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Primer

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Vitiligo

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Abstract

Vitiligo is an acquired autoimmune depigmenting disorder that affects approximately 0.36% of the global population and presents in three forms based on lesion distribution: non-segmental, segmental and mixed vitiligo. Beyond its visible impact on the skin, vitiligo deeply affects mental well-being and quality of life. The pathogenesis of non-segmental vitiligo is influenced by genetic polymorphisms that are linked to immune response and melanogenesis pathways, whereas environmental factors contribute to disease onset. Diagnosis is generally clinical, with laboratory tests or biopsies rarely required. Melanocyte loss involves mechanisms, such as cellular stress, innate immune activation and adaptive immune responses, that specifically target melanocytes, with a central role for tissue-resident memory T cells. This cascade ultimately leads to the depletion of epidermal melanocytes and impairs melanocyte stem cell regeneration. Clinical management emphasizes shared decision-making with three primary objectives: halting depigmentation, initiating repigmentation and sustaining pigment restoration. Signs of active disease help clinicians to identify patients in need of intervention. Treatments approved in the past 2 years offer potential for reversing disease progression, and emerging therapies targeting key pathways to modulate immune activation and stimulate melanocyte regeneration and differentiation are being tested in clinical trials.

Sections

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Introduction

Vitiligo is an acquired, chronic autoimmune depigmenting disorder affecting approximately 0.36% of the global population[1]. The hallmark of vitiligo is the loss of melanocytes, driven primarily by the activation of immune cells in genetically predisposed individuals. The condition affects both sexes equally, with no statistically significant differences in incidence based on Fitzpatrick skin type or ethnicity[2].

In the most recent expert recommendations published in 2023 by the international Vitiligo Task Force[3], three types of vitiligo are defined: non-segmental, segmental, and unclassified or undetermined vitiligo (Table 1). There was agreement among Task Force members to use the term 'vitiligo (non-segmental)' to replace the previous umbrella term 'vitiligo', which encompassed all forms of the disease except for segmental vitiligo; in this Primer, we use the term 'non-segmental vitiligo'. Non-segmental vitiligo is characterized by white skin patches, often symmetrical, which tend to expand over time. Segmental vitiligo refers to a clinically unilateral segmental distribution of depigmented lesions. The co-occurrence of segmental vitiligo and non-segmental vitiligo is referred to as mixed vitiligo. Unclassified or undetermined vitiligo is characterized by focal disease or isolated mucosal involvement[4].

Vitiligo imposes a substantial disease burden, as is evident from its considerable impact on the quality of life of affected individuals. Several objective scoring systems and patient-reported outcomes are used to assess disease severity. Furthermore, distinguishing between active and stable disease is crucial for management, and various signs of disease activity have now been identified.

Although vitiligo remains challenging to treat, advances in the understanding of its pathophysiology have led to the development of targeted therapies. Some, such as topical ruxolitinib (an inhibitor of JAK1 and JAK2), have already received regulatory approval from the FDA and EMA, whereas others, including systemic JAK inhibitors and biologics, are under clinical investigation. Clinical management emphasizes shared decision-making with three primary objectives: halting depigmentation, initiating repigmentation and maintaining pigment restoration.

In this Primer, we review the current knowledge of vitiligo, including its epidemiology, pathophysiology, clinical features, diagnosis, screening, management and effect on quality of life. We also discuss established treatment recommendations and explore how emerging insights into vitiligo pathophysiology are driving the development of novel targeted therapies.

Epidemiology

Prevalence and incidence

A 2024 systematic review of 71 studies, which used a Bayesian hierarchical linear mixed model, estimated that the global lifetime prevalence of physician-diagnosed vitiligo is 0.36% (95% credible interval (CrI) 0.24–0.54), affecting approximately 28 million people worldwide based on 2022 population data[1]. The prevalence is higher in adults (0.67%) than in children (0.24%), reflecting an accumulation of cases with age, and vitiligo affects male individuals and female individuals equally. Geographically, the prevalence of physician-diagnosed vitiligo shows moderate variation, ranging from 0.23% (95% CrI 0.14–0.38) in East Asia to 0.52% (95% CrI 0.33–0.82) in South Asia and 0.52% (95% CrI 0.28–1.07) in Central Europe[1] (Fig. 1). These estimates are derived from studies conducted in broad populations with substantial ancestral admixture, rather than in genetically defined groups.

However, population-based survey data indicate that the true prevalence might be considerably higher. A 2022 survey of over 35,000 adults in Europe, Japan and the USA found an overall prevalence of 1.3%, comprising diagnosed cases (0.6%), undiagnosed cases (0.4%) and those with vitiligo signs (0.3%)[5]. These data suggest that a

Table 1 | Modified classification and consensus nomenclature for vitiligo

Type	Subtype	Characteristics
Vitiligo (non-segmental)	Acrofacial	Depigmented macules limited to the distal extremities (hands and feet) and/or face and/or periorifical sites. Can progress to other body sites
	Mucosal (more than one mucosal site)	Oral and/or genital mucosae Can occur in generalized vitiligo or as an isolated condition
	Generalized	Bilateral, often symmetrical depigmented macules that occur in a random distribution over the entire body
	Universal	Complete or nearly complete skin depigmentation (80–90% of the body) Usually preceded by generalized vitiligo, gradually progresses to complete or near-complete skin and hair depigmentation
	Mixed (associated with segmental vitiligo)	First segmental lesions followed by bilateral lesions
	Rare variants	Vitiligo punctata: multiple pea-sized depigmented macules Vitiligo minor: multiple hypopigmented macules Follicular vitiligo: whitening of the hair with limited skin involvement
Segmental vitiligo	Unisegmental, bisegmental or plurisegmental	Depigmented macules that appear on one side or segment of the body (for example, dermatomal distribution) Usually stabilizes after a short period of progression Onset at an early age and can be associated with early whitening of the hair in the affected area
Undetermined/ unclassified vitiligo	Focal	Small, isolated patch, which has not evolved into non-segmental vitiligo after a period of at least 2 years and does not fit into a segmental distribution
	Mucosal	One mucosal site in isolation

Classification adapted from ref. 3.

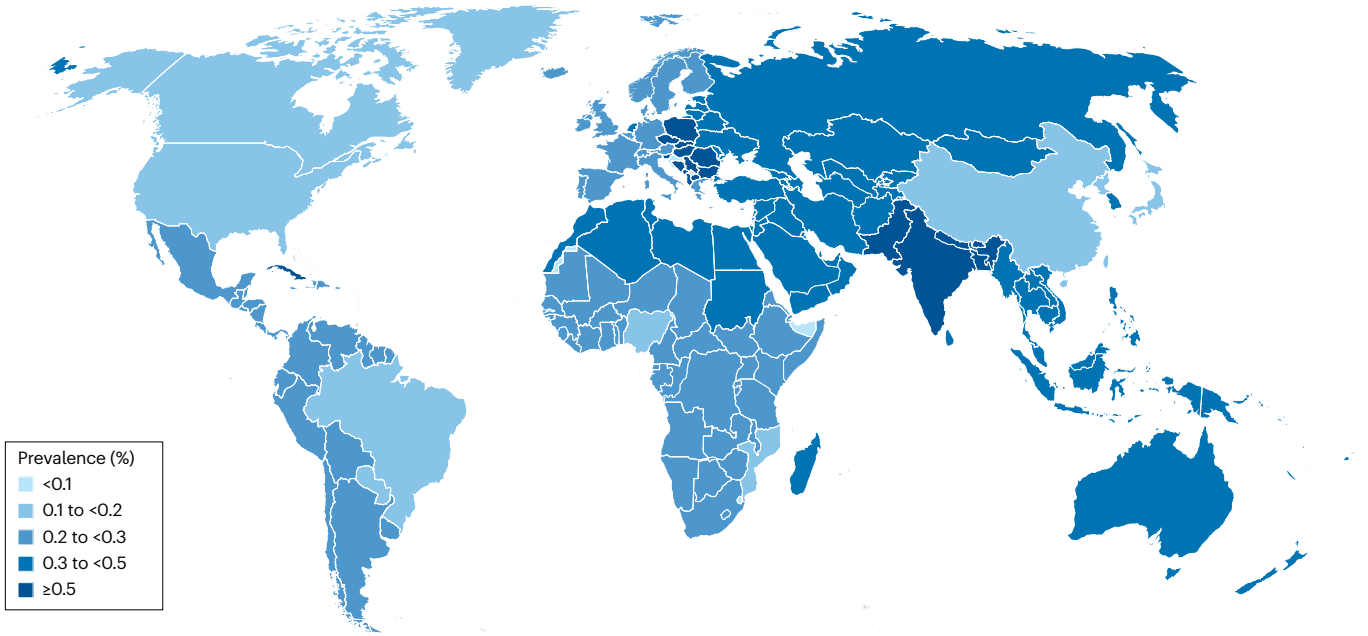


Fig. 1 | Lifetime prevalence of vitiligo. Physician-diagnosed cases for the general population for all ages are depicted. Reprinted with permission from ref. 1, Elsevier.

substantial proportion of vitiligo cases remain undiagnosed, a finding supported by a US-based study that estimates that up to 40% of adult vitiligo might be undiagnosed[6]. This under-reporting might stem from misconceptions that vitiligo is merely a cosmetic concern rather than a well-characterized autoimmune disease with major associated systemic comorbidities and a profound psychosocial impact.

Complementing prevalence data, a 2024 UK population-based cohort study of 9,460 individuals estimated a cumulative lifetime incidence of vitiligo of 0.92% by 80 years of age[7]. This study also highlighted considerable disparities across ethnic groups, with a lifetime incidence of 3.58% in individuals of Asian ethnicity and 2.18% in individuals of Black ethnicity, compared with 0.73% in white individuals.

Age of onset

Vitiligo can develop at any age, although onset most often occurs in childhood or early adulthood. Until 10 years ago, most studies indicated that approximately 50% of patients develop vitiligo by 20 years of age, with most cases (70–80%) manifesting by 30 years of age[8]. A 2019 study suggests that the age distribution of vitiligo onset follows a bimodal pattern, with one-third of patients experiencing early-onset disease (average age at onset of 10.3 years) and the remaining two-thirds developing late-onset disease (average age at onset of 34.0 years)[9]. Segmental vitiligo tends to have an earlier onset than non-segmental vitiligo (median age at onset of 14 years)[10]. The clinical features of vitiligo vary based on age of onset. Patients with adult-onset vitiligo show stronger associations with thyroid disease, stress as a triggering factor and autoimmune conditions, whereas childhood-onset vitiligo correlates with family history of vitiligo and the Koebner phenomenon[11] (the appearance of new lesions at sites of injury or trauma). Of note, very early-onset disease occurring before 3 years of age progresses more rapidly and affects a larger body surface area compared with later-onset disease[12]. Finally, a study conducted in 2019 showed that, between 1970 and 2004, the age of onset for vitiligo more than doubled, indicating a shift from paediatric to adult cases and pointing to a potential environmental trigger[13].

Risk factors

Genetic predisposition. Vitiligo risk is strongly influenced by family history, with a reported prevalence among first-degree relatives of 7–20% across various studies[14–16]. Family clustering and twin studies demonstrate that genetic factors account for approximately 80% of the risk of developing vitiligo[17,18]. Genome-wide association studies have provided substantial insight into the molecular underpinnings of the disease, identifying more than 50 susceptibility loci (Table 2). These loci predominantly comprise genes involved in immune regulation (for example, antigen presentation and T cell signalling) and melanocyte biology, and their considerable overlap with susceptibility loci for other autoimmune diseases indicates shared genetic pathways[17,18]. Polygenic risk scores derived from these genetic variants show that increased genetic burden correlates with earlier disease onset[19]. However, genetic predisposition alone does not determine vitiligo development, as is evident from monozygotic twin studies, which find concordance rates of only 23%, indicating that environmental factors have a crucial role in disease manifestation despite identical genetic backgrounds[20].

Inverse relationship with skin cancer. Epidemiological studies consistently show that patients with vitiligo have a lower risk of skin cancer compared with the general population. This protective effect applies to both melanoma and non-melanoma skin cancers. Multiple large cohort studies from the UK, Netherlands, Sweden, Israel and Italy have independently observed a reduced risk of melanoma in individuals with vitiligo[21–25]. Similarly, the risk for non-melanoma skin cancers is also markedly reduced, an observation supported by a systematic review and meta-analysis[26]. This inverse association is supported by genetic data, as several vitiligo-associated variants are linked to reduced

Table 2 | Vitiligo susceptibility loci

Locus	Gene symbol	UniProt name	Potential role in vitiligo	Refs.
1p13.2	*PTPN22*	Tyrosine-protein phosphatase non-receptor type 22	T cell signalling	206
1p31.3	*FOXD3*	Forkhead box protein D3	Neural crest and melanoblast regulator	207
1p36.23	*RERE*	Arginine-glutamic acid dipeptide repeats protein	Transcription co-repressor expressed in lymphoid cells	208
2q24.2	*IFIH*	Interferon-induced helicase C domain-containing protein 1	Innate immune response to viral infection	209,210
2q33.2	*CTLA4*	Cytotoxic T lymphocyte protein 4	CD80-mediated and CD86-mediated T cell inhibition	211,212
3p13	*FOXP1*	Forkhead box protein P1	Essential for early B cell development	213
3q13.33	*CD80*	T lymphocyte activation antigen CD80	T cell priming by B cells, T cells and dendritic cells	210
3q28	*LPP*	Lipoma-preferred partner	Potential transcription co-activator	208
4p16.1	*CLNK*	Cytokine-dependent haematopoietic cell linker	Positive regulator of mast cells	210
5q22.1	*TSLP*	Thymic stromal lymphopoietin	A cytokine alarmin capable of activating skin dendritic cells to promote a T helper 2 immune response	212
6p22.1	*HLA-B*	Human leukocyte antigen B (HLAB)	Peptide antigen presentation	208
	HLA-C	Human leukocyte antigen C (HLAC)	Peptide antigen presentation	208
6p21.32	*HLA-DRB1*	Human leukocyte antigen DRB1	Peptide antigen presentation	208
	HLA-DQA1	Human leukocyte antigen DQA1	Peptide antigen presentation	208
6Q15	*BACH2*	Transcription regulator protein BACH2	Transcription activator or repressor with roles in B cell maturation and differentiation and in the balance between effector and regulatory T cells	210
10p15.1	*IL2RA*	Interleukin-2 receptor subunit-α	IL-2-dependent T cell activation	208
10q25.3	*CASP7*	Caspase 7	Executioner protein in apoptosis	210
11p13	*CD44*	CD44 antigen	Regulator of T cell activation, migration and survival	210
11q14.3	*TYR*	Tyrosinase	Melanogenesis regulator	208
11q21	Gene desert	Not applicable	*TYR* regulator	208
12q13.2	*IKZF4*	Zinc finger protein Eos	Transcription factor that promotes the function of regulatory T cells	210
14q12	*GZMB*	Granzyme B	Protease that mediates cytotoxic lymphocyte-induced apoptosis	208
15q12-13-1	*OCA2*	P protein	Melanosomal membrane transporter	210
16q24.3	*MC1R*	Melanocortin 1 receptor	Melanogenesis regulator	210
17p13.2	*NLRP1*	NACHT, LRR and PYD domains-containing protein 1	IL-1β-mediated innate immune response	207,214,215
22q12.1	*XBP1*	X-box-binding protein 1	Major histocompatibility complex class II regulator	212
22q12.3	*C1QTNF6*	Complement C1q tumour necrosis factor-related protein 6	Immune response to light-induced apoptosis	208
22q13.2	*TOB2*	Protein TOB2	Cell cycle progression inhibitor, regulator of T cell tolerance	210
Xp11.23	*FOXP3*	Forkhead box protein P3	T cell activity and development	212

Vitiligo susceptibility loci are reviewed in refs. 15,17.

melanoma risk[27]. A potential explanation for this phenomenon is that the immune hyperactivity driving vitiligo might enhance antitumour surveillance against melanocytes, thereby providing protection against melanoma[27,28].

Environmental factors. Physical trauma to the skin is a well-known trigger for new lesions in individuals with active diseases — a process known as the Koebner phenomenon. This phenomenon is a clinical sign of underlying immune activity, with approximately 34.1% of patients reporting trauma-induced lesions[29]. Furthermore, exposure to some phenolic compounds can trigger vitiligo in predisposed individuals. This chemical-induced vitiligo, often first noted as cases of occupational vitiligo, can be caused by agents such as monobenzone, 4-tert-butylphenol and rhododendrol, which are found in some industrial products, resins and skin-lightening creams[30]. These chemicals are thought to act as tyrosine analogues, inducing melanocyte-specific stress and triggering an autoimmune response[30]. The resulting depigmentation is clinically and histologically indistinguishable from non-segmental vitiligo and can spread beyond the initial sites of contact. For all types of vitiligo, psychological stress frequently precedes initial depigmentation or disease flare-ups in about 50% of patients by disrupting neuroendocrine–immune balance[31,32].

Microbiota. The microbiota also influences vitiligo pathogenesis. Patients with vitiligo demonstrated alteration in both the cutaneous and gut microbiota, particularly depletion of commensal bacteria such as *Bifidobacterium* spp. and *Bacteroides* spp. in lesional skin[33–35]. Furthermore, research has revealed a connection between skin dysbiosis, mitochondrial damage in melanocytes and activation of the adaptive immune response in patients with vitiligo[33]. Environmental factors might also contribute to skin dysbiosis; for example, in vitro experiments with cultured keratinocytes (and confirmed with skin biopsy samples from patients) suggest that house dust mites might serve as an external source of pathogen-associated molecular patterns that induce melanocyte loss in patients with vitiligo[36]. In addition, alterations in gut microbiota metabolites, such as an overproduction of pro-inflammatory kynurenine pathway metabolites and a reduction in anti-inflammatory secondary bile acids and short-chain fatty acids, have been linked to the pro-inflammatory T cell responses that are characteristic of vitiligo[37].

Association with autoimmune comorbidities

The systemic nature of vitiligo is underscored by its strong association with other autoimmune diseases (Table 3), which stems from shared genetic and immunological pathways. The most common comorbidity is autoimmune thyroid disease, with a prevalence of 15–25% in patients with vitiligo[38,39]. Other conditions that are frequently associated with vitiligo include alopecia areata (3–8%), psoriasis (2–5%) and atopic dermatitis (10–30%)[40–43].

The autoimmune process in vitiligo also affects melanocytes in other organs, leading to an increased incidence of ocular issues and sensorineural hearing abnormalities, which are reported in 12–38% of patients[44–46]. In addition, vitiligo has a profound psychiatric impact, with high rates of depression and anxiety in patients with vitiligo (12–50%)[47–49]. These psychiatric conditions are increasingly viewed as integral comorbidities with potential biological links and not just as psychosocial reactions[50]. This web of associations highlights the need for clinicians to screen for these conditions, especially thyroid dysfunction, as part of comprehensive patient care.

Mechanisms/pathophysiology

Depigmentation in vitiligo results from the loss of melanocytes, although vitiligo does not only affect melanocytes. Genetic susceptibility creates a background of vulnerability, particularly in melanocytes, which are intrinsically prone to oxidative stress. Cellular damage then triggers activation of innate immune responses, which in turn drive the expansion of autoreactive adaptive immunity. The persistence of immune memory, coupled with failures in immune tolerance, sustains chronic depigmentation and underlies disease relapse. Of note, attempts at melanocyte regeneration are often thwarted by the inflammatory environment.

Genetic susceptibility and intrinsic melanocyte vulnerability

As discussed above, vitiligo has a strong genetic component, with genome-wide association studies identifying loci affecting pathways related to oxidative stress responses, immune regulation and melanocyte biology. Polymorphisms in antioxidant genes, including those encoding catalase and glutathione peroxidase, are associated with reduced antioxidant capacity in patients with vitiligo, thereby predisposing melanocytes to redox imbalance[51,52]. Variants in immune regulatory genes, such as HLA class I and class II alleles

Table 3 | Key comorbidities associated with vitiligo

Category	Comorbidity	Strength of association	Prevalence in vitiligo	Clinical implications	Refs.
Systemic autoimmune diseases	Thyroid diseases (Hashimoto's disease, Graves' disease)	Strong	~15–25%	Regular screening for thyroid function and antibodies is the standard of care	38,39,216
	Type 1 diabetes mellitus	Moderate	~1–4%	Enquire about related symptoms, especially with family history	39,217
	Rheumatoid arthritis	Low	~1–3%	Shared inflammatory pathways	218
	Atrophic gastritis	Moderate	~2–3%	Consider screening in patients with suggestive symptoms (for example, macrocytic anaemia, gastrointestinal complaints)	219,220
	Connective tissue diseases (for example, systemic lupus erythematosus)	Low	~0.32%	Awareness of overlapping autoimmunity; screen based on clinical suspicion	220,221
Associated skin conditions	Alopecia areata	Strong	~3–8%	Shared genetic loci and T cell-mediated immune pathways	217
	Psoriasis	Moderate	~2–5%	Reflects shared genetic loci and overlapping T cell-mediated inflammatory pathways	41
	Atopic dermatitis	Strong	~10–30%	Highlights complex immune interplay, with overlapping type 1 and type 2 pathways	222
Ocular and auditory systems	Uveitis, hearing abnormalities	Moderate to strong	Uveitis: ~1–8% Hearing abnormalities: ~12–37%	Melanocytes exist in the eye and inner ear; their destruction can cause symptoms	44–46
Psychiatric conditions	Depression, anxiety	Strong	Depression: ~12–50% Anxiety: ~21–50%	Quality-of-life assessment and psychological support are key elements of care	47–49

Table 4 | Potential sources of ROS in vitiligo pathogenesis

Category	Source	Pathophysiological role	Refs.
Exogenous triggers	Ultraviolet radiation (UVA and UVB), X-rays	Causes direct cellular damage and biopterin photooxidation, leading to p53 activation and increased cellular stress	57,69,72
	Chemical exposure (for example, phenols and quinols)	Induces direct melanocyte toxicity and ROS generation, acting as a known environmental trigger for occupational vitiligo	30
Endogenous cellular processes	Mitochondrial electron transport chain	A major source of cellular ROS, which causes mitochondrial dysfunction, leading to mtDNA release that activates the cGAS–STING pathway and inflammasomes	62,63,223
	Melanogenesis (for example, tyrosine hydroxylase)	Generates reactive intermediates (for example, quinones) that contribute to the intrinsic vulnerability and stress of melanocytes	53,57
	Enzymatic activity (for example, NADPH oxidase, xanthine oxidase)	Produces superoxide radicals and other ROS, which contribute to the overall oxidative stress state in vitiligo skin	56,57
Inflammatory signalling	Cytokines (for example, TNF)	Induces ROS production in keratinocytes and fibroblasts, forming part of the self-amplifying inflammatory feedback loop	67,70
	Growth factors (for example, TGFβ, EGF)	Alters cellular signalling and stress responses, contributing to the complex inflammatory microenvironment	57,71

mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

and immune-checkpoint regulators, further contribute to the loss of tolerance and enhanced autoreactivity.

Melanocytes are intrinsically vulnerable to oxidative stress because melanin synthesis itself generates reactive oxygen species (ROS). Tyrosinase-catalysed oxidation of tyrosine to DOPA and then dopaquinone inevitably produces ROS[53]. This physiological challenge is usually counterbalanced by antioxidant systems but, in genetically predisposed individuals, this balance is skewed, priming melanocytes for damage. Thus, genetic susceptibility and intrinsic vulnerability of melanocytes form the foundation upon which environmental and cellular stressors can initiate disease.

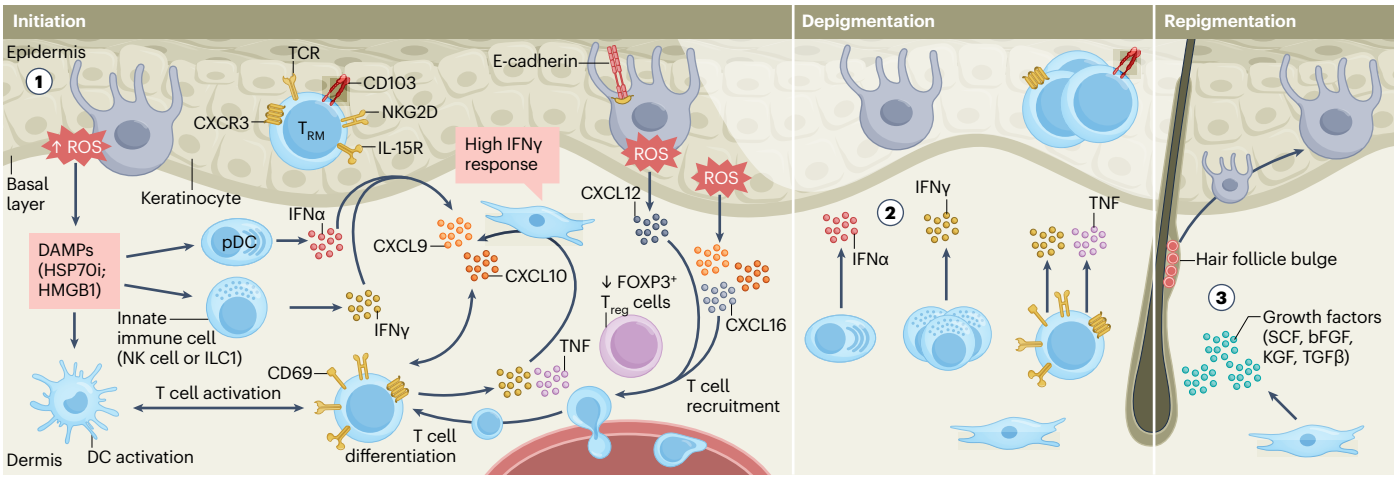
Cellular and oxidative stress

Elevated ROS have been documented in both depigmented lesions and clinically normal skin of patients with vitiligo (Table 4), affecting melanocytes, keratinocytes, fibroblasts and lymphocytes[54,55] (Fig. 2). This systemic redox imbalance causes lipid, protein, and DNA damage and weakens local antioxidant defences. Although transcription of antioxidant enzyme genes, such as *CAT* (encoding catalase) and *SOD2*, is chronically increased in vitiligo melanocytes, protein levels remain low, suggesting that turnover of these proteins is rapid and results in impaired antioxidant function[56,57].

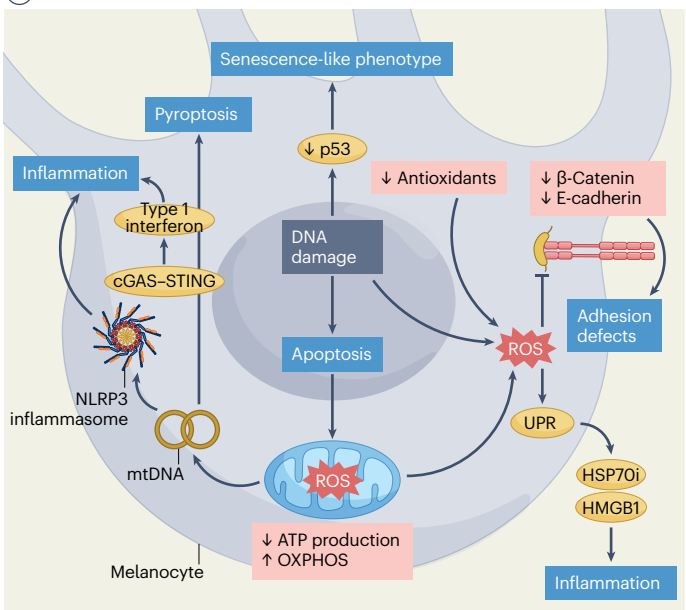
Mitochondrial dysfunction is a central feature of this stress state. In vitiligo, melanocytes and fibroblasts exhibit mitochondrial membrane depolarization, whereas keratinocytes display hyperpolarization[58] reminiscent of that in immune cells in autoimmune diseases such as type 1 diabetes mellitus[59] and systemic lupus erythematosus[60]. In autoimmune diseases, mitochondrial hyperpolarization and depletion of ATP, when associated with oxidative disequilibrium, function to induce T cell activation and apoptosis, thereby contributing to autoimmunity[60,61]. Enlarged mitochondria in melanocytes could represent a compensatory adaptation, although damaged mitochondria release mitochondrial DNA into the cytosol, where it activates cGAS–STING and inflammasome pathways, fuelling inflammation and pyroptosis[62,63] (a highly inflammatory form of programmed cell death). Impaired mitophagy in vitiligo exacerbates the accumulation of dysfunctional mitochondria, while reduced expression of mitochondrial homeostasis genes, such as *SIRT3*, links mitochondrial dysfunction to apoptosis, contributing to melanocyte loss[64–66].

Oxidative stress has additional consequences beyond cell death. ROS induce the unfolded protein response, leading to the release of damage-associated molecular patterns (DAMPs), which promote inflammation[67]. Inflammatory signalling through IFNγ disrupts melanocyte adhesion through activation of MMP9, which cleaves E-cadherin[68], and impairs regenerative WNT–β-catenin signalling, thereby compromising repigmentation and promoting senescence[69–71]. Senescent melanocytes express p53 and adopt a senescence-associated secretory phenotype by the release of inflammatory cytokines and chemokines

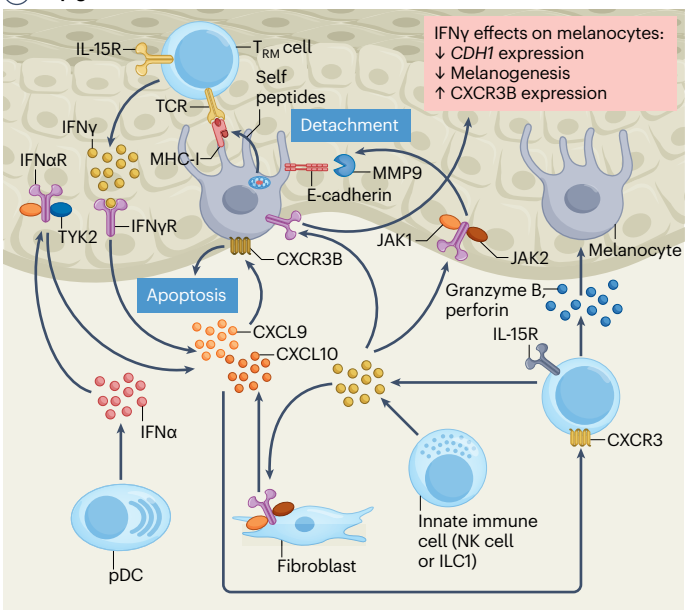
Fig. 2 | Pathogenesis of vitiligo. Initiation (1): oxidative stress in vitiligo melanocytes induces DNA damage, mitochondrial dysfunction, mitochondrial DNA (mtDNA) release, and activation of innate immune pathways (cGAS–STING, inflammasomes), leading to senescence-like phenotype or cell death and the release of damage-associated molecular patterns (DAMPs; for example, HSP70). These signals activate the innate immune system, including type 1 innate lymphoid cells (ILC1s), which produce IFNγ, and plasmacytoid dendritic cells (pDCs), which produce IFNα. In response, epidermal cells and IFNγ-responsive fibroblasts produce pro-inflammatory chemokines such as CXCL9 and CXCL10, leading to local activation of autoreactive tissue-resident memory T (T_{RM}) cells and the recruitment of additional lymphocyte populations that produce IFNγ and TNF. Lesional skin is characterized by insufficient regulatory T (T_{reg}) cell-mediated immune suppression. Depigmentation (2): melanocytes expressing the CXCR3B isoform are targeted by CXCL10. IFNγ and TNF stimulate keratinocytes to produce MMP9, which cleaves E-cadherin, contributing to melanocyte detachment and loss. Autoreactive T_{RM} cells in vitiligo require IL-15 for their maintenance in the epidermis. Repigmentation (3): ultraviolet (UV) light exposure induces the production of growth factors, such as stem cell factor (SCF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF) and TGFβ. Melanocytes and their precursors are stimulated to migrate into depigmented areas and produce pigment. This process depends on the activation of the WNT signalling pathway. DC, dendritic cell; HSP70i, inducible HSP70; MHC-I, major histocompatibility complex class I; NK, natural killer; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCR, T cell receptor; UPR, unfolded protein response.



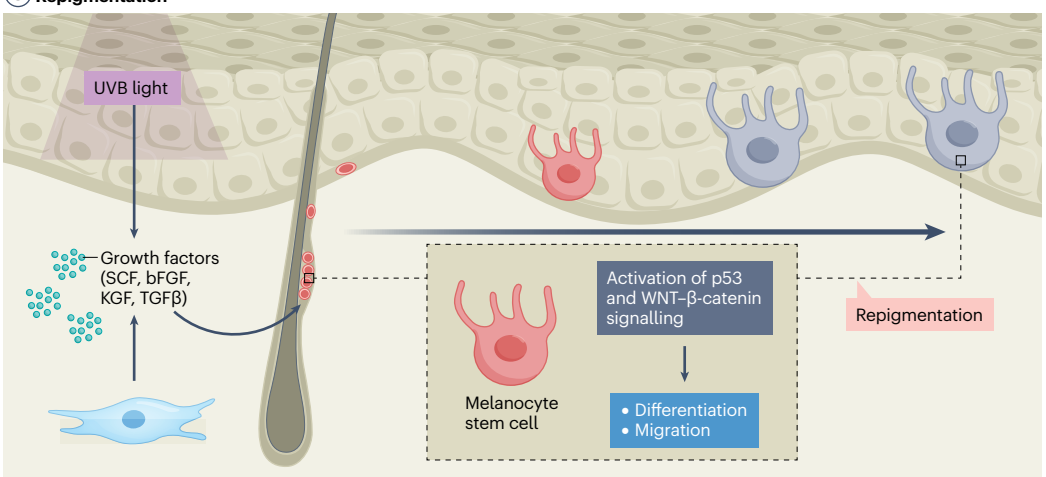
1 Initiation



2 Depigmentation



3 Repigmentation



that recruit and activate immune cells, such as $CD8^+$ T cells, promoting melanocyte-directed immune response[69]. ROS also interfere with melanosome transfer to keratinocytes, thereby contributing to early depigmentation[72].

Several strategies to support antioxidant defence have been proposed to enhance vitiligo treatments. These approaches include oral or topical supplementation with vitamin C, vitamin E, coenzyme Q, and antioxidant enzymes such as catalase and superoxide dismutase[73,74]. Direct targeting of mitochondria with mitoquinone has also emerged as a potential strategy[75,76]. Together, oxidative stress has emerged as a multifaceted driver connecting genetic susceptibility, mitochondrial dysfunction, immune activation and defective melanocyte regeneration.

Innate immune activation

Vitiligo-affected skin shows infiltration of macrophages, dendritic cells, innate lymphoid cells and natural killer cells to the leading edge of lesional sites (Fig. 2). The oxidative and metabolic stress of melanocytes and surrounding cells initiates an innate danger response involving the release of DAMPs and, potentially, self-antigens in the local environment, which are sensed by innate immune cells. DAMPs, such as HMGB1 and inducible HSP70 (HSP70i), are elevated in vitiligo-affected skin, where they activate dendritic cells, promote secretion of chemokines (such as CXCL10, CXCL16 and CXCL8), and directly induce melanocyte apoptosis[77,78]. Inhibition of HSP70i leads to repigmentation in preclinical models, emphasizing its causal role[79].

Activated innate cells and stressed keratinocytes amplify inflammation. Plasmacytoid dendritic cells release IFNα, innate lymphoid cells produce IFNγ, and keratinocytes respond by secreting CXCL9 and CXCL10 (refs. 80,81). Oxidative stress activates the NLRP3 inflammasome via the redox-sensitive TRPM2 channel in keratinocytes, resulting in IL-1β release and enhanced production of CXCL10 and CXCL16 that attracts T cells[82]. Melanocytes themselves produce CXCL12, promoting recruitment of T cells and antigen-presenting cells[83].

Thus, innate immunity bridges the gap between cellular stress and adaptive autoimmunity. The cumulative signals establish a pro-inflammatory microenvironment that favours the recruitment and activation of autoreactive T cells and primes the skin for targeted melanocyte destruction.

Adaptive immunity and immune memory

The adaptive immune response represents a critical effector phase in vitiligo. Dendritic cells present melanocyte-derived antigens or as-yet unidentified auto-antigens to naive T cells, leading to the expansion of autoreactive $CD8^+$ T lymphocytes. These cells infiltrate the skin, guided by the CXCL9/CXCL10–CXCR3 axis and directly affect melanocyte loss through cytotoxic effects or the release of the type 1 cytokines IFNγ and TNF[84–87] (Fig. 2).

Effector mechanisms. $CD8^+$ T cells specific for melanocyte antigens have been identified in both non-lesional and peri-lesional skin of patients with vitiligo and can induce melanocyte apoptosis in non-affected skin in vitro[88,89]. These $CD8^+$ T cells also release IFNγ and TNF, which act on melanocytes directly and indirectly through their effects on keratinocytes and fibroblasts. IFNγ induces expression of the CXCR3B receptor by melanocytes, which are susceptible to apoptosis in response to CXCL10 (ref. 81). Together with TNF, IFNγ induces keratinocyte secretion of MMP9, which cleaves E-cadherin and causes melanocyte detachment from the epidermal basal layer[68]. Fibroblasts are key amplifiers of pro-inflammatory signalling, producing CXCL9 and CXCL10 in response to IFNγ and thereby reinforcing T cell recruitment[90].

Vitiligo should not be viewed merely as a local depigmenting disorder but rather as an autoimmune disease with systemic immune alterations. Circulating melanocyte-specific $CD8^+$ T cells are elevated in the blood of patients, especially in active disease, and express skin-homing markers, showing that the immune system is primed to target melanocytes throughout the body[89,91–93]. Although type 1 cytokines dominate the effector phase, altered circulating and skin-homing T cell subsets, including CLA^+ T cells that produce IFNγ and IL-13, have also been reported[94–96]. The expression of chemokines, such as CCL18, CCL5, CXCL12 and CXCL16, that attract diverse T cell subsets is increased in vitiligo lesions, and T cells in affected skin also produce type 2 cytokines, particularly IL-13, suggesting a possible, although still unstudied, contribution of type 2 cytokines in vitiligo pathogenesis[83,97–99].

Memory and chronicity. Importantly, the adaptive response becomes self-sustaining through tissue-resident memory T (T_{RM}) cells. Melanocyte-specific $CD8^+$ T_{RM} cells persist in lesional and peri-lesional skin and express CXCR3, NKG2D, and the IL-15 receptor chain CD122; CD49a expression defines a subset of T_{RM} cells that have a heightened cytotoxic potential[84–87]. T_{RM} cells (probably maintained by IL-15 and TGFβ) produce high levels of IFNγ and TNF, and together with recirculating T cells, they regulate melanocyte adhesion, mitochondrial metabolism and the pro-inflammatory state through JAK signalling to sustain the disease[84–87]. Targeting IL-15 or JAK signalling restores pigmentation in mouse models of vitiligo[87,100].

In summary, T_{RM} and recirculating T cells contribute to melanocyte loss and the chronicity of vitiligo. The crosstalk of these T cells with keratinocytes, melanocytes and fibroblasts amplifies inflammation, creating a vicious cycle involving interplay between cellular stress, innate sensing and adaptive effectors.

Dysregulated immune tolerance and checkpoint failure

In physiological conditions, regulatory T (T_{reg}) cells and immune checkpoints maintain immune tolerance in the skin. In vitiligo, both systems are impaired. T_{reg} cells are reduced in number and show functional defects in the blood and skin of patients with vitiligo[101,102]. These dysfunctional T_{reg} cells exhibit a T helper 1-like phenotype and impaired immunosuppression of $CD8^+$ T cells[103]. In mouse models of vitiligo, T_{reg} cells restrain $CD8^+$ T cell function, and their presence in the skin inversely correlates with the extent of depigmentation, emphasizing their role in slowing disease progression[104]. Effective localization of T_{reg} cells in skin requires two pathways, CCR6 and CCR4 for migration and CCR5 for positioning near autoreactive $CD8^+$ T_{RM} cells, both of which are defective in vitiligo[104].

Immune-checkpoint molecules on T_{RM} and effector T cells, such as PD1, CTLA4, LAG3 and TIM3, normally prevent excessive activation of these T cells. PD1, in particular, preserves immune tolerance in the skin by limiting $CD8^+$ T cell responses to cutaneous neoantigens[105]. In vitiligo, melanocytes fail to upregulate PDL1 in response to IFNγ, which makes them more susceptible to $CD8^+$ T cell-mediated destruction[106]. Blockade of PD1 in patients with melanoma frequently induces vitiligo-like depigmentation, highlighting the potential importance of PD1–PDL1 signalling in limiting depigmentation[107]. Conversely, PDL1 administration in a mouse model of vitiligo increases the abundance of T_{reg} cells in the skin and reverses depigmentation[108].

Consequently, the loss of immune regulation, both through inadequate T_{reg} cell function and ineffective immune-checkpoint signalling, removes crucial brakes on the adaptive immune response, allowing autoimmunity to persist and contributing to the chronicity of the disease. Strategies that aim to restore tolerance in the skin could represent a promising therapeutic approach for vitiligo.

Hidden alterations in clinically normal pigmented skin

Although research has traditionally focused on depigmented lesions, clinically unaffected skin in patients with vitiligo harbours considerable subclinical abnormalities[109–111]. Melanocytes from pigmented, non-lesional skin display intrinsic defects in adhesion, increased oxidative stress and mitochondrial dysfunction, which lead to the release of DAMPs[77,111–113]. Abnormal distribution of E-cadherin and the suprabasal localization of melanocytes have been reported in pigmented skin in patients with vitiligo, suggesting a possible intrinsic defect. However, E-cadherin cleavage can also occur in response to TNF-induced and IFNγ-induced MMP9 production by keratinocytes[68], a process that is particularly sensitive to the redox status[114]. Keratinocytes and fibroblasts from pigmented, non-lesional skin also exhibit elevated ROS and an enhanced capacity to secrete inflammatory mediators[115,116].

Transcriptomic studies of non-lesional skin have revealed upregulation of innate immune and type 1 cytokine pathways[117–119]. Melanocyte-specific $CD8^+$ T_{RM} cells are already present in non-affected skin and display a partially activated phenotype, whereas T_{reg} cells are reduced in number, although enriched for IL-10 and TGFβ expression compared with lesional skin, suggesting a compensatory attempt to restrain autoimmunity[87,101,117]. CCR5 expression by T_{reg} cells allows proximity to $CD8^+$ cells, potentially modulating their activity [96].

Collectively, these data suggest that clinically 'normal' pigmented skin is in fact in a 'pre-lesional' state that is characterized by subtle oxidative stress and immune activation. This finding supports the concept that immune attack precedes the development of visible lesions.

Melanocyte regeneration and repigmentation

Despite autoimmune attack, the skin retains some capacity for repair through melanocyte regeneration from stem cells, unlike in other autoimmune diseases, which are irreversible because they lack this possibility of regeneration. Repigmentation typically arises from the hair follicles, which possess melanocyte stem cells located in the bulge region. These cells are probably spared from autoimmune destruction because of the established immune privilege of the hair follicles, which tends to exclude inflammation, similar to other privileged organs such as the eyes, brain, testes and ovaries[120,121] (Fig. 2). Consequently, repigmentation manifests as perifollicular islands that form from the growth, migration and differentiation of melanocyte stem cells (the primary reservoir for repigmentation) into melanocytes. However, areas of skin without hair follicles, or where the hair has turned white, do not repigment effectively. Differentiated melanocytes at lesion margins seem to migrate short distances, but their regenerative potential is limited[120].

Exposure to ultraviolet (UV) radiation, particularly narrow-band UVB (NB-UVB), is used as a treatment for vitiligo. UV radiation damages DNA in keratinocytes, which induces p53 activation and expression of melanocyte growth factors, leading to melanocyte proliferation, migration and repopulation of the interfollicular epidermis[120]. WNT–β-catenin signalling is essential for melanocyte regeneration induced by UV light, as it drives the differentiation of melanocyte stem cells[122]. By contrast, impaired melanocytes from individuals with vitiligo are characterized by disrupted WNT signalling[123]. During the repigmentation process, melanocyte precursors in the follicle bulge show increased expression of *KCTD10* (encoding an E3 ubiquitin-protein ligase substrate recognition adaptor), *CTNNB1* (encoding β-catenin) and RHO GTPase genes (encoding intracellular signalling proteins that influence cytoskeletal

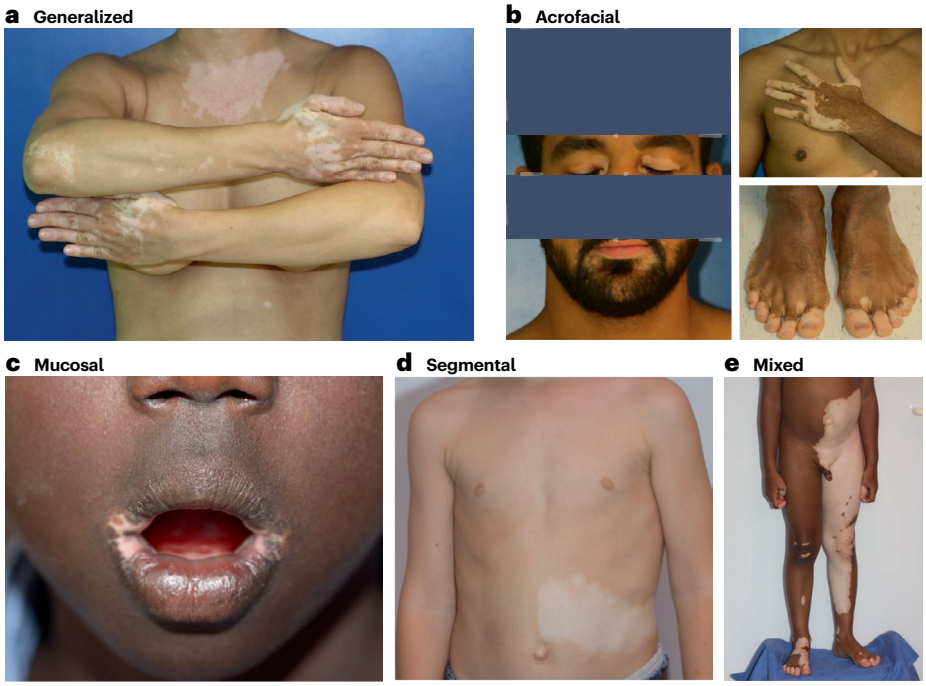


Fig. 3 | Clinical images of vitiligo. Non-segmental vitiligo subtypes include generalized (part **a**), mucosal (part **b**) and acrofacial (part **c**) vitiligo. Segmental vitiligo (part **d**). Mixed vitiligo is characterized by the coexistence of segmental vitiligo and non-segmental vitiligo over most of the body (vitiligo universalis) (part **e**).

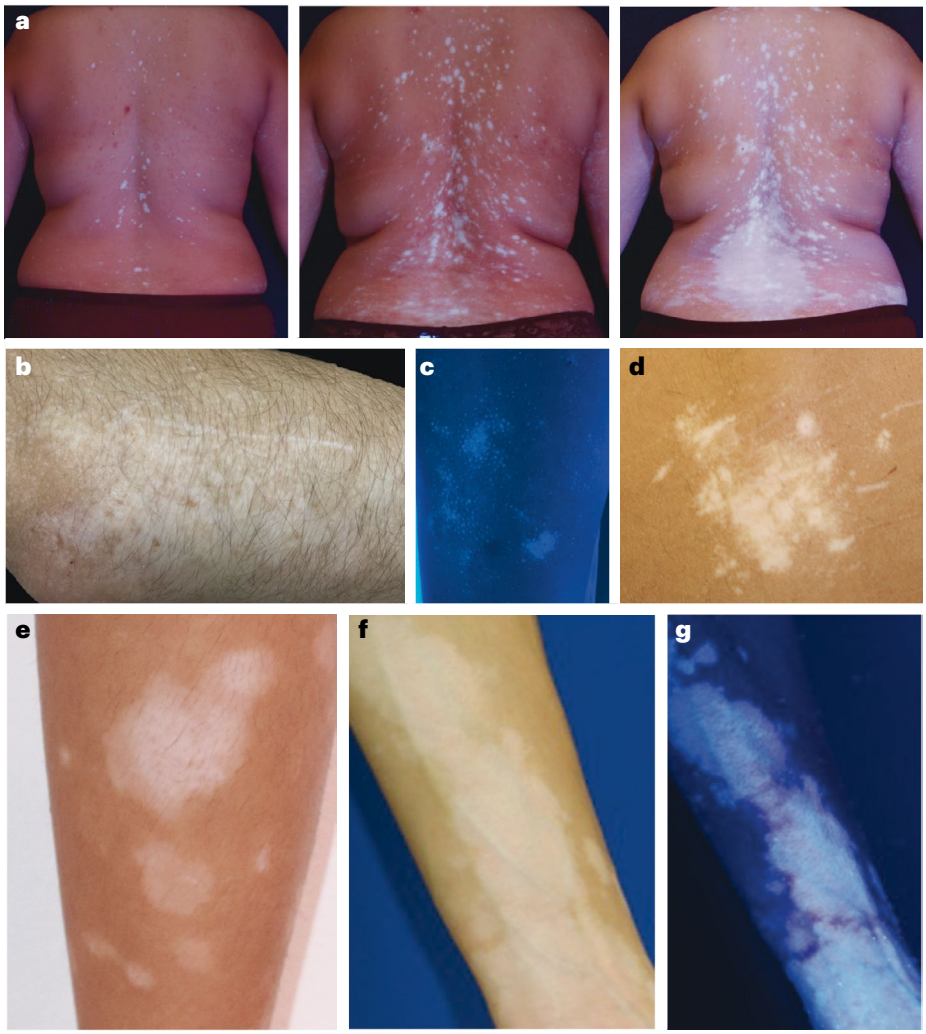


Fig. 4 | Clinical signs of disease activity. Progressive depigmentation occurring in a patient with active disease (part **a**). Confetti-like lesions under normal light (part **b**) and with a Wood lamp (part **c**). Koebner phenomenon type IIb (depigmentation induced by skin trauma) (part **d**). Trichrome areas of vitiligo lesions under normal light (parts **e** and **f**) and with a Wood lamp (part **g**).

dynamics, cell migration and cell cycle progression). These genes are known to have a role in pigmentation[124].

Therapeutic approaches increasingly aim to combine immune suppression with melanocyte regeneration. When melanocyte stem cell reservoirs are absent, transplantation of melanocytes and/or their precursors from other sites can restore pigmentation, provided that autoimmune attack is adequately controlled[125]. This finding underscores the importance of coupling regenerative strategies with interventions that target the upstream immune cascade.

Diagnosis, screening and prevention

The most recent international classification was published in 2024 by the international Vitiligo Task Force[3], and it recognizes three forms of vitiligo: segmental, non-segmental, and undetermined or unclassified vitiligo (Table 1). Diagnosis is based predominantly on physical examination and exclusion of differential diagnoses.

Clinical presentation

Clinically, vitiligo manifests primarily in two forms: segmental and non-segmental vitiligo (Fig. 3). Non-segmental vitiligo is the more prevalent type, typically presenting with bilateral, symmetrical depigmented lesions that commonly involve areas such as the face, hands, feet and body folds[3]. These lesions often expand over time. Segmental vitiligo typically presents as unilateral depigmented patches that follow a segmental distribution (for example, Blaschkoid distribution), tends to have an earlier onset than non-segmental vitiligo and stabilizes rapidly. The depigmented lesions in both types of vitiligo are usually asymptomatic (not associated with pruritic or scaly changes), well-demarcated, white in colour (Fig. 3), and can vary in size and shape. In some cases, the affected skin can exhibit poliosis, where the hair within the depigmented area turns white. Mucous membranes, including the lips and genitals, can also be involved.

Phases and signs of disease activity

The course of vitiligo typically alternates between phases of activity and stability. During active phases, new lesions appear and existing depigmented patches enlarge (Fig. 4a). By contrast, stable phases are marked by the absence of new lesions and no expansion of existing ones, often persisting for months or even years. However, assessing disease stability is not straightforward and requires a combination of patient history,

careful physical examination for clinical signs of activity and, ideally, sequential photographic documentation to confirm the absence of progression. Understanding the dynamic nature of vitiligo evolution is crucial for tailoring therapeutic strategies, as treatment approaches can differ considerably depending on whether the disease is active or stable. Visible clinical signs or indicators of disease activity are essential for clinical assessment and include several key features. One such sign is confetti-like depigmentation (Fig. 4b,c), characterized by numerous small, pinpoint white macules (a flat, circumscribed skin lesion area that is less than 1 cm in diameter and not elevated or depressed) that often appear in clusters. The Koebner phenomenon (Fig. 4d) is also linked to disease activity[126]. Two other clinical signs linked to active disease are hypochromic and inflammatory borders or areas. Hypochromic borders or areas represent partial depigmentation surrounding or within vitiligo patches and reflect an intermediate stage of pigment loss. Within this context, the term trichrome vitiligo has also been used referring to the presence of three skin tones that correspond to the extent of pigment loss: completely depigmented, hypopigmented and unaffected skin (Fig. 4e–g). Inflammatory borders are marked by erythema (redness) at the edges of lesions[3].

Objective assessment and patient-reported outcomes

Assessment of vitiligo relies on a combination of clinician-reported outcome measures (ClinROMs), patient-reported outcome measures (PROMs), and photography or digital analysis techniques to evaluate disease extent and activity. The effect of the disease on quality of life is assessed by validated PROMs. These methods ensure a comprehensive understanding of vitiligo progression and response to treatment. PROMs capture the patient's experience of vitiligo, including, for example, the perceived extent and psychosocial impact of the disease. The Self-Assessment Vitiligo Extent Score (SAVES)[127] allows patients to estimate the percentage of affected skin, providing a subjective counterpart to ClinROMs. Incorporating SAVES into standard assessment may facilitate shared decision-making and supports a more patient-centred treatment approach. There are also vitiligo-specific and general scores that provide a measure of the psychosocial and quality of life effects of vitiligo for affected individuals[128] (discussed later). For these impact-related tools, it can be useful to take skin colour into account, as is done in the Vitiligo Impact Patient Scale (VIPs)[129].

In the context of measurement instruments, it is important to consider the quality aspect (measurement properties such as validity, reliability and responsiveness) of a tool[128,130]. ClinROMs are standardized tools that are used by health-care professionals to assess aspects of the disease, for example, severity (including both extent and activity of vitiligo)[131]. Measures of depigmentation extent include the Vitiligo Area Scoring Index (VASI)[132] and the Vitiligo Extent Score (VES or VESplus)[133,134], both of which quantify the percentage of depigmented skin across different body regions[135]. To evaluate disease activity, the Vitiligo Signs of Activity Score (VSAS)[136] assesses clinical features of disease activity, such as confetti-like lesions and hypochromic borders, whereas the Vitiligo Disease Improvement Score (VDIS) and Vitiligo Disease Activity Score (VDAS) focus on lesion evolution over time, including repigmentation, the appearance of new macules or the expansion of existing depigmented patches[137].

Digital analysis techniques enhance the precision in assessing the extent of lesions[138–140]. Examination with a Wood lamp, a source of long-wave UV (UVA) light, remains an essential bedside tool for detecting early or subtle vitiligo lesions, particularly in individuals with lighter skin tones. Examination with a Wood lamp is also essential for assessing disease stability: a stable lesion appears white and sharply delineated, whereas signs of disease activity, such as confetti-like lesions or trichrome areas, indicate ongoing progression (Fig. 4b,c,e–g). Furthermore, examination with a Wood lamp can aid in visualizing lesion changes in the early stages of repigmentation following therapeutic or surgical interventions (Fig. 5). High-resolution digital photography and the use of machine learning and deep learning for the assessment of vitiligo are currently being developed and enable more objective tracking of changes in lesion size over time[139,140].

Differential diagnosis

An examination with a Wood lamp improves the detection of focal melanocyte loss by increasing the contrast between hypopigmented and normal skin, making areas of depigmentation appear more prominent[141], particularly in fair-skinned individuals (in areas such as the face) and in low-pigmented areas of darker-skinned individuals (such as the palms). Vitiligo lesions exhibit a characteristic bright white or blue-white fluorescence under a Wood lamp (Fig. 4c,g), a feature that is not observed in other acquired hypomelanotic conditions.

Differential diagnoses of vitiligo include various hypopigmentation and depigmentation disorders (Fig. 6), including pityriasis alba (Fig. 6f), hypopigmented mycosis fungoides (Fig. 6e), pityriasis versicolor (also known as tinea versicolor; Fig. 6d), and idiopathic guttate hypomelanosis, amongst others (Table 5). Vitiligo can also be misdiagnosed in fair-skinned individuals with melasma (a common skin condition characterized by brown or grey-brown patches of hyperpigmentation, usually on the face), where the presence of normal skin between melasma macules creates a vitiligo-like appearance[142] (Fig. 6g).

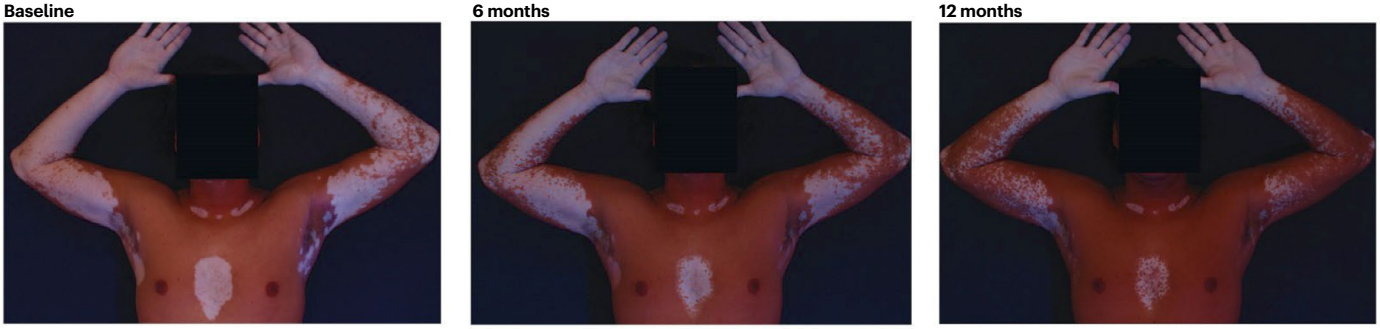


Fig. 5 | Perifollicular repigmentation in vitiligo during the course of treatment. Combined narrow-band ultraviolet B phototherapy and systemic oral minipulse of corticosteroid treatment for 24 months resulted in progressive repigmentation, with pigmented spots located around hair follicles.

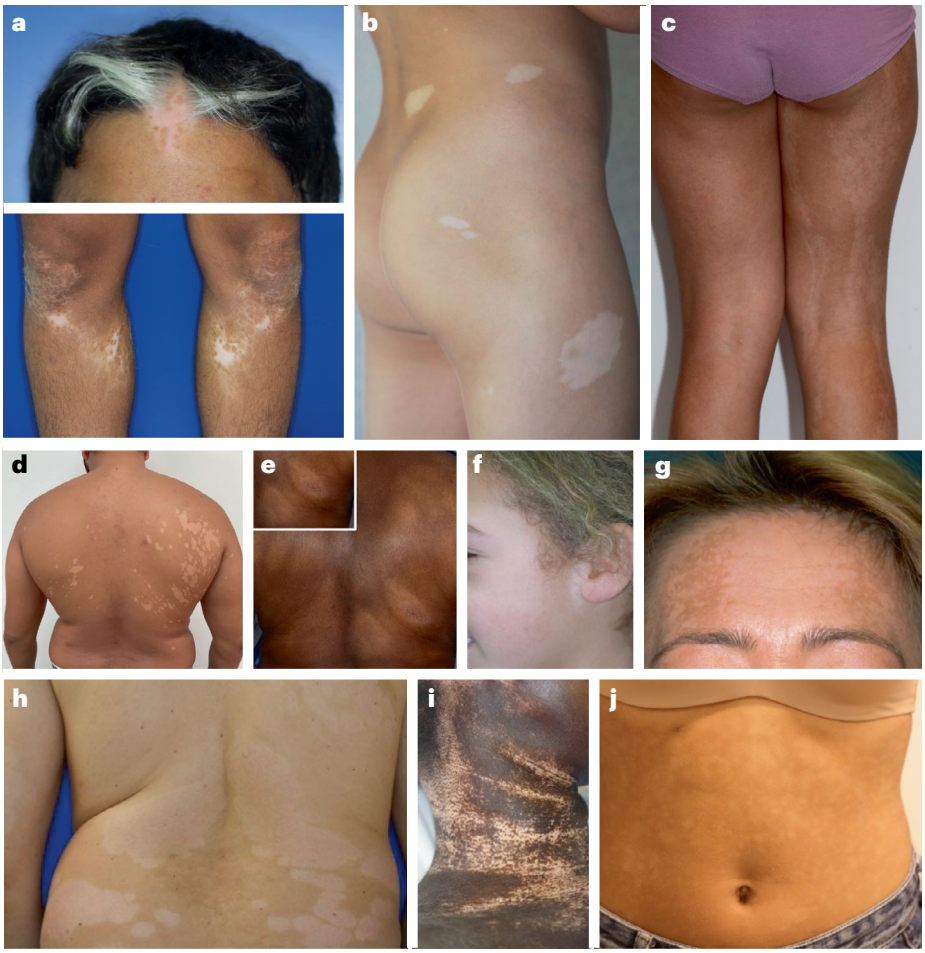


Fig. 6 | Differential diagnoses of vitiligo. Congenital loss of pigmentation (parts **a**–**c**). Piebaldism (part **a**) is a congenital condition characterized by the presence of a white forelock and ventral depigmentation. Tuberous sclerosis (part **b**) is a rare genetic disorder that includes hypopigmented areas on the trunk and limbs. Hypomelanosis of Ito (part **c**) is a systemic neurocutaneous syndrome defined by hypopigmentation along Blaschko lines (pathways of epidermal cell migration and proliferation during normal skin development). Acquired loss of pigmentation (parts **d**–**g**). Pityriasis versicolor (part **d**) is a fungal skin infection that leads to irregular, hypopigmented skin patches, which are especially noticeable in individuals with darker skin tone. Hypochromic mycosis fongoides (part **e**) is a subtype of mycosis fongoides (a form of cutaneous T cell lymphoma) that presents as hypopigmented macules. Pityriasis alba (part **f**), a mild type of dermatitis that typically occurs in children and young adults, is characterized by scaly or flaky hypomelanotic patches with feathered edges. Melasma (part **g**) is a common skin condition resulting in hyperpigmented areas, usually on the face. Post-inflammatory hypopigmentation (parts **h**–**j**). Psoriasis (part **h**) and systemic sclerosis (part **i**). Progressive macular hypomelanosis (part **j**) affects the trunk, rarely extending to the arms, legs and/or neck, and presents as multiple, circular, poorly defined pale and non-scaly spots.

Histopathology

Vitiligo is typically diagnosed by clinical examination using a Wood lamp, although a skin biopsy can be performed to rule out other conditions such as hypochromic mycosis fungoides. However, since the identification of visible clinical signs of disease activity[126], performing a skin biopsy to assess the immune infiltrate at the peri-lesional site is no longer considered necessary for therapeutic purposes, particularly for evaluating the inflammatory immune response that could justify initiating systemic therapy to halt disease progression.

Screening

Owing to the absence of identifiable preclinical markers and the unpredictable nature of its autoimmune onset, there are no established screening or prevention strategies for vitiligo. Educating patients, the public and health-care providers is crucial to ensuring early recognition and timely treatment of vitiligo. Given the high prevalence of comorbid thyroid disease, it is recommended that individuals with vitiligo undergo screening for antithyroid antibodies and thyroid function[3]. In case of family history and/or if the affected individual's history suggests the presence of additional autoimmune disorders (Table 3), further investigation could be discussed.

Prevention

Primary prevention for vitiligo is currently not possible. Heritability has a minor role in the development of the disease, and the environmental triggers of vitiligo onset remain insufficiently understood to enable primary prevention. Secondary prevention, such as avoiding skin stress to limit the Koebner phenomenon, is commonly recommended[29]. Secondary prevention may also include early detection and diagnosis to enable timely treatment and limit disease progression. Vitiligo can occur in response to laser hair removal, a condition termed laser-induced vitiligo (or leukoderma), although an international survey revealed that this complication is fairly rare[143]. Early recognition of signs of disease activity, such as confetti-like lesions, trichrome areas, an inflammatory border or the Koebner phenomenon, remains crucial for identifying patients with highly active disease who might require systemic therapy to stabilize their condition[144,145], including in young children (with parental consent). Furthermore, maintenance therapy could be a valuable option for patients to prevent disease flares.

Management

Treatment approaches are determined by various clinical factors, including the subtype of vitiligo, the extent of depigmentation and disease activity[3,146,147]. A thorough evaluation of these elements is essential before selecting an appropriate therapy. An algorithm for the treatment of

non-segmental vitiligo has been proposed by the international Vitiligo Task Force[3] (Fig. 7). The management of vitiligo is often described in terms of three key objectives: halting disease progression, promoting repigmentation through melanocyte regeneration and proliferation, and sustaining repigmentation while preventing relapse. However, this division should be regarded as a theoretical framework since, in clinical practice, these goals are closely interconnected. For example, controlling the underlying autoimmune process can lead to spontaneous repigmentation, whereas therapies primarily aimed at inducing repigmentation, such as NB-UVB phototherapy, also exert immunomodulatory effects that aid in arresting disease activity. In cases where depigmented areas cover more than 50% of the body, depigmentation therapy can be considered[148] (Fig. 7). Topical depigmenting agents include monobenzyl ether of hydroquinone (also known as monobenzone or p-benzyloxy-phenol), 4-methoxyphenol (also known as mequinol or p-hydroxyanisole) and phenol. Monobenzone is the only topical depigmenting agent that is currently approved for vitiligo by the FDA. Cryotherapy and pigment lasers are the two options for physical depigmentation therapies. Patients can experience repigmentation after the end of depigmenting treatment, which should be explained to the patient.

A patient-centred approach, known as shared decision-making, has gained recognition in vitiligo management[149]. This approach aims to inform patients about the available treatment options, engage them in discussion about their preferences, and clarify the advantages, risks and limitations of each therapeutic approach (Fig. 7). In some situations, shared decision-making can lead to a strategy of reassurance and regular monitoring (a wait-and-see approach), depending on the patient's wishes. Importantly, this process might differ based on patient age: in children and adolescents, parents or caregivers are actively involved in the decision, and particular attention must be given to treatment adherence and psychosocial consequences at school, whereas in adults, decisions are usually driven by the patient, with concerns more often related to professional or relational impact. In addition, the identification of emotional distress, including anxiety or depressive symptoms, can help to guide appropriate referral for psychological support when required (discussed later).

Early detection and prompt treatment of vitiligo are crucial for achieving optimal management outcomes. Proactive and intensive intervention at an early stage could considerably enhance the prognosis[150]. Controlling disease progression through an active immune-modulating and anti-inflammatory approach is beneficial for all forms of vitiligo, including segmental vitiligo, particularly during its early phases[151]. Based on current knowledge, initiating early and intensive systemic therapy is now considered a suitable strategy for the treatment of rapidly progressing vitiligo to prevent irreversible damage to melanocytes and melanocyte stem cells[3].

With current treatment approaches, complete or near-complete repigmentation is achievable in some cases. For example, complete repigmentation can be achieved for lesions on the face, whereas more than 50% repigmentation can be achieved for lesions on the body. However, areas such as the hands and feet remain particularly challenging to treat[152]. It is essential to assess the effectiveness of the therapy after at least 6 months, as noticeable repigmentation can take anywhere from 6 to 24 months[3,153]. Patients should be clearly informed that the treatment process is lengthy and often requires considerable patience and persistence.

Topical immunomodulatory agents

Topical immunomodulatory treatments have a crucial role in the management of vitiligo. Topical corticosteroids remain a first-line option

Table 5 | Principal differential diagnoses of vitiligo

Category	Disease	Key distinguishing features
Acquired hypopigmentation	Tinea versicolor	Fine scale; yellowish fluorescence on a Wood lamp examination; positive in the potassium hydroxide test
	Pityriasis alba	Ill-defined borders; faint scale; typically on the face of children with atopy; less distinct depigmentation
	Post-inflammatory hypopigmentation	History of preceding inflammatory skin disease (for example, eczema or psoriasis); follows a pattern of original rash; incomplete pigment loss
	Idiopathic guttate hypomelanosis	Small, discrete, porcelain-white macules ('sprinkled confetti'); typically on sun-exposed areas in older adults; non-progressive
	Progressive macular hypopigmentation	Ill-defined, non-scaly hypopigmented macules on the trunk of young adults; often coalescing; more common in darker skin types
	Hypopigmented mycosis fungoides	Irregular shape, often with slight atrophy or scale; can be pruritic; biopsy shows atypical lymphocytes
	Chemical leukoderma	History of exposure to specific chemicals (for example, phenols); often starts on hands or forearms and can spread; confetti-like macules can be similar to vitiligo
Congenital hypopigmentation	Piebaldism	Present at birth; non-progressive; characteristic white forelock; symmetrical on trunk or limbs; spares hands and feet and back
	Tuberous sclerosis	Hypopigmented macules ('ash-leaf spots'), often lanceolate-shaped; present from infancy; associated with other signs (for example, facial angiofibromas or shagreen patch)
	Hypomelanosis of Ito	Whorled, streaky or patchy hypopigmentation following Blaschko lines; present from birth or in infancy; patients can have associated extracutaneous abnormalities
	Naevus depigmentosus	Non-progressive, hypopigmented macule or patch caused by a defect in melanosome transfer from melanocytes to keratinocytes

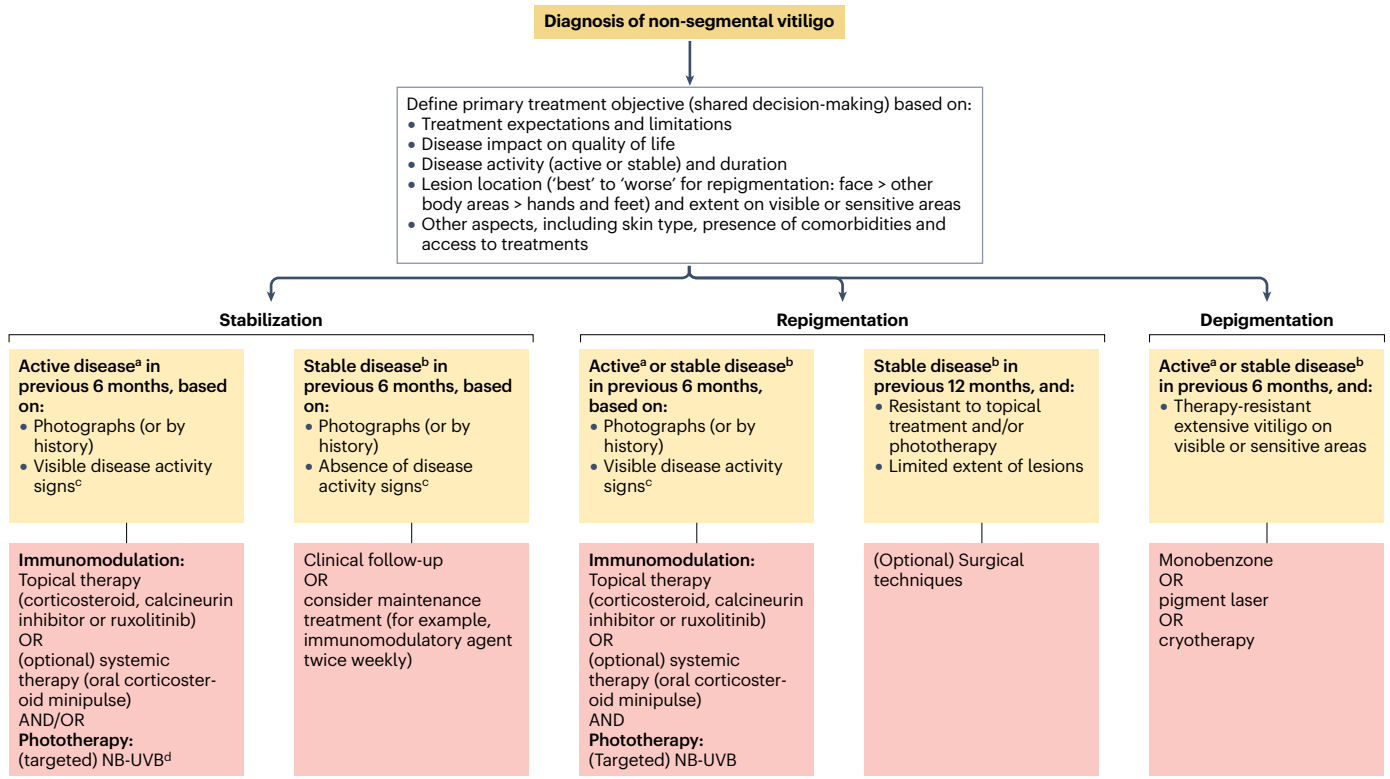


Fig. 7 | Algorithm for the management of non-segmental vitiligo. The algorithm is modified from that produced by the international Vitiligo Task Force[3]. The algorithm underscores the value of shared decision-making between clinicians and patients. Dermatologists should ensure patients are well informed about their condition, including prognosis and potential treatment outcomes, based on clinical examination. Dermatologists should provide information to the patient such as cosmetic skin camouflage, the use of sunscreens and avoidance of the Koebner phenomenon. It is essential to have a clear discussion with patients about treatment objectives, especially as strategies can vary depending on whether the goal is to halt disease progression or achieve repigmentation. Assessing disease activity continues to have a key role in personalizing care for individuals with vitiligo. NB-UVB, narrow-band ultraviolet B. [a]New lesions or increase of existing lesions. [b]No new lesions or increase of existing lesions. [c]Clear presence of confetti-like depigmentations, hypochromic borders or areas, or Koebner phenomenon. [d]NB-UVB and immunomodulatory therapy preferred (for example, phototherapy and topical immunomodulatory agent). Adapted with permission from ref. 3, John Wiley & Sons.

for localized vitiligo as they are particularly effective in halting disease progression. Repigmentation is more likely to be achievable on the face and neck, whereas acral sites and lesions with poliosis respond poorly. Most studies recommend once-daily application of potent to very potent topical corticosteroids, such as clobetasol propionate and betamethasone dipropionate, for 3–6 months, with intermittent regimens (for example, 2 weeks on/2 weeks off or 5 days/week) advised to reduce local adverse effects such as atrophy (thinning of the skin), telangiectasia (visible damaged or widened blood vessels just beneath the skin surface) or striae ('stretch marks'), and to allow longer treatment courses[154]. Topical calcineurin inhibitors, including tacrolimus and pimecrolimus, are preferred for sensitive areas such as the face, eyelids and body folds. Topical calcineurin inhibitor monotherapy can induce ≥25% repigmentation in 55% of patients and ≥75% repigmentation in 18% of patients after 3 months. When combined with NB-UVB phototherapy, efficacy can be further enhanced[3,146,155,156].

Ruxolitinib, a topical JAK inhibitor (specifically JAK1 and JAK2), is the first vitiligo treatment approved by the FDA and EMA specifically for managing vitiligo affecting the face or less than 10% of the body surface in patients older than 12 years of age, based on the results from two randomized, double-blind, phase III trials[157]. In these trials, 674 patients with non-segmental vitiligo were randomly assigned to twice daily 1.5% ruxolitinib cream or placebo treatment to all vitiligo areas on the face and body for 24 weeks, after which all patients received 1.5% ruxolitinib treatment through week 52. At week 24, 31% and 51.8% of patients achieved a Facial-VASI (F-VASI) score of 75 and 50, corresponding to the percentage improvement in the score measuring the extent (surface area of the face involved) and the degree of depigmentation (the level of pigment loss in a representative lesion), respectively, compared with 9.6% and 18.6%, respectively, in those who received placebo; 23.4% of ruxolitinib-treated patients achieved a total VASI (T-VASI) score of 50 compared with 5.9% of those treated with placebo. At week 52, 50.3% and 74.6% of patients who continued ruxolitinib treatment achieved a F-VASI score of 75 and 50, respectively, whereas 51.1% achieved a T-VASI score of 50 (ref. 157). The best response was observed in the head and neck areas, followed by the upper and lower limbs, and then the trunk. The hands and feet were the most challenging sites to repigment[158]. Most adverse events were mild or moderate, with the most common being acneiform eruptions and pruritus at the application site. Furthermore, 69% of patients who continued ruxolitinib treatment maintained a clinical response at 2 years[159]. However, among patients who discontinued treatment after 52 weeks, an F-VASI

response of 75 was sustained in less than 39% at 2 years, suggesting the need for maintenance therapy to prevent disease flares[160].

Systemic immunomodulatory agents

Systemic agents are primarily recommended for patients with progressive vitiligo to halt disease progression. Although most data are from open-label or retrospective studies, it is now widely accepted that treating highly progressive vitiligo should involve a combination of systemic immunomodulatory therapy and phototherapy[3].

Currently, systemic treatment mainly consists of oral minipulse therapy (weekly or twice weekly rather than daily treatments) with systemic corticosteroids for 3–6 months (for example, methylprednisolone 16 mg or dexamethasone 5 mg for two consecutive days each week in adults, with dosage adjustments for children)[146]. Systemic corticosteroids should always be used in conjunction with phototherapy[161]. Potential adverse effects related to both short-term and long-term oral minipulse therapy should be carefully considered. Possible side effects include weight gain, insomnia, agitation, acne, menstrual irregularities, hypertrichosis, growth retardation in children and immunosuppression, although these can be minimized through the use of intermittent, low-dose regimens[162].

Further data are needed to confirm the efficacy of other systemic therapies, such as methotrexate, ciclosporine (a calcineurin inhibitor) or azathioprine, for the management of vitiligo. There is no clear recommendation for the use of antioxidants in vitiligo management. However, there is limited evidence for improvement with the combination of phototherapy with oral antioxidants, such as extracts from the fern *Polypodium leucotomos* and gliadin-protected superoxide dismutase, compared with phototherapy alone[163,164].

Phototherapy

UV-based phototherapy has been a major treatment for vitiligo for decades. The most common form of phototherapy currently used for extensive lesions is NB-UVB. NB-UVB lamps have a sharp emission peak at 311–313 nm. NB-UVB efficacy varies by body location, in the following order from most to least efficacious: face and neck > trunk > arms and legs >> hands and feet[165]. Indeed, acral areas are the most difficult to repigment, especially the distal tips of the digits. Similarly, mucosal areas can be difficult to repigment. These areas share a lack of follicular units that are a reservoir for melanocyte stem cells. The resulting reduced density of melanocytes and stem cell signalling makes these areas less amenable to treatment with phototherapy[152]. The safety of phototherapy in vitiligo is a general concern, as UV exposure has been linked to various skin cancers[166]. However, in addition to the previously discussed lower risk of skin cancer in patients with vitiligo, a meta-analysis of more than 200,000 patients with vitiligo across multiple countries found no increased risk of skin cancers in patients receiving NB-UVB phototherapy for vitiligo compared with patients not receiving this therapy[167].

In prospective studies, the typical dosing regimen for NB-UVB begins with an initial dose of 150–250 mJ/cm^2, which is subsequently increased by 10–20% at each treatment session, as tolerated, up to a maximum of 3 J/cm^2 for the body or 1 J/cm^2 for the face[168]. NB-UVB treatment for vitiligo is typically administered two or three times per week. Although these two regimens have not been directly compared, repigmentation is generally believed to depend on the total number of treatment sessions, with a faster onset of pigmentation observed with thrice-weekly therapy[168]. Counselling patients is important for shared decision-making. Before discontinuing phototherapy owing to a lack of response, at least 48 NB-UVB sessions should be administered. Some patients can be slow responders, so up to 72 or more sessions might be considered before stopping treatment[168]. For localized areas of depigmentation, targeted phototherapy using an excimer laser or excimer lamp can be employed. For example, treatment with the xenon-chloride excimer laser, which is a high-intensity light source that emits at 308 nm, induces faster and more extensive repigmentation than NB-UVB therapy[169–172]. The protocol for excimer laser is almost identical to that for NB-UVB: the initial dose is 150 mJ/cm^2, increasing by 15% up to a maximum dose of 3 J/cm^2 for the body and 1 J/cm^2 for the face[171]. These devices deliver higher irradiance compared with other light sources and possess distinct optical properties, including collimation (making a more focused beam) and coherence, which result in a reduced required treatment duration. Home phototherapy might be an effective option if travel to and cost of in-office treatment are burdensome or if it is the patient's preference; efficacy and safety seem to be similar to in-clinic treatment[173,174].

Various adjuvant immunomodulatory therapies, including tacrolimus, oral minipulse therapy with corticosteroids, or topical or oral JAK inhibitor therapy, have been evaluated to determine whether the response to NB-UVB can be enhanced, and these combination therapies result in much improved repigmentation[175–177].

For all types of UV phototherapy, the increase in the next dose should be lowered to 5–15% if mild erythema develops without tenderness. Treatment should be halted if moderate to severe erythema or blistering occurs and can be resumed at the last well-tolerated dose once symptoms have resolved.

Surgical interventions

Surgical interventions are considered when conventional treatments show limited response. Surgical procedures, which include tissue or cellular grafting, are only recommended for stable vitiligo, indicated by the absence of new lesions or disease progression for at least 12 months[125].

Tissue grafting involves direct transplantation of melanocyte-containing skin from a donor site to a recipient depigmented site. Punch grafting, one of the simplest techniques, uses 1–2 mm punches to transfer small pieces of skin to prepared recipient sites. This method has evolved with motorized micropunch devices (which remove 0.5–0.8 mm pieces of skin) that reduce procedure time and minimize cobblestone appearance at the recipient site[178]. Suction blister epidermal grafting involves the creation of epidermal blisters using negative pressure, followed by the transplantation of the blister roofs, which contain melanocytes, to depigmented recipient sites. This technique offers precise separation of the epidermis from the dermis, minimizing donor site scarring, although considerable preparation time is required for raising blisters (15–150 min) and dermabrading the recipient site[179,180].

Cellular grafting uses either pure melanocyte or combined melanocyte-keratinocyte suspensions for transplantation. In non-cultured epidermal cell suspension, epidermal cells, including melanocytes and keratinocytes from a small donor skin sample, are enzymatically separated using trypsin and transplanted to prepared depigmented recipient sites[181,182]. With a donor-to-recipient skin area ratio of 1:5 to 1:10, non-cultured epidermal cell suspension allows treatment of larger areas while requiring limited donor skin. Cultured epidermal cell suspension involves expansion of autologous melanocytes in a laboratory and can be used to treat areas up to 40-fold larger than the donor site[183]. However, this approach remains experimental owing

Box 1 | Patient experience

I've been living with (my) vitiligo for two decades now, and it's been quite a journey! It's interesting to read today that this disease requires holistic care because it wasn't the case for a very long time. First, vitiligo wasn't even recognized as a disease, and the only 'professional advice' I had from some dermatologists was to learn to live with it. They couldn't imagine how life-changing (and challenging) it is. For example, it's not the case anymore but the summer season was a source of stress because I thought the sun was an enemy. So, I had to limit my sun exposure and my outdoor activities. Sitting with friends on a terrace became challenging because I had to change my seat each time the sun shifted. It was like a (crazy) dance around the table! Moreover, clothing and makeup to cover up were also topics to be addressed or, at least, thought about (constantly). And in terms of money as well. So, the only solution I could find back then was to hide my vitiligo, especially at work. I didn't want anyone to notice something and start asking questions when obviously I wasn't open or ready to share. Only a few people from my (very) inner circle were aware of what I was going through. But more importantly, I think it's the isolation you can feel because no one really gets it. You've received contradictory advice about a lot of things, like sun exposure, stress, phototherapy, skin friction, contagion, heredity, and so on. Today, I can understand it though due to advances in research, but back then, I had to navigate through all this alone, while some questions remain unanswered. And this 'thing' keeps growing on your skin and you're just lost. So, all of this adds a certain burden on your shoulders on a daily basis, which is not good for the anxiety rate.

Also — and I think most physicians could be surprised — but even the right treatment could be a burden sometimes. You're sticking to a certain routine: applying cream every single day, sometimes twice a day; going to phototherapy sessions also takes up a significant amount of time dedicated to the disease. This means you don't have the luxury of forgetting it!

To sum up, the burden of vitiligo is multidimensional — encompassing emotional, social and psychological challenges — and it is not easy to be candid about it. But the good news is that some peace and serenity can be found. How so? With the right support system, which means aligning your needs and expectations with the actual people's skills. I mean, your dermatologist is not psychic or a psychologist! But maybe you can ask for some relevant contacts. Don't forget that you're not alone on this journey, as 0.5–1% of the global population is having the same experience. Communities and organizations exist, so it's up to everyone to act. Try not to be obsessed with pending questions about this mysterious disease because some will be answered eventually, although some may not.

to the requirement for facilities with good manufacturing practice certification, a culture period of approximately 3 weeks and safety concerns related to the use of growth factors during cell culture. Another drawback is the reduced efficacy of pure melanocyte grafts, which lack the essential growth factors and structural support provided by co-transplanted keratinocytes.

The outcome of surgical treatments depends on multiple factors (for example, duration of the disease, vitiligo type or site of lesion), with disease stability being essential for successful results[125]. Favourable responses have been obtained for facial areas, whereas responses are poor for acral sites[125]. Segmental vitiligo is a common indication for surgical intervention because it typically affects a localized area, tends to stabilize early (often within 6–12 months of onset) and shows poor response to medical therapies. Successful surgical intervention requires careful patient selection, appropriate technique choice and, sometimes, combination approaches to achieve optimal repigmentation in refractory vitiligo. Post-operative phototherapy enhances repigmentation by stimulating melanocyte regeneration[184].

Maintenance therapy

In the absence of maintenance therapy, depigmentation occurs in almost 50% of vitiligo lesions within the first year after repigmentation[185]. Thus, maintenance therapy is important to retain repigmentation. For example, applying tacrolimus 0.1% twice weekly (without the need for sun or NB-UVB exposure) reduces the risk of relapse on the face from 40% to 9.7%[186]. The same regimen with topical corticosteroids is probably effective as well, although the suitability of this drug type for maintenance therapy needs to be confirmed. For patients with more extensive disease, maintenance treatment remains challenging. Trials are needed to test the efficacy of NB-UVB as a maintenance therapy. Future systemic treatments currently in development might help to prevent vitiligo recurrence (discussed later).

Management of segmental vitiligo

Segmental vitiligo is often associated with an autoimmune response, especially during the early phase of depigmentation[187]. Therefore, management involves early intervention with immunomodulatory treatments, such as topical corticosteroids or calcineurin inhibitors, combined with phototherapy, to halt disease progression and promote repigmentation. Topical ruxolitinib has not yet been evaluated for this indication. Systemic therapies (such as oral minipulse of systemic corticosteroids) could be considered during the early stages of segmental vitiligo development. In the stable, late phase, defined by the absence of new lesions for at least a year, the response to medical treatments is typically poor, so surgical options such as melanocyte transplantation might be considered to restore pigmentation. This approach offers a more effective and long-lasting solution for repigmentation in patients with lesions that are resistant to medical therapy[3,188].

Quality of life

Vitiligo has a major psychosocial impact on affected individuals that extends beyond its visible skin manifestations. Once considered primarily cosmetic, vitiligo is now acknowledged as an autoimmune disease with profound implications for mental health and overall well-being (Box 1). Emotional distress, anxiety and diminished self-esteem are frequently reported by individuals with vitiligo, reflecting its deep impact on daily functioning[47]. To assess this burden, various quality of life (QOL) instruments can be used. Among them, the Dermatology Life Quality Index (DLQI) is a widely used generic dermatological score; however, it is not specific to vitiligo. The vitiligo-specific QOL

(VitiQoL) instrument has been the most widely used in clinical trials[189]. However, its limited responsiveness in advanced-phase studies has underscored the need for more sensitive tools. The 12-item short-form of the VIPs (VIPs-12) has been proposed to address this gap, as it offers a more nuanced understanding of the disease's effects, particularly across different skin tones and cultural contexts[190]. Evidence from large-scale international studies[48,191–193], such as the VALIANT study spanning 17 countries, supports the relevance of tools such as the VIPs-12. This research revealed a higher QOL burden among patients with darker skin, more than 5% body surface area involvement, and lesions on the face or hands. These findings reinforce the role of visible and stigmatizing locations of lesions in amplifying emotional and social distress. Ethnicity and sex further modulate the effect of the disease. For example, involvement of the genital area substantially affects QOL in some populations such as in Thai cohorts[194]. In addition, patients of colour often report greater psychosocial distress, highlighting the intersection of clinical severity and societal perception[192,195]. Beyond individual symptoms, the psychological toll of vitiligo extends to social and familial relationships. Social isolation, internalized stigma and reduced confidence are common, with studies linking these effects to increased rates of anxiety and emotional dysregulation[196]. Resilience and coping strategies, when supported through psychotherapy, mitigate some of these effects and improve patient outcomes[196,197]. A systematic review conducted in 2022 emphasized the urgent need to integrate psychological care into dermatological treatment[198]. Addressing the mental health component of vitiligo through education, multidisciplinary support and culturally adapted tools is now considered essential. These efforts reflect an evolving understanding of vitiligo as not merely a skin condition but as a complex disease requiring holistic care to improve patient quality of life.

Outlook

In the past 10 years, a revolution has occurred in the vitiligo field, particularly in terms of treatment. With growing understanding of its pathogenesis, vitiligo has evolved from an orphan disease to a well-recognized condition, highlighted by the approval of topical ruxolitinib and the ongoing development of systemic therapies for more severe cases. Despite this progress and increased awareness of the impact of vitiligo on quality of life, achieving complete or near-complete repigmentation for all patients remains a major challenge.

Pathogenesis and management strategies

New topical and systemic treatments for vitiligo are being developed (Fig. 8 and Supplementary Table 1). The role of the JAK–STAT pathway, particularly downstream signalling via IFNγ, is now well established in vitiligo pathogenesis, which spurred the development and testing of JAK inhibitors, resulting in the regulatory approval of topical ruxolitinib for repigmentation. The most advanced emerging treatments are oral JAK inhibitors that are already used in other autoimmune diseases. In a double-blinded, placebo-controlled phase IIb trial[199], treatment with the oral JAK3 inhibitor ritlecitinib resulted in an improvement in mean F-VASI (−21.2) compared with placebo (−2.1) in patients with active non-segmental vitiligo. However, no statistically significant improvement in T-VASI was observed after the 24-week double-blind, placebo-controlled period. Both F-VASI and T-VASI scores continued to improve during the additional 24-week open-label extension phase. In another double-blinded, placebo-controlled phase II trial[200] in patients with non-segmental vitiligo (baseline F-VASI ≥0.5 and T-VASI ≥5), 11 mg and 22 mg doses (but not a 6 mg dose) of the oral JAK1 inhibitor upadacitinib improved mean F-VASI scores (−35.63 and −33.96, respectively) and T-VASI scores (−17.26 and −20.69, respectively)

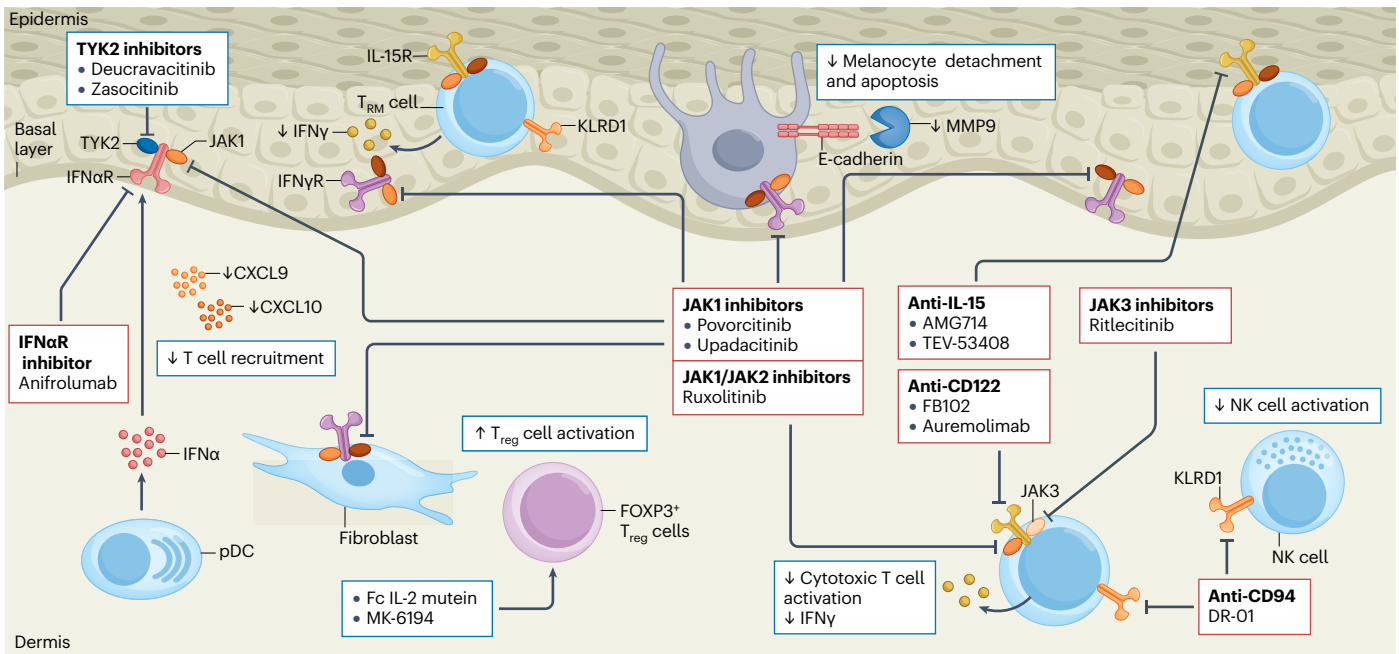


Fig. 8 | Therapeutic targets of agents being developed for vitiligo treatment. Current and emerging therapeutic targets across key pathogenesis pathways in vitiligo are depicted. Inhibition of the IFNγ–JAK–STAT axis (using inhibitors of JAK1 and JAK2, JAK3, or TYK2) aims to suppress type I and type II interferon signalling and downstream chemokine-driven T cell recruitment. Additional approaches target natural killer (NK) cell activation and IL-15-mediated signalling (for example, anti-IL-15, anti-CD122 and anti-CD94 therapies). Restoration of immune tolerance through activation or expansion of FOXP3⁺ regulatory T (T_{reg}) cells (using Fc–IL-2 muteins) promotes control of the immune response. pDC, plasmacytoid dendritic cell; T_{RM} cell, tissue-resident memory T cell.

compared with placebo (−14.36 F-VASI score and −6.42 T-VASI score) at 24 weeks. Improvements continued through week 52 during the extension phase[200]. In a phase II trial[201] of the oral JAK1 inhibitor povorcitinib in patients with extensive non-segmental vitiligo (F-VASI ≥0.5 and T-VASI ≥8), all doses led to improvement in T-VASI that was statistically superior to that with placebo (15 mg, 19%; 45 mg, 18%; 75 mg, 16%; placebo, −2%). Percentage improvement in F-VASI from baseline was statistically superior with any dose of povorcitinib (15 mg, 28%; 45 mg, 36%; 75 mg, 29%) than with placebo (5%) at 24 weeks. Continued improvements were observed up to week 52 in the extension period[201]. No new safety signals emerged in these three phase II trials. Phase III trials for these therapies are ongoing (ritlecitinib: NCT05583526, NCT06072183 and NCT06163326; upadacitinib: NCT06118411; povorcitinib: NCT06113445 and NCT06113471). JAK inhibitors are only the first generation of immune-based treatments for vitiligo, as next-generation approaches are currently in early development.

Targeting IL-15 and its receptor IL-15R to prevent $CD8^+$ T cell activation and reduce the abundance of T_{RM} cells is another promising strategy that is being assessed in phase I trials (NCT06625177, NCT06905873). The type I interferon pathway is also being targeted in vitiligo, with phase II clinical trials under way for the TYK2 inhibitors deucravacitinib (NCT06327321) and zasocitinib (NCT07108283) and for anifrolumab (NCT05917561), a monoclonal antibody against IFNαR. Enhancing T_{reg} cell responses might also offer therapeutic benefit, with a phase II trial using modified IL-2 currently under way (NCT06113328). DR-01 — an antibody that targets CD94 on cytotoxic $CD8^+$ T cells, γδT cells and natural killer cells — is currently being evaluated in a phase I trial (NCT06602232).

Treating resistant areas, such as the hands and feet, and promoting melanocyte regeneration once inflammation is controlled, remain key challenges. Currently, only UV-based phototherapies reliably activate melanocyte stem cells but more practical options (that is, approaches that do not require medical appointments or with reduced health risks) are needed to improve patient adherence. Direct stimulation of melanocyte stem cells could be an effective adjunct therapy to promote repigmentation in vitiligo. For example, subcutaneous implantation of afamelanotide, an analogue of melanocyte-stimulating hormone, accelerates repigmentation in patients treated with NB-UVB[202]. An ongoing phase III study is evaluating this analogue in combination with phototherapy versus phototherapy alone[202] (NCT06109649). Afamelanotide might be particularly beneficial for patients with darker skin tones owing to overall skin darkening with this treatment, an effect that might be less desirable in patients with fair skin[203]. WNT agonists promote maturation of melanocyte stem cells in vitiligo lesional skin and thus have been proposed as novel vitiligo treatments that could synergize with immunosuppressant therapies to accelerate patient responses[123]. In addition, exosomes from induced pluripotent stem cells offer a novel strategy for treating vitiligo by promoting melanocyte proliferation and function while reducing the immune response[204]. The use of induced pluripotent stem cell-derived exosomes is also being explored to enhance repigmentation, and a phase I trial (NCT06810869) is currently under way in individuals with mild vitiligo (that is, low surface area involved).

In addition, new concepts in the management of vitiligo are also being considered. For example, exploring the role of maintenance therapies after repigmentation and determining whether early intervention can alter disease progression will be crucial. Identifying biomarkers to predict treatment response or relapse risk will be an important step forward. Vitiligo offers a unique window into organ-specific autoimmunity owing to the accessibility of the skin, enabling direct study of the interactions between immune and non-immune cells. The shared mechanisms with other autoimmune diseases make vitiligo a valuable model for testing and developing novel immunotherapies with potential cross-disease relevance.

Challenges and future directions

The future will bring the development of additional topical and systemic treatments for vitiligo. Once these new therapies become available, real-life studies will be required to monitor the efficacy and safety of these treatments, particularly systemic therapies. In this regard, international registry initiatives are currently ongoing, such as the international registry to study pharmacovigilance of vitiligo drugs (VIRTUAL), an initiative of the Global Vitiligo Atlas (a collaboration between the International League of Dermatological Societies) and the Vitiligo International Patient Organisations Committee (VIPOC).

Although systemic JAK inhibitors have shown efficacy in clinical trials, it will be crucial to determine whether broad inhibition of circulating T cells is desirable or whether more precise, skin-targeted approaches are preferable. In this context, therapies that specifically modulate key pathogenesis pathways, such as IL-15-driven activation and maintenance of T_{RM} cells in the skin, could represent a promising strategy to dampen the memory immune response and achieve durable disease control with potentially fewer systemic adverse effects. Furthermore, it will be important to determine whether topical and/or systemic treatments can be used as maintenance therapy after patients achieve a satisfactory level of repigmentation. Future studies will also need to address whether early intervention in the disease course can alter its trajectory and prevent the accumulation of T_{RM} cells in the skin. Another important challenge is finding effective treatments for difficult-to-treat areas such as the hands and feet. Enhancing the regeneration of melanocytes, once the immune response is under control, will be another key objective for future research. To date, UV-based therapies remain the only approach that reliably activates melanocyte stem cells. The development of more convenient, reliable and safer therapeutic options could greatly improve patient adherence and satisfaction.

The identification of biomarkers for predicting therapeutic response or detecting patients at risk of relapse after treatment discontinuation will also be crucial. Vitiligo stands out as an exceptional model for understanding organ-specific autoimmunity as, unlike in many other autoimmune diseases, the affected tissue — the skin — is directly accessible, facilitating the isolation and culture of melanocytes and other resident cell types. This accessibility enables detailed investigation of the interactions between non-immune cells (for example, keratinocytes, melanocytes and fibroblasts) and immune cells, including autoreactive T_{RM} cells.

Moreover, given its shared genetic predispositions and immune mechanisms with other autoimmune diseases, vitiligo could serve as a powerful platform for the evaluation of novel immunomodulatory therapies. Treatments validated in vitiligo could have broader applications in other autoimmune conditions, making it a valuable model for both mechanistic research and therapeutic development.

Public health measures and patient support groups

Although vitiligo is not life-threatening, its increasing prevalence and visibility call for greater public health attention. Vitiligo carries a

substantial psychosocial burden that is often overlooked owing to the lack of physical disability (Box 1). As autoimmune diagnoses rise, early recognition and support become more crucial[205]. Training primary care providers through educational programmes about vitiligo and the latest available treatments, along with simulated case-based training and launching public awareness campaigns are key, especially in regions where depigmentation is stigmatized. Patient associations, such as the VIPOC, have a pivotal role in advocacy and education by helping to reshape public perceptions and improve care. Their collaboration with researchers has highlighted unmet needs and led to the development of patient-centred tools. Public health strategies should integrate vitiligo into broader skin and mental health initiatives, while ensuring equitable access to emerging treatments.

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Author contributions
Introduction (J.S.); Epidemiology (K.E. and J.M.B.); Mechanisms/pathophysiology (K.B., J.E.H., B.B. and M.P.); Diagnosis, screening and prevention (I.H., N.v.G. and J.S.) Management (T.P., I.H., J.S. and J.M.B.); Quality of life (D.P. and K.E.); Outlook (J.S.); overview of the Primer (all authors). All authors read and approved the final version of the manuscript.

Competing interests
J.S. received grants and/or honoraria from AbbVie, Bristol Myers Squibb, Calypso Biotech, Eli Lilly, Incyte, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi, Sun Pharmaceuticals, and Viela Bio and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and on a 3D model of a depigmenting disorder. N.v.G. received grants, is a consultant and/or is an investigator for AbbVie, Incyte, Merck/MSD, Pfizer, Bristol Myers Squibb, Idorsia and Novartis; she was involved in the development of several measurement instruments for vitiligo. K.E. is a consultant for AbbVie, Incyte, La Roche-Posay, Pfizer, Pierre Fabre, Sanofi and Viela Bio. K.B. has received grants and/or honoraria from Calypso Biotech, LEO Pharma, Pfizer, Pierre Fabre, Sanofi, Silab, Almirall, and AnaptysBio and has a patent on MMP9 inhibitors and uses thereof in the prevention or treatment of a depigmenting disorder and on a 3D model of a depigmenting disorder. T.P. has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceuticals, UCB and Vyne Therapeutics, is the cofounder of NIKAIA Pharmaceuticals, and has patents on WNT agonists and GSK3β antagonists for repigmentation of vitiligo and on the use of CXCR3B blockers in vitiligo. J.E.H. has served as a consultant for AbbVie, Aclaris Therapeutics, BiologicsMD, EMD Serono, Genzyme/Sanofi, Janssen, Pfizer, Rheos Medicines, Sun Pharma, TeVido BioDevices, The Expert Institute, Third Rock Ventures and Villaris Therapeutics, has served as an investigator for Aclaris Therapeutics, Celgene, Dermira, EMD Serono, Genzyme/Sanofi, Incyte Corporation, LEO Pharma, Pfizer, Rheos Medicines, Stiefel/GlaxoSmithKline, Sun Pharma, TeVido BioDevices and Villaris Therapeutics, holds equity in Aldena Therapeutics, NIRA Biosciences, Rheos Medicines, TeVido BioDevices and Villaris Therapeutics, is a scientific founder of Aldena Therapeutics, NIRA Biosciences and Villaris Therapeutics, and has patents pending for IL-15 blockade for the treatment of vitiligo, JAK inhibition with light therapy for vitiligo, and anti-human CXCR3 antibodies for treatment of vitiligo. I.H. is a consultant to Abbvie, Pfizer, Incyte, UCB, Boehringer Ingelheim, Sonoma, Union therapeutics, Novartis, Jansen, Avita, and Galderma and is investigator for Lenicura, Pfizer, Incyte, Avita and L'Oreal/La Roche-Posay. He is also a board member and past-president of the Hidradenitis Suppurativa Foundation and the Global Vitiligo Foundation. The other authors declare no competing interests.

Informed consent
The authors affirm that human research participants provided informed consent for publication of the images in Figs. 3–6 and the patient experience in Box 1.

Additional information
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