MCGA Position Paper for Healthcare Providers

GENETIC COUNSELING AND TESTING FOR HEREDITARY CANCER PREDISPOSITION SYNDROMES

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Summary

Identifying individuals and families with hereditary cancer predisposition syndromes through genetic counseling can guide clinical management and ultimately save lives. As described in published consensus guidelines and position statements, genetic counseling should include obtaining a detailed 3-4 generation medical family history (genetic pedigree), the patient's medical history including any pertinent somatic or germline genetic test results, cancer risk assessment, patient education regarding genetics, cancer risks, medical management options, 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 for the familial mutation (cascade screening). 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 support cancer genetic risk assessment and testing in two of the more common hereditary cancer predisposition syndromes, hereditary breast ovarian cancer syndrome (HBOC) and Lynch syndrome.[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. In individuals with cancer, identifying a pathogenic or likely pathogenic variant (mutation) in a cancer predisposition gene may guide treatment decisions as well.[4]

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, and psychosocial factors. Written informed consent is mandated by Michigan state law[5] prior to pre-symptomatic 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 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 widespread availability 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.[3,4]

Genetic Testing

Many national societies/organizations have stated that identifying and testing individuals for hereditary cancer syndromes is a multi-step process.[3-14] Based on these established guidelines, the following should be included 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] 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 family medical history (genetic pedigree) and the patient's medical history including any pertinent somatic genetic testing/tumor profiling results

b. conducting a risk assessment which includes generating a list of potential differential diagnoses of hereditary cancer syndrome(s)

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 and medical management and pre-test informed consent for patients considering genetic testing

e. interpreting results for those who have genetic testing and discussing implications, including reproductive risks

f. discussing with patients how to inform their 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.

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. However, there is growing acceptance of the use of telegenetics (video conferencing) and telephone genetic counseling for pre- and/or post-test counseling as a means for increasing access to qualified genetics professionals.[16]

Other Uses of Genetic/Genomic Testing in Oncology

The above guidance applies to genetic testing for inherited predisposition (germline genetic testing). Genomic testing on tumor tissue (somatic tumor profiling), which involves identifying tumor-specific mutations (pathogenic and/or likely pathogenic variants) in genes that are contributing to an individual's cancer, is increasingly being used to guide therapy. Methods to identify circulating tumor DNA via liquid biopsies to identify early stage or pre-clinical cancers are also in development. The informed consent requirements are different for these types of genomic applications. Clinicians should keep abreast of the evidence base supporting the use of such applications and provide informed consent that adequately delineates the known benefits, limitations, and harms.

Somatic tumor profiling will sometimes identify mutations (pathogenic and/or likely pathogenic variants) in genes associated with inherited cancer syndromes. When this occurs, it is important to assess whether the pathogenic variant in the cancer predisposition gene is only present in the tumor or if it is also present in the patient's germline where it could have implications for additional cancer risks and for familial inheritance. In such cases, patients should be evaluated using the processes described in the previous sections of this document.

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. All 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, psychosocial 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/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, pancreatic, gastric, and duodenal cancer, along with an increased risk for HHT in SMAD4 mutation carriers	*SMAD4, BMPR1A*
Familial Pancreatic Cancer	Pancreatic cancer. Can be an isolated finding or associated with features of other syndromes.	*BRCA1/2 (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	*BRCA1/2, 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. [16]

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 Marfanoid habitus	*RET*
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. [17]

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

Appendix 2

Adapted from the Commission on Cancer, Cancer Program Standards. Standard 4.4: Genetic Counseling and Risk Assessment, 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 (ABGC) or American Board of Medical Genetics and Genomics (ABMGG) board-certified/eligible genetic counselor or clinical geneticist
• Advanced Practice Oncology Nurse (APON) or physician assistant prepared at graduate level with specialized education in cancer genetics and hereditary cancer syndromes. Certification as an Advanced Oncology Certified Nurse Practitioner (AOCNP) or equivalent certification from the Oncology Nursing Certification Corporation (ONCC) is preferred.
• Genetics Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG), or a nurse who is Advanced Genetics Nursing-Board Certified (AGN-BC) credentialed through the American Nurses Credential Center.
• A registered nurse with specialized education in cancer genetics and hereditary cancer predisposition syndromes. Specialized education is defined as education that results in certification and leads to ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes.
• Board-certified physician with expertise in cancer genetics which is defined as providing cancer risk assessment on a regular basis and taking part in continuing medical education in cancer genetics and hereditary syndromes.