BRCA Testing for All Ashkenazi Women: A Halakhic Inquiry

By: SHARON GALPER GROSSMAN

I recently underwent testing for the BRCA mutation. Thank G-d, neither I nor anyone in my family has ever had breast or ovarian cancer. So, why would a woman who has never been diagnosed with cancer and has no family history of it undergo BRCA testing? This article presents the halakhic issues around offering BRCA testing to all Ashkenazi women regardless of family history, and introduces views of several modern poskim, who have not, until now, rendered an opinion on this topic.

Inherited mutations in BRCA1 and BRCA2 predispose one to extremely high risks of breast and ovarian cancer. Carriers of a BRCA1 mutation face a lifetime breast cancer risk of approximately 70% and an ovarian cancer risk of 30% to 40%.[1] For carriers of the BRCA2 mutation the breast cancer risk is approximately 50%, while the ovarian cancer risk is approximately 20%.[2] One in 40 Ashkenazi Jews carries a BRCA mutation.[3] BRCA mutations account for 11% of all breast cancer[4] and 40% of

1 Moslehi, R., Chu, W., Karlan, B., et al. "BRCA1 and BRCA2 Mutation Analysis of 208 Ashkenazi Jewish Women with Ovarian Cancer," *American Journal of Human Genetics* vol. 66 (Cambridge: 2000) pp. 1259–1272.

2 Ibid.

3 Roa, B.B., Boyd, A.A., Volcik, K., Richards, C.S. "Ashkenazi Jewish Population Frequencies for Common Mutations in BRCA1 and BRCA2," *Nature Genetics* vol. 14(2) (New York: 1996) pp. 185–187.

4 King, M.C., Marks, J.H., Mandell, J.B.: "New York Breast Cancer Study Group Breast and Ovarian Cancer Risks due to Inherited Mutations in BRCA1 and BRCA2." *Science* vol. 302(5645) (Washington, DC: 2003) pp. 643–646.

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all ovarian cancer in the Jewish population.[5,6] Men who carry these mutations have a 5-25% risk of prostate cancer.[7,8,9,10,11]

Initially, only women already diagnosed with cancer underwent BRCA testing. However, testing prior to a cancer diagnosis enables women with positive results to pursue risk-reducing interventions including early-onset screening with breast MRI/mammogram, pelvic ultrasound and CA-125, chemoprevention, and risk-reducing surgeries such as mastectomy and oophorectomy. In BRCA carriers, MRI surveillance of the breast increases breast cancer detection rates and the number of pa-

5 Hirsh-Yechezkel, G., et al. "Population Attributes Affecting the Prevalence of BRCA Mutation Carriers in Epithelial Ovarian Cancer Cases in Israel," *Gynecologic Oncology* vol. 89(3). (Elsevier): 2003, pp. 494–498.

6 Risch, H.A., et al. "Prevalence and Penetrance of Germline BRCA1 and BRCA2 Mutations in a Population Series of Women with Ovarian Cancer," *American Journal of Human Genetics* vol. 68(3) (Cambridge: 2001) pp. 700–710.

7 Antoniou, A., Pharoah, P.D., Narod, S., et al. "Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies," *American Journal of Human Genetics* vol. 72(5) (Cambridge: 2003) pp. 1117–1130.

8 Antoniou, A.C., Pharoah, P.D., Narod, S. et al. "Breast and Ovarian Cancer Risks to Carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT Mutations: A Combined Analysis of 22 Population-Based Studies," *Journal of Medical Genetics* vol. 42(7) (London: 2005) pp. 602–603.

9 Chen, S., Parmigiani, G. "Meta-analysis of BRCA1 and BRCA2 Penetrance," *Journal of Clinical Oncology* vol. 25(11) (Alexandria: 2007) pp. 1329–1333.

10 Struewing, J.P., Hartge, P., Wacholder, S., et al. "The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 Among Ashkenazi Jews," *New England Journal of Medicine* vol. 336(20) (Waltham: 1997) pp. 1401–1408.

11 Finkelman, B.S., Rubinstein, W.S., Friedman, S., et al. "Breast and Ovarian Cancer Risk and Risk Reduction in Jewish BRCA1/2 Mutation Carriers," *Journal of Clinical Oncology* vol. 30(12) (Alexandria: 2012) pp.1321–1328.

tients diagnosed at an earlier stage of disease, and is cost effective[12,13,14,15,16] and supported in multiple guidelines.[17,18] However, the impact of surveillance with breast MRI on mortality is not clear. Surveillance for early detection of ovarian cancer in BRCA carriers has not proven beneficial. Some BRCA carriers may opt for chemoprevention, taking tamoxifen or oral contraceptive pills as a way to reduce the risk of developing breast and ovarian cancer. However, only limited data are available regarding the preventive benefit of tamoxifen in BRCA mutation carriers. And although studies show that oral contraceptive pills reduce risk of ovarian cancer, they may theoretically increase the risk of breast cancer.[19] Prophylactic mastectomy reduces the risk of developing breast cancer by 90% and might increase survival, especially when performed at a younger

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12 Grann, V.R., Jacobson, J.S., Thomason, D., et al. "Effect of Prevention Strategies on Survival and Quality-Adjusted Survival of Women with BRCA1/2 Mutations: An Updated Decision Analysis," *Journal of Clinical Oncology* vol. 20 (Alexandria: 2002) p. 2520.

13 Kurian, A.W., Sigal, B.M., Plevritis, S.K. "Survival Analysis of Cancer Risk Reduction Strategies for BRCA1/2 Mutation Carriers," *Journal of Clinical Oncology* vol. 28 (Alexandria: 2010) p. 222.

14 Kriege, M., Brekelmans, C.T., Boetes, C., et al. "Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition," *New England Journal of Medicine* vol. 351 (Waltham: 2004) p. 427.

15 Warner, E., Hill, K., Causer, P., et al. "Prospective Study of Breast Cancer Incidence in Women with a BRCA1 or BRCA2 Mutation under Surveillance With and Without Magnetic Resonance Imaging," *Journal of Clinical Oncology* vol. 29 (Alexandria: 2011) p. 1664.

16 Plevritis, S.K., Kurian, A.W., Sigal, B.M., et al. "Cost-Effectiveness of Screening BRCA1/2 Mutation Carriers with Breast Magnetic Resonance Imaging," *JAMA: The Journal of the American Medical Association* vol. 295 (Chicago: 2006) p. 2374.

17 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Genetic/Familial High-risk Assessment: Breast and Ovarian. Version 2.2019. www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf (Accessed on September 10, 2018).

18 Saslow, D., Boetes, C., Burke, W., et al. "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography," *CA: A Cancer Journal for Clinicians* vol. 57(2) (Hoboken: 2009).

19 Iodice, S., Barile, M., Rotmensz, N., et al. "Oral Contraceptive Use and Breast or Ovarian Cancer Risk in BRCA1/2 Carriers: A Meta-Analysis," *European Journal of Cancer* vol. 46 (Elsevier): 2010 p. 2275.

age.[20,21,22,23] Compared to BRCA carriers who opt for surveillance alone, BRCA carriers who undergo risk-reducing oophorectomy decrease their risk of death by 77%, in large part due to a reduction in the incidence of ovarian cancer, but also due to a significant reduction in the incidence of breast cancer (oophorectomy reduces the incidence of breast cancer by 48%) and of breast cancer mortality.[24] Prophylactic oophorectomy is most effective at reducing the risk of cancer if a woman undergoes surgery before she turns 40. Additionally, risk-reducing surgeries have been shown to be the most cost-effective measures. Using costs, life-years (LY), and quality-adjusted life-years (QALY) as outcomes, a study that compared preventive surgery, chemoprevention, MRI, and mammography showed that prophylactic surgeries were associated with the lowest overall cost and the longest survival in LYs, dominating all other strategies.[25] Most modern *poskim* permit and some even require prophylactic surgery in BRCA carriers.[26] Identifying BRCA carriers prior to cancer diagnosis in order to initiate early surveillance and risk-reducing surgery saves lives.

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20 Domchek, S.M., Friebel, T.M., Singer, C.F., et al. "Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers with Cancer Risk and Mortality," *JAMA: The Journal of the American Medical Association* vol. 304(9) (Chicago: 2010) pp. 967–975.

21 Kurian, A.W., Sigal, B.M., Plevritis, S.K. "Survival Analysis of Cancer Risk Reduction Strategies for BRCA1/2 Mutation Carriers," *Journal of Clinical Oncology* vol. 28(2) (Alexandria: 2010) pp. 222–231. doi:10.1200/JCO.2009.22.7991.

22 Carbine, N.E., Lostumbo, L., Wallace, J., Ko, H. "Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer," Cochrane Database System Review 2018;4:CD002748.

23 https://www.health.gov.il/hozer/mk03_2020.pdf.

24 Ibid.

25 Grann, V.R., Patel, P.R., Jacobson, J.S., et al. "Comparative Effectiveness of Screening and Prevention Strategies Among BRCA1/2 Affected Mutation Carriers," *Breast Cancer Research and Treatment* vol. 125. (Springer): 2011, pp. 837–847.

26 Grossman, S.G. "The Angelina Jolie Effect in Jewish Law: Prophylactic Mastectomy and Oophorectomy in BRCA Carriers," *Rambam Maimonides Medical Journal* vol. 6(4) Haifa: 2015. e0037. doi:10.5041/RMMJ.10222. Willig MI. Catching cancer before it catches you: Medical and Halakhic implications of BRCA gene testing (Audio Lecture) Yeshiva University Medical Ethics Forum. 2008. [Accessed September 1, 2015]. Macros and Adina Katz YUTorah Online. Rabbi Willig addresses this issue 99 minutes into the recording.

1. Who Should Undergo BRCA Testing Prior to Cancer Diagnosis?

Until very recently, no one would have offered BRCA testing to someone like me, a woman with no family history of cancer. Among cancer-free women, referral for genetic assessment has been limited to those with a family history of breast and ovarian cancer. In 2014, the U.S. Preventive Services Task Force (USPSTF) reiterated its recommendation against BRCA testing for healthy women in the absence of family history of cancer.[27] This recommendation was based on the lack of data on cancer risks among BRCA carriers in the general population, as opposed to mutation carriers in severely affected families.[28] Three recent studies argue for a reassessment of this policy as they confirm that limiting BRCA testing to women with a family history of breast or ovarian cancer fails to identify the vast majority of BRCA carriers in the Ashkenazi population. In a Canadian study of 2,000 unselected[29] Ashkenazi Jewish women,[30] an Israeli study of 8,105 unselected Ashkenazi Jewish men,[31] and a British study that randomly assigned 1,034 unselected Ashkenazi Jewish men and women either to testing based on family history or testing regardless of family history,[32] BRCA testing based on family history alone failed to

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27 Moyer, V.A. "Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women," U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* vol. 160(4) (Philadelphia: 2014) pp. 271–281.

28 "Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement," *Annals of Internal Medicine* vol. 143(5) (Philadelphia: 2005) pp. 355–361.

29 In this context, the term "unselected" refers to Jewish women or men who participated in a study because of their Ashkenazi ancestry, regardless of their family history.

30 Metcalfe, K.A., Poll, A., Royer, R., et al. "Screening for Founder Mutations in BRCA1 and BRCA2 in Unselected Jewish Women," *Journal of Clinical Oncology* vol. 28(3) (Alexandria: 2010) pp. 387–391.

31 Gabai-Kapara, E., Lahad, A., Kaufman, B., et al. "Population-Based Screening for Breast and Ovarian Cancer Risk Due to BRCA1 and BRCA2," *Proceedings of the National Academy of Sciences of the United States of America* vol. 111(39) (Washington, DC: 2014) pp. 14205–14210.

32 Manchanda, R., Loggenberg, K., Sanderson, S., et al. "Population Testing for Cancer Predisposing BRCA1/BRCA2 Mutations in the Ashkenazi-Jewish Community: A Randomized Controlled Trial," *Journal of the National Cancer Institute* vol. 107 (Oxford: 2015) doi:10.1093/jnci/dju379, p. 379.

identify more than half the carriers of the mutation.[33] These studies support population-based testing for all Ashkenazi women regardless of family history.

These three studies reveal that BRCA mutations in individuals screened from the general population are no less harmful than those of carriers who were referred for screening based on family history. In the Israeli study, BRCA carriers identified from the general population, regardless of family history of breast or ovarian cancer, had very high risks of developing cancer; by age 80, their risk for either breast or ovarian cancer was 83% for BRCA1 carriers and 76% for BRCA2 carriers. These risks were even higher in more recent birth cohorts.[34] In addition, these studies confirm that women who test positive act on the results. Investigators from Ontario reported uptake of screening and prevention options in women with a BRCA mutation identified through Jewish population genetic testing and confirmed that such women do in fact seek intervention.[35] Before genetic testing, none of these women had undergone breast MRI screening, or risk reducing surgery, or had taken a chemo-preventive drug. By one year after testing, 100% of them had undergone MRI. Within two years of receiving a positive genetic test result, 16% of the women had taken a chemo-preventive drug, 11.1% had undergone prophylactic mastectomy, and 90%, a prophylactic oophorectomy. These results show that women who undergo population-based BRCA testing and are found to be carriers of the mutation, process this information and take steps to reduce their risk of developing cancer.

Mary-Claire King (the scientist who discovered the BRCA mutation) has highlighted the results of the Israeli study to support the position that all women, and not just Ashkenazi Jews, should receive genetic testing for BRCA1 and BRCA2.[36] She based her recommendation on the finding that the cancer risks associated with a BRCA mutation are high even in the

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33 Ibid. pp. 1–19.

34 Gabai-Kapara, "Population Based Screening for Breast and Ovarian Cancer Risk Due to BRCA1 and BRCA2."

35 Metcalfe, K.A., Poll, A., Llacuachaqui, M., et al. "Patient Satisfaction and Cancer-Related Distress Among Unselected Jewish Women Undergoing Genetic Testing for BRCA1 and BRCA2," *Clinical Genetics* vol. 78. (Wiley Online Library): 2010, pp. 411–17.

36 King, M.C., Levy-Lahad, E., Lahad, A. "Population-Based Screening for BRCA1 and BRCA2," 2014 Lasker Award. *JAMA: The Journal of the American Medical* Association vol. 312(11) (Chicago: 2014) pp. 1091–1092.

absence of a family history of cancer.[37] Although population-based testing might not be feasible for the entire U.S. population, these studies support population-based testing for all Ashkenazi women in Israel as a rational approach to identifying BRCA carriers, especially since there are two mutations in BRCA1 and one mutation in BRCA2 that together are present in up to 2.5% of Ashkenazi Jewish women. One of the three mutations is present in 12% of unselected patients with breast cancer[38] and in 35% of unselected patients with ovarian cancer.[39] Given that these three mutations comprise the majority of the deleterious mutations in the Jewish population, genetic testing among healthy Ashkenazi Jews without a family history of breast or ovarian cancer can be focused and limited to these three founder mutations, making such testing more straightforward and cost-effective. To this end, Efrat Levy-Lahad, director of the Medical Genetics Institute at Shaare Zedek Medical Center, has argued vociferously for offering BRCA testing to all Ashkenazi women in Israel.

Why does screening based on family history alone fail to detect such a significant number of women who carry the BRCA mutation? There are many possible answers. Families in the Israeli study were small and included few females with mutations who had reached the ages of highest cancer risk.[40] Young women in these families would not have been tested in the absence of a general screening program. Incomplete family histories might be due to limited communication within the family, lack of awareness, inaccuracies in family history, family lost in the Holocaust, family migration, paternal transmission, male preponderance, few women inheriting the mutation, and chance. Furthermore, BRCA risk prediction models are imperfect and underestimate the probability of detecting mutations at low (≤10%) and intermediate (10%–40%) probability levels, while

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37 Gabai-Kapara, "Population Based Screening for Breast and Ovarian Cancer Risk Due to BRCA1 and BRCA2."

38 Warner, E., Foulkes, W., Goodwin, P., et al. "Prevalence and Penetrance of BRCA1 and BRCA2 Gene Mutations in Unselected Ashkenazi Jewish Women with Breast Cancer," *Journal of the National Cancer Institute* vol. 91 (Oxford: 1999) pp. 1241–1247.

39 Moslehi, "BRCA1 and BRCA2 Mutation Analysis of 208 Ashkenazi Jewish Women with Ovarian Cancer."

40 Gabai-Kapara. "Population Based Screening for Breast and Ovarian Cancer Risk Due to BRCA1 and BRCA2."

overestimating mutations at high-probability thresholds.[41,42,43] Population screening enables us to identify carriers regardless of their relatives' willingness to divulge information on cancer diagnosis or genetic test results. This is a factor that can limit testing in ultra-Orthodox communities, which tend to discourage disclosure.[44] Population-based testing also identifies carriers independent of physician referral, a potentially important consideration as a recent study demonstrated that only 19% of U.S. primary care physicians accurately assessed family history for BRCA testing.[45] In families of BRCA carriers in France, most eligible relatives are not referred for testing.[46] In the population-based trial in Israel, only 35% (29 of 82) of high-cancer-incidence families had received a referral for genetic counseling, despite its availability to all Israelis through the universal health care system. Although there is an equal risk of maternal and paternal transmission of BRCA1 and BRCA2, there is often a misperception about paternal transmission of breast cancer risk. In the Ontario study, the majority of families demonstrated paternal transmission of the BRCA mutation.[47] Many women and their physicians underestimate the significance of a family history of breast cancer on the father's side of the

41 Marroni, F., Aretini, P., D'Andrea, E., et al. "Evaluation of Widely Used Models for Predicting BRCA1 and BRCA2 Mutations," *Journal of Medical Genetics* vol. 41(4) (London: 2004) pp. 278–285.

42 Barcenas, C.H., Hosain, G.M., Arun, B., et al. "Assessing BRCA Carrier Probabilities in Extended Families," *Journal of Clinical Oncology* vol. 24(3) (Alexandria: 2006) pp. 354–360.

43 Antoniou, A.C., Hardy, R., Walker, L., et al. "Predicting the Likelihood of Carrying a BRCA1 or BRCA2 Mutation: Validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester Score," *Journal of Medical Genetics* vol. 107(1). (London: 2008), pp. 425–431. Downloaded from https://academic.oup.com/jnci/article-abstract/107/1/dju379/907914 by guest on 13 December 2018 11 of 11 | JNCI J Natl Cancer Inst, 2015, Vol. 107, No. 1 articling system using data from UK genetics clinics.

44 Freund, A., Cohen, M., Faisal, A. "The Doctor Is Just a Messenger: Beliefs of Ultra-Orthodox Jewish Women in Regard to Breast Cancer and Screening," *Journal of Religion and Health* vol. 53 (Springer): 2014, pp. 1075–1090.

45 Bellcross, C.A., et al. "Awareness and Utilization of BRCA1/2 Testing Among U.S. Primary Care Physicians," *American Journal of Preventive Medicine* vol. 40(1) (Elsevier): 2011, pp. 61–66.

46 Pujol, P., et al. "Lack of Referral for Genetic Counseling and Testing in BRCA1/2 and Lynch Syndromes: A Nationwide Study Based on 240,134 Consultations and 134,652 Genetic Tests," *Breast Cancer Research and Treatment* vol. 141(1) (Springer): 2013, pp. 135–144.

47 Metcalfe, "Screening for Founder Mutation in BRCA1 and BRCA2 in Unselected Jewish Women."

family. Only 34% of women diagnosed with breast cancer knew that a father can pass an abnormal breast cancer gene to his children[48] and less than half of all physicians (including oncologists) were aware that the gene can be passed through the father.[49,50] Population-based testing obviates the need to rely on family history, family disclosure, knowledge regarding paternal transmission, or physician referral.

2. What is the Ideal Age to Undergo BRCA Testing?

Proposed ages for BRCA testing include in utero, childhood, adolescence, prior to marriage, prior to conceiving the first child, age 25–30, upon completion of childbearing, and menopause. The ideal age for testing depends on how one intends to use the results. BRCA testing is performed to initiate early screening, prevent cancer with prophylactic surgery or chemoprevention, and to identify carriers who might undergo preimplantation gestational diagnosis (PGD) to prevent transmission of BRCA to potential offspring. To prevent cancer, predisposed individuals must be identified before cancer develops. BRCA-related cancers do not typically develop in childhood and rarely occur before the age of 25.[51] Thus, it is pointless to screen for the gene in utero or in children, decades before the disease manifests itself or screening is initiated. Conversely, testing after completion of childbearing or menopause is sub-optimal because the beneficial effects of risk-reducing surgery are attenuated after age 40, there is a risk of developing cancer between age 40 and menopause, and many years of potential intensive surveillance for early detection will have been lost. This leads to the conclusion that BRCA testing should ideally be performed between the ages of 25 and 30, ages at which screening is initiated and chemoprevention can be considered. Testing at age 25 allows women to plan their families with an eye to completing childbearing by age 40, to maximize the risk-reducing benefits of prophylactic oophorectomy.

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48 Miesfeldt, S., Cohn, W., Ropka, M., et al. "Knowledge about Breast Cancer Risk Factors and Hereditary Breast Cancer Among Early-Onset Breast Cancer Survivors," *Familial Cancer* vol. 1 (Springer): 2001, pp. 135–141.

49 Pichert, G., Dietrich, D., Moosmann, P., et al. "Swiss Primary Care Physicians' Knowledge, Attitudes and Perception Towards Genetic Testing for Hereditary Breast Cancer," *Familial Cancer* vol. 2 (Springer): 2003, pp. 153–158.

50 Mouchawar, J., Klein, C.E., Mullineaux, L. "Colorado Family Physicians' Knowledge of Hereditary Breast Cancer and Related Practice," *Journal of Cancer Education* vol. 16 (Springer): 2001, pp. 33–37.

51 Metcalfe, K.A. et al. "Is It Time to Offer BRCA1 and BRCA2 Testing to All Jewish Women?" *Current Oncology* [S.l.] vol. 22 (Milton, Ontario: 2015) n. 4, p. e233-e236, June 2015. ISSN 1718–7729.

Mary-Claire King advocates BRCA testing for every woman, "at about age 30, in the course of routine medical care."[52] Rabbi Yair Hoffman proposes that *kallah* teachers instruct all women to undergo BRCA testing at age 25 or upon the first birthday of their first child.[53] He recommends testing upon reaching either of these two milestones because by age 25 many women will be married and can thus avoid discrimination in dating, and testing near marriage or near a birth might increase anxiety, and because this is the age at which intensive medical surveillance should begin. Rabbi Moshe Tendler disagrees, arguing that one should not wait until age 25 to undergo testing.[54] He believes that if you are old enough to marry, you are old enough to know your genetic future.

Should one undergo BRCA testing prior to marriage? Genetic testing before marriage for Tay Sachs has become routine. Couples can use the results of Tay Sachs testing to avoid marriage between two carriers of the mutation or to perform PGD to select embryos that do not carry both copies of the mutation. At first glance, one might consider applying this premarital testing model to BRCA screening. However, the differences in inheritance and in the diseases associated with these mutations suggest that doing so might not make sense. The Tay Sachs mutation is recessive, it does not affect the carrier, and concern arises only when two carriers marry each other and give birth to a child who harbors both copies of the recessive gene. The penetrance of Tay Sachs is 100%; all offspring who inherit both copies of the mutation will develop the disease in infancy. Tay Sachs is universally fatal in childhood. In contrast, the BRCA mutation is autosomal dominant, putting carriers themselves at increased risk of developing BRCA-related cancers. However, not all carriers of the mutation will develop BRCA-related cancers and if a BRCA-related cancer does develop, it will not do so until adulthood. Furthermore, there are screening interventions for early detection, and effective prophylactic treatments to prevent the development of BRCA-related cancers. In addition, BRCA-related cancers are curable. For the above reasons, the current model of screening the entire Ashkenazi population for Tay Sachs prior to marriage might not be appropriate for screening for the BRCA mutation.

Couples who would like to pursue pre-implantation genetic diagnosis (PGD) to prevent the birth of a child with the BRCA mutation must do BRCA testing prior to having children. However, testing before marriage

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52 King, "Population Based Screening for BRCA1 and BRCA2."

53 http://www.5tjt.com/kallah-teachers-brca-testing-and-surgery/.

54 Personal communication, phone conversation, January 17, 2019, Israel.

can lead to discrimination in dating. In addition, because dating and marriage in the religious world can occur many years before surveillance for BRCA carriers is initiated, testing before marriage introduces anxiety over the mutation at a much earlier date than necessary. PGD is a challenging process financially, psychologically, and physically. PGD for all BRCA carriers might also be impractical. Modern *halakhic* decisors debate the use of PGD to select embryos that do not carry the mutation. Some permit but do not require PGD in this situation, as the parents would fulfill the *mitzvah* of having children even by bearing a child with the BRCA mutation.[55,56] There are others who believe that PGD should be reserved for the prevention of life-threatening diseases like Tay Sachs, and forbid this approach with regard to the birth of a child with the BRCA mutation. Machon Puah advocates dealing with each case individually. In families with known carriers of the BRCA mutation or a strong family history of breast (including in males) and ovarian cancer, testing for a BRCA mutation prior to marriage to prevent the birth of a BRCA carrier might be advisable. However, in light of the lower risk of harboring a BRCA mutation in the general Ashkenazi population, the reality that not all BRCA carriers will develop cancer, the fact that these cancers can be prevented and cured, and that such testing would further complicate *shiddukhim*/marriageability, offering population-based BRCA testing prior to marriage so that couples can choose to perform PGD on potential offspring is not recommended.

3. Arguments against Ashkenazi-Based Population Testing for BRCA Mutation

Population-based screening of the Ashkenazi population does not appear to be harmful. Arguments against such testing include uncertainty regarding the management of variants of unknown significance (VUS); the claims that BRCA testing causes anxiety, raises confidentiality issues, and fosters transmitter guilt; and cultural, work-related, and racial discrimination against BRCA carriers. In addition, critics contend that women without a family history of cancer are not interested in BRCA testing; that current models of genetic counseling cannot meet the increase in patient volume of population-based testing; and that the approach is not cost-effective. Finally, there is the misperception that there is no reason to undergo BRCA testing if one would not consider prophylactic surgery.

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55 Steinberg, Avraham. *Ha-Refuah K-Halacha* vol. 2 (Schlesinger: Jerusalem, 1988) pp. 116–7.

56 Machon Puah. "*Treatment for BRCA*." http://www.ouisrael.org/tidbits/detail/Machon-Puah-Treatment-for-BRCA, 27 Dec. 2011.

However, outcomes data from studies of population-based BRCA testing in Ashkenazi women invalidate these arguments.

3a. Uncertainty Regarding Management of Variants of Unknown Significance

Variants of unknown significance (VUS) are DNA alterations of unknown pathogenicity. A diagnosis of VUS can be particularly anxiety provoking as the appropriate management of these genetic alterations is unknown. To avoid this problem, proponents of population-based testing for BRCA do not recommend reporting VUS. Testing should focus only on those BRCA mutations with known deleterious effects. In the Ashkenazi population, limiting testing to known founder mutations makes sense because the founder mutations account for 90% of the mutations identified.[57,58,59,60,61] If VUS focused founder mutation testing is performed in an Ashkenazi population, VUS are rare, eliminating this concern.[62] In addition, the increased number of test results should lead to the classification of many additional variants.

3b. Population-Based Testing Increases Anxiety

One of the reasons that Rabbi Moshe Tendler previously objected to population-based BRCA testing was his concern that mass screening might

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57 King, "Population Based Screening for BRCA1 and BRCA2."

58 Kauff, N.D., Perez-Segura, P., Robson, M.E., et al. "Incidence of Non-Founder BRCA1 and BRCA2 Mutations in High Risk Ashkenazi Breast and Ovarian Cancer Families," *Journal of Medical Genetics* vol. 39 (London: 2002) pp. 611–614.

59 Phelan, C.M., Kwan, E., Jack, E., et al. "A Low Frequency of Non-Founder BRCA1 Mutations in Ashkenazi Jewish Breast-Ovarian Cancer Families," *Human Mutation* vol. 20. (Wiley Online Library): 2002, pp. 352–357.

60 Frank, T.S., Deffenbaugh, A.M., Reid, J.E., et al. "Clinical Characteristics of Individuals with Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals," *Journal of Clinical Oncology* vol. 20 (Alexandria: 2002) pp. 1480–1490.

61 Rosenthal, E., Moyes, K., Arnell, C., et al. "Incidence of BRCA1 and BRCA2 Non-Founder Mutations in Patients of Ashkenazi Jewish Ancestry," *Breast Cancer Research and Treatment* vol. 149 (Springer): 2015, pp. 223–227.

62 Spearman, A.D., Sweet, K., Zhou, X.P., McLennan, J., Couch, F.J., Toland, A.E. "Clinically Applicable Models to Characterize BRCA1 and BRCA2 Variants of Uncertain Significance," *Journal of Clinical Oncology* vol. 26 (Alexandria: 2008) pp. 5393–5400.

cause mental anguish.[63] However, compelling scientific data proves that population-based testing has a transient and minimal impact on anxiety.

Most women who present for clinical genetic testing already have significant family or personal histories of breast or ovarian cancer, and might expect a positive genetic test result. Studies show that among women referred for BRCA testing based on family history, the discovery of a BRCA mutation does not have a negative impact on their psychosocial functioning.[64,65,66,67] To the contrary, several studies report that the testing imparts important psychological benefits,[68,69,70,71] although a few noted increased distress.[72] However, women participating in a population-based genetic

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63 Mosenkis, Ari. "Genetic Screening for Breast Cancer Susceptibility: A Torah Perspective," *Journal of Halacha and Contemporary Society* vol. 34 (Fall) (New York: 1997) pp. 5–26.

64 Schwartz, M.D., Peshkin, B.N., Hughes, C., Main, D., Isaacs, C., Lerman, C. "Impact of BRCA1/BRCA2 Mutation Testing on Psychologic Distress in a Clinic-Based Sample," *Journal of Clinical Oncology* vol. 20 (Alexandria: 2002) pp. 514–20.

65 Watson, M., Foster, C., Eeles, R., et al., on behalf of the psychosocial study collaborators. "Psychosocial Impact of Breast/Ovarian (BRCA1/2) Cancer–Predictive Genetic Testing in a UK Multi-Centre Clinical Cohort," *British Journal of Cancer* vol. 91 (Springer): 2004, pp. 1787–94.

66 Smith, A.W., Dougall, A.L., Posluszny, D.M., Somers, T.J., Rubinstein, W.S., Baum, A. "Psychological Distress and Quality of Life Associated with Genetic Testing for Breast Cancer Risk," *Psycho-Oncology* vol. 17 (Wiley Online Library): 2008, pp. 767–73.

67 Meiser, B., Butow, P., Friedlander, M., et al. "Intention to Undergo Prophylactic Bilateral Mastectomy in Women with an Increased Risk of Developing Hereditary Breast Cancer," *Journal of Clinical Oncology* vol. 18 (Alexandria: 2000) pp. 2250–7.

68 Nelson, H.D., Huffman, L.H., Fu, R., et al., "Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Systematic Evidence Review for the U.S. Preventive Services Task Force," *Annals of Internal Medicine* vol. 143(5) (Philadelphia: 2005) pp. 362–379.

69 Sivell, S., Iredale, R., Gray, J., et al. "Cancer Genetic Risk Assessment for Individuals at Risk of Familial Breast Cancer," *Cochrane Database Syst Review* vol. 2. (Wiley): 2007, CD003721.

70 Schlich-Bakker, K.J., ten Kroode, H.F., Ausems, M.G. "A Literature Review of the Psychological Impact of Genetic Testing in Breast Cancer Patients," *Patient Education and Counseling* vol. 62(1) (Elsevier): 2006, pp. 13–20.

71 Meiser, B., Butow, P., Friedlander, M., et al. "Psychological Impact of Genetic Testing in Women from High-Risk Breast Cancer Families," *European Journal of Cancer* vol. 38(15) (Elsevier): 2002, pp. 2025–2031.

72 Smith, K.R., West, J.A., Croyle, R.T., et al. "Familial Context of Genetic Testing for Cancer Susceptibility: Moderating Effect of Siblings' Test Results on Psychological Distress One to Two Weeks after BRCA1 Mutation Testing," *Cancer*

testing program often have no family history of cancer, and a positive genetic test comes as a surprise. In 98% of such women, the results of BRCA testing are negative, therefore the testing does not increase anxiety.[73] The concern is that women who test positive will experience psychological distress. A Canadian study found that in unselected Jewish women who underwent population-based genetic testing, cancer-related distress was low before testing and increased significantly by one year after receipt of positive test results (no such effect was seen after a negative test result).[74] For women who received a positive test result, distress levels decreased significantly two years after testing[75] and returned to baseline **in women who then chose preventive surgery**. Women who tested positive and decided against prophylactic surgery had high baseline anxiety prior to testing and continued to experience high levels of distress two years after testing. Future studies will determine the long-term impact of population-based testing in women who test positive and decline prophylactic surgery. Nevertheless, 92% of women were satisfied with the testing process. This study was not randomized and did not compare distress levels among women who were tested due to family history with those who underwent population-based screening. In addition, none of the women received pretest genetic counselling. In a randomized trial comparing the psychological impact of BRCA testing in women who underwent population-based testing with those who were tested based on family history, there was no difference in anxiety levels, depression, or physical/mental well-being between these two populations.[76] These results suggest that women who undergo population-based testing and receive a positive result experience a transient increase in anxiety similar to that of women who are tested based on family history. In those who opt for prophylactic surgery, distress returns to baseline at two years. Collectively, these findings confirm that for the majority of women, population-based testing does not harm their quality of life or psychological well-being and ameliorate concerns regarding the impact of population-based testing on

Epidemiology Biomarkers and Prevention vol. 8(4, part 2) (Philadelphia: 1999) pp. 385–392.

73 Metcalfe, "Patient Satisfaction and Cancer-Related Distress."

74 Ibid.

75 Metcalfe K.A., Mian, N., Enmore, M., et al. "Long-Term Follow-Up of Jewish Women with a BRCA1 and BRCA2 Mutation Who Underwent Population Genetic Screening," *Breast Cancer Research and Treatment* vol. 133 (Springer): 2012, pp. 735–40.

76 Manchanda, "Population Testing for Cancer Predisposing BRCA1/BRCA2 Mutations in the Ashkenazi-Jewish Community," pp. 1–19.

distress and anxiety. Future studies will further our understanding of the psychological impact of population-based testing especially in women who test positive and decline prophylactic surgery. However, even if population-based BRCA testing increases anxiety, one could argue in its favor because such testing leads to *pikuaḥ nefesh*.[77]

3c. Population-Based Testing Causes Discrimination

A woman who learns that she carries a BRCA mutation might confront group stigmatization, as well as discrimination in health, life, and disability insurance; in the workplace; and in *shiddukhim*.

Concerns regarding employment and legal discrimination against BRCA carriers are well founded. Although in the United States the Genetic Information Non-Discrimination Act provides federal protection against genetic discrimination of unaffected carriers, it is neither comprehensive nor easily actionable.[78] The Act protects the health insurance and employment status of individuals with hereditary cancer risks,[79] but excludes military members and veterans, and does not protect against discrimination regarding the availability of life, disability, and long-term care insurance. Even if legal protections were comprehensive and airtight, perception alone might be enough to create social stigma.

The concern that testing positive for BRCA will affect *shiddukhim* is also legitimate. Population-based genetic testing prior to marriage introduces many ethical dilemmas. Specifically, is there an obligation to disclose the results to a potential suitor? If so, what is the appropriate time frame? Before the *shiddukh* is made? On the first date? As the relationship begins to intensify? After the engagement? After marriage? If one waits until after marriage, would failure to disclose this information invalidate the marriage from a *halakhic* perspective? In one situation, where a young

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77 In a forthcoming edition of *Ha-Refua K-Halacha,* which Rav Professor Avraham Steinberg shared with the author in a personal communication in January 2019, Rav Steinberg lists all of the potential arguments against population-based testing, including the possibility that testing will cause anxiety and psychological distress, and states, "When weighing the pros and cons of population-based testing, the pros ultimately outweigh the cons because *pikuaḥ nefesh*, the value of saving a life, overrides all other concerns."

78 Baruch, S., Hudson, K. "Civilian and Military Genetics: Nondiscrimination Policy in a Post-GINA World," *American Journal of Human Genetics* vol. 83. (Elsevier): 2008, pp. 435– 444.

79 Hudson, K.L., Holohan, M.K., Collins, F.S. "Keeping Pace with the Times: The Genetic Information Nondiscrimination Act of 2008," *New England Journal of Medicine* vol. 358 (Waltham: 2008) pp. 2661–2663.

girl whose mother died of breast cancer was in the early stages of dating, the boy's family insisted that she undergo BRCA testing before it would allow the relationship to progress, although his family promised to continue the relationship even if she tested positive. The woman did not want to know her BRCA status because she feared that a positive result would cause tremendous anxiety, leading her to spend the rest of her life waiting for cancer. Rav Chaim Kanievsky ruled that she was not required to undergo genetic testing.[80] Questions such as this might proliferate if BRCA testing were offered to all Ashkenazi women. However, delaying testing until after marriage (assuming marriage occurs before the age of 30) could obviate many of these dilemmas. In addition, population-based testing would require the development of an accompanying educational initiative to inform the public of the risks of carrying a BRCA mutation and of the existence of effective interventions to reduce the risk of developing cancer. Such a campaign could reduce stigmatization of and discrimination against BRCA carriers in *shiddukhim*.

3d. Population-Based Testing Violates Confidentiality

Population-based screening for BRCA raises numerous problems relating to confidentiality. If a woman tests positive, whom should she inform? Family members? Employers? It makes sense for her to tell her immediate family members, as they are at the most risk of carrying the gene and later developing breast cancer, and because she is likely to need their emotional support. However, Nishmat Avraham asked Rabbi Elyashiv whether a third party is obligated to disclose to close relatives the BRCA status of a woman who tested positive and refused to inform her immediate family, now at increased of developing cancer. Rabbi Elyashiv permitted the woman to maintain her confidentiality because the risk to other family members is not definite; even if a relative does carry the gene, it is not certain that he/she will develop cancer; and there is no completely preventative or curative treatment for cancer in those relatives who test positive. Therefore, he found no obligation to inform other family members.[81] It is possible that Rav Elyashiv might rule differently today, given the existence of effective potentially life-saving interventions to reduce the risk of developing breast and ovarian cancer. The argument for informing distant relatives is still less compelling. Although population-based testing raises confidentiality issues that must be addressed, these

[80] https://drive.google.com/file/d/0B6Vpm_W8m0xMbmtxY1VvZFBVQk0/view.

[81] *Nishmat Avraham* (*Even Ha-Ezer* and *Ḥoshen Mishpat*) vol. 3 (Brooklyn: Mesorah Publications, 2004) p. 302.

should not discourage population-based testing, which facilitates *pikuaḥ nefesh*.

3e. Population-Based Testing Causes Transmitter Guilt

Feelings of transmitter guilt can plague parents who have passed on a harmful mutation to their children.[82,83,84,85]

3f. Women Who Are BRCA Negative Might Mistakenly Believe that They Are Not at Risk of Breast or Ovarian Cancer

Some BRCA negative women might assume that they are at no risk of developing cancer. They might fail to recognize the possibility that other factors, including mutations in other susceptibility genes and in established environmental, reproductive, and lifestyle factors can increase the risk of breast and ovarian cancer. Without appropriate counseling, women might even avoid routine screening, since they incorrectly interpret negative test results to mean that they are at zero risk of breast or ovarian cancer. A public health campaign educating Israelis about the risk of breast and ovarian cancer in women who are BRCA negative must accompany any population-based testing.

3g. Women Do Not Want to Undergo BRCA Testing

Critics of population-based BRCA testing argue that women without a family history of breast or ovarian cancer are not interested in BRCA testing. However, Ashkenazi Jews' high participation levels in genetic screening programs for Tay Sachs disease and other genetic disorders refute this

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82 Mellon, S., Gauthier, J., Cichon, M., et al. "Knowledge, Attitudes, and Beliefs of Arab-American Women Regarding Inherited Cancer Risk," *Journal of Genetic Counseling* vol. 22. (Springer): 2013, pp. 268–276.

83 Weitzel, J.N., Blazer, R.K., Macdonald, D.J., et al. "Genetics, Genomics, and Cancer Risk Assessment: State of The Art and Future Directions in the Era of Personalized Medicine," *CA Cancer: A Cancer Journal for Clinicians* vol. 61. (Wiley Online Library): 2011, pp. 327–359.

84 Allford, A., Qureshi, N., Barwell, J., et al. "What Hinders Minority Ethnic Access to Cancer Genetics Services and What May Help?" *European Journal of Human Genetics* vol. 22 (Springer): 2014, pp. 866–874.

85 Strømsvik, N., Råheim, M., Oyen, N., et al. "Men in the Women's World of Hereditary Breast and Ovarian Cancer: A Systematic Review," *Familial Cancer* vol. 8 (Springer): 2009, pp. 221–229.

claim.[86] An early study of women at high risk of carrying a BRCA mutation reported that 79% would "definitely" choose to undergo BRCA testing and 16% would "probably" do so, attesting to a substantial interest in such testing.[87] Ashkenazi Jews' widespread participation in a variety of BRCA research studies provides further evidence of women's support for population-based testing.[88] In Ontario, enthusiasm for population-based testing among Ashkenazim was overwhelming, as 2,000 women enrolled in the study within two weeks of the publication of a single newspaper article calling for participants.[89] 93% of the participants reported satisfaction with population-based testing.[90] In Israel, participation in population-based testing among Ashkenazi women is high, averaging 67%.[91]

3h. Population-Based Testing Promotes Racial Discrimination

A pitfall of population-based testing of Ashkenazi women is that this approach excludes two other groups that are at an increased risk of carrying a BRCA mutation—Ashkenazi men and Sephardim. The frequency of the BRCA mutation in men is no different than it is in women, and sons are just as likely to inherit BRCA as daughters. In men, the mutation is associated with an increased risk of prostate and male breast cancer. National Comprehensive Cancer Network (NCCN) recommends screening for breast and prostate cancer in male carriers.[92] However, the risk of cancer in male BRCA carriers is substantially lower than the risk in female carriers. In addition, there are no proven risk-reducing surgical options for

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86 Kaback, M.M. "Population-Based Genetic Screening for Reproductive Counseling: The Tay-Sachs Disease Model," *European Journal of Pediatrics* vol. 159(suppl.3) (Springer): 2000, pp. S192–S195.

87 Struewing, J.P., Lerman, C., Kase, R.G., Giambarresi, T.R., Tucker, M.A. "Anticipated Uptake and Impact of Genetic Testing in Hereditary Breast and Ovarian Cancer Families," *Cancer Epidemiology Biomarkers and Prevention* vol. 4 (Philadelphia: 1995) pp. 169–173.

88 Rubinstein, W.S. "Hereditary Breast Cancer in Jews," *Familial Cancer* vol. 3 (Springer): 2004, pp. 249–257.

89 Metcalfe, "Screening for Founder Mutation in BRCA1 and BRCA2 in Unselected Jewish Women."

90 Metcalfe, K.A., et al. "Is it Time to Offer BRCA1 and BRCA2 Testing to All Jewish Women?" *Current Oncology* vol. 22, n.4 [S.l.] (Ontario: 2015) pp. e233–e236. ISSN 1718–7729.

91 Personal communication, Professor Efrat Levy-Lahad, January 23, 2019, Israel.

92 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Genetic/Familial High-risk Assessment: Breast and Ovarian. Version 2.2019. www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf (Accessed on September 10, 2018).

male carriers. In men, current recommendations for BRCA testing are limited to those with a strong family history of such cancers.[93]

Emphasis on Ashkenazi ancestry as a risk factor for BRCA mutations could lead to misperceptions and complacency in non-Ashkenazi Jews, and population-based BRCA testing could amplify differential access to care.[94,95] In addition, some argue that targeted screening for Tay-Sachs disease in Ashkenazim has detracted attention from diseases in non-Ashkenazi Jewish populations.[96] Although specific Sephardi populations such as 'pure' Sephardim who originated in Spain and Portugal and immigrated to Israel from Iraq, Yemen, Iran, and Afghanistan appear to be at increased risk of carrying a BRCA mutation,[97] current scientific evidence does not currently support BRCA testing for the entire Sephardi population.[98] More comprehensive research is needed before a recommendation can be made regarding testing the entire Sephardi population. Ashkenazi-based population testing for the BRCA mutation should include genetic counseling for non-Ashkenazi populations.

3i. It Is Impossible to Offer Genetic Counseling to the Entire Ashkenazi Population

Traditional cancer genetic counseling, including both pre-test and post-test counseling, is impractical on a large scale. Offering intensive genetic counseling to 100 women who have no family history, with the expectation that only two will be positive, would be an inefficient allocation of limited genetic counseling resources. Population-wide BRCA screening

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93 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Genetic/Familial High-risk Assessment: Breast and Ovarian. Version 2.2019. www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf (Accessed on September 10, 2018).

94 Cancer screening: United States, 2010 MMWR Morb Mortal Wkly Rep 61: 41–45, 2012 Centers for Disease Control and Prevention (CDC) Medline.

95 Liao, Y., Bang, D., Cosgrove, S., et al. "Surveillance of Health Status in Minority Communities: Racial and Ethnic Approaches to Community Health Across the U.S." (REACH U.S.) Risk Factor Survey, United States, 2009 *MMWR Surveillance Summaries* vol. 60 (Atlanta: 2011) pp. 1– 44.

96 Brandt-Rauf, S.I., Raveis, V.H., Drummond, N.F., Conte, J.A., Rothman, S.M. "Ashkenazi Jews and Breast Cancer: The Consequences of Linking Ethnic Identity to Genetic Disease," *American Journal of Public Health* vol. 96 (Washington: 2006) pp. 1979–1988.

97 Sagi, M., Eilat, A., Ben Avi, L., Goldberg, Y., Bercovich, D., Hamburger, T., Peretz, T., Lerer, I. "Two BRCA1/2 Founder Mutations in Jews of Sephardic Origin," *Familial Cancer* vol. 10(1) (Springer): 2011, pp. 59–63.

98 Personal communication, Professor Efrat Levy-Lahad, January 23, 2019, Israel.

would generate a demand that would overwhelm the capacity of current genetic counseling practices.

All three studies of Ashkenazi-based testing offered a streamlined approach to genetic testing, limiting pre-test counseling to written educational materials and reserving post-test genetic counseling for women who tested positive or had a strong family history of breast or ovarian cancer. Women reported high levels of satisfaction with this approach.[99] Selective genetic counseling did not reduce the increase in risk-reducing interventions after a BRCA diagnosis. One year after testing, 100% of women had undergone MRI screening examination. Within two years of receiving a positive genetic test result, 11.1% had undergone prophylactic mastectomy and 90%, prophylactic oophorectomy.[100] In the Israeli study, although the pretest written materials included the phone number of a genetic counselor, only three out of 1,800 women contacted her.[101] These results confirm that Ashkenazi-based population testing can be successfully implemented using a more tailored approach to genetic counseling. To this end, future studies of population-based testing including the Screen Project in Canada, the BFOR trial in the United States, and the current proposal for population-based testing submitted to the Israel Ministry of Health, all offer selective genetic counseling.[102,103]

3j. Population-Based Screening Is Not Cost-Effective

Outcome data from two studies, including the randomized U.K. trial, strongly refute the claim that BRCA testing is not cost-effective. They show that population-based BRCA is highly cost-effective across a broad range of parameters, confirming that it would be cost-effective in the Israeli health-care system.[104,105]

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99 Metcalfe, "Patient Satisfaction and Cancer-Related Distress Among Unselected Jewish Women."

100 Ibid.

101 Personal communication, Professor Efrat Levy-Lahad, January 23, 2019, Israel.

102 Akbari, M.R., Gojska, N., Narod, S.A. "Coming of Age in Canada: A Study of Population-Based Genetic Testing for Breast and Ovarian Cancer," *Current Oncology* vol. 24(5) [S.l.] (Ontario: 2017) pp. 282-283.

103 Personal communication, Professor Efrat Levy-Lahad, January 23, 2019, Israel.

104 Rubinstein, W.S., Jiang, H., Dellefave, L., Rademaker, A.W. "Cost-Effectiveness of Population-Based BRCA1/2 Testing and Ovarian Cancer Prevention for Ashkenazi Jews: A Call for Dialogue," *Genetics in Medicine* vol. 11(9) (Springer): 2009, pp. 629–639.

105 Manchanda, R., Legood, R., Burnell, M., McGuire, A., et al. "Cost Effectiveness of Population Screening for BRCA; Mutations in Ashkenazi-Jewish Women

3k. There Is No Reason to Undergo BRCA Testing if One Will Not Pursue Prophylactic Surgery

A growing number of *poskim* believe that prophylactic surgery is *halakhically* permitted. Some even posit that a BRCA carrier is required to undergo prophylactic surgery.[106] Even if a person with a positive result does not pursue prophylactic surgery, population-based screening is still important because it will enable women who test positive to initiate intensive surveillance to facilitate early diagnosis of breast and ovarian cancer or chemoprevention.

4. How Does *Halakhah* View BRCA Testing?

Answering this question is critical to any public health initiative in Israel, as a large percentage of the population would not undergo BRCA testing without rabbinic endorsement. While one can debate the appropriateness of seeking a rabbi's guidance before undergoing a medical intervention, the recent measles epidemic illustrates the power of modern *poskim* to facilitate disease prevention: The joint statement of leading *charedi* rabbis exhorting the Israeli population to get vaccinated against measles, and referring to those who refuse as *shofekh damim,* murderers, had a profound impact on vaccine increase in the *charedi* community.[107]

Given the scientific evidence supporting BRCA testing for all Ashkenazi women, is there a *halakhic* obligation for such women to undergo BRCA testing? Am I, an Ashkenazi woman without family history of breast or ovarian cancer, obligated to undergo BRCA testing?

The *halakhic* obligation to prevent disease is based on several Biblical sources including "*ve-nishmartem me'od le-nafshoteikhem*—And you shall protect your souls exceedingly," (*Devarim* 4:15) and "*rak hishamer le-kha u-shemor nafshekha*—only guard yourself and protect your soul" (*Devarim* 4:9). Rambam *Hilkhot De'ot* explains that we are obligated to prevent disease because a healthy body is a necessary precondition to performing the commandments and serving G-d.[108] In addition, in his *Hilkhot Rotze'aḥ*

Compared to Family-History Based Testing," *Journal of the National Cancer Institute* vol. 107(1) (Oxford: 2015) pp. 1-14.

106 Grossman, S.G., "The Angelina Jolie Effect in Jewish Law: Prophylactic Mastectomy and Oophorectomy in BRCA Carriers," *Rambam Maimonides Medical Journal*, vol. 6(4) (Haifa: 2015) p. e0037. https://www.yutorah.org/lectures/lecture.cfm/730940/rabbi-mordechai-i-willig/catching-cancer-before-it-catches-you-medical-and-halachic-implications-of-brca-gene-testing/. Rabbi Willig addresses this issue 99 minutes into the recording.

107 http://rotter.net/forum/scoops1/511727.shtml.

108 Maimonides (1138–1204), *De'ot* 4:2.

11:4, Rambam lists a series of medical interventions to prevent disease, including eating only when hungry, drinking only when thirsty, and going to the bathroom when necessary. This is not an exclusive or exhaustive list but a broad one with general applicability and fluidity. Presumably, as medical knowledge evolves, the list of interventions that we are required to perform to prevent disease might expand to include a *halakhic* obligation for all Ashkenazi women to undergo BRCA testing as it helps identify women who can take steps to reduce their risk of cancer and chances of dying.

4a. Extrapolating from Tay Sachs

There are, however, two *halakhic* principles that could potentially invalidate any *halakhic* obligation to undergo genetic testing in general and BRCA testing in particular. The first principle is based on *Devarim* 18:13, "You shall be perfect in the eyes of G-d," about which Rashi writes, "and do not search after the future," which has been interpreted as a prohibition on visiting fortunetellers and seeking the future. Does genetic testing that determines our genetic future qualify as a form of fortune telling?

The second *halakhic* principle at issue is that of *"shomer peta'im, Hashem,"* or "G-d watches over the simple."[109] The implication of this verse is that one should not investigate the dangers around him or within him but ought instead to leave his fate in the hands of G-d. This verse appears throughout the Talmud as a justification for engaging in risky behavior. Why is a woman allowed to become pregnant even though doing so can be dangerous to her? Why is a woman permitted to engage in intercourse after bloodletting or on the ninetieth day of pregnancy (intercourse under these circumstances was considered dangerous)? The answer in each of these cases is that they are permitted because "G-d watches over the simple." This principle also permits us to drive cars even though there is danger of an accident and to cross streets even though there is a risk of being hit by a car. Does *shomer peta'im Hashem* override the obligation to undergo BRCA testing? Should we forgo testing and rely on G-d to prevent breast and ovarian cancer? We should not, because multiple sources suggest that the verse does not apply when the danger is easy to detect, and that instead, there is an obligation to investigate.[110]

In the early days of Tay Sachs testing, Rav Moshe Feinstein was asked about the permissibility of Tay Sachs testing. In his *teshuva,* he weighs the competing values of *ve-nishmartem*, the obligation to prevent disease, and

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109 *Psalms* 116:6.

110 *Proverbs* 14:115, *Sanhedrin* 110b, *Niddah* 31a, *Avodah Zarah* 30b, *Yevamot* 72a, *Shabbat* 129b; *Tosefta, Niddah* 2:4.

shomer peta'im, the apparent obligation to rely on G-d for a cure and the prohibition against searching after the future, including the possibility that genetic testing constitutes a form of seeking our genetic future.[111] He concludes that the prohibition against searching after the future and the principle of *shomer peta'im Hashem* do not apply to Tay Sachs testing since such testing is simple to do and refusal to test is equivalent to "closing our eyes to what one can see." Therefore, he advocates genetic testing for Tay Sachs. Can one derive an obligation for Ashkenazi women to undergo BRCA testing from Rav Moshe's mandate for Tay Sachs testing? As I noted earlier, there are significant differences in the transmission, penetrance, and prognosis of the two genetic diseases, making extrapolation from Tay Sachs testing to BRCA testing problematic. Because BRCA-related cancers occur in adulthood and not infancy, do not develop in all carriers, and are potentially preventable and curable, perhaps there is less urgency to BRCA testing. Rabbi Moshe Tendler, Rav Moshe Feinstein's son-in-law, speculates however that had his father-in-law been asked specifically about the obligation of all Ashkenazi women to undergo BRCA testing, he would have unequivocally endorsed BRCA testing for all women with the same enthusiasm that he endorsed Tay Sachs testing.[112] Nonetheless, Rabbi Moshe Tendler emphasizes that since no one ever posed the question regarding BRCA testing directly to Rav Moshe Feinstein, that conclusion is theoretical; it is impossible to discern what Rav Moshe Feinstein's true position on BRCA testing would have been.

4b. How Do Modern *Poskim* View Population-Based BRCA Testing of Ashkenazi Women?

In 2000, even before medical data confirmed that risk-reducing surgery or surveillance had life-saving potential, Rabbi J.D. Bleich wrote, "Genetic testing, including testing for BRCA1 and BRCA2, should be regarded as halakhically mandated in circumstances in which medical science believes that the results are likely to affect treatment in a manner that will enhance longevity anticipation or well-being. Certainly, a person identified as being at risk for a specific disease is obligated to pursue all available measures in order to ward off the disease or to diagnose its presence while the disease is yet in an incipient stage and still amenable to cure."[113] He bases this "halakhic mandate" to undergo BRCA testing on the verse "*Ve-nishmartem me'od le-nafshoteikhem,* And you shall be exceedingly watchful of your

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111 *Iggerot Moshe, Even He-Ezer* IV, no. 10.

112 Personal communication, Rabbi Moshe Tendler, January 16, 2019, Israel.

113 Bleich, J.D. "Genetic Screening: Survey of Recent *Halachic* Periodical Literature," *Tradition* vol. 34 (Brooklyn: 2000) pp. 63–87.

lives" (*Devarim* 4:15) and concludes that BRCA testing should be included in Rambam's *Hilkhot Rotze'aḥ* list of interventions to pursue to maintain health, because a doctor who knows that he is examining a BRCA carrier might examine her breasts a little more carefully to look for a lump. In light of recent scientific data that confirm that BRCA testing saves lives and that the benefits of testing are far greater than a more thorough breast exam, if one asked him today about the obligation of all Ashkenazi women to undergo BRCA testing, Rabbi Bleich would in all likelihood offer an even stronger endorsement. In a 2008 Yeshiva University Conference on Medical Ethics, Rabbi Mordechai Willig also supported BRCA testing in all Ashkenazi women.[114]

Until recently, few other *poskim* had weighed in on the obligation of Ashkenazi women to undergo population-based testing for the BRCA mutation. However, because of their lengthy discussions with this author, several modern *poskim* have begun to consider this issue. In the forthcoming edition of *Ha-Refua K-Halakha*, Rav Professor Avraham Steinberg writes that there is a *halakhic* obligation for women with a family of history of breast and ovarian cancer to undergo BRCA testing and that testing in such women is strongly recommended. Rav Steinberg strongly recommends that all women with a strong family history of breast or ovarian cancer undergo BRCA testing before their first pregnancy. This will give those who test positive the opportunity to consider PGD in order to avoid the birth of a child who will carry the mutation. He also recommends BRCA testing for all Ashkenazi women at age 25-30 when surveillance would begin, a recommendation that would avoid discrimination in *shiddukhim* as many women would already be married at this age.[115] He writes that because genetic testing is straightforward and without risk, and because those who test positive face a 70% chance of being diagnosed with cancer during the course of their lives, BRCA testing falls under the commandment, "*ve-nishmartem me'od l-nafshotekhem.*" Rav Professor Steinberg states that BRCA testing does not violate the prohibition against searching after the future because the danger of carrying a BRCA mutation is known and common. He writes that ultimately *pikuaḥ nefesh,* the opportunity to

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114 http://curiousjew.blogspot.com/2007/01/yu-medical-ethics-genetic-screening.html; https://www.yutorah.org/lectures/lecture.cfm/730940/rabbi-mordechai-i-willig/catching-cancer-before-it-catches-you-medical-and-halachic-implications-of-brca-gene-testing/.

115 Personal communication with Rav Professor Steinberg occurred on January 2019. The forthcoming edition of *Ha-Refua K-Halacha* has not yet been published

save lives, overrides all other concerns regarding any potential arguments against BRCA testing.

In 1997, Rabbi Moshe Tendler was quoted in a personal communication as strongly opposing population-based testing for BRCA because he feared that a positive test result would cause anxiety and discrimination, especially in *shiddukhim*.[116] Over the last 22 years, several subsequent publications have cited this original article and reiterated Rabbi Tendler's strong objection to BRCA testing in Ashkenazi women without a family history of breast or ovarian cancer. In fact, as recently as May 2017, Dr. Daniel Eisenberg wrote, "Rabbi Moshe Dovid Tendler, chairman of biology at Yeshiva University, once described genetic testing for BRCA genes as an issue of 'tyranny of knowledge.' He rightly stated that when information causes anxiety, but offers no way to reduce that anxiety, it controls us. In the case of screening for the BRCA genes, where no absolutely reliable diagnostic tool exists, the patient is faced with the prospect that she may develop breast or ovarian cancer, diseases which she cannot guard against without radical prophylactic surgery."[117]

Rabbi Moshe Tendler has since modified his position on BRCA testing for all Ashkenazi women.[118] His earlier concerns regarding testing were only that the mere act of undergoing genetic testing could make *shiddukhim* difficult and thus he advised his students to be tested in Israel, rather than in America, so as to keep people from knowing that they had done it. However, he now declares, "I am in full support of BRCA testing for all Jewish women, not just Ashkenazi women, and you can quote me on that. I believe that today it is a חיוב דאורייתא. It is an absolute *halakhic* requirement to do the testing since we have the means to respond to a positive test. It's not just finding out and not being able to do anything about it." In fact, he does not think that women should delay testing until the age of 25–30 when surveillance can begin. He recommends that women undergo BRCA testing as soon as they are married. "If you are old enough to get married, you are old enough to know what your genetic future holds for the next 20–30 years. There are enough cases of it (cancer) occurring in your twenties and thirties for the test to be done and provide valuable information." The obligation to undergo BRCA testing is so strong that Rabbi Tendler believes there is no situation in which one is permitted to refuse BRCA testing. Only the *gedolei Yisrael* of the past, such as Yosef *ha-tzadik,* who achieved such a high level of spirituality that G-d performed miracles for him on a daily basis, can rely on *Hashem* for

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116 Mosenkis, "Genetic Screening for Breast Cancer Susceptibility."

117 http://www.aish.com/ci/sam/Genetic_Screening_for_Breast_Cancer_Genes.html.

118 Personal communication, Rabbi Moshe Tendler, January 16, 2019, Israel.

cure. "A person does not have that individual right unless he is of the stature of Yosef *ha-tzadik*. Anyone less than Yosef *ha-tzadik* is criticized by our *ḥakhamim* for failure to take advantage of whatever can be helpful to him. There is a חיוב of a person to help himself. G-d allowed it in the laws of nature for us to be vaccinated to prevent disease, for us to do testing so that we can control disease, then you are required to do so. Period." Rabbi Tendler's endorsement of BRCA testing for *all* Jewish women is unequivocal and unconditional.

Rabbi Yuval Cherlow has also stated that all Ashkenazi women must undergo testing. "If an individual Ashkenazi woman asked me if she should undergo BRCA testing, I would tell her absolutely. I would tell her to run. If testing were only being done on *Shabbat*, she may undergo testing on *Shabbat*. The larger question is whether we as a Jewish society should fund such testing."[119] As more modern *poskim* become aware of the medical benefits of population-based testing for all Ashkenazi women, I believe that the number of rabbinic leaders who obligate testing will increase.

Future Directions

In the United States, The BFOR Trial (Breast Cancer Founder Research Study) is offering free BRCA testing to 4,000 Ashkenazi men and women in four U.S. cities.[120] Study participants register via their smartphone or computer, complete an online education module, provide their informed consent electronically, and have their lab test order sent directly to a local Quest Diagnostics Patient Service Center to which the participant then goes to supply a DNA sample. The participant's primary care physician or a BFOR cancer genetics specialist will provide test results, follow-up genetic counseling, and order additional genetic testing if appropriate. Most health insurance covers intensive screening or risk-reducing surgery for those found to carry a BRCA mutation.

Canada launched the Screen Project in March 2017 to offer BRCA testing to all women and men 18 years of age or older.[121] It uses a guided direct-to-consumer approach through the study's web site (http://www.thescreenproject.ca/) to enroll individuals. A team of genetic counselors contacts all individuals with a mutation in person or by

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119 Personal communication, Rabbi Yuval Cherlow, February 19, 2019, Israel.

120 https://www.bforstudy.com/release.

121 Akbari, M.R., Gosjka, N., Narod, S.A. "Coming of Age in Canada: A Study of Population-Based Genetic Testing for Breast and Ovarian Cancer," *Current Oncology* [S.l.], v. 24(5) (Ontario: 2017) pp. 282–283.

telephone to discuss their options for cancer prevention and to facilitate a referral to a local genetic clinic for long-term follow-up. The cost of this BRCA genetic test is 165 Canadian dollars.

On January 17, 2020, the Israel Ministry of Health announced that it will include BRCA testing for Ashkenazi women in the basket of health services.[122] In the United States, the organization, "1 in 40," has petitioned the National Comprehensive Cancer Network, a non-profit alliance of 28 leading cancer centers devoted to creating clinical practice guidelines and standards for clinical policy in cancer care, to recommend BRCA testing for all Ashkenazi women regardless of family history. Future studies will determine the feasibility of BRCA testing for all Ashkenazi women and the appropriate management of Ashkenazi men and non-Ashkenazi populations.

Conclusion

"To identify a woman as a carrier only after she develops cancer is a failure of cancer prevention,"[123] writes Mary Claire King. Dr. Kenneth Offit, chief of the clinical genetics service at Memorial Sloan Kettering Cancer Center in New York, who discovered one of the most common BRCA gene mutations for Ashkenazi Jews, estimates, "In the [Ashkenazi] Jewish community, where these mutations are quite common, we think that probably 90% of people who could be tested have not been tested."[124]

BRCA testing identifies women at increased risk of cancer who will benefit from surveillance, chemoprevention, and risk-reducing surgery. That limiting BRCA testing to women with a family history of cancer fails to identify more than 50% of carriers provides a compelling scientific argument for testing *all* Ashkenazi women. The *halakhic* argument for BRCA testing of all Ashkenazi women derives from the obligation to ward off disease and the reality that the information obtained from testing can be used not only to prevent disease but also to save lives. Recognizing this reality, several modern *poskim* believe that BRCA testing for all Ashkenazi women is *pikuaḥ nefesh*, which overrides any other consideration. A growing number of rabbinic leaders in the United States and Israel endorse and even require BRCA testing for all Ashkenazi women. ☙

122 https://www.health.gov.il/NewsAndEvents/SpokemanMesseges/Pages/17012020_1.aspx.

123 King, "A Population Based Screening for BRCA1 and BRCA2."

124 https://www.timesofisrael.com/new-study-on-cancer-risk-in-ashkenazi-jews-aims-to-be-model-for-genetic-testing/.