March 18, 2019

Douglas K. Owens, MD, MS
Chairperson
U.S. Preventive Services Task Force
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Rockville, MD 20857

Dear Dr. Owens and esteemed members of the U.S. Preventive Services Task Force,

On behalf of our organizations and millions of Americans at risk of, or diagnosed with, hereditary cancers please see the following comments regarding the Draft Recommendation Statement: Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer.

The USPSTF recommendations impact two crucial areas of health care in the U.S.:

1. The Task Force provides evidence-based guidelines on preventive services such as screenings, counseling services, and preventive medications with a focus on primary care clinicians.
2. The panel's guidelines are cited in the Patient Protection and Affordable Care Act (ACA); thereby influencing access to care and insurance coverage of crucial preventive health services for a majority of Americans.

All of our concerns and remarks relate to one or both of these areas.

Rationale (and Guideline scope)
The Task Force focuses explicitly on risk assessment and testing for germline BRCA1 and BRCA2 genetic mutations.

PROPOSED REVISION:
Extend the evaluation and letter grade to encompass multi-gene panel testing.
The focus on BRCA mutations was appropriate six years ago, but the science has advanced exponentially since then. Several other clinically actionable genetic mutations have been identified. In 2015, the National Comprehensive Cancer Network (NCCN) published guidelines for high-penetrance gene mutations as well as a number of moderate-penetrance mutations associated with hereditary breast and ovarian cancer. These include TP53, CDH1, PALB2, CHEK2 and ATM. Guidelines also exist for Lynch syndrome genes, which include MLH1, MSH2, MSH6, PMS2, and EPCAM. Mutations in Lynch syndrome genes are more common than BRCA mutations, and predispose to overlapping phenotypes (e.g. breast cancer) in some cases, yet these genes are not addressed in the USPSTF guidelines.

Science has evolved significantly since 2013 and testing beyond BRCA has become standard of care. Multiple studies have demonstrated that compared with multi-gene NGS

panels, traditional testing of BRCA1/2 alone misses potentially actionable findings in a substantial proportion of cases.[1,2,3,4,5,6] As such, BRCA testing alone gives a very limited picture of potential risk. Ultimately, patients benefit from multi-gene panel testing. Knowledge about a mutation—whether classified as moderate- or high-risk—is useful in guiding risk management and preventive measures, providing tremendous health benefits to patients and their families.

Patient Population Under Consideration

The USPSTF recommendation states that it applies to: "*asymptomatic women with unknown BRCA mutation status. It includes women who have never been diagnosed with BRCA-related cancer, as well as those with a previous breast, ovarian, or peritoneal cancer diagnosis; women who have completed treatment; and women who are considered cancer free.*"

PROPOSED REVISION:

Extend the evaluation and letter grade to include men.

Men carry gene mutations associated with increased risk of cancer at the same rate as women and benefit from increased screening for associated cancers. The Task Force recognizes this stating, "*Clinical practice guidelines recommend that BRCA mutation testing begin with a relative with known BRCA-related cancer, including male relatives, to determine if a clinically significant mutation is detected in the family before testing individuals without cancer*." With this knowledge, why are men excluded from the "Patient Population Under Consideration"?

Men with an abnormal BRCA2 gene are seven times more likely than the average risk population to develop prostate cancer.[7] While BRCA2 is the most common gene mutation found in men with breast cancer, a significant proportion of patients have a mutation in another cancer susceptibility gene, particularly CHEK2, PALB2, and ATM.[8,9] These cancers occur earlier, have a more aggressive phenotype, and are associated with reduced survival times.[10] Men with Lynch syndrome have a 60% to 80% lifetime risk of developing colon cancer, higher than their female counterparts with the same mutation. These numbers are similar to the breast cancer risk in women with BRCA1 mutations.

Men benefit from genetic testing; those identified with a pathogenic mutation can undergo earlier, increased screening for prostate, breast, colon and other related cancers.[11] Lack of inclusion in these guidelines presents a barrier to genetic testing for men. This results in a lost opportunity to prevent or detect cancer early when it is most likely to respond to treatment. In addition, it is a lost opportunity to inform biological relatives of male mutation carriers of their increase cancer risk especially in those families with few females.

PROPOSED REVISION:

Clarify that the evaluation and letter grade applies to anyone with a known mutation in the family.

As written, the USPSTF acknowledges that women with a relative with a known mutation in BRCA1/2 should receive genetic counseling and consideration for testing but this should be made clear in the "Patient Population Under Consideration" section. Not clearly stating

that individuals with a known familial mutation are included in this section could preclude these individuals from testing, especially if there is not a strong family history of cancer.

- The data on genetic counseling and testing for someone who has a known germline mutation in the family is even stronger and likely to be more informative than for individuals without a known mutation in the family.
- The USPSTF could alter the guidelines to clearly state that people with a first-degree relative with a known mutation should also receive genetic counseling and testing.

PROPOSED REVISION:
Extend the evaluation and letter grade to individuals diagnosed with cancer and meet criteria for genetic counseling and testing based on personal and family history of cancer.
We applaud inclusion of those with a previous diagnosis of cancer who are no longer in treatment. However, knowing that a pathogenic mutation such as BRCA1/2 conveys the risk of multiple primary cancers, inclusion of patients already diagnosed with a potentially related cancer—regardless of whether they are currently in treatment—would serve to prevent future cancers in this population. As the Task Force notes, "*clinical practice guidelines recommend that BRCA mutation testing begin with a relative with known BRCA-related cancer, including male relatives*."

- Research indicates that women with a BRCA mutation who have already been diagnosed with breast cancer are at very high risk for a second primary breast cancer and for ovarian cancer.[12,13,14]
- Cancer screening and prevention options for a new cancer diagnosis in this cohort of breast cancer survivors are similar to those for women with a mutation who have not had cancer.
- The prospective PROSE study showed decreased ovarian cancer-associated mortality in BRCA mutation carriers who chose risk-reducing salpingo-oophorectomy. This study included breast cancer survivors with BRCA mutations.[15]
- Testing within a family is more cost-effective and most likely to yield a conclusive result if it begins with an individual who has had a cancer diagnosis consistent with a hereditary cancer syndrome. Despite mention of testing affected family members, omission of this population under "Patient Population Under Consideration" implies that testing unaffected women in a family where there has been no identified mutation is a more appropriate approach. Further, under ACA, exclusion of survivors from these guidelines impacts access to care and coverage of genetic testing in this population. This may inadvertently increase inappropriate and more costly initial genetic tests of unaffected family members, rather than first screening the family member who is most likely to test positive—and then testing unaffected individuals for the identified mutation. In addition, testing often occurs at the time of diagnosis. Failing to test at this time is a missed opportunity to identify mutations carriers and to prevent future cancers.

Assessment of Risk
The Task Force states, *"…primary care providers should ask about specific types of cancer, primary cancer sites, which family members were affected, relatives with multiple types of primary cancer, and the age at diagnosis and sex of affected family members*."

As demonstrated throughout our comments, a family history of breast, ovarian cancer and other cancers may be linked with Lynch Syndrome or other clinically relevant mutations such as ATM, CHEK2 or PALB2. By providing guidelines limited to the individuals who may carry a BRCA mutation, the Task Force is missing the opportunity to improve the health of more Americans by guiding practitioners to identify individuals who may carry a mutation in other cancer predisposing genes for which preventive care options are available.

PROPOSED REVISION:
Expand scope, review evidence, and develop guidelines for "Risk Assessment, Genetic Counseling, and Genetic Testing for Hereditary Cancer Syndromes."
One of the USPSTF goals is to "improve the health of all Americans." With this in mind, the Task Force would better serve clinicians and the public by developing a single set of evidence-based guidelines that address the collection and evaluation of personal and family medical history to identify individuals appropriate for genetic counseling and testing for all clinically actionable genetic mutations associated with increased risk of cancer. These should include assessment for Lynch syndrome genes, BRCA1 and BRCA2, and other genes for which there is evidence of clinical utility.

Establishing one, comprehensive set of practice guidelines for collecting family history and referral of appropriate individuals for genetic counseling, testing, and related preventive services will serve the greater good and align these recommendations with the current standard of care.

Genetic Counseling
Under "Detection" the USPSTF recommendation states, "*Risk for clinically significant BRCA mutations can be further evaluated with genetic counseling by suitably trained health care providers…*" The "Genetic Counseling" section goes on to explain, "*Genetic counseling about BRCA mutation testing should be done by trained health professionals, including trained primary care providers*."

PROPOSED REVISION:
Genetic counseling must encompass risk of mutations other than BRCA 1/2.
As detailed in our "Population Under Consideration" comments, the focus on BRCA is insufficient given our knowledge about other mutations, found in an estimated 50% of patients who carry an actionable pathogenic mutation. Counseling must cover the possibility of these mutations and the potential implications of not testing for genes beyond BRCA.

PROPOSED REVISION:
Define health care providers who provide genetic counseling to clarify "genetics training and clinical experience." Adopt the Commission on Cancer's guidelines. Stipulate that training by commercial laboratories does not constitute adequate genetics training.
Genetics is a rapidly evolving area of medicine. Most primary care providers and gynecologists do not have formal training in genetics and receive their information from the laboratories performing the testing.[16,17]

The American College of Surgeons, Commission on Cancer (CoC) is a consortium of professional organizations dedicated to improving survival and quality of life for cancer patients through standard-setting, prevention, research, education, and the monitoring of comprehensive quality care. In regard to which experts should provide genetic counseling services, the CoC states: "*Please note, specialized training in cancer genetics should be ongoing; educational seminars offered by commercial laboratories about how to perform genetic testing are not considered adequate training for cancer risk assessment and genetic counseling*."[18]

While there is some concern in the cancer community about a purported shortage of certified genetic counselors, the growth in telegenetics and partnerships between large cancer centers and smaller, community-based health care settings has increased patient access to qualified genetics experts. Studies show that videoconference consultations are generally well accepted by both patients and clinicians, and satisfaction rates are similar with in-person counseling. This type of remote counseling has been successfully integrated into clinical practice and should be seen as a viable delivery model.[19,20,21]

Treatment and Interventions

The Task Force mentions risk-management interventions but indicates, "*Management of BRCA mutations to reduce risk of future cancer is beyond the scope of this recommendation statement.*" This reasoning is faulty as the USPSTF provides recommendations for cancer screening interventions including mammography, colonoscopy, PSA testing, and more—but the focus is on the average-risk population.

PROPOSED REVISION:

Review research and assign letter grades to screening, preventive, and risk-management options for those at increased risk of cancer.

Women and men with germline mutations are managed with a variety of interventions, including intensive cancer screening at younger ages, chemoprevention, and risk-reducing surgeries. Note that these are not "treatments"—they are PREVENTION. The community needs clear guidelines and recommendations for appropriate screening and preventive modalities for individuals at increased risk of cancer.

Many health insurers look to the USPSTF and ACA to determine which services are medically necessary for prevention of disease. Without Task Force guidelines and letter grades for specific preventive, screening, and risk-management options many patients struggle to access services such as breast screening MRIs, mammograms before age 40, risk-reducing surgeries, earlier/more frequent colonoscopies, etc.

The current grade "B" recommendation acknowledges that genetic counseling and testing have clinical utility as preventive services; the value of genetic testing lies in an individual's ability to access interventions that will lower their risk or detect cancers at an earlier stage. Without a letter grade assigned to the interventions, these preventive services are not covered under the ACA, and may not be covered by health insurers.

Interventions reviewed and graded should include, but not be limited to:

- Breast Screening, such as MRI and Mammography. Research shows that increased breast screening with mammography and breast MRI leads to earlier detection of breast cancer in this cohort.[22,23,24]
- Prostate Cancer Screening. NCCN Guidelines currently recommend that men with BRCA2 mutations start prostate cancer screening at age 45 and men with BRCA1 mutations consider the same.
- Colonoscopy. NCCN guidelines recommend starting colonoscopies at age 20-25 (or 2-5 years prior to the earliest colon cancer in the family) for those with Lynch syndrome.
- Prophylactic Mastectomy. Prospective data shows that bilateral risk-reducing mastectomy lowers the risk for breast cancer in high-risk women.[25]
- Prophylactic Bilateral Salpingo-Oophorectomy and Hysterectomy. Data demonstrates that risk-reducing bilateral salpingo-oophorectomy lowers cancer-specific and overall mortality in BRCA mutation carriers.[26] NCCN guidelines recommend hysterectomy and bilateral salpingo-oophorectomy be offered to women who have completed child bearing and carry MLH1, MSH2, or MSH6 mutations.[27]
- Oral Contraceptives. Research shows that use of oral contraceptives is associated with a lower risk of ovarian and endometrial cancer.[28,29,30]
- Chemoprevention. Evidence supporting the role of chemoprevention agents in reducing the risk of breast cancer in high-risk women has been previously described.[31,32,33]

We support the USPSTF retaining parenthetical statements on the need for more research for risk-management interventions where evidence is lacking or inconclusive.

In summary, USPSTF guidelines play a critical role in guiding clinical decisions and access to care. The Task Force must expand its recommendations to encompass current science and medical practice to meet the needs of clinicians and patients. We welcome the opportunity to discuss the concerns and suggestions outlined herein.

Sincerely,

AliveAndKickin
Cancer*Care*
CCARE Lynch Syndrome
Don't be a Chump! Check for a Lump!
FORCE: Facing Our Risk of Cancer Empowered
HIS Breast Cancer
Living Beyond Breast Cancer
Malecare
National Ovarian Cancer Coalition
NothingPink
Ovarian Cancer Research Alliance
Research Advocacy Network
SHARE Cancer Support
Sharsheret
Triage Cancer
ZERO

CC: Senator Lisa Murkowski
Representative Jamie Raskin
Senator Chris Van Hollen Jr.
Representative Debbie Wasserman Schultz

[1] Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, et al. Clinical evaluation of a multiple gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol*. 2014;32:2001–9. 15.
[2] Tung N, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer*. 2015;121:25–33. 16.
[3] LaDuca H, Stuenkel AJ, Dolinsky JS, Keiles S, Tandy S, Pesaran T, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2000 patients. *Genet Med*. 2014;16:830–7. 17.
[4] Maxwell KN, Wubbenhorst B, D'Andrea K, Garman B, Long JM, Powers J, et al. Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer. *Genet Med*. 2015;17:630–8. 18.
[5] Lincoln SE, Kobayashi Y, Anderson MJ, Yang S, Desmond AJ, Mills MA, et al. A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. J Mol Diagn. 2015;17:533–44 *JAMA Oncol*. 2017 Dec 1;3(12):1647-1653. doi: 10.1001/jamaoncol.2017.1996.
[6] Walsh T, Mandell JB, Norquist BM3, Casadei S, Gulsuner S, Lee MK, King MC. Genetic Predisposition to Breast Cancer Due to Mutations Other Than BRCA1 and BRCA2 Founder Alleles Among Ashkenazi Jewish Women. *JAMA Oncology*. 2017 Dec 1;3(12):1647-1653. doi: 10.1001/jamaoncol.2017.1996.
[7] Reid R, DiGiovanni M, Bernhisel R, Brown K, Saam J, Lancaster J. Inherited germline mutations in men with prostate cancer. *Journal of Clinical Oncology* 2018 36:6_suppl, 357-357.
[8] Pritzlaff M, Summerour P, McFarland R, et al. Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results. *Breast Cancer Res Treat*. 2016;161(3):575-586.
[9] Brown K, Calip GS, Bernhisel R, Evans B, Rosenthal ET, Saam J, Lancaster J, Hoskins K. Multi-gene hereditary cancer testing among men with breast cancer. *Journal of Clinical Oncology* 2017 35:15_suppl, 1532-1532.
[10] NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. Version 1.2019. January 31, 2019.
[11] Ibrahim M, Yadav S, Ogunleye F, Zakalik D. Male BRCA mutation carriers: clinical characteristics and cancer spectrum. *BMC Cancer*. 2018;18(1):179. Published 2018 Feb 13. doi:10.1186/s12885-018-4098 -y
[12] Metcalfe KA, Lynch HT, Ghadirian P, Tung N, Olivotto IA, Foulkes WD , Warner E, Olopade O, Eisen A, Weber B, McLennan J, Sun P, Narod SA. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers, *Gynecologic Oncology*, Volume 96, Issue 1, January 2005, Pages 222-226, ISSN 0090-8258, 10.1016/j.ygyno.2004.09.039.
(http://www.sciencedirect.com/science/article/pii/S0090825804007772)
[13] Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, Sun P, Foulkes WD, Narod SA. Contralateral Breast Cancer in BRCA1 and BRCA2 Mutation Carriers, *JCO,* Volume 22, Number 12, June 2004, Pages 2328-2335.
(http://jco.ascopubs.org/content/22/12/2328.full.pdf)
[14] Rhiem K, Engel C, Graeser M, Zachariae S, Kast K, Kiechle M, Ditsch N, Janni W, Mundhenke C, Golatta M, Varga D, Preisler-Adams S, Heinrich T, Bick U, Gadzicki D, Briest S, Meindl A, Schmutzler RK. The risk of contralateral breast cancer in patients from*BRCA1/2* negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study, *Breast Cancer Research,* Volume 14, Number 6, December 2012. (http://breast-cancer-research.com/content/pdf/bcr3369.pdf)
[15] Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber J, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality, *JAMA,* Volume 304, Number 9, September 2010, Pages 967-975. (http://jama.jamanetwork.com/article.aspx?articleid=186510)

[16] Klitzman R, Chung W, Marder K, Shanmugham A, Chin LJ, Stark M, Leu CS, Appelbaum PS. Attitudes and practices among internists concerning genetic testing, *J Genet Couns*. Volume 22, Number 1, February 2013, Pages 90-100.

[17]Pal T, Cragun D, Lewis C, Doty A, Rodriguez M, Radford C, Thompson Z, Kim J, Vadaparampil ST. A Statewide Survey of Practitioners to Assess Knowledge and Clinical Practices Regarding Hereditary Breast and Ovarian Cancer. *Genetic Testing and Molecular Biomarkers*, Volume 17, Number 5, May 2013, Pages 367 - 375. (http://online.liebertpub.com/doi/abs/10.1089/gtmb.2012.0381)

[18] Commission on Cancer, Cancer Program Standards 2012: Ensuring Patient-Centered Care, American College of Surgeons, 2012, Page 68-69. (http://www.facs.org/cancer/coc/programstandards2012.pdf)

[19] Solomons NM, Lamb AE, Lucas FL, McDonald EF, Miesfeldt S. Examination of the Patient-Focused Impact of Cancer Telegenetics Among a Rural Population: Comparison with Traditional In-Person Services. Telemed J E Health. 2018 Feb;24(2):130-138. doi: 10.1089/tmj.2017.0073. Epub 2017 Jul 21.

[20] Vrečar I, Hristovski D, Peterlin B. Telegenetics: an Update on Availability and Use of Telemedicine in Clinical Genetics Service. *J Med Syst*. 2017 Feb;41(2):21. Epub 2016 Dec 17.

[21] Buchanan AH, Datta SK, Skinner CS, Hollowell GP, Beresford HF, Freeland T, Rogers B, Boling J, Marcom PK, Adams MB. Randomized Trial of Telegenetics vs. In-Person Cancer Genetic Counseling: Cost, Patient Satisfaction and Attendance. *J Genet Couns*. 2015 Dec;24(6):961-70. doi: 10.1007/s10897-015-9836-6. Epub 2015 Apr 3.

[22] Passaperuma K, Warner E, Causer PA, Hill KA, Messner S, Wong JW, Jong RA, Wright FC, Yaffe MJ, Ramsay EA, Balasingham S, Verity L, Eisen A, Curpen B, Shumak R, Plewes DB, S A Narod SA. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations, *British Journal of Cancer,* Volume 107, Number 1, January 2012, Pages 24-30. (http://www.nature.com/bjc/journal/v107/n1/full/bjc2012204a.html)

[23] Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, Foulkes WD, Ghadirian P, Lynch H, Couch F, Wong J, Wright F, Sun P, Narod SA. Prospective Study of Breast Cancer Incidence in Women With a BRCA1 or BRCA2 Mutation Under Surveillance With and Without Magnetic Resonance Imaging, *JCO*, Volume 29, Number 13, May 2011, Pages 1664-1669. (http://jco.ascopubs.org/content/early/2011/03/28/JCO.2009.27.0835.full.pdf)

[24] Sardanelli F, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, Vergnaghi D, Federico M, Cortesi L, Corcione S, Morassut S, Di Maggio C, Cilotti A, Martincich L, Calabrese M, Zuiani C, Preda L, Bonanni B, Carbonaro LA, Contegiacomo A, Panizza P, Di Cesare E, Savarese A, Crecco M, Turchetti D, Tonutti M, Belli P, Maschio AD, for the High Breast Cancer Risk Italian 1 (HIBCRIT-1) Study, Multicenter Surveillance of Women at High Genetic Breast Cancer Risk Using Mammography, Ultrasonography, and Contrast-Enhanced Magnetic Resonance Imaging (the High Breast Cancer Risk Italian 1 Study): Final Results, *Investigative Radiology,* Volume 46, Number 2, February 2011, Pages 94-105. (http://journals.lww.com/investigativeradiology/Abstract/2011/02000/Multicenter_Surveillance_of_Women_at_High_Genetic.3.aspx)

[25] Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van ’t Veer L, Garber JE, Evans GR, Narod SA , Isaacs C, Matloff E, Daly MB, Olopade OI, Weber BL. Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group, *JCO,* Volume 22, Number 6, March 2004, Pages 1055-1062. (http://jco.ascopubs.org/content/22/6/1055.full)

[26] Marchetti C, De Felice F, Palaia I, Perniola G, Musella A, Musio D, Muzii L, Tombolini V, Panici PB. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. *BMC Women's Health*201414:150. (https://doi.org/10.1186/s12905-014-0150-5)

[27] NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version I.2018. July 12, 2018.

[28] Whittemore AS, Balise RR, Pharoah PDP, DiCioccio RA. Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), Oakley-Girvan I, Ramus SJ, Daly M, Usinowicz MB, Garlinghouse-Jones K, Ponder BAJ, Buys S, Senie R, Andrulis I, John E, Hopper JL, Piver MS, Oral

contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations, *British Journal of Cancer*. Volume 91, Number 11, November 2004, Pages 1911-1915.

[29] Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. *JAMA Oncology* 2018; doi:10.1001/jamaoncol.2017.4942.

[30] Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. *Lancet Oncology*2015; 16(9):1061-1070.

[31] Wuttke M, Phillips KA. Clinical management of women at high risk of breast cancer. *Curr. Opin. Obstet. Gynecol*. 2015;27:6–13. doi: 10.1097/GCO.0000000000000140.

[32] Evans D.G., Howell S.J., Howell A. Personalized prevention in high risk individuals: Managing hormones and beyond. *Breast*. 2018;39:139–147. doi: 10.1016/j.breast.2018.03.009.

[33] Nazarali SA, Narod SA. Tamoxifen for women at high risk of breast cancer. Breast Cancer. 2014;6:29–36. doi: 10.2147/BCTT.S43763.