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Date of request: May 21, 2021
NCCN Guidelines Panel: Uterine Neoplasms

Dear NCCN panel members,

On behalf of Ambry Genetics, GeneDx, Inc., Illumina, Myriad Genetic Laboratories, Inc., and Quest Diagnostics laboratories, we respectfully request your review of the enclosed request for modifications within the High-Risk Assessment: Uterine Neoplasms, Version 1.2021 – October 20, 2020.

Specific Changes Requested:

On page UN-1, change the 5th initial evaluation bullet point from:

- Consider genetic evaluation (See ENDO-A)

to

- Recommend genetic evaluation of tumor and evaluate for inherited cancer risk (See ENDO-A)

Insert the following page(s) to ENDO-A between the current pages 3 and 4:

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR UTERINE NEOPLASMS

- It is estimated that 5 to 10% of uterine neoplasms occur in women with an inherited cancer syndrome. Identification of these cases is important to:
  - Inform screening and prevention strategies to address the risk for additional malignancies.
  - Guide surgical decisions (i.e., hysterectomy alone vs hysterectomy/bilateral salphingo-oophorectomy).
  - Provide opportunities for early detection and prevention of cancer in family members.
- Lynch syndrome is the most common hereditary cancer syndrome associated with uterine cancer risk. Universal testing of endometrial carcinomas for MMR proteins/MSI status is recommended to identify women with Lynch syndrome (see ENDO-A 2 of 5).

- Inherited conditions with established or emerging evidence for uterine cancer risk are listed in the table below. Genetic counseling and testing should be considered for any patient with a uterine neoplasm when and if the following are present:
  - There is a relative with a known pathogenic variant in a hereditary cancer gene.
  - Diagnosis occurred <50 yrs, especially in the absence of other known uterine cancer risk factors.
  - There is a family history of uterine neoplasms in close (first, second and/or third degree) female relatives.
  - Any of the clinical features listed in the table below are present in the patient and/or relatives. Detailed information regarding testing criteria, cancer risks, and management recommendations for each listed condition are available in the cited NCCN guidelines.

Syndrome	Gene(s)	Clinical Features	NCCN Guidelines
Lynch syndrome	*MLH1*/*MSH2*/*EPCAM* *MSH6*/*PMS2*	MMR deficient tumor (see Endo-A 2 0f 5). Lynch Syndrome testing can still be considered for patients whose tumors are not MMR deficient, or for whom tumor testing was not performed, if there is a significant history of colorectal cancer, ovarian cancer, gastric cancer, small bowel cancer or other features of Lynch Syndrome in the patient and/or family	Genetic/Familial High-risk Assessment: Colorectal
BRCA-related Breast/Ovarian Cancer syndrome (HBOC)	*BRCA1*/*BRCA2*	Serous endometrial cancer, breast cancer, ovarian cancer, pancreatic adenocarcinoma, prostate cancer	Genetic/Familial High-risk Assessment: Breast, Ovarian and Pancreatic
PTEN Hamartomatous Tumor syndrome (PHTS)/Cowden	*PTEN*	Breast cancer, thyroid cancer, colorectal cancer, uterine cancer, GI hamartomatas, macrocephaly, mucocutaneous lesions, Llermitte-Duclos disease	Genetic/Familial High-risk Assessment: Breast, Ovarian and Pancreatic
Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)	*FH*	Uterine leiomyosarcoma, uterine and skin leiomyomas, renal cancer	Kidney Cancer
Polymerase Proofreading-associated syndrome (PPAS)	*POLD1*/*POLE*	Colorectal cancer and/or polyposis	Genetic/Familial High-risk Assessment: Colorectal

Rationale:

The current NCCN guidelines for Uterine Neoplasms appropriately recommends assessment for the inherited cancer condition Lynch Syndrome through tumor testing for MMR proteins and MSI status in all women with endometrial carcinoma. However, there are no recommendations for assessment for other inherited cancer syndromes associated with the risk for uterine neoplasms. The proposed additions to the guidelines add information to facilitate the identification of women who may have one of these other conditions, which can provide an opportunity to inform management for the patient, as well as allow for early detection or prevention of cancer in relatives.

The association of PHTS/Cowden with uterine cancer is well-established, as is the risk for leiomyosarcoma/leiomyomatosis in HLRCC. A growing body of evidence indicates that women with mutations in *BRCA1* and possibly *BRCA2* have a slightly increased risk for endometrial carcinoma overall, but a significantly higher risk for the less common and more aggressive serous sub-type. There is an emerging body of evidence for endometrial cancer risk in women with pathogenic variants in the genes *POLD1* and *POLE*.

The proposed changes are consistent with the approach to genetic risk assessment in other NCCN treatment guidelines (i.e., see pages GAST-D in NCCN guidelines for Gastric Cancer, pages HRCC-1, 2, A, B, C, D in NCCN guidelines for Kidney Cancer).

We also request that the wording in the bullet point in the flow chart on page UN-1 be adjusted from “consider” to “recommend” for consistency with the wording on page ENDO-A-2.

Sincerely,

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Citations:

de Jonge MM, et al. Endometrial Cancer Risk in Women with Germline BRCA1 or BRCA2 Mutations: Multicenter Cohort Study. J Natl Cancer Inst. 2021 Epub ahead of print. PMID: 33710348.

Dörk T, et al. Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management. Cancers (Basel). 2020 12:2407. PMID: 32854222.

Hampel H, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015 17:70-87. PMID: 25394175.

Nahshon C, et al. Should the risk for uterine cancer influence decision making for prophylactic hysterectomy in BRCA1/2 mutated patients- a systematic review and meta-analysis. Gynecol Oncol. 2021 160:755-762. PMID: 33309051.

Shu CA, et al. Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations. JAMA Oncol. 2016 2:1434-1440. PMID: 27367496.

Spurdle AB, et al. Endometrial cancer gene panels: clinical diagnostic vs research germline DNA testing. Mod Pathol. 2017 30:1048-1068. PMID: 28452373.

Cited NCCN Clinical Practice Guidelines in Oncology

Gastric Cancer, Version 1.2021, February 9, 2021

Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic, Version 1.2021, September 8, 2020

Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2020, July 21, 2020

Kidney Cancer, Version 2.2021, February 3, 2021