

## Supplementary Data

### **Racial/ethnic and sex differences in somatic cancer gene mutations among patients with early-onset colorectal cancer**

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## Supplementary Tables

Table S1. Clinical and demographic characteristics of the colorectal cancer (CRC) patient study population by race/ethnicity and age at sequencing: AACR Project GENIE.

| Characteristic                               | Age at Colorectal Cancer (CRC) Sequencing |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
|--|---|--------|-----------------------------|-------|------|-------|------|-------|------|-------|----------------------------|-------|------|-------|------|-------|------|-------|
|  | Total                                     |        | Early-Onset CRC (<50 years) |       |      |       |      |       |      |       | Late-Onset CRC (50+ years) |       |      |       |      |       |      |       |
|  |   |        | Total                       |       | NHW  |       | NHB  |       | API  |       | Total                      |       | NHW  |       | NHB  |       | API  |       |
| N  | %   | N      | %                           | N     | %    | N     | %    | N     | %    | N     | %                          | N     | %    | N     | %    | N     | %    |       |
| <b>Total</b>                                 | 6903                                      |        | 2016                        | 29.2  | 1666 | 82.6  | 166  | 8.2   | 184  | 9.1   | 4887                       | 70.8  | 4190 | 85.7  | 369  | 7.6   | 328  | 6.7   |
| <b>Age at Sequencing</b>                     |   |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
| <30 Years                                    | 108                                       | 1.6    | 108                         | 5.4   | 88   | 5.3   | 11   | 6.6   | 9    | 4.9   |                            |       |      |       |      |       |      |       |
| 30-39 Years                                  | 550                                       | 8.0    | 550                         | 27.3  | 450  | 27.0  | 46   | 27.7  | 54   | 29.3  |                            |       |      |       |      |       |      |       |
| 40-49 Years                                  | 1358                                      | 19.7   | 1358                        | 67.4  | 1128 | 67.7  | 109  | 65.7  | 121  | 65.8  |                            |       |      |       |      |       |      |       |
| 50-59 Years                                  | 1875                                      | 27.2   |                             |       |      |       |      |       |      |       | 1875                       | 38.4  | 1560 | 37.2  | 173  | 46.9  | 142  | 43.3  |
| 60-69 Years                                  | 1808                                      | 26.2   |                             |       |      |       |      |       |      |       | 1808                       | 37.0  | 1561 | 37.3  | 123  | 33.3  | 124  | 37.8  |
| 70-79 Years                                  | 889                                       | 12.9   |                             |       |      |       |      |       |      |       | 889                        | 18.2  | 780  | 18.6  | 61   | 16.5  | 48   | 14.6  |
| 80+ Years                                    | 315                                       | 4.6    |                             |       |      |       |      |       |      |       | 315                        | 6.4   | 289  | 6.9   | 12   | 3.3   | 14   | 4.3   |
| Mean, Years (std)                            | 57.0                                      | (13.1) | 41.4                        | (6.3) | 41.5 | (6.3) | 40.9 | (6.1) | 41.0 | (6.1) | 63.4                       | (9.2) | 63.6 | (9.3) | 61.9 | (8.6) | 61.9 | (8.9) |
| <b>Sex</b>                                   |   |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
| Female                                       | 3181                                      | 46.1   | 942                         | 46.7  | 756  | 45.4  | 90   | 54.2  | 96   | 52.2  | 2239                       | 45.8  | 1916 | 45.7  | 164  | 44.4  | 159  | 48.5  |
| Male   | 3722                                      | 53.9   | 1074                        | 53.3  | 910  | 54.6  | 76   | 45.8  | 88   | 47.8  | 2648                       | 54.2  | 2274 | 54.3  | 205  | 55.6  | 169  | 51.5  |
| <b>Tumor Mutational Burden (TMB) Status*</b> |   |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
| Non-hypermutated                             | 6250                                      | 90.5   | 1832                        | 90.9  | 1511 | 90.7  | 157  | 94.6  | 164  | 89.1  | 4418                       | 90.4  | 3771 | 90.0  | 342  | 92.7  | 305  | 93.0  |
| Hypermutated                                 | 653                                       | 9.5    | 184                         | 9.1   | 155  | 9.3   | 9    | 5.4   | 20   | 10.9  | 469                        | 9.6   | 419  | 10.0  | 27   | 7.3   | 23   | 7.0   |
| <b>Histological Subtype/Site</b>             |   |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
| Colon Adenocarcinoma                         | 4481                                      | 64.9   | 1220                        | 60.5  | 1003 | 60.2  | 112  | 67.5  | 105  | 57.1  | 3261                       | 66.7  | 2815 | 67.2  | 266  | 72.1  | 180  | 54.9  |
| Rectal Adenocarcinoma                        | 1352                                      | 19.6   | 454                         | 22.5  | 382  | 22.9  | 31   | 18.7  | 41   | 22.3  | 898                        | 18.4  | 751  | 17.9  | 62   | 16.8  | 85   | 25.9  |
| Colorectal Adenocarcinoma                    | 910                                       | 13.2   | 300                         | 14.9  | 249  | 14.9  | 19   | 11.4  | 32   | 17.4  | 610                        | 12.5  | 517  | 12.3  | 35   | 9.5   | 58   | 17.7  |
| Colorectal Mucinous Adenocarcinoma           | 160                                       | 2.3    | 42                          | 2.1   | 32   | 1.9   | 4    | 2.4   | 6    | 3.3   | 118                        | 2.4   | 107  | 2.6   | 6    | 1.6   | 5    | 1.5   |
| <b>Sample Type</b>                           |   |        |                             |       |      |       |      |       |      |       |                            |       |      |       |      |       |      |       |
| Primary Tumor                                | 4664                                      | 67.6   | 1407                        | 69.8  | 1163 | 69.8  | 114  | 68.7  | 130  | 70.7  | 3257                       | 66.6  | 2796 | 66.7  | 228  | 61.8  | 233  | 71.0  |
| Metastasis                                   | 2027                                      | 29.4   | 543                         | 26.9  | 450  | 27.0  | 48   | 28.9  | 45   | 24.5  | 1484                       | 30.4  | 1278 | 30.5  | 126  | 34.1  | 80   | 24.4  |
| Unknown                                      | 212                                       | 3.1    | 66                          | 3.3   | 53   | 3.2   | 4    | 2.4   | 9    | 4.9   | 146                        | 3.0   | 116  | 2.8   | 15   | 4.1   | 15   | 4.6   |

\*Predicted by tumor mutational burden (TMB) at a cutoff of  $10^{1.25}$ .

Abbreviations: NHW, non-Hispanic white; NHB, non-Hispanic black; API, Asian or Pacific Islander; N, number; std, standard deviation.

Table S2. Baseline mutation probability, comparison and heterogeneity of non-silent somatic gene mutations among patients with early-onset and late-onset non-hypermutated colorectal cancer. Genes ranked by false discovery rate (FDR).

| Gene Symbol   | Baseline mutation probability | Baseline mutation probability by age at cancer sequencing |                | OR*  | 95% CI*     | P        | FDR    |
|---------------|-------------------------------|---|----------------|------|-------------|----------|--------|
|               |                               | Early-Onset CRC   | Late-Onset CRC |      |             |          |        |
| <i>TP53</i>   | 0.76                          | 0.80  | 0.74           | 1.39 | 1.22 - 1.60 | 1.39E-06 | 0.0001 |
| <i>LRP1B</i>  | 0.08                          | 0.15  | 0.06           | 2.96 | 1.53 - 5.73 | 0.001    | 0.049  |
| <i>TCF7L2</i> | 0.08                          | 0.10  | 0.08           | 1.38 | 1.12 - 1.69 | 0.002    | 0.049  |
| <i>KDR</i>    | 0.02                          | 0.02  | 0.03           | 0.56 | 0.37 - 0.85 | 0.006    | 0.12   |
| <i>FBXW7</i>  | 0.11                          | 0.12  | 0.11           | 1.27 | 1.06 - 1.52 | 0.009    | 0.13   |
| <i>FLT4</i>   | 0.02                          | 0.02  | 0.03           | 0.64 | 0.42 - 0.98 | 0.04     | 0.49   |
| <i>AMER1</i>  | 0.05                          | 0.03  | 0.05           | 0.69 | 0.48 - 1.00 | 0.048    | 0.52   |
| <i>WRN</i>    | 0.02                          | 0.01  | 0.03           | 0.51 | 0.26 - 1.03 | 0.06     | 0.52   |
| <i>SMAD3</i>  | 0.03                          | 0.04  | 0.03           | 1.43 | 0.98 - 2.10 | 0.07     | 0.52   |
| <i>DOCK8</i>  | 0.04                          | 0.06  | 0.04           | 1.64 | 0.96 - 2.79 | 0.07     | 0.52   |
| <i>BRAF</i>   | 0.08                          | 0.07  | 0.09           | 0.84 | 0.68 - 1.04 | 0.11     | 0.66   |
| <i>PIK3CG</i> | 0.02                          | 0.01  | 0.02           | 0.63 | 0.35 - 1.11 | 0.11     | 0.66   |
| <i>PTEN</i>   | 0.03                          | 0.04  | 0.03           | 1.27 | 0.94 - 1.72 | 0.12     | 0.66   |
| <i>RNF43</i>  | 0.04                          | 0.03  | 0.04           | 0.77 | 0.55 - 1.08 | 0.13     | 0.66   |
| <i>AXIN2</i>  | 0.03                          | 0.02  | 0.03           | 0.72 | 0.47 - 1.11 | 0.14     | 0.66   |
| <i>CTNNB1</i> | 0.04                          | 0.03  | 0.04           | 0.80 | 0.59 - 1.08 | 0.14     | 0.66   |
| <i>MGA</i>    | 0.03                          | 0.02  | 0.03           | 0.72 | 0.46 - 1.13 | 0.15     | 0.69   |
| <i>SMAD4</i>  | 0.15                          | 0.15  | 0.15           | 1.11 | 0.95 - 1.30 | 0.18     | 0.74   |
| <i>ROS1</i>   | 0.03                          | 0.03  | 0.03           | 1.26 | 0.89 - 1.78 | 0.18     | 0.74   |
| <i>PTPRT</i>  | 0.05                          | 0.04  | 0.05           | 0.80 | 0.56 - 1.14 | 0.21     | 0.77   |
| <i>ERBB3</i>  | 0.03                          | 0.03  | 0.03           | 0.81 | 0.58 - 1.14 | 0.22     | 0.77   |
| <i>ATM</i>    | 0.06                          | 0.05  | 0.06           | 0.86 | 0.67 - 1.10 | 0.22     | 0.77   |
| <i>KAT6A</i>  | 0.03                          | 0.04  | 0.03           | 1.38 | 0.81 - 2.36 | 0.24     | 0.77   |
| <i>SMAD2</i>  | 0.03                          | 0.03  | 0.03           | 1.20 | 0.88 - 1.64 | 0.25     | 0.77   |
| <i>MED12</i>  | 0.03                          | 0.02  | 0.03           | 0.79 | 0.53 - 1.19 | 0.26     | 0.77   |
| <i>AR</i>     | 0.02                          | 0.02  | 0.02           | 0.79 | 0.52 - 1.20 | 0.26     | 0.77   |
| <i>RIF1</i>   | 0.04                          | 0.03  | 0.05           | 0.71 | 0.38 - 1.35 | 0.30     | 0.84   |
| <i>MTOR</i>   | 0.03                          | 0.02  | 0.03           | 0.83 | 0.59 - 1.19 | 0.32     | 0.85   |
| <i>IKZF1</i>  | 0.02                          | 0.02  | 0.02           | 0.81 | 0.53 - 1.23 | 0.33     | 0.85   |
| <i>PREX2</i>  | 0.03                          | 0.03  | 0.04           | 0.80 | 0.50 - 1.27 | 0.34     | 0.85   |
| <i>GLI2</i>   | 0.05                          | 0.05  | 0.05           | 1.21 | 0.79 - 1.85 | 0.37     | 0.85   |
| <i>CARD11</i> | 0.03                          | 0.03  | 0.03           | 0.86 | 0.61 - 1.20 | 0.37     | 0.85   |

|                |      |      |      |      |      |   |      |      |      |
|----------------|------|------|------|------|------|---|------|------|------|
| <i>BRCA2</i>   | 0.04 | 0.03 | 0.04 | 0.87 | 0.64 | - | 1.18 | 0.38 | 0.85 |
| <i>APC</i>     | 0.74 | 0.74 | 0.74 | 1.06 | 0.93 | - | 1.21 | 0.39 | 0.85 |
| <i>FANCM</i>   | 0.03 | 0.03 | 0.03 | 0.76 | 0.41 | - | 1.42 | 0.39 | 0.85 |
| <i>KRAS</i>    | 0.45 | 0.43 | 0.46 | 0.95 | 0.85 | - | 1.07 | 0.41 | 0.86 |
| <i>ASXL1</i>   | 0.02 | 0.02 | 0.03 | 0.86 | 0.59 | - | 1.25 | 0.43 | 0.86 |
| <i>ARID1B</i>  | 0.04 | 0.04 | 0.04 | 1.13 | 0.84 | - | 1.52 | 0.43 | 0.86 |
| <i>PTPRS</i>   | 0.04 | 0.04 | 0.04 | 1.15 | 0.80 | - | 1.66 | 0.45 | 0.87 |
| <i>SMARCA4</i> | 0.02 | 0.02 | 0.03 | 0.87 | 0.59 | - | 1.28 | 0.48 | 0.89 |
| <i>FAT1</i>    | 0.04 | 0.04 | 0.04 | 1.11 | 0.81 | - | 1.52 | 0.50 | 0.89 |
| <i>NOTCH1</i>  | 0.03 | 0.02 | 0.03 | 0.88 | 0.62 | - | 1.27 | 0.50 | 0.89 |
| <i>PIK3C2B</i> | 0.03 | 0.03 | 0.02 | 1.20 | 0.71 | - | 2.03 | 0.50 | 0.89 |
| <i>EPHA3</i>   | 0.03 | 0.02 | 0.03 | 0.89 | 0.60 | - | 1.31 | 0.55 | 0.90 |
| <i>EPHA5</i>   | 0.03 | 0.03 | 0.03 | 0.89 | 0.60 | - | 1.31 | 0.55 | 0.90 |
| <i>PRKDC</i>   | 0.05 | 0.05 | 0.05 | 1.12 | 0.76 | - | 1.65 | 0.56 | 0.90 |
| <i>SETD2</i>   | 0.02 | 0.02 | 0.02 | 0.89 | 0.60 | - | 1.32 | 0.56 | 0.90 |
| <i>KMT2A</i>   | 0.02 | 0.03 | 0.02 | 1.11 | 0.78 | - | 1.58 | 0.58 | 0.91 |
| <i>PIK3CA</i>  | 0.17 | 0.16 | 0.18 | 0.96 | 0.82 | - | 1.12 | 0.59 | 0.91 |
| <i>GRIN2A</i>  | 0.03 | 0.03 | 0.03 | 1.12 | 0.73 | - | 1.72 | 0.60 | 0.91 |
| <i>NOTCH3</i>  | 0.03 | 0.03 | 0.03 | 0.92 | 0.64 | - | 1.30 | 0.63 | 0.94 |
| <i>NRAS</i>    | 0.05 | 0.04 | 0.05 | 0.94 | 0.72 | - | 1.23 | 0.66 | 0.96 |
| <i>TSC2</i>    | 0.02 | 0.02 | 0.02 | 0.92 | 0.62 | - | 1.38 | 0.70 | 0.96 |
| <i>KMT2C</i>   | 0.03 | 0.03 | 0.03 | 0.92 | 0.60 | - | 1.42 | 0.71 | 0.96 |
| <i>BCOR</i>    | 0.02 | 0.02 | 0.02 | 0.93 | 0.64 | - | 1.36 | 0.72 | 0.96 |
| <i>POLE</i>    | 0.02 | 0.02 | 0.02 | 1.07 | 0.72 | - | 1.59 | 0.74 | 0.96 |
| <i>BCORL1</i>  | 0.02 | 0.02 | 0.02 | 1.09 | 0.62 | - | 1.90 | 0.76 | 0.96 |
| <i>EP300</i>   | 0.03 | 0.02 | 0.03 | 0.95 | 0.66 | - | 1.36 | 0.77 | 0.96 |
| <i>COL7A1</i>  | 0.09 | 0.09 | 0.09 | 1.06 | 0.70 | - | 1.60 | 0.79 | 0.96 |
| <i>NF1</i>     | 0.02 | 0.02 | 0.03 | 0.95 | 0.66 | - | 1.37 | 0.79 | 0.96 |
| <i>ATR</i>     | 0.02 | 0.02 | 0.02 | 1.05 | 0.71 | - | 1.56 | 0.80 | 0.96 |
| <i>SETBP1</i>  | 0.02 | 0.02 | 0.02 | 0.92 | 0.50 | - | 1.70 | 0.80 | 0.96 |
| <i>ERBB4</i>   | 0.04 | 0.03 | 0.04 | 0.96 | 0.71 | - | 1.32 | 0.82 | 0.96 |
| <i>KMT2B</i>   | 0.02 | 0.02 | 0.03 | 0.94 | 0.53 | - | 1.66 | 0.83 | 0.96 |
| <i>EPHB1</i>   | 0.03 | 0.03 | 0.03 | 1.05 | 0.68 | - | 1.61 | 0.84 | 0.96 |
| <i>PIK3R1</i>  | 0.03 | 0.03 | 0.03 | 0.97 | 0.69 | - | 1.36 | 0.84 | 0.96 |
| <i>ERBB2</i>   | 0.03 | 0.03 | 0.03 | 1.03 | 0.74 | - | 1.45 | 0.85 | 0.96 |
| <i>ATRX</i>    | 0.03 | 0.03 | 0.03 | 0.98 | 0.70 | - | 1.36 | 0.88 | 0.98 |
| <i>SOX9</i>    | 0.10 | 0.10 | 0.10 | 1.01 | 0.84 | - | 1.23 | 0.90 | 0.98 |
| <i>KMT2D</i>   | 0.06 | 0.05 | 0.06 | 0.98 | 0.77 | - | 1.26 | 0.90 | 0.98 |
| <i>CIITA</i>   | 0.02 | 0.02 | 0.02 | 0.97 | 0.53 | - | 1.78 | 0.92 | 0.98 |
| <i>ARID1A</i>  | 0.06 | 0.05 | 0.06 | 1.01 | 0.79 | - | 1.29 | 0.93 | 0.98 |
| <i>ARID2</i>   | 0.02 | 0.02 | 0.02 | 1.01 | 0.69 | - | 1.48 | 0.95 | 0.99 |
| <i>CREBBP</i>  | 0.03 | 0.03 | 0.03 | 1.01 | 0.72 | - | 1.42 | 0.96 | 0.99 |

|             |      |      |      |      |      |   |      |      |      |
|-------------|------|------|------|------|------|---|------|------|------|
| <i>ALK</i>  | 0.03 | 0.03 | 0.03 | 0.99 | 0.71 | - | 1.39 | 0.97 | 0.99 |
| <i>POLQ</i> | 0.05 | 0.05 | 0.05 | 1.00 | 0.60 | - | 1.67 | 1.00 | 1.00 |

Abbreviations: CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; FDR, false discovery rate.  
 \*ORs, 95% CIs, P and FDR values were calculated for genes from models adjusted for patient race/ethnicity, sex, histology and site, sequencing assay, sample type and tumor mutational burden.



|                |      |      |      |      |      |        |      |      |      |      |      |      |      |        |      |       |      |      |      |      |      |         |      |      |
|----------------|------|------|------|------|------|--------|------|------|------|------|------|------|------|--------|------|-------|------|------|------|------|------|---------|------|------|
| <i>PTPRS</i>   | 0.04 | 0.05 | 0.04 | 1.27 | 0.85 | - 1.90 | 0.24 | 0.73 | 0.04 | 0.04 | 0.04 | 0.78 | 0.19 | - 3.15 | 0.72 | 0.999 | 0.05 | 0.04 | 0.06 | 0.59 | 0.17 | - 2.02  | 0.40 | 0.93 |
| <i>KRAS</i>    | 0.44 | 0.42 | 0.45 | 0.94 | 0.83 | - 1.07 | 0.37 | 0.76 | 0.57 | 0.57 | 0.57 | 1.08 | 0.70 | - 1.66 | 0.72 | 0.999 | 0.41 | 0.40 | 0.42 | 0.93 | 0.61 | - 1.43  | 0.75 | 0.99 |
| <i>FANCM</i>   | 0.03 | 0.02 | 0.03 | 0.67 | 0.33 | - 1.36 | 0.27 | 0.76 | 0.04 | 0.04 | 0.04 | 0.74 | 0.12 | - 4.64 | 0.75 | 0.999 | 0.02 | 0.06 | 0.00 | -    | -    | -       | -    | -    |
| <i>EPHB1</i>   | 0.03 | 0.03 | 0.03 | 1.18 | 0.73 | - 1.90 | 0.49 | 0.87 | 0.04 | 0.03 | 0.04 | 0.82 | 0.22 | - 3.04 | 0.77 | 0.999 | 0.02 | 0.01 | 0.03 | 0.23 | 0.03 | - 2.10  | 0.20 | 0.79 |
| <i>CARD11</i>  | 0.03 | 0.03 | 0.03 | 0.91 | 0.63 | - 1.30 | 0.61 | 0.89 | 0.02 | 0.03 | 0.02 | 1.22 | 0.30 | - 4.95 | 0.78 | 0.999 | 0.03 | 0.01 | 0.05 | 0.27 | 0.06 | - 1.30  | 0.10 | 0.72 |
| <i>IKZF1</i>   | 0.02 | 0.02 | 0.02 | 0.79 | 0.49 | - 1.25 | 0.31 | 0.76 | 0.02 | 0.02 | 0.02 | 0.83 | 0.21 | - 3.32 | 0.79 | 0.999 | 0.02 | 0.02 | 0.02 | 1.02 | 0.19 | - 5.38  | 0.98 | 1.00 |
| <i>ATR</i>     | 0.02 | 0.02 | 0.02 | 1.05 | 0.68 | - 1.62 | 0.84 | 0.92 | 0.02 | 0.02 | 0.02 | 0.85 | 0.19 | - 3.77 | 0.83 | 0.999 | 0.02 | 0.03 | 0.02 | 1.43 | 0.34 | - 6.01  | 0.63 | 0.99 |
| <i>POLE</i>    | 0.02 | 0.02 | 0.02 | 0.98 | 0.62 | - 1.54 | 0.94 | 0.95 | 0.03 | 0.03 | 0.03 | 0.87 | 0.21 | - 3.54 | 0.85 | 0.999 | 0.03 | 0.04 | 0.02 | 1.87 | 0.47 | - 7.41  | 0.37 | 0.93 |
| <i>PTPRT</i>   | 0.05 | 0.04 | 0.05 | 0.83 | 0.55 | - 1.24 | 0.36 | 0.76 | 0.04 | 0.04 | 0.04 | 1.11 | 0.32 | - 3.88 | 0.87 | 0.999 | 0.06 | 0.03 | 0.07 | 0.50 | 0.16 | - 1.61  | 0.25 | 0.79 |
| <i>GRIN2A</i>  | 0.03 | 0.03 | 0.03 | 1.16 | 0.72 | - 1.85 | 0.54 | 0.89 | 0.02 | 0.02 | 0.02 | 0.87 | 0.16 | - 4.73 | 0.87 | 0.999 | 0.02 | 0.02 | 0.03 | 1.20 | 0.27 | - 5.32  | 0.81 | 0.99 |
| <i>SMAD4</i>   | 0.15 | 0.15 | 0.15 | 1.13 | 0.95 | - 1.34 | 0.16 | 0.59 | 0.15 | 0.15 | 0.14 | 1.04 | 0.59 | - 1.85 | 0.89 | 0.999 | 0.13 | 0.14 | 0.13 | 0.95 | 0.52 | - 1.75  | 0.88 | 1.00 |
| <i>KMT2D</i>   | 0.06 | 0.05 | 0.06 | 1.03 | 0.78 | - 1.34 | 0.85 | 0.92 | 0.05 | 0.05 | 0.05 | 0.94 | 0.37 | - 2.41 | 0.90 | 0.999 | 0.04 | 0.03 | 0.05 | 0.67 | 0.22 | - 2.11  | 0.50 | 0.99 |
| <i>SOX9</i>    | 0.10 | 0.09 | 0.10 | 1.03 | 0.83 | - 1.27 | 0.81 | 0.92 | 0.08 | 0.08 | 0.08 | 0.96 | 0.45 | - 2.04 | 0.91 | 0.999 | 0.11 | 0.11 | 0.11 | 1.22 | 0.62 | - 2.41  | 0.56 | 0.99 |
| <i>DOCK8</i>   | 0.04 | 0.06 | 0.04 | 1.68 | 0.95 | - 2.97 | 0.08 | 0.49 | 0.06 | 0.07 | 0.06 | 1.10 | 0.16 | - 7.69 | 0.93 | 0.999 | 0.04 | 0.08 | 0.02 | -    | -    | -       | -    | -    |
| <i>MGA</i>     | 0.03 | 0.02 | 0.03 | 0.81 | 0.51 | - 1.29 | 0.38 | 0.76 | 0.01 | 0.00 | 0.02 | -    | -    | -      | -    | -     | 0.02 | 0.01 | 0.03 | 0.27 | 0.03 | - 2.45  | 0.25 | 0.79 |
| <i>ARID2</i>   | 0.03 | 0.02 | 0.03 | 1.08 | 0.73 | - 1.59 | 0.72 | 0.92 | 0.01 | 0.01 | 0.01 | -    | -    | -      | -    | -     | 0.02 | 0.01 | 0.02 | 0.23 | 0.02 | - 2.13  | 0.19 | 0.79 |
| <i>PIK3C2B</i> | 0.03 | 0.02 | 0.03 | 0.96 | 0.54 | - 1.73 | 0.90 | 0.93 | 0.01 | 0.04 | 0.00 | -    | -    | -      | -    | -     | 0.03 | 0.04 | 0.03 | -    | -    | -       | -    | -    |
| <i>WRN</i>     | 0.02 | 0.01 | 0.03 | 0.53 | 0.26 | - 1.11 | 0.09 | 0.54 | 0.02 | 0.00 | 0.03 | -    | -    | -      | -    | -     | 0.02 | 0.02 | 0.01 | 1.70 | 0.09 | - 33.63 | 0.73 | 0.99 |
| <i>PIK3CG</i>  | 0.02 | 0.02 | 0.03 | 0.72 | 0.40 | - 1.30 | 0.28 | 0.76 | 0.01 | 0.00 | 0.02 | -    | -    | -      | -    | -     | 0.01 | 0.00 | 0.02 | -    | -    | -       | -    | -    |
| <i>BCORL1</i>  | 0.02 | 0.03 | 0.02 | 1.35 | 0.75 | - 2.43 | 0.31 | 0.76 | 0.01 | 0.00 | 0.01 | -    | -    | -      | -    | -     | 0.05 | 0.02 | 0.06 | 0.69 | 0.05 | - 9.27  | 0.78 | 0.99 |

Abbreviations: CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; FDR, false discovery rate.

\*ORs, 95% CIs, P and FDR values were calculated for genes from models adjusted for patient sex, histology and site, sequencing assay, sample type and tumor mutational burden.

†P-values were derived from Cochran's Q test for heterogeneity across the racial/ethnic groups. Only genes with significant associations for non-silent somatic mutations between early-onset and late-onset non-hypermutated CRC cases in at least one racial/ethnic group were tested.

Table S4. Baseline mutation probability, comparison and heterogeneity of non-silent somatic gene mutations among patients with early-onset and late-onset non-hypermuted colorectal cancer by sex.

| Gene Symbol | Female                        |   |                |      |             |          |       |                               | Male  |                |      |             |       |      |          |                  | Mutation frequency |  | Heterogeneity |  |
|-------------|-------------------------------|---|----------------|------|-------------|----------|-------|-------------------------------|---|----------------|------|-------------|-------|------|----------|------------------|--------------------|--|---------------|--|
|             | Baseline mutation probability | Baseline mutation probability by age at cancer sequencing |                | OR*  | 95% CI*     | P        | FDR   | Baseline mutation probability | Baseline mutation probability by age at cancer sequencing |                | OR*  | 95% CI*     | P     | FDR  | P        | Cochran's Q test | P-Hett†            |  |               |  |
|             |                               | Early-Onset CRC   | Late-Onset CRC |      |             |          |       |                               | Early-Onset CRC   | Late-Onset CRC |      |             |       |      |          |                  |                    |  |               |  |
| TP53        | 0.75                          | 0.80  | 0.73           | 1.54 | 1.26 - 1.88 | 2.73E-05 | 0.002 | 0.76                          | 0.79  | 0.75           | 1.29 | 1.07 - 1.55 | 0.007 | 0.51 | 0.45     | 1.57             | 0.21               |  |               |  |
| BRAF        | 0.09                          | 0.06  | 0.10           | 0.58 | 0.42 - 0.81 | 0.002    | 0.057 | 0.08                          | 0.08  | 0.07           | 1.16 | 0.87 - 1.54 | 0.32  | 0.81 | 0.03     | 9.35             | 0.002              |  |               |  |
| EP300       | 0.02                          | 0.01  | 0.03           | 0.30 | 0.13 - 0.67 | 0.004    | 0.09  | 0.03                          | 0.04  | 0.03           | 1.59 | 1.04 - 2.43 | 0.03  | 0.64 | 0.00003  | 12.71            | 0.0004             |  |               |  |
| KDR         | 0.03                          | 0.01  | 0.03           | 0.43 | 0.23 - 0.82 | 0.01     | 0.16  | 0.02                          | 0.02  | 0.03           | 0.67 | 0.38 - 1.18 | 0.17  | 0.75 | 0.74     | 1.04             | 0.31               |  |               |  |
| LRP1B       | 0.09                          | 0.17  | 0.06           | 3.55 | 1.34 - 9.38 | 0.01     | 0.16  | 0.07                          | 0.13  | 0.05           | 2.21 | 0.80 - 6.09 | 0.12  | 0.75 | 0.026    | 0.43             | 0.51               |  |               |  |
| WRN         | 0.03                          | 0.01  | 0.03           | 0.17 | 0.04 - 0.72 | 0.02     | 0.17  | 0.02                          | 0.02  | 0.02           | 1.06 | 0.46 - 2.46 | 0.89  | 0.95 | 0.006    | 4.63             | 0.03               |  |               |  |
| SMAD2       | 0.03                          | 0.04  | 0.03           | 1.71 | 1.09 - 2.68 | 0.02     | 0.17  | 0.03                          | 0.03  | 0.04           | 0.89 | 0.57 - 1.39 | 0.61  | 0.95 | 0.21     | 4.11             | 0.04               |  |               |  |
| TCF7L2      | 0.09                          | 0.11  | 0.09           | 1.41 | 1.06 - 1.88 | 0.02     | 0.17  | 0.08                          | 0.09  | 0.07           | 1.40 | 1.04 - 1.87 | 0.025 | 0.63 | 0.16     | 0.00             | 0.97               |  |               |  |
| AXIN2       | 0.02                          | 0.01  | 0.03           | 0.36 | 0.15 - 0.85 | 0.02     | 0.17  | 0.03                          | 0.03  | 0.03           | 1.00 | 0.60 - 1.66 | 0.99  | 0.99 | 0.003    | 4.02             | 0.04               |  |               |  |
| APC         | 0.73                          | 0.74  | 0.72           | 1.21 | 1.00 - 1.47 | 0.049    | 0.35  | 0.75                          | 0.73  | 0.76           | 0.93 | 0.78 - 1.12 | 0.45  | 0.81 | 0.61     | 3.79             | 0.05               |  |               |  |
| KRAS        | 0.49                          | 0.50  | 0.49           | 1.08 | 0.91 - 1.27 | 0.40     | 0.73  | 0.41                          | 0.36  | 0.43           | 0.83 | 0.71 - 0.98 | 0.02  | 0.63 | 1.72E-09 | 4.73             | 0.03               |  |               |  |
| FBXW7       | 0.12                          | 0.12  | 0.11           | 1.26 | 0.98 - 1.63 | 0.08     | 0.41  | 0.10                          | 0.11  | 0.10           | 1.27 | 0.99 - 1.63 | 0.06  | 0.68 |          |                  |                    |  |               |  |
| FLT4        | 0.02                          | 0.02  | 0.02           | 0.75 | 0.41 - 1.40 | 0.37     | 0.73  | 0.02                          | 0.02  | 0.03           | 0.58 | 0.33 - 1.04 | 0.07  | 0.68 |          |                  |                    |  |               |  |
| TSC2        | 0.02                          | 0.02  | 0.02           | 1.54 | 0.88 - 2.71 | 0.13     | 0.47  | 0.02                          | 0.01  | 0.02           | 0.57 | 0.31 - 1.06 | 0.08  | 0.68 |          |                  |                    |  |               |  |
| POLQ        | 0.05                          | 0.02  | 0.06           | 0.36 | 0.12 - 1.04 | 0.06     | 0.37  | 0.05                          | 0.07  | 0.04           | 1.77 | 0.94 - 3.35 | 0.08  | 0.68 |          |                  |                    |  |               |  |
| ERBB2       | 0.03                          | 0.02  | 0.03           | 0.59 | 0.32 - 1.08 | 0.09     | 0.42  | 0.03                          | 0.04  | 0.03           | 1.45 | 0.95 - 2.21 | 0.09  | 0.68 |          |                  |                    |  |               |  |
| SMAD3       | 0.03                          | 0.03  | 0.03           | 1.32 | 0.73 - 2.37 | 0.36     | 0.73  | 0.03                          | 0.04  | 0.03           | 1.56 | 0.93 - 2.60 | 0.09  | 0.68 |          |                  |                    |  |               |  |
| MGA         | 0.02                          | 0.02  | 0.03           | 0.87 | 0.46 - 1.66 | 0.68     | 0.91  | 0.03                          | 0.02  | 0.03           | 0.61 | 0.33 - 1.13 | 0.11  | 0.75 |          |                  |                    |  |               |  |
| SETD2       | 0.02                          | 0.02  | 0.02           | 1.29 | 0.71 - 2.32 | 0.40     | 0.73  | 0.03                          | 0.02  | 0.03           | 0.65 | 0.37 - 1.15 | 0.14  | 0.75 |          |                  |                    |  |               |  |
| PIK3CG      | 0.02                          | 0.01  | 0.02           | 0.73 | 0.31 - 1.71 | 0.47     | 0.77  | 0.02                          | 0.01  | 0.03           | 0.56 | 0.25 - 1.22 | 0.14  | 0.75 |          |                  |                    |  |               |  |
| PRKDC       | 0.05                          | 0.05  | 0.05           | 0.93 | 0.53 - 1.63 | 0.79     | 0.91  | 0.04                          | 0.05  | 0.04           | 1.47 | 0.85 - 2.52 | 0.17  | 0.75 |          |                  |                    |  |               |  |
| KMT2B       | 0.03                          | 0.03  | 0.02           | 1.75 | 0.79 - 3.89 | 0.17     | 0.55  | 0.02                          | 0.01  | 0.03           | 0.53 | 0.22 - 1.30 | 0.17  | 0.75 |          |                  |                    |  |               |  |
| ARID1A      | 0.06                          | 0.07  | 0.06           | 1.26 | 0.89 - 1.76 | 0.19     | 0.58  | 0.05                          | 0.04  | 0.06           | 0.78 | 0.54 - 1.12 | 0.18  | 0.75 |          |                  |                    |  |               |  |
| SMAD4       | 0.16                          | 0.16  | 0.16           | 1.05 | 0.84 - 1.32 | 0.66     | 0.91  | 0.14                          | 0.15  | 0.14           | 1.15 | 0.93 - 1.44 | 0.20  | 0.81 |          |                  |                    |  |               |  |
| PREX2       | 0.04                          | 0.03  | 0.04           | 0.97 | 0.51 - 1.83 | 0.93     | 0.95  | 0.03                          | 0.02  | 0.04           | 0.63 | 0.31 - 1.30 | 0.21  | 0.81 |          |                  |                    |  |               |  |
| ATM         | 0.06                          | 0.06  | 0.07           | 0.92 | 0.65 - 1.31 | 0.65     | 0.91  | 0.06                          | 0.05  | 0.06           | 0.81 | 0.57 - 1.15 | 0.23  | 0.81 |          |                  |                    |  |               |  |
| SMARCA4     | 0.02                          | 0.02  | 0.02           | 1.13 | 0.64 - 1.99 | 0.67     | 0.91  | 0.03                          | 0.02  | 0.03           | 0.72 | 0.42 - 1.24 | 0.24  | 0.81 |          |                  |                    |  |               |  |
| MTOR        | 0.03                          | 0.02  | 0.03           | 0.86 | 0.51 - 1.46 | 0.58     | 0.88  | 0.03                          | 0.02  | 0.03           | 0.76 | 0.47 - 1.24 | 0.27  | 0.81 |          |                  |                    |  |               |  |
| CTNNB1      | 0.04                          | 0.03  | 0.04           | 0.82 | 0.53 - 1.27 | 0.38     | 0.73  | 0.04                          | 0.03  | 0.04           | 0.79 | 0.52 - 1.21 | 0.28  | 0.81 |          |                  |                    |  |               |  |
| KMT2D       | 0.06                          | 0.05  | 0.06           | 0.80 | 0.55 - 1.17 | 0.25     | 0.67  | 0.05                          | 0.06  | 0.05           | 1.19 | 0.85 - 1.67 | 0.32  | 0.81 |          |                  |                    |  |               |  |
| AMER1       | 0.05                          | 0.04  | 0.06           | 0.67 | 0.40 - 1.11 | 0.12     | 0.47  | 0.04                          | 0.03  | 0.04           | 0.77 | 0.45 - 1.31 | 0.33  | 0.81 |          |                  |                    |  |               |  |
| ROS1        | 0.03                          | 0.03  | 0.02           | 1.31 | 0.78 - 2.21 | 0.31     | 0.73  | 0.03                          | 0.03  | 0.03           | 1.26 | 0.79 - 2.00 | 0.34  | 0.81 |          |                  |                    |  |               |  |
| FANCM       | 0.04                          | 0.04  | 0.04           | 0.85 | 0.38 - 1.90 | 0.69     | 0.91  | 0.02                          | 0.02  | 0.03           | 0.61 | 0.22 - 1.68 | 0.34  | 0.81 |          |                  |                    |  |               |  |



|         |      |      |      |      |      |        |      |      |      |      |      |      |      |        |      |      |
|---------|------|------|------|------|------|--------|------|------|------|------|------|------|------|--------|------|------|
| ATR     | 0.02 | 0.03 | 0.02 | 1.53 | 0.88 | - 2.67 | 0.13 | 0.47 | 0.02 | 0.02 | 0.02 | 0.76 | 0.43 | - 1.35 | 0.35 | 0.81 |
| PTEN    | 0.04 | 0.04 | 0.04 | 1.35 | 0.89 | - 2.05 | 0.16 | 0.54 | 0.03 | 0.03 | 0.03 | 1.24 | 0.79 | - 1.96 | 0.35 | 0.81 |
| NRAS    | 0.05 | 0.05 | 0.05 | 1.07 | 0.73 | - 1.58 | 0.73 | 0.91 | 0.04 | 0.04 | 0.05 | 0.84 | 0.57 | - 1.23 | 0.37 | 0.81 |
| FAT1    | 0.04 | 0.04 | 0.04 | 1.07 | 0.67 | - 1.70 | 0.78 | 0.91 | 0.04 | 0.04 | 0.04 | 1.21 | 0.79 | - 1.86 | 0.38 | 0.81 |
| ALK     | 0.03 | 0.03 | 0.03 | 1.19 | 0.75 | - 1.88 | 0.45 | 0.77 | 0.03 | 0.02 | 0.03 | 0.80 | 0.48 | - 1.34 | 0.39 | 0.81 |
| ASXL1   | 0.02 | 0.02 | 0.02 | 0.98 | 0.56 | - 1.72 | 0.95 | 0.96 | 0.03 | 0.02 | 0.03 | 0.80 | 0.48 | - 1.33 | 0.39 | 0.81 |
| DOCK8   | 0.05 | 0.08 | 0.04 | 1.87 | 0.91 | - 3.83 | 0.09 | 0.42 | 0.04 | 0.04 | 0.03 | 1.41 | 0.64 | - 3.15 | 0.40 | 0.81 |
| ARID2   | 0.02 | 0.02 | 0.02 | 1.32 | 0.76 | - 2.29 | 0.32 | 0.73 | 0.02 | 0.02 | 0.03 | 0.79 | 0.46 | - 1.37 | 0.40 | 0.81 |
| CIITA   | 0.02 | 0.02 | 0.01 | 1.91 | 0.69 | - 5.30 | 0.21 | 0.60 | 0.03 | 0.02 | 0.03 | 0.71 | 0.32 | - 1.59 | 0.41 | 0.81 |
| BCOR    | 0.03 | 0.02 | 0.03 | 0.69 | 0.39 | - 1.21 | 0.19 | 0.58 | 0.02 | 0.02 | 0.02 | 1.24 | 0.73 | - 2.10 | 0.42 | 0.81 |
| PTPRS   | 0.05 | 0.04 | 0.05 | 1.13 | 0.65 | - 1.97 | 0.65 | 0.91 | 0.04 | 0.05 | 0.04 | 1.22 | 0.75 | - 2.00 | 0.43 | 0.81 |
| BRCA2   | 0.04 | 0.03 | 0.04 | 0.84 | 0.54 | - 1.33 | 0.46 | 0.77 | 0.04 | 0.03 | 0.04 | 0.85 | 0.55 | - 1.29 | 0.44 | 0.81 |
| RIF1    | 0.04 | 0.03 | 0.04 | 0.67 | 0.24 | - 1.84 | 0.44 | 0.77 | 0.04 | 0.03 | 0.05 | 0.73 | 0.31 | - 1.68 | 0.46 | 0.81 |
| MED12   | 0.03 | 0.03 | 0.04 | 0.80 | 0.47 | - 1.36 | 0.40 | 0.73 | 0.02 | 0.02 | 0.02 | 0.79 | 0.42 | - 1.50 | 0.47 | 0.82 |
| NOTCH1  | 0.03 | 0.02 | 0.03 | 0.93 | 0.55 | - 1.60 | 0.80 | 0.91 | 0.03 | 0.02 | 0.03 | 0.84 | 0.51 | - 1.38 | 0.49 | 0.83 |
| EPHA3   | 0.03 | 0.03 | 0.03 | 0.93 | 0.53 | - 1.64 | 0.80 | 0.91 | 0.03 | 0.02 | 0.03 | 0.86 | 0.49 | - 1.51 | 0.60 | 0.95 |
| CARD11  | 0.03 | 0.02 | 0.03 | 0.80 | 0.47 | - 1.34 | 0.39 | 0.73 | 0.03 | 0.03 | 0.03 | 0.90 | 0.58 | - 1.41 | 0.65 | 0.95 |
| IKZF1   | 0.02 | 0.02 | 0.02 | 0.77 | 0.43 | - 1.40 | 0.39 | 0.73 | 0.02 | 0.02 | 0.02 | 0.87 | 0.48 | - 1.58 | 0.65 | 0.95 |
| KMT2C   | 0.03 | 0.03 | 0.03 | 1.03 | 0.54 | - 1.99 | 0.92 | 0.95 | 0.03 | 0.03 | 0.03 | 0.87 | 0.48 | - 1.58 | 0.65 | 0.95 |
| GLI2    | 0.05 | 0.07 | 0.05 | 1.67 | 0.91 | - 3.05 | 0.10 | 0.44 | 0.05 | 0.04 | 0.05 | 0.87 | 0.47 | - 1.61 | 0.67 | 0.95 |
| KMT2A   | 0.02 | 0.02 | 0.02 | 1.10 | 0.64 | - 1.91 | 0.73 | 0.91 | 0.03 | 0.03 | 0.03 | 1.11 | 0.69 | - 1.78 | 0.67 | 0.95 |
| SOX9    | 0.11 | 0.10 | 0.11 | 1.09 | 0.83 | - 1.44 | 0.52 | 0.83 | 0.10 | 0.09 | 0.10 | 0.94 | 0.72 | - 1.24 | 0.68 | 0.95 |
| EPHA5   | 0.03 | 0.02 | 0.03 | 0.75 | 0.39 | - 1.43 | 0.38 | 0.73 | 0.03 | 0.03 | 0.03 | 1.11 | 0.67 | - 1.83 | 0.69 | 0.95 |
| PIK3CA  | 0.19 | 0.17 | 0.20 | 0.97 | 0.78 | - 1.20 | 0.77 | 0.91 | 0.16 | 0.14 | 0.16 | 0.96 | 0.77 | - 1.19 | 0.69 | 0.95 |
| PIK3R1  | 0.03 | 0.03 | 0.03 | 0.96 | 0.61 | - 1.53 | 0.88 | 0.95 | 0.02 | 0.02 | 0.03 | 0.91 | 0.55 | - 1.52 | 0.73 | 0.95 |
| ARID1B  | 0.03 | 0.03 | 0.03 | 1.18 | 0.74 | - 1.88 | 0.50 | 0.80 | 0.04 | 0.04 | 0.04 | 1.07 | 0.73 | - 1.58 | 0.73 | 0.95 |
| AR      | 0.02 | 0.02 | 0.03 | 0.73 | 0.40 | - 1.33 | 0.30 | 0.73 | 0.02 | 0.02 | 0.02 | 0.91 | 0.50 | - 1.65 | 0.75 | 0.95 |
| POLE    | 0.02 | 0.02 | 0.02 | 1.10 | 0.60 | - 2.01 | 0.77 | 0.91 | 0.03 | 0.02 | 0.03 | 1.09 | 0.64 | - 1.86 | 0.75 | 0.95 |
| GRIN2A  | 0.03 | 0.03 | 0.03 | 1.11 | 0.61 | - 2.02 | 0.73 | 0.91 | 0.02 | 0.02 | 0.02 | 1.10 | 0.59 | - 2.06 | 0.76 | 0.95 |
| COL7A1  | 0.10 | 0.10 | 0.10 | 1.04 | 0.58 | - 1.85 | 0.90 | 0.95 | 0.07 | 0.07 | 0.08 | 1.10 | 0.60 | - 2.01 | 0.76 | 0.95 |
| BCORL1  | 0.03 | 0.04 | 0.03 | 1.21 | 0.62 | - 2.37 | 0.58 | 0.88 | 0.01 | 0.01 | 0.01 | 0.86 | 0.30 | - 2.50 | 0.78 | 0.95 |
| KAT6A   | 0.04 | 0.05 | 0.03 | 1.62 | 0.78 | - 3.36 | 0.20 | 0.58 | 0.03 | 0.03 | 0.02 | 1.11 | 0.49 | - 2.51 | 0.80 | 0.95 |
| ERBB3   | 0.03 | 0.02 | 0.03 | 0.63 | 0.37 | - 1.10 | 0.10 | 0.44 | 0.03 | 0.03 | 0.04 | 0.95 | 0.61 | - 1.47 | 0.81 | 0.95 |
| RNF43   | 0.04 | 0.03 | 0.05 | 0.60 | 0.36 | - 1.00 | 0.05 | 0.35 | 0.03 | 0.03 | 0.03 | 0.95 | 0.60 | - 1.51 | 0.83 | 0.95 |
| ATRX    | 0.04 | 0.04 | 0.05 | 0.96 | 0.64 | - 1.45 | 0.86 | 0.95 | 0.02 | 0.02 | 0.02 | 0.94 | 0.53 | - 1.67 | 0.83 | 0.95 |
| CREBBP  | 0.03 | 0.03 | 0.03 | 1.01 | 0.61 | - 1.66 | 0.97 | 0.97 | 0.03 | 0.03 | 0.03 | 0.96 | 0.60 | - 1.53 | 0.85 | 0.95 |
| PTPR    | 0.04 | 0.03 | 0.05 | 0.57 | 0.32 | - 1.03 | 0.06 | 0.37 | 0.05 | 0.05 | 0.05 | 0.96 | 0.61 | - 1.52 | 0.86 | 0.95 |
| NOTCH3  | 0.03 | 0.02 | 0.03 | 0.78 | 0.45 | - 1.37 | 0.39 | 0.73 | 0.03 | 0.03 | 0.03 | 1.04 | 0.66 | - 1.65 | 0.87 | 0.95 |
| PIK3C2B | 0.03 | 0.03 | 0.02 | 1.39 | 0.65 | - 2.95 | 0.39 | 0.73 | 0.03 | 0.02 | 0.03 | 1.06 | 0.50 | - 2.26 | 0.88 | 0.95 |
| ERBB4   | 0.03 | 0.03 | 0.04 | 0.98 | 0.61 | - 1.57 | 0.93 | 0.95 | 0.04 | 0.03 | 0.04 | 0.98 | 0.64 | - 1.49 | 0.93 | 0.96 |
| SETBP1  | 0.02 | 0.02 | 0.02 | 0.76 | 0.27 | - 2.14 | 0.60 | 0.89 | 0.03 | 0.03 | 0.03 | 1.03 | 0.48 | - 2.21 | 0.94 | 0.96 |
| EPHB1   | 0.03 | 0.03 | 0.03 | 1.08 | 0.57 | - 2.03 | 0.82 | 0.91 | 0.03 | 0.03 | 0.03 | 0.98 | 0.54 | - 1.78 | 0.95 | 0.96 |
| NF1     | 0.03 | 0.02 | 0.03 | 0.91 | 0.53 | - 1.55 | 0.73 | 0.91 | 0.02 | 0.02 | 0.02 | 1.02 | 0.61 | - 1.69 | 0.95 | 0.96 |

Abbreviations: CRC, colorectal cancer; OR, odds ratio; CI, confidence interval; FDR, false discovery rate.

\*ORs, 95% CIs, P and FDR values were calculated for genes from models adjusted for patient race/ethnicity, histology and site, sequencing assay, sample type and tumor mutational burden.

†P-values were derived from Cochran's Q test for heterogeneity by sex. Only genes with significant associations for non-silent somatic mutations between early-onset and late-onset non-hypermutated CRC cases in at least one sex-specific group were tested.

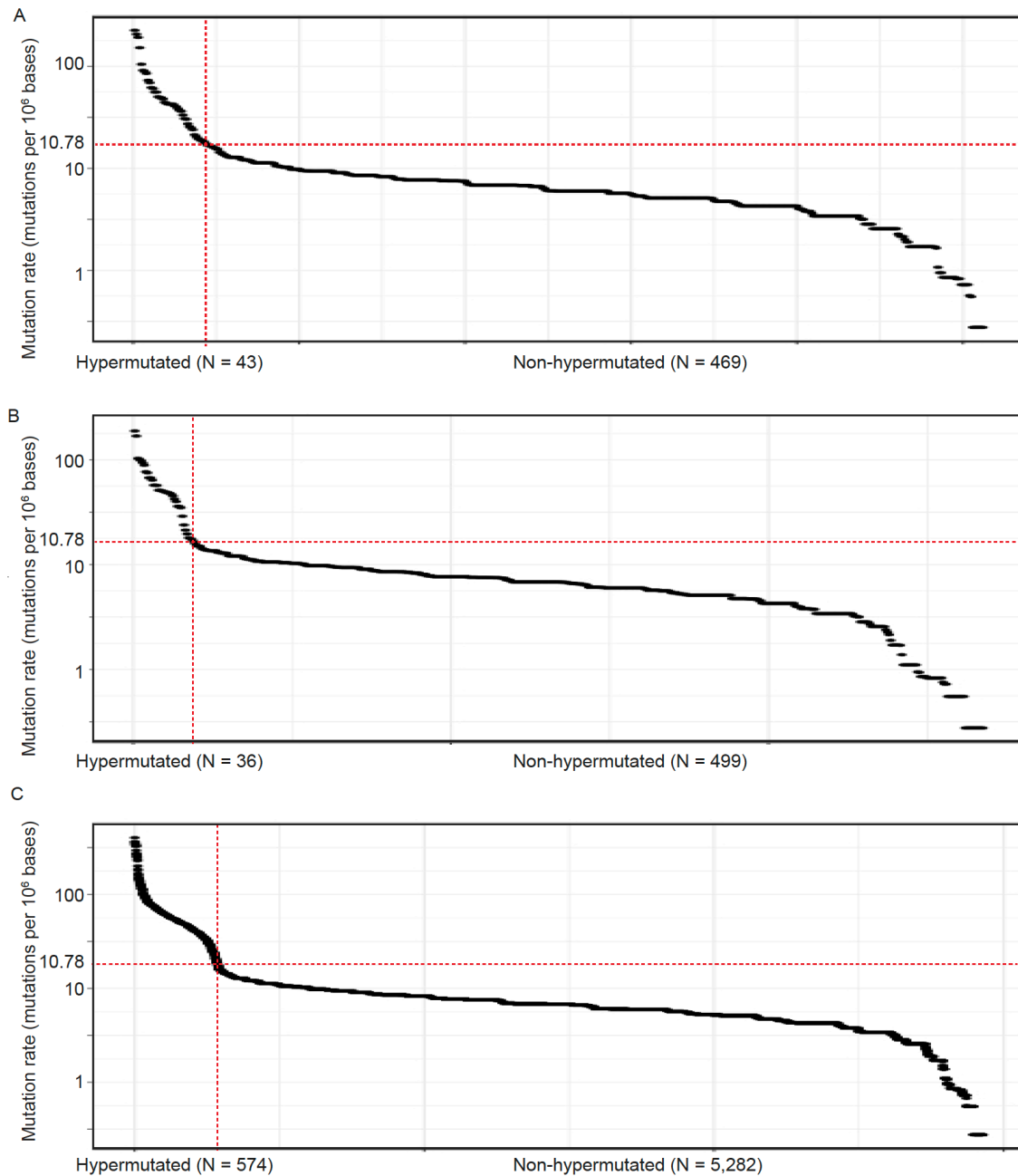
Table S5. Read depth for clinical-grade targeting sequencing data from tumor tissues and case counts by early-onset and late-onset groups and sequencing center.

| <b>Participating GENIE Center</b>                                   | <b>Center Abbreviation</b> | <b>Number of Panels/ Pipelines per Center</b> | <b>Read depth*</b> | <b>Early-Onset CRC (No. Patients)</b> | <b>Late-Onset CRC (No. Patients)</b> |
|---|----------------------------|---|--------------------|---------------------------------------|--------------------------------------|
| Memorial Sloan Kettering Cancer Center                              | MSK                        | 4   | 750X               | 1124                                  | 2636                                 |
| Dana-Farber Cancer Institute  | DFCI                       | 3   | 350X               | 674                                   | 1660                                 |
| Duke Cancer Institute, Duke University Health System                | DUKE                       | 3   | 750X-1000X         | 63                                    | 182                                  |
| Johns Hopkins Sidney Kimmel Comprehensive Cancer Center             | JHU                        | 2   | 500X               | 49                                    | 171                                  |
| Vanderbilt-Ingram Cancer Center                                     | VICC                       | 4   | 1000X              | 56                                    | 150                                  |
| University of California, San Francisco                             | UCSF                       | 2   | 500X               | 34                                    | 64                                   |
| The University of Texas MD Anderson Cancer Center                   | MDA                        | 3   | 250X               | 8                                     | 14                                   |
| The Herbert Irving Comprehensive Cancer Center, Columbia University | COLU                       | 3   | 1000X              | 2                                     | 5                                    |
| Providence Cancer Institute   | PROV                       | 3   | --                 | 0                                     | 3                                    |
| Princess Margaret Cancer Centre, University Health Network          | UHN                        | 5   | 500X               | 6                                     | 2                                    |

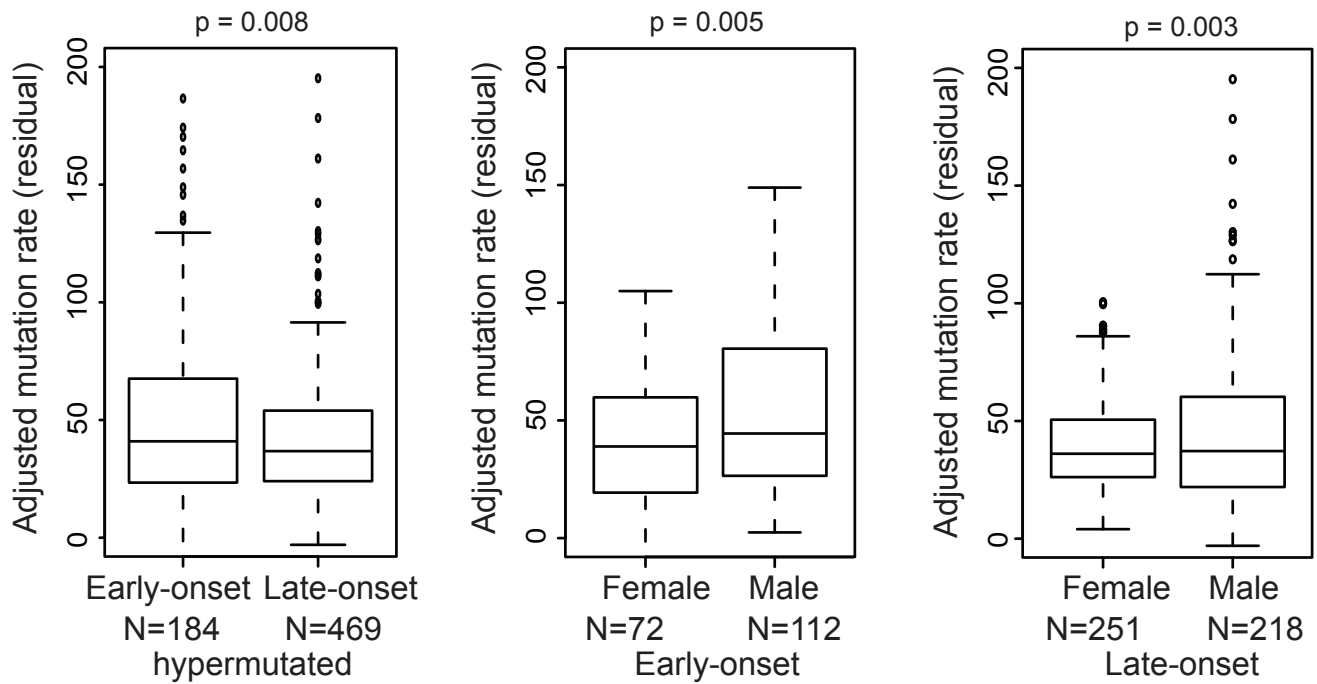
\*Read depth as provided by each participating center. This includes mean (MSK, DFCI, JHU, VICC, UCSF, COLU and UHN), range (DUKE) or minimum (MDA) read depth coverage.

## Supplementary Figures

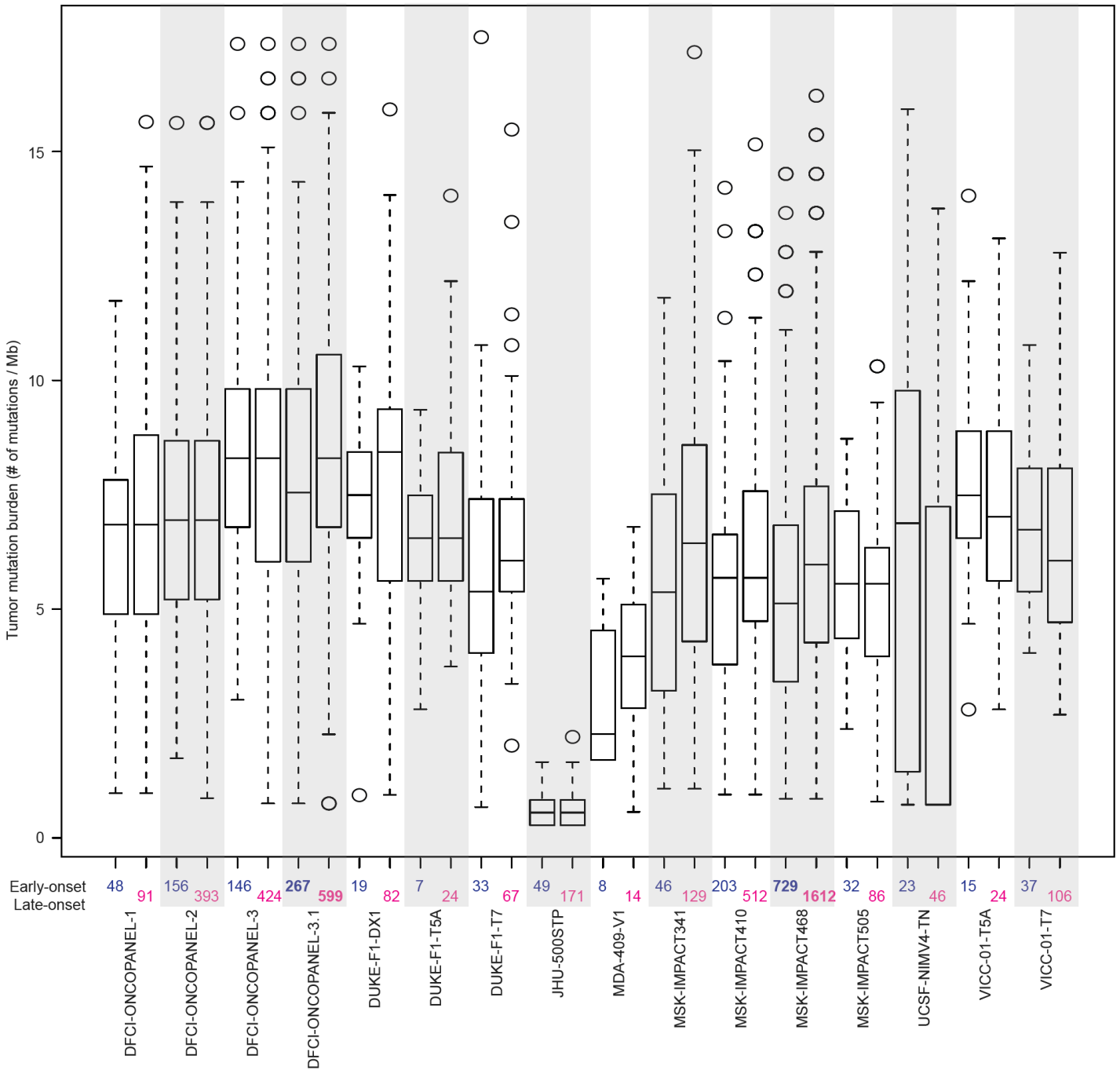
**Figure S1. Mutation rates among 6,903 tumor samples from colorectal cancer patients across racial/ethnic groups for (A) Asian or Pacific Islander [API], (B) Non-Hispanic Black [NHB], and (C) Non-Hispanic White [NHW] individuals. Non-hypermuted tumors were defined using a cutoff (red line) of 17.78+ mutations/Mb.**



**Figure S2. Adjusted mutation rates in 653 hypermutated colorectal tumors: AACR GENIE.** Boxplots of adjusted mutation rates between early-onset and late-onset cases with hypermutated CRC (left), and by sex for early-onset (middle) and late-onset (right) cases with hypermutated colorectal tumors. The residual of adjusted mutation rates and *P*-values were derived from models adjusted for race/ethnicity, sex, site and histology, sequencing assay, and sample type, as appropriate.



**Figure S3. Tumor mutational burden (TMB) across sequencing assay/platform for early-onset and late-onset non-hypermutated colorectal cancer cases: AACR Project GENIE.** TMB is defined by number of mutations per Mb. Sequencing assays/platforms with greater than 5 early-onset non-hypermutated colorectal cancer cases are presented with frequency counts (a total of 14 early-onset non-hypermutated cases excluded).



**Figure S4. Frequency of non-silent somatic mutations in commonly assayed and mutated genes between early-onset and late-onset non-hypermuted CRC cases (mutation frequency >10%).**

