Leveraging Predictive Risk Models to Navigate the Diagnostic Challenges of Positive Antinuclear Antibodies

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Disclosures

- I have no financial disclosures.

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The problem with the ANA

- “First Day of Rheumatology” Dr. Glaucomflecken

https://www.youtube.com/watch?v=ykZLc7iYRW0

Objectives

- Review antinuclear antibody (ANA) testing and discuss strengths and limitations of different methods
- Review limitations of ANA testing and name non-rheumatic conditions associated with positive ANAs
- Explain the significance of ANA titer and pattern and identify factors that are associated with developing autoimmune disease
- Discuss strategies to help triage and evaluate individuals with positive ANAs

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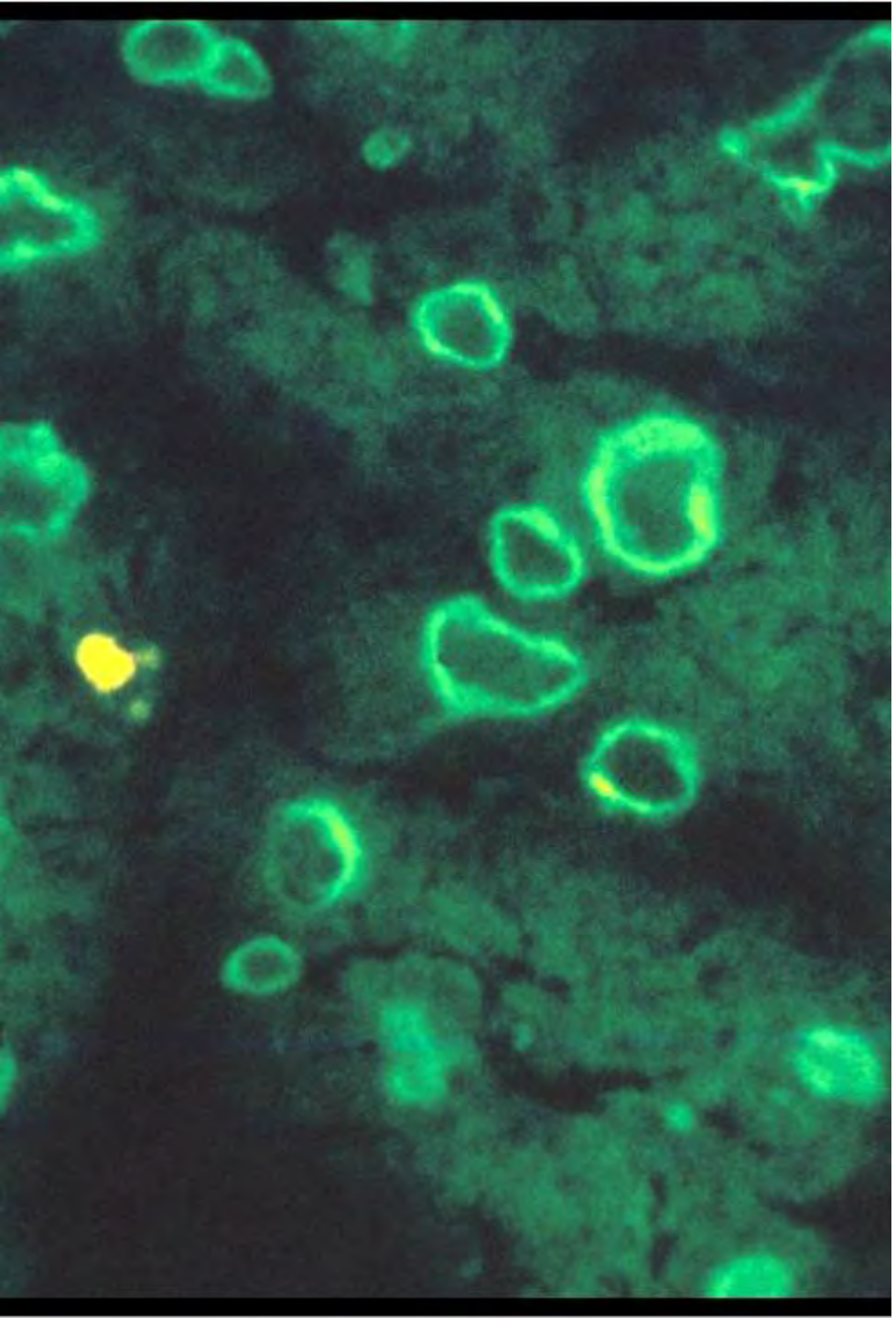
Recommended literature

- Bossuyt X et al. Understanding and interpreting antinuclear antibody tests in systemic rheumatic diseases. Nat Rev Rheumatol 2020 Dec; 16(12): 715-726.

- Olsen NJ et al. Finding lupus in the ANA haystack. Lupus Sci Med 2020 Feb 2:7(1):e000384.

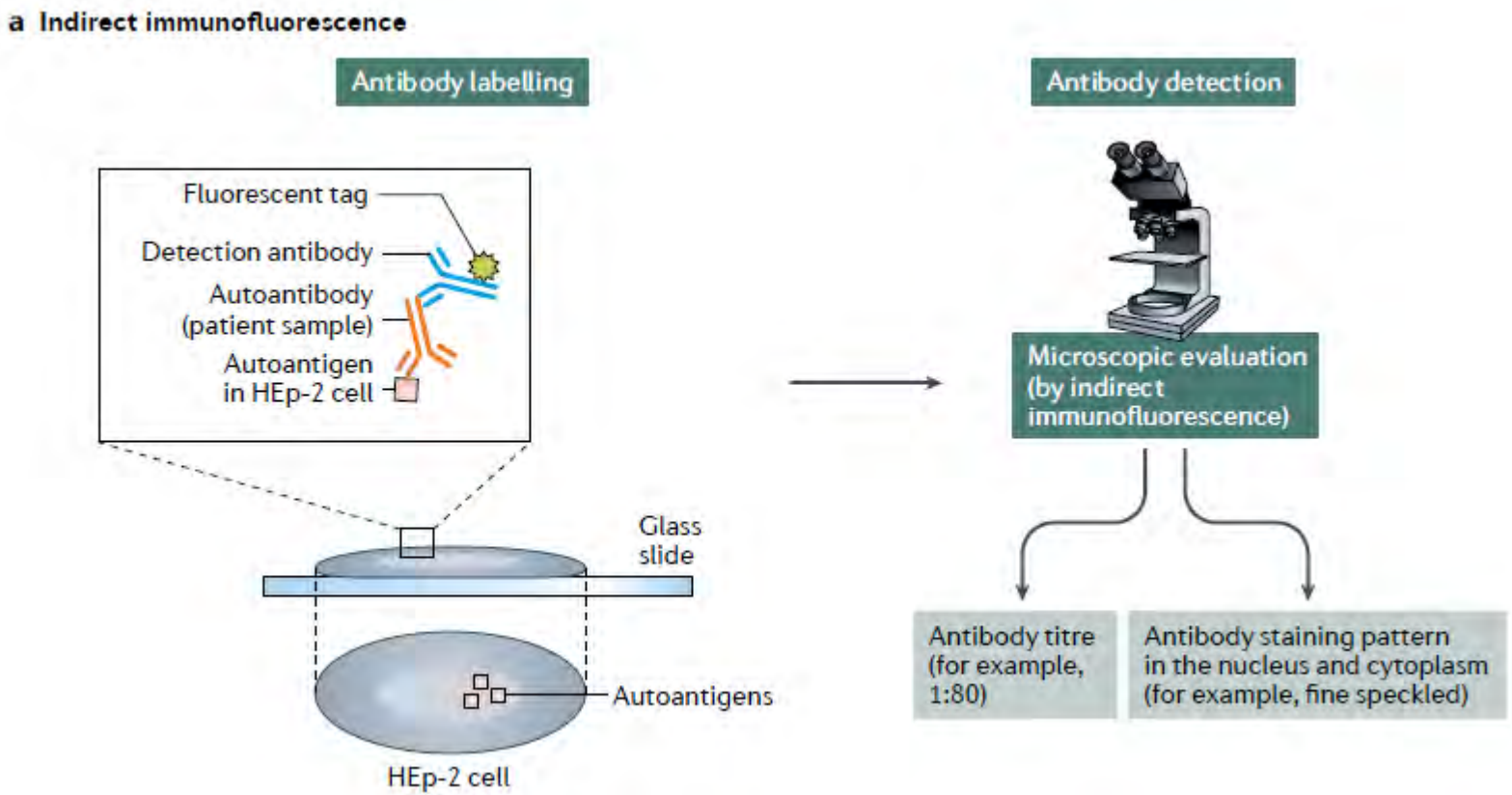
- Barnado A et al. Identifying antinuclear antibody positive individuals at risk for developing systemic autoimmune disease: development and validation of a real-time risk model. Front Immunol 2024 Mar 20:15:1384229.



Antinuclear Antibodies (ANAs)

- Antinuclear antibodies serve as diagnostic criteria for multiple autoimmune diseases.
  - Highly sensitive for autoimmune diseases but not specific
  - Other causes: chronic infections (hepatitis B, C, tuberculosis) and malignancy
- Up to **20% of the general population has a positive ANA without having autoimmune disease.**
- Only **11-20% of patients with a positive ANA will ultimately have an autoimmune disease.**

ANA testing

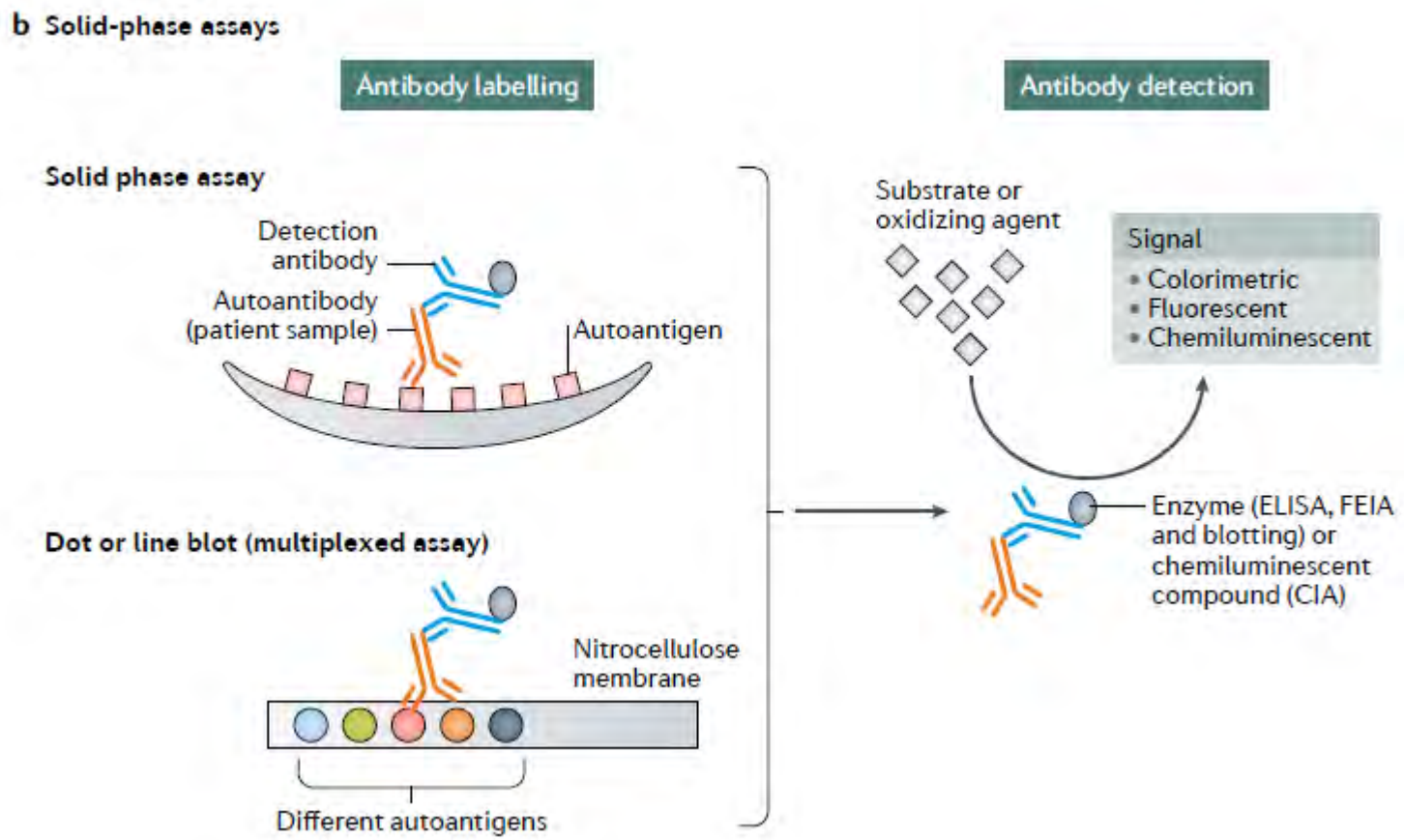


Bossuyt X et al. Nat Rev Rheumatol 2020

<u>Indirect immunofluorescence (HEp-2 cell)</u>

- **Considered gold standard ANA testing by ACR**
- Not dichotomous result
- Significance of result based on titer and staining pattern
- Can visualize cytoplasmic patterns
- Can detect novel autoantibodies, useful for research
- Manual and more time intensive, inter and intra-operator variability
- Different HEp-2 IIF kits may give different results

ANA testing

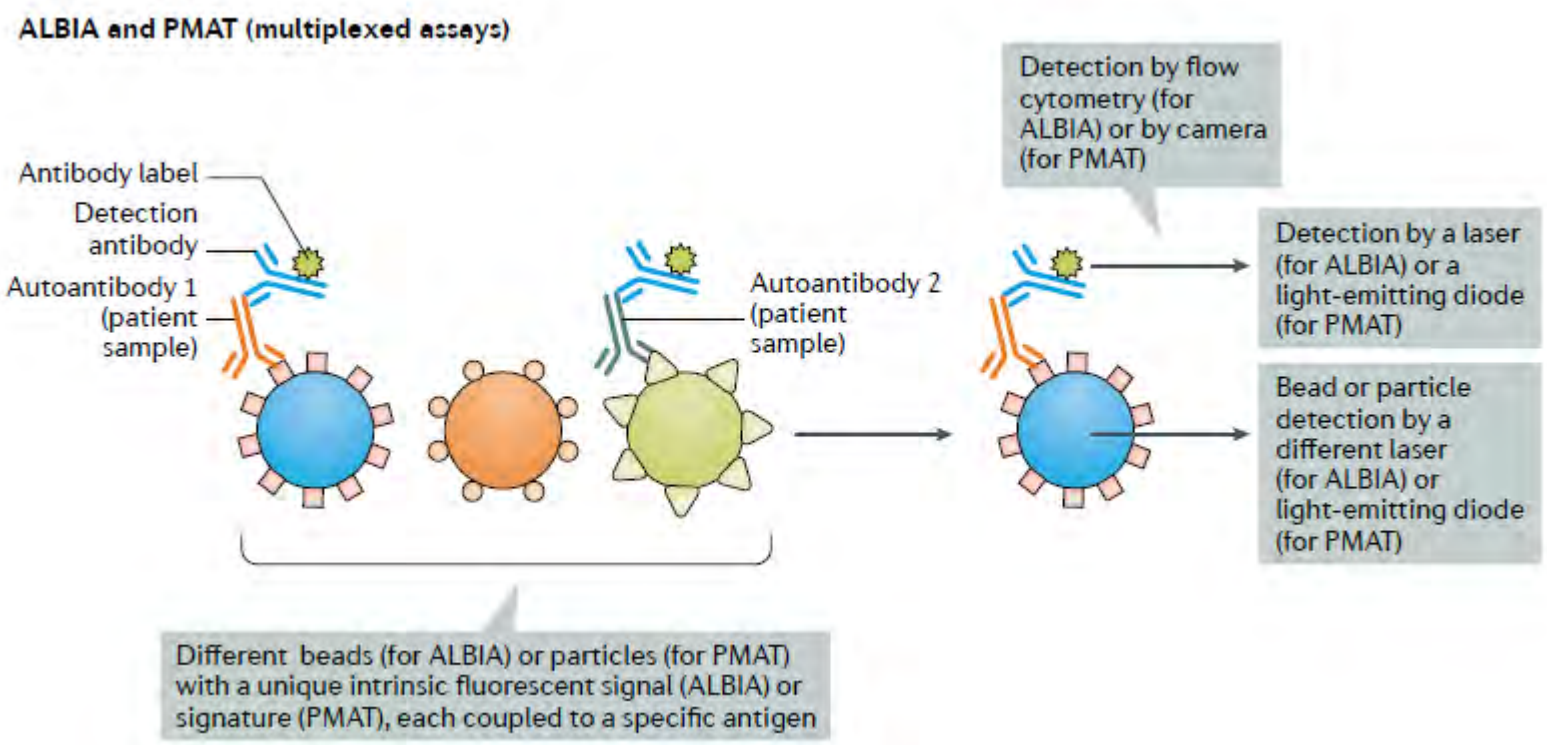


<u>Solid phase assays:</u>

- **ELISA** (Enzyme-Linked Immunosorbent Assay), **FEIA** (Fluorescent Enzyme Immunoassay), **CIA** (chemiluminescent compound)
- Often reported as positive, negative, indeterminate
- **More efficient, cost effective, and specific than Hep-2 IIF**
- Less sensitive than Hep-2 IIF depending on solid phase assay kit cut-off

Bossuyt X et al. Nat Rev Rheumatol 2020

ANA testing



ALBIA and PMAT (multiplexed assays):

- Addressable laser bead immunoassay (ALBIA) and particle-based multi-analyte technology (PMAT) assay
- Analyzed by flow cytometry using two lasers (ALBIA) or camera (PMAT)
- Simultaneous detection of multiple antibodies with high specifities
- **High degree of automation allows for efficient screening** of multiple antibodies

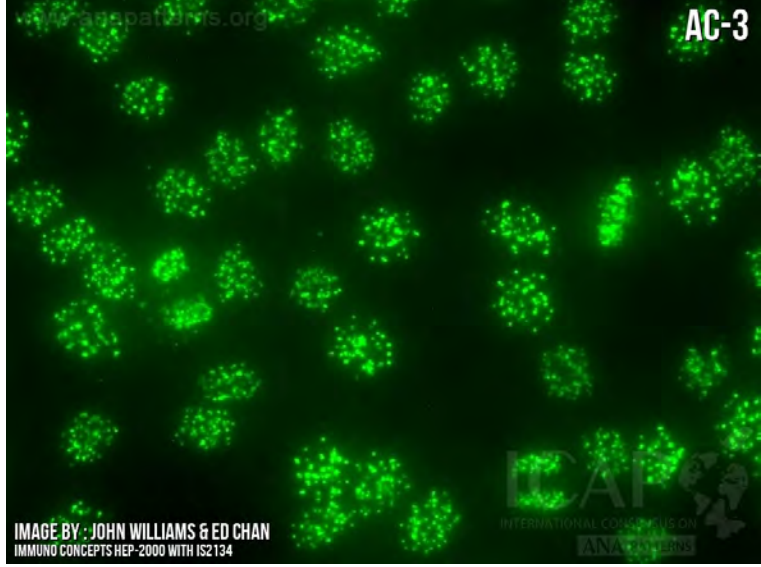
Bossuyt X et al. Nat Rev Rheumatol 2020

ANA titer

- **As titer increases, risk of autoimmune disease increases**
- HEp-2 IIF cutoff for “positive:” ≥ 1:160
  - Based on titer that corresponds to 95th percentile of age and gender-matched healthy individuals
- Note discrepancy of Hep-2 IIF and solid phase assays may be that solid phase assays have a cut-off of ≥ 1:40 or ≥ 1:80
- Value of combining tests
  - When Hep-2 IIF and solid phase assay (FEIA) are both negative or positive, helpful in ruling out or ruling in disease
  - For discordant results, a positive FEIA and negative Hep-2 IIF is more likely for disease than the alternative combination
- Note SLE classification criteria requires ANA ≥ 1:80 for entry
  - Cutoff chosen to optimize sensitivity (98%), specificity (75%)

Bossuyt X et al. Nat Rev Rheumatol 2020

ANA patterns



Centromere

- Highest PPV for ANA-associated rheumatic diseases
- Highly associated with but not pathognomonic for systemic sclerosis
- 93% with centromere ANA pattern had positive centromere antibody

Titer	1:160	1:320	1:640	1:1280
PPV	29%	42%	77%	82%

Vulsteke J-B et al, Ann Rheum Dis 2021

ANA patterns

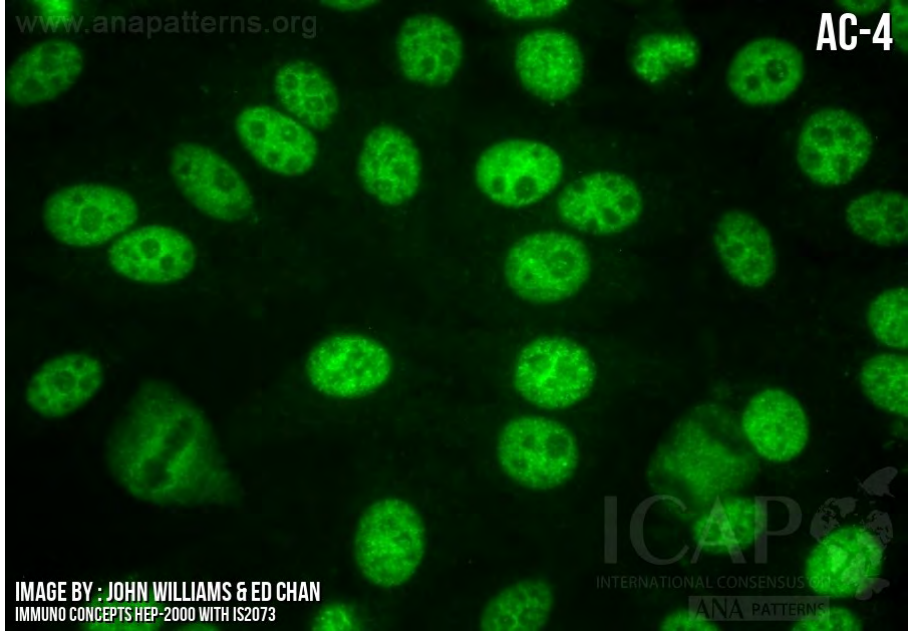
Nucleolar

- Most commonly associated with systemic sclerosis but also SLE, idiopathic inflammatory myopathy
- Associated with PM/Scl, anti-fibrillarin (U3 RNP)

Titer	1:160	1:320	1:640	1:1280
PPV	19%	31%	-	61%

Vulsteke J-B et al, Ann Rheum Dis 2021

ANA patterns



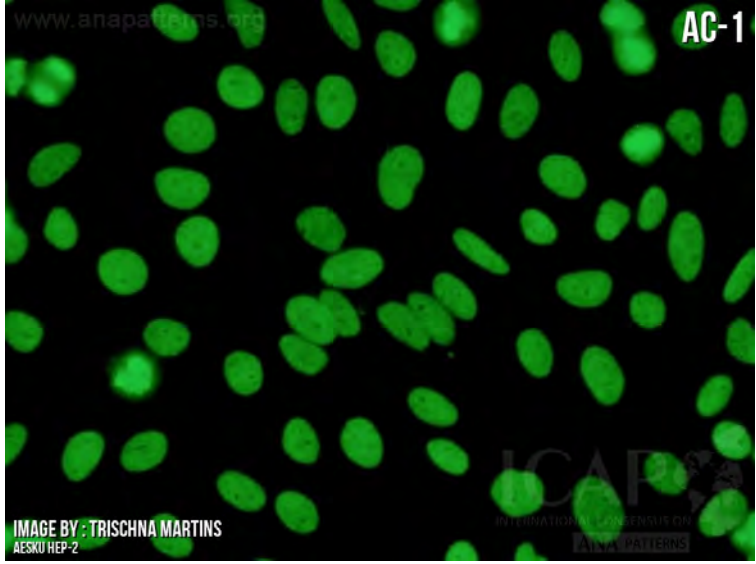
Speckled

- Can be seen in all ANA-associated rheumatic diseases
- Associated with RNP/Smith (coarse) and SSA/Ro-60 (fine)
- PPV for ANA 1:80 speckled ~ 4%

Titer	1:160	1:320	1:640	1:1280
PPV	13%	39%	32%	71%

Vulsteke J-B et al, Ann Rheum Dis 2021

ANA patterns



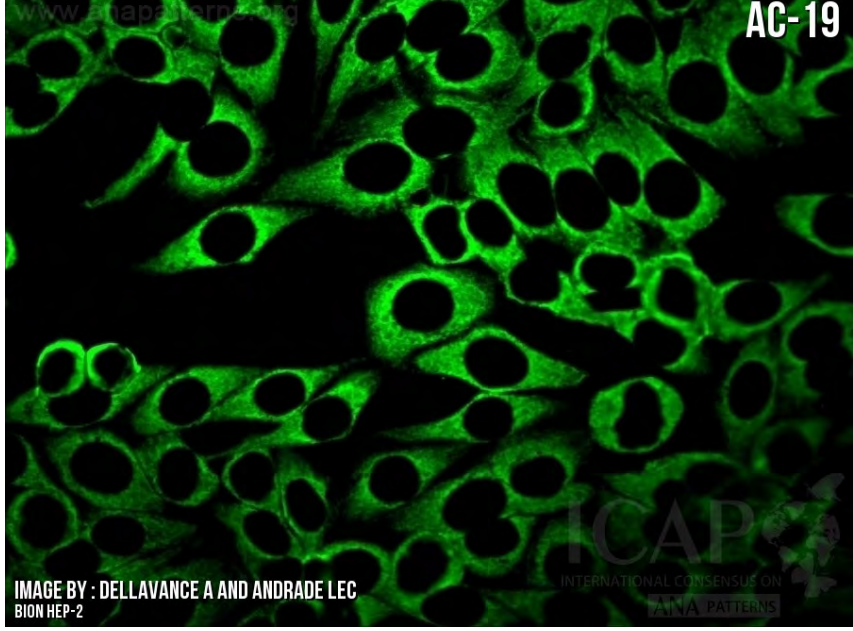
Homogeneous

- Associated with SLE and systemic sclerosis
- Also associated with non-autoimmune disease
- ~15% with positive dsDNA

Titer	1:160	1:320	1:640	1:1280
PPV	6%	9%	29%	39%

Vulsteke J-B et al, Ann Rheum Dis 2021

ANA patterns



Cytoplasmic

- ANAs can result as negative as not nuclear pattern
- Patterns associated with anti-synthetase syndrome

Vulsteke J-B et al, Ann Rheum Dis 2021

ANAs in the healthy US population

- Cross-sectional analysis of 4,754 US individuals from NHANES (1999-2004)
- Positive ANA prevalence in individuals ≥ 12 yo: **13.8%**
- Positive ANA prevalence **increases with age**
- **More prevalent among females vs. males** (17.8% vs. 9.6%)
  - Female to male ratio peaked at ages 40-49 years
- **Modestly higher prevalence in African Americans vs. Whites**
- Positive ANAs were less common in overweight and obese individuals vs. individuals with normal weight
- No significant associations with education, family income, alcohol use, smoking history

Satoh M et al, Arthritis Rheum 2012

Frequency of ANA in Malignancy

Neoplasm	Pts	% ANA (+)	ANA titers
Breast	39	28.2%	1:80-1:320
Colorectal	68	27.9%	1:80-1:640
Gastric	13	7.7%	1:80-1:160
Hepatocellular	10	30%	1:80-1:320
Lung	64	26.6%	1:80-1:320
Lymphoma	22	31.8%	1:80-1:320
Pancreatic	10	20%	
Prostate	17	23.5%	1:80-1:320
Gynecologic	16	43.7%	1:80-1:320
Ovarian	7	28.6%	
Uterine	9	55.5%	
Urinary bladder	9	33.3%	1:80-1:160

Lupus **2004**, 13, 159-164

Frequency of “Specific” Autoantibodies in Malignancy

- Monoclonal gammopathy unclear significance
  - 141 pts - 22% with anti-RNP, 11% with anti-Sm
  - 340 pts – 13.5% bound Ro/SSA and 23.2% bound La/SSB
  - 125 pts – 4.8% p-ANCA, 4.8% c-ANCA (IgM and IgG)
- Lymphoma
  - 61 pts with NHL – 3.5% dsDNA + 12.5% aPL
- Prolactinoma
  - 19 pts, 30.3% dsDNA, 27.2% aCL, 27.2% SSA, 27.2% Sm, 24.2% PR3

J Autoimmun 1995, 8, 415-424

J Clin Lab Immun 1990, 32(4), 153-159

Clin Exp Immun 1989, 75(3), 349-353

Human Antibodies 1992, 3(2), 75-80

Leukemia and Lymphoma 2000, 40(1-2), 119-122

Frequency of ANA in Infection

Infection	ANA frequency	Citation
HIV	~20% “low titer” 3%	Curr Opin Infect Dis **2009,** 22(1), 49-56
HBV	20-27%	Gastroenterology **1995**, 108, 157-164
HCV	22-29% > 1:80	Medicine **2000,** 79(1), 47-56
Subacute Endocarditis	30% (1:40 to 1:640)	QJM **1975**, 172, 537-550
Tuberculosis	7% predominately low titer	J Chron Dis **1970**, 22, 717-725
Malaria	38%	Clin Exp Immun **1982**, 49(2), 310-316

- Positive ANAs can be seen with **acute viruses**: hepatitis A, Zika, chikungunya, and dengue

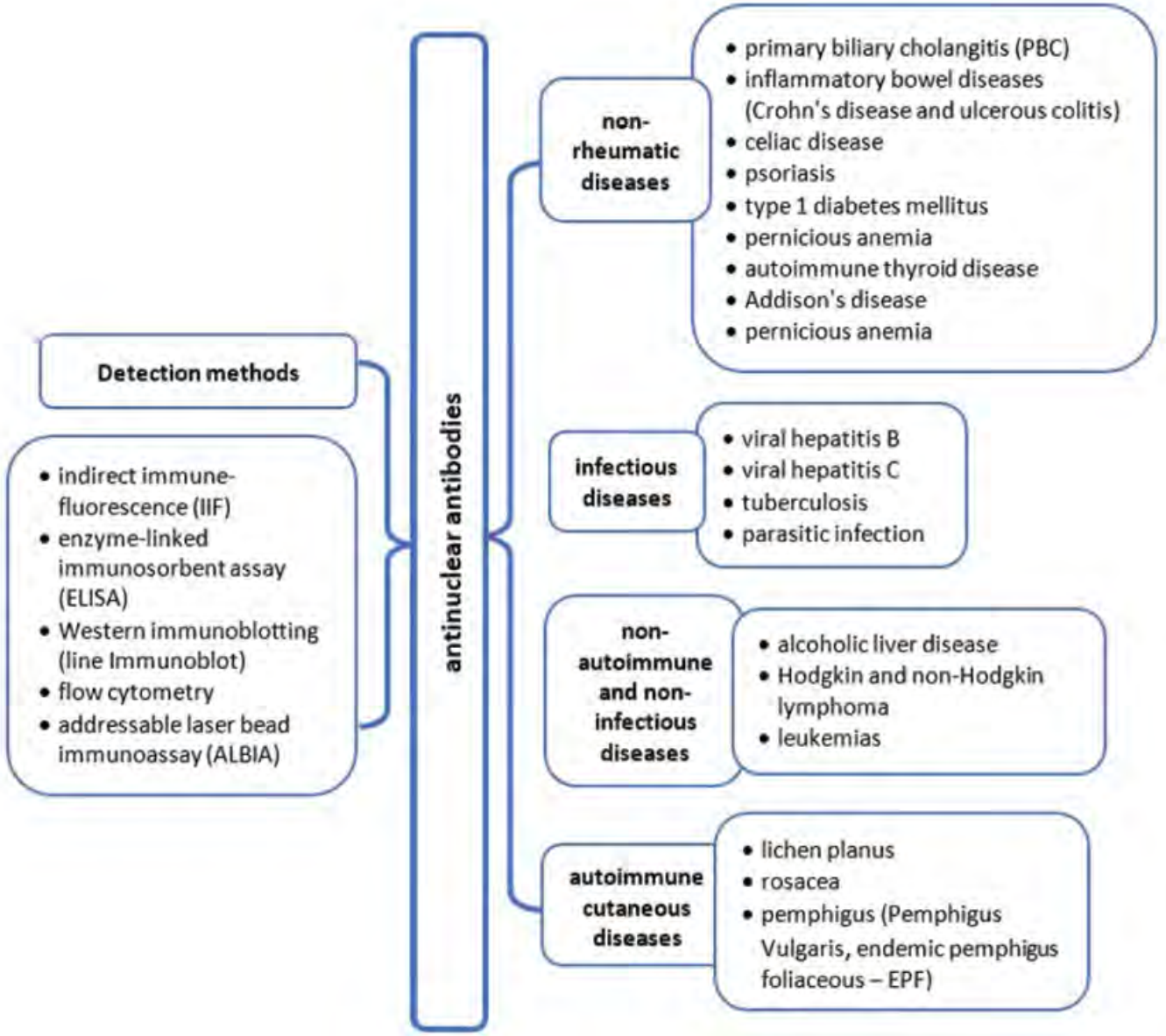
IM JH et al. Infectious Diseases 2019

ANA and Infection

- In single center Korean study with 9,320 individuals seen in the infectious disease
  - 1,111 underwent ANA testing – 110 tested positive
  - Remaining 82 patients who tested positive without underlying autoimmune disease
    - Mycobacterium tuberculosis (n = 10) (extrapulmonary)
    - Treponema pallidum (n = 5)
    - Orientia tsutsugamushi (n = 5) (Rickettsial mite-bourne disease)
    - E coli (n = 5)
    - Bartonella (n = 3)
    - HIV (n = 3)
  - Immune response to intracellular pathogen that induces ANA?

IM JH et al. Infectious Diseases 2019

ANA and non-rheumatic diseases



ANA positivity in non-rheumatic diseases

- 15-26% in psoriasis
- 27% type 1 diabetes
- 8-24% in Crohn’s disease
- 9-24% in Celiac disease
- 80% in Grave’s disease
  - Low titers (1:80 or 1:160)
- 35% in autoimmune thyroid disease
  - ANA positivity due to anti-thyroglobulin and anti-thyroperoxidase antibodies
  - Can also see positive dsDNA and SSA

Kumar NN, et al. Archivum Immunologiae et Thrapiae Experimentalis 2025

Immunologic profiles of positive ANA individuals

- Positive ANA individuals (asymptomatic) have similar immunologic abnormalities compared to individuals with autoimmune diseases[1,2,3]
  - B cell activation
  - T cell activation and changes[1,3]
    - Reductions in invariant natural kill T cells (iNKT)
    - Increases in T follicular helper cells (Tfh)
    - Increases in T regulatory cells (Treg)
  - Immunologic changes correlated with ANA titer and having additional autoantibodies[1]
  - Healthy ANA positive African Americans with increased T cell activation, IL-6 levels[3]
  - Healthy ANA positive European Americans with suppressive immune phenotype to protect against T cell expansion, increase in interferon[3]

[1]Baglaenko Y, et al. Arth Res Ther 2018
[2]Slight-Webb S, et al. Arthritis Rheumatol 2016
[3]Slight-Webb S, et al. J Allergy Clin Immunol 2020

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Antinuclear Antibodies

- **Don’t order ANA and ENA (i.e. SSA, SSB, Smith) unless the patient is suspected to have a connective tissue disease.**
- Avoid in investigation of widespread pain or fatigue alone
- Consider pre-test probability knowing false positive results lead to further unnecessary testing
- Repeat testing is not recommended unless the clinical picture changes significantly
- National shortage of both pediatric and adult rheumatologists in the US

Tozzoli R, et al. Am J Clin Pathol 2002.
Solomon DH, et al. Arthritis Rheum 2002.
Ferrari R. Clin Rheumatol 2015.

Long diagnostic journeys for patients with autoimmune diseases

- On average, **SLE patients are diagnosed 6.9 years from time of symptom onset**
- Some patients are **diagnosed up to 10 years** from time of symptom onset

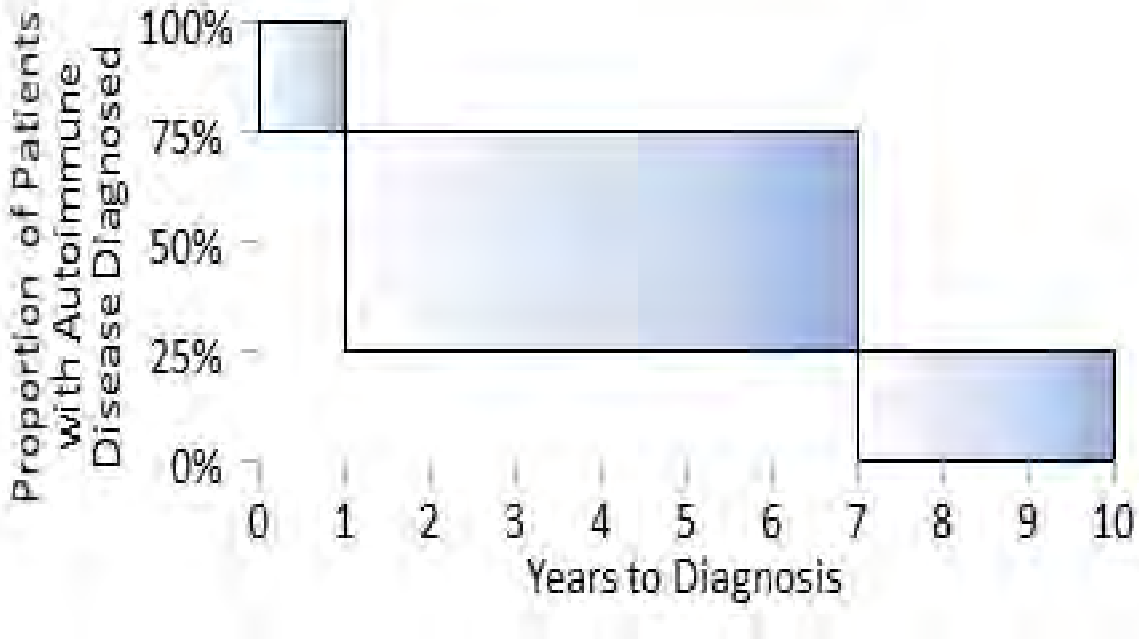


Figure adapted from data in Sloan M, et al. Rheumatol Adv Pract 2020

Interventions to reduce positive ANA referrals

- **Up to 22% of rheumatology referrals are for positive ANAs[1,2]**
  - **Only 11-20% of these referrals result in an autoimmune disease diagnosis[3-6]**
- **Triage systems[7]**
  - Incomplete and missing data (up to 50%) even with standardized forms
  - Rheumatologists cannot determine who is high or low risk

[1]Olsen NJ, et al. Lupus Sci Med 2020
[2]McGhee JL, et al. BMC Pediatr 2004
[3]Slater CA, Arch Intern Med 1996
[4]Dinser R et al. Scand J Rheumatol 2007
[5]Abeles AM, Am J Med 2013
[6]Soto ME, et al. Results Immunol 2015
[7]Speed CA, et al. Rheum (Oxford) 2005

Interventions to reduce positive ANA referrals

- **Electronic consults (e-consults)[1,2]**
  - Allow communication to reduce missing data (internal providers)
  - Mixed results if shorten rheumatology wait times
- **Quality improvement and education initiatives[3,4]**
  - Some improvement in quality of positive ANA referrals (PPV went from 16% to 26%) with an educational poster and hard-stop prompt in the electronic ANA order
  - Some improvement with educational sessions to reduce number of positive ANA referrals but didn't reduce ANA ordering
  - Institution specific, how reach external providers
  - Impact may wane over time and vary by provider type/specialty

[1]Patel VD, et al. BMC Rheumatol 2020
[2]Rostom K, et al. J Rheumatol 2018
[3]Patel V, et al. Clin Rheumatol 2021
[4]Basson YP, et al. Clin Rheumatol 2024

Predictive Risk Models

Develop and validate risk models in the EHR to identify patients at risk for adverse outcomes.

- Through adaptive and pragmatic clinical trials, assess if risk models improve outcomes

AVAIL (Advanced Vanderbilt Artificial Intelligence Laboratory)

- **Biostatistics –** rigorous regression modeling techniques, novel machine learning methods
- **Biomedical informatics –** expertise in programming and partner with HealthIT to deploy and randomize risk models in EHR
- **Clinical informatics –** physician scientists with expertise in clinical implementation, decision support
- **Clinical infrastructure -** Health IT, nursing, administration leadership

Predictive Risk Models

AVAIL process

- Build robust predictive models that are informed by the literature, clinicians, and biostatisticians
- Identify high risk patients
- Randomly assign intervention vs. standard of care (usual care)
- Assess if intervention impacts clinical outcomes

Prior successes

- Hospital readmissions
- Suicide
- Pediatric venous thromboembolism
- Postpartum hemorrhage

Predictive risk models: expanding from studying to impacting outcomes

No tools exist to help clinicians risk stratify patients with a positive ANA.

- **Aim: Refine and validate features available in the EHR to distinguish positive ANA patients who develop autoimmune disease from positive ANA patients who do not develop autoimmune disease.**

- **Expand** our model to examine risk not just for SLE but for multiple systemic autoimmune diseases.
- **Automate** our model so providers do not have to input data or calculate risk scores.
- **Assess** our model in clinical practice through a systems-based approach to determine if they improve patient outcomes.

Proposed EHR data for the model

Demographics
Age at time of positive ANA
Sex
Race
Ethnicity

Billing code categories
Arthritis
Rash
Alopecia
Raynaud's
Sicca
Fatigue
Serositis
Interstitial lung disease or pulmonary hypertension

Laboratory data
ANA titer (1:80 or = 1:160)
Lowest white blood cell count
Lowest platelet count
Highest serum creatinine
Ever present rheumatic disease-associated autoantibody

- Developed *a priori*
- Informed by the literature (SLE risk models) and clinical relevance
- Selected based on EHR availability

Risk factors for developing autoimmune disease with a positive ANA

- **Demographics**
  - Younger
  - Female
  - African American race and Hispanic ethnicity
- **Clinical factors**
  - Inconsistent studies on most predictive signs and symptoms
    - Joint pain, skin rash
  - Higher titer ANA
  - Additional autoantibodies
- **Genetics, biomarkers**
  - Modest predictive value for genetic risks scores in RA and SLE
  - Biomarkers not clinically available, not validated in real-world settings
- Overall, limited studies with low sample sizes and lack of robust modeling methods

SLE risk models

UK SLE risk model[1]

- Logistic regression model using UK biobank
- **Female sex, younger age, and higher number of clinic visits, and billing codes** (arthritis, rash, sicca, fatigue, serositis, Raynaud's) **most predictive for SLE**
- Model AUC 0.75, PPV 7-9%, sensitivity of 24-34%
- **Strengths:** large sample, control group, used variables readily available in the EHR, validation
- **Limitations:** model performance, not a diverse population, did not deploy in clinical practice to assess feasibility and if helped make earlier SLE diagnoses

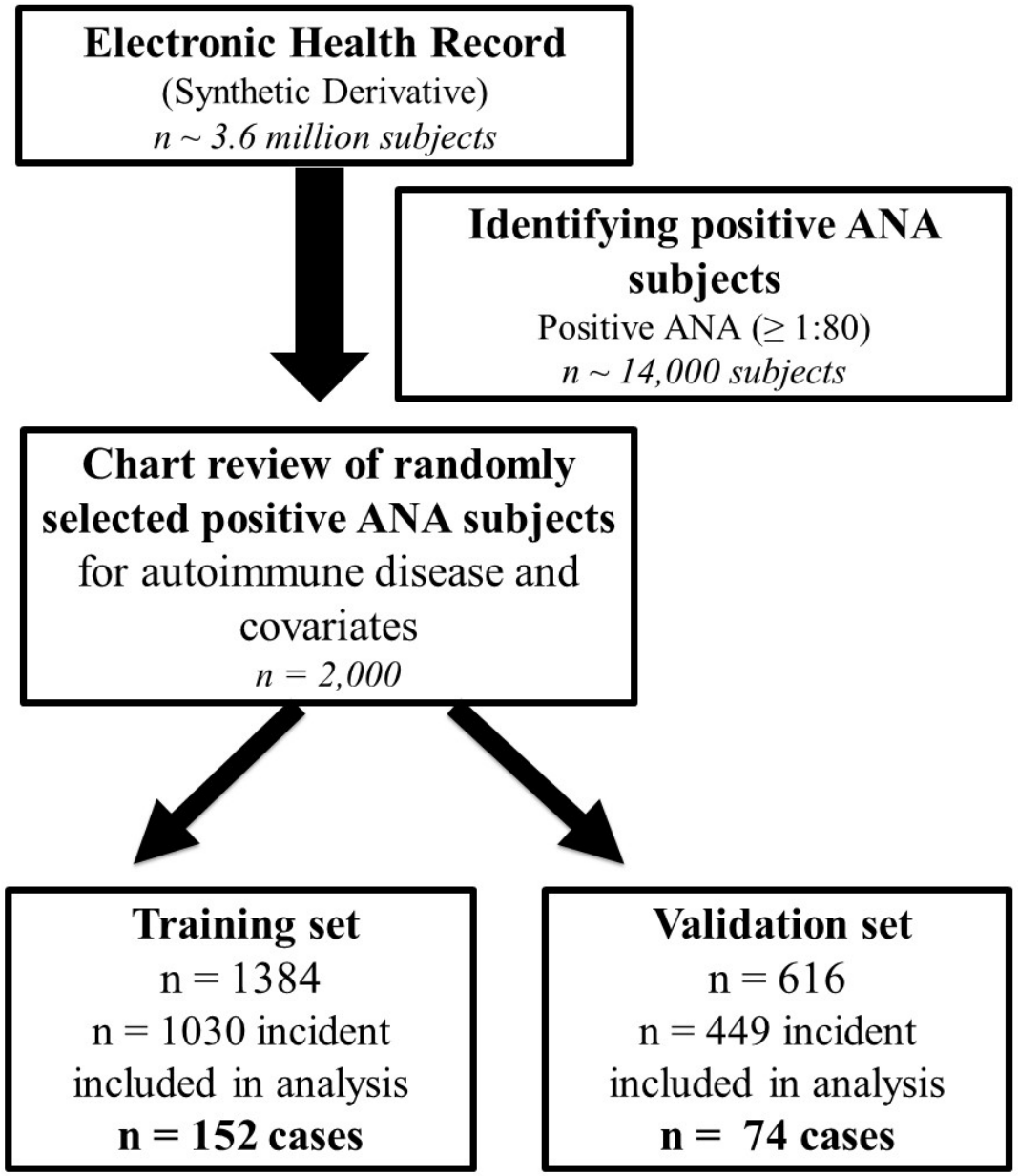
Greek SLE risk model[2]

- Machine learning methods (random forests, LASSO)
- Developed in an academic center rheumatology clinic, mined rheumatology notes for ACR/EULAR SLE classification criteria
- AUC ~ 0.98
- **Strengths:** large sample, validation, good model performance
- **Limitations:** not a diverse sample, not generalizable to general practice setting, challenging to deploy and automate in the EHR, not assessed in clinical practice

[1]Rees F et al. Arthritis Care Res 2017
[2]Adamichou C et al. Ann Rheum Dis 2021

Study Flow

- Identified positive ANA subjects in the Synthetic Derivative
- Randomly selected ~2,000 subjects for a training and validation set
- Analyzed subjects who were incident
  - 15% had systemic autoimmune disease



Training set

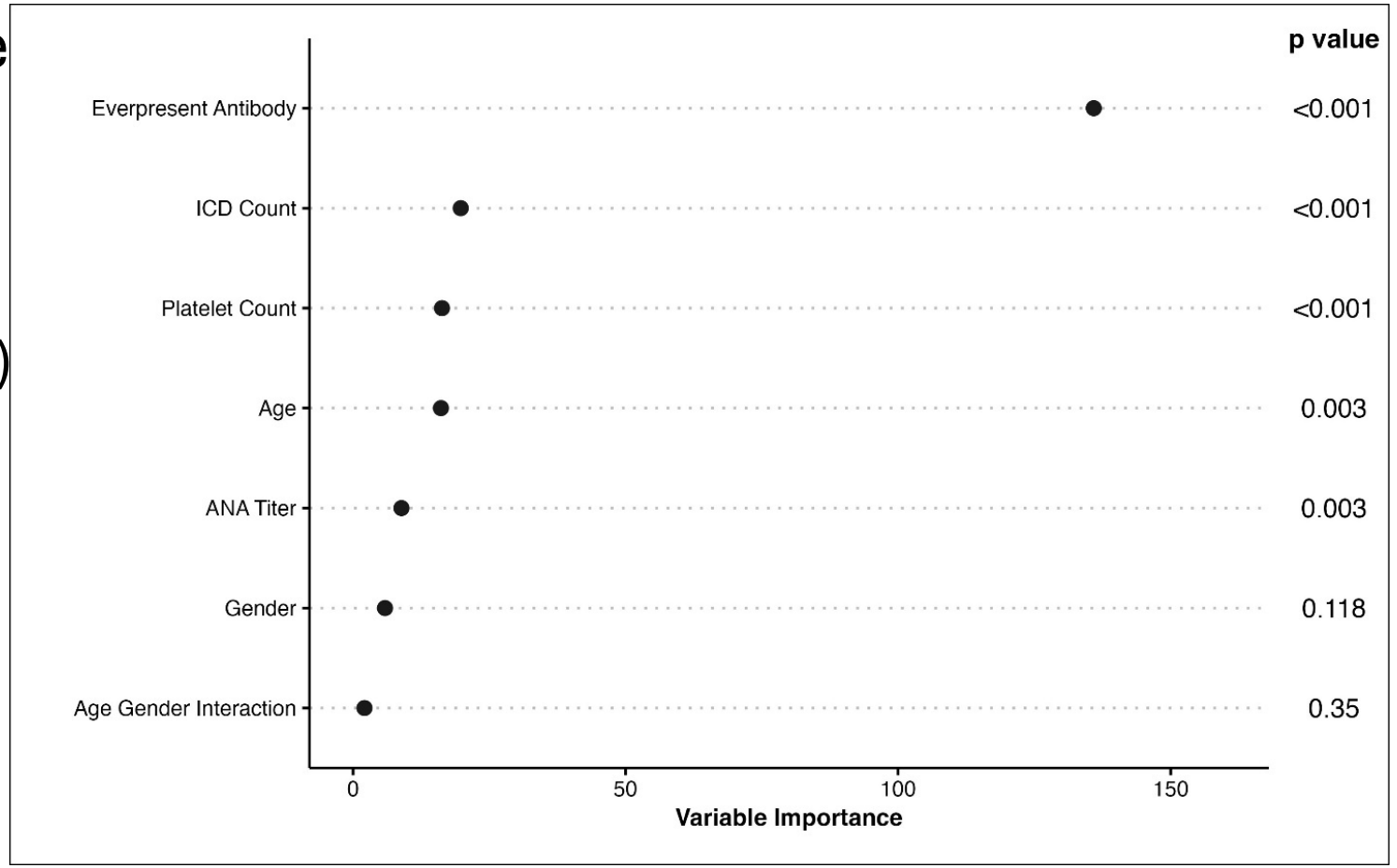
- 15% with systemic autoimmune disease (n = 152)
- **<u>Systemic autoimmune disease more likely</u>**:
  - **Younger** age (41.8 ± 21.5 vs. 47.9 ± 19.3, p = 0.003)
  - **Females** (84% vs. 70%, p < 0.001)
  - **Higher titer ANA** (≥ 1:160 vs. 1:80) (90% vs.79%, p = 0.002)
  - **Higher platelet count** (274 ± 113 vs. 229 ± 96, p < 0.001)
  - Presence of **disease-specific autoantibody** (i.e. dsDNA, RF)
    - (51% vs. 9%, p < 0.001)
  - **Higher billing code count** for symptoms of autoimmune diseases
    - (0.9 ± 0.9 vs. 0.6 ± 0.8, p < 0.001)

ANA Risk Model Results

- Developed a preliminary mode
  - Age, sex, (interaction term),
  - Billing code counts,
  - ANA titer, platelet count,
  - **Autoantibodies** (i.e. dsDNA, RF)
- Used logistic regression,

XGBoost, and neural networks

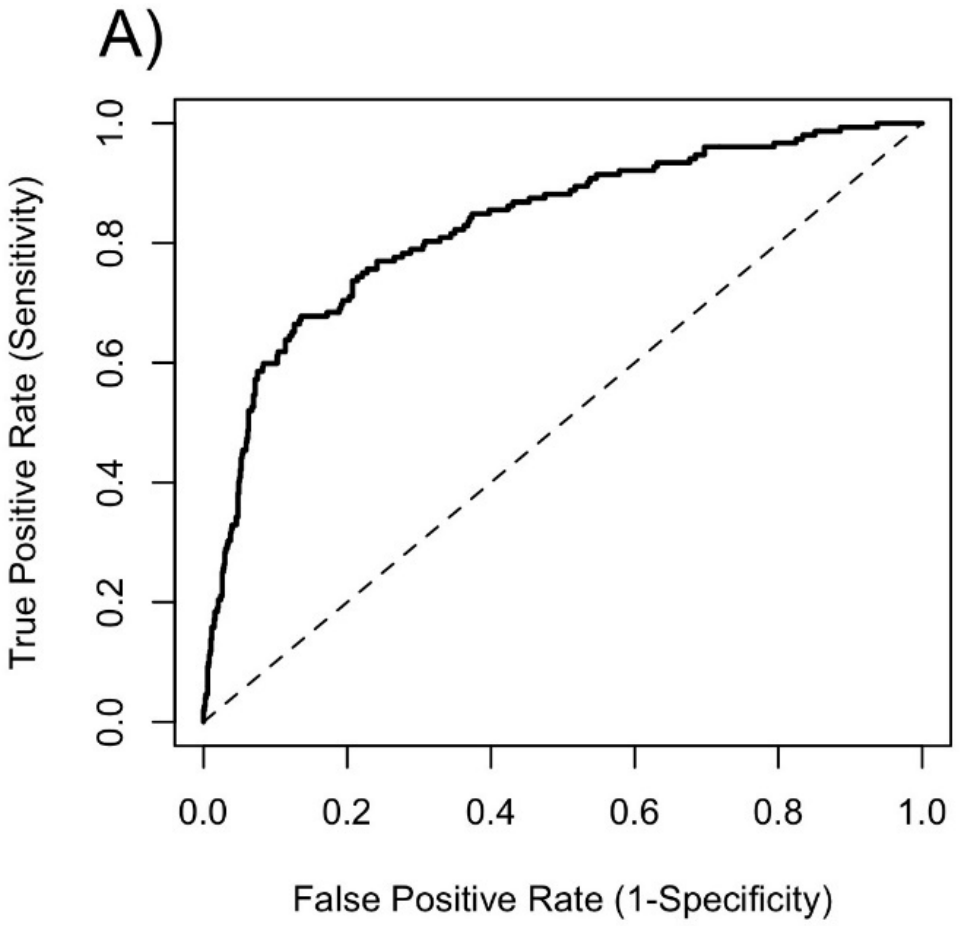
  - Final model used logistic regression
  - Logistic regression performed similarly to machine learning methods



Barnado A, et al. Front Immunol 2024

Training set

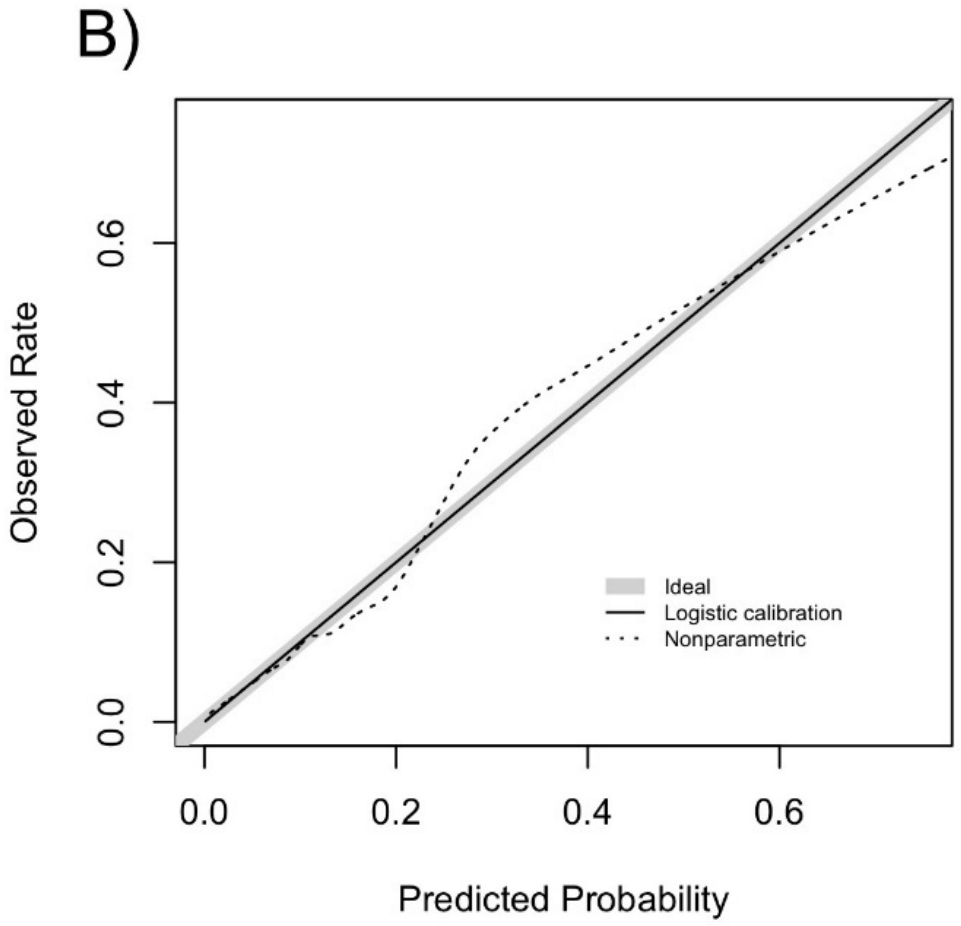
ROC



AUC = 0.83

(95% CI 0.79-0.86)

Calibration curve



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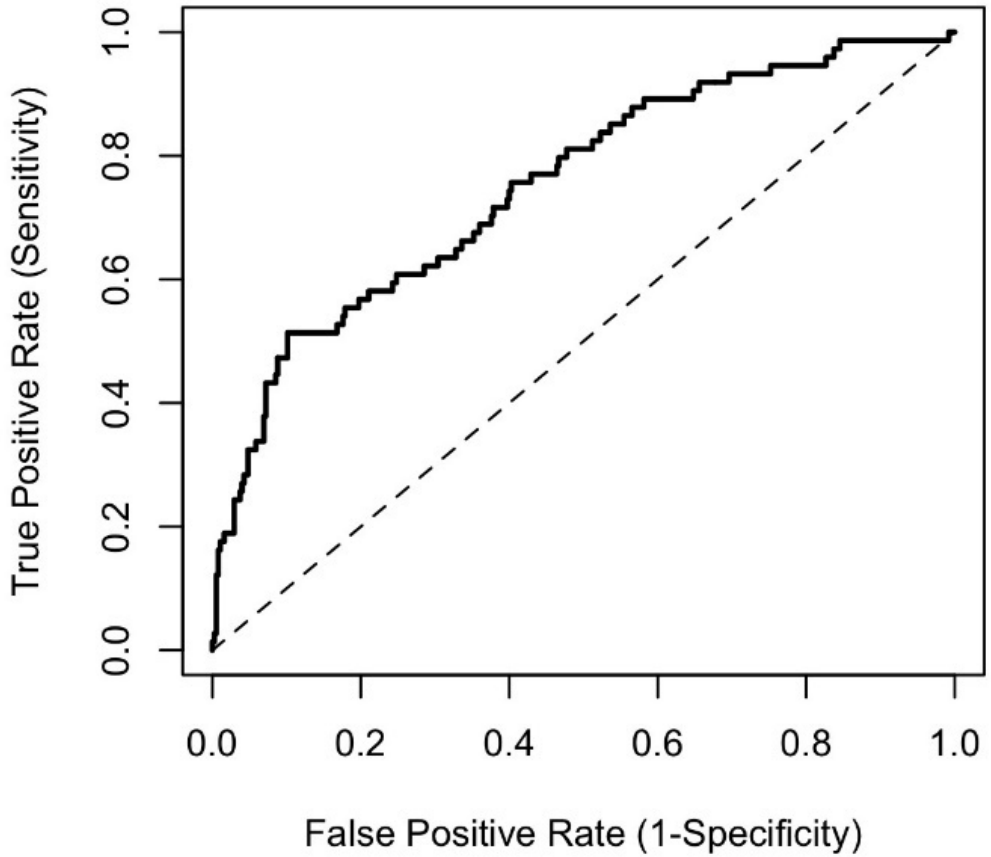
Validation set

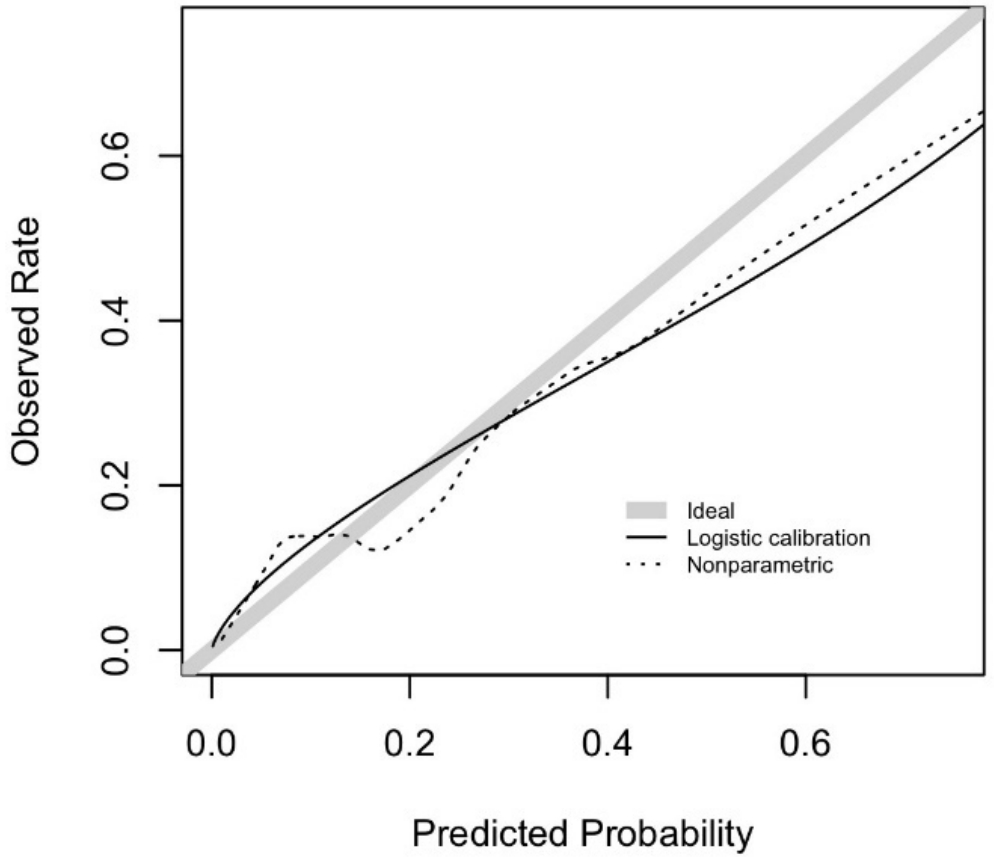
C) ROC



AUC = 0.75

(95% CI 0.68-0.81)

D) Calibration curve



Barnado A, et al. Front Immunol 2024

Risk Model in Real Time

Predicted Risk of Autoimmune Disease Calculator

What is the patients gender?

- ○ Male
- ◉ Female

ANA titer

- ◉ 1:160 or greater
- ○ 1:80

Does the patient have another autoantibody in addition to the ANA?*

- ○ No
- ◉ Yes

What is the patient's age (years)?

0 24 99

0 10 20 30 40 50 60 70 80 90 99

What is the patient's platelet count? Enter 237 if missing.

424

How many relevant ICD codes does the patient have?**

2

Estimated risk of Autoimmune Disease

91.7%

Shiny Application Developed by:

Ryan Moore, Hank Domenico, Dan Byrne

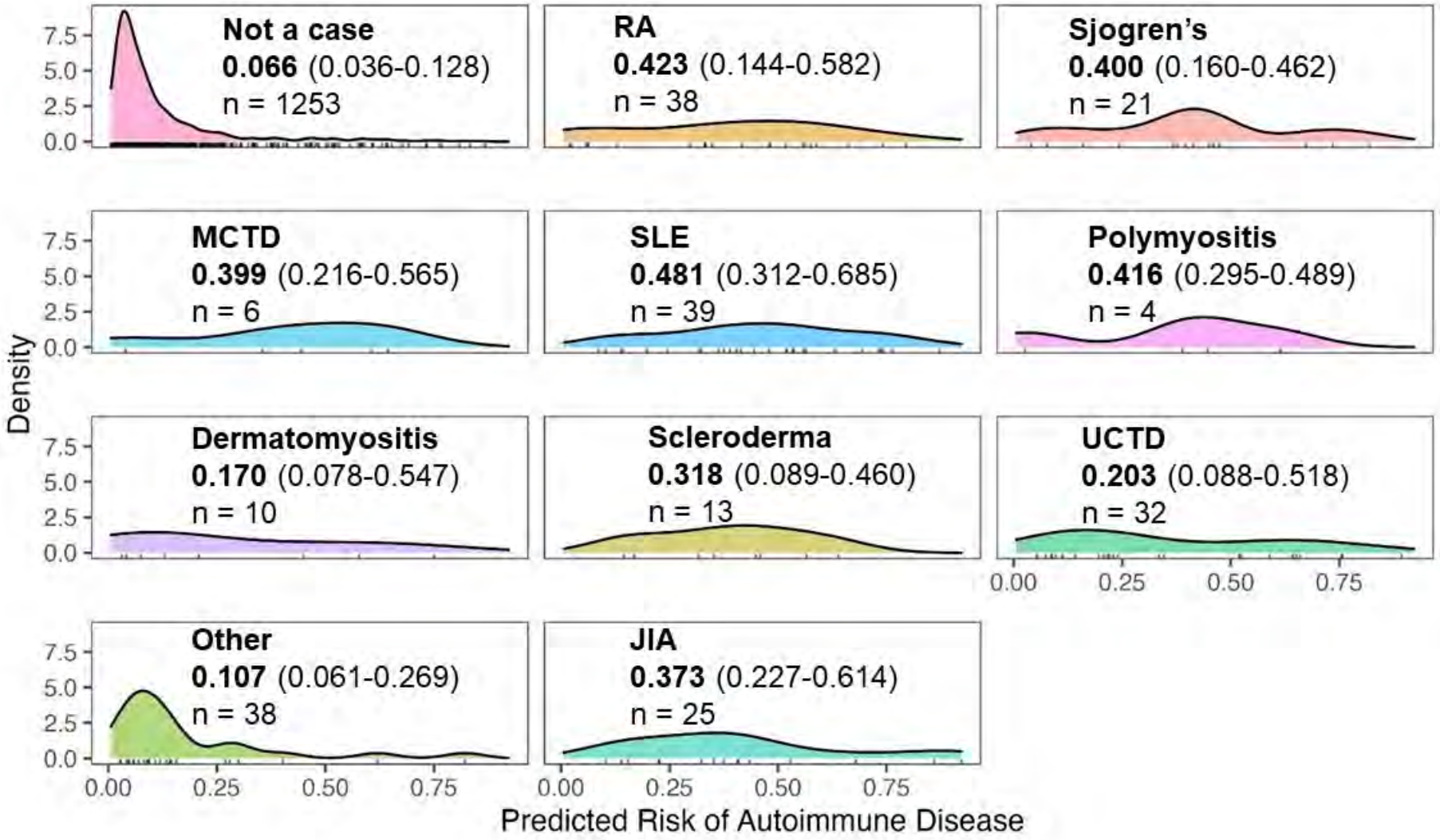
Disclaimer:

This calculator has been developed for use in research and has been retrospectively evaluated at Vanderbilt University Medical Center; thus it should not be used for general clinical practice at this time. This model is intended to be used as an evidence-based tool and does not replace a clinician's clinical judgment

* Antibodies include: Rheumatoid factor, Cyclic citrullinated peptide (CCP), SSA (Ro), SSB (La), Scl-70, Centromere, RNP, Smith, dsDNA, ANCA, Jo-1, and any antibody from myositis antibody panel

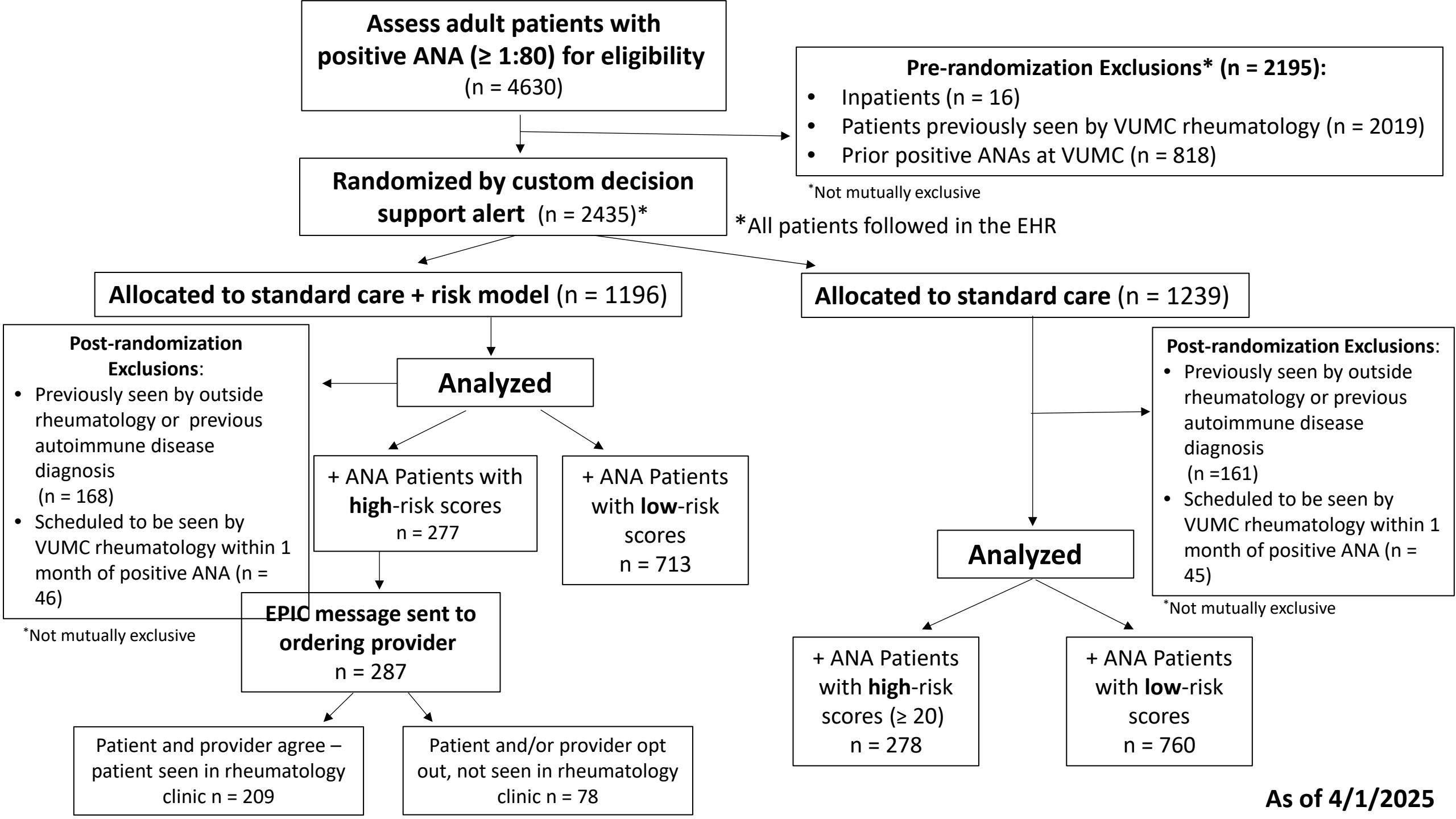
** Relevant ICD code names include: Arthritis (pain in joint, symptoms and disorders of joints), Fatigue, Interstitial Lung Disease, Hypertension, Rash (disorder of skin, dermatitis due to solar radiation), Raynauds, Serositis (pericarditis, pleurisy, pleural effusion), Sicca, and Alopecia. A full list of ICD-9 and ICD-10 codes are available in the supplemental table 4

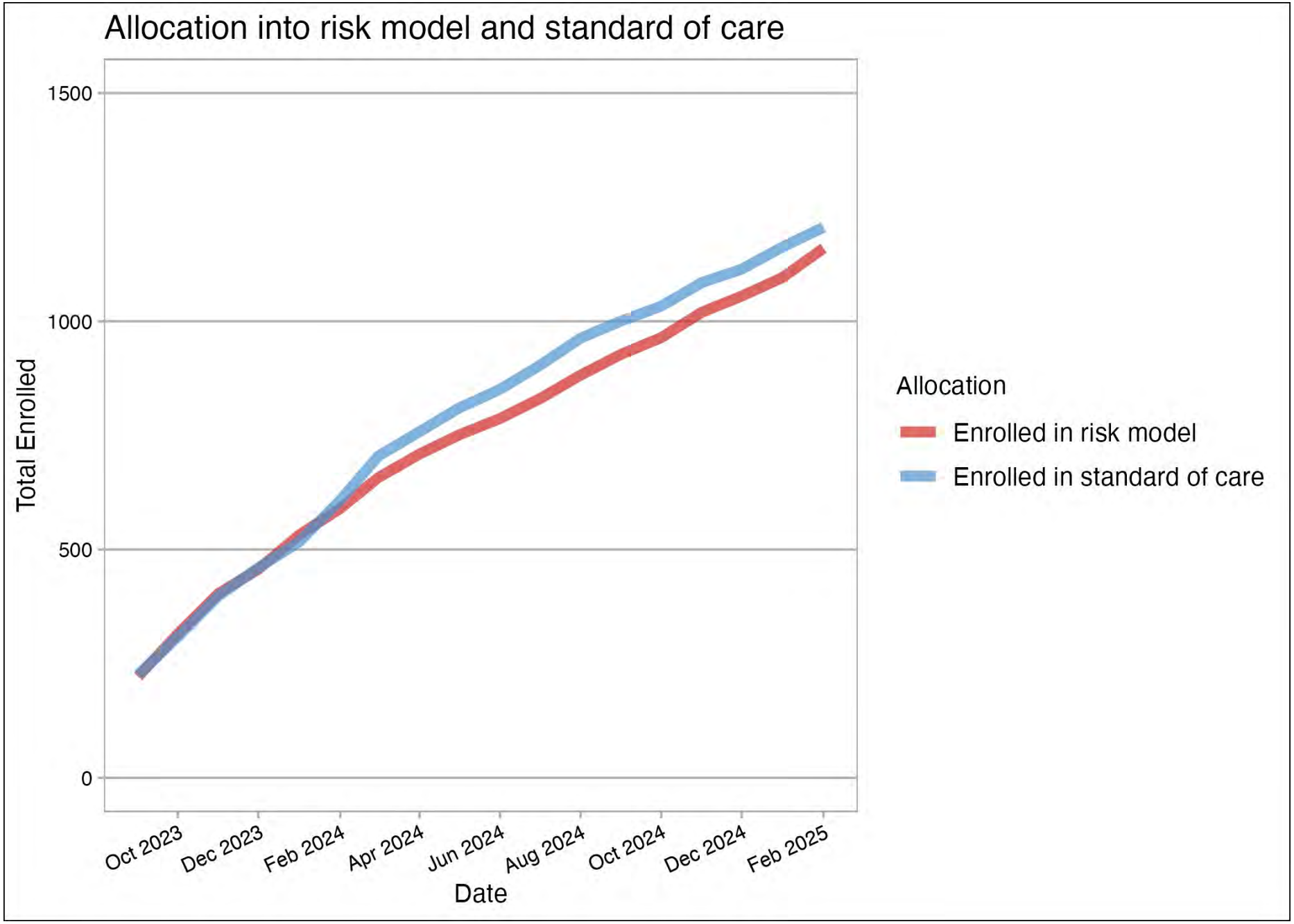
https://cqs.app.vumc.org/shiny/AutoimmuneDiseasePrediction/



- SLE and RA individuals had the highest risk scores
- Individuals labeled as "other" had the lowest risk scores
  - Seronegative conditions: psoriatic arthritis, inflammatory bowel disease
- **Seropositive individuals had higher median scores than seronegative individuals** (0.385 vs. 0.107, $p < 0.001$)

Barnado A, et al. Front Immunol 2024


Assess adult patients with positive ANA (≥ 1:80) for eligibility
(n = 4630)
Pre-randomization Exclusions* (n = 2195):
• Inpatients (n = 16)
• Patients previously seen by VUMC rheumatology (n = 2019)
• Prior positive ANAs at VUMC (n = 818)
*Not mutually exclusive
Randomized by custom decision support alert (n = 2435)*
*All patients followed in the EHR
Allocated to standard care + risk model (n = 1196)
Allocated to standard care (n = 1239)
Post-randomization Exclusions:
• Previously seen by outside rheumatology or previous autoimmune disease diagnosis (n = 168)
• Scheduled to be seen by VUMC rheumatology within 1 month of positive ANA (n = 46)
*Not mutually exclusive
Analyzed
+ ANA Patients with high-risk scores n = 277
+ ANA Patients with low-risk scores n = 713
EPIC message sent to ordering provider n = 287
Patient and provider agree – patient seen in rheumatology clinic n = 209
Patient and/or provider opt out, not seen in rheumatology clinic n = 78
Post-randomization Exclusions:
• Previously seen by outside rheumatology or previous autoimmune disease diagnosis (n =161)
• Scheduled to be seen by VUMC rheumatology within 1 month of positive ANA (n = 45)
*Not mutually exclusive
Analyzed
+ ANA Patients with high-risk scores (≥ 20) n = 278
+ ANA Patients with low-risk scores n = 760
As of 4/1/2025



- From study start (8/2/2023) to 3/31/2025

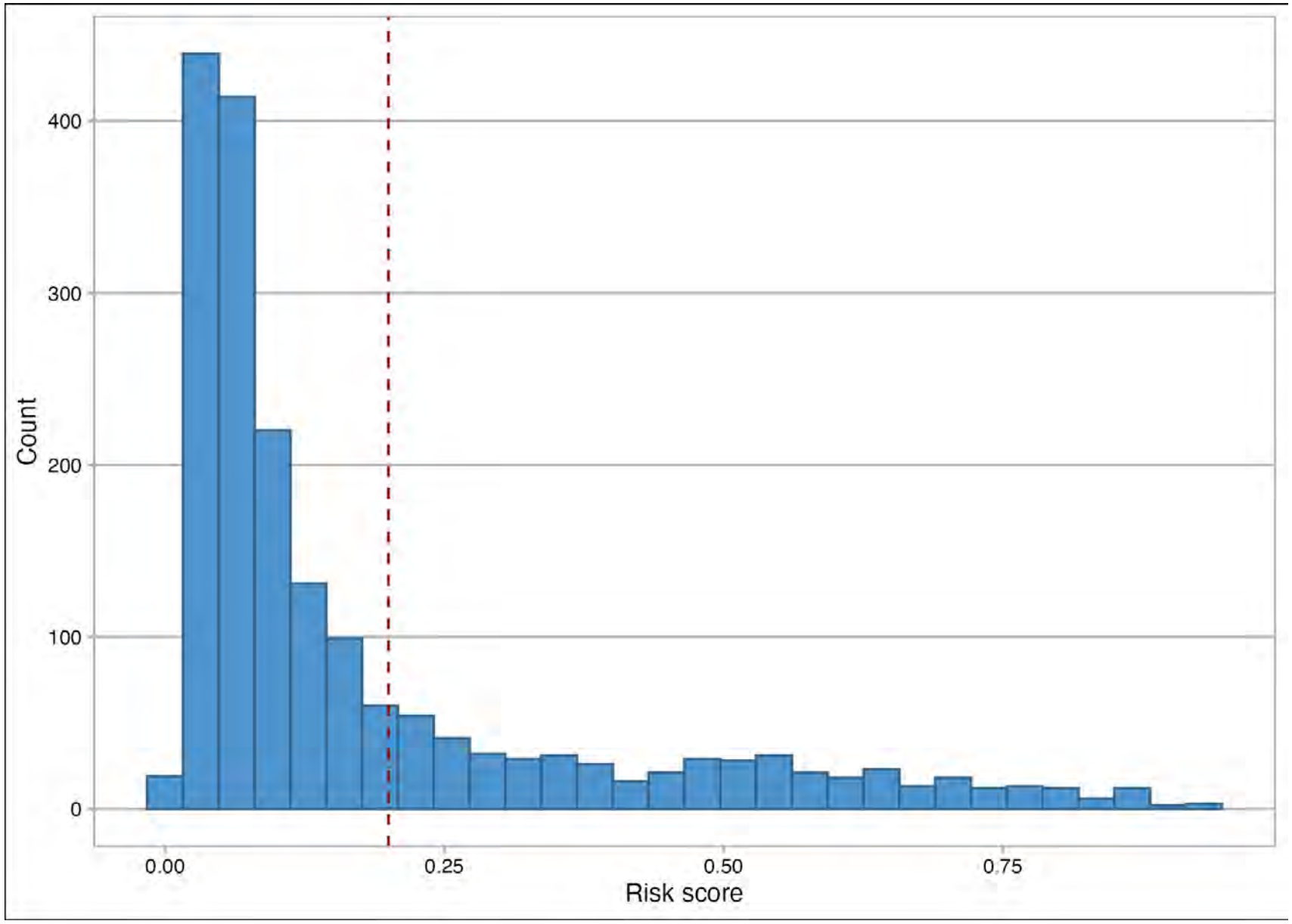
- Planned **2-year study**
- Met enrollment goal of randomizing 2,000 individuals with positive ANAs
- Goal to see ~ 300 individuals in clinic

Randomized Individuals

Individual characteristics	**Control arm (n = 973)**	**Risk model arm (n = 900)**
Age (years) mean ± standard deviation	55 ± 17	56 ± 17
Sex % (n) Female Male	 69% (673) 31% (300)	 70% (629) 30% (271)
ANA titer % (n) 1:80 1:160 1:320 1:640 1:1280 ≥ 1:2560	 7% (68) 41% (396) 35% (343) 12% (112) 2% (24) 3% (29)	 7% (65) 39% (353) 36% (327) 9% (85) 3% (31) 4% (39)
Additional antibody Yes No	 15% (149) 85% (824)	 19% (169) 81% (731)

Randomized Individuals

Individual characteristics	**Control arm (n = 973)**	**Risk model arm (n = 900)**
Risk group % (n) High risk Low risk	 26% (256) 74% (717)	 28% (248) 72% (652)
Risk model score mean ± standard deviation	18 ± 20	19 ± 21
Autoimmune diagnosis % (n) Yes No	 3% (n = 26) 97% (n = 947)	 8% (n = 69) 92% (n = 831)



- **Most positive ANA individuals had low risk model scores**
- **≥ 20 = "high" risk score** using Youden's cut point to maximize sensitivity and specificity

Ordering provider specialties

The most frequent ordering specialties:

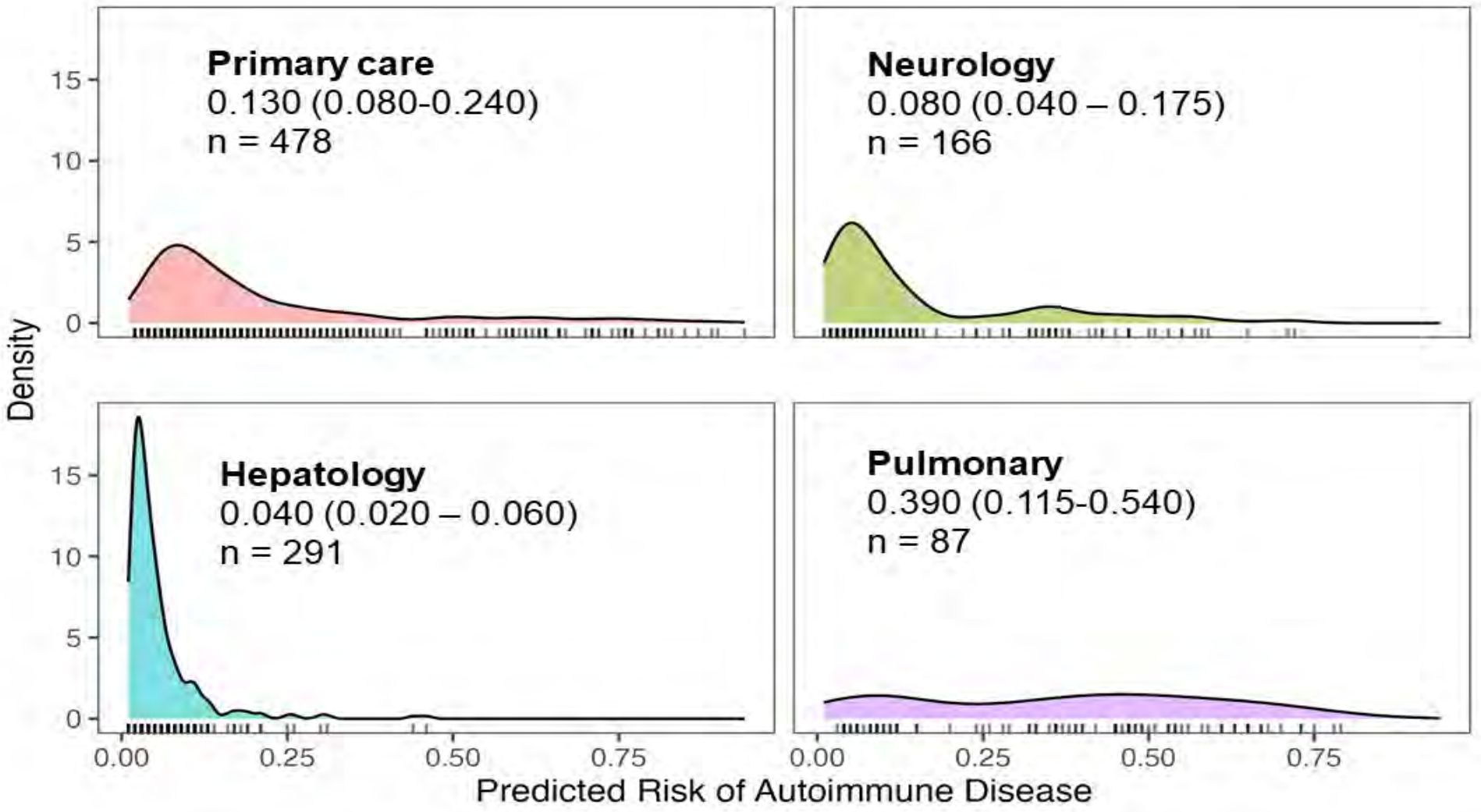
- primary care (36%)
- hepatology (22%)
- neurology (13%)
- pulmonary (7%)

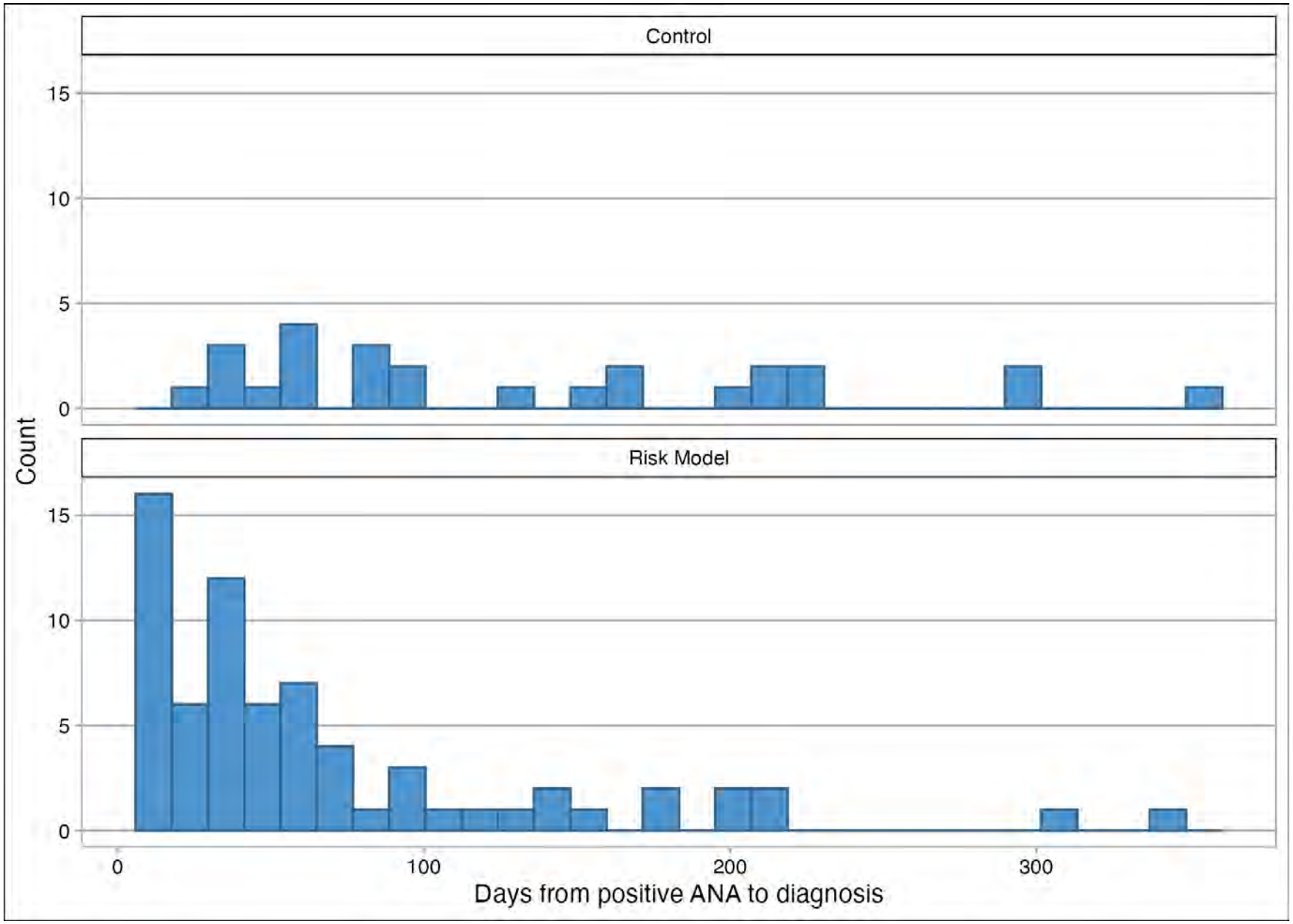
The most frequent reasons for ordering ANAs were:

- liver abnormalities (21%)
- joint pain (15%)
- neurologic complaints (7%).

- There were 2166 distinct billing codes used for ordering ANAs.

Risk score by ordering provider specialty



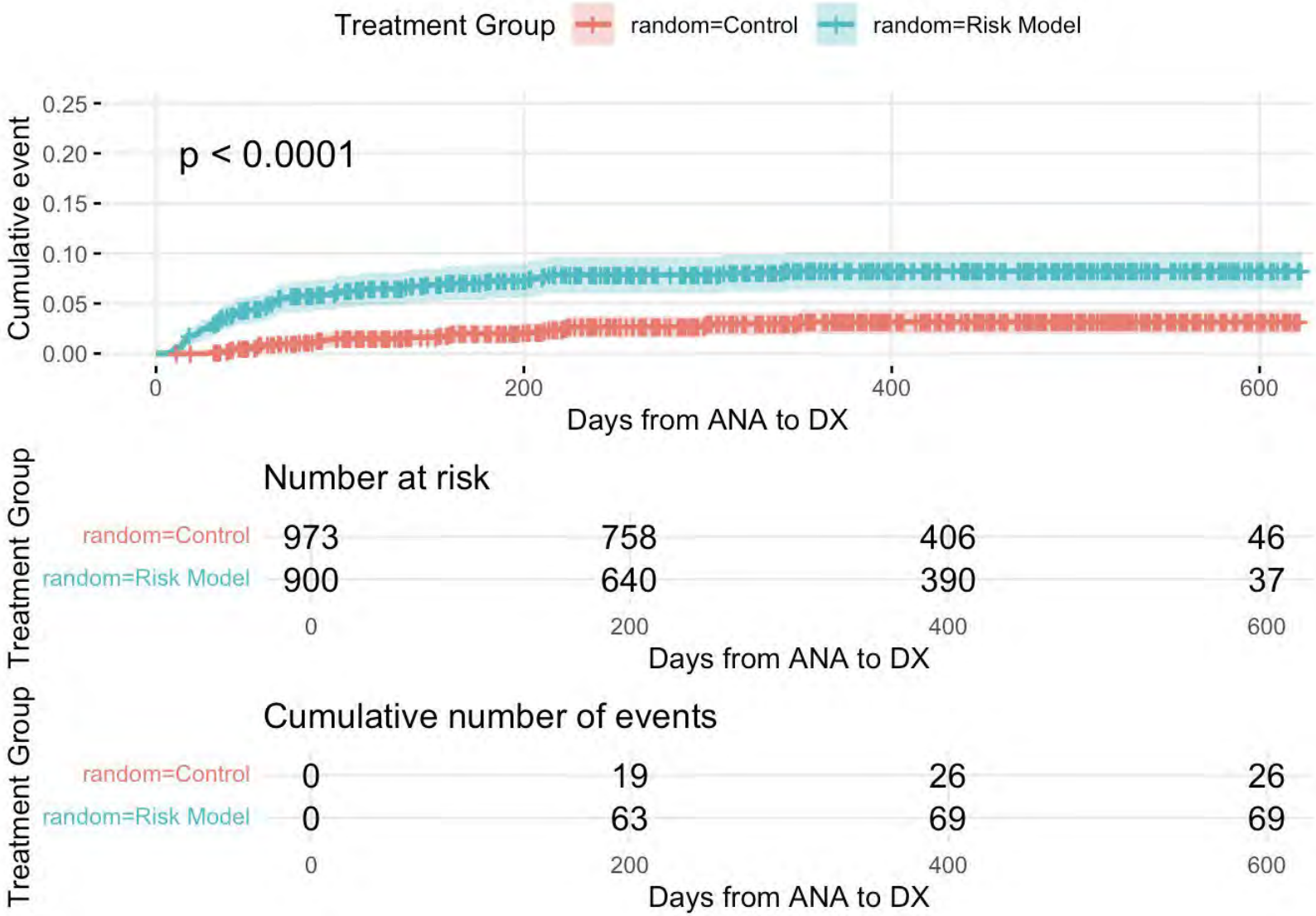


- **<u>Primary outcome</u>: time from positive ANA to autoimmune disease diagnosis**

- Perform chart review on all positive ANA individuals to assess if saw rheumatology and if received autoimmune diagnosis

- Perform interim analyses every 6 months of study

Preliminary 18-month results



- **<u>Primary outcome</u>**: time from positive ANA to diagnosis
- **HR = 2.99 (95% CI 1.90 – 4.69), p < 0.001**
- Median time to diagnosis in risk model vs. control arm: **42 vs. 94 days**

Preliminary 18-month results

Diagnoses

- Inflammatory arthritis (n = 9)
- Rheumatoid arthritis (n = 7)
- Sjogren’s (n = 6)
- SLE (n = 5)
- IPAF (n = 5)
- UCTD (n = 4)
- Systemic sclerosis (n = 2)
- Giant cell arteritis (n = 2)

Future directions

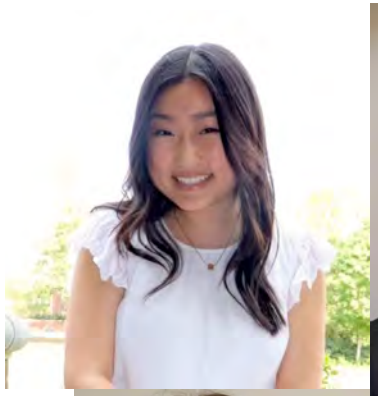
- Continue 2-year study with 1 year follow-up in EPIC
- Pilot study of applying risk model to outside positive ANA referrals
  - Use of advance practice provider and telehealth
- Nailfold capillaroscopy in high-risk individuals
- Serum, plasma, DNA, and RNA collection in high-risk individuals
- External validation in other EPIC sites

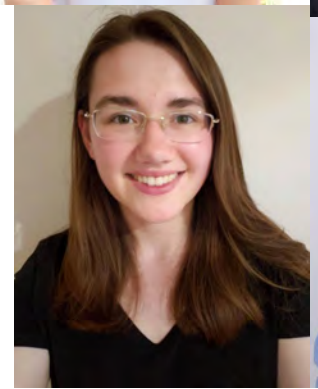
Conclusions

- Multiple methods can be used for ANA testing, each with their own limitation and strengths
- Positive ANAs can be seen in individuals with infections, malignancies, non-rheumatic diseases, and healthy individuals
- Age, sex, race, ANA titer and pattern are associated with increased risk of developing autoimmune diseases
- The electronic health record (EHR) can be repurposed to conduct pragmatic studies and improve patient outcomes

Acknowledgements

- **Mentoring**
  - Leslie Crofford (Rheumatology)
  - Josh Denny (Biomedical Informatics)
- **Funding**
  - NIAMS K08, ACR RRF K Supplement Award
  - DBMI Catalyzing Informatics Innovation
  - **R01 NIAMS Katz Award**
- **Collaborators**
  - Robert Carroll, Allison McCoy, Trent Rosenbloom (DBMI)
  - Yu Shyr, Dan Byrne, Ryan Moore, Hank Domenico (Biostatistics)
- **Research Team**
  - Emily Grace PA-C
  - Sarah Green, Ashley Suh, Bryan Han





NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Rheumatology Research Foundation