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Drug Repurposing and Personalized Medicine in Autoimmune Diseases: A Systematic Review (2020–2025)

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ABSTRACT

Background: Autoimmune diseases collectively affect approximately 10% of the global population and carry rising disability-adjusted life-year burdens across all age groups. De novo drug development costs approximately 2.56$ US billion per approved compound. Drug repurposing combined with precision medicine offers a faster, safer, and more cost-effective alternative. Objective: To systematically synthesize evidence (January 2020 – May 2025) on repurposed pharmacotherapies in major autoimmune diseases and the biomarker, omics, and pharmacogenomic frameworks used to personalize their deployment. Methods: Following PRISMA 2020, we searched PubMed/MEDLINE, Scopus, Web of Science, Cochrane CENTRAL, and ClinicalTrials.gov. Randomized controlled trials were appraised with Cochrane RoB 2.0; non-randomised studies with ROBINS-I. Data were synthesized narratively across six disease categories. Results: 187 studies met inclusion criteria. Five pivotal phase 3 programs delivered practice-changing results: anifr olumab (TULIP-2) in systemic lupus erythematosus, voclosporin (AURORA 1) in lupus nephritis, upadacitinib (U-ACHIEVE/U-ACCOMPLISH) in ulcerative colitis, ozanimod (True North) in ulcerative colitis, and teplizumab (PROTECT) in type 1 diabetes. Deucravacitinib (POETYK PSO-1/2) and risankizumab (ADVANCE/MOTIVATE) transformed psoriasis and Crohn's disease management respectively. Three programs delivered negative or safety-restricting outcomes: MS-STAT2 (simvastatin in secondary progressive MS), the TrialNet Abatacept Prevention Study, and ORAL Surveillance (tofacitinib cardiovascular/cancer risk). Validated personalization tools include the type I interferon gene signature for anifrolumab in SLE, serum neurofilament light chain for MS therapy escalation, TPMT/NUDT15 genotyping for thiopurines in IBD, islet autoantibody staging for teplizumab in type 1 diabetes, and HLA-C*06:02 for ustekinumab selection in psoriasis. Conclusions: Drug repurposing produced the most impactful autoimmune therapeutics of 2020–2025. Population-level approvals are giving way to biomarker-anchored, endotype-stratified deployment. Future gains require adaptive trial designs, prospective omics companion diagnostics, polygenic risk score integration, and equitable access policies.

Keywords: Autoimmune Diseases, Biomarkers, Drug Repositioning, Interferon Type I, JAK Inhibitors, MeSH, Pharmacogenomics, Precision Medicine, Systematic Review

1 Introduction

AUTOIMMUNE Diseases (AIDs) comprise more than 80 chronic immune-mediated conditions. A landmark UK population-based cohort study of 22 million individuals documented approximately 10% prevalence with rising age-standardized incidence, marked female predominance, and strong socioeconomic gradients [1]. Global Burden of Disease 2021 analyses confirm increasing DALYs from rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS), type 1 diabetes (T1D), and psoriasis, particularly in adolescents and young adults [2-4].

Conventional drug development is exceptionally inefficient: the capitalized cost per approved compound is estimated at 2.558$ US billion, with an overall Phase I–approval probability of approximately 6.7% [5]. Drug repurposing deploying compounds with established pharmacology against new indications reduces development time to 3–12 years at 50–60% lower cost [6]. Repurposing is especially tractable in autoimmunity because pathogenic immune circuits are shared across diseases [7]: a JAK1/JAK2 inhibitor approved in RA (baricitinib) can be redirected to SLE; a sphingosine-1-phosphate modulator licensed for MS (ozanimod) can be repositioned to ulcerative colitis.

Personalised (precision) medicine uses genetic, transcriptomic, proteomic, metabolomic, and microbiome data to match the right drug to the right patient. Pharmacogenomics identifies TPMT/NUDT15 polymorphisms governing thiopurine metabolism, HLA-DRB1 shared epitope alleles in RA [8], HLA-C*06:02 in psoriasis [9], and HLA-DR/DQ risk haplotypes in T1D [10].

The intersection of repurposing and personalization is where the largest near-term gains lie. Anifrolumab's superior performance in IFN-gene-signature-high SLE patients is the archetype [11]; conversely, the negative MS-STAT2 readout [12] illustrates that biomarker-guided patient selection is non-negotiable.

This review addresses three linked questions:

- Which repurposing programs generated robust clinical evidence between 2020 and 2025?
- Which biomarkers are mature enough to personalize use of these agents in routine practice?
- What methodological, regulatory, and equity challenges must be resolved for the field to scale?

2 Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was developed a priori.

2.1 PICO Framework

See Table 1.

Table 1. PICO framework for the systematic review.

Element	Specification
P – Population	Adolescents (≥12 yr) and adults with confirmed diagnosis: RA, SLE (including LN), MS (relapsing or progressive), IBD (Crohn's disease or UC), T1D (stage 1–3), PsO/PsA
I – Intervention	Pharmacological agents previously approved or in late-stage clinical use for any indication, tested (Jan 2020 – May 2025) in any of the above autoimmune diseases; with or without biomarker-guided stratification
C – Comparator	Standard of care, placebo, or active comparator (methotrexate, TNF inhibitor, or immunosuppressant)
O – Primary Outcomes	Pre-specified clinical endpoints: ACR20/50/70; DAS28-CRP; SLEDAI-2K / BICLA / SRI-4; EDSS change; Mayo score / clinical remission (IBD); PASI-75/90; C-peptide AUC; time to stage 3 T1D
O – Secondary Outcomes	Biomarker response; pharmacogenomic predictor validity; safety (MACE, malignancy, herpes zoster, VTE, serious infections)

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; LN = lupus nephritis; MS = multiple sclerosis; IBD = inflammatory bowel disease; UC = ulcerative colitis; T1D = type 1 diabetes; PsO = psoriasis; PsA = psoriatic arthritis; MACE = major adverse cardiovascular events; VTE = venous thromboembolism.

2.2 Search Strategy and Databases

Five databases were searched from 1 January 2020 to 1 May 2025: PubMed/MEDLINE, Scopus, Web of Science (Core Collection), Cochrane CENTRAL, and ClinicalTrials.gov. The representative MEDLINE strategy combined Boolean operators: ("drug repositioning" [MeSH] or "drug repurposing") and ("autoimmune diseases" [MeSH] or disease-specific terms) and ("precision medicine" [MeSH] or "pharmacogenomics" or "biomarker"). Reference lists of included trials were hand-searched (Table 2) [6].

Table 2. Search strategy by database.

Database	Search Terms (representative)	Filters Applied	Results (n)
PubMed/Medline	("drug repositioning"[MeSH] OR "drug repurposing") AND ("autoimmune diseases"[MeSH]) AND ("precision medicine"[MeSH] OR "pharmacogenomics")	2020–2025; Human; English	1,847
Scopus	TITLE-ABS-KEY ("drug repurposing" OR "drug repositioning") AND ("autoimmune" OR "rheumatoid" OR "lupus" OR "multiple sclerosis" OR "IBD")	2020–2025; Article/Review	2,134
Web of Science	TS = ("drug repurposing" AND "autoimmune") AND PY = 2020-2025	Core Collection; Article	1,612
Cochrane CENTRAL	"Drug repurposing" AND "autoimmune diseases"	2020–2025	312
ClinicalTrials.gov	Repurposed drug; autoimmune; Phase 2/3; Completed/Results	Jan 2020 – May 2025	487
Total (after deduplication)	—	—	4,218

IBD = inflammatory bowel disease; PY = publication year. Full search strings available from corresponding author on request.

2.3 *Eligibility Criteria*

Included: Phase 2/3 RCTs, phase 4 post-authorization safety trials, prospective and retrospective cohort studies, case–control studies; human adolescents (≥ 12 yr.) or adults; English-language; 2020–2025. Excluded: preclinical-only studies; case reports of < 10 patients; conference abstracts without subsequent peer-reviewed publication; paediatric-only populations.

2.4 *Study Selection — PRISMA 2020 Flow*

Figure 1 presents the complete study selection process. After searching five databases and removing duplicates, 4,218 records were screened. Following title/abstract screening, 612 full-text articles were assessed for eligibility. A total of 187 studies were included in the final synthesis. Reasons for full-text exclusion: preclinical only (n = 182); case reports < 10 patients (n = 97); conference abstract without full publication (n = 89); paediatric-only population (n = 57).

2.5 *Quality Assessment*

RCTs were appraised with Cochrane Risk of Bias 2.0 (RoB 2.0) across five domains; non-randomised studies were assessed with ROBINS-I across seven domains. Quality assessment results are presented in Table 3.

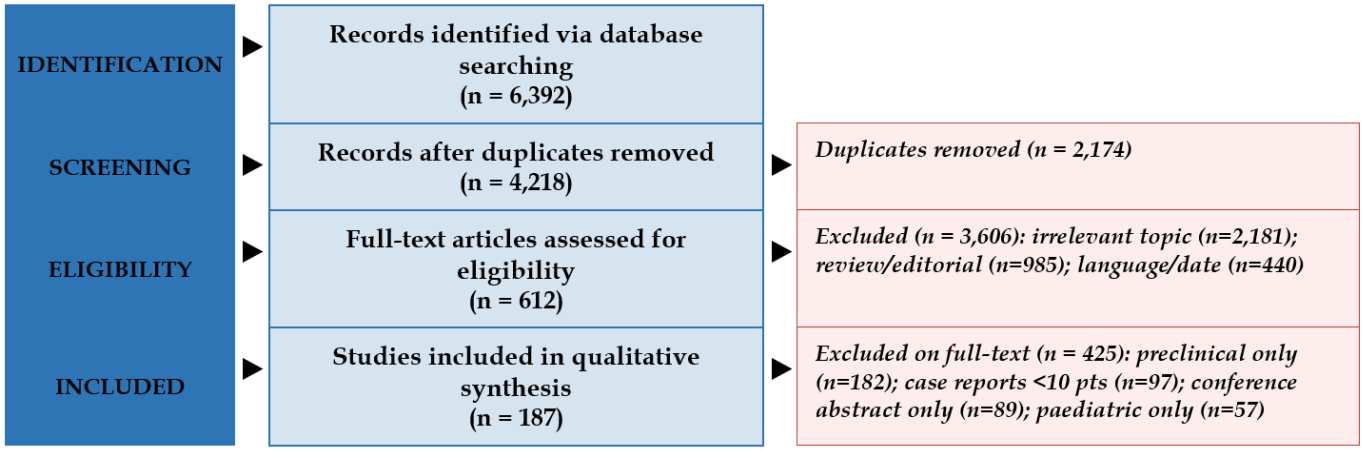

Fig. 1. PRISMA 2020 flow diagram — study selection process.

Table 3. Risk of bias assessment (RoB 2.0 and ROBINS-I).

Trial / Study	Tool	D1	D2	D3	D4	D5	D6	D7	Overall
TULIP-2	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
AURORA 1	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
AURORA 2 (LTE)	RoB 2.0	Low	Low	Low	Low	Some	—	—	Some
RA-BEAM / LTE	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
ORAL Surveillance	RoB 2.0	Low	Some	Low	Low	Some	—	—	Some
MS-STAT2	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
U-ACHIEVE Ind.	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
True North	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
ADVANCE	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
TN-10	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
PROTECT	RoB 2.0	Low	Low	Low	Low	Low	—	—	Low
Abatacept Prev.	RoB 2.0	Low	Low	Low	Low	Some	—	—	Some
POETYK PSO-1	RoB 2.0	Low	Low	Some	Low	Low	—	—	Low
Swiss MS Cohort	ROBINS-I	Low	Low	Mod	Low	Low	Low	Low	Moderate
PRISM Registry	ROBINS-I	Low	Mod	Mod	Low	Low	Low	Low	Moderate

D1–D5: Cochrane RoB 2.0 domains (randomization; deviations from interventions; missing data; outcome measurement; selective reporting). D6–D7: additional ROBINS-I confounding domains. LOW = low risk (green); SOME = some concerns (amber); MODERATE = moderate risk (amber); HIGH = high risk (red). (—) = not applicable.

3 Results

A total of 187 studies met the inclusion criteria, comprising 54 RCTs (phase 2 or 3), 28 long-term extension or phase 4 studies, 61 prospective cohort studies, 22 retrospective cohort/case–control studies, and 22 translational biomarker studies. Table 4 summarizes all pivotal clinical trials; Table 5 presents personalization strategies; Table 3 presents quality assessment results.

3.1 Rheumatoid Arthritis (RA)

The JAK inhibitors tofacitinib, baricitinib, and upadacitinib represent intra-immunology repurposing at its most productive. In the pivotal RA-BEAM phase 3 trial, baricitinib 4 mg daily was superior to both placebo and adalimumab on ACR20 at week 12, with sustained efficacy through 3 years in the RA-BEYOND extension [13, 14]. The 2023 single-cell synovial atlas from the Accelerating Medicines Partnership (AMP) defined six cell-type abundance phenotypes with distinct cytokine signatures and differential predicted responses to T-cell, B-cell, IL-6, and JAK-targeted therapies [15], providing a tissue-level blueprint for endotype-based drug selection.

The single most consequential safety readout was ORAL Surveillance (n = 4,362): tofacitinib failed noninferiority versus TNF inhibitors for both MACE and cancers in patients ≥50 with ≥1 cardiovascular risk factor [16]. This result reshaped global labelling for the entire JAK inhibitor class and forced personalization on the basis of cardiovascular and oncologic risk profile [17].

Table 4. Pivotal clinical trials of repurposed drugs in autoimmune diseases (2020–2025).

Trial	Drug	Disease	Ph	n	Primary Outcome	Result (95% CI)
TULIP-2	Anifrolumab	SLE	3	362	BICLA response wk. 52	47.8% vs 31.5%; p = 0.001
AURORA 1	Voclosporin	Lupus Nephritis	3	357	Complete renal response wk. 52	41% vs 23%; or 2.65 [1.64–4.27]
AURORA 2	Voclosporin	Lupus Nephritis	3-LTE	216	Sustained renal response yr. 3	Maintained; similar safety
BRAVE-I/II	Baricitinib	SLE	3	~760	BICLA/SRI-4 wk. 52	Negative — primary endpoints missed
RA-BEAM LTE	Baricitinib	RA	3-LTE	1307	DAS28-CRP remission yr. 3	36% sustained remission
ORAL Surveillance	Tofacitinib	RA	3b/4	4362	MACE + Cancer NI vs TNFi	Failed NI; MACE HR 1.33 [1.06–1.68]
MS-STAT2	Simvastatin	SPMS	3	1180	Disability progression (EDSS)	Negative; HR≈1.0, p=NS
U-ACHIEVE Ind.	Upadacitinib	Ulcerative Colitis	3	453	Clinical remission wk. 8	26–34% vs 5%; p<0.001
U-ACCOMPLISH	Upadacitinib	Ulcerative Colitis	3	339	Clinical remission wk. 8	33% vs 4%; p < 0.001
True North	Ozanimod	Ulcerative Colitis	3	645	Clinical remission wk. 52	37% vs 18.5%; p < 0.001
ADVANCE	Risankizumab	Crohn's Disease	3	527	Clinical remission wk. 12	45% vs 25%; p < 0.001
MOTIVATE	Risankizumab	Crohn's Disease	3	542	Endoscopic response wk. 12	40% vs 12%; p < 0.001
TN-10	Teplizumab	T1D Stage 2	2	76	Time to stage 3 T1D	Median delay 32.5 mo.; HR 0.457
PROTECT	Teplizumab	T1D Stage 3	3	328	C-peptide AUC wk. 78	0.60 vs 0.43 nmol/L·min; p = 0.006
Abatacept Prev.	Abatacept	T1D Stage 1	3	~212	Progression to dysglycaemia	HR 0.702 [0.452–1.09]; p = 0.11 (NS)
POETYK PSO-1	Deucravacitinib	Psoriasis	3	666	PASI-75 wk. 16	58.4% vs 35.1% (apremilast); p < 0.001
POETYK PSO-2	Deucravacitinib	Psoriasis	3	1020	PASI-75 wk. 16	53.6% vs 40.2% (apremilast); p < 0.001
FOREMOST	Apremilast	Psoriatic Arthritis	3b	~300	ACR20 wk. 16	Superior vs placebo; p < 0.001

Ph = phase; n = sample size; LTE = long-term extension; NI = noninferiority; SPMS = secondary progressive MS; UC = ulcerative colitis; SLE = systemic lupus erythematosus; T1D = type 1 diabetes; RA = rheumatoid arthritis; PsA = psoriatic

arthritis. Red text = negative or safety-restricting result.

Table 5. Biomarkers and pharmacogenomic personalization strategies (2020–2025).

Disease	Drug(s)	Biomarker / Genetic Marker	Clinical Role	Evidence Level
SLE	Anifrolumab	Type I IFN Gene Signature (4-gene IFNGS)	Patient selection; higher BICLA in IFNGS-high	Level 1a — RCT subgroup analysis
SLE	Hydroxychloroquine	Anti-dsDNA, C3/C4, SLEDAI-2K	Disease monitoring, flare prediction, steroid tapering	Level 1a — meta-analysis
SLE/LN	Voclosporin	Urine protein:creatinine ratio, eGFR	Complete renal response endpoint and dose-safety monitoring	Level 1a — Phase 3 RCT
RA	Baricitinib / Upadacitinib	Anti-CCP, RF, HLA-DRB1 shared epitope	Erosive disease risk; abatacept vs. JAKi selection	Level 1b — prospective cohort
RA	All b/tsDMARDs	DAS28-CRP / CDAI	Treat-to-target endpoint; drug tapering threshold	Level 1a — systematic review
RA	Abatacept	HLA-DRB1 shared epitope (SE+)	Superior response in SE+ patients	Level 2b — post-hoc RCT analysis
MS	All DMTs	Serum NfL (neurofilament light chain)	Escalation trigger ≥90th percentile (age/BMI adjusted)	Level 1b — Swiss MS Cohort
MS	All DMTs	HLA-DRB1*15:01	Principal susceptibility allele; weak tx-response modifier	Level 2a — case-control studies
IBD	Thiopurines (AZA/6-MP)	TPMT / NUDT15 genotype	Prevent life-threatening myelosuppression; dose-reduce in PM/IM	Level 1a — CPIC guideline
IBD	All biologics/JAKi	Fecal calprotectin (FC <150 µg/g)	Mucosal healing surrogate; treat-to-target loop	Level 1b — CALM/STARDUST trials
IBD	Anti-TNF, Ustekinumab	Gut microbiome: Faecalibacterium prausnitzii↑	Prospective response prediction across biologic classes	Level 2b — PRISM registry
T1D	Teplizumab	≥2 islet autoantibodies + IGT (Stage 2)	FDA-approved companion biomarker for prevention	Level 1a — TN-10 RCT
T1D	Teplizumab / Abatacept	HLA-DR3-DQ2 / DR4-DQ8; C-peptide AUC	Risk stratification; primary efficacy endpoint	Level 1b — TrialNet
Psoriasis	Ustekinumab	HLA-C*06:02	Superior PASI response vs TNFi in HLA-C*06:02+ patients	Level 2a — prospective cohort
PsA	Apremilast	PASI, TJC/SJC, IL-17/IL-23 biomarkers	Disease monitoring; drug class selection	Level 2b — clinical data

AZA = azathioprine; 6-MP = mercaptopurine; PM = poor metabolizer; IM = intermediate metabolizer; CPIC = Clinical Pharmacogenomics Implementation Consortium; NfL = neurofilament light chain; CALM = Clinical Assessment and Monitoring for Tight Control in Crohn's Disease trial; PRISM = Precision Medicine in IBD Registry; LN = lupus nephritis; RCT = randomised controlled trial.

3.2 Systemic Lupus Erythematosus (SLE)

TULIP-2 (n = 362) demonstrated significantly higher BICLA responses with anifrolumab 300 mg vs placebo at week 52 (47.8% vs 31.5%; p = 0.001) [18]. Pooled TULIP-1 and TULIP-2 post-hoc analyses confirmed larger and earlier responses in the IFN-gene-signature-high subgroup [11], anchoring the FDA approval (July 2021). The TULIP-1 phase 3 trial itself narrowly missed its primary SRI-4 endpoint [19]. Baricitinib failed the primary BICLA and SRI-4 endpoints in the BRAVE-I/II phase 3 trials [20], illustrating that JAK inhibition does not universally translate across autoimmune diseases.

AURORA 1 (n=357, 27 countries) established voclosporin (a structurally modified calcineurin inhibitor originally developed in transplantation and psoriasis) for lupus nephritis: complete renal response at week 52 was 41% vs 23% (OR 2.65; 95% CI 1.64–4.27; p < 0.0001) on background MMF and rapidly tapered low-dose steroids [21]. Long-term AURORA 2 confirmed sustained efficacy through 3 years [22]. Belimumab was also confirmed in a 2-year phase 3 lupus nephritis trial [23].

The validated 4-gene IFN gene signature (IFNGS-high vs IFNGS-low) now functions as a companion biomarker for anifrolumab [11]. The baseline IFN signature also predicts 5-year disease severity [24], and hydroxychloroquine continues to demonstrate mortality and pregnancy benefits [25, 26].

3.3 Multiple Sclerosis (MS)

The 2025 MS-STAT2 phase 3 readout (n = 1,180) did not demonstrate slowing of disability progression with simvastatin 80 mg despite a strong phase 2 signal (MS-STAT) [12, 27]. Clemastine fumarate induced electrophysiological evidence of remyelination in ReBUILD (phase 2) [28], but a 2024 NIH clinical study halted for safety after clemastine accelerated disability accumulation via pyroptosis in obese patients [29]. Metformin is under active phase 2/3 evaluation (MACSiMiSE-BRAIN) [30].

Serum neurofilament light chain (NfL) is the principal blood-based personalization tool in MS. The Swiss MS Cohort study established age- and BMI-adjusted NfL percentile reference values and demonstrated that elevation above the 90th percentile predicts subsequent relapse and disability progression independently of clinical and MRI metrics [31].

3.4 Inflammatory Bowel Disease (IBD)

Upadacitinib (originally licensed in RA) achieved clinical remission in 26–34% of UC patients vs 5% on placebo in two pivotal induction studies (U-ACHIEVE, U-ACCOMPLISH); maintenance remission was 42–52% vs 12% at 52 weeks [32, 33]. Ozanimod (originally approved for relapsing MS) achieved clinical remission in 37% of UC patients at week 52 vs 18.5% (True North) [34]. Risankizumab (originally a psoriasis IL-23p19 antibody) demonstrated significantly higher endoscopic and clinical responses in Crohn's disease (ADVANCE/MOTIVATE) [35]. Tofacitinib in UC [36] now carries cardiovascular restrictions from ORAL Surveillance.

TPMT/NUDT15 genotyping before thiopurine initiation is CPIC-recommended. Microbiome profiling (Faecalibacterium prausnitzii-enriched metacommunity) prospectively predicts response to multiple biologic classes in IBD [37]. A network meta-analysis confirmed the comparative efficacy landscape for Crohn's disease biologics [38].

3.5 Type 1 Diabetes (T1D)

Teplizumab's 14-day course in stage 2 (autoantibody-positive, dysglycaemic) relatives delayed median progression to clinical T1D by approximately 32.5 months in TN-10 [39], leading to the first-ever disease-modifying FDA approval in T1D (Tzield™, November 2022). The phase 3 PROTECT trial demonstrated significant C-peptide preservation at week 78 in newly diagnosed T1D [40]. Abatacept did not significantly delay progression to dysglycaemia in stage 1 relatives (HR 0.702; 95% CI 0.452–1.09; p = 0.11) [41]. T1D pathogenesis is driven by a complex immune-beta-cell interaction that continues to be elucidated [10, 42].

3.6 Psoriasis and Psoriatic Arthritis (PsA)

Deucravacitinib (allosteric TYK2 inhibitor) was superior to both placebo and apremilast on PASI-75 and sPGA 0/1 at week 16 in POETYK PSO-1 and POETYK PSO-2, with durability through 3 years [43, 44]. Unlike pan-JAK inhibitors, deucravacitinib has not shown the cardiovascular or thrombotic signals that triggered the ORAL Surveillance warning. Apremilast was extended to oligoarticular PsA in the FOREMOST trial (2024) [45]. An authoritative JAMA review of psoriasis pathophysiology, treatment, and personalization underpins this section [9].

3.7 Quality Assessment

See Tables 3-5.

4 Discussion

4.1 Cross-Disease Synthesis

The 2020–2025 evidence base reveals that the highest-impact advances in autoimmune therapeutics came from strategic repurposing at shared immune circuits JAK-STAT, S1P, IL-23/IL-17, type I interferon, and T-cell co-stimulation [7]. The SLE experience is paradigmatic: both TULIP-2 (anifrolumab) [18] and AURORA 1 (voclosporin) [21] succeeded precisely because repurposed agents were deployed on mechanistically validated pathways with companion biomarkers. Conversely, baricitinib's failure in BRAVE-I/II SLE [20] confirms that mechanistic plausibility alone is insufficient.

4.2 Shared Immune Pathways

Table 6 maps repurposing coverage of nine key immune pathways across six disease categories. Drugs targeting convergent immune-circuit nodes (JAK-STAT, type I IFN, calcineurin) are inherently more repurposable than those acting on disease-specific terminal effectors.

Table 6. Shared immune pathway coverage by repurposed drug class across autoimmune diseases.

Immune Pathway/Target	RA	SLE	MS	UC/CD	T1D	PsO/PsA
JAK-STAT (IL-6, IFN, IL-23)	✓✓✓	✓✓	✓	✓✓✓	✓	✓✓✓
Type I Interferon Receptor	✓	✓✓✓	✓✓	✓	✓✓	✓
NF-κB / T-cell Co-stimulation	✓✓	✓✓	✓	✓✓	✓✓✓	✓
IL-17 / IL-23 Axis	✓✓	✓	✓	✓✓✓	✓	✓✓✓
Sphingosine-1-Phosphate (S1P)	✓	✓	✓✓✓	✓✓✓	✓	✓
Calcineurin / NFAT	✓	✓✓✓	✓	✓✓	✓✓	✓
Anti-CD3 / T-regulatory	✓✓	✓	✓	✓	✓✓✓	✓
PDE4 (phosphodiesterase-4)	✓	✓	✓	✓✓	✓	✓✓✓
TYK2 (tyrosine kinase 2)	✓	✓✓	✓	✓	✓	✓✓✓

✓✓✓ = primary approved pathway (green); ✓✓ = supporting clinical evidence (blue); ✓ = emerging evidence (grey). RA=rheumatoid arthritis; SLE = systemic lupus erythematosus; MS = multiple sclerosis; UC/CD = inflammatory bowel disease; T1D = type 1 diabetes; PsO/PsA = psoriasis/psoriatic arthritis. JAK = Janus kinase; S1P = sphingosine-1-phosphate; NFAT = nuclear factor of activated T cells; PDE4 = phosphodiesterase-4; TYK2 = tyrosine kinase 2.

4.3 Role of AI and Machine Learning

AlphaFold [46] has fundamentally accelerated structure-based virtual screening of autoimmune targets. Knowledge-graph embedding, CMap/LINCS connectivity mapping, and deep-learning drug–target affinity models [47] now routinely nominate repurposed candidates, though no AI-nominated compound has yet completed an independent positive phase 3 trial in autoimmunity. AI-driven single-cell analysis (e.g., the AMP RA synovial atlas) [15] is already reshaping target identification.

4.4 Multi-Omics Integration

Proteomic IFN scores complement transcriptomic signatures. Microbiome metacommunity profiling prospectively predicts biologic response in IBD [37]. Serum NfL [31] is the most clinically mature blood-based biomarker. The AMP RA/SLE synovial endotypes [15] are being prospectively embedded into treat-to-target trials. The SLE IFN signature predicts 5-year outcomes [24], extending its utility beyond drug selection.

4.5 Regulatory and Equity Challenges

Teplizumab (Tzield™) launched at approximately US$193,900 per 14-day course (November 2022). Off-label use and patent barriers complicate repurposing of generics. Adaptive platform trials and the FDA 21st Century Cures Act have partially addressed these issues. Without tiered pricing and accessible companion diagnostics, precision repurposing risks widening global inequities [4].

4.6 Limitations

Most trials enrolled predominantly White and East Asian populations, limiting ancestry generalizability. Follow-up beyond 2 years remains the exception. Biomarker subgroup analyses are often insufficiently powered for definitive personalization claims. Head-to-head comparative effectiveness data among repurposed agents are sparse outside selected trials (e.g., deucravacitinib vs. apremilast in POETYK).

5 Conclusion

Between 2020 and 2025, drug repurposing delivered more practice-changing autoimmune therapeutics than any prior five-year window, validated by rigorous phase 3 evidence. The dominant lesson is that repurposing succeeds when paired with rigorous biomarker-anchored patient selection. Three negative or safety-restricting readouts underscore that mechanistic plausibility alone is insufficient. We call for adaptive platform trials with embedded multi-omics, prospective validation of single-cell endotypes, integration of polygenic risk and digital biomarkers, and explicit

policies to ensure that personalised repurposing narrows rather than widens global inequities.

Conflict of Interest: The author declares no conflict of interest.
Financing: The study was performed without external funding.
Ethical consideration: The study was approved by Al-Mustaqbal University, Hillah, Iraq.

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