

POD01

Using a Novel Approach to Evaluate the Population-Level Burden of Disability Among Working-Age Individuals with Rheumatoid Arthritis

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Methods: We conducted a population-based repeated cross-sectional study using Ontario health administrative databases to assess annual trends from 2000 to 2022. We identified medication claims funded through the Ontario Disability Support Program (ODSP) within the Ontario Drug Benefit (ODB) database. We identified individuals with RA from the Ontario Rheumatoid Arthritis Database. Annual denominators comprised the number of RA individuals between the ages of 20-64 years, alive, with Ontario Health Insurance Plan coverage in the given measurement year. Individuals contributed to annual denominators until death, outmigration, attainment of age 65 (transitioning to ODB Seniors Program) or study end date. Annual numerators comprised the number of RA individuals with at least one ODSP-attributed medication claim for biologic, conventional, or targeted synthetic DMARDs, NSAIDs, opioids, or systemic glucocorticoids. We further quantified the total volume and medication-related costs attributed to these claims funded through ODSP. For comparison, we ascertained disability-related claims (for any medication class) amongst the general Ontario population aged 20 to 64 years.

Results: Over the 23-year period, the number of RA individuals aged 20-64 years grew from 34,394 to 74,182 individuals, while the number of RA individuals with a disability RA medication claim increased from 2,805 individuals in 2000 to 6,270 individuals in 2022, corresponding to a stable annual disability prevalence of 8-9% of all RA working aged individuals (a pattern driven by individuals transitioning to ODB Senior Program at 65). Regional disability prevalence was lowest in the Central region (4.8%) and highest in the North East (12.6%). The annual volume of ODSP RA medication claims ranged from 55,611 in 2000 to a peak in 2020 of 255,810 claims, corresponding to annual costs of \$1,894,925CAD and \$33,215,527CAD respectively (Figure). In contrast, the disability prevalence in the general population ranged from 2.7-3.8% during the study period.

Conclusion: Over two decades, the number of working-age RA individuals receiving disability benefits doubled, and RA disability prevalence was twice that of the general population. Nearly 1 in 11 younger RA adults were on disability annually, contributing to substantial medication use and economic costs. Investment in effective, evidence-based care models is needed to preserve work participation and reduce the long-term impacts of RA-related disability.

POD02

Feasibility Study to Implement Quality Indicator Toolkits for Rehabilitation After Total Hip and Knee Replacement: Patient and Clinician Toolkit User Metrics

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Methods: We gave clinicians access to the QUICK toolkit after 3 months of providing usual care and a training webinar. Six weeks later patients could access the EQUIP toolkit. Toolkit resources included videos, checklists, booklets and QUICK guides and were available to both groups for the duration of the study. We determined toolkit usage through Google analytics and post-intervention questionnaires. Questionnaire data were analyzed descriptively and exploratory analysis performed to examine relationship between toolkit access in past 3 months and adherence to 10 QIs. Analyses were conducted using SAS (V9.4, Cary, NC).

Results: In total, 46 patients participated in the study and 22 of them received THR/TKR rehabilitation during the toolkit implementation and maintenance phases. Of these, 12 completed end of rehabilitation questionnaires and 5 (42%) reported being introduced to the EQUIP toolkit. The most frequently accessed resources were the TKR (64 total views) and THR (48 total views) booklets. (Fig 1) Overall, patients rated the QI questionnaire and video as being most helpful; 60% agreed the toolkit helped them understand what to expect during rehabilitation and 80% to engage in and make decisions about their own care. There was no difference in patient-reported QI adherence between those who accessed the toolkit and those who did not ($p=0.55$). Seven of 14 (50%) of clinicians accessed the QUICK toolkit during maintenance phase. Based on Google analytics, the QUICK toolkit landing page was accessed 237 times and clinicians reported they most often used the QI checklists and QUICK guides (both 86%). Of the clinicians with recent toolkit use, 86% agreed it increased their knowledge of the TJR rehabilitation evidence and 43% said it helped to identify care gaps and areas for improvement. There was no difference in clinicians with improved QI adherence comparing those who accessed the toolkit in previous 3 months and those who did not ($p=0.58$).

Conclusion: Only a small proportion of patients and clinicians accessed the toolkits and total views and active users markedly declined during the maintenance phase. We will need to further explore facilitators and barriers to access and develop targeted strategies to improve uptake of the THR/TKR rehabilitation QIs.

POD03

Lupus Double-Negative B Cells Harbor Expanded Somatic Mutations in Lymphoma-Relevant Pathways

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Methods: In a cohort of 35 SLE patients, we performed whole exome sequencing on FACS-isolated naïve (CD19+, IgD+), memory (MBC; CD19+, IgD-, CD27+), and DN B-cells (CD19+,

IgD-, CD27-) from peripheral blood. Patient-matched buccal DNA was used to filter out germline variants, and somatic mutations detected by ≥ 2 callers (Mutect2, Strelka2, and CaVEMan) were retained. Variant allele frequencies (VAFs) were compared across subsets to assess clonal dynamics. Associations with disease activity (SLEDAI-2KG), time since diagnosis, and age were evaluated. Pathway enrichment and lymphoma-associated mutations were evaluated by interrogating mutations detected in MBC and DN cells across all patients.

Results: DN and MBC proportions correlated with disease activity ($p=0.443$, $p=0.008$; $\rho=0.354$, $p=0.037$). DN and MBC had significantly higher somatic mutation burdens than naïve cells ($p=0.001$ and $p=0.017$), consistent with expansion of antigen-experienced and/or autoreactive compartments under chronic inflammation (Figure 1A-B). Mutation burden in DN correlated with time since diagnosis, but not age, suggesting disease-associated acquisition and/or selective growth of mutated clones (Figure 1C). Among mutations shared between MBC and DN, a disproportionate fraction expanded in DN (Figure 1D), consistent with a competitive advantage of mutated DN subclones. Shared mutations expanded in DN were enriched for B-cell activation and proliferation pathways, including NF- κ B and B-cell receptor signaling (FDR <0.05 ; Figure 1E). In patients with high mutation burden, both MBC and DN harbored non-synonymous variants in lymphoma-associated genes, including IGLL5 and CARD11 (Figure 1F-H).

Conclusion: Our results identify DN B-cells as a clonally evolving population that acquires a high burden of somatic mutations under chronic inflammatory conditions, with some variants affecting genes and pathways relevant to malignant transformation. These results highlight DN cells as a plausible cell of origin for transformation in SLE and underscore the value of DN-focused molecular profiling to identify patients with high-risk clonal features and improve monitoring for progression and lymphoma transformation potential.

POD04

Distinct Fever Resolution Trajectories and Phenotypic Clustering in PFAPA and Surf: A Survival and Dimensional Analysis

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Methods: The primary outcome was time to fever resolution, defined as at least 12 months follow up period after the most recent clinic visit with reported absence of the recurrent fevers and assessed using Kaplan-Meier survival analysis and Cox proportional hazards modeling. Principal Component Analysis (PCA) was applied to explore phenotypic clustering based on symptom patterns.

Results: In this retrospective cohort study, 235 pediatric patients followed at the Autoinflammatory Clinic of The Hospital for Sick Children from 2016 to 2024 were classified as

PFAPA (n = 155) or SURF (n = 80) based on validated Eurofever/PRINTO classification criteria for PFAPA and proposed empirical indications for SURF. The median time to fever resolution was significantly longer in the SURF group compared to PFAPA (2,068 vs. 1,738 days; log-rank p = 0.037). In a semi-parametric Cox regression model, SURF diagnosis was independently associated with a lower likelihood of resolution over time (Hazard Ratio [HR] = 0.683; 95% [CI]: 0.476–0.980; p = 0.038). Inclusion of tonsillectomy status in a multivariable model did not significantly alter the outcome (HR for tonsillectomy = 1.046; p = 0.803). PCA revealed three major clusters: a classic PFAPA phenotype (tonsillopharyngitis, cervical adenitis), a GI-dominant cluster (abdominal pain, nausea, diarrhea), and an intermediate group (with mix of the symptoms in lower frequency). The GI cluster was predominantly composed of patients with SURF and correlated with longer disease persistence.

Conclusion: Children with SURF exhibit significantly delayed fever resolution compared to those with PFAPA. PCA-derived clusters support the presence of a gastrointestinal-dominant phenotype within the SURF spectrum, suggesting that these syndromes may exist along a clinical continuum. These findings have implications for prognosis and management, highlighting the need for phenotype-driven approaches in pediatric autoinflammatory conditions.

POD05

Characterizing Memory T Cells Associated with Systemic Lupus Erythematosus Pathogenesis

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Methods: CITE-seq and TCR-seq were performed to assess the transcriptomic profiles of CD4+ memory T cells in flaring and quiescent SLE patients. CD4+ memory T cells were isolated from PBMCs by negative selection using magnetic sorting, stained with oligo-conjugated antibodies against surface proteins for subset classification, and subsequently partitioned, barcoded, and sequenced. We examined samples from 15 distinct patients at two separate clinical visits spaced one year apart, yielding 30 samples. The longitudinal nature of our data allows us to inspect transcriptional changes both between and within patients.

Results: Integrated analysis of 30 samples identified 10 immune cell clusters (Fig.1.A). At baseline, flaring patients (n=9) were significantly enriched for Tfh, Th2, Th17 cells, and a Treg subset, while quiescent patients (n=6) had increased Th1 cells. TCR repertoire analyses at baseline revealed a higher proportion of expanded clonotypes in flaring patients, which was not seen in quiescent patients. Interestingly, we also found that there was a higher proportion of expanded clonotypes at followup in various subsets of interest, particularly in flaring patients

that later became quiescent – suggesting tissue egress and recirculation following resolution of inflammation. Clonal overlap among subsets was markedly greater in flaring patients, suggesting shared antigen specificity and differentiation from common progenitors. More specifically, we identified two functionally deviated/exhausted Treg subsets (ISGhi/ISGlo) (Fig.1.B) and, at baseline, found notable clonal overlap between the ISGhi Treg subset and Th2/17 cells and between the ISGlo subset and Tfh/Tph cells in flaring patients, which was absent in quiescent patients (Fig.1.C). This suggests that there are two distinct subsets of cells with shared antigen exposure and/or functional plasticity; one that is exposed to an IFN-rich environment in the tissue, and another that is more involved in T-B cell interactions within lymphoid compartments. **Conclusion:** We found abnormal Treg subsets with features of exhaustion and functional deviation that shared antigen specificity with other T helper cells. Their increased prevalence during flare suggests that dysregulated immunoregulation may contribute to SLE pathogenesis.

POD06

Sialic Acid-Binding Ig-Like Lectin 1: A Serological Biomarker for Pulmonary Involvement in Idiopathic Inflammatory Myopathies

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Methods: Baseline sera and clinicodemographic data from IIM patients enrolled in a multi-centre registry with routine bio-banked serum samples were included. SIGLEC1 levels were tested using a capture immunoassay (Aviva Systems Biology, San Diego CA). Pulmonary involvement was assessed using pulmonary disease activity defined on the Myositis Disease Activity Assessment Visual Analogue Scales Tool (score \geq 1.0 cm), parenchymal abnormalities on chest X-ray or high-resolution CT (including ground-glass opacities), and dyspnea due to ILD. Median serum SIGLEC1 levels (ng/mL) were compared between patients with and without these features using the Mann-Whitney U test.

Results: The study included 87 IIM patients (67.8% female, mean age 55.4 \pm 14.3 years) with dermatomyositis (DM, n=31), polymyositis (n=4), antisynthetase syndrome (ASyS, n=9), immune-mediated necrotizing myopathy (n=6), inclusion body myositis (n=9), and overlap myositis (OM, n=28). Median serum SIGLEC1 levels were significantly higher in IIM patients with pulmonary disease activity (5.1 vs. 2.6 ng/mL; difference 2.5 ng/mL; P<0.05) and parenchymal abnormalities (5.1 vs. 2.6 ng/mL; difference 2.5 ng/mL; P<0.05) compared with those without these features. There were no significant differences in median serum SIGLEC1 levels between IIM patients with and without dyspnea due to ILD (4.7 vs. 3.4 ng/mL; difference 1.3 ng/mL). Higher median serum SIGLEC1 levels differentiated between the presence and absence of pulmonary disease activity (5.2 vs. 2.6 ng/mL; difference 2.6 ng/mL; P<0.05) when patients with DM, OM, and ASyS were grouped together. DM patients with pulmonary disease activity (5.3 vs. 2.6 ng/mL; difference 2.7 ng/mL), parenchymal abnormalities (5.4 vs. 3.2

ng/mL; difference 2.2 ng/mL), and dyspnea due to ILD (7.3 vs. 3.8 ng/mL; difference 3.5 ng/mL) had higher median serum SIGLEC1 levels; however, these differences were not significant.

Conclusion: SIGLEC1 levels are a promising biomarker for assessing pulmonary involvement in patients with IIM. This finding reinforces IFN-I activity as a hallmark of IIM-ILD. Future studies are underway to evaluate SIGLEC1 levels as a biomarker of IIM-ILD.

POD07

Citrullination of Neutrophil Serine Proteases Enhances Proteolytic Activity, Stability and Autoantigenicity in Rheumatoid Arthritis

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Methods: The activity of proteases (NE, PR3, CTG) and various biospecimens were analyzed using fluorogenic substrate after citrullination with PAD2/4 (confirmed by a cit-specific probe). Active protease sites were labelled and visualized using a probe (TAMRA-FP). Degradation of aggrecan, a proteoglycan found in cartilage, was determined using various biospecimens exposed to PAD isoforms. ACPA targeting cit-proteases was measured in serum from RA patients, ACPA positive and ACPA negative controls with ELISA.

Results: Using both recombinant proteases and neutrophil supernatant, proteolytic activity of NE, PR3 and CTG increased markedly after citrullination with PAD2, and to a lesser extent, PAD4 (Fig1A). For example, the activity of cit-PR3 increased by 13-fold compared to native PR3. Citrullination level with increasing concentrations of PAD2 correlated strongly with proteolytic activity ($R=0.95$, $p<0.0001$). PAD2 citrullination also lead to enhanced stability of proteases, with persistently detectable activity after 72 hours in-vitro, and evidence of protection from autoprolysis in PR3 and NE, which was not observed with PAD4 (Fig1B). Protection from Trypsin degradation in cit-PR3 was also observed. In the recombinant proteases, supernatant, and NETs, PAD2 citrullination opened new catalytic sites as demonstrated by labelling using an activity-based probe (Fig1C), suggestive of a conformational change which was confirmed by in-silico modelling. Aggrecan degradation was enhanced by PAD2-citrullination of NE and NETs. Serum cit-PR3 and serum PR3 activity was higher in RA compared to healthy controls (Fig1D). In synovial fluid, PR3, NE and CTG activity were all increased in RA compared to OA (Fig1E). Autoantibodies to PAD4/2 cit-proteases were higher in RA and ACPA positive controls compared to ACPA negative controls (Fig1F).

Conclusion: PAD enhances neutrophil serine protease activity and stability through conformational changes induced by citrullination, possibly providing a biological advantage for host defense. Enhanced proteolytic activity was apparent in RA biospecimens, leading to degradation of cartilage components and autoantibody formation. PAD isoforms may play functionally distinct roles in the pathogenesis of RA.

POD08

Perimenopause is Associated with Increased Disease Activity in Psoriatic Arthritis

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Methods: We analyzed data on female patients with PsA followed in a prospective cohort from 1978 to 2024. Data on PsA disease activity, medications, co-morbidities, and age at menopause were collected using standard protocols. Pre-perimenopause and post-menopause stages were defined as >2 years before and after the final menstrual period (FMP), respectively, while the perimenopause stage was within 2 years (before or after) of the FMP. PsA disease activity was assessed at each visit using Disease Activity in PsA (DAPSA), tender and swollen joint counts, PASI, CRP, and FACIT-fatigue. Disease activity during the perimenopause stage was compared to the pre-perimenopause and post-menopause visits. The association between menopausal stages and PsA disease activity measures was assessed with a Generalized Additive Model with splines (considering time from FMP as continuous) and with linear mixed-effects models (menopausal stages as categorical variables). Each model was adjusted for age, disease duration, and medication use, and accounted for repeated observations via a subject-specific random effect. We assessed the mediating effects of BMI and fatigue on the change in DAPSA across menopause stages.

Results: A total of 477 female patients provided data for 8381 visits over a mean follow-up of 12.1 years. Mean age at first visit was 44.9±13.9 years and mean age at menopause was 48.7 years. Hormone replacement therapy had only been used during 1.5% of visits. A rise in DAPSA scores was found during perimenopause years, followed by a slight drop post menopause (Figure 1A). Linear mixed models found an association between being in perimenopause and higher DAPSA vs. pre-perimenopause ($\beta=1.92$, $p<0.001$) and post-menopause stages ($\beta=1.56$, $p=0.001$, Figure 1B). Significantly higher tender and swollen joint counts were found in perimenopause vs. both pre- and post-menopause. Higher PASI was found in perimenopause vs. post-menopause stage. Increase in fatigue levels during perimenopause only partially mediated the increase in DAPSA score during perimenopause, explaining 12% to 18% of this change. BMI did not have a mediating effect on DAPSA change during perimenopause.

Conclusion: Perimenopause is associated with an increase in PsA disease activity which includes both patient-reported outcomes but also objective measures of activity. These findings may warrant consideration of hormone replacement therapy in perimenopausal PsA patients.

POD09

Increased Risk of Intrahepatic Cholestasis of Pregnancy in Women with Systemic Lupus Erythematosus Exposed to Azathioprine

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Methods: The Lupus in prEGnAnCY (LEGACY) cohort is conducted at SLICC centres in Canada, South Korea, Peru, and Mexico. Pregnant women with SLE are enrolled before 17 weeks and followed in the second (20–24 weeks), third (30–34 weeks) trimesters, and postpartum (8–12 weeks). Since ICP occurs after 20 weeks, only pregnancies with a second-trimester visit were included. Follow-up began at that visit and continued until delivery. AZA exposure was modelled as time-varying. The primary outcome was delivery for ICP and/or early-onset ICP (<28 weeks). Multivariable Cox proportional hazards models with frailties adjusted for maternal demographics, co-morbidities, disease activity, and glucocorticoid use. At the Montreal site, thiopurine metabolites and shunting were assessed, using established cut-offs.[3]

Results: Of 127 SLE pregnancies, 46 were AZA-exposed and 81 unexposed (Table 1). Ten ICP cases occurred (each in a distinct woman): 8 among AZA-exposed (17.4%, 95%CI 9.1-30.7) and 2 among unexposed (2.5%, 95%CI 0.7-8.6). AZA was continued until and beyond delivery in most (6/8) exposed ICP cases. All ICP cases required delivery except one AZA-exposed case (who stopped AZA at ICP diagnosis). AZA exposure was associated with a substantially increased risk of ICP (unadjusted HR 9.1, 95%CI 1.9-44.5; adjusted HR 11.9, 95%CI 2.2-65.1). Of note, all ICP cases with metabolite data (4/4) exhibited second-trimester shunting. Among all pregnancies with second-trimester metabolite data (n=22), 36.4% (95%CI 19.7-57.0) were shunting, and 50.0% (95%CI 21.5-78.5) of these developed ICP. No ICP occurred with tacrolimus alone (n=14). All ICP pregnancies resulted in live births, although AZA-exposed cases tended to have higher bile acid levels, earlier delivery, and lower birth weight for gestational age versus unexposed cases.

Conclusion: We observed that AZA exposure was strongly associated with ICP in SLE pregnancies. Second-trimester thiopurine shunting may identify women at highest risk, supporting the value of metabolite monitoring. **Supported by a CIORA grant.**

POD10

A Rare SAT1 Variant in Early-Onset SLE: Case Report with Case-Control Functional Assay

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Background: Objective: SAT1 (Xp22) is an X-linked gene that encodes spermidine/spermine

N¹-acetyltransferase. Rare SAT1 variants have been reported in early-onset systemic lupus erythematosus among males^{1,2}. We report a case of a male diagnosed with systemic lupus erythematosus (SLE) at 6 years of age who carries a rare, predicted damaging variant in SAT1. Methods: Trio whole-genome sequencing (WGS) was performed on the proband and both biological parents. Variant annotation and filtering were used to prioritize rare coding variants with predicted functional impact, and segregation was confirmed within the trio. Case-control functional assays on fibroblasts were performed using the proband and two independent controls. One was internal laboratory reference control (healthy individual) and the second was a (non-SLE control). diABZI (STING agonist) time-course western blots and an interferon-stimulated gene (ISG) qPCR panel were performed under unstimulated and stimulated conditions.

Case Report: Results: The patient presented at 6 years of age with fever, malar rash, a Kawasaki-like inflammatory picture and macrophage activation syndrome (MAS). An echocardiogram demonstrated pericardial effusion, and mild left main coronary artery (LMCA) dilation. Following Kawasaki disease therapy with intravenous immunoglobulin, he developed nephrotic-range proteinuria and hypertension, which led to a kidney biopsy confirming class IV lupus nephritis. Laboratory testing showed leukopenia, hemolytic anemia, thrombocytopenia, hypocomplementemia, and positive ANA, anti-dsDNA, anti-Sm, and anti-RNP autoantibodies. He was treated with pulse methylprednisolone, mycophenolate sodium, and ACE inhibition. Neurologic and neurodevelopmental features emerged later in his disease course: absence epilepsy was identified earlier in adolescence (13 years) and was responsive to valproic acid, and upper-motor-neuron-patterned findings (hyperreflexia and clonus) were observed (starting at age 16 years, mild intellectual disability and ADHD became evident around mid-adolescence (15 years). Whole genome sequencing of the proband and parents identified an X-linked hemizygous SAT1 missense variant: NM_002970.3:c.26C>A (p.Ala9Asp) on Xp22 inherited from mom. This variant has a CADD = 31, 5/5 pathogenicity tools deleterious. In functional assays, the proband ISG qPCR panel showed higher induction of several ISGs (IFI44, RSAD2, MX1, IRF7, CXCL1, CCL2) after diABZI compared with controls. In the ISD experiment, the control sample showed stronger pTBK1 and pSTING responses than the proband.

Conclusion: We identified a previously unknown variant in SAT1, with evidence demonstrating its association with early-onset SLE in a male diagnosed at an extreme young age. In addition to bioinformatic tools predicting the variant is deleterious, our functional validation studies provide evidence for downstream immune dysregulation. Our report provides important evidence for the causal nature of this rare variant for monogenic lupus.

References: (1) Xu L. *Ann Rheum Dis* 2022;81:1712–1721. (2) Zhao C. *Immunity* 2023;56:2508–2522.

POD11

Health Canada Indications and Formulary Coverage of Biologic and Synthetic Disease Modifying Anti-Rheumatic Drugs for Juvenile Arthritis: Are We Meeting Current Guidelines?

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Methods: Provincial formularies and NIHB program were reviewed to compile coverage of bDMARD/sDMARD for the treatment of all JIA subtypes and JIA-associated uveitis. This was compared to the Health Canada (HC) indications for these drugs and current Canadian/American treatment guidelines for polyarticular JIA (pJIA), enthesitis-related arthritis (ERA) systemic JIA (sJIA), and uveitis.[1,2] In the absence of North American guidelines, recently published literature helped us identify recommended evidence-informed treatment strategies for juvenile psoriatic arthritis (JPsA).[3] Health Canada, NIHB and all provinces were evaluated for their overall performance with bDMARD/sDMARD treatment recommendations for JIA and uveitis. A parallel assessment was conducted in adults, focusing on inflammatory arthritis and informed by recently published treatment guidelines.

Results: Overall, Ontario had the highest capacity to follow paediatric bDMARD/sDMARD recommendations followed by HC and Quebec (Figure 1). For JIA subtypes, all pJIA-recommended drugs were indicated and approved by HC, funded through NIHB, and covered by most provinces. For sJIA, HC and half the provinces fully met recommendations, whereas NIHB and remaining provinces ranked lower. Only Ontario met ERA treatment guidelines. HC approved one anti-IL-17 agent for ERA, which is recommended for adult ankylosing spondylitis (AS) but not included in ERA guidelines. However, it remains unfunded by NIHB and all provinces. JPsA treatment recommendations were not met by NIHB nor any province. Notably, HC has approved JPsA indications for anti-IL-17 and tofacitinib, which are included in these recommendations and in adult psoriatic arthritis (PsA) guidelines. Ontario approved half of the drugs recommended in current uveitis treatment guidelines; HC, NIHB, British Columbia and Quebec approved 25% while other provinces did not meet guidelines. Adults with inflammatory arthritis generally fully met treatment guidelines, whereas Adult Still's disease guidelines were not met by NIHB or any province.

Conclusion: Access to publicly funded bDMARDs/sDMARDs for JIA and uveitis is highly variable, with most provinces and NIHB unable to fully meet treatment guidelines. Adults with inflammatory arthritis generally have full access to recommended therapies, highlighting major inequities in paediatric care and a barrier to delivering evidence-based therapies for children.

POD12

Unraveling Sex-Specific Genetic Markers in Psoriatic Arthritis: Insights from a Genome-Wide Association Study

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Methods: Data were extracted from the UK Biobank, including 459 female and 497 male PsA patients. To minimize population stratification, only Caucasian participants were included, resulting in 444 female and 423 male patients, along with 226,198 female and 191,928 male

Caucasian controls. A genome-wide association study (GWAS) was conducted, comparing 97,013,422 SNPs between males and females among PsA patients and controls, focusing exclusively on autosomes. Only SNPs with allele frequencies greater than 0.005 in affected cases and controls were included, and associations were considered significant at $P < 1 \times 10^{-6}$.

Results: In males, 2,596 SNPs were identified across 104 genes, and in females, 4,542 SNPs were associated with 108 genes. Among these genes, 72 were shared between sexes, including PSORS1C1, the strongest genetic associated locus for psoriatic disease. Additionally, 32 unique genes were identified in males, including ERAP-1 and TRAF3IP2, whereas 35 were identified in females, including HLA-DRB1 and HLA-DQA1. Notably, sex-specific genes have been previously documented to exhibit sex-specific differences in immune responses. Ongoing studies are focusing on pathway enrichment analysis of sex specific genes for both genders.

Conclusion: The identification of unique genes in each sex, alongside shared genetic markers, highlights the complexity of PsA's genetic landscape. These findings suggest that sex-specific genetic factors may play a role in the manifestation and progression of the disease. Further research is essential to validate these results and explore their clinical and molecular implications, which could ultimately lead to more tailored therapeutic strategies for PsA patients.

POD13

Complex-, Difficult-To-Manage, and Treatment-Refractory Psoriatic Arthritis: Insights from a Prospective Cohort Study

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Methods: This analysis was conducted on PsA patients evaluated in the Gladman Krembil Psoriatic Arthritis Program between July 1, 2024, and July 1, 2025. Patients were classified into C2M/D2M and TR categories according to GRAPPA and EULAR criteria [1, 2]. Demographic, clinical, radiographic variables as well as treatment, and comorbidity data were analyzed to characterize the C2M/D2M and TR groups. C2M/D2M patients were compared to non-C2M/D2M, and TR patients compared to C2M/D2M patients who did not meet TR criteria, using both GRAPPA and EULAR classification frameworks.

Results: Of 630 patients assessed, GRAPPA criteria identified 225 (35.7%) as C2M and 81 (12.9%) as TR, while EULAR criteria identified 122 (19.4%) as D2M and 79 (12.5%) as TR. Patients fulfilling C2M/D2M definitions, including TR, showed significantly higher disease activity and treatment intensity compared with non-C2M/D2M groups. These patients had higher patient and physician global assessment scores, increased tender and swollen joint counts (TJC/SJC), higher Psoriasis Area and Severity Index (PASI) scores, and higher enthesitis (tender) point count. C-reactive protein (CRP) and Disease Activity index for Psoriatic Arthritis (DAPSA) were also markedly elevated, accompanied by greater biologic use and a higher

number of biologic DMARDs (bDMARDs). The TR subset demonstrated more severe articular involvement (higher TJC/SJC), elevated CRP, and substantially greater treatment exposure, reflected by higher bDMARD use (Figure 1). Female sex and higher BMI were associated with C2M/D2M but not consistently with TR disease.

Conclusion: GRAPPA and EULAR criteria both effectively identify PsA patients with high disease burden but differ in sensitivity and thresholds. GRAPPA captured a broader subset, whereas EULAR applied more stringent definitions. C2M/D2M disease appears multifactorial, potentially driven by non-PsA and comorbidity-related factors such as elevated BMI, while TR disease primarily reflects persistent, objectively active inflammation despite adequate therapeutic exposure.

POD14

Characterizing Subjective Cognitive Impairment in Systemic Lupus Erythematosus Using The Perceived Deficits Questionnaire-20 and Associations with Objective Neuropsychological Testing

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Methods: We performed a cross-sectional study of 214 adult SLE patients from a single-centre longitudinal cohort who completed both the PDQ-20 and ACR-NB. The PDQ-20 assesses four domains—attention/concentration, planning/organization, retrospective memory, and prospective memory—across 20 items scored 0–4 (higher = worse). Objective cognition was evaluated using a modified ACR-NB assessing six domains: manual motor speed, attention/processing speed, visuospatial construction, language, learning/memory, and executive function. CI was defined as impairment ($z \leq -1.5$) in ≥ 2 domains. Spearman correlations examined construct validity between PDQ-20 items/domains and ACR-NB tests, while Wilcoxon rank-sum tests compared PDQ-20 scores between CI and non-CI groups.

Results: Participants were predominantly female (90%), with a mean age of 31 ± 17 years; 43% met criteria for objective CI. The mean PDQ-20 score was 31.1 ± 16.9 (out of 80), indicating moderate subjective impairment. The most frequently reported difficulties were “mind wandering,” “forgetting names,” “losing train of thought,” and “forgetting why one entered a room,” reflecting deficits in attention and working memory. The highest domain scores were observed in attention/concentration and planning/organization. Correlations between PDQ-20 and ACR-NB scores were generally weak. The strongest associations were between PDQ-20 items related to working memory (e.g., Q17 “trouble holding phone numbers,” Q4 “trouble organizing”) and the ACR-NB Auditory Consonant Trigrams test ($r \approx -0.25$ to -0.29). No significant difference in PDQ-20 total scores was observed between CI (33.4 ± 17.5) and non-CI (29.3 ± 15.9) groups ($p = 0.15$), nor were there differences between individual PDQ-20 items (Figure 1).

Conclusion: SLE patients frequently report cognitive challenges, particularly in attention and planning, which correlate only weakly with objective CI. The PDQ-20 captures everyday cognitive experiences not reflected by formal testing, highlighting the need to assess both

subjective and objective cognition in SLE. Integrating patient-reported cognitive screening may enhance understanding, monitoring, and support for cognitive health in clinical practice.