Predictive Genetic Testing: Can Specialized Advanced Practitioners Quell Consumer Confusion?

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Author's disclosures of potential conflict of interest are found at the end of this article.

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Abstract

It is currently common to see advertisements on television, in magazines, and on the Internet for genetic tests to evaluate one's own risk for cancer. Medical direct-to-consumer (DTC) marketing is not new to us—we are used to seeing advertisements for medications, medical tests, and treatments to "ask your doctor about." But how well do these DTC campaigns, specifically those for genetic tests for cancer susceptibility, inform the general public about hereditary cancer and the risk of carrying a mutation? More importantly, how much do general health-care providers and even oncology practitioners understand about genetic testing for hereditary cancer syndromes? This article will discuss hereditary cancer syndromes, the genetics of inherited mutations, and the process of evaluating who is an appropriate candidate to undergo predictive genetic testing (PGT) for hereditary cancer syndrome–associated mutations. Psychosocial and family implications as well as the ethical, legal, regulatory, and social issues associated with PGT will be briefly touched upon. Both the positive and negative implications of DTC marketing of genetic testing as well as a discussion of research and lessons learned related to DTC marketing for PGT will be presented. As information and understanding of genetics continues to grow and evolve, a health-care provider dedicated to cancer genetics is crucial. Advanced practitioners who further specialize and credential in genetics are the ideal health-care professionals to fill this important role.

J Adv Pract Oncol 2011;2:71–85

The basics of our understanding of cancer are changing daily. Our knowledge base about the genetic and molecular components of cancer is continuously evolving, as are the ways in which we screen for, diagnose, and treat cancer. Genetic testing for cancer susceptibility is one field that is growing exponentially. Health-care providers have long been performing risk assessments for cancer susceptibility by obtaining information about personal and family history of cancer, age, exposure to known carcinogens, and lifestyle. The discovery of certain inherited genes associated with cancer syndromes has added an extra piece of information to use when assessing patients' risk of cancer. Germ-line testing for in-

herited predisposition to certain types of cancers is currently a well-accepted component of oncology medicine for those individuals who are identified as potentially having hereditary risk factors (Robson, Storm, Weitzel, Wollins, & Offit, 2010).

It is important to note that genetic information, albeit an important part of the equation, is only a piece of the picture when it comes to trying to predict one's risk of developing cancer. It seems that much of the population took the success of sequencing the human genome to mean that we *understand* the human genome. In fact, we have a long way to go when it comes to understanding genotype/phenotype correlations when applied to complex diseases such as cancer (Farkas & Holland, 2009). The science that genetic risk evaluation is based upon has evolved very quickly and will continue to change our understanding and clinical applications of predictive genetics for years to come (Shirts & Parker, 2008).

With the continual growth of information and the ever-evolving understanding of genetics and its correlation to cancer predisposition, the public, general health-care professionals, and even oncology specialists cannot be expected to remain fully informed on this complex topic, much less provide the complicated care required for patients and their families in the setting of genetic testing—a health-care provider dedicated to the specialty of cancer genetics is necessary. Further, an individual's genetic test result does not change over time, yet its interpretation over time likely will change (Shirts & Parker, 2008). Therefore, the concern of whose responsibility it is to recommend the appropriate screening and prophylactic treatments and follow up with patients at the necessary intervals must be addressed. With the prominent presence of direct-to-consumer (DTC) advertising and marketing of genetic tests for cancer susceptibility, demand for genetic testing as well as the need for interpretation of and education about these results will likewise increase in the setting of the coming oncology provider shortage (Erikson, Salsberg, Forte, Bruinooge, & Goldstein, 2007).

Finally, as with any genetic information, issues related to ethical, regulatory, advocacy, family, and psychosocial dynamics must be continuously addressed. The advanced practitioner (AP) who further specializes and credentials in genetics is the ideal health-care professional to fill this growing need in predictive genetic testing.

Predictive Genetic Testing

Predictive genetic testing (PGT) is generally ordered in individuals with high-risk features in order to determine (a) the presence of a mutation and (b) the likelihood of developing a particular disease (Hildt, 2009). For cancer, which is clearly a multifactorial disease, PGT is really a susceptibility test that provides information about the likelihood of developing cancer (genetic predisposition) (Hildt, 2009). This is in comparison with PGT for autosomal dominant diseases in which the specific disease almost surely will be present in an individual with that mutation present (e.g., Huntington's chorea); it also differs from genetic analyses to identify heterozygous *carriers* of a disease—those who will not develop the disease (e.g., cystic fibrosis) but whose status may affect their children (Hildt, 2009).

It is very important to be clear that when talking about PGT for cancer predisposition, the type of genetic testing being performed is *susceptibility testing*—we are gaining one piece of evidence about the risk of developing a multifactorial related disease. It is crucial to be sure the individual undergoing PGT for cancer susceptibility fully understands that the result will certainly not produce concrete predictions as to whether or not he will develop cancer, when he will develop cancer, or what the severity or the type of cancer would be. Also, for many of the available genetic tests for cancer susceptibility, there is the possibility of detecting a variant mutation of unknown significance (VUS) in the person being tested—which means at this time the risk of developing cancer is unknown, we are not able to say what the mutation means about their risk of developing cancer in the future.

Most of the inherited cancer syndromes can be explained by Knudson's Two-Hit Hypothesis, which states that two genetic alterations, or "hits," have to occur in order for cancer to develop. In people with hereditary cancer, the first hit (the mutated gene) is acquired through the germ line and is present in every cell. The second hit is a somatic (or sporadic) mutation which then clonally develops into a tumor (Bunz, 2008). So, cancer related to the inheritance of a mutated gene is not phenotypically expressed (tumor develop-

ment), as the presence of the normal allele masks it. The phenotypic expression does not occur until a somatic mutation occurs to the nonmutated allele (Bunz, 2008). The Two-Hit Hypothesis is depicted in Figure 1.

Genes associated with hereditary cancer syndromes may be highly penetrant (Bunz, 2008), but they are also extremely rare in the population (Lindor, McMaster, Lindor, & Greene, 2008). Penetrance is defined as the probability that disease will appear when a disease-related genotype is present (Calzone, Masny, & Jenkins, 2010). That is, a percentage of individuals who carry a gene for a hereditary cancer syndrome will develop the associated cancer, yet a percentage of people carrying that mutation will not develop cancer. Breast cancer is a good example to illustrate how although hereditary cancer syndromes may be highly penetrant, they are also rare in the population. Breast cancer is a common disease in women but only about 5% to 10% of all breast cancer is hereditary and less than 1% of the general population carries a mutation in the *BRCA1* or *BRCA2* gene (Matloff & Caplan, 2008). Yet although *BRCA1* or *BRCA2* mutations are rare in the population and do not account for most cases of breast cancer, these mutations are highly penentrant—approximately 60% of mutation carriers will develop breast cancer (National Cancer Institute, 2010).

It is crucial for health-care professionals who provide genetic testing services for cancer susceptibility to not only understand the mechanisms of genetics behind inherited cancer syndromes, carcinogenesis, and genetic pathways of cancer, but also have the ability to effectively educate patients. Being able to assess the learner's educational needs and explain difficult concepts in a way that matches the learner's style and education level are crucial skills.

Syndromes of Inherited Cancer Predisposition

Table 1, though not comprehensive, shows the complexity of genetic tests available for some inherited cancer syndromes. This table demonstrates that genetic testing is not straightforward, even when setting out to test for a specific cancer type. As one can clearly see, breast cancer, for example, is involved in many of the inherited syndromes; the clinician considering PGT for a patient would need to be astute in both gaining additional information as part of the risk assessment and performing the correct genetic test—perhaps testing for the *PTEN* gene for Cowden syndrome may be more appropriate than testing for *BRCA1/2* for hereditary breast and ovarian cancer. This is just one example of how a health-care professional who is not specialized in the field, much less the general public, would not

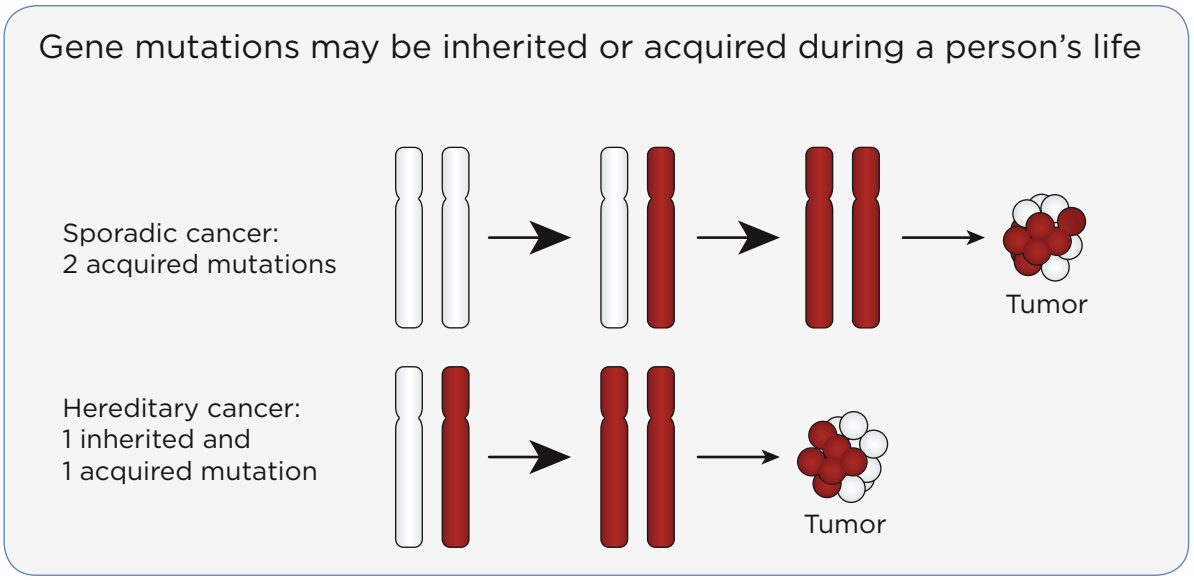

Figure 1. The Two-Hit Hypothesis (Demmer, 2005).

Table 1. Inherited Cancer Syndromes

Syndrome	Gene	Associated cancers
Hereditary breast/ovarian cancer (HBOC) syndrome	*BRCA1* *BRCA2*	Male and female breast, ovarian, pancreatic, prostate, melanoma
Cowden syndrome	*PTEN*	Endometrial, male and female breast, thyroid
Li-Fraumeni syndrome	*TP53*	Sarcoma, breast, brain, leukemia, lymphoma, adrenocortical carcinoma
Peutz-Jeghers syndrome	*STK11*	Breast, colorectal, endometrial, cervical, gastric, lung, pancreatic, ovarian
Lynch syndrome	*MLH1* *MSH2* *PMS2* *MSH6*	Colorectal, endometrial, adenocarcinoma, gastric, biliary tract, urinary tract, ovarian, small bowel, pancreatic
Family adenomatous polyposis (FAP)	*APC*	Gastric, duodenal, colon, pancreatic
MYH-associated polyposis	*MYH*	Colon, duodenal
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric and lobular breast carcinoma
Hereditary pancreatic cancer	*PALLD*	Adenocarcinoma of pancreas
Hereditary prostate cancer	*HPC1* *HPC2* *HPCX*	Prostate
Hereditary cell nevus syndrome or Gorlin syndrome	*PTCH*	Multiple basal cell carcinoma, medulloblastoma, ovarian fibrosarcoma
Hereditary melanoma	*CDKN2A*	Melenoma, pancreatic
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	Adrenal cortical, carcinoid, islet cell pancreatic
MEN type 2	*RET*	Medullary thyroid, bilateral pheocromocytomas

Note. Adapted from Calzone et al., 2010.

necessarily be positioned to provide the highest level of genetic testing for cancer predisposition.

Benefits

Screening for cancer in nonsymptomatic, high-risk individuals is done with the purpose of early detection of precancerous lesions or localized disease at a stage that may increase the chance for cure, slow progression, prevent complications, limit disability, and enhance quality of life (Tranin, Masny, & Jenkins, 2003). The National Comprehensive Cancer Network (2010) provides recommended guidelines for screening and risk reduction strategies for carriers of mutations for familial cancer syndromes. For individuals who carry a genetic mutation that greatly increases their risk of developing cancer, healthcare providers are responsible for educating them about the importance of appropriate risk reduction strategies as well as increased screening for early detection of the type of cancer they are at increased risk of developing. As with all healthcare education, the focus should be done in the context of giving control to the patient when it comes to informed decision-making. This includes decisions about prophylactic surgery, chemoprevention, and screening. Clearly, careful consideration must be taken when recommending surgery or prescribing chemopreventive agents to healthy individuals, with attention paid to toxicity, cost, and morbidity (Zon et al., 2009). Risks and benefits of surgical and chemopreventive agents should be assessed in the context of the individual's current health status, life expectancy, and level of risk for developing cancer (Zon et al., 2009). Advanced practitioners should also

strive to enable these specific patients to take an active role in their health through self-examination, nutrition, and close follow-up, focusing on reducing morbidity and mortality and increasing quality of life.

Testing an individual who is affected (already has a diagnosis of cancer) can be beneficial in helping to identify the cause of their cancer and make health-care decisions for themselves and their family based on the information gained.

Psychosocial and Familial Implications

The potential for a negative psychosocial response of unaffected (no cancer diagnosis) individuals to a positive genetic test result (deleterious mutation identified) has been a major concern of clinicians since testing first became available (Raymond & Everett, 2009). Certainly a test result that provides definitive information may have significant psychological significance. A negative test in an individual from a family with a known deleterious mutation may produce relief for his/her risk as well as the risk of their children, who are now at the same risk level as the general population. Thus, unnecessary medical and surgical interventions can be avoided (ASCO, 2003). Noncarriers, however, may also feel guilt or worry about the future health of a family member who is a mutation carrier (van Oostrom et al, 2007). Feelings of guilt and anger can be expected among members of a family who carry a hereditary mutation (i.e., parents that passed on the gene, between siblings, etc.).

A positive test result and its subsequent interventions surely may cause an individual and family distress (ASCO, 2003). An identified mutation carrier may also experience positive benefits from knowing her genetic status, such as feelings of empowerment and relief about finally having some knowledge about her situation. In the absence of a known familial mutation in the gene being analyzed, a negative genetic test may falsely give relief, when in fact, the individual may remain at heightened risk of cancer by virtue of family history and lifestyle behaviors (smoking, high-fat diet, etc.; ASCO, 2003). The potential for misinterpretation of negative test results or nondefinitive results certainly has the potential to lead to a false sense of risk level and mismanagement of patient care. The physical risk of having blood drawn or a sample of saliva taken is quite minimal, yet the impact of the test results on the patient and her family is a significant risk associated with PGT.

Family implications are also a consideration to be addressed both prior to and after genetic testing results are disclosed, as clearly the genetic test of an individual will have an impact on the family. The serious legal and ethical issue of disclosing information must be considered in the context of confidentiality of the patient's genetic information vs. the family members' right to know about their genetic risk. Further complicating this ethical issue is the right *not* to know; that is, some family members may not want to be informed of their genetic risks, and according to the principle of nonmaleficence, this may be particularly significant for diseases for which there are no prevention or treatment options (Godard et al., 2006). Current laws being developed are inconsistent regarding a health-care professional's duty to warn family members about their potential risk (ASCO, 2003). The importance of disclosure to all at-risk family members is clear, as this information may impact their decision to undergo PGT.

Certainly this issue will continue to be one of debate ethically and legally as PGT continues to grow; as providers of PGT, APs certainly should be involved with policy and clinical guideline development. Providers of PGT services must be able to offer support and appropriate recommendations to patients and their families, and who better to do this than a specialized advanced practitioner?

Who Should Undergo PGT?

It is commonly, but mistakenly, assumed that the availability of testing for deleterious mutations for cancer predisposition syndromes means that testing can and should be routinely applied to anyone who is concerned about their familial cancer risk. However, the rarity of these mutations in the general population leads to unacceptable predictive value when applied to general population screening (Lindor et al., 2008). Obviously it can be confusing to the public, and even nonspecialized health-care professionals, to figure out who should undergo PGT, especially in light of increasing media for PGT. As stated earlier, genetic testing is only one piece of the puzzle of determining cancer risk. An accurate personal and in-depth family history is always the first

Table 2. Features suggestive of hereditary cancer syndrome

Unusually early age of cancer onset (e.g., premenopausal breast cancer)
Multiple primary cancers in a single individual (e.g., colorectal and endometrial cancer)
Bilateral cancer in paired organs, or multifocal disease (e.g., bilateral breast cancer or multifocal renal cancer)
Clustering of the same type of cancer in close relatives (e.g., mother, daughter, and sisters with breast cancer)
Cancers occurring in multiple generations of a family (autosomal dominant inheritance)
Occurrence of rare tumors (e.g., retinoblastoma, adrenocortical carcinoma, granulosa cell tumor of the ovary, ocular melanoma, hepatoma, or duodenal cancer)
Unusual presentation of cancer (e.g., male breast cancer)
Uncommon tumor histology (e.g., medullary thyroid carcinoma)
Rare cancers associated with birth defects (e.g., Wilms tumor and genitourinary abnormalities)
Geographic or ethnic populations known to be at high risk of hereditary cancers. Genetic testing candidates may be identified based solely on ethnicity when a strong founder effect is present in a given population (e.g., Ashkenazi heritage and *BRCA1/BRCA2* mutations)

Note. Obtained from National Cancer Institute.

step in cancer risk assessment, which is then used to select what genetic test, if any, is indicated (Calzone & Soballe, 2008). Even when evaluating individuals who are known to be mutation carriers in the family, a thorough family history is necessary as more than one gene mutation can be segregated in a family (Calzone & Soballe, 2008). Pathology reports and death certificates are often required to confirm family history, as inaccurate reports of family history are common (Calzone & Soballe, 2008), and criteria for appropriateness of PGT varies according to syndrome. Identifying who should undergo PGT requires sufficient time and knowledge. Table 2 indicates general features that are suggestive of the presence of a hereditary cancer syndrome.

The decision to offer PGT extends beyond the evidence from the personal and family history for a possible inherited susceptibility mutation to include the ability to interpret and the potential benefit of the information gained. The American Society of Clinical Oncology (2003) recommends that PGT be offered in the setting of pre- and posttest counseling when all of the following conditions are met:

- The individual has personal or family history features suggestive of a genetic cancer susceptibility condition
- The genetic test can be adequately interpreted
- The test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

With direct-to-consumer marketing efforts, patients will drive the demand for genetic testing. It is the responsibility of providers of genetic testing services to evaluate the appropriateness of predictive genetic testing, accurately interpret test results and their implications, and assess the potential impact on patients and their families.

Education, Counseling, and Informed Consent

Pre- and posttest education and counseling, an integral component of the PGT process, includes the following: education regarding essential information on the suspected syndrome and gene; assessment of psychosocial issues associated with testing; review of the risks, benefits, and limitations of testing; considerations of possible test outcomes and implications; and discussion of disclosure of test results and the implications to family (Calzone & Soballe, 2008). The underlying principles of genetic counseling are education, autonomous decision-making, and assessment of and attention to psychosocial issues that may impact adjustments to test outcomes. Special considerations should be given to facilitating autonomous decision-making when there is no evidence

of effective screening or prevention options, such as for the *p53* mutation associated with Li-Fraumeni syndrome (Calzone & Soballe, 2008).

A meta-analysis was conducted by Braithwaite, Emery, Walter, Prevost, and Sutton (2006) to determine the quality and strength of evidence relating to psychological outcomes of genetic counseling for cancer syndromes. Their findings indicate that genetic counseling improved knowledge of cancer genetics but did not alter the level of perceived risk in the short term; however, prospective studies did report improvements in the accuracy of perceived risk. No long-term increases in general anxiety, worry, distress, or depression were found as a result of genetic counseling. It is clear that a provider of cancer genetic testing must have specialized knowledge of genetics and oncology, but it is also critical that they also have the specific skills needed to assess, educate, and counsel individuals and families. Evidence suggests that this type of highly specialized service should unquestionably be provided by individuals who are experts in PGT as competency of genetics remains limited across all health-care disciplines, with the exceptions of trained genetic specialists (Freedman et al., 2003; Harvey et al., 2007).

Informed consent is a crucial component to the genetic testing process, as the potential for discrimination, implications for the individual and their family, and the predictive nature of the information has resulted in a well-defined and accepted approach to consenting for PGT (Calzone & Soballe, 2008). Informed consent for PGT should only be offered by providers who can provide or make available adequate genetic education and counseling, fully explain benefits and risks of testing, and appropriately interpret results, and who have sufficient knowledge of preventive and surveillance options (Robson et al., 2010).

Interpretation of Results

There are three possible test results for PGT, which are either informative or uninformative:

1. A mutation is identified. This is, of course, very *informative,* and results indicate an increased risk of cancer. Again, the individual's actual cancer risk is not only based on the presence of a mutation but also based on the penetrance associated with specific mutations in specific genes.

2. No mutation is identified. If there is a known mutation in a family, a negative test will be *informative*—that individual did not inherit the known mutation. Not finding a mutation in the absence of a known mutation in the family is *uninformative* because a hereditary basis for cancer in the individual or the family has not been established and, therefore, a genetic predisposition to cancer cannot be ruled out. Reasons for an uninformative test result include the following: the cancer in the family may be associated with a cancer susceptibility gene other than the one being tested for, the cancer in the family is associated with a gene mutation but the cancer in the individual who underwent testing is not associated with that mutation, there is a limited sensitivity of the testing techniques used to detect mutations leading to false negatives, the cancer tracking in the family may be due to shared environmental conditions rather than a germline mutation, and the gene has not yet been identified within the hereditary cancer syndrome (NCCN, 2010; Calzone & Soballe, 2008).

3. A variant of uncertain significance is identified. This means that a genetic mutation has been found, yet the extent that this mutation increases cancer risk, or whether it is associated with the history of cancer in the family, is uncertain (NCCN, 2010). As our genetic knowledge increases, a particular VUS may be reclassified later as either benign or deleterious, but this may not happen for years (Calzone & Soballe, 2008), making this result *uninformative* in the meantime for this individual. Close follow-up of these individuals is crucial and notifications of changes in the status of this result (e.g., whether the mutation is upgraded to deleterious or downgraded to polymorphism) are imperative to report to the patient. Enrollment of these individuals into research studies is often appropriate.

The interpretation of these three possible outcomes as being either informative or uninformative is far from clear-cut, and depends on whether there is a known deleterious mutation in the family for that individual being tested. The ideal person to undergo testing for a hereditary cancer syndrome is always an individual affected by the cancer of concern, as this yields the most useful information for establishing the genetic basis for cancer. If no mutation in the affected person is detected, genetic testing is considered uninformative (as far as the cause of the affected individual's cancer or that of his family members) and there is no basis for test-

ing relatives for that mutation (NCCN, 2010).

Testing performed in an individual from a family in which a deleterious mutation is known is the most informative and can yield one of two possible results: the mutation known to the family is detected or it is not (NCCN, 2010). If the mutation in the family is detected in an individual, cancer risks are then based on the penetrance data for mutations in that specific gene. For example, 20% or more of men and women with mutations in the *MLH1* or *MSH2* genes will never develop colon cancer (Calzone et al., 2010). Environmental factors and possibly other inherited factors also affect penetrance (Calzone et al., 2010). If the mutation is not found in an individual from a family with a known mutation, their risk of cancer is equivalent to that of the general population (NCCN, 2010). It should be noted that other risk factors and family history from the individual's other side of the family not associated with a documented mutation may increase their risk of cancer above that of the general population (NCCN, 2010).

When no familial mutation has previously been identified, the interpretation of genetic tests is much more complex (Calzone & Soballe, 2008). Figure 2 shows the complexity of interpreting genetic results and determining cancer susceptibility. It is evident that the interpretation of test results is very complex. It is easy to conceive of a health-care professional who is not specialized in PGT making inaccurate interpretations and therefore inappropriate recommendations for the individual undergoing testing. Advanced practitioners trained in interpreting these complex results are also capable of the close follow-up required of individuals who are not only identified as carriers of a known mutation, but also of individuals who have uninformative (though maybe significant) results.

Direct-to-Consumer PGT

Direct-to-consumer advertising (DTCA) or marketing (DTCM) is a promotional effort by a pharmaceutical company or other provider of medical services to present information about medications or medical services to the public in the lay media (Wilkes, Bell, & Kravitz, 2000). There are two types of DTCA (Abel, Burstein, Hevelone, & Weeks, 2009): the type that targets undiagnosed individuals with the goal of encouraging potential patients to seek primary evaluation and treatment, vs. the type that targets patients who already have a disease with the aim of prompting them to request changes to their treatment. In the United States, we are very familiar with DTCA for medications and medical interventions. Susceptibility testing for disease is now theoretically applicable to everyone, where previously genetic testing was limited to particular contexts such as pregnancy, high-risk family histories, and clinical findings (Wade & Wilfond, 2006). Direct-to-consumer advertising for genetic testing for hereditary cancer syndromes is relatively new.

Until recently, genetic tests were only ordered by health-care professionals. The preceding discussion indicates the very real need for a highly specialized health-care professional to provide PGT for cancer syndromes. Recently a number of companies have begun to offer genetic tests and genomic risk profiles directly to consumers, usually through the Internet (Genetics and Public Policy Center, 2010), with results being reported directly to the consumer without an independent health-care provider. These DTC genomic profiles are out of the scope of this paper; however, APs providing genetic testing will need to remain knowledgeable about available DTC tests in order to provide accurate interpretation and recommendations to patients and other health-care professionals regarding appropriate interventions based on results obtained from these tests. Direct-to-consumer advertising refers to tests advertised but not directly sold directly to the consumer (Hudson, Javitt, Burke, Byers, with ASHG Issues Committee, 2007); these types of campaigns for PGT will be the focus of this discussion.

Benefits and Drawbacks of DTC Campaigns

Successful DTC marketing campaigns for PGT that target the general public may significantly and repeatedly increase public knowledge regarding health topics (Mansfield, Mintzes, Richards, & Toop, 2005) such as hereditary cancer syndromes. It may also empower patients to seek medical care for undiagnosed conditions and possibly even facilitate patient-provider communication (Abel, Lee, & Weeks, 2007). Certainly a potential benefit of DTC campaigns for PGT is the ability to reach a large portion of the population, including those individuals who may

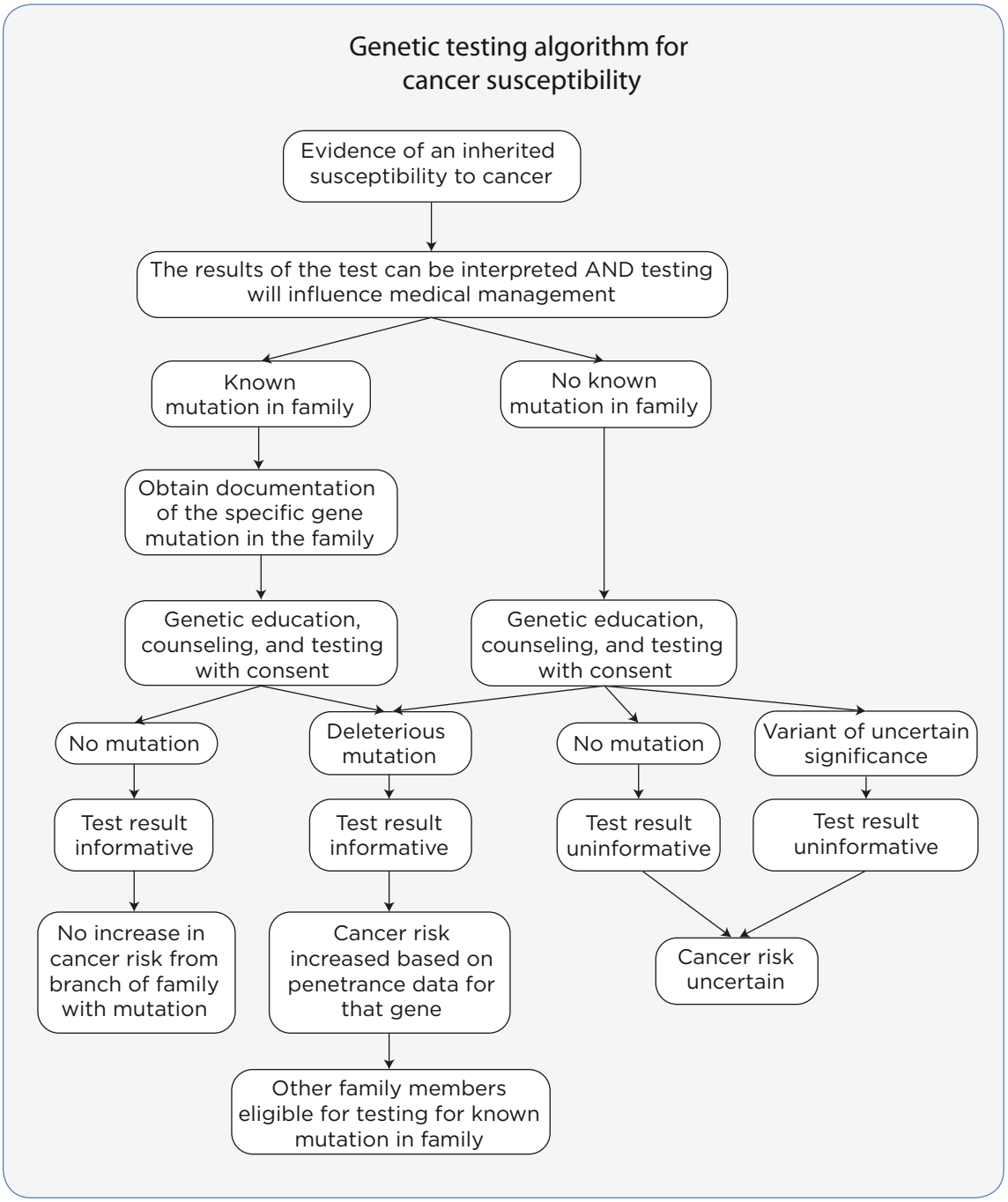

Figure 2. Interpretation of genetic testing results. Adapted from NCI, 2010.

be appropriate for testing; of course identifying carriers of deleterious mutations provides the opportunities for prevention, screening, and early detection discussed previously. Ethical notions of autonomy and self-determination back the argument of a patient's "right to know" about one's own body and genetic makeup (Wasson, 2008). One major drawback of DTC campaigns specific to PGT is the current lack of regulatory oversight. The US Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications monitors compliance with set regulations for advertising and marketing of medications in order to protect public health (Ameer & Krivoy, 2009). A similar oversight system is not yet in place for consumer-directed advertising of genetic testing. There is the potential for misrepresentation of the general public's risk of hereditary

Table 3. Potential Benefits and Drawbacks of DTC Marketing for Predictive Genetic Testing

Potential benefits of DTC marketing for PGT

- Individuals able to pursue insight into genetic makeup
- Increase in public knowledge and awareness of hereditary cancer syndromes
- Improved patient/health-care provider communication
- Sense of relief/empowerment for individuals who receive an informative result
- Opportunity for prevention, screening, early detection in identified mutation carriers
- Campaigns have ability to reach large portion of population, including individuals who should be tested

Potential drawbacks

- Current lack of marketing regulations that exist for pharmaceutical DTC campaigns
- Individuals who are not appropriate for PGT compelled to be tested
- Health-care providers feel pressure to perform tests, even when not appropriate
- Wasting of health-care resources as follow-up to inappropriate genetic tests
- Misinterpretation of test results
- Misrepresentation of general public risk leading to fear and confusion
- Campaigns too broad, reaching many individuals who are not appropriate to testing
- Socioeconomic status differences in access to PGT

cancer. The broadness of these campaigns will reach many individuals who are not appropriate candidates for testing, which in turn leads to an increased demand for testing and potential wasting of health-care resources when applied to the general population. Table 3 provides this author's opinions about the potential benefits and drawbacks of DTCA when applied to PGT.

Some of these benefits and drawbacks have been shown by Myriad Genetics Laboratories (a Utah-based biopharmaceutical and genomics company) in their campaign related to the BRAC*Analysis* genetic susceptibility test for hereditary breast and ovarian cancer. This campaign was the first mass media effort to promote genetic testing to the general population (Lowery, Byers, Axell, Ku, & Jacobellis, 2008; Myers et al., 2006). In 2002, Myriad Genetics launched a pilot consumer awareness campaign in the Denver and Atlanta media markets to promote awareness of *BRCA1* and *BRCA2* genes that significantly increase risk for breast and ovarian cancer and for its BRAC*Analysis* test (Lowery et al., 2008; Williams-Jones, 2006). The campaign targeted women between the ages of 25 and 54 who had a relative with breast or ovarian cancer (Lowery et al., 2008). Television advertisements showed young, healthy, ethnically diverse women talking about having family members with breast cancer and wanting to learn about their personal risk in order to gain control over the disease (Mykitiuk, 2004). "After BRAC*Analysis*, I realized I could choose to do something now," states one woman, suggesting that by using the BRAC*Analysis* test, women are empowered to learn their risk status and explore appropriate prevention and treatment options (Williams-Jones, 2006).

According to Myriad's media campaign website, the reason they were launching their campaign was because hereditary breast and ovarian cancer syndrome is underdiagnosed, and they hoped to educate women and their physicians about the syndrome and ways to take action to reduce cancer risk (Williams-Jones, 2006). Myriad's advertising stated that only 5% to 10% of breast cancers have a hereditary cause, but did not mention that the *BRCA* test will detect positive mutations in only 17% to 25% of patients with a strong family history, defined as a first-degree relative with breast cancer (Williams-Jones, 2006). Further, Myriad's criteria for testing included having only one affected relative. Because breast cancer is common in the general population, most of the people purchasing the test will be found not to carry a mutation, which would have been predicted by the person's lack of significant family history without PGT (Williams-Jones, 2006).

There is certainly cause for concern about

women being misinformed regarding the appropriateness of self-testing. Ethical issues arise about whether this campaign exploits the general public's fear of cancer and their lack of understanding about genetic susceptibility, as well as the potential for financial gain by companies at the cost to consumers who are not appropriate candidates for testing. A study by Lowery et al. (2008) assessed the impact of the Myriad DTC marketing for genetic testing for breast and ovarian cancer in Denver. They found that the campaign did in fact reach a large audience, including women at increased risk (i.e., those with a first-degree relative with breast or ovarian cancer). These women, who would be candidates for genetic testing, were more likely to recall seeing the advertisements than women at general risk. About half of the high-risk women who recalled seeing or hearing the advertisements stated that they were more interested in having testing, indicating that the campaign was effective in impacting its target population. At least one-third of general risk women who were surveyed, who would not be appropriate for testing, however, also expressed interest in having genetic testing for *BRCA1* or *BRCA2* mutations, suggesting that the campaign was too broad in its scope and that women were misinformed about their risk and the appropriateness for undergoing testing. It becomes imperative, therefore, for knowledgeable health-care professionals to educate patients about their given risks and the fact that they may not be appropriate candidates for genetic testing.

Impact of DTC Campaigns on Referrals

Another study conducted by Mouchawar et al. (2005) in Colorado found an increase in genetic counseling referrals during and after the time of the Myriad campaign. The majority of these referrals were for women who were of general risk and not appropriate candidates for testing, again implying that the marketing campaign was leading women to believe they were at a higher risk than they actually were, requiring genetic testing. Yet another study, conducted by the Centers for Disease Control and Prevention (2004), compared the impact of the marketing campaign on the public and health-care providers from the pilot cities (Denver and Atlanta) with two comparison cities (Raleigh-Durham and Seattle). This study found that there was an increase in both consumer and provider awareness of *BRCA1* and *BRCA2* testing in the pilot cities. Providers in the pilot cities also perceived of being asked a higher incidence of questions about *BRCA* testing, more *BRCA* tests being requested by patients, and more tests actually being ordered by physicians. In all four cities, primary care providers reported that they lacked the knowledge to adequately advise their patients about hereditary breast and ovarian cancer and genetic testing. These findings all show that such a marketing campaign targeted at the general population is effective in raising awareness, but is without the necessary corresponding understanding (by both the public and health-care professionals) of genetic testing for cancer susceptibility or of the applicability of the tests to the general public.

Myriad Genetics launched another large marketing campaign for BRAC*Analysis* in the Northeast in 2007, with "Be Ready Against Cancer Now" advertisements promising viewers that "cancer doesn't have to be inevitable" (Matloff & Caplan, 2008). Again, they omit the fact that the majority of breast cancer is not hereditary, or that the population rate for *BRCA* mutations is less than 1% (Matloff & Caplan, 2008). They do not clearly provide the risk factors that make a person a good candidate for testing. The advertisements seem to oversimplify the benefits ("Reduce my cancer risk now"), suggesting an easy and definitive answer, while none of the possible risks of testing are mentioned (uninformative results, psychological distress, genetic discrimination, cost, etc.; Matloff & Caplan, 2008). It seems that despite the criticism generated by the pilot campaign, subsequent marketing ventures, although billed as a "public awareness campaigns," omit most of the information necessary to actually educate the public (Matloff & Caplan, 2008) about who should undergo PGT.

Direct-to-consumer advertising may play an important role in educating the general public about hereditary cancer syndromes and increasing our ability to identify individuals who are appropriate candidates for testing. These campaigns should be held to regulations to protect the public and the health-care system as a whole from inappropriate use of PGT. Advanced practitioners need to be involved in the ongoing efforts to ensure adequate oversight of advertising claims made by genetic test manufacturers. With

the increasing demand for genetic testing that will accompany DTCA, specialized health-care providers will be necessary to identify and educate those who are and who are not appropriate candidates for testing.

Financial, Ethical, Legal, and Social Considerations

In the United States, we are afforded a huge degree of freedom and choice when it comes to making decisions about one's own body and health (Wasson, 2008). The medical community is ethically bound to respect patients' decisions about their health choices—even those that go against medical advice—as long as those choices are made in an informed manner. It is hard to argue that genomic and genetic testing should be any different. If we believe this, then individuals should have the right to undergo PGT, even if not deemed appropriate by an educated health-care professional and not resulting in informative results. It should also be acknowledged that insurance companies should not be held accountable for paying for tests in these circumstances. Genetic testing is expensive, with costs ranging anywhere from several hundred to several thousand dollars with variable insurance coverage (NIH, 2010). In many cases, when a physician recommends genetic testing for a hereditary cancer syndrome, health insurance companies will pay these costs (if the patient meets their testing criteria, which vary between companies). If a person does not meet the criteria for coverage by insurance (or decides not to have insurance pay for personal reasons, such as fear of discrimination), he is able to pay out of pocket (NIH, 2010).

Genetic testing cannot be discussed without mentioning the ethical concerns about confidentiality; genetic discrimination with regard to employment, health, and life insurance; equity of access; and stigmatization (Zimmerman & Kroese, 2007). These ethical, legal, and social implications of genetic testing are beyond the scope of this paper but they are extremely important. With the Genetic Information Non-discrimination Act as the "law of the land," individuals should be free to seek out their genetic information as they choose (Farkas & Holland, 2009). However, with the lack of regulations and oversight, what is done with genetic information and how privacy is protected is not always very clear. Further, with concerns about genetic discrimination with regard to health or life insurance, DTC genetic testing offers individuals a means of obtaining their genetic makeup privately without going through standard medical channels; this may be another benefit of DTC testing (Wasson, 2008). In fact, a selling point of some DTC companies is their increased privacy. However, patients are not told that failure to indicate results of genetic testing in life insurance or disability applications could be considered fraud (ACOG, 2008).

Finally, as with other health-care disparities, individuals of higher socioeconomic status may have a higher uptake of PGT services (Bowen, Harris, Jorgense, Myers, & Kuniyuki, 2010), whether that be due to level of education or access to health-care or insurance coverage. Specialists in the area of PGT should continue to critically examine the spectrum of DTC advertising and tests and the ethical, legal, and social issues associated with them.

Role of the Advanced Practitioner

Oncology professionals at all levels practice, to some degree, in genetics, with one level to the next being distinguished by educational preparation, professional experience, practice specialty, and specific job roles and responsibilities (Tranin et al., 2003). Understanding the genetic and genomic mechanisms of caner etiology, diagnosis, and treatment is now central to the role of the AP and is reflected by an action plan in progress for the integration of genetic competencies into nursing curricula, licensure, and registration examinations; specialty certification processes; and continuing nursing education (Calzone et al., 2010).

As has been shown in the preceding discussion, PGT for cancer syndromes is extremely complex—there is far more to it than just obtaining a blood or saliva sample from a patient. Considerations include increased time necessary to devote to genetic counseling, lack of educational preparation of most health-care professionals to provide this service, along with the increasing number of individuals requiring genetic service. Advanced practitioners have been able to, and should continue to, fulfill a vital role in providing this essential service (Snyder, Lynch, & Lynch, 2009; Tranin et al., 2003). The Oncology Nursing Society, the International Society of Nurses in

Genetics (ISONG), and the American Nurses Association (ANA) have developed standards and/or guidelines to define the role and scope of practice of APNs providing cancer genetic counseling. The ISONG and the ANA have published a Statement on the Scope and Standards of Genetics in Clinical Nursing Practice (Snyder et al., 2009). Further, the Genetic Nursing Credentialing Commission (GNCC, 2010) provides an opportunity to be credentialed for master's prepared APNs in genetics (APNG). Achieving credentialing for nurses in genetics is a great milestone in nursing history (Greco & Mahon, 2003).

Snyder et al. (2009) describe the logistics of an APN-led hereditary breast cancer prevention clinic from referral logistics, completion of an in-depth health and family history and pedigree, educating and counseling to facilitate autonomous decision-making, communicating results, and managing follow-up. They have found that APNs, given their background and experience in the oncology setting, when coupled with intensive training in hereditary cancer syndromes, become the ideal professionals for helping patients at high risk for hereditary breast cancer in collaboration with the patient's family and interdisciplinary team. The standards for the accomplishment of APNG status are extremely high, indicating the competency of an APN providing PGT, who must demonstrate the ability to apply extensive genetic knowledge according to the scope and standards of practice (Greco & Mahon, 2003). Table 4 describes the APGN credentialing requirements.

As the field of PGT continues to grow in complexity and demand, the need for highly specialized practitioners will increase. Advanced practitioners with a specialty in genetics are the ideal candidates to fill this role, as not only do they receive extensive education and training in hereditary cancer syndromes, they have also been prepared to provide preventative and screening services in order to reduce morbidity, mortality, and costly health problems. Providers in this role perform thorough risk assessments, provide education and counseling, and offer appropriate screening guidelines for all referrals or patients seeking PGT.

Follow-up for patients and their family members who are identified as carriers of a mutation for a hereditary cancer syndrome (as well as those with VUS or uninformative results) is critical and complex. With the growing field of genetics, the role of the oncology genetic nurse specialist will become more in demand by institutions by proving financial gains in multiple ways: freeing up the general provider's time through referrals by assuming responsibility for the lengthy assessments, education, and counseling appointments, as well as the recommendation of appropriate screening, medical treatments, and follow-up. All of these areas will generate revenue for the institution and attract new patients through effective community education.

Conclusion

Cancer is very complex, and our knowledge base is expanding daily from the areas of molecular genetics, diagnostics, treatments, and follow-up to survivorship. The complexity of hereditary cancer syndromes is also extremely intricate. This is an evolving field that requires specialized health-care providers who have an understanding of the biology of genetics as well as the psychosocial implications that may affect an individual and their families. Knowledge and communication skills are essential for this role, as counseling is the mainstay of providing genetic information.

It is clear that APs who have specialized training in genetics are prepared to competently and effectively meet the complex needs of patients at risk of carrying a deleterious mutation specific for a cancer syndrome, for patients who have been found to carry such a mutation (or a VUS),

Table 4. APNG Credentialing Requirements

- RN license in good standing
- Graduation from an accredited graduate program in nursing
- 300 hours of Genetic Practicum experiences as a clinical genetic nurse with greater than 50% genetic practice component
- Documentation of 50 cases providing genetic health care in past 5 years
- Four in-depth genetic case histories reflecting ISONG standards of genetic nursing practice
- Minimum of 50 contact hours of genetic content in the past 5 years

Note. ISONG = International Society of Nurses in Genetics. Information obtained from GNCC (2010).

and for the general public whose misconceptions and questions must be addressed appropriately. It is this author's opinion that it is very apparent that APs are prepared to provide evidenced-based recommendations to patients regarding the appropriateness of testing, screening, and follow-up. Specifically, they have the expertise to effectively follow up with patients as the clinical interpretation of genetic results change with our rapidly evolving understanding of genetics (Shirts & Parker, 2008). Advanced practitioners also have the skills to address complicated psychosocial, family, ethical, legal, policy, regulatory, and financial issues that accompany genetic testing at this point in time.

It is not feasible to expect general practitioners to be able to meet all of the complex needs of this group of patients. It is also not reasonable that busy practitioners will be able to advocate at system-wide, state, and national levels for these patients. Therefore, APs who specialize in PGT and all of its associated complexities are the ideal practitioners to provide this very important and necessary service to this unique group of individuals.

DISCLOSURES

The author has no conflicts of interest to disclose.

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