# Supplementary Online Content

Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. Published online February 7, 2019. *JAMA Oncol*. doi:10.1001/jamaoncol.2018.6760



This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Demographic Information for 3607 Patients with a Personal History of Prostate Cancer Who Underwent Germline Genetic Testing Between 2013 and 2018**

| | Total Cohort (n = 3607) | Patients with a Positive Finding (n = 620) | Patients with a Positive Finding (% of Total) |
|---|---|---|---|
| **Age at Testing (Years)** | | | |
| <50 | 134 | 20 | 13.4 |
| 50–59 | 629 | 111 | 15.7 |
| 60–69 | 1308 | 237 | 16.9 |
| 70–79 | 1214 | 189 | 14.5 |
| 80–89 | 297 | 58 | 18.2 |
| >90 | 24 | 5 | 20.8 |
| | | | |
| **Ancestry/Ethnicity** | | | |
| White/white | 2594 | 462 | 17.8 |
| Ashkenazi Jewish | 234 | 52 | 22.2 |
| Black/ African American | 227 | 23 | 10.1 |
| Hispanic | 78 | 5 | 6.4 |
| Asian | 73 | 11 | 15.1 |
| Other | 401 | 67 | 16.7 |
| | | | |
| **Family History (Cancer)** | | | |
| Prostate | 1547 | 256 | 16.6 |
| Breast | 1450 | 262 | 18.1 |

| | Total Cohort (n = 3607) | Patients with a Positive Finding (n = 620) | Patients with a Positive Finding (% of Total) |
|---|---|---|---|
| **Family History (Cancer)** | | | |
| Ovarian | 355 | 81 | 22.8 |
| Colon | 659 | 107 | 16.2 |
| Pancreatic | 402 | 78 | 19.4 |
| Other | 548 | 96 | 17.5 |
| | | | |
| **Gleason Score** | | | |
| 3 | 2 | 0 | 0 |
| 4 | 5 | 0 | 0 |
| 5 | 2 | 0 | 0 |
| 6 | 139 | 21 | 15.1 |
| 7 | 691 | 110 | 15.9 |
| 8 | 246 | 44 | 17.9 |
| 9 | 393 | 62 | 15.8 |
| 10 | 60 | 10 | 16.7 |
| Unknown | 2069 | 374 | 18.0 |

**eTable 2. Distribution by Ethnicity of Pathogenic/Likely Pathogenic/Risk Allele Variants Detected in Men with Prostate Cancer**

| Gene | White (n = 2594) | Ashkenazi Jewish (n = 234) | Black/African American (n = 227) | Hispanic (n = 78) | Asian (n = 73) | Other (n = 401) | Total |
|---|---|---|---|---|---|---|---|
| ***APC*** | 9 | 16 | 0 | 0 | 0 | 5 | 30 |
| ***ATM*** | 48 | 7 | 2 | 0 | 2 | 6 | 65 |
| ***BLM*** | 3 | 2 | 0 | 0 | 0 | 1 | 6 |
| ***BMPR1A*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***BRCA1*** | 29 | 7 | 3 | 0 | 2 | 2 | 43 |
| ***BRCA2*** | 119 | 13 | 6 | 3 | 3 | 20 | 164 |
| ***BRIP1*** | 7 | 0 | 0 | 0 | 0 | 0 | 7 |
| ***CDH1*** | 3 | 0 | 0 | 0 | 0 | 0 | 3 |
| ***CDKN1B*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***CDKN1C*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***CDKN2A*** | 3 | 0 | 0 | 0 | 0 | 0 | 3 |
| ***CFTR*** | 3 | 1 | 1 | 1 | 0 | 0 | 6 |
| ***CHEK2*** | 74 | 8 | 1 | 0 | 0 | 12 | 95 |
| ***EPCAM*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***F5*** | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| ***FANCA*** | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| ***FANCC*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***FANCL*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***HFE*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***HOXB13*** | 24 | 0 | 3 | 0 | 0 | 3 | 30 |
| ***MITF*** | 7 | 0 | 0 | 0 | 0 | 0 | 7 |
| ***MLH1*** | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| ***MSH2*** | 19 | 1 | 0 | 0 | 0 | 3 | 23 |
| ***MSH6*** | 9 | 3 | 0 | 1 | 1 | 1 | 15 |

| Gene | White (n = 2594) | Ashkenazi Jewish (n = 234) | Black/African American (n = 227) | Hispanic (n = 78) | Asian (n = 73) | Other (n = 401) | Total |
|---|---|---|---|---|---|---|---|
| ***MUTYH*** | 49 | 1 | 2 | 0 | 0 | 3 | 55 |
| ***MYH7*** | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| ***NBN*** | 10 | 0 | 0 | 0 | 0 | 0 | 10 |
| ***NF1*** | 1 | 0 | 0 | 0 | 0 | 1 | 2 |
| ***PALB2*** | 13 | 0 | 2 | 0 | 1 | 1 | 17 |
| ***PMS2*** | 10 | 1 | 1 | 0 | 1 | 5 | 18 |
| ***PTCH1*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***RAD50*** | 5 | 0 | 0 | 0 | 0 | 2 | 7 |
| ***RAD51C*** | 4 | 0 | 1 | 0 | 0 | 0 | 5 |
| ***RAD51D*** | 3 | 1 | 0 | 0 | 0 | 0 | 4 |
| ***RECQL4*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***RET*** | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| ***SDHA*** | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| ***SDHB*** | 3 | 0 | 0 | 0 | 0 | 0 | 3 |
| ***SMAD4*** | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| ***SPINK1*** | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| ***TINF2*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| ***TMEM127*** | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| ***TP53*** | 19 | 0 | 0 | 0 | 0 | 3 | 22 |
| ***TSC2*** | 1 | 0 | 0 | 0 | 0 | 1 | 2 |
| ***VHL*** | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| ***WRN*** | 1 | 0 | 0 | 0 | 0 | 0 | 1 |

**eTable 3. Pathogenic/Likely Pathogenic/Risk Allele (Positive Variants) and Variants of Unknown Significance Detected in This Study**

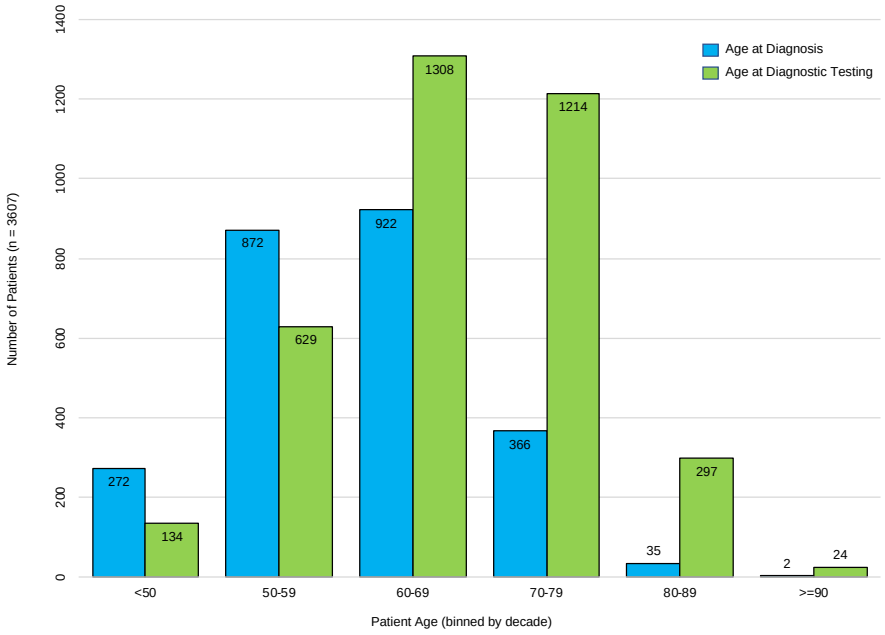
| Gene | Number of Requisitions | Number of Positive Variants Detected | Number of Variants of Uncertain Significance Detected |
|---|---|---|---|
| ***BRCA2*** | 3459 | 164 | 75 |
| ***BRCA1*** | 3436 | 43 | 38 |
| ***MSH2*** | 3350 | 23 | 48 |
| ***MSH6*** | 3346 | 15 | 75 |
| ***PMS2*** | 3345 | 18 | 50 |
| ***MLH1*** | 3343 | 2 | 25 |
| ***EPCAM*** | 3331 | 1 | 5 |
| ***TP53*** | 3329 | 22 | 30 |
| ***CHEK2*** | 3300 | 95 | 71 |
| ***ATM*** | 3207 | 65 | 160 |
| ***NBN*** | 3145 | 10 | 41 |
| ***PALB2*** | 3014 | 17 | 42 |
| ***RAD51D*** | 2689 | 4 | 12 |
| ***HOXB13*** | 2667 | 30 | 0 |
| ***PTEN*** | 2641 | 0 | 4 |
| ***STK11*** | 2622 | 0 | 9 |
| ***CDH1*** | 2504 | 3 | 28 |
| ***BRIP1*** | 2461 | 7 | 36 |
| ***RAD51C*** | 2438 | 5 | 21 |
| ***NF1*** | 2347 | 2 | 35 |
| ***APC*** | 2345 | 30 | 76 |
| ***BARD1*** | 2336 | 0 | 29 |
| ***MUTYH*** | 2322 | 55 | 27 |
| ***SMAD4*** | 2282 | 1 | 4 |

**eTable 4. Comparison of Frequency of Mutations among Tested Patients From This Data Set Compared with Those in the Pritchard et al[5] Metastatic Series.**

| Gene | This Study (%) | Pritchard et al., 2016 (%) | Difference (%) | 95% CI | P Value |
|---|---|---|---|---|---|
| ***APC*** | 1.28 | NT | | | |
| ***ATM*** | 2.03 | 1.59 | 0.44 | (-0.8683 to 1.3292) | 0.4480 |
| ***BRCA1*** | 1.25 | 0.87 | 0.38 | (-0.6822 to 1.0169) | 0.3997 |
| ***BRCA2*** | 4.74 | 5.35 | 0.61 | (-1.0213 to 2.6557) | 0.4950 |
| ***BRIP1*** | 0.28 | 0.18 | 0.10 | (-0.7383 to 0.4345) | 0.6756 |
| ***CDKN2*** | 0.13 | NT | | | |
| ***CDH1*** | 0.12 | NT | | | |
| ***CHEK2*** | 2.88 | 1.87 | 1.01 | (-0.6140 to 2.0679) | 0.1847 |
| ***HOXB13*** | 1.12 | NT | | | |
| ***MLH1*** | 0.06 | 0.00 | | | |
| ***MSH2*** | 0.69 | 0.14 | 0.55 | (-0.1547 to 0.9113) | 0.0870 |
| ***MSH6*** | 0.45 | 0.14 | 0.31 | (-0.3794 to 0.6227) | 0.2378 |
| ***MUTYH*** | 2.37 | NT | | | |
| ***NBN*** | 0.32 | 0.29 | 0.03 | (-0.7430 to 0.3698) | 0.8985 |
| ***NF1*** | 0.09 | NT | | | |
| ***PALB2*** | 0.56 | 0.43 | 0.13 | (-0.7278 to 0.5705) | 0.6727 |
| ***PMS2*** | 0.54 | 0.29 | 0.25 | (-0.5345 to 0.6257) | 0.3947 |
| ***RAD50*** | 0.32 | NT | | | |
| ***RAD51C*** | 0.21 | 0.14 | 0.07 | (-0.6070 to 0.3694) | 0.7123 |
| ***RAD51D*** | 0.15 | 0.43 | 0.28 | (-0.0880 to 1.1166) | 0.1487 |
| ***TP53*** | 0.66 | NT | | | |

Abbreviations: CI, confidence interval; NT, not tested.

**eFigure 1. Age at Diagnosis Compared With Age at Testing in Men with a Personal History of Prostate Cancer.** A distinctive rightward shift was identified and indicated a lag between the initial diagnosis of prostate cancer and referral for germline genetic testing.



**eFigure 2. Distribution of Genes in Which Pathogenic, Likely Pathogenic, and Increased Risk Allele Variants Were Detected in This Study.** The number of positive findings detected in each gene is listed above the histogram. A small number of genes had several positive findings, whereas there was a long tail of genes in which only one positive finding was detected.