5. Ethics in the cancer clinic

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Abstract. While acquired genetic alterations are the basis of most cancers, a small but noticeable portion of cancers results from germ line mutations. There are some commercially available tests for mutation detection in these cancers. Although the tests would be useful from many aspects, it should be noted that many ethical dilemmas will emerge from the knowledge of the genetic susceptibility of an individual to cancer. The purpose of this chapter is to explain some hereditary cancer predisposing syndromes and ethical considerations for genetic testing by practitioners to offer some proper and practical recommendations.

Introduction

While acquired genetic alterations are the basis of most cancers, a small but noticeable portion of cancers result from germ line mutations. Several major types of these mutations have been characterized in the past few years by significant advances in molecular genetics. Nowadays, there are some
commerically available tests for mutation detection in cancer predisposing
genes, which can be used to identify people at high risk for hereditary cancers
and their referral for preventive options. These options include targeted
surveillance, chemoprevention, and surgical procedures.

Although genetic testing would be useful from many aspects, it should be
noted that many ethical dilemmas will emerge from the knowledge of the
genetic susceptibility of an individual to cancer. One of the major dilemmas
arises when a person with positive test results does not want to inform his/her
family members of their risks. Thus, the practitioner will be faced with a
challenge between confidentiality of the patient and his/her duty to warn the
index patient’s relatives. In the case of high penetrance cancers with effective
preventive options, this issue would be more pronounced. Therefore, the need
for outlining ethical principles and rules for clarifying such challenges and
offering proper options would be more realized.

There are more examples of such dilemmas, and because they are
common in cancer genetics clinics, practitioners should be aware of these
issues and relevant ethical rules and remedies. The purpose of this section is
to explain some of these issues to offer some proper and practical
recommendations. The 2003 statement of American Society of Clinical
Oncology (ASCO) policy on genetic testing for cancer susceptibility, its
update (Genetic and Genomic Testing for Cancer Susceptibility, 2010), and
Ethical Guidelines for Genetic Research in Iran will be used as the basis for
defining the ethical rules [1-3].

Hereditary cancer predisposition syndromes

The hereditary component of many cancers was recognized many years
ago. Epidemiologic studies showed that some cancers cluster in certain
families, and they have hereditary basis. For example, in 1865, Broca
described the incidence of hereditary breast cancer in four generations [4],
and in 1913, Aldrin Warthin characterized a family with a cluster of
gastrointestinal and gynecologic malignancies, which seemed to be hereditary
nonpolyposis colorectal cancer (HNPCC) [5,6].

Nowadays, Genetic testing for predisposing cancer mutations has been
widely implemented in the clinical setting. Recent studies indicate that
5–10% of the common cancers (i.e., colon, breast, and prostate) occur in
individuals that have inherited predisposing cancer genes, which can be
passed onto their offspring [7-9].

Most cancer syndromes are related to single-gene mutations not multiple-
loci gene mutations. The onset of some hereditary cancer syndromes are in
the earlier stages of life. For example, retinoblastoma is generally diagnosed
before the age of 4 years. However, most cancers have a late-onset and are commonly diagnosed during the middle period of life [9]. Different hereditary cancer syndromes have different penetrance (i.e., the lifetime risk of developing cancer) and expression risks among mutation carriers. However, the risk for a particular cancer can approach 85–100% over a lifetime.

Hereditary cancers mainly develop at a younger age and often prior to the time when general screening is done. Nowadays, the risk assessment by genetic testing is mostly offered for well-defined hereditary cancers with high penetrance. Examples include mutations of the BRCA1 and BRCA2 genes, which predispose the carriers to breast and ovarian cancer, and the mismatch-repair genes that predispose one to Lynch syndrome (hereditary non-polyposis colon cancer [HNPCC]) [10].

This section focuses primarily on the above mentioned cancers, including breast-, ovarian- cancers and Lynch syndrome (Table 1) because breast and ovarian cancers are the most common cancers in women and colorectal cancer is one of the most important causes of cancer related deaths in men.

Table 1. Brief clinical descriptions of HNPCC and HBOCS [11].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genes</th>
<th>Families are characterized by</th>
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<tbody>
<tr>
<td><strong>HNPCC</strong> (hereditary nonpolyposis colorectal cancer.)</td>
<td><em>MLH1</em>, <em>MSH2</em>, <em>MSH6</em>, <em>PMS2ab</em>, <em>PMS1ab</em></td>
<td>Colorectal and endometrial cancer, age of onset 50 yrs. May observe extracolonic cancers such as stomach, small bowel, ureter or renal-pelvis, ovary, brain, sebaceous skin tumors. Autosomal dominant transmission: multiple cases of HNPCC-related tumors in paternal or maternal lineage, and in more than one generation.</td>
</tr>
<tr>
<td><strong>HBOCS</strong> (hereditary breast and ovarian cancer)</td>
<td><em>BRCA1</em>, <em>BRCA2</em></td>
<td>Breast cancer, age at onset 50 yrs. Nonmucinous epithelial ovarian cancer. Autosomal dominant transmission: multiple cases of breast and/or ovarian cancer in paternal or maternal lineage, and in more than one generation.</td>
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</tbody>
</table>
Hereditary colorectal cancer

There are two main types of hereditary colorectal cancer syndromes: Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC), and the familial adenomatous polyposis (FAP) syndrome [6]. Most FAP syndromes are related to mutations in the adenomatous polyposis coli (APC) gene (5q21–q22), which encodes a protein that controls apoptosis, others may be caused by biallelic mutations in the MYH gene [12]. The penetrance of FAP is near 100% by age 35 and the risk of colon cancer is close to 100% with an average age of onset of 39 years [4]. FAP has an autosomal dominant inheritance pattern. Thus, the offspring of a carrier will have a 50% chance of predisposition to colorectal cancer or other cancers [9].

Lynch syndrome (hereditary nonpolyposis colon cancer [HNPCC]) is defined by microsatellite instability (MSI) in the tumor. MSI is characterized by appearance of multiple repeats of small snippet DNAs in the polymerase chain reaction as an indication of a DNA-mismatch-repair defect in cells. At present, MSI detection is mainly substituted with immunohisotchemical staining of the protein products of the DNA-repair genes [13-14]. About 45–70% of HNPCC families have germ line mutations in one of the hMSH2, hMLH1 and hMSH6 genes. In addition, mutations in hPMS1 and hPMS2 genes have also been defined as the cause of the HNPCC syndrome. All of the above mutations contribute to 3–5% of all colorectal cancers [4, 15].


- Colorectal cancer diagnosed in a patient less than 50 years of age
- Presence of synchronous, metachronous colorectal, or other tumors associated with Lynch syndrome (HNPCC) regardless of age (Lynch syndrome–related tumors include cancers of the colon, rectum, endometrium, stomach, ovaries, pancreas, ureter, renal pelvis, biliary tract, small bowel, and brain, usually glioblastomas (Turcot syndrome), sebaceous gland adenomas, or keratoacanthomas (Muir–Torre syndrome).
- Colorectal cancer with the MSI-high histology diagnosed in a patient less than 60 years of age [MSI-high refers to peaks in more than one of the recommended microsatellites (BAT25, BAT26, D2S123, D5S346, and D17S250)].
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPPC-related tumor and with one of the cancers being diagnosed at less than 50 years of age.
Table 2. Clinical management and genetic status [11].

<table>
<thead>
<tr>
<th>Genetic testing status</th>
<th>Endometrial cancer</th>
<th>Colonoscopy</th>
</tr>
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<tbody>
<tr>
<td>No testing information (family history alone) uninformative negative test result</td>
<td>Endometrial biopsies and transvaginal ultrasound every year</td>
<td>Every 1–3 yrs.</td>
</tr>
<tr>
<td>Positive for mutation</td>
<td>Endometrial biopsies and transvaginal ultrasound annually; consideration prophylactic hysterectomy, oophorectomy</td>
<td>Annually</td>
</tr>
<tr>
<td>Negative for familial mutation</td>
<td>None</td>
<td>Every 5 years starting at age 50 yrs.</td>
</tr>
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</table>

HNPCC syndrome usually arises before 50 years of age, and its related tumors include colorectal, endometrial, stomach, ovarian, and pancreatic carcinoma, with the risk of colon and endometrial cancers ranging from 70-90% and 30-60%, respectively [4, 16]. The burden for both FAP and HNPCC is devastating for the patients and their families. Furthermore, genetic testing (Box 1) can refer patients to surveillance or surgical intervention programs (Table 2) [9, 11, 17]. Because these programs can prevent or diagnose cancer at an early stage, genetic testing and disclosure of the information to the other family members is likely to have an important role in improvement of their health and a reduction in morbidity and/or mortality.

Hereditary breast and ovarian cancer

Hereditary breast and ovarian cancers are mainly associated with BRCA1 and BRCA2 mutations [18]. There are some blood tests available that can identify the germ line mutation carriers. One in 300-800 individuals in the population carry genetic susceptibility (usually BRCA1 and/or BRCA2 mutations) to breast or ovarian cancer, and this accounts for 3-10 percent of all cases of breast cancer. The penetrance of mutations has been estimated to be in the range of 50–80% for BRCA1 and 40–70% for BRCA2, with the range influenced by the studied population [4, 18]. The ovarian cancer risk among BRCA gene mutation carriers is about 40% over a lifetime.
Children of a patient with BRCA1/BRCA2 germline mutation have a 50% risk of inheriting that mutation. However, because of the incomplete penetrance and variable expression, the development and onset of cancer cannot be precisely predicted. Women of reproductive age with BRCA1/2 mutations often are faced with family-planning and reproductive issues that will raise important ethical dilemmas, especially in pre-implantation and prenatal diagnosis procedures [19].

**Ethical considerations for genetic testing practitioners**

**Ethical principles**

Every healthcare provider should initiate his/her activity in the medical clinic by adhering to the original ethical principles. The four original principles of biomedical ethics are: 1) respect for autonomy; 2) beneficence; 3) justice; and 4) nonmaleficence [20-24].

**Autonomy**

The principle of autonomy defines the right of an individual to self-determination. It relies on having the ability to make informed decisions about one’s own personal matters. The respect for this principle requires that action of a medical professional never have harmful effects upon the patient’s autonomy, even if that professional disagrees with that individual’s decision.

**Beneficence**

The principle of beneficence means doing well unto others. It emphasizes serving the best interest of the patients. Practitioners must regularly ask themselves who will benefit from their actions, and in what way.

**Justice**

The principle of justice means that the benefits and burdens should be shared equally among the population. In practice, practitioners should be certain of equitable treatment of patients, especially the more vulnerable groups (e.g. children and mentally retarded persons). Furthermore, the equity of access to genetic testing should be considered seriously.
Non-maleficence

The principle of non-maleficence means “above all [or first], to do no harm,” and states an obligation not to inflict harm intentionally. Practitioners should recognize those who may be harmed by a particular's action, and inform them in an open and truthful manner.

Ethical rules

Although ethical principles are important, the ethical rules, and the “informed consent and confidentiality,” derived from those principles are more efficient. These two rules underline the majority of the dilemmas practitioners encounter for either genetic testing recommendations, or passing on the results. Generally speaking, practitioners should be aware of both international and national laws regarding informed consent, confidentiality, and genetic counselling and discrimination [21].

Informed consent

Informed consent is based on autonomy to protect patient’s autonomous decision. To make an informed and autonomous decision, a person should be aware of the available preventive options and their implications [25]. A patient’s decision must be free from coercive impacts, and it must be based on the patient’s own beliefs [25]. Informed consent is an important part of genetic testing for hereditary cancer syndromes, and it includes a careful discussion of the possible outcomes, benefits, risks, and limitations of the genetic testing, as well as a discussion of the alternatives [26]. Deciding to accept or decline the test should be made autonomously in line with the patient’s own desires and plans [1].

ASCO states (Table 3) that oncologists should consider offering genetic testing only if they are able to provide or make available adequate genetic education and counseling as well as access to preventive and surveillance options. Otherwise, they should consider referring the patient and his/her family to these services. Because of the medical, social, and legal ramifications associated with the results of genetic testing, ASCO strongly recommends that genetic testing should be done only when paired with pre- and post-test counseling [1,2]. Pre-test counseling ensures that patients are aware of the potential implications of their test results and post-test counseling will also ensures that patients make informed medical decisions after receiving their test results.
Table 3. Basic Elements of Informed Consent for Cancer Susceptibility Testing (modified from American Society of Clinical Oncology 2003 statement) [2].

1. Information on the specific genetic mutation(s) or genomic variant(s) being tested, including whether the range of risk associated with the variant will impact medical care
2. Implications of a positive and negative result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic or genomic testing
5. Risk of passing a genetic variant to children
6. Technical accuracy of the test including, where required by law, licensure of the testing laboratory
7. Fees involved in testing and counseling and, for DTC testing, whether the counselor is employed by the testing company
8. Psychological implications of test results (benefits and risks)
9. Risks and protections against genetic discrimination by employers or insurers
10. Confidentiality issues, including, for DTC (direct to consumer) testing companies, policies related to privacy and data security
11. Possible use of DNA testing samples in future research
12. Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing
13. Importance of sharing genetic and genomic test results with at-risk relatives so that they may benefit from this information
14. Plans for follow-up after testing

Table 4. Questions to Ask Patients With and Without Cancer [26].

<table>
<thead>
<tr>
<th>Questions to ask all patients</th>
<th>Questions to ask patients who have had cancer/or regarding relatives with cancer</th>
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<tbody>
<tr>
<td>Age</td>
<td>Organ in which tumor developed</td>
</tr>
<tr>
<td>Personal history of benign malignant tumors</td>
<td>Age at time of diagnosis</td>
</tr>
<tr>
<td>Major illnesses</td>
<td>Number of tumors</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Pathology, stage, and grade of malignant tumor</td>
</tr>
<tr>
<td>Surgeries</td>
<td>Pathology of benign tumors</td>
</tr>
<tr>
<td>Biopsy history</td>
<td>Treatment regimen (surgery, chemotherapy, radiation)</td>
</tr>
<tr>
<td>Reproductive history</td>
<td></td>
</tr>
<tr>
<td>Cancer surveillance</td>
<td></td>
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<tr>
<td>Environmental exposures</td>
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Pretest genetic counselling

The first step of counselling is the collection of a patient’s personal and family medical history. The information to be obtained includes the frequency of cancer surveillance, the date and results of recent screening examinations and details about pertinent environmental exposures (Table 4,5) [26,27].

The information that a practitioner is required to be provided to a patient:

1. Why the test is recommended and who should be tested.
2. Reviewing the relevant information about cancer genes and their risks.
3. Defining the implications of all possible test results
   a. Positive result: The possibility of developing various cancers depends upon different genes, their penetrance, and expressivity.
   b. Negative result: In the absence of a known mutation in a family, genetic heterogeneity should be considered.
   c. Variants with unknown significance which would be alterations in sequences not known to be involved with mRNA processing.
4. Possibility of a positive result using statistical models and pedigree assessment in order to provide qualitative and quantitative information for the patient.
5. Explaining likelihood of a false-positive or a false-negative result for the patients.
6. Informing the patient regarding the cost of genetic testing
7. Informing the patient about potential risk for discrimination
8. Explaining the possible psychosocial aspects.
   a. Anticipated reaction to results.
   b. Timing and readiness for testing.
   c. Family issues.
   d. Preparing for results.
9. Discussion of confidentiality issues when the results would be disclosed to other family members.
10. Reviewing utilizations of the test including medical surveillance and preventative procedures.
11. Discussing the alternatives to genetic testing.
12. Informing the patient about storage and potential reuse of genetic material [26].
Table 5. Components of a typical genetic counselling session [27].

<table>
<thead>
<tr>
<th>Information gathering</th>
<th>Collecting personal medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collecting family medical history</td>
</tr>
<tr>
<td></td>
<td>Physical examination to evaluate features related to inherited syndromes</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Analyzing the information gathered to develop a list of differential diagnoses</td>
</tr>
<tr>
<td>Education</td>
<td>Communicate information to the patient and their family about the condition, inheritance, and medical management</td>
</tr>
<tr>
<td>Psychosocial counseling</td>
<td>Promoting conversation about the patient’s feeling regarding how a diagnosis of a hereditary condition may affect their health and impact their family members, their fears, and their anticipated responses to the outcome of genetic testing</td>
</tr>
</tbody>
</table>

Confidentiality and disclosure

Confidentiality is a central and essential part of a doctor–patient relationship. In general, no medical information can be disclosed to any other person without the consent of the tested individual. However, when family-specific mutations are identified, individuals should be encouraged to disclose the results to other at-risk relatives to facilitate predictive testing, especially when proven surveillance and prophylactic measures are available. Furthermore, sharing of this information could influence other family members’ reproductive decisions. In case this disclosure to other relatives can be a burden for the index patient, the practitioner should consult the situation with the ethics committees [28].

Possible reasons for patient’s non-disclosure include: absence of interest, denial, difficult relationships with the family members, reluctance to deliver bad news, and practical barriers to communication. Non-disclosure is most important for high-penetrant genes (as in familial adenomatous polyposis and hereditary breast and ovarian cancer), for which there are surveillance or surgical procedures available, and diagnosis at an early stage results in significant reduction of morbidity and mortality [9, 25].
Post-test counseling

This is a multi-step process, optimally done during a face-to-face meeting.

1. Disclosure of the results. After obtaining the client’s consent, inform him/her of the result.
2. Significance of the test results. Review the specificity and sensitivity of the test and discuss how the client’s result affects his/her cancer risk.
3. Impact of the results. Assess the emotional impact of the result on the client and his/her support person through verbal and nonverbal cues; provide support as needed.
4. Medical management. Review screening recommendations and options of cancer-risk reduction, such as chemoprevention or prophylactic surgery, if available, and also include the benefits, risks, and limitations of such options. Provide referrals to other medical professionals for additional discussions of these topics and strongly encourage compliance with screening recommendations.
5. Informing other relatives. Discuss cancer risks to other relatives and the importance of informing the family members about family history and the genetic test results. Written documentation that the client can share with relatives may be provided, safeguarding confidentiality as desired by the client. If a high-risk client refuses to contact the at-risk relatives, consulting with the ethics committee would be an option [26, 29].
6. Future contact. In case the follow-up care will be managed elsewhere, encourage the client to maintain his/her contact with the cancer risk assessment center for updates about their family history, the genetics of familial cancer disorders, and the management of inherited predisposition to cancer. The same applies to high-risk families with negative test results who maybe candidates for future testing. When available, offer clients the option of participating in long-term follow-up studies.
7. Resources. Provide the client with resources for cancer genetics and possibility of contacts with other willing clients, if desired and available. This could serve as a psychosocial support resource for the client or refer to other qualified individuals if additional support is needed [26].

Different kinds of discrimination

Discrimination based on genetic information may be in many forms including insurance and employment. Thus, practitioners should make their patients aware of potentials for discrimination during the pre-test counseling session. ASCO supports establishing a federal law to prohibit discrimination
by health insurance providers and employers on the basis of an individual’s inherited susceptibility to cancer [14, 21].

### Ethical dilemmas

#### Prenatal diagnosis or pre-implantation genetic diagnosis for cancer-predisposition genes

Prenatal diagnosis means identification of a family specific mutation in a cancer-predisposition gene and collection of a fetal sample by chorionic-villus sampling or amniocentesis to find out whether or not the fetus is affected. Such testing provides an option to terminate the pregnancy if the fetus is affected. Pre-implantation genetic diagnosis involves the use of in-vitro fertilization to create several embryos. By day 3, the embryo consist of six to ten cells, one or two of which could be removed for analysis. PCR is used to amplify the DNA to detect single gene diseases [30]. Then, only unaffected embryos are re-implanted. This technique has been used for a range of genetic disorders for which family-specific mutations have been identified, including Huntington’s disease, cystic fibrosis, and Duchenne muscular dystrophy [25, 30].

Although many cancer predisposing genes do not have full penetrance and they can be early detected, many believe that PGD is ethically acceptable because of the heavy burden imposed on the carrier patients and their quality of life by preventive measures in cancer predisposition syndromes [30].

### Genetic testing of children

Cancer genetic testing not only provides useful information regarding the susceptibility of at-risk individuals to cancer and early death, but also reveals genetic information about the health of their family members including the offspring. Identification of an individual’s susceptibility to a particular hereditary cancer syndrome may eventually allow their family members to benefit from preventive and therapeutic modalities based on their genotypes. Testing for cancer-predisposition genes in children is recommended if a malignant disease is likely to develop in childhood and if evidence-based-risk-reduction strategies exist that could be implemented in childhood. Examples include retinoblastoma-gene testing (to avoid eye examinations under anaesthesia every 3 months), RET gene testing for multiple endocrine neoplasia 2 (to guide the need for thyroidectomy), and APC-gene testing for familial adenomatous polyposis (to guide the need for sigmoidoscopy).
ASCO advises that if there is no cancer risk in childhood, testing should be deferred until adulthood. The reasoning behind this advice is to protect the child's future autonomy and right not to know, to ensure that the child is not treated differently by the parents and is not stigmatized with limited education, marriage, and reproduction opportunities [31]. However, some argue that the idea of the child's best interests includes more than medical interests; predictive testing in children can have important psychosocial benefits including self knowledge and planning [31].

Conclusion

Genetic testing in cancer genetic clinics predicts future health and tries to facilitate the practice of preventive oncology for the individual and for his/her family members. The task of regulating ethical rules for protection of genetic information is essential to ensure that the most good and the least harm come to patients and their family.

References


