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PRENATAL SCREENING FOR BREAST CANCER

An Interactive Qualifying Project Report

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1. Prenatal Screening
2. Genetic Testing
3. Bioethics

Abstract

Prenatal screening for breast cancer via the *BRCA1* and *BRCA2* genes is explored. The bioethical issues involved with the testing for a late onset disease via correlational genes are discussed both from a literature standpoint as well as based on surveys carried out with scientific professionals and religious leaders.

Executive Summary

The field of bioethics is an incessantly kinetic area of study, changing with each new development in biomedical technique. Because of a constant influx of new technology into the medical arena, bioethical issues must be continually re-evaluated. Prenatal screening is a procedure decades old, and yet still remains at the forefront of ethical debate due to increasing diagnostic ability. No longer is prenatal diagnosis limited to neural tube defects, Down's syndrome, or other such chromosomal disorders. With the advent of genetic screening, it has become feasible that any disease with a genetic marker could be screened for prenatally. Yet, though the technology is there to screen for all genetically linked disorders, the question remains: when is it unethical to screen a fetus for a disorder?

This study examines the issue of prenatal screening for a genetically linked late-onset disease, breast cancer. Because breast cancer has only recently been linked to the *BRCA1* and *BRCA2* genes, and adult genetic screening is still fresh, prenatal screening for breast cancer via *BRCA1* or *BRCA2* mutations has not yet been tried or even evaluated. Still, we need to examine the possibility now to help set a framework for ethical analysis should this possibility become a reality. The research documented in this report analyzes the possibility of prenatal screening for breast cancer by first investigating the scientific literature to confirm that we currently have the technology to perform such screening. Next bioethical and other such literature is examined to establish a background of ethical issues that might surround prenatal screening for breast

cancer. Finally, fieldwork in the form of questionnaires and an interview are documented which elucidate current professional opinions on the matter.

It was towards the beginning of the 1990's that breast cancer was first linked to the *BRCA1* gene, and just a few years later that *BRCA2* was also added as a breast cancer linked gene. Both genes have since been extensively studied and sequenced. In addition, common mutations present in these genes in breast cancer patients have been recorded, and the correlational statistics between *BRCA1* and *BRCA2* mutations and the onset of breast cancer determined. Overall, approximately 10% of breast cancer patients are thought to have a mutation in either gene, while those with a mutation have around an 85% chance of developing breast cancer at some point in their life.

While no alternative treatment or cure for breast cancer has thus far been developed from this genetic linkage, the knowledge does allow for advanced genetic screening for breast cancer. Mutations in *BRCA1* or *BRCA2* are far more likely to be found in patients with a strong family history of breast or ovarian cancer, thus they make the most likely candidates for genetic screening. However, because the overall population shows little preference for specific mutations in *BRCA1* and *BRCA2* the entire gene sequences must be screened for mutation, creating a rather costly procedure. Still, the procedure is currently being performed as a means to allow patients to take the necessary cautions for breast cancer screening.

Likewise, if a fetus were to be prenatally screened for breast cancer, its *BRCA1* and *BRCA2* gene sequences would be examined for mutations just as with an adult. Prenatal genetic screening is not a new concept and has been performed successfully with numerous disorders such as cystic fibrosis and Huntington's disease. The screening for

Huntington's disease is of particular note for our study, in that it is a late onset disease as is breast cancer.

The fact that breast cancer is late-onset, however, increases the ethical issues surrounding prenatal screening for breast cancer. The question can be raised: is it ethical to screen for a disease, causing anxiety, insurance issues, or potential selective abortion, which will not affect a person until adulthood? Compounding this issue further is the approximately 15% chance that a fetus testing positive for a mutation would never develop breast cancer in her lifetime. Because the current law states that genetic screening results are accessible to insurance companies, any screening done can expose the future person to discrimination. However, is it ethical to dictate how much information a woman is allowed to obtain about her fetus? Certainly it is easy to sit at a distance and decide whether prenatal screening for breast cancer is ethical, but much more of a challenging and emotion-wrought decision when face to face with the mother who herself has a familial history of breast cancer, inquiring about obtaining screening for her fetus.

For this reason, opinions on prenatal screening for breast cancer were obtained via survey from various medical professionals and religious representatives who might one day be "face to face" with this issue. The medical professionals included oncologists, registered nurses familiar in breast cancer patients, and genetic counselors. Religious representatives included Catholic priests, Protestant ministers, and Jewish rabbis. The resounding opinion of the medical professionals was that prenatal screening for breast cancer should without a doubt *not* be performed or even made available, feeling the quality life of the future person must be taken into account. On the other hand, the

religious leaders consented that perhaps if the testing were used merely to gain all information possible about the fetus it would be beneficial. However, the religious leaders generally showed concern that any testing be used towards selective abortion.

Overall, our literature review in combination with survey results seem to indicate that prenatal screening for breast cancer is not a worthwhile procedure to allow at this point in time. The cost of the procedure is too great for many people to handle themselves, but involving the insurance companies allows for potential discrimination. In addition, because 90% of all breast cancer patients do not have *BRCA1* or *BRCA2* mutations, even a negative screening result (no mutations) does not provide security against developing breast cancer. Still, as mentioned previously, prenatal diagnosis and genetic screening are constantly changing fields, and the issue of prenatal screening for breast cancer could be skewed entirely by new developments in medical technology. While this study provides evidence that the procedure of prenatal screening for breast cancer currently is not practical to allow, perhaps one day in the future advances in cancer or genetic therapy could make this screening a viable option.

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- Genetic Counselor Jan Warsing, University of Massachusetts Medical School, MA for her interview

- Professor William E. Stempsey, Department of Philosophy, College of Holy Cross, MA.

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1. Introduction

As medical research progresses, and biotechnology advances accordingly, the number of ethical issues involved with these advances also increases. Two such medical research areas, genetic testing and prenatal screening, are surrounded by numerous bioethical controversies. These controversies stem from the issue of knowledge. How much knowledge about personal health and the health of the fetus is beneficial, and where does medical research cross the line into detrimental knowledge? Or is garnering the maximum amount of information about our health always best? In addition, how reliable is the knowledge our doctors might give to us?

When the technologies behind genetic testing and prenatal screening are put together, allowing for genetic testing of the fetus, even more issues can be raised. If genetic testing is done for a disease that will not afflict the fetus until he/she is an adult, do parents have a right to obtain that information for the fetus without the consent of the person the fetus will one day become? If the parents decide to abort a fetus with a predisposition towards a certain disease, does that decision begin to approach eugenics? All of these questions apply to the issue of prenatal screening for breast cancer. In this report, these questions as well as many others will be addressed in terms of their relation to the concept of prenatal screening for breast cancer. Prenatal screening for breast cancer remains a concept, because it has not yet been performed. Yet, because the technology to perform this test is already present, and the desire for better prevention of breast cancer is a vital issue in our society, it remains a realistic possibility.

2. Scientific Background

Prenatal screening for breast cancer would not even be a possibility were there not incredible progress in the research of both breast cancer and prenatal diagnosis. The newfound correlation between *BRCA1* and *BRCA2* mutations and a predisposition towards breast cancer allows for advanced screening determining an increased risk of developing the disease. Simultaneously, advances in prenatal diagnosis allow for more reliable and less intrusive tests, which are broader in their range of potential diagnosis as a result of DNA screening. Both these advances together provide the opportunity for prenatal diagnosis of breast cancer. The following pages will elucidate the details of these advances and the techniques required to perform prenatal screening for breast cancer.

2.1 *BRCA1* and *BRCA2*

2.1.1 BRCA1 and BRCA2 genes

Though their discovery will be discussed in more detail further on, certainly the search for *BRCA1* and *BRCA2* was a long and expensive process. The question then arises: what benefits come from finding genes that relate to diseases such as breast cancer? *BRCA1* and *BRCA2* mutations do not cause breast cancer, in that the vast majority of breast cancer patients do not have mutations in either gene and there are certain people with mutations in one of the two genes that never develop breast cancer in their lifetime.

Yet, while the discovery of *BRCA1* and *BRCA2* has not led to an instant understanding of the cause or cure for breast cancer, it can give scientists clues as to the nuances of cancer development. For example, by knowing, as will be discussed later, that both genes have a tumor suppressor function, and that a mutation in those genes which causes them to malfunction leads often to breast cancer, we can determine exactly how their tumor suppressor functionality works and use drugs that mimic this functionality to treat breast cancer. Another benefit to knowledge of correlation genes such as *BRCA1* and *BRCA2* to breast cancer is the ability to perform advanced screening. Early screening for mutations in a person with a strong family history of cancer can give that person the chance to take as many precautions as possible. This screening is important whether the person is male or female, as these mutations, particular those in *BRCA2* affect male breast cancer as well as female breast cancer. This screening will not guarantee a successful fight against cancer, but can increase a person's chance of surviving their fight with breast cancer.

Another question arises from the discussion of *BRCA1* and *BRCA2*: how exactly do they work to influence the formation of a malignant tumor in the breast? Both *BRCA1* and *BRCA2* are genes found in all human DNA. Both genes are made up of segments known as exons and introns. Exons are essentially the useful parts of the DNA that will end up encoding for a specific protein. The function of introns is not yet known; instead all that is known is that, as far as we can tell, they are not used by the cell to make any proteins. In order to get from DNA to protein, the exons must first be transcribed into RNA, a different kind of nucleic acid from DNA, which is then translated into an amino acid sequence, which in turn forms a protein. It is these proteins that then go on to carry out the function of the particular gene. For *BRCA1* and *BRCA2*, both tumor suppressor genes, the proteins they encode somehow work to prevent or destroy tumor formation. Thus, if there is a mutation in either gene that in turn causes its corresponding protein to be non-functional, it will not successfully suppress tumors.

In order to discover genes such as *BRCA1* and *BRCA2*, scientists frequently work backwards. For example, in searching for *BRCA1*, various groups of researchers simultaneously analyzed numerous families with strong breast cancer histories looking for a common link. Once this link was pinpointed to somewhere on the 17^{th} chromosome, the researchers job became a task of merely narrowing in with more family analysis and sequencing of the genome. The first reported isolation and cloning of the *BRCA1* gene was led by Mark Skolnick, PhD in 1990 at the University of Utah Medial Center in affiliation with Myriad Genetics (18), currently the primary supplier of *BRCA1* and *BRCA2* genetic testing. The gene was first fully sequenced in 1994. *BRCA2* was

fully sequenced later in 1995, also in collaboration with scientists from Myriad Genetics (18).

2.1.2 Their properties

Certain details concerning the properties of both genes are important in their function and the recognition of them when screening. *BRCA1* is a 81kb gene located on the 17th chromosome. It is composed of 24 exons, with a high density of *Alu* repetitive segments. *Alu* repeats comprise 41.5% of the genome (25). While *Alu* repeats to not appear to contribute greatly to the overall function of the gene, they are important in recognizing BRCA1. Other repetitive elements also contribute to the overall genome. The entire protein encoded by the *BRCA1* gene is 1,863 amino acids in length (18) [See Appendix pp.2-6 for detailed diagrams of *BRCA1* properties].

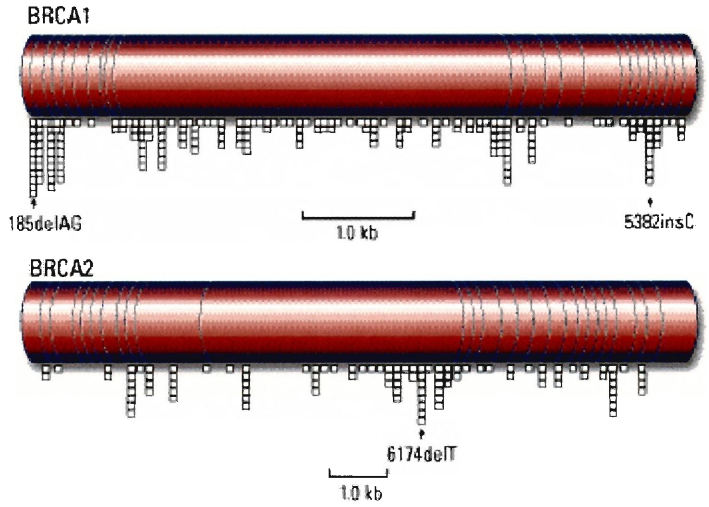
BRCA2 was the second of the two genes to be sequenced. Located on the 13th chromosome, the gene is comprised of a 10,257bp-coding region and a 2,799bp non-coding region (28). *BRCA2* codes for a protein 3,418 amino acids in length (18).

Because *BRCA2* only more recently began to be sequenced and studied, less is known about its function in the body other than, like *BRCA1*, the knowledge that it is a tumor suppressor (18). There are more extensive studies, however, detailing the role of *BRCA1* in tumor suppression. For example, experiments have shown that there is an accelerated growth of normal and malignant mammary epithelial cells when *BRCA1* expression is inhibited. Likewise, when *BRCA1* is over expressed in experiments with mice, malignant breast cancer cell growth is hindered (25).

2.1.3 Mutations

A wide variety of mutations, estimated to be over 200 in number, contribute to the inhibited activity of the *BRCA1* and *BRCA2* function, resulting in increased risk for breast cancer. An overview of a portion of the mutations is represented below. [Figure 1] For the general population, no particular mutation in either gene seems to predominate as a precursor to breast or ovarian cancer. Studies show a wide range of mutations in the *BRCA1* and *BRCA2* genes found in patients with breast cancer. Yet, certain ethnic groups, more specifically Ashkenazi Jewish women, demonstrate specific mutations correlating to breast cancer. (As indicated by black arrows in Figure 1) [See appendix pp. 7-10 for various mutations found in different studies.]

Figure 1: Mutation sites in BRCA1 and BRCA2 correlating with breast cancer.
Square blocks correspond to mutation sites and relative number of cases reported with the particular mutation.

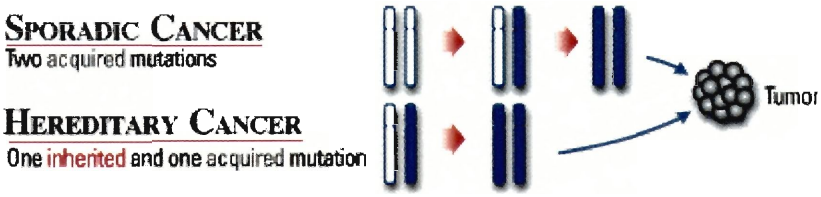


(18)

The way in which the mutations act to increase a person's chance of developing breast cancer in their lifetime demonstrates the difference between inherited and acquired mutations. A person without an inherited *BRCA1* or *BRCA2* mutation might still develop a mutation in either one or both of his/her *BRCA1* or *BRCA2* genes during his/her

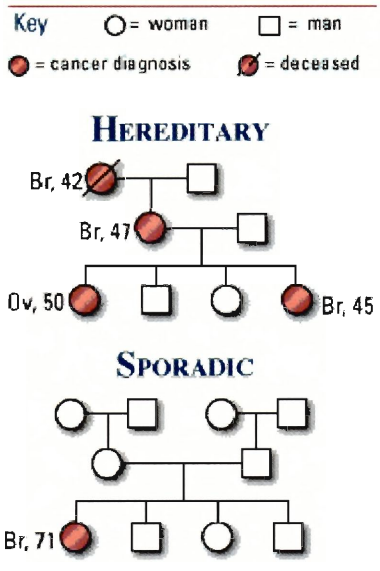
lifetime. A mutation in a pair of either gene would then in turn inhibit its tumor suppressing function and enable malignant breast tumors to form. These mutations, developed during a person's lifetime are termed sporadic mutations. Yet, the risk of mutations in a pair of either gene randomly forming over a lifetime is relatively small. On the other hand, a person born with an inherited *BRCA1* or *BRCA2* mutation need only acquire one sporadic mutation in order to develop inhibited tumor suppressor function. [Figure 2] Thus, the inherited mutation leads to an overall increased chance of developing breast or other form of cancer. [Figure 3]

Figure 2: Sporadic vs. Inherited mutations and steps to tumor development



(18)

Figure 3: Sporadic vs. Inherited pedigree



(18)

Frequently, doctors and genetic counselors use bilateral breast cancer (found in both breasts) as a good indicator of potential *BRCA1* or *BRCA2* inherited mutation (32). This indicator relates to the concept of sporadic and inherited mutations, in that a person who inherits a *BRCA1* or *BRCA2* mutation is more likely of inhibiting function via sporadic mutation formation. Thus, they are more likely than a person without an inherited mutation to develop tumor suppressor inhibition in two different locations, i.e. both breasts.

2.1.4 Methods for gene detection via DNA sample

2.1.4.1 Full Sequence

Because so many mutations in the *BRCA1* and *BRCA2* genes correlate with breast cancer, for a person without any ethnic heritage or previous familial sequencing, the entire *BRCA1* and *BRCA2* genes must be sequenced in order to discover a deleterious mutation corresponding to an increased risk for breast cancer. The primary lab that performs sequencing for *BRCA1* and *BRCA2* mutations is Myriad Genetic Laboratories located in Salt Lake City, UT (18). The following represents a basic procedure used to sequence DNA for deleterious *BRCA1* and *BRCA2* mutations performed by Myriad Genetics Laboratory for a study published in the Journal of Clinical Oncology.

The first step that must be undertaken is exon amplification. Exons are the portion in the DNA that encodes proteins as opposed to the introns or "nonsense" DNA. Exon amplification essentially consists of cutting the segment containing the exon out of the original gene. Then the fragment is transfected into a specific cell from which the

cytoplasmic RNA produced from the exon DNA can be isolated. cDNA can then be made from the RNA, which in turn can be analyzed. [Figure 4]

Figure 4: Diagram of exon amplification

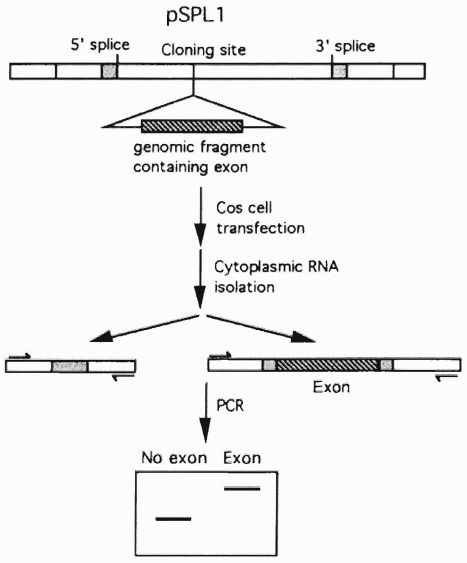


Figure 1. Outline of exon amplification method for isolating coding sequences.

(9)

For the particular sequencing experiment, exons number 2 through 24 of *BRCA1* and exons 2 through 27 of *BRCA2* were sequenced. First, the exons were amplified via Polymerase Chain Reaction (PCR). Due to the large amount of DNA, 82 different pairs of PCR primers were required in order to amplify the entire sequence equally on both alleles. The PCR reaction products are then electrophoresed and sequenced via the Perkin Elmer Applied Biosystems sequencing apparatus. Finally, the sequences are analyzed with software developed by Myriad Genetics. The entire process is repeated for DNA in which mutations are found (9).

As stated in the introduction, the gene has a certain function because it is translated into a protein that carries out that function. Not all mutations in the gene will alter the protein enough that it cannot function. Mutations that do affect the resulting protein, and cause it to not function properly are termed deleterious. When analyzing DNA, a guideline must be made as to what mutations are deleterious so that researchers aren't left with the time consuming task of analyzing the function of each protein formed from the mutant DNA.

In the protocol developed by Myriad Genetics, a mutation was identified as deleterious if it "led to premature truncation of the *BRCA1* protein product at least 10 amino acids from the C terminus or premature truncation of the *BRCA2* protein product at least 270 amino acids from the C terminus" (9). In addition, there are a few *BRCA1*mutations defined as deleterious that do not fit into the above criteria, but have been shown in previous studies to inhibit normal protein function. A database entitled the Breast Cancer Information Core contains information about which *BRCA1*and *BRCA2* mutations are considered deleterious (9).

While this full sequencing method has a greater than 99% analytical sensitivity rating and is the most intensive screening method available, there is the possibility that it could miss large deletions or mutations located far away from the protein encoding region of the genes (18).

2.1.4.2 Specific Mutations

There are cases, however, in which a person might only need to be tested for the presence of a *BRCA1*and *BRCA2* mutation in specific locations. This selectivity might be

due to an instance in which a family member has already been testing via full sequence analysis and a deleterious mutation was found. In this case, any family member would most likely possess the same inherited mutation, if any. Another situation in which only specific mutations need to be tested for involves specific ethnic groups, namely people of Ashkenazi Jewish heritage. There are three *BRCA1* and *BRCA2* mutations that predominate amongst Ashkenazi women with a familial history of breast cancer (9).

Single site or the three different Ashkenazi Jewish mutations are detected via essentially the same protocol as used to sequence the entire genome. Yet, because only a small portion of the genome requires sequencing, the procedure is considerably less time consuming, and requires fewer materials. As a result, the cost of single site or three site Ashkenazi Jewish testing is significantly less than that of a full sequence analysis. For example, the cost of a full sequence analysis done by Myriad Genetics is approximately $2,400.00. On the other hand, the cost of a single site analysis is approximately $395.00 and the cost of a three-site analysis for Ashkenazi Jewish people is $450.00 (18). Certain insurance coverage plans will cover *BRCA1* and *BRCA2* genetic testing. Yet, many people choose not to inform their insurance companies of the testing for reasons discussed later in this report.

Nonetheless, despite the clear economic advantage of the specific site analysis, there are advantages to the full sequence analysis. Even if a specific mutation has been demonstrated previously in other family members, there is a slight chance that two mutations could be present in the family pedigree. In addition, mutations other than the three most prevalent ones have been demonstrated in the Ashkenazi Jewish population. In the study published in the Journal of Clinical Oncology mentioned previously, 2 of the

20 mutations found in Ashkenazi women were distinct from the 3 predominant mutations (9). Thus, certain genetic counselors recommend considering the full sequence analysis if the single site or triple site analysis turns up negative.

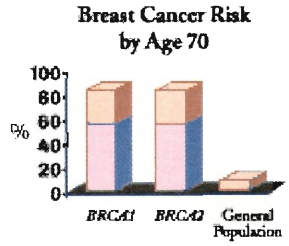
2.1.5 Correlation between BRCA1, BRCA2 and breast cancer

The worth of genetic testing for *BRCA1* and *BRCA2* is highly dependent on the strength of the correlation between *BRCA1* or *BRCA2* mutations and development of breast cancer. Numerous studies have been performed to quantify this correlation. While there is some variance between data from different studies, approximately ten percent of women with breast cancer have a *BRCA1* or *BRCA2* mutation, while approximately 85% of women with *BRCA1* or *BRCA2* mutations will develop breast cancer during the course of their lifetime. Figures 5 and 6 diagram these generalized statistics.

Figure 5: Fraction of breast cancer patients with inherited mutation

(18)

Figure 6: Relative likelihood of acquiring breast cancer



(18)

The following represents the results of three different studies done to demonstrate the correlation between breast cancer and either *BRCA1*, *BRCA2* or both. The first is research published in the Journal of the American Medical Association (JAMA) in 1997 and focuses on *BRCA1* (24). The subjects these scientists tested for *BRCA1* mutations consist of 798 women all recommended for screening due to an elevated risk for *BRCA1* mutation in their family pedigree. The criteria that contributed to the elevated risk included multiple cases of breast cancer, early age onset of breast cancer, and cases of ovarian cancer in the family (24). Of the final group of subjects: 554 had unilateral breast cancer (one breast only), 84 had bilateral breast cancer, 30 had unilateral breast cancer and ovarian cancer, and 11 did not have cancer but had a family history of breast and ovarian cancer (24). Ashkenazi decent was established prior to testing, though the full sequence of the *BRCA1* gene was sequenced for all subjects, via PCR as in the full sequence reaction described in detail previously (24).

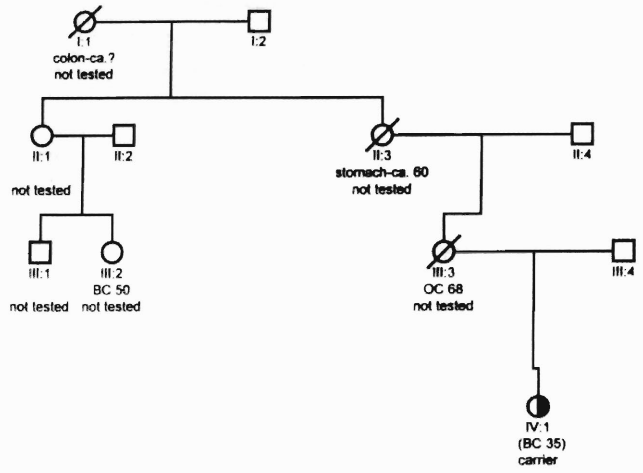
Deleterious mutations were detected in 12.8% of the subjects (24). From their data, the researchers extrapolated certain statistics. They determined that a 30 year old, non-Ashkenazi woman with only unilateral breast cancer as an 8.3% chance of carrying a

deleterious *BRCA1* mutation. On the other hand, a woman of Ashkenazi decent of the same age and condition has a 27% chance of the mutation. Similarly, a 50-year-old woman with both unilateral breast cancer and ovarian cancer has a 37.6% chance of carrying a deleterious mutation if she is of Ashkenazi heritage, or a 12.8% chance if she is not (24).

In a second study published in a 1999 issue of Human Molecular Genetics, the researchers studied subjects from all around the world and analyzed their DNA for *BRCA2* mutations. Subjects were selected on the basis of a family history of breast/ovarian cancer or a personal incident of breast or ovarian cancer. The final study included 71 families with a history of breast or ovarian cancer (28). While the object of the study was not specifically to determine the correspondence between breast cancer and *BRCA2*, but instead was to determine different *BRCA2* mutations globally, the article still brings up certain important statistics.

Of the breast or ovarian cancer families, 8% were found to have a deleterious *BRCA2* mutation. This number is lower than certain other studies of *BRCA2,* but is explained by the authors in saying that previous studies showing a higher percentage of mutation have required more incidences of family breast or ovarian cancer before being eligible for the study (28). Figure 7 shows a pedigree of one of the families shown to have a deleterious *BRCA2* mutation. An important point of this pedigree is that not only is there a family history of breast and ovarian cancer, but also of colon and stomach cancer. While few studies have currently been done to explore the relation between colon and stomach cancer and *BRCA1* and *BRCA2* mutations, it is an important subject of further research.

Figure 7: Pedigree of BRCA1 deleterious mutation family



M47, BRCA2 Mutation del CTTAA 6633

Figure 1. Pedigrees of the six HBC/HBOC families with apparently disease-associated *BRCA2* mutations.

(28)

Deleterious mutations in both *BRCA1* and *BRCA2* were the focus of a 1998 article published in the Journal of Clinical Oncology. Subjects for this study were referred from 12 different institutions by the following criteria: "diagnosed with invasive breast cancer before age 50 or ovarian cancer at any age and had at least one first- or second- degree female relative with either diagnosis." The final number of subjects came to 70 women (9).

39% of the women studied were determined to have a deleterious mutation, 32 in *BRCA1* and 31 in *BRCA2*. Broken down, 50% of these women with mutations came from families with a history of ovarian cancer, and 29% from families without ovarian cancer. A deleterious mutation was found in 20% of the women who developed breast cancer before the age of 50 with only one other relative who'd been diagnosed with breast or ovarian cancer. These percentages are clearly much greater than the results of

the previous studies. This could be due to the fact that one of the criteria for selection in this study was early onset, which is a strong indicator of inherited mutation.

43% of the women who identified themselves as being from Ashkenazi Jewish decent were found to have a deleterious mutation. Finally, 88% of the women with both breast and ovarian cancer were found to have a deleterious mutation in *BRCA1* or *BRCA2*. As with the previous study, this result clearly indicates the importance of the relationship between *BRCA1* and *BRCA2* and other forms of cancer, specifically ovarian cancer. Below in Figure 8 is a table of probabilities of deleterious mutations based on the results of this study.

Figure 8: Probabilities of BRCA1 and BRCA2 mutations

Table 3. Modeled Probabilities of Women With Breast Cancer Under 50 Years of Age Carrying a Mutation in *BRCA1* or *BRCA2*

Any Relative With BrCa Under 50 Years[a]	Any Relative With OvCa[a]	Proband Bilateral BrCa or OvCa[a]	Proband BrCa 40[a]	Modeled Probability of Mutation in *BRCA1* (%)	Modeled Probability of Mutation in *BRCA2* (%)	Modeled Probability of Mutation in *BRCA1* or *BRCA2* (%)
•				10.1	14.5	25
•			•	28.2	11.6	40
•		•		41.5	9.5	51
•		•	•	71.1	4.7	76
	•			22.9	12.5	35
	•		•	22.9	12.5	35
	•	•		65.0	5.7	71
	•	•	•	65.0	5.7	71
•	•			22.9	12.5	35
•	•		•	50.9	7.9	59
•	•	•		65.0	5.7	71
•	•	•	•	86.7	2.2	89

(9)

Though the results of these studies vary, they all give similar results in that only relatively small portions of women with breast cancer carry a *BRCA1* or *BRCA2* mutation. These portions increase as only women with a strong familial history of breast

cancer are considered or as a familial or personal history of other cancers enter into the family pedigree. None of the studies performed used men as subjects, though the first study mentioned did predict based on the data for women and knowledge of other factors involved in male breast cancer that males with a mutation in *BRCA1* or *BRCA2* have approximately a 9% chance of developing breast cancer by the age of 70 years. While this figure has not been studied, it corresponds with the fact that in families with a history of breast cancer, male breast cancer occurs at a frequency of approximately 11% the occurrence of female breast cancer (24). This, however, does not take into account that men with *BRCA1* or *BRCA2* mutations might face an increased risk for stomach or colon cancer.

The following is a table created by Myriad Genetics to demonstrate the probability women with different pedigrees have of carrying a *BRCA1* or *BRCA2* mutation.

Figure 9: Myriad Genetics BRCA1 or BRCA2 probabilities

Modelled probabilities of women with breast cancer under 50 carrying a mutation in *BRCA1* or *BRCA2*. [24]
(based on analysis of women with at least one first- or second-degree relative with breast cancer before 50 years or ovarian cancer)

Any relative with breast cancer <50 years?	Any relative with ovarian cancer?	Proband: Bilateral breast cancer or ovarian cancer	Proband: Breast cancer <40?	Modelled probability of mutation in *BRCA1*	Modelled probability of mutation in *BRCA2*	Modelled probability of mutation in *BRCA1* or *BRCA2*
x				10.1%	14.5%	**25%**
x			x	28.2%	11.6%	**40%**
x		x		41.5%	9.5%	**51%**
x		x	x	71.1%	4.7%	**76%**
	x			22.9%	12.5%	**35%**
	x		x	22.9%	12.5%	**35%**
	x	x		65.0%	5.7%	**71%**
	x	x	x	65.0%	5.7%	**71%**
x	x			22.9%	12.5%	**35%**
x	x		x	50.9%	7.9%	**59%**
x	x	x		65.0%	5.7%	**71%**
x	x	x	x	86.7%	2.2%	**89%**

(18)

In summary, while there is certainly a correlation between breast cancer and the *BRCA1* and *BRCA2* genes, gene mutations account for a decidedly small percentage of the overall breast cancer. This doesn't mean that they aren't still useful for screening purposes and in understanding different methods for treating breast cancer. Yet, the advanced screening for a mutation, if positive, will not guarantee the development of breast cancer or that successful preventative measures can be carried out. Or if the test turns out to be negative, there is still a chance that breast cancer could develop regardless

of the mutation. Advanced screening is advantageous in many cases in terms of taking preventative measures for personal care and the care of future generations, but should be undertaken with caution and knowledge as to the statistics.

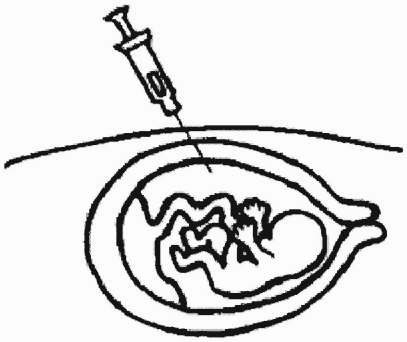
2.2 Prenatal Screening

Prenatal screening is not in itself a new practice, having been practiced for over two decades, but the conditions or potential conditions we can now screen for are rapidly growing in number. Likewise, prenatal diagnosis for certain diseases with a genetic marker, such as cystic fibrosis, has been done since the beginning of the decade. Yet, as the number of genetic markers discovered increases, the more we are able to test for prenatally. In order to screen for a gene that relates to a particular disease, fetal DNA must first be isolated. This isolation can be performed in a few different ways, as will be discussed in more detail later. Once the DNA is isolated, the same procedure is carried out as though it was an adult's DNA. Thus, the procedure carries a certain amount of error just as with the adult procedure. Likewise, there is a certain amount of risk involved in the actual isolation of fetal DNA from the mother, though the risk differs greatly between different procedures.

2.2.1 Amniotic Fluid

Certainly one of the most common and long-standing methods for obtaining fetal DNA for prenatal diagnosis is via amniotic fluid, in a procedure termed an amniocentesis. A doctor viewing the fetus via an ultrasound precedes an amniocentesis. A thin long needle is then inserted through the mother's abdomen, and a small amount (less than one ounce) of the fluid surrounding the fetus in the womb, known as the amniotic fluid, is removed. [Figure 10] Because this fluid contains cells shed from the fetus, DNA can be extracted from the fluid and then tested (10).

Figure 10: Amniocentesis:



(10)

Amniocentesis can be used to test for chromosomal abnormalities and neural tube defects as well as genetic markers (10). Amniocentesis is approximately 99.4% accurate (13). However, there are certain risks and problems associated with amniocentesis. Amniocentesis cannot be carried out with the utmost safety until the woman is in her 16th week of pregnancy. As this is already in the second trimester, and results aren't received until approximately one week after the procedure is carried out, the pregnancy has significantly progressed before any diagnosis is received. For many women, the fetus has even begun to kick before the amniocentesis results are received. The late diagnosis leads to a more difficult decision as to how to deal with the results. An abortion carried out towards the middle or end of the second trimester becomes much more stressful and involved than one carried out earlier on in the pregnancy. Even if an abortion is not considered, the stress of having to wait so long for any diagnosis can be very stressful for the parents.

Another problem associated with amniocentesis is the risk of miscarriage. Approximately 1/200 women experience a miscarriage after going through

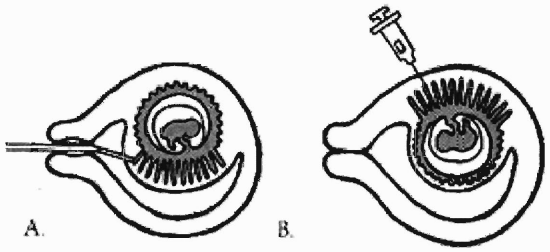
amniocentesis. This figure increases to 1/100 women if the test is carried out earlier than 16 weeks in the pregnancy. However, these figures are difficult to interpret in that it cannot clearly be determined whether the fetus would have miscarried regardless of the amniocentesis. In addition, some women experience bleeding, cramping, or a leaking of fluid through the vagina after undergoing amniocentesis. Finally, there is a slight risk of infection due to the amniocentesis procedure (10). Still, for a large percentage of women, the risks of amniocentesis are outweighed by the reassurance or knowledge the results of an amniocentesis can provide them.

2.2.2 Chorionic Villi Sampling

Chorionic Villi Sampling is also a procedure commonly used for prenatal diagnosis (13). Chorionic Villi are present on the outer edge of the placenta in the womb. Cells are obtained from these villi, from which DNA is isolated and then can be tested for various disorders. There are two different methods for obtaining the villi cells. [Figure 11] In the transcervical method, a sterile catheter is inserted through the aseptically prepared vagina and cervix. While the doctor monitors the catheter's position via an ultrasound, 15-30 mg of chorionic villi is aspirated via a syringe. On the other hand, in the transabdominal approach, a procedure similar to the amniocentesis is carried out, in that a long thin needle is put through the mother's abdomen in order to obtain chorionic villi cells (10).

Figure 11: Chorionic Villi Sampling

A = transcervical method B = transabdominal method



(10)

Just as with amniocentesis, there are certain advantages and risks associated with chorionic villi sampling. Chorionic villi sampling can be safely performed as early as the 10^{th} week of pregnancy, clearly an advantage over the 16^{th} week testing by amniocentesis, with a 99.5% accuracy rating. Yet, the risk of miscarriage is significantly higher with chorionic villi sampling, with 1/100 fetuses miscarrying after the procedure. Still, just as with amniocentesis, this figure is difficult to interpret in that it is never clear exactly how many fetuses would have miscarried regardless of the procedure (10).

Another problem that arises with chorionic villi sampling is that of mosaicism, occurring in approximately 1% of patients. Mosaicism occurs when there is a mixture of both normal and abnormal DNA present in the sample taken from the fetus. In many cases, it is predicted that the mosaicism is present in the placenta but the fetus contains only normal DNA. In these cases, the true status of the fetus can be determined via amniocentesis. In addition, 1.8% of specimens experience contamination by maternal cells. The fetal cells can be differentiated from maternal cells by careful laboratory techniques. Finally, chorionic villi sampling cannot detect neural tube defects; thus other

procedures must be performed to test for these defects (10). Still, despite all its flaws, for many women, the earlier testing that can be performed with chorionic villi sampling outweighs the slightly increased risks associated with it over amniocentesis.

2.2.3 Maternal Blood

Though this procedure is not yet performed to detect genetic markers for disease, studies are exploring isolating fetal DNA for testing from maternal serum or blood. This procedure, were it to become commonplace, would clearly be more safe and convenient for parents. Not only are fetal cells present in maternal blood as early as 7 weeks into the pregnancy, the procedure of taking blood from the mother would be almost entirely non-invasive and pose no risk to the fetus. Below are the results of two studies done to determine the amount and accuracy of fetal DNA isolated from maternal blood.

For a study published in 1997 in the American Journal of Human Genetics, women attending the department of Obstetrics and Gynecology at the Prince of Wales Hospital in Hong Kong were recruited to donate blood two times during the pregnancy. The first donation was given prior to amniocentesis or chorionic villi sampling, while the second donation was given shortly after delivery (15). The researchers found that the blood collected during early pregnancy contained an average of 3.4% (range of 0.39%-11.9%) fetal cells. On the other hand, in the blood collected during late pregnancy, an average of 6.2% (2.33-11.4%) fetal cells was found (15). These results seem to indicate that the percentage increases with the duration of the pregnancy, though they are not conclusive.

In another study published in 1997 for the American Journal of Human Genetics, the researchers studied the accuracy of fetal cells present in maternal blood. The researchers compared the gender of the fetus as determined by cells present in the maternal blood as compared to the actual fetal gender determined after birth. 230 samples were used from clinical sites around the United States, and were taken either just before or after amniocentesis (2). The study showed that in 99.3% of the women carrying male fetuses, male fetal DNA was detectable. Though the researchers did not use a unique marker to distinguish female DNA, they assume the figure should be similar. On the other hand, in 25.7% of the women carrying female fetuses, small amounts of male DNA was discovered. The vast majority of these women had previously given birth to a male child; thus, the researchers postulate that this is the origin of the male DNA (2). Though the amount of male DNA in these cases was miniscule, the fact that it was present still lends inaccuracy to the procedure.

Both of these studies indicate that testing for genetic markers prenatally via maternal blood will perhaps be a possibility, but that considerably more research must be done before the testing will become a reality. While the procedure would certainly be preferable to other current modes of prenatal screening, its current inaccuracy would make prenatal diagnosis via this method decidedly unreliable.

2.2.4 Prenatal Testing for Genetic Markers

As stated previously, prenatal testing for genetic markers has been performed for over a decade. Numerous diseases have been tested prenatally, as shown by Figure 12, a table from 1991 showing diseases then considered acceptable to test for via genetic

markers prenatally. Notice that Huntington's disease, a late onset disease like breast cancer, was approved for testing.

Figure 12: Disease tested for by genetic marker prenatally

TABLE 1.
DISORDERS CONSIDERED ACCEPTABLE BY VARIOUS STATES FOR DNA ANALYSIS OR PRENATAL SCREENING[a]

Disorder	Birth Incidence (1 in)	Comments
Anencephaly/spina bifida	700	High maternal serum alpha protein level
Adrenal hyperplasia (congenital)	15,000	DNA chromosome test—chromosome 6p recessive—21 hydroxylase deficiency
Adult polycystic kidney disease	1,250	DNA chromosome test—chromosome 16p
Becker muscular dystrophy	Uncertain	DNA test—chromosome Xp
Biotinidase deficiency	40,000	Non-DNA test—semiquantitative colorimetric analysis of a dried blood spot
Cystic fibrosis	2,500 (whites)	DNA test—autosome 7q—gene isolated—cystic fibrosis transmembrane conductor regulator
Down's syndrome	770	Trisomy 21—chromosome cytology non-DNA low maternal serum alpha protein level
Duchenne muscular dystrophy	4,000 (men)	DNA X-linked recessive (Xp)
Fragile—X syndrome	2,000 (men)	DNA X-linked recessive (Xq)
Galactosemia	40,000	Non-DNA test—heel stick enzyme screening assay—blood galactose level urine shows presence of nonglucose-reducing substances
Hemophilia A	10,000 (males)	DNA test, X-linked recessive (chromosome Xq) gene defect for Factor VIII
Hemophilia B	30,000 (males)	DNA test, X-linked recessive (chromosome Xq) for Factor IX
Huntington disease	10,000	DNA chromosome 4p (dominant)
Hypothyroidism (congenital)	5,000	Non-DNA test—heel stick blood spot test for thyroxine radioimmunoassay
Phenylketonuria	8,000 to 16,000 (whites)	Heel stick blood spot specimen shows high levels of phenylalanine detected with Guthrie inhibition assay test. Also DNA recessive chromosome 12q—phenylalanine hydroxylase deficiency
Retinoblastoma	20,000	RFLP linkage chromosome 13—loss of heterozygosity
Sickle cell anemia	350 (blacks)	DNA chromosome 11p—β-globin gene defect
Tay-Sachs disease	3,600 (Ashkenazi Jews)	Hexosaminidase A (DNA Chromosome 15q)—DNA deletion gene 28
Homocystinuria	240,000	Non-DNA dried blood spot enzyme assay. Also DNA chromosome 21q
A—Thalassemia	400	DNA test chromosome 16p (recessive) gene defect alpha globin
B—Thalassemia	400	DNA test chromosome 11p B-globin (recessive)
Maple syrup urine disease	120,000	Non-DNA test, urine has sweet odor; identification of leucine on heel stick blood spot
Tyrosinemia	100,000	Non-DNA test, enzyme heel stick assay denotes defect in tyrosine aminotransferase

[a] From References 1, 6, and 8.

(13)

The manners in which these diseases are tested for prenatally are essentially the same as the way in which they are tested in adults. For example, the following is a protocol used by a study in which the researchers were testing prenatally for cystic fibrosis. Note how similar the procedure is to the one described above for the testing of *BRCA1* and *BRCA2* mutations.

The cells are first isolated via centrifugation and are placed on glass slides, so that individual cells can be isolated. These cells were lysed (so as to isolate the DNA) and set up for a procedure known as fluorescent PCR because the PCR products are labeled fluorescently. Two sets of primers were required for the PCR, one to amplify the site on the genome where the mutation characteristically is in cystic fibrosis patients, and another that marks the X and Y chromosome, so that the researchers could verify the fetus's gender simultaneously. The PCR products were then prepared for analysis and analyzed by the Genescan 672 software (11). Figure 13 shows the output given by the software, with the peaks corresponding to DNA fragments. Note that 100 base pairs (bp) is the normal fragment signal on the cystic fibrosis gene, while the 97bp fragment is caused by the mutant allele of the cystic fibrosis gene (11). Thus, the output shown is for a female fetus that is a carrier for the mutant cystic fibrosis gene.

Figure 13: Signal for detection of cystic fibrosis mutation

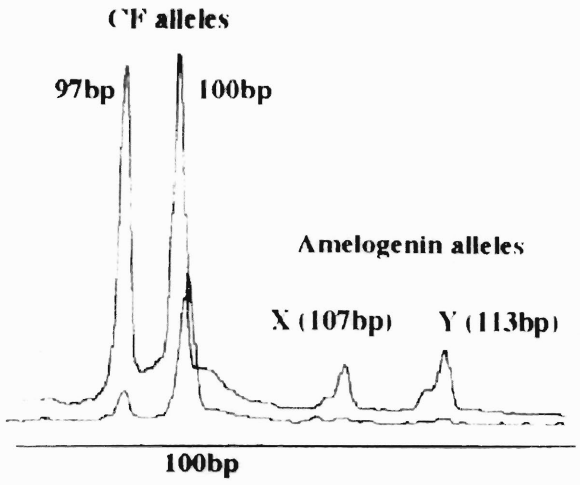


Fig. 1—Genescan profile showing signals for X and Y amelogenin, ΔF508 and normal CF alleles using 10 fetal cells

(11)

Prenatal screening for breast cancer could be performed in a similar manner for a family with a history of a specific *BRCA1* or *BRCA2* mutation. If a family member has not previously been shown to carry a specific mutation, or if more security in the mutation-free diagnosis is desired, the fetal DNA would then have to undergo full sequencing, as with adult DNA. Though the full sequencing would certainly be possible for fetal DNA just as it is for adult DNA, the time it would require to receive results if the DNA requires full sequencing would undoubtedly be much longer than were only a single site mutation focused on. This time difference might be critical if the fetal DNA was acquired through Chorionic Villi Sampling or Amniocentesis and the pregnancy has thus progressed fairly far before testing was even started. Overall, however, the protocol by which a fetus could be screened for *BRCA1* or *BRCA2* mutations is fairly straightforward and supported by numerous procedures already proven effective for similar cases.

3. Social and Ethical Implications

3.1 Decisive Factors and Decision Makers

3.1.1 Severity, Probability and Age of Onset

With the enhanced ability to detect mutations for multi-factorial or polygenic diseases, certain factors need to be taken into consideration, while evaluating the feasibility and usefulness of prenatal screening. There has been considerable argument for and against obtaining this type of sensitive information because it steers an individual towards a web of complicated issues.

Knowing whether an individual will develop the disease or not can free an individual from uncertainty and doubts of continuing risk. For some, even a positive diagnosis may be preferable to continuing uncertainty. The state of knowing can alleviate the emotional wellbeing of an individual and grant the individual time to prepare for the outcome, whatever that might be. Where medical treatment is effective, the individual may opt for early treatment or preventive measures before the symptoms develop. And for those who test negative, they can discontinue or avoid medical procedures.

Individuals may wish to pursue genetic testing for the benefit of family members in the present or future or to make reproductive choices. In most cases, the reason for testing may be some or all of the above reasons and will vary due to different circumstances. Prenatal diagnosis, too, can be construed to have similar motivational factors.

However, whatever be the result of a prenatal diagnosis, the reaction to the information is processed depending on the severity, probability and age of onset on the

disease or disability. In all diseases, one or the other of these factors may predominate. Beyond the dynamics that are built into the way a disease is expressed, any individual may have varying tolerability and sensitivity to a disease (22).

For example, in a disease like Turner's syndrome, that affects girls, the disease results in shortness, infertility and odd appearance (shield chest and webbed feet) but does not affect life expectancy. In fact, most women with Turner's syndrome cases are able to lead a normal life with little or no assistance and cases have been reported where women with the disease have been able to bear children by employing new reproductive technologies like artificial insemination etc. In this case, it is possible to overcome the disease due to the low degree of severity.

The probability of occurrence of the disease once a genetic defect has been traced is unique for each disease. Several genetic diseases are directly correlated to a specific genetic information and, therefore, the likelihood that the disease will develop is extremely high. With the ongoing effort to map the entire human genome, the weight of genetic markers and the correlation to a particular human trait, ability or disability has to be assessed cautiously. However, in the case of sickle cell anemia, the genetic condition definitely indicates the presence of disease but it has also been acknowledged that sickle cell anemia imparts immunity towards malaria for the individual (16). This immediately poses the question that although the genetic evidence suggests that development of breast cancer is a possibility, should the genetic changes be deemed as unwanted and unnecessary? Several researchers have suggested that these genetic mutations could be the course of natural genetic divergence. They may or may not have a greater benefit

immediately but over time may prove to be useful. Also, it is difficult to verify this possibility because such genetic evolution is cumulative and occurs over generations.

Age of onset is self-explanatory and inevitably demands a quantitative evaluation of the fetus' life, whatever length it may be. In diseases, like Huntington's, once the genetic susceptibility has been determined, the symptoms are expected to definitely develop around mid-life and cause progressive deterioration.

In the case of breast cancer, all of these factors are extremely relevant and need evaluation. Not only is this evaluation necessary but it needs to be conducted by an informed panel of members. It cannot be categorized as a grave birth defect and has been reported to manifest itself within a large age range, from mid-twenties to above sixty years. In the case of breast cancer, quality of life remains unaffected until the onset of disease. Even so, breast cancer does not physically impair a person's independence or self-reliance until advanced and irreversible stage of disease.

Because of this unpredictable nature of breast cancer, several options become available to the individual. Breast cancer can be controlled through preventive therapy. With the potential of prenatal diagnosis, it is possible to adopt a lifestyle that may reduce or postpone the possibility of disease. Also, the new chemotherapies are extremely potent and the numbers of breast cancer survivors are ever increasing. But this same unpredictability in the nature of breast cancer may backfire if the disease expresses itself very aggressively and overpowers all medical efforts to control it. Also, the likelihood of a carrier of the BRACA1 and BRACA2 mutations being lucky and leading an unaffected life cannot be eliminated entirely. On the other extreme, the chance that an individual with no previous familial history of breast cancer will develop and succumb to it due to

random mutagenic factors is also a possibility. These circumstances suggest that prenatal diagnosis for breast cancer creates many different options and needs to be handled very prudently with reference to the particular situation.

3.1.2 Selective Abortion

Abortion, the medical termination of a pregnancy, can be a chosen course of action for several reasons: mother's physical and mental health, unwanted pregnancy due to ineffective contraception, sexual assault, incest, unplanned or economic reasons or fetal health. In general, if the pregnancy has been initiated voluntarily, reasons for abortion are fewer and less compelling and typically focus on the genetic profile of the fetus.

In most cases, the hope for treatment of fetus during the pregnancy, i.e. in vivo, is unrealistic and untenable. This lack of available therapy implies that abortion remains the solution to most inheritable diseases. Any prenatal screening technique is of little significance if the parents are unwilling to at least entertain the thought of terminating the pregnancy, if the diagnosis reveals a serious genetic abnormality or mutation.

This situation can be examined by taking into account the emotional tumult that parents face. Parents feel responsible for their child's well-being in all respects and are known to go to any extent for the benefit of their child. This is one of the many reasons that they even choose to consider exposing themselves and their fetus to medical diagnosis, realizing completely that it may compel them to address and make extreme choices.

Most practitioners stress that diagnosis most often reveals a normal fetus and thus merely reassures anxious parents of the normal and progressive development of their child. Sometimes, the anxiety can be caused in part by the recommendation of the test, when the reasons to do so may not be justifiable. However, if the diagnosis does detect a genetic mutation, then it only compounds the complex issues that the parents will need to address.

The procedure places undue stress and anxiety on parents since the decision to abort or not to abort must be made by them only. The strong desire for a healthy child combined with knowledge that the termination of the life of their child may follow, creates great moral suffering.

Several ethicists argue that selective abortion is justified as it protects the family or marriage from financial and emotional strain of rearing defective or children who will need continuing medical assistance. The availability of the option of selective abortion can be simply viewed as an extension of the fundamental rule in prenatal diagnosis that the parents are the sole decisions makers for both diagnosis and abortion (12). Another concern amongst ethicists is that the increasingly acceptable notion of selective abortion may thwart a development of treatment or therapy for the disease, when another solution is available. Even the presence of an option that is more effective and cheaper can bias the decision of parents and create a trend of taking the easy way out.

The continued presence of this easy and convenient choice contradicts and defeats the idea of medical treatment because eradicating or reducing the occurrence of the disease in the population via selective abortion takes precedence and rules out the opportunity and possibility of finding a cure or treatment for the disease. This undermines

the potential benefit of genetic therapy by dangerously entangling prenatal diagnosis and selective abortion.

Most prospective parents begin to believe that implementation of prenatal diagnosis could or should be followed by selective abortion. Parents are steered towards a decision for selective abortion as they feel they do not want their child to be discriminated against due to his or her genetic constitution. And this may be a real possibility in the future, if the trend of selective abortion continues, and individuals with particular genetic defects find themselves in a minority (12).

Also, the pressure of early diagnosis and early abortion creates a very short time lag between diagnosis and a decision to abort. Technological limitations make early detection difficult and the situation gets more complicated when the question of reliability and accuracy of the test is taken into account.

On the other hand, prenatal diagnosis can be employed as an information gathering procedure and this genetic input can be utilized in future therapy for the individual or by the parents in making reproductive decisions. The extent of therapy and its effectiveness for different diseases is under investigation like cystic fibrosis is under investigation.

Prenatal screening for breast cancer involves taking into consideration all the above arguments for and against selective abortion that will aid parents to reach a decision.

3.1.3 Role of Parents: Decision-Makers

In most cases of genetic testing, genetic counselors or family physicians recommend genetic testing only if there is a history of a particular disease in the family. Also, the receiver of the information is an adult, the carrier and is the one responsible for determining the consequences of the information.

In prenatal diagnosis, the receivers of the information are the parents of the fetus. They become the decision-makers and the people who will evaluate the information and arrive at a decision. The argument remains that physicians or genetic counselors are more qualified technically to assess the status of the fetus. Nevertheless, these technical assessments are purely medical judgements and should be considered, but not as the final determinant.

This leads to the most accepted and prevalent status where, traditionally, the parents are granted utmost rights to decide the future of the fetus. This is also based on the assumption that parents are able to determine and pursue the course of action that is in their child's best interest. As substitute decision-makers, the parents will come as close to making a decision in the child's best interest as possible.

One of the more prominent reasons for giving precedence to the parents rather than medical experts is the difference in perception. Parents and physicians have different values and perceptions and may or may not arrive at the same conclusion after evaluating the information. Even if they do agree to the plan of action or inaction, they may have different motivating factors. Parents may be inspired by their devotion to the fetus, on one hand, or, on the other hand, are motivated to safe guard the interests of the family as

a whole. The physicians may want to promote the needs of the fetus or the general genetic health of society.

The privilege is generally granted to the parents, whatever is the motivation of either the parents or the physician. The decision-makers are the parents because it is their lifestyle and quality of life that will be affected and their values that will undergo scrutiny depending on what they decide to do with the genetic information of the fetus. The parents will have to examine a tremendous amount of medical and technical diagnostic information and will also have to explore their own individual values, their values as a family and the values of their social structure (23).

Even though the role of parents, as decision-makers, predominates most debates about decisions regarding child's health care, rarely, if ever, does this accord them unlimited discretionary power. Most ethicists tend to agree that parents should, after weighing out medical information and advice, have reasonable authority to make decisions for their child, subject to certain ethical and legal constraints.

This conditional acceptance of the parental role implies that the privilege of decision making should be viewed as a responsibility too. Parents exercise this responsibility throughout the period of child's life when they are under parental care. Judgements about what is good and right for the children, frequently, without their consent, is an important part of executing parental duty. If parents can make these judgements after children are born, then by advancing this argument, parents should be allowed to make responsible choices prenatally for they are in the best position to weigh factors and their consequences. Hence, the parents don a role that bestows a lot of privilege but also demands a lot of responsibility.

Lately, there has been an increase in number of cases of child abuse, state support of dependent children and lack of fertility control by those who are unable to raise children. In the circumstances, when the parents are physically or mentally ill, living in an environment that is not suitable for raising children like severe alcoholics and history of violent behavior, or when they are financially strained like unable to afford domestic expenses, parents become incapable to rear children. The increase in the incidence of such situations is alarming and leads to another general concern regarding the unreliability of parental responsibility, where parents may choose not to satisfy the dire needs of their child. Parents may, as mentioned earlier, choose to protect what they may consider as the greater interests of their family unit, as opposed to the interest of their unborn child. In the case of breast cancer, however, it does pose a problem because there is no in vitro corrective procedure. But this does not bar the possibility that parents may have concerns of maintaining and improving the gene pool of their family, such that future generations may not have those particular genetic mutations.

Prenatal diagnosis may create complicated choices but under the above circumstances may be exploited or misused. For instance, it is expected that under stressful circumstances of having to make a decision, parents become vulnerable and easy to mislead by either an over-optimistic or bleak outlook of the physician. Also, it cannot be ascertained without doubt that doctors and genetic counselors are giving accurate and unbiased, objective advice.

As a result of technological advances like prenatal diagnosis, there have been gradual reductions in the reliability of the assumed state of stability and inviolability of parent-child relationships (3). With the technology for prenatal diagnosis becoming more

readily available, other technologies to correct or delete the problem itself are also thriving. These technologies provide an easier solution by ending the cause of the dilemma rather than to facing the choices. This increase in exploiting technology has raised doubts whether the parents can always be relied on to make sound decisions.

By law, the woman's right to privacy outweighs the fetus' right to life for the first six months (32). Whether or not the fetus possesses any rights at all is debatable. However, this problem of whose rights should be given more importance can be resolved by considering it as a question of best interest of the fetus. This has become the more favored view as it minimizes the parental role as decision-makers or of any other lone authority or group of people.

The best interest perspective attributes more emphasis on the fetus's life and comfort when compared to any other entity i.e. parents, family and society. The best interests of the fetus vary from case to case but can have certain basic parameters that require careful analysis. These variables include the presence and evaluation of a medical condition that may impose on the future life of the fetus, reliability of the medical diagnosis, the severity, probability, age of onset of disease and life expectancy. If a treatment or possible therapy exists then the benefit of treatment versus it's possible physical, emotional and/or financial burdens need to be carefully assessed.

Following this, it is possible that the best interests of the fetus are undermined. Under such conditions, where there can be an obvious condition of conflict between the parents and fetus, the competency of the parents as decision-makers, should be realistically assessed. Some ethicists suggest that to alleviate this possible imbalance of

control, where a decision is being made on behalf of the fetus, it is important to consider the fetus as the weak party and accorded the privileged position (12).

In the case of breast cancer, however, it is almost impossible to predetermine the fate of the fetus before it is born, i.e. whether it will develop breast cancer, therefore, the best interests of the fetus remain ambiguous. In this light, it is up to the parents to evaluate all variables carefully and make a decision with reference to their particular situation.

3.2 Ethical Factors

3.2.1 Moral Dilemmas

3.2.1.1 Parental Anxiety

Pregnancy in general is a very stressful condition. Anxiety and dilemmas increase especially when the fetus is diagnosed with some kind of disease. A couple whose a fetus is diagnosed with a certain disease will not be the only people going through the anxiety and the dilemmas about their decision of whether to abort the fetus or not. Family and friends also might get involved in their decision. This decision is especially difficult when the couple is not a believer of a particular religion or spirituality.

Without religion their decision-making will be mostly based on the situation that the couple or the pregnant woman will be in. For example, age is a major factor. If the couple is very young, the most reasonable solution might be abortion since they might not be mature enough to be parents. Another reason might be biological. For a woman who is very young, pregnancy might be very dangerous for her young body. She might not be able to support two organisms and abortion will be a good solution.

Many young people are not wealthy or able to support a second person other than themselves. A couple will have a lot of struggle in raising a child. They will have to find a job that pays enough money to support another life. They will have to make a lot of free time for them and the child to spend together. Privacy (personal time, time for self) will be limited, as will be time with friends. If the couple wants to start a successful career it will be hard to fulfill their dream if they have a child. The child will need a parent to be

home at times that business needs their employees at work. It is best to start a career before a child arrives in the family.

Maturity will be another good example. Some people, who are in their late 20^s, late 30^s may feel that they are not mature enough (mentally) to have a child. For whatever reasons there might be (fear of commitment, fear of lost personal freedom, fear of dependence like a child depends on parents, etc) these people will make no effort to have a child. Therefore when a pregnancy in which has a certain disease comes along in their relationship, they vote for abortion. It is sad to hear or listen to these kinds of situations since it seems like these people are making zero effort to support another life, another human being. It seems like with the smallest difficulty they give up. It's not that easy though. When a woman feels some life in her body, she becomes very concerned and sensitive to life and is very hard to make a decision for abortion, even if the child is diagnosed with a deadly disease.

When a couple believes in a particular religion, the decision for the fetus is often more straightforward. Many people who believe in God believe that abortion is a sin. The fetus should have the right to come in life even if there is a certain disease in his/her organism. Therefore, no matter when the pregnancy takes place, the fetus will be given a chance to live even if only for a few days or weeks.

The anxiety of a couple does not arise only from the decision making of the fetus life, but from the economical issues too. The couple having the fetus has to think if their economical status will be able to support all the necessary treatments needed for the decease. Parents of the couple might be part of this decision since they might be able to contribute financially and help the couple.

It is hard on everyone (theist, atheist) to go through some decision-making about a life when a disease is involved, especially when the disease is breast cancer, since there is no guarantee that it will ever develop. If they decide to keep the child, they will have to be prepared in case that their child will develop, for example, breast cancer. Parents will need to have resources for the treatments if breast cancer develops. If their child never develops breast cancer, then they will be very happy that their decision at the start of pregnancy was not abortion.

3.2.1.2. Disclosure

Disclosure is a rather big moral dilemma for a couple having a fetus diagnosed with the certainty of contracting a disease. There are several issues involved with disclosure; however three general issues will be discussed in this paper. The first issue deals with be the priority of receiving the information. The second issue deals with the appropriate age of the child receiving his/her health information. The third issue deals with the proper source of this information given to the child.

Most pregnant women have a strong need to know about the health condition of their unborn baby, regardless of whether of not there is a familial history of a particular disease or a decision regarding abortion has to be made. When the pregnant woman visits the doctor and finds that the fetus has a certain disease or will develop this disease later on life, the first dilemma is faced: "What decision should be made about this situation?"

Parents will be concerned about the fetus, but at the same time they will be concerned about themselves too. The worse the health condition of the child, generally the greater the harm will be to the parents. Parents' harms include emotional pain,

suffering, loss of a child, opportunities, isolation, fear, guilt, loneliness, and financial expenses. (4) It must be said that the harm of parents is not necessarily correlated to harm that a child goes through. Therefore the parents will make a decision about the fetus based on the conditions previously described.

If the parents decide to keep the child and give him/her a chance to live they (parents) will be faced with the second issue of the dilemma. This issue deals with the appropriate age of the child to receive his/her health information. This issue is very delicate because the person (child) receiving the information might react in various ways, some of which might not be expected by the parents and the society.

Parents with children in this condition will be very concerned and worried about finding the appropriate age for their child to learn of his/her health condition. Parents will be conflicted when or if they should inform their child: at an early age, when they are dealing with their teenage issues, or at a later age (adulthood) when they have resolved most of their personal and social issues. This is a very big decision for parents since they want to protect and not harm their child. If parents decide to let their child know about his/her health condition, the child (teenager or adult) might react in a lot of ways. A child (teenager or adult) might see this situation from a very dark point of view. The child (teenager or adult) might get very depressed, anxious, stressed, and angry with the parent who decided to let him/her live. The child might not want to make any effort for a better and brighter future since their disease might develop in the middle of the career and take life away. An adult might be angry for not being informed at an early age since he/she might have made a different career choice. A child (teenager or adult) might think that developing a deep and serious relationship with a woman/man might be a waste of time.

Another person might feel strongly about having a serious relationship, but having a child will be not an option. Another might choose to have a lot of partners in their life and unknowingly get HIV virus and die of it instead of the decease diagnosed prior to their birth.

However a person (teenager or adult) might see his/her disease from a positive point of view. The person might be grateful that he/she had a chance to meet the parents, be grateful for being alive, for being loved, and having friends who like his/her character and don't mind of the disease of their friend. This person (teenager or adult) might be more cautious about the disease and get screened often so the disease (example breast cancer) will be caught in time and might have better chances to be fought.

Parents who have a child diagnosed with a late on set disease (breast cancer) might be very tempted not to let their child know about his/her health problem since they don't want to hurt their child. This might sound like a very good solution at first, but if the child develops cancer than he/she might be very angry with the parents. The child might be very angry since he/she might have a family of their own and children and this kind of news will bring their world upside down. Therefore when to inform the child depends on the parents' decision. It also depends on the child's character and point of view. This is a very difficult decision for a parent to make.

A less stressful yet important issue that parents have to face will be the third issue of the dilemma. The third issue deals with the proper source of this information to the child. After the parents make the decision of informing the child about his/her condition, someone has to tell him/her about it. Who should it be: parents or doctor? Who will be more tactful? Which one will make it less shocking? This again could lead a person to

different points of views. A person might find it more helpful if his/her parents were the one to reveal this information. He/she might find this way appropriate since parents are the ones who stay by the children's side all the time in all situations and it could even ensure them about parental love. Another person might find it more comfortable if the doctor is the one to reveal the news since the doctor will be well informed about the disease. If there are going to be any questions about the disease, the doctor will be most likely to have a scientific answer about it. Parents might be as well informed as the doctor, but sometimes the words coming out of doctor's mouth sound more convincing and accurate. Therefore as mentioned before, it depends on the character and point of view that a person will see the situation.

3.2.2 Social Factors

3.2.2.1 Risk Budget

Almost every young person dreams of having a happy family, healthy and smart children. There are not that many people who think about having a family and not caring if their child will be born with a deadly disease. One of the reasons that people feel this way is because of the conception that we built when we see a sick person. We seem to divide people in two categories (intentionally or not) "normal" people and "non-normal" people. What is a "normal" person? A "normal" person is someone who is born with no disease kind (deadly or late on set disease) or handicap, or blind, or deaf. "Normal" people are better physically, intellectually, spiritually, genetically, etc. It includes being advanced on the evolutionary tree (31) If someone is born with any kind of disease or is disabled, he/she will be looked with pity by others ("normal" people). "Normal" people

will emphasize how unhappy and sad and lonely these people might feel since they look or act different. It is like the physical and/or mental conditions are put in a spotlight mostly by the normal people. Why does this happen? Part of it might be that "normal" people might fear the unknown. These diseases are unknown to their ("normal" people) body and they don't really know how it feels to have a deadly or late of set disease. They don't know how it is to live with a handicap such as blindness or deafness. By not being able to experience the same physical or mental conditions "normal" people think people with special needs might be very depressed, sad and unhappy. Therefore there should be more of "us" (normal people) and fewer of "them". Excluding "them" from "our" gene pool presumably will keep our breeding stock healthy and happy. For this reasons people are seeking perfection and believe that perfection brings happiness. It seems like "we" are taking too much advantage of "our" advanced evolutionary tree (31).

People today are fascinated by the way that technology has developed. They are fascinated by the way that technology can make a wish come true. If the couple wants a specific gender for their child, they can have it. If they want to see if their child's gene has any mutation or might develop any in the future, they can do it. If they want to abort children till their gene sequence doesn't show any kind of mutation later in life, they might do it. But what is the use of this kind of technology? If people want to screen their fetus' genes and decide to abort till there is perfection, they can do it. However if the majority of people will have courage and desire to follow this pathway, then we will go to extinction? This could happen even if we are considering breast cancer. Yes, breast cancer is a late on-set disease but if people think that aborting their fetus of any gender (especially female, since they have a higher rate of getting the mutation) will be the best

solution to their problem, then what will be the future of our kind? It is true that no one wants trouble and extra work in their life (by having a child with special needs, parents will have to spend a lot of time and money on them). But do we really want to eliminate every single possibility of any later on set mutations? If people will feel that this will be the only way to eliminate any kind of non-perfection in society, then the only way to receive babies might be in laboratories (experimentally). But are we ready to give up the old fashion way of having children (God's children) and devote ourselves a hundred percent to technology?

3.2.2.2. Implications on Insurance Coverage

Our civilization has gone through a lot of changes and it's still changing year after year. Since our civilization has changed so much we try to figure out how to keep up with technology for most of our needs and wants. One of the beneficial steps that happened in this evolution is the time when people thought of having insurance coverage for their health. Health insurance coverage is important during personal or familial illnesses. When a person or a family has need of lab work, surgery, or just to make a visit to a doctor, insurance coverage makes a very helpful contribution to the bills of this person or family. It is very important that every one has insurance coverage because without it bankruptcy soon might be knocking at the door.

There are people, though, who do not have health insurance because they are illegal aliens, employed in a business with no insurance coverage, employed part time work in different work places, or are unemployed. What do these people do when sickness knocks on the door? There are a few alternatives that a person in this category

can choose. Illegal aliens are the most problematic since they have to pay everything in full. They have neither rights nor any government help since they are not American citizens. People who are employed in a part time job(s) have the privilege of applying for free insurance coverage in certain hospitals. These hospitals will cover all the expenses if the patient is in no condition to cover any of the payments. This option is available even for the unemployed people.

As is known, health insurance coverage has positive and negative futures. A positive future is that it helps citizens pay their medical bills. A negative future may be that a person does not have full coverage and will be unprotected on the most critical time of his/her life. For example, when a person is diagnosed with a deadly or long lasting decease and very expensive treatments have to be followed, the health insurance coverage may cover only a very small amount of the treatment or cover only few treatments for a certain length of time. The person who is going under this treatment not only is under stress because of the disease that is progressing inside the body but the problem with insurance coverage is not making it any easier for this person to follow through all the treatments needed for the particular decease. If a person is not wealthy, it is going to be hard to complete all the necessary treatments since there may be limited coverage offered from a health insurance. However, the limited coverage is not the worst thing that health insurance can bring to a person or a family. There are so many other things that make people very angry about the health insurance system. People have lost jobs or promotions and even have been turned down for adoption based up on their genetic status.

Women have lost jobs when their employers found out about their health status (26). Women who had a family history of cancer or any other disease that the insurance company found to be a preexisting cause may not receive coverage. Women have had to be laid off since the claim was denied by the employer's insurance coverage. They have lost opportunities of getting a promotion for the same reason (26). Another reason for not getting a promotion may be the life span of the person. If people are informed that the woman who is asking for a promotion has tested positive for breast cancer and her remaining life span is unknown, many employers may not want to give a promotion to a woman in this condition. People have the perception that if the genetic test (for breast cancer) is positive, then the chance of a person developing the disease is 100%.

Women with positive genetic testing have been denied the adoption of a child (26). These women were not good enough to be mothers of foster children. They posed a risk of early death. But how can these people predict the lifetime of a person? How do they know that other women who want to adopt children but have never tested for breast cancer nor have it in their family records, won't develop breast cancer some time in their life? People forget or misunderstand a very important fact that genetic tests find mutations, not diseases. These women had a genetic test because they wanted to know if they were at risk of developing cancer, not because they wanted to be discriminated against by the whole society. An accurate gene test can tell if a mutation of BRAC1 or BRCA2 is present, but this finding does not guarantee that breast cancer will develop. Since there is no guaranty that breast cells will mutate and develop cancer, then how can an insurance company do so much damage to so many women? If a genetic test can't be accurate enough to determine if a woman will truly develop breast cancer at a certain age

(40-50 and up), then insurance companies can't declare a woman as a truly breast cancer patient. In fact, several states have prohibited insurance companies from using genetic test results as a criterion on which to deny coverage. However, women whose health insurance is paid for by their employers are exempt from these laws (26).

"What does it cost?" This has been the refrain repeat with increasing intensity over the last decade on the issue of financial coverage of patient care. In the past, the answer to this question, to the frustration of health care payers and providers, has been, "We don't know." In recent years, the financial coverage of patient care in clinical trials has become an urgent question. Mayo Clinic in 1988 was able to start a clinical trial. They were able to estimate from 1988-1995 a realistic amount for breast cancer treatments.

The cost of the genetic test only is:

Test	Total Charge	20% Co-Pay
Comprehensive BRACAnalysis –BRCA1 and BRCA2 gene sequence analysis for susceptibility to breast and ovarian cancer	$2,400.00	$480.00
Single Site BRACAanalysis-Single-mutation analysis for susceptibility to breast and ovarian cancer for individuals with known BRCA1 or BRCA2 mutations in the family	$ 395.00	$79.00
Multisite 3 BRACAnalysis-Three-mutation BRCA1 and BRCA2 analysis for susceptibility to breast and ovarian cancer For Ashkenazi individuals	$450.00	$90.00
Comprehensive BRACAnalysis for Individuals whose results from *Multisite* 3 BRACAnalysis are negative	$2,050.00 (additional)	$410.00

BRACAnalysis Services (http://www.myriad.com)

As it is seen even, the co-pay is still expensive for an individual. If there is a family who has two or three people having one of these tests done, this ends up being very expensive for a middle class family. The insurance company might cover approximately 80% of the fee, but there are times when the insurance company denies the claim and the patient is responsible for the whole amount.

The National Cancer Institute (NCI), through its Office of Clinical Research Promotion, has been in the forefront of addressing the yearly cost of which negotiating agreements with such organizations as Medicare and the American Association of Health Plans for coverage of patient care in clinical trials sponsored by the National Institutes of Health (NIH) (21). "Legislation ruling coverage of patient care costs for specific cancer clinical trials has been decided in Maryland, Rhode Island, and Georgia and is under consideration in several other states"(19). A similar law is also under consideration at the federal level as part of the proposed Patient's Bill of Rights Act of 1998 (20). These proposals must be "costed out," by such agencies at the Congressional Budget Office (8) as they are considered, and many of these proposals and agreements contain requirements for continued evaluation of the economic impact of clinical trial coverage as the programs go into effect (20, 8, 1). Until now, the entities responsible for "costing out" the financial impact of coverage proposals have had to operate in the absence of empirical information. Because predicting financial exposure into the future is always risky business, these analyses have tended to err on the high side. Now, with the data provided by Wagner et al. (27) it will be possible to begin to place more realistic and, as it turns out, lower ceilings on these estimates. Wagner et al. (27) examined the patient care cost of 61 cancer patients enrolled in NCI-sponsored at the Mayo Clinic from 1988 through

1994 and compared these costs with the 61 "control" patients receiving standard care in Olmsted County, MN. The 61 control patients were carefully pair-matched with the clinical trial patients on the basis of age, sex, site of primary cancer, stage of cancer, date of diagnosis, and clinical trial eligibility. Total cumulative medical care costs, for each case and control patient, were tracked at 1 month, 3 months, 6 months, 1 year, and 5 years after the date of diagnosis. In the analysis of 5-year cumulative costs, statistical methods were used to take effects of examining into account. The study found that trial participants experienced only slightly higher costs compared with control patients and that this difference was not statistically significant. At 1 year after diagnosis, the average cost for trial enrollees was $24, 645 compared with $23, 964 for comparable patients receiving standard care. The respective costs at 5 years were $46, 424 and $44, 133. These results should be considered preliminary because of the small size of this study and the notoriously high variance of medical cost data (5). Nevertheless, the results of this study and other preliminary work presented at a NCI-sponsored symposium in July 1998 (17) strongly suggest that, until more definitive results are available, several thousand dollars can be considered a reasonable estimate of the incremental cost of patient care in clinical trials.

There are women who have been diagnosed with breast cancer and after some treatments they have the option of mastectomy. After this process they might consider having breast prosthesis. Breast prosthesis is an option for a woman's confidence for it gives the illusion of symmetry to the body. An A cup prosthesis costs $400. Some insurance companies will pay for only one per lifetime, so if a woman changes breast size

with age or weight, too bad. The breast prosthesis is made for white woman; perhaps the manufacturers feel sure that women of color will tolerate this prosthesis (7).

Even if it sounds impossible, there are solutions to keep the insurance company from getting this information. The solution is confidentiality. Before women go through the test procedure, they need to ask their doctor what kind of information the insurance company requires. They can find out how their physician or health care plan protects their records. They have to let the physician and the health plan know that confidentiality is very important. These steps might seem very simple, but this might help a lot of women out there who do not know their rights.

There are a lot of issues that a woman can face when she is faced with the possibility of developing beast cancer. One of the most intense issues is health insurance coverage. She might be denied a job opportunity, a promotion, child adoption and health coverage.

3.2.2.3 Religious Convictions

In one sense American society has become increasingly secular over the past few decades: Religious icons are forbidden in public space and the religious significance of major holidays has diminished with celebrations focusing on exchanging gifts and eating jellybeans. Yet even in the face of this trend, there is simple evidence that people in our society are increasingly eager to find a spiritual niche. Books about angels and the soul appear regularly on best-seller lists. "More than 95% of Americans say that they believe in God. The majority also believes in prayer, or after life and other religious ideas" (14).

Religion is an important force in most people's lives. Most pregnant women sometimes rely on this force too closely when the fetus has some kind of deadly disease. They will be more likely to practice their religious believes a little more often during their pregnancy than they did before getting pregnant. What makes these believers feel so close to God and pray for His grace now that they are carrying a new life in them? It might be the mentality that the fetus, as a new soul in his or her mother's wound, is pure and does not know evil. In conjunction to this God is considered as a pure soul too who does not know evil either. Therefore a fetus (as a pure soul) could be considered His son/daughter since they both (fetus and God) are pure and know only good. In Catholic perspectives the fetus is of a pure soul and God's progeny, it will be considered a sin (although Catholic claims about abortion is not narrowly religious, abortion is viewed negatively) not to want to give life to the fetus under any circumstances. These circumstances might be the fetus dying of cystic fibrosis, Down syndrome, sickle cell anemia or many other deadly diseases.

When a Catholic pregnant woman is faced with one of these circumstances, she will be faced with a dilemma of ether considering her fetus as a human soul (without a sufficient developed body) or considering her fetus as soulless entity. If she considers the first option than she has no right to take away this soul it will be considered a sine. However if she considers the other option she still can't have abortion since it is considered a serious sine because it interfered with the procreative outcome of sexual act. (29). Hence her only alternative to this matter is to search and find a cure for her fetus,

and if a cure is not available hope that when the fetus will be born the cure for the disease will be found during the life of the newborn.

As mentioned earlier in this subject women become more pious when their tragedy befalls them. They pray to God and hope for a miracle to save their fetus from the deadly disease. Prayer it also provides therapy for the bereaved parents.

There are other pregnant women who are faced with the same circumstances and do not consider themselves religious. They do not believe on anything but what is presented in front of their eyes (if it is not seen and touched is not worth believing in). This fact will lead someone to believe that these women are free to make any decision they want because they are not entangled by the dilemma of being sinful. They can choose to abort the fetus, they can choose to give life to their fetus and give him/her up for adoption, or they can give life to their fetus and do whatever it takes to fight for his/her life. However in reality things are different. Like the religious woman, the non-religious woman will start debating the same dilemma of either considering her fetus as a human soul (without a sufficient developed body) or considering her fetus as soulless entity. This is a very strong issue since abortion of a human soul (considered as a formed fetus) will be considered killing, homicide. But, if the woman will consider the other option (her fetus as a soulless entity), then there will not be so much of a burden in her soul if she considers abortion.

This decision making (of abortion) gets more stressful when woman's rights are taken into consideration. Foes of abortion claim that the act of terminating a pregnancy does interfere with the right of another (fetus), while advocates of a woman's right to

procure an abortion deny that killing a fetus is a violation of rights (fetus as an entity is denied of any rights) (29).

Many of these women non-Catholic will be intimidated on keeping the child when they will be told by their doctor, or any other source of information about breast cancer, that breast cancer might not be developed by the newborn life. This news is very powerful yet not accurate enough to convince parents about the future of their newborn. Their decision upon abortion will depend on the way that they will view their pregnancy and if they will take into consideration the woman's rights. Therefore when a woman (religious or not) is pregnant with a fetus which caries a late on-set disease decision making will depend on a lot of factors that are part of her life.

4. Surveys

To supplement the literature review of the topic of prenatal screening for *BRCA1* and *BRCA2* mutations, professionals were asked their opinions on issues concerning the subject matter. Professionals in the scientific area consisted of oncologists, registered nurses (RNs) dealing with breast cancer, and genetic counselors. "Professionals" in the issue of morality consisted of religious leaders. Our selection of these groups as professionals will be discussed just prior to the discussion of the survey results.

4.1 Scientific/professional

In order to obtain a general idea of the opinions of people intricately involved in the issues of cancer and genetic screening, oncologists, registered nurses, and genetic counselors were questioned. This was done by means of a questionnaire in all cases as well as a interview in one specific case. A survey group of 10 oncologists and breast cancer specialized RNs, as well as 2 genetic counselors was presented with our questionnaire [shown in Appendix p.11] In addition, one of the genetic counselors whose questionnaire answers are mentioned in the tabulation of survey results was interviewed.

As stated above, these particular professions were chosen as questionnaire recipients because of their intimate dealings with either breast cancer or genetic screening. Oncologists and registered nurses were chosen from numerous local hospitals, including University of Massachusetts Medical School Cancer Center in Worcester, MA, Beth Israel Deaconess Hospital in Boston, MA, and University of Massachusetts Memorial Hospital in Worcester, MA, as well as independent practitioners from Hartford, CT. Genetic counselors from University of Massachusetts Medical School and

University of Massachusetts Memorial Hospital also responded to the questionnaire. The questionnaire was either mailed, faxed, or hand delivered to the recipients with a cover letter explaining the overall theme and purpose of our research.

The questionnaire was developed as a means to get an overall impression of the opinions of these professionals on genetic screening as well as specifically screening, both adult and prenatal, for breast cancer via the *BRCA1* gene. The following represents each question present on the questionnaire, why it was chosen as a question, and the resulting statistics from the 12 professionals on that particular question. The percentages represent the number of people selecting a certain response out of the entire group, regardless of whether all subjects responded to the particular question.

1. In general, would you advise patients with a familial history of a disease such as breast cancer to be screened for any genes that have shown a relationship to the disease?

This question was designed to obtain an idea of the subjects overall opinion on genetic screening. Two of the subjects commented that this question was vague and difficult to answer, thus not all answered the question, and those answers that were given could be skewed by difficulty answering such a general question.

Results:

Yes	No	Not Sure
25%	17%	25%

Unfortunately, little information can be garnered from these responses other than that few people were outright against screening for genes that have a relationship to a disease.

2. Do you feel that advanced knowledge of an increased risk for breast cancer would increase the patient's chances of successfully surviving breast cancer?

This question was designed to obtain professional opinion on the benefits of increased screening. Clearly, the value of screening increases if it benefits the patient's chances of survival.

Results:

Yes	No	Not Sure
50%	17%	17%

A large number of subjects did feel there is an increased chance of survival with early screening. This certainly adds to the value of screening.

3. In your opinion, are there any negative effects that advanced knowledge of an increased risk for breast cancer might cause for the patient?

This question provides the counterbalance to the previous question, in that it attempts to determine opinions about the harmful effects of early screening. Our potential ideas for harmful effects included insurance problems or anxiety, though we felt including these ideas in the question might bias the subjects towards an answer of yes.

Results:

Yes	No	Not Sure
17%	83%	

These results, like those of the previous question, help to support the value of early screening in that benefits with few negative effects can be garnered from screening. It is, however, interesting to note that of the two subjects who felt there are negative effects to screening, one was a genetic counselor and the other a registered nurse. This brings up the issue that perhaps some oncologists are not in an intimate enough relationship with their patients to determine negative effects of screening.

4. Do you find most breast cancer patients of yours or your colleagues' have a familial history of breast cancer?

This question was designed to determine professional opinion on the weight of inherited genetic breast cancer compared to sporadic breast cancer.

Results:

Yes	No	Not Sure
25%	67%	8.3%

These results correlate with the literature provided data that states that the majority of breast cancer cases are not caused by inherited genetic mutations. It should be noted that one of the subjects who answered yes to this question mentioned on the questionnaire that she specializes in patients with a familial history of the disease. Thus, other subjects with a similar patient unbalance could skew the data.

5. From your experience, do you find breast cancer is more common in certain ethnic groups? If so, circle any ethnic groups you feel have a great predominance to breast cancer. [Options shown in results table]

This question was designed to bring out the prevalence of breast cancer in the Ashkenazi Jewish population that has been shown in certain studies.

Results:

White/ Caucasian	Jewish	Asian	African American	Hispanic	Native American	Other
42%	25%					

Though the increased percentage of Ashkenazi Jewish breast cancer patients is illustrated in a few responses, because Caucasians represent the majority of patients seen overall by many practitioners in the area, this probably accounts for their higher prevalence. Another factor that could skew these data could be if the subject is not aware of their patient's religious backgrounds and thus would not separate Jewish patients from Caucasian patients when categorizing.

6. Would you recommend your patient visit a genetic counselor if they were to receive genetic testing?

The literature states that many doctors go ahead with genetic testing, bypassing a genetic counselor. Thus, this question was designed to get a feel for the overall opinion towards the value of genetic counselors.

Results:

Yes	No	Not Sure
100%		

Clearly, even disregarding the result of the genetic counselors who are certainly biased in answering this question, the results show the importance placed in the role of a genetic counselor.

7. Were prenatal screening for BRCA1 mutations made available, would you advise a pregnant patient with a personal or familial history of breast cancer to obtain this prenatal screening for their fetus?

This question delves into the overall issue of our research, with the qualification that women receiving testing have a history of breast cancer.

Results:

Yes	No	Not Sure
	100%	

These results very clearly demonstrate the overriding opinion against prenatal screening for breast cancer for people with a background of breast cancer.

8. In your opinion, should prenatal screening for the BRCA1 and BRCA2 genes be offered to all pregnant women?

This question reiterates the previous question except that it expands the testing to all women, not just those with a family background of breast cancer. In addition, it delves into the idea as to whether this sort of testing should be offered at all, not just whether it is advisable to receive.

Results:

Yes	No	Not Sure
	100%	

These results confirm the results of the previous question, adding in the opinion that these tests should not even be offered to women as an option.

The following are relevant comments made by subjects in the space provided on their questionnaire. These comments serve to elucidate on some of reasons behind the adamant opposition to prenatal screening for breast cancer and reemphasize certain points brought out in the literature review on this topic.

> "These genes only contribute to a small fraction of breast cancer. Only patients with a very strong history of breast cancer should consider testing."
>
> "At this point it would be ethically and morally wrong to do prenatal screening for BRCA and genes! The HG Project is against such testing."
>
> "Less than 5% of all breast cancers are genetic. I don't think that knowing the gene will make any effect on screening and precaution. Until there is more research and advancement in successfully preventing this disease there is no value in getting a prenatal BRCA1/2 test. i.e. – what good is the information? Won't change anything. i.e. – outcome/prognosis. Only will increase anxiety and will not be lost effective; no value for over 95% of other BRCA victims and may also be damaging to patient as the insurance companies may not give them health insurance or life insurance."

Overall, these questionnaire responses as well as comments rather clearly indicate that those surveyed strongly oppose the idea of prenatal screening for breast cancer. Because of the small subject group size as well as the lack of diversity in location of doctors, little can be extrapolated from these results to give an impression of the overall view of prenatal screening in the scientific community. Still, the results give some

impression of how those specializing in breast cancer or genetic screening might react to prenatal screening for breast cancer. In any further research done on this subject, it would be interesting to see the results of questions focusing on prenatal screening for other diseases, particularly late onset diseases such as Huntington's Disease. Perhaps specific questions about certain screening for other diseases as well as prenatal screening could replace some of the first questions on the survey that subjects found ambiguous. In addition, it would be interesting to add OBGYN's into the subject group as another group knowledgeable about prenatal screening.

In addition to the questionnaire, Jan Warsing, a genetic counselor at University of Massachusetts Medical School was interviewed concerning the subject of prenatal screening for breast cancer. She was also presented with the questionnaire and her results are included to the results listed above. The interview, however, complemented the survey responses with detailed reasoning behind each answer. Warsing, as indicated by the questionnaire results, is opposed to prenatal screening for breast cancer. In fact, she says she generally advises her adult patients not to receive testing for the *BRCA1* and *BRCA2* genes unless they are absolutely determined and well aware of the consequences. She feels that the slim potential benefits that can come from the knowledge of genetic mutations in *BRCA1* or *BRCA2* are usually outweighed by the anxiety caused by a mutation and the difficulty that can arise with insurance companies.

Another issue involving such screening that Jan Warsing brought up was the issue of cost. Because genetic screening for *BRCA1* and *BRCA2* is expensive even when partially covered by insurance, it places an economic barrier on who can receive the testing. Warsing contends that genetic testing frequently becomes a luxury not accessible

by everyone because of the cost. Finally, Warsing brought in the issue of "quality of life" for a fetus found to have a *BRCA1* or *BRCA2* mutation. She feels that prenatal testing for breast cancer could severely injure the quality of life of the fetus, and that selective abortion due to a *BRCA1* or *BRCA2* mutation would clearly also be a step to far.

In all, the questionnaire and interview with scientific professionals provided us with some interesting and surprising insights. For example, it is interesting to note that even the final question of the questionnaire which asked not only whether the subject agreed personally with prenatal screening for breast cancer but also whether it should be made an option at all produced a unanimously negative response. It was somewhat surprising that not one subject felt that the choice of whether the test should be performed should be left up to the patient rather than the scientific community. Perhaps this reflects on the general advanced knowledge about genes and their relationship to disease that professionals see in the patients. This is an interesting contrast to the response of the religious leaders who largely feel that the choice should be left up the patient, as will be discussed later on. Still, the questionnaire results undoubtedly demonstrate the opinion of our subject group of professionals closely involved with breast cancer and genetic screening that prenatal screening for breast cancer should not be performed.

4.2 Religious Leader Opinion

Because not only scientific professionals are affected by issues such as that of prenatal screening for breast cancer, other opinions were sought to get a more broad set of opinions on this issue. Because questioning a large diverse spectrum of the general public is difficult to accomplish via a questionnaire merely handed out to random people, community members were sought who represented a large part of our society as well as were familiar with moral issues, if not necessarily scientific ones. Religious leaders were decided upon as good representatives of a fairly large portion of the population in their moral attitudes.

For purposes of our survey, twenty-five religious organizations were contacted. Of these twenty-five, seven religious figures completed and returned the questionnaire sent to them. Though questionnaires were sent to a variety of religious denominations such as Buddhism, Muslim, Jewish, Christian, etc., the final respondents consisted only of Jewish and Christian religious leaders. Specifically, there were three Jewish, one Catholic, one Russian Orthodox, one Baptist (Protestant) and one Episcopal (Protestant) respondent. Because the four Christian denominations of the respondents correspond with different beliefs, these groups were kept separate in the analysis of questionnaire responses. Questionnaire responses are reported for each separate denomination, as well as in total.

The questionnaire [shown in Appendix, p.12] was sent to each consenting (consent determined via phone call) religious organization with only a cover letter stating the purpose of our research. No background concerning genetic testing or prenatal

screening was given. This tests the overall knowledge about these scientific issues in addition to opinions. The reason for this lack of background information lies in the fact that were a pregnant woman to go to her religious leader asking advice about prenatal screening, the leader would not, at that point, be given any background knowledge prior to what he/she already has. Thus, knowledge about the subject is vital to their decisions on these matters.

The survey questions, along with the reasoning behind them, the results, and conclusions to be drawn from them are listed below. Numbers in tables represent the number of respondents answering in that particular way to a question. If a respondent added additional comments to his/her response, these comments are listed below the overall percentage responses for each question.

1. With the latest medical advancements, the power to fight, overcome and prevent disease has increased greatly. Do you think this has put a strain on your community's religious beliefs?

This question was designed to ascertain the subject's overall feeling concerning medical research and how it relates to religion. Though an affirmative answer does not necessarily imply disapproval of medical research, it does indicate that the subject might be more leery of new techniques and their affect on the community.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Yes		1				1
No	3		1	1	1	6

Clearly, the responses indicate that these subjects are open to medical advances and do not feel that they strain religious beliefs, with the exception of one negative response.

2. Are you familiar with the concept of genetic counseling and prenatal screening?

The purpose of this question was to ascertain the background knowledge of the subject, as mentioned previously.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Yes	3	1		1	1	6
No			1			1

Once again the response is nearly unanimous, and indicates the background scientific knowledge of these subjects is fairly good. It should be noted, however, that the definition of familiarity could differ amongst subjects. For example, a subject might answer in the affirmative even if they have only heard the terms mentioned a couple of times on the news.

3. Are you aware that prenatal screening for familial diseases like breast cancer can be accomplished using genetic tools?

The purpose of this question is to follow up on the previous question with slightly more detail to determine more specifically the background knowledge of the subjects.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Yes	3	1		1		5
No			1			1
Other					1 "somewhat"	1

These results indicate a bit more disagreement between subjects. While the majority of subjects still consider themselves familiar with these scientific issues, the same addendum about the definition of familiarity as was mentioned in the previous question applies again here. The no respondent confirms his answer of no on the previous question with his answer here.

4. If it is determined that the fetus is a carrier for breast cancer, what would your recommendations be?

The purpose of this question is to determine what the subject's stance about actions taken concerning the fetus is, after the testing has already been completed. Though this question will not ascertain opinions about testing itself, it will provide insights as to beliefs about the rights of fetuses.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Abortion						0
Mother's Decision	1					1
Prof. Counseling for parents	2			1		3
Other		1	1		1	3

Other responses:

Catholic: "No direct attack against innocent human life at any stage"

Russian Orthodox: "Trust in God's holy will."

Baptist: "I would recommend (as a pastor) that the parents get complete medical information in understandable lay terminology, including accurate, current statistics about the percentage of "carriers" who actually get breast cancer. Are these numbers even available now?"

These responses are interesting in their variety. The sentiment against abortion is clear in the lack of any affirmative answers for abortion. The other responses are fairly well divided. The majority of respondents, with the possible exceptions of Catholic and Russian Orthodox, seem to stress obtaining the most knowledge as possible about the disease in this scenario.

5. In general, would you recommend couples in your community with a familial history of a disease such as breast cancer to opt for prenatal screening?

The purpose of this question is to delve into the main issue of the research, determining opinions about prenatal screening for breast cancer. While this question does not exclude prenatal screening for other diseases, an affirmative answer implies approval of prenatal screening for breast cancer because of the question's wording.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Yes	2					2
No	1	1			1	3
Not aware/Not Sure			1	1		2

The results of this question give no clear overall opinion concerning prenatal screening. While the affirmative answers were most numerous, they did not greatly outnumber the negatives and unsures. These results also show the most dramatic disparity amongst the Jewish leaders thus far, with two saying yes and one no. Overall, these responses indicate the general opinion amongst the subjects concerning prenatal screening for genetic markers is mixed.

6. In your opinion, prenatal screening for breast cancer... (Please check all that apply).

1. Causes unnecessary anxiety for parents.

2. Prepares and informs parents about their child's potential health issues.

3. Opposes your religious convictions.

The purpose of this question is to expand upon the previous question, now giving reasons for support or disapproval of prenatal screening for breast cancer.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
1		1	1		1	3
2	3			1	1	5
3						0

The results of this question indicate that none of the subjects feel that prenatal screening for breast cancer is directly against their religious beliefs, though a significant number feel it would be anxiety causing. Still, the majority of subjects feel the testing would be informative and allow for better preparation.

7. Does your religious community have an official position on Prenatal Screening? If yes, please explain.

The purpose of this question is to determine just what it asks, various official positions on prenatal screening. Clearly, an official position would strongly influence the position of the individual religious leader, as well as the members of that organization.

Results:

	Jewish	Catholic	Russian Orthodox	Episcopal	Baptist	**Total**
Yes	1	1	0	0	0	2
No	2	0	1	1	1	5

Jewish: "Affirmed by the committee on Bioethics of the Union of American Hebrew Congregation."

Catholic: "Screening is ok, though the knowledge gained must not result in abortion."

While the official positions given correlate with the previous question responses, one of the interesting points in the results to this question concerns the disparity between Jewish figures. This could indicate that some Jewish leaders are not aware of the official position, or that that position applies to only certain Jewish disciplines. Either way, the previous answer responses of the Jewish leaders correspond with the official position.

These questionnaire responses can clearly not be used to make any wide-sweeping generalizations due to the small subject size. Yet, some interesting impressions do come out of them. It is interesting to note the large amount of support for prenatal screening for breast cancer, particularly when compared with the absolute disapproval of it demonstrated by the scientific professionals. This difference could be due to a number

of reasons. For example, scientific professionals could be more informed about the nature of the correlation between *BRCA1* and *BRCA2* and breast cancer, and thus more doubtful of the benefits of prenatal screening for it. Along those lines, scientific professionals could also be more skeptical about the general public's knowledge about these issues, causing potential parents to make rash decisions or falsely feel there is no longer a threat of breast cancer with a negative result.

Another potential reason for the difference could come from the opinions about what might be the resulting action taken if a positive result is given. Scientific professionals might be more likely to assume that abortion will be the consequence, while religious leaders might assume the test is just for precaution and information. Overall, the results are surprising. We had predicted before receiving the replies that scientific professionals, generally, by profession, interested in obtaining the most information possible, would be in favor of the testing. On the other hand, we predicted that religious leaders would oppose the testing, preferring the mother rely on faith, as she should not act on results with abortion anyway. Yet, the responses were the reverse.

For future studies, it would be interesting to sample a larger number of doctors and religious figures, from more diverse backgrounds. In addition, it would be useful to obtain opinions from pregnant women, as well as women who have gone through breast cancer. Still, these responses give a beginning impression of the opinions concerning prenatal screening for breast cancer: a resounding, "No, it should not be done!" from the scientific professionals, and the belief that maybe it would provide useful information from the religious leaders.

5. Conclusion

The issues surrounding prenatal screening leave an ambiguous picture as to the benefits and negativities associated with the diagnosis of a fetus. A parent who chooses to undergo prenatal screening for her fetus gains information about the unborn child's well being, yet this information also becomes accessible to insurance companies, thus bringing up the issue of fetal confidentiality. Yet a parent who does not get this same screening for her fetus faces the prospect of guilt that could come should the future child develop the unscreened-for disease. Neither of these scenarios even addresses the problem of abortion. Each prospective parent faces the question, "under what conditions, if any, will I abort my fetus?" And who should be the regulator of all these issues? Can we trust each individual to make educated decisions for themselves, or do we need professionals or even the government to regulate these issues?

Certainly, prenatal screening should not be universally banned. The legality of abortions establishes the control of the woman over her own reproductive choices. These choices include the decision to abort a fetus as a result of prenatal diagnosis. After all, certain diseases currently screened for prenatally lead to terribly painful lives for the future child. A parent's right to decide that they do not want to force their child into such a life of pain should not be abolished. Likewise, a parent must be able to gauge his or her own parenting abilities. A woman who intends to return to work after the birth of their child and feels she is unable to undertake the care of a disabled or diseased child should not be forced into care she feels unfit to perform. In addition, for mary crippling genetic diseases, the child never reaches emotional or physical maturity enough to have children of their own. Thus the only means for the propagation of the disease is for carrier parents

to give birth to an afflicted child. "Selective abortion," as such abortion after prenatal diagnosis is termed, is perhaps the only, albeit grim, means to halt the progress of the disease.

However, all of these justifications apply to debilitating diseases with early onset. In addition, they can be prenatally diagnosed with fairly accurate certainty. These justifications for prenatal diagnosis do not apply to a disease such as breast cancer, which is a late onset disease. If a fetus is diagnosed as having a *BRCA1* or *BRCA2* mutation, they are not guaranteed to develop the disease (only an 85% correlation between mutation and breast cancer for women). If the future woman does develop breast cancer, it will not be until at least her twenties, though more probably not until much later in life. Finally, if the fetus is screened to be free of *BRCA1* or *BRCA2* mutations, these mutations only correlate to approximately 10% of breast cancer cases. Thus, even a negative screening does not ensure a clear bill of health for breast cancer.

Yet, deciding that breast cancer prenatal screening should not be performed is not the end of the issue. The question next arises, even if it should not ethically be performed, does that mean women should not have the right to receive prenatal screening for breast cancer? This question is not so clear of an issue, yet the practical decision is that prenatal screening should not be available even as an option. This decision does not comply with the overall scientific consensus of open information available to all, but when looked at from a realistic and practical viewpoint becomes the wisest decision. Clearly, the scientific professional surveys indicate that those involved with breast cancer and prenatal screening unanimously agree that prenatal diagnosis should not be made available for this particular situation.

Numerous reasons lead to this decision. One of the most prevalent reasons is the involvement of insurance companies with prenatal diagnosis. Prenatal diagnosis for a disease such as breast cancer is an incredibly expensive procedure, even with insurance companies involved, let alone when paid for privately. Yet, if the insurance companies become involved, as the laws stand right now, they have access to the genetic information. This information can then be the cause of repeated discrimination and bias against the future woman. Current debate is taking place concerning issues of confidentiality and insurance. If such debates progress in favor of confidentiality, the involvement of insurance in the decision against testing for breast cancer could require re-evaluation.

Still, even if the screening for breast cancer is performed, the benefit that can be drawn from it remains small. True, a fetus that has tested positive for a *BRCA1* or *BRCA2* mutation will be able to be screened for breast cancer as soon as possible once grown. Yet, only women with a strong family history of breast and ovarian cancer contain these mutations, thus the future woman will already be taking the necessary steps towards early detection of breast cancer. As with the issue of insurance, scientific advances can always give cause for re-evaluation of the benefits of this testing. Technologies such as gene therapy could one day lead to a means of prevention that could be taken as early as childhood for a fetus testing positive for a mutation. However, it is still to early in the development of these technologies for a future woman to benefit from them currently.

Another reason against the prenatal testing of breast cancer is an oft-mentioned word when genetic testing is discussed: eugenics, or creating a "perfect" race of human

beings. While the fear of eugenics with genetic testing is often greatly exaggerated, it is an ever-present concern considering the prevalence of bigotry and prejudice in our society. Granted, the formation of a race prejudiced against those with breast cancer seems highly unlikely, yet a line must be drawn somewhere. Ideally, screening prenatally for breast cancer would be used as a tool for gathering information on the fetus to be used towards prevention. Yet, it remains probable that certain parents might use such screening as a means to get as near to a "flawless" child as possible, via selective abortion.

Still, who should have the authority to draw this line? The distinction between early onset debilitating diseases and late onset diseases such as breast cancer is clear, and certainly the regulations involving prenatal screening should vary with the characteristics of each individual condition or disease. Yet the question still remains, who creates these regulations? In an ideal world, all people could come together to decide their own medical options. Yet the fact remains that realistically, not everyone has the time, access, or desire to make a truly informed decision about such issues. Additionally, not everyone has the confidence to make such decisions for themselves. When the issue of health is concerned, many people will trust their doctor's word rather than risk making the improper decision themselves.

Thus, the best means of handling regulation of prenatal screening seems to be to rely on a group of informed professionals from diverse backgrounds, including doctors, genetic counselors, bioethicists, OBGYNs, etc. Certainly, relying on a small group to make the decisions for the masses is not a perfect system, but it is the best solution for an imperfect world. These individuals can come together and weigh the pros and cons of

prenatal screening for each disease and condition individually, making guidelines based on this analysis. These guidelines should not be considered permanent, as continuing advances in science and ethical issues surrounding such things as insurance remain ever changing.

Yet, no amount of regulation can ever obliterate the emotional stress of a prospective parent. It is for this reason that prenatal screening remains a difficult and volatile issue. No decision about whether to allow or prohibit screening for a particular disease or condition is without debate. Nonetheless, decisions must be made via careful, open-minded analysis of the benefits and drawbacks of screening. While this objective analysis is possible from an emotional distance, it is more difficult when the decisions directly affect one's life. In the end, no amount of regulation or analysis can make decisions concerning breast cancer and prenatal screening any less emotional for those involved.

Humorous Reflection on Prenatal Screening

Soliloquy on Screening

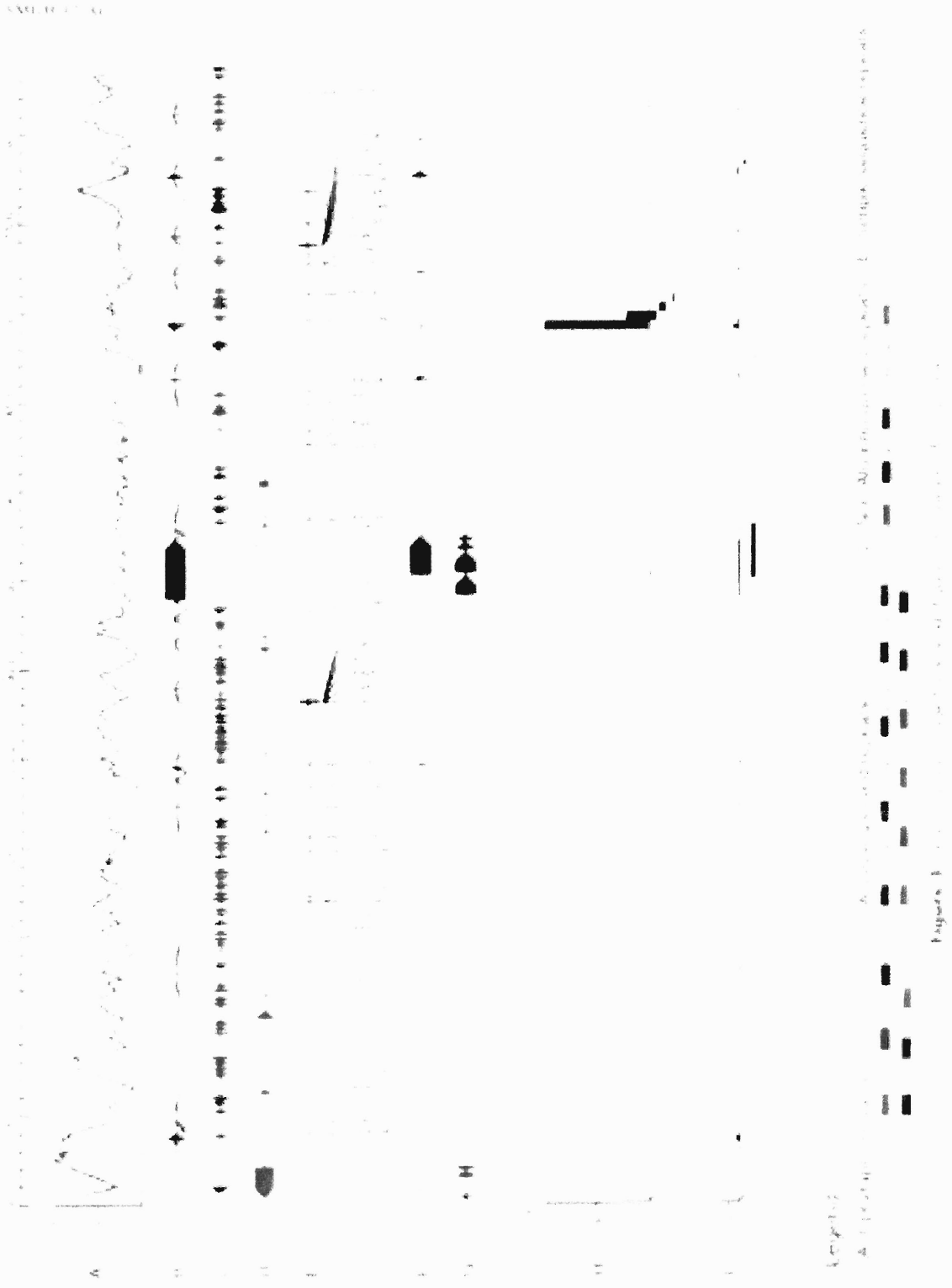
With apologies to William Shakespeare

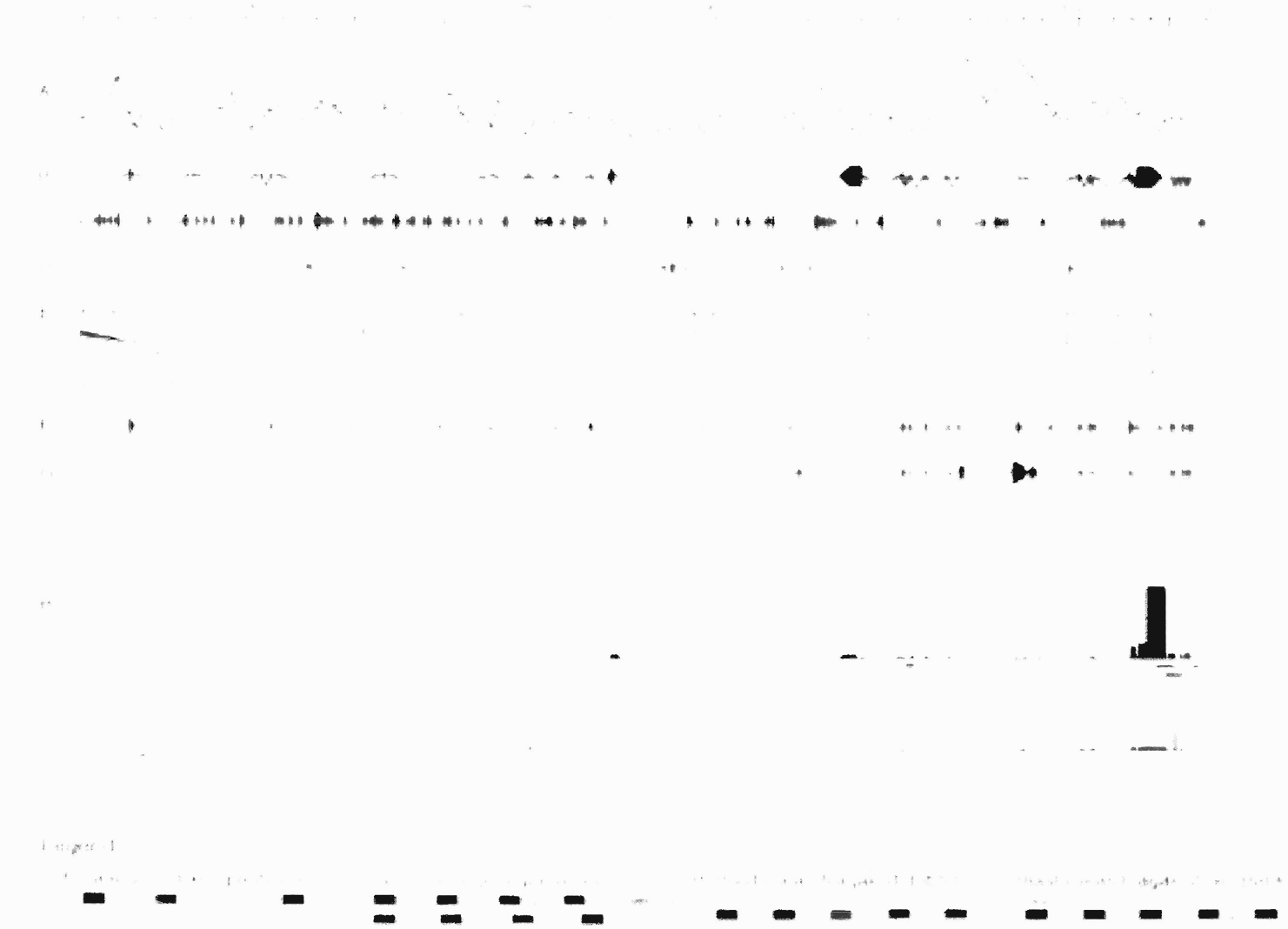
To screen or not to screen
That is the question!
Whether it be nobler to proceed
With a test for mutant genes
Only after the minds of all have been
prepared by proper education
Or to begin to test, anon, because
It is the thing to do.
One should not ask to test
Without informed consent
Alas, in time
Ignorance and confusion
In the minds of parents and screenees
May cause pain, suffering, stigmatization
To those innocents who ask not
For the genes they are heir to
And, may at some distant day
Defame those who screen.
For whether one should test a
pound of flesh
A single cell of a drop of blood
It is that person tested who must
Live with and adjust to –the label
"carrier"
And therein lies the rub!

Robert F. Murray, Associate Professor
Pediatrics and Medicine
Howard University
College of Medicine
Washington, D.C.

Appendix

1. Full *BRCA1* genome (Smith, 1032-1033)





2. *BRCA1* exons (Smith, 1036)

Table 4 Positions of Exons for Genes in the *BRCA1* Contig

Start	End	Exon	Start	End	Exon
[illegible]			[illegible]		
3114	3864	1a	95051	96083	9
3e2[illegible]	3998	1b	100302	100654	5
46[illegible]0	4776	2	100663	101539	6
[illegible]9[illegible]5	5606	3	101555	101442	7
5[illegible]2[illegible]	5[illegible]78	4	102774	102687	8
53758	53966	5	103386	103285	9
5[illegible]4[illegible]3	54e[illegible]2	6	[illegible]		
5[illegible]8[illegible]3	5[illegible]9[illegible]6	7	10e659	10[illegible]89	1
[illegible]1[illegible]1	[illegible]4[illegible]9	8	109927	[illegible]0[illegible]3	2
52[illegible]0	52866	9	[illegible]3620	[illegible]4[illegible]1	3
[illegible]8[illegible]2	57297	10	11[illegible]96	[illegible]885	4
[illegible]7[illegible]1	[illegible]7[illegible]4	11	12[illegible]1	[illegible]2[illegible]5	5
6[illegible]1[illegible]6	4e[illegible]2[illegible]	12	[illegible]2[illegible]4	[illegible]3[illegible]0	6
[illegible]2[illegible]6	62[illegible]4	13	[illegible]		
6[illegible]2[illegible]	6[illegible]4[illegible]0	14	13[illegible]76	[illegible]3[illegible]3	15
[illegible]8[illegible]4	6[illegible]9[illegible]8	15	[illegible]3[illegible]6	[illegible]4[illegible]2	16
[illegible]0[illegible]8	[illegible]1[illegible]2	[illegible]	[illegible]e8[illegible]6	[illegible]5[illegible]2	17
64[illegible]2	64[illegible]0	17	[illegible]e8[illegible]5	[illegible]7[illegible]4	18
65360	65[illegible]0	18	[illegible]3e22[illegible]	[illegible]6[illegible]2[illegible]	19
71[illegible]8	[illegible]168[illegible]	20			
[illegible]7620	[illegible]76[illegible]4	21			
[illegible]9[illegible]83	[illegible]9[illegible]6[illegible]4	22			
81[illegible]34	82[illegible]94	23			
8293e	83852	24			
84012	84486	24			

[illegible]

3. *BRCA1* repeats in gene sequence (Smith, 1035)

Table 3 Non *Alu* SSRs in the *BRCA1* Contig

Repeat type	Begin (nucleotide)	End (nucleotide)	Gene	Intron	Marker
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

4. Abbreviated *BRCA1* genome (Smith, 1037)

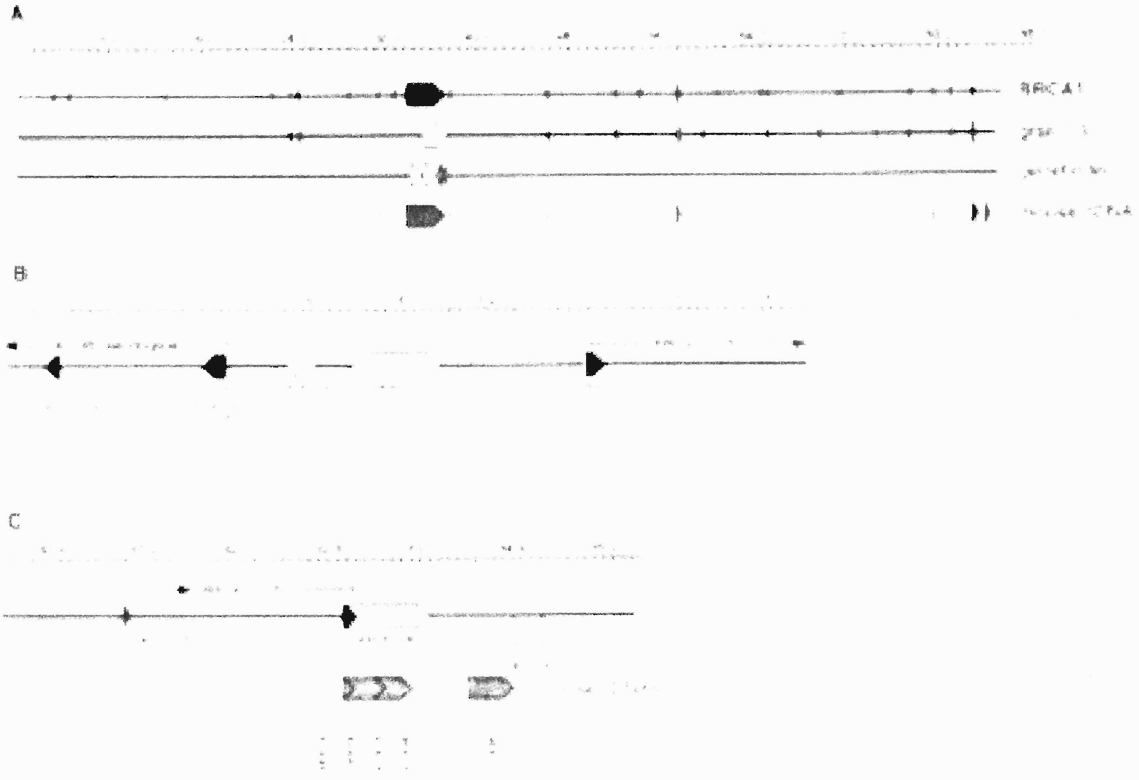


Figure 2

5. *BRCA1* and *BRCA2* mutations (Frank, 2420)

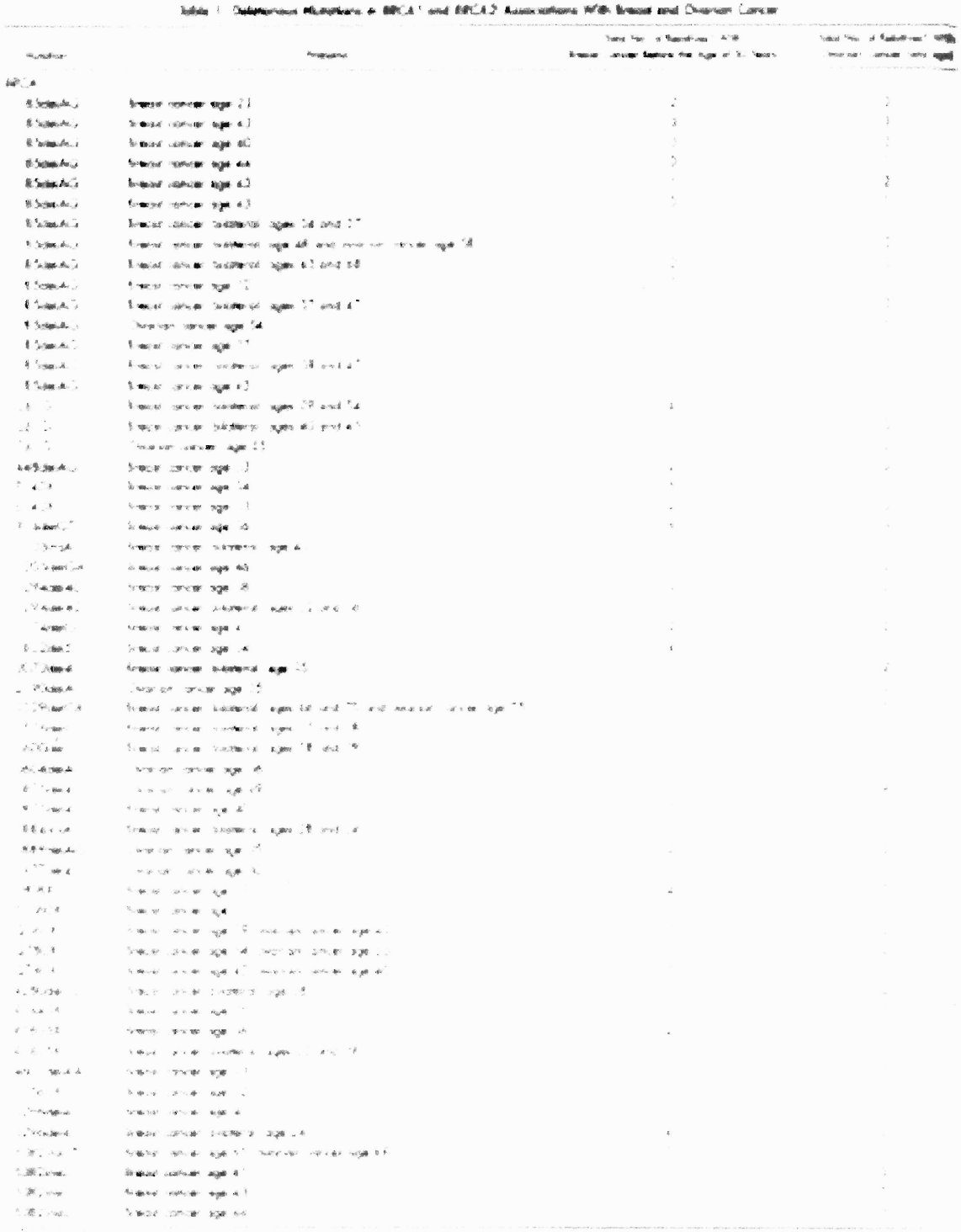
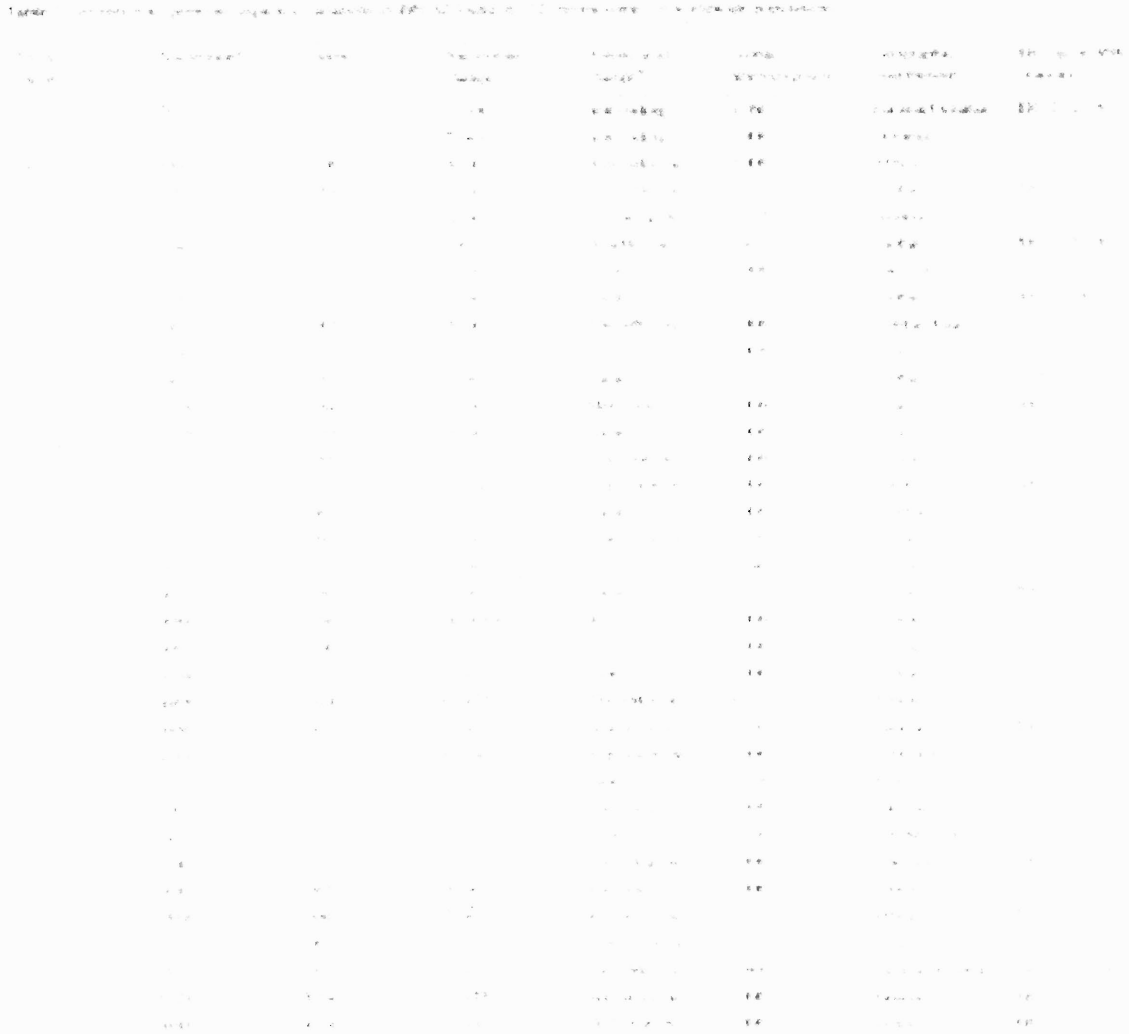


Table [illegible] Deleterious Mutations in BRCA1 and BRCA2 Associations With Breast and Ovarian Cancer, cont'd

6. Worldwide *BRCA2* mutations (Wagner, 414)



7. Scientific Professionals Questionnaire

1. In general, would you advise patients with a familial history of a disease such as breast cancer to be screened for any genes that have shown a relationship to the disease? Yes ☐ No ☐ Not Sure ☐

2. Do you feel that advanced knowledge of an increased risk for breast cancer would increase the patient's chances of successfully surviving breast cancer?
   Yes ☐ No ☐ Not Sure ☐

3. Have you ever known a patient of yours or a colleague's who received gene testing and then experienced negative effects such as failure to receive insurance coverage, etc.?
   Yes ☐ No ☐ Not Sure ☐

4. Do you find most of breast cancer patients of yours or your colleagues have a familial history of breast cancer?
   Yes ☐ No ☐ Not Sure ☐

5. From your experience, do you find breast cancer is more common in certain ethnic groups? If so, circle any ethnic groups you feel have a great predominance to breast cancer.

   White/Caucasian Jewish Asian African American
   Hispanic Native American Other _____

6. Would you recommend your patient to visit a genetic counselor if they were to receive gene testing?
   Yes ☐ No ☐ Not Sure ☐

7. Were prenatal screening for *BRCA1* mutations made available, would you advise a pregnant patient with a personal or familial history of breast cancer to obtain this prenatal screening for their fetus?
   Yes ☐ No ☐ Not Sure ☐

8. In your opinion, should prenatal screening for the *BRCA1* and *BRCA2* genes offered to all pregnant women?
   Yes ☐ No ☐ Not Sure ☐

Any Additional Comments: _____

_____

_____

_____

8. Religious Questionnaire

1. With the latest medical advancements, the power to fight, overcome and prevent disease has increased greatly. Do you think this has put a strain on your community's religious beliefs?
   ❑ Yes ❑ No

2. Are you familiar with the concept of genetic counseling and prenatal screening?
   ❑ Yes ❑ No

3. Are you aware that prenatal screening for familial diseases like breast cancer can be accomplished using genetic tools?
   ❑ Yes ❑ No

4. If it is determined that the fetus is a carrier for breast cancer, what would your recommendations be?
   ❑ Abortion ❑ Mother's decision
   ❑ Professional Counseling for parents
   Other _____
   _____

5. In general, would you recommend couples in your community with a familial history of a disease such as breast cancer to opt for prenatal screening?
   ❑ Yes ❑ No ❑ Not aware/Not sure

6. In your opinion, prenatal screening for breast cancer
   Please check all that apply.

❑ Causes unnecessary anxiety for parents.
❑ Prepares and informs parents about their child's potential health issues.
❑ Opposes your religious convictions.

7. Does your religious community have an official position on Prenatal Screening?
   ❑ No ❑ I don't know ❑ Yes

   If yes, please explain: _____
   _____
   _____

Any Additional Comments: _____
_____
_____
_____

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