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Position Paper for Healthcare Providers

GENETIC COUNSELING AND TESTING FOR HEREDITARY CANCER PREDISPOSITION SYNDROMES

Summary

Identifying individuals and families with hereditary cancer predisposition syndromes is a process and hereditary cancer genetic testing should be provided in the context of pre- and post- test genetic counseling either in person or by telehealth. As described in published consensus guidelines and position statements, this process should include: obtaining a detailed 3-4 generation pedigree; cancer risk assessment; patient education regarding genetics, cancer risks, genetic testing (including cost), and medical management options; and psychosocial assessment and counseling. Pre-test informed consent must be provided and documented in writing in compliance with Michigan state law. When testing is performed, the genetic counseling process also includes results interpretation, personalized management recommendations, and a discussion about notifying relatives of their risks and the availability of testing when a familial mutation is detected (cascade testing). Genetic counseling and testing should be performed by those with sufficient professional expertise in recognizing the entire scope of hereditary cancer syndromes (Appendix 1, Tables 1 & 2).

Background

Overall, approximately 5-10% of cancers are the result of a hereditary cancer predisposition syndrome. Individuals with an inherited predisposition are at increased risk to develop certain types of cancer compared to the general population. Inherited predisposition is often associated with an earlier age of onset than usual and an increased risk of multifocal or multiple primary tumors. Most hereditary cancer syndromes are inherited in an autosomal dominant fashion with incomplete penetrance meaning that relatives are also at substantial risk. Evidence-based guidelines supporting cancer genetic risk assessment and testing in two of the more common hereditary cancer predisposition syndromes, hereditary breast and ovarian cancer syndrome and Lynch syndrome, are available.[1,2] Expert-based national guidelines for risk assessment and testing for these and other hereditary cancer predisposition syndromes have also been published. [3,4] Identifying individuals at risk can lead to increased surveillance, and in some cases, options for surgical and/or pharmaceutical risk reduction. These strategies are aimed at decreasing morbidity and mortality.

Although genetic testing for hereditary cancer predisposition syndromes usually involves just a specimen collection (e.g., peripheral blood, saliva, or cheek swab sample), the issues surrounding genetic testing for inherited susceptibility are much more complex. There is a wide array of potential risks, limitations, and benefits, which include but are not limited to medical, legal, economic, and psychosocial factors. Written informed consent is mandated by Michigan state law[5] prior to presymptomatic or predictive genetic testing. In addition to state law, numerous medical societies/organizations have concluded that any genetic testing for hereditary cancer syndromes should be performed in the context of informed consent, and be provided by a professional with expertise in cancer genetics[3--14].

The American Society of Clinical Oncology (ASCO) stipulates that a health care professional with cancer genetics expertise should be competent in recognizing key features of hereditary cancer predisposition syndromes, should be knowledgeable about cancer genetics practice recommendations, risk assessment models, syndrome-specific screening and prevention guidelines, and should be able to engage patients in a thorough discussion of the benefits, risks, and limits of genetic testing in light of their individual situations[12]. The American College of Surgeons Commission on Cancer (CoC) and the National Accreditation Program for Breast Centers (NAPBC) have issued standards for provision of cancer risk assessment, genetic counseling and genetic testing services, including specific definitions of qualified genetic professionals that are based on genetic education, credentials and/or experience (Appendix 2).[13, 14] Considering the advent of multigene testing panels and the complexities of selecting the appropriate panel and interpreting the clinical significance of results, the National Comprehensive Cancer Network further recommends that such tests be ordered in consultation with a cancer genetics professional[4].

Genetic Testing is a Process

Many national societies/organizations have stated that identifying and testing individuals for hereditary cancer syndromes is a process. [3-14] Based on these established guidelines, the following should be required as part of this process to standardize care in the state of Michigan:

1) Michigan health care professionals should examine their own competence to provide cancer genetic risk assessment, and adequate, appropriate, and comprehensive pre- and post- test genetic counseling. Resources such as ASCO's recommended competencies[12] and those developed by the National Coalition for Health Professional Education in Genetics[15] (Appendix 3) can serve as guides for self-evaluation. If a healthcare professional deems that hereditary cancer predisposition syndromes are beyond his/her expertise, referral of identified patients to a qualified genetics expert is recommended.

2) The process of cancer genetic risk assessment and counseling should include the following:

a. obtaining a 3-4 generation genetic pedigree

b. conducting a risk assessment which includes a differential diagnosis of which hereditary cancer syndrome(s) is the most likely diagnosis

c. developing surveillance and management recommendations as indicated based on the patient's personal and family medical histories and/or genetic test results

d. providing patient education about risks, genetic testing (including costs) and medical management and pre-test informed consent for patients considering genetic testing.

e. interpreting results for those who have genetic testing

f. discussing with patients how to inform other relatives about potential risks

3) Written informed consent is required by law in the State of Michigan[5]. Pre-test informed consent requires fully informing the patient of the risks, benefits, and limitations of a genetic test. Several

groups, including ASCO[11] and the National Society of Genetic Counselors[9], have described the elements of pre-test informed consent specific to cancer genetics. These include the purpose of testing, who to test, alternatives to testing, possible test results, confidentiality, and protections and limits of genetic nondiscrimination legislation. Cost can have an impact on a person's decision to have genetic testing and as such should be discussed as well.

4) The ethical and legal principles of autonomy, privacy, equity and confidentiality should be applied to each patient and family seeking genetic testing.

5) The psychosocial aspects of cancer genetic risk assessment and testing should be addressed during the pre-test and post-test counseling session(s).

The above process has typically been provided in person. But there is growing evidence for and acceptance of the use of telegenetics (videoconferencing) and telephone genetic counseling for pre- and/or post-test counseling as a means for increasing access to qualified genetics professionals. [16-18]

Conclusions

The Michigan Cancer Genetics Alliance (MCGA) concludes that any hereditary cancer predisposition syndrome testing should be offered to patients by following the current standards of care established by professional societies/organization guidelines. [3-17] All of these guidelines explicitly state that genetic testing is a process during which patients undergo pre- and post-test counseling with a qualified genetics expert or person with sufficient competence in cancer genetics. Centers performing genetic testing should provide patients with risk assessment, education to facilitate informed consent for genetic testing, test interpretation, psychological support, and options for further medical care tailored to their circumstances. There should also be a discussion of the importance of informing other relatives of cancer risks and how this might be achieved.

References:

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Appendix 1

Table 1: Hereditary Cancer Syndromes with an Increased Risk of Common Cancers*

Syndrome	Features/Associated Cancers	Gene(s) Causing Syndrome
Hereditary breast cancer; Hereditary Breast and Ovarian Cancer (HBOC) Syndrome	Early-onset breast cancer, male breast cancer, ovarian, prostate cancer, pancreatic cancer, melanoma (cutaneous and ocular)	*BRCA1*, *BRCA2*, probably other gene(s)
Lynch Syndrome (HNPCC=Hereditary Nonpolyposis Colorectal Cancer)	Early-onset colorectal cancer, early-onset endometrium cancer, ovarian, stomach, small bowel, pancreas, ureter, renal pelvis cancers.	DNA mismatch repair genes- *MLH1*, *MSH2*, *MSH6, PMS2 and EPCAM*
Cowden Syndrome	Breast, thyroid, endometrial cancer, colon, and renal cancer, and benign hamartomatous lesions of skin, oral mucosa and intestine, and benign breast and thyroid disease	*PTEN*
Familial Adenomatous Polyposis (FAP); Attenuated FAP (AFAP)	Adenomatous polyposis (>100 colonic polyps), colorectal cancer, papillary thyroid cancer, gastric cancer, periampullary cancer, adrenal cancer, hepatoblastoma, and extracolonic manifestations; Less than 100 colonic polyps, later-onset colorectal cancer (>40). May be increased risk of gastric and duodenal adenomas and/or cancer	*APC*
MUTYH-Associated Polyposis	Adenomatous polyposis with features ranging from AFAP to classic FAP. Recessive inheritance.	*MYH*
Juvenile Polyposis Syndrome	Hamartomatous polyps, increased risk colorectal,	*SMAD4*, *BMPR1A*

	pancreatic, gastric, and duodenal cancer, along with an increased risk for HHT in SMAD4 mutation carriers	
Familial Pancreatic Cancer	Pancreatic cancer. Can be an isolated finding or associated with features of other syndromes.	*BRCA2 (HBOC), STK11/LKB1 (Peutz Jegher), mismatch repair genes (Lynch), APC (FAP), CDKN2A (FAMMM), PALB2, ATM*
Hereditary Prostate Cancer	Prostate cancer, possible increased risk of other cancers	*HPC1/RNASEL, HPC2/ELAC2, HPC9/HoxB13, others*
Li-Fraumeni Syndrome	Early-onset breast, soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, leukemia, lung,brain tumors	*TP53, CHEK2*
Peutz-Jeghers Syndrome	Breast cancer, benign ovarian tumors, testicular tumors, pancreatic cancer, polyps of the ureter, bladder, GI tract (hamartomatous polyps), renal pelvis, bronchus, nasal passage. Melanin spots on lips, buccal mucosa and digits	*STK11/LKB1*
Hereditary Diffuse Gastric Cancer	Diffuse gastric cancer, lobular breast cancer, signet cell colorectal cancer	*CDH1*
Basal cell nevus syndrome; Gorlin syndrome	Basal cell nevi, characteristic facies, palmar and plantar pits, odontogenic keratocysts, rib abnormalities, increased risk of basal cell carcinoma, ovarian cancer, ovarian fibromata	*PTCH*
Familial Atypical Mole Malignant Melanoma syndrome (FAMMM)/ Hereditary dysplastic nevus syndrome	Multiple primary melanomas, dysplastic nevi, pancreatic cancer	*CDKN2A (p16 / p14), CDK4*

Adapted from the American College of Medical Genetics and National Society of Genetic Counselors practice guideline on referral indications for cancer predisposition assessment. [17]

Lists of syndromes to consider based on tumor type is available in the source document and is an excellent resource for providers.

Table 2: Rare Hereditary Cancer Syndromes*

Birt-Hogg-Dube syndrome	Renal tumors (benign and malignant), lung cysts, skin lesions, spontaneous pneumothorax	*FLCN*
Carney Complex	Primary pigmented nodular adrenocortical disease, lentigenes, myxomas of the heart, skin and breast, large cell calcifying Sertoli cell tumors, psammomatous melanotic schwannoma, breast ductal adenomas	*PRKAR1A*
Familial gastrointestinal stromal tumor (GIST)	Gastrointestinal stromal tumors	*KIT, PDGFRA, SDHB, SDHC*
Hereditary Leiomyomatosis and Renal Cell Cancer	Renal cancer, cutaneous and uterine leiomyomas	*FH*
Hereditary Mixed Polyposis Syndrome	Multiple polyps of mixed histology, increased risk of colorectal cancer	*BMPR1A, GREM1*
Hereditary Retinoblastoma	Retinoblastomas, often bilateral or multifocal, other malignancies like osteosarcomas, especially in response to radiation exposure	*RB1*
Melanoma-Astrocytoma Syndrome	Melanoma, astrocytoma (I am wondering if we should move this and combine with FAMM)	*CDKN2A,p14ARF*
Multiple Endocrine Neoplasia type I; MENI	Zollinger-Ellison syndrome. Parathyroid tumors, hyperparathyroidism, pituitary tumors, pancreatic islet tumors	*MEN1*
Multiple Endocrine Neoplasia type II; MEN2	MEN2A: Medullary thyroid carcinoma (MTC), pheochromocytoma, parathyroid tumors/parathyroid hyperplasia. MEN2B: earlier onset of MTC and pheochromocytomas as well as mucosal neuromas and a	*RET*

	Marfanoid habitus	
Pheochromocytoma	Adrenal medullary tumors, isolated pheochromocytomas and/or paragangliomas	*RET/VHL/SDHD, SDHB*
Nonchromaffin Paraganglioma	Paragangliomas, chemodectomas, carotid body tumors, glomus jugular tumors, pheochromocytoma	*PGL1/SDHD PGL2, PGL3/SDHC*
Rhabdoid Tumor Predisposition Syndromes Types I and II	Rhabdoid tumors	*SMARCCB1, SMARCA4*
Serrated Polyposis Syndrome	Serrated polyps, increased risk colorectal cancer	*Unknown genes*
Tuberous Sclerosis Complex	Brain lesions (e.g., subependymal nodules, cortical harmartomas), cardiac rhabdomyomas, renal angiomyolipomas or cysts, skin manifestations,	*TSC1, TSC2*
von Hippel-Lindau Syndrome	Hemangioblastomas of the brain, spine, and retina, pheochromocytoma, renal cell carcinoma, epididymal cystadenoma, endolymphatic sac tumors	*VHL*
Wilms tumor	Nephroblastoma; can also be associated with WAGR, Beckwith-Wiedmann and other abnormal urogenital development syndromes	*WT1*

Adapted from the American College of Medical Genetics and National Society of Genetic Counselors practice guideline on referral indications for cancer predisposition assessment. [19]

Lists of syndromes to consider based on tumor type is available in the source document and is an excellent resource for providers.

Appendix 2

From the Commission Commission on Cancer. Cancer Program Standards. Standard 2.3: Risk Assessment and Genetic Counseling, and National Accreditation Program for Breast Centers. NAPBC Standards Manual. Standard 2.16.[13, 14]

Qualified Genetic Professionals to Provide Genetic Counseling include:
• American Board of Genetic Counseling board-certified/eligible genetic counselor
• American College of Medical Genetics physician board certified in medical genetics
• Advanced Practice Oncology Nurse prepared at graduate level with specialized education in cancer genetics and hereditary cancer syndromes (certification by the Oncology Nursing Certification Corporation as AOCNP or AOCNS preferred)
• Genetics Clinical Nurse or an Advanced Practice Nurse in Genetics, credentialed through the Genetics Nursing Credentialing Commission
• Board-certified physician with expertise and experience in cancer genetics (defined as providing cancer risk assessment on a regular basis) employing a model that includes both pre-test and post-test counseling

Appendix 3

From the National Coalition for Health Professional Education in Genetics (NCHPEG)
Core Competencies in Genetics – September 2007 [15]

BASELINE COMPETENCIES: ***At a minimum, each health-care professional should be able to:***
a. Examine one's competence of practice on a regular basis, identifying areas of strength and areas where professional development related to genetics and genomics would be beneficial.
b. Understand that health-related genetic information can have important social and psychological implications for individuals and families.
c. Know how and when to make a referral to a genetics professional.

SKILLS: ***All health professionals should be able to:***
2.1 Gather genetic family history information, including at minimum a three-generation history.
2.2 Identify and refer clients who might benefit from genetic services or from consultation with other professionals for management of issues related to a genetic diagnosis.
2.3 Explain effectively the reasons for and benefits of genetic services.
2.4 Use information technology to obtain credible, current information about genetics.
2.5 Assure that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question