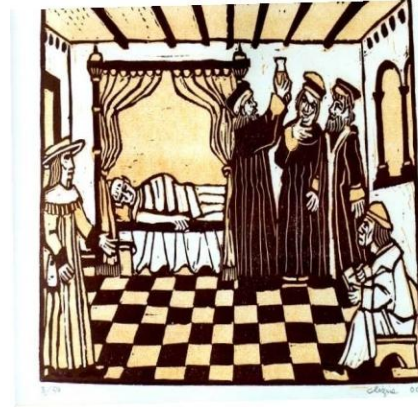
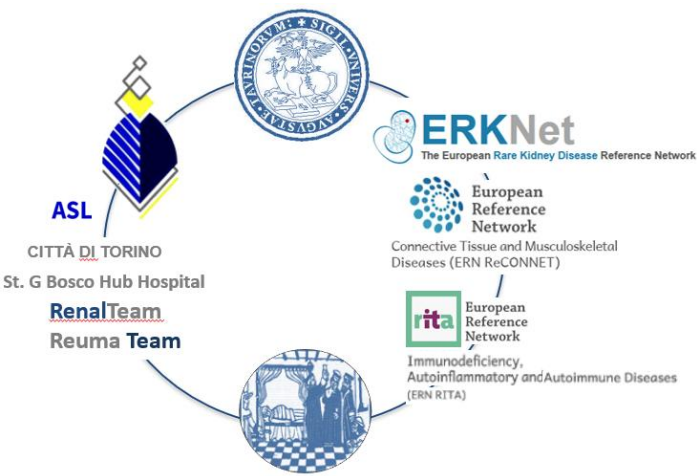




Predicting progression from undifferentiated connective tissue disease to clinically overt disease using particle-based multi-analyte technology

Savino Sciascia

Department of Clinical and Biological Sciences of the University of Turin, and University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-net, ERN-Reconnect and RITA-ERN Member) with Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley (North-West Italy), San Giovanni Bosco Hub Hospital, Turin, Italy

Clinical Challenge



Rita:

22 years-old art student presenting with a +ANA, +anti-Ro/SSA, oral aphthosis and arthralgia

Clinical Challenge

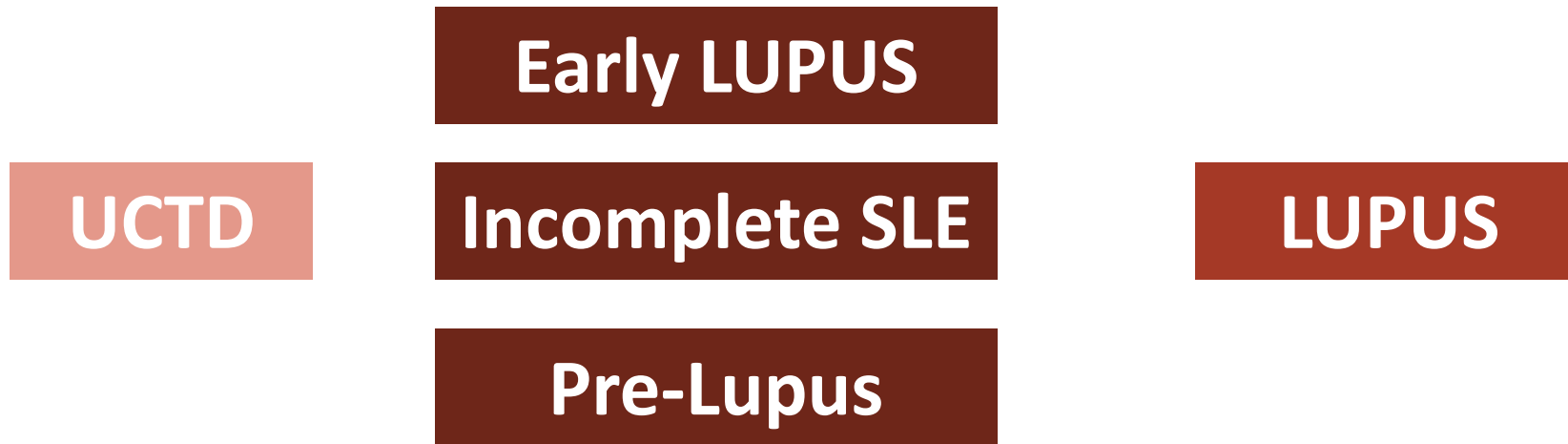
UCTD

LUPUS

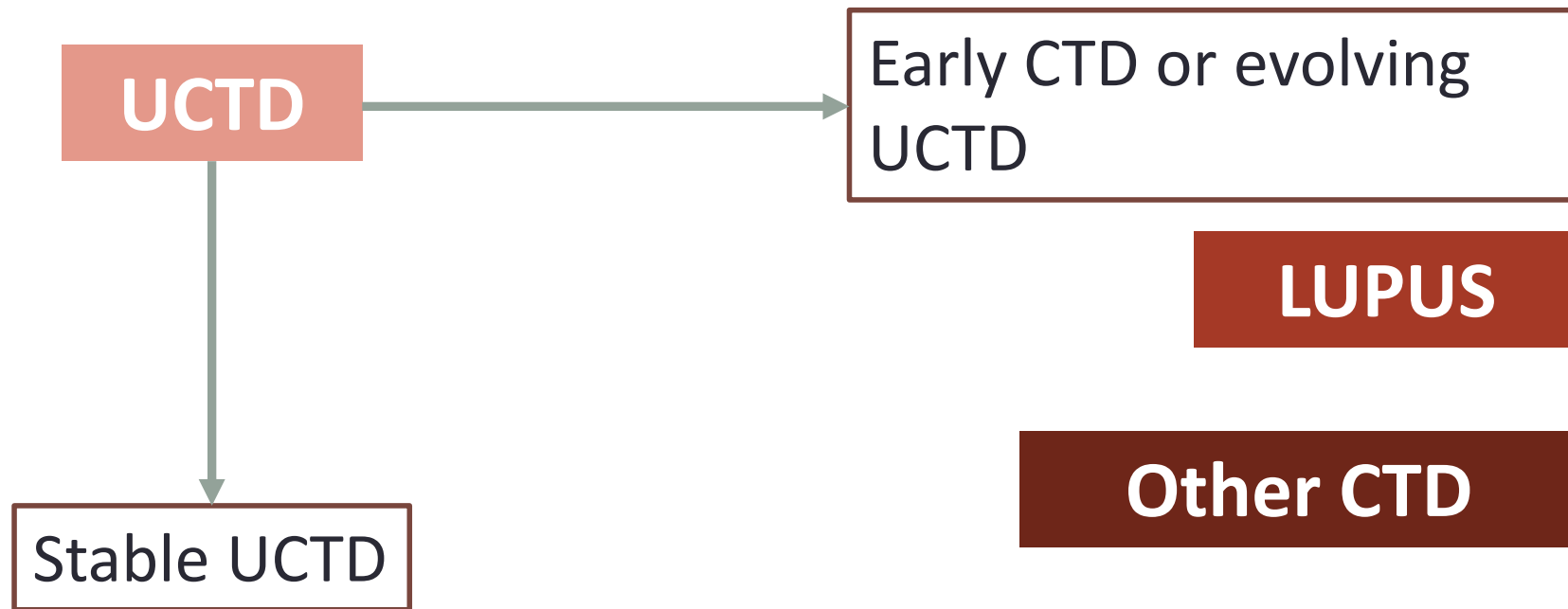
Other CTD

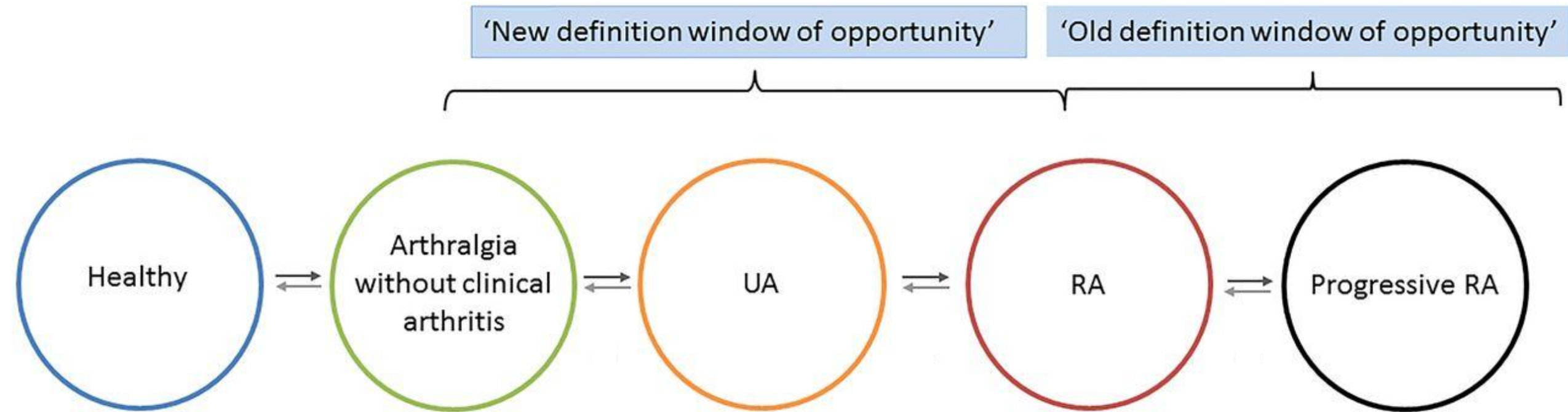


Clinical Challenge



Clinical Challenge





If accepted in RA, why not in CTD?

Clinical Challenge

Diagnostic Challenges (identify early to prevent damage accrual)

Prognostic Challenge (who is going to evolve to a definite CTD to guide therapy)

Management Challenges (F/U plan)

2012 SLICC
classification
criteria
fulfilment in
early-SLE
and UCTD

Characteristic	Al Daabil et al. (2014) ⁹⁴	Swaak et al. (2001) ⁸³	Rua-Figueroa et al. (2015) ²³	Chen et al. (2015) ²⁸	Mosca et al. (2019) ³²	Lastrup et al. (2009) ⁸⁴	Vaz et al. (2009) ¹⁶	Tiao et al. (2016) ⁸⁵	Overall range (%)
Demographics									
Number of patients	161	100	345	77	389	26	74	30	NA
Diagnosis	Potential SLE	Incomplete SLE	Incomplete SLE	Incomplete lupus syndromes	Early SLE	Incomplete SLE	Lupus-like UCTD	Sub-acute CLE with SLE	NA
Clinical criteria (%)									
Malar rash	11.0	4.0	11.0	9.1	49.6	19.2	13.0	43.3	4.0–49.6
Discoid rash	1.0	4.0	7.1	0.0	9.3	3.8	NR	NR	0.0–9.3
Photosensitivity	22.0	NR	20.5	1.3	31.6	46.1	25.0	96.7	1.3–96.7
Oral ulcers	11.0	NR	7.3	7.8	21.6	7.7	22.0	60.0	7.3–60.0
Arthritis	57.0	15.0	44.2	20.8	57.6	30.7	49.0	60.0	15.0–60.0
Serositis (pleuritis/ pericarditis)	13.0	NR (NR/4.0)	8.8	20.8	NR (22.4/18.8)	19.2	4.0	3.3	4.0–20.8
Renal disorder	1.0	NR	4.3	16.9	13.1	15.3	NR	19.2	1.0–19.2
Persistent proteinuria	NR	4.0	NR	NR	NR	NR	NR	NR	NA
Cellular cast	NR	3.0	NR	NR	NR	NR	NR	NR	NA
Neurological disorder	4.0	NR	1.2	6.5	NR	4.0	NR	6.7	1.2–6.7
Seizures	NR	1.0	NR	NR	2.8	NR	NR	NR	1.0–2.8
Psychosis	NR	0.0	NR	NR	1.0	NR	NR	NR	0.0–1.0
Haematological disorder	30.0	NR	43.5	51.9	NR	30.7	NR	50.0	30.0–51.9
Haemolytic anaemia	NR	2.0	NR	NR	4.6	NR	NR	NR	2.0–4.6
Leukopenia	NR	36.0	NR	NR	16.2	NR	28.0	43.3	16.2–36.0
Thrombocytopenia	NR	8.0	NR	NR	6.6	NR	14.0	16.7	6.6–16.7
Immunological criteria (%)									
Anti-dsDNA antibodies	16.0	NR	NR	22.1	71.7	100.0	29.0	50.0	16.0–100.0
Anti-Sm antibodies	3.0	NR	NR	5.2	30.2	NR	4.0	35.7	3.0–35.7
aCL antibodies	14.0	NR	NR	NR	18.1	NR	NR	37.5	14.0–37.5
LA	4.0	NR	NR	NR	15.1	NR	NR	33.3	4.0–33.3
ANA	98.0	100.0	94.7	97.4	99.5	100	100.0	96.6	94.7–100.0

2012 SLICC
classification
criteria
fulfilment in
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ANA	98.0	100.0	94.7	97.4	99.5	100	100.0	96.6	94.7–100.0

Time matters: UCTD Vs SLE VS early SLE

At the time of the diagnosis, patients with UCTD are **older** compared to early SLE (42.9 vs 34.6 years old)

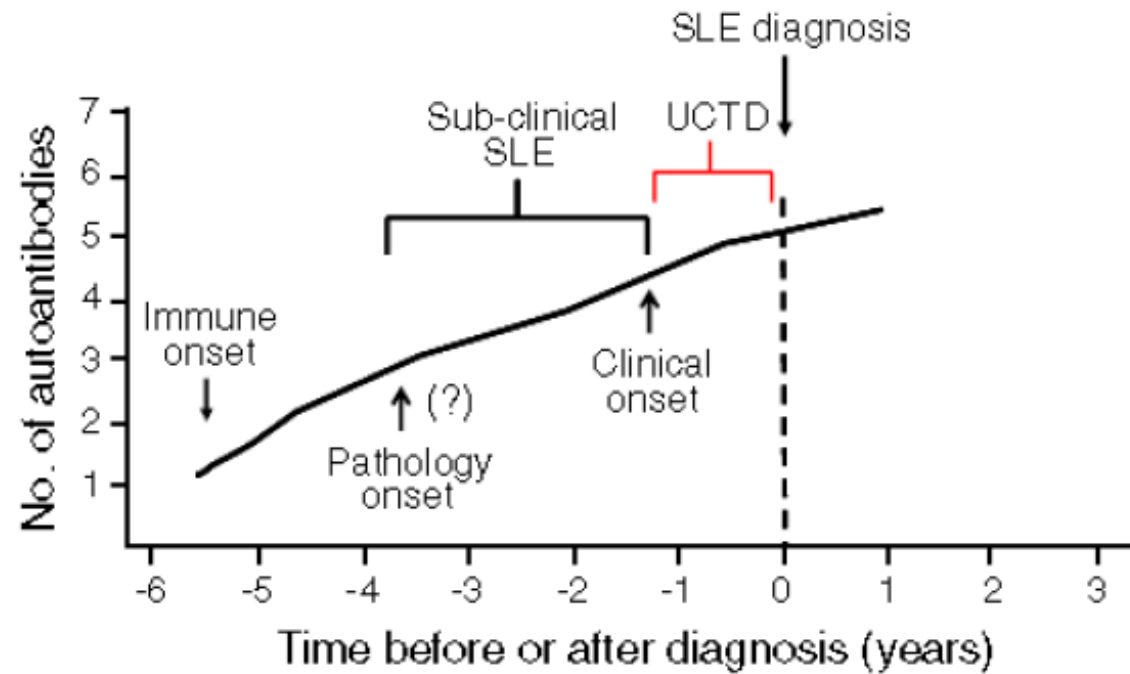
Rua-Figueroa I et al, Medicine 2015

UCTD patients present **lower rate of yearly progression** to a severe manifestations (3-13%) than early SLE (3-57%)

Bortoluzzi A, Lupus 2017
Hallengren C.S Lupus 2004

→ **IN PRACTICE:** Absence of new clinical and laboratory manifestations over a 3-year period and lack of a CTD- specific serological profile support the diagnosis of UCTD.

THE IMPORTANCE OF ANA AND ENA PROFILING



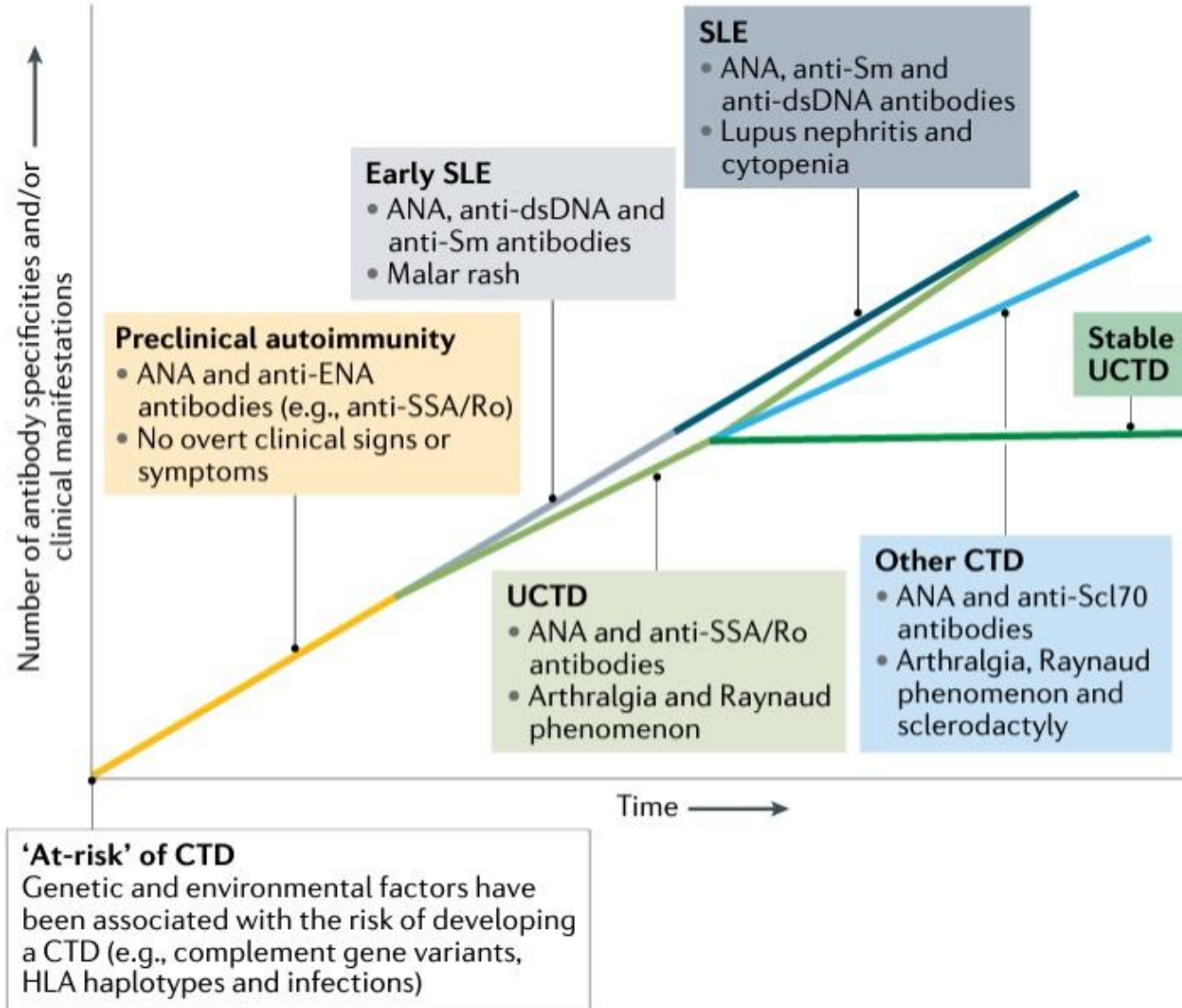
ANA+

7% → SLE



67% → UCTD

33 % → CTD



The cumulative number of positive Abs can represent an indicator of the evolution to a definite diagnosis of CTD

Lu et al. showed that SLE subjects have a mean of 0.3 new antibody specificities per year and a mean of 3 antibody specificities at the time of diagnosis

[Arbuckle, M. R. et al. NEJM 2003.](#)

[Lu, R. et al. Journal of autoimmunity 2016.](#)

Term	Description	Example
At-risk of SLE	Genetic or environmental risk factors that pre-dispose the individual to SLE	25-year-old woman who has an identical twin with SLE but no features of the disease herself
Preclinical SLE	Evidence of autoimmunity and immune dysregulation but no clinical features of disease	25-year-old woman who is positive for ANA and anti-Sm antibodies but has no other features of SLE
Early SLE	Evidence of autoimmunity and some clinical features of SLE but fewer than required to meet classification criteria	25-year-old woman who is positive for ANA and anti-SSA/Ro antibodies and has a malar rash, but no other signs or symptoms of SLE
SLE	Symptoms, signs and laboratory features that meet classification criteria for SLE	25-year-old woman who is positive for ANA and anti-dsDNA antibodies and has lymphopenia, arthritis and lupus nephritis
UCTD	Evidence of autoimmunity and some clinical features of connective tissue diseases such as SLE, Sjögren syndrome, systemic sclerosis, rheumatoid arthritis or myositis, but not enough to meet the classification criteria for any of these conditions. Usually, disease has not progressed for at least 3 years with signs and symptoms remaining stable over time	25-year-old woman who is positive for ANA and has Raynaud phenomenon and sicca symptoms, but no other features of connective tissue diseases

ANA, antinuclear antibody; dsDNA, double-stranded DNA; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.

Early SLE

Rita:

22 years-old art student presenting with a +ANA, +anti-Ro/SSA, oral aphthosis and arthralgia +**anti-dsDNA**

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Early SLE

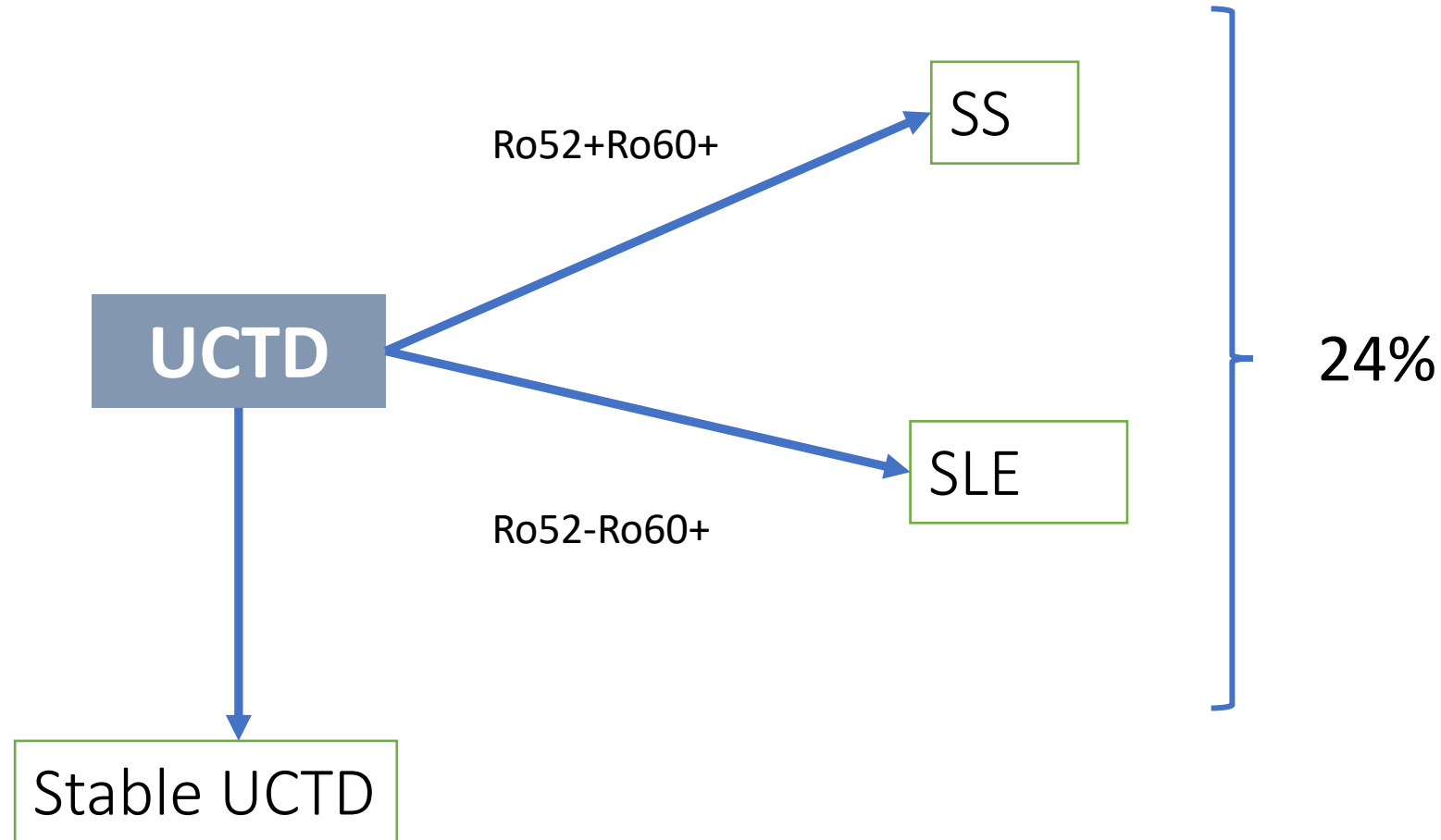
Rita:

22 years-old art student presenting with a +ANA, +anti-Ro/SSA, oral aphthosis and arthralgia **+anti-dsDNA**

Rita:

22 years-old art student presenting with a +ANA, +anti-Ro/SSA, oral aphthosis and arthralgia **+malar rash**

UCTD & anti-Ro/SSA



Cavazzana, I. *CER* 2001

Belfiore *Revue du Rhumatisme* 2000

Murng, SHK *Journal of Clinical Pathology* 2018

Robbins, *Front Immunol* 2019



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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev



Review

Predicting progression from undifferentiated connective tissue disease to definite connective tissue disease: A systematic review and meta-analysis

Sarah Dyball^a, Mia Rodziewicz^{a,1}, Claudia Mendoza-Pinto^{b,1}, Ian N. Bruce^c, Ben Parker^{c,*}

^a Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Stopford Building, Oxford Road, Manchester, UK

^b Systemic Autoimmune Diseases Research Unit Specialties Hospital UMAE-CIBIOR, Mexican Social Security Institute, Puebla, Mexico

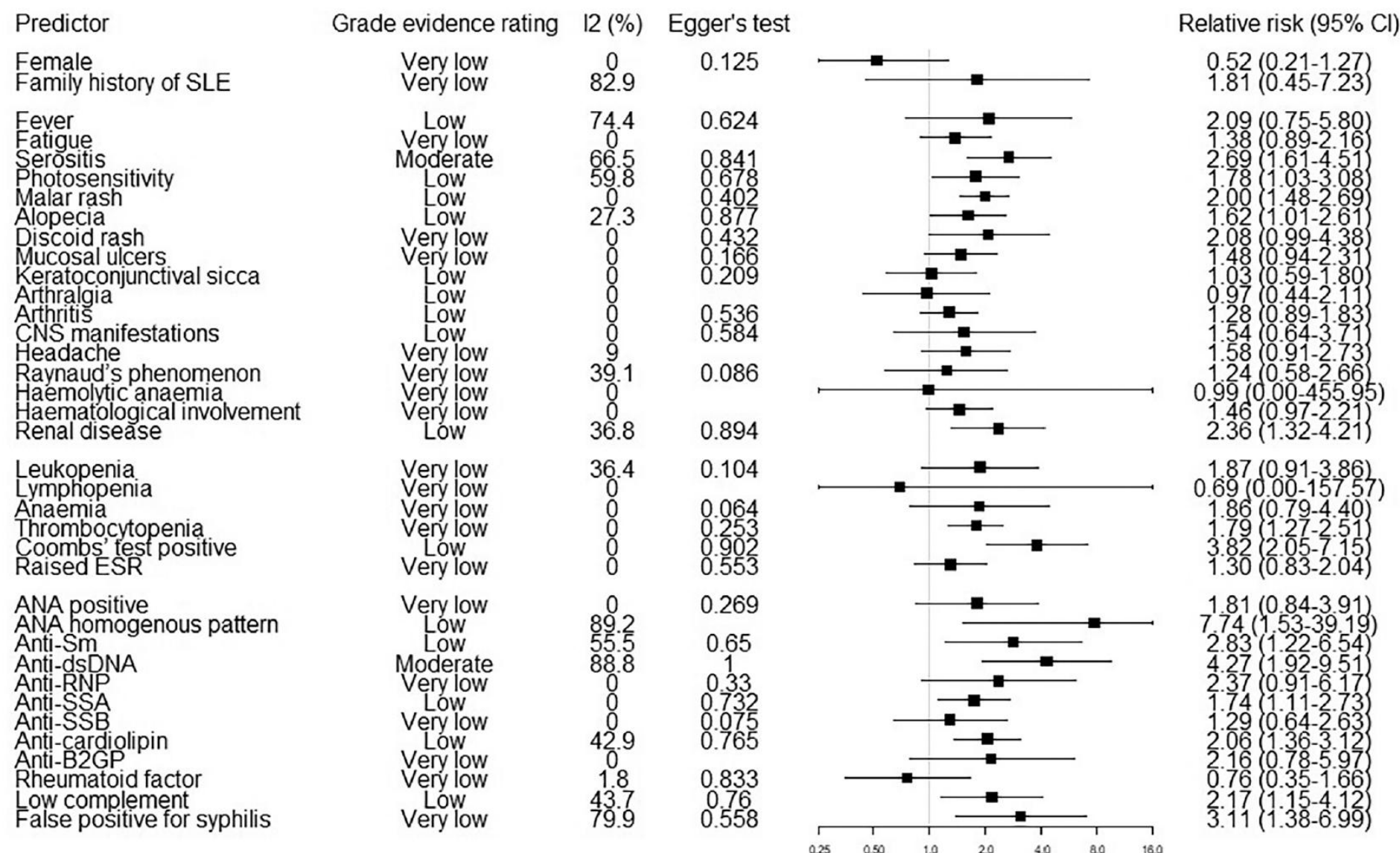
^c National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, UK

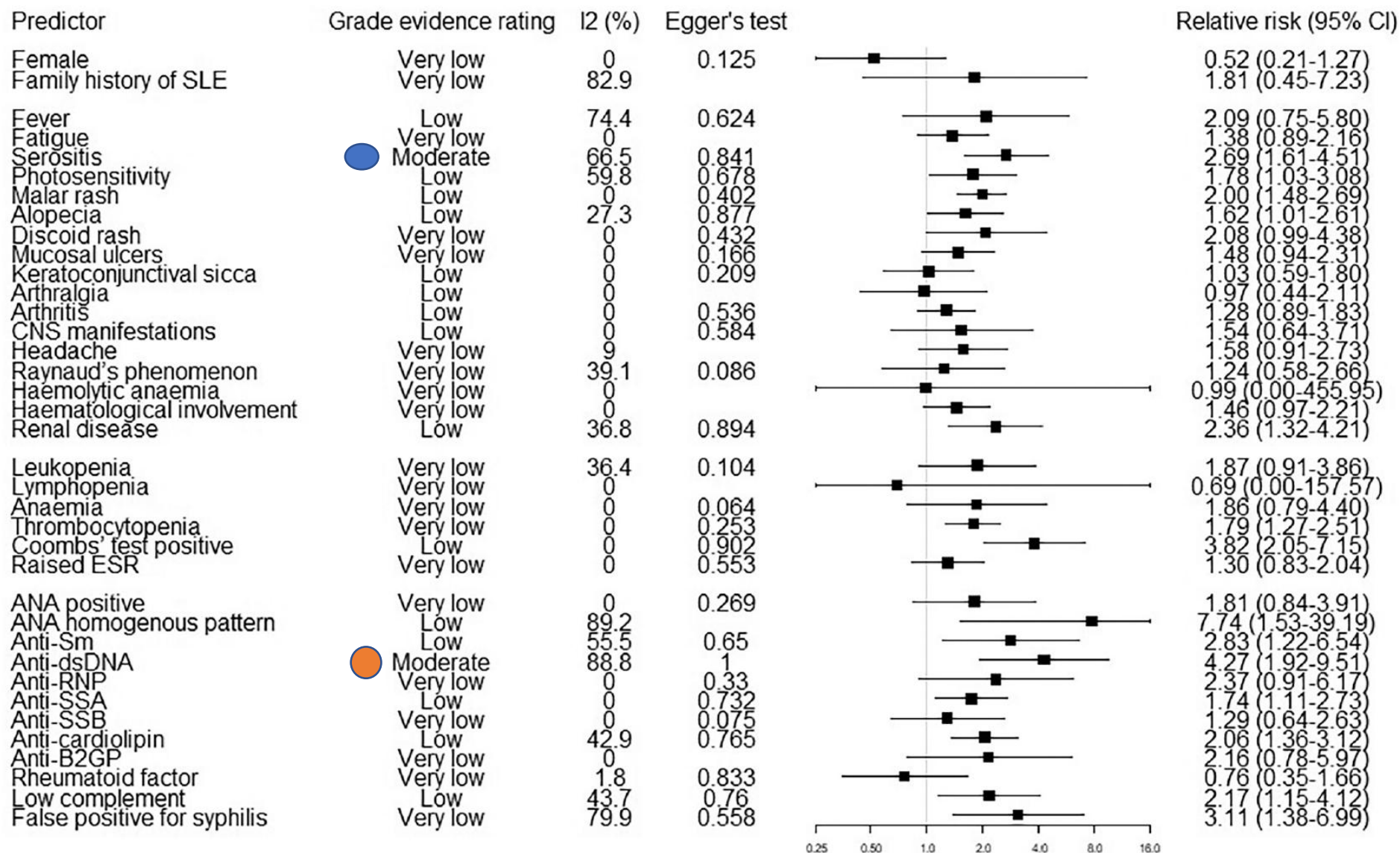


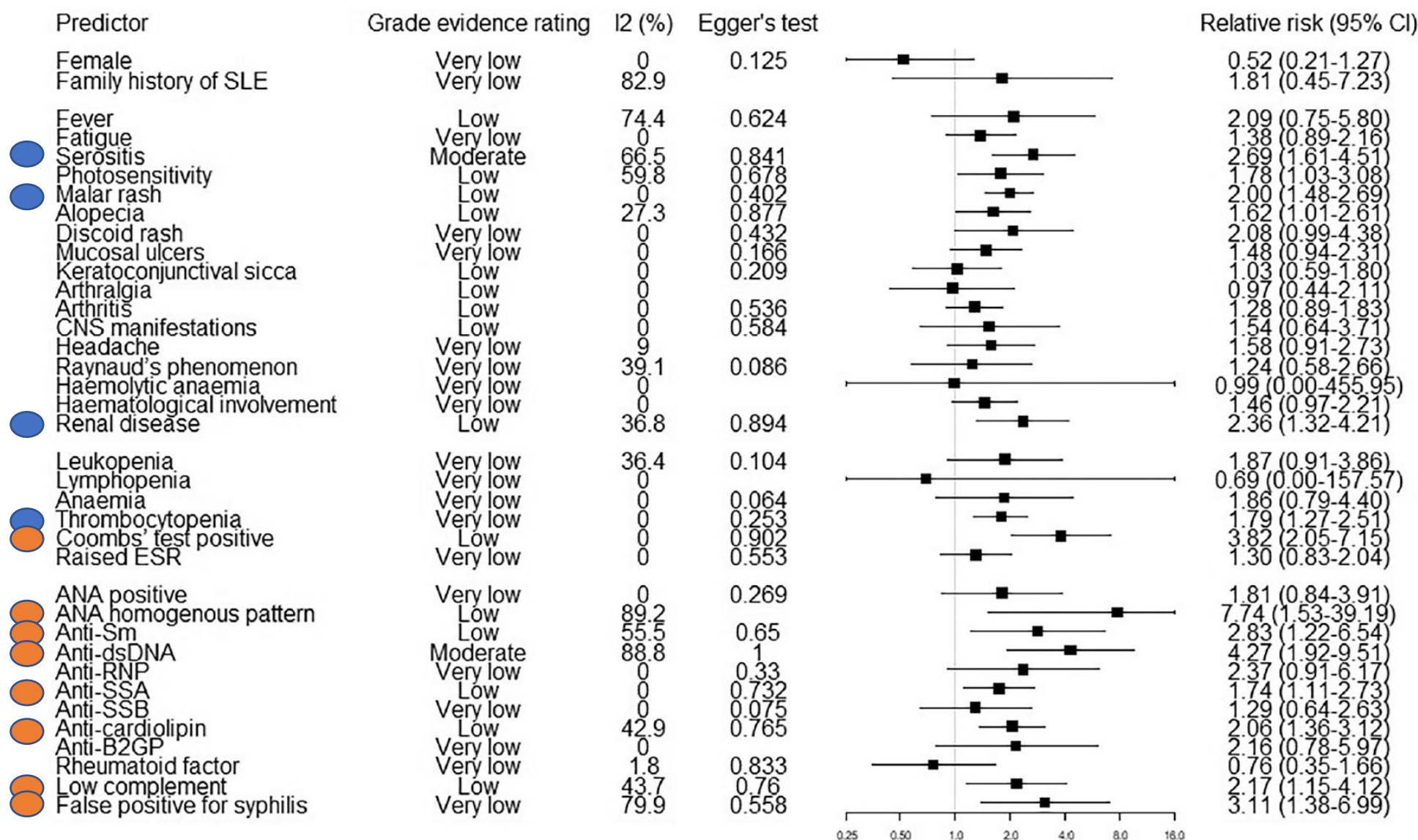
UCTD



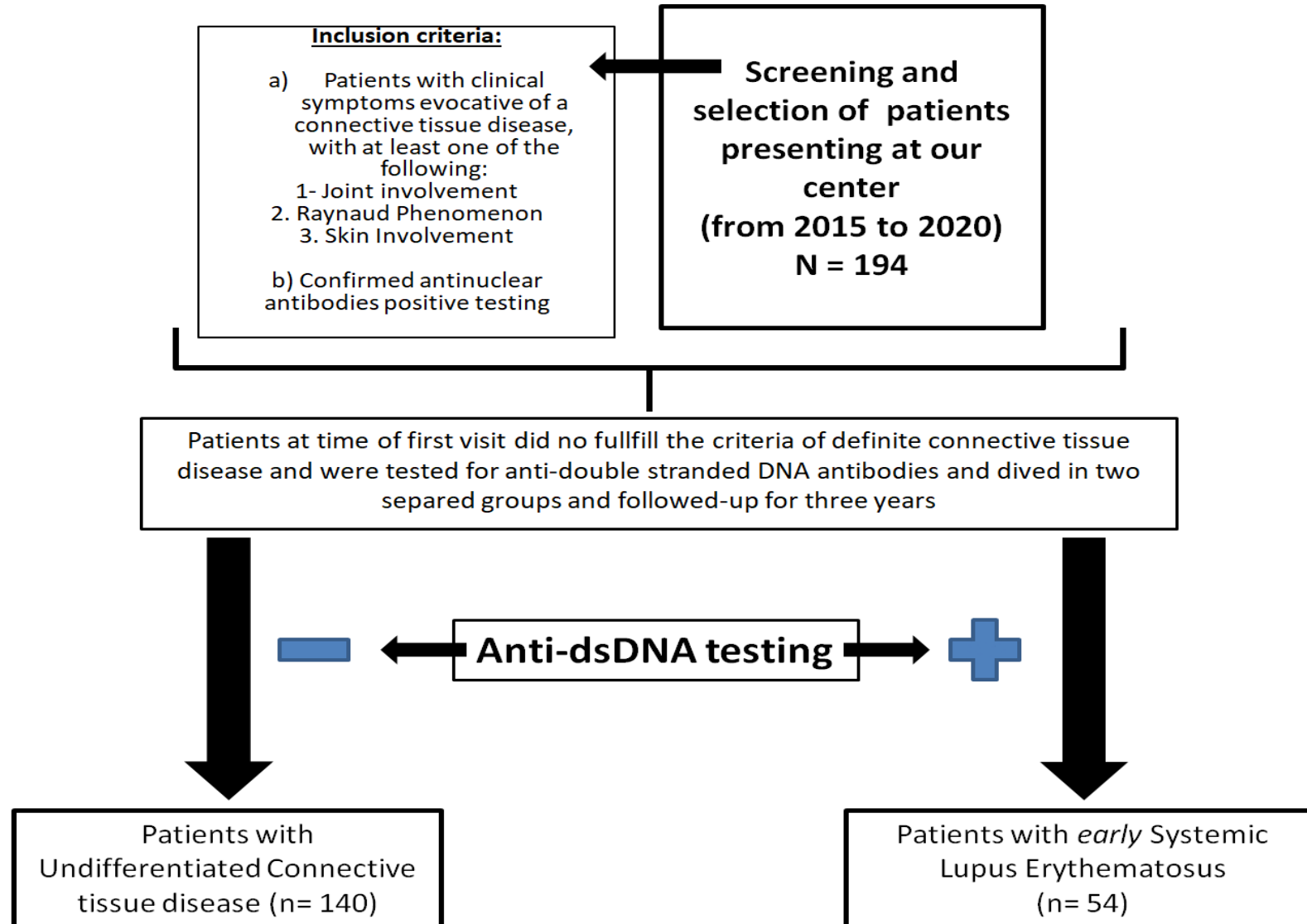
LUPUS





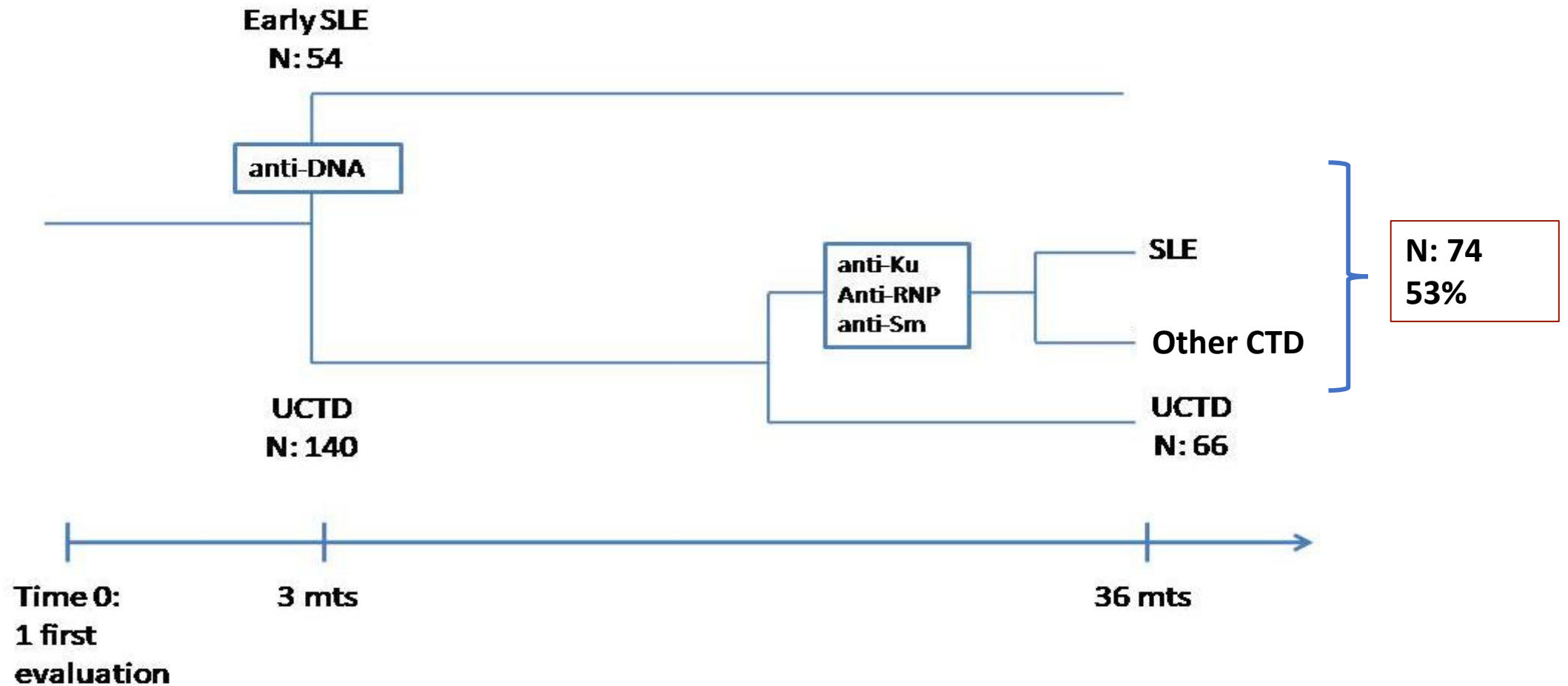


Our Experience in 194 patients with UCTD



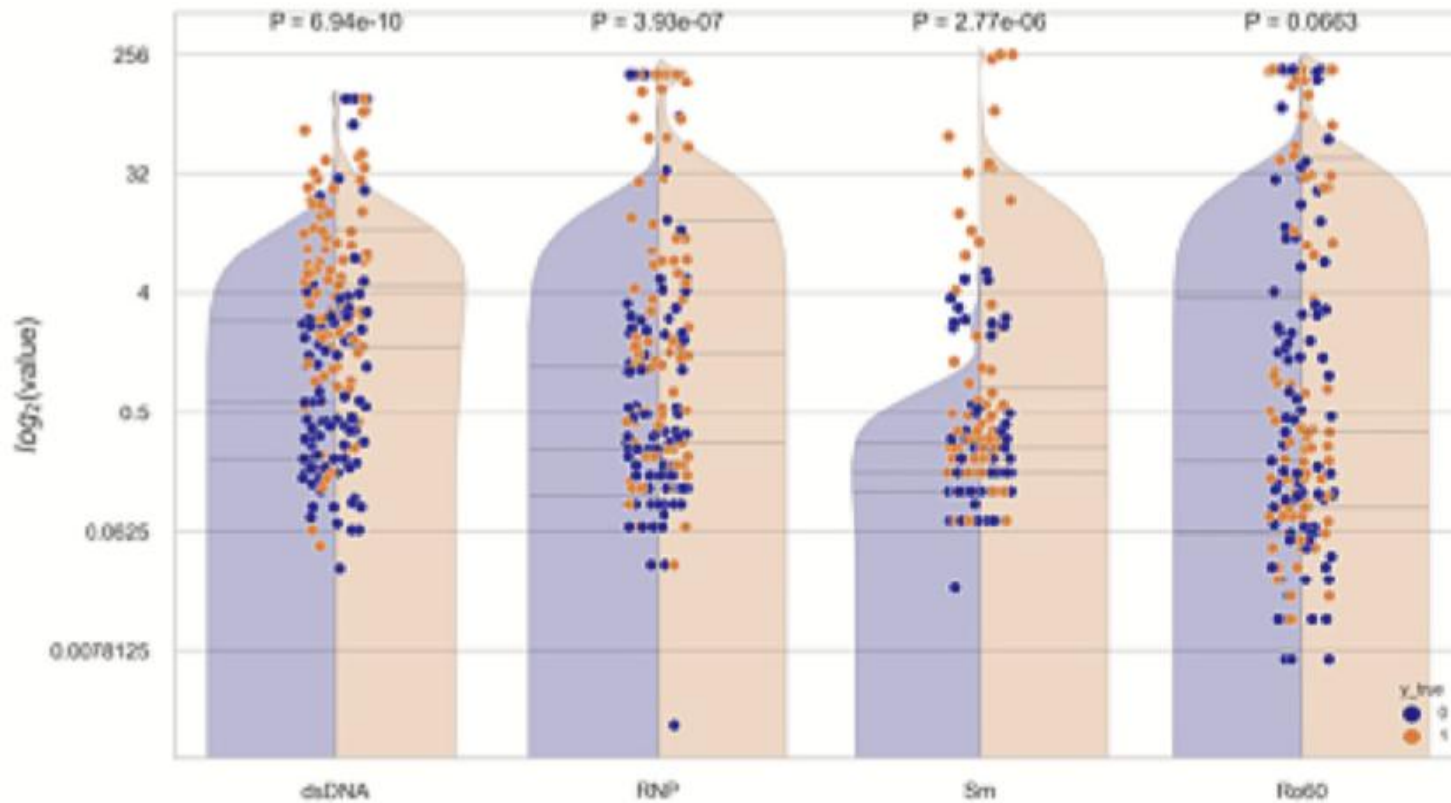
Our Experience in 194 patients with UCTD

Particle-based
multi-analyte
technology-
PMAT

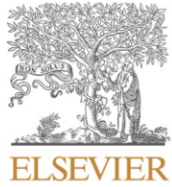


Diagnosis evolution during follow-up	Early SLE (n=54)	UCTD (n=140)	p-value
Systemic Lupus Erythematosus	45 (83.3%)	50 (35.7%)	<0.001
Systemic sclerosis	/	19 (13.6%)	N/A
Sjögren's syndrome	/	8 (5.7%)	N/A
Mixed connective tissue disease	2 (3.7%)	/	N/A
Vasculitis	/	4 (2.9%)	N/A

Antibody Specificities	Early SLE (n=54)	UCTD (n=140)	p-value
ANA positive $\geq$ 1:640	21 (38.9%)	34 (24.3%)	0.04
RNP	23 (42.6%)	20 (14.3%)	<0.001
Sm	11 (20.4%)	6 (4.3%)	<0.001
Ro52	11 (20.4%)	39 (27.9%)	ns
Ro60	18 (33.3%)	40 (28.6%)	ns
SS-B	6 (11.1%)	18 (12.9%)	ns
Scl-70	3 (5.6%)	11 (7.9%)	ns
Jo-1	/	2 (1.4%)	N/A
Centromere	1 (1.9%)	27 (19.3%)	0.002
DFS70	3 (5.6%)	15 (10.7%)	0.26
Ribo-P	6 (11.1%)	11 (7.9%)	ns
Ku	6 (11.1%)	3 (2.1%)	0.008
PmScl	2 (3.7%)	1 (0.7%)	ns
BICD2	4 (7.4%)	7 (5%)	ns
SMN1	2 (3.7%)	/	N/A
FHL1	1 (1.9%)	6 (4.3%)	ns
RNPC-3	1 (1.9%)	1 (0.7%)	ns
PUF60	7 (13%)	7 (5%)	0.054
RNA Pol III	/	1 (0.7%)	N/A
Th/To (Rpp38)	/	2 (1.4%)	N/A
Fibrillarin	/	3 (2.1%)	N/A



The levels of all four antibodies were significantly higher in individuals that had CTD after follow-up, compared to individuals that did not ($p < 0.0001$)

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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Identifying subsets of patients with undifferentiated connective tissue disease: Results from a prospective, real-world experience using particle-based multi-analyte technology[☆]

Massimo Radin^{a,b}, Irene Cecchi^{a,b}, Alice Barinotti^{a,b}, Georgia Wilson Jones^{a,b}, Marta Arbrile^{a,b}, Paolo Miraglia^{a,b}, Michael Mahler^c, Chelsea Bentow^c, Daniela Rossi^{a,b}, Elisa Menegatti^{a,b}, Dario Roccatello^{a,b,1}, Savino Sciascia^{a,b,1,*}

^a University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-Net, ERN-Reconnect and RITA-ERN Member) with Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

^b School of Specialization of Clinical Pathology, Department of Clinical and Biological Sciences, University of Turin, Italy

^c Werfen Autoimmunity, San Diego, CA 92131, USA

➤ [Clin Exp Rheumatol](https://doi.org/10.55563/clinexprheumatol/7vp1bo). 2022 Mar;40(3):575–580. doi: 10.55563/clinexprheumatol/7vp1bo. Epub 2021 Jun 26.

Disease evolution in a long-term follow-up of 104 undifferentiated connective tissue disease patients

Massimo Radin¹, Elena Rubini², Irene Cecchi², Silvia Grazietta Foddai², Alice Barinotti², Daniela Rossi², Savino Sciascia², Dario Roccatello²

Affiliations + expand

PMID: 34251309 DOI: [10.55563/clinexprheumatol/7vp1bo](https://doi.org/10.55563/clinexprheumatol/7vp1bo)

Learning lesson 1:

Our Experience in 194 patients with UCTD

Antibodies			HR (95% CI)	p-value
ANA > 1:640			2 (1.1 - 3.9)	0.045
RNP			4.5 (2.2 - 9.1)	<0.001
Sm			5.7 (2 - 16.4)	0.001
Ku			5.7 (1.4 - 23.7)	0.017
PUF60			2.9 (1.1 - 8.6)	0.046

Our Experience in 194 patients with UCTD

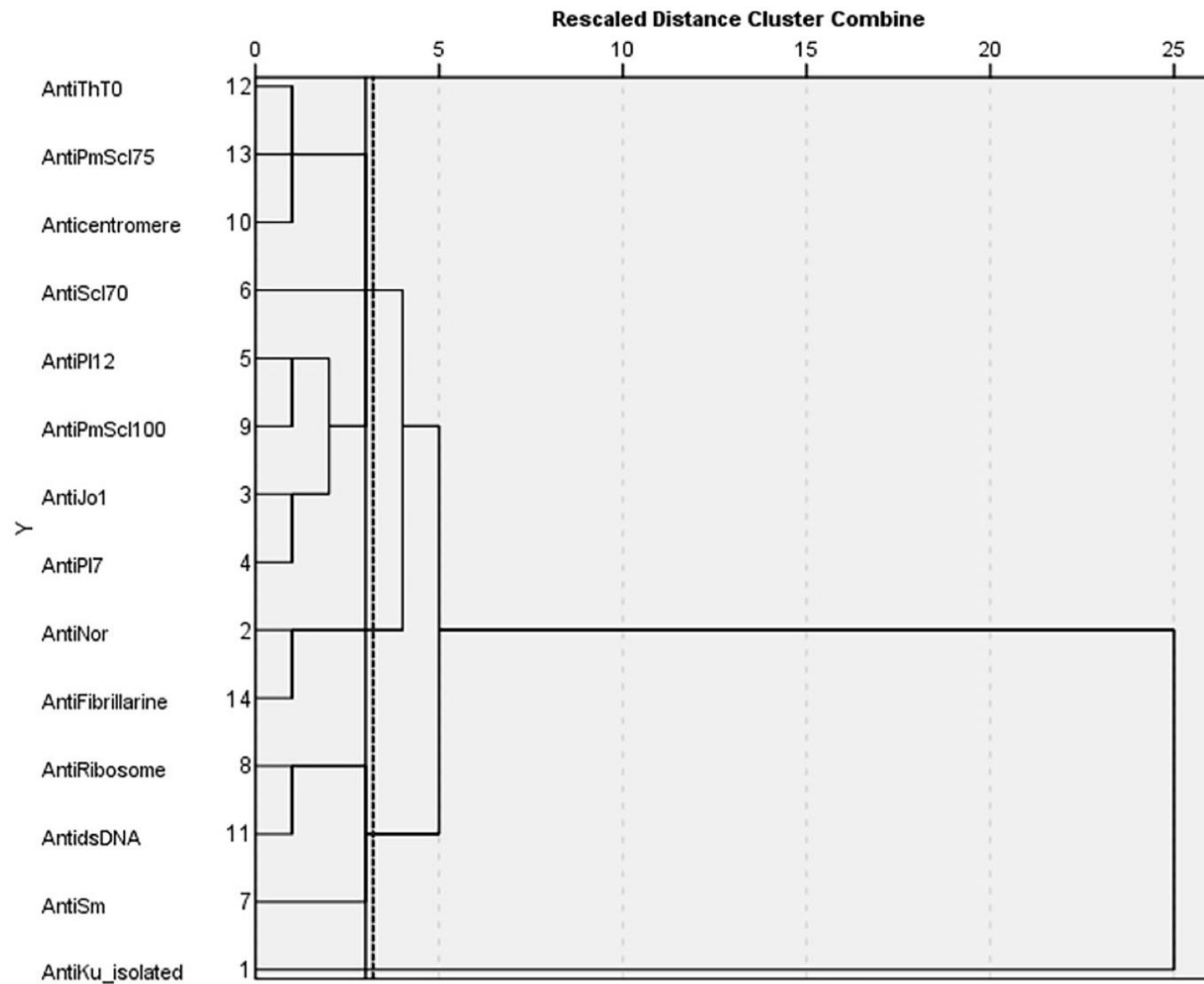
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Diagnosis evolution during follow-up	Early SLE (n=54)	UCTD (n=140)
Systemic Lupus Erythematosus	52	55
Systemic sclerosis	/	19
Sjögren's syndrome	/	8
Mixed connective tissue disease	2	6
Vasculitis	/	4 (2.9%)

Anti-Ku antibodies

Dendrogram using Average Linkage (Between Groups)



Moving forward to CTD profiling

Anti-Ku antibodies can be found in SLE patients with overlap features of a myopathy or overlap between myositis and systemic sclerosis.

Increased creatine and a high risk of interstitial lung diseases,
anti-Ku-positive patients with anti-dsDNA antibodies having a high risk of nephritis

Mahler M, Ann Rheum 2019.
Sousa Rheumatology 2023

PUF60 represents a newly described autoantigen in patients with Sjögren's syndrome and dermatomyositis

Fiorentino Ann Rheum Dis 2016

Moving forward to CTD profiling

Conventional CTD Antibodies Target suggestive for SLE	dsDNA, Sm, RNP, Ro60, Ro52, SS-B, Ribo-P, anti-C1q, (LA, aCL, aB2GP1)
Conventional CTD Antibodies Target suggestive for other CTD	Scl-70, Jo-1, Centromere
Novel CTD Antibodies Target	DFS70, RNA Pol III, Th/To, Ku, BICD2, PM/Scl, aPS/PT
DifferentialDiagnosis (vasculitis)	MPO, PR3, GBM
Differential Diagnosis (RA)	CCP3, RF, PAD3, PAD4, CarP
Differential Diagnosis (Miopathies)	Mi-2, HMGCR, NXP2, MDA5, PL-7, PL-12, EJ, SRP, TIF1γ, SAE, OJ

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Over 1/3 of Th/To abs+ scleroderma patients develop pulmonary hypertension

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**Bicaudal D2
abs have be
found in
patients with
SSc and
interstitial lung
disease**

Why these new autoAb matter?



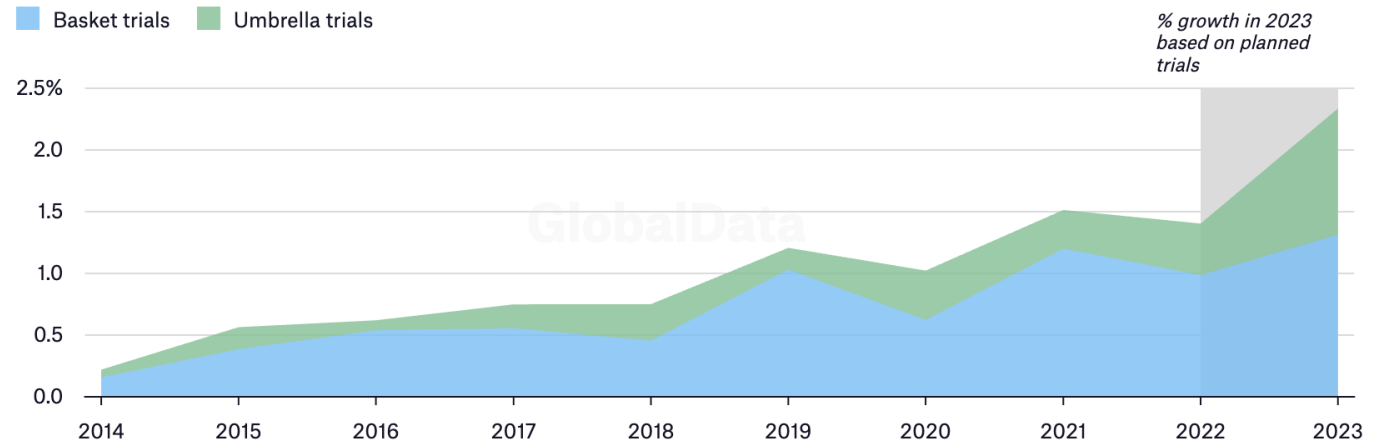
- Better clinical outcome, with lower flare rates and damage accrual
- Less healthcare utilization
- Lower costs
- Better Quality of life

Why these new autoAb matter?



Oncology basket and umbrella trials are on the rise

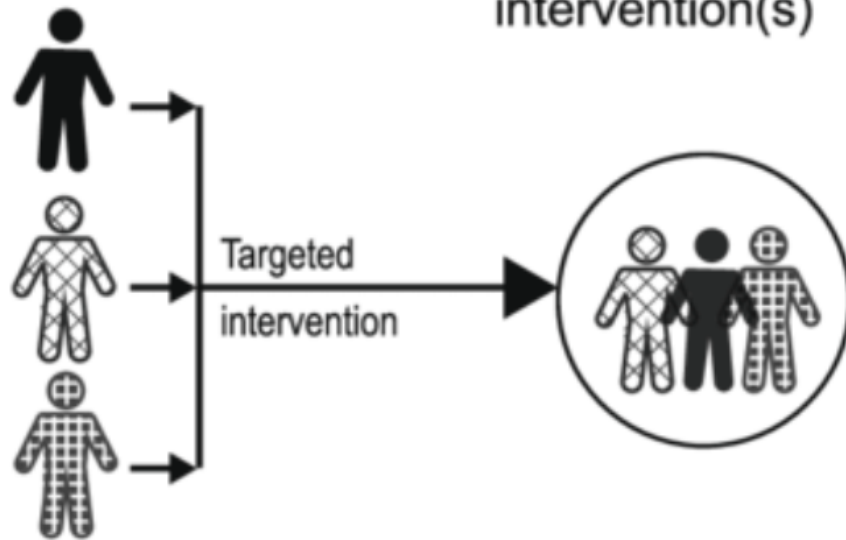
Phase I-III oncology basket and umbrella trials as a percentage of total oncology trials initiated each year



Basket trial

Multiple diseases

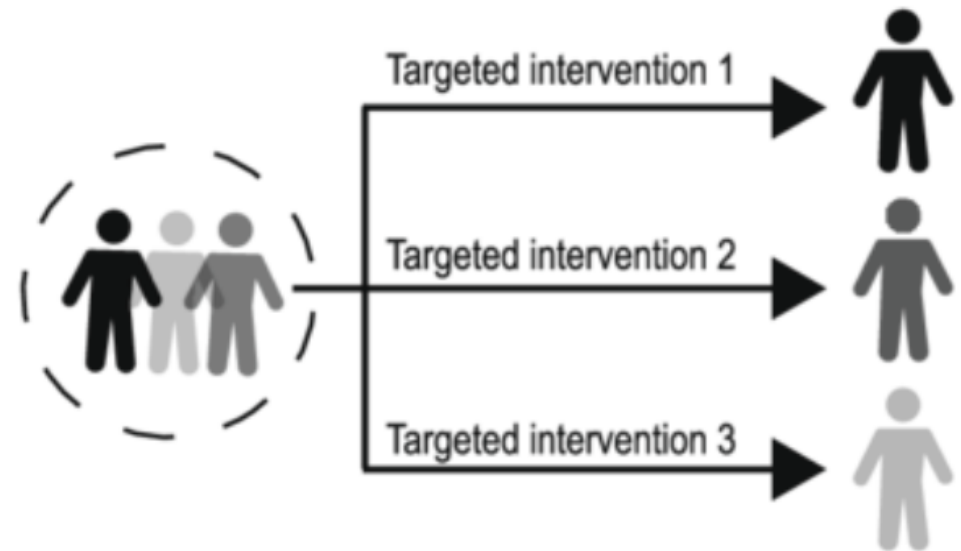
Common targeted
intervention(s)



Umbrella trial

Single disease

Multiple targeted
interventions





5 The **right** patient
The **right** drug
The **right** dose
R The **right** route of administration
The **right** time