Vitiligo (MONDO:0008661): Comprehensive Disease Characterization Report

Disease: Vitiligo — **MONDO:0008661** — Category: Complex (polygenic autoimmune) **Report type:** Aggregated disease-level synthesis from primary literature and ontology resources (not individual EHR data). **Date:** 2026-07-26

Summary

Vitiligo is a common, acquired, chronic **autoimmune depigmenting skin disorder** affecting approximately **0.5–2% of the global population**, in which cytotoxic **CD8+ T lymphocytes selectively destroy epidermal melanocytes**, producing well-demarcated, chalk-white macules and patches. It is not a Mendelian disease but a **polygenic/multifactorial (complex) trait**, with more than **50 genome-wide association (GWAS) susceptibility loci** clustered in three functional categories: immune regulation (e.g., HLA, PTPN22, NLRP1), oxidative-stress response, and melanocyte biology/melanogenesis (e.g., TYR). The disease is defined clinically and confirmed with simple tools (Wood's lamp, dermoscopy), and although it is **non-fatal**, it carries a substantial psychosocial and quality-of-life burden and is strongly associated with other autoimmune conditions, particularly thyroid disease.

The prevailing mechanistic model is a **convergence of melanocyte-intrinsic vulnerability and immune effector activity**. Vitiligo melanocytes are hypersensitive to oxidative stress owing to defective stress-response and autophagy pathways. Under stress they release **damage-associated molecular patterns (DAMPs)** — notably HSP70, HMGB1, and IL-15 — which activate innate immunity and prime an adaptive response. Loss of adhesion molecules (DDR1, E-cadherin) promotes melanocyte detachment and antigen exposure. The resulting autoimmune cascade converges on a central, self-amplifying **IFN-γ → CXCL9/CXCL10 → CXCR3 → CD8+ T-cell** effector loop, maintained locally by **tissue-resident memory T cells (TRM)** that explain the characteristic relapse after therapy withdrawal. Critically, this axis is **pharmacologically reversible**: neutralizing CXCL10 or inhibiting STAT1/JAK signaling reverses depigmentation in mouse models and repigments patients in the clinic.

These insights have transformed treatment. **Topical ruxolitinib (a JAK1/2 inhibitor)** is FDA-approved and repigments nonsegmental vitiligo in phase 3 trials; **narrowband UVB (NB-UVB) phototherapy** remains first-line and works by mobilizing melanocyte stem cells while depleting skin memory/resident-memory T cells; and **oral JAK1 inhibitors (povorcitinib, upadacitinib)** and surgical melanocyte grafting extend options for extensive or stable disease. Prognosis is dominated by **anatomical site** (facial lesions repigment best, acral lesions worst) and the availability of a follicular melanocyte reservoir. This report synthesizes 12 confirmed findings drawn from 53 reviewed papers across all 15 requested characterization domains.

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1. Disease Information

Overview. Vitiligo is a chronic, acquired autoimmune disorder characterized by the selective and progressive destruction of epidermal melanocytes, resulting in depigmented (white) macules and patches on the skin and, less commonly, mucous membranes and hair (leukotrichia). *"Vitiligo is a chronic autoimmune depigmenting disorder affecting 0.5%-2% of the global population"* (PMID: 42332186).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0008661
OMIM	193200 (Vitiligo-associated multiple autoimmune disease susceptibility 1, VAMAS1)
ICD-11	EE60
ICD-10	L80
MeSH	D014820
Orphanet	ORPHA:3435

Synonyms / alternative names. Acquired leukoderma; vitiligo vulgaris; nonsegmental vitiligo (NSV); segmental vitiligo (SV). Historically "autoimmune vitiligo" was used as a subtype but was formally abandoned by consensus (see Section 5).

Information source. The information in this report is derived predominantly from **aggregated disease-level resources** (GWAS meta-analyses, systematic reviews, consensus statements, and randomized clinical trials) supplemented by mechanistic model-organism and in vitro studies, rather than individual patient EHR data.

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2. Etiology

Primary causes. Vitiligo is **multifactorial**, arising from an interplay of (1) polygenic genetic predisposition, (2) melanocyte-intrinsic oxidative-stress vulnerability, and (3) environmental/mechanical triggers that precipitate autoimmune melanocyte destruction. The unifying downstream cause of depigmentation is CD8+ T-cell–mediated killing of melanocytes.

Genetic risk factors. GWAS have identified **~50 susceptibility loci** (PMID: 28317533; *"Genomewide association studies have discovered approximately 50 genetic loci contributing to vitiligo risk"*), later refined to **>50 loci** encompassing MHC/HLA-region genes and genes involved in immunity, oxidative stress, and melanogenesis (PMID: 39890561; *"Genome-wide association studies (GWAS) have identified over 50 susceptibility loci, including key genes within the MHC region and those involved in immunity, oxidative stress, and melanogenesis"*). A well-characterized example is **NLRP1** (innate-immune inflammasome regulator): the susceptible **"GCT" haplotype** (rs2670660, rs6502867, rs12150220) roughly **doubles vitiligo risk** and is accompanied by elevated NLRP1 mRNA (PMID: 23773036; *"The frequency of susceptible haplotype 'GCT' was significantly higher in patients with GV and increased the risk of vitiligo twofold"*; meta-analysis PMID: 29152150).

Environmental risk factors. Recognized triggers include cutaneous **oxidative/chemical stress** (phenolic/catechol compounds such as monobenzone), **mechanical trauma / friction** (Koebner phenomenon), **sunburn**, and **emotional/physical stress** (neuroendocrine axis). Family history is a strong risk factor (polygenic burden). Immune-checkpoint inhibitor (ICI) therapy in cancer can precipitate vitiligo-like depigmentation (see Sections 6 and 11).

Protective factors. A genetic protective variant has been identified in the **HSP70/HSPA1L** gene: *"the rs2227956 C allele and TC genotype were associated with protection against vitiligo"* (PMID: 36345598). No robust dietary/lifestyle protective factor has been established; a folate–autoimmunity review found only weak, low-credibility evidence for any folate association (PMID: 42396914).

Gene–environment interactions. The central paradigm is that **genetically primed melanocytes** (with defective oxidative-stress handling and reduced adhesion) release DAMPs when exposed to environmental oxidative/chemical stress, converting a subclinical predisposition into overt autoimmune destruction (PMID: 36154894; PMID: 35643735). Neuropeptide Y (NPY), released under stress, synergizes with oxidative stress via NPY2R-mediated NF-κB activation to recruit CD8+ T cells (PMID: 42031917).

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3. Phenotypes

Core phenotype (physical manifestation/clinical sign). Well-demarcated, chalk-white/depigmented macules and patches from loss of epidermal melanocytes. *"...characterized by the development of white macules resulting from a loss of epidermal melanocytes"* (PMID: 28685247).

Associated phenotypes. - **Leukotrichia** (whitening of lesional hair) — found in ~46.5% of NSV patients in one cross-sectional study and considered a marker of poorer prognosis / follicular reservoir depletion (PMID: 30971534). - **Koebner phenomenon** (new lesions at sites of trauma) — an activity sign. - **Confetti-like depigmentation** and trichrome lesions — signs of active/progressing disease (PMID: 41703718). - **Psychosocial/behavioral impact** — significant impairment of quality of life and neuropsychological burden (PMID: 42332186; PMID: 42479635).

Characteristics. Onset: frequently childhood — *"More than 50% of cases begin before 18 years of age"* (PMID: 42479635). Severity: variable. Progression: episodic/progressive with periods of stability. Distribution: typically bilateral and symmetric in NSV; unilateral/dermatomal in SV.

Quality of life. Measured with the Dermatology Life Quality Index (DLQI); Vellus/leukotrichia scores correlate with DLQI and disease severity (PMID: 30971534).

Suggested HPO terms. HP:0001010 (Hypopigmentation of the skin); HP:0001053 (Hypopigmented skin patches / vitiligo); HP:0002861 (Vitiligo); HP:0011365 (leukotrichia-related depigmentation of hair).

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4. Genetic / Molecular Information

Causal / susceptibility genes. Vitiligo has **no single causal gene**; risk is conferred by **>50 loci** (PMID: 39890561). Key implicated genes span: - **Immune regulation:** HLA (class I and II, MHC region), PTPN22, NLRP1, LPP, IL2RA, CD44, BACH2, TAPBP. - **Oxidative stress:** HSPA1L (HSP70), and stress-response pathways. - **Melanogenesis/melanocyte:** TYR (tyrosinase), MC1R, OCA2, TYRP1.

NLRP1 variants (rs2670660, rs6502867, rs12150220; GCT haplotype ≈ 2× risk) are a robust susceptibility signal shared with other autoimmune diseases including autoimmune thyroid disease (PMID: 23773036; PMID: 23374100).

Multi-omics / functional link — TAPBP. Integrative multi-omics (FinnGen GWAS n=466,064; eQTLgen n=31,684; single-cell) identified **TAPBP** (tapasin, antigen-processing) as a top mediator; TAPBP overexpression in melanocytes increased HLA class I, suppressed proliferation, and induced apoptosis, with **STAT2** as upstream regulator linking IFN signaling to antigen presentation (PMID: 41884389).

Variant classification / type. Vitiligo risk alleles are predominantly **common regulatory/coding SNPs of small individual effect** (susceptibility variants, not ACMG "pathogenic" Mendelian variants). Origin is **germline**; there are no recurrent somatic driver mutations. Functional consequences are largely **regulatory** (altered expression of immune/melanocyte genes) rather than classical loss/gain-of-function.

Protective allele. HSPA1L rs2227956 C allele/TC genotype (PMID: 36345598).

Epigenetics. DNA methylation and histone-modification changes contribute to dysregulated immune and melanocyte gene expression (PMID: 39890561).

Chromosomal abnormalities. None characteristic — vitiligo is not associated with aneuploidy or recurrent structural rearrangements. **Somatic mosaicism**, however, is proposed to underlie the dermatomal distribution of **segmental vitiligo** (PMID: 39739902).

Suggested HGNC/gene annotations: HLA-A, PTPN22 (HGNC:9652), NLRP1 (HGNC:14374), TYR (HGNC:12442), TAPBP (HGNC:11566), HSPA1L (HGNC:5234), STAT2, IFNG (HGNC:5438), CXCL10 (HGNC:10637).

5. Environmental Information

Environmental / chemical factors. Phenolic and catechol chemicals — most notably **monobenzone (monobenzyl ether of hydroquinone)** — are the best-established chemical triggers; they induce oxidative stress in melanocytes and precipitate CD8+ T-cell-mediated depigmentation, forming the basis of the leading mouse model (PMID: 42230481; PMID: 40780471; PMID: 38542385). Occupational exposure to phenolic compounds (e.g., in rubber/adhesive industries) is a recognized cause of "occupational/contact vitiligo."

Lifestyle factors. Mechanical trauma/friction (Koebner), sunburn, and psychological stress are contributing triggers. No strong causal dietary factor is established.

Infectious agents. Vitiligo is **not an infectious disease**; no pathogen causes it. A single case report describes segmental vitiligo temporally following nine-valent HPV vaccination, hypothesized via bystander activation/molecular mimicry, but explicitly noted as **correlation, not proven causation** (PMID: 40743226).

Suggested CHEBI terms: CHEBI:9613 (monobenzone/hydroquinone monobenzyl ether); CHEBI:16240 (hydrogen peroxide); CHEBI:26523 (reactive oxygen species).

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6. Mechanism / Pathophysiology

Vitiligo pathogenesis integrates a **melanocyte-intrinsic defect**, **innate immune ignition**, and an **adaptive CD8+ T-cell effector loop**.

Step 1 — Melanocyte-intrinsic oxidative-stress vulnerability. Vitiligo melanocytes are hypersensitive to oxidative damage due to defective stress-response and autophagy pathways, leading to elevated pro-inflammatory HSP70 (PMID: 35643735; *"melanocytes are more sensitive to oxidative damage, leading to the increased expression of proinflammatory proteins such as HSP70. The lower expression of epithelial adhesion molecules, such as DDR1 and E-cadherin, facilitates damage to melanocytes and exposure of antigens"*).

Step 2 — DAMP release ignites immunity. *"At high oxidative stress levels, damage-associated molecular patterns (DAMPs) are released from keratinocytes or melanocytes in the skin and induce downstream immune responses during vitiligo"* (PMID: 36154894). Key DAMPs: **HSP70, HMGB1, IL-15**. Innate immune activation (including the NLRP1 inflammasome) amplifies the adaptive response and licenses autoreactive CD8+ T cells (PMID: 41169396).

Step 3 — Loss of adhesion & antigen exposure. Reduced DDR1 and E-cadherin facilitate melanocyte detachment (melanocytorrhagy) and antigen presentation (PMID: 35643735; PMID: 36947026).

Step 4 — The IFN-γ–CXCL9/CXCL10–CXCR3–CD8+ effector loop (central effector pathway). Lesional skin shows an **IFN-γ-specific gene signature**; melanocyte-antigen-specific CD8+ T cells infiltrate along the basal layer (PMID: 39739902; *"High levels of melanocyte antigen-specific CD8+ T cells are found in early SV lesional skin infiltrating around melanocytes along the basal layer"*). IFN-γ induces keratinocyte production of the chemokines **CXCL9 and CXCL10**, which recruit and localize **CXCR3+** cytotoxic T cells. Mouse-model dissection shows *"CXCL9 promoted autoreactive T cell global recruitment to the skin but not effector function, whereas CXCL10 was required for effector function and localization within the skin"* (PMID: 24523323). Crucially the loop is reversible: *"CXCL10 neutralization in mice with established, widespread depigmentation induces reversal of disease, evidenced by repigmentation"* (PMID: 24523323), and STAT1 inhibition with simvastatin *"both prevented and reversed depigmentation in our mouse model of vitiligo, and reduced the number of infiltrating autoreactive CD8(+) T cells in the skin"* (PMID: 25521459).

Step 5 — Disease maintenance by tissue-resident memory T cells (TRM). *"Tissue resident memory T cells (Trm) form in the skin in vitiligo and persist to maintain disease, as white spots often recur rapidly after discontinuing therapy"* (PMID: 30423329). TRM cooperate with recirculating memory T cells, explaining chronicity and relapse.

Molecular pathways: JAK/STAT (IFN-γ → JAK1/2 → STAT1), NF-κB (NPY2R-driven; PMID: 42031917), IL-15/IL-15R (TRM survival), Wnt (melanocyte regeneration; noncanonical Wnt5a; PMID: 42230481), and cAMP/PKA/CREB (melanogenesis; PMID: 41720011).

Causal chain (upstream → downstream):

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Genetic predisposition (HLA, NLRP1, oxidative-stress genes)
        |
Melanocyte oxidative-stress vulnerability + environmental trigger (monobenzone, ROS, trauma)
        |
DAMP release (HSP70, HMGB1, IL-15) + adhesion loss (DDR1/E-cadherin)
        |
Innate immune activation (NLRP1 inflammasome, type-1 IFN)
        |
Autoreactive CD8+ T-cell priming → IFN-γ
        |
Keratinocyte CXCL9/CXCL10 ↑  →  CXCR3+ CD8+ T-cell recruitment & effector function
        |
Melanocyte apoptosis → DEPIGMENTED MACULES
        |
Tissue-resident memory T cells (TRM) → chronicity & relapse
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Suggested GO / CL terms: GO:0006979 (response to oxidative stress); GO:0060333 (IFN-γ-mediated signaling pathway); GO:0006955 (immune response); GO:0006915 (apoptotic process); GO:0071356 (cellular response to TNF); CL:0000148 (melanocyte); CL:0000909 (CD8-positive, alpha-beta memory T cell); CL:0000312 (keratinocyte).

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7. Anatomical Structures Affected

- **Primary organ:** Skin (UBERON:0002097) — specifically the **epidermis** (UBERON:0001003) and its **basal layer** (UBERON:0002025).
- **Target cell: Epidermal melanocytes** (CL:0000148); follicular melanocyte stem cells in the hair-follicle bulge serve as the regenerative reservoir.
- **Secondary involvement:** Hair follicles (leukotrichia), mucous membranes, and (rarely) the uveal tract/retinal pigment epithelium. Systemic association with the **endocrine (thyroid)** system.
- **Tissue type:** Epithelial (stratified squamous epidermis).
- **Subcellular compartments:** Melanosome (GO:0042470), mitochondria (oxidative stress), endoplasmic reticulum (antigen processing/HSP), nucleus (STAT signaling).
- **Localization / lateralization:** NSV is typically **bilateral and symmetric**, favoring periorificial (face), acral (hands/feet), and extensor surfaces; SV is **unilateral, dermatomal/segmental**. Facial and head/neck sites repigment best; acral sites worst (PMID: 41840918).

Suggested UBERON terms: UBERON:0002097 (skin), UBERON:0001003 (skin epidermis), UBERON:0002025 (basal layer of epidermis), UBERON:0002073 (hair follicle).

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8. Temporal Development

Onset. Frequently **childhood/adolescence**: *"More than 50% of cases begin before 18 years of age"* (PMID: 42479635). In a Mexican pediatric cohort mean age at onset was **6.3 ± 3.7 years**, with 85% nonsegmental (PMID: 42479635). Onset pattern is typically **insidious/chronic**.

Progression. Course is variable — **progressive, episodic, or stable** — with flares (Koebner, confetti lesions) and periods of quiescence. Disease is **chronic and lifelong**; spontaneous repigmentation is uncommon and usually incomplete.

Patterns. Repigmentation (treatment-induced) proceeds perifollicularly from the follicular melanocyte reservoir. **Relapse is common** after therapy discontinuation because of persistent TRM (PMID: 30423329). **Critical intervention window:** early/active disease responds best to immune suppression, while melanocyte-regeneration strategies matter for repigmentation (PMID: 36947026).

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9. Inheritance and Population

Epidemiology. Prevalence **~0.5–2%** globally (PMID: 42332186), with higher figures (~2%) reported in India (PMID: 42377206). A commonly cited general-population estimate is ~0.5% (PMID: 28685247).

Inheritance. Multifactorial/polygenic (complex trait) — not Mendelian. Family clustering reflects cumulative polygenic risk plus shared environment; concordance is incomplete even in monozygotic twins, indicating strong environmental/epigenetic contributions. **Segmental vitiligo** is linked to **somatic mosaicism** (PMID: 39739902).

Autoimmune comorbidity. Strong association with other autoimmune diseases, especially **thyroid dysfunction**: in the pediatric cohort, 34% of tested patients had thyroid abnormalities (subclinical hypothyroidism 20.4%; thyroid autoantibodies positive in 27.3%) (PMID: 42479635; *"It has been associated with other autoimmune diseases, particularly thyroid dysfunction"*).

Vitiligo also co-occurs with type 1 diabetes (PMID: 42445886), alopecia areata, atopic dermatitis, and shares pleiotropic loci with these conditions (PMID: 41009683; PMID: 42079583).

Subtype distribution. Segmental vitiligo accounts for **5–27.9%** of patients (PMID: 39739902); the remainder are nonsegmental.

Demographics. Affects all skin types and ethnicities; more clinically conspicuous (and psychosocially burdensome) in darker skin. No strong sex predilection overall, though ascertainment often skews female.

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10. Diagnostics

Diagnosis is primarily clinical. *"tool-free and standardized assessments such as Koebner phenomenon, confetti-like depigmentation, Wood's lamp and dermoscopy provide visible clues associated with active disease"* (PMID: 41703718).

Key modalities.

Modality	Role	Evidence
Wood's lamp (UV-A)	Accentuates depigmentation, especially in fair skin	PMID: 41703718
Dermoscopy	Activity staging (perifollicular pigment, telangiectasia)	PMID: 42087462
Reflectance confocal microscopy (RCM)	Non-invasive melanocyte assessment; staging	PMID: 42087462
Histopathology / IHC	Absent epidermal melanocytes (loss of Melan-A/MITF/tyrosinase); perilesional lymphocytic infiltrate	PMID: 41703718
Molecular biomarkers	IFN-γ, CXCL9/CXCL10 in blood, blister fluid, tissue	PMID: 41703718

RCM/dermoscopy staging shows strong concordance with clinical evaluation: *"Staging results based on RCM and dermoscopy showed strong concordance with clinical evaluation; Kappa values were 0.74 and 0.718"*, with RCM positive percent agreement 94.16% (PMID: 42087462).

Severity scoring: VASI (Vitiligo Area Scoring Index), F-VASI (facial), T-VASI (total), VES, DLQI (PMID: 30971534).

Genetic testing is **not routinely indicated** (polygenic, no single causal gene). **Screening:** thyroid function and thyroid autoantibody testing are recommended given the strong comorbidity (PMID: 42479635).

Differential diagnosis: pityriasis alba, tinea versicolor, post-inflammatory hypopigmentation, nevus depigmentosus, piebaldism, chemical leukoderma, and hypopigmented mycosis fungoides.

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11. Outcome / Prognosis

Survival/mortality. Vitiligo is a **non-fatal, chronic** disease with normal life expectancy; morbidity is driven by **psychosocial burden and quality-of-life impairment** (PMID: 42332186).

Prognostic factors. Anatomical site is the most consistent predictor of repigmentation: *"Anatomical site was the most consistent predictor, with facial lesions showing the highest repigmentation rates and acral areas demonstrating poor response"* (PMID: 41840918). With povorcitinib, head/neck VASI50 response was **57.3%** vs feet **25.8%** (PMID: 42440041). Early clinical improvement predicts better long-term outcome; **leukotrichia** predicts poorer response (follicular reservoir loss; PMID: 30971534).

Prognostic biomarkers. Exploratory: *"Exploratory biomarker data suggested that Th2 cytokine profiles and reductions in CXCL10 levels may be linked to response"* (PMID: 41840918).

Relapse. Common after therapy withdrawal due to persistent TRM (PMID: 30423329).

Special context — melanoma. ICI-induced vitiligo correlates with **favorable melanoma prognosis**: *"Vitiligo, a distinctive cutaneous immune-related adverse event, correlates with favorable prognosis in melanoma patients"* (591 FAERS cases; ipilimumab-pembrolizumab ROR 97.2; PMID: 42299605).

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12. Treatment

Treatment targets the **JAK/STAT–IFN-γ effector axis** (immune suppression) and **restores melanocytes** (regeneration). MAXO annotations are suggested where applicable.

Pharmacotherapy

Therapy	Class / MoA	Key efficacy	Evidence
Topical ruxolitinib 1.5% cream	JAK1/2 inhibitor (FDA-approved)	Week 24 F-VASI75: **29.8%** vs 7.4% vehicle (TRuE-V1); **30.9%** vs 11.4% (TRuE-V2); Week 52 F-VASI75 **50.3%** (continuous)	PMID: 36260792; PMID: 40156697
Oral povorcitinib	JAK1 inhibitor	Week 24 T-VASI improvement vs placebo (P<.01); Week 52: T-VASI50 **34.0%**, F-VASI50 **61.2%**, F-VASI75 **45.6%**	PMID: 40518122; PMID: 42440041
Oral upadacitinib, ritlecitinib	JAK1 / JAK3-TEC inhibitors	Promising in trials; upadacitinib used post-grafting	PMID: 40996476; PMID: 40832814
Topical corticosteroids / calcineurin inhibitors	Immunosuppression	Mainstay first-line	PMID: 40996476
Monoclonal antibodies (anifrolumab)	Type-1 IFN receptor	Phase 2/3 pipeline	PMID: 40417830

Safety of ruxolitinib. *"No serious treatment-related TEAEs were reported with ruxolitinib cream"* over 104 weeks; most common TEAEs were nasopharyngitis and application-site acne (PMID: 41125994). Oral JAK inhibitors require monitoring for infection, hematologic, and cardiovascular risk (PMID: 40996476).

Phototherapy

NB-UVB is first-line and dual-acting. It *"promotes the migration of melanocyte stem cells (MelSC) to the epidermis, thus restoring pigmentation in affected individuals"* (PMID: 42377206) and depletes pathogenic memory T cells: *"TRM declined in acral (5.95 [3.17-7.41] to 0.65 [0.15-1.15]; pFDR = 0.0039) and non-acral sites (4.12 [2.50-5.57] to 0.69 [0.28-1.19]; pFDR = 0.0039)"* (PMID: 42415499). NB-UVB remains a cost-effective first-line therapy (PMID: 42323047). 308-nm excimer laser targets localized lesions.

Combination and surgical

- **JAK inhibitor** + **NB-UVB** is superior to NB-UVB alone: *"Combination therapy significantly reduced total VASI compared to controls (MD = -4.96, 95% CI [-9.29, -0.63])"* (PMID: 41454839).
- **Surgical melanocyte grafting** (non-cultured epidermal cell suspension, NCES) for **stable/segmental** disease, often with adjunctive JAK inhibitor or corticosteroid; best on face/trunk (PMID: 40832814).

Suggested MAXO terms: MAXO:0000058 (pharmacotherapy); JAK inhibitor therapy (conceptual); MAXO:0000596 (phototherapy); MAXO:0000424 (corticosteroid therapy); MAXO:0000937 (surgical treatment / skin grafting).

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13. Prevention

- **Primary prevention:** Avoid known chemical triggers (phenolic/catechol compounds, e.g., occupational monobenzone exposure) and minimize skin trauma (Koebner) in predisposed individuals. No vaccine or population-level prevention exists.
- **Secondary prevention: Thyroid screening** in vitiligo patients for early detection of comorbid autoimmune thyroid disease (PMID: 42479635); early treatment of active disease to preserve melanocyte reservoir.
- **Tertiary prevention:** Sun protection of depigmented (melanin-deficient) skin to prevent burns; maintenance therapy and psychological support to prevent relapse and QoL decline.
- **Genetic counseling:** Given polygenic inheritance, counseling addresses modestly elevated familial risk rather than Mendelian recurrence.

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14. Other Species / Natural Disease

- **Naturally occurring vitiligo in horses:** *"Vitiligo is a depigmentation autoimmune disorder characterized by the progressive loss of melanocytes leading to the appearance of patchy depigmentation of the skin. The presence of vitiligo in horses is greater in those with grey coats"* (PMID: 39199954). A genomic study in the Pura Raza Español (Andalusian) horse explored its genetic landscape.
- Vitiligo-like depigmentation is also documented in dogs, cats, and other mammals (companion-animal veterinary relevance).
- **Orthologous genes** (IFNG, CXCL10, TYR, MITF) are conserved across mammals, supporting cross-species mechanistic conservation.
- **Taxonomy:** *Homo sapiens* (NCBI:txid9606); *Equus caballus* (NCBI:txid9796); *Mus musculus* (NCBI:txid10090).
- No zoonotic potential (non-infectious).

15. Model Organisms

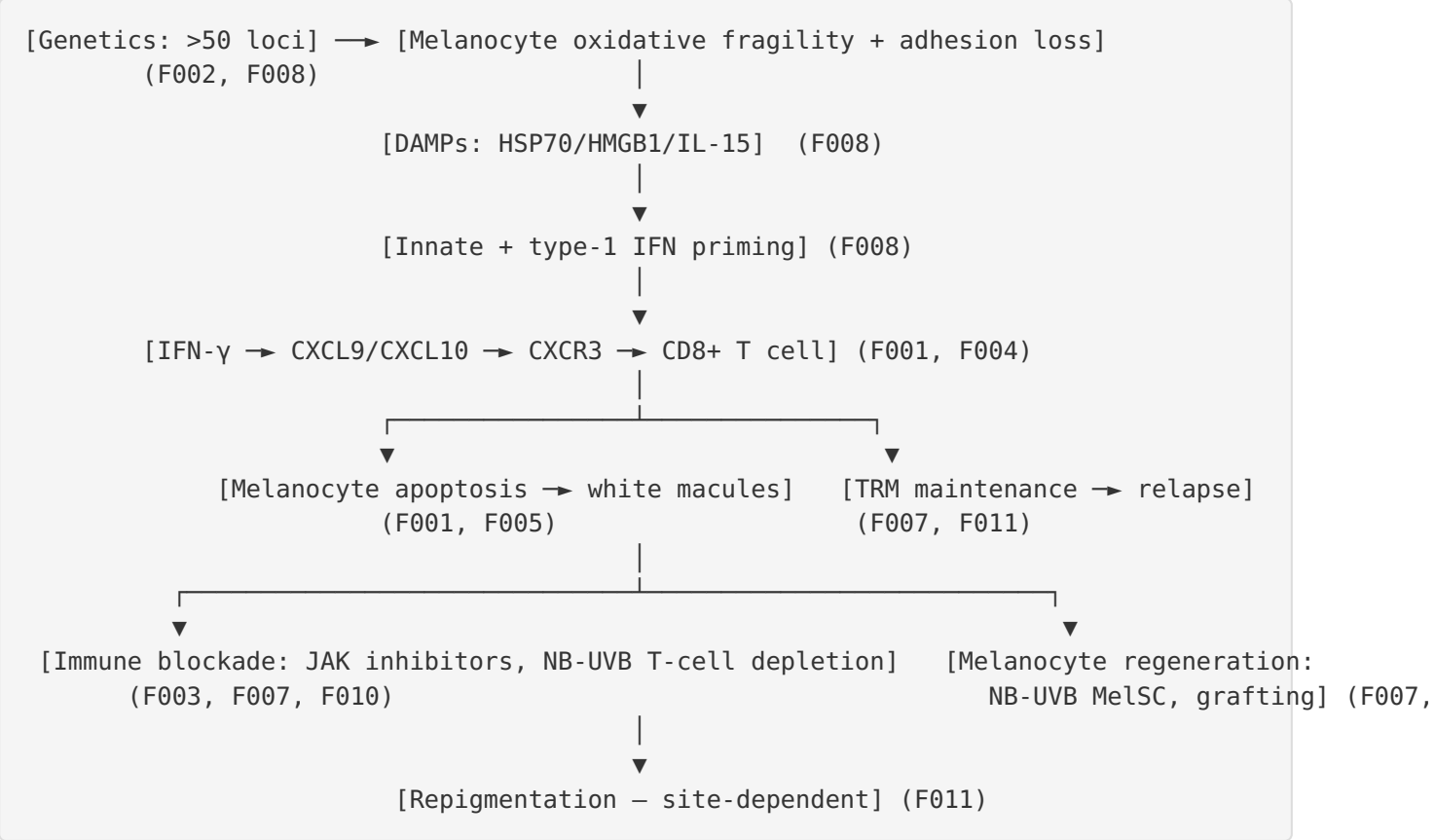
Model	Type	Key features / recapitulation	Evidence
Monobenzone-induced C57BL/6 mouse	Chemical/ environmental	Oxidative-stress- and CD8+ T-cell-mediated depigmentation; standard therapeutic testbed	PMID: 42230481; PMID: 40780471; PMID: 38542385
Melanocyte-specific CD8+ T-cell adoptive-transfer mouse	Genetic/ immunologic	IFN-γ signature, skin CXCL10, CXCR3 upregulation; TRM/Tcm maintain disease and relapse	PMID: 24523323; PMID: 30423329
H2O2-induced mouse	Oxidative stress	NPY/NF-κB-driven CD8+ infiltration	PMID: 42031917
Zebrafish; B16F10 & PIG1 cells	In vitro / lower vertebrate	Melanogenesis (MITF, TYR, cAMP/PKA/CREB)	PMID: 41720011

Applications: These models dissect the oxidative-stress→immune cascade, validate the CXCL10/JAK-STAT axis as a therapeutic target, and screen candidate drugs. The adoptive-transfer mouse specifically models TRM-maintained relapse: *"Tissue resident memory T cells*

(Trm) form in the skin in vitiligo and persist to maintain disease, as white spots often recur rapidly after discontinuing therapy" (PMID: 30423329). **Limitations:** mouse models are typically induced (not spontaneous polygenic), may not fully capture human HLA-restricted antigen specificity, disease chronicity, or the psychosocial dimension. **Resources:** MGI (mouse), ZFIN (zebrafish), Cellosaurus (PIG1, B16F10).

Mechanistic Model / Interpretation

Vitiligo is best understood as a **two-hit convergence disease**: a *genetically encoded melanocyte fragility* (hit 1) meets an *environmental/oxidative trigger* (hit 2), and the collision releases DAMPs that convert local stress into a systemic, self-sustaining autoimmune attack. The 12 confirmed findings assemble into a single, therapeutically actionable pathway:



The **IFN-γ–CXCL10–CXCR3** node is both the mechanistic hub and the clinical fulcrum: every effective modern therapy (topical/oral JAK inhibitors, NB-UVB, combination) suppresses this node, while durable cure is limited by **TRM persistence** — the single best explanation for the

field's central clinical frustration (relapse). Prognosis tracks the **follicular melanocyte reservoir**, which is why facial lesions (rich in follicles) outperform acral lesions (sparse follicles), and why leukotrichia is a bad sign.

Evidence Base

PMID	Contribution	Supports
42332186	Definition, 0.5–2% prevalence	F001
39739902	CD8+ T cells in early SV; SV mosaicism/fraction	F001, F005
28317533, 39890561	~50→>50 GWAS loci; immunity/oxidative/ melanogenesis	F002
23773036, 29152150	NLRP1 GCT haplotype ≈2× risk	F002
41884389	STAT2–TAPBP multi-omics axis	F002
36260792, 40156697, 41125994	Topical ruxolitinib efficacy & long-term safety	F003
24523323	CXCL9 vs CXCL10 roles; reversal by neutralization	F004
25521459	Simvastatin/STAT1 prevents & reverses	F004
22417114, 28685247	VGICC classification; prevalence/defining lesion	F005
42479635, 42299605	Childhood onset, thyroid comorbidity; ICI-vitiligo/melanoma	F006
42377206, 42415499, 42323047	NB-UVB MelSC migration + TRM depletion	F007
36154894, 35643735, 36345598, 36947026	DAMPs, adhesion loss, HSPA1L protective allele	F008
30423329, 42230481, 39199954	Mouse models; TRM; horse natural disease	F009
40518122, 42440041, 41454839, 40832814	Oral povorcitinib; JAK+NB-UVB; grafting	F010
41840918	Site as key prognostic factor; biomarkers	F011
41703718, 42087462	Clinical/RCM diagnostics; IFN-γ/CXCL biomarkers	F012

Limitations and Knowledge Gaps

1. **No primary dataset of origin.** This report synthesizes published aggregate/disease-level evidence rather than analyzing a raw patient dataset; effect sizes are quoted from source studies.
2. **TRM eradication remains unsolved.** No approved therapy durably eliminates skin-resident memory T cells; relapse biology (IL-15/IL-15R, TRM survival) is an open target.
3. **Predictive biomarkers are exploratory.** CXCL10/Th2 signatures show promise but lack prospective validation and standardized cutoffs.
4. **Genetic risk is incompletely explained.** >50 loci account for only part of heritability; gene–environment and epigenetic contributions are underquantified; monozygotic-twin discordance is unexplained mechanistically.
5. **Acral disease is refractory.** The follicular-reservoir hypothesis explains but does not solve poor acral repigmentation.
6. **Segmental vitiligo mechanism** (somatic mosaicism vs neuronal) is not definitively resolved.
7. **Model limitations.** Induced mouse models may not capture human HLA-restricted antigen specificity, chronicity, or psychosocial burden.

Proposed Follow-up Experiments / Actions

1. **TRM-targeted therapy trials:** Test IL-15/IL-15Rβ (CD122) blockade or JAK inhibitors specifically for durable, relapse-free maintenance after repigmentation.
2. **Prospective biomarker validation:** Validate serum/skin CXCL10 (and Th2 profiles) as predictive/response biomarkers in a prospective multicenter cohort with standardized thresholds.
3. **Acral-specific regeneration strategies:** Combine melanocyte-stem-cell mobilizers (Wnt/PKA-CREB agonists; PMID: 41720011) with immune blockade and grafting for acral lesions.
4. **Genotype-guided precision medicine:** Correlate HLA/NLRP1/TAPBP genotypes with JAK-inhibitor response to enable stratified treatment.
5. **Systematic thyroid & autoimmune screening protocol:** Formalize periodic thyroid function/antibody screening in vitiligo care pathways (PMID: 42479635).

6. **Head-to-head and combination RCTs:** Directly compare topical ruxolitinib vs NB-UVB vs their combination, and oral vs topical JAK inhibitors, with QoL endpoints.
7. **Neuro-immune axis exploration:** Investigate NPY2R antagonism and vagus-nerve stimulation (PMID: 42031917; PMID: 38542385) as adjuncts targeting stress-driven flares.

Report compiled from 12 confirmed findings across 53 reviewed papers spanning genetics, immunology, clinical trials, diagnostics, and comparative/model biology. Evidence source types span human clinical (GWAS, RCTs, cohorts), model organism (mouse, horse, zebrafish), and in vitro (melanocyte/keratinocyte) studies.
