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SEX DIFFERENCES IN MELANOMA: HORMONAL, BIOLOGICAL, AND CLINICAL PERSPECTIVES – A LITERATURE REVIEW

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ABSTRACT

Background: Melanoma is one of the most aggressive forms of skin cancer, with increasing global incidence and significant mortality. Despite advances in diagnosis and treatment, it remains a major public health concern. Consistent sex-related differences have been observed in melanoma epidemiology, clinical presentation, and survival outcomes.

Aims: The aims of this review are to analyze sex-related differences in melanoma, focusing on epidemiology, biological mechanisms, clinical characteristics, and treatment outcomes, as well as their implications for public health and personalized medicine.

Methods: A narrative literature review was conducted using PubMed and Google Scholar databases. Relevant studies published primarily within the last decade were included, with a focus on epidemiology, hormonal influences, immune system variability, tumor microenvironment, and treatment response in melanoma.

Results: Women demonstrate a consistent survival advantage compared to men, partly explained by earlier diagnosis and more favorable tumor characteristics. However, biological factors, including hormonal influences and immune system differences, play a significant role in disease progression. Sex-related differences were also observed in treatment response, particularly in the context of immunotherapy, as well as in tumor biology and clinical presentation.

Conclusion: Sex is an important factor influencing melanoma development, progression, and treatment outcomes. Understanding these differences may contribute to improved prevention strategies, earlier diagnosis, and more personalized therapeutic approaches. Incorporating sex-specific considerations into clinical practice and research may help reduce disparities in melanoma outcomes.

KEYWORDS

Melanoma, Sex Differences, Immunotherapy, Tumor Microenvironment, Epidemiology, Public Health

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1. Introduction

Melanoma is one of the most aggressive forms of skin cancer and represents a growing global health concern. Although it accounts for a relatively small proportion of all skin cancers, it is responsible for the majority of skin cancer-related deaths. Over recent decades, its incidence has been steadily increasing worldwide, particularly in populations with high exposure to ultraviolet (UV) radiation and lighter skin phenotypes (GBD 2023 Cancer Collaborators, 2025; Shah et al., 2025). Despite advances in diagnosis and treatment, melanoma remains a significant clinical and public health challenge.

The development of melanoma is influenced by a complex interaction of environmental, genetic, and behavioral factors. Ultraviolet radiation is the most important modifiable risk factor, with both intermittent and cumulative exposure contributing to disease risk (Liu-Smith et al., 2017). Additional risk factors include fair skin, light eye and hair color, a high number of melanocytic nevi, and a family history of melanoma. However, these factors alone do not fully explain the variation in melanoma incidence and outcomes observed across different populations.

In recent years, melanoma has become an increasingly important global health issue, with substantial variation in incidence across regions. The highest rates are reported in countries with predominantly fair-skinned populations, such as Australia, New Zealand, and parts of Europe, whereas lower incidence is observed in populations with darker skin types. These geographic differences are closely linked to ultraviolet radiation exposure, genetic susceptibility, and environmental factors. Despite these variations, the global burden of melanoma continues to increase, placing growing pressure on healthcare systems and highlighting the need for improved prevention and early detection strategies (GBD 2023 Cancer Collaborators, 2025).

In addition to environmental and genetic factors, increasing attention has been directed toward individual-level determinants that may influence melanoma risk and outcomes. These include biological

characteristics, immune system variability, and hormonal influences, which may contribute to differences in disease behavior. Understanding these factors is essential for developing more targeted and effective approaches to melanoma management.

One of the most consistently reported observations is the presence of sex-related differences in melanoma. These differences are evident in incidence, clinical presentation, and survival outcomes. Men are more likely to develop melanoma at older ages and tend to present with more advanced disease, whereas women are more frequently diagnosed at earlier stages and demonstrate better survival outcomes (Buja et al., 2022; Murali et al., 2025). Notably, women often present with thinner tumors and lower metastatic potential, which are key prognostic factors.

Behavioral factors, such as sun exposure patterns and preventive practices, partially explain these differences. Women are generally more likely to engage in protective behaviors and seek medical attention earlier, while men are more likely to delay diagnosis (D'Ecclesiis et al., 2021). However, behavioral explanations alone are insufficient to fully account for the observed disparities.

Increasing evidence suggests that biological mechanisms play a central role. Hormonal influences, particularly those related to estrogen and androgen signaling, may affect tumor progression and immune regulation (Hill et al., 2021). In addition, differences in immune system function between males and females may influence tumor surveillance and response to treatment (Li et al., 2024). Recent studies have also highlighted the importance of the tumor microenvironment and molecular signaling pathways in melanoma progression, which may differ between sexes (Chhabra et al., 2024).

From a public health perspective, melanoma continues to impose a substantial burden worldwide, emphasizing the need for improved prevention and early detection strategies.

The recognition of sex as an important biological variable has gained increasing attention in recent years across multiple areas of medical research. In oncology, incorporating sex-specific analyses has improved the understanding of disease mechanisms and treatment responses.

In the context of melanoma, these differences may have important implications for both clinical practice and public health strategies, particularly in relation to prevention, early detection, and personalized treatment approaches. Taken together, these findings suggest that sex should be considered an important factor in both melanoma research and clinical practice. The aim of this review is to summarize current evidence on sex differences in melanoma, with a focus on biological mechanisms and public health implications. In addition to clinical and biological aspects, melanoma also represents a significant socioeconomic burden. The costs associated with diagnosis, treatment, and long-term follow-up continue to increase, particularly with the introduction of advanced therapies such as immunotherapy and targeted treatments. These factors further emphasize the importance of effective prevention strategies and early detection, which may reduce both healthcare costs and disease-related morbidity.

2. Methodology

This study was designed as a narrative literature review aimed at summarizing current evidence on sex-related differences in melanoma. A structured search of PubMed and Google Scholar databases was conducted to identify relevant publications. The search strategy included combinations of keywords such as “melanoma,” “skin cancer,” “sex differences,” “gender differences,” “hormones,” “immune response,” “immunotherapy,” and “public health.” The search focused primarily on studies published within the last decade, although earlier key studies were also included where relevant.

The inclusion criteria comprised peer-reviewed original research articles, systematic reviews, and meta-analyses addressing epidemiology, biological mechanisms, clinical outcomes, and prevention strategies in melanoma, with particular emphasis on sex-related differences (D'Ecclesiis et al., 2021). Studies investigating hormonal influences, immune system variability, tumor microenvironment, treatment response, and survival outcomes were prioritized.

Exclusion criteria included non-peer-reviewed publications, conference abstracts without full text, studies lacking sufficient methodological quality, and articles not available in English. Studies focusing exclusively on non-melanoma skin cancers were excluded.

The selected studies were analyzed qualitatively and grouped into thematic categories, including epidemiology, clinical presentation, hormonal influences, immune system differences, treatment outcomes, molecular mechanisms, and public health aspects. Due to heterogeneity in study designs and reported outcomes, a quantitative meta-analysis was not performed. Instead, a narrative synthesis approach was used.

3. Results

3.1. Epidemiology of melanoma

Melanoma incidence has increased significantly over recent decades and continues to rise globally (GBD 2023 Cancer Collaborators, 2025; Shah et al., 2025). The highest rates are observed in populations with lighter skin types and high exposure to ultraviolet radiation, reflecting the combined influence of environmental factors, lifestyle behaviors, and genetic susceptibility (Liu-Smith et al., 2017).

Clear sex-related differences are evident in epidemiological patterns. In younger age groups, incidence rates in women are comparable to or slightly higher than in men, which has been associated with intermittent sun exposure and tanning behaviors. However, after the age of 50, melanoma occurs more frequently in men, who also account for a higher proportion of advanced cases (Olsen et al., 2020).

Mortality patterns further emphasize these differences, with men consistently demonstrating higher melanoma-related mortality compared to women across different populations (Stålhammar, 2023). These disparities may reflect delayed diagnosis, differences in tumor biology, and variations in healthcare utilization.

In addition, population-based analyses suggest that sex differences in melanoma incidence and mortality remain consistent across geographic regions, supporting the hypothesis that both environmental and biological factors contribute to these patterns.

3.2. Clinical presentation

Sex differences are also observed in clinical presentation at diagnosis. Men are more likely to present with thicker tumors and more advanced stages of disease, both of which are associated with poorer prognosis (Buja et al., 2022). In contrast, women are more frequently diagnosed at earlier stages and tend to have thinner melanomas with lower metastatic potential (Whiteman et al., 2025).

These differences are partly explained by earlier detection and more proactive health-seeking behavior in women (D'Ecclesiis et al., 2021), although biological factors may also contribute. Tumor localization varies between sexes, with melanoma more commonly found on the trunk in men, particularly on the back, whereas in women it is more often located on the lower extremities (Hoyt et al., 2024).

These anatomical differences may be related to patterns of sun exposure, clothing habits, and behavioral factors. However, emerging evidence suggests that anatomical distribution may also be influenced by biological mechanisms, including variations in skin structure and regional immune responses.

It has been suggested that a substantial proportion of survival differences between sexes may be explained by clinical factors such as tumor thickness, stage at diagnosis, and anatomical location, although these variables do not fully account for the observed disparities (Afshar et al., 2024). This indicates that additional biological determinants contribute to sex-specific disease outcomes. These epidemiological differences are closely reflected in clinical outcomes, indicating a strong link between incidence patterns and disease progression.

3.3. Survival differences and prognostic factors

One of the most consistent findings in melanoma research is the survival advantage observed in women. Female patients demonstrate better outcomes across different stages of disease, including both early and advanced melanoma (Joosse et al., 2011; Murali et al., 2025).

Importantly, sex appears to act as an independent prognostic factor. Although earlier diagnosis and more favorable tumor characteristics contribute to improved survival in women, they do not fully explain the observed differences (Afshar et al., 2024).

Large population-based studies have confirmed that women experience significantly better short- and long-term survival compared to men (Shaw et al., 2024). This advantage is particularly pronounced in younger age groups but remains evident across the lifespan. Additional analyses suggest that women may have a lower risk of disease progression and metastasis, which further contributes to improved outcomes. These findings indicate that biological mechanisms, rather than solely clinical factors, play a key role in determining survival differences.

Taken together, these findings suggest that sex-related differences in melanoma survival are multifactorial and cannot be explained by clinical factors alone.

3.4. Hormonal influences

Hormonal factors are considered an important component of sex-related differences in melanoma. Estrogen has been associated with reduced tumor aggressiveness and may influence immune function and tumor growth, whereas androgen-related pathways may promote tumor progression (Hill et al., 2021).

Hormonal signaling may affect cell proliferation, apoptosis, and tumor invasion, thereby contributing to differences in disease behavior. Sex steroid hormones may also interact with molecular pathways involved in melanoma development, and receptor-mediated mechanisms have been proposed as potential drivers of sex-related differences in tumor behavior (Aguirre-Portolés et al., 2021).

For example, the ZIP9 receptor has been identified as a potential mediator of androgen signaling in melanoma cells, influencing tumor growth and progression. These findings support the hypothesis that endocrine factors contribute to differences in disease progression and clinical outcomes.

3.5. Immune system differences

Differences in immune system function between males and females may play a central role in melanoma outcomes. Females generally exhibit stronger innate and adaptive immune responses, which may enhance tumor surveillance and slow disease progression (Li et al., 2024).

This enhanced immune activity may partly explain the better survival observed in women. At the same time, this heightened immune response may contribute to increased susceptibility to immune-related adverse events, particularly in the context of immunotherapy (Gaeta et al., 2026). Sex-related differences in cytokine production, immune cell activation, and inflammatory pathways may further influence disease progression and treatment outcomes. These findings highlight the importance of immune regulation as a key factor in melanoma biology.

3.6. Immunotherapy and treatment response

Recent advances in melanoma treatment, particularly the introduction of immune checkpoint inhibitors, have significantly improved survival outcomes. However, sex-based differences in treatment response remain evident.

Studies suggest that response to immunotherapy may differ between males and females, with men achieving better outcomes in some treatment settings, while women may experience stronger immune activation and a higher incidence of treatment-related adverse events (Kudura et al., 2022; Pasello et al., 2024).

Differences in serum biomarkers, immune regulation, and tumor microenvironment may further influence treatment effectiveness (Pasello et al., 2024). These differences may be related to variations in immune system activation, cytokine profiles, and hormonal regulation, which can influence both treatment efficacy and toxicity.

These findings suggest that sex-specific immune mechanisms may play an important role in determining therapeutic outcomes and highlight the need for more personalized treatment approaches.

3.7. Tumor microenvironment and molecular mechanisms

The tumor microenvironment plays a crucial role in melanoma progression and treatment resistance, involving complex interactions between tumor cells, immune cells, and surrounding tissues. Recent studies indicate that these interactions may differ between sexes, with variations in gene expression, signaling pathways, and cellular composition influencing tumor invasion and resistance to therapy (Chhabra et al., 2024).

Sex-related differences in the tumor microenvironment may also involve variations in immune cell infiltration, angiogenesis, and signaling pathways, which can affect tumor progression and response to therapy. Molecular mechanisms, including hormone-related signaling and receptor activity, may further contribute to sex-related differences in melanoma biology (Orlandi et al., 2024).

These findings emphasize the importance of integrating molecular and immunological perspectives in understanding melanoma progression.

In addition, emerging evidence suggests that genetic and epigenetic differences between sexes may influence melanoma susceptibility and tumor behavior, further contributing to observed disparities.

3.8. Age-related patterns

Age is an important factor influencing melanoma incidence and outcomes and interacts with sex in shaping disease patterns. Younger women may exhibit similar or slightly higher incidence rates compared to men, whereas older men demonstrate higher incidence and mortality (Olsen et al., 2020; Stålhammar, 2023). These patterns may reflect both behavioral factors and biological changes associated with aging. Age-related hormonal changes, particularly the decline in estrogen levels, may influence melanoma progression and immune function. In addition, aging is associated with alterations in immune system activity, which may further contribute to differences in disease outcomes between sexes.

3.9. Lifestyle and behavioral factors

Lifestyle factors contribute significantly to melanoma risk and outcomes. Differences in sun exposure patterns, use of sunscreen, and health-seeking behavior are observed between males and females (D'Ecclesiis et al., 2021).

Women are generally more likely to engage in preventive measures, such as sunscreen use and skin examinations, and are more likely to seek medical attention earlier. In contrast, men are less likely to adopt protective behaviors and more likely to delay diagnosis, which may contribute to more advanced disease at presentation (Buja et al., 2022).

These behavioral differences, combined with biological factors, contribute to observed disparities in melanoma outcomes.

3.10. Sunscreen and prevention

Photoprotection plays a key role in melanoma prevention. Sunscreen reduces ultraviolet-induced skin damage and is widely recommended as part of preventive strategies (Micha et al., 2025).

However, its effectiveness depends on correct and consistent use. In practice, many individuals apply insufficient amounts or fail to reapply sunscreen regularly, and behavioral factors such as prolonged sun exposure may reduce its protective effect (Brunner et al., 2025).

Public health campaigns aimed at improving sunscreen use and increasing awareness of skin cancer risk have shown some effectiveness, but adherence remains suboptimal. These findings highlight the need for improved education and targeted prevention strategies.

3.11. Public health implications

Melanoma represents a growing public health challenge due to its increasing incidence and potential severity (GBD 2023 Cancer Collaborators, 2025).

Sex-related differences in disease outcomes highlight the need for targeted prevention strategies and more personalized approaches to care. Public health interventions should focus on increasing awareness, promoting early detection, and encouraging protective behaviors, particularly among high-risk populations such as men, who are more likely to present with advanced disease (Shah et al., 2025).

Integrating sex-specific considerations into public health strategies may help reduce disparities in melanoma outcomes and improve overall disease management.

Overall, the evidence consistently demonstrates that sex-related differences in melanoma are present across multiple levels, including epidemiology, tumor biology, clinical presentation, and treatment response, highlighting the complexity of this phenomenon.

An overview of sex-related differences in melanoma and their clinical implications is presented in Table 1.

Table 1. Overview of Sex-related Differences in Melanoma and their Clinical Significance

Domain	Key Findings	Clinical Interpretation
Epidemiology	Higher incidence in younger women; higher incidence and mortality in older men	Age-dependent sex differences should be considered in screening and prevention strategies
Tumor characteristics	Women present with thinner melanomas and earlier-stage disease; men with thicker tumors and advanced stages	Significant impact on prognosis and survival outcomes
Anatomical distribution	Predominantly lower extremities in women; trunk (especially back) in men	Reflects differences in sun exposure patterns and biological factors
Survival outcomes	Female patients demonstrate consistently improved survival across stages	Supports the role of sex as an independent prognostic factor
Immune response	Stronger immune activation in females compared to males	Improves tumor control but increases susceptibility to immune-related toxicity
Immunotherapy response	Higher incidence of adverse events in females; variable efficacy between sexes	Indicates need for sex-adapted therapeutic strategies
Hormonal influence	Estrogen-associated protective effects; androgen-related pathways linked to tumor progression	Suggests endocrine modulation of melanoma biology
Tumor microenvironment	Sex-specific differences in immune infiltration and signaling pathways	May influence disease progression and resistance to therapy
Pharmacokinetics	Differences in drug metabolism, distribution, and clearance between sexes	Potential impact on treatment efficacy and toxicity
Behavioral factors	Greater use of preventive measures in women; delayed diagnosis in men	Contributes to disparities in stage at diagnosis and outcomes

Note. Adapted from a synthesis of findings reported in Buja et al. (2022), D'Ecclesiis et al. (2021), Joosse et al. (2011), Kudura et al. (2022), Pasello et al. (2024), and Chhabra et al. (2024).

4. Discussion

The findings of this review confirm that sex-related differences in melanoma are consistent, multifactorial, and clinically relevant. These differences are observed not only in epidemiology and clinical presentation but also in survival outcomes and response to treatment. While behavioral factors contribute to these disparities, the available evidence strongly suggests that biological mechanisms play a fundamental role (D'Ecclesiis et al., 2021; Bellenghi et al., 2020).

One of the most significant observations is the consistent survival advantage observed in women. Although earlier diagnosis and more favorable tumor characteristics contribute to improved outcomes, these factors alone are insufficient to explain the magnitude of the difference. This indicates that sex acts as an independent prognostic factor in melanoma (Murali et al., 2025; Afshar et al., 2024). It is likely that a combination of hormonal, immunological, and molecular factors contributes to this survival advantage.

Hormonal influences appear to be particularly important in shaping melanoma progression. Estrogen has been associated with reduced tumor aggressiveness and may enhance immune surveillance, whereas

androgen-related pathways may promote tumor growth and invasion (Hill et al., 2021). In addition, receptor-mediated mechanisms, such as those involving ZIP9, may further contribute to sex-specific differences in melanoma biology (Aguirre-Portolés et al., 2021). These findings highlight the complex interaction between endocrine regulation and tumor behavior.

The role of the immune system is also central to understanding sex-related differences in melanoma. Females generally exhibit stronger innate and adaptive immune responses, which may improve tumor control and delay disease progression (Li et al., 2024). However, this heightened immune activity may also increase the risk of immune-related adverse events, particularly in the context of immunotherapy (Gaeta et al., 2026). These observations suggest that immune system variability plays a dual role, influencing both disease outcomes and treatment-related toxicity.

The introduction of immune checkpoint inhibitors has significantly changed the therapeutic landscape of melanoma. However, accumulating evidence indicates that treatment response may differ between sexes. Men may achieve better outcomes in certain settings, whereas women may experience stronger immune activation and higher rates of adverse effects (Kudura et al., 2022; Pasello et al., 2024). These differences may be related to variations in immune regulation, cytokine profiles, and hormonal influences, which affect both treatment efficacy and toxicity. Understanding these mechanisms is essential for optimizing therapeutic strategies.

The tumor microenvironment represents another key factor contributing to sex-related differences in melanoma. Interactions between tumor cells, immune cells, and surrounding tissues may vary between males and females, influencing tumor progression and resistance to therapy (Chhabra et al., 2024). Differences in gene expression, signaling pathways, and cellular composition may further contribute to these variations (Orlandi et al., 2024). These findings emphasize the importance of integrating molecular and immunological perspectives in melanoma research.

From a clinical perspective, these findings have important implications. Sex-specific factors should be considered in risk assessment, treatment selection, and follow-up strategies. Incorporating sex as a variable in clinical decision-making may improve patient stratification and contribute to more personalized approaches to melanoma management.

Sex-related differences in melanoma are also evident in patterns of disease progression and metastasis. Several studies suggest that men are more likely to develop aggressive disease with a higher risk of distant metastases, including brain involvement, which is associated with poorer prognosis (Cioffi et al., 2024). In contrast, women may exhibit slower disease progression and a lower risk of metastatic spread in early stages. These differences may reflect variations in tumor biology, immune response, and hormonal regulation, which together influence disease trajectory.

Sex differences may also influence the pharmacokinetics and pharmacodynamics of anticancer therapies. Variations in body composition, metabolism, and drug clearance can affect treatment exposure and response (Delahousse et al., 2024). These factors may partly explain differences in both efficacy and toxicity observed between male and female patients. Understanding sex-related variability in drug metabolism is particularly important in the era of personalized medicine and may contribute to optimizing treatment strategies.

In addition to clinical outcomes, sex differences are also observed in psychosocial aspects of melanoma. Studies indicate that female patients may report different quality-of-life outcomes compared to males, including higher levels of psychological distress but also greater engagement in follow-up care and health monitoring (Vogel et al., 2021). These findings highlight the importance of considering not only survival but also long-term survivorship and patient-reported outcomes in melanoma management.

The growing understanding of sex-related differences in melanoma supports the need for more personalized approaches to treatment. Incorporating sex as a biological variable may improve risk stratification, treatment selection, and monitoring strategies. Personalized medicine approaches should consider not only genetic and molecular factors but also sex-specific differences in immune response, hormonal regulation, and treatment tolerance. Future research should focus on integrating sex-specific analyses into clinical trials and translational studies. Many existing studies do not stratify results by sex, which limits the ability to identify clinically relevant differences. Standardizing the inclusion of sex as a variable in research design may improve the quality of evidence and support the development of more targeted therapeutic strategies.

From a public health perspective, melanoma continues to represent a significant and growing challenge. Increasing incidence rates, combined with persistent sex-related disparities in outcomes, underline the need for targeted prevention strategies (GBD 2023 Cancer Collaborators, 2025; Shah et al., 2025). Public health

interventions should focus on increasing awareness, promoting early detection, and encouraging protective behaviors, particularly among men, who are more likely to present with advanced disease.

The integration of sex-specific perspectives into melanoma research may also contribute to improving healthcare system efficiency. Better understanding of risk profiles and treatment responses may support more precise allocation of resources and enhance the effectiveness of screening and prevention programs.

Despite the growing body of evidence, several limitations should be acknowledged. The heterogeneity of study designs, differences in population characteristics, and variability in reported outcomes may affect the comparability of findings. In addition, many studies do not fully account for confounding factors, including socioeconomic status, access to healthcare, and lifestyle differences, which may influence the observed disparities.

Future research should focus on further elucidating the biological mechanisms underlying sex differences in melanoma, particularly in the context of immunotherapy and targeted treatments. A better understanding of how hormonal, immunological, and molecular factors interact may help identify new therapeutic targets and improve patient outcomes. In addition, integrating sex-specific considerations into clinical trials and treatment strategies may contribute to more precise and effective melanoma management.

These findings highlight the importance of incorporating sex as a biological variable in both clinical research and routine medical practice. A better understanding of these differences may contribute to improved patient outcomes and more effective, individualized treatment strategies.

5. Conclusions

Melanoma remains a significant global health challenge, with increasing incidence and substantial mortality. This review highlights consistent sex-related differences in melanoma across epidemiology, clinical presentation, and survival outcomes. Women demonstrate a clear survival advantage, which is only partially explained by earlier diagnosis and more favorable tumor characteristics.

The available evidence suggests that biological mechanisms, including hormonal influences, immune system variability, and tumor microenvironment interactions, play a central role in shaping these differences. In addition, sex-specific variations in treatment response, particularly in the context of immunotherapy, further emphasize the importance of considering sex as a relevant clinical factor.

From a public health perspective, these findings underline the need for targeted prevention strategies, improved awareness, and early detection, especially among high-risk populations. Addressing behavioral differences between sexes may contribute to reducing disparities in outcomes.

Future research should focus on further elucidating the molecular and immunological mechanisms underlying sex differences in melanoma. Integrating sex-specific factors into clinical trials and treatment strategies may support the development of more personalized and effective therapeutic approaches.

Overall, incorporating sex as a key variable in both research and clinical practice may improve melanoma management and contribute to better patient outcomes.

Disclosure

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