J Genet Counsel (2015) 24:388–399
DOI 10.1007/s10897-014-9805-5

PROFESSIONAL ISSUES

Aligning Policy to Promote Cascade Genetic Screening for Prevention and Early Diagnosis of Heritable Diseases

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Received: 14 February 2014 / Accepted: 1 December 2014 / Published online: 11 January 2015

Abstract Cascade genetic screening is a methodology for identifying and testing close blood relatives of individuals at increased risk for heritable conditions and follows a sequential process, minimizing testing costs and the number of family members who need to be tested. It offers considerable potential for cost savings and increased awareness of heritable conditions within families. CDC-classified Tier 1 genomic applications for hereditary breast and ovarian cancer syndrome (HBOC), Lynch Syndrome (LS), and familial hypercholesterolemia (FH) are recommended for clinical use and support the use of cascade genetic screening. Most individuals are unaware of their increased risk for heritable conditions such as HBOC, LS, and FH. Consistent implementation of cascade genetic screening could significantly increase awareness and prevention of heritable conditions. Limitations to effective implementation of cascade genetic screening include: insufficient genetic risk assessment and knowledge by a majority of healthcare providers without genetics credentials; a shortage of genetic specialists, especially in rural areas; a low rate of reimbursement for comprehensive genetic counseling services; and an individual focus on prevention by clinical guidelines and insurance coverage. The family-centric approach of cascade genetic screening improves prevention and early diagnosis of heritable diseases on a population health level. Cascade genetic screening could be better supported and augmented through changes in health policy.

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Keywords Cascade genetic screening · Familial hypercholesterolemia · Genetic counseling · Healthcare reform · Hereditary breast and ovarian cancer syndrome · Hereditary conditions · Heritable disease · Lynch syndrome · Policy change

Introduction

Cascade genetic screening is a methodology for identifying and testing close blood relatives of individuals at increased risk for heritable conditions and follows a sequential process, minimizing testing costs and the number of family members who need to be tested. Identifying asymptomatic carriers in families provides opportunities to assess hereditary risk, prevent disease by risk reduction, diagnose disease in early stages, and improve clinical outcomes. Cascade genetic screening can be more cost-effective than population screening, as the risk of being a carrier is considerably higher among close blood relatives for certain conditions (Krawczak et al. 2001). A PubMed search of the terms 'cascade genetic screening' and 'cascade genetic testing' lists articles that describe emerging applications for cascade genetic screening, as well as approaches to increase participation in cascade genetic screening for conditions that are well-supported by clinical guidelines.

Cascade genetic screening for autosomal dominant conditions, such as familial hypercholesterolemia (FH), heritable breast and ovarian cancer syndrome (HBOC), and Lynch syndrome (LS), have proven highly effective at identifying at-risk individuals, since there is a 50 % risk of first degree relatives inheriting a familial mutation (Jasperson 2013; Hardcastle et al. 2014; Krawczak et al. 2001). These three conditions are among several genetic conditions where there is proven efficacy from cascade genetic screening (Table 1). Modes of inheritance, screening depth, and degree of

Table 1 Information for 3 conditions with tier 1 genomic applications

Condition	*BRCA* 1 & 2 (HBOC) [a]	Familial hypercholesterolemia (FH), heterozygous (HeFH) & homozygous (HoFH)	Lynch syndrome (LS)
Prevalence in general population	1:300–500 (Petrucelli et al. 1998)	HeFH: 1:200–500 (Youngblom and Knowles 2014; Nordestgaard et al. 2013) HoFH: 1:160,000–1,000,000 (Youngblom and Knowles 2014; Nordestgaard et al. 2013)	1:370–440 (Hampel and de la Chapelle 2011; Kohlmann and Gruber 2004)
	Prevalence varies in specific populations (Petrucelli et al. 1998)	Prevalence varies in specific populations (Youngblom and Knowles 2014)	
Est. US population affected [b]	632,000–1,054,000	632,000–1,581,000 (HeFH) 300–2000 (HoFH)	719,00–854,000
Disease characteristics	Increased risk for breast, ovarian, prostate, pancreas, and skin cancer (melanoma) (Petrucelli et al. 1998) Lifetime risks (Petrucelli et al. 1998) ·Breast cancer 40–80 %, often seen by age 50 years ·Ovarian cancer 11–17 % (generally seen at age 30 years or older (NCI, 2014a) ·Male breast cancer 1–10 % ·Prostate cancer Up to 39 % ·Pancreatic cancer 1–7 %	Severely elevated LDL cholesterol (LDL-C) levels (Youngblom and Knowles 2014) HeFH (Youngblom and Knowles 2014) ·20× increase in risk for coronary heart disease ·Untreated men are at a 50 % risk for a coronary event by age 50 years; untreated women are at a 30 % risk by age 60 years HoFH (Youngblom and Knowles 2014) ·Individuals experience severe coronary heart disease by mid-20s	Increased risk for colon, endometrium, ovarian, stomach, small intestine, hepatobillary tract, urinary tract, brain and skin cancers (Kohlman and Gruber 2004) Lifetime risks and mean age at diagnosis (Kohlman and Gruber 2004) ·Colorectal cancer: 52–82 %, 44–61 years ·Endometrial cancer: 25–60 %, 48–62 years ·Gastric cancer: 6–13 %, 56 years ·Ovarian cancer: 4–12 %, 42.5 years (~30 % diagnosed before age 40 years)
Genes involved	*BRCA1* and *BRCA2* (Petrucelli et al. 1998)	*APOB*, *LDLR*, and *PCSK9* (Youngblom and Knowles 2014)	Mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*; and *EPCAM* (Kohlman and Gruber, 2004)
Recommendations/ guidelines	US Preventive Services Task Force (USPSTF), *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women*, 2013 National Comprehensive Cancer Network (NCCN), *Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian*, 2014	National Institute for Healthcare Excellence (NICE), *Identification and management of familial hypercholesterolaemia*, 2008	National Comprehensive Cancer Network (NCCN), *Genetic/Familial High-Risk Assessment: Colorectal*, 2014 Evaluation of Genomic Applications in Practice and Prevention (EGAPP™), *Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives*, 2009

[a] *BRCA 1 & 2* mutations are used as a 'marker' for HBOC prevalence, HBOC can also result from deleterious mutations in other genes (known and unknown)

[b] Calculation based on prevalence data and the 2013 US Census population estimate

penetrance are key factors that influence the effectiveness of cascade genetic screening (Krawczak et al. 2001). Using screening methodologies in addition to cascade genetic screening can improve case ascertainment of at-risk carriers when following algorithms based on carrier status, ancestry, family health history, closeness of relatives, and clinical indications. For example, cascade genetic screening for hemochromatosis, a common autosomal recessive disorder of iron storage, has stronger evidence of effectiveness when testing first degree relatives of symptomatic patients than other close relatives (Dubois and Kowdley 2004). While still a growing area of study, appropriate uses of cascade genetic screening have been shown to effectively increase case ascertainment of asymptomatic carriers, provide options for prevention and risk reduction, improve clinical management and treatment, and lower testing and healthcare costs (Krawczak et al. 2001).

Medical genetics and public health disciplines have opportunities to share their approaches to improve health outcomes in those with or at risk for heritable conditions. Public health aims to promote health, prevent and detect disease early, and extend life for populations (World Health Organization n.d.). The knowledge that individuals are at increased risk for or

affected by a hereditary condition can inform measures to reduce risk and prevent disease in their close blood relatives. Family-centered genetic screening offers enormous potential to improve population health outcomes by increasing early awareness among individuals who share the same hereditary condition. It provides substantial cost-savings for individuals, their health payers, and healthcare systems since the cost of evidence-based cascade genetic screening strategies are lower than additional costs for disease management (Krawczak et al. 2001). Healthcare reform, including the Affordable Care Act (2010), is focusing on improving population health outcomes, lowering healthcare costs, and increasing coordination within healthcare systems. Cascade genetic screening aligns well with the goals of healthcare reform, but could be better supported. This article discusses how cascade genetic screening could be promoted by increasing awareness about this screening methodology, reducing systemic barriers, and encouraging coordination within and among healthcare systems.

Coordinating Genetic Services Through Cascade Genetic Screening

Genetic specialists are healthcare professionals who are credentialed in genetics and have comprehensive education and experience in genetics, hereditary conditions, and counseling. Genetic specialists utilize the practice of cascade genetic screening to test close blood relatives in a sequential process informed by an understanding of molecular genetics, inheritance, genetic testing methodologies, and evidence-based guidelines, when available. They help individuals and families identify their risk for certain genetic disorders, examine their family health history, and provide guidance on genetic screening and testing, results interpretation, prevention, and management (National Society of Genetic Counselors [NSGC] n.d.).

Cascade genetic screening minimizes the involvement of family members in unnecessary genetic testing and screening and reduces costs by identifying the most appropriate individual to test first. Each step in cascade genetic screening uses an algorithm to re-evaluate risk for other family members. If a clinician identifies a positive gene mutation in a family, further genetic testing of family members only requires single-site testing for the specific gene mutation, rather than testing for an entire gene or panel of genes associated with a heritable condition. Single-site testing is generally a much less costly endeavor. Sometimes, symptomatic family members might choose not to get tested because they do not feel well enough to be seen for testing, may not understand their own increased risk for a second primary cancer, or be uninterested in testing for other reasons. In cases where a symptomatic relative is unavailable, an obligate carrier may sometimes be identified for testing who is asymptomatic, but would carry a mutation based on patterns of family inheritance.

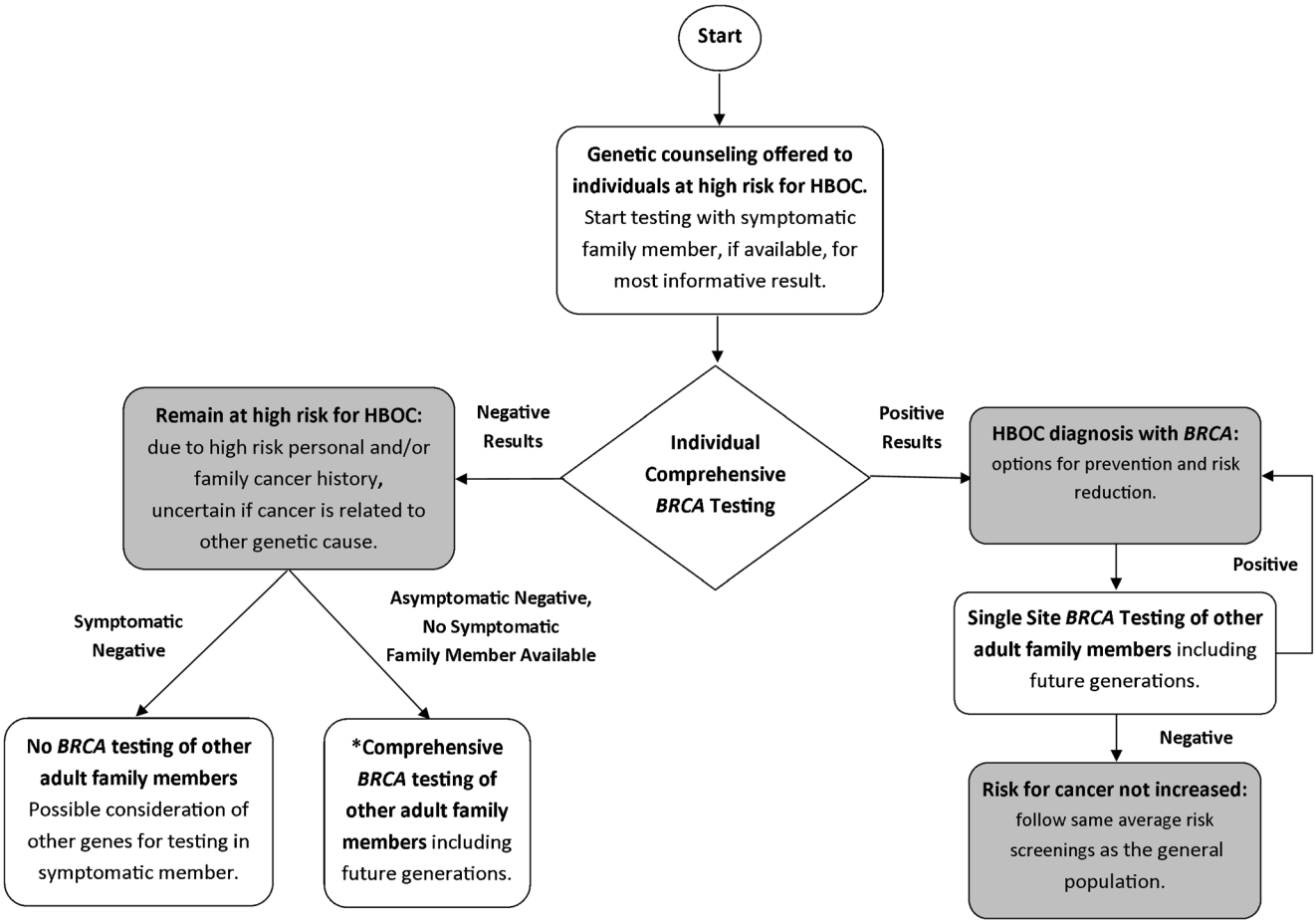
The most common classifications of mutations identified through genetic testing are negative (no deleterious mutation found), true negative (known family mutation is not found), positive (deleterious mutation associated with disease of interest found), or variant of unknown significance (VUS). Advances in genetic research allow for the possibility of reinterpretation of test results, such as when a VUS is reclassified into a negative or positive result. Standard practice does not initiate cascade screening when a VUS is identified. However, when a VUS is reclassified into a positive result, the individual who had been tested would need to be re-contacted and family members would then follow a cascade genetic screening protocol accordingly. Future testing of other genes is also possible if other gene variants become associated with the disease. In this case, cascade genetic screening would follow the same protocol for any future genetic testing by first testing affected family members, if available.

Cascade Genetic Screening for Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

Effective implementation of cascade genetic screening for hereditary breast and ovarian cancer syndrome (HBOC) could save lives and reduce healthcare costs. When an individual has a family history that indicates an increased risk for having HBOC, the standard practice among genetic specialists is to first offer comprehensive testing (See Fig. 1) to the closest blood relative available who has been diagnosed with an HBOC-related cancer (a symptomatic relative). Individuals with Ashkenazi Jewish ancestry have an increased risk for HBOC and would first be screened with a *BRCA* test for the three most common mutations found in this population. *BRCA* 1 & *BRCA* 2 genes have roles in tumor suppression and deleterious mutations in these genes are the most strongly-associated known markers for HBOC (NCI 2014b).

Comprehensive *BRCA* testing costs between $1500 and $3300 (or more, if multiple-gene panels are ordered, an increasingly common practice; Ambry Genetics [AG] 2014; Invitae n.d.; Myriad n.d.). In this most efficient scenario, where a symptomatic family member is available for testing, a positive result not only allows opportunities for prevention and early diagnosis of future primary cancers in the individual, but also allows all close blood relatives who choose to be tested to receive the much less expensive single-site testing. For example, *BRCA* single-site testing costs about $200–475 (AG 2014; Invitae n.d.; Myriad n.d.). In addition, any subsequent family member who has a negative test result for the familial mutation will know that they are not at increased risk of developing HBOC-related cancers, and can return to the general population-risk cancer screenings recommended for the general public.

In this example, a negative result of the symptomatic family member might lead to consideration of other genes to determine the etiology of the cancer family history, and



*Asymptomatic family members who wish to be tested will need comprehensive *BRCA* testing until a positive mutation is identified or a symptomatic family member becomes available for testing. Symptomatic is defined as being diagnosed with an HBOC-related cancer.

Fig. 1 Cascade genetic screening of *BRCA* mutation for hereditary breast and ovarian cancer (*HBOC*) syndrome

provisionally eliminate the gene(s) tested as the cause of the increased risk. Asymptomatic family members would not need to be tested unless a familial mutation is identified. Asymptomatic family members are not generally tested first because if the result is negative, it remains uncertain if the disease is unrelated to known genetic mutations altogether, if that individual did not inherit the familial mutation, or if the gene(s) tested were not the ones involved in the familial disease. This uncertainty means that other family members who want to be tested and are appropriate for testing will need to repeat the more comprehensive and costly testing.

The most appropriate relative may not be available for testing for many reasons, including no or inadequate health insurance coverage for genetic testing, lack of interest in pursuing testing, being too ill, or deceased with no banked sample available. Not initially testing the most appropriate relative adds considerable cost to the individual and other family members in terms of health outcomes, emotional distress, time, and healthcare costs. The following example (See Fig. 2) describes an individual with a family history indicating a high risk for HBOC. The most appropriate close blood relatives symptomatic for cancer were either unavailable or lacked medical coverage for genetic testing (some information in the family history has been changed or not disclosed to protect the privacy of the individuals). The referred patient was a 31-year old female who reported a family history of five paternal relatives with breast cancer under age 50 years, two of whom had second primary breast cancers. In total, there were 30 close blood relatives at risk (expanded pedigree not shown). Four of the five affected women were deceased; the surviving affected family member was the patient's paternal aunt. The aunt was 16 years out from her cancer diagnosis, uninsured, and not being actively screened for cancer recurrence or second primary cancers.

With cascade genetic screening, the clear choice for HBOC-related gene testing is the paternal aunt of the referred patient - not only for her own health management, but also to help inform her many at-risk relatives. A positive result would allow single-site cascade genetic screening for all at-risk relatives. Without testing the index case, testing all 30 at-risk relatives via comprehensive *BRCA* testing would cost a minimum of $66,000 (median *BRCA* comprehensive cost: $2200) and does not include multi-gene panels. If the index case has

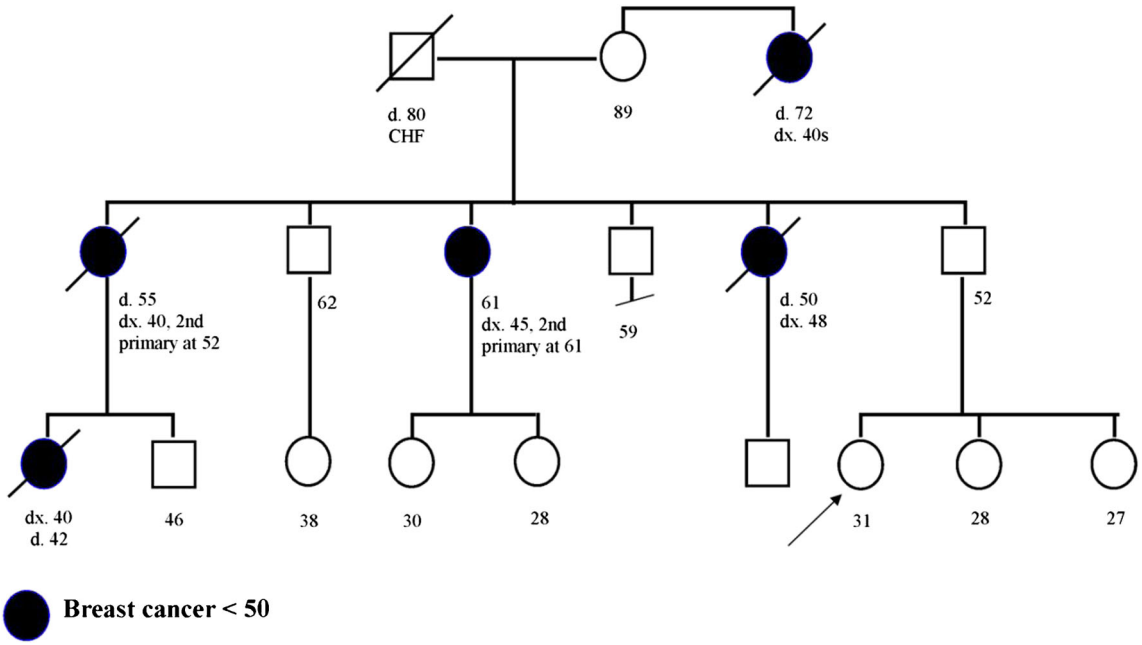


Fig. 2 Pedigree of a 31 year old female patient (*arrow*) who reported a family history of five paternal relatives with a history of breast cancer

comprehensive testing first and a mutation is found, and the at-risk relatives subsequently have single-site testing, the total cost would be about $12,000 (median *BRCA* single-site cost: $400). Due to a lack of adequate insurance coverage, genetic counseling and testing was inaccessible for the aunt until a grant and financial assistance from the testing company covered costs. If the aunt had an individual insurance plan with a high deductible, she likewise may not have been able to receive genetic counseling and testing due to large out-of-pocket costs. As part of our ongoing data collection with Oregon cancer genetic clinics, we see anecdotal evidence that such situations occur regularly. That is, no or inadequate insurance coverage stalls appropriate care for both patients and their family members (Oregon Health Authority, Oregon Genetics Program [OGP] 2013).

Cascade Genetic Screening Recommended for CDC Tier 1 Genomic Applications

Scientific advisory panels conduct systematic reviews of certain genomic and family health history applications to assess evidence on the relative benefits and harms for their use in clinical settings (Centers for Disease Control and Prevention [CDC], Office of Public Health Genomics [OPHG] 2013). The CDC Office of Public Health Genomics (OPHG) has categorized these applications based on three levels of evidence using a tier-ordered approach. Tier 1 applications meet the criteria for all three categories of analytic validity, clinical validity, and clinical utility, and are recommended for clinical use (OPHG 2013). These clinical scenarios support the use of cascade genetic screening to identify at-risk individuals for HBOC, FH, and LS, to name just a few conditions (Bowen et al. 2012; OPHG 2013). Table 1 provides a brief summary of these conditions. All three conditions are inherited in an autosomal dominant manner; the level of penetrance varies by the gene involved and the specific mutation for all conditions (Kohlmann and Gruber 2004; Petrucelli et al. 1998; Youngblom and Knowles 2014).

In the US population, there are over 2 million carriers of HBOC, FH, and LS (Table 1). Most of these individuals remain unaware of their increased risk status. Among individuals with FH, fewer than 1 % are diagnosed (Nordestgaard et al. 2013), and it is estimated that fewer than 2 % of individuals with LS are aware of their increased hereditary colorectal cancer risk (Hampel and de la Chapelle 2011). An annual statewide telephone survey of adults, the 'Behavioral Risk Factor Surveillance System' (BRFSS) coordinated by the CDC, was conducted in Oregon (2011) and indicated that only 30 % of women with family histories indicating an increased risk for HBOC (Question respondents n<100, statistically reliable; OGP 2011a; U.S. Preventive Services Taskforce [USPSTF] 2005) responded that they had heard of the '*BRCA* genetic test'. Among those women who had heard of the *BRCA* test, 70 % responded that they did not think they needed a genetic test to assess their risk for hereditary breast and ovarian cancer (OGP 2011a). Consistent implementation of genetics risk assessment and cascade genetic screening could considerably improve awareness.

Challenges to Consistent Implementation of Cascade Genetic Screening

Provider Factors

One of the limitations in fostering increased awareness of personal risk for heritable conditions is that clinicians without

genetics expertise may not be identifying patients at increased genetic risk. If offering genetic testing, a non-genetic provider may have neither the knowledge nor time to conduct comprehensive genetic counseling, including interpretation of results and making recommendations for cascade genetic screening (Bensend et al. 2014; Brierley et al. 2012; Radford et al. 2013). In addition, identifying the most appropriate sequence of close blood relatives to test, understanding the applicable gene(s) for testing, and promoting contact and discussion with family members are all integral to the cascade genetic screening process, which can be time consuming and especially challenging for healthcare providers not experienced in those areas.

Surveys of healthcare provider knowledge in genetics have shown that a majority have deficiencies in their understanding of genetics risk assessment and testing, such as the ability to consistently identify and differentiate risk status based on personal and family histories of HBOC (Bellcross et al. 2011; Trivers et al. 2011; Wood et al. 2008). The Oregon Genetics Program conducted a Healthcare Provider Survey (N=1211) in 2010 and found that only 30 % of clinicians reported that they felt moderately or very confident in their genetics knowledge of breast and ovarian cancer, and 26 % felt moderately or very confident for colorectal cancer genetics (Cox et al. 2012; OGP 2011c). Less than 50 % of health care providers reported that they used family history of patients without cancer to decide whether to refer those patients to a genetic specialist (OGP 2011c).

Clinicians with inadequate genetics knowledge are more likely to miss opportunities to identify patients who could benefit from genetic counseling, incorrectly recommend genetic counseling and testing to patients at low risk, and not have the expertise or time to offer cascade genetic screening (Brierley et al. 2012; Wood et al. 2008). When genetic testing is provided without cascade genetic screening, at-risk close blood relatives in a family might receive genetic counseling and testing only on a case-by-case basis and the most appropriate members in the family may not be tested. Such an approach to genetic services becomes more costly and may leave many close blood relatives uninformed of their increased risk for heritable conditions. Additionally, the growing sophistication of genetic testing (e.g., choosing among different labs offering similar tests, next generation sequencing, and multiple-gene panel testing) adds to the genetic competencies needed by healthcare providers for accurate test interpretation and differential diagnosis.

Another barrier to expanding cascade genetic screening is an insufficient number of clinicians who have the genetics expertise to offer comprehensive genetic counseling. The American College of Surgeons' Commission on Cancer (CoC) provides accreditation to cancer clinics. One of their established quality standards is the availability of genetic counseling by a qualified genetic specialist, such as a certified genetic counselor or an advanced practice nurse in genetics (American College of Surgeons 2012). There is a shortage of genetic specialists throughout the U.S., especially in rural areas (Radford et al. 2013). There are over 3500 certified genetic counselors, 70 certified genetic nurse specialists, and 1500 clinical geneticists in the U.S., which is a ratio of one clinical genetic specialist for every 63,000 U.S. residents not including area of specialty (American Board of Genetic Counseling 2013; American Board of Medical Genetics and Genomics 2013; Genetic Nursing Credentialing Commission n.d.; U.S. Census Bureau 2014).

In Oregon, five of the six Oregon clinics with credentialed cancer genetic specialists are located in the Portland metropolitan area. Healthcare providers who practice more than 80 miles from Eugene or Portland, Oregon's two largest cities, are significantly more likely (63 %) to have indicated in the Healthcare Provider Survey (2010) that they would not refer their patients to a genetic specialist compared to providers who practice within 80 miles of Portland or Eugene (7 %) (p<0.05; OGP 2011c). More recently, cancer genetic specialists have begun partnering with other healthcare providers and have been using telemedicine as one method to improve access to genetic services (Radford et al. 2013). Some cancer clinics are also partnering with companies that provide telephone genetic counseling, which helps them meet CoC accreditation standards (Cohen et al. 2013). Such partnerships can foster genetics awareness in the healthcare community and help establish cooperative learning relationships. By recognizing the value of comprehensive genetic services, many opportunities exist to create changes in healthcare systems and increase the number of healthcare providers with genetic expertise.

Genetics Specialist Factors

Financial reimbursement policies are inconsistent for genetic counseling and do not adequately support comprehensive genetic services, including case preparation and follow-up to encourage familial communication (Engel et al. 2012; Harrison et al. 2010; McPherson et al. 2008). The ability of genetic counselors to bill independently for genetic counseling varies from state to state and by health plan (NSGC 2011, 2014). Genetic counseling can be a time-intensive practice that requires considerable case preparation, documentation, and follow-up outside of face-to-face patient care (McPherson et al. 2008). Patient-related activities can take at least half of the time spent for a patient when including telephone disclosure, which is not typically reimbursed by payers (Heald et al. 2013; McPherson et al. 2008; Wham et al. 2010). Wham et al. (2010) reported in a survey of NSGC cancer genetic counselors (N=161) that almost all (96 %) were not reimbursed for time spent on case preparation. There is little financial incentive to provide cascade

genetic screening, unless comprehensive genetic counseling services are encouraged by better reimbursement schemes.

Efforts to encourage family communication of hereditary risk may be constrained by time, as well as financial and administrative limitations. Wham et al. (2010) found only 71 % of surveyed cancer genetic counselors would discuss the importance of sharing genetic test results with at-risk relatives during the initial consultation when given a case example of a 40-year old patient with early-onset breast and ovarian cancer. Findings from an international survey of genetic counselors and geneticists (N=626) indicated that, although respondents consistently advised patients about familial implications of hereditary conditions, other types of support for family communication were limited, mainly due to lack of time, administrative assistance, and clinical support (Forrest et al. 2010). Forrest et al. (2010) reported the following differences in follow-up practices among genetic specialists: prepare a summary letter for their patient (79 %); offer a follow-up appointment to their patient (59 %); sometimes/always prepare a separate generic family letter (59 %); and offer appointments for at-risk family members (66 %). More research is needed regarding which types of genetic counseling interventions are most efficacious in encouraging cascade genetic screening, given the time and clinical constraints of genetic specialists. One such study taking place is a randomized controlled study using a patient-centered approach that looks at how telephone genetic counseling interventions might improve family uptake of genetic counseling (Gaff and Hodgson 2014; Hodgson et al. 2014).

Healthcare systems may also need to reexamine their systems of care, as many are not encouraged financially to provide an integrated model of care for individuals at high-risk for hereditary cancer syndromes. Magee-Women's Hospital in Pittsburgh developed a program of coordinated care in a multidisciplinary clinic for women at a high risk clinic for breast and ovarian cancer and reported getting reimbursement of only 59 % for their direct costs for genetic services annually (Engel et al. 2012). Gustafson et al. (2011) found that a large medical system received reimbursement for 63 % of encounters from third-party private payers (N=289) with the integration of genetic services consistently across non-genetics specialty departments.

Patient Factors

Patients themselves may not fully participate in cascade genetic screening by deciding not to disclose test results to their family members or not be tested as a symptomatic family member. Patients have described various reasons for not contacting some or all of their at-risk relatives including not being in close communication with relatives or deciding that the result would be less relevant to certain family members, such as older relatives. (Dugan et al. 2003; Fehniger et al. 2013; Chivers Seymour et al. 2010; Dilzell et al. 2014). Fehniger et al. (2013) looked at the uptake of *BRCA* testing in racially diverse family members (N=606) and found that 73 % of first and second-degree relatives knew about the *BRCA* test results as reported by patients who were *BRCA* positive, and 31 % of eligible family members had testing. The frequency of communication and degree of relationship were the only significant and independent predictors of both disclosure of results and testing after adjusting for participant characteristics (Fehniger et al. 2013). African Americans and Asian Pacific Islanders were significantly less likely to disclose their *BRCA* mutation status, in comparison to Whites (Fehniger et al. 2013). Fehniger et al. also highlighted the importance of finding ways to reduce racial disparities, including culturally-specific genetic counseling and educational materials, to support family communication.

Due to the Health Insurance and Portability Act of 1996, healthcare providers are not permitted to disclose protected health information to relatives. There are exceptions when the risk of harm not to disclose health information outweighs protecting a patient's privacy, such as for certain infectious diseases or threats of physical harm (Dugan et al. 2003; Tarasoff v. Regents 1976). Non-disclosure of hereditary risk of genetic disease by the healthcare provider to relatives is further reinforced by a dominant ethos that the healthcare provider's respect for their patient's confidentiality and autonomy is stronger than the duty to warn at-risk relatives (Dugan et al. 2003; Laberge and Burke 2009; Offit et al. 2004; Sharaf et al. 2013).

Several medical societies have placed emphasis on the role of the healthcare provider to communicate with the patient about the importance of sharing relevant test results with family members (Laberge and Burke 2009). The American Society of Human Genetics (1998) Statement on professional disclosure of familial genetic information describes a set of 'exceptional circumstances' in which a healthcare professional's legal and ethical obligations makes disclosure permissible, including when serious harm is likely to occur and the disease is preventable, treatable, or risk reduction possible. Some family members, as well as genetic specialists (Dugan et al. 2003), have challenged the principle of non-disclosure of genetic test results to family members, and several lawsuits have been filed by family members against providers regarding non-disclosure of test results (Offit et al. 2004). The role of the healthcare provider in informing at-risk family members may be changing and a revised clinical guideline for LS recommends a stepwise approach by providers to encourage familial communication, and also includes the possibility of informing a family member without the patient's consent (Menko et al. 2013).

Chivers Seymour et al. (2010), in a systematic review of research on family communication about late-onset hereditary cancer, identified the supportive role of the healthcare

provider as one key factor to aid family communication. When patients share genetics information with relatives, communication barriers may occur as a result of a lack of comfort with sharing test results or misunderstanding test results, especially with variants of unknown significance results (Vos et al. 2011). Support from a healthcare provider can help improve understanding of genetic test results and the validity of the information received (Chivers Seymour et al. 2010; Vos et al. 2011). Based on telephone interviews, Crotser et al. (2010) described at-risk family members (N=8) as feeling isolated and anxious from learning about a familial mutation, as well as after receiving their own test results. They expressed a need for better decision-support, counseling, and educational resources from healthcare providers (Crotser et al. 2010).

Educational materials are a useful aid in supporting informational needs by family members. Dilzell et al. (2014) in a survey of patients diagnosed with LS (n=74), found that patients informed 88 % of their first-degree relatives and half shared a genetic counseling note with their relatives. The results from the Dilzell et al. study (2014) showed that family members who received any educational material, whether it was a genetic counseling note or information from an educational website, were more likely to follow-up with a clinician (74 vs. 22 %, $p \leq .001$) and attend a genetic counseling appointment (43 vs. 16 %, $p \leq .001$). A higher mean number of educational materials shared with relatives was also positively correlated with increased likelihood of both seeing a clinician and having genetic counseling (Dilzell et al. 2014).

LaPointe et al. (2013) looked at patients who had *BRCA* testing and how life events, such as a cancer diagnosis or a death in the family, helped generate family discussion about cancer risk. There was considerable interest among patients in having multiple informational resources to support family communication (LaPointe et al. 2013). Individuals with a higher education level had a stronger association with interest in an educational website, whereas family members who were less open to discuss cancer in their family were more likely to be interested in support groups (LaPointe et al. 2013). A newer, promising development includes educational websites that offer communication tools for families to share individual risk information, such as KinTalk for LS, HBOC, and other hereditary cancer syndromes (Kardashian et al. 2012; Jasperson 2013; University of California at San Francisco n.d.). Considering the evidence that healthcare providers play an important role in decision management and improving family communication, having a genetic specialist and informational resources available to support patients can have a strong impact in reducing anxiety, improving the accuracy of information received, and helping family members make informed decisions about seeking genetic counseling.

Policy Factors

Healthcare policies are oriented toward improving health outcomes for individuals only, and do not necessarily address their close blood relatives. Financial barriers to cancer genetic services, as seen in our case study, are significant for many individuals and their families. Males and symptomatic females do not qualify for a no-cost sharing policy (as applicable to non-grandfathered health plans) under the Affordable Care Act (ACA) for HBOC genetic counseling and testing, which is based on the U.S. Preventive Task Force (USPSTF) clinical preventive guidelines (USPSTF 2013; U.S. Department of Health and Human Services 2012). The USPSTF recommendations do not include either at-risk males or females with a personal history of an HBOC-related cancer (USPSTF 2013), since males do not have a strong individual preventive benefit from HBOC testing and the prevention of new primary cancers in symptomatic females is considered management. In some clinical scenarios, a male or a symptomatic female may be the most appropriate individual for testing in a family, yet the USPSTF recommendations result in policy barriers to following this best approach. For patients with a grandfathered health plan not covered by the ACA policy or a symptomatic female with any health plan, co-pays and deductibles can be a barrier to pursuing testing even if the service is a covered benefit. Decisions on family planning may be another reason that an individual at high risk for a hereditary condition might choose to be tested. When healthcare policies only address an individual, short-term perspective on prevention, the most appropriate family members may not receive necessary testing due to cost. As a result, genetic services may be less well-coordinated and cost-effective than is optimal.

Health insurance companies also have policies based on an individual approach in which they will only reimburse covered members for genetic services, even if their member may not be the most informative person in a family for testing (OGP 2011b, 2014). Some health insurance plans have started recognizing the economic value and health benefits of genetic testing for non-covered members, such as a symptomatic family member, if the result will influence management of the covered individual (OGP 2014). In a recent review of written policies among the top eight Oregon healthcare insurers (representing 86 % of the privately covered lives), there are two plans that will cover testing costs of HBOC for a family member (OGP 2014). All but one insurer has at least some coverage for HBOC testing for individuals with cancer, if it will affect their medical management, but not if the testing is solely for risk determination of other family members. This creates a dilemma if the appropriate relative to test has completed treatment or they are an obligate carrier; the additional information gained from genetic testing may not affect their personal management. Without testing for a genetic mutation(s) in a symptomatic individual, the at-risk family

members may either need to undergo more costly genetic testing or unnecessary screening (e.g., MRI scans), depending on the condition. This barrier to cascade genetic screening could be addressed with a policy change by insurers to cover genetic testing based on clinical guidelines for genetic services, regardless of their personal healthcare management.

An additional area to explore might be the business model of health insurance companies as a whole, where individual companies retain their customers on a scale of just a few years. For many chronic illnesses, health plan coverage and reimbursement for preventive and disease management services are based on a short-term and limited return on investment (ROI) point of view. In an investigation of the ROI of disease management (DM) programs, Goetzel et al. (2005) noted that, although almost all health plans have one or more DM programs, all 44 cost-benefit analyses of DM programs for selected chronic illnesses were between 3 months and 5 years. A short-term view of ROI when applied to genetic services limits the potential financial benefits of cascade genetic screening, as it can take many years for covered individuals and their family members to gain the rewards of cancer prevention. Health insurance companies may better reconcile their needs and those of their clients, if policies were developed to encourage a coordinated effort of sharing population risks within the health insurance community and include private and public health partners (Bowen et al. 2012).

Discussion

Cascade genetic screening offers the opportunity to more broadly increase awareness, prevention, and screening among individuals at higher risk of developing heritable diseases. The scope of genetic services encompasses prevention for a lifetime and impacts multiple generations of family members. A family-centric approach to screening promotes disease prevention and early diagnosis of heritable conditions on a population health level. The rapid growth in the availability of predictive genetic testing, and the opportunities for coordinated care from cascade genetic screening, provides impetus to envision a wider view of prevention and a more family-centric approach to clinical care.

Public health efforts could emulate other models to improve the efficacy of cascade genetic screening. Public health departments offer reduced or no-cost testing for those unable to afford testing for sexually transmitted diseases and partner referral services. Similar approaches could be provided to increase family member referrals and reduce financial barriers to genetic counseling and testing services (Bowen et al. 2012). Cancer or genetic registries could be used to help patients and at-risk family members learn about their risk for hereditary conditions (Bowen et al. 2012; Cox et al. 2014; Forrest et al. 2010).

In Oregon, state health reform initiatives focus on the "Triple Aim" of better population health, better quality of care, and lower costs (Institute for Healthcare Improvement n.d.). Coordinated Care Organizations have been created to bring together payers, public health professionals, and healthcare providers from different disciplines to work together (Oregon Health Policy Board n.d.). Cascade genetic screening aligns well with the "Triple Aim" in each of its goals: *better population health* - increasing awareness of hereditary conditions among family members; *better quality of care* - coordinating services for those who need testing; and *lower costs* – testing individuals within a family in the most cost-effective way and preventing hereditary diseases. The Oregon Genetics Program has ongoing efforts in the state to educate payers, healthcare providers, and policy makers about cascade genetic screening as a model that supports the goals of healthcare reform.

Conclusion

Cascade genetic screening offers considerable potential for cost and life savings, as well as increased awareness of heritable conditions within families. A more coordinated effort to fund and support cascade genetic screening would benefit individuals, healthcare systems, and health insurance companies. Consistent implementation of cascade genetic screening could significantly increase awareness, risk management, and prevention of many heritable conditions such as HBOC, LS, and FH. The family-centric approach of cascade genetic screening improves prevention and early diagnosis of heritable diseases on a population health level and could be better supported and augmented through changes in health policy.

Acknowledgments The Centers for Disease Control and Prevention (CDC) Cooperative Agreement, Division of Cancer Prevention and Control, provided funding for project activities through the Enhancing Breast Cancer Genomic Practices through Education, Surveillance, and Policy; CDC-RFA-DP11-1114; FOA DP11-114 award #5U58DP003790. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

Conflict of Interest The authors declare no conflicts of interest.

Animal or Human Studies No animal or human studies were carried out by the authors for this article. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients being included in the study.

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