Cancer-specific risks associated with germline *PALB2* pathogenic variants from a large clinical genetic testing cohort

Yen Y. Tan[1], Chunling Hu[2], Huaizhi Huang[2], Nicholas Boddicker[2], Wenan Chen[2], Medha Kaul[2], Tara Rao[2], Alvaro N.A. Monteiro[3], Tina Pesaran[4], Rachid Karam[4], Susan M. Domchek[5], Siddhartha Yadav[2], Marcy E. Richardson[4*], Fergus J. Couch[2]

[1]Medical University of Vienna, Vienna, AU; [2]Mayo Clinic, Rochester MN; [3]Moffitt Cancer Center, Tampa, FL;[4]Ambry Genetics, Aliso Viejo, CA; [5]University of Pennsylvania, Philadelphia, PA

Background: Pathogenic variants (PVs) in *PALB2* are known to confer high-to-moderate risk for breast cancer. However, breast cancer risk estimates for *PALB2* PVs for different populations are not well defined and associations with other cancers are still unclear. Using data from a large clinical genetic testing cohort we have established cancer-specific risks associated with *PALB2* PVs.

Methods: We analyzed the associations of *PALB2* PVs with breast, ovarian, prostate, and pancreatic cancers in individuals tested at Ambry Genetics. Cancer-specific odds ratios (ORs) and 95% confidence intervals (CI) were estimated by comparing PV carrier frequencies in cancer cases to population controls from AllofUs adjusting for age and genetic ancestry and gnomAD v4.1 adjusting for ancestry only. Two-sided p-values are reported.

Results: Of 1,119,667 individuals tested, 357,109 had breast cancer, 37,468 ovarian cancer, 22,112 pancreatic cancer and 32,738 prostate cancer. *PALB2* PVs were observed in 0.79% of breast cancer cases, 0.30% of ovarian cancer cases, 0.78% of pancreatic cancer cases, and 0.47% of prostate cancer cases, with mean age at diagnosis of 54.2 years for breast, 60.1 years for ovarian, 62.8 years for pancreatic and 66.7 years for prostate. Whereas only 2.4% of breast cancers with PVs had a personal history of ovarian or pancreatic, 13.4% of ovarian cases had a prior history of breast cancer, and 33.3% of pancreatic cancers had a prior history of breast cancer. Analysis of PV types found that frameshift PVs accounted for 50% of PVs, nonsense for 30%, canonical splice sites for 5% and copy number variants for 8-9% of cases in all cancer types.

To refine estimates of risks for breast cancer, association studies were performed separately with GnomAD v4.1 and AllofUs controls. *PALB2* PVs were consistently associated with high risks of breast cancer (GnomADv.4.1 OR=6.74, 95%CI=5.86-7.82, $p=3.87x10^{-146}$; AllofUs OR=5.65, 95%CI=4.83-6.65, $p=2.54x10^{-155}$) with confidence intervals above OR=4. This was significantly different and increased over breast cancer risk estimates from the CARRIERS and BRIDGES population-based studies (OR=4.67, 95%CI=3.73-5.85, $3.95x10^{-27}$) and the UK Biobank population-based study (OR=3.87, 95%CI=3.09-4.83, $p=4.62x10^{-27}$). Similarly, high risks of pancreatic cancer were confirmed (GnomADv.4.1 OR=5.23, 95%CI=3.85-6.99, $p=1.49x10^{-27}$). Importantly, associations between *PALB2* PVs and moderate risks of both ovarian cancer (GnomADv.4.1 OR=2.63, 95%CI=2.07-3.33, $p=1.81x10^{-15}$; AllofUs OR=2.15, 95%CI=1.62-2.85, $p=2.97x10^{-7}$) and prostate cancer (GnomADv.4.1 OR=2.45, 95%CI=2.01-2.97, $p=1.52x10^{-19}$) were observed.

Conclusions: This large-scale study provides robust estimates of *PALB2* PV prevalence and associated cancer risks in a U.S. clinical genetic testing population. The findings provide refined risk estimates for breast and pancreatic cancers but also establish that *PALB2* PVs confer increased risk for ovarian and prostate cancers. These results help clarify ongoing

uncertainty, particularly for ovarian and prostate cancer, and highlight the importance of *PALB2* in broader hereditary cancer risk assessment and multigene panel testing.