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ORIGINAL RESEARCH

Rare Melanomas and Quality of Life: A Report From the Melanoma Research Alliance's RARE Registry

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Background: Acral melanoma (AM) and mucosal melanoma (MM) are rare melanoma subtypes with poorer outcomes compared with the most common cutaneous melanoma (CM) subtype. Limited patient-centered research on quality of life (QOL) has been conducted in these rare melanomas. We characterized patient-reported physical and mental functioning among individuals enrolled in the Melanoma Research Alliance's RARE Registry. **Methods:** We performed a cross-sectional analysis of 230 registry participants (64 AM, 107 MM, 59 non-acral CM) who completed the Short Form-12 (SF-12); Physical (PCS) and Mental (MCS) Component Summary T-scores were categorized (≤ 1 SD, ± 1 SD, ≥ 1 SD) and compared with expected normative proportions. Differences in PCS and MCS T-scores among cohorts were assessed while controlling for demographic and health variables. **Results:** In AM and MM, PCS and MCS scores deviated significantly from normative expectations ($p < .004$), with more falling ≥ 1 SD below the US population mean. In CM, MCS but not PCS scores differed from expected norms (MCS: $p < .001$; PCS: $p = .566$). Unadjusted PCS scores were significantly lower in AM and MM compared to CM ($p = .005$), whereas MCS scores did not differ among cohorts ($p = .172$). Multiple clinical covariates were significant predictors of PCS and MCS scores. **Conclusions:** Participants with AM and MM report clinically meaningful differences in physical and mental QOL compared with population norms; CM participants showed normal physical but poor mental functioning. Routine screening for physical and mental functioning is recommended to identify unique patient needs. Early referral to appropriate supportive care may be warranted, independent of medical and global prognostic factors.

Melanoma is a malignant neoplasm arising from melanocytes and most frequently develops on sun-exposed skin (cutaneous melanoma; CM). Rarer forms of melanoma can also occur at anatomical sites with little to no sun exposure, including acral sites (acral melanoma; AM), mucosal surfaces (mucosal melanoma; MM), and ocular structures (uveal melanoma; UM).

Cutaneous melanoma accounts for approximately 90% of all melanoma diagnoses (Schadendorf et al., 2015) and typically develops on skin with either chronic or intermittent ultraviolet radiation exposure (Arnold et al., 2018). Cutaneous melanoma occurs predominantly in White individuals, is more common in women < 50 years old, and is associated with higher mortality in males (Buja et al., 2022; Venzel et al., 2023; Nowowiejska et al., 2025). Improvements in early detection and approved therapies, particularly targeted and immune therapies, have substantially improved survival outcomes for many patients with CM; nevertheless, nearly 50% of patients with advanced disease will not benefit from these treatments (Tasdogan et al., 2025).

Compared to CM, advances in the clinical management of rare melanoma subtypes such as AM and MM have progressed more slowly, owing in part to their rarity, unknown etiologies, and distinct genetic and biological characteristics (Shannon et al., 2024). Acral melanoma and MM represent two rare and aggressive subtypes of melanoma with poorer health outcomes than CM; they account for approximately 2% to 3% and 1% of all melanoma cases, respectively (Perez et al., 2023; Sergi et al., 2023; Shannon et al., 2024). Acral melanoma arises on largely sun-protected, glabrous skin of the palms of the hands, soles of the feet, or nail apparatus, and affects individuals of all races and ethnicities (Elder et al., 2020; Holman et al., 2023). Acral melanoma is associated with an inferior 10-year melanoma-specific survival rate relative to CM (67.5% vs. 87.5%; Bradford et al., 2009). Mucosal melanoma arises on mucosal epithelium, including from the lower GI tract, nasal cavity and paranasal sinuses, gynecological sites, oral cavity, urological sites, upper GI tract, and others (conjunctiva; Elder et al., 2020), and is the predominant melanoma subtype in Asians and other non-White populations (Mao et al., 2021). Mucosal melanoma carries a substantially poorer prognosis than CM, with a more than two-fold higher mortality rate (Hahn et al., 2019).

Both AM and MM represent underserved patient populations with substantial, unmet clinical needs. While modern therapies for melanoma have improved patient care and survival outcomes in patients with CM (Tasdogan et al., 2025), such benefits have not been equitably realized for patients with AM and MM (Alicea & Rebecca, 2021; Nadelmann et al., 2025a, 2025b; Sergi et al., 2023). This disparity likely reflects multiple factors: a delayed or missed diagnosis, advanced stage at presentation, distinct tumor genetics and biology, reduced efficacy of current melanoma therapies, and limited evidence to inform disease management, among others (Alicea & Rebecca, 2021; Mao et al., 2021; Nowowiejska et al., 2025).

To address these gaps, the Melanoma Research Alliance (MRA), together with patient advocates, launched the RARE Registry (www.raremelanoma.org), which was designed in part to collect patient-reported life history and clinical data to better understand patient quality of life (QOL) in individuals diagnosed with AM, MM, or CM. Although QOL outcomes have been extensively studied across many cancer populations (Low et al., 2024), including CM (Beutel et al., 2015; Toma et al., 2023; Weitman et al., 2018) and UM (Amaro et al., 2010; Gollrad et al., 2022), limited published studies have characterized patient-reported QOL data among patients with AM and MM (Kim et al., 2022; Nakajima et al., 2026). In this study, we evaluated patient-reported physical and mental QOL using the 12-Item Short Form Survey (SF-12) among RARE Registry participants with AM, MM, or non-acral CM, encompassing patients at all points in the disease journey. Quality of life data derived from RARE address a significant knowledge gap, informing supportive care of these patients across the treatment continuum, from diagnosis through survivorship.

METHODS

RARE Registry

The RARE Registry (RARE; raremelanoma.org) is the first direct-to-patient, web-based, bidirectional, and interactive registry and was established in

2022 with sponsorship by the MRA. RARE was designed to collect patient-reported and clinical data from individuals diagnosed with AM and MM, and was expanded in 2023 to include patients with non-acral CM. The RARE Registry was developed in close collaboration with advocates who serve on an Oversight Committee alongside scientific advisors.

Study Population and Eligibility Criteria

RARE operates under an Institutional Review Board–approved protocol (NB200070) administered by the North Star Review Board (www.learningirb.org) in compliance with human subjects–based research. All participants are required to provide electronic consent prior to enrollment and may withdraw from the registry at any time. Eligible participants include adults (generally ≥ 18 years of age), male or female, English-speaking, with a self-reported diagnosis of AM, MM, or non-acral CM. Individuals at any stage of the disease can participate, including patients who are newly diagnosed, in remission, or experiencing relapse or disease progression.

Data Collection

RARE is ongoing, and was built and is operated on the Ordinal Data CURE open-source platform (Ordinal Data, Inc.; www.ordinaldata.com), and operates in a HIPAA-compliant and SSAE 16-certified hosting center. Data were collected on an ongoing basis from October 2022 to November 2025 (a period of 37 months) through surveys assessing (1) demographics, (2) disease history, (3) genetics and tumor biomarkers, (4) disease monitoring, (5) overall health and lifestyle, (6) QOL, (7) treatment overview, and (8) treatment timeline. Surveys could be completed all at once or over multiple sessions. For this study, data from select survey questions were analyzed.

Quality of life was assessed using a standardized self-report measure, the SF-12, which is a validated health-related QOL instrument developed to assess perceptions of personal capabilities and limitations in both physical and mental domains of functioning (Ware et al., 1996; Ware et al., 1995). Based on available data, on average, participants completed the survey approximately 3 years after their initial diagnosis (range: 1 month to 20 years post-diagnosis). SF-12 scores were represented as standardized T-scores (using a mean of 50 and a standard deviation [SD] of 10 in the general US population) for each of the two component summary scores, the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score.

Data Analysis

Data were analyzed using SPSS (v31.0) and R (v4.5.1). A p value of less than .05 was considered statistically significant.

Demographics and Health-Related Variables

The Chi-square (χ^2) test of independence with Cramér's V and non-parametric Kruskal-Wallis (H) test with Dunn's post-hoc test (Z) for multiple comparisons were used to compare descriptive demographic and clinical variables across melanoma cohorts as well as associations between categorical health-related variables and melanoma subtype.

Quality of Life

Correlations between PCS and MCS scores were assessed using Pearson correlation (r).

SF-12 Scores by Subtype

The Kruskal-Wallis (H) test with Dunn's test (Z) for multiple comparisons was used to assess melanoma subtype–specific differences in PCS and MCS scores.

US Population Norm-Based Comparison

Consistent with established normative interpretation of SF-12 T-scores, values were categorized into three groups (≤ 1 SD, ± 1 SD, ≥ 1 SD) and compared with expected normative proportions (15.865%, 68.27%, and 15.865%, respectively) using Chi-square (χ^2) goodness-of-fit tests within each melanoma subtype.

Demographic and Health-Related Variables and QOL Associations

Analysis of covariance (ANCOVA) was used to assess PCS and MCS T-scores among cohorts while adjusting for clinical variables. Covariates were selected based on adequate distribution across cohorts to ensure stable and interpretable estimates

and included age, disease status (active or no evidence of disease [NED]), and metastatic disease history (metastasis present or absent). Health-related factors not included in covariate analyses are shown in Table 1.

Adjusted PCS and MCS scores were derived using estimated marginal means from multiple linear regression models, and statistical significance was evaluated using analysis of variance (F) followed by Tukey's honestly significant difference (HSD) test. For PCS scores, a significant interaction between melanoma subtype and current disease status indicated a violation of the homogeneity of regression slopes assumption. Accordingly, pairwise comparisons between cohorts were conducted within subgroups (NED vs. active disease) using model-adjusted means.

Individual Item Comparison

Individual SF-12 items underwent ordinal encoding to assign categorical variables as integer values, with higher values indicating higher self-reported health. A Kruskal-Wallis (H) test and Dunn's post-hoc test (Z), when appropriate, were performed to compare individual SF-12 item responses across cohorts.

RESULTS

The SF-12 response rate for all RARE participants was 35.8% (230/643 total enrolled). For this study, only SF-12 survey completers were included: 64 (27.8%) with AM, 107 (46.5%) with MM, and 59 (25.7%) with CM (Table 1, Appendix A).

Demographic and Health-Related Variables

Demographics

Across all melanoma cohorts, most participants were located in the United States (78.7%), female (79.6%), White (95.2%), and non-Hispanic (96.5%; Table 1). The mean age (± SD) of participants with AM, MM, and CM at the time of SF-12 survey completion was 55.9 ± 12.0 years (n = 61), 60.4 ± 11.3 years (n = 105), and 46.7 ± 13.3 years (n = 55), respectively, with CM participants significantly younger than participants with AM and MM ($H(2) = 38.4$, $p < .001$; CM vs. AM $p < .001$; CM vs. MM $p < .001$; AM vs. MM $p = .084$). The mean duration between melanoma diagnosis and SF-12 survey completion was 3.1 ± 3.3 years (n = 44) for participants with AM, 2.1 ± 2.9 years (n = 54) for MM, and 4.2 ± 4.7 years (n = 36) for CM, with MM participants completing the SF-12 survey earlier in their disease journey than participants with CM ($H(2) = 7.3$, $p = .026$; CM vs. AM $p = .999$; CM vs. MM $p = .029$; AM vs. MM $p = .212$). As the date of initial diagnosis was unavailable for nearly 42% of the study population, health-related variables such as current disease status and metastatic disease progression were evaluated as a surrogate for survivorship in evaluating QOL outcomes.

Health-Related Variables

Cutaneous melanoma participants were significantly younger when diagnosed than participants with AM and MM ($H(2) = 19.9$, $p < .001$; CM vs. AM $p = .004$; CM vs. MM $p < .001$; AM vs. MM $p = .787$); the mean age (± SD) of participants at the time of diagnosis was 54.0 ± 11.4 years (n = 44) for AM, 56.8 ± 12.3 years (n = 54) for MM, and 43.9 ± 13.5 years (n = 36) for CM. At the time of initial diagnosis, the general disease stage (primary local, regional metastatic, distant metastatic) did not differ among cohorts ($\chi^2(4) = 2.61$, $p = .625$, Cramér's $V = 0.078$); the majority (> 62.5%) of participants were initially diagnosed with local primary disease independent of melanoma subtype. The anatomic sites of primary tumors for each cohort are provided in Appendix A. Local, regional metastatic, and distant metastatic stages did not differ among cohorts ($\chi^2(4) = 2.61$, $p = .625$, Cramér's $V = 0.078$). Metastatic disease was reported by 34.4% with AM, 47.7% with MM, and 47.5% with CM ($\chi^2(2) = 3.52$, $p = .172$, Cramér's $V = 0.125$). Current disease status, defined as NED or active disease, was significantly different across cohorts ($\chi^2(2) = 7.14$, $p = .028$, Cramér's $V = 0.178$), with active disease reported by 37.5% with AM, 53.3% with MM, and 33.9% with CM.

Quality of Life

SF-12 Scores by Subtype

T-scores (± SD) for the PCS and MCS of the SF-12 are presented in Figure 1. Pearson correlations (r) between PCS and MCS scores were negligible across subtypes (AM: $r = 9.46 \times 10^{-2}$, $p = .457$; MM: $r = -8.25 \times 10^{-5}$, $p = .999$; CM: $r = 4.07 \times 10^{-2}$, $p = .759$), indicating that PCS and MCS scores functioned independently within these cohorts. The mean PCS

Table 1. Characteristics of RARE Participants by Melanoma Cohort

Variable	Option	AM, *n* (%)	MM, *n* (%)	CM, *n* (%)
Geography	United States	47 (73.4%)	79 (73.8%)	55 (93.2%)
	Australia	5 (7.8 %)	8 (7.5%)	0 (0.0%)
	Canada	3 (4.7%)	5 (4.7%)	0 (0.0%)
	Great Britain	4 (6.3%)	7 (6.5%)	0 (0.0%)
	Other	5 (7.8%)	8 (7.5%)	4 (6.8%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex	Male	18 (28.1%)	17 (15.9%)	10 (16.9%)
	Female	45 (70.3%)	90 (84.1%)	48 (81.4%)
	Missing	1 (1.6%)	0 (0.0%)	1 (1.7%)
Race	Asian	1 (1.6%)	4 (3.7%)	0 (0.0%)
	American Indian/Alaskan Native	0 (0.0%)	1 (0.9%)	0 (0.0%)
	Black/African American	2 (3.1%)	0 (0.0%)	0 (0.0%)
	White	58 (90.6%)	102 (95.3%)	59 (100.0%)
	Other	2 (3.1%)	0 (0.0%)	0 (0.0%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Ethnicity	Hispanic	1 (1.6%)	3 (2.8%)	2 (3.4%)
	Non-Hispanic	63 (98.4%)	104 (97.2%)	55 (93.2%)
	Missing	0 (0.0%)	0 (0.0%)	2 (3.4%)
Education level	High school	6 (9.4%)	20 (18.7%)	6 (10.2%)
	College/University	36 (56.3%)	51 (47.7%)	22 (37.3%)
	Advanced degree	21 (32.8%)	36 (33.6%)	31 (52.5%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Stage at initial diagnosis	Primary local	40 (62.5%)	70 (65.4%)	41 (69.5%)
	Regional metastatic	16 (25.0%)	18 (16.8%)	12 (20.3%)
	Distant metastatic	4 (6.3%)	10 (9.3%)	3 (5.1%)
	Not sure	1 (1.6%)	5 (4.7%)	0 (0.0%)
	Missing	3 (4.7%)	4 (3.7%)	3 (5.1%)
Metastatic disease	Present	22 (34.4%)	51 (47.7%)	28 (47.5%)
	Absent	41 (64.1%)	54 (50.5%)	29 (49.2%)
	Missing	1 (1.6%)	2 (1.9%)	2 (3.4%)
Current disease status	Active disease, on observation	7 (10.9%)	12 (11.2%)	7 (11.9%)
	Active disease, on therapy	17 (26.6%)	45 (42.1%)	13 (22.0%)
	No evidence of disease	39 (60.9%)	48 (44.9%)	37 (62.7%)
	Missing	1 (1.6%)	2 (1.9%)	2 (3.4%)

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; *n* = number of participants. Percentages (%) were calculated from a sample size of 22 for AM, 51 for MM, and 28 for CM.

score (± SD) was below the US population norm of 50.0 for participants with AM (45.0 ± 13.3) and MM (45.6 ± 10.5), and slightly above 50.0 (50.9 ± 9.3) for participants with CM. The mean MCS score (± SD) was below 50.0 for all melanoma subtypes (AM: 43.9 ± 11.9, MM: 47.4 ± 11.0, CM: 45.3 ± 11.5). Unlike MCS scores, PCS scores differed significantly by melanoma subtype (PCS: $H(2) = 10.71$, $p = .005$; MCS: $H(2) = 3.52$, $p = .172$). Participants with AM and MM had significantly worse physical functioning (CM vs. AM: $Z = 2.45$, $p = .043$; CM vs. MM: $Z = 3.19$, $p = .004$; AM vs. MM: $Z = 0.470$, $p = .999$). The distribution of SF-12 scores across melanoma subtypes displayed significant kurtosis and bimodality, although both modes fell within the broad range of normal (± 1 SD; Appendix B).

US Population Norm-Based Comparison

When clinically relevant T-score categories were created, analyses indicated that, generally, participants functioned poorer than population norms. This was characterized by both an overrepresentation of scores falling ≤ 1 SD below the mean and underrepresentation of scores ≥ 1 SD above the mean. χ^2 goodness-of-fit tests were conducted to compare observed distributions of PCS and MCS T-score categories with expected normative proportions (Table 2).

Table 1. Characteristics of RARE Participants by Melanoma Cohort (cont.)

Variable	Option	AM, *n* (%)	MM, *n* (%)	CM, *n* (%)
History of other cancers	No	47 (73.4%)	79 (73.8%)	51 (86.4%)
	Yes	16 (25.0%)	26 (24.3%)	8 (13.6%)
	Missing	1 (1.6%)	2 (1.9%)	0 (0.0%)
Chronic disease (pre-diagnosis)	No	45 (70.3%)	76 (71.0%)	55 (93.2%)
	Yes	18 (28.1%)	29 (27.1%)	4 (6.8%)
	Missing	1 (1.6%)	2 (1.9%)	0 (0.0%)
Chronic disease (post-diagnosis)	No	47 (73.4%)	78 (72.9%)	43 (72.9%)
	Yes	16 (25.0%)	26 (24.3%)	16 (27.1%)
	Missing	1 (1.6%)	3 (2.8%)	0 (0.0%)
Treatment side effects	No	17 (26.6%)	11 (10.3%)	22 (37.3%)
	Yes	38 (59.4%)	85 (79.4%)	31 (52.5%)
	Not sure	2 (3.1%)	1 (0.9%)	0 (0.0%)
	Missing	7 (10.9%)	10 (9.4%)	6 (10.2%)
Surgery	No	10 (15.6%)	27 (25.2%)	10 (16.9%)
	Yes	53 (82.8%)	80 (74.8%)	49 (83.1%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Radiation therapy	No	52 (81.3%)	68 (63.6%)	51 (86.4%)
	Yes	11 (17.2%)	39 (36.4%)	8 (13.6%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Infused/injected medications	No	41 (64.1%)	33 (30.8%)	36 (61.0%)
	Yes	22 (34.4%)	74 (69.2%)	23 (39.0%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Intralesional/ topical medications	No	56 (87.5%)	96 (89.7%)	56 (94.9%)
	Yes	7 (10.9%)	11 (10.3%)	3 (5.1%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Oral medications	No	58 (90.6%)	88 (82.2%)	51 (86.4%)
	Yes	5 (7.8%)	19 (17.8%)	8 (13.6%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Clinical trials	No	57 (89.1%)	90 (84.1%)	53 (89.8%)
	Yes	6 (9.4%)	17 (15.9%)	6 (10.2%)
	Missing	1 (1.6%)	0 (0.0%)	0 (0.0%)
Concerns about metastatic disease[a]	Length of life	19 (86.4%)	44 (86.3%)	24 (85.7%)
	Effects on family/friends	12 (54.5%)	19 (37.3%)	14 (50.0%)
	Treatment side effects	9 (40.9%)	31 (60.8%)	19 (67.9%)
	Ability to continue work	7 (31.8%)	13 (25.5%)	12 (42.9%)
	Financial concerns	7 (31.8%)	9 (17.6%)	11 (39.3%)
	Access to care	5 (22.7%)	9 (17.6%)	7 (25.0%)
	Other	2 (9.1%)	3 (5.9%)	2 (7.1%)
	Missing	0 (0.0%)	1 (2.0%)	1 (3.6%)

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; *n* = number of participants.
[a]Data based on the RARE participants with metastatic disease. Percentages (%) were calculated from a sample size of 22 for AM, 51 for MM, and 28 for CM.

Physical QOL. PCS distributions deviated from expected norms in the AM cohort (PCS: $\chi^2(2) = 27.17$, $p < .001$) and MM cohort (PCS: $\chi^2(2) = 29.41$, $p < .001$) and were similar to normative expectations in participants with CM ($\chi^2(2) = 1.14$, $p = .566$).

Mental QOL. MCS scores ≤ 1 SD below the mean were overrepresented across all three subtypes (AM: $\chi^2(2) = 34.30$, $p < .001$; CM: $\chi^2(2) = 22.21$, $p < .001$; MM: $\chi^2(2) = 11.03$, $p = .004$).

Demographic and Health-Related Variables and QOL Associations

Physical QOL Associations

Age. Participant age at survey completion was not a significant predictor of PCS scores (ANCOVA; $B = 0.0007$, standard error [SE] = 0.062, $p = .914$); adjusted mean PCS scores in AM and MM cohorts were 5.35 and 5.44 lower than in CM, respectively (CM vs. AM: $p = .035$; CM vs. MM: $p = .022$; Appendix C and D).

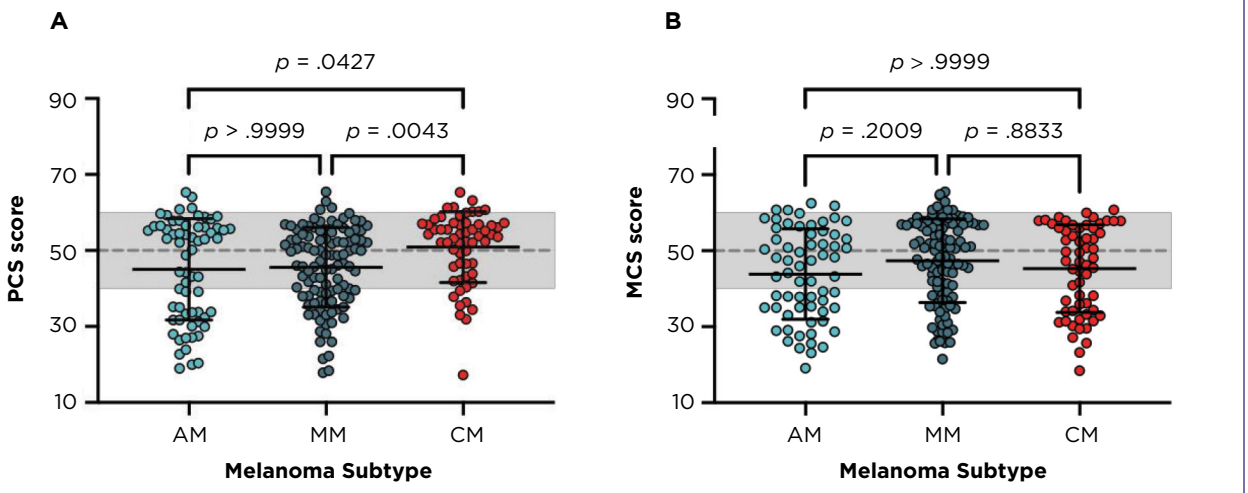


Figure 1. Distribution of SF-12 PCS and MCS T-scores across melanoma subtypes. (A and B) Individual RARE participant PCS T-scores (A) and MCS T-scores (B) are shown as colored symbols across melanoma subtypes. Horizontal grey bar indicates scores that fall within ±1 SD of the US general population mean (T-score of 50; grey dashed line). Data are graphed as mean with error bars representing the SD. Mean ± SD PCS T-scores are 45.04 ± 13.32 for AM, 45.60 ± 10.51 for MM, and 50.88 ± 9.28 for CM; PCS scores are significantly different between cohorts (H(2, 230) = 10.71, p = .005). Mean ± SD MCS T-scores are 43.86 ± 11.89 for AM, 47.37 ± 11.00 for MM, and 45.28 ± 11.53 for CM; MCS scores are similar among cohorts (H(2, 230) = 3.52, p = .172). *P* values shown are derived from Dunn's pairwise comparisons post-hoc test. AM = acral melanoma; CM = cutaneous melanoma; MCS = Mental Component Summary; MM = mucosal melanoma; PCS = Physical Component Summary; SD = standard deviation; SF-12 = 12-item Short Form Survey.

Disease Progression and Status. Both a history of metastatic progression (present vs. absent) and current disease status (active vs. NED) were significant predictors of PCS scores. Participants with active disease (B = -4.82, SE = 1.48, p = .001) and metastatic progression (B = -5.08, SE = 1.46, p = .001) had lower PCS scores. After adjusting for metastatic progression, PCS scores remained significantly different across cohorts (F(2, 221) = 5.35, p = .005); adjusted mean PCS scores in AM and MM cohorts were 6.13 and 4.75 lower than in CM, respectively (CM vs. AM: p = .006; CM vs. MM: p = .022; Appendix D). A significant interaction between melanoma subtype and current disease status on PCS scores was observed (F(2, 221) = 3.95, p = .021), indicating that differences in PCS scores across cohorts depend on disease status. Stratified analyses showed that the adjusted mean PCS score was 7.25 lower in MM compared to CM (SE = 2.34, p = .006) in the NED subgroup and 6.17 lower in AM compared to MM in the active disease subgroup (SE = 2.60, p = .049; Appendix E).

Mental QOL Associations

Age. Participant age was a significant positive predictor of MCS (B = 0.321, SE = 0.06, p < .001). Mental Component Summary scores did not differ by melanoma subtype after adjusting for age (Appendix C).

Disease Progression and Status. Metastatic disease progression was not significantly associated with MCS scores (B = −0.562, SE = 1.54, p = .715); covariate-adjusted MCS scores were similar among cohorts (Appendix C). Compared to participants with NED, active disease status at the time of survey completion was a significant negative predictor of MCS scores (B = -6.26, SE = 1.49, p < .001). Adjusting for current disease status revealed marginally significant differences in MCS scores between the AM and MM cohorts, with AM participants reporting worse mental functioning (F(2, 221) = 3.24, p = .041; AM vs. MM: p = .049; Appendix C and D).

Table 2. Distribution and Chi-Square Statistics of SF-12 PCS and MCS Scores Across Melanoma Cohorts

Score	AM, *n*, expected *n* (%)[a]	MM, *n*, expected *n* (%)[a]	CM, *n*, expected *n* (%)[a]
SF-12 PCS Score			
0–39.999 (< -1 SD)	25, 10.2 (39.1%)	35, 17.0 (32.7%)	8, 9.4 (13.6%)
40–60 (± 1 SD)	35, 43.7 (54.7%)	68, 73.1 (63.6%)	44, 40.3 (74.6%)
60.001–100 (> +1 SD)	4, 10.2 (6.3%)	4, 17.0 (3.7%)	7, 9.4 (11.9%)
χ^2(df, n), *p* value	$\chi^2(2, 64) = 27.17$, $p < .001$	$\chi^2(2, 107) = 29.41$, $p < .001$	$\chi^2(2, 59) = 1.14$, $p = .566$
SF-12 MCS Score			
0–39.999 (< -1 SD)	27, 10.2 (42.2%)	28, 17.0 (26.2%)	21, 9.4 (35.6%)
40–60 (± 1 SD)	33, 43.7 (51.6%)	70, 73.1 (65.4%)	37, 40.3 (62.7%)
60.001–100 (> +1 SD)	4, 10.2 (6.3%)	9, 17.0 (8.4%)	1, 9.4 (1.7%)
χ^2(df, n), *p* value	$\chi^2(2, 64) = 34.30$, $p < .001$	$\chi^2(2, 107) = 11.03$, $p = .004$	$\chi^2(2, 59) = 22.21$, $p < .001$

Note. AM = acral melanoma; CM = cutaneous melanoma; df = degrees of freedom; MCS = Mental Component Summary; MM = mucosal melanoma; *n* = number of participants; PCS = Physical Component Summary; SD = standard deviation; SF-12 = 12-item Short Form Survey; χ^2 = chi-square test statistic
[a]Expected percentage (%) for each cohort is based on the normal distribution (15.865%, 68.27%, 15.865%) used in the Chi-square goodness-of-fit test.

Individual SF-12 Item Responses

Exploratory analyses of individual items on the SF-12 (Table 3) were conducted to assess whether specific domains contributed to observed differences across melanoma subtypes. Non-parametric testing showed that three items were different across groups: limitations in moderate activities (p = .013), limitations in daily activities due to physical health (p = .041), and the impact of physical and emotional health on social activities (p = .016). Post-hoc comparisons suggested that participants with AM and MM had greater limitations in moderate activities than those with CM, and those with MM had greater limitations in activities due to physical health. Participants with AM also experienced greater social impact of health compared to those with CM. Given the number of comparisons and exploratory nature of these analyses, these findings should be interpreted cautiously and considered hypothesis-generating (Appendix F).

CONCLUSIONS

This study presents the first QOL data from the MRA's RARE Registry, a patient-driven, non-institutional initiative to advance rare melanoma research. Patients with rare melanomas have been historically underrepresented in patient-reported outcomes research. Patient-reported SF-12 responses from patients with AM, CM, and MM indicate complex and clinically meaningful differences in QOL that are not explained by demographic and health-related variables alone.

The participants that completed study questionnaires were somewhat demographically homogeneous. However, their reported health-related features, including stage of disease, primary site, and treatment pathway, varied significantly, constituting a clinically representative sample across melanoma subtypes.

Quality of Life

Physical and mental QOL were reflected in subscales of the SF-12 (PCS and MCS) and were not significantly associated with one another. Outcomes in this study varied. Interestingly, most participants, across all diagnosis types, reported QOL within the broad range of normal.

Physical QOL

Scores from the SF-12 PCS subscale indicate that a significant proportion of AM and MM patients had lower physical functioning than US population norms. Individual item analyses showed that nearly half of all participants with AM or MM experienced limitations in daily activities and accomplished less due to physical health and that these difficulties impacted their social activities.

Table 3. Individual SF-12 Item Responses by Melanoma Cohort

SF-12 item	AM (*n* = 64), %	MM (*n* = 107), %	CM (*n* = 59), %
General rating of health			
Excellent	10.9	7.5	16.9
Very good	37.5	45.8	40.7
Good	26.6	35.5	30.5
Fair	20.3	8.4	11.9
Poor	4.7	2.8	0.0
Limitations in moderate activities due to health			
Yes, limited a lot	21.9	13.1	1.7
Yes, limited a little	14.1	25.2	16.9
No, not limited at all	64.1	61.7	81.4
Limited in climbing stairs due to health			
Yes, limited a lot	25.0	9.3	3.4
Yes, limited a little	18.8	37.4	27.1
No, not limited at all	56.3	53.3	69.5
Accomplished less due to physical health			
Yes	46.9	51.4	32.2
No	53.1	48.6	67.8
Limited in daily activities due to physical health			
Yes	42.2	44.9	25.4
No	57.8	55.1	74.6
Accomplished less due to emotional health			
Yes	54.7	39.3	47.5
No	45.3	60.7	52.5
Less careful due to emotional health			
Yes	34.4	26.2	28.8
No	65.6	73.8	71.2

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; *n* = number of participants; SF-12 = 12-item Short Form Survey.

In contrast, PCS scores of participants with a diagnosis of CM primarily fell within the broad range of normal, and item analyses showed a significantly lower degree of these limitations.

However, this pattern has not been shown consistently in previous research. For example, a German registry of long-term survivors of melanoma showed lower physical function and greater pain in women than the population norm (Beutel et al., 2015). A qualitative study showed that many patients with CM reported limitations in physical functioning (Weitman et al., 2018).

When comparing physical QOL in AM, CM, and MM, PCS scores were lower, indicating worse functioning, for participants with rare melanomas than CM. This pattern persisted when adjusting for other demographic factors, including age. A study in Romania that used the SF-12 also showed a role for age but instead reported higher physical scores in younger compared to older patients with melanoma (Toma et al., 2023). Other health-related factors, including metastatic progression and active disease, were associated with worse physical functioning across all subtypes, and differences in PCS scores across subtypes remained after adjusting for these covariates.

The broad interval between melanoma diagnosis and QOL survey completion (1 month to 20 years) could feasibly contribute to variability in PCS scores by capturing patients at different phases of survivorship. This interval was shorter among participants with rare melanomas, particularly MM, than those with CM, and may have captured physical QOL earlier in the disease journey (e.g., undergoing intensive treatment) and contributed to the greater physical impairments observed in patients with MM and AM.

Table 3. Individual SF-12 Item Responses by Melanoma Cohort (cont.)

SF-12 item	AM (*n* = 64), %	MM (*n* = 107), %	CM (*n* = 59), %
Pain affected normal work			
Extremely	9.4	3.7	1.7
Quite a bit	9.4	5.6	6.8
Moderately	15.6	15.9	8.5
A little bit	23.4	30.8	28.8
Not at all	42.2	43.9	54.2
Felt calm and peaceful			
All of the time	4.7	4.7	3.4
Most of the time	23.4	34.6	35.6
A good bit of the time	20.3	17.8	23.7
Some of the time	31.3	28.0	27.1
A little of the time	17.2	12.1	6.8
None of the time	3.1	2.8	3.4
Had a lot of energy			
All of the time	3.1	4.7	8.5
Most of the time	21.9	18.7	22.0
A good bit of the time	17.2	18.7	23.7
Some of the time	25.0	34.6	20.3
A little of the time	25.0	16.8	20.3
None of the time	7.8	6.5	5.1
Felt downhearted and blue			
All of the time	0.0	0.0	1.7
Most of the time	7.8	2.8	8.5
A good bit of the time	14.1	11.2	13.6
Some of the time	28.1	29.9	22.0
A little of the time	31.3	33.6	33.9
None of the time	18.8	22.4	20.3
Physical/emotional health affected social activities			
All of the time	4.7	4.7	0.0
Most of the time	17.2	4.7	3.4
A good bit of the time	10.9	7.5	11.9
Some of the time	17.2	24.3	16.9
A little of the time	25.0	19.6	23.7
None of the time	25.0	39.3	44.1

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; *n* = number of participants; SF-12 = 12-item Short Form Survey.

Mental QOL

A significant proportion of MCS scores fell below the US norm across all subtypes; a large proportion of participants reported clinically meaningful fatigue, cognitive difficulties, and social withdrawal. This is consistent with previous research that indicates, at least in CM, that concerns about limitations in social activities are common (Weitman et al., 2018). Notably, participants with CM reported relatively normal physical QOL but poorer mental QOL than US norms.

Several demographic and health-related factors appear to be related in some way to mental QOL in our study population. Participant age at the time of survey completion was a significant predictor of mental functioning, with older age associated with better mental QOL. After adjusting for age at the time of the survey, MCS scores were similar across melanoma subtypes. Consistent with our observations, a previous study showed that older patients had a higher mental than physical score on the SF-12 (Toma et al., 2023). Additionally, younger patients are more likely than older patients to have concerns about social rejection and body self-image (Ahmad et al., 2026). Thus, the significantly younger age of participants with CM may be a contributing factor to the pattern of relatively lower mental QOL in this study compared with physical QOL.

Our data also suggest that disease status is associated with mental QOL across diagnosis types.

Participants with active disease at the time of survey completion had lower MCS scores than those with NED in all diagnosis types. Notably, the CM cohort exhibited the largest interval between diagnosis and survey completion, suggesting that impairments in mental QOL may persist long after diagnosis and treatment, and highlights a potential need for psycho-oncology support beyond the initial CM diagnosis (Toma et al., 2023).

Strengths and Limitations

Strengths of this study include utilization of a multinational, direct-to-patient registry to examine QOL in rare melanoma subtypes that are underrepresented in clinical research. The use of a normed, validated measure of QOL (SF-12) allows for standardized, norm-based comparisons with the general population and across groups. Melanoma subtypes were broadly comparable across key clinical characteristics, supporting the validity of cross-group QOL comparisons. In addition, the use of covariate-adjusted analyses, interaction testing, and stratified models provides a more nuanced understanding of the relationship among melanoma subtype, disease status, and patient-reported QOL.

Limitations include the voluntary and web-based nature of the registry, which resulted in a self-selected and less representative sample; participants were mostly White and female with at least some secondary education, which may limit generalizability. Although certain melanoma subtypes disproportionately affect specific demographic groups, the degree of homogeneity observed in this sample exceeded expected distributions. Covariate analyses were conducted to evaluate associations between medical and demographic variables and QOL scores; however, non-normal distributions and smaller subgroup sizes may limit the sensitivity and stability of these analyses.

FUTURE DIRECTIONS

This study represents an important step toward characterizing the lived experience of individuals with rare melanomas. The findings highlight the need for continued research to better understand the multidimensional impact of rare melanoma diagnoses. Greater efforts are needed to obtain a more demographically representative sample to further clarify QOL across the rare melanoma population. One clinically relevant pattern observed in this study is that physical and mental QOL vary significantly across diagnosis type, demographic and health-related factors, and even within one person. A patient who is functioning well physically may be experiencing significant mental distress. As the RARE Registry continues to enroll participants, future studies should include longitudinal analyses to evaluate physical and mental QOL at defined intervals or distinct stages of the disease, particularly for AM and MM. Future investigations should also consider treatment era and treatment history, particularly given advances in the clinical management of melanoma, such as targeted therapies and immune checkpoint inhibitors beginning in 2011 (Sullivan et al., 2013), which may influence long-term QOL (Saw et al., 2022).

Cutaneous melanoma diagnoses are seen frequently within the advanced practice oncology setting. Patients with a rare melanoma often face more aggressive treatment pathways and may interact more frequently with clinical practice as a result. Our research suggests that QOL in rare melanoma is widely variable, and often below population norms for both physical and mental QOL, highlighting the importance of assessing the impact of the diagnosis and treatments on QOL for each patient. The advanced practitioner in the oncology setting is ideally positioned to screen for current QOL and support patients in accessing appropriate psycho-oncology support (Toma et al., 2023) and palliative care, including referrals to psycho-oncology, rehabilitation medicine, physical therapy, or fatigue management programs, even in patients without active disease when functional impairments exist (Low et al., 2024). ●

Disclosure

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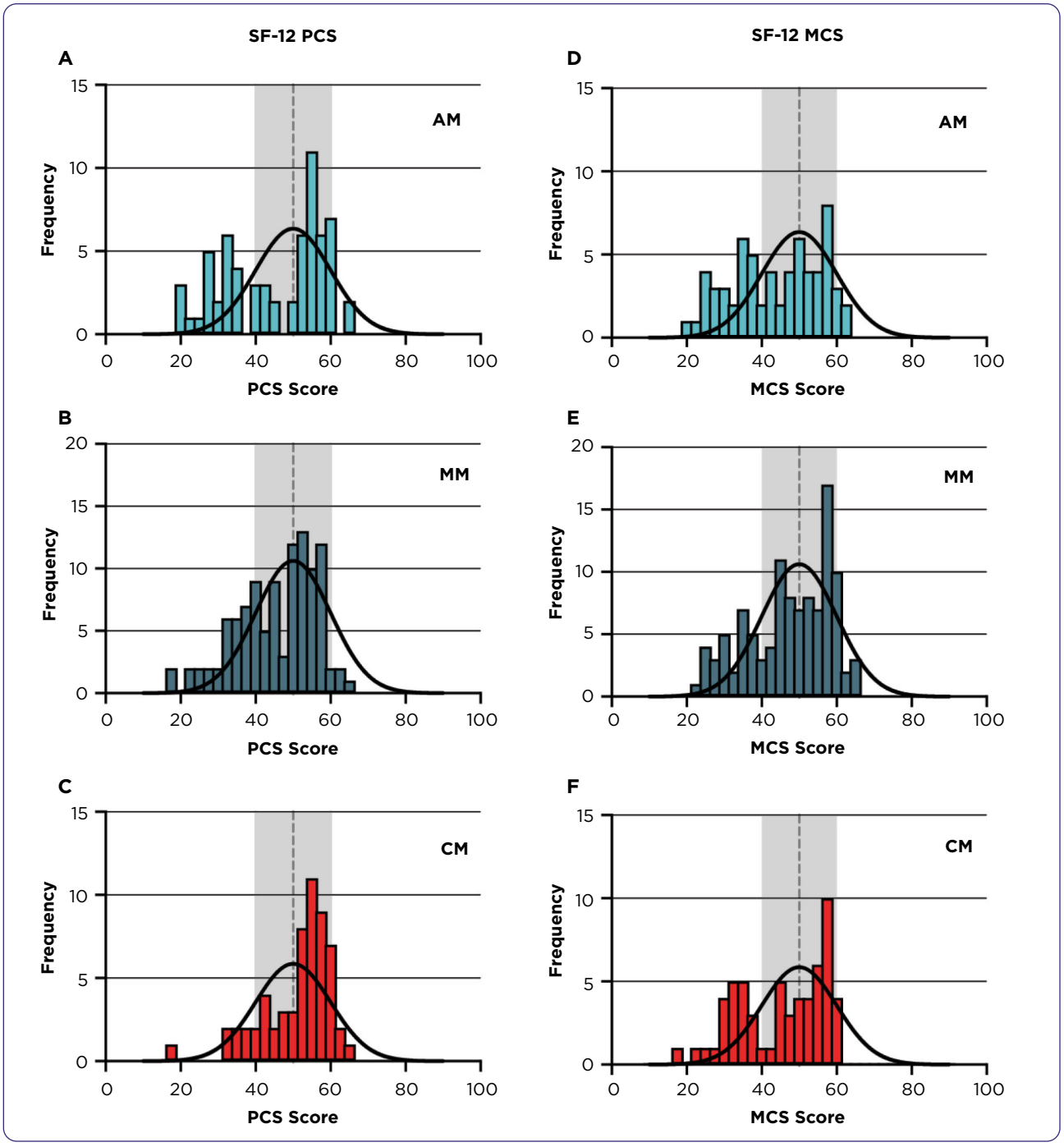
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Appendix A. Anatomic Site of Primary Melanoma at Initial Diagnosis

Subtype	Origin site	*n* (%)
AM	Fingernail	8 (12.5%)
	Palm of hand	0 (0.0%)
	Sole of foot	40 (62.5%)
	Toenail	13 (20.3%)
	Unknown/missing	3 (4.7%)
MM	Anus	32 (29.9%)
	Bladder	0 (0.0%)
	Conjunctiva	1 (0.9%)
	Esophagus	0 (0.0%)
	Gallbladder	0 (0.0%)
	Gastrointestinal tract	2 (1.9%)
	Nose	14 (13.1%)
	Oral cavity/mouth	3 (2.8%)
	Penis	0 (0.0%)
	Sinuses	12 (11.2%)
	Urethra	1 (0.9%)
	Vagina	11 (10.2%)
	Vulva	25 (23.4%)
	Other	2 (1.9%)
	Unknown/missing	4 (3.7%)
CM	Head/neck/face	6 (10.2%)
	Back	11 (18.6%)
	Chest	3 (5.1%)
	Arms/shoulders	13 (22.0%)
	Legs/hips	21 (35.6%)
	Hands	1 (1.7%)
	Feet	1 (1.7%)
	Unknown/missing	3 (5.1%)

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; *n* = number of participants.



Appendix B. Distribution of SF-12 PCS and MCS T-scores across melanoma cohorts. Histogram with bars representing the frequency of RARE participants within each bin (2.5-point intervals) of PCS T-scores (A–C) and MCS T-scores (D–F) across melanoma subtypes (A and D = AM; B and E = MM; C and F = CM). PCS scores for AM and MM both show slight negative skewness (−0.41 and −0.56, respectively), indicating modest left-tailed distributions; PCS scores for CM exhibit a slightly stronger left-tail skew (−1.24). MCS scores show slight negative skewness across all subtypes (AM: −0.22, MM: −0.51, CM: −0.43). Negative values of kurtosis are evident for PCS scores (AM: −1.23, MM: −0.31) and MCS scores (AM: −1.15, MM: −0.78, CM: −1.09) across subtypes, indicating a slight-to-moderate platykurtic distribution, apart from PCS scores for CM (1.77). A normal distribution curve ($\mu = 50$, $\sigma = 10$) is shown in black. Vertical grey bar marks the T-score interval from 40 to 60, representing ± 1 SD from the US general population mean (T-score of 50; vertical grey dashed line). AM = acral melanoma; CM = cutaneous melanoma; MCS = Mental Component Summary; MM = mucosal melanoma; PCS = Physical Component Summary; SF-12 = 12-item Short Form Survey.

Appendix C. Covariate-Adjusted SF-12 PCS and MCS Scores (Estimated Marginal Means) and ANCOVA Results

Variable	Subtype	*n*	Adj. mean score (95% CI)	ANCOVA F(df_1, df_2)	*p* value
SF-12 PCS Score					
Age at survey completion[a]	AM	61	45.56 (42.77–48.35)	4.15 (2, 217)	.017
	MM	105	45.47 (43.27–47.68)		
	CM	55	50.91 (47.77–54.05)		
Metastatic disease[b]	AM	63	44.44 (41.72–47.15)	5.35 (2, 221)	.005
	MM	105	45.81 (43.74–47.89)		
	CM	57	50.56 (47.74–53.38)		
SF-12 MCS Score					
Age at survey completion[a]	AM	61	43.89 (41.16–46.62)	1.83 (2, 217)	.163
	MM	105	46.01 (43.85–48.16)		
	CM	55	47.82 (44.74–50.89)		
Metastatic disease[b]	AM	63	44.08 (41.22–46.94)	1.68 (2, 221)	.190
	MM	105	47.32 (45.13–49.51)		
	CM	57	45.32 (42.35–48.29)		
Current disease status[c]	AM	63	43.42 (40.68–46.16)	3.24 (2, 221)	.041
	MM	105	47.59 (45.48–49.70)		
	CM	57	44.39 (41.50–47.29)		

Note. AM = acral melanoma; ANCOVA = analysis of covariance; CI = confidence interval; CM = cutaneous melanoma; df_1 = degrees of freedom; df_2 = residual (error) degrees of freedom; MCS = Mental Component Summary; MM = mucosal melanoma; n = number of participants; PCS = Physical Component Summary; SF-12 = 12-item Short Form Survey.
[a]Age at survey completion is derived from the difference between participant's date of birth and date of QOL survey submission in RARE. Percentages (%) reflect the number of participants among QOL survey responders who provided date of birth data.
[b]Metastatic disease, categorized as present or absent, refers to whether the participant's melanoma has metastasized.
[c]Current disease status refers to no evidence of disease and active disease (either on therapy or on observation).

Appendix D. Pairwise Comparisons (Tukey's HSD) of Covariate-Adjusted SF-12 PCS Scores

Variable	Comparison	Adj. mean score difference (95% CI)[d]	*p* value
SF-12 PCS Score			
Age at survey completion[a]	CM vs. AM	5.35 (0.31–10.39)	.035
	CM vs. MM	5.44 (0.65–10.23)	.022
	AM vs. MM	0.08 (-4.17–4.34)	.999
Metastatic disease[b]	CM vs. AM	6.13 (1.44–10.81)	.006
	CM vs. MM	4.75 (0.56–8.94)	.022
	AM vs. MM	-1.38 (-5.46–2.71)	.707
SF-12 MCS Score			
Current disease status[c]	CM vs. AM	0.97 (-3.75–5.70)	.8781
	CM vs. MM	-3.20 (-7.51–1.11)	.1878
	AM vs. MM	-4.17 (-8.33 to -0.01)	.0490

Note. AM = acral melanoma; CI = confidence interval (lower, upper); CI = confidence interval; CM = cutaneous melanoma; HSD = honestly significant difference; MM = mucosal melanoma; PCS = Physical Component Summary; MCS = Mental Component Summary; SF-12 = 12-item Short Form Survey
[a]Age at survey completion is derived from the difference between participant's date of birth and date of QOL survey submission in RARE. Percentages (%) reflect the number of participants among QOL survey responders who provided date of birth data.
[b]Metastatic disease, categorized as present or absent, refers to whether the participant's melanoma has metastasized.
[c]Current disease status refers to no evidence of disease and active disease (either on therapy or on observation).
[d]Positive adjusted mean differences reflect higher scores in the reference group (e.g., CM in CM vs. AM comparisons).

Appendix E. Pairwise Comparisons (Tukey's HSD) of Adjusted SF-12 PCS scores by Melanoma Cohort, Stratified by Current Disease Status

Current disease status subgroup	Comparison	Adj. mean difference[a]	SE	*t*(df)	*p* value
No evidence of disease	CM vs. AM	4.71	2.45	1.92	.135
	CM vs. MM	7.25	2.34	3.10	.006
	AM vs. MM	2.53	2.30	1.10	.516
Active disease	CM vs. AM	5.88	3.24	1.82	.166
	CM vs. MM	-0.28	2.78	-0.10	.994
	AM vs. MM	-6.17	2.60	-2.37	.049

Note. AM = acral melanoma; CM = cutaneous melanoma; df = residual (error) degrees of freedom; HSD = honestly significant difference; MM = mucosal melanoma; PCS = Physical Component Summary; SE = standard error; SF-12 = 12-item Short Form Survey.
[a]Positive adjusted mean differences reflect higher scores in the reference group (e.g., CM in CM vs. AM comparisons).

Appendix F. Assessment of Individual SF-12 Item Responses Across Melanoma Cohorts Using the Kruskal-Wallis Test With Dunn's Post-Hoc Test for Multiple Comparisons

SF-12 Item	*H*	*p* value	Comparison	*Z*	Adj. *p* value
General rating of health	2.81	.245	–	–	–
Limitations in moderate activities due to health	8.62	.013	CM vs. AM	2.51	.036
			CM vs. MM	2.69	.021
			AM vs. MM	-0.10	1.000
Limited in climbing stairs due to health	5.84	.054	–	–	–
Accomplished less due to physical health	5.73	.057	–	–	–
Limited in daily activities due to physical health	6.35	.041	CM vs. AM	1.89	.173
			CM vs. MM	2.45	.043
			AM vs. MM	0.35	1.000
Accomplished less due to emotional health	3.93	.140	–	–	–
Less careful due to emotional health	1.31	.521	–	–	–
Pain affected normal work	3.96	.138	–	–	–
Felt calm and peaceful	2.93	.231	–	–	–
Had a lot of energy	1.86	.400	–	–	–
Felt downhearted and blue	1.43	.490	–	–	–
Physical/emotional health affected social activities	8.23	.016	CM vs. AM	2.76	.017
			CM vs. MM	0.96	.090
			AM vs. MM	-2.17	1.000

Note. AM = acral melanoma; CM = cutaneous melanoma; MM = mucosal melanoma; SF-12 = 12-item Short Form Survey.