5-2016

Exploring the Role of Genetic Counselors in Tumor Genomic Sequencing : A Survey of Genetic Counselors

Michelle Weinberg
Sarah Lawrence College, mweinberg1@gm.slc.edu

Exploring the Role of Genetic Counselors in Tumor Genomic Sequencing

: A Survey of Genetic Counselors

May 2016

Michelle Weinberg

Joan H. Marks Graduate Program in Human Genetics

Sarah Lawrence College

Submitted in partial completion of the Master of Science Degree at Sarah Lawrence College, May 2016

ABSTRACT

In the emerging era of genomics-driven medicine, tumor genomic profiling in particular has begun to revolutionize the field of oncology. As the integration of such technologies evolves and affects the management and treatment of cancer, questions arise with regards to the changing roles of healthcare professionals involved in cancer care. One hundred and twenty-eight members of the National Society of Genetic Counselors (NSGC) responded to a survey to assess the current roles of genetic counselors in oncology and the perceived roles that genetic counselors will have in the clinical use of tumor genomic profiling. With regards to current roles in cancer care, the majority reported that they provide genetics cancer-related expertise to other medical professionals (85.0%, n=85). With respect to perceived roles in the clinical use of tumor genomic sequencing, most responders (80.0%, n=80) indicated that they feel there is a role for genetic counselors. The majority of responders identified 5 roles that genetic counselors would be equipped to play in regard to tumor genomic analysis. The largest number, 91 (97.9%) report identifying and discussing incidental germline findings uncovered by testing, followed by serving as a resources for physicians who may not be comfortable with genomic testing 76.3% (n=71), educating medical students, residents and fellows about tumor genomic sequencing 69.9% (n=65), educating medical professionals on issues around informed consent 67.7% (n=63), and post-test counseling of patients to help interpret tumor sequencing results 65.6% (n=61). The duty of pre-test counseling for patients to help explain tumor sequence testing and informed consent is reported as a significant role by smaller numbers of responders 44.1% (n=41). When prompted to choose the most significant, the majority (56.7%, n=51) report identifying and discussing

incidental germline findings as the primary role. Responses show that participants foresee multiple duties that genetic counselors are adept to handle in the context of tumor genomic analysis, with information involving germline findings specified as the most important and relevant to the training of genetic counselors.

KEY WORDS:

Next-generation sequencing, Tumor genomic profiling, Genetic counselors, Germline findings

INTRODUCTION

Considerable attention has been given to the field of oncology in the emerging era of genomics-driven medicine. Since cancer is a disease of the genome, oncology is at the frontline of the personalized healthcare movement (Garraway, Verweij, & Ballman, 2013). President Obama has made it a priority to fund scientific research during his administration, and his Precision Medicine Initiative (PMI) promotes the shift in medical practice from a "one-size-fits-all" strategy to a more tailored approach, taking into account each individual's genetic makeup (or the genetic profile of an individual's tumor) (White House, Office of the Press Secretary, January 30, 2015).

Although cancer largely arises as a result of the accumulation of genomic damage that one acquires throughout life, each cancer has its own genetic makeup. Accordingly, genome-profiling technologies play an integral role in the emerging field of "precision oncology" as described by editors Garraway, Verweijj and Ballman (2013), in the *Journal of Oncology Special Series: The Era of Genomics-Driven Cancer Medicine*. The

aggregation of this genomic data holds great value for oncologists, ultimately working to improve clinical oncology disease management (Garraway et al., 2013).

Although such advances have the potential to narrow the gap between the knowledge gained from genomic data and its practical use in the clinic, Van Allen, Wagle and Levy (2013) acknowledge that there is an increasing disparity between the levels of complexity that such technologies are beginning to attain and the analytical capacity of oncology professionals. Guan et al. (2012) affirm that it will require ongoing dedication to the application of NGS technology in oncology to enable the success of genome-driven cancer care.

BACKGROUND

Next generation sequencing technology in oncology: the process

Contributors to the *American Medical Association: Journal of Ethics*, Erin W. Hofstatter, MD and Allen E. Bale, MD (2013) have described the process of sequencing technology in the field of oncology as "conceptually logical and simple." They explain that a patient's tumor is first sequenced and compared to a standard control genome so that all of the genetic differences can be detected. Hofstatter and Bale point out that since all humans have benign genetic variants that differ from any control, the patient's constitutional genome is also sequenced to distinguish between germline mutations of the individual's constitutional genome and somatic mutations of the tumor. They note that while somatic mutations are potentially pathogenic, germline mutations are seldom related to cancer (but should be established nonetheless). Mutation databases of known cancer genomes are then accessed to determine whether the somatic alterations identified

are actionable genetic variations, meaning that they are treatable with emerging anticancer drugs (Hofstatter & Bale, 2013).

Case studies have illustrated some exceptional clinical outcomes for cancer patients as a result of tumor sequencing that altered treatment. Chung et al. (2014) detected an EML4-ALK rearrangement in a 53-year-old nonsmoker with poorly differentiated malignant neoplasm in the lung and right upper extremity using the fully informative genomic panel (FoundationOne) developed by Foundation Medicine Inc. Based on this mutation, crizotinib was administered, and the "patient responded with rapid and significant volume decreases of the masses from both sites" (Chung et al., 2014). In another case, Palma et al. (2015) identified an FGFR3 activating mutation via tumor sequencing in a patient with urothelial carcinoma. As a result, the individual responded exceptionally to targeted drug, pazopanib (Palma et al., 2015).

Advances in genomic sequencing in oncology

Massively parallel ("next-generation") sequencing (MPS) has become more widely implemented due to significant benefits over its predecessors. Laura MacConaill, PhD, (2013) of Dana-Farber Cancer Institute describes the advantages as follows: The launch of MPS dramatically reduced cost of sequencing a single patient from US$70 million by the Sanger method in 2007 to under US$5,000 in 2013. Simultaneously, tremendous improvement in both sensitivity and scalability has allowed for more comprehensive studies with initial reports of 100-fold improved throughput over Sanger sequencing (2013). Additionally, MPS is able to identify various types of aberrations in

the cancer genome such as "base mutations, indels, copy number alterations, and rearrangements" (MacConaill, 2013).

Consequently, there has been growing use of next-generation sequencing (NGS) in a variety of academic and commercial settings. For example, Memorial Sloan Kettering Cancer Center (MSKCC), a cancer treatment center in New York, uses next-generation sequencing in their latest diagnostic test known as Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT™). MSKCC announced, "…MSK-IMPACT™ gives doctors an unparalleled amount of information about individual people's cancers to guide their treatment" (Kiesler, 2014). The technology has also spawned the creation of specialized sequencing technology companies (e.g., Illumina, Life Technologies) as well as companies that specialize in applying sequencing technology to cancer care (e.g., Foundation Medicine Inc., Caris Life Sciences) (Carlson, 2012).

Clinical utility of genomic sequencing in oncology

Researchers have demonstrated clinical utility of NGS for targeted tumor profiling in expanded studies. Lipson et al. (2012) analyzed 24 non-small cell lung cancer (NSCLC) and 40 colorectal cancer (CRC) tissue specimens to detect alterations linked to available clinical treatments or targeted clinical trials of new therapies. They identified actionable mutations in 72% of the NSCLCs and 52.2% of CRCs. A separate retrospective investigation performed by Johnson et al. (2014) detected potentially actionable genetic mutations (defined as associated with susceptibility to an approved treatment or experimental therapy) in multiple cancer types (breast carcinoma, head and

neck cancers and melanoma). The majority of their patients (83% of 103) had additional treatment options based on targeted NGS tumor sequencing. At a median follow-up of 4.1 months, 21% of patients received genotype-directed therapies and 61% of patients were in clinical trials (Johnson et al., 2014). Since the small number of geographic locations limited the number of patients in trials, Johnson et al. (2014) expected that patient enrollment would increase as studies expand nationally. In another study, Andre et al. (2012) recruited metastatic breast cancer patients to identify therapeutic targets based on genomic alterations. They anticipated that up to 30% of patients would receive genome-directed therapy, concluding that personalized medicine is feasible for metastatic breast cancer.

There are experts in the field that view such findings differently. Sparano, Ostrer and Kenny (2013) categorize the data obtained by Andre et al. (2012), as exemplifying the inadequacy of NGS in oncology, with fewer than 30% of screened breast cancer patients expected to receive targeted therapy according to initial preliminary reports (Sparano, Ostrer, & Kenny, 2013). Hofstatter and Bale (2013) also cite this analysis in "The Promise and Pitfalls of Genomics-Driven Cancer Medicine," questioning the cost-benefit ratio of NGS in clinical oncology since most patients are not receiving clinically actionable results. Garraway (2013) makes a similar argument in his article titled "Genomics-Driven Oncology: Framework for an Emerging Paradigm," explaining that despite advances in sequencing technologies, the practical clinical impact of NGS "still pushes the limits of logistical feasibility, remains costly, and may exceed the present developmental therapeutic need by a large margin" (Garraway, 2013).

In the same article, however, Garraway ultimately asserts that a significant

number of cancers harbor actionable variants for which targeted therapies may exist. He argues that a genomics-driven approach is unlikely to benefit all cancers, but "the proportion with plausibly actionable genetic mutations is sufficiently high as to provide credence to the overarching hypothesis that tumor genetic information may ultimately provide widespread clinical benefit" (Garraway, 2013). Furthermore, Johnson et al. (2014) argue that even "negative" sequencing results can have a clinical impact, steering patients toward appropriate non-targeted clinical studies (i.e., immunotherapy, chemotherapy) or possibly no additional treatments (Johnson et al., 2014). They also claim that novel genomic findings can precipitate additional pre-clinical studies and future clinical trials(Johnson et al., 2014).

Although there are conflicting opinions about the degree of utility of NGS in oncology today, many experts foresee its potential to revolutionize clinical practice in the future. Meldrum, Doyle and Tothill (2011) suggest that discoveries made in refining our ability to study and understand the human genome, and in turn, the cancer genome will be responsible for bridging to a new era of personalized cancer medicine. They argue that not only will sequencing technologies improve our understanding of the pathogenesis of cancer, they will impact detection, management and treatment of disease. In acknowledging how sequencing technologies have already greatly advanced cancer research efforts, MacConaill (2013) claims that they are "poised to similarly transform the translational oncology landscape."

Challenges of applying tumor-sequencing technology to oncology

Most experts agree that for sequencing technologies to revolutionize oncology,

there are multiple obstacles that need to be addressed. Oncology professionals identify the intrinsic biological nature of cancer tissue as a challenge for evaluating a specimen by any method because malignancies exhibit multiple degrees of histological heterogeneity (e.g., varying ratios of healthy cells to cancer cells, different histologic tumor grades within a single specimen) (Hofstatter & Bale, 2013; Kamalakaran et al., 2013). Kamalakaran et al. (2013) identify crucial steps that must be taken to examine and quantify the tissue sample, along with appropriate checkpoints to ensure integrity and quality of data.

Genomic heterogeneity also interferes with the ability to accurately interpret genomic data. Hofstatter and Bale (2013) describe some of the complexities involved. They begin by explaining that cancers, being exceedingly unstable by nature, accumulate a great number of genetic alterations. As a result, detecting actionable or "driver" mutations proves difficult because most of the alterations are "passenger" mutations, or not pathogenic. In addition, they mention the potential for variants of uncertain significance(Hofstatter & Bale, 2013). Even when found in genes that are known to cause cancer, the impact of genetic changes is often unknown or yet to be established. Guan et al. (2012) also note that few detected alterations are pathogenic, and describe the interpretation and clinical translation of genetic variants as a bottleneck for routine use of NGS in clinical oncology. Furthermore, Guan et al. (2012) explain that the driver and passenger mutations can change as a tumor develops, so even if a targeted therapy proves successful, it may suddenly stop working if the tumor develops resistance. In the book *Cancer Genomics: From Bench to Personalized Medicine,* Dellaire, Berman and Acreci (2014) acknowledge this challenge and state the potential need to re-evaluate cancer care

moving forward, possibly coming full circle by ordering additional genomic sequencing of serial tumor biopsies.

Guan et al. (2012), Kamalakaran et al. (2013) and Roychowdhury et al. (2011) discuss the difficulties in translating complex genomic data into clinically actionable cancer care at scale. They emphasize the challenges in storing, filtering, processing and analyzing huge amounts of data and the need for specialized computational infrastructure. While describing the "superb potential" of sequencing technologies in accelerating precision cancer medicine, MacConaill (2013) also points out the need for a rigorous interpretive framework to identify and decipher complex underlying genomic information.

Finally, several experts in cancer genetics have documented the ethical challenges that arise from the examination of comprehensive genomic data in the clinical setting, and the subsequent disclosure of results to oncologists and patients. Hofstatter and Bale (2013) point out the potential for unanticipated incidental germline findings, indicating that most patients carry a "handful" of germline variants that are disease-causing in the homozygous state. They explain that although such findings might not have much of an effect on the patient in question, they could have serious implications for family members. Hofstatter and Bale (2013) also discuss circumstances when incidental germline findings simultaneously unveil additional diagnoses for cancer patients, such as Hereditary Breast and Ovarian Cancer (HBOC) Syndrome. Since these types of findings are not always entirely unanticipated, they say that pre-test counseling to review potential types of findings could assist in the appropriate disclosure of such results. Hoffstater and Bale (2013) go on to claim that the incidental or "unsolicited" findings that prove to be

more problematic are the diagnoses of untreatable diseases unrelated to cancer, illustrating an example case involving a mutation known to cause a heritable form of early-onset Alzheimer dementia. Lolkema et al. (2013) evaluate the ethical issues that pertain to the possible moral duty to return such germline findings. They mention that in ongoing debates over whether to disclose such genetic information to patients, most agree that there is an ethical duty to return genetic data that is truly actionable. Hall et al. (2014b), Kamalakaran et al. (2013), and Roychowdhury et al. (2011) acknowledge the significant need for an informed consent process that includes a way to handle germline incidental findings. Meldrum et al. (2011) agrees that such ethical issues must be resolved, and proposes that a "more targeted approach to genome sequencing may be a logical next step towards widespread implementation of the technology."

Lack of knowledge of healthcare professionals working in oncology

The latest report of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) noted significant gaps in the education and training of health professionals regarding the implementation of genetic testing and the competency in genetics and genetic testing (Ferreira-Gonzalez et al., 2008). While tumor-sequencing tests have the potential to offer transformative genomic findings relevant to disease management, evidence suggests that medical oncologists in particular feel ill-equipped to implement the technology (Innocent, Ruth, & Boland, 2014). A survey conducted of oncologists in varied settings to assess perceived understanding and preparedness to use NGS technology indicated that community oncologists were found to be "less knowledgeable and less experienced with it, and felt less prepared to use it clinically"

(Innocent et al., 2014). Hall et al., (2014b) cite this investigation in the *Journal of Surgical Oncology*, stating that the ability of oncologists to use this rapidly emerging technology for their patients is affected by setting and confidence level. Furthermore they mention that according to several studies, provider confidence in genomic proficiency influences their decision-making with regards to ordering behaviors towards tumor-sequencing tests (Hall, Forman, Montgomery, Rainey, & Daly, 2015). Presumably, low levels of confidence would disadvantage the delivery of genomics-driven cancer medicine. In another article titled "Conflicted Confidence: Academic Oncologists' Views on Multiplex Pharmacogenomic Testing," Hall (2014) mentions that the lack of experience or minimal experience beyond basic single-gene testing suggests the need for provider-orientated education regarding routine aspects of somatic testing, such as communicating potential germline implications of somatic tests.

Benefits of a Team Approach

Professionals in the field have suggested that a multidisciplinary environment in genomics-driven cancer care could address the oncologists' lack of confidence. Robert R. McWilliams, MD, of the Mayo Clinic demonstrated the need for a team approach among colleagues. He distributed an informal survey that revealed that "70% of respondents 'commonly' did not know what to do with genomic results, and more than 80% of respondents would find it helpful to be able to query a genomic tumor board with multidisciplinary expertise regarding the result" (American Society of Clinical Oncology: Daily News, 2015). Kamalakaran et al. (2013) mention a collaborative approach in an article titled *Translating next generation sequencing to practice*: "For the oncology

experts, the decision support is usually performed by a team of bioinformaticians, statisticians and genetic counselors. The importance and relevance of the mutations must be ascertained and presented to the oncologist in an intuitive manner." In describing how oncologists will handle the return of comprehensive genomic data, Garraway (2013) points out the need for additional support stating, "Considerable personnel resources (e.g., genetic counselors with specialized training) may be needed to ensure that patients understand the potential benefits and risks of receiving somatic and germline data and to support physicians in conveying such information."

Potential role of genetic counselors in genomics-driven oncology

The roles of genetic counselors have expanded across multiple specialties, but particularly in oncology due to more widespread use of panel-based genetic testing resulting in variants of uncertain significance (Ormond, 2013). Genetics experts at Illumina, Inc., express an increased need for genetic counselors in the implementation of NGS stating the following: "The complex nature and volume of the reported results requires professional interpretation of the testing in order to translate and synthesize the meaning and potential benefit to patients, and genetic counselors are uniquely suited to provide this service" (Swanson, Ramos, & Snyder, 2014).

Although genetic counselors have elements of the skill-set to translate genomic data into purposeful information for patient care, evidence suggests that education is needed to improve their knowledge base of rapidly emerging sequencing technologies (Hall et al., 2014). A survey regarding tumor NGS was distributed among members of the National Society of Genetic Counselors (NSGC) of which 693 participants responded.

It assessed the experience, objective knowledge (i.e., advantages/disadvantages, clinical barriers, clinical applicability) and perceptions of personal competence related to NGS genomic testing (NGSGT) in oncology. The study revealed that genetic counselors (GC) are uncertain of their professional role in genomic sequencing and feel inadequately prepared to support NGS of tumors in the clinic setting. Only 13% indicated that they had counseled for NGS tumor-sequencing tests. While 46% of GCs in the study anticipated a role in tumor panel testing, almost all participants (97%) agreed that GCs have a role in associated germline testing. Additionally, the survey revealed that the majority desire more education about NGSGT in tumors (84%) and germline (87%). In concluding the study, Hall et al. (2014) suggested the following: "Lack of experience and knowledge deficits may adversely impact GC perceived clinical competence to help patients make important decision using this new technology."

Conclusion

NGS technology is rapidly improving the field of precision oncology, but with this advancement comes a host of challenges, ranging from the interpretation of the complex cancer genome to the clinical applicability of genomic data, and of course the ethical delivery of genomic results. It has been proposed that a multidisciplinary approach may be best suited for comprehensive cancer medicine, but studies need to investigate how genetic counselors, in particular could help bridge the gap between the genomic results of tumor profiling and the implications for the patient and family members.

Purpose of the study

The increasing disparity between the genomic data attained by NGS technology and the analytical capacity of healthcare providers raises the need for a multidisciplinary team. This paper aims to establish the current roles that genetic counselors, in particular, play in oncology and their perceived roles in the application of tumor-sequencing technologies.

METHODS

Participants

Genetic counselors that work in cancer genetics in any capacity (e.g., clinical, laboratory and industry) were eligible to participate.

Instruments

The study consisted of a voluntary and anonymous 25-question survey distributed among members of NSGC. The survey consisted of multiple choice and free-response questions within varied categories: demographic information, tumor-sequencing experience, perceived obstacles of tumor-sequencing technologies in its application and perceived roles of genetic counselors in the field. The survey was generated via Survey Monkey, and it consisted of both mandatory and optional questions. Participants were able to return to questions and change their answers. IP addresses were not collected, and participants were not asked any identifying questions. Participants did not receive any compensation for their participation.

Procedures

The Sarah Lawrence College Institutional Review Board determined that the research project was exempt from ongoing IRB review (#00009775) on December 2, 2015. An invitation to participate in the study was distributed through the Genetic Counseling Student Research Survey Program to the NSGC distribution list on December 28, 2014 (N=3245). The objectives of the research project were stated in the email, along with a link for the survey and contact information for the primary investigator and research supervisor. The link directed participants to complete the survey. An additional reminder email was sent out on January 14, 2016. The survey was open until January 31, 2016.

Data Analysis

A total of 128 submissions were collected (n=128). One hundred respondents were considered in the analysis of the project based on having completed at least 96.0% of the survey. The data analysis was done using Survey Monkey and SPSS. Qualitative questions were analyzed by classifying relevant information into common themes (open-coding). The primary investigator categorized the answers first; followed by an additional coder who was otherwise uninvolved in the project. The inter-rater reliability was 92.4%.

RESULTS

Demographic Information

Participants answered questions with regards to cancer patient load, work setting and years of experience (Table I).

Table I: Respondent demographic information			
Variable		N = 100	
Percentage of the patients seen for cancer counseling		**N**	**%**
	0%	5	5.0
	1-25%	11	11.0
	25-50%	6	6.0
	51-75%	3	3.0
	75-100%	75	75.0
Type of practice	Community Hospital	42	42.0
	University Hospital	41	41.0
	Private Office	7	7.0
	Laboratory	10	10.0
Length of time in practice	4+ years	44	44.0
	1-3 years	39	39.0
	<1 year	17	17.0

Current Practice

Participants were asked to reflect on the use of tumor genomic sequencing in their institution (Table IIa), the obstacles for use of tumor profiling (Table IIb), along with ways in which they currently provide genetics cancer-related expertise to other medical professionals (Table IIc). Two open-ended questions were included that prompted participants to elaborate. One asked why participants identified a particular obstacle for the use of tumor profiling as the most significant, for which 52.0% (n=52) responded. The other open-ended question asked about the ways in which participants currently provide cancer-related expertise to other medical professionals. Sixty-six (66.0%)

individuals elaborated, and the types of cancer-related expertise were classified into common themes (Table IIc).

Table IIa: Current practice			
Do you work regularly with an oncology group(s)?		N = 100 **N**	**%**
	Yes	86	86.0
	No	14	14.0
If yes, how would you rate the knowledge of oncology group(s)?		N = 91 **N**	**%**
	Somewhat informed	59	64.8
	Very informed	20	22.0
	Slightly informed	12	13.2
	Not at all informed	0	0.0
To your knowledge, are the oncologists at your institution using tumor genomic sequencing at least some of the time?		N = 100 **N**	**%**
	Yes	87	87.0
	No	13	13.0

Table IIb: Current practice			
Which of the following do you perceive as primary obstacles to wider use of tumor genomic sequence testing? Check all that apply.			
		N = 100 **N**	**%**
	Information not yet valuable in most cases	66	66.0
	Insurance reimbursement	62	62.0
	Lack of familiarity among medical professionals	62	62.0
	Test not available	11	11.0
	Unsure	16	16.0
Which of the obstacles do you think is the most significant?			
		N = 100 **N**	**%**
	Insurance reimbursement	29	29.0
	Information not yet valuable in most cases	29	29.0
	Lack of familiarity among medical professionals	23	23.0
	Unsure	18	18.0
	Test not available	1	1.0

Table IIc: Current practice			
As part of your job, do you provide genetics cancer-related expertise to other medical professionals?		N = 100 **N**	**%**
	Yes	85	85.0
	No	15	15.0
If you provide genetics cancer-related expertise to other medical professionals, please elaborate.			
	Open-ended theme	N = 66 **N**	**%**
	Teaching (e.g., lectures, presentations, conferences)	47	71.2
	Intra-hospital meetings (e.g., tumor boards, grand rounds)	35	53.0
	Consult (e.g., recommendations for testing/management/referrals, interpretation of results)	34	51.5
	Support (e.g., provide support in hospital/ community events)	7	10.6
	Germline (e.g., clarify implications of germline mutations)	9	13.6

Potential Areas of Practice

Participants were asked to consider the potential roles that genetic counselors would be equipped to play with regards to the application of tumor genomic sequencing (Table III). An open-ended question was included that asked participants why they identified a particular role as most significant, for which 56.0% (n=56) responded.

Table III: Future practice

Do you feel there is a role for genetic counselors in the use of tumor genomic sequence testing?

	N = 100	
	N	**%**
Yes	80	80.0
Unsure	20	20.0
No	0	0.0

If yes, which of the following roles do you believe genetic counselors can play in regard to tumor genomic sequencing? Check all that apply.

	N = 100	
	N	**%**
Identify and discuss incidental germline information uncovered by testing	91	97.9
Serve as a resource for physicians who may not be comfortable with genomic testing	71	76.3
Educate medical students, residents and fellows about tumor genomic sequencing	65	69.9
Educate physicians and medical professionals on issues around informed consent	63	67.7
Post-test counseling of patients to help interpret tumor sequence testing results	61	65.6
Pre-test counseling of patients to help explain tumor sequence testing/ informed consent	41	44.1

If you answered the previous question, which role do you think is the most significant?

	N = 90	
	N	**%**
Identify and discuss incidental germline information uncovered by testing	51	56.7
Post-test counseling of patients to help interpret tumor sequence testing results	11	12.2
Educate physicians and medical professionals on issues around informed consent	9	10.0
Pre-test counseling of patients to help explain tumor sequence testing/ informed consent	8	8.9
Serve as a resource for physicians who may not be comfortable with genomic testing	7	7.8
Educate medical students, residents and fellows about tumor genomic sequencing	2	2.2
Unsure	2	2.2

Interest in Further Education

Additional questions asked participants to rate their levels of interest in further education with respect to tumor profiling and potential topics to be covered in a tumor genomic sequencing course (Table IV). Of the 97.0% of participants that were interested, 43 agreed that they would be interested in participating in a course on tumor genomics, 54 indicated that they strongly agreed and 3 were neutral.

Table IV: Further Education

I would be interested in participating in a course on tumor genomics aimed at genetic counselors.

	N = 100	
	N	**%**
Strongly Agree	54	54.0
Agree	43	43.0
Neutral	3	3.0

Below are potential topics to be covered in a tumor genomics course for genetic counselors. Please rate your interest in each of the following topics.

	N = 97	
	Total	**Weighted Average**
Information about tumor genotyping (e.g., driver vs. passenger mutations)	97	4.22
How to identify patients who are good candidates for sequencing	96	4.32
The relationship between tumor sequencing results and germline information	95	4.86
How results of tumor sequencing can influence treatment decisions	97	4.37
Current companies offering tumor sequencing and tumor sequencing information services (e.g., Foundation Medicine, N-of-One, etc.)	97	3.92
Advantages and disadvantages of various sequencing technologies	97	4.29
Available resources for interpretation of tumor genomic sequencing	97	4.72

DISCUSSION

Current Practice

Most participants reported that they provide genetics cancer-related expertise to other medical professionals (85.0%, n=85). Of the 66 individuals who elaborated, open-ended responses most frequently involved teaching other healthcare providers through lectures, presentations and conferences (71.2%, n=47), followed by collaborating in intra-hospital meetings such as tumor boards and grand rounds (53.0%, n=35). A significant number of counselors described consulting with other healthcare providers, which included recommendations for referrals, surveillance, management and genetic testing (51.5%, n=34). Other common responses involved providing support internally and/or throughout the community (10.6%, n=7) and clarifying the implications of germline findings (13.6%, n=9).

The majority of respondents indicated that they had more than one role in educating other medical professionals (69.7% n=46). One responder described multiple categories in providing expertise to other hospital providers: "I have given a talk for GI fellows at my hospital, and started to teach a nursing class this year. I also attend solid tumor conference at my hospital to provide input on cases that may need germline genetic testing, and consult less formally about genetic testing for patients with medical professional from various departments."

Other participants specifically reported educating physicians with oncology training. One genetic counselor said, "I have given genetics presentations to various oncology specialists about the updates in cancer genetics in-services and tumor board education to medical oncologists, surgeons and radiation oncologists." Another

described assisting oncology clinicians with the interpretation of tumor genomic sequencing results: “I work closely with the pediatric hematologist-oncologists at my institution. I explain results of previously tested patients, as well as clarifying cases I have consulted on. I also help them understand tumor-sequencing results (such as Foundation Medicine) testing.”

Among the large number of responders, 86 (86.0%) that reported working regularly with an oncology group or several oncology groups, only 22.0% (n=20) rated the knowledge of cancer genetics by their oncology groups as very informed. Still 87 (87.0%) reported that oncologists at their institution were using tumor genomic sequencing at least some of the time.

A majority of the responders (62.0%, n=62) identified a lack of familiarity among medical professionals with regards to tumor genomic sequencing as a significant obstacle to its wider application, along with insurance reimbursement (62.0%, n=62) and information not yet valuable in most cases (66.0%, n=66). A smaller number (11.0%, n=11) identified testing not yet available as an obstacle to more widespread use. When responders were prompted to choose the most significant obstacle, the same three choices were selected with the most frequency at 23.0%, 29.0% and 29.0% respectively, and one responder (1.0%) chose ‘test not yet available’ (Table III).

Among the 29 participants who chose insurance reimbursement as the primary barrier, both expense to patients and insurance company policies were identified as issues. Approximately a third of the 29 (34.5%, n=10) expressed that medical professionals are weary of the cost, mentioning that the out of pocket expense is too high, especially for middle and low-income populations. A few other participants said that

insurance companies have not instituted policies in this area of genetic testing, as they still view tumor profiling as exploratory, and thus will not fund it. One responder wrote, "Internal 3rd party insurance payers have internal policies that deem this 'experimental;' there is no peer reviewed literature proving the utility of the testing."

Limited clinical utility was also mentioned by 17 of the 29 participants that indicated that the primary obstacle to the widespread use of tumor genomic sequencing is that 'information is not yet valuable in most cases.' Respondents often noted in comments that the testing rarely benefits the patient in terms of adjusting medical management. As one participant reported: "Thus far, in the results that I have seen, it is uncommon for the result of tumor sequencing to alter the patient's treatment options." Another respondent stated, "Most genomic alterations identified on tumor NGS do not yet have a matched FDA-approved drug or clinical trial." Four participants argued that 'information not yet valuable' is the biggest limitation due to a lack of guidelines in terms of how to handle tumor genomic sequencing results. One genetic counselor said, "It ties into lack of ability to and/or understanding of how to interpret and apply results to help determine appropriate treatment course." Another respondent said, "I think that the lack of information and the subsequent lack of NCCN Guidelines for these test results are stopping our docs (who rely heavily on NCCN) from ordering this kind of testing."

Concerns about to a gap in knowledge were similarly expressed by the 23 (23.0%) respondents who chose a lack of familiarity among health care providers as the primary barrier to tumor profiling. Eight (34.8%) of these respondents indicated that oncologists are less likely to order tumor genomic sequencing because they are often uninformed about how and when to request testing and how to best use the resulting information.

Two individuals reported that the current developments in technology are very difficult for busy oncologists to keep up with. One respondent who chose lack of familiarity as a barrier was more specific: "Data regarding clinical applicability of results; too many labs with varying yet similar tests and MDs do not know when to order which."

Potential Areas of Practice

With respect to anticipated roles in the clinical application of tumor genomic sequencing, most responders (80.0%, n=80) felt that genetic counselors should play a part. In fact, the majority of responders identified 5 roles that genetic counselors would be equipped to play in tumor genomic analysis. The largest number, 91 (97.9%) indicated identifying and discussing incidental germline findings uncovered by testing, followed by serving as a resource for physicians who may not be comfortable with genomic testing 76.3% (n=71), educating medical students, residents and fellows about tumor genomic sequencing 69.9% (n=65), educating medical professionals on issues around informed consent 67.7% (n=63), and post-test counseling of patients to help interpret tumor sequencing results 65.6% (n=61). The duty of pre-test counseling for patients to help explain tumor sequence testing and informed consent was identified as a potential role by a smaller number of responders 44.1% (n=41).

When asked which role was most significant, the most common response was 'review of germline results' (56.7%, n=51). Other responses were fairly evenly split between 'post-test counseling' (12.2%, n=11), 'educate physicians and professionals around informed consent' (10.0%, n=9), 'pre-test counseling' (8.9%, n=8), and 'resource for physicians' (7.8%, n=7), however, comments suggested considerable overlap in the

concerns and expectations among respondents regardless of their answer. The issue of germline mutations was reflected in the open-ended response from a participant who indicated that the primary role was pre-test counseling: "I chose this as the most significant since it educates the patient in the very beginning that way there is no surprise of a germline incidental result afterwards." Among the 11 responders who chose post-test counseling of patients one stated, "Post-test counseling will allow GCs to explain the results fully and appropriately to the patients, while simultaneously allowing for the identification and proper subsequent germ line testing." One of the 10 participants who indicated that the primary role was educating physicians who may not be comfortable with informed consent said, "Many patients have no idea about the difference between somatic and germline testing. Additionally they are not informed that the testing could yield information that could be relevant for family members."

Respondents also commonly expressed their confidence with regards to the application of genomic testing, in contrast with oncologists' lack of experience or minimal experience beyond basic single-gene testing (Hall 2014). One respondent, speaking of post-test counseling to help interpret tumor sequence results, said: "This seems to be the area where there is the most confusion and where a GC could have the most significant role." Participants indicated that these roles were consistent with the skill set and training of genetic counselors. One respondent wrote, "I think that explaining incidental germ line information is an area where GCs bring expertise above and beyond that of the patient's oncologist." Others stated, "It is the most relevant to the genetic counseling profession and least well-addressed by other medical professionals."

and “Physicians only briefly consent to germline findings when ordering tumor tests, but these can have a larger implication of global health of the patient and family members.”

Another theme among open-ended responses was the shortage of genetic counselors (6.0%, n=6). A respondent speaking of pre-test counseling said, “I think this role would be the most difficult to implement as there are not enough genetic counselors to likely cover this new demand.” A respondent among those who favored distinguishing incidental germline findings wrote, “I end up explaining what the test even was most of the time, which definitely speaks to the need for pre-test counseling but it's not something GCs have time for.” Due to the shortage, a genetic counselor suggested the importance of educating medical professionals about informed consent stating, “If paired tumor/germline testing begins, this would be extremely important and there are not enough GCs to do the pre-test counseling and consent so education and handouts would be necessary.” Another participant added: “There won't be enough GCs to provide pre and post test-counseling for all patients having tumor profiling, but being a resource for the questions that come up will really help.”

Study limitations

Since the research survey was distributed through the distribution list of the National Society of Genetic Counselors (NSGC), only NSGC members were able to participate. For this reason, the study did not account for experiences and opinions of non-NSGC members. As with any research study, the individuals who were most likely to participate are those who had interest or strong feelings on the topic being investigated. This is a concern considering the low response rate of 3.1% among NSGC members (N =

3245), although eligibility criteria may have limited response, as only those who specialize in oncology could participate.

Conclusion

Based on this study, genetic counselors today already play a significant role as part of multidisciplinary care in oncology. With regards to tumor genomic sequencing, survey results indicate that there is variability in the opinions of what the obstacles are to widespread use. Nevertheless, the data suggests that genetic counselors foresee multiple roles that they are adept to handle in the context of tumor genomic analysis, with information involving germline findings consistently specified as the most important and relevant to the profession. Given the shortage of genetic counselors, some respondents suggest that a comprehensive role as a resource in educating other medical professionals might inevitably be the most feasible way to ensure the appropriate delivery of germline information.

References

American Society of Clinical Oncology: Daily News. (2015, May 31). Cancer genetics: Multidisciplinary panels: Putting sequencing data to work. Message posted to http://am.asco.org/multidisciplinary-panels-putting-sequencing-data-work

André, F., Bachelot, T., Campone, M., Arnedos Ballester, M., Commol, F., & Gonçalves, A. (2012). Array CGH and DNA sequencing to personalize therapy for metastatic breast cancer: A prospective national trial (UNICANCER SAFIR-01). *Ann Oncol, 23*(Suppl. 9)

Carlson, B. (2012). Next generation sequencing: The next iteration of personalized medicine: Next generation sequencing, along with expanding databases like the cancer genome atlas, has the potential to aid rational drug discovery and streamline clinical trials. *Biotechnology Healthcare, 9*(2), 21-25.

Chung, J. H., Ali, S. M., Davis, J., Robstad, K., McNally, R., Gay, L. M., et al. (2014). A poorly differentiated malignant neoplasm lacking lung markers harbors an EML4-ALK rearrangement and responds to crizotinib. *Case Reports in Oncology, 7*(3), 628-632.

Dellaire, G., Berman, J., & Arceci, R. (Eds.). (2014). *Cancer genomics: From bench to personalized medicine*. London, UK: Elsevier Inc.

Ferreira-Gonzalez, A., Teutsch, S., Williams, M. S., Au, S. M., FitzGerald, K. T., Miller, P. S., et al. (2008). US system of oversight for genetic testing: A report from the

SecretaryΓÇÖs advisory committee on genetics, health and society. *Personalized Medicine, 5*(5), 521-528.

Garraway, L. A. (2013). Genomics-driven oncology: Framework for an emerging paradigm. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31*(15), 1806-1814.

Garraway, L. A., Verweij, J., & Ballman, K. V. (2013). Precision oncology: An overview. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31*(15), 1803-1805.

Hall, M. J., Boland, P., Ruth, K., Matro, J. M., Rainey, K., Fang, C. Y., et al. (2014). Incorporating genomic testing using next-generation sequencing (NGS) into clinical practice: Genetic counselors' (GC) experience, knowledge and perceived competence.(J Clin Oncol 32, 2014 (suppl; abstr e17624))

Hall, M. J. (2014). Conflicted confidence: Academic oncologists' views on multiplex pharmacogenomic testing. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 32*(13), 1290-1292.

Hall, M. J., Forman, A. D., Montgomery, S. V., Rainey, K. L., & Daly, M. B. (2015). Understanding patient and provider perceptions and expectations of genomic medicine. *Journal of Surgical Oncology, 111*(1), 9-17.

Hofstatter, E. W., & Bale, A. E. (2013). The promise and pitfalls of genomics-driven cancer medicine. *The Virtual Mentor : VM, 15*(8), 681-686.

Innocent, J., Ruth, K., & Boland, P., et al. (2014). Academic (AO) and community (CO) oncologists' knowledge, understanding, and preparedness for clinical next-generation sequencing genomic testing (NGSGT)<*br />* *J.Clin.Oncol.,* (suppl; abstr e17635)

Johnson, D. B., Dahlman, K. H., Knol, J., Gilbert, J., Puzanov, I., Means-Powell, J., et al. (2014). Enabling a genetically informed approach to cancer medicine: A retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. *The Oncologist, 19*(6), 616-622.

Kamalakaran, S., Varadan, V., Janevski, A., Banerjee, N., Tuck, D., McCombie, W. R., et al. (2013). Translating next generation sequencing to practice: Opportunities and necessary steps. *Molecular Oncology, 7*(4), 743-755.

Kiesler, E. P. D. (2014). *Tumor sequencing test brings personalized treatment options to more patients.* Retrieved July 17, 2015, from https://www.mskcc.org/blog/new-tumor-sequencing-test-will-bring-personalized-treatment-options-more-patients

MacConaill, L. E. (2013). Existing and emerging technologies for tumor genomic profiling. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31*(15), 1815-1824.

Meldrum, C., Doyle, M. A., & Tothill, R. W. (2011). Next-generation sequencing for cancer diagnostics: A practical perspective. *The Clinical Biochemist.Reviews / Australian Association of Clinical Biochemists, 32*(4), 177-195.

Ormond, K. E. (2013). From genetic counseling to "genomic counseling". *Molecular Genetics & Genomic Medicine, 1*(4), 189-193.

Palma, N., Morris, J. C., Ali, S. M., Ross, J. S., & Pal, S. K. (2015). Exceptional response to pazopanib in a patient with urothelial carcinoma harboring FGFR3 activating mutation and amplification. *European Urology, 68*(1), 168-170.

Sparano, J. A., Ostrer, H., & Kenny, P. A. (2013). Translating genomic research into clinical practice: Promise and pitfalls. *American Society of Clinical Oncology Educational Book / ASCO.American Society of Clinical Oncology.Meeting,* , 15-23.

Swanson, A., Ramos, E., & Snyder, H. (2014). Next generation sequencing is the impetus for the next generation of laboratory-based genetic counselors. *Journal of Genetic Counseling, 23*(4), 647-654.

White House, Office of the Press Secretary. (January 30, 2015). *FACT SHEET: President obama's precision medicine initiative.* Retrieved July 18, 2015 https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative