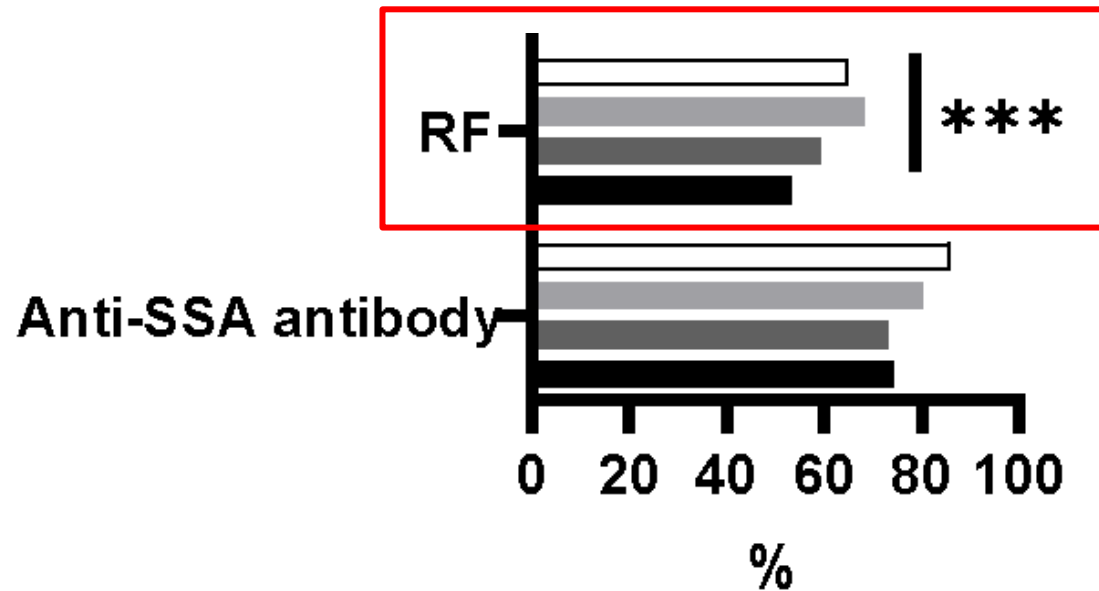
High symptom burden cluster use of cholinomimetics, NSAIDs, DMARDs & biologics



Dry, high pain cluster has the highest sicca frequency

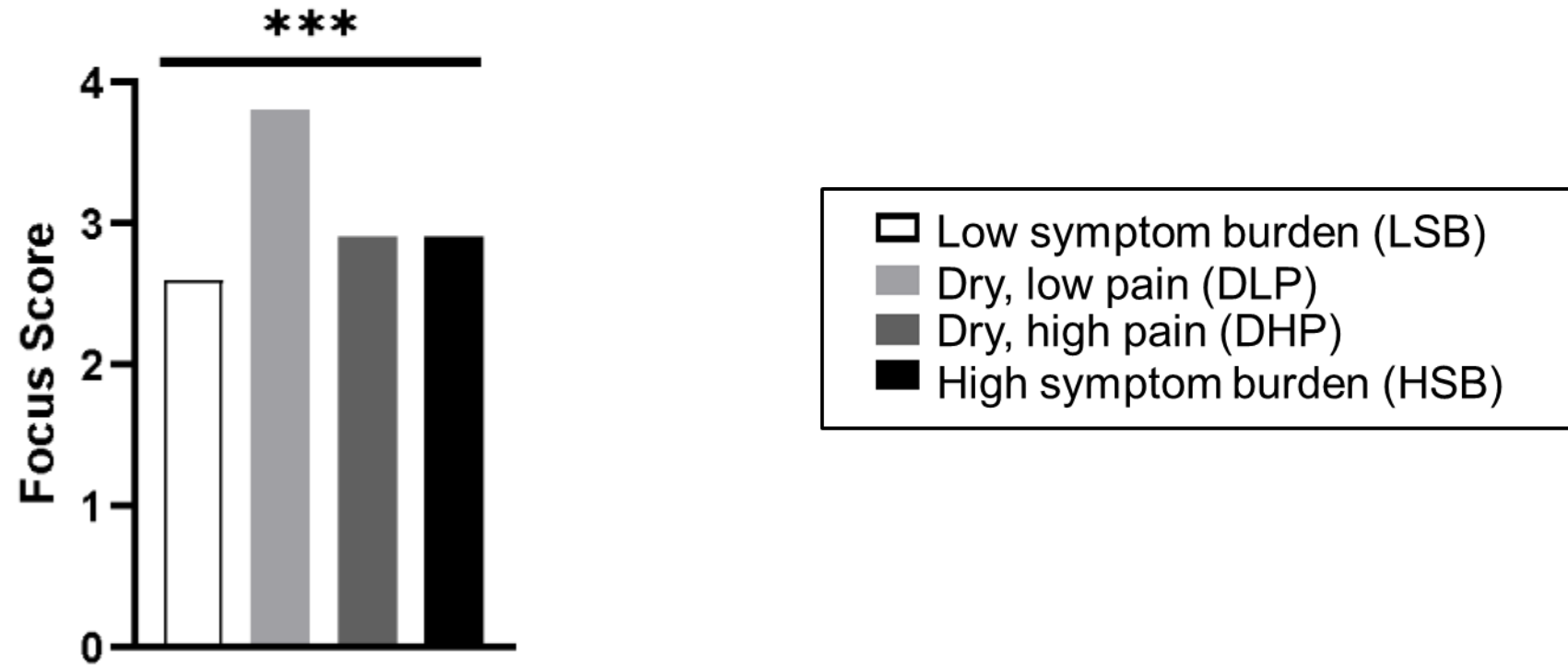


High symptom burden cluster has lowest RF & IgG

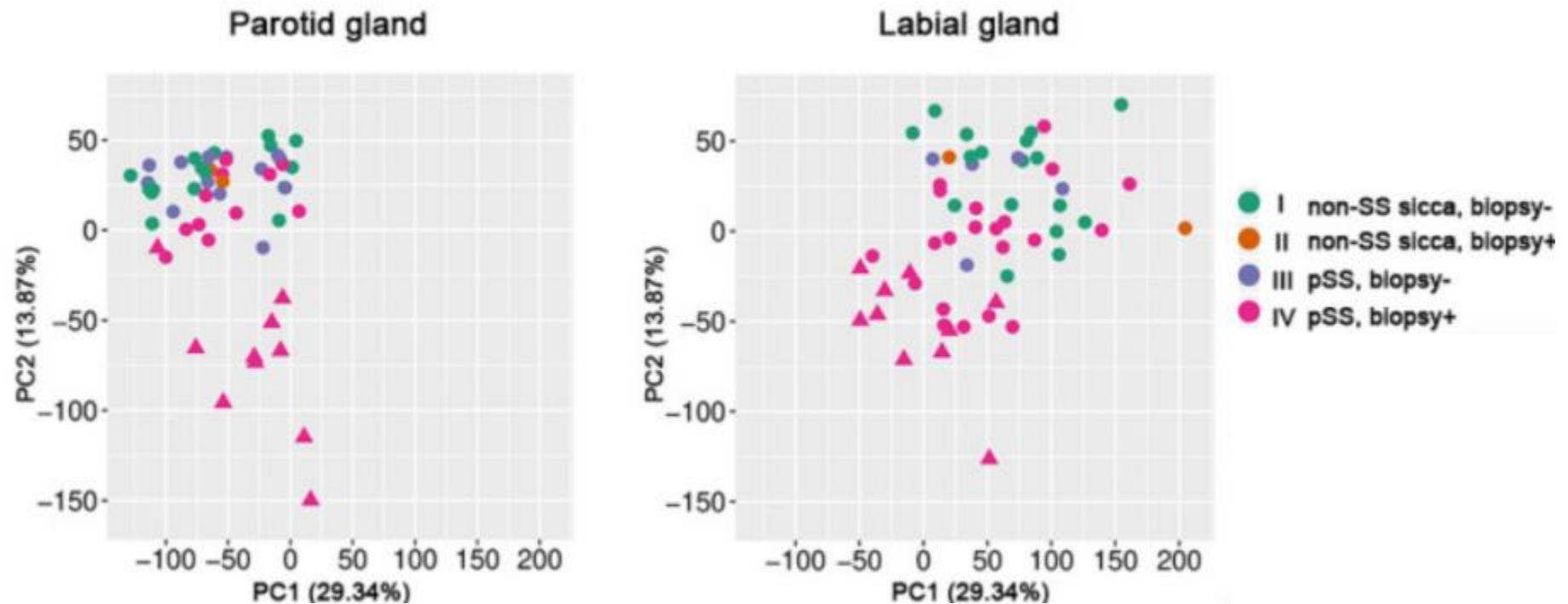


- Low symptom burden (LSB)
- Dry, low pain (DLP)
- Dry, high pain (DHP)
- High symptom burden (HSB)

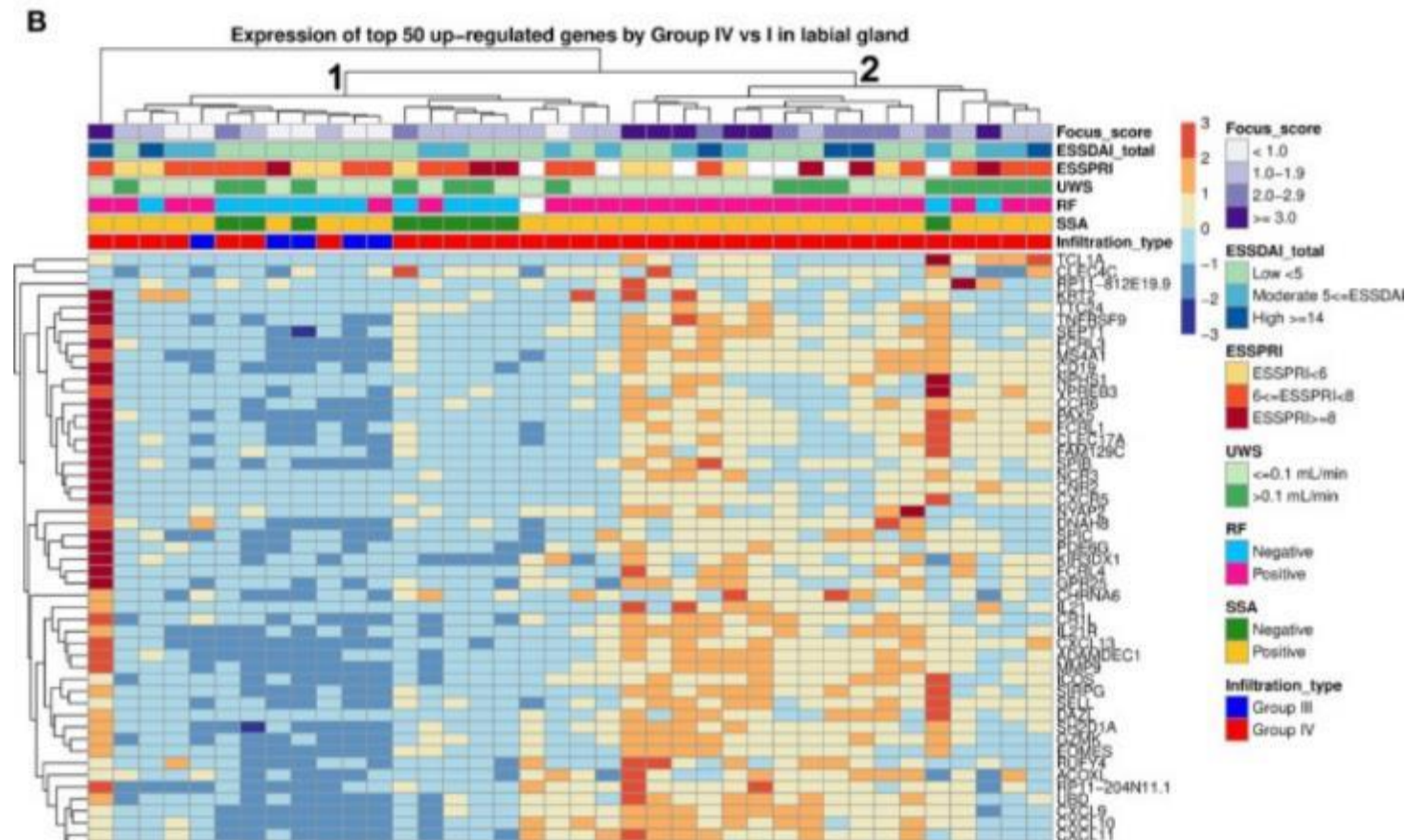
Dry, low pain cluster has highest focus score



Subtypes: gland transcriptome



Subtypes: gland transcriptome



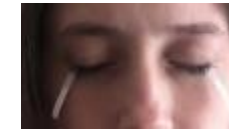
Etiopathogenesis summary

- **Evolving role for sex hormones in SjD**
- **Increased understanding of SjD endotypes**
- **Future directions**
 - scRNAseq
 - Tissue-based methods

2. Diagnosis

Diagnosis: ACR/EULAR Classification Criteria

Category	Score
Schirmer ≤ 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 (Or RF + ANA?)	3



Criteria does not = diagnosis

Further testing-Minor salivary gland (lip) biopsy

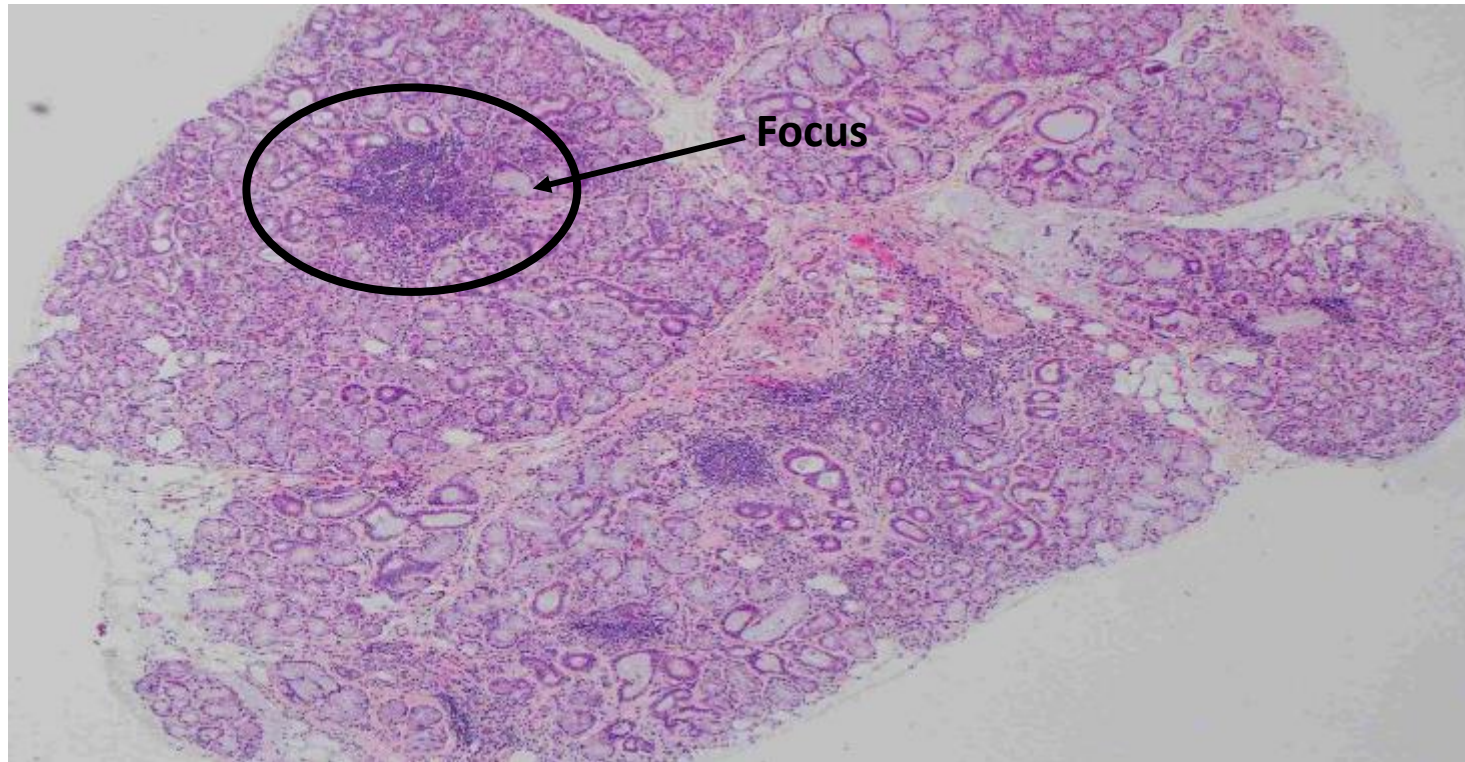


Minor Salivary Gland

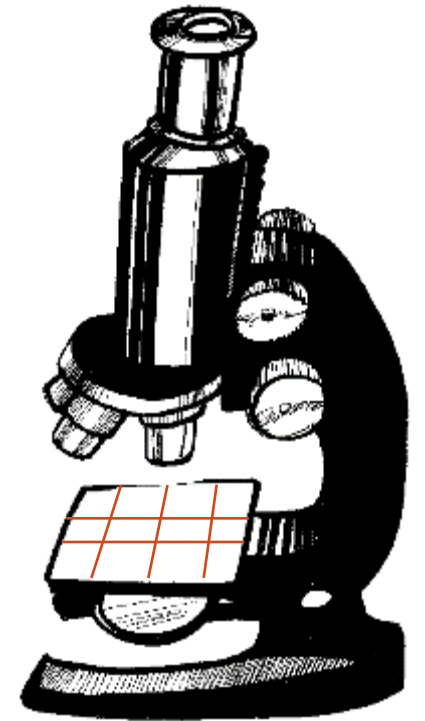


Focus Score

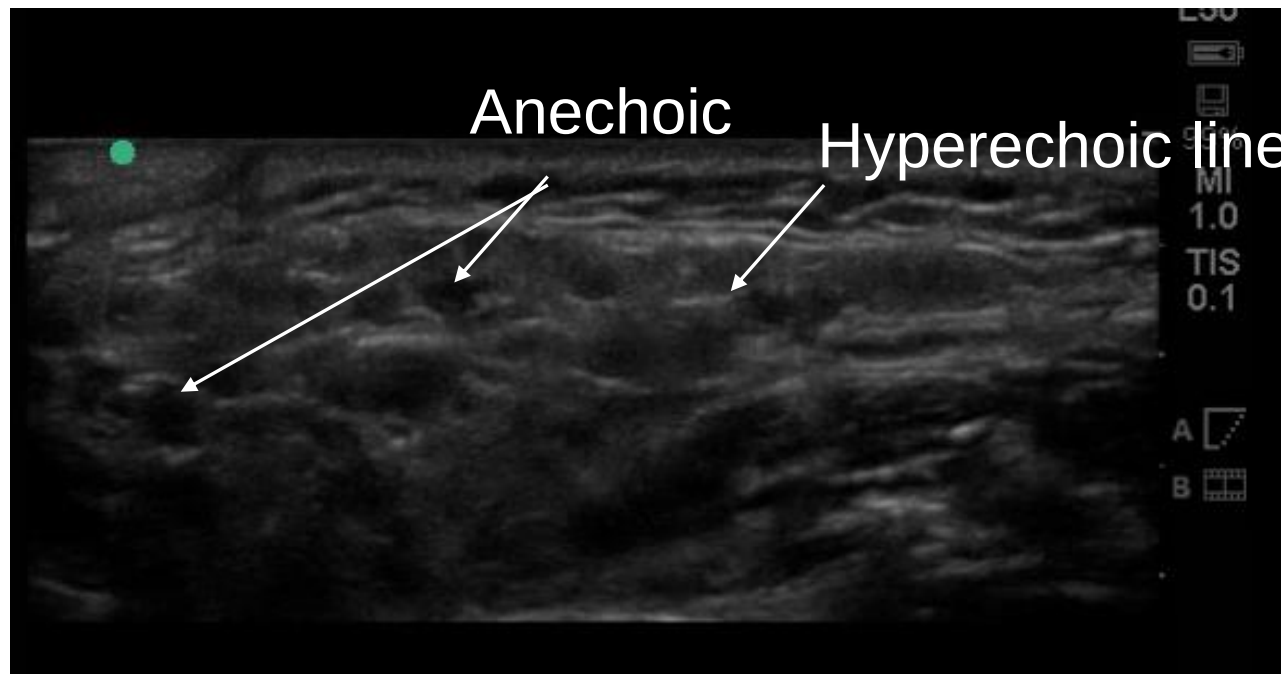
Number of foci (50 lymphocytes) per 4 mm²



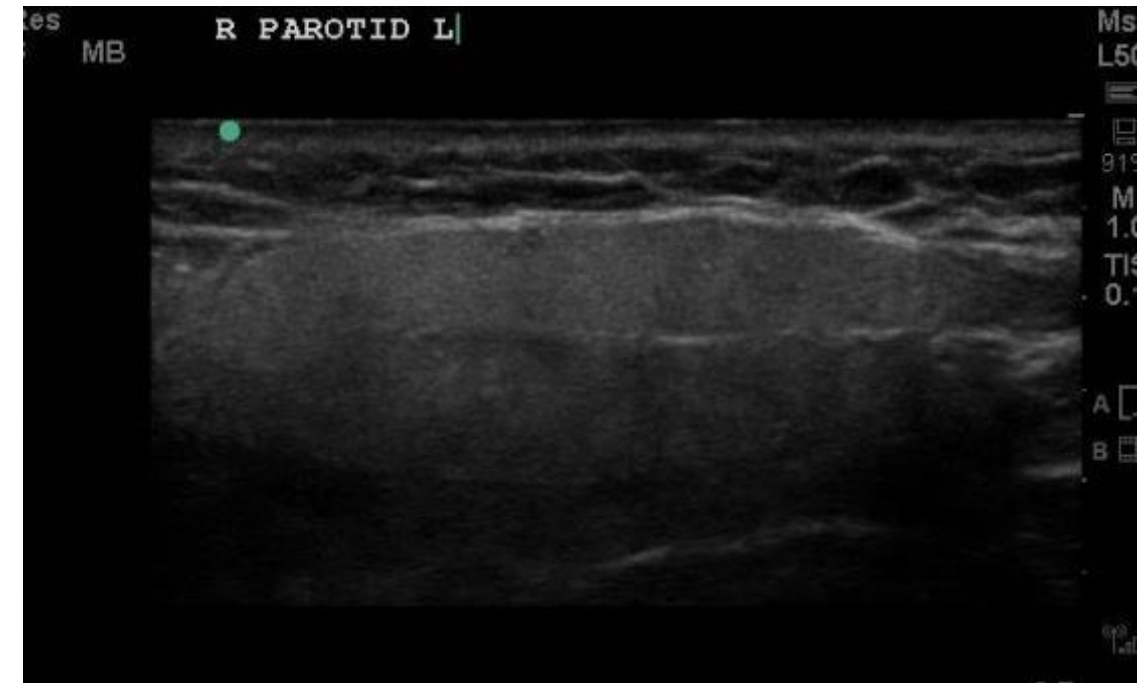
Focus score ≥ 1 foci/4mm² supports diagnosis



SjD imaging characteristics

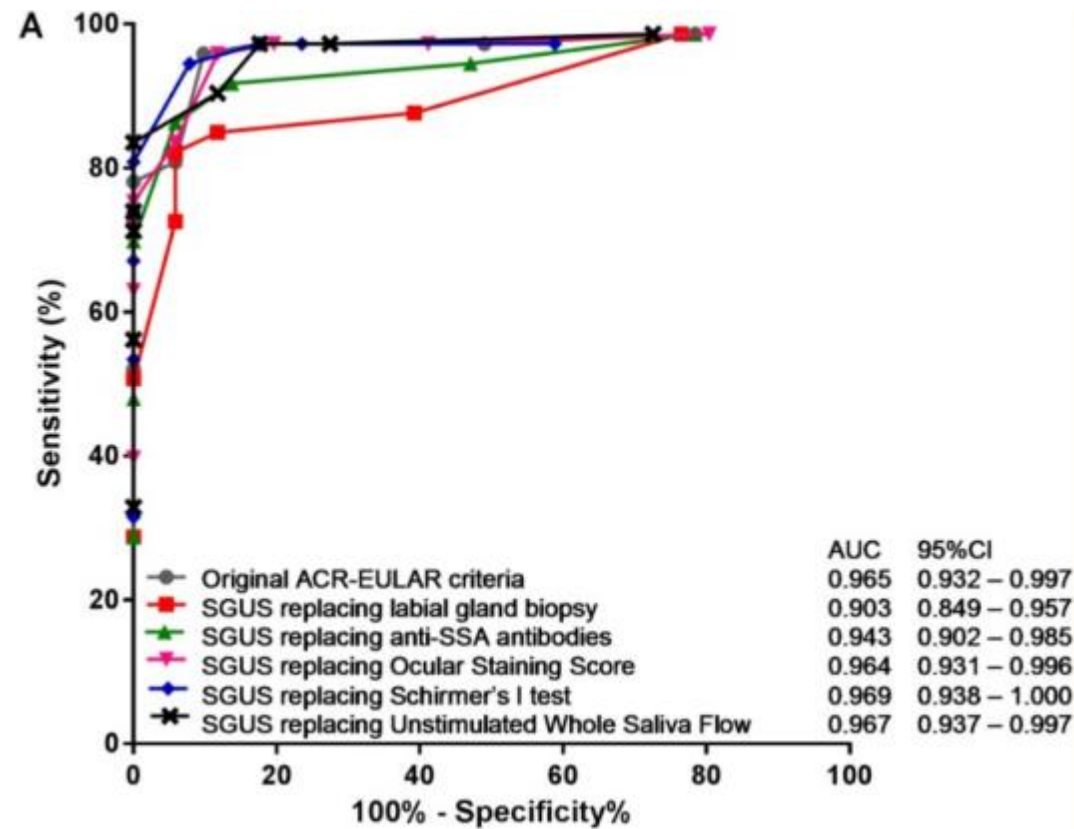


Sjögren's parotid gland



Normal parotid gland

SGUS in ACR/EULAR criteria



3. Evaluation

Evaluation: SjD history

History

- ESSPRI/PROMIS
- Medication use
- Constitutional
- Gland
- Neuropathy

1) How severe has your dryness been during the last 2 weeks ?

No dryness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Maximal imaginable dryness
	0	1	2	3	4	5	6	7	8	9	10	

2) How severe has your fatigue been during the last 2 weeks ?

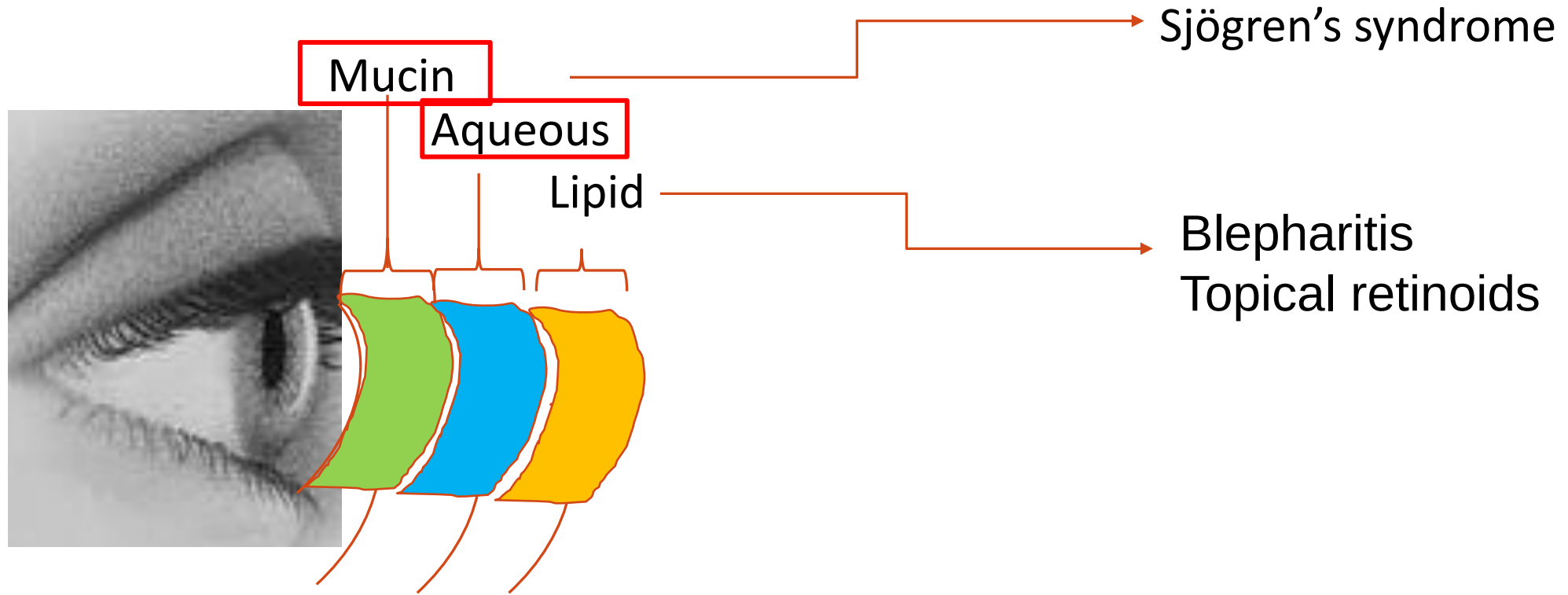
No fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Maximal imaginable fatigue
	0	1	2	3	4	5	6	7	8	9	10	

3) How severe has your pain (joint or muscular pains in your arms or legs) been during the last 2 weeks ?

No pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Maximal imaginable pain
	0	1	2	3	4	5	6	7	8	9	10	

Ocular Exam

- Rule out other causes



Ocular Exam

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	0	0	0	0-9	0	0
	1	10-32	1	1-5	1	10-32	1	1-5
	2	33-100	2	6-30	2	33-100	2	6-30
	3	>100	3	>30	3	>100	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.

Oral Exam

- Rule out other causes
- Salivary pooling
- Glandular exam
- Unstimulated Salivary Flow
 - Weigh collection receptacle
 - Position/prepare patient
 - Collect in receptacle x 5 minutes
 - Weigh collection receptacle
 - Classification criteria: ≤ 0.1 ml/minute
 - 1 g = 1mL



Evaluation: SjD labs & imaging

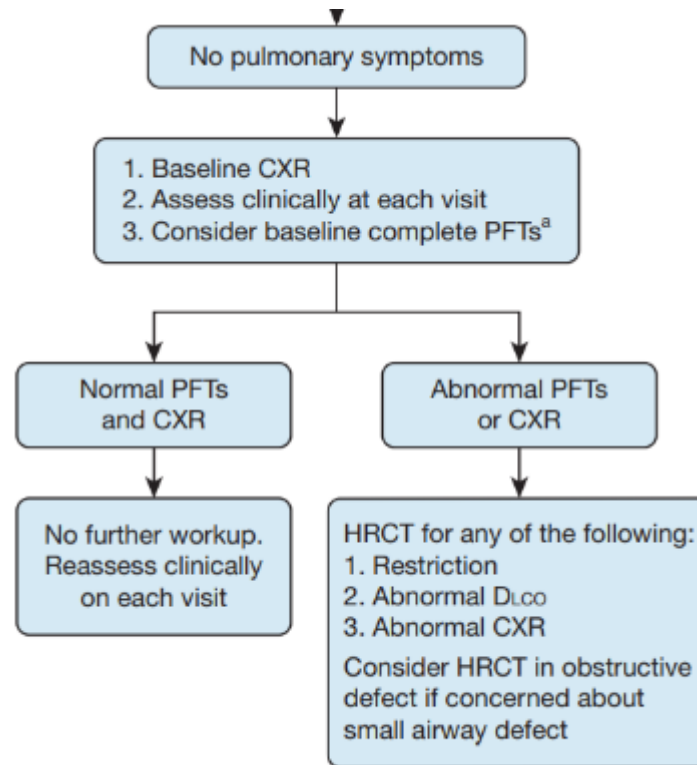
Labs

- CBC
- CMP
- Urinalysis/UPC
- B2 macroglobulin, C3, C4, Cryos, IgG, SPEP/UPEP

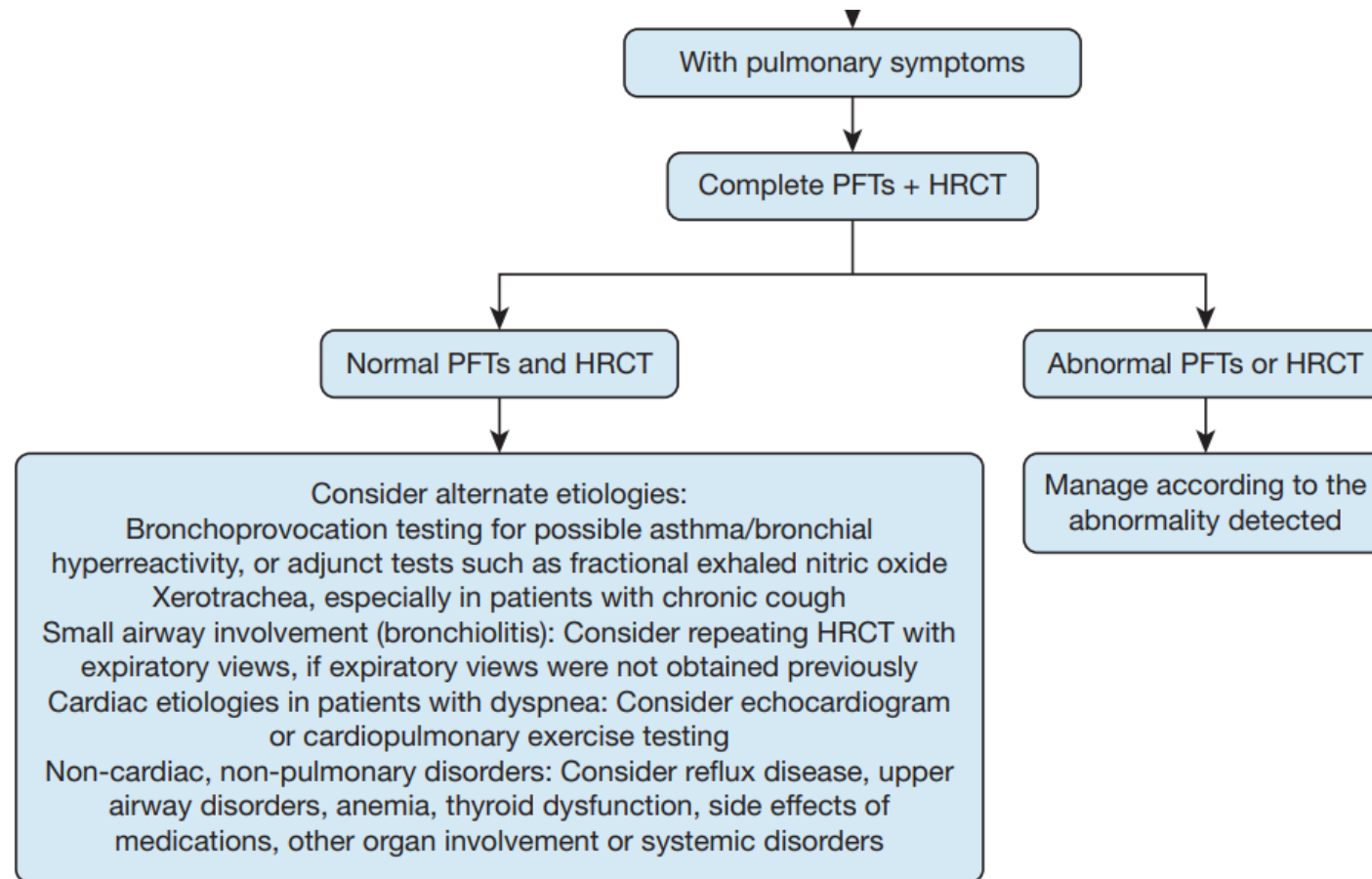
Imaging

- Salivary scintigraphy
- X-ray sialography
- MR sialography
- PET
- US

New Pulm Screening Guidelines



New Pulm Screening Guidelines



4. Management

Treatment-Dry Eye

Evaluate for other causes

- ie blepharitis

Over the counter wetting drops/gels

- Preservative free

Protection/humidification

- Moisture chamber eyewear

Punctal Plugs

Prescriptions

- Cyclosporine
- Lifitigrast

Scleral Lens

Serum Tears



Treatment-Dry mouth

- Avoid mouthwash or rinse containing astringents (e.g., alcohol)
- Use sugar-free gum, candies, or lozenges (Xylitol preferred)
- Wetting sprays (for short term relief)
- Moisturizing gels and oils (coconut oil, sesame oil, olive oil)
- Treat concomitant candida infections
- Sialagogues

Treatment-Caries Prevention

- Nightly use of prescription-strength toothpaste
- Fluoride varnish applied by a dentist every 3 months
- Promote saliva production
- Avoid tooth abrasives
- If acids are consumed, rinse the mouth with 1 tsp baking soda mixed in 8 oz of water

Disease modifying drugs

- No FDA-approved disease modifying SjD treatment
- Limited by disease heterogeneity
- ESSDAI
 - Anti-CD40: **ESSDAI** ≥ 6 or <6
 - Anti-CD40 Ligand: **ESSDAI** ≥ 5 or <5
 - Anti-BAFF Receptor: **ESSDAI** ≥ 6
 - Anti-Baff/anti-CD20: **ESSDAI** ≥ 5
 - JAK/STAT inhibitors: **ESSDAI** 0-13
 - BTK inhibitors: **ESSDAI** ≥ 5
 - RNase-Fc fusion protein

Polling Question 2

What factors are associated with increased mortality in SjD?

- A. Age
- B. Sex
- C. Parotid gland enlargement
- D. Small fiber neuropathy
- E. All of the above

ESSDAI

Domain	No	Low	Mod	High
Constitutional	0	3	6	
Lymphadenopathy/lymphoma	0	4	8	12
Glandular	0	2	4	
Articular	0	2	4	6
Cutaneous	0	3	6	9
Pulm	0	5	10	15
Renal	0	5	10	15
Muscular	0	6	12	18
PNS	0	5	10	15
CNS	0		10	15
Heme	0	2	4	6
Biological	0	1	2	

CRESS

Item	Measurement	Definition of response
Systemic disease activity	ClinESSDAI	Score <5 (low disease activity)
Patient-reported symptoms	ESSPRI	Decrease of ≥1 point or ≥15% from baseline
Tear gland*	Schirmer/OSS**	If abnormal score at baseline: • Or increase of ≥5 mm in Schirmer • Decrease of ≥2 points in OSS Or if both normal at baseline: • No change to abnormal in Schirmer and OSS
Salivary gland*	UWS/SGUS	• Increase of ≥25% or if score is 0 at baseline any increase in UWS • Or decrease of ≥25% in total Hoyer score
Serological	RF/IgG	• Decrease of ≥25% in RF • Or decrease of ≥10% in IgG
Total CRESS responder		Response on ≥3 items of 5

Wrap up

1. Increasing pathogenic insights into SjD endotypes will hopefully yield improved care for SjD patients
2. Growing use of SGUS
3. New pulmonary guidelines support ILD screening
4. Promising new drugs-but not might be applicable to all

Acknowledgements

Mentors/Collaborators

- Jacques Galipeau
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- Franklin Zhao



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Questions?

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

-William Osler