Published in final edited form as:

Cancer Invest. 2019 ; 37(1): 39–45. doi:10.1080/07357907.2018.1564926.

Practice Implications of Expanded Genetic Testing in Oncology

Diane M. Korngiebel,

University of Washington, Biomedical Informatics and Medical Education

Jennifer M. Zech,

University of Washington, Medicine¹

Amelia Chappelle,

University of Washington, Medicine

Wylie Burke,

University of Washington, Bioethics and Humanities

Jan D. Carline,

University of Washington, Biomedical Informatics and Medical Education

Thomas H. Gallagher, and

University of Washington, Medicine and Bioethics and Humanities

Stephanie M. Fullerton

University of Washington, Bioethics and Humanities

Abstract

Genetic test use in oncology is growing, yet providers' experiences with evolving testing norms and their implications for patient care remain under-explored. In interviews with oncologists and cancer genetics professionals, 22 key informants described the increasing importance of germline results for therapeutic decision-making, preference for ordering tests directly rather than referring, and rapid adoption of cancer gene panels for testing. Implications for informed consent, result interpretation, and patient management were identified. These results suggest concerns raised by the transition of genetic test delivery from cancer genetics professionals to oncologists that must be addressed in practice guidelines and provider training.

Keywords

Cancer; inherited risk; genetic testing; clinical practice; genomic medicine

Corresponding author Stephanie M. Fullerton, Box 357120, Department of Bioethics and Humanities, University of Washington School of Medicine, Seattle, WA 98195, Telephone: (206) 616-1864, FAX: (206) 685-7515, smfltrn@uw.edu.

¹Currently at ICAP at Columbia University, Mailman School of Public Health

DECLARATION OF INTEREST STATEMENT

The authors declare no conflicts of interest.

INTRODUCTION

Genetic testing plays an increasingly prominent role in oncology practice. Genomic profiling of somatic mutations in tumors is recommended by the National Comprehensive Cancer Network (NCCN) for some cancers to inform choice of molecularly targeted therapeutic agents such as cetuximab (1) or imatinib (2). Information about inherited (germline or constitutive) risk, as opposed to somatic variation, is also now regarded as relevant to choice of therapeutic agent (e.g., olaparib) and surgical approach (3). Changes in the salience of germline genetic risk information for cancer-related patient care is particularly noteworthy, given traditional responsibilities and existing clinical practice guidelines which recommend referral and genetic counseling for most patients suspected of a familial/hereditary cancer predisposition (4, 5). Yet providers' experiences with evolving genetic testing norms and their implications for patient care remain under-explored. Emerging evidence, for example, suggests that patients are often tested without seeing a genetic counselor and that subsequent patient management may be inappropriate (6). Less is known about the practice realities driving provider choices in this regard or their perceived implications for test ordering and interpretation, counseling and referral, and patient management.

Here, we report the results of a qualitative investigation of the views of medical oncologists and clinical genetics professionals who care for patients in a variety of settings, including large academically affiliated cancer centers and smaller community cancer clinics. Our key informants described widespread use of testing for genetic risk in the context of patient care and numerous challenges posed by rapidly changing genetic testing practices.

MATERIALS AND METHODS

Recruitment

Thirty-one oncologists and cancer genetics professionals were recruited from 12 different academic and community institutions in six states; 22 agreed to participate, for a response rate of 71% (Table 1). Purposive and snowball sampling were used to ensure a relevant sample that would encompass a range of viewpoints and settings. Interviews were conducted between November 2014 and September 2015.

Data collection

Interviews were conducted by telephone using a semi-structured guide designed to elicit participants' narrative accounts of cancer-related genetic testing experiences (7). Questions covered test ordering to interpretation and follow-up (Table 2). Because of the narrative focus of the interviews, participants were emailed 1-2 days before their interviews and asked to be prepared to discuss a typical cancer-related genetic testing experience and a more "atypical" example where the process did not go as well as they thought it should have. Interviews lasted 30-60 minutes and were conducted by one of four experienced interviewers, audio-recorded, transcribed, and de-identified. This study was approved by the University of Washington Institutional Review Board, and all participants provided informed consent.

Data analysis

Atlas.ti 7 (8) was used for coding and content analysis (9, 10). The codebook was based on categories drawn from interview question domains with iterative revisions made during data analysis to accommodate novel concepts and themes. Three coders analyzed transcripts and two experienced coders reviewed all coding; discordant codes were resolved via consensus. Two coders then performed thematic analysis across coding categories to capture relationships between and across codes, and a third coder reviewed their analysis. All coders reviewed themes for final consensus and results reporting.

RESULTS

Our key informants described three main ways in which the uses of testing for inherited risk in oncology are currently evolving in their practice settings, including the increasing importance of genetic results for therapeutic decision-making, the preference for ordering genetic tests directly rather than referring patients to genetic specialists, and the widespread adoption of cancer gene panels for testing. Respondents described the implications of these changes for informed consent, result interpretation, and patient management.

Genetic testing for therapeutic decision-making

Most of our respondents noted the central role that genetic testing (both somatic and germline) now plays in surgical decision-making and choice of chemotherapeutic regimen. For newly diagnosed patients, oncologists will often recommend testing for inherited risk to inform decision-making about a preferred treatment plan.

“A decent number [of cancer patients]...are trying to decide about their surgery type, whether it be a breast conserving therapy,...lumpectomy or...bilateral mastectomy in the event that they tested positive. So their decisions are pending the results of the genetic testing...We’re now getting more ovarian cancer referrals as well to decide whether or not they’d be eligible for PARP inhibitors...” (P10, genetic counselor)

In other cases, variants with relevance to cancer predisposition are identified subsequent to a genetic investigation of the tumor, either through the order of paired tumor/germline genetic testing or, in many cases, incidentally. Patients with suspect risk variants are then referred for confirmation and counseling.

“We have physicians who...find a somatic mutation in a tumor that could be a germline mutation. And recently this played out in a case of a pancreas patient who has Jewish ancestry and they found a BRCA2 mutation in the tumor, which is a founder mutation in the Jewish population and we did see him for genetics and he did carry a germline mutation.” (P2, genetic counselor)

The oncologists we interviewed recognized the potential for incidental identification of information about inherited risk but, at least for some, that was regarded as less important than the advantages of obtaining comprehensive information without additional invasive procedures.

“I often let them know that I’m doing screening just on their tumor specimen. Usually their first question is, ‘Do we need to do more biopsies? Do they have other procedures?’ And so the answer is no, and so then they’re generally okay with whatever additional testing I want to order... We talk about this being other testing that could help understand their risk for cancer or understand how they might do after being diagnosed with cancer, and then we just discuss results as they come in.” (P7, GI oncologist)

Implications for patient informed consent—When patients are referred to genetics professionals for testing, there is an opportunity to be counseled about the possibility of learning that they have an inherited cancer predisposition and, if they prefer, to decline testing. When tumor testing is done, however, patients may not realize the potential for information about inherited risk to be generated.

“You get diagnosed with cancer, you go to the doctor, they draw 10 tubes of blood...you’re fearing for your life and they tell you... ‘We’re going to do some tests about your cancer.’ And if one of those is a genetic test, which is not all that uncommon, or it gets lumped in with other blood tests, then when the results come back, patients can be blindsided basically.” (P16, genetic counselor)

Several of the oncologists we spoke to suggested that this prospect is an unavoidable by-product of current testing practices, arguing that post-test genetics referral and counseling will likely become the norm.

“Then the tumor identifies the problem and you get referred...It just has to be part of the reflex testing. We don’t ask a patient whether they want their receptors to be checked on their breast cancer. It’s determined that it’s part of their care and that’s what has to be done...I think people are just going to do the genetics and ask questions later.” (P18, medical geneticist)

Genetic test ordering managed directly by oncologists

Many of our respondents, both cancer genetics professionals and oncologists, acknowledged that oncologists often order genetic testing for inherited risk directly rather than refer patients to genetic services (as is recommended by current testing guidelines). In straightforward cases, oncologist-led counseling and genetic testing was felt to be both clinically appropriate and cost-effective.

“We have obstetrical doctors and gynecologists and oncologists who order these tests. They’re perfectly capable of doing the simple kind of genetic counseling for some of the simpler testing.” (P20, other geneticist)

While not ideal in more complex cases, informants also acknowledged barriers to accessing routine genetic services for their patients, including genetic workforce shortages, as well as billing limitations that discourage institutions from hiring more genetic counselors.

“Genetic counselors provide an essential service in educating patients and providers, but they cannot bill at all. So the institution is very reluctant to increase genetic counselor FTE because they see it as a loss leader.” (P15, GI oncologist)

One solution to addressing such access barriers, and (for some of those with whom we spoke) a prerequisite for more routine test ordering by oncologists, would be having a genetics specialist readily available for *ad hoc* consultation and advice.

“I don’t necessarily think that it’s a bad thing for non-genetics providers to order testing if they have someone they work closely with who they can ask questions to, who does have genetics training, because I think that it would be difficult at best for patients to be able to get genetic testing if everybody had to see a genetic counselor.” (P2, genetic counselor)

Implications for interpretation of complex results—The perceived downside to more widespread genetic test ordering by oncologists are the difficulties posed by the return of unanticipated or otherwise hard-to-interpret results.

“I’m a community physician...I’ve got a medical license, I can order any blood test I want to, and I may or may not be well-trained in the precise implications of that test. Heck, I may not even be able to interpret the report because what used to be about a half page report has now grown to about a two or three page report and there’s more BRCA’s that you have to know the meaning of.” (P11, breast oncologist)

Some respondents also suggested that oncologists might be challenged by genetic risk results outside the range of typical patients.

“For the most part, a clinician...will be able to look in the NCCN guidelines...They won’t mess it up too much. It’s extremes of youth or age [i.e., patients who present in a manner inconsistent with clinical practice guidelines] that challenge them. It’s ambiguous findings that challenge them...They [i.e., clinicians outside of highly experienced centers without genetics expertise] try to apply the same kind of management criteria...when it’s completely inappropriate.” (P18, medical geneticist)

These concerns, as well as barriers to accessing genetic services, led several to suggest that an emerging practice challenge for oncology is determining when it is appropriate to consult and/or refer.

“I think we need to be utilizing genetics experts appropriately, by making sure that we’re handling the more complicated stuff and that we are developing more collaborative relationships with people to handle the more straightforward stuff.” (P14, genetic counselor)

Multigene test panels have replaced single gene tests

Many respondents noted that multigene test panels have largely replaced single gene testing for genetic predisposition in oncology because they provide more comprehensive information more quickly than other tests.

“... that [it] is basically becoming faster, easier, cheaper to do panel testing and other tests that aren’t as well proven, which is great because it generates a lot of

information that we can learn things from and potentially either better understand our patients or better understand how we can help them.” (P7, GI oncologist)

In some cases, the advantages of panel tests relative to simpler forms of genetic testing become apparent only in hindsight.

“[A] patient was tested for BRCA1 and 2 mutations because there was breast cancer in the family, and she was negative...Two years later she developed a sarcoma and she had a p53 mutation...If you had tested her today with the testing panels, a p53 mutation would have come up. Now does that mean we would have known that she would have developed a uterine sarcoma? No. But at least...nobody would have been so unprepared when it happened.” (P1, breast oncologist)

In addition to providing more comprehensive information, an additional perceived advantage of multigene tests is that they simplify decision-making about test ordering. However, as one medical geneticist noted, this can also complicate result interpretation.

“We have these huge multi-gene test panels...So we don’t have to be smart about guessing [where to start testing], is one way to put it. We don’t have to be astute clinicians and look for subtle signs...because there’s so many genes on the panel. The downside to it is that...if you don’t have that high [pretest probability] going in, then it’s more difficult to discriminate among false positives [i.e., variants of uncertain significance].” (P6, medical geneticist)

Implications for patient management—Several respondents commented on the fact that multigene test panels, insofar as they include many genes that have not been as well characterized as *BRCA1/2*, often generate Variants of Uncertain Significance (VUS) and that this complicates patient management.

“I think that uncertainty is more difficult to manage than it is being told specifically you have a deleterious mutation...I mean, there are so many VUS in panels now...I don’t believe that it’s ethical as a clinician to have data about a patient and...not share it...I think our duty is to disclose this information. The problem is, as soon as we disclose this information, we’ve created a new problem.” (P21, breast oncologist)

In addition to increased uncertainty associated with panel test results, the clinical significance of genetic findings can change with variant reclassification, requiring reassessment of treatment or surveillance goals.

“So...three or six months later I get a phone call from the genetic counselor who says, ‘Gee, I’m sorry, it’s been reclassified.’...And now I have to suddenly disengage...[an intensified screening protocol] because what was thought to be an actionable or pathogenic mutation is now reclassified as a variant of unknown significance.” (P12, medical oncologist)

DISCUSSION

Our interviews with oncologists and cancer genetics professionals highlight practice trends and emerging issues in the use of genetic testing in cancer care. Hereditary cancer risk is regarded as important for therapeutic decision-making and sought out ahead of finalizing the treatment plan (3), or encountered either as an incidental by-product of tumor profiling (11, 12) or in the context of paired germline-tumor testing (13). To enable timely acquisition of treatment-relevant results, oncologists often order tests for inherited risk themselves rather than referring patients to genetic specialists (14). Cancer gene panels increase diagnostic yield (15) and simplify test ordering by providing a comprehensive, rapid assessment of key candidate genes, and are becoming the preferred mode of testing (16). Hence, genetic risk information, once the exclusive purview of cancer genetics professionals, is increasingly a central practice focus and responsibility of oncologists.

These evolving genetic testing norms entail significant new practice challenges. Respondents described patients “blindsided” by news of a cancer genetic predisposition identified subsequent to analysis of their tumor and, despite the implied need for adequate and consistent pre-test counseling, several respondents questioned the feasibility of obtaining adequate informed consent for genetic testing among the barrage of tests that accompany an initial cancer diagnosis. Timely referral to genetic services is not possible in many cases due to a shortage of available genetic counselors, so oncologists are left to assess patients for testing and order tests themselves. Multigene cancer test panels, while simpler to order, generate more complex and uncertain information than single gene tests (17, 18), complicating subsequent interpretation and patient management. A key concern for our respondents was how best to incorporate genetic consultation when the resources typically recommended for pre- and post-genetic counseling and interpretation support (19) are not readily available.

Current clinical practice guidelines for the assessment and management of genetic and/or familial risk of breast and ovarian cancer, as well as colorectal cancer, do not fully address these on-the-ground realities or their potential implications. The NCCN guidelines for high-risk assessment of breast and/or ovarian cancer (5), for example, acknowledge that the recent introduction of multigene testing “has rapidly altered the clinical approach to testing at-risk patients and their families” and provide additional information about some of the moderate penetrance genes that appear on such panels. However, they preface that information with the disclaimer that “the inclusion of a gene on this table below does not imply endorsement either for or against multi-gene testing for moderate-penetrance genes” and recommend that multigene testing be “ideally offered in the context of professional genetic expertise”(5). NCCN recommendations for multigene testing in the context of genetic/familial high-risk assessment for colorectal cancer (4) are similarly caveated. Neither account for the fact that the supply of genetic counselors is not projected to meet demand until between 2024 and 2030 (20).

In addition, NCCN breast and ovarian cancer guidelines now include “*BRCA1/2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis” as a new criterion for BRCA testing, acknowledging the potential for incidental

detection of inherited risk variants (21). But there is no discussion of the complexities posed by the detection of a likely inherited risk variant *prior to* the recommended risk assessment and counseling by a cancer genetics professional, nor is any distinction drawn between women who may meet criteria due to a suggestive family history versus an incidentally discovered risk variant. While innovative solutions, such as telemedicine approaches to virtual consultation with genetic counselors (22), training oncology nurses in genetic services delivery (23), and related collaboration of genetic counselors with non-specialists, (24), have been proposed to alleviate the growing demand for genetic risk assessment and counseling, without changes to consent practices in the context of tumor profiling, unexpected and potentially unwelcome identification of inherited risk is likely to persist as a central practice concern.

Our study is subject to several limitations. First, although we recruited providers from several different institutions across the United States, our sample size was modest and our observations may therefore not be wholly representative of current practice. In particular, we spoke to only a small number of community-based oncologists, so our results may not capture the full range of experiences in those settings. Second, our study was qualitative and focused on the self-reports of providers, many at the front lines of cancer genetics services; although our interviews identified the types of challenges that may be in play, they provide no estimate of the scale of these challenges in current oncology practice. These findings informed the development of a subsequent national survey of oncologists, designed to address this limitation (manuscript in preparation).

Our results highlight both the central importance of genetic testing to oncology practice and concerns raised by the transition of responsibility for the management of germline genetic information from cancer genetics professionals to oncologists. Addressing the practice challenges identified in this study will require concerted attention to practice guidelines and provider training, as well as the identification of new approaches to obtaining genetics consultation in the absence of patient referral.

ACKNOWLEDGEMENTS

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the authors' affiliated institutions or organizations.

The authors acknowledge the contributions of Anne Acosta, Valora Consulting, for her work on data analysis.

Special thanks to study participants.

This work was supported by the National Human Genome Research Institute under Grants R21 HG007578 (Fullerton) and K01 HG008180 (Korngiebel).

REFERENCES

1. Bertotti A, Papp E, Jones S, Adleff V, Anagnostou V, Lupo B, et al. The genomic landscape of response to EGFR blockade in colorectal cancer. *Nature*. 2015;526(7572):263–7. [PubMed: 26416732]
2. Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2016;101(4):407–16. [PubMed: 27033238]

3. Bayraktar S, Arun B. BRCA mutation genetic testing implications in the United States. *Breast (Edinburgh, Scotland)*. 2017;31:224–32.
4. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. 10 10, 2017, Version 3.2017.
5. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. National Comprehensive Cancer Network; 10 3, 2017, Version 1.2018.
6. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(20): 2232–9. [PubMed: 28402748]
7. Sankar P, Jones NL. Semi-structured Interviews in Bioethics Research In: Jacoby L, Siminoff LA, editors. *Empirical Methods for Bioethics: A Primer*. 11 San Diego, CA: Elsevier Ltd.; 2008 p. 117–36.
8. ATLAS.ti 7. Berlin: Scientific Software Development; 2012.
9. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qualitative health research*. 2005;15(9):1277–88. [PubMed: 16204405]
10. Patton MQ. *Qualitative Evaluation and Research Methods*. Thousand Oaks, CA: Sage Publications, Inc.; 2002.
11. Meric-Bernstam F, Brusco L, Daniels M, Wathoo C, Bailey AM, Strong L, et al. Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2016;27(5): 795–800. [PubMed: 26787237]
12. Bombard Y, Robson M, Offit K. Revealing the incidentalome when targeting the tumor genome. *Jama*. 2013;310(8):795–6. [PubMed: 23982363]
13. Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. *Jama*. 2017;318(9):825–35. [PubMed: 28873162]
14. Gray SW, Kim B, Sholl L, Cronin A, Parikh AR, Klabunde CN, et al. Medical Oncologists' Experiences in Using Genomic Testing for Lung and Colorectal Cancer Care. *Journal of oncology practice*. 2017;13(3):e185–e96. [PubMed: 28095174]
15. Rosenthal ET, Bernhisel R, Brown K, Kidd J, Manley S. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. *Cancer genetics*. 2017;218–219:58–68.
16. Graffeo R, Livraghi L, Pagani O, Goldhirsch A, Partridge AH, Garber JE. Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. *Breast cancer research and treatment*. 2016;160(3):393–410. [PubMed: 27734215]
17. Cragun D, Radford C, Dolinsky JS, Caldwell M, Chao E, Pal T. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory. *Clinical genetics*. 2014;86(6):510–20. [PubMed: 24506336]
18. Shirts BH, Casadei S, Jacobson AL, Lee MK, Gulsuner S, Bennett RL, et al. Improving performance of multigene panels for genomic analysis of cancer predisposition. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2016;18(10):974–81. [PubMed: 26845104]
19. Van Allen EM. The Potential and Challenges of Expanded Germline Testing in Clinical Oncology. *Jama*. 2017;318(9):801–3. [PubMed: 28873143]
20. Hoskovec JM, Bennett RL, Carey ME, DaVanzo JE, Dougherty M, Hahn SE, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. *Journal of genetic counseling*. 2017.
21. Hofstatter E, Mehra K, Yushak M, Pusztai L. Tumor profiling and the incidentalome: patient decisions and risks. *Future oncology (London, England)*. 2015;11(24):3299–305.
22. Weissman SM, Zellmer K, Gill N, Wham D. Implementing a Virtual Health Telemedicine Program in a Community Setting. *Journal of genetic counseling*. 2017.

23. Kelly PA. Next Generation Sequencing and Multi-Gene Panel Testing: Implications for the Oncology Nurse. *Seminars in oncology nursing*. 2017;33(2):208–18. [PubMed: 28390840]
24. Goedde LN, Stupiansky NW, Lah M, Quaid KA, Cohen S. Cancer Genetic Counselors' Current Practices and Attitudes Related to the Use of Tumor Profiling. *Journal of genetic counseling*. 2017.

TABLE 1.

Participant Demographics (n=22)

Gender		
Male	8	
Female	14	
Medical specialty		
Oncologists	8	
Breast oncologists	3	
GI oncologists	2	
Medical oncologists	2	
Hematologist oncologist	1	
Genetic specialists	14	
Genetic counselors	8	
Medical geneticists	3	
Genetic pathologists	2	
Other	1	
Practice setting		
Academic-based	15	
Community-based	7	
Region		
Midwest	4	
Northeast	3	
South	2	
West	13	

Table 2.

Sample Interview Questions and Domains

Domains	Sample questions and protocol guidance
Clinical background and Experience	Can you tell me about your role at [INSTITUTION]? What are your primary responsibilities?
	In what ways does your practice involve genetic testing of cancer patients?
Typical genetic testing experience	Describe what is – for you – a typical and recent example of cancer-related genetic testing. Please begin your description from the point that the patient (OR, if more relevant, the patient's sample or clinical data) arrives in your care.
	Where is the patient in his/her cancer treatment plan, i.e. recently diagnosed, under-going treatment, or perhaps asymptomatic (i.e. referred due to suspected family history)?
	After the first encounter with the patient (or data) what are the next steps in the process? What is your role?
	Do you interact with other healthcare providers in the course of this process? [wherever possible, gather information on whether/how team interactions change as testing process moves from order > interpretation > follow-up]
	IMPORTANT: If the respondent has only referenced genetic testing related to cancer susceptibility (sometimes called "germline" testing) ask about their experience, if any, with tumor genotyping (sometimes called "somatic" testing) OR vice-versa.
Atypical Genetic Testing Experience	IMPORTANT: If the respondent has difficulty coming up with a specific case, first try: Any example that you could give me about what happens when your otherwise "well-oiled machine" breaks down in some way would be incredibly helpful for us in our work. Otherwise, return to the prior "typical case" and ask about places in that narrative where there appeared – at least theoretically – to be potential for miscommunication/misunderstandings among providers.
	What specifically was atypical/challenging about this particular testing experience? (reference the prior account, where possible)
	At what point was a problem identified?
	IMPORTANT: Why do you think that this happened?
	IMPORTANT: What could have made this instance go more smoothly?