Clinical heterogeneity in Sjogren's disease

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20e Groninger Symposium Systeemziekten

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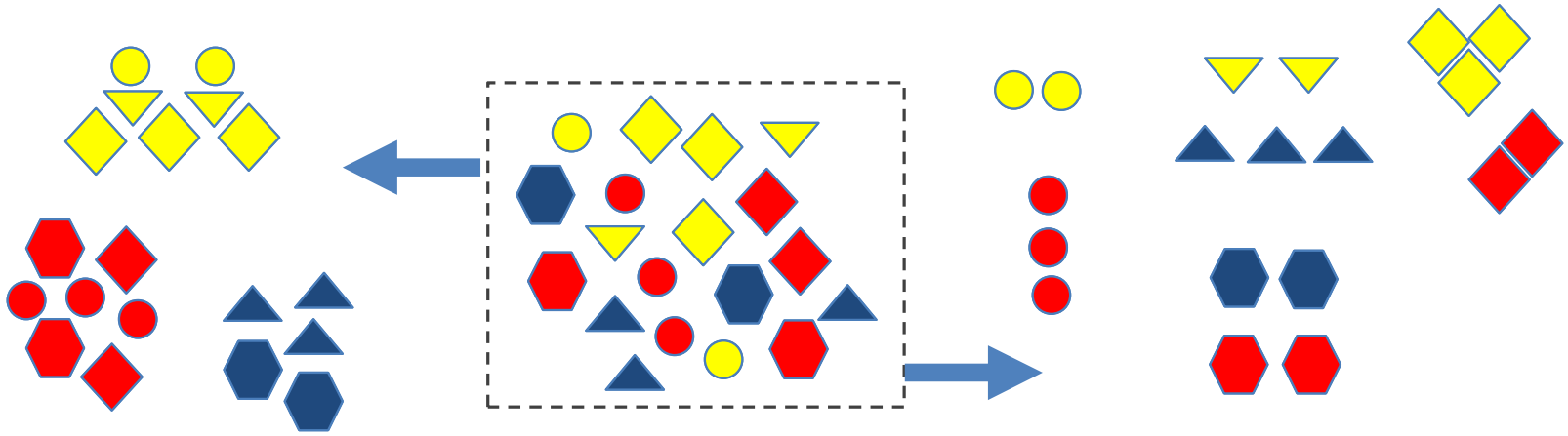
Disclosure slide

Conflict of interests	None / see below
Relevant relationship with companies	Companies
• Sponsoring or research money • Fee or other reimbursement	• Johnsons & Johnsons • Bristol Myers Squibb • Sanofi • Novartis • Argenx • IQVIA • Flagship • Resolves Therapeutics

Stratified Medicine in Sjogren's

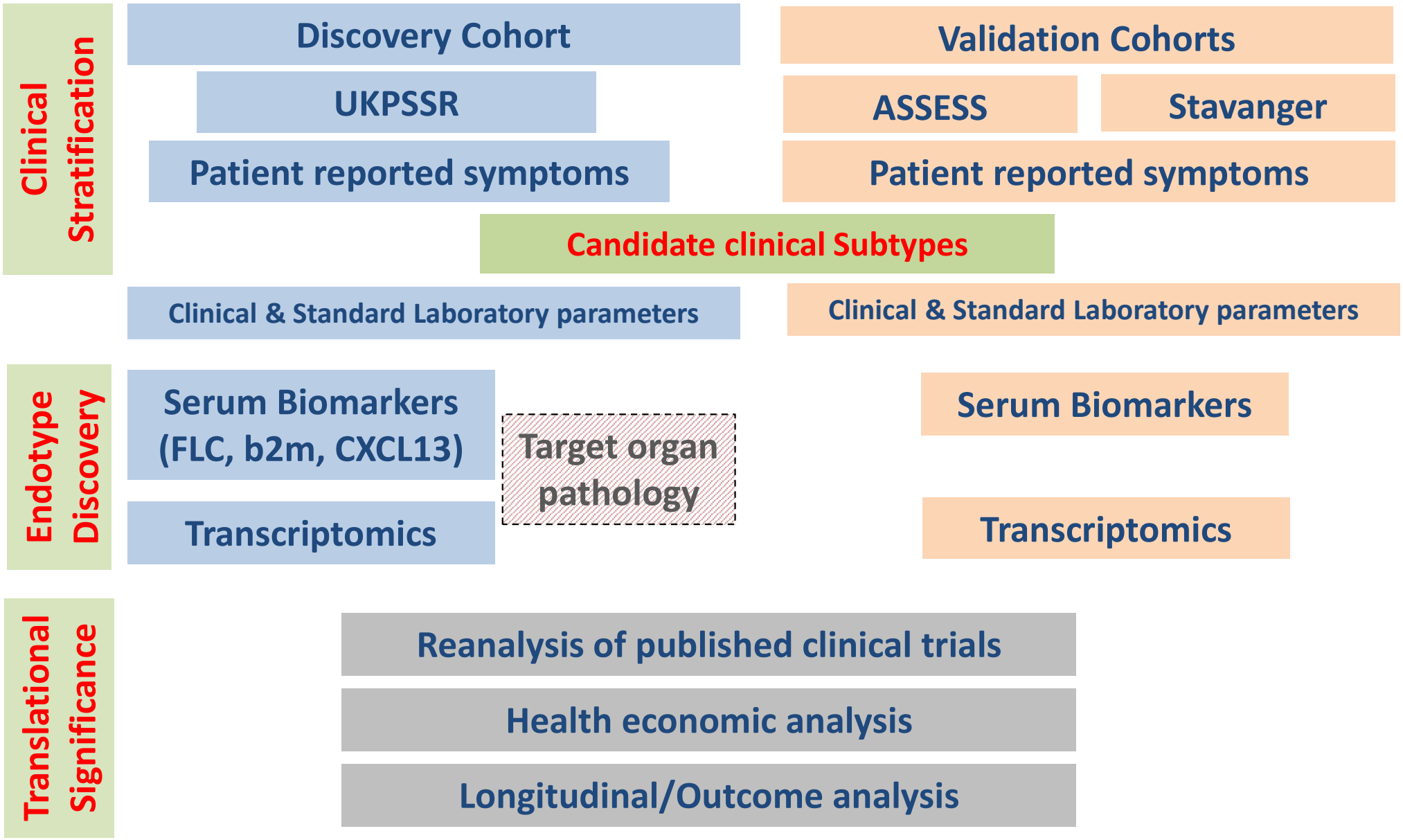
Why	Heterogeneity (clinical, biological, health economical, attitude to therapies, etc)
Who	Patients, clinicians, scientists, industry, payers
What	Clinical features, pathophysiology, prognosis (e.g. lymphoma development), therapeutic responses
When	At diagnosis, treatment decision, evaluate therapeutic responses/adverse effects
Where	Probably not relevant
How	??



Conventional view of clinical subsets of Sjögren's

- Mainly "glandular" with high levels of pain and fatigue
- "Severe" extra-glandular manifestations such as lymphoma

- But, do all SjD patients belong to either one of these two subgroups?
- No "consensus" on what constitute "severe" extra-glandular manifestations or "mainly glandular features"

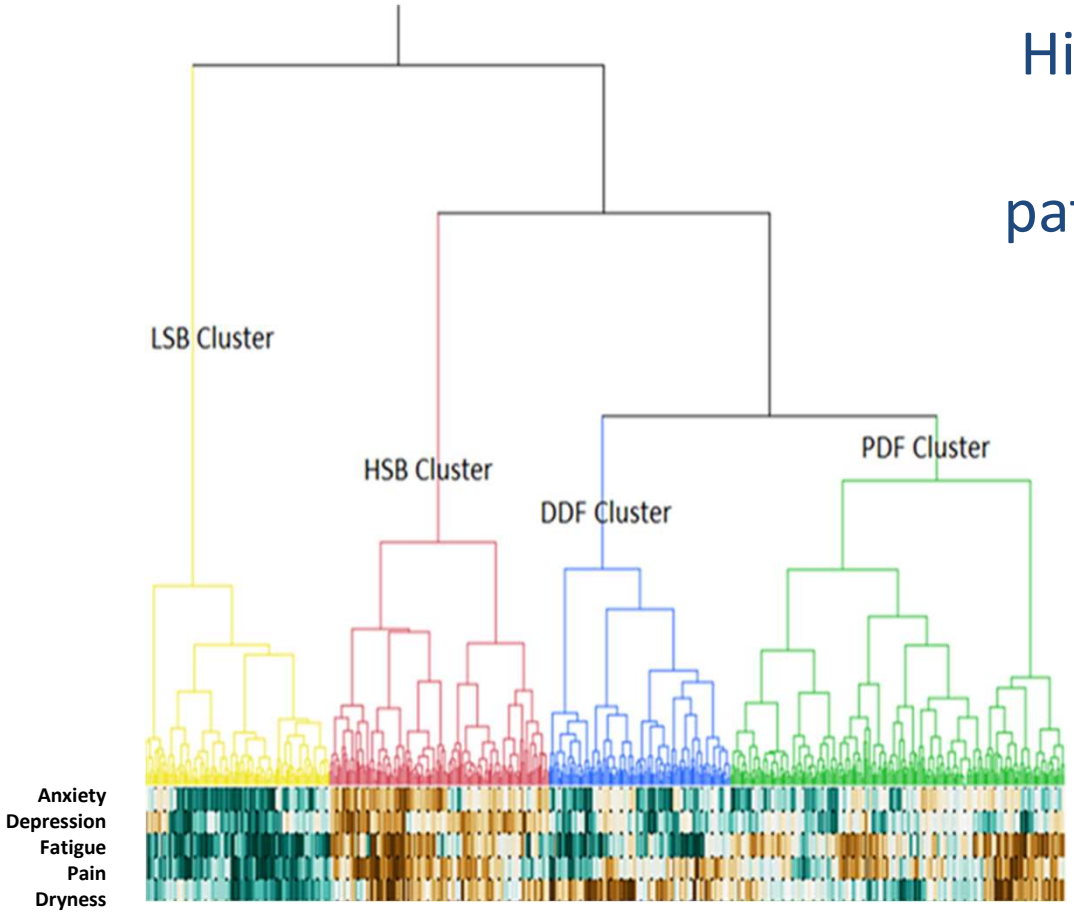

Clinical Stratification
Discovery Cohort
UKPSSR
Patient reported symptoms
Validation Cohorts
ASSESS
Stavanger
Patient reported symptoms
Candidate clinical Subtypes
Clinical & Standard Laboratory parameters
Clinical & Standard Laboratory parameters
Endotype Discovery
Serum Biomarkers (FLC, b2m, CXCL13)
Transcriptomics
Target organ pathology
Serum Biomarkers
Transcriptomics
Translational Significance
Reanalysis of published clinical trials
Health economic analysis
Longitudinal/Outcome analysis

Cohort characteristics

	UKPSSR	ASSESS	Stavanger
Sample size	608	334	62
Median Age (Years)	61	58	62
Female (%)	95	93	82
BMI	25.8	23.4	24.7
AECG duration (years)	5	5	11
ESSDAI (median)	3	3	5
ESSPRI (median)	5.7	5.3	6.0

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Hierarchical cluster analysis of five key symptoms of SjD patients reveals 4 main clusters



PRS	LSB	HSB	DDF	PDF
ESSPRI-Dryness (0-10)	3 (2, 4)	7 (6, 8)	8 (7, 9)	6 (4, 7)
ESSPRI-Fatigue (0-10)	2 (1, 3)	7 (6, 9)	6 (4, 7)	6 (5, 8)
ESSPRI-Pain (0-10)	1 (0, 2)	7 (5, 8)	2 (0.25, 3)	6 (5, 8)
HADS-Anxiety (0-21)	5 (3, 7)	14 (11, 15)	5 (3, 8)	7 (5, 9)
HADS-Depression (0-21)	2 (1, 4)	11 (9, 13)	4 (2, 6.75)	5 (3, 7)

LSB = Low symptom burden

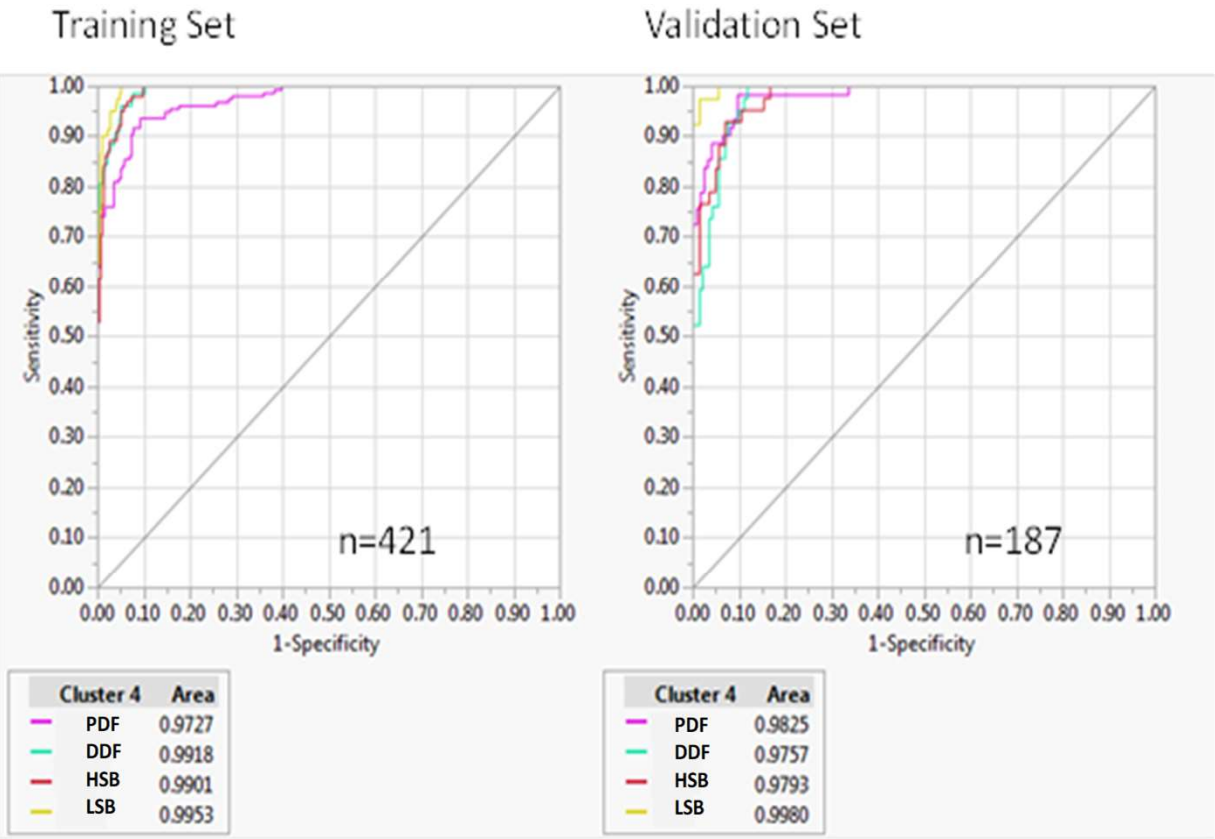
HSB = High symptom burden

DDF = Dryness Dominant with fatigue

PDF = Pain dominant with fatigue

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Model development and validation



Area Under the Curve (AUC) for the ROC curves >0.95 for all four groups

Newcastle Sjögren's syndrome Stratification Tool (NSST)

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Differences in clinical parameters

Parameter	Cohort	LSB	HSB	DDF	PDF	P value
USF	UKPSSR	0.4	0.2	0.05	0.3	0.0097
	ASSESS	0.26	0.4	0.002	0.22	<0.0001
	Stavanger	1.65	0.8	0.2	0.9	0.1212
	Combined	0.3	0.25	0.005	0.3	<0.0001
Schirmer's	UKPSSR	3	3	2	4	0.0136
	ASSESS	5.25	5.75	7	7.75	0.2644
	Stavanger	7	6.75	1.5	5.5	0.0240
	Combined	3.9	5	2.3	5	<0.0001
ESSDAI	UKPSSR	2	4	4	4	0.0193
	ASSESS	3	5	5	5	0.8902
	Stavanger	3	3	3	3	0.8824
	Combined	2	3	4	4	0.4183

No differences in age, gender, symptom duration, disease duration

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Differences in “routine” clinical laboratory parameters

Parameter	Cohort	LSB	HSB	DDF	PDF	P value
Lymphocytes	UKPSSR	1.2	1.5	1.27	1.32	<0.0001
	ASSESS	1.32	1.48	1.18	1.48	0.0251
	Stavanger	1.35	1.9	1.2	1.8	0.0303
	Combined	1.25	1.5	1.2	1.4	<0.0001
IgG	UKPSSR	17.97	14.1	16.63	14.35	<0.0001
	ASSESS	15	12.8	15.2	12.45	0.0028
	Stavanger	13.95	13.4	15.95	11.7	0.0054
	Combined	16.6	13.4	15.95	13.1	<0.0001
SSA/SSB	UKPSSR	93	87	94	85	0.0238
	ASSESS	70	59	74	54	0.0490
	Stavanger	90	60	100	59	0.0018
	Combined	85	75	89	72	0.0001

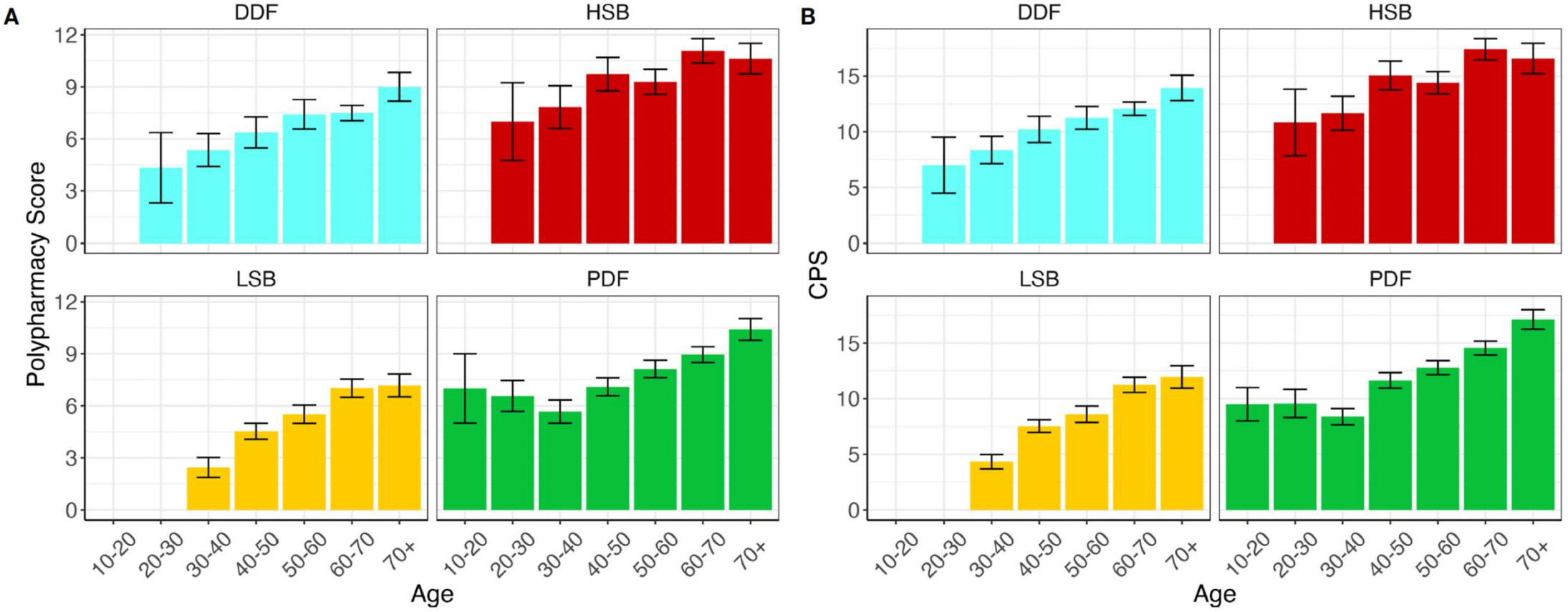
No differences in CRP and ESR

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

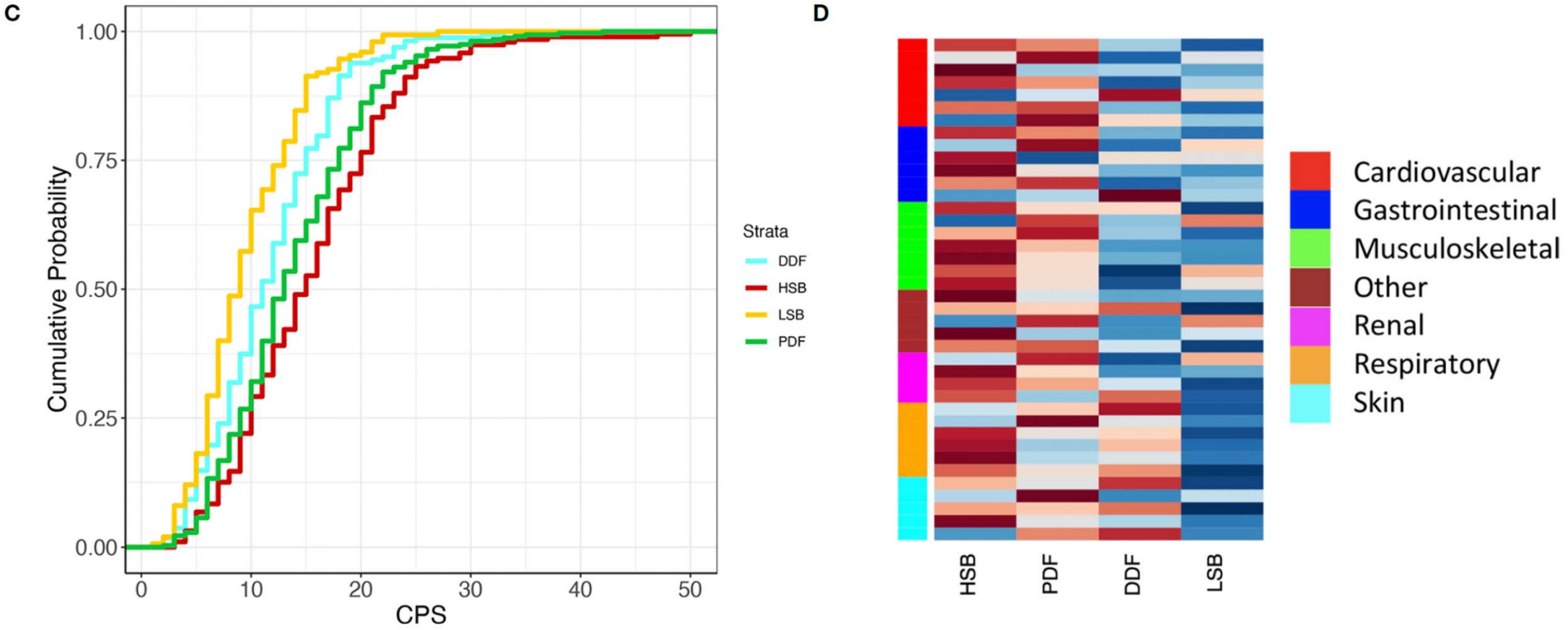
Differences in serum protein markers

Parameter	Cohort	LSB	HSB	DDF	PDF	P value
Log κ-FLC	UKPSSR	3.2	3.06	3.25	3.08	0.0336
	ASSESS	2.8	2.72	2.89	2.59	0.0106
Log λ-FLC	UKPSSR	2.94	2.86	3	2.86	0.0485
	ASSESS	2.75	1.69	2.78	2.63	0.3375
Log β2m	UKPSSR	1.34	1.3	1.38	1.32	0.0336
	ASSESS	1.2	1.14	1.25	1.12	0.0031
Log CXCL13	UKPSSR	4.86	4.97	5.33	5	0.04
	ASSESS	4.74	4.93	4.98	4.48	0.001
Lymphoma (%)	UKPSSR	1.6	5.6	11.2	2.6	0.0113

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019



Tarn JR et al, 2022. Front Immunol.



Tarn JR et al, 2022. Front Immunol.

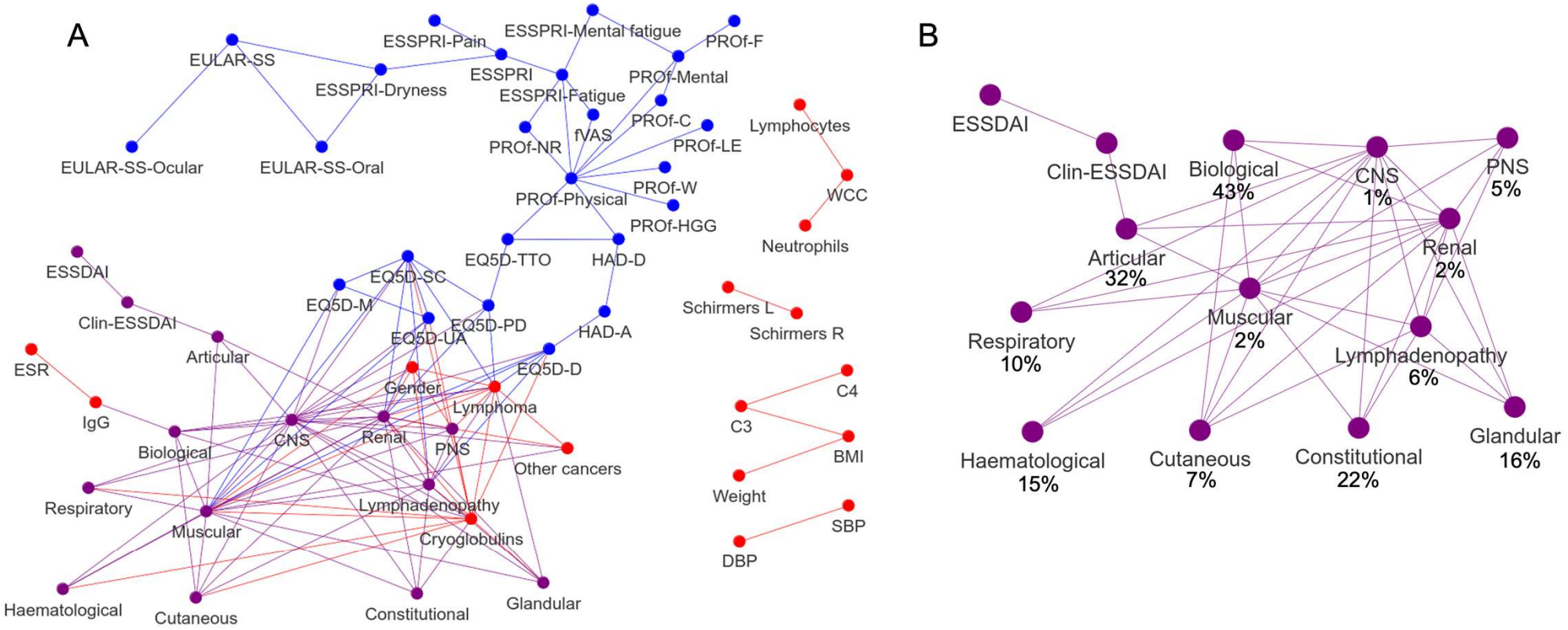


Figure 1. A) ARACNE Clinical network reconstruction for a cross-sectional dataset of 624 patient reported outcome measures and objective clinical and laboratory observations in SS. Edges between nodes represent shared information between the nodes. B) Sub-network of the ESSDAI subdomains showing the connections between them. Percentages in brackets represent the proportion of non-zero scores for each domain.

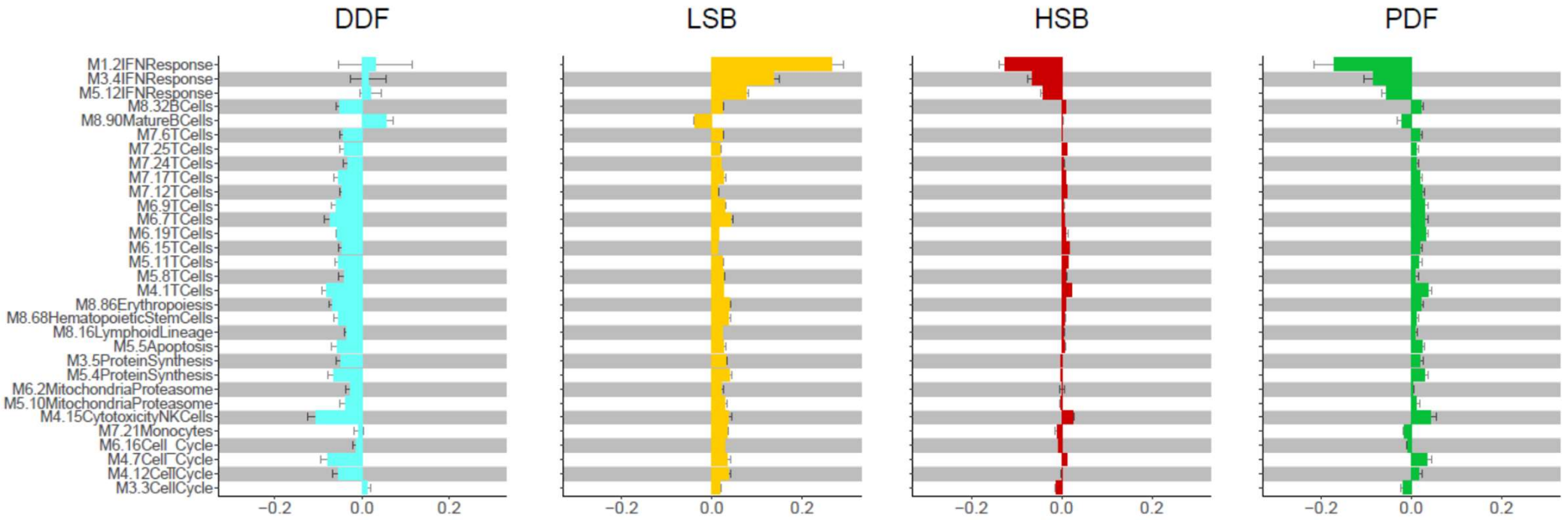
Tarn JR et al. (accepted).

Molecular profiles of the NSST subtypes

Approaches

- Peripheral blood transcriptomic profiles
- Serum proteomic profiles

Transcriptomic profiles of the NSST subtypes are distinct

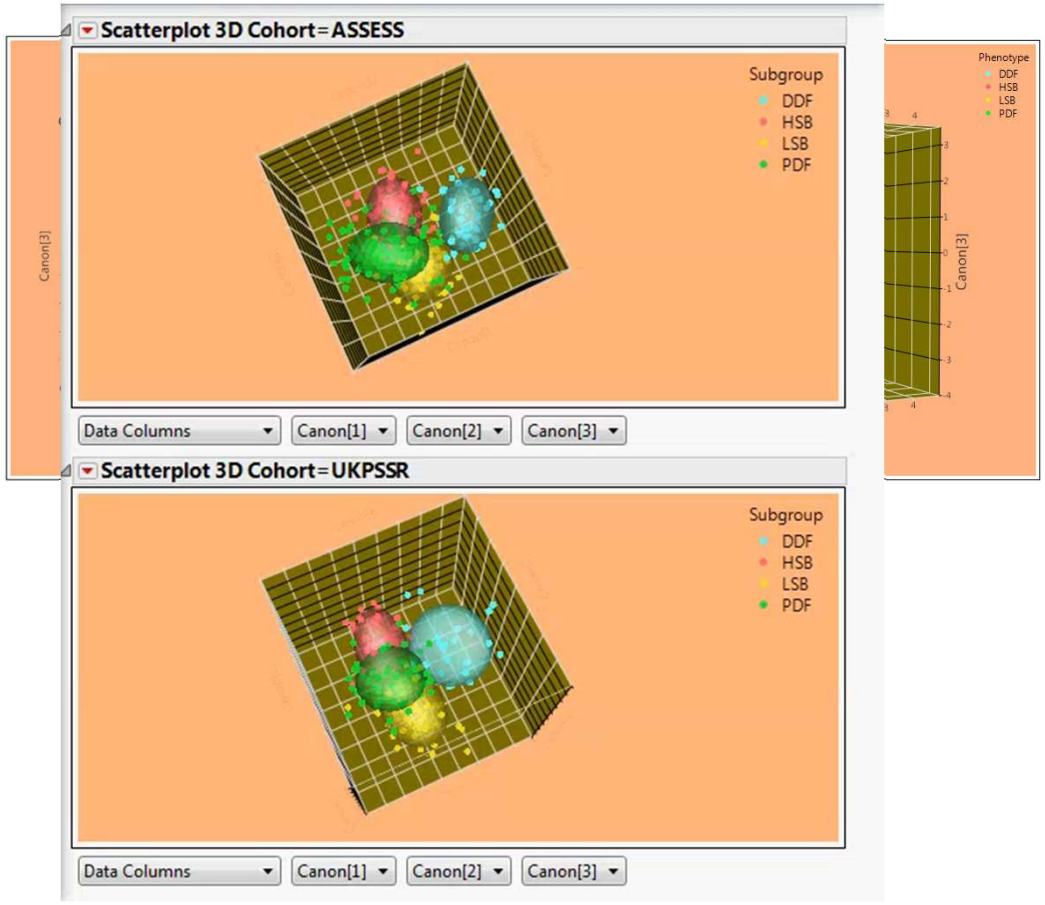


Differentially expressed transcriptomic modules

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Transcriptomic profiles of the 4 NSST subtypes are similar in independent cohorts and distinct from each other

UKPSSR



ASSESS

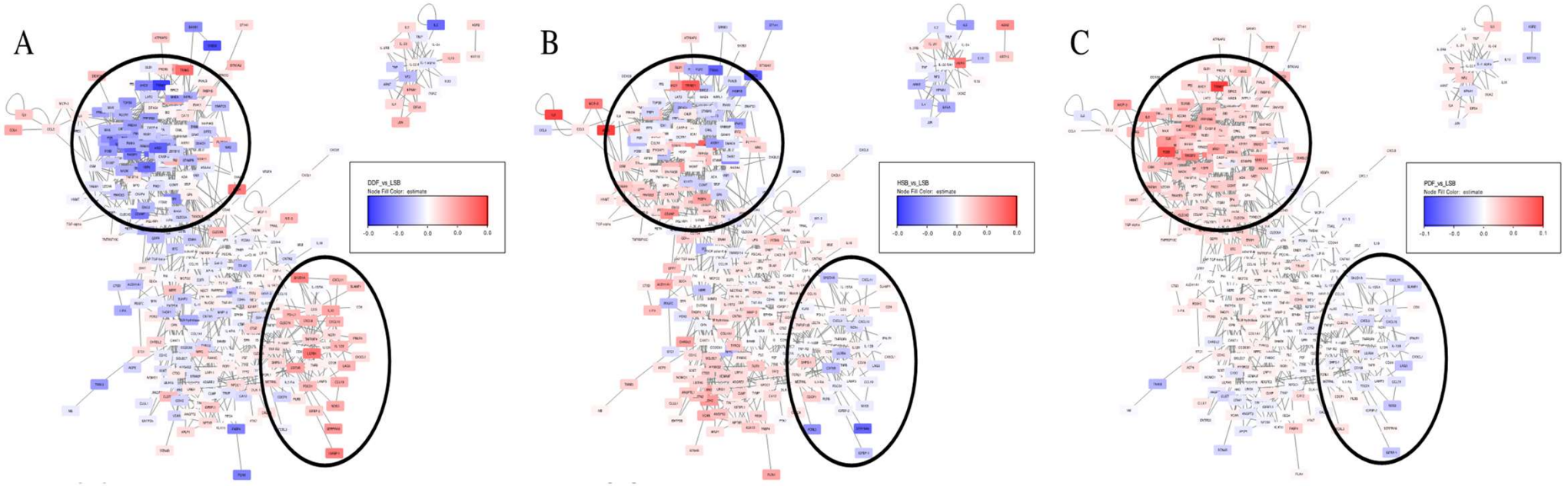
Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Serum proteomic profiles

- Profiled serum proteins of 180 SS patients from the UKPSSR (45 from each subtype)
- Five O-Link proteomics panels included a total of 454 unique proteins
- Network reconstruction using ARACNE algorithm (*Margolin AA et al, 2006*) using all patients
- Differential expression estimates were overlaid on these networks to highlight subnetworks of differential expression

Berry JS, et al. Ann Rheum Dis, 2023

O-link ARACNE Network



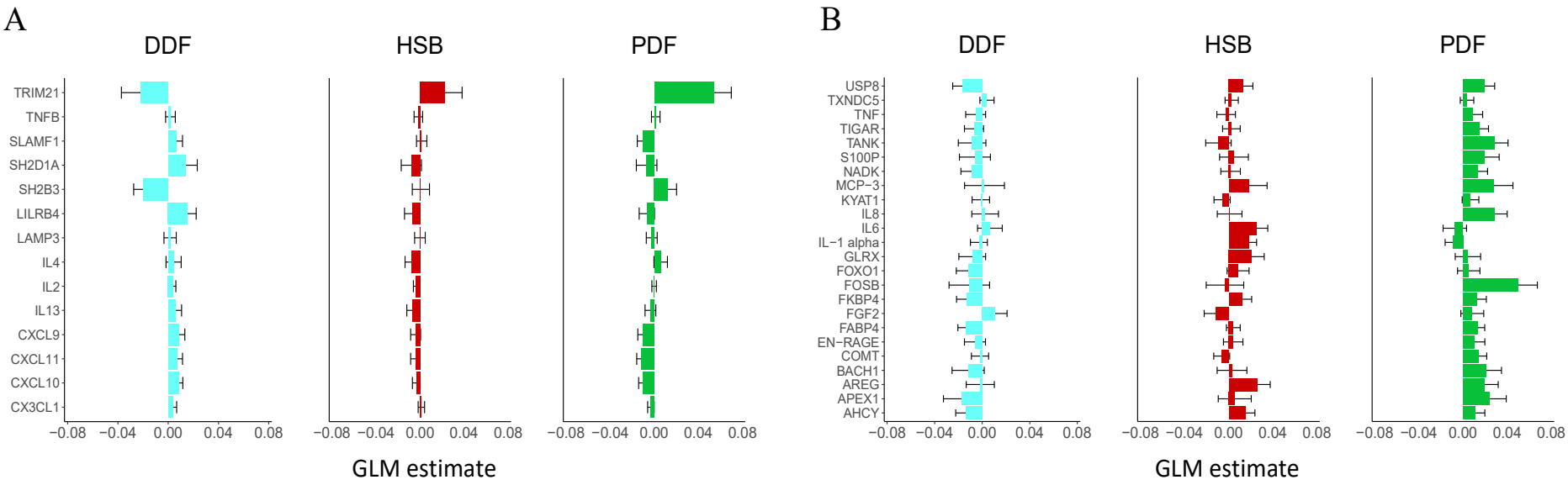
DDF HSB PDF

Nodes represent individual proteins and edges the mutual information between them.
Node color represents differential protein expression (Using LSB as a comparator)

Black ellipses highlight subnetworks with differential protein expression between the subtypes.

Berry JS, et al. Ann Rheum Dis, 2023

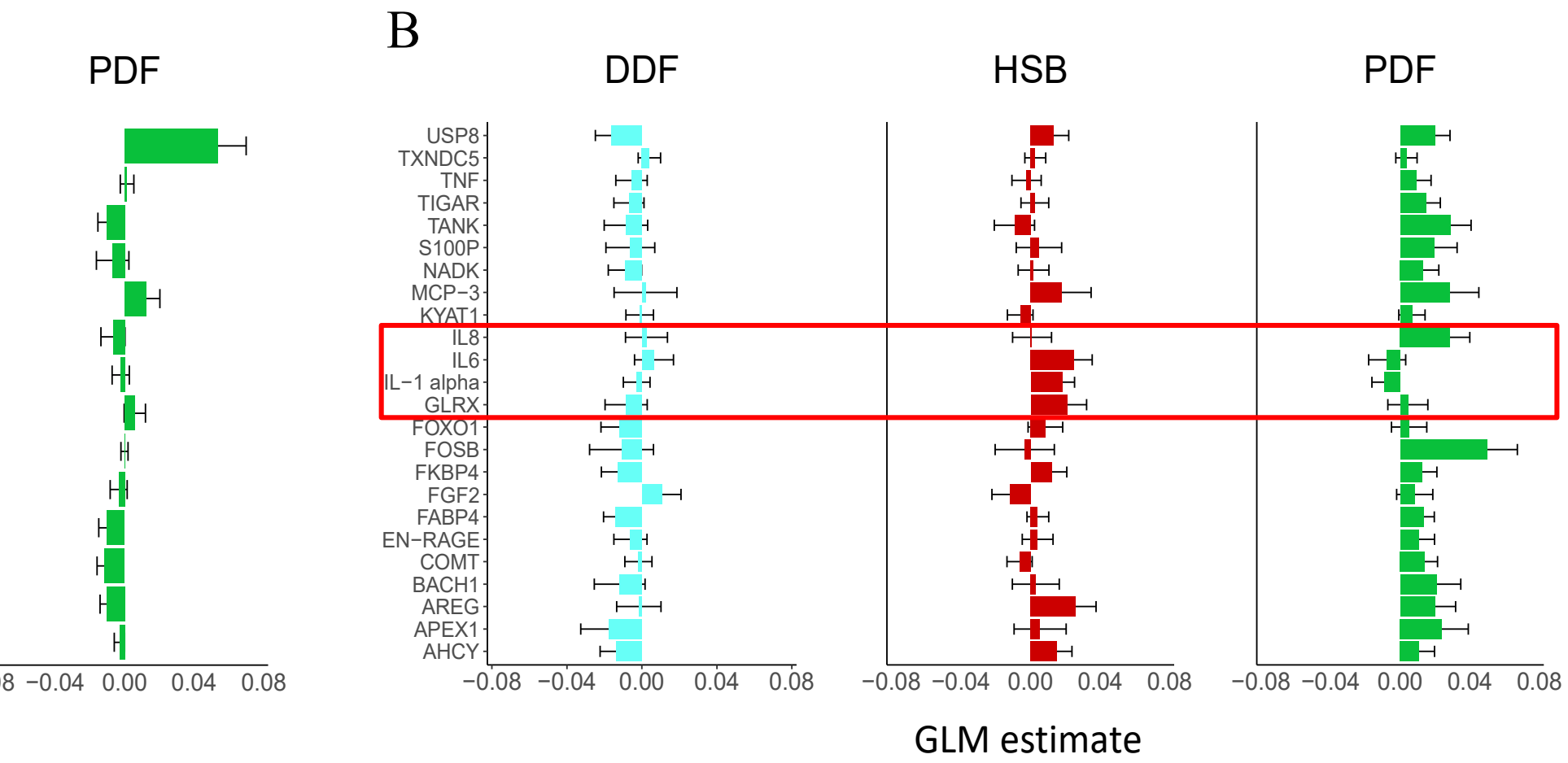
Protein expression between subtypes

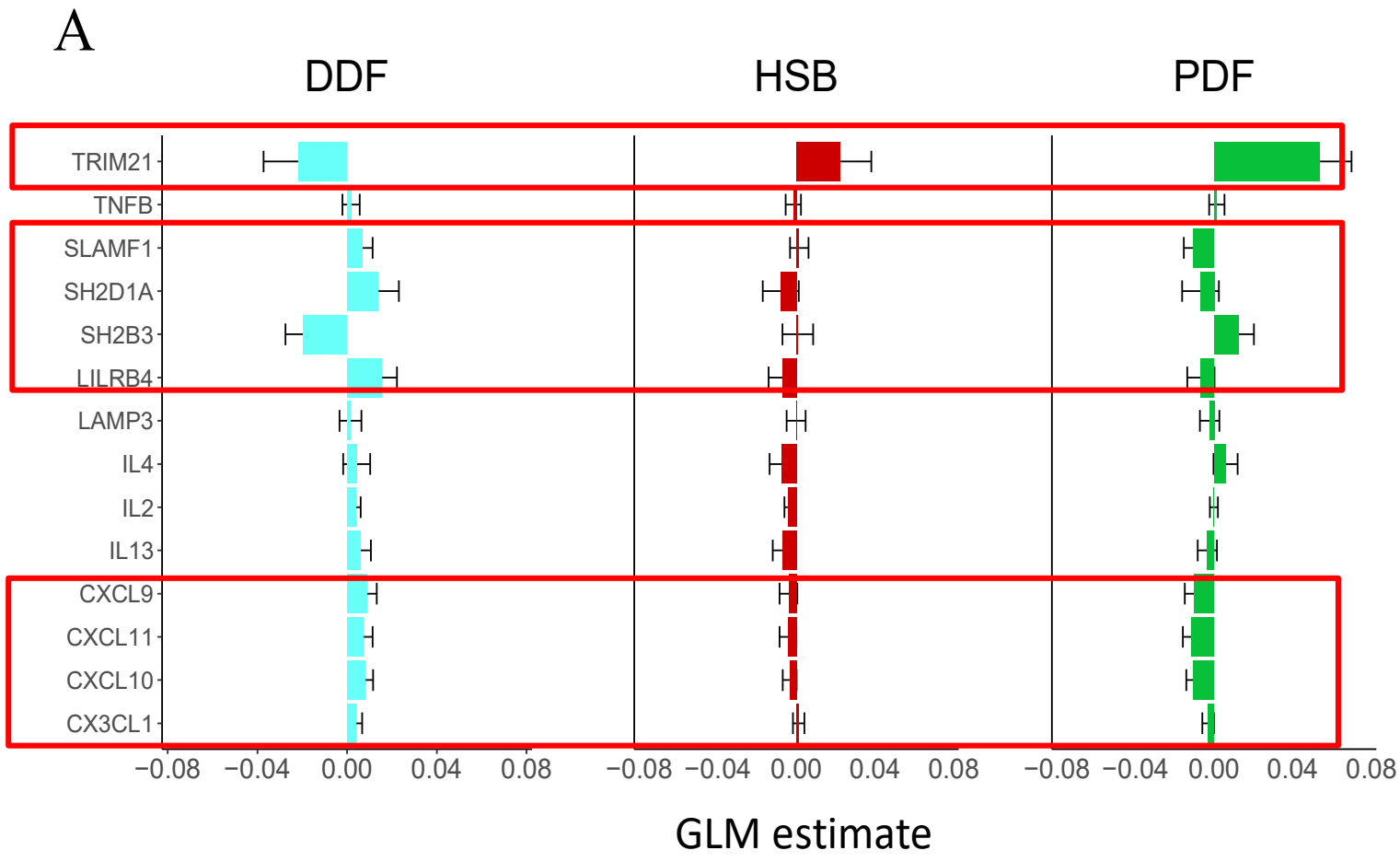


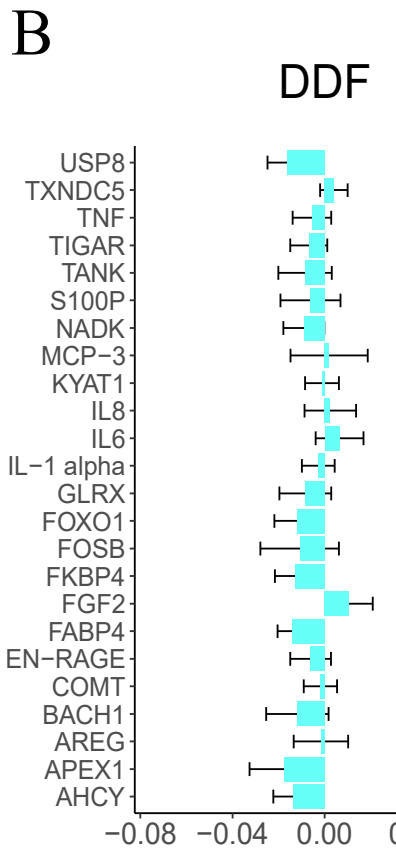
A. Selected proteins from the inferior subnetwork showing differences in inflammatory cytokines and chemokines associated with the DDF subtype

B. Selected proteins from the superior subnetwork showing the major differences associated with the DDF, HSB, and PDF subtypes.

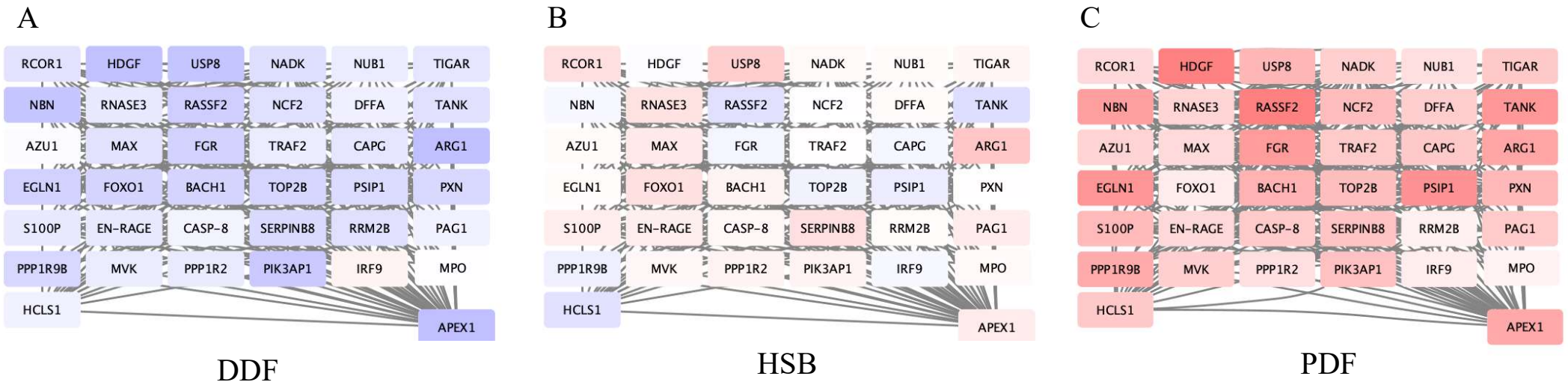
Berry JS, et al. Ann Rheum Dis, 2023


B
PDF
DDF
HSB
PDF
USP8
TXNDC5
TNF
TIGAR
TANK
S100P
NADK
MCP−3
KYAT1
IL8
IL6
IL−1 alpha
GLRX
FOXO1
FOSB
FKBP4
FGF2
FABP4
EN−RAGE
COMT
BACH1
AREG
APEX1
AHCY
−0.08 −0.04 0.00 0.04 0.08
GLM estimate


A
DDF
HSB
PDF
TRIM21
TNFB
SLAMF1
SH2D1A
SH2B3
LILRB4
LAMP3
IL4
IL2
IL13
CXCL9
CXCL11
CXCL10
CX3CL1
−0.08
−0.04
0.00
0.04
0.08
GLM estimate


B
DDF
USP8
TXNDC5
TNF
TIGAR
TANK
S100P
NADK
MCP−3
KYAT1
IL8
IL6
IL−1 alpha
GLRX
FOXO1
FOSB
FKBP4
FGF2
FABP4
EN−RAGE
COMT
BACH1
AREG
APEX1
AHCY
−0.08
−0.04
0.00

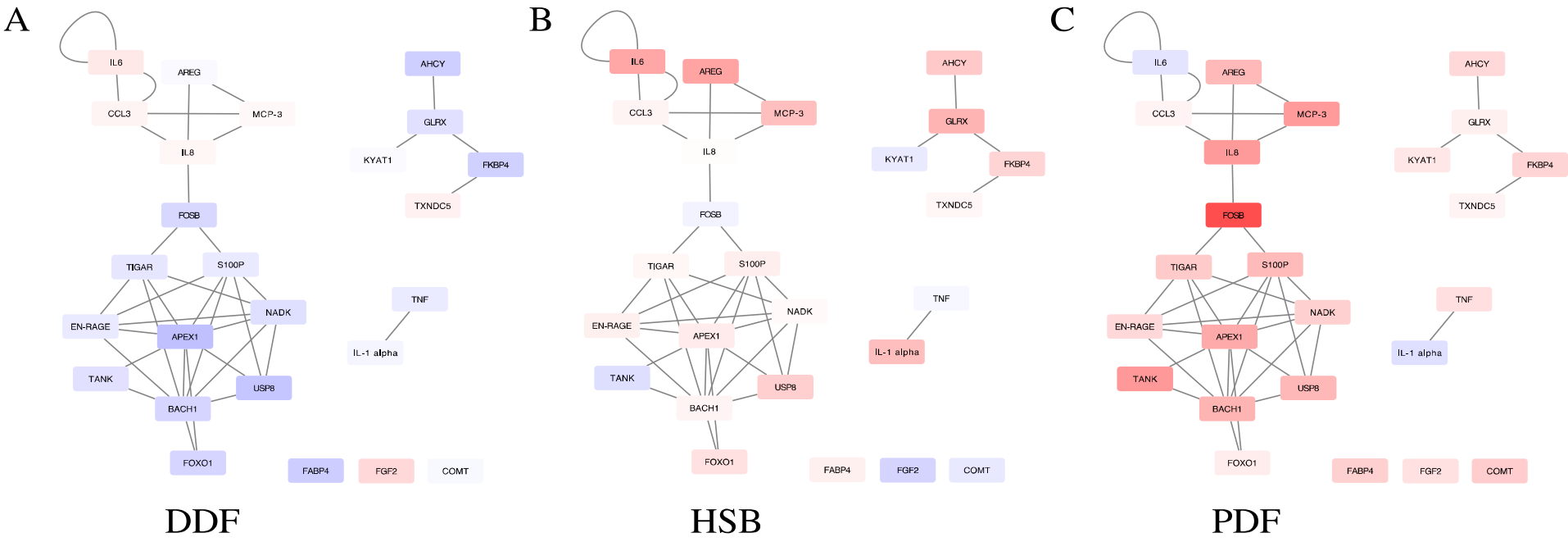
Examples of “hub” proteins



APEX Nuclease (Multifunctional DNA Repair Enzyme)

Berry JS, et al. Ann Rheum Dis, 2023

Examining the superior subnetwork



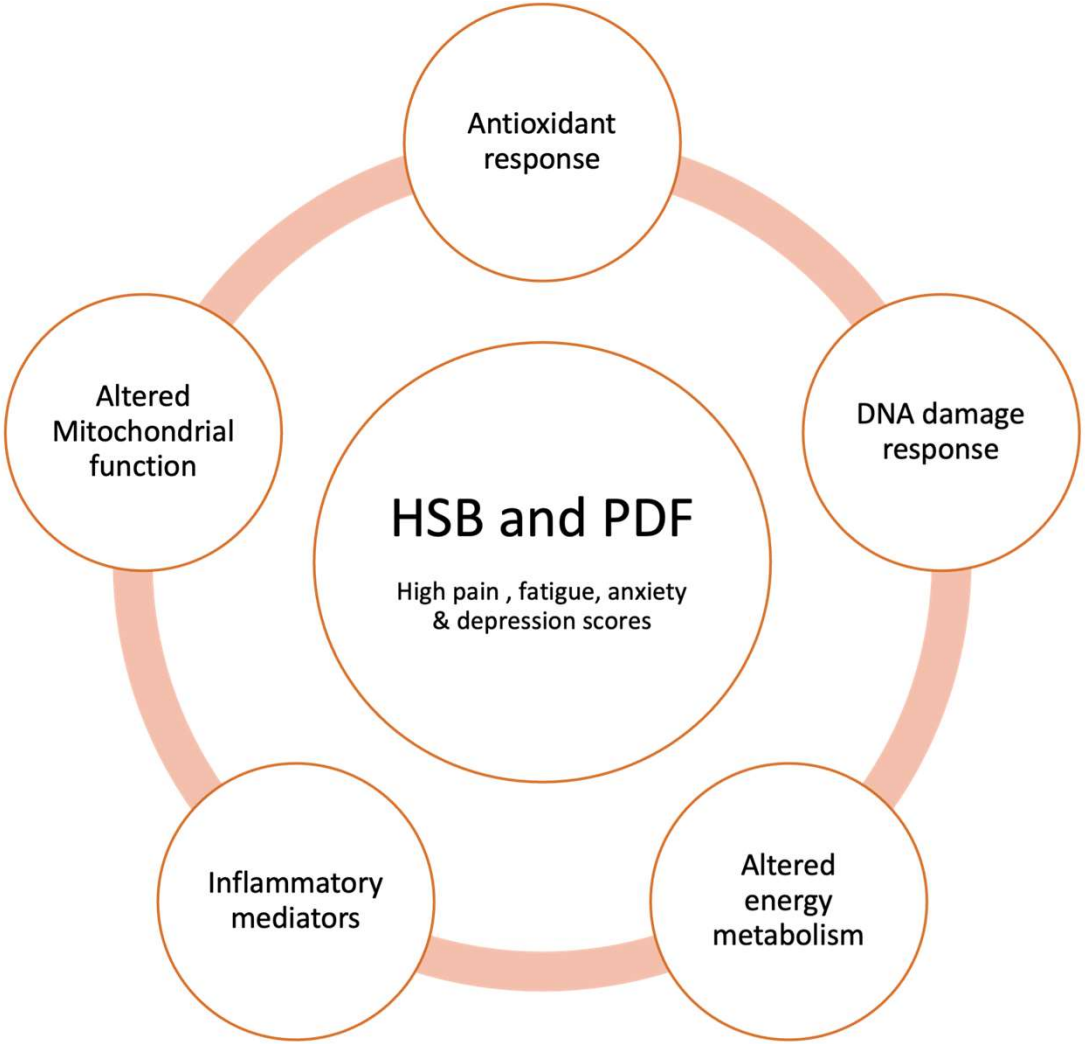
Selected proteins from the superior subnetwork showing the major differences in expression between the subtypes. Transcription factors such as APEX1, BACH1, TIGAR and FOXO1 demonstrate significant influence within the network.

Berry JS, et al. Ann Rheum Dis, 2023

Functional proteomic profiles of SS subtype

DDF	HSB	PDF
Glandular dysfunction & B-cell hyperactivity Increased expression of IFN-γ induced chemokines (CXCL9, CXCL10, CXCL11) Increased expression of chemokines associated with ELS (CXCL19, CXCL13, CX3CL1) Increased expression of B-cell stimulating cytokines (IL-2, IL-4, IL-10, IL-13, TNFB) Highest IFN module activity score Lowest level TRIM21 with highest Anti-SSA positivity	**Inflammation, antioxidant response & altered cellular metabolism** Increased expression of proteins associated with inflammation and innate immune response, oxidative stress response (GLRX, NADK, AHCY), and DNA repair (APEX1, TIGAR) Increase expression of transcription factors affecting energy metabolism (APEX1, TIGAR, FOXO1, BACH1) High levels of IL-6 and IL-1a Altered neuroimmunendocrine pathways associated with anxiety and depressive symptomatology (KAT1, COMT, IL-6, FGF2, FKBP4)	**Inflammation, antioxidant response & altered cellular metabolism** Increased expression of proteins associated with inflammation and innate immune response, oxidative stress response (GLRX, NADK, AHCY), and DNA repair (APEX1, TIGAR, HEXIM1, NBN) Increase expression of transcription factors affecting energy metabolism (APEX1, TIGAR, FOXO1, BACH1) Low levels of IL-6 and IL-1a High levels of FOSB

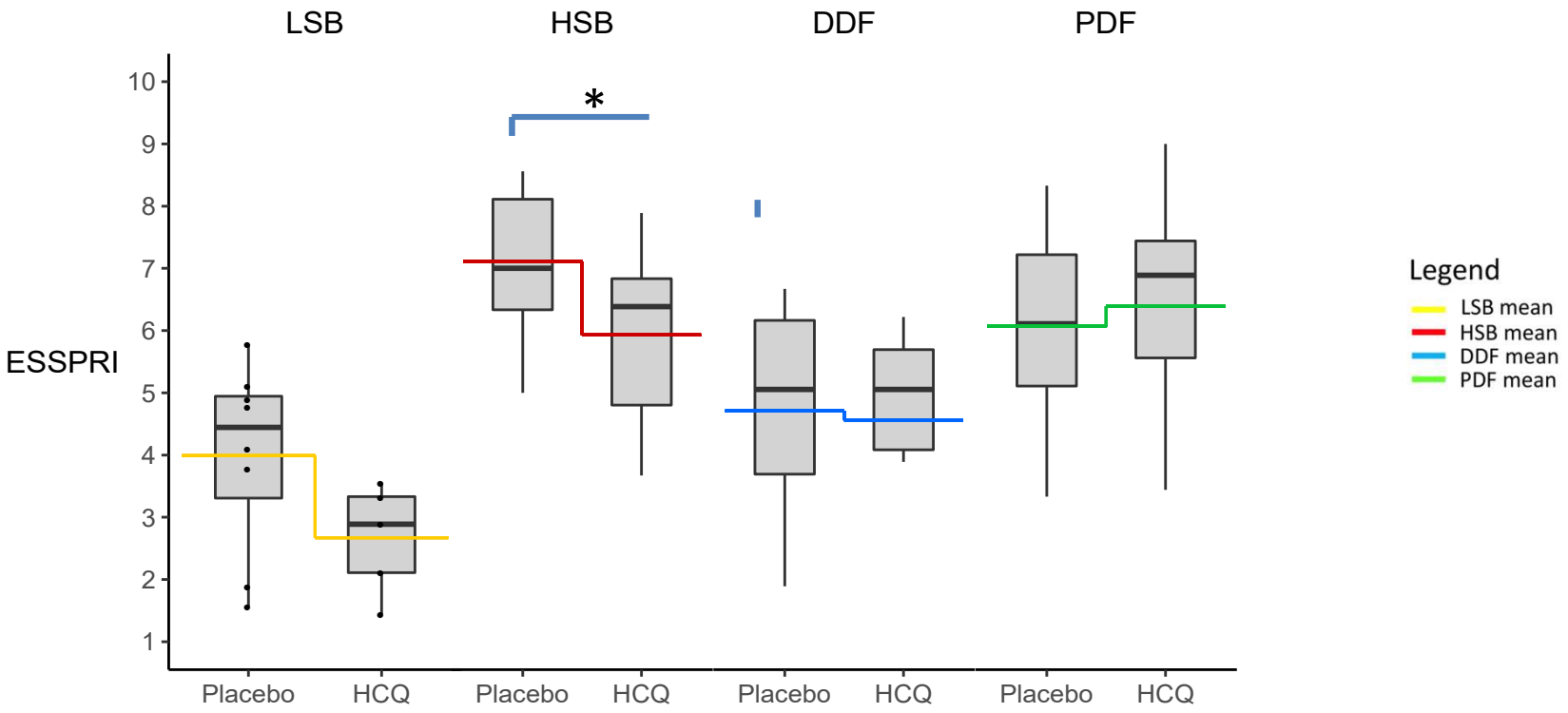
Berry JS, et al. Ann Rheum Dis, 2023



Berry JS, et al. Ann Rheum Dis, 2023

Translational potential of the NSST subtypes

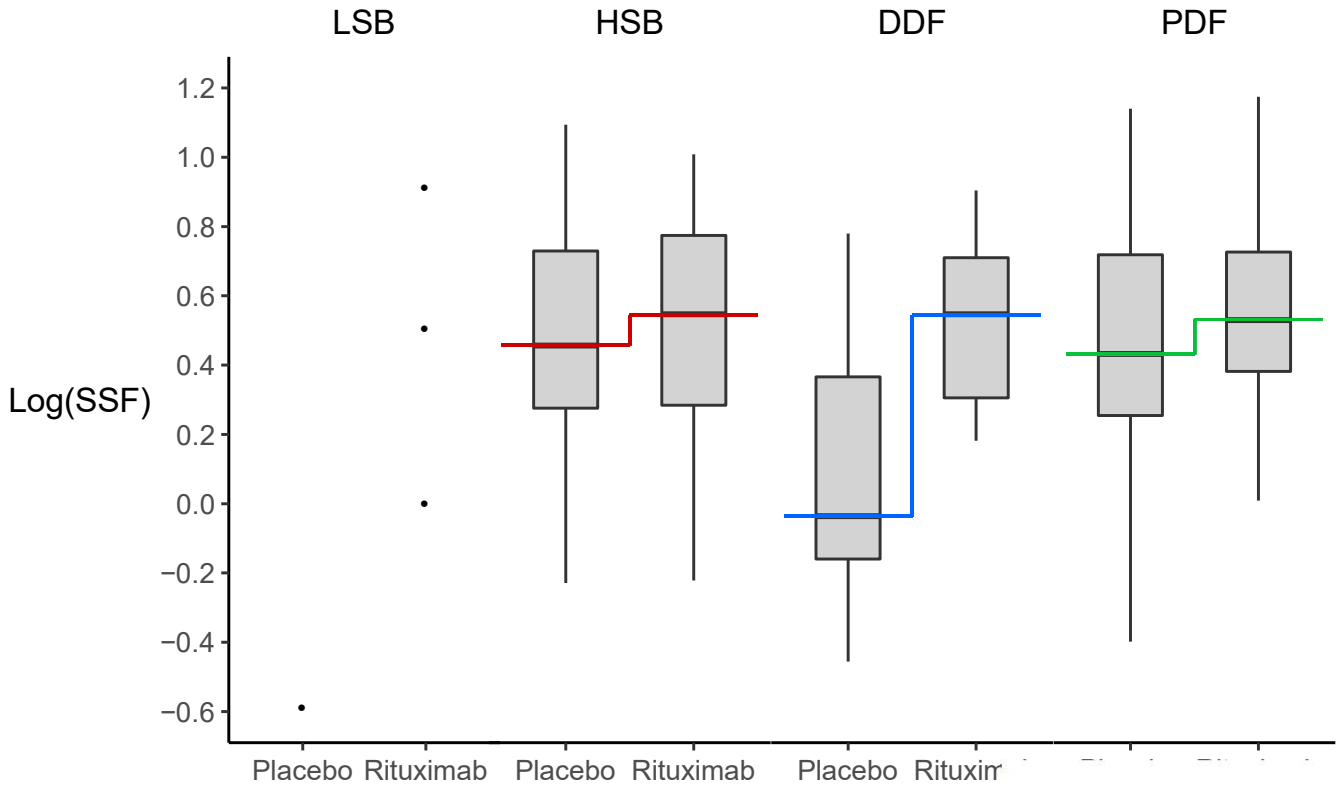
Differential response of SjD subtypes to hydroxychloroquine



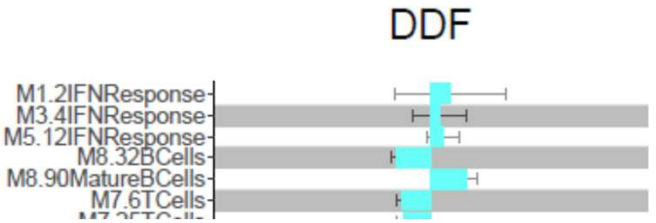
Reanalysis of the JOQUER trial using NSST

Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Differential response of SjD subtypes to rituximab

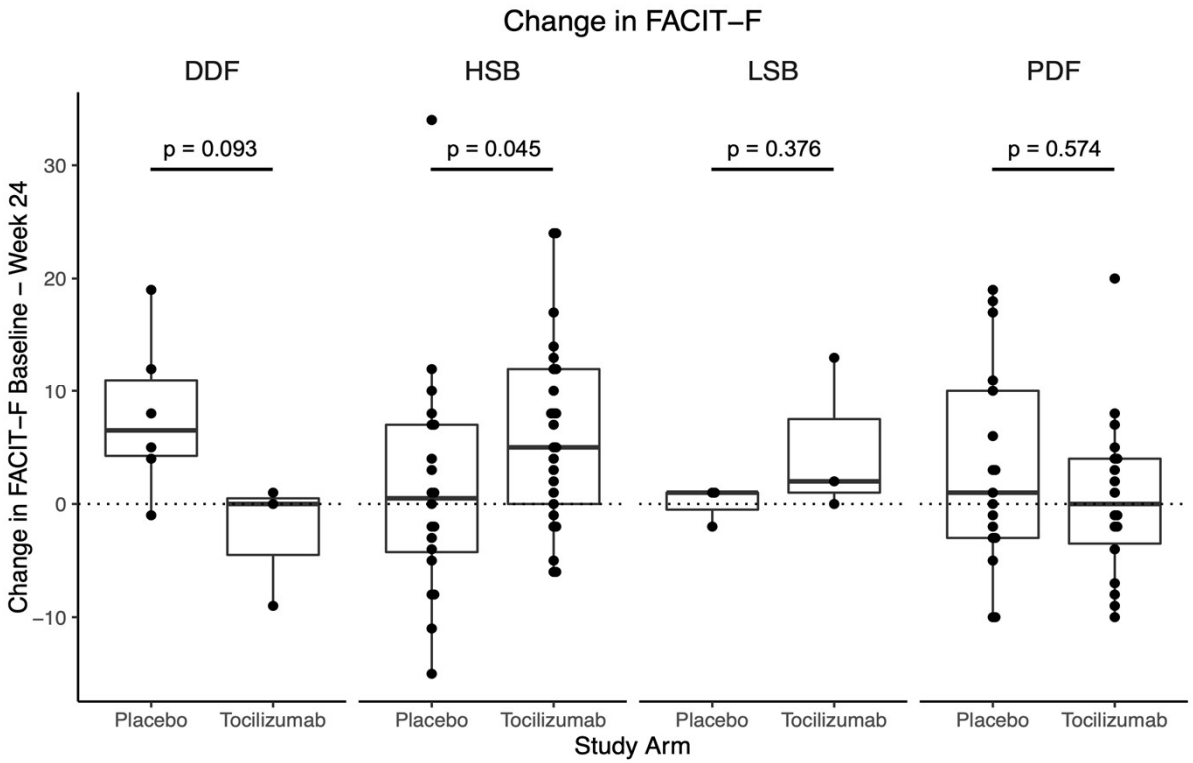


Reanalysis of the TRACTISS trial using NSST



Tarn, Howard-Tripp, Lendrem, et al. Lancet Rheumatology, 2019

Reanalysis of the phase 3 Tocilizumab trial



DDF: N=8 (PBO 5, TOC 3)
HSB: N=50 (PBO 20, TOC 30)
LSB: N=6 (PBO 3, TOC 3)
PDF: N=39 (PBO 20, TOC 19)

Stratified reanalysis of the Tocilizumab clinical trial (Felten R et al, 2021) using the four NSST symptom-based subgroups

NSST subtypes and health-related quality of life of Sjögren's patients – longitudinal data

- EQ-5D is a standardized instrument for the measurement of health outcomes.
- Used in cost-utility analyses for interventions / Quality Adjusted Life Years (QALY).
- 2 part questionnaire:
  1. Assess quality of life on 5 dimensions:
     - Mobility
     - Self-care
     - Usual Activities
     - Pain/discomfort
     - Anxiety/depression
  2. Global health state scale (0-100):
     - worst imaginable -> best imaginable health state

- A "Time Trade Off (TTO)" score ranging from -1 to +1 can be generated
  - 1 = best imaginable health state, 0 = rather be dead, <1 indicated health state worse than dead
- An EQ-5D TTO score of <0.5 is considered poor

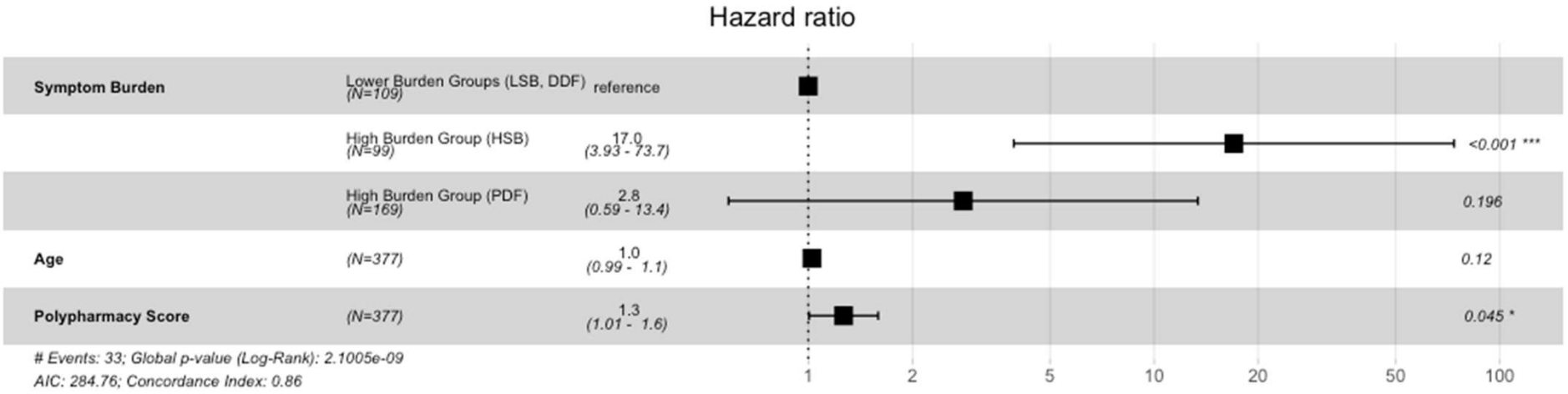
Longitudinal data on QoL- survival analysis

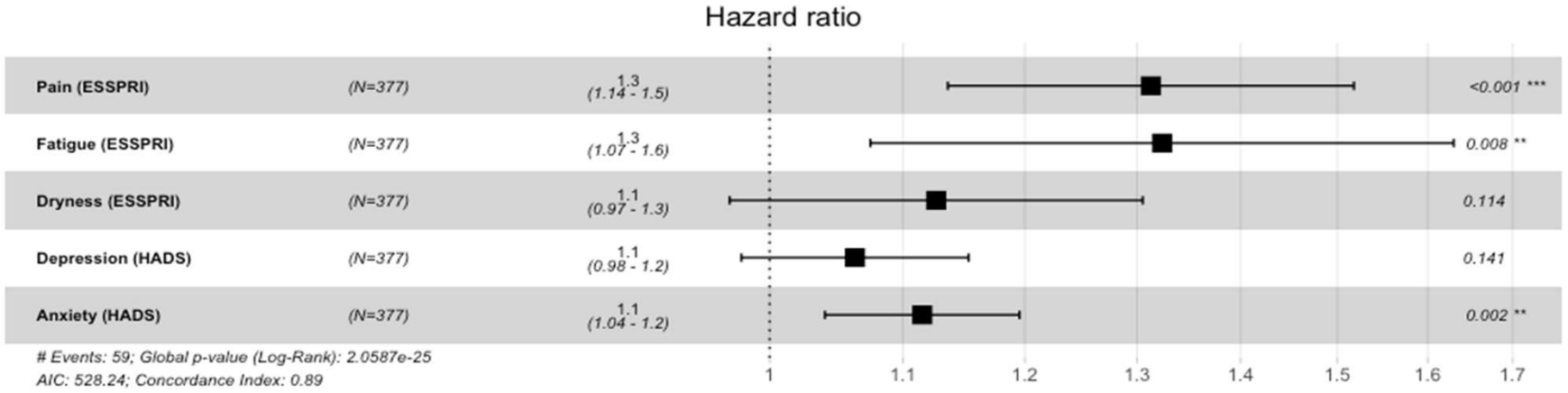
- Longitudinal EQ-5D-3L data from the Newcastle SjD cohort
- n = 377, median follow up time of 6.35 years
- Survival analysis / time-to-event analysis
  - The follow up time at which EQ-5D TTO ≤ 0 was recorded as an 'EQ-5D event'.

- How does quality of life differ between SjD clinical parameters?
  - Symptom burden (including NSST subtypes)
  - SjD outcome measures – ESSDAI, ESSPRI
  - Demographics
  - Comorbidity

Tarn JR et al, 2022. J Intern Med.

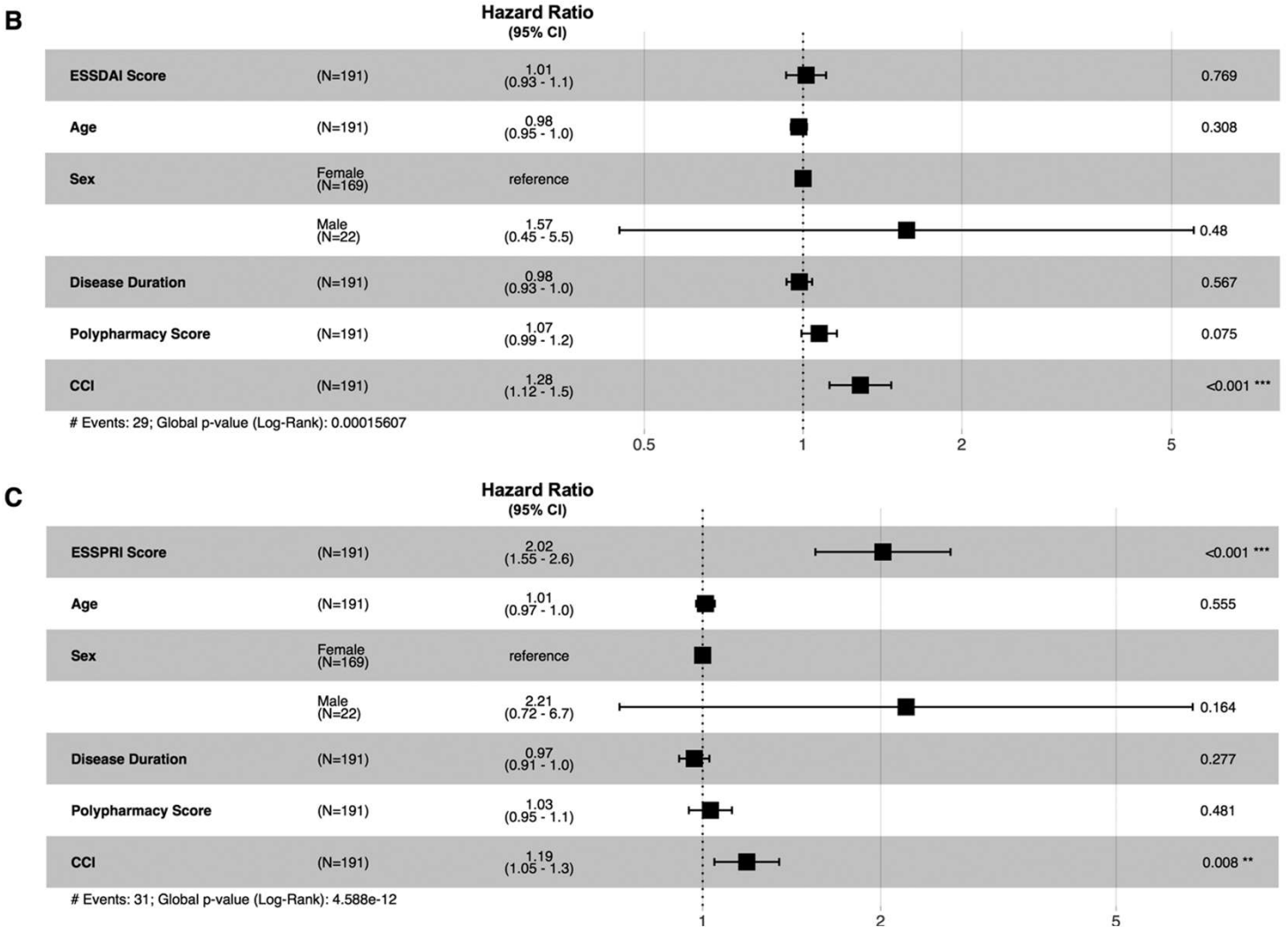
Symptom burden strongly predicts EQ-5D decline





Tarn JR et al, 2022. J Intern Med.

Disease activity and other factors are poor/weak predictors of EQ-5D decline

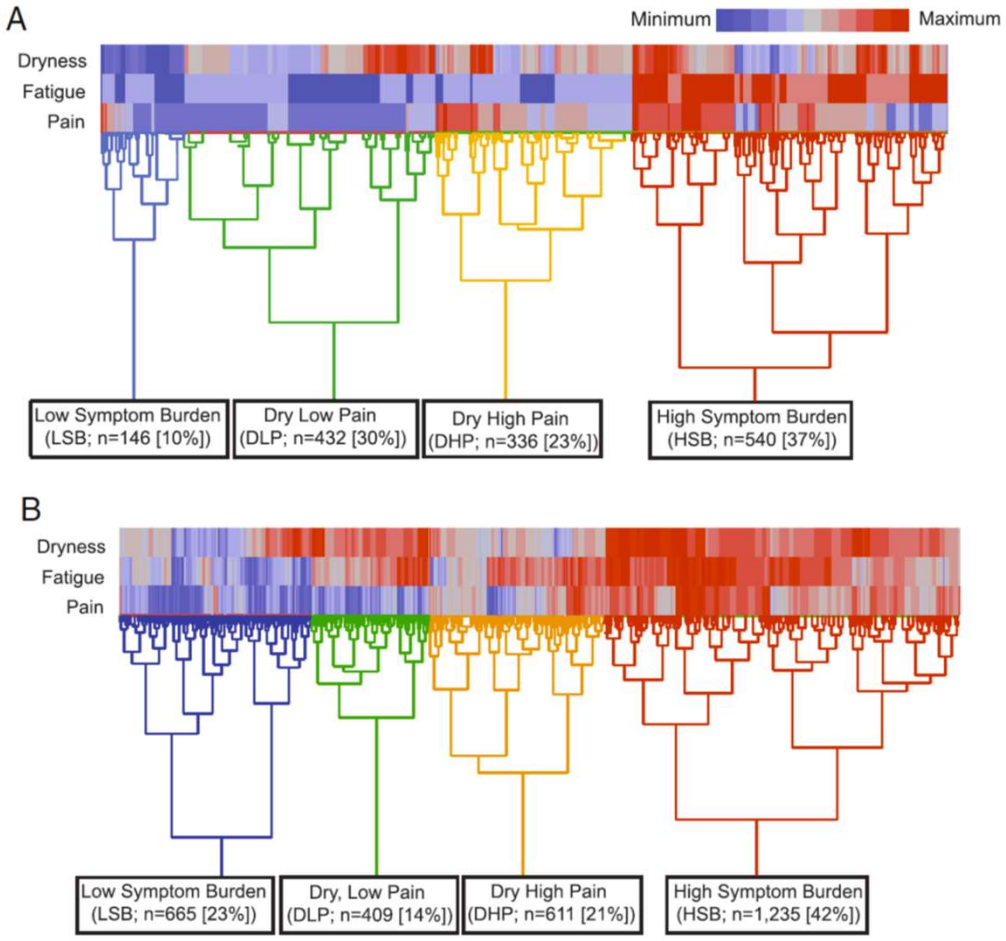


Tarn JR et al, 2022. J Intern Med.

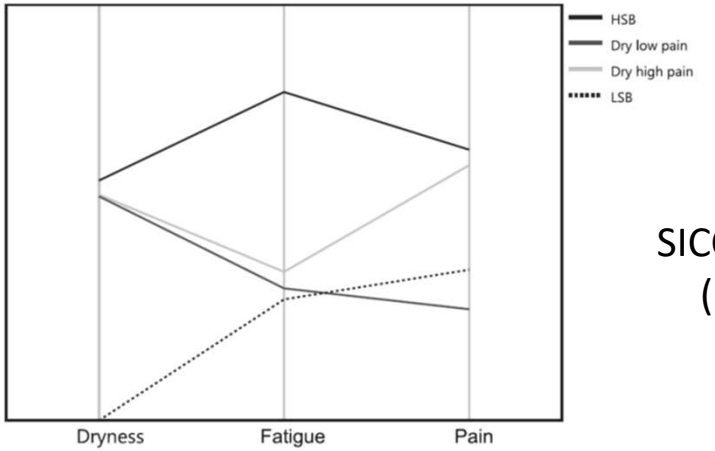
Conclusions

- Sjögren's can be stratified into distinct subtypes based on their symptom profiles
  - This stratification approach (NSST) is simple and can be done at the bedside
- These NSST subtypes have distinct laboratory and transcriptomic profiles
- The NSST subtypes may respond differently to therapies

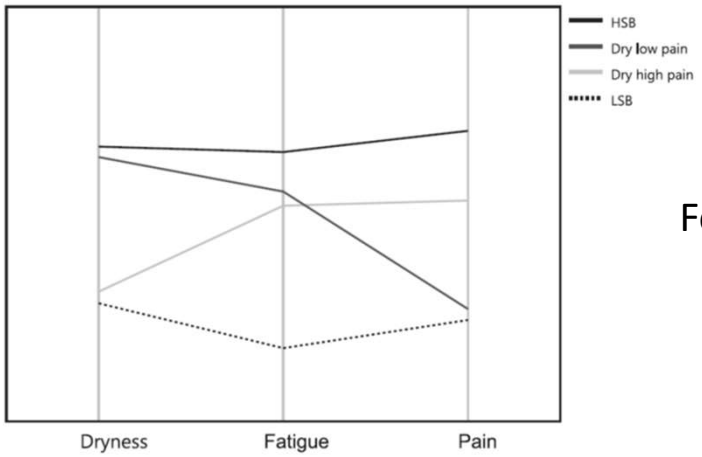
Other clinical stratification approaches



Hierarchical cluster analysis

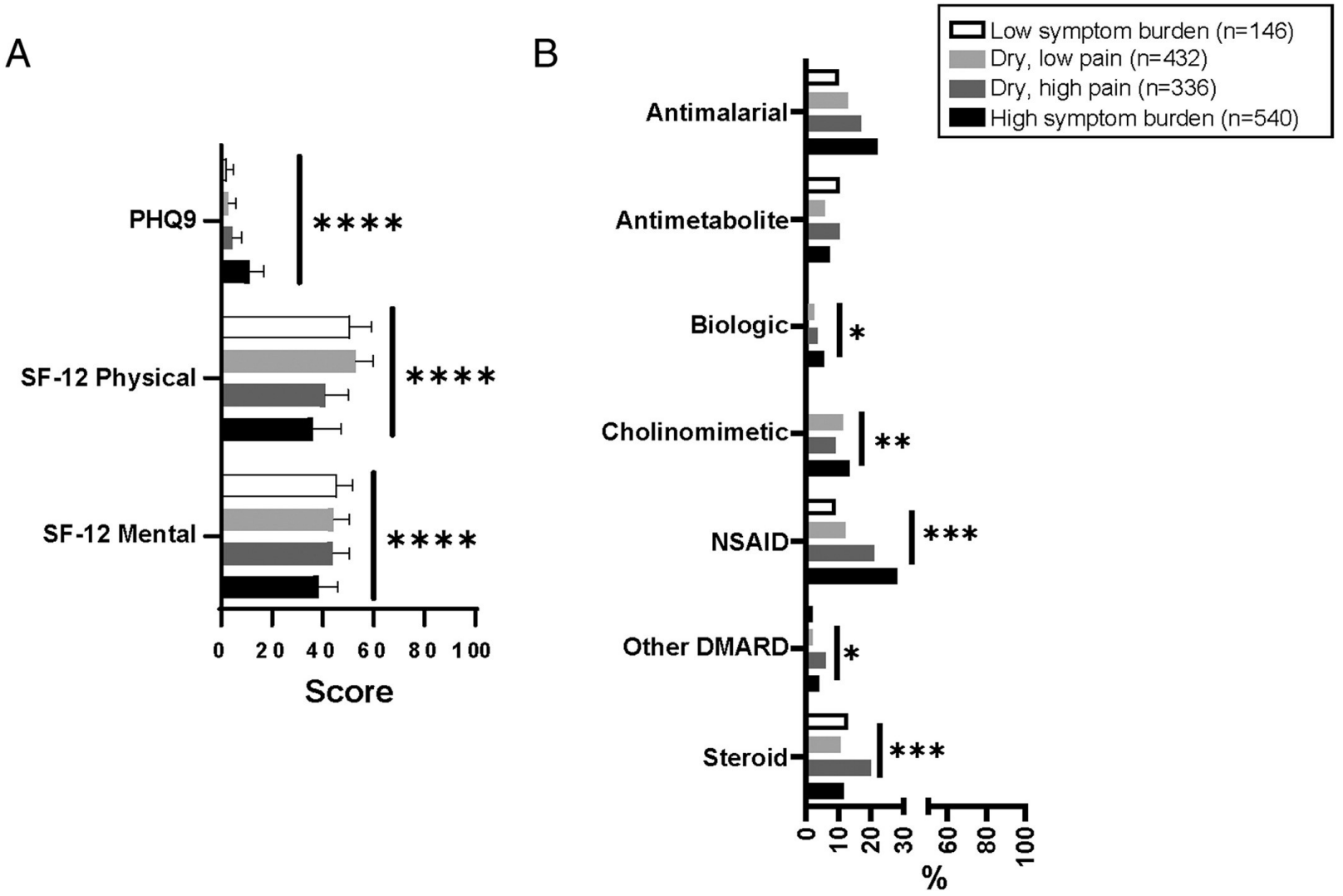


SICCA registry (n=1454)

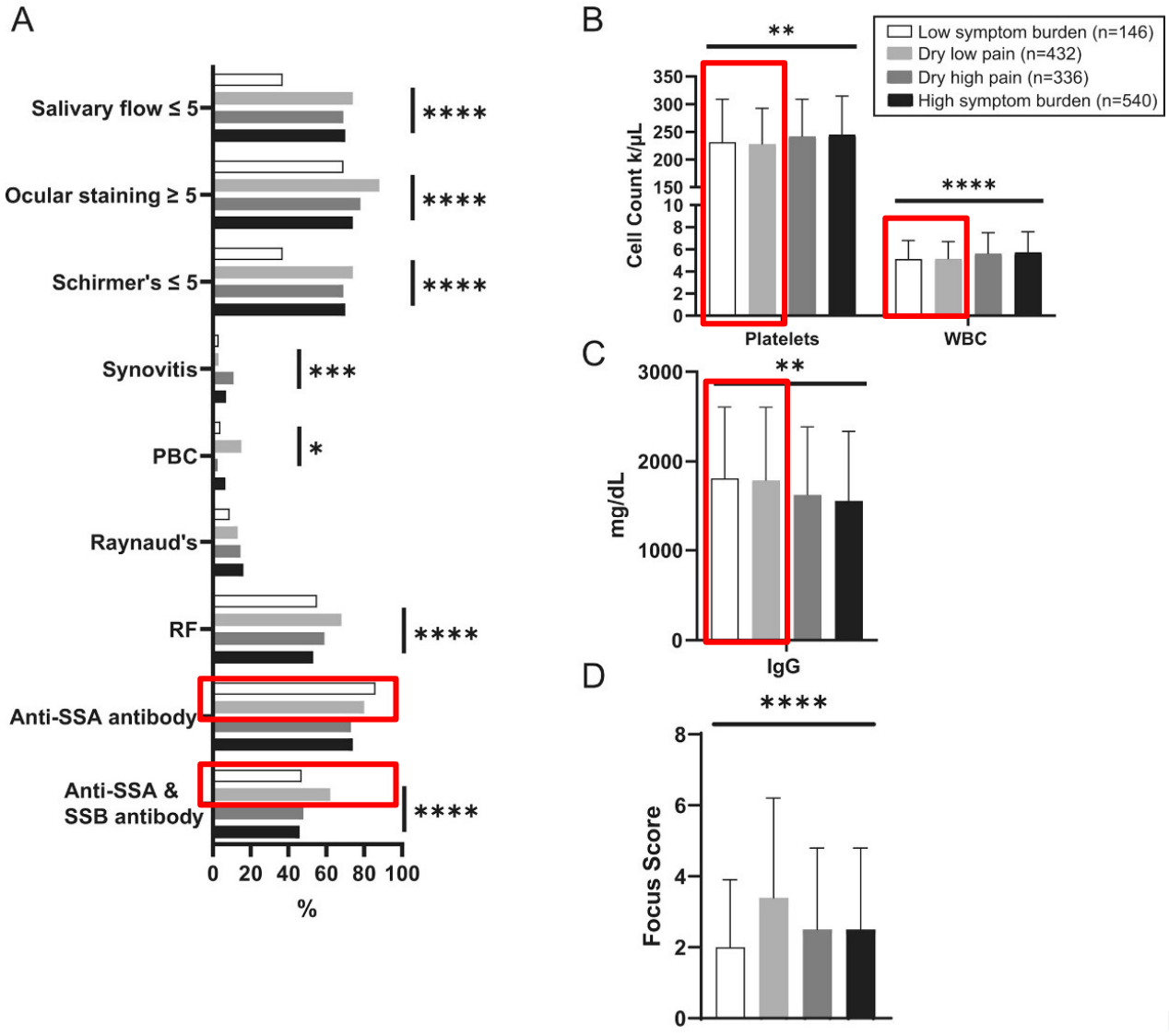


Sjogren Foundation survey (n=2920)

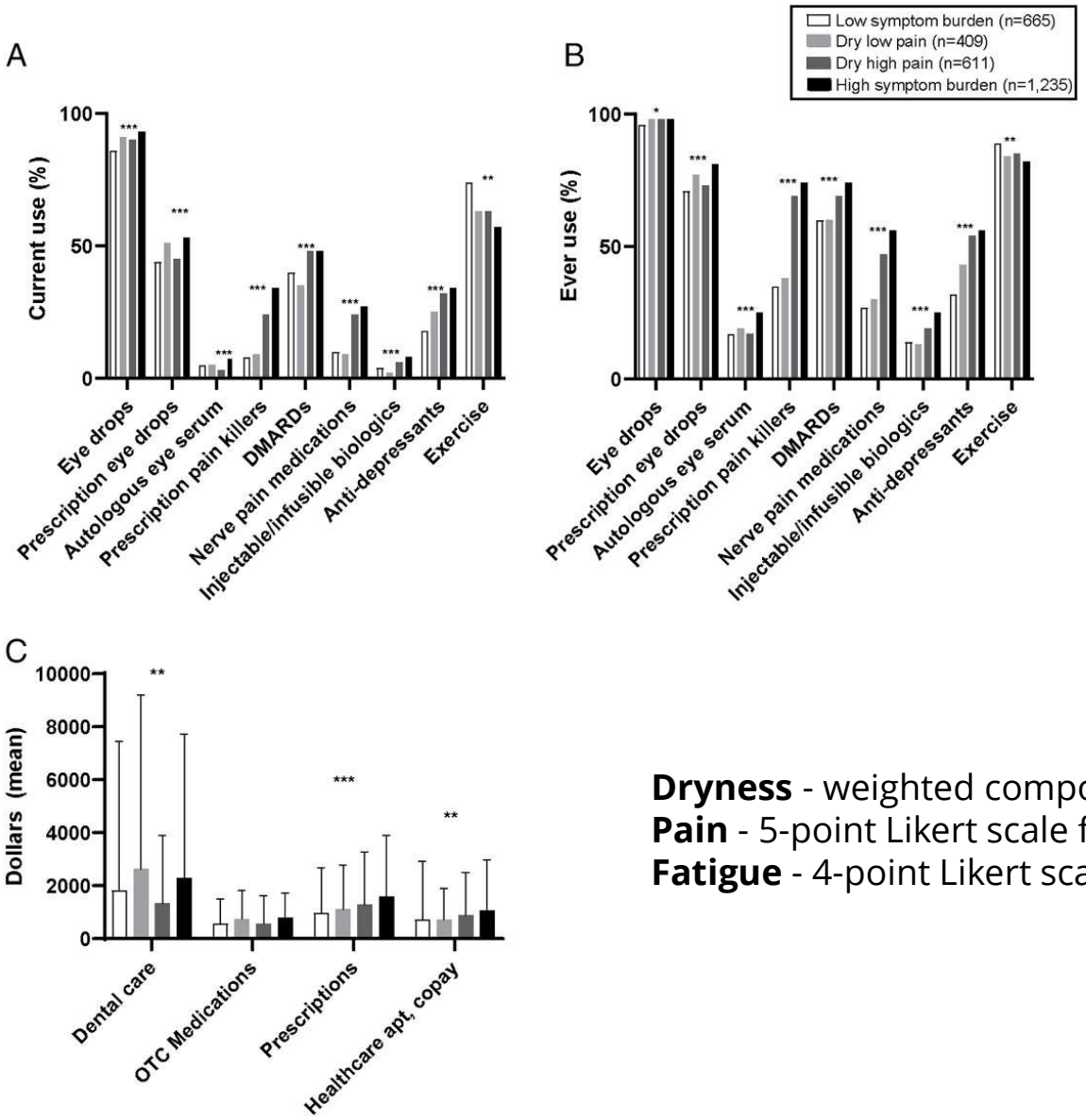
McCoy SS et al, Arthritis & Rheumatol, 2022



McCoy SS et al, Arthritis & Rheumatol, 2022



McCoy SS et al, Arthritis & Rheumatol, 2022



Dryness - weighted composite score of responses to 5 questions
Pain - 5-point Likert scale from “not at all” to “extremely,”
Fatigue - 4-point Likert scale from “not at all” to “nearly every day”

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Other symptom-based subtypes

- Korean Initiative Sjogren's syndrome (KISS)
- Five (? Four) symptoms:
  - ESSPRI Dryness (0-10), >5 as cut-off
  - ESSPRI Pain (0-10), > 3 as cut-off
  - ESSPRI Fatigue (0-10), > 7 as cut-off
  - EQ-5D* Anxiety/Depression, $\geq$ 3

Table 1 Baseline demographic and clinical characteristics of each class

	Class 1 Dryness dominant (n = 66)	Class 2 High symptom burden (n = 134)	Class 3 Low symptom burden (n = 121)	*P*
Pain	0 [0–3]	5 [4–7]	2 [0–3]	< 0.001
Fatigue	5 [4–6]	7 [6–8]	5 [3–5.5]	< 0.001
Dryness	8 [8–10]	8 [7–9]	5 [5–7]	< 0.001
Anxiety/depression	2 [1, 2]	3 [2, 3]	2 [1, 2]	< 0.001
Schirmer's test (OD)	n = 62 3 [1.75–5]	n = 112 4.5 [2–8]	n = 104 3.5 [2.25–7]	0.006
OSS (OD)	4 [2–6.25]	3 [1–5]	3 [1–5]	0.004
OSDI	35 [21.5–56.5]	48 [32–64]	28 [14–43]	< 0.001
uSFR (mL/5 min)	n = 46 0.1 [0–0.25]	n = 97 0.1 [0–0.4]	n = 89 0.25 [0.1–0.5]	< 0.001
sSFR (mL/5 min)	n = 40 1.5 [0.85–4.38]	n = 83 2.8 [1.5–5]	n = 70 2.75 [1.15–6.05]	0.091
Fibromyalgia	1 (1.5%)	12 (9.0%)	3 (2.5%)	0.021
Peripheral neuropathy	3 (4.5%)	25 (18.7%)	7 (5.8%)	0.001
Cryoglobulin positivity	n = 63 2 (3.2%)	n = 130 1 (0.8%)	n = 113 0 (0%)	0.116

Latent class analysis (n = 341)

Lee JJ et al, J Transl Med, 2021

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Dryness	8 [8–10]	8 [7–9]	5 [5–7]	< 0.001
Anxiety/depression	2 [1, 2]	3 [2, 3]	2 [1, 2]	< 0.001
Arthralgia/arthritis	13(19.7%)	81 (60.4%)	50 (41.3%)	< 0.001
Cutaneous involvement	6 (9.1%)	28 (20.9%)	13 (10.7%)	0.027
ESSPRI	5 [4.3–5.7]	6.7 [6–7.7]	4 [3–4.7]	< 0.001
ESSDAI	3 [1–6]	4 [2–8]	3 [1–5.75]	0.03
Articular	0	0[0–1]	0	0.004
PNS	0	0	0	0.027
Corticosteroid	24/66 (36.4%)	63/134 (47.0%)	33/121 (27.3%)	0.0049

- Low C3 level was more frequently found in dryness dominant group (24.6% vs 18.5% (high symptom burden) vs 10.7% (low symptom burden, p=0.041)
- HSB group was more frequently treated using NSAIDs (18.7% vs. 4.5% (DD) and 13.2% (LSB), p=0.024)

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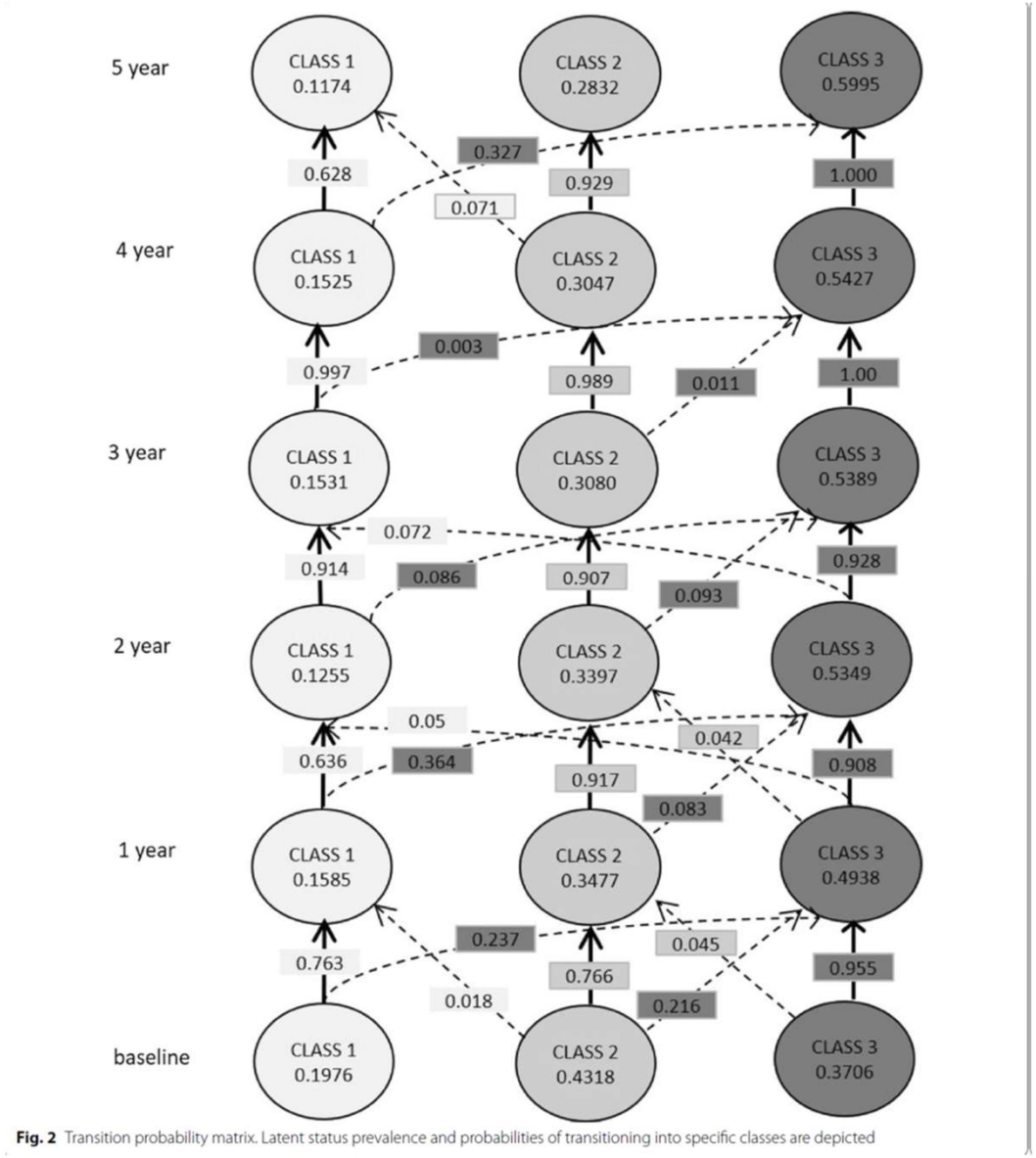

Fig. 2 Transition probability matrix. Latent status prevalence and probabilities of transitioning into specific classes are depicted

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Other “clinical” stratification

- Cross-sectional survey “real world data”
- 5 countries (France, Italy, Spain, Germany, US)
- Eligibility: Adults with pSS **and current or past systemic disease** activity according to physician opinions.
  - Not all SS included
  - Diagnosis is clinically based
- 316 physicians, 1879 patient record forms, 888 patient-completed PROs
- Latent class analysis

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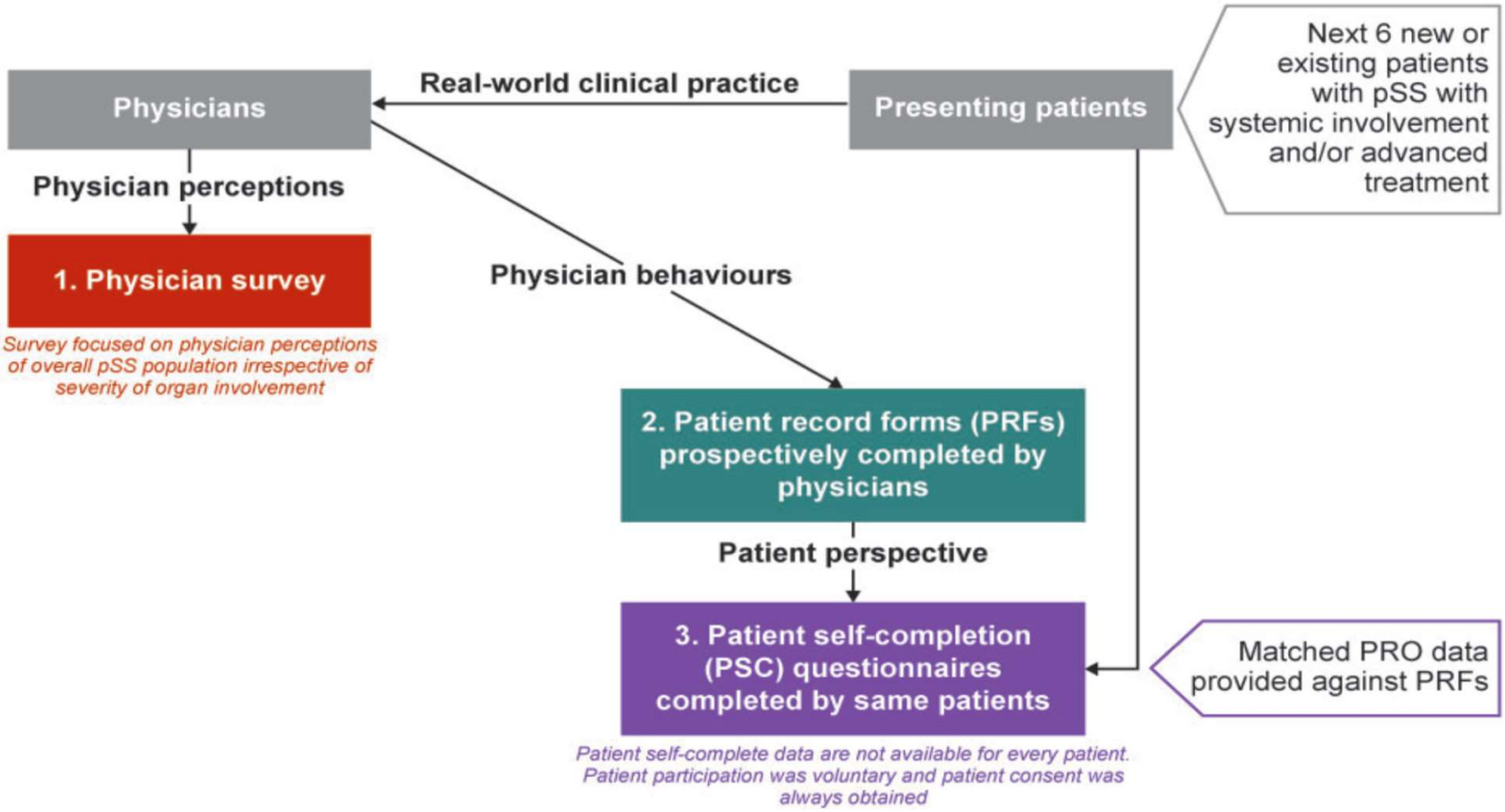
Fig. 1 Summary of DSP methodology



DSP: Disease-Specific Programme; PRO: patient reported outcome; pSS: primary Sjögren's syndrome.

Variables included in the first model of the latent class analysis

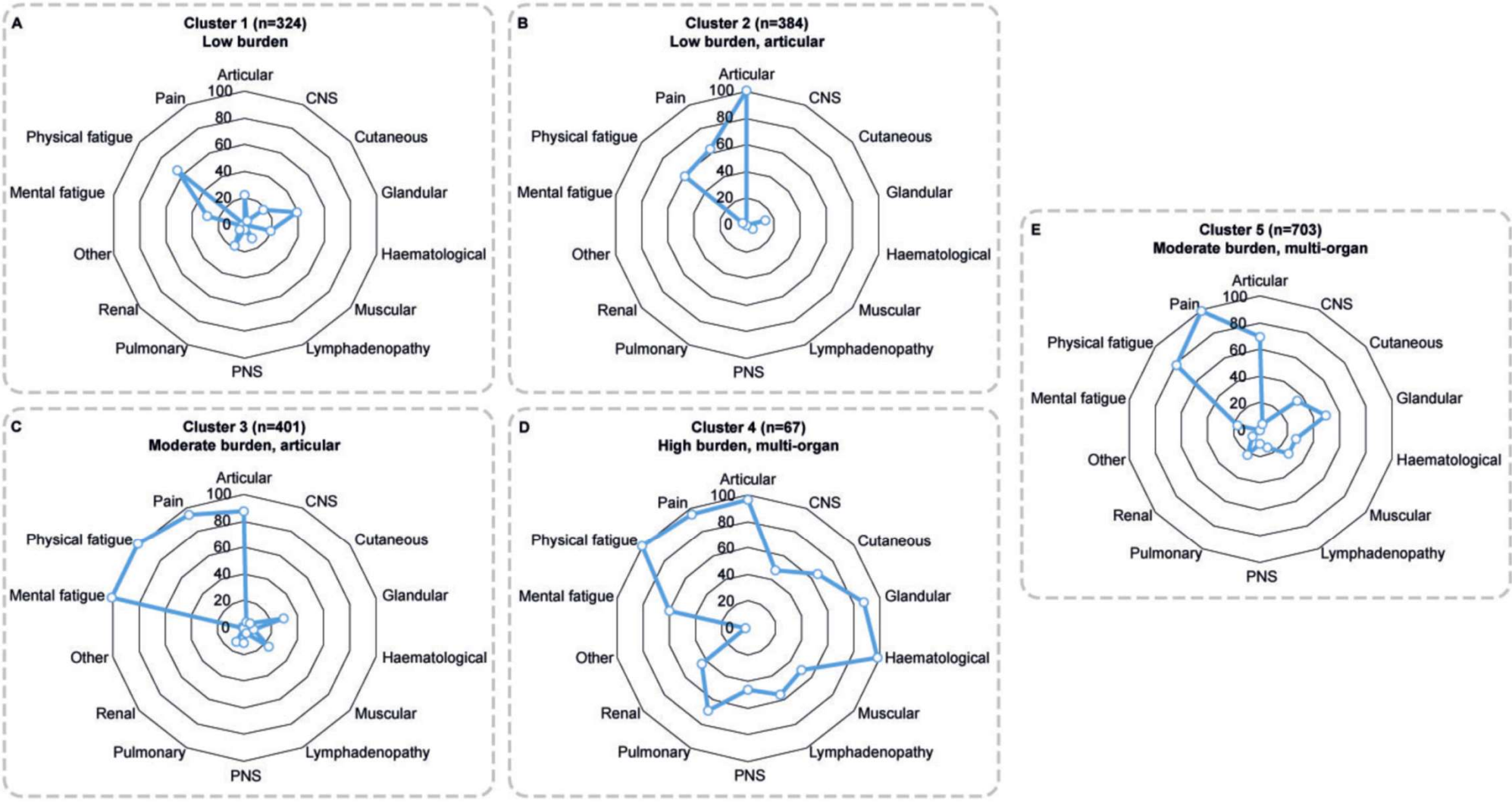
- Patient demographics, age, gender, BMI, employment status
- Current signs and symptoms (sicca, pain, fatigue and organ involvement) and severity of involvement
- Objective test results (unstimulated/stimulated salivary flow rate, Schirmer's test result, serum anti-SSA/Ro positivity, serum anti-La/SSB positivity, complement levels [C3 and/or C4])
- Time to onset of organ involvement
- Time between first symptoms and diagnosis
- Time since diagnosis
- Physicians' Global Assessment of disease activity
- Physician assessment of disease progression
- Concomitant conditions
- Treatment response
- Satisfaction with treatment

Variables included in the final model of the latent class analysis

- Type of organ involvement,
- Presence of pain (at the time of the survey)
- Presence of fatigue (at the time of the survey)

- Duration of the pSS diagnosis was retained
  - to aid interpretation of cross-sectional dataset.

Choice of cluster solution was based on the Bayesian information criterion and clinical input.



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Conclusions

- Clinical stratification of SjD may have important role in understanding disease pathogenesis, therapeutic development and clinical management
- Different approaches have been described, each approach may have their merits in different contexts of utility

danken

Sjögren's registry

Patients & healthy volunteers

Newcastle Sjogren's Group

Jessica Tarn
Dennis Lendrem
Joe Berry
Karl Wood
Nadia Howard-Tripp
Emmanuella Traianos
Sheryl Mitchell
Ben Hargreaves
David Storey
James Locke
Christine Downie
Alexis Collins
Katherine James

Victoria Macrae
Sheryl Mitchell
Ben Hargreaves
Kristen Davies
Jade Walton
Sarah Legg

Also:
Clare Lendrem
Andrew Skelton
Graham Smith
John Casement
Peter McMeekin

Thank you....

Newcastle Musculoskeletal CLRN
Newcastle Biomedical Research Centre