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Ethical, cultural and religious aspects of hereditary cancer in Jewish communities

Review Article

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Summary

Acceptance and compliance with screening and genetic programs for genetic illness depends crucially on the compatibility and fit of their design with the social, cultural and religious concerns and mores of target communities. As a case in point, genetic screening programs that are currently in use within Jewish populations are considered on the background of ethical and religious concerns. Implications to design of programs for surveillance and screening of hereditary cancer syndromes are discussed.

I. Introduction

The recently defined ability to identify patients and families genetically at increased risk for developing specific cancers has important ramification for ethnic and religious communities composed of individuals with higher risk of carrying the offending alleles. The effects on a community's self-image, the potential for stigmatization of healthy disease carriers as unfit marriage prospects, and the impact on traditional patterns of behavior in the sphere of matchmaking and marriage are poorly understood but are of potentially great import to the design of screening and surveillance programs. The stresses will likely be accentuated as the genomic revolution makes personal genetic profiles commercially available in the near future. Regrettably, these issues have so far remained unexplored, yet they will affect acceptance of the scientific advances and the milieu in which medical treatment will be offered or provided. Self referral to screening, acceptance of early diagnosis and prevention programs, and maintaining communal and organizational support for population based genetic research is crucially dependent on exploring and defining these issues. What follows is an exploration of the impact of genetic knowledge in the sphere of hereditary cancer on the Jewish community, as a case in point. BRCA associated cancers represent an instructive example in-as-far as their impact on families and communities at risk. It is particularly important to bring together the scientific and social/ ethical issues and investigate how they interact and affect screening and surveillance for cancer. After all, a program rejected by the very community that it attempts to help will be of little practical use. The issues that concern us in this paper are especially those issues that would impact on the design and formulation of a surveillance and screening program that would be accepted and internalized by the communities that it would benefit. The hope is that the issues raised by this paper may serve to crystallize points of concern in other communities and groups at risk.

II. The Background: Genetics, genomics and the Jews

The "Jewish" genetic illnesses can be roughly divided or assigned into three groups. It is estimated that 1 in 4 Ashkenazi Jews carries one or another genetic mutation (Levin, 1999), In itself, this is not unusual in historically interbreeding populations; however, these facts interact poignantly and differently than they do, say in Iceland, with specific social, political and communal concerns.

First, the Jewish populations, especially those of Eastern European origin, carry genes for certain genetic diseases at a rate much higher than the general population. These include the recessive Canavan Disease, Gaucher Disease, Tay-Sachs, Familial Dysautonomia, Bloom's Syndrome, Mucolipidosis IV, Torsion Dystonia, Fanconi Anemia and Nieman-Pick Syndrome. These diseases affect primarily children, can be diagnosed in the carrier state in the unaffected heterozygotes (who carry the gene and can pass it on to their children) and can be prevented through early detection of carriers and, in certain cases, via prenatal testing. The strategies for detection of these conditions have been uniformally supported and well-accepted by the Jewish community and grass-roots screening programs have been designed and implemented.

The second group includes conditions equally common in Jews and non-Jews, such as Down's

Syndrome, Cystic Fibrosis, and those that represent common condition for which only probabilities of development can be currently predicted. As an example or the latter group, genetic make-up can predict whether an individual has a 5% or 40% risk of developing heart disease or diabetes. The interaction of poly-genic factors that determine such risk in populations is now popularly termed genomics.

The third group of illnesses includes those that increase the risk of serious conditions later in life but do not guarantee that illness will develop. Screening, surveillance and prevention strategies for this group are being refined but have already shown promise. BRCA associated cancers, while also affecting certain other ethnic groups, typify this kind of condition. The Jewish community is at a particular risk; it is estimated that some 2.5% of Jewish women of Ashkenazi (Eastern and Central European) origin carry one of the BRCA genes (Tonin et al, 1995; Moslehi et al, 2000), and one in ten Jewish women with breast cancers is a BRCA carrier while almost 40% of Jewish ovarian cancer victims carry this gene. (Tonin et al, 1996)

Women with the BRCA I and II mutations are thought to have a lifetime risk of developing breast cancer of up to 85%. The incidence risk rises after age 50, with BRCA II carriers lagging a few years behind in age as compared to BRCA I carriers. Those with BRCA I have an approximately 49% lifetime risk of developing ovarian cancer with risk beginning in lower 30s and rising thereafter. For BRCA II mutation the lifetime risk is approximately 20%, with incidence mostly after age 40 and rising sharply after age 50; incidence rates of both ovarian and breast cancer do vary in different reports (Thompson and Easton, 2001). Parity appears to increase breast cancer risk in mutation carriers, at least in some surveillance studies, inverse to the usual relation of parity and risk in the general population. Similarly use of oral contraceptive use increases risk in some reports among women at high risk but may decrease it in BRCA carriers (Narod et al, 1998; Warner, 2003).

As in general, hereditary cancers ultimately affect a large proportion of affected individuals and include familial breast, prostate and ovarian cancer and a type of colon cancer. These cancers tend to occur at earlier ages and strike multiple members of families. These devastating effects on individuals and families can be prevented or at least ameliorated through surveillance or prevention strategies. Unlike the previously discussed groups of disorders, these conditions present unique and specific challenges. This paper will specifically focus on this group of conditions.

Traditionally, the Jewish community has supported and encouraged premarital genetic testing for the conditions in the first group; however, it realized more than 20 years ago that the existing screening programs, though ultimately screening more than a million people (Kaback et al, 1992), did not address some important communal and religious concerns. Foremost among these were concern for privacy, confidentiality and the impact on the traditional courting and marriage patterns in the Orthodox communities. Rabbi M. Feinstein, the leading expert on religious law in the United States, laid the following guidelines in a 1974 responsum: "it is advisable for one preparing to be married, to have himself tested. It is also proper to publicize the fact…that such a test is available. It is clear that absolute secrecy must be maintained to prevent anyone form learning the results of such a test performed on another. The physician must not reveal these to anyone…these tests should be performed in private". Encouraged by these guidelines, a grass root organization was formed in 1974; by 1997, it has screened 80.000.00 individuals for Tay-Sachs, Canavan and Cystic fibrosis. Currently, anonymous screening for 10 conditions, most recently including familial dysautonomia is available. The program has been immensely successful essentially wiping out Tay-Sachs disease in the New York metropolitan area. The details of this program and its design have been well described [1]. One must, however, realize that this program was designed for recessive conditions, ones that can be easily identified, with risk well quantified and with the goal of preventing marriage between carriers. As designed, it is not suitable for BRCA related cancers or other variable penetrance inherited cancer syndromes that remain a significant challenge for organized Jewish communities. The very anonymity of this program makes it a poor vehicle for screening for complex conditions with possible but not certain onset of symptoms at a far-removed future date and for which a variety of interventions is available.

III. Approach to woman with a diagnosed BRCA mutation

The options for a woman with a diagnosed BRCA mutation include five potential courses of action:

1. Doing nothing. This course of action has in the past been advocated by some community activists, primarily for its purported benefits in allaying individual and group anxiety. However, as new options for early detection and potential curative intervention have developed, this option has become much less attractive.

2. Surveillance. To better define terms that are used in this field – screening refers to low or average risk population while surveillance is the term applied to high risk groups.

For ovarian cancer, we know little securely about screening in high risk populations because screening has not yet been proven to reduce mortality in the general population. Two randomized studies that utilized CA125 screening in combination with trans-vaginal ultrasound failed to show benefit in the general population (Rosenthal and Jacobs, 1998), In addition, there are no randomized studies in BRCA carriers. Unlike the situation in breast cancer screening, where an over aggressive screening strategy leads to more unnecessary biopsies, false positives in ovarian cancer screening result not only in a biopsy but often in a laparotomy (abdominal surgery) and significant morbidity. Observational studies in this population have led some to recommend trans-vaginal ultrasound with color flow Doppler and serum CA125

measurements once or twice yearly starting at age 30 (Fishman et al, 2003).

Clearly, an ability detect pre-malignant mammary changes in this population would be of great benefit and may enable avoidance of use or, at very least, wiser and better tailored use of prophylactic mastectomy and/ or oophorectomy or timely initiation of chemoprevention with tamoxifen. Although these modalities can markedly reduce the risk, it remains unacceptably high, reinforcing the need for more effective surveillance options. Many women refuse prophylactic surgery out of concern for side effects, because cancer development is not inevitable, curability of breast cancer when detected early, and their faith in development of new, less invasive options in the future. As an alternative to prophylactic mastectomy, surveillance can only be justified if it enables detection at a very early stage, such as T1a, b No (cure rate of 90%), or DCIS(99% survival rate). If the risk of dieing form breast cancer overall is 20%, that with surveillance should be no greater than 6%; 3% if tamoxifen is a part of the prevention regimen. On the other hand, most BRCA carriers develop cancer at a younger age, potentially affecting more years of life (Narod et al, 1998).

The current recommendations for surveillance in high risk population by the National Cancer Network consist of breast self examination (BSE) starting at age 18, clinical breast exam by a health care professional at age 25 and annual mammography after 25 years of age (Daly et al, 2002). It must be noted, however, that two large screening studies of women at average risk, the Shanghai and the St. Petersburg study that included BSE and CBE respectively, did not reveal an advantage in terms of breast cancer mortality (Thomas et al, 2002; Semiglazov et al, 1999). Thus breast exams may not be a very useful or effective component of surveillance approaches.

Prospective follow-up studies of women with BRCA mutations during surveillance reveal that cancers tend to be diagnosed at sizes greater than 1 cm or with lymph node positivity. Neither mammography nor ultrasound appear to fulfill the criteria for effectiveness set forth; earlier and better methods are needed (Kolb et al, 2002). Mammography usefulness is vitiated by the well-appreciated clinical fact that it is less sensitive in young women with denser breasts. Several studies suggest that BRCA related cancers are less mammographically detectable because of fewer diffuse calcifications, and less tissue distortion; they tend to have a fleshy border and less distortion effect on the surrounding tissue. In surveillance studies of BRCA carriers, cancers have tended to be detected in between screening visits. In other words, they may appear and grow rapidly and not be detectable at set intervals.

Other cancers that have been associated with BRCA mutations are prostate, pancreatic, melanoma and buccal cancers; no screening recommendations have been published for these diseases.

Magnetic Resonance Imaging (MRI) is a potentially useful modality for screening. MRI presents certain advantages as a screening tool for it does not use ionizing radiation and does not require breast compression. On the other hand, it has a lower sensitivity for DCIS, it is expensive, and biopsies under MRI are technically difficult. Some 5-10% of the women require sedation due to claustrophobia to be able to tolerate the MRI procedure. Nevertheless, the clinical advantages are real and there is great interest in using this modality for screening or surveillance (Kuhl et al, 2000). Two recent reports at the American Society of Clinical Oncology meeting in 2003, have presented encouraging data in this regard (Kuhle and Krieg, 2003).

An alternative strategy focuses on methods that aim to obtain breast tissue for a pathological evaluation. The goal is to detect pre-malignant change that may trigger prophylactic interventions or to detect very early cancers. Since the vast majority of BRCA related cancers arise in the ductal system of the breast, nipple aspiration(NA) and/or ductal lavalge(DL) appear to be reasonable approaches. In addition, periareolar fine needle aspiration (FNA) has been extensively studied (Fabian and Kimler, 2001; Dooley et al, 2001)

Methods being explored for application to NA and DL specimens are proteomics, hormone levels, detection of methylation abnormalities, proliferation indices and estrogen hormone expression. Hopefully, these will farther increase our ability to detect incipient malignant change or to detect such change early in women at high risk for breast cancer. We will then be able to intervene at the right time and with the right therapy.

3. Prophylactic tamoxifen

A case control study has demonstrated effectiveness of prophylactic Tamoxifen for breast cancer prevention in BRCA carriers (Narod et al, 2000); however, a subset analyses of the large prospective Breast Cancer Prevention Trial (NSABP-P2) failed to confirm these results in subset analyses of women with BRCA mutation (King et al, 2001). The evidence is likewise mixed in terms of the ability of oral contraceptives to prevent ovarian cancer risk in BRCA carriers (Modan et al, 2001) One study has raises an intriguing notion that tubal ligation may in some way reduce cancer risk among BRCA heterozygites (Narod et al, 2001).

4. Prophylactic mastectomy

Prophylactic mastectomy has long been considered an effective option for women at higher risk of breast cancer. It does appear to reduce risk substantially but does not remove all breast tissue and breast cancers have been reported to occur after prophylactic mastectomies (Hartmann et al, 1999, 2001).

5. Prophylactic oophorectomy

Prophylactic oophorectomy results in markedly decreased estrogen levels and is an equivalent of menopause. As such, it may be protective of breast cancer (Kauff et al, 2002; Rebbeck et al, 2002) while also completely obviating the risk of ovarian cancer (Rebbeck et al, 1999).

BRCA related breast and ovarian cancers represent a significant problem for the health and well-being of Jewish communities. While several effective options currently exist, no preferred option has emerged to

universal acceptance. Surveillance strategies appear to represent a potentially appealing alternative as they promise to decrease the incidence of breast and ovarian cancers while leaving the responsibility for prevention in the patients' hands, at the same time, avoiding morbidity of prophylactic surgery in the here and now. Unfortunately, there is no consensus as to how survaeillance should be marketed or promoted. As a community we could certainly benefit from more discussion and consideration of ethical and religious aspects of difficult decision making in the environment of lack of certainty and rapid scientific progress. Acceptance of surveillance and screening options will certainly be affected by their design and sensitivity to community concerns. The solution may well ultimately lie in development of better surveillance options and new pharmacological interventions to reduce risk without causing significant morbidity and design of programs organic to the mores and lifestyle patterns of Jewish communities.

IV. The impact of BRCA cancers on the Jewish communities

Traditionally, the Jewish community has enthusiastically welcomed and participated in mass screenings and genetic research. Unlike the African-American or American Indian community that essentially rejected community based screening strategies, Jews in major metropolitan centers in the United States provided organizational and financial support to TaySachs screening and other screening programs. Screening efforts have often been led by members of the community in academic and political positions. Levels of support for genetic testing remain high. A recent study found that the majority of Jewish women in Boston would agree to undergo BRCA testing, if offered. A minority of women (17%) in this study expressed concern or discomfort with Jews being singled out to offer BRCA testing. Most women, however, believed there were scientific reasons for testing Jews (71%), and only 5% of women felt that research that focused on Jews was bad for Jews as a group. Increased concern about genetic discrimination, however, was associated with women who were highly educated. Forty percent of women surveyed were interested in BRCA1/2 testing, 40% were not interested, and 20% were uncertain about whether they would obtain BRCA1/2 testing (Lehmann et al, 2002). In general, women from high- risk families who here already diagnosed with breast or ovarian cancer have a very high rate of agreement for BRCA testing of 87% (Meijers-Hejboer et al, 2003). These attitudes toward testing reflect acceptance in the communities at risk. As recently as 1999, The Women of Reform Judaism passed a resolution urging more genetic screening and counseling for recessive genetic disorders. (rj.org/wrj/reso/completehealth.html) More recently, however, with the description of BRCA associated cancers and the identification of familial non-polyposis colon cancer mutation at higher rates in persons of Eastern European Jewish origin, a backlash has began to develop in some segments of the Jewish community. One frequently hears the sentiment that the exemplary co-operation of the Jewish community with genetic researchers has exposed it to the danger of stigmatization as a community of "sick" individuals and that it, in some way and in some minds, may validate Nazi claim on racial purity (Nelson, 1998). Needless to say, that is not the outcome that individual Jews or community leaders would like to see. This concern has been expressed on both the local and national level (Lehrman, 1997). The United Synagogue, the body of Conservative Judaism in the USA, passed a resolution in 1999 stating that concern "about discrimination is currently dissuading members of the Jewish community and other racial/ ethnic groups from participating in potentially important research and diagnostic projects" and urged inclusion of comprehensive genetic counseling and informed consent into such programs (www.uscj.org/scripts/usjc/paper/Article.as?ArticleID+673).

V. Stigma and the Jews

The concept of stigma as a key-determinant of individual behavior has been gaining currency in healthcare delivery research and policy. Eric Gorfman has pioneered the use of this concept to understand how individual and communities respond to "culturally inacceptable" conditions, traits, attributes or behavior (Gorfman, 1963). Much investigation has confirmed the essential role of the concept of "spoilt identity" in interaction with membership of a despised or persecuted group to eventuate in compensatory mechanism and the use of irony, concealment or defiance by individuals in the affected group to minimize and lessen the psychological impact of stigmatization. It has become apparent that stigma functions not only on the level of an individual also in the settings of kinship, family and community. Numerous reports have demonstrated that concealment of a disability or disease is a widespread strategy that often leads to serious consequences for the affected individuals, their families and marital partners, and the population as a whole. Stigmas often influence social policy, prioritization of research resources and access to healthcare. Fears of contagion often lead to state sponsored denial of basic rights. "Discourses on stigma are deeply implicated in the fault lines of racism, sexism and other discrimination (www.stigmaconference.nih.gov/FinalDasPaper.htm)
Neither is such concern misplaced. It wasn't that long ago that a twice Nobel laureate suggested in an article in the UCLA Law Review that "…there should be tattoed on the forehead of every young person a symbol showing possession of the sickle cell gene or whatever similar gene…If this was done, two young people carrying the same seriously defective gene in single dose would recognize the situation at first sight and would refrain form falling in love with one another." (Pauling, 1968)

It would surprise no one that the Jewish community is particularly sensitive to issues of stigmatization, eugenics and genetic discrimination. After all, tattoing a symbol on a forehead is not that different than legislating a yellow star on one's garment; as recent subjects of Nazi eugenic pseudo-science, Jews remain deeply troubled by

population registries, ethnic demarcation policies, or population control strategies. Most of all, any suggestion that they, as a people, carry "defective" genes, will be viscerally resisted as an echo of Nazi propaganda. The fact that many other populations carry their own genetic illnesses does not carry currency with Anti-Semites. Although time and tolerance has began to heal wounds, they remain fairly close to the surface. As a community, Jews will be loath to embrace any screening strategy that partakes of or suggests above notions.

VI. Communal responses

Jewish communities have been slow to respond to the new ethical challenges in an organized and planned fashion; to a large degree this has been due to fragmentation along religious, ethnic and national lines. In the Unites States as well as in Israel, there are religious and non-religious Jews, Orthodox of various gradations and shadings, Reform and Conservatives; there are immigrants and natives, those originating from Europe, those originating from the Middle East and so on. However, it is possible to characterize the responses of the most insular and therefore most homogenous populations – the Chassidic and other ultra-orthodox groups. As the most rapidly growing sub-group, these communities in many ways define responses that influence and impact other religious and cultural Jewish populations; in addition, with average of 6.4 children per family they meet and tackle reproductive, genetic and related social issues to a greater extent than any other Jewish population. That is not to say that the description that follows is universally applicable; however, it is characteristic of an increasing and easily identifiable population that is concentrated in major metropolitan centers and serves as the most easily identifiable subject for genetic investigation and screening.

VII. Cultural and religious correlates of attitudes to genetic screening

Matters of genetics and family health are amply discussed in the traditional Jewish sources. As a religious duty, procreation assumes a duty to marry wisely and to avoid spouses with known genetic illness so as to improve and support the resulting progeny (Rosner, 1988). As a practical matter, matches in this insular community occur at a young age and are promoted and often arranged by parents; as a consequence, knowledge of a presence of a genetic defect becomes quickly and widely disseminated, jeopardizing future marriage prospects of all other family members. Put another way, if the information leaks out, the marriage prospects of all of the children of a large family are affected. This state of affairs leads to deplorable but easily understood reluctance to take advantage of genetic screening and, stubborn guarding of genetic information, even to what sometimes appears to be a detriment.

The Dor Yeshorim program has incorporated these concerns through designing a truly anonymous program. The results of genetic screening are literally unknown to any participant in the process; neither functionaries nor participants in screening. The program codes each participant with a number which is provided solely to the participant. When a marriage is contemplated, the two individuals call the program anonymously and provide their codes and these are matched. If both are carriers of the same disease, they are told that they are not "compatible'; no specific diagnostic information is provided. Thus neither side knows who is " at fault" and can go on to consider other partners in good conscience. This process is repeated with each potential partner. Dor Yesharim markets its services as most appropriate early in relationship, before significant emotional entanglement is likely to have developed. In addition, the program sponsors annual drives aimed at graduating classes of religious schools and seminaries; thus, building large databases of participant codes. In consequence, anxiety is minimized and privacy is assured.

Unfortunately, what works for a recessive and incurable conditions, does not work well for a disease with variable penetrance or expression or for one that, if identified, can be prevented or treated. Can one inform participants who carry a gene for the eminently treateable Gaucher disease that they are "not compatible" and leave it at that? How about a BRCA carrier? Is the screening program under an obligation to provide follow-up counseling and referral to treatment? How does on counsel an individual who finds himself repeatedly "incompatible" and whose responsibility is it? The ethical and moral issues are staggering. Do we break the code to inform carriers of cancer risk or do we lead them through the imperfect options for surveillance or prevention? What are the costs in terms of resultant anxiety, broken engagements, stigmatization of prospective marriage partners and the cost to the community? Clearly the Dor Yesharim model does not suffice for the much more complex situations of inherited pre-dispositions for cancer and other dominant diseases and a different approach must be identified and implemented in order to be accepted by the community. In fact, the newly reported association between Fanconi's anemia, a condition for which Dor Yesharim tests, and BRCA related cancers presents this program with an immediate ethical quandary (Venkitaraman, 2003).

Are there novel surveillance and screening strategies that can satisfy the community's concern about confidentiality, avoid stigmatization, and become widely accepted while providing the kind of robust reduction in disease incidence and impact that one expects from a first class screening methodology (Khoury et al, 2003)? The experience of the past three decades has shown us that screening or surveillance program will only be accepted by a community if they are sensitive to that community's cultural and religious/ethical concerns, supported by community's activists and opinion leaders, and enthusiastically carried into the community by its members. No program can accomplish this goal if it does not go through the time consuming but crucial process of consultation, consensus building and internal marketing. Some steps to begin this conversation have already been taken in the form of symposia, community events and

informal discussions. More discussion must surely follow to culminate in a creation of a community wide task force to formulate recommendations for design and implementation of community wide screening and surveillance approach. The process cannot be rushed but the results, should they follow, have a real potential to markedly improve health and well-being of countless individuals. It is a goal that we must all surely support.

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