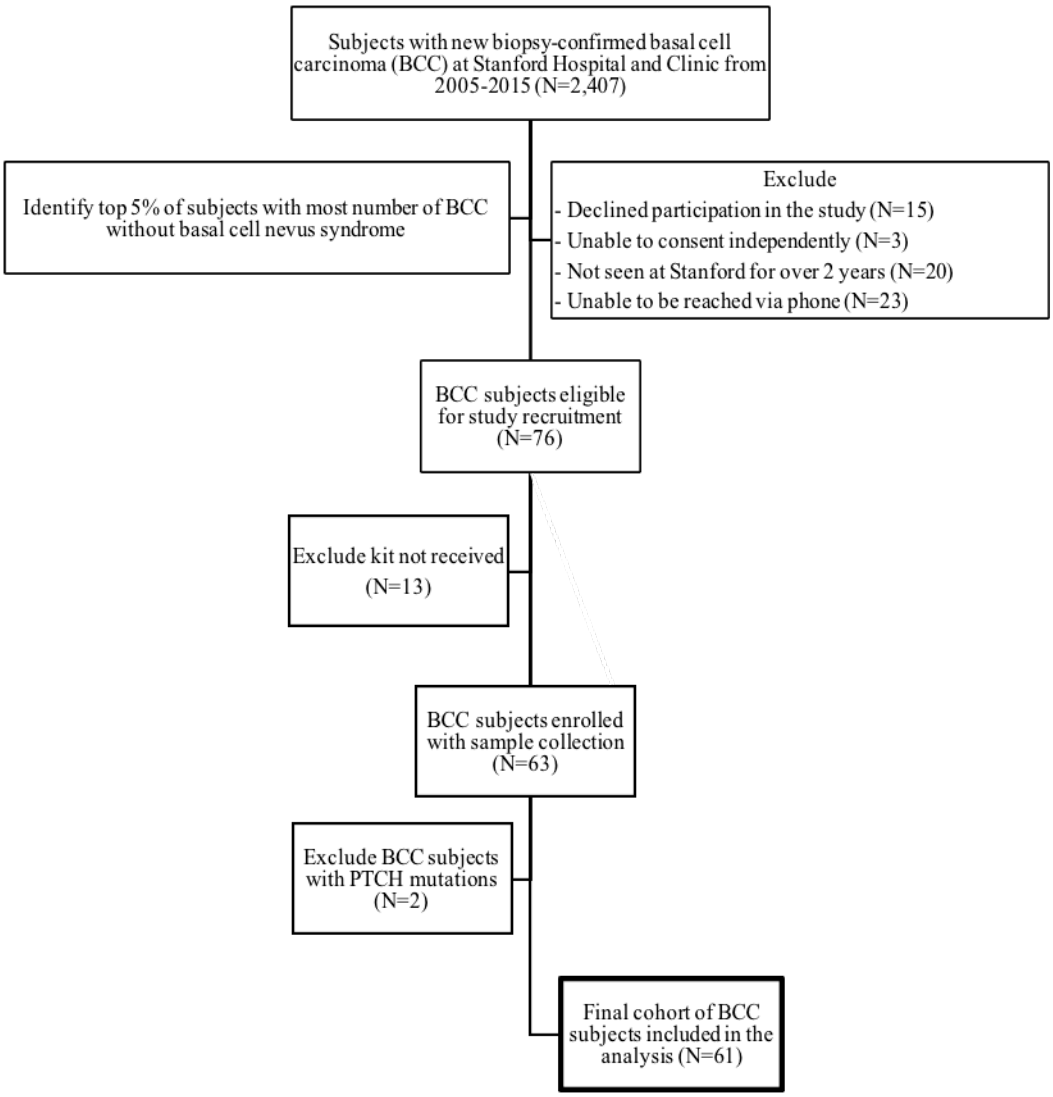
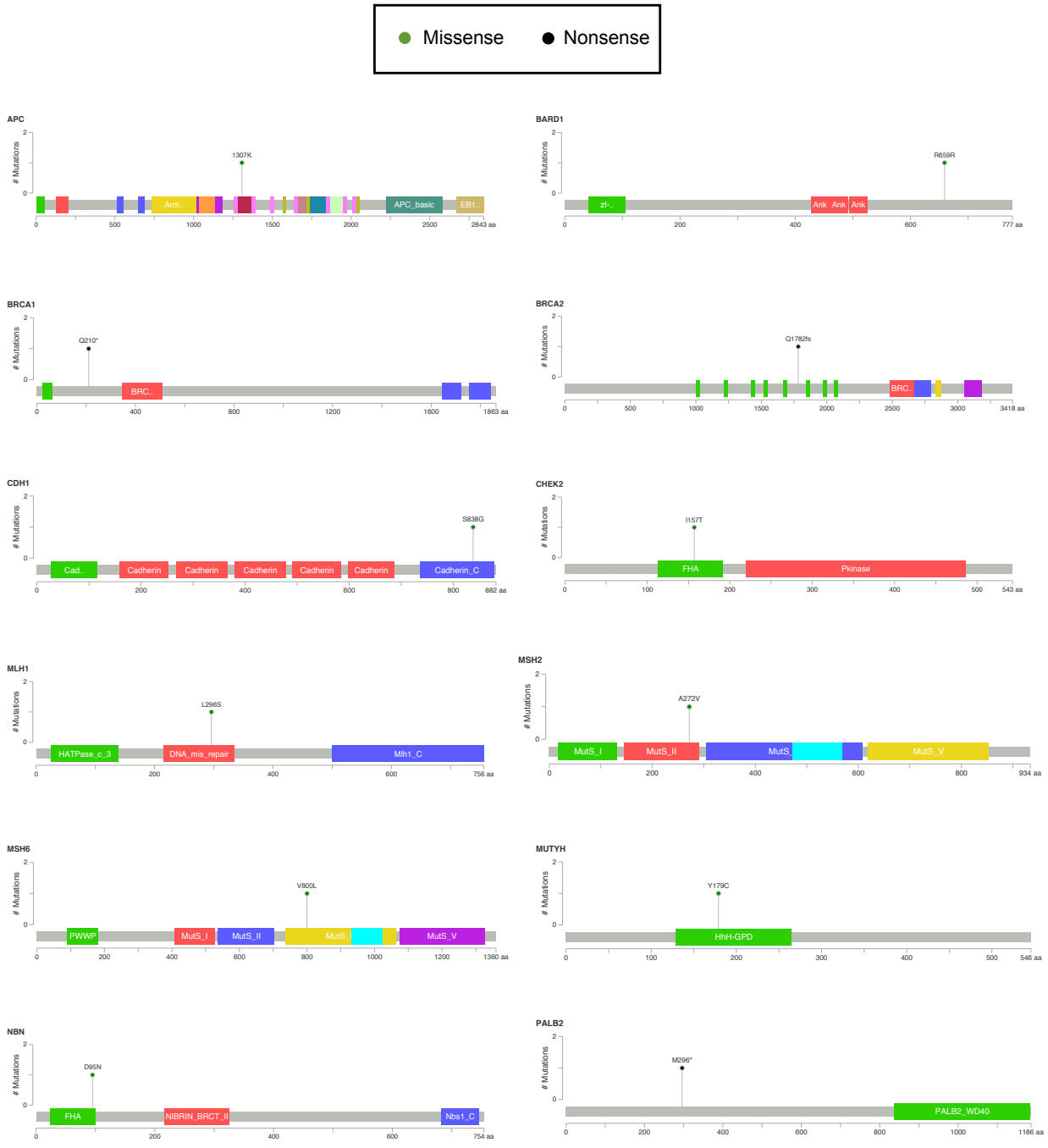
## SUPPLEMENTARY MATERIALS

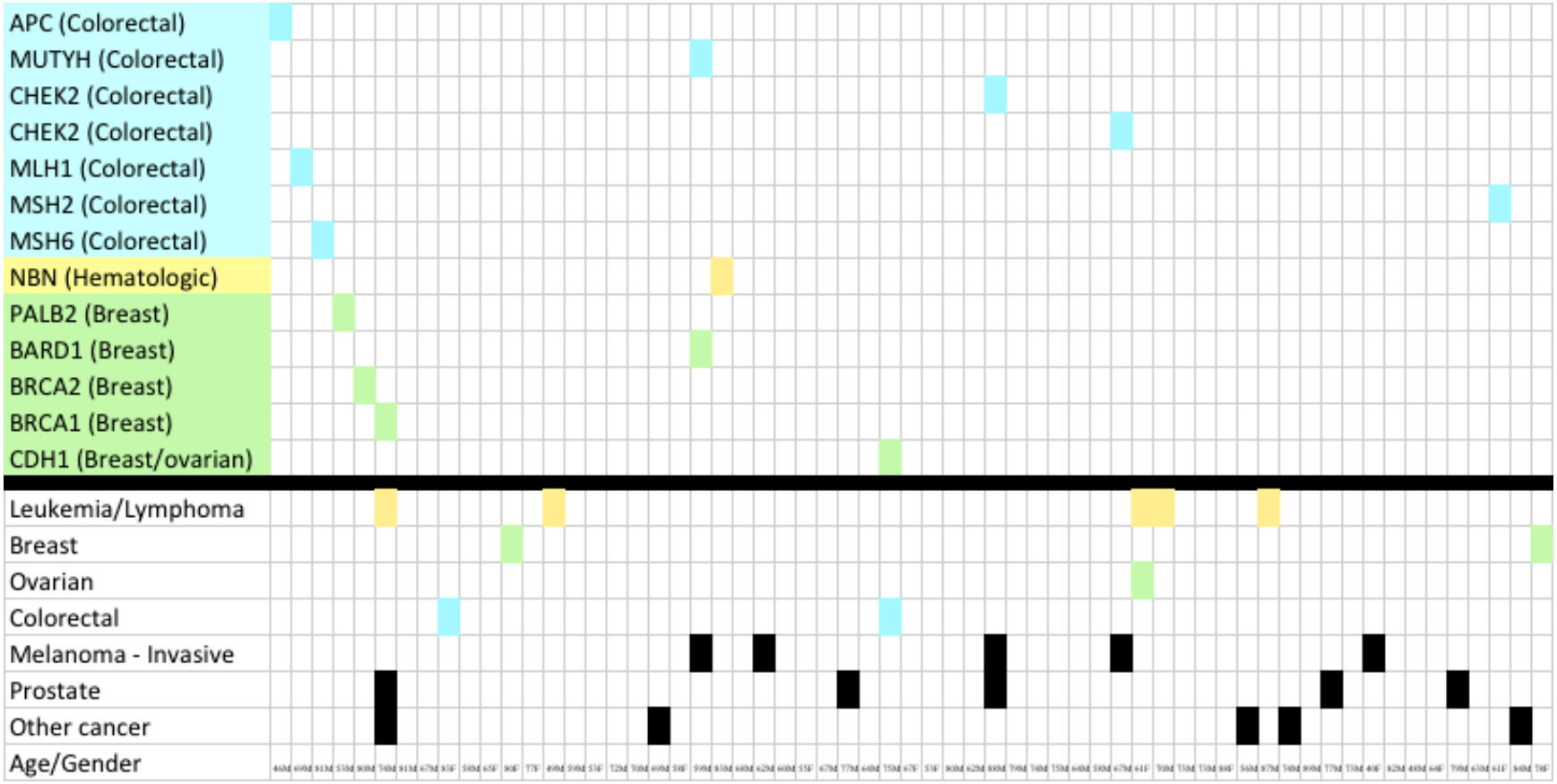
**Supplementary Figure S1.** Schema of basal cell carcinoma (BCC) cohort recruitment and enrollment. Top 5% of subjects with biopsy-confirmed non-recurrent, non-residual basal cell carcinoma without documented basal cell nevus syndrome were recruited to participate. A final cohort of 69 BCC subjects was included in the study. Approval for this study was obtained from the Stanford Institutional Review Board (IRB protocol 36263).



**Supplementary Figure S2.** All reported pathogenic mutations. A total of 13 reported pathogenic variants were identified in 12 genes, including *APC, MUTYH, CHEK2, MLH1, MSH2, MSH6,* 438 *NBN, PALB2, BARD1, BRCA2, BRCA1*, and *CDH1*.



**Supplementary Figure S3.** Heatmap
The heatmap of germline mutations and personal history of other cancers in the enrolled subjects, ordered from left to right per number of BCCs (range 6-65). The color is coded in following association: Blue (colorectal cancer), yellow (hematologic cancer), green (breast/ovarian), black (other).



**Supplementary Table S1**. DNA repair pathway genes in the 29 cancer susceptibility gene panel.

| | |
|---|---|
| Base excision repair | *MUTYH* |
| Mismatch excision repair | *MSH1, MSH2, MSH6, PMS2* |
| Homologous recombination | *BRCA1, BRCA2, MRE11A, NBN, RAD50, RAD51C, RAD51D* |
| DNA polymerases | *POLD1, POLE* |
| Genes defective in diseases associated with sensitivity to DNA damaging agents | *ATM, BRIP1, PALB2* |
| Other conserved DNA damage response genes | *CHEK2, TP53. APC, BARD1, CDH1* |

**Supplementary Table S2.** ICD-9 and CPT codes used to query Truven MarketScan database

| Diagnosis or Procedure | ICD-9 or CPT codes |
|---|---|
| Basal cell carcinoma | 173.01, 173.11, 173.21, 173.31, 173.41, 173.51, 173.61, 173.71, 173.81, or 173.91 |
| Biopsy procedure | 11310, 11311, 11312, 11313, 11300, 11301, 11302, 11303, 11305, 11305, 11306, 11307, 11308, 11100, 11101, 67810 |
| Destruction procedure | 17261, 17262, 17263, 17264, 17265, 17266, 17270, 17271, 17272, 17273, 17274, 17276, 67850, 17280, 17281, 17283, 17284, 17286 |
| Excision procedure | 11600, 11601, 11602, 11603, 11604, 11606, 11620, 11621, 11622, 11623, 11624, 11626, 11620, 11621, 11622, 11623, 11624, 11626, 11640, 11641, 11642, 11643, 11644, 11646, 67840, 67961, 67966 |
| Mohs procedure | 17311, 17312, 17313, 17314, 17315 |
| Breast cancer | 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9 |
| Lung cancer | 162.3, 162.4, 162.5, 162.8, 162.9 |
| Stomach cancer | 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9 |
| Colon cancer | 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9 |
| Pancreatic cancer | 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9 |
| Liver cancer | 155.0, 155.1, 155.2 |
| Bladder cancer | 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9 |
| Renal / Urinary cancer | 189.0, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9 |
| Prostate cancer | 185 |
| Brain cancer | 191.0, 191.1, 191.2, 191.3, 191.4, 191.5, 191.6, 191.7, 191.8, 191.9 |
| Non-Hodgkin lymphoma | 200.20, 200.21, 200.22, 200.23, 200.24, 200.25, 200.26, 200.27, 200.28, 200.30, 200.31, 200.32, 200.33, 200.34, 200.35, 200.36, 200.37, 200.38, 200.40, 200.41, 200.42, 200.43, 200.44, 200.45, 200.46, 200.47, 200.48, 200.60, 200.61, 200.62, 200.63, 200.64, 200.65, 200.66, 200.67, 200.68, 200.70, 200.71, 200.72, 200.73, 200.74, 200.75, 200.76, 200.77, 200.78 |
| Hodgkin's disease | 201.0*, 201.1*, 201.2*, 201.4*, 201.5*, 201.6*, 201.7*, 201.9* |
| Leukemia | 204.*, 205.*, 206.*, 207.* |
| Melanoma | 172.0, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9 |
| Uterine cancer | 179, 182.0, 182.1, 182.8 |
| Ovarian cancer | 183.0, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9 |

**Supplementary Table S3**. Pathogenic germline mutations in high frequency BCC cohort compared to Exome Aggregation Consortium (ExAC)

| Gene | BCC cohort (N=59) | ExAC (N=60,706) | P value of BCC cohort vs ExAC |
|---|---|---|---|
| *APC* | 1 (1.7) | 0.32% | 0.061 |
| *BARD1* | 1 (1.7) | 0.01% | <0.001 |
| *BRCA1* | 1 (1.7) | 0.17% | 0.005 |
| *BRCA1* | 1 (1.7) | 0.18% | 0.006 |
| *CDH1* | 1 (1.7) | 0.46% | 0.160 |
| *CHEK2* | 2 (3.4) | 0.76% | 0.020 |
| *MLH1* | 1 (1.7) | 0.09% | <0.001 |
| *MSH2* | 1 (1.7) | 0.06% | <0.001 |
| *MSH6* | 1 (1.7) | 0.04% | <0.001 |
| *MUTYH* | 1 (1.7) | 0.67% | 0.332 |
| *NBN* | 1 (1.7) | 0.19% | 0.008 |
| *PALB2* | 1 (1.7) | 0.05% | <0.001 |

**Supplementary Table S4**. Demographics for Truven MarketScan dataset

| | BCC = 0 (N=926,265) | BCC=1 (N=111,562) | BCC>=6 (N=13,264) | BCC >= 12 (N=2,920) |
|---|---|---|---|---|
| **Age at first enrollment,** mean (SD) | 49.0 (7.7) | 48.7 (7.8) | 50.1 (6.8) | 50.0 (7.0) |
| **Age groups, N (%)** | | | | |
| <30 | 18,490 (2.0) | 2,475 (2.2) | 141 (1.1) | 39 (1.3) |
| 30-39 | 97,515 (10.5) | 12,630 (11.3) | 930 (7.0) | 209 (7.2) |
| 40-49 | 303,245 (32.7) | 37,250 (33.4) | 4,188 (31.6) | 919 (31.5) |
| 50-59 | 472,535 (51.0) | 55,281 (49.6) | 7,547 (56.9) | 1,653 (56.6) |
| 60-69 | 34,480 (3.8) | 3,926 (3.5) | 458 (3.5) | 100 (3.4) |
| **Gender, N (%)** | | | | |
| Male | 462,165 (49.9) | 53,866 (48.3) | 8,050 (60.7) | 1,903 (65.2) |
| **Region, N (%)** | | | | |
| Northeast | 191,843 (20.7) | 19,958 (17.9) | 2,440 (18.4) | 550 (18.8) |
| North Central | 207,915 (22.4) | 20,822 (18.7) | 2,833 (21.4) | 657 (22.5) |
| South | 361,672 (39.0) | 49,901 (44.7) | 5,292 (39.9) | 1,100 (37.7) |
| West | 162,094 (17.5) | 20,610 (18.5) | 2,668 (20.1) | 609 (20.9) |
| Unknown | 2,741 (0.3) | 271 (0.2) | 31 (0.2) | 4 (0.1) |
| **Years enrolled from 2012-2015, median (min, max)** | 4.0 (3.0, 4.0) | 4.0 (3.0, 4.0) | 4.0 (3.0, 4.0) | 4.0 (3.0, 4.0) |
| **Years enrolled from 2007-2015, median (min, max)** | 6.0 (3.0, 9.0) | 6.0 (3.0, 9.0) | 6.6 (3.0, 9.0) | 6.4 (3.0, 9.0) |

**Supplementary Table S5**. Cancer incidences in Truven MarketScan dataset

| Cancer, N (%) | BCC = 0 (N=926,265) | BCC=1 (N=111,562) | BCC>=6 (N=13,264) | BCC >=12 (N=2,920) |
|---|---|---|---|---|
| Breast | 18,602 (2.0) | 2,851 (2.6) | 325 (2.5) | 84 (2.9) |
| Lung | 3,332 (0.3) | 384 (0.3) | 83 (0.6) | 28 (1.0) |
| Stomach | 807 (<0.1) | 67 (<0.1) | 15 (0.1) | 8 (0.3) |
| Colon | 5,091 (0.5) | 617 (0.6) | 111 (0.8) | 30 (1.0) |
| Pancreatic | 941 (0.1) | 103 (0.1) | 20 (0.2) | 6 (0.2) |
| Liver | 1,205 (0.1) | 139 (0.1) | 30 (0.2) | 6 (0.2) |
| Bladder | 2,803 (0.3) | 361 (0.3) | 54 (0.4) | 9 (0.3) |
| Renal / Urinary | 3,101 (0.3) | 419 (0.4) | 73 (0.6) | 14 (0.5) |
| Prostate | 13,303 (1.4) | 1,661 (1.5) | 324 (2.4) | 83 (2.8) |
| Brain | 1,376 (0.1) | 218 (0.2) | 53 (0.4) | 17 (0.6) |
| Non-Hodgkin lymphoma (minus CNS) | 1,813 (0.2) | 300 (0.3) | 72 (0.5) | 19 (0.7) |
| Hodgkin's disease | 1,043 (0.1) | 285 (0.3) | 133 (1.0) | 50 (1.7) |
| Leukemia | 2,371 (0.3) | 494 (0.4) | 117 (0.9) | 46 (1.6) |
| SCC | 8,210 (0.9) | 9,112 (8.2) | 4,072 (30.7) | 1,119 (38.3) |
| Melanoma | 5,857 (0.6) | 3,696 (3.3) | 1,264 (9.5) | 337 (11.5) |
| Uterine | 2,746 (0.3) | 317 (0.3) | 27 (0.2) | 7 (0.2) |
| Ovarian | 2,301 (0.2) | 278 (0.3) | 31 (0.2) | 10 (0.3) |
| Any Cancer | 59,247 (6.4) | 10,894 (9.8) | 2343 (17.7) | 633 (21.7) |

**Supplementary Table S6**. Age at cancer for BCC and other malignancies in Truven MarketScan dataset

| Cancer age, mean (SD) | BCC = 0 (N=926,265) | BCC=1 (N=111,562) | BCC>=6 (N=13,264) | BCC>=12 (N=2,920) | p-value, BCC 6+ vs 0 | p-value, BCC 12+ vs 0 |
|---|---|---|---|---|---|---|
| BCC | - | 53.2 (7.8) | 53.9 (6.7) | 53.5 (6.9) | - | - |
| NMSC* | 57.0 (5.5) | 53.0 (7.7) | 52.4 (6.8) | 51.9 (7.0) | <0.001 | <0.001 |
| Breast | 53.4 (6.0) | 53.1 (6.1) | 63.1 (6.2) | 52.7 (6.1) | 0.530 | 0.283 |
| Lung | 56.2 (5.7) | 55.8 (6.1) | 56.4 (5.0) | 55.3(5.2) | 0.896 | 0.199 |
| Stomach | 55.6 (6.0) | 56.2 (5.4) | 58.0 (4.9) | 55.8 (4.1) | 0.125 | 0.788 |
| Colon | 54.9 (5.7) | 54.4 (6.4) | 55.2 (5.3) | 54.9 (5.8) | 0.718 | 0.830 |
| Pancreatic* | 56.1 (5.8) | 56.2 (5.7) | 54.0 (6.9) | 49.5 (8.7) | 0.151 | 0.049 |
| Liver | 55.9 (5.9) | 56.2 (5.7) | 57.6 (5.5) | 57.0 (6.1) | 0.101 | 0.665 |
| Bladder | 56.1 (5.3) | 55.7 (5.6) | 57.0 (4.5) | 58.1 (3.9) | 0.287 | 0.162 |
| Renal / Urinary | 55.3 (5.9) | 54.9 (6.0) | 55.3 (6.1) | 54.9 (6.5) | 0.929 | 0.804 |
| Prostate | 56.8 (4.3) | 56.6 (4.4) | 57.0 (4.1) | 57.3 (3.4) | 0.518 | 0.615 |
| Brain* | 53.2 (7.4) | 52.6 (8.3) | 49.4 (10.7) | 43.7 (14.8) | 0.012 | 0.016 |
| Non-Hodgkin lymphoma (minus CNS) | 54.8 (6.3) | 54.4 (6.5) | 54.3 (6.6) | 54.1 (6.8) | 0.504 | 0.585 |
| Hodgkin's disease | 51.4 (7.8) | 50.0 (8.3) | 50.8 (7.3) | 50.6 (6.8) | 0.263 | 0.239 |
| Leukemia | 54.6 (6.4) | 53.6 (7.1) | 53.4 (8.2) | 53.6 (9.2) | 0.400 | 0.938 |
| Melanoma | 54.2 (6.7) | 55.3 (6.0) | 54.0 (6.4) | 54.6 (6.2) | 0.141 | 0.540 |
| SCC* | 57.6 (4.9) | 55.6 (6.2) | 55.8 (5.8) | 55.7 (5.8) | <0.001 | <0.001 |
| Uterine | 54.9 (5.8) | 55.3 (6.0) | 54.8 (5.0) | 52.0 (6.7) | 0.700 | 0.217 |
| Ovarian | 53.2 (6.7) | 52.6 (7.0) | 52.5 (7.3) | 51.7 (8.0) | 0.825 | 0.718 |
| Any Cancer* | 54.6 (6.0) | 53.7 (6.7) | 54.0 (6.4) | 53.9 (6.8) | <0.001 | 0.037 |