Incyte Dermatology

Vitiligo

Understanding the Burden and Pathophysiology of Disease

MSL-DIS-US-0010 04/24

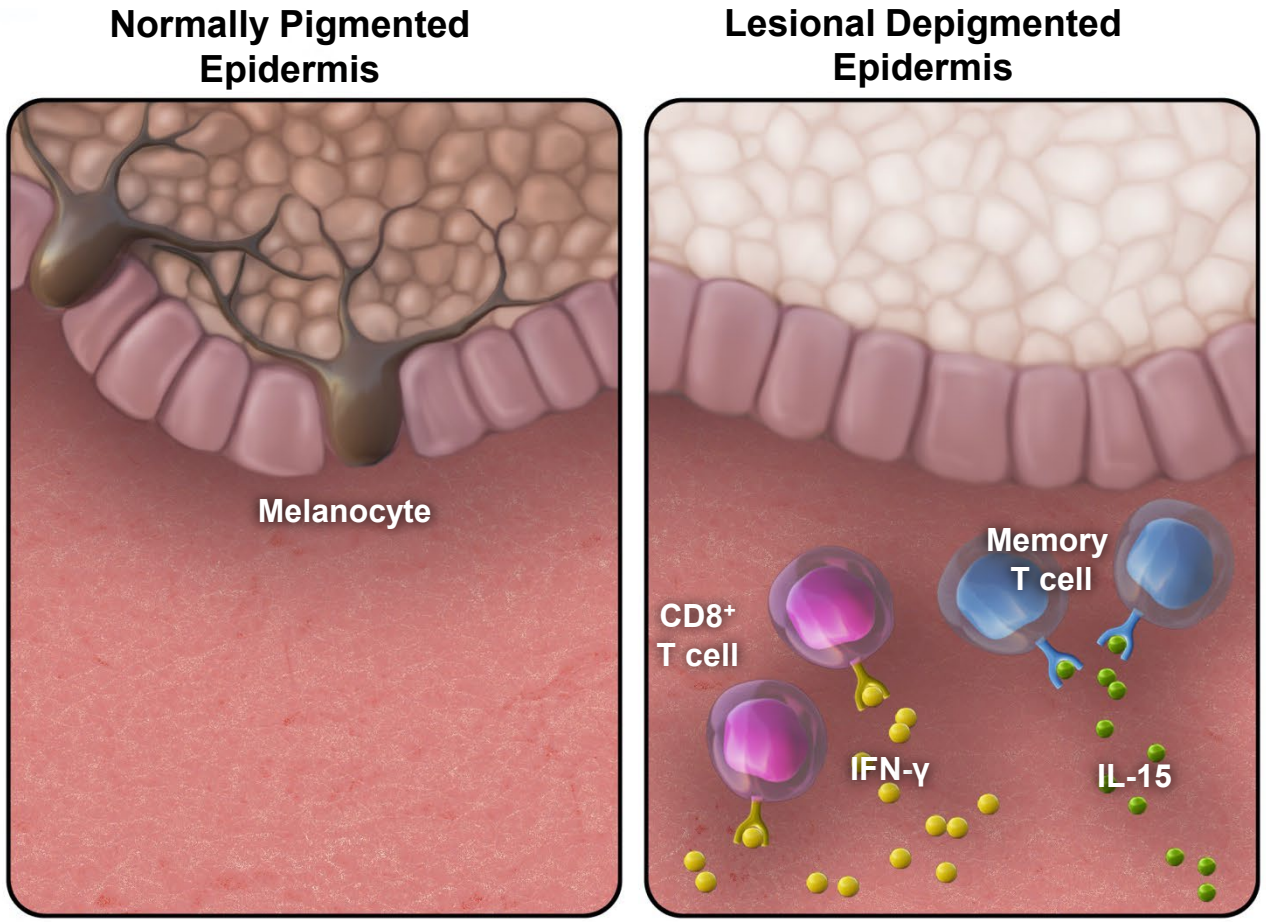
Burden of Disease

Vitiligo Is a Chronic Autoimmune Disease of the Skin

Vitiligo is a chronic, autoimmune skin depigmenting disease that is associated with[1]:

A complex immunopathogenesis[1]

Various autoimmune comorbidities (thyroid disease is most common)[2]



Inflammation-driven destruction of melanocytes and epidermal depigmentation is caused by IFN-γ–producing CD8⁺ T cells, and maintained by CD8⁺ skin resident memory T cells[3]

IFN-γ, interferon gamma; IL-15, interleukin 15.

1. Bergqvist C, Ezzedine K. *Dermatology*. 2020;236:571-592. **2.** Liu J, et al. Academy of Managed Care (AMCP) Nexus 2023, Orlando, FL, October 16-19, 2023. **3.** Frisoli ML, et al. *Annu Rev Immunol*. 2020;38:621-648.

Vitiligo Is the Most Common Depigmenting Skin Disorder[1]

Affects different populations **irrespective of skin color, ethnic origin, or race**[2-4]

US Prevalence

1.4%

of individuals reported having vitiligo[5,a]

Estimated

1.9M

diagnosed cases in 2020[2,b]

>65%

of individuals experience disease onset at

≤30 years of age[3]

Prevalence is generally

similar across genders[2,5,6]

Estimated

40%

may be **undiagnosed**[2,b]

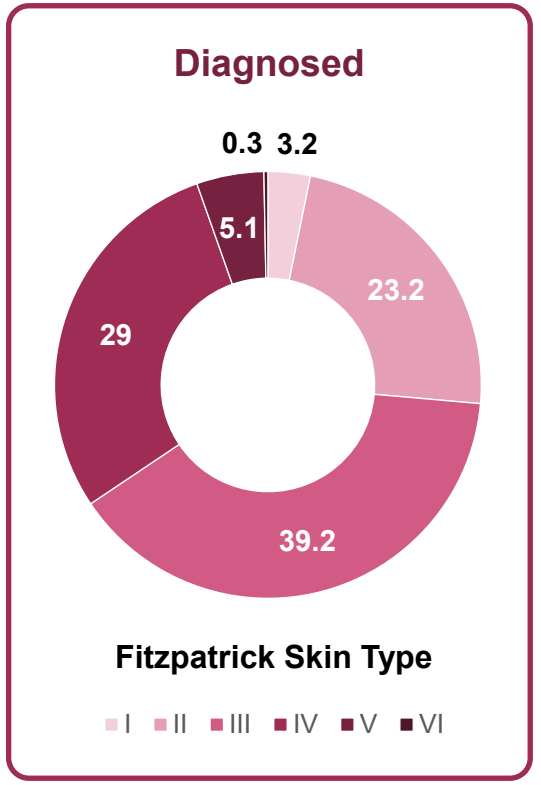
[a]From an online survey of self-reported signs of vitiligo among 35,694 respondents (EU, n=18,785; US, n=8517; Japan, n=8392). [b]From a clinician-adjudicated point prevalence estimate based on an online survey of self-reported signs of vitiligo among 40,888 US respondents.

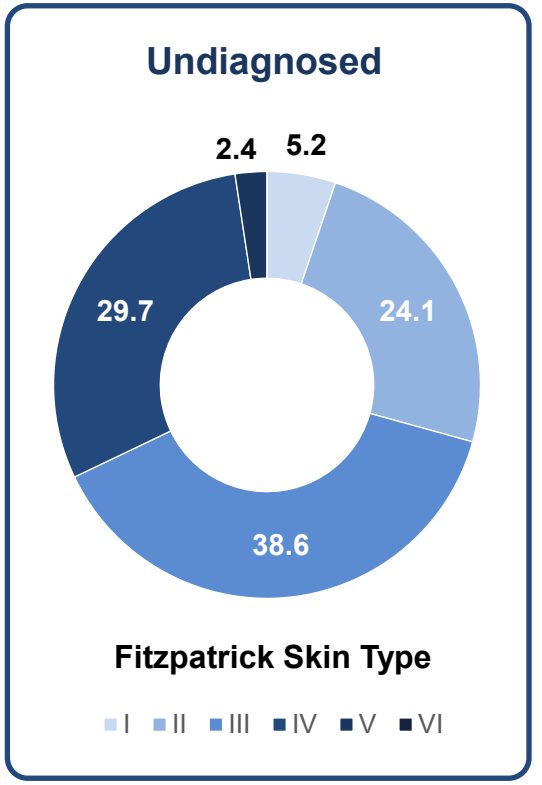
1. Bergqvist C, Ezzedine K. *Dermatology*. 2020;236:571-592. 2. Gandhi K, et al. *JAMA Dermatol*. 2021;e214724. 3. Zhang Y, et al. *Dermatol Ther*. 2014;27:298-303. 4. Sharma CK, et al. *J Environ Pathol Toxicol Oncol*. 2015;34:321-334. 5. Bibeau K, et al. *J Eur Acad Dermatol Venereol*. 2022;36:1831-1844. 6. Harris JE, et al. American Academy of Dermatology Annual Meeting, Denver, CO, March 20-24, 2020. Poster 177555.

Vitiligo Affects Different Populations Irrespective of Skin Color, Ethnic Origin, or Race

Data from a cross-sectional, population based survey[a] that assessed point prevalence of vitiligo in the US showed that vitiligo affects adults of all races and ethnicities

Race and ethnicity, n (%)	All adult participants (N=40,888)	Diagnosed (n=314)	Undiagnosed (n=249)
White	30,428 (74.4)	215 (68.5)	149 (59.8)
Black or African American	5253 (12.8)	49 (15.6)	47 (18.9)
Hispanic, Latino, or Spanish origin	4225 (10.3)	48 (15.3)	53 (21.3)
Other	2086 (5.1)	13 (4.1)	12 (4.8)
Asian	1481 (3.6)	13 (4.1)	10 (4.0)
Multiracial[b]	1188 (2.9)	18 (5.7)	19 (7.6)
American Indian or Alaska Native	367 (0.9)	4 (1.3)	12 (4.8)
Native Hawaiian or other Pacific Islander	85 (0.2)	2 (0.6)	0



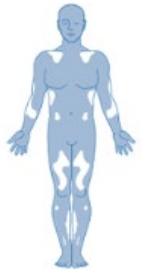


A cross-sectional, population-based survey was conducted between December 2019 and March 2020 to estimate point prevalence of vitiligo in the US and to describe demographic and clinical characteristics of this patient population. The patient survey included demographics, clinical characteristics, comorbidities, and vitiligo screening questions adapted from published screening tools, the patient-administered Vitiligo Screening Tool, and a self-reported questionnaire. A representative sample of the US adult general population (18-85 years) was recruited by email invitation and stratified quotas were set to be representative of the 2017 US census estimates with respect to age (4-85 years), gender, race, household income level, and geographic region. [b]Multiracial was captured indirectly on the participant survey: if >1 race category was selected then the participant was considered multiracial and is included only in the multiracial category.

Gandhi K, et al. *JAMA Dermatol*. 2022;4724158:43-50.

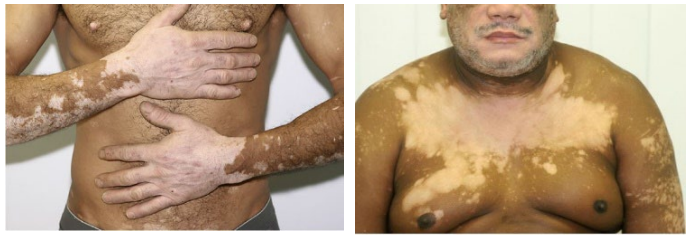
Vitiligo Is Classified Based on 3 Clinical Phenotypes

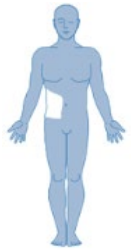
Classification of Vitiligo



Vitiligo (Nonsegmental Vitiligo):
Immune system attacks functional melanocytes[1-4]

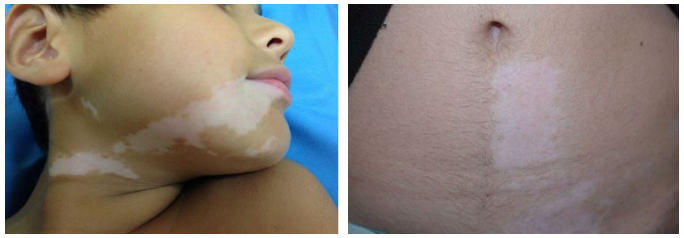
- Most common type; presents with bilateral lesions or scattered symmetrical lesions over the entire body[3,4]
- Progresses slowly and has unpredictable course[3-5]
- Subtypes: Acrofacial, focal, mucosal, generalized, universal[6]





Segmental Vitiligo:
Related to somatic mosaicism[6]

- Usually unilateral and has an earlier onset[3-5]
- Progresses rapidly and then stabilizes[3-5]



Mixed-Type Vitiligo[3,4]

- Initially presents with segmental lesions, followed by development of bilateral lesions
- Usually more refractory to treatment

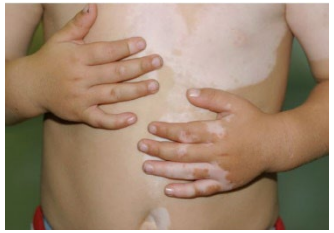
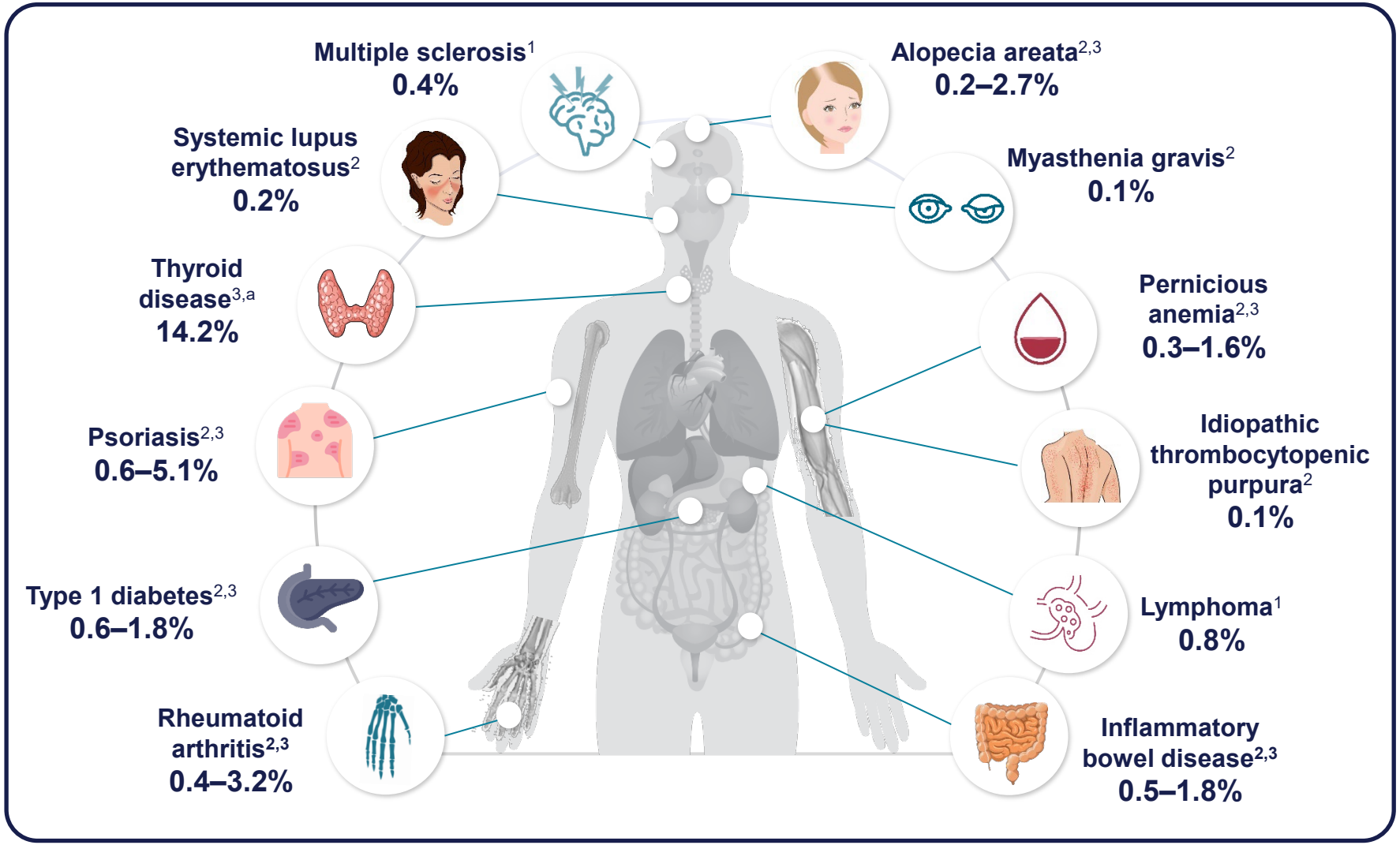


Image [top left] reprinted from *Dermatology*, Vol. 236, Bergqvist C, et al, Vitiligo: a review, doi: 10.1159/000506103, Pages 571-592, Copyright (2020), with permission from Karger. Images [top right, bottom] reprinted from *The Lancet*, Vol 386, Ezzedine K, et al, Vitiligo, Pages 74-84, Copyright (2015), with permission from Elsevier. Images [middle] reprinted from *J Am Acad Dermatol*, Vol 77, Rodrigues M, et al, New discoveries in the pathogenesis and classification of vitiligo, doi: 10.1016/j.jaad.2016.10.048, Copyright (2017), with permission from Elsevier.

1. Bergqvist C, Ezzedine K. *Dermatology*. 2020;236:571-592. **2.** Ezzedine K, et al. *Pigment Cell Melanoma Res*. 2012;25:E1-13. **3.** Picardo M, et al. *Nat Rev Dis Primers*. 2015;1:15011.
4. Ezzedine K, et al. *Lancet*. 2015;386:74-84. **5.** Rodrigues M, et al. *J Am Acad Dermatol*. 2017;77:17-29. **6.** Rodrigues M, et al. *J Am Acad Dermatol*. 2017;77:1-13.
Images created by Teitge Design (www.teitgedesign.com/); original available at https://www.umassmed.edu/vitiligo/blog/blog-posts1/2020/05/patterns-of-vitiligo/. Accessed Mar 2022.

Vitiligo Is Associated With Various Autoimmune Comorbidities



In a retrospective study, 15.3% of individuals with vitiligo had 1 or more significant comorbid autoimmune condition[1]

Of the autoimmune disorders reported, thyroid disease is the most common[1,3]

[a] Includes all types of thyroid disease including hypothyroidism and hyperthyroidism.[3]

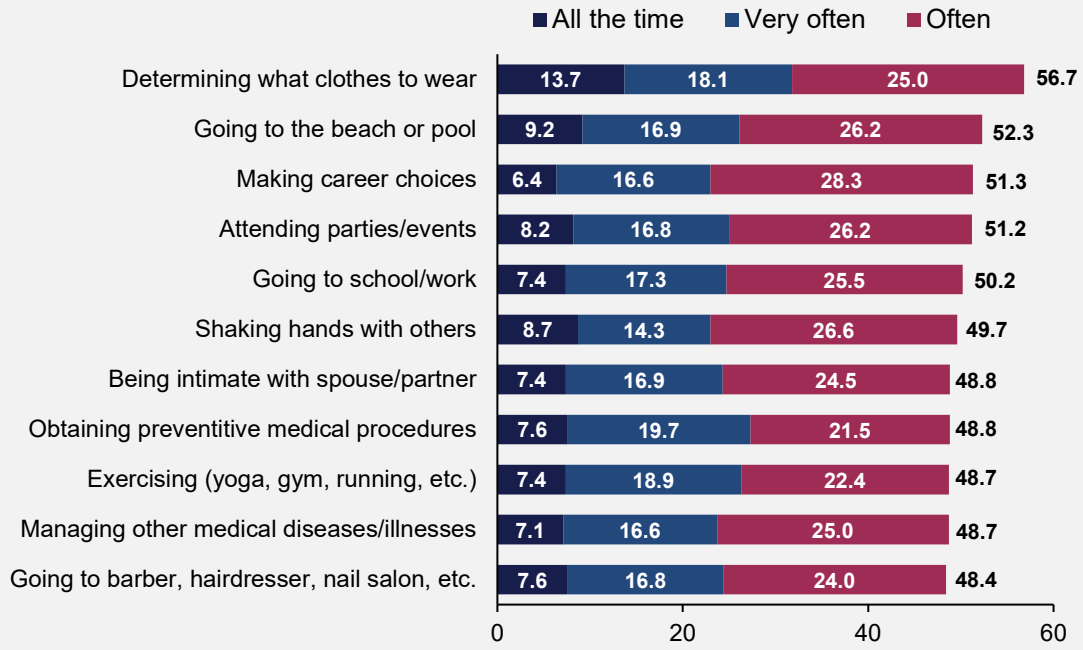
1. Hadi A, et al. *J Am Acad Dermatol.* 2020;82:628-633. 2. Ezzedine K, et al. *Dermatol Ther (Heidelb).* 2023;13:2265-2277. 3. Liu J, et al. Academy of Managed Care (AMCP) Nexus 2023, Orlando, FL, October 16-19, 2023.

Vitiligo Can Impact QoL in Routine Activities, Employment, and Psychosocial Health

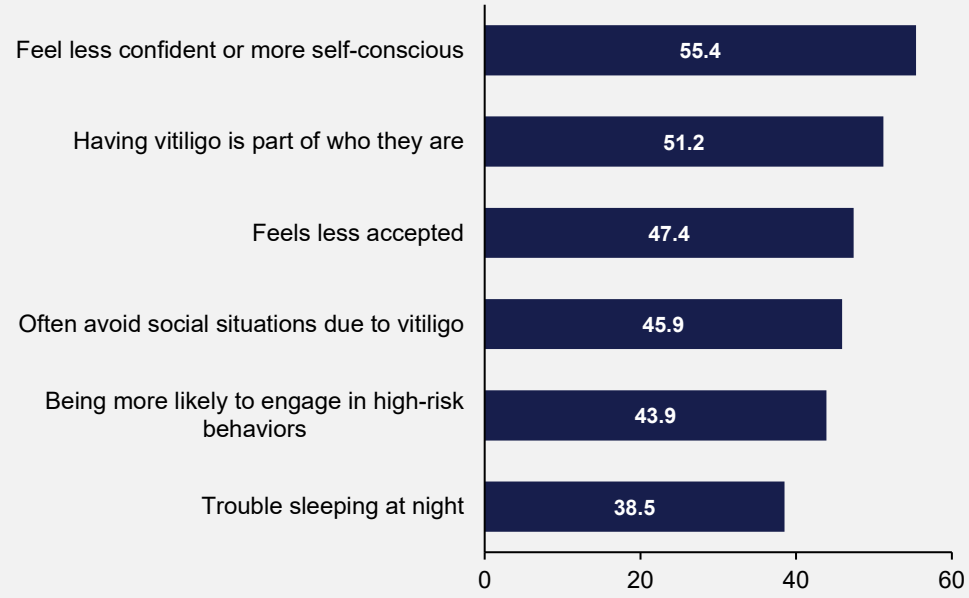
In a cross-sectional online survey of 608 US adults diagnosed with vitiligo[1,a]:

- Vitiligo impacted participants' daily lives by affecting their choice of clothing, going to social activities, and making career choices
- More than half reported that having vitiligo made them feel less confident and more self-conscious

Daily Impact of Vitiligo[1]



Perceived Effect of Vitiligo on Well-Being[2]
(Includes response of strongly agree or agree)

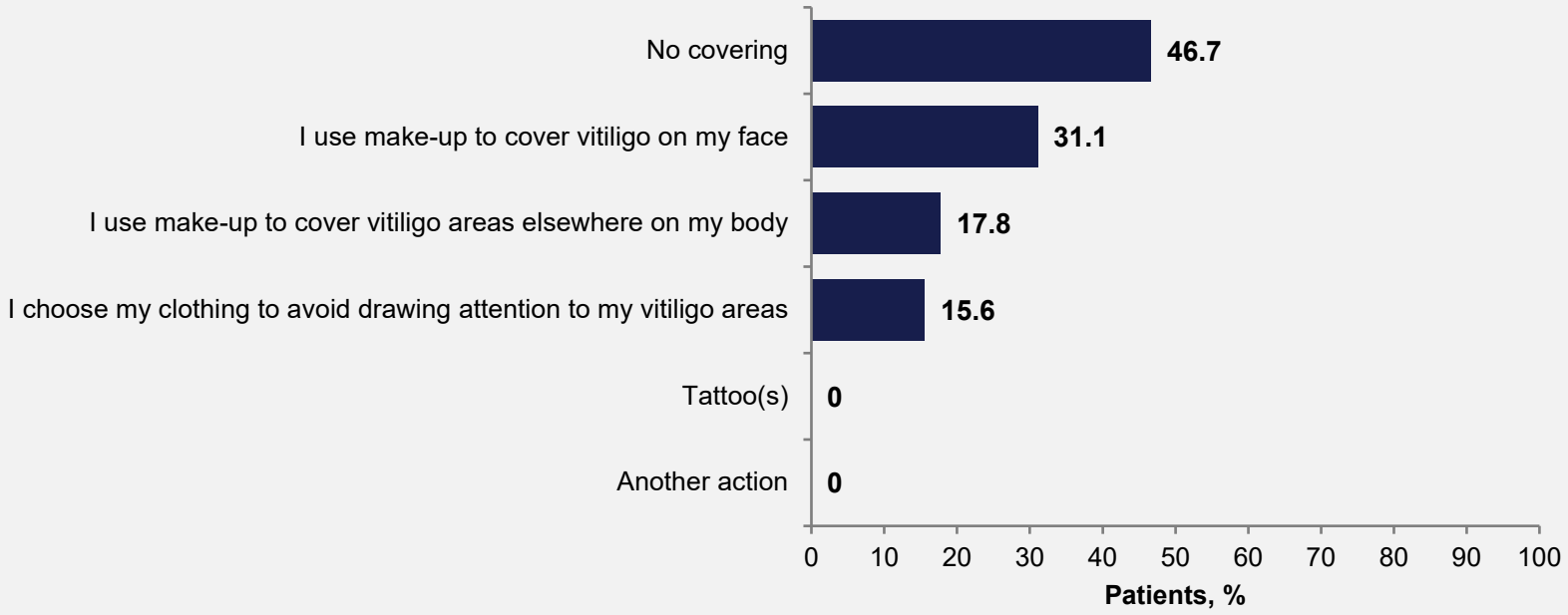


[a]US data from the population-based Vitiligo and Life Impact Among International Communities (VALIANT) study which sought to understand the burden of vitiligo. Adults ≥18 years of age diagnosed with vitiligo by a healthcare professional were recruited for the study. Participants completed a self-administered online screener designed to capture high-level demographics, confirm diagnosed vitiligo, and provide consent before continuing to the 25-minute survey. Participant responses regarding their emotional well-being were sought to understand the effect of vitiligo on various attitudinal metrics, including daily life and activities, impact on self-esteem, depression, anxiety, and stigmatization.[1,2] QOL, quality of life.

1. Bibeau K, et al. American Academy of Dermatology Annual Meeting, Boston, MA, March 25-29, 2022. Poster 34630. 2. Bibeau K, et al. American Academy of Dermatology Annual Meeting, Boston, MA, March 25-29, 2022. Poster 34631.

Individuals With Vitiligo Spend a Considerable Amount of Time Each Day Covering Up Their Lesions

How Individuals With Vitiligo Reported Covering Up Their Lesions[1]



Data from the Adelphi Vitiligo Disease Specific Program™ patient burden survey of 90 US participants reported[1,a]:

- About half of the participants (53.3%) cover up or hide their vitiligo
- Mean amount of time taken every day to cover up vitiligo with make-up:
  - **Face:** ~57 minutes
  - **Other body parts:** ~30 minutes

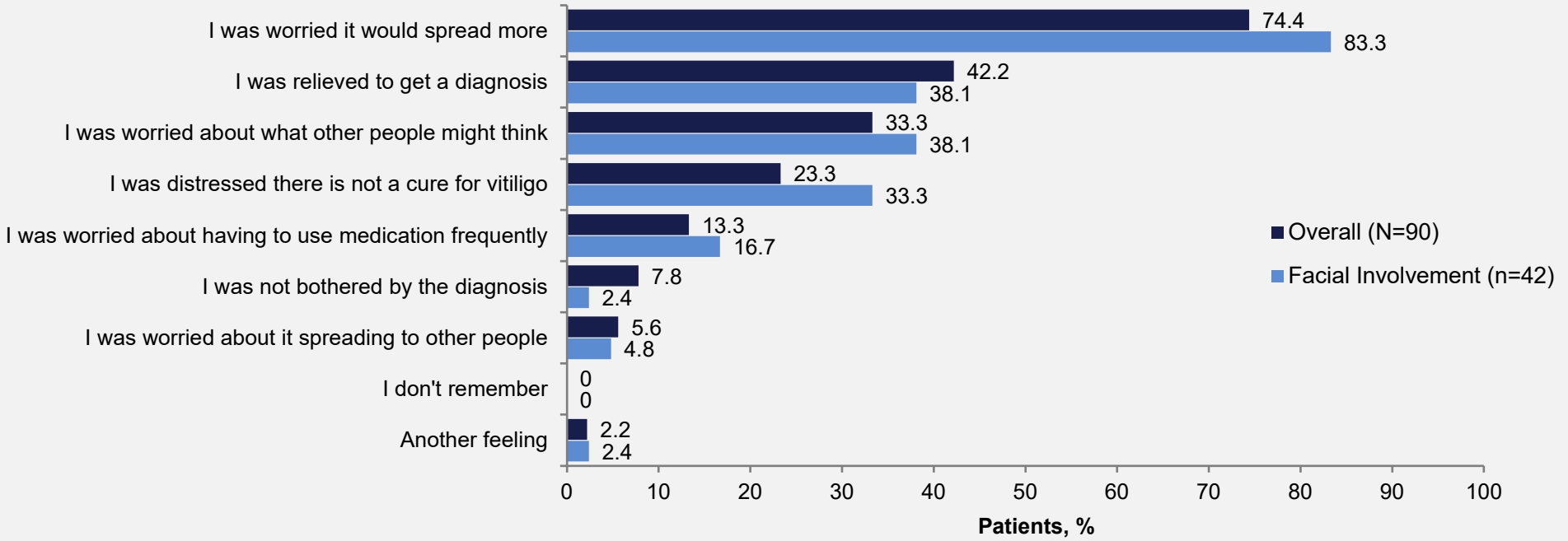
[a]Reported data from the Adelphi Vitiligo Disease Specific Program database which captured patient demographics, disease characteristics, treatment history, and self-reported patient burden to understand the impact vitiligo has on patient quality of life. Data collection included physician-completed medical record data abstraction, and physician- and patient-completed surveys. US dermatologists treating patients ≥12 years of age with NSV completed surveys and patient record forms for 6 consecutive adults and 2 adolescents. Patients aged ≥12 years diagnosed with NSV, affecting ≤10% total BSA, not involved in ongoing clinical trials, and completed the patient burden survey were eligible for data collection. The self-reported patient burden survey included metrics on: vitiligo concealment, feelings at first vitiligo diagnosis, psychosocial burden, support network of patients, work productivity and activity impairment, patient perspective noticeability of vitiligo lesions, and impact on quality of life and mental health conditions such as anxiety and depression.[1] BSA, body surface area; NSV, nonsegmental vitiligo. 1. Rosmarin D, et al. Global Vitiligo Foundation Annual Scientific Symposium, New Orleans, LA, March 16, 2023. Oral Presentation.

Individuals With Vitiligo Experience a Range of Feelings at First Diagnosis, Especially Those With Facial Involvement

Data from the Adelphi Vitiligo Disease Specific Program™ patient burden survey of 90 US participants showed[1,a]:

- Most were worried about their vitiligo spreading when they first received the diagnosis
- A greater proportion of participants with facial involvement felt worried or distressed compared to those without facial involvement

How Patients Reported They Felt When First Diagnosed With Vitiligo[1]



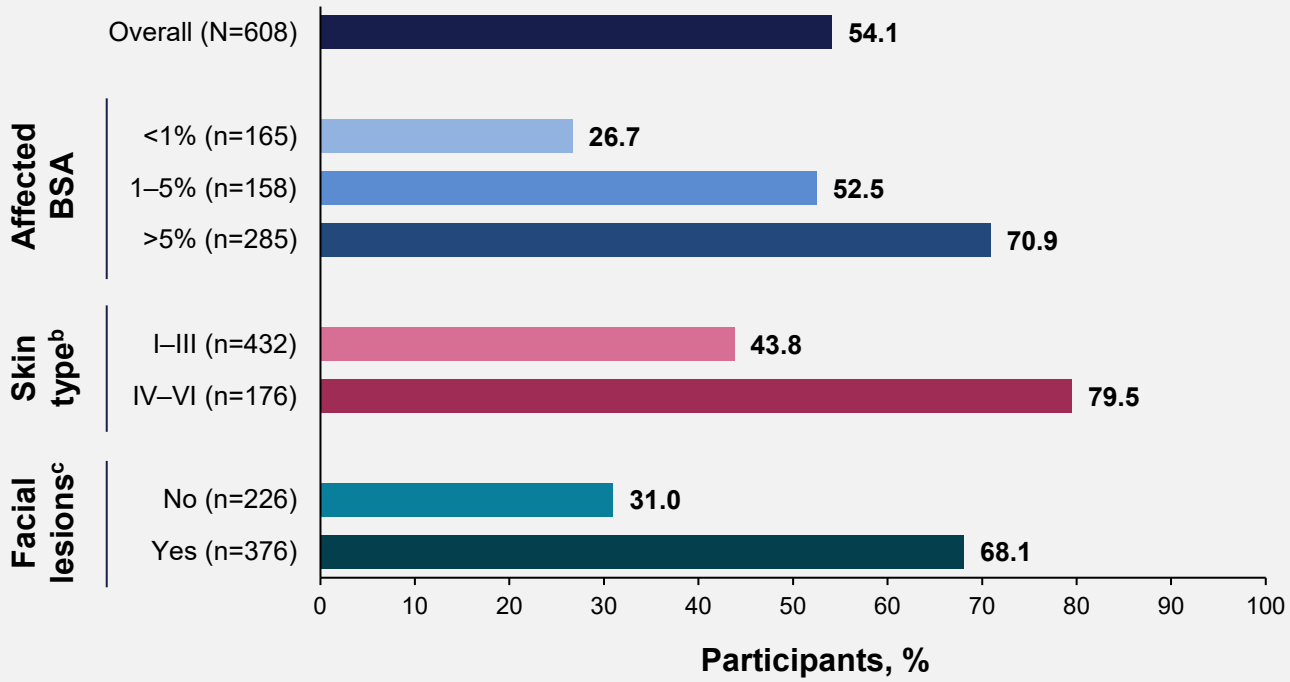
[a]Reported data from the Adelphi Vitiligo Disease Specific Program database which captured patient demographics, disease characteristics, treatment history, and self-reported patient burden to understand the impact vitiligo has on patient quality of life. Data collection included physician-completed medical record data abstraction, and physician- and patient-completed surveys. US dermatologists treating patients ≥12 years of age with NSV completed surveys and patient record forms for 6 consecutive adults and 2 adolescents. Patients aged ≥12 years diagnosed with NSV, affecting ≤10% total BSA, not involved in ongoing clinical trials, and completed the patient burden survey were eligible for data collection. The self-reported patient burden survey included metrics on: vitiligo concealment, feelings at first vitiligo diagnosis, psychosocial burden, support network of patients, work productivity and activity impairment, patient perspective noticeability of vitiligo lesions, and impact on quality of life and mental health conditions such as anxiety and depression.[1] BSA, body surface area; NSV, nonsegmental vitiligo. 1. Rosmarin D, et al. Global Vitiligo Foundation Annual Scientific Symposium, New Orleans, LA, March 16, 2023. Oral Presentation. All trademarks are the property of their respective owners.

Many Adults With Vitiligo Experience Substantial Psychological Burden

In a cross-sectional online survey of 608 US adults diagnosed with vitiligo[a]:

- About half reported having a diagnosed mental health condition by a medical professional
  - Anxiety and depression were the most common diagnoses
- Most had symptoms consistent with depression regardless of having a formal diagnosis
  - More than half exhibited moderate to severe symptoms of depression

Moderate to Severe Depressive Symptoms as Assessed by the PHQ-9

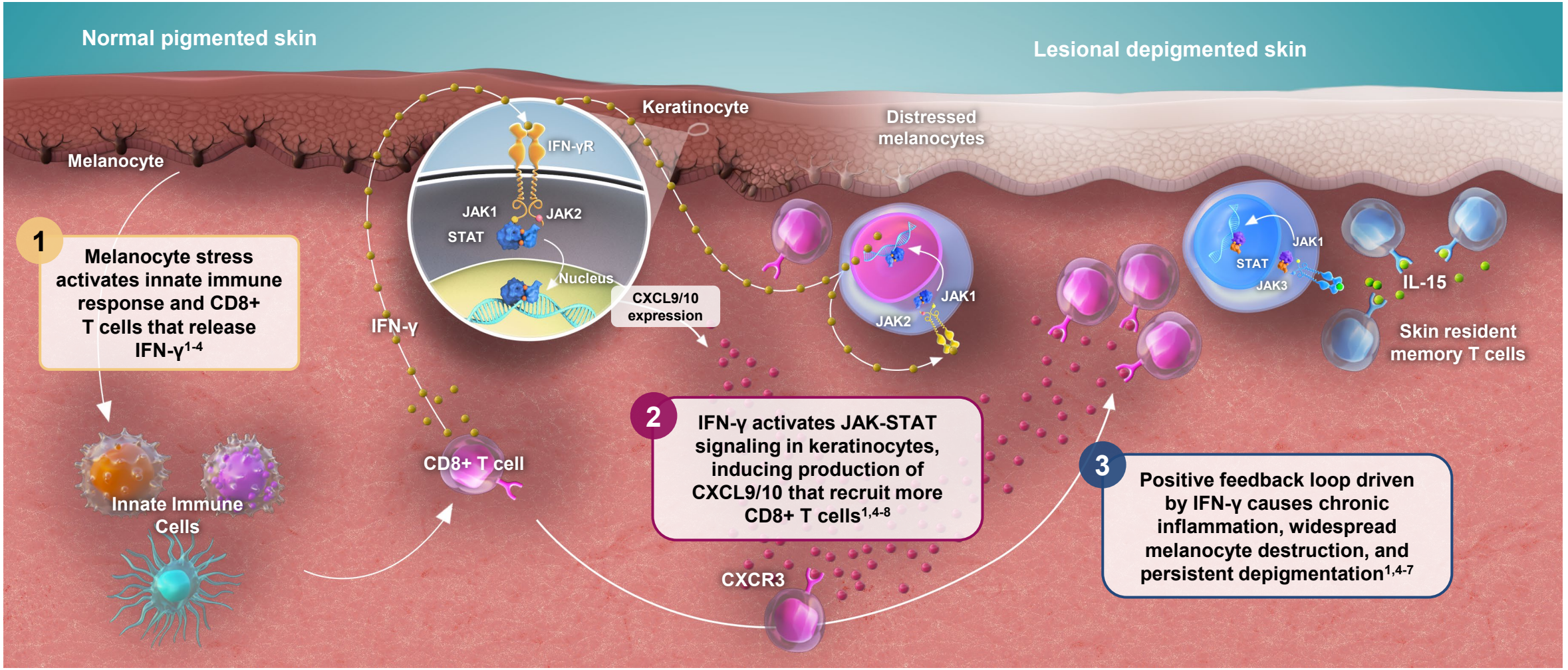


[a]US data from the population-based Vitiligo and Life Impact Among International Communities (VALIANT) study which sought to understand the burden of vitiligo. Adults ≥18 years of age diagnosed with vitiligo by a healthcare professional were recruited for the study. Participants completed a self-administered online screener designed to capture high-level demographics, confirm diagnosed vitiligo, and provide consent before continuing to the 25-minute survey. Participant responses regarding their emotional well-being were sought to understand the effect of vitiligo on various attitudinal metrics, including daily life and activities, impact on self-esteem, depression, anxiety, and stigmatization. Symptoms consistent with depression were screened via the validated nine-item PHQ-9 depression screener. [b]Fitzpatrick skin phototypes I–III were characterized as fairer skin types and phototypes IV–VI as darker skin types. [c]Individuals with 0% affected BSA (n=6) were excluded from analysis of facial lesions. BSA, body surface area; PHQ-9, nine-item Patient Health Questionnaire.

Bibeau K, et al. American Academy of Dermatology Annual Meeting, Boston, MA, March 25-29, 2022. Poster 34630.

Pathophysiology of Vitiligo

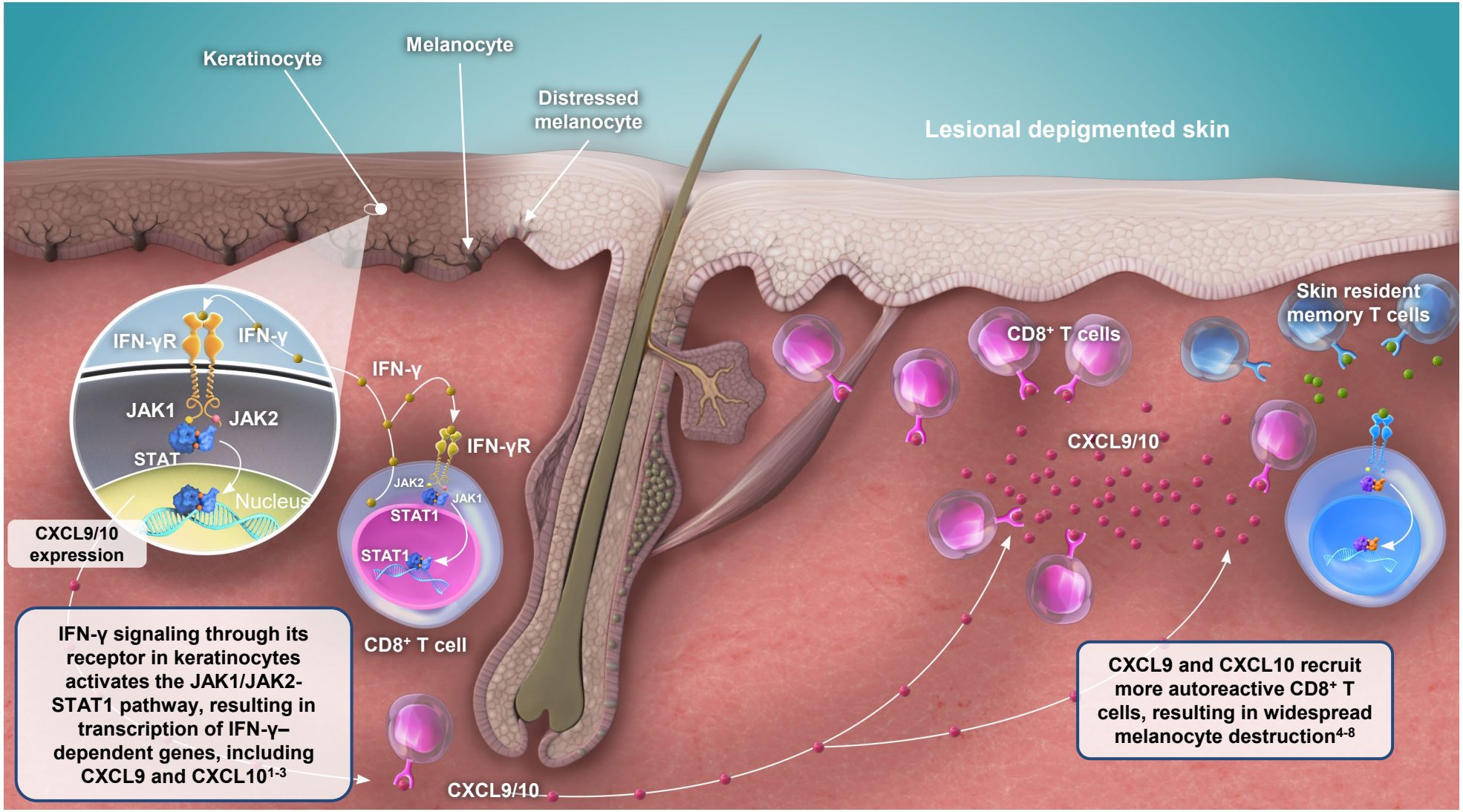
Depigmentation in Vitiligo Is the Result of CD8+ T-Cell–Mediated Destruction of Melanocytes



[a]Vitiligo may be more complex than previously thought, with prominent combined activities of both Th1- and Th2-related cytokines inducing inflammatory responses. Moreover, melanocytes may not only be a target of T cells but could actively contribute to perpetuate inflammation. CXCL9, chemokine ligand 9; CXCL10, chemokine ligand 10; CXCR3, chemokine receptor 3; IFN-γ, interferon gamma; IFN-γR, interferon gamma receptor; IL-15, interleukin-15; JAK, Janus kinase.

1. Bergqvist C, Ezzedine K. *J Dermatol*. 2021;48:252-270. 2. Strassner JP, Harris JE. *Curr Opin Immunol*. 2016;43:81-88. 3. Richmond JM, et al. *Curr Opin Immunol*. 2013;25:676-682. 4. Frisoli ML, et al. *Annu Rev Immunol*. 2020;38:621-648. 5. Howell MD, et al. *Front Immunol*. 2019;10:2342. 6. Rashighi M, Harris JE. *Dermatol Clin*. 2017;35:257-265. 7. Rosmarin D, et al. *Lancet*. 2020;396:110-120. 8. Martins C, et al. *J Invest Dermatol*. 2022;142(4):1194-1205.e7. 9. Chen X, et al. *Free Radical Biology Med*. 2019;139:80-91. 10. Richmond JM, et al. *Sci Transl Med*. 2018;10:eaam7710. 11. Atwa MA, et al. *J Cosmet Dermatol*. 2021;20:2640-2644.

JAK-1 and JAK-2 Mediated IFN-γ Signaling Drives Inflammation in Vitiligo



CXCL9, chemokine ligand 9; CXCL10, chemokine ligand 10; CXCR3, chemokine receptor 3; IFN-γ, interferon gamma; JAK, Janus kinase; STAT, signal transducer and activator of transcription. 1. Strassner JP, Harris JE. *Curr Opin Immunol*. 2016;43:81-88. 2. Regazzetti C, et al. *J Invest Dermatol*. 2015;135:3105-3114. 3. Abdallah M, et al. *Pigment Cell Melanoma Res*. 2018;31:330-336. 4. Rashighi M, et al. *Ann Transl Med*. 2015;3:1-5. 5. Rashighi M, Harris JE. *Dermatol Clin*. 2017;35:257-265. 6. Frisoli ML, et al. *Annu Rev Immunol*. 2020;38:621-648. 7. Richmond JM, et al. *J Invest Dermatol*. 2017;137:350-358. 8. Rosmarin D, et al. *Lancet*. 2020;396:110-120.

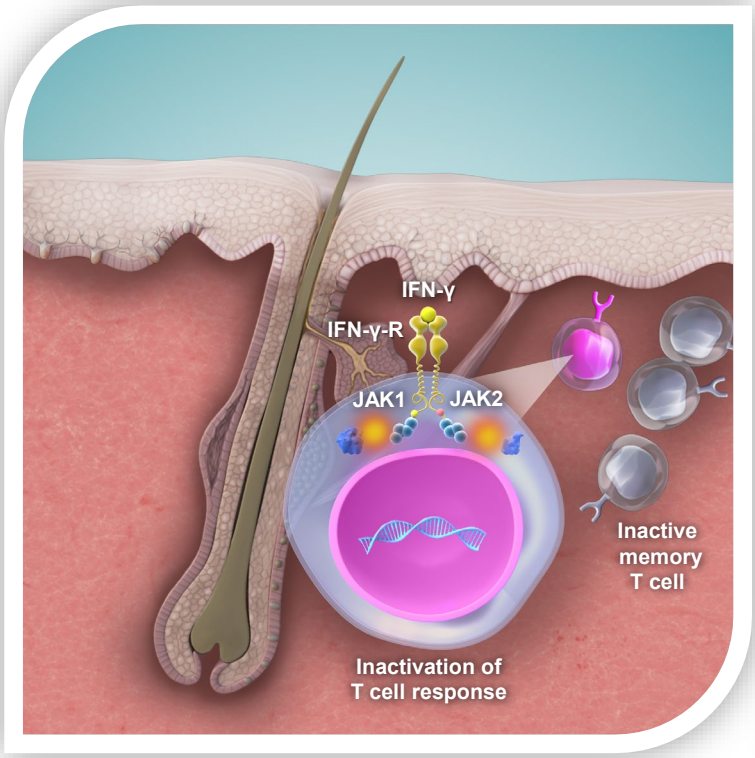
Management of Vitiligo

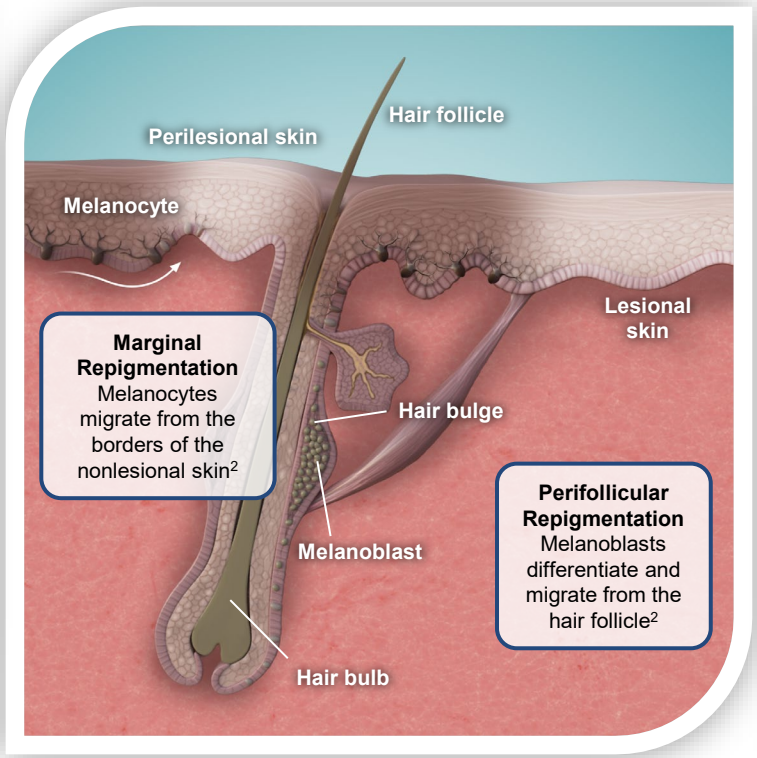
The Goal of Vitiligo Therapy Is to Inhibit Autoimmune Response, Promote Repigmentation, and Maintain Repigmentation[1-3]

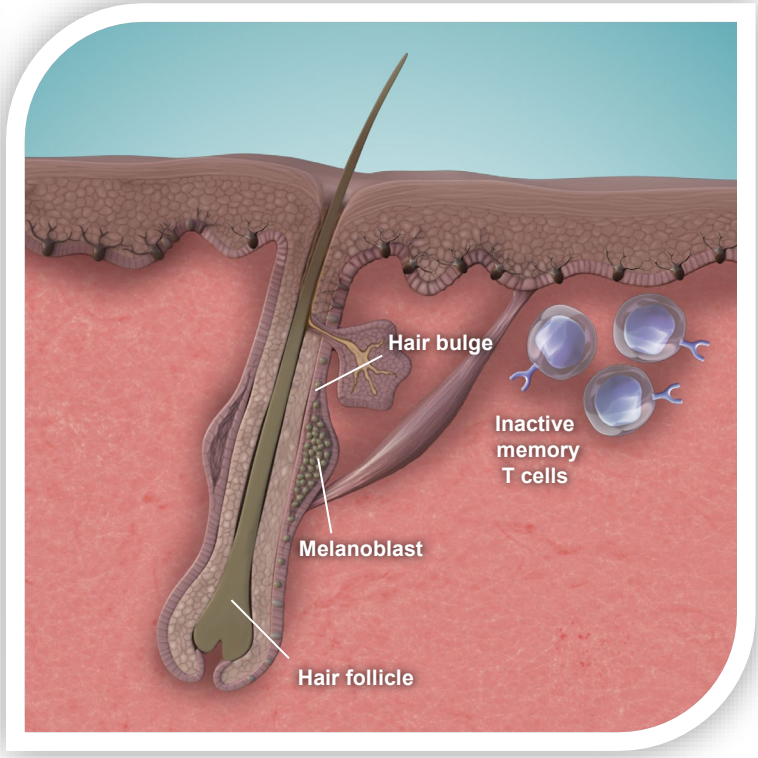
Inhibit Autoimmune Response
by reducing inflammation and further destruction of melanocytes[2]

Promote repigmentation
via differentiation and proliferation of melanocyte stem cells[2,3]

Maintain repigmentation
by preventing activation of skin T_{RM}[1]





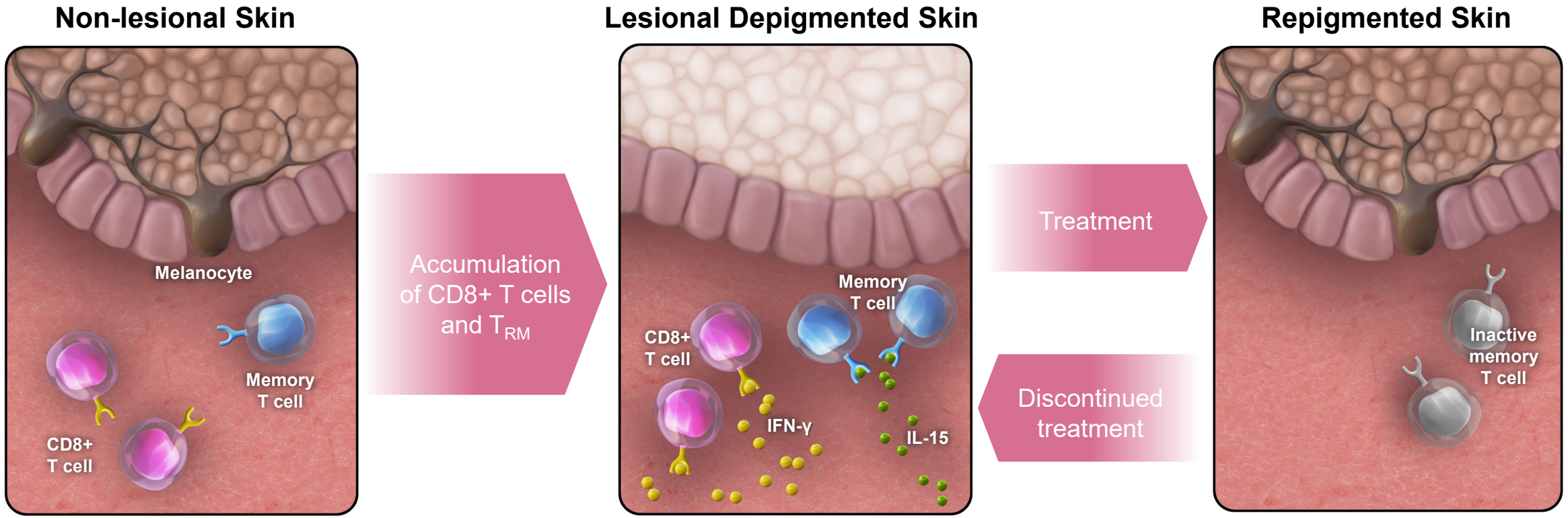


IFN-γ, interferon gamma; JAK, Janus kinase; T_{RM}, resident memory T cells.

1. Boniface K, Seneschal J. *Exp Dermatol*. 2019;28:656-661. 2. van Geel N, et al. *J Eur Acad Dermatol Venereol.* 2023;37(11):2173-2184. 3. Seneschal J, et al. *J Eur Acad Dermatol Venereol.* 2023;37(11):2185-2195.

Consistent and Continuous Therapy Following Repigmentation Is Important to Prevent Progression and Depigmentation of Repigmented Lesion

- Vitiligo is considered a skin memory disorder in which skin resident memory T cells play a prominent role in disease development, progression, and flare-up after treatment is stopped
- Many patients will re-develop vitiligo in the same area following discontinuation of treatment due to skin resident memory T cells that remain in the skin



IFN-γ, interferon gamma; IL-15, interleukin-15; T_{RM}, resident memory T cells.

Boniface K, Seneschal J. *Exp Dermatol*. 2019;28:656-661.

Repigmentation Is a Slow Process That Can Take Weeks to Months Depending on Lesion Location

Areas that begin to repigment the fastest with therapy (weeks)

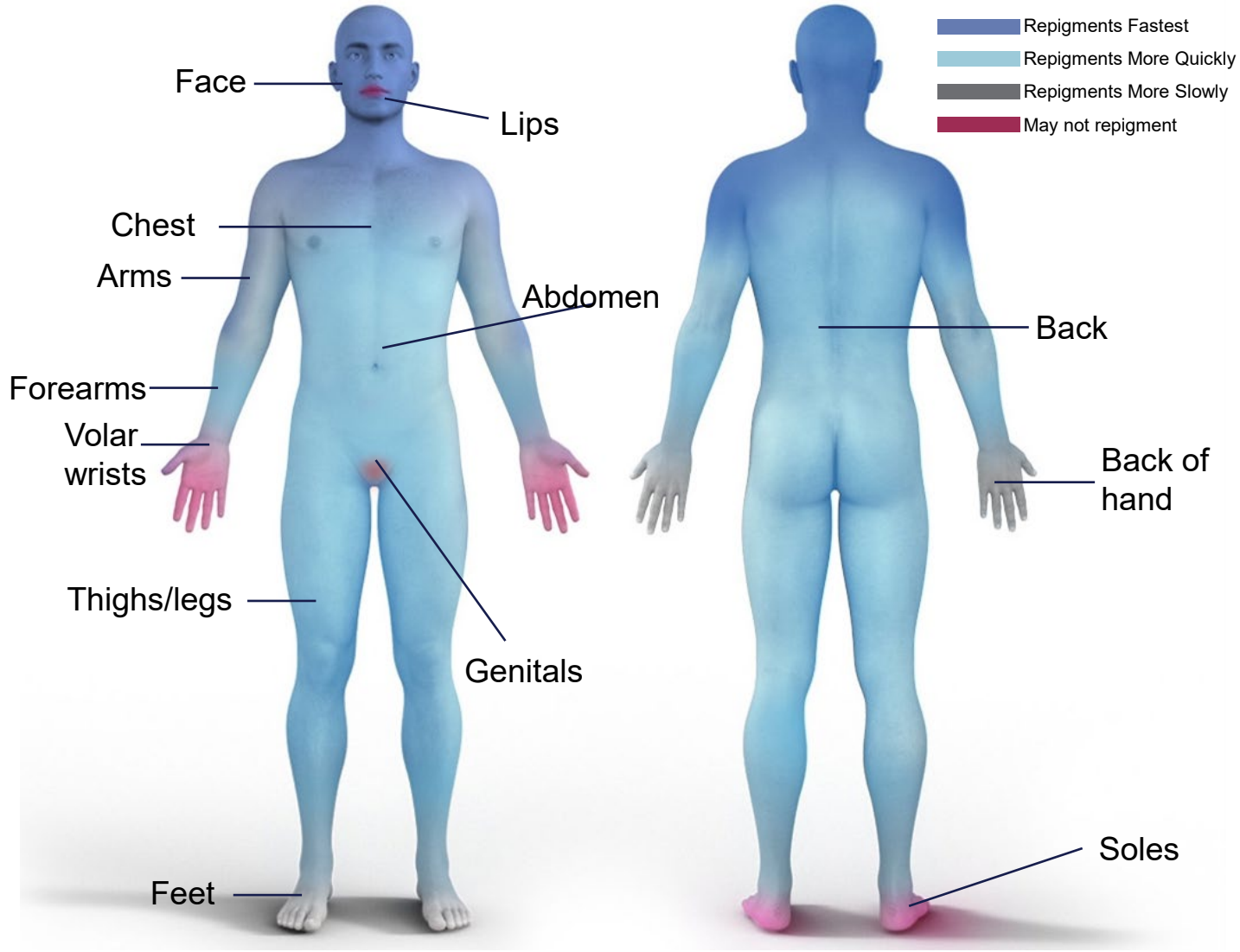
Areas with higher density of hair follicles (eg, **face, arms, forearms, thighs, legs, abdomen, back**)

Areas that repigment more slowly with therapy (months) or are more difficult to repigment

Areas with lower density of hair follicles (eg, **dorsal hands, dorsal feet**)

Areas that may not repigment with therapy

Areas where hair follicles are absent or low in density (eg, **palms, soles, volar wrists, genital sites, mucosal and semimucosal surfaces**) and areas with **no pigmented hair**

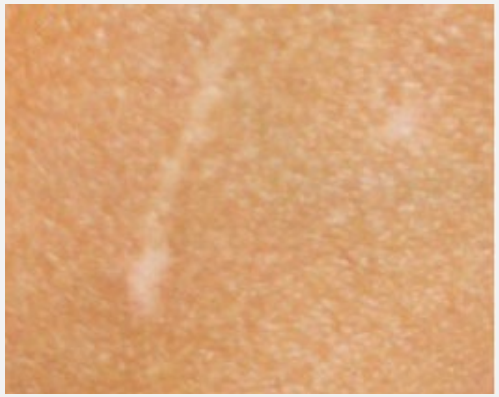


Birlea S, et al. *Dermatol Clin*. 2017;35:205-218.

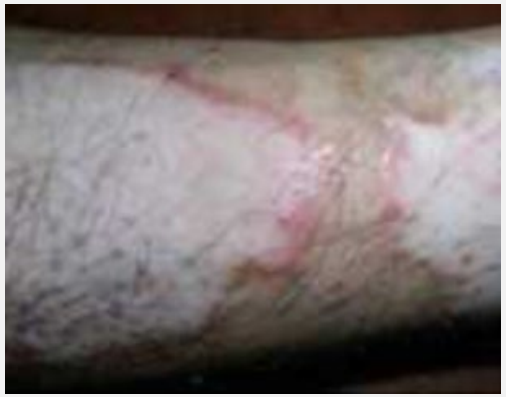
Early Detection and Treatment of Vitiligo Are Critical for Optimal Management

- Vitiligo management requires careful initial assessment to determine the severity and extent of disease and individual prognostic factors[1,2]
- Treatment of vitiligo should be started early to maximize efficacy and improve prognosis[2]
- Early and aggressive treatment should be considered if there are signs of rapidly progressing disease to prevent irreversible damage to pigment cells and improve prognosis[2]

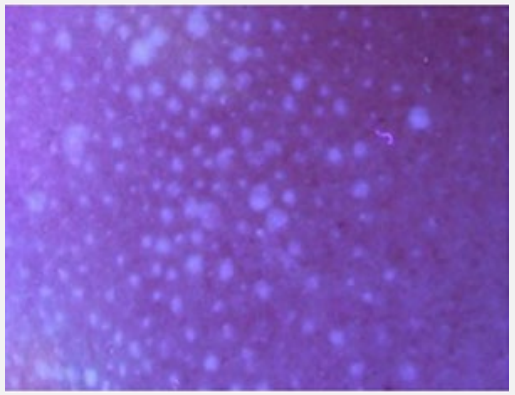
Signs of Disease Activity Include:



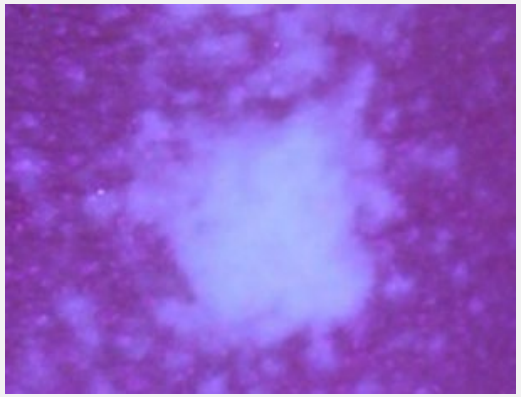
Koebner phenomenon[3]



Inflammatory vitiligo[4]



Confetti-like depigmentation[3]



Hypochromic/blurry borders[3]

Images reprinted from *J Eur Acad Dermatol Venereol*, Vol 33, van Geel N, et al, Clinical visible signs of disease activity in vitiligo: a systematic review and meta-analysis, doi: 10.1111/jdv.15604, Pages 1667-1675, Copyright (2019), with permission from John Wiley and Sons; Verma SB. *Dermatol Online J*. 2005;11. doi: 10.5070/D351m233wk. Figure reproduced under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives (CC BY-NC-ND) license (https://creativecommons.org/licenses/by-nc-nd/4.0/ [creativecommons.org]), only edits for style were made.1. Bergqvist C, Ezzedine K. *Dermatology.* 2020;236:571-592. 2. van Geel N, et al. *J Eur Acad Dermatol Venereol*. 2023;37:2173-2184. 3. van Geel N, et al. *J Eur Acad Dermatol Venereol*. 2019;33:1667-1675. 4. Verma SB. *Dermatol Online J.* 2005;11(3):13. https://doi.org/10.5070/D351m233wk.

Therapeutic Options for the Treatment of Vitiligo

	Topicals	Systemic	Phototherapy	Surgical
Therapies and MOA	**Ruxolitinib (RUX) Cream:** Direct inhibition of IFN-γ signaling by inhibiting JAK1/JAK2 **Topical Calcineurin Inhibitors (TCI):** Inhibits T-cell activation[3] **Topical Corticosteroids (TCS):** Local immunosuppression	**Systemic Corticosteroids:** OMP[a] with oral corticosteroids; IM triamcinolone x 1 dose **Systemic Immunosuppressants:** Cyclosporine, methotrexate, mycophenolate mofetil **MOA:** Immunosuppression to stabilize progressive disease	**Types of Phototherapy:** NB-UVB; excimer laser and lamps (targeted phototherapy) **MOA:** Local immunosuppression to stabilize vitiligo; increases melanocyte proliferation and melanogenesis	**Types of Surgical Procedures:** Tissue grafts; cellular grafts; hair follicle transplantation; autologous melanocyte cultures **MOA:** Transfer of a reservoir of healthy melanocytes to vitiliginous skin for proliferation and migration into areas of depigmentation
Use	RUX used as monotherapy to treat individuals with ≤10% BSA[4] TCS and TCI are used alone when ≤5%-10% BSA affected; in combination when sensitive areas are involved; or in combination with phototherapy in recalcitrant disease	Treatment used in individuals with >5–10% BSA that have active/ rapidly progressive vitiligo Often used in combination with topical therapies and phototherapy to promote repigmentation	Whole-body phototherapy used for extensive disease >5–10% BSA and rapidly spreading disease Targeted phototherapy used when <10% BSA is affected and lack of response to TCS and TCI	Surgical procedures are used to treat stable,[b] localized, depigmented areas unresponsive to medical intervention Often used in combination with phototherapy to shorten time to repigmentation

[a]OMP (oral mini pulse) therapy refers to discontinuous administration of suprapharmacologic doses of steroids. Regimens usually consist of betamethasone or dexamethasone for 3–6 months on 2 consecutive days and is usually administered in combination with other therapies. [b]Disease stability must be evaluated before surgery and is defined by the absence of new or expanding lesions over 6 months to 2 years. MOA, mechanism of action.

1. Grimes PE, et al. Vitiligo: Management and Prognosis. UpToDate. Available: https://www.uptodate.com/contents/vitiligo-management-and-prognosis#!. 2. Rodrigues M, et al. *J Am Acad Dermatol*. 2017;77:1-13. 3. Protopic (tacrolimus). Prescribing information. Astella Pharma US, Inc.; May 2012. 4. OPZELURA® (ruxolitinib) cream. Prescribing information. Incyte Corporation; July 2022.

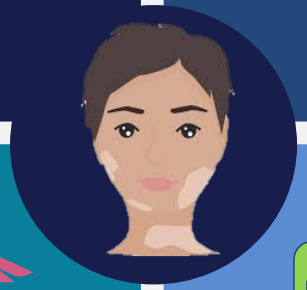
Management of Vitiligo Includes Patient Education and Shared Decision-Making

Patient Education

- Provide education on pathogenesis, chronicity of disease and prognosis, and duration of treatment

Treatment Goals

- Explain the process of repigmentation and set expectations for extent and time to repigmentation based on lesion location to align on attainable treatment goals



Treatment Options

- Discuss available treatment options and patient's preference for treatments to align on most appropriate therapy

Adherence

- If previously treated, evaluate patient adherence to therapy and barriers to adherence
- Reinforce that patient adherence to therapy is key to attaining treatment goals

van Geel N, et al. *J Eur Acad Dermatol Venereol*. 2023;37:2173-2184.

Summary

Vitiligo is a chronic depigmenting autoimmune skin disorder that affects adults of all skin colors, regardless of race and ethnicity[1-3]

Individuals with vitiligo report experiencing psychological conditions, including anxiety and depression and most are concerned about their vitiligo spreading[4,5]

Depigmentation in vitiligo is driven by an inflammatory process through JAK-1/JAK-2 mediated IFN-γ signaling that results in the destruction of melanocytes by CD8+ T cells[1,6]

- Skin resident memory T cells also contribute to disease persistence and depigmentation after treatment discontinuation or interruption

The goal of vitiligo therapy is to stabilize the autoimmune response, promote repigmentation, and maintain repigmentation[1,7]

- Early detection and treatment of vitiligo are critical to optimize management[7]
- Vitiligo management includes educating patients on the chronicity of the disease, setting expectations around duration of treatment and time to repigmentation, and shared-decision making to ensure patient adherence to treatment[7]

CD8+, cluster differentiation 8; FDA, Food and Drug Administration; IFN, interferon; JAKs, Janus kinases.

1. Bergqvist C, Ezzedine K. *Dermatology*. 2020;236:571-592. 2. Ezzedine K, et al. Presented at the 2021 Virtual GVF Annual Scientific Symposium. 3. Gandhi K, et al. *JAMA Dermatol*. 2022;4724158:43-50. 4. Bibeau K, et al. Presented at the American Academy of Dermatology Annual Meeting 2022. Poster 34630. 5. Rosmarin D, et al. Presented at the 2023 GVF Annual Scientific Symposium. 6. Frisoli ML, et al. *Ann Rev Immunol*. 2020;38:621-648. 7. van Geel N, et al. *J Eur Acad Dermatol Venereol*. 2023;37:2173-2184.

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