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Question 26: What is the natural history of the disorder?
Question 27: What is the impact of a positive (or negative) test on patient care?
Question 28: If applicable, are diagnostic tests available?
Question 29: Is there an effective remedy or acceptable action, or other measurable benefit?
Question 30: Is there general access to that remedy or action?
Question 31: Is the test being offered to a socially vulnerable population?
Question 32: What quality assurance measures are in place?
Question 33: What are the results of pilot trials?
Question 34: What health risks can be identified for follow-up testing and/or intervention.
Question 35: What are the financial costs associated with testing?
Question 36: What are the economic benefits associated with actions resulting from testing?
Question 37: What facilities/personnel are available or easily put in place?
Question 38: What educational materials have been developed and validated, and which of these are available?
Question 39: Are there informed consent requirements?
Question 40: What methods exist for long term monitoring?
Question 41: What guidelines have been developed for evaluating program performance?

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Question 26. What is the natural history of the disorder?

To be completed

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Question 27. What is the impact of a positive (or negative or indeterminate) test on patient care?

Summary

- Recommended interventions for women with a *BRCA1/2* mutation and/or a strong family history are based on expert opinion with limited scientific documentation and include:
  - Early detection of breast/ovarian cancer by
    increased surveillance
  - Reducing the risk of developing breast/ovarian cancer by
    surgeries (e.g., mastectomy and/or oophorectomy)
    chemoprevention
    lifestyle modifications
- The impact of *BRCA1/2* mutation testing is dependent upon the woman's family history, availability of an affected relative for initial testing, test results, and personal choice.

Positive *BRCA1/2* mutation test result

A Consensus Statement was developed by a multidisciplinary task force, convened by the Cancer Genetics Studies Consortium and organized by the National Human Genome Research Institute, directed at women with an inherited predisposition to breast and/or ovarian cancer. (Burke et al., 1997) Few data exist on the outcomes of interventions to reduce risk for women in this category. As a result, recommendations contained in the consensus statement are primarily based on expert opinion. These are summarized below (more complete discussion will follow later in Question 29).

Breast Cancer Surveillance

- breast self-examination monthly, beginning by age 18-21 years of age
- clinician breast examination annually or semi-annually, beginning at age 25 to 35 years
- mammography annually, beginning at age 25 to 35 years

Ovarian Cancer Surveillance

- serum CA-125 testing, annual or semi-annual
- transvaginal ultrasound study, annual or semi-annual

Surgical Options

- risk-reducing mastectomy
- risk-reducing oophorectomy

Chemoprevention

- Estrogen therapy
- Oral contraceptives
- Tamoxifen/Raloxifene

Lifestyle Modifications

- Low-fat, high fiber diets
- Adequate intake of fruits and vegetables

- Regular exercise
- Avoidance of carcinogenic agents, such as cigarettes

Because mastectomy and oophorectomy may significantly reduce, but not eliminate, risk for breast and ovarian cancer, it has been proposed that this type of surgery be labeled "risk reduction" as opposed to prophylactic surgery. (Stefanek et al., 2001) This term is not only more accurate but may also facilitate understanding among health care disciplines and between women at risk and their health care providers. All of the above recommendations are offered to women with strong family histories of breast and/or ovarian cancer whether or not they are found to carry a *BRCA1/2* mutation. Other breast imaging modalities, such as ultrasound and magnetic resonance imaging (MRI), are currently being investigated.

Negative *BRCA1/2* mutation test result

BRCA1/2 mutation known to be present in an affected relative. If a mutation in *BRCA1/2* is identified as co-segregating with cancer in a family, then women in that family who do not carry that mutation have no greater risk of breast and/or ovarian cancer than the general population. This assumes that there is no mutation on the other side of the family. These women can avoid unnecessary medical interventions and may derive psychological benefits from this knowledge. They need to be reminded, however, that it is important to follow standard recommendations for breast cancer screening.

BRCA1/2 mutation status not known in an affected relative. When it has not been possible to test an affected family member, a negative test result in a woman without cancer reduces, but does not eliminate, the likelihood of hereditary cancer. Her risk is still higher than that of the general population. Patterns of care for this woman may include some or all of the recommendations listed for those women with a *BRCA* mutation, depending on the strength of the family history.

Indeterminate *BRCA1/2* mutation test result

Indeterminate test results (genetic variants of unknown clinical significance) occur in approximately 13 percent of all tests. Testing affected family members to determine whether this variant "tracks" with cancer may be informative. Care of women in this category is not standardized and varies according to treating physician and other risk factors. Nearly all of these indeterminate results are not associated with an increased risk of cancer (personal communication, Brian Ward, Myriad Genetic Laboratories).

References:

Burke, W., Daly, M., Garber, J., Botkin, J., Kahn, M. J., Lynch, P., McTiernan, A., Offit, K., Perlman, J., Petersen, G., Thomson, E., and Varricchio, C. 1997. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *JAMA* **277**(12)**:**997-1003.

Stefanek, M., Hartmann, L., and Nelson, W. 2001. Risk-reduction mastectomy: clinical issues and research needs. *J Natl Cancer Inst* **93**(17):1297-306.

CLINICAL UTILITY

Question 28. If applicable, are diagnostic tests available?

Summary

- For predicting hereditary breast/ovarian cancer
  - Family history is the initial screening test
  - If family history indicates the likelihood of an inherited form of cancer, *BRCA1/2* mutation testing is then offered first to an affected relative. If a deleterious mutation is found, testing can be offered to unaffected women in that family.
  - Women with a *BRCA1/2* mutation are at very high risk for these inherited cancers
  - There is no further diagnostic test to allow definitive prediction, on an individual basis

For identifying and diagnosing breast/ovarian cancer once it has occurred

- Clinical breast exam and mammography are screening tests aimed at identifying breast cancer
- Measurement of CA125 and ultrasound are screening tests aimed at identifying ovarian cancer
- Histologic examination of tissue/fluid samples is the diagnostic test for both breast and ovarian cancer

Predicting risk for hereditary breast/ovarian cancer

For women whose family history indicates high risk for hereditary breast/ovarian cancer, *BRCA1/2* mutation testing is recommended, with initial testing done in an affected relative. When the relative does not carry a *BRCA1/2* mutation, mutation testing is not recommended for the woman, and further assessment of cancer risk is based only on family history. When a *BRCA1/2* mutation is identified in an affected relative, the woman is offered mutation testing to determine whether she carries the same mutation. Such testing might be considered a second level screening test for determining hereditary breast/ovarian cancer predisposition, keeping in mind that not all women with a mutation will develop breast or ovarian cancer in their lifetime. For example, the risk for breast/ovarian cancer to occur during one's lifetime ranges from 9 to 85 percent when a mutation is present, and this risk is high enough that definitive primary prevention options such as risk-reducing surgery might be considered. However, when a disease-causing mutation is found in an affected family member but not in an unaffected woman, the unaffected woman's risk is reduced to that in the general population.

Identifying and diagnosing breast cancer, once it has occurred

Diagnosis of breast cancer is typically made through clinical breast exam, mammography, and needle biopsy. Screening for breast cancer by self-breast exam, clinical breast exam, and mammography are well-established, effective methods for detecting most breast cancers at an early stage. (Question 29) High-resolution mammography is used to evaluate the patient with clinical signs and/or symptoms and to characterize and localize further abnormalities detected

on screening mammography. It is a low-dose x-ray procedure that allows visualization of the internal structure of the breast and may be supplemented by breast sonography, which increases specificity. There are five assessment categories in the Breast Imaging Reporting and Data System (BI-RADS):

1. Normal
2. Benign
3. Probably benign
4. Suspicious
5. Highly suggestive of malignancy

Tissue diagnosis is recommended for categories 4 and 5. The likelihood of malignancy is between 2 and 90 percent for category 4 and more than 90 percent for category 5 lesions.

Percutaneous breast biopsy

1. Fine needle aspiration biopsy is relatively simple, relatively atraumatic for the patient, and is ideally suited for the aspiration of a simple cyst. However, it is optimal to have an experienced cytopathologist available for immediate evaluation of the adequacy of the sample. Sensitivity varies with the experience of the clinician and the cytopathologist, ranging from 65-98 percent. (Scott and Morrow, 1999) Specificity ranges from 34 to 100 percent, and the false-negative rate is between 0 and 4 percent. (Scott and Morrow, 1999) A limitation of this procedure is the inability of cytology to distinguish invasive cancer from *in situ* disease.
2. Core needle biopsy creates greater trauma for the patient but is generally able to determine level of invasion. Another advantage is that a cytopathologist is not required to interpret the histologic material. Sensitivity and specificity approach 100 percent when larger needle sizes are used and five or more tissue samples are obtained. (Vargas et al., 2000) A potential disadvantage of core needle biopsy is the risk for seeding the needle tract with tumor cells.
3. Advanced Breast Biopsy Instrumentation (ABBI®) is the latest approach to increase the volume of breast tissue excised utilizing a percutaneous application. The ABBI biopsy "gun" ranges from 5 to 20 mm and, thus, can potentially completely excise a small breast neoplasm. Hematoma complications occur at less than 5 percent with this methodology. As with core needle biopsy, sensitivity approaches 100 percent, but ABBI is more invasive and traumatic for the patient.

Open surgical breast biopsy

1. *Incisional biopsy* - Because of the multiple forms of percutaneous biopsy available, there are few remaining indications for an open surgical biopsy. A clinician may, however, occasionally find a palpable breast mass that is suspicious for locally advanced breast cancer but a core needle biopsy is unavailable, or it reveals ductal carcinoma *in situ* (DCIS). In this case an incisional biopsy would be warranted to rule out the presence of a large palpable form of DCIS versus an advanced cancer.
2. *Excisional biopsy* – Any breast lesion that requires definitive histopathologic evaluation is a candidate for excisional biopsy. An open diagnostic biopsy is indicated for the following reasons: 1) it is not technically possible to obtain a sample via one of

the needle biopsy techniques, 2) there is concern that the lesion represents a radial scar, or 3) a needle biopsy results in atypical findings.

Diagnosing ovarian cancer, once it has occurred

The lack of obvious early symptoms has been a major obstacle in trying to diagnose ovarian cancer at an early stage. Approximately 70 percent of cases are diagnosed at an advanced stage of disease. (Schwartz, 2002) Clinical history, physical examination of the pelvis, diagnostic imaging (e.g., endovaginal ultrasound), and serum CA-125 are typically used to identify candidates for surgical exploration. These methods have not been recommended for use in the general population and are currently being used only in women with family histories of breast/ovarian cancer or a known *BRCA1/2* mutation. (Question 3) Research continues for effective methods for detecting early stage ovarian cancer. The potential for novel markers from emerging technologies of transcriptional profiling and proteomics are currently being investigated for use in the general population. (Mills et al., 2001) Diagnosis, staging and initial treatment of ovarian cancer are determined through surgery, usually by a laparotomy, but occasionally by laparoscopy. (Schwartz, 2002) Any fluids found in the abdominal cavity are aspirated and sent for cytologic evaluation. If no fluid is present, peritoneal cytology is obtained. The abdominal cavity is explored, looking for any intraperitoneal abnormalities suggestive of metastatic disease. The pelvic and para-aortic retroperitoneum are palpated, looking for enlarged lymph nodes.

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Question 29. Is there an effective remedy, acceptable action or other measurable benefit?

Summary

- The effectiveness and acceptance of surveillance/treatment options for women with a *BRCA1/2* mutation vary considerably.
- Increased surveillance:
  - Adherence to mammography/imaging ranges from 57 to 97 percent
  - Sensitivity of clinical surveillance for breast cancer is 65.7 percent (95% CI 48-87). Specificity has not been assessed.
  - Specificity of surveillance for ovarian cancer is about 96 percent; in other words, a false positive rate of 4 percent (95% CI 3.1-6.5). Sensitivity has not been addressed, but is likely to be lower than for breast cancer surveillance.
  - Adherence to recommendations for CA-125 testing and transvaginal ultrasound ranges from 11 to 73 percent
- Chemoprevention:
  - Based on a single study, acceptance of tamoxifen for breast cancer prevention is 4.7 percent (2/43, 95% CI, 0.6-15.8)
  - Tamoxifen reduced the occurrence of breast cancer by 34 percent in a pooled analysis of the four major prevention trials (random effects model)
  - Tamoxifen reduced the occurrence of breast cancer in 8 women with *BRCA2* mutations by 62 percent**,** but no effect was seen in 11 women with *BRCA1* mutations
  - Tamoxifen reduced the occurrence of contralateral breast cancer by 62 and 37 percent**,** respectively, in women with *BRCA1* and BRCA2 mutations,
  - Raloxifene is undergoing clinical trials for use in breast cancer prevention
  - The protective effect of oral contraceptives for ovarian cancer is not consistent or well-defined (one study reports a protective effect and one study reports no effect**,** and both studies have important methodological limitations).
- Risk-reducing surgeries - mastectomy (RRM) and oophorectomy (RRO)
  - RRM appears to be less acceptable than RRO, and acceptance varies by age, education level, and whether childbearing is complete.
  - RRM was chosen by 0-15 percent of U.S. women.
  - RRO was chosen by 13-50 percent of all U.S. women and by 64-78 percent of women aged 40 years or older.
  - RRM reduces occurrence of breast cancer from between 89.5 and 100 percent
  - RRO reduces occurrence of breast cancer by about 55 percent (95% CI, 24-74)
  - RRO reduces occurrence of ovarian cancer by about 97 percent (95% CI, 86-95.5)
- Modeling The Impact of Three Risk Reducing Strategies on Life Expectancy
  Life expectancy in women choosing preventive options is expected to increase as follows:
  - Tamoxifen 1.8 to 1.9 years (2.7 to 2.8 quality-adjusted life years [QALYs])
  - RRM 3.4 to 4.1 years (2.1 to 2.6 QALYs)
  - RRO 0.8 to 2.6 years (2.1 to 4.4 QALYs)
  - RRM + RRO 4.3 to 5.3 years (2.1 to 2.6 QALYs)
  - Tamoxifen + RRO 4.6 years (6.3 QALYs)

Breast and Ovarian Cancer Surveillance

Adherence to breast and ovarian cancer screening

The proportion of women that is compliant with screening further limits the efficacy of breast and ovarian cancer screening, which was discussed above. Studies that describe adherence to breast and ovarian cancer surveillance in women with either a *BRCA1/2* mutation or a strong family history of breast/ovarian cancer are briefly described below. The proportion of women that participates in the recommended breast and ovarian cancer surveillance varies considerably. The reported ranges are as follows:

Mammography	57 to 97%
CA-125	21 to 68%
Transvaginal ultrasound	11 to 73%

- 79 women with *BRCA1/2* mutations who received counseling at two university hospitals in Canada between 1994 and 1998 participated in a retrospective survey study that included identification of breast and ovarian cancer surveillance practices. (Metcalfe et al., 2002) No reasons were reported for the variable denominators. These self-reported data are as follows:
  - breast self exam, 72 percent (53/76);
  - clinical breast exam, 87 percent (66/76);
  - mammogram (excludes women with bilateral breast cancer or double mastectomy), 87 percent (48/55);
  - pelvic ultrasound (excluding women with oophorectomy), 67 percent (26/39);
  - CA-125 (excluding women with oophorectomy), 55 percent (22/40). Eight of the 40 women eligible for CA-125 testing were not aware of this test.
- At the Memorial Sloan-Kettering Cancer Center, 170 women 35 years of age or older and who carried a *BRCA1/2* mutation were followed for an average of two years. Of the 72 women who chose surveillance for ovarian cancer, 63 provided surveillance data. Surveillance by ultrasonographic and/or CA-125 based-surveillance was reported by 81 percent (51/63). Among the women with intact breast tissue in this group, 88 percent (51/58) also underwent regular mammographic exam. In the 65 women who had chosen risk-reducing oophorectomy and provided surveillance data, 97 percent (63/65) underwent regular mammographic examination. (Kauff et al., 2002)
- 216 women without cancer, aged 25 years and older and who were members of extended families genetically linked to *BRCA1/2*, participated in this study. Of these, 29 of the 143 women with intact breasts were identified as carriers of the *BRCA1/2* mutation, and one had a risk-reducing mastectomy within 12 months following genetic testing. The results of mammography utilization pre- and post-genetic testing are shown in Table 4-2. The only statistically significant predictor of mammography uptake among all women was age; 38 percent of women ages 25-39 years had mammography within 1 year of *BRCA1/2* testing, compared to 60 percent for women 40 years of age and older ($p<0.01$). Of the 131 women with intact ovaries, 39 were identified as mutation carriers and 5 of these reported a risk-reducing oophorectomy within 1 year following genetic testing. The results of ovarian cancer surveillance utilization pre- and post-genetic testing are shown in Table 4-1. Because of the small number of women receiving ovarian cancer surveillance, no multivariate analyses were performed. (Lerman et al., 2000)

Table 4-1. Use of Breast and Ovarian Cancer Surveillance by Women from Families with *BRCA1/2*-Associated Breast Cancer. (Lerman et al., 2000)

	Mammography		CA-125	Transvaginal Ultrasound
	Pre-genetic testing (%)	Post-genetic testing (%)	Post-genetic testing (%)	Post-genetic testing (%)
Carrier	68	68	21	15
No carrier	55	44	6	
Declined Testing	67	54	7	7

- 759 adult members of a large kindred with hereditary breast and ovarian cancer (*BRCA1* mutation) were approached to assess the use of health care interventions by women following genetic testing. (Botkin et al., 2003) 189 women completed baseline and post-test interviews. Women over 25 years without breast cancer and with intact breasts and/or ovaries, were asked about mammography, CA-125 measurements, and transvaginal ultrasound studies performed within the 12 months before the baseline interview and at 1 and 2 years after the baseline interview. The results are shown in Tables 4-2 and 4-3.

Table 4-2. Use of Mammography by Women from a Large Kindred Where a Specific *BRCA1* Mutation Co-segregates with Breast and Ovarian Cancer. (Botkin et al., 2003)

	Mammography		
***BRCA1* Status**	**Baseline**	**1 year**	**2 year**
All ages	**(%)**	**(%)**	**(%)**
Carrier (N=37)	22	62	57
No carrier (N=92)	30	53	49
Unknown (N=15)	0	27	20
25-39 years			
Carrier (N=20)	10	45	35
No carrier (N=32)	13	19	16
Unknown (N=8)	0	0	0
40 years or older			
Carrier (N=17)	35	82	82
No carrier (N=60)	40	72	67
Unknown (N=7)	0	57	43

Table 4-3. Use of CA-125 and Transvaginal Ultrasound by Women from a Large Kindred Where a Specific *BRCA1* Mutation Co-segregates with Breast and Ovarian cancer. (Botkin et al., 2003)

	CA-125			Transvaginal Ultrasound		
***BRCA1* Status (N)**	**Baseline (%)**	**1 year (%)**	**2 year (%)**	**Baseline (%)**	**1 year (%)**	**2 year (%)**
Carrier (19)	0	32	37	0	26	11
No carrier (66)	0	5	5	0	5	2
Unknown (12)	0	0	8	0	8	8

- 251 women with *BRCA1/2* mutations who received genetic test results at Memorial Sloan-Kettering Cancer Center from June 1995 to October 2000 participated in this study. (Scheuer et al., 2002) A portion of this study compared breast and ovarian cancer surveillance before and after genetic counseling. Overall, 165 women were eligible for the breast cancer screening portion of the study (intact breast tissue), and 89 women were eligible for the ovarian cancer screening portion of the study (intact ovaries). Some women were eligible for both. The results are shown in Table 4-4.

Table 4-4. Changes in Breast and Ovarian Cancer Surveillance Among Women with *BRCA1/2* Mutations. (Scheuer et al., 2002)

		Before Counseling	After Counseling
	N	**N (%)**	**N (%)**
Mammography	136	111 (82)	127 (93)
Clinical Breast Exam	117	113 (97)	114 (97)
Breast Self Exam	114	88 (77)	95 (83)
CA-125	74	20 (27)	50 (68)
Transvaginal Ultrasound	70	25 (36)	51 (73)

- 134 women with *BRCA1/2* mutations and breast tissue at risk seen at Memorial Sloan-Kettering Cancer Center between 1995 an 2001 were retrospectively studied to assess breast cancer screening compliance. The average follow-up time was 38.4 months. At the time of receiving genetic test results, 112/134 (84%) had undergone mammography in the previous year. At follow-up, 128/134 (95%) had undergone mammography (p=0.03). (Huang et al., 2003)
- 289 women who received free genetic counseling and testing through Lombardi Cancer Center's Cancer Assessment and Risk Evaluation program from 1995 to 2000 participated in this study. (Schwartz et al., 2003) Probands (women previously affected with breast or ovarian cancer) received either positive (deleterious mutation) or uninformative *BRCA1/2*

mutation test results. Relatives of the proband who were found not to carry the mutation known to segregate with cancer in their family were given negative test results. Participation in surveillance for ovarian cancer is reported in Table 4-5.

Table 4-5. Use of CA-125 and Transvaginal Ultrasound by Women from a Large Kindred Where a Specific *BRCA1* Mutation Co-segregates with Breast and Ovarian Cancer. (Schwartz et al., 2003)

	CA-125		Transvaginal Ultrasound	
***BRCA1* Status**	**Baseline (%)**	**1 year (%)**	**Baseline (%)**	**1 year (%)**
Carrier (N=79)	12	43	16	40
No carrier (N=44)	19	9	19	21
Uninformative (N=166)	21	27	27	29

Increased breast cancer surveillance

Efficacy Increased breast cancer surveillance (self and clinical breast examination and mammography/MRI) is recommended for women with *BRCA1/2* mutations who choose not to undergo risk-reducing mastectomy. (Burke et al., 1997) An issue of concern in breast cancer surveillance is interval cancer, described as cancers detected between regularly scheduled clinical examinations. These interval cancers can occur either because lesions present at the time of screening are not detected (e.g., due to dense breast tissue) or because new lesions appear and the rate of tumor growth is rapid. Studies that assessed the effectiveness of breast cancer surveillance in younger women with either a *BRCA1/2* mutation or a strong family history of breast/ovarian cancer for a two to three year time period are briefly described below. A summary is provided in Table 4-6 using the Der Simonian and Laird methodology for combining studies. (Berlin et al., 1989) Among women with known *BRCA1/2* mutations or a strong family history of breast/ovarian cancer, between 4 and 12 percent developed breast cancer. The sensitivity of clinical breast examination in these women is 65.7 percent (33/51, 95% CI 48.2-87.2%). Specificity is not assessed. This estimate provides an upper limit due to high compliance, good equipment and highly trained study personnel utilized for these high-risk women.

Table 4-6. The Sensitivity of Clinical Surveillance in Detecting Interval Cancers in Women at High Risk for Breast Cancer.

Study	High-risk women N	Breast cancer cases N	Breast cancer cases detected by surveillance N	Sensitivity % (95% CI)
1	749	31	22	71.0 (52.0-85.8)
2	165	12	7	58.3 (27.7-84.8)
3	63	8	4	50.0 (15.7-84.3)
Total	977	51	33	65.7 (48.2-87.2)

Reference: 1 (Brekelmans et al., 2001), 2 (Scheuer et al., 2002), 3 (Meijers-Heijboer et al., 2001)

Study 1. the Netherlands - This study included 128 *BRCA1/2* mutation carriers (mean age of 37 years, range 21-63 years) and 621 women with high familial risk (≥ three 1st or 2nd degree relatives with breast cancer or two 1st or 2nd degree relatives whose breast cancer occurred before 50 years of age; mean age of 38 years, range 22-70 years). Surveillance consisted of monthly breast self-examination, bi-annual clinical breast examination and annual mammography and/or MRI. In the 128 *BRCA1/2* mutation carrier group, 9 women (7%) developed invasive breast cancer (average follow-up 2.1 years). Five were detected by clinical surveillance (56%), and four were interval cancers (two of these were ≤ 10 mm). Among the 621 women with high familial risk, 17 of 22 cases of breast cancer (77%) were detected clinically, including four cases of ductal carcinoma *in situ*. Of 18 cases of invasive cancer (22-4), 16 reported tumor size. Seven of these were ≤ 10 mm. (Brekelmans et al., 2001)

Study 2. New York, NY - 165 *BRCA1/2* mutation carriers who received genetic test results at Memorial Sloan-Kettering Cancer Center were followed for an average of 24.1 months. Surveillance consisted of monthly breast self-examination, clinical breast examination 2-4 times a year, annual mammography, and, in some women, breast ultrasound or MRI. Seven percent (12/165) were diagnosed with a new primary breast cancer. Palpable masses were detected by breast self-exam in five cases and by physician exam in one case. Of these six cases, five were less than 20 mm and one had lymph node metastases. Five cases were detected by mammography and one by MRI. All of the three invasive cases were less than 20 mm. (Scheuer et al., 2002)

Study 3. the Netherlands - 63 *BRCA1/2* mutation carriers were prospectively followed for an average of 3 years. Surveillance consisted of a monthly breast self-examination, a clinical breast examination every six months, and yearly mammography. MRI, ultrasound, and fine-needle aspiration were also used where appropriate. Overall, 8 of 63 (13%) were diagnosed with breast cancer. Two of these women had a prior oophorectomy. Four of these 8 cancers were initially detected by self-examination. The interval from screening to diagnosis was 2-5 months. (Meijers-Heijboer et al., 2001)

Another study compared findings on physical examination, mammography, and MRI with histologic findings following risk-reducing surgery in high-risk women, most of whom were *BRCA1/2* mutation carriers. None of the women had clinical evidence of breast cancer. A high percentage of pathologic lesions was identified by histology, but there was no control group for comparison.

- 67 women who underwent risk-reducing mastectomy (RRM) had their breasts examined for pre-malignant and malignant lesions. To exclude overt malignancy, palpation was performed by a skilled practitioner the day before RRM, mammography was done in all patients three months prior to RRM, and MRI was performed in 27/67 women (40%) three months prior to RRM. In all women, palpation, mammography, and MRI were without signs of breast cancer. 26 of these women had a unilateral RRM, contralateral to a previous breast cancer, and 41 women had a bilateral RRM. 44/67 women (66%) were known *BRCA1/2* mutation carriers. High-risk histopathologic lesions (ALH, ADH, lobular carcinoma *in situ*, ductal carcinoma *in situ*) were found in 18/26 women (69%) who had undergone unilateral mastectomy. High-risk lesions were found in both breasts of 13/41 women (32%) that had undergone bilateral RRM. In 7/41 women, a single breast was affected (17%). (Hoogerbrugge et al., 2003)

Gaps in knowledge: 1) although the impact of breast cancer surveillance on invasive breast cancer can be estimated, its impact in reducing breast cancer mortality among women with *BRCA1/2* mutations is not well documented, and 2) data on "false positives" (e.g. women with a suspicious lump or imaging study who are referred for biopsy) are missing from the reported studies.

Increased ovarian cancer surveillance

Efficacy Increased ovarian cancer surveillance is recommended for women with *BRCA1/2* mutations who elect to retain their ovaries. (Burke et al., 1997) This surveillance may consist of semi-annual transvaginal ultrasonography, preferably with color Doppler, and serum CA-125 measurement. Other imaging techniques (e.g., MRI and CT) and tumor markers may be used in addition to, or in place of, sonography and CA-125. Combinations of serum test/imaging may increase the sensitivity of either test alone. Studies that describe ovarian cancer surveillance in women with either a *BRCA1/2* mutation or a strong family history of breast/ovarian cancer are briefly described below. A summary is provided in Table 4-7. Among the 1,533 women collectively studied, 9 cases of ovarian cancer were identified. An additional 68 women underwent surgical exploration based on surveillance results. No ovarian cancers were identified in this group. Thus, the false positive rate of ovarian cancer screening is 68/1,524 or 4 percent (95% CI 3.1-6.5) based on the Der Simonian and Laird pooling methodology. (Berlin et al., 1989)

Table 4-7. The Results of Clinical Surveillance in Detecting Ovarian Cancers in Women at High Risk for Ovarian Cancer

Study	High-risk women N	Ovarian cancer cases detected by surveillance N	Surgical exploration without ovarian cancer N
1	62	5	5
2	384	0	15
3	311	1	8
4	776	3	40
Total	**1,533**	**9**	**68**

Study 1 (Scheuer et al., 2002), 2 (Muto et al., 1993), 3 (Laframboise et al., 2002), 4 (Bourne et al., 1991)

Study 1. New York, NY - 89 *BRCA1/2* mutation carriers who retained their ovaries were prospectively followed for an average of 17 months. Of the 89 women, 62 (70%) received ovarian cancer surveillance. Five of the 89 (5.6%) were found to have ovarian or primary peritoneal cancer. Surgical exploration was indicated by an abnormal transvaginal ultrasound in 4 of these cases. CA-125 levels were elevated in two cases, normal in one and not measured in one. Two of the four ovarian cancer cases were stage I, one was stage II, and one was incompletely staged. The woman diagnosed with peritoneal cancer had a solitary implant on a fallopian tube. Abnormal transvaginal ultrasonograms or CA-125 measurements were noted in 22 of the 62 women under surveillance, which resulted in surgical exploration in five women without cancer. (Scheuer et al., 2002)

Study 2. Boston, MA - 384 women with either a first degree or multiple second degree relatives with confirmed ovarian cancer participated in a study to assess the utility of screening with transvaginal sonography (TVS), color flow doppler, and CA-125. The mean age of the women was 41 years, and 214 (56%) were pre-menopausal. CA-125 levels varied significantly according to menopausal status, phase of menstrual cycle, and oral contraceptive use. The initial serum CA-125 assay was abnormal in 42 of the women (11%). Eight women had persistently elevated levels, and three of these also had abnormal ultrasound studies. Five of these 8 went on to surgical exploration. Transvaginal ultrasound successfully visualized both ovaries 87 percent of the time in pre-menopausal women but only 57 percent of the time in post-menopausal women. Despite multiple attempts and the use of transabdominal sonography, 22 percent of post-menopausal ovaries could not be visualized. Overall, 89 out of 384 women (23%) had a scan that was defined as abnormal. Ten of these women were referred for surgical intervention. No malignancies were detected in the 15 women (5 with abnormal CA-125 measurements and 10 with abnormal TVS results) undergoing surgery. (Muto et al., 1993)

Study 3. Ontario, Canada - 311 women with a high-risk pedigree assessment for ovarian cancer or a known *BRCA1/2* mutation were retrospectively studied using both CA-125 and ultrasound. Over a seven year time period (1992-1999), all women had at least one screening visit (range 1-17), with an average of five visits. Among the 1,209 CA-125 tests, 33 (2.7%) were abnormal. The number of ultrasound studies performed was 1,342 (range 1-14 per patient), with an average of four per patient. Ultrasound abnormalities were reported in 226 studies (16.8%). Twenty patients underwent risk-reducing oophorectomy based on their cancer risk (all had normal screening test results). Nine women underwent surgery because of an abnormal screening result: two had only abnormal CA-125 measurements, six had only abnormal ultrasound results, and one had abnormal findings for both. Three of the nine were known *BRCA1/2* mutation carriers. The only woman in this study found to have ovarian cancer at the time of surgery had an abnormal ultrasound study. Her *BRCA1/2* mutation status was not known. (Laframboise et al., 2002)

Study 4. London, UK - 776 women with at least one first or second degree relative with ovarian cancer were recruited through advertisement in local and national press in the U.K. These women were examined using a transabdominal and transvaginal ultrasound. 636 women (82%) had a negative result. An additional 64 women (8.2%) initially had a positive result but were reclassified negative on repeat scans. A total of 43 women (5.5%) had positive results on more than one scan and were referred for surgical investigation; 39 (91%) underwent laparotomy. Three cases of primary ovarian cancer were identified, all stage 1. Another 33 women (4.3%) were either waiting for a re-scan or dropped out of the study. (Bourne et al., 1991)

> **Gaps in knowledge**: 1) The efficacy of available surveillance options in reducing ovarian cancer mortality is not established. 2) Data demonstrating that screening will detect early cancer are lacking.

Chemoprevention

Tamoxifen

Efficacy The only Food and Drug Administration (FDA)-approved risk-reduction agent for breast cancer is tamoxifen. This approval was based on the results from the Breast Cancer Prevention Trial (BCPT), conducted between 1992 and 1998 by the National Surgical Adjuvant Breast and Bowel Project. (Fisher et al., 1998) The purpose of the BCPT was to determine whether tamoxifen use by cancer-free, high-risk women significantly altered incidence of invasive breast cancer. Similar studies have been performed with conflicting results. These studies are summarized in Table 4-8, and brief descriptions are found below. Several published reports have presented possible reasons for the differences in breast cancer risk among the trials. (Eeles and Powles, 2000; Fisher et al., 2000; Kuschel et al., 2000) These include:

- issues related to power to detect a difference and large drop-out rates
- compliance with taking therapy
- timing and use of concurrent hormone replacement therapy
- study population differences including: entry criteria, strength of family history, and prior procedures known to affect breast cancer risk (e.g. oophorectomy)

A pooled analysis of these four trials reported a 38 percent (95% CI 28-46; p<0.0001) reduction in breast cancer incidence with tamoxifen using a fixed-effects model. The reduction in risk was 34 percent when analyzed with a random-effects model. (Cuzick et al., 2003)

Table 4-8. Summary of Four Published Tamoxifen Trials for Breast Cancer Prevention

	Fisher *et al.* (1998)	**Powles *et al.* (1998)**	**Veronesi *et al.* (1998)**	**Cuzick *et al.* (2002)**
Number of women randomized	13,388	2,494	5,408	7,139
Number of women with follow-up	13,175	2,471	3,837	7,051
Median follow-up (months)	55	70	46	50
Breast cancer cases (n)	368	70	41	170
Placebo	244	36	22	101
Tamoxifen	124	34	19	69
Odds Ratio (95% CI)	0.51 (0.39-0.66)	1.1 (0.7-1.7)		0.68 (0.5-0.9)
P value	< 0.001	0.8	0.6	0.013

Study 1: (Fisher et al., 1998) - Women from 131 clinical centers in the U.S. and Canada were eligible for this trial, if they were: 1) older than 60 years of age, 2) 35 years or older with a breast biopsy showing lobular carcinoma *in situ***,** or 3) between the ages of 35 and 59 years with an estimated risk for developing breast cancer equal to that of a 60 year old woman (5-year predicted risk of at least 1.66 percent, estimated using the Gail model (Gail et al., 1989)). Tamoxifen reduced the risk of invasive breast cancer by 49 percent (RR=0.51, 95% CI 0.39-0.66). The extent of risk reduction based on age was as follows: women aged 49 years of younger (44%), 50-59 years (51%), and 60 years or older (55%). The trend is statistically significant. The occurrence of estrogen receptor-positive tumors was decreased by 69 percent, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Women who received tamoxifen had a 2.5 times greater risk of developing invasive endometrial cancer compared with women who received placebo. There was also an increase in the number of thromboembolic vascular events among the postmenopausal women who received tamoxifen. Stroke, transient ischemic attack, deep vein thrombosis, and pulmonary embolism were all increased in women receiving tamoxifen, although the latter was the only event rate to reach statistical significance.

Study 2: (Powles et al., 1998) – Women identified in the screening and symptomatic breast clinics of the Royal Marsden Hospital, Surrey, U.K. were eligible if between 30 and 70 years of age, with no clinical or screening evidence of breast cancer, and with an increased risk of breast cancer because of family history. The frequency of breast cancer in this trial is the same for women on tamoxifen or placebo (RR=1.1, 95% CI 0.7-1.7).

Study 3: (Veronesi et al., 1998) – The Italian Tamoxifen Prevention Study includes healthy women aged 35-70 years of age who had a total hysterectomy for reasons other than neoplasms. These women were not at increased risk for breast cancer. Nearly 50 percent (n = 2,595) had a bilateral oophorectomy and 19 percent (n = 998) had a unilateral oophorectomy. Forty-one breast cancer cases developed, 19 in the tamoxifen arm and 22 in the placebo arm (NS). Women on tamoxifen were more likely to suffer a vascular event (p=0.0053), such as thrombophlebitis, phlebothrombosis, or embolus. Addition analyses were conducted after 81 months of follow-up. (Veronesi et al., 2003) While there continued to be no difference in breast cancer incidence between the placebo and tamoxifen arms, a high-risk group for estrogen-receptor positive breast cancer was identified. This group comprised 702 (13%) women taller than 160 cm (the median height of the group), with at least one functioning ovary, who had menarche at no older than age 13 and no full-term pregnancy before age 24. The remaining 4693 (87%) women were classified as the low-risk group. Intervention with tamoxifen significantly reduced the incidence of breast cancer in the high-risk group by 82 percent (HR = 0.18, 95% CI = 0.05-0.62, p=0.003).

Study 4: (Cuzick, 2002) – Women aged 35-70 years were recruited for the International Breast Cancer Intervention Study (IBIS) from the U.K., Australia, New Zealand, and some European countries. Entry criteria required that these women have risk factors for breast cancer indicating at least a two-fold relative risk for ages 45-70 years, a four-fold relative risk for ages 40-44 years, and a roughly ten-fold relative risk for ages 35-39 years. The rate of breast cancer was 32 percent lower in the tamoxifen group (95% CI, 8-50) than in the placebo group (p=0.01). Age, degree of risk, and use of hormone replacement therapy did not affect the reduction. The reduction in risk of estrogen receptor positive invasive tumors was 31 percent. There was no reduction in risk of estrogen receptor negative invasive tumors. The tamoxifen group experienced more thromboembolic events (OR=2.5 [95% CI, 1.5-4.4], p=0.001) and excess deaths from all causes (25 vs. 11, p=0.028).

Tamoxifen and BRCA1/2 Mutation Status The observation that the reduction in breast cancer due to tamoxifen was consistent for women both with and without a family history of breast cancer led to the theory that it may have a similar effect among women with inherited mutations in *BRCA1/2*. However, *BRCA1* tumors lack estrogen and progesterone receptors. This, and other differences, raise the possibility that tamoxifen might be effective in reducing breast cancer risk among women with *BRCA2* mutations, but not among those with *BRCA1* mutations. To address this issue, King *et al*. (King et al., 2001) did a retrospective study utilizing 288 out of 320 breast cancer cases (90%) from the BCPT. Eight *BRCA1* and 11 *BRCA2* mutation carriers were identified (n = 19, 6.6%). Tamoxifen reduced breast cancer incidence among healthy *BRCA2* carriers by 62 percent, while no effect was seen among *BRCA1* carriers. This stratified analysis resulted in rather small sample sizes. Larger trials are necessary to achieve statistical significance.

Tamoxifen and bilaterial breast cancer Another study investigated the effect of tamoxifen on the risk of contralateral breast cancer in *BRCA1/2* mutation carriers. (Narod et al., 2000) This case-control study used 209 women with bilateral breast cancer and a *BRCA1/2* mutation as cases and 384 women with unilateral disease and a *BRCA1/2* mutation as controls. Women

reporting tamoxifen use were 50 percent less likely to have bilateral breast cancer than non-users (95% CI 0.28-0.89). Tamoxifen protected against bilateral breast cancer for carriers of *BRCA1* mutations (odds ratio 0.38, 95% CI 0.19-0.74) and for *BRCA2* mutations (odds ratio 0.63, 95% CI 0.2-1.5, NS). Tamoxifen use for two to four years was associated with the greatest risk reduction (odds ratio 0.25, 95% CI 0.07-0.91). A smaller protective effect was seen for use less than two years (odds ratio 0.47, 95% CI 0.23-0.99) and an increased risk seen with use for more than four years (odds ratio 1.53, 95% CI 0.44-5.27, NS). Estrogen receptor status of the tumors was available for 130 patients (56 bilateral cases and 74 controls). There was no difference in the protective effect of tamoxifen, based on estrogen receptor status.

A statistical model was developed to estimate the preventive effect of tamoxifen in women with *BRCA1* or *BRCA2* mutations for breast cancer. (Duffy and Nixon, 2002) Using data from the two primary prevention trials that stratified results by estrogen receptor status (Duffy and Nixon, 2002; Fisher et al., 1998; Veronesi et al., 1998), an estimated reduction in risk from tamoxifen therapy was 5 percent (95% CI 0.51-1.76)) for women with *BRCA1* mutations and 37 percent (95% CI 0.34-1.15) for women with *BRCA2* mutations.

> **Gap in knowledge**: Limited empiric data exist on the balance between risks and benefits of long-term tamoxifen use.

Acceptance/Adherence for Tamoxifen Therapy _A single study has formally evaluated patients' acceptance of tamoxifen and their willingness to take it. (Port et al., 2001) Forty-three patients who qualified to take tamoxifen for primary breast cancer prevention were counseled in a neutral manner regarding risks and benefits of this therapy. Of these patients, two (5%) elected to start taking tamoxifen. Fifteen patients (35%) declined immediately, and 26 patients (60%) were undecided initially and eventually declined. Fear of side effects (endometrial cancer, thromboembolic events, and menopausal symptoms) was the most commonly cited reason for declining to take tamoxifen. Additional evidence on adherence to tamoxifen therapy can be found in the breast cancer chemoprevention trials. The frequency of noncompliance was high in each of these studies (Table 4-9).

Table 4-9. Proportion of Noncompliant Patients in the Breast Cancer Chemoprevention Trials.

	Noncompliance Rate (%)	
Study	**Tamoxifen**	**Placebo**
Fisher *et al*., 1998	24	20
Powles *et al*., 1998	46	37
Veronesi *et al*., 1998	28	25
Cuzick *et al*., 2002	36	26

Other chemoprevention strategies undergoing pilot or clinical trials

Raloxifene, which was approved by the FDA in 1997 for the prevention of osteoporosis in postmenopausal women, is another drug that holds promise as an agent for breast cancer risk reduction. Raloxifene and Tamoxifen are Selective Estrogen Receptor Modulators or SERMs.

The Study of Tamoxifen and Raloxifene Trial (STAR) for the Prevention of Breast Cancer is a randomized, double-blind study designed to determine whether raloxifene is more or less effective than tamoxifen in reducing the incidence of invasive breast cancer in postmenopausal women. Additionally, it will evaluate the toxicity of these drugs and their effect on the quality of life of participants. More than 22,000 women are expected to be recruited from over 400 centers in the United States, Canada, and Puerto Rico.

The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial randomized 9,366 postmenopausal women with operable breast cancer to assess efficacy in preventing contralateral breast cancer. A total of 84 percent of the tumors was estrogen- and/or progestogen-receptor positive. With a median follow-up of 31 months, Arimidex (anastrozole) reduced the risk of contralateral breast cancer by 42 percent, compared with tamoxifen. Arimidex is a nonsteroidal compound and is the first of a new class of third-generation selective oral aromatase inhibitors. Inhibition of aromatase reduces the production of estrogen. (Tobias, 2002)

A randomized trial of fenretinide (a retinoic acid derivative) to prevent a second breast cancer in women with stage I breast cancer or ductal carcinoma *in situ* included nearly 3,000 women. At a median observation time of 97 months, there was no statistically significant difference in the occurrence of contralateral or ipsilateral breast cancer. A beneficial effect was observed in pre-menopausal women (contralateral breast cancer, hazard ratio=0.66, 95% CI 0.41-1.07, ipsilateral breast cancer, hazard ratio=0.65, 95% CI 0.46-0.92). The opposite effect was seen in post-menopausal women. (Veronesi et al., 1999)

Oral Contraceptives and Ovarian Cancer

The general impression that oral contraceptives (OC) provide protection against ovarian cancer is based on studies involving the general population. (Franceschi et al., 1991; Parazzini et al., 1992; Wu et al., 1988) This protection is not consistently supported in well-designed studies among women with BRCA1/2 mutations. Below is a summary of studies involving OC in women with BRCA1/2 mutations, along with comments about the study design and interpretation.

- The first study to examine the effect of OC in women with *BRCA1/2* mutations was a retrospective case-control study. Cases were 207 women with a *BRCA1/2* mutation diagnosed with invasive epithelial ovarian cancer (average age of 54 years). Women were identified in three ways. Sixteen women had been diagnosed with cancer in Ontario after 1995. Twenty-six were Ashkenazi Jewish women from 11 gynecology-oncology hospitals in North America, and 165 were identified by the Breast Cancer Linkage Consortium (37 from the U.K., 39 from other European countries, 67 from the U.S. and 22 from Canada). The 161 controls were living sisters of the cases, regardless of *BRCA1/2* mutation status (average age of 52 years). Use of OC at any time or any duration was reported by 50 percent of the cases compared with 70 percent of the controls ($p<0.001$). Average duration of OC use was 4 years in cases and 6 years in controls ($p<0.01$). The odds ratio for ovarian cancer associated with OC use was 0.5 (95% CI, 0.3-0.8) using all control women. The odds ratio was 0.4 (95% CI, 0.2-0.7) using only *BRCA1/2* mutation positive control women. There was a statically significant trend for length of OC use and risk of ovarian cancer. Several biases exist in this study that would overestimate the protective

effect of OC usage. These including using controls who did not have intact ovaries and requiring that the control sister be alive at the time of the study. A limitation of the study is that a proportion of cases and controls has unknown timing of OC use in relation to learning about their *BRCA1/2* status. In addition, 30 percent of cases had a personal history of breast cancer compared with 18 percent of controls. (Narod et al., 1998)

- A second case-control study evaluated the risk of ovarian cancer and OC use in Jewish women with and without one of the three BRCA1/2 founder mutations. A total of 2,269 controls was matched to 1,115 cases for age, area of birth, and place and length of residence in Israel. A total of 840 patients (75%) and 751 controls (33%) underwent *BRCA1/2* mutation testing. Only the 840 cases who underwent mutation testing were included in the analyses. Ignoring mutation status, women who reported OC use for 5 or more years had a statistically significant reduction in ovarian cancer risk (odds ratio = 0.69, 95% CI 0.48 - 0.98). However, this effect was limited to *BRCA1/2* mutation non-carriers (odds ratio = 0.53, 95% CI 0.34 - 0.84). Women with *BRCA1/2* mutations were not at reduced risk of ovarian cancer (odds ratio = 1.07, 95% CI 0.63-1.83). Because only 13 controls were mutation carriers, controls were not separated according to mutation status. This study may not be relevant to non-Jewish populations or to all types of oral contraceptives. (Modan et al., 2001)
- Using a subgroup of Ashkenazi Jewish women in North America with *BRCA1/2* mutations from previously reported data summarized above (Narod et al., 1998), Narod *et al.* report *de novo* an odds ratio for ovarian cancer of 0.54 among women who had used OC (95% CI, 0.35-0.84). (Narod et al., 2001) The same limitations discussed earlier apply to this analysis.

Gap in Knowledge Although a consistent reduction in ovarian cancer risk associated with OC use has been documented for the general population, it is not yet clear whether such an effect is found among women with *BRCA1/2* mutations.

Risk Reduction Surgery

Definitions and Biases

Because mastectomy and oophorectomy may significantly reduce, but not eliminate, risk for breast and ovarian cancer, it has been proposed that this type of surgery be labeled "risk reduction" as opposed to prophylactic surgery. (Stefanek et al., 2001) This term is not only more precise but may also facilitate understanding among health care disciplines and between women at risk and their health care providers.

A recent publication warns that the value of risk-reducing surgeries for the prevention of breast and ovarian cancer in high-risk women may be over- or under-estimated, because of potentially unrecognized biases in study design. (Klaren et al., 2003) These biases include:

- Confounding by indication
  Example: Comparing surgery and non-surgery patients who are from families with different baseline risk of breast and ovarian cancer. This form of bias may lead to an under-estimation of risk reduction after risk-reducing surgery.
- Survival bias
  Example: The occurrence of ovarian cancer may reduce available person-years at risk, especially among those not undergoing oophorectomy. These deaths change the risk of

breast cancer in the remaining study group (i.e. families with *BRCA1* mutations in the ovarian cancer cluster region). This may result in an over-estimation of the breast cancer risk reduction.

- Detection bias
  Example: A clinically undetected tumor is found in tissue removed during risk-reducing surgery. For a conservative estimate of the efficacy of the risk-reducing surgery, the cancer should be counted as an event in the surgery group. It is also clinically important to estimate the efficacy of the surgery after exclusion of the women diagnosed at surgery.
- Ascertainment bias
  Analyses that include cancer occurrences prior to the date the first family member started to be screened or counseled (date of ascertainment) can over-estimate the cancer risk.
- Cancer-induced testing bias
  The differential selection of identified mutation carriers with cancer from the total group of mutation carriers may lead to an over-estimation of cancer incidence in the non-surgery group, if the cancer event is included in the analysis.
- Familial-event bias
  Example: The decision by women with an increased risk for breast/ovarian cancer to choose risk-reducing surgery is often influenced by a recently diagnosed cancer or cancer-related death in a family member. Thus, if members of the same family are included in the study population, the date of risk-reducing surgery should be considered. If follow-up is started at the date of testing, the cancer risk among women in the non-surgery group is overestimated, and, consequently, an overestimation of the cancer risk reduction after risk-reducing surgery occurs.
- Confounding by other risk factors
  Oophorectomy confounds the efficacy of mastectomy. Parity and hormone replacement therapy are also confounders in evaluating breast and ovarian cancer risk. These risk factors have not been included in most efficacy studies.

<u>Mastectomy</u>

The recommendation for risk-reducing mastectomy (RRM) in individuals with a hereditary predisposition to breast and ovarian cancer remains controversial. The actual risk-reduction potential of RRM is a critical component of the decision-making process for health care providers and women at increased risk of breast cancer. The effectiveness of RRM relative to chemoprevention and bilateral oophorectomy has not yet been resolved. The identification of appropriate surgical candidates and the penetrance estimates for cancer phenotypes lack clear definition. The impression that early cancer, detected by intensive surveillance, can be treated effectively also makes RRM less appealing. Cost and willingness of insurance companies to provide coverage (Question 30) can also affect the use of RRM. Finally, the acceptance of this surgery is also influenced by the fact that it is disfiguring, contributes to early menopause, and has negative sexual function implications.

Acceptance

Among women with a *BRCA1/2* deleterious mutation, approximately 22 percent undergo RRM (Table 4-10). These data were pooled using the Der Simonian and Laird methodology. (Berlin et al., 1989) There are clear cultural differences in acceptance rates of RRM between the Netherlands and the United States. In the three studies that took place in the Netherlands,

between 35 and 67 percent of eligible women chose RRM, while three U.S. studies reported 15 percent or less choosing this preventive option. These studies are summarized in the following table.

Table 4-10. Proportion of Women Considering or Accepting Risk-Reducing Mastectomy (RRM) by Mutation Status

Study		Consider RRM	Accept RRM (%)	
Number	Site	% (N)	All Women	*BRCA1/2* Positive
1	U.S.	65 (107/164)	9 (15/165)	n/a
2	U.S.	n/a	n/a	3 (1/ 29)
3	U.S.	n/a	n/a	15 (29/194)
4	U.S.	11 (4/ 37)	n/a	0 (0/ 37)
5	Netherlands	66 (21/ 32)	n/a	67 (8/ 12)
6	Netherlands	n/a	n/a	51 (35/ 68)
7	Netherlands	n/a	n/a	35 (35/101)
8	Australia	19 (63/333)	n/a	n/a
All (95% CI)		30 (13.6-68.0)	9 (5.2-14.6)	22.4 (8.3–60.2)

n/a = Not assessed
Reference: 1 (Stefanek et al., 1995), 2 (Lerman et al., 2000), 3 (Scheuer et al., 2002), 4 (Botkin et al., 2003), 5 (Unic et al., 2000), 6 (Meijers-Heijboer et al., 2000), 7 (Meijers-Heijboer et al., 2003) 8 (Meiser et al., 2000)

Study 1. Maryland – 164 women were assessed in a clinic for women at increased risk for the development of breast cancer at Johns Hopkins Oncology Center. While 107 (65%) expressed initial interest in RRM, only 15 (9%) had the procedure. There were no differences between those opting for the procedure and those opting for surveillance in either the number of first-degree relatives affected with breast cancer or the objective 30-year risk of breast cancer development. (Stefanek et al., 1995)

Study 2. U.S. - 216 unaffected females, aged 25 years and older and who were members of extended *BRCA1/2* linked families participated in this study. 143 were eligible for RRM (they had intact breasts). Of these, 29 were identified as carriers of a *BRCA1/2* mutation. Only one of these women reported having a RRM within the following 12 months. (Lerman et al., 2000)

Study 3. New York City - 233 women with known *BRCA1/2* mutations who received genetic test results at Memorial Sloan-Kettering Cancer Center participated in this study. Twenty (8.6%) had previously undergone RRM, and 19 had undergone bilateral mastectomies for breast cancer. Of the remaining 194 women, 29 (15%) underwent RRM at a median of 5.3

months (range, 0.1 to 34.8 months) after receiving mutation testing results. Women electing RRM were younger than those not opting for surgery (mean 43.0 v 46.8 years, p=0.015) and had a greater number of breast and ovarian malignancies in first- and second-degree relatives (mean, 2.7 v 2.1 cancers, p=0.046). (Scheuer et al., 2002)

Study 4. Utah - 759 adult members of a large kindred with evidence of hereditary breast and ovarian cancer (*BRCA1* mutation) were approached to assess the use of health care interventions by women following genetic testing. Women known to carry the kindred specific *BRCA1* mutation, but without breast cancer, with intact breasts, and over 25 years were informed of mastectomy as a preventive option (N=37). None of the women had obtained RRM during the 2 year follow-up period. However, 2/20 women under age 40 and 2/17 women 40 years and older were considering this procedure at 2 years following testing. (Botkin et al., 2003)

Study 5. the Netherlands - A prospective pilot study of women's treatment choices and medical and decision-analytic recommendations was conducted in the Netherlands from 1995 to 1997. Forty-eight women with a family history of breast cancer completed the protocol. Of the 12 women with a *BRCA1/2* mutation, eight (67%) chose RRM and four (33%) chose close surveillance. Of the 36 women awaiting DNA test results, 32 made hypothetical treatment choices: 21 (66%) chose RRM and 11 (34%) chose close surveillance. Predictors for choosing RRM included being married and having children. (Unic et al., 2000)

Study 6. the Netherlands – Of 411 unaffected women from 53 consecutive families with an identified *BRCA1/2* mutation at a Family Cancer Clinic in the Netherlands, 275 had a 50 percent risk of carrying a *BRCA1/2* mutation and 136 had a 25 percent risk of carrying a *BRCA1/2* mutation. All were offered DNA testing, and 198 (48%) accepted. Of the women with a pre-test genetic risk of 50 percent, 69/158 (44%) had a mutation. Among the women with a 25 percent risk, 6/40 (15%) had a mutation. Sixty-eight mutation carriers aged 25 years and older were eligible for RRM, and 35 (51%) had the procedure. The uptake rate by age group was as follows: 21/38 (55%) of women under 40 years, 13/21 (62%) of women 40-54 years, and 1/9 (11%) of women 55 years and older. Thirty-three of 54 (61%) women with children opted for RRM compared with 2/14 (14%) of women without children. RRM was performed within 9 months of the DNA testing results in 31/35 (89%). The other 4 women waited 11, 13, 28, and 33 months, respectively. Breast reconstruction was done in all but one woman. Chemoprevention was not an option for the women in this cohort. (Meijers-Heijboer et al., 2000)

Study 7. Netherlands - A consecutive series of 112 families with a *BRCA1/2* mutation wasused to identify 220 women that had breast cancer (n=172), ovarian cancer (n=33), or both breast and ovarian cancer (n=15). These women were eligible for RRM if they were free from metastatic disease at the moment of personal genetic diagnosis and had intact breast tissue. RRM was performed in 35/101 women (35%). The mean time interval from the genetic diagnosis to RRM was 9 months. At a follow-up of 1 and 2 years, 15 (22%) and 18 (35%), respectively, of eligible women had their breasts removed. After this period, one additional woman requested the procedure. (Meijers-Heijboer et al., 2003)

Study 8. Australia – 333 out of 374 eligible unaffected women at increased risk of developing hereditary breast cancer were enrolled from familial cancer clinics and associated outreach clinics in five Australian states. Clinic staff judged 223 (67%) to have a 50 percent mutation carrier risk, 37 (11%) to have a 25 percent mutation carrier risk, and the remaining 73 (22%) to be at moderately increased risk of developing breast cancer. Of the 192 women eligible for and interested in genetic testing, only 13 percent (24) had received a genetic testing result at the time of manuscript submission. 47 high-risk women (14%) were not eligible for genetic testing because they did not have a living, affected relative who could undergo mutation detection. Five (3%) of the 192 women reported participating in a placebo-controlled tamoxifen chemoprevention trial. Sixty-three of the 333 women reported that they would consider RRM (19%), and 157 (47%) reported that they would not consider RRM, should mutation testing results be positive. Four had already undergone the procedure, and the remaining women were uncertain about their choice. Consideration of RRM was significantly correlated with breast cancer anxiety, overestimating one's risk, and age. Only women age 30-39 years were more likely to consider RRM compared with women 50 years of age and older. This study reports on intentions to undergo RRM. Thus, it is not known if this would reflect actual behavior. This cohort is highly educated, which may limit generalizations to be made to all women at increased hereditary risk of breast cancer. (Meiser et al., 2000)

Efficacy

Two retrospective studies report on the efficacy of bilateral RRM. The first was restricted to women with a family history of breast cancer but did not include information about *BRCA1/2* mutations. The second utilized a subgroup of the same population that was tested for *BRCA1/2* mutations. A third study reported prospectively on the efficacy of RRM in unaffected *BRCA1/2* mutation carriers. These studies all reported a 90 percent or higher decrease in risk for breast cancer.

- In the first study, 639 women with a family history of breast cancer who had undergone a RRM were assigned to high risk or moderate risk groups. Established criteria for high-risk status include the following: one or more relatives with breast cancer, early age at the diagnosis of cancer, and a family history of ovarian cancer, bilateral breast cancer, or breast cancer in male members. A total of 214 women met all of these high risk criteria. The remaining 425 women were assigned to the moderate risk group. A total of 268 had at least one affected first-degree relative, 46 had 2 aunts, cousins, or both with breast cancer, and 111 had family histories of breast cancer involving fewer second-degree or third-degree relatives. The median length of follow-up was 14 years. Breast cancers developed in 7 women at an average of 6 years after RRM (range, 2-25 years). Using the Gail model (Gail et al., 1989) to predict incidence of breast cancer, the reduction in the risk of breast cancer in the moderate risk group was 89.5 percent ($p<0.001$). Comparisons between the participants in the high risk group and their 403 sisters not having RRM were used to estimate that the reduction in the incidence of breast cancer in this group was 90 percent (95% CI, 70.8-97.9). (Hartmann et al., 1999)
- In the second study, blood samples were obtained from 176 of the 214 high-risk women from the first study to ascertain *BRCA1/2* mutation status. Deleterious *BRCA1/2* mutations were found in 18 women, and 8 had genetic variants of uncertain clinical significance. None of the 26 women developed breast cancer after a median follow-up of 13.4 years (range, 5.8-28.5 years). Three of the 214 women developed breast cancer after

RRM; two were *BRCA1/2* mutation negative; the other's *BRCA1/2* mutation status was unknown. Estimations of efficacy of RRM were performed considering this woman as both a mutation carrier and a non-carrier. Risk reduction of breast cancer among *BRCA1/2* mutation carriers ranged from 89.5 to 100 percent (95% CI, 41.4-100%). (Hartmann et al., 2001)

- 139 women with a *BRCA1/2* mutation, but without breast cancer, were enrolled in a breast cancer surveillance program at the Rotterdam Family Cancer Clinic. They were followed prospectively for an average of 2.9 years. 76 of these women underwent RRM, while the remaining 63 maintained regular surveillance. No cases of breast cancer were observed after RRM, whereas 8 cases developed in women under regular surveillance (hazard ratio, 0; 95% CI, 0-0.36). The results of this study are limited by the relatively short follow-up period. Also, women were not excluded from this study for having an oophorectomy. Although the authors adjusted for this variable and reported that the estimate was still statistically significant, the adjusted hazard ratios were not reported. (Meijers-Heijboer et al., 2001)

Oophorectomy

Risk-reducing oophorectomy (RRO) is generally more accepted than RRM in individuals with a hereditary predisposition to breast and ovarian cancer, particularly among women who have completed childbearing. Although the risk of ovarian cancer in carriers of *BRCA1/2* mutations is considerably lower than the risk for breast cancer, screening and early detection of ovarian cancers is substantially more difficult. The majority of ovarian tumors are diagnosed at stage III and IV, and mortality from these advanced stage cancers is high. While there are no outward physical changes, RRO contributes to the onset of menopausal symptoms, is associated with adverse changes in lipid profiles, increased risk of coronary artery disease and osteoporosis, and may promote sexual dysfunction. Cost and willingness of insurance companies to provide coverage (Question 30) can also influence the use of RRO.

Acceptance

Among women with a *BRCA1/2* deleterious mutation, approximately 36 percent undergo RRO (Table 4-11). These data were pooled using the Der Simonian and Laird methodology. (Berlin et al., 1989) The mean age for ovarian cancer in hereditary breast/ovarian families is in the mid-40s. The National Institutes of Health Consensus conference recommends that women with two or more first-degree relatives with ovarian cancer be offered RRO after completion of childbearing or at age 35 years. (1995) Three of the six studies in Table 4-11 provide data on women 40 years of age or older. Sixty-eight percent of women in this age group choose to undergo RRO. These studies are summarized in the following table.

Table 4-11. Proportion of Women with a *BRCA1/2* Mutation Accepting Risk-Reducing Oophorectomy (RRO)

Study Number	Site	Accept RRO: All Women % (N)	Accept RRO: Women ≥ 40 years % (N)
1	Netherlands	60 (36/60)	79 (22/28)
2	Netherlands	49 (47/95)	n/a
3	U.S.	13 (5/39)	n/a
4	U.S.	50 (90/179)	64 (77/120)
5	U.S.	46 (12/26)	78 (7/9)
6	U.S.	27 (21/79)	n/a
All (95% CI)		36 (23–58)	68 (58-80)

n/a = Not assessed
Reference: 1 (Meijers-Heijboer et al., 2000), 2 (Meijers-Heijboer et al., 2003), 3 (Lerman et al., 2000), 4 (Scheuer et al., 2002), 5 (Botkin et al., 2003), 6 (Schwartz et al., 2003)

Study 1. Netherlands - 411 unaffected women with unknown BRCA1/2 mutation status were recruited from 53 consecutive families in which a *BRCA1/2* mutation had been identified. The study was performed at a Family Cancer Clinic in the Netherlands. Of these, 275 of the women had a 50 percent risk of carrying a *BRCA1/2* mutation, and 136 had a 25 percent risk. All were offered DNA testing, and 198 (48%) accepted. Of the women with a pre-test risk of 50 percent, 69 (44%) had a mutation identified. Of those with a 25 percent risk, 6 (15%) had a mutation identified. A total of 60 women aged 30 years and older were eligible for RRO, and 36 (60%) had the procedure. Although RRO is usually advised for women 35 years of age or older, seven women less than 35 years of age underwent RRO simultaneously with RRM. The uptake rate by age group was as follows: 14/32 of women under 40 years (44%), 18/20 of women 40-54 years (90%), and 4/8 of women 55 years and older (50%). Overall, 27/40 of women with children opted for RRO (68%), compared with 2/5 of women without children (40%). RRO was performed within 9 months of the DNA testing in 24/29 (83%). The remaining 5 women waited between 10 and 25 months. Chemoprevention was not an option for the women in this cohort. (Meijers-Heijboer et al., 2000)

Study 2. Netherlands - A consecutive series of 112 families with a *BRCA1/2* mutation was used to identify 220 women who had breast cancer (n=172), ovarian cancer (n=33), or both breast and ovarian cancer (n=15). These women were eligible for RRO if they were 35 years of age or older, free from metastatic disease at the moment of personal genetic diagnosis, and had intact ovaries. RRO was performed in 47/95 women (49%). The mean time interval from the genetic diagnosis to RRO was 8 months. At a follow-up of 1 and 2 years, 19 (40%) and

14 (47%), respectively, of eligible women had their ovaries removed. After this period, two additional women requested the procedure. (Meijers-Heijboer et al., 2003)

Study 3. U.S. - 216 unaffected females, aged 25 years and older and who were members of extended *BRCA1/2* linked families participated in this study. Of these, 131 were eligible to receive RRO (they had intact ovaries). Of the 84 mutation carriers enrolled in this study, 29 were less than 40 years of age. No data were provided on acceptance of RRO stratified by age or status of childbearing. The follow-up period of this study was limited to 12 months. Thirty-nine were identified as carriers of the *BRCA1/2* mutation, and five of these women (13%) reported having a RRO within 12 months. No data were provided on the ages of the women choosing or not choosing RRO. (Lerman et al., 2000)

Study 4. New York - 233 women with known *BRCA1/2* mutations who received genetic test results at Memorial Sloan-Kettering Cancer Center participated in this study. Twenty-nine (12%) had previously undergone RRO, and 25 (11%) had a personal history of ovarian cancer. Of the remaining 179 women, 90 (50%) underwent RRO at a median of 3.4 months after receiving mutation testing results (range, 0.1 to 49.7 months). Women electing RRO were older than those not opting for surgery (mean 47.3 vs 41.6 years, $p<0.001$) and more likely to have a prior breast cancer diagnosis (74% vs 49%, $p=0.001$). Two women were found to have stage I malignancies in their RRO specimens. Transvaginal sonograms obtained within 1 month of surgery were not considered suspicious in either case, and a preoperative CA-125 measurement available in one case was also normal. (Scheuer et al., 2002)

Study 5. Utah – 759 adult members of a large kindred with evidence of hereditary breast and ovarian cancer (*BRCA1* mutation) were approached to assess the use of health care interventions by women following genetic testing. Women known to carry the kindred specific *BRCA1* mutation, but without breast/ovarian cancer, with intact ovaries, and over 25 years were informed of oophorectomy as a preventive option (N=26). Twelve of the women (46%) obtained RRO during the 2-year follow-up period. Of nine women age 40 years or older, 7 had an RRO (78%). (Botkin et al., 2003)

Study 6. Washington D.C. - 289 women who received free genetic counseling and testing through Lombardi Cancer Center's Cancer Assessment and Risk Evaluation program from 1995 to 2000 participated in this study. Probands (women previously affected with breast or ovarian cancer) received either positive (deleterious mutation) or uninformative *BRCA1/2* mutation test results. Relatives of the proband who were found not to carry the mutation known to segregate with cancer in their family were given negative test results. Among mutation carriers, 21 out of 79 (27%) underwent RRO in the year following testing. Five percent (8/166) and 2 percent (1/44) of women who received uninformative and negative results, respectively, underwent RRO. (Schwartz et al., 2003)

Efficacy

Oophorectomy is known to reduce the risks for both ovarian cancer and breast cancer. The efficacy of this intervention is described in the studies below. Two studies report a hazard ratio for developing breast cancer in women with *BRCA1/2* mutations who underwent

oophorectomy: the first, 0.32 (95% CI 0.08-1.2) is not statistically significant; the second, 0.47 (95% CI 0.29-0.77). One study reported an odds ratio of 0.45 (95% CI 0.24-0.75) for developing breast cancer in women with *BRCA1/2* mutations who underwent oophorectomy. While ovarian cancer cannot develop after removal of the ovaries, peritoneal cancers arise from the same cell lineage as ovarian cancer and are clinically indistinguishable from stage III ovarian cancer. The risk of developing ovarian (peritoneal) cancer after oophorectomy in women with *BRCA1/2* mutations has been reported by several studies. The hazard ratios from three studies ranged from 0.02 to 0.15.

- Women with breast cancer and a *BRCA1/2* mutation (cases) were matched to women without breast cancer and a BRCA1/2 mutation (controls) by year of birth and mutation (*BRCA1* or *BRCA2*). The risk for breast cancer was reduced in both *BRCA1* (OR=0.39, 95% CI=0.02-0.75) and *BRCA2* mutation carriers (OR=0.56, 95% CI=0.16-0.60). Overall, oophorectomy was associated with an odds ratio of 0.45 (95% CI 0.24 to 0.75). The risk reduction was greatest for oophorectomy performed before age 40 (OR=0.24, 95% CI=0.10-0.60). The risk reduction was not statistically significant in other age groups. (Eisen et al., 2000a; Rebbeck et al., 1999)
- 248 women with cancer and *BRCA1/2* mutations who underwent RRO (case) were matched with 245 women with BRCA1/2 mutations without cancer (controls). Matching was on cancer status at time of case RRO, ascertainment center, locus of mutation, and year of birth. Average follow-up was 9.4 years. One woman developed ovarian cancer after RRO and five women were diagnosed with ovarian cancer at the time RRO. After excluding those women diagnosed at the time of surgery, an adjusted hazard ratio of 0.02 (95% CI, 0.002-0.12) was reported. In addition, 25 women (10%) developed breast cancer after RRO. The hazard ratio for breast or ovarian cancer risk reduction was 0.46 (95%CI, 0.29-0.73). (Weber et al., 2000)
- 170 women age 35 years or older who carried a *BRCA1/2* mutation were followed for a mean of two years at the Memorial Sloan-Kettering Cancer. 98 underwent RRO at a median of 3.6 months after receiving genetic testing results, and 72 chose surveillance for ovarian cancer. Ovarian cancer or a papillary serous carcinoma of the peritoneum developed in 5 of the 72 women (7%) in the surveillance group. Of the remaining 98 women who underwent RRO, 3 (3%) had early-stage tumors that were diagnosed at the time of surgery, and primary peritoneal cancer developed in one patient during follow-up. The hazard ratio for ovarian cancer was 0.15 (95% CI 0.02-1.31). Among women who had not undergone RRM, breast cancer developed in 8 of 62 (13%) of the surveillance group and 3 of 69 (4%) in the RRO group. The hazard ratio of *BRCA* mutation-related breast cancer after RRO was 0.32 (95% CI 0.08-1.2). The hazard ratio of either cancer after RRO was 0.25 (95% CI, 0.08-0.74). (Kauff et al., 2002)
- 259 women with *BRCA1/2* mutations who reported having undergone RRO were identified from 11 North American and European registries. 292 controls who did not undergo RRO were matched with respect to *BRCA1/2* status, year of birth, and the center where the surgery was performed. Follow-up duration was 8.8 years. A diagnosis of ovarian or papillary serous peritoneal cancer was made in 8 (3%) of the cases compared with 58 (20%) of the controls ($p<0.001$; hazard ratio=0.04, 95% CI=0.01-0.16). Six of the 8 cancers in the cases were diagnosed at the time of RRO. The incidence of breast cancer was studied in a subgroup of 99 cases and 142 controls, which was followed for 11 years.

21 cases (21%) and 60 controls (42%) were diagnosed with breast cancer (hazard ratio: 0.47, 95% CI=0.29-0.77). (Rebbeck et al., 2002)

- 16 families with at least 2 first-degree relatives with documented ovarian carcinoma were identified from the NCI registry. 28 women in these families elected to have prophylactic oophorectomy and were followed for 1-20 years. During this time 3 (10.7%) developed intra-abdominal carcinomatosis, which was indistinguishable histopathologically from ovarian carcinoma. (Tobacman et al., 1982)
- 931 families with two or more first- or second-degree relatives were identified from the Gilda Radner Familial Ovarian Cancer Registry. 324 women in these families had prophylactic oophorectomy. Primary peritoneal cancer (indistinguishable from primary ovarian cancer) developed in 6 (2%) of these women 1-27 years after their surgery. (Piver et al., 1993)

Gap in knowledge: Although data exist to quantify the efficacy of RRM and RRO in reducing the occurrence of breast cancer and/or ovarian cancer, there are few empiric data to document the expected reduction in mortality that is likely to be associated with these procedures.

Gap in knowledge: It is also important to evaluate effectiveness by type of mastectomy (subcutaneous or total mastectomy), and this information is not presently available.

Modeling The Impact of Three Risk Reducing Strategies on Life Expectancy

Four papers describe a decision analysis using a Markov model to examine the effect of surveillance, tamoxifen therapy, and risk reducing surgeries (RRM and RRO) on life expectancy for *BRCA1/2* mutation positive women. Three of these studies focus on women with mutations but without cancer. (Grann et al., 2002; Grann et al., 2000; Schrag et al., 1997) The probabilities used in these models include the likelihood of developing breast and/or ovarian cancer, and the effectiveness of RRM, RRO, tamoxifen, raloxifene, and oral contraceptives. Two models also include the complications of tamoxifen therapy. (Grann et al., 2002; Schrag et al., 2000) Results from the three studies that estimated survival in women without cancer report that life expectancy in those choosing preventive options is expected to increase as follows:

Tamoxifen	1.8 to 1.9 years (2.7 to 2.8 quality-adjusted life years [QALYs])
RRM	3.4 to 4.1 years (2.1 to 2.6 QALYs)
RRO	0.8 to 2.6 years (2.1 to 4.4 QALYs)
RRM + RRO	4.3 to 5.3 years (2.1 to 2.6 QALYs)
Tamoxifen + RRO	4.6 years (6.3 QALYs)

- The first analysis compares chemoprevention and risk reducing surgery to surveillance in *BRCA1/2* mutation positive women. After accounting for increased risks of thrombophlebitis, pulmonary emboli, and endometrial cancer from chemoprevention, survival at age 30 is extended by 2.2, 1.9, and 0.9 years for raloxifene, tamoxifen, and oral contraceptives, respectively. For RRM, RRM + RRO, and RRO, life expectancy is extended by 3.4, 4.3, and 0.8 years, respectively. These advantages diminish slightly in comparison with surveillance from age 30 years to 40 years and more sharply from 40

years to 50 years. When expected survival duration is adjusted for quality, raloxifene adds 3.2 quality-adjusted life years (QALYs), tamoxifen adds 2.7 QALYs, and oral contraceptives add 1.4 QALYs. Risk reducing surgery adds 2.1-2.5 QALYs. (Grann et al., 2000)

- A second analysis stratifies a simulated cohort of 30-year-old women with *BRCA1/2* mutations by risk of breast and ovarian cancer. Gains in life expectancy are computed for women undergoing RRM, RRO, and RRM + RRO at 30, 40, 50, and 60 years of age. For a 30 year old *BRCA1/2* mutation positive woman (with a 60% risk of breast cancer and a 20% risk of ovarian cancer by age 70), life expectancy is increased 4.1 years with RRM, 1.0 years with RRO, and 5.3 years with RRM + RRO. These gains decrease with each decade in age and became minimal at age 60 years. (Schrag et al., 1997)
- A third analysis, by this same author, computes life gain expectancies from secondary breast cancer prevention strategies in women with *BRCA1/2* mutations who have breast cancer. Depending on the penetrance of the *BRCA1/2* mutation, gains in life expectancy for a 30-year-old woman are: tamoxifen, 0.4-1.3 years; RRO, 0.2-1.8 years; tamoxifen + RRO, 0.5-3.2 years; contralateral mastectomy, 0.6-2.1 years; tamoxifen + contralateral mastectomy, 0.7-2.3 years; both surgeries, 0.8-4.2 years; and tamoxifen + both surgeries, 0.8-4.4 years. As in previous analyses, these gains in life expectancy are reduced when interventions are undertaken at older ages. (Schrag et al., 2000)
- Another decision analysis looks at prevention strategies on survival and quality-adjusted survival of women with *BRCA1/2* mutations. A 30-year-old woman could prolong her survival beyond that associated with surveillance alone by use of preventive measures: 1.8 years with tamoxifen, 2.6 years with RRO, 4.6 years with tamoxifen + RRO, 3.5 years with RRM, and 4.9 years with both RRO and RRM. Quality adjusted survival would add 2.8 years with tamoxifen, 4.4 years with RRO, 6.3 years with tamoxifen + RRO, and 2.6 years with RRM or both RRO and RRM. (Grann et al., 2002)

Lifestyle Modifications

Numerous studies have identified lifestyle modifications, such as reduction in dietary fat (Greenwald et al., 1997; Hunter and Willett, 1993), reduction in alcohol intake (Schatzkin and Longnecker, 1994; Smith-Warner et al., 1998), increasing physical activity (McTiernan, 2000), and increasing antioxidant vitamin intake (Hunter and Willett, 1993; Sato et al., 2002), that may be associated with a decreased risk in breast and ovarian cancer. Although the effects of these modifiers on *BRCA1/2* mutation-positive women have not been directly studied, patients at increased risk may welcome the opportunity to be in control of these aspects of their lives and may enjoy improved health.

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CLINICAL UTILITY

Question 30. Is there general access to that remedy or action?

Summary

- Data from a single study of 150 insurers suggest that less than 30 percent have policies that cover risk reducing mastectomy and approximately 20 percent cover risk reducing oophorectomy for women at high risk for breast and ovarian cancer
- Access to remedies such as chemoprevention and risk-reducing surgeries may be limited by:
  - lack of insurance or insurance coverage,
  - lack of these services in certain areas,
  - inability to take time off from work,
  - lack of referral patterns.

Financial costs of risk-reducing surgeries may preclude consideration of these options for some women. Recently, a confidential, cross-sectional nationwide survey was sent to 481 medical directors from the American Association of Health Plans (AAHP), Medicare, and Medicaid to investigate the existing coverage policies for risk-reducing mastectomy (RRM) and oophorectomy (RRO). (Kuerer et al., 2000)

- The overall response rate was 31 percent (n=150). The response rate was 25 percent (n=98) for members of the AAHP, 65 percent (n=20) for regional Medicare carriers, and 62 percent (n=32) for state Medicaid plans.
- The overall coverage for risk-reducing surgeries was similar for patients with a strong family history of breast cancer and for those with a *BRCA1/2* gene mutation: 29 and 28 percent for RRM, respectively, and 18 and 20 percent for RRO, respectively.
- The coverage for these procedures was significantly higher among AAHP members than with governmental plans (Medicare and Medicaid): RRM – 44 percent v. 2 percent in patients with a family history, 38 v. 10 percent in patients with a *BRCA1/2* mutation; RRO – 26 v. 4 percent in patients with a family history, and 24 v. 12 percent in patients with a *BRCA1/2* mutation.
- Insurers with no coverage policy for one or more of these procedures ranged from 40 to 64 percent.
- The final decision concerning coverage for RRM and RRO was reported to be made by the medical director (66%), a committee (11%), chief executive officer/president (1%), financial representative (1%), or other (21%) of these respondents.

The overall low response rate indicates that actual coverage rates for these procedures may be even lower than those reported. In addition, the responses may not represent actual plan practices.

Another study examined a cohort of 35 women who underwent 39 risk-reducing surgeries at Memorial Sloan-Kettering Cancer Center. (Kauff et al., 2001) Of these procedures, 38 out of the 39 were reimbursed in full, after payment of coinsurance and deductibles. One patient with a personal and family history of premenopausal breast cancer was denied reimbursement.

A major limitation to this type of study is that women who undergo these procedures have likely received pre-authorization from their insurance carrier for reimbursement.

> **Gap in Knowledge:** An ideal study design to assess financial barriers would be to assemble a cohort of women with *BRCA1/2* mutations or with a high risk of breast/ovarian cancer who would like to have a risk-reducing surgery and determine: a) the number with insurance, and b) the prevalence of reimbursement for these procedures among women with insurance coverage.

Other limiting factors to access for remedies include the time necessary for and availability of, services related to the remedies. Genetic counseling often serves as the "gateway" to *BRCA1/2* mutation testing. A one-hour session is recommended prior to testing, with one or two additional hours of counseling, if testing is actually performed. These services are not readily available in all areas or may not be accessible due to lack of referral patterns. Even if services are available, women may not be able to take time away from work to attend. Similar barriers exist for the actual surgical procedures. RRM and BSO are usually performed in tertiary care hospitals and require recovery periods that necessitate time off from work. Additional counseling and/or mental health care may be necessary following these surgeries.

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CLINICAL UTILITY

Question 31. Is the test being offered to a socially vulnerable population?

Summary

- There is no universally accepted definition of social vulnerability
- A suggested definition of social vulnerability includes economic and psychosocial risks
- Limited research shows no documented cases of insurance or employment discrimination. However, women and their families are concerned about the potential for discrimination
- There is a variety of family issues within the context of social concerns

A definition of social risk, in the context of genetic testing, has not been universally accepted. It has been suggested that vulnerability encompasses a range of economic and psychosocial issues. (Burris et al., 2000) Economic issues include losing access to health/life insurance, a decrease in employability, and loss of economic support (e.g. divorce due to genetic information). Psychosocial vulnerability includes stigma, loss of social status or marriageability, and exposure to social hostility because of genetic information. While there have been no documented cases of health insurance or employment discrimination against carriers of *BRCA1* and *BRCA2* mutations, women and their families continue to be very concerned about the potential for genetic discrimination. (Armstrong et al., 2003; Peterson et al., 2002) This fear causes some people to decline testing or genetic counseling appointments despite the appropriateness of the referral. Fear of genetic discrimination keeps some individuals from sharing positive test results with their physicians. (See also Question 42)

> **Gap in Knowledge:** There are no empirical data for stigmatization, loss of social status or marriageability, and exposure to social hostility due to genetic information.

BRCA1/2 mutation testing, like other genetic susceptibility tests, has an impact on not only the persons being tested but also all of their blood relatives. Family issues related to *BRCA1/2* mutation testing include: dilemmas about disclosure, variability in the extent and value of genetic information among family members, conflict regarding testing, differences in decision making and coping, guilt about transmitting the mutation to children, and unresolved conflict and grief. (Speice et al., 2002) When the woman seeking mutation testing has no personal history of breast or ovarian cancer, it is recommended that an affected family member undergo testing first. This affected individual will have to weigh the personal risks and benefits of *BRCA1/2* mutation testing prior to consenting to undergo this test.

Women seeking *BRCA1/2* mutation testing may be considered socially vulnerable due to their fear of perceived stigmatisation associated with being a mutation carrier and/or having cancer, along with the fear of developing cancer. Consultation with a genetic counselor and the informed consent process for testing are strongly recommended. (1994a; 1994b; 1996; 1999b; Biesecker et al., 1993; Geller et al., 1997; McKinnon et al., 1997; Schneider, 1997)

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CLINICAL UTILITY

Question 32. What quality assurance measures are in place?

Summary

- A quality assurance plan assists laboratories in ensuring reproducible, high quality results in a timely manner that are clinically useful to patients and providers.
- A quality assurance plan focuses on all three phases of testing: pre-analytic, analytic and post-analytic.
- The components of a generic molecular quality assurance program are well described and are available from national and state regulatory agencies and professional organizations.
- Specific professional guidelines for quality assurance do not exist for breast and ovarian cancer predisposition testing.
- Quality assurance oversight is provided by the laboratory certification process administered by Federal or State agencies (Clinical Laboratory Improvement Amendments and New York State) or by professional organizations (College of American Pathologists).

Definition Quality assurance is all systematic activities taken to ensure that the laboratory meets the needs of the medical community for timely accurate services. It encompasses the pre-analytical, analytical, and post-analytical components of laboratory testing. A major goal is to minimize the human error that accounts for the majority of laboratory errors.

Standards, guidelines and checklists

Clinical molecular genetic testing laboratories must follow good laboratory practice guidelines and subscribe to external quality assessment programs. Guidelines, recommendations, and checklists are available from national and state regulatory agencies and professional organizations regarding quality control/quality assurance, inter-laboratory comparison/proficiency testing, and laboratory personnel requirements (Table 4-12). While multiple standards and guidelines exist, only three are enforceable and require laboratory inspection for certification. These include: Clinical Laboratory Improvement Amendments (CLIA), College of American Pathologists (CAP), and New York State. All other guidelines are efforts of professional organizations to regulate the genetic testing industry, but are without enforcement.

Testing for *BRCA1/2* mutations is a high complexity laboratory procedure, which benefits from a uniform testing policy and test interpretation. Because of this, testing should to be restricted to laboratories with the necessary expertise, experience, and resources. Due to patent issues, only one laboratory in the U.S. (Myriad Genetic Laboratories, Salt Lake City, UT) currently offers *BRCA1/2* sequencing in a clinical setting. Most generic components of quality assurance are well established and consistent among the published guidelines. However, some are controversial. For example, the qualifications for clinical laboratory directors have not been universally agreed upon by professional and licensing organizations. Overall, the components of quality assurance can be subdivided into three stages: pre-analytic, analytic, and post-analytic.

Table 4-12. Guidelines, Recommendations, and Checklists Addressing Quality Assurance

Guidelines, Recommendations and Checklists	Source / Reference
Clinical Laboratory Improvement Amendments of 1988	Federal Register 1992;57:7002-3
Genetic Testing Under the Clinical Laboratory Improvement Amendments	Federal Register 2000;65: 25928-24934
NY State Department of Health Laboratory Standards (9/00)	www.wadsworth.org/labcert/clep/clep.html
Molecular Diagnostic Methods for Genetic Diseases: Approved Guidelines	National Committee for Clinical Laboratory Standards MM1-A Vol 20 #7
CAP Checklist	College of American Pathologists www.cap.org
Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling and Testing Guidelines	American College of Medical Genetics with support from the New York State Health Department www.health.state.ny.us/nysdoh/cancer/obcancer/contents.htm

Pre-analytic components of quality assurance

The pre-analytic components of a quality assurance program include those activities that occur prior to the sample being tested. A general overview of these components is provided below.

The laboratory should be available to assist in determining the appropriate level of consent. The requisition must include a space for the person ordering the test to signify that the appropriate level of consent was obtained. The inclusion of a check-off box indicating acceptance (or rejection) for use of remaining sample for other purposes should also be on the consent form.

- Confidentiality: All genetic testing is confidential. Health Insurance Portability and Accountability Act (HIPAA) Final Regulation, published December 28, 2000, addresses confidentiality of personal health information (Question 44).
- Specimen types: Specimen types include blood (for all types of testing) or paraffin embedded tumor tissue (for targeted mutation testing only). Each laboratory determines the exact sample type and amount required for its testing method, and furnishes that information to referring centers.
- Standard information for the requisition slip: This includes patient-specific information such as name, date of birth, sex, ethnicity and family history, and sample information such as sample type, date of collection, and indication for testing. Also included is reporting and billing information, such as referring physician/health professional and source of payment.
- Criteria for sample rejection: Each laboratory develops its own written criteria for sample rejection (Question 11).
- Accessioning: Each specimen is assigned a unique identifier. Specimens from the same patient will have individual identifiers.

- Specimen transport and storage: Each laboratory determines its own criteria based upon experience and furnishes that information to clients.

Analytic components of quality assurance

- Test validation and characterization: All guidelines agree that the laboratory is responsible for documenting the validity of its tests. However, the components of test validation have only been addressed by the NYS guidelines and guidelines proposed by the US Food and Drug Administration. The ACMG has issued generic Standards and Guidelines for test validation (www.acmg.net). Literature review and analytical/clinical studies provide necessary information, including description of the mutations tested, the performance properties of the test, the clinical utility, and limitations. One controversial area in test validation surrounds the number of probands (positive controls) that must be tested in order to validate a test. The Genetic Testing Workgroup for CLIA Committee recommended that the appropriate number of positive probands required for test validation should be subject to professional guidelines rather than regulations and be disease-specific. These recommendations have been endorsed by ACMG. There currently are no disease specific guidelines for validation of *BRCA1/2* mutation analyses. Thus, the number of required positive controls has not been determined.

- Control of PCR contamination: A major concern for any clinical molecular laboratory is false-positive results due to contamination by PCR products. This concern can be addressed by following the recommended guidelines for laboratory design, laboratory practice, selection and preparation of controls. This quality assurance standard is generic but applies to *BRCA1/2* mutation testing.
  - Laboratory design: physically separated into three areas: reagent preparation, specimen preparation, and PCR and product detection
  - Laboratory practice: the use of positive displacement pipettors, cotton plug tips, gloves, lab coats, and careful preparation of reagents
  - Selection and preparation of controls: positive controls for each allele targeted in the test. Positive controls should amplify weakly to minimize large quantities of PCR product. No-DNA controls should be included in every run. Assays based on the presence or absence of PCR product must include a known positive control as an amplification control. Include a sizing ladder if the assay is based on fragment size. Include appropriate controls in mobility shift assays. Confirm unexpected results.

New York State (NYS) requirements for test validation as part of the licensing process: Myriad Genetic Laboratories (Salt Lake City, UT) has a current NYS license for *BRCA1/2* mutation testing. The following information is required by NYS for each new test:

- A description of the disease, the gene, the test, the principle of the test, and indications for testing.
- Assay description, including: all information relevant to the test, DNA extraction protocol, dilution, quantitation; reagent recipes; vendor/catalog information; reagent quality control (in/out dates, storage requirements); required equipment/vendors; step-by-step protocol; primer list with sequences, source of primers; description of positive controls, source, how verified; description of negative controls; technical limitations and troubleshooting guide; equipment, and procedures for quality control.

- Description of expected results from controls and what an indeterminate result looks like.
- Sample requisition form, including physician name, address, phone number, fax, date specimen collected, patient name, and accession number.
- Sample reports for negative, positive, indeterminate or rejected results, including interpretive statement explaining test results for each example, test limitations and relevant disclaimers, specimen information, and signature of laboratory director.
- Consent form.
- Explanation of how validation studies were performed, results, and interpretation. High quality original results showing homozygous normal, carrier, homozygous mutant.
- Reproducibility, sensitivity, specificity, positive predictive value.

ACMG requirements for test validation: The following information has been proposed as the components of test validation that would be completed prior to offering testing.

- Intended use of test
- Indications of test
- Method category
- Methodology, specific
- Examples of test results
- Analytical validity (control specimens, number tested, types of specimens, results, sensitivity, specificity, accuracy, reproducibility, confirmation, proficiency testing, statistical analysis)
- Quality control procedures (external controls, checks of results, repeat specimens, frequency of QC assessments)
- Clinical validity (literature citations or study results and summary)
- Clinical interpretation (report templates, information for risk analysis)
- Limitations (technical, biological)
- Clinical utility (interventions available for positive test result; level of efficacy)
- Ethical, legal and social implications

External proficiency testing in the United States: The goal of proficiency testing, which is currently the main indicator of quality assurance, is to allow laboratories to identify individual areas of weakness and take steps to improve. CAP requires participation in proficiency testing as part of the laboratory accreditation process. The ACMG/CAP proficiency testing program for breast cancer began in 2001 and provided participating laboratories in the MGL (molecular genetic laboratory) survey with three challenges once a year. Myriad Genetic Laboratories is the only laboratory in the U.S. performing *BRCA1/2* mutation testing by sequencing for clinical purposes. Other participating laboratories have either been licensed by Myriad to test for specific mutations for clinical purposes or test only as part of a non-clinical research protocol. Interpretive questions are also included in this survey (Questions 11 and 12). Proficiency test performance is anonymously reviewed and analyzed. The ACMG/CAP MGL Committee develops a report for each participating laboratory, and consumer groups have access to aggregate information. Laboratories that test patients from New York State must obtain a license from the New York State Department of Health. While the New York State program does not provide proficiency testing for *BRCA1/2* mutations, it does require these laboratories to participate in an established proficiency testing program, internal or

external, at least twice each year. New York State certified laboratories must undergo on-site inspections every other year and submit validation materials for each assay performed.

External proficiency testing programs outside the United States The European Molecular Genetics Quality Network (EMQN) is focused on improving the standards of European clinical molecular genetics laboratories by providing external quality assessment programs and best practice guidelines. A basic difference between the ACMG/CAP proficiency testing program and that of EMQN is survey administration. The ACMG/CAP program coordinates all disease-specific challenges from a single source, while EMQN identifies a management group to develop disorder-specific proficiency testing and a national partner to disseminate the results to participating laboratories.

Post-analytic components of quality assurance

Some issues of post-analytical testing, such as reporting, mutation nomenclature, and retention of records, are held in general agreement by various professional societies and regulatory groups.

- Laboratory reports: Laboratory reports are to the physician or healthcare professional, not the patient. The report should echo any information collected on the requisition slip that is used for identification or as part of the interpretation. In addition, test-specific information should be included such as laboratory identifiers, testing method, test result, interpretation, recommendations (e.g., genetic counseling) and the signature of the laboratory director.
- Nomenclature for mutations: The nomenclature developed by the Nomenclature Working Group (Antonarakis, 1998) is followed by the Breast Cancer Information Core (Szabo et al., 2000). There are discrepancies between some mutations named previous to the adoption of this nomenclature. Myriad Genetic Laboratories uses the convention of Beaudet and Tsui (Beaudet and Tsui, 1993). In addition, the discovery of genomic rearrangements has necessitated that mutations not only be identified by the nucleotide number in the transcript (cDNA), but also the nucleotide number in the genomic DNA (gDNA).
- Retention of records and specimens: The CLIA Committee Workgroup recommended that a minimum of 10 years was appropriate for records retention of both positive and negative results. However, guidelines for specimen retention time have not been agreed to. There is some controversy over specimen retention, particularly surrounding the opt-out requirement.
- Genetic counseling: All current standards and guidelines address the responsibility of the laboratory to recommend genetic counseling, when appropriate. However, none require the laboratory to actually provide genetic counseling to patients. The laboratory can help guide healthcare professionals to genetic counseling resources.

Is there ongoing review of quality assurance?

The CAP/ACMG Molecular Genetics Resource Committee has the main responsibility for reviewing external proficiency testing results. In addition, the ACMG Quality Assurance Subcommittee of the Laboratory Practice Committee reviews these same proficiency testing results at semi-annual meetings. This Committee is composed of clinical laboratory directors

(including molecular, biochemical, and cytogenetic laboratories) and representatives from the ACMG/CAP proficiency testing program. Threshold indicators are set for addressing laboratory problems related to specific disease testing. An additional charge for this committee is to develop disease-specific technical standards and guidelines. Additional goals of the Committee include the development of technology-specific guidelines.

CDC recommendations for quality assurance programs

The following are genetic testing quality assurance recommendations developed for the Centers for Disease Control and Prevention. (1999a) They include:

- conducting pilot research to develop positive controls and testing reference samples in pilot performance evaluation programs
- developing pilot evaluation programs to supplement what already exists, particularly for diseases and/or methodologies not covered by existing programs
- establishing laboratory-oriented, disease-specific consortia to provide quality assurance support as a forum for information networking, and providing methods validation through results comparison
- establishing and linking laboratory oriented and disease-specific databases with other appropriate internet resources
- improving training and continuing education for physicians, laboratory scientists, and technicians

References

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CLINICAL UTILITY

Question 33. What are the results of pilot trials?

Summary

Pilot trials of *BRCA1/2* mutation testing for predisposition to breast/ovarian cancer have been published.

- Populations were usually non-Hispanic Caucasian and/or Ashkenazi Jewish women at high risk for developing breast/ovarian cancer
- Fewer than 10 percent of U.S. physicians have ordered a *BRCA1/2* mutation test for a patient. They are more likely to refer for genetic counseling.
- DNA testing for *BRCA1/2* mutations was selected by 52 percent (95% CI 27-75%) of women at elevated risk for breast/ovarian cancer in 6 pilot trials and by 68 percent (95% CI 49-96%) of women with breast/ovarian cancer in 4 studies.
- Of 64 women with *BRCA1/2* mutations, 35 (55%) chose to have or were considering risk reducing mastectomy.
- Of 76 women with *BRCA1/2* mutations, 62 (82%) chose to have or were considering risk reducing oophorectomy.
- The majority of women undergoing genetic counseling and testing for *BRCA1/2* mutations was satisfied with the process and found it helpful in future medical decision making.

Pilot trials are an important step in translating research knowledge into practice. Types of data collected in pilot trials that cannot be obtained in other ways include:

- the proportion of health practitioners that offers testing
- the proportion of the target population that chooses testing
- overall satisfaction with the screening/counseling/testing process
- the decision-making process when a mutation is identified
- performance of the analytic testing process in a routine testing environment
- verification of prevalence estimates in the 'real world'
- financial costs and health benefits of screening

The last three listed topics are addressed further in other sections. Pilot trials should be run in an environment where the data can be collected, analyzed and reported promptly. Often, pilot trials are short-lived and test relatively few subjects; these constraints place limitations on reliable estimates. This disadvantage can sometimes be overcome by combining information from multiple trials. In addition, some trials are translated into routine practice upon completion. In such instances, it might be possible to obtain supplementary information that accumulates after the trial itself has been analyzed and published.

There have been few true pilot trials in the area of *BRCA1/2* mutation testing. Therefore, much of the data we are looking at are surrogates that may or may not be accurate indicators.

Utilization of *BRCA1/2* mutation testing by health practitioners

Initially, *BRCA1/2* mutation testing was exclusively offered by large cancer centers, which were usually associated with academic institutions. The patents for the *BRCA1* and *BRCA2* genes were awarded to Myriad Genetic Laboratories in late 1997 and early 1998, respectively. Since that time, *BRCA1/2* mutation testing has become available to physicians and other select health practitioners. Direct-to-consumer advertising for genetic testing for the predisposition to breast/ovarian cancer has recently been initiated by Myriad. Thus, women may be inquiring about and/or requesting this service from their health care providers. It is likely that fewer than 10 percent of U.S. physicians have ordered a *BRCA1/2* mutation test for a patient. A higher proportion has referred a patient for genetic counseling and testing. One of the strongest predictors for ordering or referring for a test is having a patient request one. Suther and Goodson (Suther and Goodson, 2003) report the most common barriers cited for provision of genetic services, as follows:

- inadequate knowledge of basic genetics
- lack of detailed or updated family histories
- lack of confidence for delivering genetic services
- lack of confidence in assessing and managing risk
- lack of simple referral guidelines or tools to facilitate their use.

Several studies have reported the utilization of *BRCA1/2* mutation testing or cancer susceptibility testing by health care providers in the United States. These are summarized below.

Colorado - 170 out of 380 (45%) family practitioners responded to a mailed survey in late 1998. This survey assessed the physicians' practice behaviors in regard to cancer genetic test ordering, cancer genetic counseling and/or testing referral, and also to patient requests for ordering testing or referring patients. In addition, six knowledge questions pertaining to *BRCA1/2* were included. Two physicians (1%) reported having personally ordered *BRCA1/2* mutation testing in the previous year. One physician referred between 11 and 25 patients for genetic counseling and/or testing. An additional 25 physicians (15%) referred between 1 and 10 patients. Correct responses to the individual knowledge questions ranged from 17 to 52 percent. (Mouchawar et al., 2001)

U.S. - 1,251 out of 1,763 (71%) primary care providers (PCP - internists, general practice, family practice, and obstetrics/gynecology) and tertiary care providers (TCP - oncology, general surgery, urology, and gastroenterology) responded to a questionnaire by their preferred participation mode (telephone interview, mailed/faxed questionnaire, or encrypted online questionnaire accessible by a password-protected Internet site). Information was ascertained about genetic test use and physician characteristics/demographics. The weighted proportions of U.S. physicians who ordered a *BRCA1/2* mutation test are 5.8 percent (95% CI 4.2-7.4) for PCPs and 5.4 percent (95% CI 3.0-7.8) for TCPs. Among the PCPs, 10.5 percent of obstetricians/gynecologists ordered a *BRCA1/2* mutation test, compared with 3.3 percent of general or family practitioners, and 6.3 percent of internists. Among TCPs, 24 percent of oncologists ordered this test. Small numbers did not permit analysis of other TCP specialists. Factors associated with cancer susceptibility test use included Northeast region of the U.S. (OR 2.3, 95% CI 1.5-3.6), feeling very well or somewhat qualified to recommend testing (OR

1.96, 95% CI 1.4-2.7), receiving advertising materials in the past 12 months (OR 1.97, 95% CI 1.4-2.8), and having patients during the past 12 months who asked whether they could or should get tested (OR 5.5, 95% CI 4.0-7.7). (Wideroff et al., 2003)

Pennsylvania/New Jersey - 433 out of 726 primary care physicians (PCPs) (60%) completed a survey by mail or telephone. One of the components of this survey was to ask if the PCP had ordered or referred patients for any cancer susceptibility testing during the previous year. Cancer susceptibility testing use was reported by 159 (37%) responders. Of these, 113 PCPs (71%) only referred for cancer susceptibility testing, 16 (10%) only ordered cancer susceptibility testing directly, and 30 (19%) had both ordered testing directly and referred patients for cancer susceptibility testing. Among the 159 PCPs who reported cancer susceptibility testing use, 122 (77%) had referred only one or two patients and 105 (66%) ordered testing in only one or two patients. Breast/ovarian cancer was the most common indication for ordering cancer susceptibility testing. Patient inquiry was strongly associated with physician cancer susceptibility testing use (OR 24.7, 95% CI 14.1-43.3). (Sifri et al., 2003)

Texas – A survey was mailed in 2001 to a random sample of primary care physicians in Texas. The results were compared with those obtained in 1996. 59 out of 342 physicians (17%) responded in 2001. 105 out of 350 (30%) responded in 1996. Twenty percent had requested genetic testing for a patient for cancer risk in 2001 compared with 4 percent in 1996. In 2001, 51 percent said they would have requested testing and 44 percent said they would have referred patients if services were available. When asked if "you have ever referred a patient for genetic evaluation for cancer risk", 39 percent said yes in 2001, compared with 19 percent in 1996. (Friedman et al., 2003)

Utilization of *BRCA1/2* mutation testing by patients

The uptake of *BRCA1/2* mutation testing has been examined in women at high risk for hereditary breast/ovarian cancer and in women with breast and/or ovarian cancer. These studies are summarized below. Among unaffected women at high risk for hereditary breast/ovarian cancer, approximately 52 percent (95% CI 29-91) chose *BRCA1/2* mutation testing (Table 4-13). Approximately 68 percent of women with breast and/or ovarian cancer (95% CI 49-96) chose testing (Table 4-13). These estimates were pooled using the der Simonian and Laird methodology. (Berlin et al., 1989) Although a summary estimate is provided, the individual estimates are heterogeneous, indicating that factors other than chance are responsible for the differences.

Table 4-13. Utilization of *BRCA1/2* Mutation Testing by Women at High Risk for Hereditary Breast/Ovarian Cancer or Women with Breast and/or Ovarian Cancer.

Study Number	Number of Women	Number Chosing Testing N (%)	Comments
High Risk but Without Cancer			
1	129	85 (66)	*BRCA1* Family members
2	277	133 (48)	
3	181	35 (19)	
4	99	70 (71)	
5	75	65 (87)	*BRCA1* Family members
Total	**761**	**388 (52)**	**95% CI 29-91**
With Cancer			
3	77	33 (43)	*BRCA1* Family members
4	41	28 (68)	
5	30	25 (83)	*BRCA1* Family members
6	220	192 (87)	*BRCA1/2* Family members
Total	**368**	**278 (68)**	**95% CI 49-96**

Study: 1 (Lerman et al., 1996), 2 (Armstrong et al., 2000), 3 (Lee et al., 2002), 4 (Loader et al., 1998), 5 (Julian-Reynier et al., 2000), 6 (Meijers-Heijboer et al., 2003)

Study 1. Omaha, Nebraska - A prospective cohort study from July 1994 to November 1995 included 279 members of 13 extended families with *BRCA1*-linked hereditary breast/ovarian cancer. Of these family members, 192 (69%) completed a baseline telephone interview. Included in those completing the baseline interview were 129 women. Eighty-five out of these 129 women (66%) requested and received genetic testing. Predictors of test utilization included possessing health insurance, greater number of first-degree relatives with breast cancer, higher baseline knowledge of *BRCA1* mutation testing, and perceived benefits of testing. (Lerman et al., 1996)

Study 2. Philadelphia, Pennsylvania - This retrospective cohort study involved 277 women who participated in a university-based clinic offering breast cancer risk assessment, genetic counseling and *BRCA1/2* mutation testing between January 1996 and April 1998. In this study, 133 (48%) had undergone or were undergoing *BRCA1/2* mutation testing, 86 (31%) had declined testing, and 40 (14%) were undecided. Factors associated with choosing testing were having a family member with a known mutation, Ashkenazi Jewish descent, wanting cancer risk information for family members, wanting information about ovarian cancer risk, and being less concerned about insurance or job discrimination. (Armstrong et al., 2000)

Study 3. Baltimore, Maryland - A retrospective cohort study of 258 high risk patients seen at the Johns Hopkins Breast and Ovarian Surveillance Service between February 1996 and December 1999 was used to evaluate the utilization of *BRCA1/2* mutation testing in a clinical setting. A total of 68 patients (26%) elected to undergo testing. The proportions by year were as follows: 20/48 (42%) in 1996, 11/56 (20%) in 1997, 13/54 (24%) in 1998, and 24/100 (24%) in 1999. Of note, 18 of 20 patients who were tested in 1996 had access to free testing during Myriad Genetic Laboratories' beta-testing period. Out of the 258 study participants, 77 had a personal history of breast and/or ovarian cancer. Thirty-three (43%) underwent mutation testing. Thirty-five of the 181 participants without cancer (19%) pursued genetic testing. Twelve of these 35 had an affected relative undergo testing, while the remaining 23 proceeded with testing without first testing an affected family member. Factors associated with genetic testing uptake included access to testing at no cost, prior diagnosis of breast or ovarian cancer, and Ashkenazi Jewish heritage. (Lee et al., 2002)

Study 4. Rochester, NY - Women were identified by physician referral (n not given) or through a regional tumor registry (n=170) to participate in a study to evaluate receptivity to testing for genetic susceptibility to breast/ovarian cancer. To qualify for this trial, an unaffected woman had to have at least two first-degree relatives or one first- and one-second degree relative with breast and/or ovarian cancer. An affected woman had to have at least one first-degree relative with breast or ovarian cancer and a first- or second-degree relative without cancer willing to be tested. 140 women returned a baseline questionnaire, 112 (80%) came for pre-test education, and 98 (70%) chose to be tested. Forty-one women had a personal and family history of breast or ovarian cancer and 28 chose testing (68%). Of the 99 women with no personal history, 70 chose testing (71%). Those women choosing to undergo genetic susceptibility testing were more educated and rated their families as closer than women declining testing. The most common reasons for choosing testing were to take extra precautions if a mutation was found and to determine if their offspring were at risk. (Loader et al., 1998)

Study 5. France - A retrospective study of 49 French *BRCA1* families was undertaken to determine the uptake of genetic testing in first- and second-degree relatives of an identified *BRCA1* mutation carrier. Within 8 months after the family index case was given a positive *BRCA1/2* mutation test result, 133 out of 419 first- and second-degree relatives (32%) attended a cancer genetics clinic. This included 75 of 208 women without cancer (36%), 30 of 36 women with cancer (83%), and 28 of 175 men without cancer (16%). 122 out of these 133 were either in the process of genetic testing or had been given their result (84%). The proportions of relatives that were either in, or had completed, the genetic testing process for affected women, unaffected women and unaffected men were 83, 87, and 79 percent, respectively. (Julian-Reynier et al., 2000)

Study 6. Rotterdam, the Netherlands - A consecutive series of 112 families with a *BRCA1/2* mutation was used to identify 220 women who either had breast cancer (n=172), ovarian cancer (n=33), or both breast and ovarian cancer (n=15). Genetic testing was used by 192/220 women (87%). In multivariate analysis, the correlation of genetic testing with young age and with having multiple primary cancers reached statistical significance (p=0.04 and p=0.02,

respectively). 171 women (89%) underwent testing within 3 months after the first invitation for testing. (Meijers-Heijboer et al., 2003)

Three other studies, described below, report the proportion of women that chooses *BRCA1/2* mutation testing, but do not provide sufficient detail to be included in the summary table (Table 4-14).

Madison, WI - A prospective study of 125 individuals who met the criteria for *BRCA1/2* genetic testing at a familial cancer genetic counseling program from November 1994 to August 1999 assessed interest in, and utilization of, genetic testing services. Of the 125 counseled patients, 30 (18%) elected to undergo testing. An additional 18 (11%) chose to store DNA from an affected individual for possible testing in the future. (Hartenbach et al., 2002)

Ottawa, Canada - A retrospective cohort of 78 women diagnosed with breast cancer before the age of 50 within the previous 2 years and treated at a regional cancer center in Canada was identified. 60 (77%) completed survey materials for this study. They were offered genetic counseling and testing free of charge. Of these women, 8 (13%) declined, 3 (5%) were lost to follow-up and 2 (3%) died between initial contact and follow-up. Of the remaining 47 women, 23 (38%) contacted and met with a genetic counselor, while 24 (40%) had not yet contacted the genetic counselor. Of the women in the former group, 5 did not meet the criteria for genetic testing, 9 proceeded to have the *BRCA1* test, 3 opted to not have the test, and 6 had not yet reached a decision regarding testing. (Cappelli et al., 1999)

Oslo, Norway – 75 known *BRCA1* mutation carriers identified 84 female first-degree relatives older than 18 years of age. Fifty-three of these women (63%) chose genetic testing. The uptake of genetic testing by age was as follows: 9/30 (30%), 18-29 years; 28/34 (82%), 30-49 years; and 16/20 (80%), 50+ years. Three of these women were affected with either breast or ovarian cancer. (Bodd et al., 2003)

Decision making about options for risk reduction

Studies that report the use of surveillance, chemoprevention, and risk-reducing surgeries are described and summarized in Question 29. The following three studies provide further information regarding the medical decision making process by women at high risk for breast/ovarian cancer, including those with *BRCA1/2* mutations.

- The impact of *BRCA1* testing on risk-reducing surgery decisions was examined among 135 women in families with hereditary breast/ovarian cancer. Among the 57 *BRCA1* positive women, 31 were eligible for RRM. 10 (32%) were considering it prior to testing results and 11 (35%) were considering RRM after receiving results. Among the 78 women negative for a *BRCA1* mutation, 68 were eligible for RRM. 15 (22%) were considering it prior to receiving test results, and none were considering RRM after receiving results. Among the 57 *BRCA1* positive women, 37 were eligible for RRO. 27 (73%) were considering it prior to testing results and 28 (76%) were considering RRO after receiving results. Among the 78 women negative for a *BRCA1* mutation, 58 were eligible for RRO. 23 (40%) were considering it prior to testing results, and none were considering RRO after receiving results. (Lynch et al., 1997)

- A retrospective study of premenopausal women from the U.K at high risk of breast and ovarian cancer assessed factors that influence a woman's decisions about RRO. Women were recruited from an ovarian cancer registry, a risk advisory clinic, and a cancer family history clinic. Women who chose surgery (n=23) and those who chose close surveillance (n=26) participated in this descriptive interview study. The five main factors that influenced surgical decisions were: 1) risk perception and risk of cancer, 2) witnessing a relative's experience of ovarian cancer, 3) family and social obligations, 4) fertility and menopause, and 5) fear of surgical procedures in general. (Hallowell et al., 2001)
- A study to evaluate the process and early outcomes of *BRCA1/2* mutation testing as a clinical service in the community setting enrolled 646 participants from August 1998 to July 2000. Among 198 cancer-free subjects who had not had prior risk-reducing surgeries or chemoprevention, 28 were *BRCA1/2* mutation carriers, 21 had variants of uncertain clinical significance, and 144 had no deleterious mutation (no data were given on the remaining 5 subjects). These subjects were asked how genetic test results would influence their decision to pursue various cancer prevention strategies. Mutation carriers were more likely to seek chemoprevention (n=18, 67%), RRM (n=19, 68%), and RRO (n=23, 82%) than subjects with unclassified variants or no mutation. Less than 5 percent of subjects with no mutation were likely to seek risk-reducing surgery. The proportions of women with a variant of uncertain clinical significance that were more likely to consider RRM and RRO after receiving genetic test results were 38 percent and 24 percent, respectively. (Chen et al., 2002)

Gap in knowledge: There are no true pilot studies that follow women who are identified as being at risk for hereditary breast/ovarian cancer through the genetic testing decision process and their subsequent medical decision making.

Satisfaction with the screening/counseling/testing process

Studies that have evaluated patients' satisfaction with genetic counseling and testing for *BRCA1/2* mutations are described below. The majority of patients were satisfied with the process or found the process helpful in guiding their medical decision making.

- A pilot study was performed in 1996 to evaluate the experiences of individuals with a family history of any type of cancer at three familial cancer clinics in the Netherlands. Thirty-six individuals participated. Twenty-seven were female, and 24 were being seen due to a family history of breast/ovarian cancer. Twenty-nine (80%) were either satisfied or very satisfied with the care provided by the geneticist. Highest levels of dissatisfaction (64%) were found on the following statement, "I have the feeling that my clinical geneticist has had sufficient contact with my family doctor". Of those respondents who received genetic test results, 25 (37%) were dissatisfied with length of time that they had to wait for the test results. (Bleiker et al., 1997)
- 79 women with *BRCA1/2* mutations who received counseling at two university hospitals in Canada between 1994 and 1998 participated in this study to identify needs of women undergoing genetic counseling and testing for *BRCA1/2* mutations. The respondents were asked to rate their overall satisfaction with their experience on a scale of one to five, one indicating extremely dissatisfied and five indicating extremely satisfied. A total of 51 (65%) said they were very or extremely satisfied. Three patients (4%) were very or extremely dissatisfied. (Metcalfe et al., 2000)

- A prospective pilot study of 35 U.S. women with breast and/or ovarian cancer was conducted to evaluate the psychological impact of genetic testing and counseling and to obtain recommendations for improving the process. A majority of women (64%) thought the genetic counseling process had been extremely helpful in future medical decision making. The most helpful aspect of the protocol was the multidisciplinary counseling effort provided by the genetic counselor and oncologist. One suggested area for improvement included assistance in communicating with family (54%). (Wood et al., 2000)
- In Wales, 735 women with at least one first-degree relative with breast cancer before age 50 were offered a surgical consultation. Half were randomly assigned to an additional consultation with a clinical geneticist and genetic nurse specialist that included the possible offer of pre-symptomatic genetic testing. Women in this group were further categorized as low risk (< 10% residual lifetime risk of breast cancer), moderate risk (10-24%), or high risk (≥ 25%). The 30 women in the high risk group reported significantly lower satisfaction with the provider's perceived skills and ability to give the required treatment and reassurance when compared with the women at low or moderate risk. The 137 women at moderate risk reported lower satisfaction than those at low risk. (Brain et al., 2002)
- A U.S. study to evaluate the process and early outcomes of *BRCA1/2* mutation testing as a clinical service in the community setting enrolled 646 participants from August 1998 to July 2000. More than 75 percent of the respondents indicated that they were "very satisfied with the counseling received" (highest ranking on a 4-point scale), with no significant difference by *BRCA1/2* mutation result. Respondents also expressed satisfaction with specific aspects of genetic counseling, including provider expertise, sensitivity, and caring. A higher percentage of patients was satisfied (≥ 3 on a 4-point scale) when counseled by a physician or genetic counselor ($p < 0.001$) compared to nurses or other providers, and when more than 60 minutes were spent on counseling ($p < 0.001$). *BRCA1/2* mutation test results were delivered during an office visit (n=365, 57%), telephone (n=253, 39%), or mail (n=17, 3%, including 3 mutation carriers). Satisfaction did not differ whether results were delivered in person or by telephone or mail. (Chen et al., 2002)

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CLINICAL UTILITY

Question 34. What health risks can be identified for follow-up testing and/or intervention?

Summary

- *BRCA1/2* mutations are identified in 10.6 percent of women without breast or ovarian cancer who undergo genetic susceptibility testing, usually because of a positive family history.
- Health risks associated with increased surveillance include repeated radiation exposure and false positive screening tests that may result in biopsies or exploratory surgery.
- Women who use tamoxifen are about twice as likely to develop venous thromboembolism as women not using tamoxifen
- Complications from risk-reducing mastectomies are short-term and procedure related. They include hematoma, seroma, pain, infection, tissue necrosis and, in rare instances, death.
- Complications associated with breast re-construction include capsular contracture, implant rupture, hematoma, wound infection and, in rare instances, death.
- Complications from risk-reducing oophorectomy are short-term and procedure related. They include infection, bleeding, urinary tract and bowel injury and, in rare instances, death.
- Endocrine changes induced by oophorectomy are associated with adverse effects on the lipid profile, increased incidence of coronary artery disease and osteoporosis. These changes also induce menopause and its associated symptoms.

Health risks associated with increased cancer surveillance

In a publication reporting the results of 10,000 *BRCA1/2* analyses from 1998 to 2000, 350 of 3,310 women (10.6%) who specifically indicated no personal history of breast or ovarian cancer carried a deleterious *BRCA1/2* mutation. (Frank et al., 2002) The majority of these women had a family history of breast and/or ovarian cancer. Increased surveillance is one available option for these women. While the health risks associated with surveillance are believed to be minimal, there is a link between radiation exposure and breast cancer in the general population. (Gofman, 1996; Goss and Sierra, 1998; Mettler et al., 1996) There is also some evidence to suggest that increased exposure to mammography (radiation) among women with genetic predisposition to breast cancer can induce this malignancy. (Chakraborty and Sankaranarayanan, 1998; den Otter et al., 1993, 1996; Friedenson, 2000; Goss and Sierra, 1998) These women typically start mammography at an early age, increasing their radiation exposure. In addition, relatively low doses of x-rays cause single- and double-stranded breaks in DNA. Ionizing radiation also damages DNA bases and results in the loss of bases. *BRCA1* and *BRCA2* gene products are both involved in repairing DNA. This is the basis for the assumption that women with *BRCA1/2* mutations will be less able to repair radiation damage to their DNA than women without these mutations. The finding that a lack of functional

BRCA1/2 led to defective repair of DNA double-stranded breaks in irradiated cells supports this assumption. (Foray et al., 1999)

Nationally, an average of 11 percent of screening mammograms are read as abnormal and necessitate further diagnostic evaluation. (Brown et al., 1995) One study estimated that after 10 mammograms, about half of women will have had a false positive result. (Elmore et al., 1998) Among women who do not have breast cancer, approximately 20 percent will undergo a biopsy after 10 mammograms. Variables that influence the false positive rate of mammography include: the woman's age, breast density, an increasing number of breast biopsies, a positive family history of breast cancer, estrogen use, an increasing interval between mammograms, availability of previous mammograms for comparison, and radiologist threshold. (Christiansen et al., 2000) Other forms of surveillance utilized for increased risk for ovarian cancer, such as vaginal ultrasound or serum CA125 measurements, are also associated with false positive results which, in turn, require invasive diagnostic procedures.

> **Gap in knowledge** – It is not known whether there Is a higher false positive rate associated with mammography (or other forms of surveillance) when women are under close surveillance (i.e., *BRCA1/2* mutation positive).

Risks of chemoprevention

Complications from tamoxifen use in women choosing chemoprevention are summarized in Table 4-14. The most consistent health risk appears to be venous thromboembolism; all four studies found similar effects, and in three of the four, the effect was statistically significant.

Table 4-14. Health risks associated with tamoxifen therapy for chemoprevention of breast cancer.

	Risks expressed as odds ratios (95% confidence interval)			
	Fisher *et al.* (1998)	**Powles *et al.* (1998)**	**Veronesi *et al.* (1998)**	**Cuzick *et al.* (2002)**
Venous thromboembolism	1.8 (1.1-3.0)	1.7 (0.5-7.1)	2.2 (1.2-4.1)	2.5 (1.4-4.6)
Thrombophlebitis				3.0 (1.4-6.9)
Endometrial cancer	2.5 (1.4-5.0)	0.8 (0.4-1.5)		2.2 (0.8-6.1)
Fractures	0.8 (0.6-1.0)			

Risks of surgery

Mastectomy

There are few data about the complications of mastectomy performed for the prevention of breast cancer, and those available from breast cancer patients may not be generalizeable to a group of relatively healthy women undergoing an elective procedure. A summary of the literature on surgical complications of mastectomy has been published. (Eisen et al., 2000b) The frequency of hematoma, pain, infection, seroma, and tissue/nipple necrosis ranges between 5 and 15 percent. These frequencies were observed with surgical techniques in use over 20 years ago and should be less than 5 percent with modern techniques. Breast

reconstruction may also be associated with complications. There is a large body of literature on the medical complications of silicone implants. Surgical intervention was required in 28 of 92 women (30%) who had implant reconstruction after risk reducing mastectomy. (Gabriel et al., 1997) The most common indications were capsular contracture, implant rupture, hematoma, and wound infection. In a retrospective study comparing breast cancer patients treated with mastectomy with or without reconstruction, 16 of 94 patients (17%) with reconstruction developed complications, half of which required surgical intervention. (O'Brien et al., 1993) As with any major surgery, death may occur in rare instances.

Oophorectomy

Eisen *et al*. also summarized the surgical complications attributable to risk reducing oophorectomy. That study found only a single report of four women who underwent risk-reducing oophorectomy reported no adverse effects from the operative procedure. (Menczer and Ben-Baruch, 1991) More data exist that describe the complications related to elective gynecologic surgery. Possible non-fatal complications include infection, bleeding, and urinary tract and bowel injury. These occur in less than 3 percent of these procedures. In addition to the loss of fertility and onset of menopausal symptoms, oophorectomy is associated with other important physiologic changes. These include:

- Alterations in the lipid profile, which increase risk of coronary artery disease
- Increased risk of osteoporosis
- Sexual dysfunction
- Urinary complications

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CLINICAL UTILITY

Question 35. What are the financial costs associated with testing?

To be completed

CLINICAL UTILITY

Question 36. What are the economic benefits associated with actions resulting from testing?

To be completed

CLINICAL UTILITY

Question 37. What facilities/personnel are available or easily put in place?

To be completed

CLINICAL UTILITY

Question 38. What educational materials have been developed and validated, and which of these are available?

To be completed

CLINICAL UTILITY

Question 39. Are there informed consent requirements?

The term "informed choice" rather than "informed consent" is recommended for breast/ovarian cancer predisposition testing by the American College of Medical Genetics to emphasize that, for the present, the provider is viewed as *offering* testing, not *recommending* it. In deciding whether or not to be tested, patients may benefit from learning how much their estimated risk, based on their family history, may increase or decrease as a result of DNA testing. It should also be made clear that the patient may not receive any useful information from testing. Testing should be voluntary and not be the result of coercion by a third party. A person considering testing primarily to benefit a relative should be encouraged to sufficiently weigh the personal implications of the result before consenting to testing. Signing the informed choice document does not itself constitute the informed choice process, but rather is intended to confirm that the appropriate communications have taken place.

General recommendations about informed consent for genetic testing vary. The New York State regulation is that the laboratory makes a reasonable effort to document consent prior to testing. This can be in the form of a patient or physician signature. New York State (NYS) requires that informed consent states the purpose of testing and includes genetic counseling, the meaning of a positive test result in the context of disease, the positive predictive value of the test, the test disclosure process and the stipulation that no additional testing be allowed on the specimen without consent. Existing Clinical Laboratory Improvement Amendments (CLIA) regulations do not require that laboratories document informed consent, but current CLIA Committee recommendations support this requirement. The National Committee for Clinical Laboratory Standards (NCCLS) Molecular Guidelines state that the referring clinician has the primary responsibility for informing patients of the risks, costs and benefits of testing. Whether or not the laboratory is required to document consent is left to the discretion of the laboratory and any applicable federal, state or local requirements.

CLINICAL UTILITY

Question 40. What methods exist for long-term monitoring?

To be completed

CLINICAL UTILITY

Question 41. What guidelines have been developed for evaluating program performance?

To be completed