

Supplemental Table 1: Description of cohort and incidence of *BRAF* gain-of-function mutation by primary tumor location (detailed).

| Characteristic | Overall, N = 51,560 ¹ | BRAF_wt, N = 49,044 ² | BRAF_GOF, N = 2,516 ² |
|------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Colon | 14,350 (28%) | 12,794 (89%) | 1,556 (11%) |
| Pancreas | 14,300 (28%) | 14,041 (98%) | 259 (1.8%) |
| Rectum | 5,479 (11%) | 5,235 (96%) | 244 (4.5%) |
| Esophagus | 3,316 (6.4%) | 3,286 (99%) | 30 (0.9%) |
| Stomach | 3,029 (5.9%) | 2,981 (98%) | 48 (1.6%) |
| Intrahepatic bile duct | 2,370 (4.6%) | 2,244 (95%) | 126 (5.3%) |
| Liver | 1,585 (3.1%) | 1,566 (99%) | 19 (1.2%) |
| Gallbladder | 1,023 (2.0%) | 1,004 (98%) | 19 (1.9%) |
| Rectosigmoid junction | 827 (1.6%) | 789 (95%) | 38 (4.6%) |
| Biliary tract | 792 (1.5%) | 763 (96%) | 29 (3.7%) |
| Appendix | 788 (1.5%) | 770 (98%) | 18 (2.3%) |
| Extrahepatic bile duct | 738 (1.4%) | 712 (96%) | 26 (3.5%) |
| Gastrointestinal tract | 665 (1.3%) | 636 (96%) | 29 (4.4%) |
| Anus | 553 (1.1%) | 545 (99%) | 8 (1.4%) |
| Ampulla of Vater | 508 (1.0%) | 485 (95%) | 23 (4.5%) |
| Small intestine | 489 (0.9%) | 475 (97%) | 14 (2.9%) |
| Duodenum | 414 (0.8%) | 395 (95%) | 19 (4.6%) |
| Intestinal tract | 144 (0.3%) | 144 (100%) | 0 (0%) |
| Jejunum | 104 (0.2%) | 94 (90%) | 10 (9.6%) |
| Ileum | 86 (0.2%) | 85 (99%) | 1 (1.2%) |

¹ n (%), note that percentage indicates column percent

² n (%), note that percentage indicates row percent

Supplemental Table 2: Frequency of *BRAF* gain-of-function alteration by primary cancer location

| Characteris tic | Overall, N = 2,516 ¹ | CRC, N = 1,838 ¹ | Other GI, N = 678 ¹ | p-value ² |
|--------------------|---------------------------------------|-----------------------------------|--------------------------------------|----------------------|
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| BRAF alteration class | | | | <0.001 |
|----------------------------------|-------------|-------------|-----------|--------|
| SV | 2,367 (94%) | 1,791 (97%) | 576 (85%) | |
| Fusion | 116 (4.6%) | 35 (1.9%) | 81 (12%) | |
| CNA | 25 (1.0%) | 6 (0.3%) | 19 (2.8%) | |
| SV, Fusion | 6 (0.2%) | 6 (0.3%) | 0 (0%) | |
| CNA, Fusion | 1 (<0.1%) | 0 (0%) | 1 (0.1%) | |
| SV, CNA | 1 (<0.1%) | 0 (0%) | 1 (0.1%) | |
| Short variant | 2,374 (94%) | 1,797 (98%) | 577 (85%) | <0.001 |
| Copy number amplification | 27 (1.1%) | 6 (0.3%) | 21 (3.1%) | <0.001 |
| Fusion | 123 (4.9%) | 41 (2.2%) | 82 (12%) | <0.001 |

¹n(%)

²Fisher's exact test; Pearson's Chi-squared test

Supplemental Table 3: *BRAF* fusion by patient, orientation agnostically listed

| Fusion Gene | Overall, N = 2,516 | CRC, N = 1,838 | Other GI, N = 678 |
|--------------------|---------------------------|-----------------------|--------------------------|
| BRAF-SND1 | 31 (1.2%) | 3 (0.2%) | 28 (4.1%) |
| BRAF-TRIM24 | 11 (0.4%) | 5 (0.3%) | 6 (0.9%) |
| BRAF-MKRN1 | 7 (0.3%) | 4 (0.2%) | 3 (0.4%) |
| BRAF-CCNY | 3 (0.1%) | 0 (0%) | 3 (0.4%) |

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| BRAF-RP1-167F1.2 | 3 (0.1%) | 2 (0.1%) | 1 (0.1%) |
| AGAP3-BRAF | 2 (<0.1%) | 1 (<0.1%) | 1 (0.1%) |
| AKAP9-BRAF | 2 (<0.1%) | 1 (<0.1%) | 1 (0.1%) |
| BRAF-COBLL1 | 2 (<0.1%) | 0 (0%) | 2 (0.3%) |
| BRAF-GTF2IRD1 | 2 (<0.1%) | 2 (0.1%) | 0 (0%) |
| BRAF-NRF1 | 2 (<0.1%) | 1 (<0.1%) | 1 (0.1%) |
| BRAF-ZC3HAV1 | 2 (<0.1%) | 1 (<0.1%) | 1 (0.1%) |
| AC073934.6-BRAF | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| AGAP1-BRAF | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| ANK3-BRAF | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| ATP11B-BRAF | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BAIAP2L1-BRAF | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-CCDC186 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-CEP290 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-CERT1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-CHCHD3 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-COG3, BRAF-PHF2P2 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-COG5 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-CUX1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-DENND2A | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-DENND2A, BRAF-POLR1D | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-ERC1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-ESRP1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-EXOC4 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-GOLGB1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-KDM7A | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-KIAA0754, BRAF-MACF1 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-KIAA1217 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-KTN1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-LINC00882 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-MCC | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |

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| BRAF-MGAM | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-MKLN1 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-PRSS1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-PTPN1 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-PTPN12 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-PTPRN2 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-RAVER2 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-RP11-689K5.3, BRAF-SEC31A | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-RPL12 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-RPS25 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-RRBP1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SEC24D | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SGK3 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SLC37A3 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SLC4A4 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SND1, BRAF- TBXAS1 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SPAG16 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-SPECC1L | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-STK39 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-STRN3 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-TMEM178B | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-TMEM44 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-TNS3 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| BRAF-TRIM44 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| BRAF-ZKSCAN5 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| CN amp, BRAF- DENND11, BRAF-HIPK2 | 1 (<0.1%) | 0 (0%) | 1 (0.1%) |
| p.Asp594Gly, BRAF- MKRN1, BRAF-TRIM24 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| p.Gly469Ala, p.Gly466Ala, BRAF- NDUFB2 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| p.Val600Glu, ATR-BRAF, BRAF-MIGA2 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |

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| p.Val600Glu, BRAF-TRIM24 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| p.Val600Glu, BRAF-UBE3C | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |
| p.Val600Glu, BRAF-ZW10 | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) |

Supplemental Table 4: Microsatellite instability and tumor mutation burden among patients with *BRAF* gain-of-function mutation by primary cancer location.

| | Overall, N = 2,516 ¹ | CRC, N = 1,838 ¹ | Other GI, N = 678 ¹ | p-value ² |
|-------------------------|------------------------------------|--------------------------------|-----------------------------------|----------------------|
| TMB (mut/Mb) | | | | <0.001 |
| Not TMB-high | 1,409 (75%) | 940 (69%) | 469 (93%) | |
| TMB-high | 459 (25%) | 425 (31%) | 34 (6.8%) | |
| Unknown | 648 | 473 | 175 | |
| MSI | | | | <0.001 |
| Not detected/Low/Stable | 2,007 (80%) | 1,358 (74%) | 649 (96%) | |
| High | 505 (20%) | 476 (26%) | 29 (4.3%) | |
| Unknown | 4 | 4 | 0 | |

* TMB-high is defined as ≥ 10 mutations/megabase in tissue and ≥ 15 mutations/megabase in blood.

¹ n (%)

² Pearson's Chi-squared test

Supplemental Table 5. Prevalence of co-mutations in colorectal cancers and non-colorectal GI cancers with *BRAF* alterations.

| | CRC, N = 1,838¹ | Other GI, N = 678¹ | p- value² | q- value³ |
|---------------|---------------------------------------|--|---------------------------------|---------------------------------|
| TP53 | 1,295 (70%) | 350 (52%) | <0.001 | <0.001 |
| APC | 781 (42%) | 85 (13%) | <0.001 | <0.001 |
| CDKN2A | 96 (5.2%) | 220 (32%) | <0.001 | <0.001 |
| RNF43 | 548 (30%) | 35 (5.2%) | <0.001 | <0.001 |
| SMAD4 | 410 (22%) | 117 (17%) | 0.006 | 0.008 |
| PIK3CA | 389 (21%) | 67 (9.9%) | <0.001 | <0.001 |
| CDKN2B | 73 (4.0%) | 137 (20%) | <0.001 | <0.001 |
| MSH3 | 337 (18%) | 21 (3.1%) | <0.001 | <0.001 |
| KMT2D | 324 (18%) | 40 (5.9%) | <0.001 | <0.001 |

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|---------------|---------------|--------------|--------|--------|
| ARID1A | 317 (17%) | 114 (17%) | 0.8 | 0.8 |
| PTEN | 305 (17%) | 27 (4.0%) | <0.001 | <0.001 |
| KRAS | 212 (12%) | 112 (17%) | <0.001 | 0.001 |
| FBXW7 | 294 (16%) | 25 (3.7%) | <0.001 | <0.001 |
| MTAP | 36 (2.0%) | 106 (16%) | <0.001 | <0.001 |
| ALK | 271 (15%) | 103 (15%) | 0.8 | 0.8 |
| MSH6 | 233 (13%) | 16 (2.4%) | <0.001 | <0.001 |
| RET | 210 (11%) | 85 (13%) | 0.4 | 0.5 |
| ACVR2A | 228 (12%) | 20 (2.9%) | <0.001 | <0.001 |
| UGT1A1 | 156 (8.5%) | 78 (12%) | 0.021 | 0.026 |
| KMT2C | 195 (11%) | 33 (4.9%) | <0.001 | <0.001 |
| BRCA2 | 192 (10%) | 49 (7.2%) | 0.015 | 0.02 |
| NTRK3 | 132 (7.2%) | 70 (10%) | 0.01 | 0.013 |
| NOTCH1 | 189 (10%) | 43 (6.3%) | 0.002 | 0.003 |
| ZNRF3 | 182 (9.9%) | 16 (2.4%) | <0.001 | <0.001 |
| LRP1B | 180 (9.8%) | 33 (4.9%) | <0.001 | <0.001 |
| RAD50 | 177 (9.6%) | 11 (1.6%) | <0.001 | <0.001 |
| ASXL1 | 173 (9.4%) | 15 (2.2%) | <0.001 | <0.001 |
| HNF1A | 159 (8.7%) | 8 (1.2%) | <0.001 | <0.001 |
| B2M | 147 (8.0%) | 11 (1.6%) | <0.001 | <0.001 |

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|---------------|---------------|--------------|--------|--------|
| NRG1 | 146 (7.9%) | 49 (7.2%) | 0.6 | 0.6 |
| ATM | 145 (7.9%) | 40 (5.9%) | 0.09 | 0.11 |
| BCOR | 144 (7.8%) | 25 (3.7%) | <0.001 | <0.001 |
| CREBBP | 141 (7.7%) | 8 (1.2%) | <0.001 | <0.001 |
| FLCN | 141 (7.7%) | 13 (1.9%) | <0.001 | <0.001 |
| BCL6 | 140 (7.6%) | 45 (6.6%) | 0.4 | 0.4 |
| CYP1B1 | 132 (7.2%) | 41 (6.0%) | 0.3 | 0.4 |
| TCF7L2 | 132 (7.2%) | 6 (0.9%) | <0.001 | <0.001 |
| NTRK2 | 52 (2.8%) | 46 (6.8%) | <0.001 | <0.001 |
| CIC | 123 (6.7%) | 17 (2.5%) | <0.001 | <0.001 |
| RPL22 | 122 (6.6%) | 9 (1.3%) | <0.001 | <0.001 |
| BCORL1 | 120 (6.5%) | 14 (2.1%) | <0.001 | <0.001 |
| CASP8 | 115 (6.3%) | 7 (1.0%) | <0.001 | <0.001 |
| PTCH1 | 115 (6.3%) | 7 (1.0%) | <0.001 | <0.001 |
| ARID1B | 114 (6.2%) | 20 (2.9%) | 0.001 | 0.002 |
| PIK3R1 | 111 (6.0%) | 14 (2.1%) | <0.001 | <0.001 |
| TERT | 40 (2.2%) | 40 (5.9%) | <0.001 | <0.001 |
| ZFHX3 | 107 (5.8%) | 13 (1.9%) | <0.001 | <0.001 |
| ARID2 | 95 (5.2%) | 38 (5.6%) | 0.7 | 0.7 |

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|------------------------|------------|-----------|--------|--------|
| MTAP-downstream | 9 (0.5%) | 37 (5.5%) | <0.001 | <0.001 |
| NF1 | 100 (5.4%) | 29 (4.3%) | 0.2 | 0.3 |
| FAT1 | 99 (5.4%) | 17 (2.5%) | 0.002 | 0.003 |
| PMS2 | 95 (5.2%) | 28 (4.1%) | 0.3 | 0.3 |
| GNAS | 85 (4.6%) | 35 (5.2%) | 0.6 | 0.6 |
| ATR | 94 (5.1%) | 7 (1.0%) | <0.001 | <0.001 |
| CHD2 | 94 (5.1%) | 4 (0.6%) | <0.001 | <0.001 |
| MLH3 | 93 (5.1%) | 4 (0.6%) | <0.001 | <0.001 |
| FGFR3 | 69 (3.8%) | 34 (5.0%) | 0.2 | 0.2 |
| MYB | 56 (3.0%) | 34 (5.0%) | 0.018 | 0.024 |
| AMER1 | 92 (5.0%) | 12 (1.8%) | <0.001 | <0.001 |

* Somatic alterations include short variant pathogenic/likely pathogenic mutations and copy number alterations (loss or amplification, copy number 0 or ≥ 8 , respectively)

¹ n (%)

² Pearson's Chi-squared test

³ False discovery rate correction for multiple testing