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Global Team of Cancer Genetic Specialists Provides New Guidance for Individuals with *PALB2* Gene Variants: ACMG Clinical Practice Resource to Help Guide Clinical Management of Patients at Increased Risk of Breast, Pancreatic and Ovarian Cancers

Bethesda, MD – May 11, 2021| The American College of Medical Genetics and Genomics (ACMG) has released an important new clinical practice resource from a global team of specialists in cancer genetics that will help inform the clinical management of patients who are at increased risk of breast cancer, pancreatic cancer and likely ovarian cancer.

"Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)" was published in ACMG's official journal, *Genetics in Medicine.*

PALB2 (Partner and Localizer of *BRCA2*) germline pathogenic variants are associated with substantially increased breast cancer risk and smaller increased risk for pancreatic and ovarian cancer. Germline pathogenic/likely pathogenic (P/LP) variants in *PALB2* were first associated with increased cancer risk in 2007 and clinical testing has been available since then. It has come to be considered as the third most important breast cancer gene after *BRCA1* and *BRCA2*. Despite the emerging importance of this gene, there has been a dearth of resources to guide clinical management of women and men with *PALB2* germline *P/LP* variants.

"*PALB2* is sometimes referred to as *'BRCA3,'* given its importance in risk of breast cancer. People who harbor a germline pathogenic or likely pathogenic variant in *PALB2* face challenging questions, especially about their personal risk to develop cancers of the breast, ovaries and pancreas, and how to manage that risk. In developing this clinical practice resource, we sought to help guide patients and their treating providers to make the best possible decisions based on current high-quality peer-reviewed evidence and a worldwide network of practicing physicians with expertise in cancer genetics," said Douglas R. Stewart, MD, FACMG, author and past chair of the ACMG Professional Practice and Guidelines Committee.

Key recommendations include the following:

- Personalized risk estimates (e.g., CanRisk) should be used in guiding clinical management.
- *PALB2 VUS* (variants of uncertain significance) should not be used to guide clinical management.
- Prospective collection of clinical data from *PALB2* patients should be used to establish clear metrics on treatment outcome and survival.
- *PALB2* patients should be offered similar surveillance to *BRCA1/2*, modified according to individual risk.

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- Risk reducing mastectomy can be considered as an option, guided by personalized risk assessments.
- Pancreatic cancer surveillance may be considered in the context of family history, ideally as part of a clinical trial.
- Ovarian cancer surveillance should not be offered; risk reducing salpingo-oophorectomy (surgery to remove the ovaries and fallopian tubes) should include shared decision making and should rarely be considered before the age of 50.
- Given the mechanistic similarities, *PALB2* patients may be considered for therapeutic regimens and trials as those for *BRCA1/2.*
- ACMG does not recommend testing partners of *PALB2* patients in the reproductive setting unless it can be justified by the partner's family history of cancer.

This Clinical Practice Resource concludes that this guidance is similar to those for patients with *BRCA1/2.* While the range of the cancer risk estimates overlap with *BRCA1/2*, it is lower in *PALB2,* so individualized estimates are important for management decisions. Systematic prospective data collection is needed to determine, as yet, unanswered questions, such as the risk of contralateral breast cancer and survival after cancer diagnosis.

"This new document is landmark for the ACMG in a couple of ways," said Marc S. Williams, MD, FAAP, FACMG, FACMI, president of the American College of Medical Genetics and Genomics. "First, it reflects a commitment of the ACMG to develop guidance for use of germline genetic information for the treatment of patients with cancer. Second, this represents the first of what we hope will be many guidance documents that reflect a diverse, global perspective. The working group included experts on *PALB2* from around the world so that the guidance will have relevance for patients from diverse backgrounds receiving care in a variety of settings," he said.

The global team of authors for this new Clinical Practice Resource includes Marc Tischkowitz, MD, PhD, Judith Balmana, MD, PhD, William D. Foulkes, MBBS, PhD, Paul James, MD, PhD, Joanne Ngeow, MBBS, MPH, Rita Schmutzler, MD, Nicoleta Voian, MD, MPH, Myra J. Wick, MD, PhD, Douglas R. Stewart, MD and Tuya Pal, MD and the ACMG Professional Practice and Guidelines Committee. They are experts in clinical cancer genetics, breast and gynecologic surgery and medical oncology and practice in Australia, Asia, the United States, Canada, the United Kingdom and Europe.

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About the American College of Medical Genetics and Genomics (ACMG) and ACMG Foundation

Founded in 1991, the American College of Medical Genetics and Genomics (ACMG) is the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics, and the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization. The ACMG is the largest membership organization specifically for medical geneticists, providing education, resources and a voice for more than 2,500 clinical and laboratory geneticists, genetic counselors and other healthcare professionals, nearly 80% of whom are board certified in the medical genetics specialties. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health. Four overarching strategies guide ACMG's work: 1) to reinforce and expand ACMG's position as the leader and prominent authority in the field of medical genetics and genomics, including clinical research, while educating the medical community on the significant role that genetics and genomics will continue to play in understanding, preventing, treating and curing disease; 2) to secure and expand the professional workforce for medical genetics and genomics; 3) to advocate for the specialty; and 4) to provide best-in-class education to members and nonmembers. *Genetics in Medicine*, published monthly, is the official ACMG journal. ACMG's website, www.acmg.net offers resources including policy statements, practice guidelines, educational programs and a 'Find a Genetic Service' tool. The educational and public health programs of the ACMG are dependent upon charitable gifts from corporations, foundations and individuals through the ACMG Foundation for Genetic and Genomic Medicine.

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