Advances and Opportunities in Lupus

for the

National Academies Autoimmunity Panel

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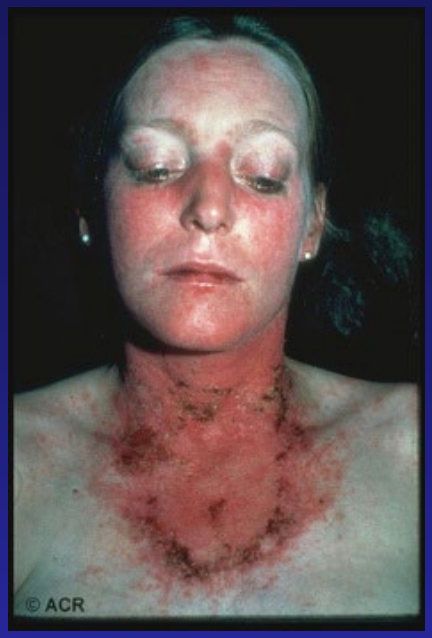
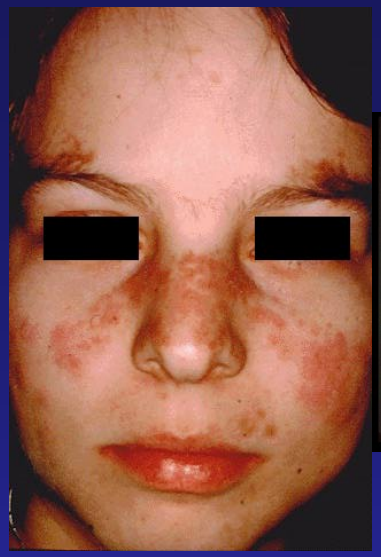
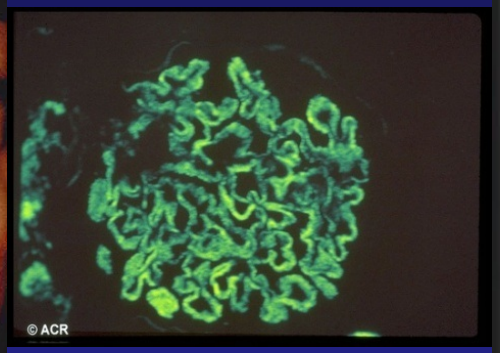
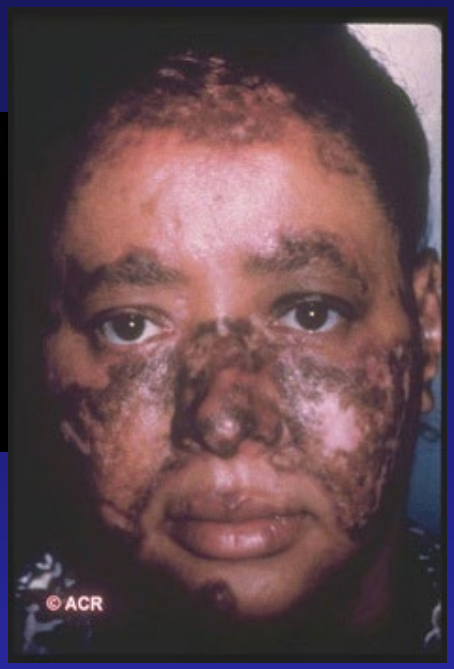
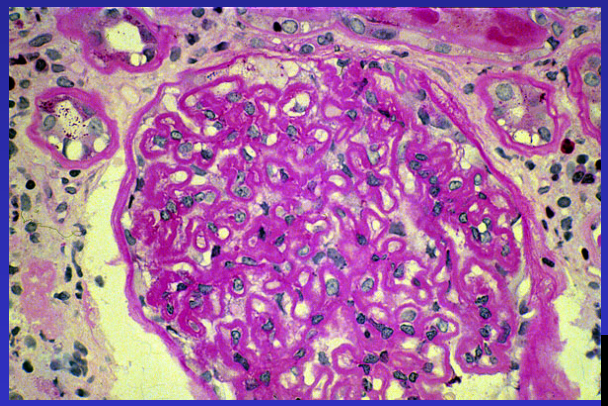
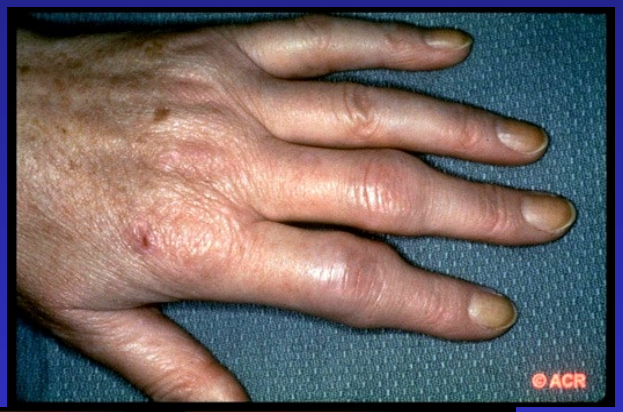


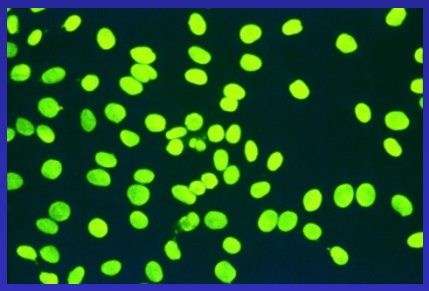




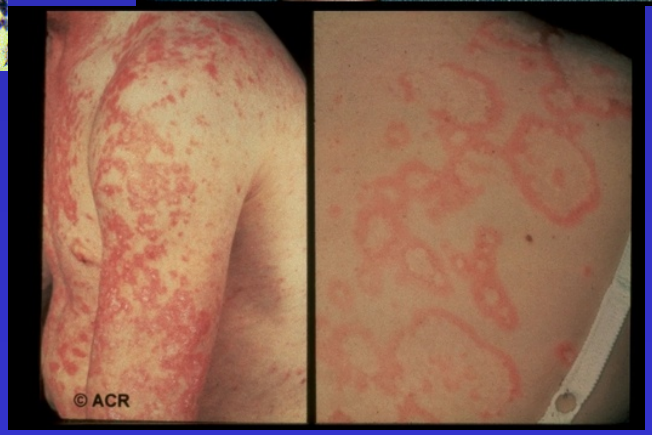


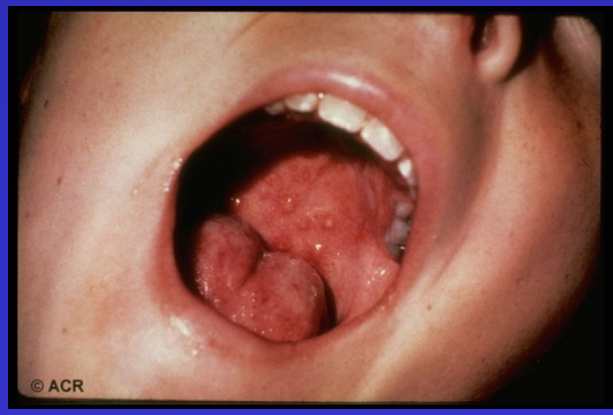




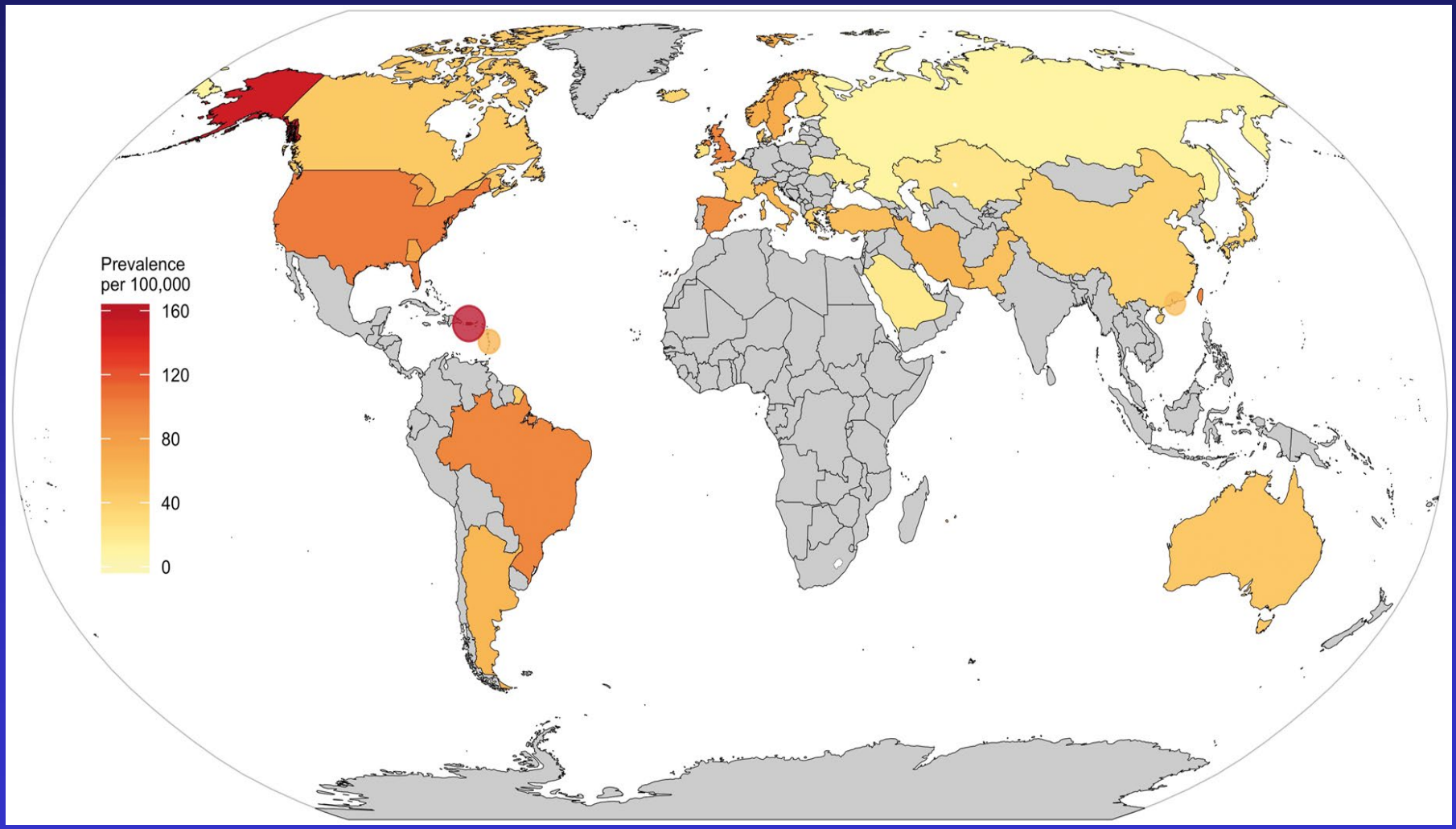


SLE is a clinically and biologically diverse autoimmune disease with a complex pathogenesis.





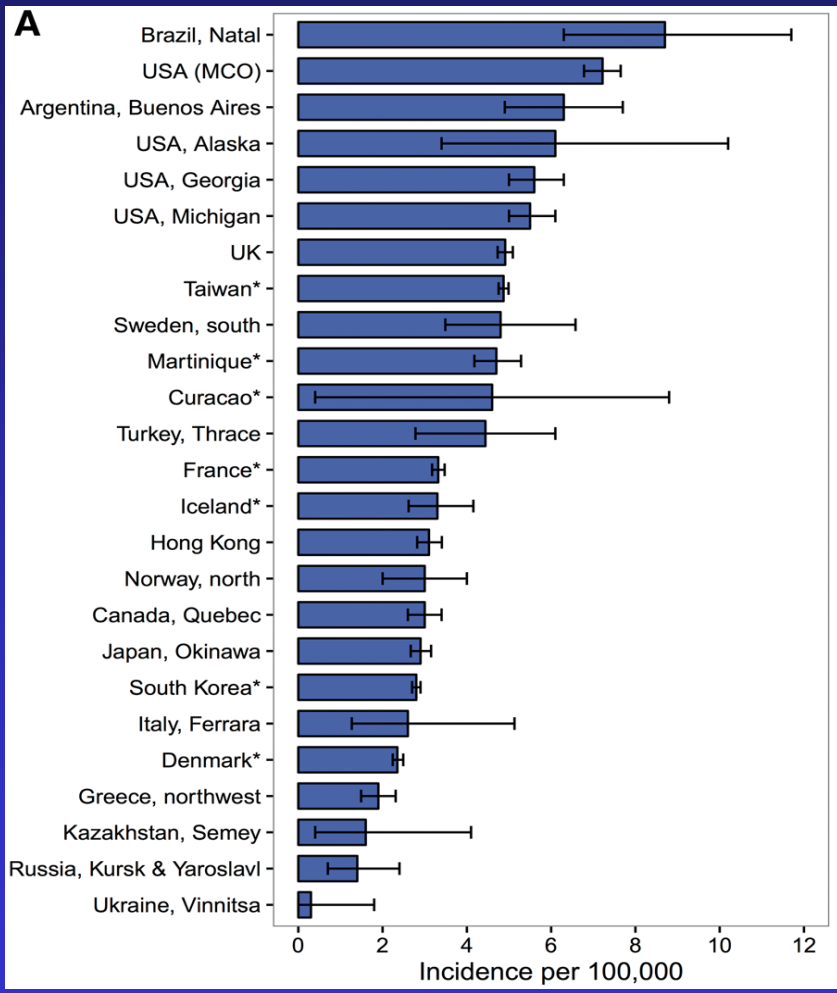
Lupus around the World



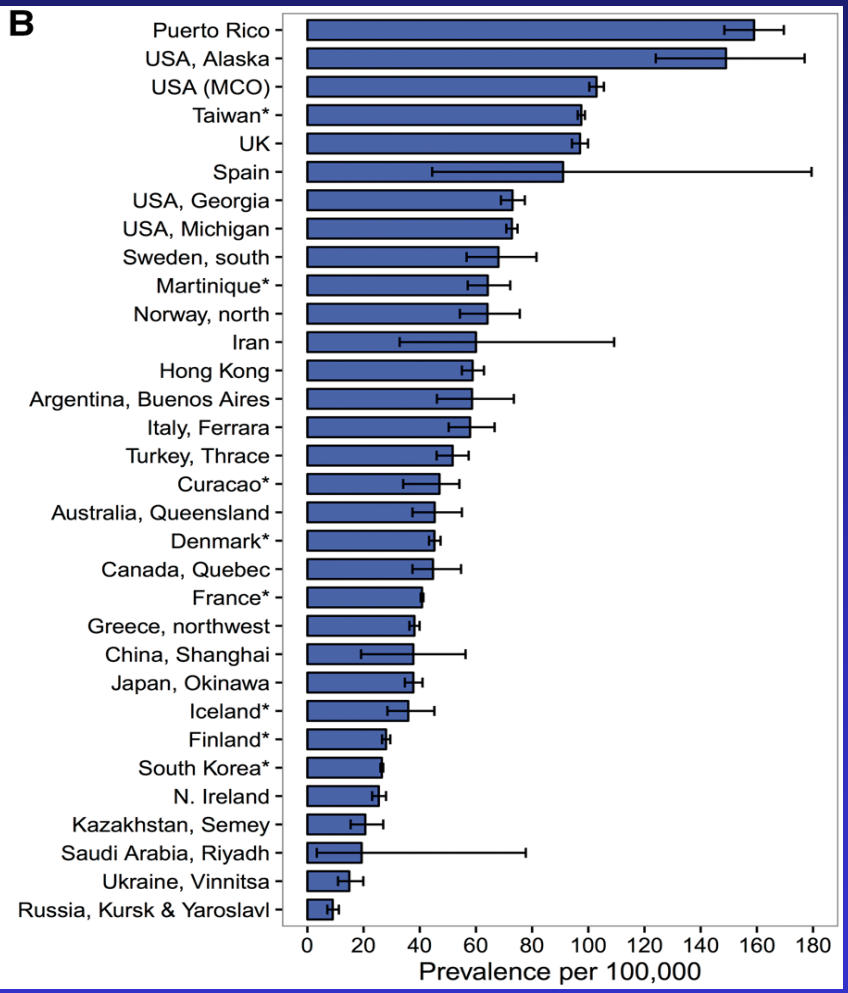
Rheumatology (Oxford), Volume 56, Issue suppl_1, April 2017, Pages i67–i77,
https://doi.org/10.1093/rheumatology/kew399

Epidemiological studies of SLE in different countries around the World

Incidence

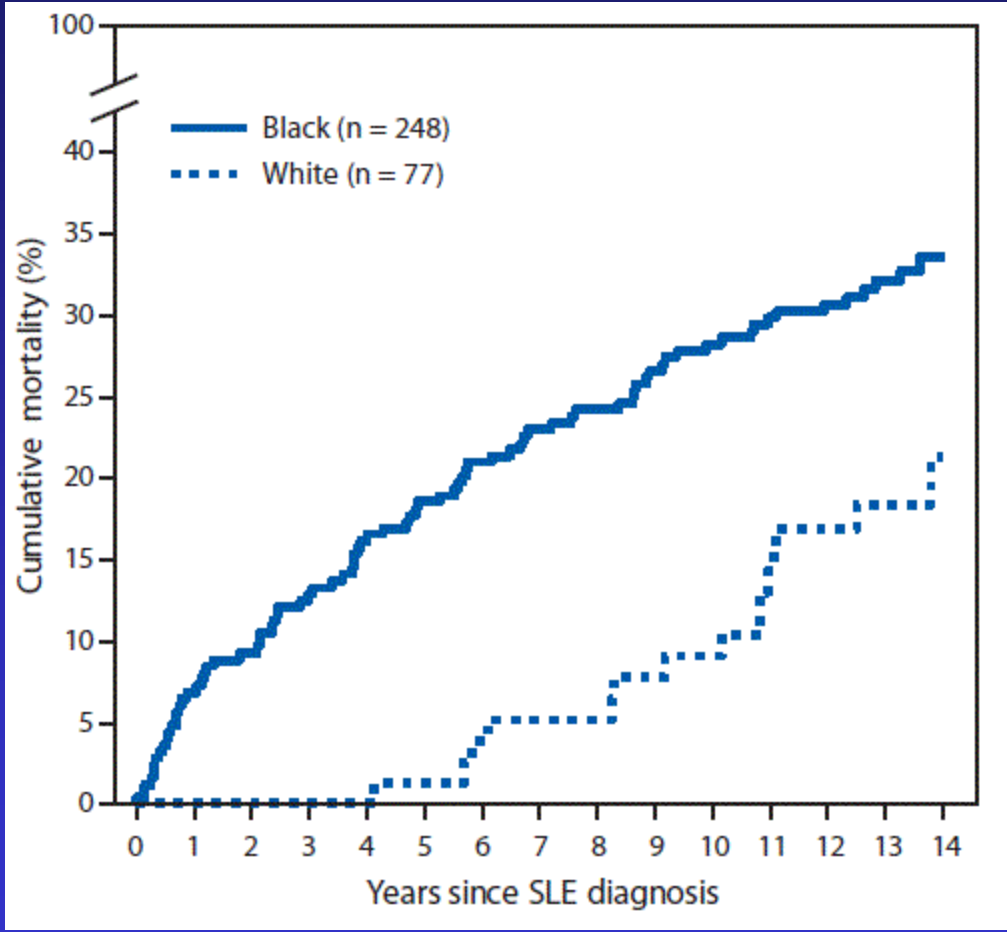


Prevalence



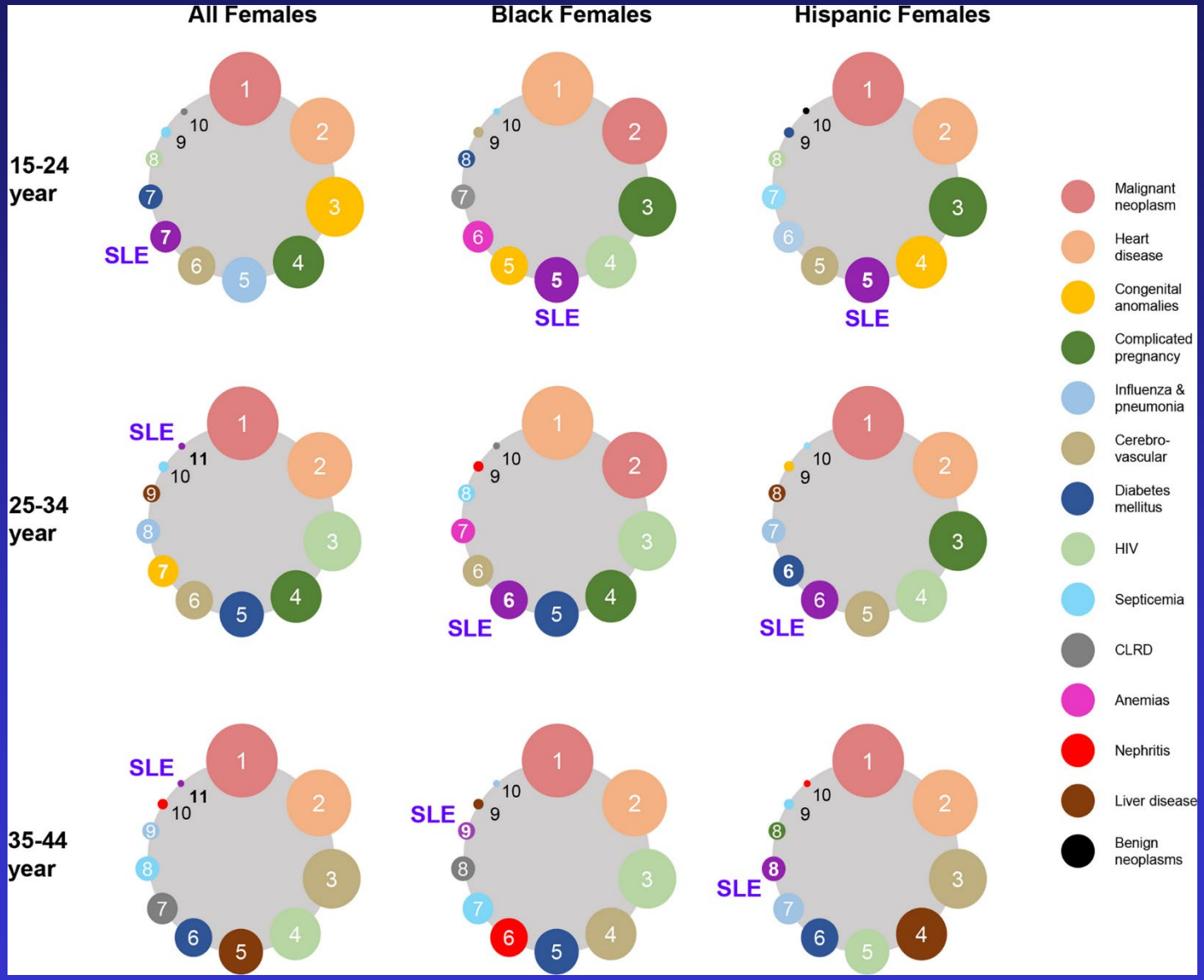
Rheumatology (Oxford), Volume 56, Issue suppl_1, April 2017, Pages i67–i77,
https://doi.org/10.1093/rheumatology/kew399

Mortality Rates for AA SLE Patients Remain High



Lim et al. MMWR. CDC. 2019

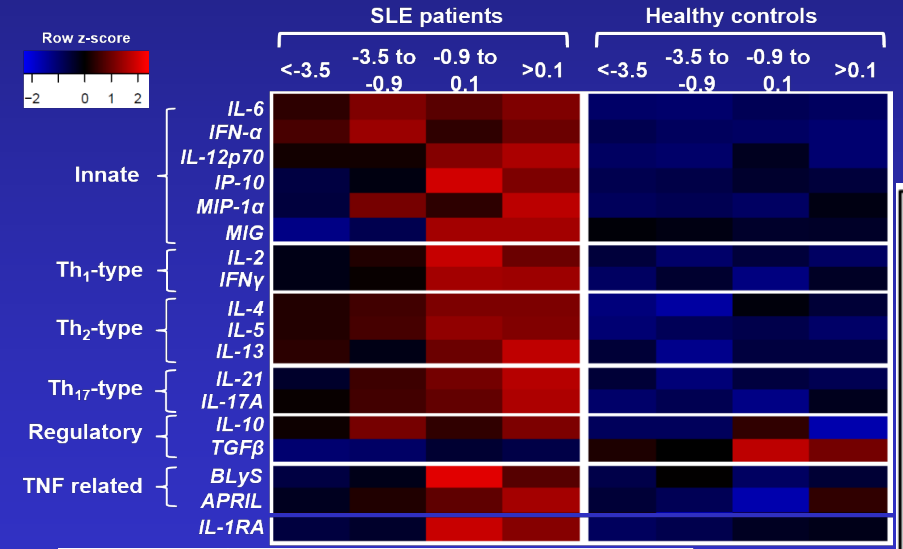
Leading causes of medical deaths of U.S. females of reproductive age by race/ethnicity and age

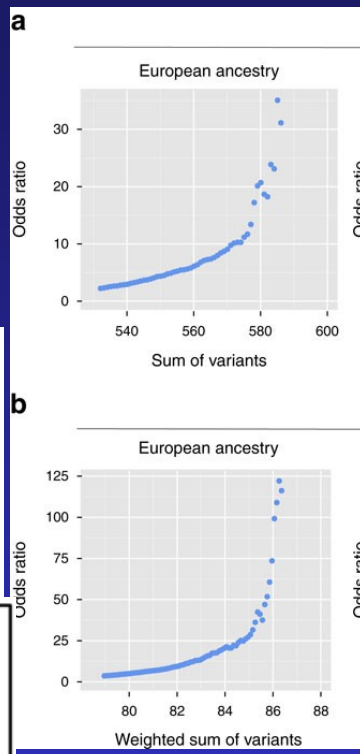


Yen and Singh. Lupus—An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000–2015. Arthritis Rheumatol. 2018;70(8): 1251-5. DOI: (10.1002/art.40512)

Recent SLE Research Advances

- Defining preclinical lupus and the start of SLE prevention trials
  - Extensive genetic associations and confirmations[1,2]
  - Definition of preclinical serologic and gene-environment interactions that lead to clinical SLE[3]
  - -- SLE prevention trial[4]



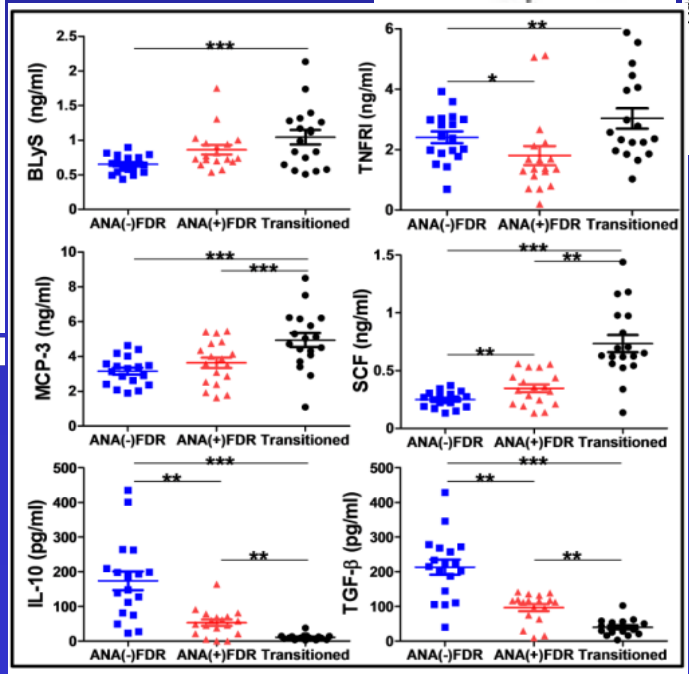


Baseline Variable	Model 1 OR (95% CI)	P-value	Model 2 OR (95% CI)	P-value
Age	1.01 (.97, 1.05)	0.668	1.01 (.96, 1.06)	0.745
Gender	0.41 (.09, 1.84)	0.246	0.28 (.04, 2.13)	0.219
Race:				
EA	0.68 (.12, 3.89)	0.665	0.61 (.08, 4.73)	0.633
AA	1.08 (.22, 5.29)	0.929	0.98 (.10, 9.56)	0.985
ACR Score	-		4.23 (1.78, 10.1)	**0.0011**
CSQ Score	-		1.31 (1.02, 1.69)	**0.0350**
SCF	3.75 (2.05, 6.84)	**<0.0001**	2.88 (1.45, 5.73)	**0.0026**
TGFb	0.20 (0.08, 0.52)	**0.0010**	0.34 (.13, .93)	**0.0352**

ROC Curves
Test (n=158)
Val (n=77)

Model 1
AUC (95% CI)
0.85 (0.78, 0.92)
0.75 (0.59, 0.91)

Model 2
AUC (95% CI)
0.94 (0.89, 0.98)
0.89 (0.81, 0.97)



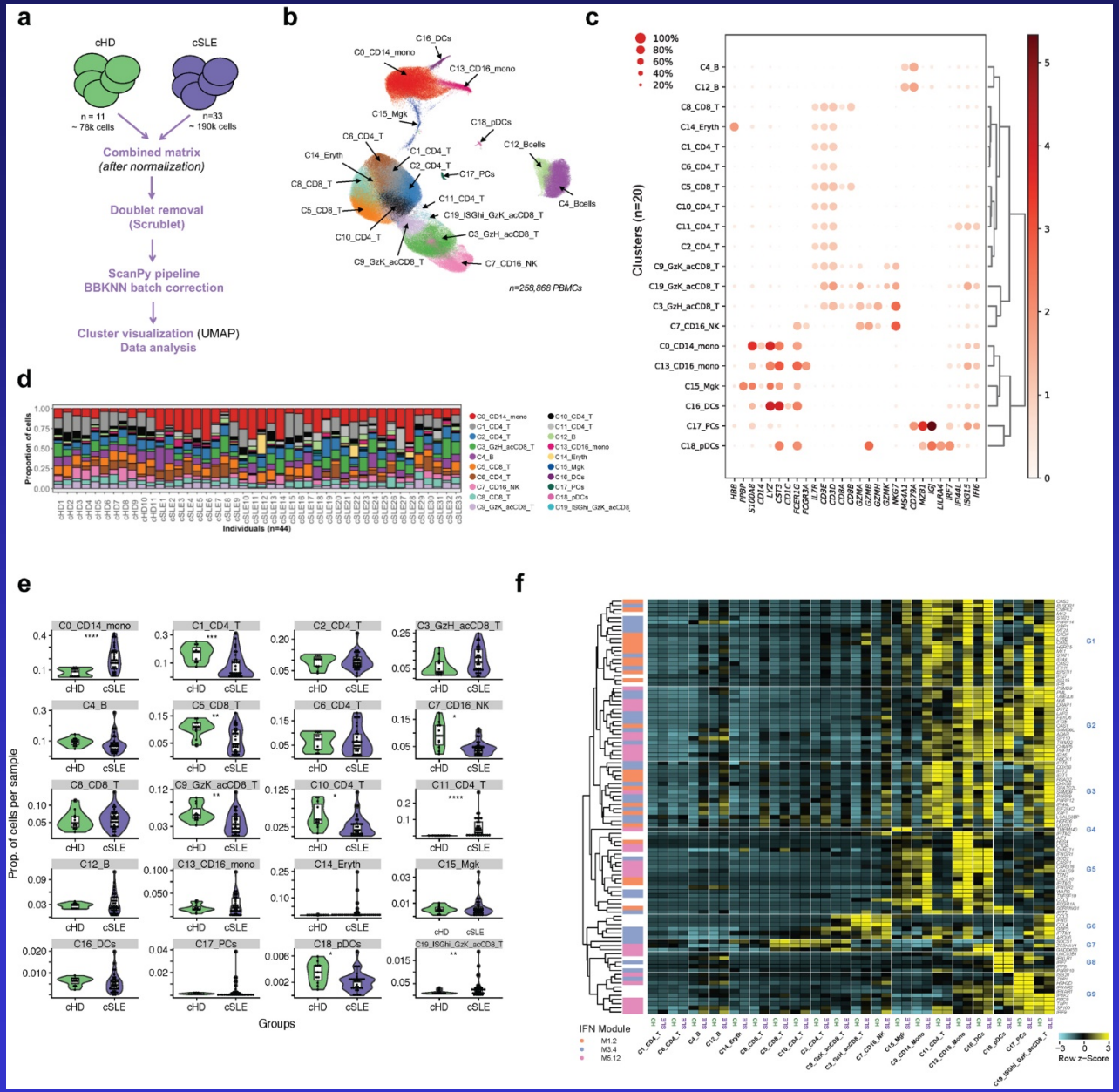
[1]Langefeld, et al. Nature Genetics 2017; [2]Wang et al. Nat Comm 2021; [3]Slight-Webb, Holers, James. Curr Opinion Immunol 2018; [4]Olsen, et al. Trials 2018. [5]Lu et al. J Autoimmun 2017. [6]Munroe et al. Arthritis Rheum 2017.

Recent SLE Research Advances

- Single cell technologies in SLE
  - "Single cell Mapping in SLE"[1]
    - scRNAseq of peripheral blood from pediatric and adult SLE patients (and controls)
    - Defines cell subpopulations with the highest interferon-associated gene signature correlate with disease activity
  - Accelerating Medicines Partnerships RA/SLE[2-4]
    - scRNAseq of lupus nephritis renal biopsies along with parallel urine and blood samples
  - Impact of standard lupus medication of immune subsets[5]
    - CyTOF, soluble mediators, phospho-CyTOF
  - Unique endotype present in AutoAb positive individuals[6]
  - Similarities between SLE and COVID19: extrafollicular B cell activation and shared B cell repertoires

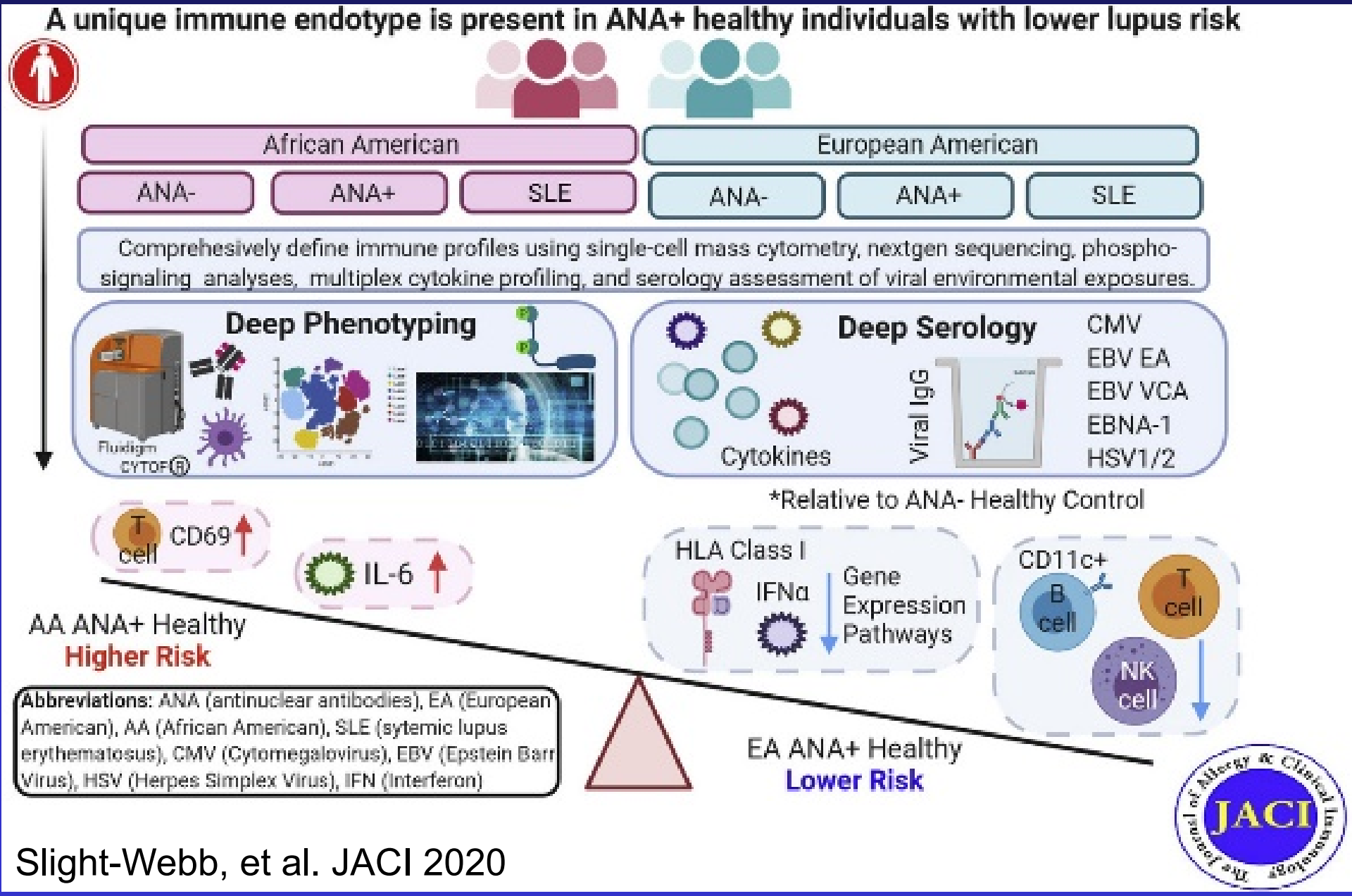
[1]Nehar-Belaid, et al. Nature Immunol 2020; [2]Der, et al. Nature Immunol 2019; [3]Arazi, et al. Nature Immunol 2019; [4]Bocharnikov AV et al. JCI Insight 2019; [5]Slight-Webb et al. JCI Insight 2019; [6]Slight-Webb, et al. JACI 2020; [7]Woodruff et al. Nat Immunol. 2020

Mapping SLE at the single-cell Level



- Profiled 276,000 PBMCs from 33 children with SLE and 11 controls
- High interferon signature genes distinguished SLE from control and driven by monocytes, CD4/CD8 T cells, NK, cDCs, pDNs, B cells and plasma cells

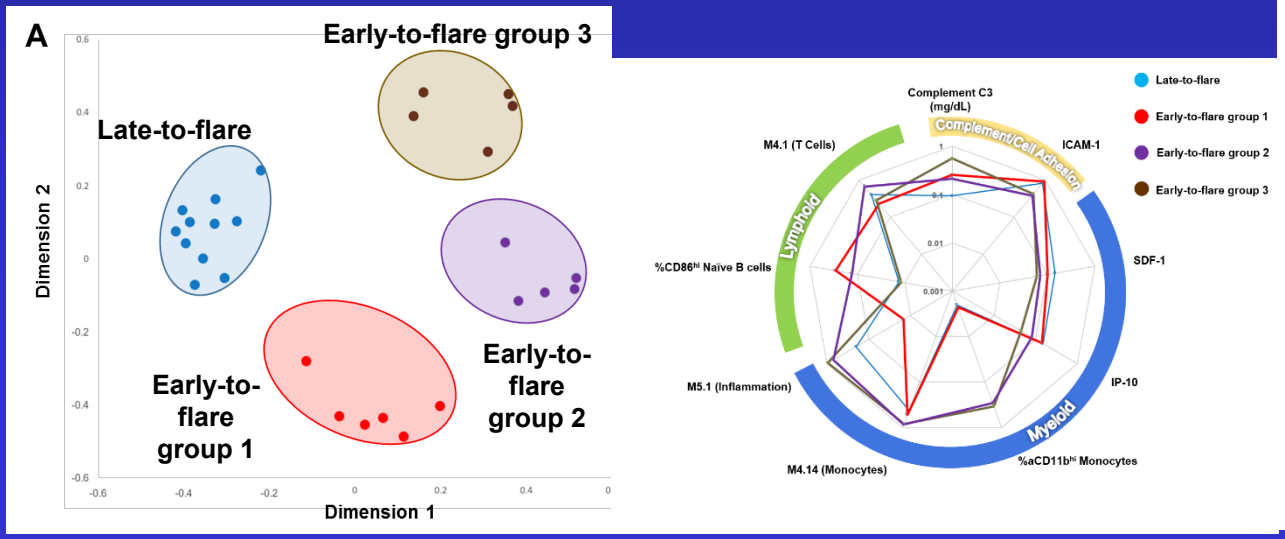
Nehar-Belaid D, et al. Nat Immunol 2020



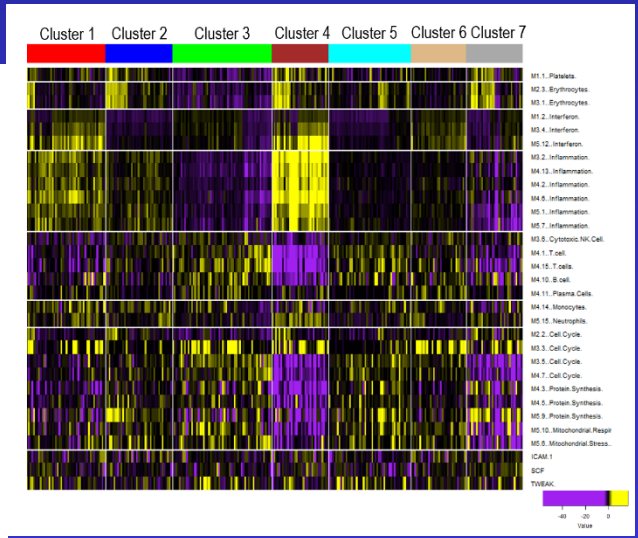
Slight-Webb, et al. JACI 2020

Recent SLE Research Advances

- Dissecting heterogeneity
  - Pediatric and Adult lupus investigation
  - Multiple groups have identified molecular clusters of pediatric and adult lupus patients
  - Patients in select clusters respond to treatment
  - Variability in flares and timing of flares



Lu et al. Sci Rep 2019



Guthridge et al. EClinicalMed 2020

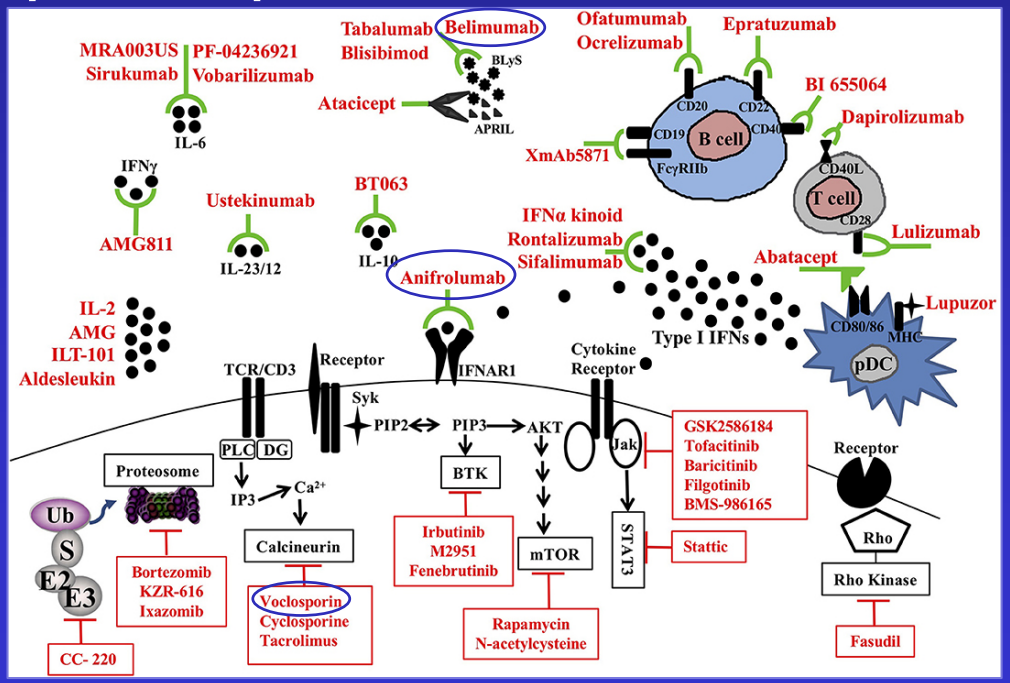
Recent SLE Research Advances

- Pathogenic pathways
  - Complement genes contribute sex-biased vulnerability to SLE[1]
    - C4 alleles 7-fold variation in risk for SLE (more strongly in men)
  - C1q restrains autoimmunity and viral infection by regulating CD8 T cell metabolism[2]
  - Augmented PKR phosphorylation and circRNA reduction are found in SLE PBMCs, impairing the control of innate immunity[3]
  - Digestion of chromatin in apoptotic cell microparticles prevents autoimmunity (null mutations/hypomorphic variants of DNASE1L3) [4]
  - Translocation of a gut pathobiont drives autoimmunity in mice and humans *(Enterococcus gallinarum).*[5]
  - Broad immune activations underlies shared vaccine responses in health and disease activity in lupus.[6]
  - A distinct phenotype of CD4+ T cells drives celiac disease and other autoimmune diseases like SLE[7]
  - CD4+ T cell subpopulation is expanded in lupus and provides B cell help through IL-10 and succinate[8]

[1]Kamitaki N, et al. Nature 2020; [2]Ling GS, et al. Science 2018; [3]Liu et al. Cell. 2019; [4]Sisirak V, et al. Cell 2016; [5]Manfredo Vieira S, et al. Science 2018; [6]Kotliarov Y, et al. Nat Med 2020; [7]Chistophersen A, et al. Nat Med 2019; [8]Caielli S, et al. Nat Med 2019.

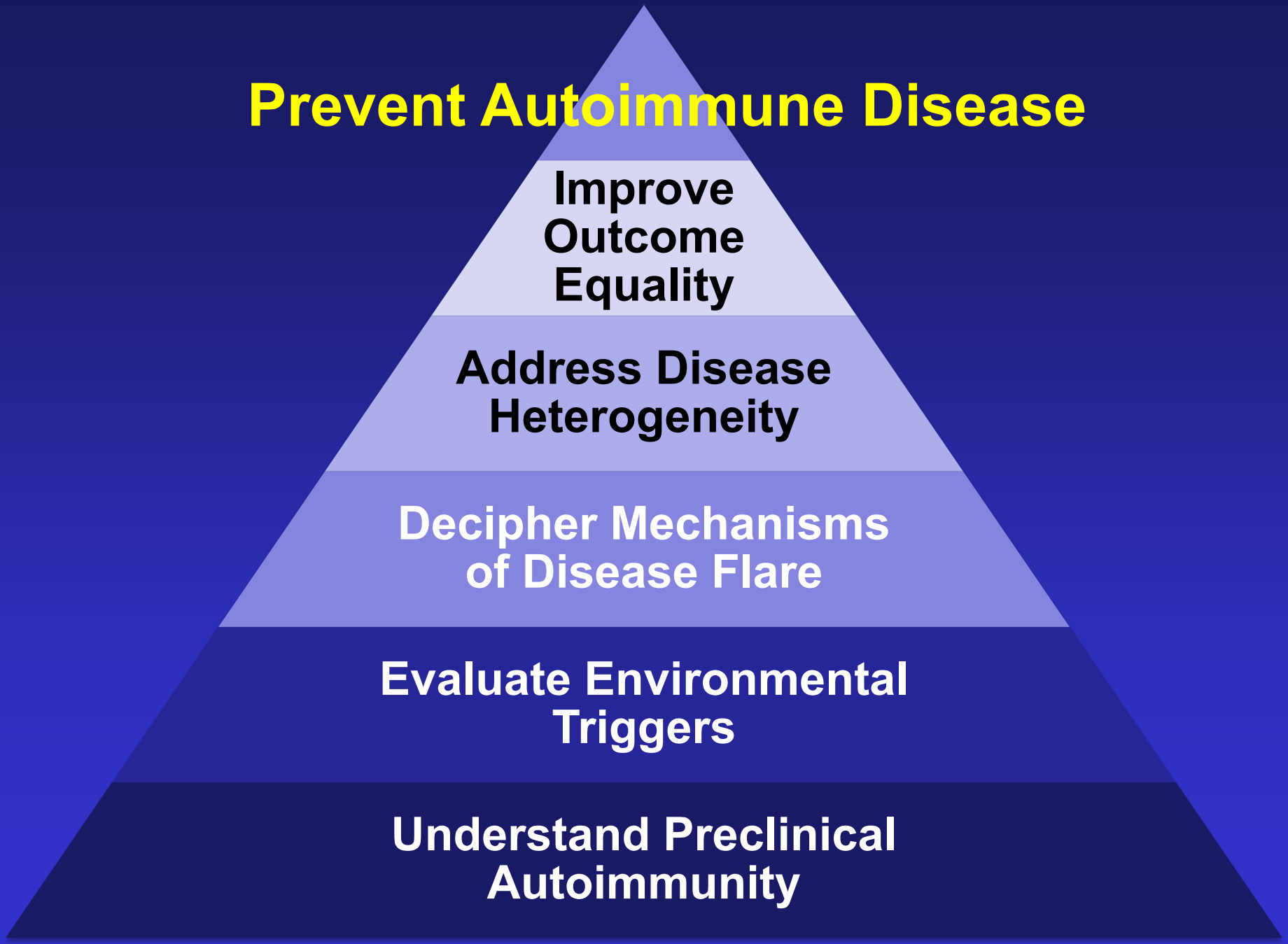
Recent Research Advances

- Improving trials and trial outcomes
  - No new FDA-approved drugs for more than 50 years until belimumab (2011)
  - Past few months saw approval of belimumab[1] and voclosporin[2] for lupus nephritis
  - Other therapeutics are hopefully close (e.g. anifrolimab[3])
  - Partnering patient enrichment strategies novel trial designs for improved outcomes



[1]Furie et al, NEJM 2020; [2]Rovin et al. Kid Int 2019; [3]Morand, et al. NEJM; 2020;

Vukelic, Li, Kyttaris, Front Immunol 2018


Prevent Autoimmune Disease
Improve Outcome Equality
Address Disease Heterogeneity
Decipher Mechanisms of Disease Flare
Evaluate Environmental Triggers
Understand Preclinical Autoimmunity

Suggested Opportunities

- Natural history studies across autoimmune diseases to identify shared and unique mechanisms of disease transition
- Prevention trials for specific autoimmune diseases and autoimmunity
- Dissect molecular homogeneity across autoimmune disease to identify shared pathways and similar patients (regardless of diagnosis) who could benefit from the same/similar treatments
- Perturb-omics
  - Cellular level – single cell work after stimulation
  - Person level – study vaccines or infections in autoimmune disease individuals
- Pathogenic mechanisms, hypothesis testing and discovery science

Suggested Opportunities

- Functional genomics to understand the mechanistic impact of genetic associations
- The “GWAS” for cumulative environmental exposures in autoimmunity; expanded methodologies for gene-gene, gene-environment and cumulative interactions
- Direct therapies to the cells of interest
- Development of trial approaches to allow small, nimble, fast-to-fail/fast-to-work clinical trials for autoimmune disease targets
- Understanding co-morbidities in autoimmunity as accelerated or severe phenotypes of the co-morbidities (e.g. accelerated osteoporosis, accelerated cardiovascular diseases, brain aging, etc.)

Suggested Opportunities

- Health equality for autoimmune disease patients
  - Understand molecular mechanisms of different presentations, severity and outcomes
  - Improve outcomes in African American, American Indian, and Hispanic patients
- Re-analysis/mining of NIH-funded datasets for new questions or to apply novel approaches
- Dissemination and implementation science in autoimmunity
- COVID and autoimmunity
  - Mechanisms and outcomes of SARS-CoV-2 induced autoimmunity
  - COVID vaccination responses and impact on autoimmune diseases
  - COVID infection in autoimmune disease patients and those taking immunomodulatory medications

Role of the NIH

CDC: Epidemiology
RRF: Training
Disease Foundations
FNIH

DoD: Translational
AHRQ/HHS: D&I/Equity
Pharma
Biotech

NIH

Roles of the NIH

- Provide foundational support for Discovery Science for Autoimmune Diseases and for Understanding Autoimmunity
- Develop, lead and implement a cohesive program across NIH Institutes/Centers, Intra-/Extramural NIH communities and with other funders to address these critical health problems
- Forge novel private and public partnerships to support the broad spectrum of science and scientific training needed to improve the lives of patients with autoimmune diseases
- Work with patient groups and patient advisory councils to ensure the clinical areas of top importance are addressed
- Serve as the central leadership for the science, scientifically-driven clinical care, improved diagnostics/prognostics/therapeutics and ultimately prevention to improve the health and health outcomes of patients with autoimmunity and autoimmune diseases and of potential patients

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