Communicating Genetic Risk:
Pros, Cons, and Counsel

RICHARD T. PENSON, MICHAEL V. SEIDEN, KRISTEN M. SHANNON, MARCIE L. LUBRATOVICH, MARIA ROCHE, BRUCE A. CHABNER, THOMAS J. LYNCH, JR.

Hematology-Oncology Department, Massachusetts General Hospital, Boston, Massachusetts, USA

Key Words. Genetic counseling · BRCA-1 · BRCA-2 · Breast cancer · Ovarian cancer · Psychosocial

ABSTRACT

Shortly before his death in 1995, Kenneth B. Schwartz, a cancer patient at Massachusetts General Hospital (MGH), founded The Kenneth B. Schwartz Center at MGH. The Schwartz Center is a non-profit organization dedicated to supporting and advancing compassionate health care delivery, which provides hope to the patient, support to caregivers, and encourages the healing process. The center sponsors the Schwartz Center Rounds, a monthly multidisciplinary forum where caregivers reflect on important psychosocial issues faced by patients, their families, and their caregivers, and gain insight and support from fellow staff members.

This case is of a woman with a personal, and a strong family history of breast cancer, who considered genetic testing for mutations in the BRCA1 and BRCA2 genes. The details of the case have been altered to protect the patient’s anonymity. The patient was very anxious and there was disagreement between her healthcare providers about the potential benefits of genetic testing. The discussion of the case focused on several controversial issues, particularly the ownership of genetic information, and who is responsible for disseminating information to the family members at risk. The difficulties in communicating risk, providing emotional support and coping with the continuing uncertainties about screening and intervention are reviewed with an overview of the molecular biology, inheritance, and epidemiology of the BRCA1 and BRCA2 genes. The Oncologist 2000;5:152-161

PRESENTATION OF CASE

The clinical details and family history in this case have been altered to protect the patient’s anonymity.

Clinical Nurse Specialist: Miss D is a 55-year-old woman presented with a six-month history of a painless breast mass. There was no associated skin or nodal involvement. Mammography was negative, but ultrasound confirmed a suspicious lesion and fine needle aspirate of the breast lesion was highly suggestive of carcinoma. Metastatic work-up was unremarkable. Partial mastectomy with axillary node dissection revealed a grade 2, invasive carcinoma, with lobular and ductal features, 1.8 cm in diameter and extending focally to a deep fascial margin, and more broadly extending to an adjacent margin. Lymph nodes were negative and there was no lymphovascular invasion. The tumor was associated with ductal carcinoma in situ of intermediate grade. Four cycles of adjuvant chemotherapy with doxorubicin and cyclophosphamide (CA) were recommended. In view of the positive margins, she also received chest wall irradiation. She was aware that the sequential addition of paclitaxel in women with node-positive disease appears to be associated with a reduction in the risk of recurrence.
and a survival advantage. After completion of therapy, she felt very strongly that she wanted further chemotherapy with paclitaxel. As this has not been investigated in women with negative nodes, the therapy was initially not recommended. She is a very anxious person who had extensively researched the issues on the Internet and demanded paclitaxel. Her rationale was that the lesion in her breast was a medial lesion and so involvement of internal mammary lymph nodes could not be ruled out. She felt so strongly that she should get paclitaxel that, in the end, her providers agreed to give her paclitaxel.

Her emotional well-being is an important issue, and indeed this was reflected in some of the decisions that she made. She is extremely anxious and she pushed very hard for a number of different things in her care, including staging and extra therapy. She would have a minor complaint or worry, for which she’d demand extensive investigation, for example, MRI scans for musculoskeletal pains. Her partner was very supportive through all this, but would also push a little bit and would call for results from people who were not supposed to give out clinical information. They were just a very anxious couple. They were also very well educated, and had done a lot of homework, but were a little bit aggressive in getting the kind of care that they wanted, without always thinking things through. Since finishing treatment Miss D has continued to be very anxious with a number of ongoing issues.

Genetic Counselor: Miss D came to the risk assessment session alone. Her family history revealed that her mother was diagnosed twice with breast cancer, once at age 43 and again at age 48. She had an aunt who had some type of gynecologic cancer, but she was unsure whether this was ovarian cancer or endometrial cancer. Her maternal grandmother was diagnosed with breast cancer at age 75 (Fig. 1). Based on the family history, Miss D was told that it was possible that the cancer in her family could be due to an altered cancer predisposition gene. Her risk of having an altered BRCA1 or BRCA2 gene was estimated in a statistical model to be approximately 40%. Genetic testing was outlined and she said that she was interested in pursuing testing, but first wanted to review this with her partner, and promised to call us to schedule a pretest education visit. She was encouraged to bring her partner to the next session.

Three months later, she came in for a pretest education session, which lasted about two and a half-hours. Her partner was with her, and we talked about many, many issues. For the purposes of this presentation, I will concentrate on three; the medical implications of testing, the emotional ramifications, and the communication of this genetic information to other family members.

The first major issue we talked about was the medical implications of testing. She is a 55-year-old woman who has just finished her treatment for breast cancer. Based solely on her cancer diagnosis, she has a slightly increased chance of developing a second primary breast cancer and perhaps a 25% chance of having a recurrence. If she is tested and is found to be negative, nothing is going to change in terms of those risks. If she is tested and found to have a BRCA1 or BRCA2 mutation, her risk of having a recurrence is unchanged, her risk of getting a contralateral breast cancer is greatly increased, and her risk of developing ovarian cancer is substantial. We talked about how she would manage those risks in terms of screening. We also talked about the option of prophylactic surgery; whether or not she would consider having her other breast and/or her ovaries removed before a cancer develops. Both Miss D and her partner seemed confident that if she were found to have an alteration, she would pursue prophylactic surgery and indicated that this was a major reason that they’d pursued genetic testing.

The second main issue we discussed was the emotional implications of testing. This patient was extremely anxious at baseline. She described herself as being “obsessed” that she still had cancer in her, because of the one positive margin that all the experts here said was an unimportant factor in her treatment.
The implications of learning that she had a gene mutation and thus a high chance of developing a second cancer were explored, particularly with respect to her anxiety and whether this would push her over the edge, emotionally. We also discussed the fact that not finding a mutation in BRCA1 or BRCA2 provides her with little information about her future cancer risks (i.e., she could carry an inherited cancer predisposition gene that is not known about at this time). We talked about her emotional support, which predominantly comes from her partner, and how her partner’s feelings impacted her decision whether to get tested or not. We also talked a lot about the emotional support she was getting from her providers here. Some of her providers were not supportive of her decision to consider genetic testing, and had strongly advised her against seeking genetic counseling. That and the ambivalence of other care providers who said, “well, it is up to you,” made her feel that she wasn’t fully backed by her providers. Finally, the impact that these results could have on her self-image was discussed. She commented that she would feel “flawed” if she found out that she had an altered gene.

The third big topic we explored was family communication. Miss D described herself as not being very close to other members of her family. It was pointed out that if she was found to have an altered gene, then her brother would have a 50-50 chance of having the gene. It was also stressed that this information could have important implications for her 21-year-old niece. She had not thought about how she would disseminate this information to other members of her family at all. If she were negative, she would not have to talk about it to anyone, but if she were positive, she indicated that she would have to think about it extensively before telling anyone. She did not have a plan at this point, so we suggested that she contact her relatives before she learned her results to see how they felt about receiving this information.

At the conclusion of the visit, she decided not to get tested. This is relatively unusual. The majority of the people that we see for genetic counseling opt to have genetic testing. She went home, and we have not heard from her since.

**Dialogue**

**Facilitator:** Who was against testing? What were their reasons?

**Clinical Nurse Specialist:** Some of her providers felt that genetic testing was an important thing for her to know about. Others, who didn’t feel strongly about this one way or another, said that if she wanted it, she should go and discuss it with the genetic counselors. But some of her providers who have spoken out against genetic testing were against it for two reasons. First, they felt that her management would not be changed by the results of genetic testing as she clearly has a strong family history. Their bias is that the information is so full of uncertainty that the results provide patients with no clearly helpful information. Secondly, they were concerned that the genetic test results could be the one thing that tipped her “over the edge,” being as anxious as she is. She has been reluctant to see a psychiatrist, although we have recommended it several times. I think the patient was very concerned about how she would react emotionally to seeing a psychiatrist.

**Physician:** I am a supporter of genetic counseling and testing, yet I don’t think people should be forced to have genetic testing. I don’t even think people should be strongly encouraged to have genetic testing. But for people who think this information will be useful to them or to their kids, brothers, or sisters, we should provide a mechanism to give them this information in a careful and professional setting.

**Physician:** Genetics raises the issue of how paternalistic physicians should be. Genetics is a little bit different than some of the other issues we deal with in health care, not only because of family issues, but it is hard to be genuinely neutral about this topic. The patient will ask, “Well, you take care of me; will this information be useful to you?” Miss D was anxious, but not any worse than many other patients dealing with these same sorts of issues. Regarding how much responsibility they have for other family members, most patients will say, “If I am negative, I will tell everyone. But if I am positive, I don’t know who I will tell.” Most people have not really worked out how

---

**Some of her providers were not supportive of her decision to consider genetic testing, and had strongly advised her against seeking genetic counseling.**
to tell a sister they have not talked to in years. What about
this 21-year-old niece; do they tell her directly? Is that any
of their business? Is it right not to tell her? This adds to the
anxiety of the genetics issues. Miss D asked lots of good
questions. She was clearly well prepared intellectually for
the discussion, but she was not so well prepared for work-
ing her way through all the emotional ramifications of the
information.

Physician: The thing to recognize is, even if we think of our-
selves as relatively non-directive, the way we communi-
cate is a powerful influence on how patients process
information. For example, a lady comes into your office
and says, “My mother had ovarian cancer and now I have
ovarian cancer. Should I be concerned about the genetic
implications?” You reply, “Look, it might be due to genes,
but your genes are your genes and we can’t fix your genes;
you have enough things to worry about, let’s worry about something else
right now.” This patient would walk out of your office
with a very different
impression than the
patient who is told, “I
am actually very con-
cerned that this might be due to a gene in your family. It
could have implications for your daughter. We do
have free genetic counseling here, if you would like
more information.”

Physician: Another common scenario is the patient who
says, “I have breast cancer. I’m not interested in genetic
testing, but I’m here for my daughter’s sake.” To which
my response is, “It’s not up to your daughter. You don’t
have to be tested.” Their response is typically to say, “I
don’t have a choice.” There are lots of ways that you
could respond to this. You could say, “I feel you’re
being extorted, the session is over (laughter).” On the
other hand you could say, “I understand that you’re
under a lot of pressure. It really is up to you. But I can’t
make the decision for you.” In many cases the daughter
is with the patient, her mother, which makes a candid
discussion much more difficult.

Physician: Actually, if there is pressure from the daughter, it
is often physician generated. Imagine that the 25-year-old
daughter walks into her gynecologist’s office and asks,
“Should I have my ovaries out?” or into a surgeon’s
office and demands mammograms because her mother
and aunt have breast cancer. Now, the well-meaning doc-
tor asks, “Does your mother have a BRCA-1 mutation?”
This relatively innocent question generates a phone call
or two, and all of a sudden the daughter has called the
mother and says, “My doctor will start my screening early if you get your BRCA genes checked.” It’s often the
daughter who takes the initiative in getting genetic coun-
seling for the mother. To compound things further, the
logical search for a gene mutation typically starts with the
mother who has cancer since her test provides more infor-
mative genetic testing. If the patient with breast cancer is
BRCA1 and BRCA2 negative despite a strong family
history, clearly the predisposition does not relate to
these genes. So the medical profession is often comp-
licit in our encouragement to bring potentially
ambivalent individuals into the testing arena.

Even if we think of ourselves as relatively non-directive, the way we communicate is a powerful influence on how patients process information.

Clinical Nurse Specialist: One of my concerns is whose knowledge it is, and does that informa-
tion create a moral burden on the patients? If someone says, “No thank you, I don’t want this information.” The daughter
then makes claims on mother to meet the daughter’s
needs. The primary relationship is with the mother and
the hope is to stay neutral. But this is a chess game
playing out, with real lives, in real time.

Facilitator: I think this splits us as caregivers. You see the
21-year-old niece on the diagram and think, “Oh, my gosh, if we could intervene and do something to change her risk, that would be important.” Yet, our primary
responsibility is toward the patient.

Clinical Nurse Specialist: I think we do have a responsibil-
ity to the patient. We have to ensure that the person has a
chance to explore their motives and the implications of
their decision.

Social Worker: We need to ask, “Who is responsible for what we ‘set off’ in the family?” We need to appreciate that we typically ask the patient to carry that burden. Nobody
wants to be the bearer of bad news, everyone wants to
shoot the messenger, and this information does alter a
patient’s relationship with her family. How do you give
medical information and help them deal with that news?
Physician: Well, there are medical and, I guess in the future, legal ramifications of the information. Right now, the genetic information is the patient’s, and solely theirs. But I’m not exactly sure where the patient’s responsibilities lie with other family members. For example, if the person had a BRCA1 mutation, didn’t inform the niece, and the niece subsequently developed ovarian cancer 15 years later, could the niece sue her aunt for keeping the information from her? The suit might go something like this. “The genetic counselor actually told you at a meeting that I (the niece) had a 25% chance of having a BRCA1 mutation, that put me at a 10-20\times higher risk of getting ovarian cancer which is typically lethal. If I had known that information, I would have had my ovaries removed. You kept that information from me, even though you knew that it had implications on my chance of surviving through adulthood. You are liable for my death.” As far as I am aware, that hasn’t happened yet. Nevertheless, there have been suits against physicians for withholding information about the implication that strong family histories of cancer may indicate mutations in cancer predisposition genes.

Physician: I have been impressed in these sessions by how many dysfunctional families there are in America, “pathogenetic households.” You march through the family tree and over half of the people I see say, “Oh, I would never tell them,” or “I never talk to them,” or “I could never share this sort of information with them.” If you add, “Well, your brothers have three daughters in their 20s. Shouldn’t you mention your gene mutation to these relatives?” “No, way,” they say, “They would never listen.” It’s tricky to know how you get around these family dynamics.

Social Worker: I think it is true that there are a lot of dysfunctional families. But, there is something particularly difficult about genetic information and being the carrier of an altered gene in a family. It really puts you in a different position in the family and people are shocked. It’s often a case of “There but for the grace of God go I,” and yet they look the other way, they are afraid to ask or afraid to be compassionate.

Genetic Counselor: No one wants to be the bearer of bad news. We’ve had families who haven’t known how to disseminate the information, and we’ve written a letter to relatives that provides some basic information about BRCA1 and BRCA2, lets the relative know she is at risk for having an alteration in one of these genes and encourages her to call us. This is always done with the patient’s full consent. In fact, the patient identifies which relatives should be sent a letter and provides all the details.

Social Worker: Do you think that you should set this as protocol that all those implicated should be invited to come and ask questions?

Physician: We rigorously review with people exactly who in their family will be told and ask if there’s someone who should be told that they are undergoing genetic testing before they get the result. We suggest they tell that relative that they’ve seen a genetic counselor and that they are at risk of being a carrier of a mutated gene, and ask, “When I find out my gene status, do you want to know?” The response has been interesting. Some are shocked and say, “My brother is really smart, but he really didn’t want to know.” Knowing which relatives want the information ahead of time can be very helpful. We can also offer to help people deal with their family. We offer to counsel both them and their relative, and because of the generous support from the Cancer Center, we can offer these as free services, including the physician’s time.

Social Worker: It seems to me that how you inform your family is the big issue. I think we put unreasonable expectations on the patient who already has cancer. It would be very difficult for any of us. I think that we should try to come up with some models or rules. I have to say the rules we design to protect some people appear to be hurting others.

Physician: Take for instance one of our patients who really wrestled with the fact that she may be positive. She wanted to be tested, and the test results demonstrate that she does not have a mutation. We set up a rule to protect patients that requires that the patients
come to the office to get their results. This lady has been so worried about her results that she has repeatedly canceled her appointments. So for the last nine months we have known that she does not have a BRCA1 or BRCA2 mutation. Yet, she is so worried that she is positive, she won’t keep the appointment. So we need to constantly review our guidelines to ensure that they are ethical.

**Physician:** One of the questions I would be interested to hear about is insurance and medical jeopardy.

**Physician:** We are a lot more concerned about members of a family with a BRCA mutation, but no cancer. The insurance risk for a person with cancer is already affected, and genetic information is not going to change her insurability. It is the 21-year-old niece in this family that should be concerned about the potential insurance consequences, if her gene status was evaluated.

**Facilitator:** What if the patient had children? For example, if you knew that she had three daughters, would that change the way that you, as a caregiver, pitch the information?

**Genetic Counselor:** I think it does. We definitely do everything in our power to remain non-directive, give clear information, and help them make their own decisions. But there are instances when we are a bit directive, based upon the specifics in the case. I think you have to take this into account. When counseling a woman with daughters who is unaware of the implications of the family history, I think it’s my duty to explain the gravity of the issue.

**Facilitator:** This must impact the caregiver. The reason you do this is to reduce the number of women who will die of breast or ovarian cancer. What keeps getting at me is seeing that 21-year-old niece. You must root for people to want to know the information. How did you feel when she walked out of there, knowing that she had a 40% chance of being positive and that the 21-year-old would probably alter some part of her medical care if she knew she was a carrier of the gene. How do you deal with that concern?

**Genetic Counselor:** That’s a good question. I make myself feel better by looking at the family tree and convincing myself that based on the family history alone, the 21-year-old niece should be worried. She should be taking care of herself and should be cared for as a “high risk” patient by medical professionals. In a way, no one needs this genetic information; you know you’re at risk simply by the presence of cancer in the family. It is also true that at this point there is nothing we can do to prevent cancer in these families. Not even prophylactic surgery is 100% effective, even if you have your breasts and ovaries removed you can still get cancer. Just based on her family history, you’d hope that she is aware of the need for close surveillance.

**Genetic Counselor:** In fact, many patients we see are not at high risk and we don’t offer them genetic testing. That information can be reassuring for these women.

**Physician:** What about someone without a strong family history? Is genetic counseling appropriate for them?

**Genetic Counselor:** In fact, many patients we see are not at high risk and we don’t offer them genetic testing. That information can be reassuring for these women.

**DISCUSSION**

**Genetics and Tumor Suppressor Genes**

Cancer is a genetic disease, but rarely inherited. It is becoming clear that in the face of uncontrolled proliferation and failure of programmed, or apoptotic, cell death, some cells survive a senescence crisis and have all of the credentials of transformation to cancer [1]. Although several specific mutations in both oncogenes and tumor suppressor genes have been identified in breast cancer, there remain many more unidentified genetic changes with deletions identified on chromosomes 1, 3, 6, 7, 8, 9, 11, 13, 15, 16, 17, 18, and 20.

Seminal studies by Broca in the 19th century established that breast cancer is associated with a familial pattern in 5% to 10% of cases [2]. A hypothesis was proposed that such families inherit a defective or lost allele encoding a tumor suppressor gene. This was based on work by Knudson, who suggested that the inactivation of the second allele produced the “inherited” form of the tumor retinoblastoma [3], and by Harris, who demonstrated that certain chromosomes could suppress malignancy in vitro in cell hybrid studies [4]. Because only one allele confers the...
increased risk of cancer, there is a 50:50 chance that a parent who develops an inherited cancer will pass on this gene to each child.

BRCA1 and BRCA2

BRCA1 was cloned in 1994, following the observation of considerable loss of heterozygosity affecting chromosome 17q12-21 [5, 6]. BRCA2 is located on chromosome 13q13 and shares homology with BRCA1 [7].

The BRCA1 and BRCA2 genes encode for proteins involved with DNA damage repair [8]. Both genes are essential genes and participate with Rad51 in DNA repair of radiation-induced breaks in DNA. The addition of phosphate groups to the BRCA1 protein is essential for the recombination repair of DNA double-strand breaks. The kinase, ATM (ataxia telangiectasia mutated gene on chromosome 11) phosphorylates BRCA-1 protein, in the presence of DNA. ATM mutations are found in 1% of the population and may contribute to up to 4% of sporadic breast cancer [9]. There are relatively few data on the prognostic implications of BRCA1/2 positive tumors. Although studies are hampered by small sample size or selection bias, the most consistent findings are a high frequency of tumors that are negative for estrogen and progesterone receptors, and a moderately increased frequency of tumors with p53 gene mutations [10]. Concerns that these tumors may have a worse prognosis do not seem to be born out by epidemiological studies [11].

Radiation exposure is an etiological factor in breast cancer [12]. Patients with defective BRCA genes may be more sensitive to radiation. The risk of mammogram-induced cancer has been estimated to be as high as 1 in 200 in women aged less than 50 years [13]. The theory is supported by mouse knockout models and cell line studies. Some investigators have reported that women at risk of harboring a BRCA1 or BRCA2 mutation who are treated with adjuvant radiation as part of conservation surgery have a high rate of ipsilateral tumors [14]. However, this is not supported by larger studies, which suggest that the risk of ipsilateral recurrence following radiotherapy in women with hereditary breast cancer is similar to those with non-hereditary disease [15]. Furthermore, the time to development of ipsilateral tumors appears to be longer, and radiation may be more effective in eradicating tumors that have BRCA mutations [16].

Epidemiology and Risk

In the general population, the risk of developing breast cancer is 11% [17]. Features that suggest a hereditary component to breast or ovarian cancer are multiple affected family members in multiple generations, with either the same or related cancers, earlier than average onset of breast or ovarian cancer, bilateral breast cancer, or two separate primaries and male breast cancer. For a woman that has an altered BRCA1 gene, the lifetime risk of breast cancer risk ranges from 50% to 90%, with a similar risk associated with an alteration in the BRCA2 gene. Germline mutations of BRCA1 or BRCA2 genes are associated with a five- or sixfold higher rate of recurrence in the contralateral breast (e.g., 12% versus 2%) [10].

Men who have two normal copies of the BRCA1 and BRCA2 gene have a <1% risk of breast cancer. This risk is not increased in a man with an altered BRCA1 gene. However, a man with an altered BRCA2 gene has a lifetime risk of approximately 7%.

Other tumors associated with mutations in the BRCA2 gene are colon and pancreatic cancer, and with a BRCA1 mutation there is a slightly increased risk of prostate cancer.

The risk of ovarian cancer in the general population is between 1% and 2%. A woman with an altered BRCA1 gene has a lifetime risk of 20%-40%, and a woman with an altered BRCA2 gene has a lifetime risk of ovarian cancer of 10%-20% [18]. Somatic mutations of BRCA genes in sporadic ovarian cancers are rare. However, hypermethylation of the promoter region occurs in 12% of sporadic ovarian cancers and may lead to transcriptional silencing of expression, implying a role in tumorigenesis [19]. A small number of cancers are attributable to mutations in mismatch repair genes that predispose to the hereditary nonpolyposis colorectal cancer syndrome [20].

Table 1. Genetic counseling

Pretest counseling:

Risk assessment visit:
1. Obtain family history (pedigree) and confirm critical diagnoses.
2. Review the natural history of the condition.
3. Discuss the predictive value of the test and determine who is the best family member to test first.
4. Review the risks, benefits, implications, and limitations of testing.

Pretest visit:
1. Review risk assessment visit.
2. Explore the patient’s motivation for testing.
3. Discuss and explore psychosocial issues, including family issues and readiness for testing.
4. Discuss confidentiality and insurance issues.
5. Outline testing logistics, including the cost of testing.
6. Discuss alternatives to testing.
7. Provide written materials regarding cancer risks and testing issues.
8. Obtain written informed consent.

Post-test counseling:
1. Provide test results face-to-face whenever possible.
2. Discuss implications of test results to patient and family.
3. Assess patient’s psychological reaction and offer follow-up support.

*Modified from NSGC position statement [29].
Approximately 7% to 10% of women with early-onset breast cancer, aged ≤40, have mutations in either BRCA1 or BRCA2 [21, 22], with a median age of presentation of 40 rather than the usual peak age of 75-79 for sporadic breast cancer [23]. Among women with breast cancer at any age, presenting to a high-risk oncology clinic with a strong family history of breast cancer, about 16% harbor a germline mutation in BRCA1 [24]. In women who have both familial breast and ovarian cancer or who belong to a population in which founder mutations may be prevalent, such as Ashkenazi Jews, this frequency is increased to between 30% and 40% [11]. Computer programs, such as BRCA PRO, are now available that predict the probability of carrying a germline BRCA1 or BRCA2 mutation [25, 26].

The availability of a commercial test for the breast cancer susceptibility genes, BRCA1 and BRCA2, has generated huge interest [27]. Although age, socioeconomic, and ethnic characteristics may mitigate against awareness of genetic risk, a majority of people are in favor of gene testing, although uptake is low [28].

**GENETIC COUNSELING**

Genetic counseling deals with complex and often highly charged information [30, 31]. For this reason, genetic counselors are trained to be non-directive. The National Society of Genetic Counselors (NSGC) and the National Institute of Health’s, Cancer Genetics Studies Consortium (CGSC) recommend that predisposition testing should only be offered in the context of a comprehensive program of pre- and post-test counseling, by professionals with appropriate knowledge and experience with the issues involved [29, 32]. Genetic counseling is a process and may or may not include genetic testing (Table 1). Typically there is a risk assessment visit and a pretest visit separated by some time during which the person can consider her decision. If a person chooses to be tested, her blood is drawn and approximately four weeks later, full gene sequencing (BRCAAnalysis™, Myriad, Salt Lake City, Utah) results are available. The American Society of Clinical Oncology recommends that for those individuals with a modest risk (>10%), genetic testing may be offered [33].

The psychological outcomes of genetic testing for other inherited diseases such as Huntington’s Chorea (HD) have been evaluated, and most of the genetic counseling for BRCA genes has been modeled on HD programs [34]. In a study by Lawson et al., there was no evidence for an association between age, gender, marital status, education, psychiatric history, general psychiatric distress, or social supports at baseline and an adverse outcome to genetic testing. However, clinical depression appeared to be associated with a higher incidence of serious psychiatric repercussion in the first 10 days after test results were made available, with an incidence of clinical depression of 15% overall. Women consistently cite fear of breast cancer as their primary concern and find the “burden of uncertainty” for the future a difficult adjustment [35]. Although anxiety levels may be high, there is evidence that women seen in specialist clinics do not have a higher level of anxiety compared with “at risk” women with no family history [35]. Indeed, they may have lower levels of anxiety than women “at risk” who have a positive family history [36]. Misunderstandings, excess anxiety, and non-compliance are commonly blamed on poor doctor-patient communication [37]. Reassurance that plays down the seriousness of the situation appears to be counterproductive, and successful reassurance seems to depend on the ability to acknowledge patients’ perspective [38].

**Very rapidly the advance of our knowledge base is impacting the advice that is given to people at high risk of developing cancer.**

**RECOMMENDATIONS FOR BRCA1 AND BRCA2 MUTATION CARRIERS**

Few concrete recommendations can be made in individuals who carry cancer-predisposing mutations, based on the present literature [39]. Efficacy of cancer surveillance or risk reduction is unknown. However, based on expert opinion concerning presumptive benefit, early breast cancer and ovarian cancer screenings are recommended for individuals with BRCA1 and BRCA2 mutations.

Breast cancer screening involves monthly self-examination, clinical examination twice a year, and annual mammography. Mammographic screening appears to reduce mortality from breast cancer by 30% in women aged 50-59 years [40]. The benefit is perhaps halved in women aged under 50 and there are no data in women who have multiple first-degree relatives with breast cancer or who are known to carry BRCA1 or BRCA2 mutations [41]. However, most physicians faced with such a patient would, at a minimum, suggest increased and earlier screening for breast cancer by routine mammography [42].

Although there are no standard recommendations for screening women at risk for ovarian cancer, options for surveillance include pelvic examinations and transvaginal ultrasound done twice a year and in postmenopausal women, a CA-125 blood test is typically done with the pelvic...
ultrasound. Screening recommendations are highly controversial [43]. However, a combination of sequential CA-125 testing and ultrasound has recently been reported as a strategy for identifying women with lower stage ovarian cancer, raising the hope that this will improve survival [44].

The benefit of PAP smear screening for cervical cancer in the general population is established, and the American Cancer Society recommends that screening for colorectal and prostate cancer begin at age 50. In patients with strong family histories or BRCA mutations, fecal occult blood testing and digital rectal examination is typically done at clinic visits and flexible sigmoidoscopy or colonoscopy and PSA performed every one to three years, commencing in the decade before the age that the youngest member of the family developed cancer.

Prophylactic surgery is an option for mutation carriers, but direct evidence of benefit is lacking, and the occurrence of cancer following prophylactic surgery has been documented. Prophylactic oophorectomy is often considered after child-bearing years and may reduce the risk of subsequent breast cancer as well as ovarian cancer, although these benefits may need to be balanced with the increased risk of osteoporosis and the risk of extraovarian peritoneal cancer [45]. Tamoxifen and raloxifene have both been investigated as potential agents for primary chemoprophylaxis, although their role in preventing inherited breast cancer is not proven [46, 47]. Clearly, research designed to evaluate clinical outcomes will be an important source of future information.

CONCLUSION

Even Heisenberg’s Uncertainty Principle can be reduced to $\Delta x \Delta p \geq \hbar/2$. Like Adams, “We demand guaranteed and rigidly defined areas of doubt and uncertainty” [48]. Genetic counseling is an emotive area. Very rapidly the advance of our knowledge base is impacting the advice that is given to people at high risk of developing cancer. Although the lack of proven benefit to screening, prophylactic surgery, or chemoprevention compounds anxiety, this is a field where clear and supportive communication particularly facilitates adjustment.

REFERENCES