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Research Article

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A Comprehensive Review of Integrated Psychosocial and Medical Approaches to Pediatric Vitiligo: Current Therapies, Suicide Risk, and Future Gene-Targeted Innovations

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Abstract

Background: *Pediatric vitiligo is a chronic autoimmune skin disorder marked by depigmentation, often causing profound psychological distress during key developmental stages. Emerging treatments such as topical Janus kinase (JAK) inhibitors and oral compound glycyrrhizin target immune-mediated melanocyte destruction but overlook the significant psychosocial burden on affected children. This review evaluates the clinical efficacy and psychosocial outcomes of integrative treatment approaches for pediatric vitiligo, with attention to cultural factors and evolving gene-based therapies.*

Methods: *A systematic search was conducted in May 2025 across PubMed, Embase, PsycINFO, Web of Science, and the Cochrane Library using terms related to pediatric vitiligo, repigmentation therapies, psychosocial outcomes, and novel molecular interventions. Included studies (2010–2025) involved patients aged 0–18 and reported on clinical or psychological outcomes. Five independent reviewers screened studies and assessed bias using Cochrane and ROBINS-I tools. Evidence strength was graded using the GRADE framework.*

Results: *Topical JAK inhibitors, glycyrrhizin-phototherapy combinations, prostaglandin analogs, and Wnt/β-catenin agonists showed promising repigmentation and safety profiles in pediatric populations. However, psychological distress, stigma, and reduced quality of life—especially in children of color—remain under-addressed. Integrated psychosocial support, including culturally tailored cognitive behavioral therapy (CBT) and family-based interventions, improved emotional resilience and adherence. Experimental treatments such as CRISPR, mRNA-based therapies, and melanocyte transplantation represent future directions.*

Conclusion: *Effective pediatric vitiligo management must combine medical and psychological care. Multicenter, longitudinal trials assessing both clinical and psychosocial outcomes are needed to establish holistic, culturally responsive, and personalized treatment models.*

Keywords: Gene Therapy, Glycyrrhizin Phototherapy, JAK Inhibitors, Pediatric Vitiligo, Psychosocial Interventions, Suicide Risk

1. Introduction

Vitiligo is a chronic autoimmune disorder characterized by cell death of melanocytes, which creates depigmented skin macules. The destruction of melanocytes occurs mainly through cytotoxic $CD8^+$ T lymphocytes that detect melanocyte-associated antigens to execute specific cell death mechanisms. The pathogenesis of vitiligo exists as a complex interplay between genetic inheritance, oxidative stress, and immune system dysfunction. The release of HMGB1 and calreticulin from melanocytes due to oxidative stress produces damage-associated molecular patterns, which both enhance localized inflammation and antigen presentation, according to.[1] $CD8^+$ T cell recruitment and activation occur through a chemokine cascade dominated by interferon-gamma (IFN-γ) and CXCL9 and CXCL10, which signal through the CXCR3 receptor.[2] The IFN-γ–CXCL10–CXCR3 axis maintains a self-reinforcing cycle that drives the destruction of melanocytes and expansion of the lesions. [2] The disease progresses and continues due to disrupted melanocyte adhesion and keratinocyte-derived IL-15 trans-presentation together with increased expression of the pro-apoptotic pathway CXCR3B.[3 4,5]

Medical approaches to vitiligo have mainly focused on skin color restoration while ignoring the severe psychological consequences that affect children with the disease. Children and adolescents experience their most crucial psychosocial growth during these developmental periods because social awareness, body image development, and peer connections stand out as

essential elements. Children with vitiligo experience teasing and bullying as well as social exclusion most strongly when their skin lesions appear on their face or hands. [6, 7]The negative social experiences result in lowered self-esteem and increased anxiety and depression while affecting academic achievement and social participation. [6, 7] Patients with darker skin tones typically experience an intensified emotional effect from depigmentation because their skin lacks natural pigment density. The mental suffering caused by pediatric vitiligo creates distress for both the affected children and their entire family system. The emotional state of parents and caregivers suffers from stigma fears, which, together with concerns about their child's mental health, demonstrate the disease's impact across generations. [8] Many families struggle to find care models that unite dermatologic therapy with psychological help despite social support being beneficial for treatment outcomes.

The review examines existing research about clinical and psychosocial treatments and integrated intervention strategies for children with vitiligo. The review evaluates treatment methods for repigmentation along with psychological intervention techniques like family-based therapy and cultural adaptation approaches to develop complete care protocols that handle all aspects of disease impact. Longitudinal studies with cultural sensitivity are necessary to achieve optimal results for children and adolescents who must manage their skin diseases and mental health challenges simultaneously.

2. Methods

The aim of this systematic review is to examine clinical, psychosocial, and combined interventions for pediatric vitiligo to inform future treatment approaches as to comprehensively address both skin restoration and psychological support.

Search

In May 2025, we conducted a literature search for studies related to clinical or psychosocial therapies for pediatric vitiligo using the following databases: PubMed, Embase, PsycINFO, Web of Science, and Cochrane Library. Search terms included a combination of the keywords “pediatric vitiligo,” “JAK inhibitors,” “glycyrrhizin,” “psychotherapy,” “CBT,” “suicide risk,” “mental health,” “gene therapy,” “CRISPR,” “Wnt signaling,” “OCG,” and “β-catenin.”

Inclusion and Exclusion Criteria

Peer-reviewed articles published between January 2010 and May 2025 and printed in English were screened for inclusion. Literature Reviews were excluded. Full-text publications of studies that met inclusion criteria were retrieved and independently assessed by five reviewers. Studies included in the final review described pediatric (0-to-18 year old) patients diagnosed with vitiligo, reported psychosocial outcomes, mental health, or suicide risk of pediatric vitiligo patients, evaluated medical or combination therapies for pediatric vitiligo patients, or indicated non-white or global populations with pediatric vitiligo.

Screening and Analysis

Risk of bias was assessed and reported with Cochrane Risk of Bias Tool for randomized controlled trials and ROBINS-I for non-randomized studies. GRADE was used to assess all studies for general evidence strength and was reported with findings.

The examination was performed in agreement with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) reporting guidelines using publicly available data. This review did not require institutional review board approval because it did not utilize human participants or original data collection at any specific hospital or clinical site.

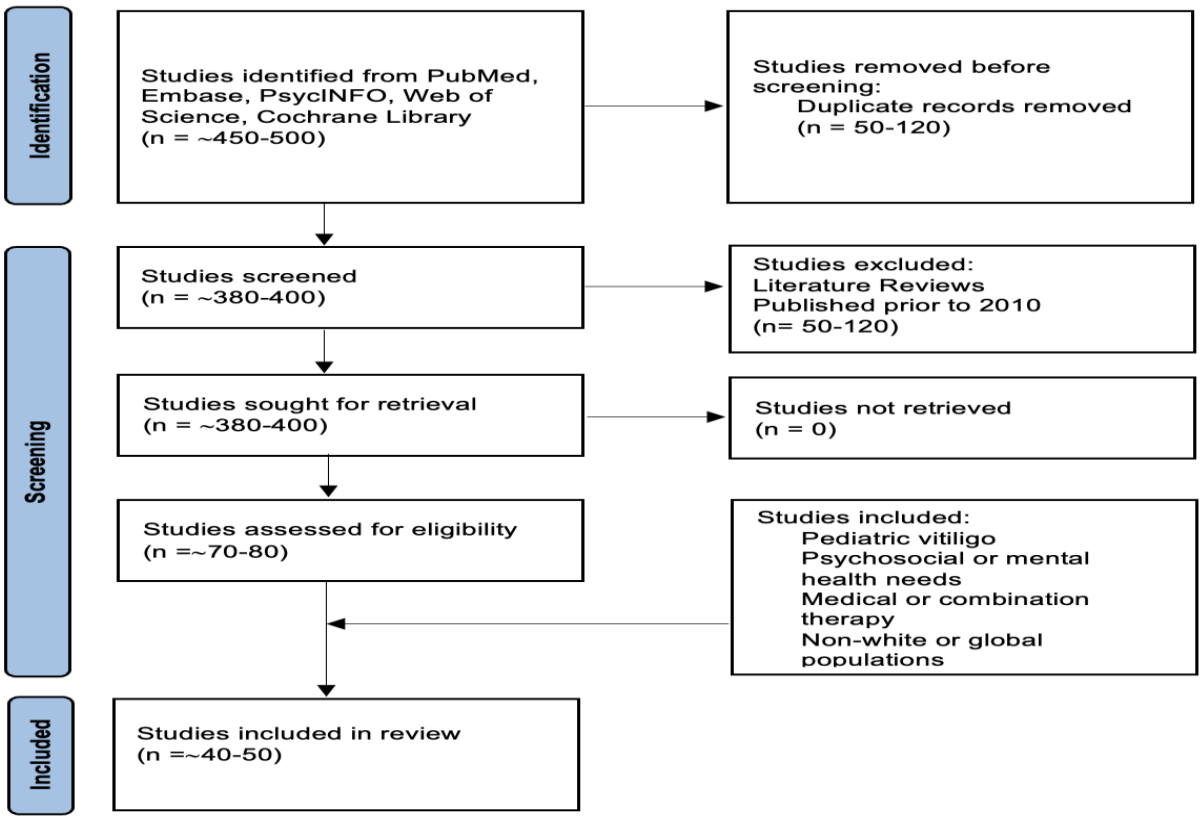

Fig 1: Literature Review Flow Diagram.

3. Results

Medical Interventions and Mechanistic Basis

Vitiligo management in pediatric populations has advanced beyond topical corticosteroids and calcineurin inhibitors, with emerging therapies targeting the immunologic and oxidative mechanisms underlying melanocyte destruction (Table 1). The following summarizes four therapeutic classes with growing relevance in pediatric care: oral compound glycyrrhizin, topical Janus kinase inhibitors, prostaglandin analogues, and Wnt/β-catenin signaling agonists.

3.1. Oral Compound Glycyrrhizin (CG) + Phototherapy

Compound glycyrrhizin, a licorice root extract with glucocorticoid-like and immunomodulatory properties, has gained attention for its role in inhibiting high-mobility group box 1 (HMGB1) protein release, thereby reducing oxidative stress and preventing autophagic melanocyte death. [9] In a meta-analysis of 39 randomized controlled trials involving nearly 4,000 patients, CG combined with phototherapy significantly outperformed phototherapy alone in achieving >50% repigmentation (RR = 1.28, $p < 0.001$. [9] Recent pediatric-specific data by Zhang et al. further support OCG's efficacy.[10] In a 52-week RCT involving 50 children with vitiligo, OCG combined with narrowband UVB (NB-UVB) achieved a 52.3% reduction in Vitiligo Area Scoring Index (VASI), comparable to oral prednisone (55.7%), but with a safer side effect profile. Serum HMGB1 levels also significantly decreased in both arms, confirming the compound's biological activity. Although most trials have been conducted in China and lack stratification by age or race, the favorable safety profile of CG, especially its steroid-sparing effects, makes it a promising candidate for pediatric populations in skin-of-color communities where long-term steroid use poses heightened risks[9, 11].

3.2. Topical Janus Kinase (JAK) Inhibitors

JAK inhibitors represent a major shift in vitiligo treatment by targeting the interferon-gamma (IFN-γ)/JAK/STAT signaling axis implicated in $CD8^+$ T-cell–mediated melanocyte destruction.[12] Topical ruxolitinib, a selective JAK1/2 inhibitor, is now FDA-approved for adolescents (≥12 years) with non-segmental vitiligo and has demonstrated significant facial repigmentation in phase III trials.[13] In pediatric studies, ruxolitinib 1.5% cream applied twice daily has achieved up to 90% facial repigmentation in children as young as 3 years old, particularly when used early in the disease course. [14,15,16]

Combination therapy with NB-UVB or 308-nm excimer laser further enhances outcomes. Importantly, the treatment is well tolerated, with the most common adverse events being localized acne and transient irritation.[17] Despite these promising results, most JAK inhibitor trials lack pediatric representation, especially among children of color, a population disproportionately affected by vitiligo and psychosocial burden.[18, 19] Nonetheless, consensus guidelines now recommend topical ruxolitinib as a first-line therapy for pediatric non-segmental vitiligo when conventional treatments fail.[20]

3.3. Prostaglandin Analogues (e.g., Latanoprost)

Prostaglandin F2α analogues such as latanoprost and bimatoprost promote melanogenesis by activating melanocyte PG receptors, increasing intracellular cyclic AMP, and enhancing melanosome transfer via filopodia formation.[21] These agents mimic the melanogenic effects of UV radiation and upregulate tyrosinase and cyclooxygenase-2 expression via α-MSH pathways. In children with facial vitiligo and darker skin tones, PGAs have demonstrated high repigmentation rates, especially when combined with microneedling and NB-UVB.[21] In Jha et al.'s pediatric case series, Grade 4 facial repigmentation was observed with bimatoprost monotherapy, while Neinaa et al. showed enhanced outcomes with latanoprost triple therapy.[22, 23] Adverse effects were minimal and localized, including hypertrichosis and transient burning, with no systemic reactions reported. PGAs remain underutilized in pediatric care, possibly due to limited familiarity and lack of standardized protocols. Their low toxicity and synergy with light-based therapies render them a particularly attractive option for pediatric patients with stable or facially localized disease.[24]

3.4. Wnt/β-Catenin Signaling Agonists

The Wnt/β-catenin pathway is critical in melanocyte stem cell activation, differentiation, and migration, essential for epidermal repigmentation in vitiligo. Activation of this pathway, particularly through Wnt3a, Wnt7a, or Wnt10b, has shown melanogenic effects in preclinical models.[25, 26] Bellei et al. demonstrated that adipose-derived extract (AT-Ex) can activate β-catenin signaling in vitiligo melanocytes, promoting the expression of melanogenesis-related genes like Sox9 and tyrosinase while enhancing antioxidant defenses through Nrf2 pathways.[25] Similarly, Yamada et al. showed that Wnt7a stimulated melanocyte stem cell differentiation in UVB-treated mouse models, while Goldstein et al. identified β-catenin as the top upstream regulator during NB-UVB–induced repigmentation in humans.[26,27] Additionally, vitamin D has been shown to stabilize β-catenin by promoting GSK3β phosphorylation, thereby protecting melanocytes from oxidative damage and promoting their survival.[28] While these studies underscore the therapeutic potential of Wnt agonists in repigmentation, no pediatric clinical trials have yet tested their application in children with vitiligo. Nevertheless, the mechanistic rationale remains strong, and non-invasive Wnt-based adjuvants like AT-Ex may offer future alternatives to UVB therapy in younger populations, particularly those with skin of color.[18, 25]

Table 1: Mechanism of Action and Clinical Data for Emerging Pediatric Vitiligo Therapies.

Therapy Class	Mechanism of Action	Pediatric Efficacy	Safety Profile	Population Notes
Oral Compound Glycyrrhizin (CG)	Inhibits HMGB1 release → ↓ oxidative stress, ↓ autophagic melanocyte death	Comparable to prednisone in VASI reduction (52.3% vs. 55.7%)[10]	Favorable; steroid-sparing; no severe AEs	Pediatric trial (n=50); underrepresented in U.S./diverse skin types
Topical JAK Inhibitors (Ruxolitinib)	Blocks JAK1/2 → ↓ IFN-γ–JAK–S TAT1 signaling → ↓ cytotoxic T-cell–driven melanocyte death	90% facial repigmentation in some children as young as 3[14]	Mild AEs: acne, site irritation; systemic absorption minimal	Approved ≥12 years; off-label use in younger children promising
Prostaglandin Analogues (Latanoprost, Bimatoprost)	Activates PGF2α receptors → ↑ cAMP → ↑ tyrosinase, melanosome transfer, melanogenesis	Grade 4 repigmentation in pediatric facial vitiligo (skin of color) 22; triple therapy superior[23]	Mostly mild: hypertrichosis, burning; no systemic reactions	Pediatric cases included; studies often combine with microneedling/NB-UVB
Wnt/β-Catenin Agonists (AT-Ex, Vitamin D)	Activates Wnt3a/7a/10b → β-catenin stabilization → ↑ melanocyte stem cell proliferation and migration	No clinical pediatric trials yet; strong preclinical evidence 19, 26	Preclinical safety only; AT-Ex and Vitamin D have favorable profiles in vitro	Lacks pediatric data; promising in regenerative, non-genetic repigmentation strategies for children

Psychosocial Burden and Interventions

Patients with vitiligo experience a significant psychosocial burden, appearing as lower body-image satisfaction, reduced peer acceptance, and increased internalized stigma. [29, 30] This burden is even more pronounced among non-white patients, for whom societal and cultural beauty standards emphasize even-toned, pigment-rich skin.[31, 32] An analysis of vitiligo patients participating in the *All of Us* campaign showed that 27% of self-identifying non-Caucasian patients reported fair or poor quality of life versus 7% of self-identifying Caucasian patients.[31] This disparity highlights how cultural beauty ideals surrounding skin tone intensify the psychosocial impact for people of color, who may face compounded discrimination both from peers and society at large.[32] Boza et al. emphasizes this point in a South America-based study showcasing that stigma contributed heavily to low quality of life index scores, reinforcing that perceived social rejection and internalized shame significantly impacts the psychological well-being of individuals with vitiligo.[33] Adding to this point, a similar study conducted in Turkey found that lower quality of life scores correlated to lower self-esteem and body image perception.[30] Though this study was conducted on adult participants, this evidence supports the argument that vitiligo's visibility can directly impact a child's self-concept and confidence. This connection between visible skin difference, cultural stigma, and negative self-perception shows that vitiligo can have a deeply detrimental psychosocial effect, particularly during childhood when identity formation is most sensitive to peer and societal input.

The psychosocial distress associated with vitiligo may lead to more serious mental health consequences. A growing body of evidence links vitiligo to a higher risk for developing depression, anxiety, and suicidal ideation. School-age children with visible depigmentation are particularly at greater risk for bullying and social rejection. This developmental stage is already marked by heightened sensitivity to appearance and peer evaluation, making young patients with vitiligo especially susceptible to psychological decline. [29] Kruger et al. found that 66.2% of the 74 pediatric patients evaluated experienced distress due to their vitiligo.[34] Alarmingly, 44.6% dealt with nasty comments, and 21.7% were bullied, leading to avoidance of social settings for fear of being stigmatized.[34] This pattern of peer rejection and social withdrawal can lead to chronic low self-esteem, which is an eventual pathway towards suicidal ideation if not appropriately addressed. The severity of vitiligo lesions and involvement of more visible regions on the body have a negative correlation to quality of life in children.[35] Lesions are often more pronounced in darker skin tones, perhaps contributing to this disparity in quality of life amongst different ethnicities. African American patients with vitiligo were found to experience higher rates of depression and anxiety and other psychiatric illnesses when compared to non-vitiligo patients.[36] Thompson et al.emphasizes this point in a large, population-based UK study which concluded that Black and ethnic minority populations with newly diagnosed vitiligo had up to a 75% risk of developing anxiety and depression.[37]

While medical treatments for vitiligo focus on pigmentation restoration, psychological interventions play a critical role in improving quality of life and mental health outcomes, particularly for pediatric patients. Cognitive Behavioral Therapy (CBT) can help children reframe negative self-perceptions and assist in developing healthy coping mechanisms to improve their quality of life and self-esteem.[38] Acceptance and Commitment Therapy (ACT) offers an alternative therapy tactic by focusing on improving psychological flexibility through modulating

internal and external responses to stressful circumstances.[39] ACT can provide vitiligo patients with the mental fortitude to accept their physical appearance and reduce feelings of depression. Family-based therapy models are especially valuable for pediatric patients, as parental attitudes and behaviors strongly influence a child's emotional adjustment.[40] Family-based therapy (FBT) addresses psychological concerns amongst the entire family unit and showcases greater improvement in depression symptoms in children than individual therapy.[40] Other potential therapy options can include peer support groups or the use of digital mental health tools tailored to the needs of the individual.

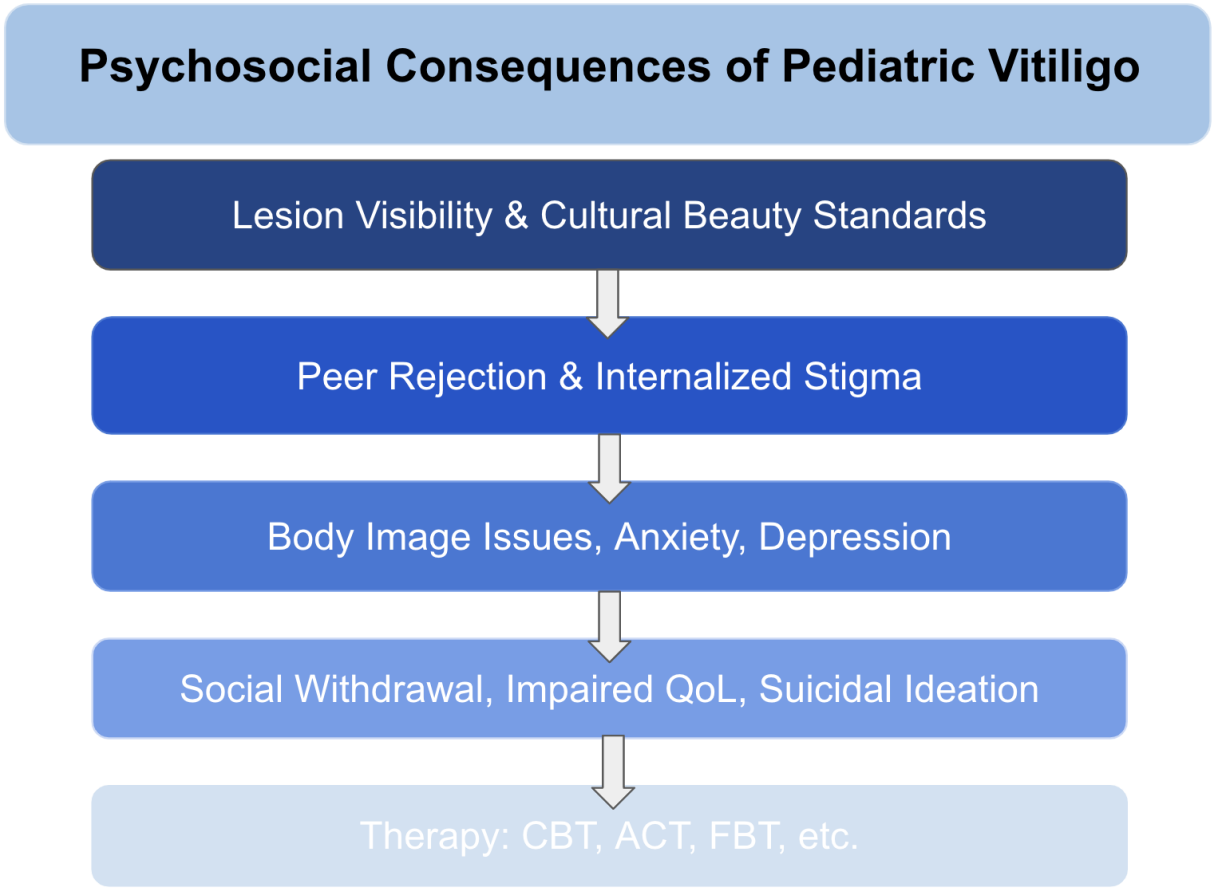

Fig. 1: Psychosocial Consequences of Pediatric Vitiligo.

Synergy Between Medical and Psychosocial Treatments

Synergy between medical and psychosocial treatments would enhance care for pediatric vitiligo in several ways. Evidence suggests that psychological support improves medical compliance and quality of life, while improved skin appearance increases therapy adherence and self-esteem. Current vitiligo treatment often separates physical repigmentation from emotional recovery, creating a gap in care, particularly for the pediatric patient population. Mental illness may contribute to treatment non-adherence and should be carefully considered in the management of pediatric vitiligo, as there are much higher rates of depression, anxiety, and social anxiety in vitiligo patients.[41, 42] Although there are limited studies on the psychological impact of vitiligo on non-adherence, a study on non-adherence in psoriasis treatment found that there was an association between non-adherence and feelings of anxiety (adjusted odd ratios [AORs]: 1.42 to 1.57), depression (AORs: 1.78 for both), and perceived stress (AORs: 1.86 to 1.57).[43] Thus, addressing psychological factors is critical to improving treatment compliance in pediatric vitiligo.

Bridging this gap between physical and psychological care requires recognizing that psychological stress not only influences treatment adherence but may also contribute directly to disease progression. While the exact cause of melanocyte destruction in vitiligo is not understood; it is well-known that psychological stress can activate the hypothalamic-pituitary-adrenal (HPA) axis in the brain. This activation leads to increased corticotropin-releasing hormone (CRH), which acts on receptor CRHR1, both of which are present in the skin. A recent study demonstrated a significant increase in CRH and CRHR1 presence in both lesional and nonlesional skin of vitiligo patients, with a significant direct association with stress.[44] There have also been some recent trials that have begun to evaluate the benefits of combining psychotherapy with the standard vitiligo treatments. For instance, one controlled trial assessing the combination of camouflage and psychotherapy found that patients with a higher initial Chinese version of the Vitiligo Life Quality Index (VLQI-C) experienced significant reductions in VLQI-C scores within four weeks of treatment compared with those with routine care alone [45]. Further, this integrated care model was associated with decreased biomarkers of stress and immune function, such as melanin-concentrating hormone and neuropeptide-Y, compared to the conventional

treatment group.[45] Together, these findings highlight the importance of an integrated care model in the treatment of vitiligo—one that addresses both repigmentation and the psychosocial consequences of vitiligo—to improve clinical outcomes and patients' well-being.

Despite growing appreciation of the need for integrated care in treating vitiligo, current data supporting integrated approaches remains limited and is based mostly on anecdotal reports and small cohort studies. The absence of randomized controlled trials (RCTs) evaluating integrated care models in children with vitiligo emphasizes the need for further investigation into how psychosocial and medical interventions can be combined successfully. Specifically, there is a need for RCTs that measure both clinical (e.g., percent repigmentation) and psychosocial outcomes (e.g., DLQI, PHQ-9 [Table 2]) simultaneously. Future studies should stratify patients by age group, disease severity, and lesion visibility to better evaluate differences in psychosocial burden. For pediatric populations, family-centered interventions, in which parents are involved in the psychological support aspect of treatment, may be especially effective. Additionally, integrating mental health screening tools into dermatologic clinics could aid in identifying high-risk youth earlier, allowing for prompt psychosocial support and comprehensive care.

Table 2: Comparison of Dermatologic and Psychological Outcome Measures in Vitiligo.

Domain	Outcome Metric	Description	Scoring	Type of Outcome
Psychological	**DLQI (Dermatology Life Quality Index)**	Assesses patient's quality of life impairment from dermatologic diseases over the past week for ages 16 and older[46]	0 (no impact) to 30 (maximum impact)	Psychosocial outcome
Psychological	**CDLQI (Children's Dermatology Life Quality Index)**	Assesses patient's quality of life impairment from dermatologic diseases over the past week for ages 4-16 years old [47]	0 (no impact) to 30 (maximum impact)	Psychosocial outcome
Psychological	**PHQ-9 (Patient Health Questionnaire-9)**	Screens and measures severity of depressive symptoms for ages 12 and older [48]	0 (no depressive symptoms) to 27 (severe depressive symptoms)	Psychosocial outcome
Psychological	**GAD-7 (Generalized Anxiety Disorder-7)**	Screens and measures severity of anxiety symptoms for ages 11 and older [48]	0 (no anxiety symptoms) to 21 (severe anxiety symptoms)	Psychosocial outcome
Psychological	**CDI (Children's Depression Inventory)**	Screens and measures severity of depressive symptoms in children 7-17 years old 49	0 (no depressive symptoms) to 54 (severe depressive symptoms)	Psychosocial outcome
Dermatologic	**Percent repigmentation**	Evaluates percentage of previously depigmented skin that has regained pigment	Varies widely	Clinical outcome outcome
Dermatologic	**VASI (Vitiligo Area Scoring Index)**	Quantifies vitiligo involvement by assessing affected body surface area and degree of depigmentation [50]	0 (no involvement) to 100 (complete involvement)	Clinical outcome

Cultural & Regional Differences

The psychosocial impact of pediatric vitiligo is often impacted by the cultural norms. In South Asian, Middle Eastern, and Sub-Saharan African societies, vitiligo is sometimes associated with contagion or divine punishment.[51] Affected children are often victims of social isolation as a result. These stigmatizing beliefs may result in delayed care, parental distress, or concealment of the condition. [52] All of these have the potential to complicate

early diagnosis and intervention. Furthermore, the cultural imperative of physical "perfection" in marriage markets or educational settings may subject children, especially girls, to long-term psychosocial consequences, which can include restricted opportunities and internalized shame.[53] These patterns highlight that psychosocial burden cannot be universally addressed without acknowledging culturally specific drivers of distress.

Colorism is prejudice based on skin tone, and it adds to these identified challenges in many non-Western communities. In cultures that idealize lighter skin tones, vitiligo's hypopigmented lesions disrupt prevailing beauty norms.[54] When visible skin changes intersect with sociocultural biases, they can worsen the emotional trauma associated with vitiligo beyond what is typically observed in depigmentation alone.[55] In such cases, dermatologic outcomes are inseparable from a child's social context, and psychosocial interventions must be appropriately tailored. For instance, culturally adapted cognitive behavioral therapy (CBT) that incorporates local metaphors or values has shown greater receptivity and effectiveness in other pediatric conditions and may warrant exploration in vitiligo care models.[56] These approaches honor the lived experience of patients rather than imposing a Western therapeutic framework without adjustment.

Community-based strategies may also bridge access gaps where mental health stigma or logistical barriers worsen conventional therapy. Partnering with religious leaders, school counselors, or local health advocates has been shown to reduce stigma around visible skin disorders and improve engagement in psychosocial services.[57] Educational campaigns delivered through culturally respected figures or in native languages can foster more accepting environments for children with vitiligo, normalizing variation in skin appearance and reducing the urge to hide the condition. In low-resource regions, mobile-based or teletherapy platforms adapted to local languages could improve access where in-person mental health infrastructure is limited.[58] This is important in communities where internet access or literacy levels may vary.

There remains a need for qualitative research that focuses on the voices of children and families navigating vitiligo within their own cultural landscapes. Western measures of quality of life or depression may not fully capture the challenges faced by children whose communities interpret disease through spiritual or moral frameworks. Including ethnographic interviews or culturally validated mental health instruments in future studies could provide more insights into how pediatric vitiligo is understood, experienced, and addressed across the world.

Emerging Innovations: Gene Therapy & Molecular Targets

Recent emerging therapies for pediatric vitiligo are exploring gene therapy and molecular targets. CRISPR-Cas9-based therapies are currently in the conceptual and preclinical stages, with a focus on immunomodulation. The genes targeted are associated with melanocyte autoimmunity, such as *TYR* (tyrosinase), *NLRP1*, and specific human leukocyte antigen (HLA) alleles known to contribute to an increased risk of autoimmune disorders like vitiligo.[59] The aim of these innovative therapies is to attenuate autoreactive immune responses that target melanocytes. Current research emphasizes somatic gene editing approaches, which include *ex vivo* strategies, such as the modification of autologous T cells or regulatory T cells to suppress melanocyte-directed autoimmunity, and *in vivo* approaches, targeting resident stem cells of the skin. Ex vivo editing allows for proper safety screening before reintroduction of modified cells.[60] In vivo strategies, like CRISPR-Cas9 delivery via lipid nanoparticles or ribonucleoprotein complexes, aim to correct gene function directly within skin tissue.[61] These innovations have made advancements, but are still currently limited in delivery efficiency, off-target effects, and immune responses to gene-editing components.

Similar to gene editing, mRNA-based therapies are in development to be a temporary alternative. These therapies deliver synthetic mRNA encoding melanogenic proteins, like tyrosinase, directly to melanocytes or progenitor cells to transiently restore pigment production.[62] However, there is no mRNA-based treatment currently approved for vitiligo. Current preclinical efforts aim to establish the safety of transient gene expression and evaluate delivery methods, such as nanoparticles and microneedles. These mRNA-based therapeutic approaches are beneficially reversible and have fewer risks compared to genome-integrating technologies like CRISPR.

Beyond molecular and gene therapies, *cultured melanocyte transplantation* has been an investigated intervention for stable vitiligo. Clinical studies have shown that autologous melanocyte transfer can result in significant repigmentation, especially when combined with narrowband UVB therapy.[63] However, this approach is limited by challenges in melanocyte proliferation and quality. To address these, continued investigations explore the use of melanocytes derived from pluripotent or somatic stem cells as a more reliable source. Stem cell-based therapies can be enhanced by co-administration with immunosuppressive agents or immunomodulatory cells. Experimental studies have demonstrated that mesenchymal stem cells (MSCs) can suppress autoreactive T cells and promote regulatory T cell activity, potentially improving engraftment and longevity of transplanted melanocytes.[64] Recent protocols combining melanocyte transplantation with MSCs or pharmacologic immunosuppression are under experimentation in the preclinical or early translational stages, hence the need for further clinical trials and research in this area.

In summary, gene therapy, mRNA delivery, epigenetic modulation, and innovative cell transplantation strategies are emerging and may lead to significant advancements for pediatric vitiligo treatment. While these approaches remain largely investigational, they pose potential for targeted, durable, and personalized interventions for future immunosuppressive treatments. Ethical considerations remain paramount as gene therapy advances. Long-term safety, durability of gene correction, and equitable access to these therapies are crucial considerations in their clinical translation.

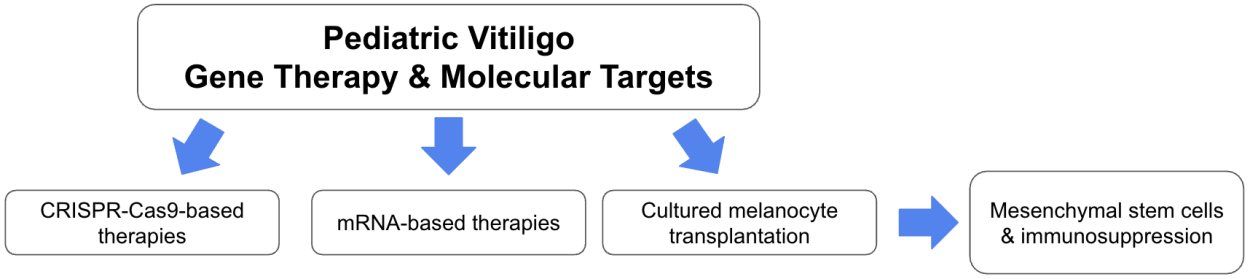

Fig. 3: Emerging Molecular and Cellular Interventions for Pediatric Vitiligo

4. Discussion

Vitiligo is an autoimmune skin disorder that is due to the selective loss of melanocytes from the epidermis and presents clinically as well-demarcated, non-scaly, chalky white patches on the body. Roohaninasab et al. reports that while there have been many advancements in the treatment of this disease, such as UVB phototherapy combined with oral glycyrrhizin and the emergence of topical JAK inhibitors, there are still critical gaps in the research.[65] Much of the available data is extrapolated from adult populations and focuses on short-term outcomes such as repigmentation, without including standardized, pediatric-specific guidelines and long-term safety or recurrence data for newer therapies. There is also a lack of research regarding optimal dosing, duration, and comparative efficacy of treatments in children. As a result, despite their potential benefits, current research does not support the widespread use of novel treatments in the pediatric population, and there is yet to be a gold standard treatment established.

In addition to these clinical limitations, the psychosocial effects of vitiligo in children are widely under-addressed. The studies done have revealed that children experience lower body image satisfaction, less peer acceptance, and more internalized stigma, which eventually can lead to lowered self-esteem and even suicidal ideation.[66] However, despite this recognition, there is a lack of integrated care models that include both medical and psychological management. Cadmus et al. explored various therapeutic modalities that address the psychosocial aspect, such as cosmetic cover-up, psychotherapies including cognitive behavioral therapy, and disease support groups, but there remains limited data determining their long-term success in improving mental health of the patients.[67] Silverberg emphasized a comorbidity of vitiligo being psychological distress, further implying the care of vitiligo is multifaceted and should include guidelines recommending psychological screening of the children and parents to determine the need for referral in addition to therapy.[68]

Equity issues further complicate care, with children of color facing a greater psychosocial burden due to an increased contrast between the depigmented lesions and their skin. In the first international survey exploring the burden of vitiligo, Bibeau et al. found that individuals with darker skin reported more quality of life impairment. However, these findings were not separated by age, leaving a gap in understanding how these disparities specifically affect pediatric populations.[69] As a result, existing care fails to address the needs in children of various skin tones, and it is important to conduct inclusive, stratified clinical trials that develop appropriate guidelines and interventions.

Despite promising developments in care, there is still a lack of studies focused on pediatric vitiligo, and there is a need for more long-term data regarding the effectiveness of both pharmacological and psychosocial therapies. Many studies exploring new therapies have called for future research that tests the safety and efficacy, not only in halting the disease, but also sustaining repigmentation in children with vitiligo. To advance the data available, it is important to conduct well-designed multi-arm randomly controlled trials that test integrated treatment protocols. This would mean combining topicals, phototherapy, novel therapies, as well as psychosocial interventions to assess safety, efficacy, and quality of life. These studies would be designed to incorporate large randomized populations and include various aspects of the disease, such as vitiligo subtype, age group, skin tone, and severity, all of which will help decide the best standardized care for pediatric vitiligo patients.

5. Conclusion

Vitiligo treatment in children must move its focus beyond repigmentation to also prioritize emotional recovery by addressing psychosocial factors. The nature of a visible dermatological condition like vitiligo during the development of a child can have lasting psychological effects, emphasizing the importance of comprehensive care. This means shifting the current therapies towards incorporating a more holistic, patient-centered approach, which in turn can transform clinical outcomes and quality of life for children with vitiligo worldwide. Furthermore, integrated interventions and future gene-based therapies present as exciting new possibilities; however, meticulous clinical validation is necessary for proper implementation. With the call for increasing pediatric studies, there is great potential to transform outcomes for pediatric vitiligo patients.

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