Rethinking the Family Cancer History Questionnaire in the Era of Next Generation Sequencing Panels - Are We Asking the Right Questions?

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Differential Diagnosis and Genetic Testing Strategy

Background: In primary care and medical/surgical oncology settings, the Family History Questionnaire is often used as a screening tool in identifying patients who may benefit from a genetics evaluation. Studies have shown however, that inherited cancer syndromes remain underdiagnosed, largely because clinicians often limit their investigation to immediate family members and do not document cancers in the extended family.[1] Recent studies have also demonstrated that oncologists lack confidence in their ability to interpret risk from family history, particularly in cases where the patient presents with a rare cancer or has an unusual pattern of cancer in his or her family. Moreover, many providers focus only on collecting family history data for cancers associated with the more common conditions, such as hereditary breast and ovarian cancer syndrome (HBOC), and do not recognize overlapping features of other syndromes.[2,3]

To address the problems clinicians face in interpreting complex family histories, we designed a cancer history questionnaire with embedded clinical decision support that assists clinicians with creating a differential diagnosis.

Specifically, we propose a two-step questionnaire (a simple, open-ended form for patients and a follow-up form for the clinician) that is designed to guide the patient and clinician to investigate family history by systematically reviewing major organ systems/tumor sites of affected relatives. This "check-list" format leads to a preliminary differential diagnosis and an associated condition/gene list. This approach allows for consideration of multiple conditions, and may be a time-saving way to collect more detailed family history data.

Methods: The PubMed database was searched for publications between 2007 to August 2014 for information regarding the following topics: 1) barriers to family history collection; 2) inaccurate or incomplete documentation of family history; 3) problems with interpretation of family history; 4) low rates of referral for eligible patients; 5) misidentified cancer syndromes and incorrect ordering of a genetic test; 6) professional society practice guidelines for referral to genetic counseling/testing; and 7) professional education issues regarding the collection of cancer histories. The search was purposely broad and designed to capture information that described barriers to the accurate documentation of cancer family histories.

Information was also obtained by doing a web search for family history questionnaires and reviewing multiple cancer history forms used in oncology and primary care settings.

References:
[1]Cragun and Pal (2013), Identification, Evaluation, and Treatment of Patients with Hereditary Cancer Risk within the United States. *ISRN Oncology*, Volume 2013, Article ID 260847.

[2]Lu et al. (2014), American Society of Clinical Oncology Expert Statement: Collection and Use of a Cancer Family History for Oncology Providers. *Journal of Clinical Oncology*, (March 10, 2014), pp. 833-840.

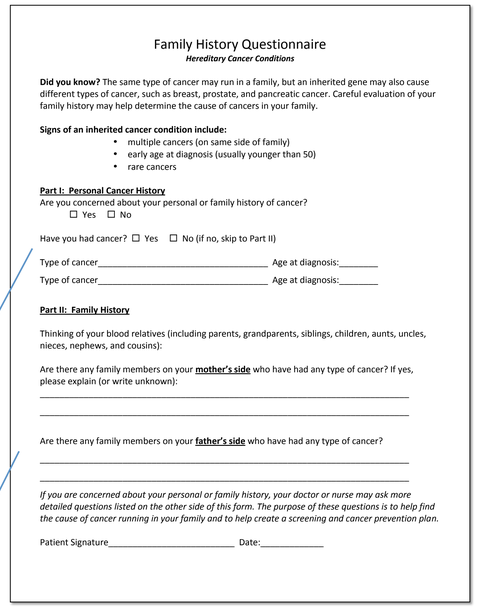
[3]Wood et al. (2014), Quality of Cancer Family History and Referral for Genetic Counseling and Testing Among Oncology Practices: A Pilot Test of Quality Measures As Part of the American Society of Clinical Oncology Practice Initiative. *Journal of Clinical Oncology*, (March 10, 2014), pp. 824-829.

Step 1: Patient-Facing Cancer History Form

Background: This form is intended for unaffected individuals with perceived or recognized familial cancer risk, and for affected individuals who have a diagnosis of cancer.
It differs from other forms in that the first section is designed to educate the patient regarding the "red flags" of inherited cancer syndromes.

A direct question about whether the patient is concerned about personal or family cancer history may prompt the clinician to ask about affected family members.

An open-ended question about family cancer history is the starting point of the documentation process. Follow-up to these answers occurs in Step 2.



Family History Questionnaire
Hereditary Cancer Conditions

Did you know? The same type of cancer may run in a family, but an inherited gene may also cause different types of cancer, such as breast, prostate, and pancreatic cancer. Careful evaluation of your family history may help determine the cause of cancers in your family.

Signs of an inherited cancer condition include:
- multiple cancers (on same side of family)
- early age at diagnosis (usually younger than 50)
- rare cancers

Part I: Personal Cancer History
Are you concerned about your personal or family history of cancer?
☐ Yes ☐ No

Have you had cancer? ☐ Yes ☐ No (if no, skip to Part II)

Type of cancer_____ Age at diagnosis:_____
Type of cancer_____ Age at diagnosis:_____

Part II: Family History

Thinking of your blood relatives (including parents, grandparents, siblings, children, aunts, uncles, nieces, nephews, and cousins):

Are there any family members on your **mother's side** who have had any type of cancer? If yes, please explain (or write unknown):
_____
_____

Are there any family members on your **father's side** who have had any type of cancer?
_____
_____

If you are concerned about your personal or family history, your doctor or nurse may ask more detailed questions listed on the other side of this form. The purpose of these questions is to help find the cause of cancer running in your family and to help create a screening and cancer prevention plan.

Patient Signature_____ Date:_____

Future Direction

The primary aim of this project was to design a family history questionnaire with embedded clinical decision support. The next step is to evaluate this tool in a variety of clinical settings and determine whether it helps the practitioner to:

- Make a preliminary assessment of a patient's inherited predisposition for cancer
- Prompt further investigation in complex cases
- Generate a differential and genetic testing strategy in high-risk patients

Other potential areas of research include an assessment of how effectively and efficiently the redesigned family history questionnaire helps clinicians capture and interpret cancer history compared to general health history forms. Additionally, the authors would like to assess whether targeted questions result in the clinician recognizing rare syndromes based on the "red flags" identified during the patient interview. Finally, we plan to evaluate the ease of use and the need for specialized training.

Step 2: To Be Filled Out By Clinician

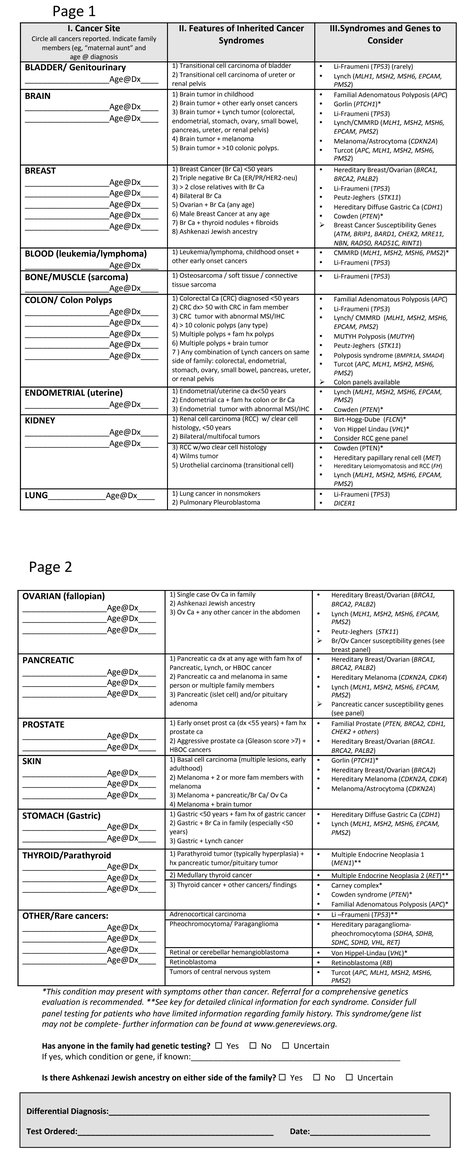
How to use the clinician form: Starting with the cancers reported by the patient, the clinician circles the tumor site(s) in column I and documents the relationship of the family member to the proband as well as ages of onset.

Next, the clinician reviews the features of inherited cancer syndromes listed in column II. Unusual combinations of tumor types or histological features are listed as a prompt to ask further questions.

Column III contains a list of possible syndromes as well as the genes most commonly associated with the condition. The syndromes are in alphabetical order so that a clinician can quickly review whether the same syndrome shows up in different rows (i.e., common to different types of cancers).

Creating a broad differential: Column III also indicates whether a panel is a consideration for a specific cancer type.

Referral to Genetics: Many of these rarer cancer syndromes require a comprehensive genetics evaluation to establish a diagnosis. A key containing detailed information about each syndrome as well as criteria for testing is available for reference.



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I. Cancer Site Circle all cancers reported. Indicate family members (eg, "maternal aunt" and age @ diagnosis	II. Features of Inherited Cancer Syndromes	III.Syndromes and Genes to Consider
BLADDER/ Genitourinary _____Age@Dx____	1) Transitional cell carcinoma of bladder 2) Transitional cell carcinoma of ureter or renal pelvis	• Li-Fraumeni (*TP53*) (rarely) • Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*)
BRAIN _____Age@Dx____ _____Age@Dx____	1) Brain tumor in childhood 2) Brain tumor + other early onset cancers 3) Brain tumor + Lynch tumor (colorectal, endometrial, stomach, ovary, small bowel, pancreas, ureter, or renal pelvis) 4) Brain tumor + melanoma 5) Brain tumor + >10 colonic polyps.	• Familial Adenomatous Polyposis (*APC*) • Gorlin (*PTCH1*)* • Li-Fraumeni (*TP53*) • Lynch/CMMRD (*MLH1, MSH2, MSH6, EPCAM, PMS2*) • Peutz-Jeghers (*STK11*) • Melanoma/Astrocytoma (*CDKN2A*) • Turcot (*APC, MLH1, MSH2, MSH6, PMS2*)
BREAST _____Age@Dx____ _____Age@Dx____ _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Breast Cancer (Br Ca) <50 years 2) Triple negative Br Ca (ER/PR/HER2-neu) 3) > 2 close relatives with Br Ca 4) Bilateral Br Ca 5) Ovarian + Br Ca (any age) 6) Male Breast Cancer at any age 7) Br Ca + thyroid nodules + fibroids 8) Ashkenazi Jewish ancestry	• Hereditary Breast/Ovarian (*BRCA1, BRCA2, PALB2*) • Li-Fraumeni (*TP53*) • Peutz-Jeghers (*STK11*) • Hereditary Diffuse Gastric Ca (*CDH1*) • Cowden (*PTEN*)* ➢ Breast Cancer Susceptibility Genes (*ATM, BRIP1, BARD1, CHEK2, MRE11, NBN, RAD50, RAD51C, RINT1*)
BLOOD (leukemia/lymphoma) _____Age@Dx____	1) Leukemia/lymphoma, childhood onset + other early onset cancers	• CMMRD (*MLH1, MSH2, MSH6, PMS2*)* • Li-Fraumeni (*TP53*)
BONE/MUSCLE (sarcoma) _____Age@Dx____	1) Osteosarcoma / soft tissue / connective tissue sarcoma	• Li-Fraumeni (*TP53*)
COLON/ Colon Polyps _____Age@Dx____ _____Age@Dx____ _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Colorectal Ca (CRC) diagnosed <50 years 2) CRC dx< 50 with CRC in fam member 3) CRC tumor with abnormal MSI/IHC 4) > 10 colonic polyps (any type) 5) Multiple polyps + fam hx polyps 6) Multiple polyps + brain tumor 7) Any combination of Lynch cancers on same side of family: colorectal, endometrial, stomach, ovary, small bowel, pancreas, ureter, or renal pelvis	• Familial Adenomatous Polyposis (*APC*) • Li-Fraumeni (*TP53*) • Lynch/ CMMRD (*MLH1, MSH2, MSH6, EPCAM, PMS2*) • MUTYH Polyposis (*MUTYH*) • Peutz-Jeghers (*STK11*) • Polyposis syndrome (*BMPR1A, SMAD4*) • Turcot (*APC, MLH1, MSH2, MSH6, PMS2*) ➢ Colon panels available
ENDOMETRIAL (uterine) _____Age@Dx____	1) Endometrial/uterine ca dx<50 years 2) Endometrial ca + fam hx colon or Br Ca 3) Endometrial tumor with abnormal MSI/IHC	• Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*) • Cowden (*PTEN*)*
KIDNEY _____Age@Dx____ _____Age@Dx____	1) Renal cell carcinoma (RCC) w/ clear cell histology, <50 years 2) Bilateral/multifocal tumors	• Birt-Hogg-Dube (*FLCN*)* • Von Hippel Lindau (*VHL*)* • Consider RCC gene panel
	3) RCC w/wo clear cell histology 4) Wilms tumor 5) Urothelial carcinoma (transitional cell)	• Cowden (*PTEN*)* • Hereditary papillary renal cell (*MET*) • Hereditary leiomyomatosis and RCC (*FH*) • Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*)
LUNG_____Age@Dx____	1) Lung cancer in nonsmokers 2) Pulmonary Pleuroblastoma	• Li-Fraumeni (*TP53*) • *DICER1*

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OVARIAN (fallopian) _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Single case Ov Ca in family 2) Ashkenazi Jewish ancestry 3) Ov Ca + any other cancer in the abdomen	• Hereditary Breast/Ovarian (*BRCA1, BRCA2, PALB2*) • Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*) • Peutz-Jeghers (*STK11*) ➢ Br/Ov Cancer susceptibility genes (see breast panel)
PANCREATIC _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Pancreatic ca dx at any age with fam hx of Pancreatic, Lynch, or HBOC cancer 2) Pancreatic ca and melanoma in same person or multiple family members 3) Pancreatic (islet cell) and/or pituitary adenoma	• Hereditary Breast/Ovarian (*BRCA1, BRCA2, PALB2*) • Hereditary Melanoma (*CDKN2A, CDK4*) • Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*) ➢ Pancreatic cancer susceptibility genes (see panel)
PROSTATE _____Age@Dx____ _____Age@Dx____	1) Early onset prost ca (dx <55 years) + fam hx prostate ca 2) Aggressive prostate ca (Gleason score >7) + HBOC cancers	• Familial Prostate (*PTEN, BRCA2, CDH1, CHEK2* + others) • Hereditary Breast/Ovarian (*BRCA1, BRCA2, PALB2*)
SKIN _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Basal cell carcinoma (multiple lesions, early adulthood) 2) Melanoma + 2 or more fam members with melanoma 3) Melanoma + pancreatic/Br Ca/ Ov Ca 4) Melanoma + brain tumor	• Gorlin (*PTCH1*)* • Hereditary Breast/Ovarian (*BRCA2*) • Hereditary Melanoma (*CDKN2A, CDK4*) • Melanoma/Astrocytoma (*CDKN2A*)
STOMACH (Gastric) _____Age@Dx____ _____Age@Dx____	1) Gastric <50 years + fam hx of gastric cancer 2) Gastric + Br Ca in family (especially <50 years) 3) Gastric + Lynch cancer	• Hereditary Diffuse Gastric Ca (*CDH1*) • Lynch (*MLH1, MSH2, MSH6, EPCAM, PMS2*)
THYROID/Parathyroid _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	1) Parathyroid tumor (typically hyperplasia) + hx pancreatic tumor/pituitary tumor	• Multiple Endocrine Neoplasia 1 (*MEN1*)**
	2) Medullary thyroid cancer	• Multiple Endocrine Neoplasia 2 (*RET*)**
	3) Thyroid cancer + other cancers/ findings	• Carney complex* • Cowden syndrome (*PTEN*)* • Familial Adenomatous Polyposis (*APC*)*
OTHER/Rare cancers: _____Age@Dx____ _____Age@Dx____ _____Age@Dx____ _____Age@Dx____	Adrenocortical carcinoma	• Li –Fraumeni (*TP53*)**
	Pheochromocytoma/ Paraganglioma	• Hereditary paraganglioma-pheochromocytoma (*SDHA, SDHB, SDHC, SDHD, VHL, RET*)
	Retinal or cerebellar hemangioblastoma	• Von Hippel-Lindau (*VHL*)*
	Retinoblastoma	• Retinoblastoma (*RB*)
	Tumors of central nervous system	• Turcot (*APC, MLH1, MSH2, MSH6, PMS2*)

**This condition may present with symptoms other than cancer. Referral for a comprehensive genetics evaluation is recommended. **See key for detailed clinical information for each syndrome. Consider full panel testing for patients who have limited information regarding family history. This syndrome/gene list may not be complete- further information can be found at www.genereviews.org.*

Has anyone in the family had genetic testing? ☐ Yes ☐ No ☐ Uncertain
If yes, which condition or gene, if known:_____

Is there Ashkenazi Jewish ancestry on either side of the family? ☐ Yes ☐ No ☐ Uncertain

Differential Diagnosis:_____

Test Ordered:_____ **Date:**_____

Sources for Questionnaire:
Hodgson, Foulkes, Eng, and Maher, *A Practical Guide to Human Cancer Genetics 4th ed.*, Springer-Verlag London 2014. Print.

Pazdur et al, *Cancer Management: A Multidisciplinary Approach, 12th ed.*, Oncology Group of CMPMedica, Print. Also see www.cancernetwork.com.

Website: www.GeneReviews.org