Variations in Practice and Geographic Disparities Between Dedicated Multidisciplinary Clinics for *BRCA1/BRCA2* Mutation Carriers in Israel

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ABSTRACT **Background:** Population screening for the BRCA mutations in Ashkenazi Jewish women was recently implemented in Israel and is expected to lead to a 10-fold increase in the diagnosis of asymptomatic carriers. Performing the screening follow-up within multidisciplinary dedicated clinics for carriers is recommended for early detection and risk reduction.

Objectives: To determine the availability, capacity, and practices of dedicated screening clinic for *BRCA* carriers in Israel.

Methods: A telephone-based survey of all public hospitals in Israel was conducted October 2020 to August 2021 to determine whether they had a dedicated clinic. Dedicated clinics were defined as multidisciplinary screening clinics offering at least breast and gynecological screening and risk reducing services on site. The clinic director or nurse navigator answered a questionnaire about screening practices followed by a semi-structured interview.

Results: Of the ten dedicated *BRCA* clinics found in Israel, nine participated. Approximately 4500 *BRCA* carriers are currently being followed. No specialized clinics are available in the southern district or in the northernmost half of the northern district of Israel, leading to a disparity between periphery and center. Screening recommendations, although asserted as adhering to international guidelines, vary among clinics including age at initiating of clinical exam, use of adjunct imaging modalities, and follow-up during lactation and after risk reducing surgery.

Conclusions: There is a suboptimal distribution of dedicated clinics for BRCA carriers in Israel. Nationally centralized attempt to create guidelines that will unify screening practices is warranted, especially considering the expected increase in demand.

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KEY WORDS: BRCA, breast neoplasms / genetics, Hereditary Breast and Ovarian Cancer Syndrome, risk management

Strict surveillance and early diagnosis of breast cancer in *BRCA* mutation carriers has been shown to positively affect morbidity and decrease mortality [1,2]. Breast and ovarian cancer risks are substantially increased in *BRCA* mutation carriers [3] and can be diagnosed at a younger age compared with the average risk population [4]. These high-risk women are therefore offered frequent screening for breast cancer starting at a young age, using sensitive imaging modalities such as breast magnetic resonance imaging (MRI), as reflected in internationally accepted guidelines [5-8]. *BRCA* mutation carriers are encouraged to participate in specialized multidisciplinary high-risk clinics, offering a biannual one-stop shops where all screening tests are performed during a single visit [7]. Such clinics are important not only for assuring adherence to the recommended surveillance and increasing compliance, but also for addressing additional *BRCA*-related specific issues such as fertility, sequelae of risk reducing strategies, psychosocial support, and referral to other disciplines as needed (e.g., plastic surgeons, assisted reproduction specialists) [9,10].

In 2020 the Israeli Ministry of Health introduced the funding for population testing for the predominant *BRCA* mutations in all Ashkenazi Jewish (AJ) women, as a screening option without the need for a pre-test counseling [11]. An estimated 2.5% of AJ (1:40) were expected to be found as carriers of one of three pathogenic sequence variants in *BRCA1* [185delAG (NM_007294.3:c.68_69delAG; p.Glu23fs; rs80357914); 5382insC (NM_007294.4:c.5266dup (p.Gln1756fs); rs80357906)], and *BRCA2* [6174delT (NM_000059.4:c.5946del (p.Ser1982fs); rs80359550)] genes, regardless of whether there was a known family history of *BRCA*-related cancers [12]. With an estimated population of 2.8 million AJ women in Israel (and about 10 million worldwide), this finding could mean that several thousand newly diagnosed *BRCA* mutation carriers would be identified in Israel.

The specialized clinics for *BRCA* mutation carriers in Israel were mostly designed as part of the breast centers within public hospitals. At the time this manuscript was written, a year after the ministry of health recommendation, there was no official list of the dedicated high-risk clinics in Israel, their location, availability, or the screening practices offered at each clinic. The aim of this study was to fill the gap in knowledge and compare the practices in the clinics currently operating in Israel.

PATIENTS AND METHODS

We defined specialized high-risk screening clinics as multidisciplinary clinics offering a long-term screening program that included at least breast and gynecological screening and risk-reducing services for carriers of deleterious mutations in *BRCA* genes. All surgical departments at Israeli public hospitals [13] were contacted by the principal investigator (NH). The director at each breast surgical oncology clinic, center, or unit was contacted by telephone or email and asked whether they had a dedicated clinic for screening of *BRCA* mutation carriers. The initial survey was conducted through the surgical departments as clinical breast exam are performed by surgeons in Israel, so they were most likely to know if such a high-risk clinic existed in their hospital. Subsequently, the director or nurse coordinator of each specialized clinic was contacted and asked to respond to a questionnaire about the practices of screening and risk reduction recommendations in their clinic. In addition, personal, semi-constructed interviews were conducted by telephone with each director (by NH). The interviews included reviewing the questionnaire responses and listening to the experiences in managing and operating a high-risk clinic. They were also asked if they were aware of other such clinics, to verify that none were overlooked.

RESULTS

All 26 surgical departments at public hospitals in Israel were contacted, and all agreed to comment on whether they had a specialized high-risk screening clinic for female *BRCA* carriers. A total of nine hospital-based clinics were identified. Through personal interviews with the clinic's directors and/or coordinators, one additional clinic in a community-based facility was identified. These clinics and their locations in Israel are shown in Figure 1. Of the ten dedicated *BRCA* clinics, nine agreed to participate in the study.

GEOGRAPHIC DISTRIBUTION OF DEDICATED BRCA CLINICS

Most clinics were located in the center of Israel (Gush Dan and the Jerusalem area), with no dedicated centers north of Tiberias or south of Jerusalem [Figure 1].

CLINIC CAPACITY

The reported number of patients currently undergoing screening in any of the high-risk specialized clinics was approximately 4500. Two of the clinics were full and could not accommodate more *BRCA* carriers, even on a waiting list basis. Waiting time for admittance was reported to be under 1 month in three clinics, and 1–6 months in other four.

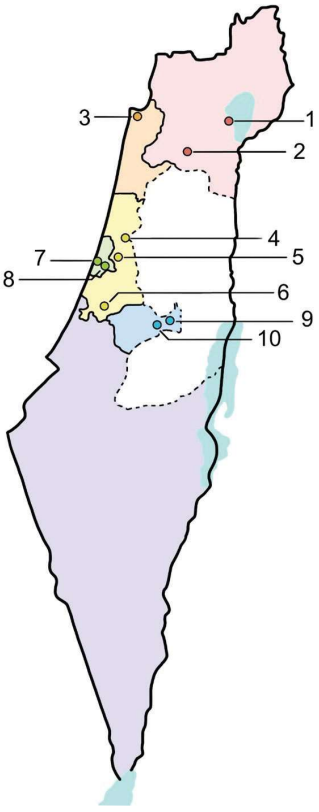
VARIABILITY IN SCREENING PRACTICES

All clinics recommended surveillance every 6 months. Each visit to participating clinics included a physical breast examination and gynecological examination. Other than that, practices and screening recommendation varied.

- *Age to start and discontinue screening:* Six of nine clinics recommended staring screening at age 25 years, and three clinics began screening at 18–20 years of age. One clinic discontinued screening at age 70 years, two clinics at age 80 years, one at age 85 years, and the other five continued screening with no upper age limit.

Figure 1. Geographic distribution by districts of dedicated BRCA clinics* (August 2021)

Northern District	1. Tiberias (Clalit Health Services)
	2. Emek Medical Center
Haifa District	3. Rambam Health Care Campus
Central District	4. Meir Medical Center
	5. Rabin Medical Center
	6. Kaplan Medical Center
Tel Aviv District	7. Tel Aviv Sourasky Medical Center
	8. Sheba Medical Center
Jerusalem District	9. Shaare Zedek Medical Center
	10. Hadassah Medical Center (Ein Kerem campus)
Southern District	No clinics



*Numbers on the map correspond with the numbers of the clinics

- *Breast imaging:* All clinics recommended annual MRI starting at age 25 years. Four clinics offered annual breast ultrasound starting at age 25 years, 6 months after breast MRI; three clinics started breast ultrasound at diagnosis as young as 18 years; and two clinics started ultrasound screening after age 30 years. An annual mammogram (replacing the breast ultrasound) was performed at one clinic starting at age 25 years, in six clinics starting at 30 years, in one starting age 35, and in one at the age of 40 years.
- *Transvaginal ultrasound:* Conducted as part of the routine screening in all clinics, most started at age 25 years. In seven clinics the exam was conducted every 6 months, and in the remaining two every 12 months.
- *Serum markers:* All clinics recommended testing serum CA-125 levels. Most started at age 25 years, with six clinics performing semiannual tests and three clinics performing annual examinations.
- *Risk reduction:* All clinics conducted planned discussions about risk reducing surgeries, such as bilateral mastectomy and salpingo-oophorectomy, and suggested the option of pre-implantation genetic diagnosis (PGD) for women of childbearing age. Five clinics recommended oral contraceptive pills for decreasing ovarian cancer risk, and only two discussed chemoprevention for breast cancer; one clinic offered tamoxifen and one clinic offered raloxifene for post-menopausal women.
- *Screening after risk reducing surgeries:* Breast imaging screening recommendations after bilateral risk reducing mastectomy for cancer free carriers varied. At one clinic, breast imaging was discontinued altogether, one clinic recommended a one-time MRI to assess residual breast tissue, and continued screening with an annual ultrasound unless there was a significant amount of residual breast tissue. In these cases, MRI screening was ongoing. The remaining clinics recommended alternating ultrasound and MRI annually or semiannually. Five clinics recommended an annual transvaginal ultrasound after bilateral salpingo-oophorectomy.
- *Pregnancy and breast feeding:* All clinics recommended breast physical examination and ultrasound during pregnancy, with frequencies varying between 2 to 6 months. During breast feeding, all recommended resuming regular physical examination protocol. Most clinics performed only ultrasound for lactating women and two perform mammogram and/or breast MRI (Diffusion tensor imaging protocol) for women breastfeeding > 6 months.
- *Additional services and screening:* Five of the clinics offered screening for male *BRCA* carriers, either at the same clinic or at a distinct clinic. All clinics referred carriers who had a family history of pancreatic or colon cancer (in at least one first degree relative or two second degree relatives from the same family side where the mutation originated from) for the relevant gastroenterology screening. Five clinics offered or referred to routine dermatology screening aimed at early detection of cutaneous melanoma.
- *Other high-risk participants:* Five of the clinics also provided screening for other high and intermediate risk carriers of germline mutations in other cancer susceptibility genes (e.g., *TP53, PTEN, ATM, CHEK2*). Two clinics offered breast cancer screening for individuals who are at a high breast cancer risk due to previous mantle radiation.

DISCUSSION

The current study showed that the dedicated screening clinics for *BRCA* mutation carriers in Israel were mostly designed as part of breast centers within public hospitals. As there is no official updated list of the dedicated high-risk clinics in Israel, their location, availability, or the type screening offered within each clinic, the clinic directors noted that patients were often referred to them by word of mouth, which may have potentially led to delays in screening. More concerning is the fact that the geographic distribution of these dedicated clinics in Israel was disproportionate, with a paucity of facilities in the southern and northern districts.

Currently, the specialized screening clinics in Israel that participated provided service for fewer than 5000 *BRCA* mutations carriers. Even if all existing clinics were able to double their current capacity, it would still not accommodate the expected rise in demand after the implementation of population screening in Israel. Two of the clinics were already at full capacity and did not accept new patients. The main limiting factor in most clinics was imaging capabilities (predominantly MRI) that should cater to the needs of these high-risk women.

There are no national Israeli guidelines for screening and risk-reduction practices in female *BRCA* carriers. Hence, each clinic independently developed or adopted its own approach and recommendations for screening. This result is the main reason for the significant variability in the practices among the surveyed clinics in Israel. The uniform recommendations included performing an annual MRI starting at age 25 years, performing breast and gynecological examinations every 6 months, and discussing the risk reducing surgeries. Age ranges for screening, frequency, and modality of imaging tests at different age groups, and frequency of serum marker tests vary. Issues such as screening during pregnancy and breast-feeding, imaging after risk reducing surgery and screening by additional medical disciplines were inconsistent. When asked how they decided on their screening protocols, most directors replied that their practices are based on the NCCN guidelines [5] making the differences in practice between the clinics even more surprising. These differences in national recommendations and intercountry variability into the optimal surveillance scheme for *BRCA* carriers not unique to the reality in Israel, as previously noted by some of us [14].

Table 1 displays surveillance and risk reduction recommendations for *BRCA* mutation carriers according to the

NCCN and ESMO guidelines, and the Israeli practice at clinics for high-risk patients.

National guidelines are important to harmonize the care within these high-risk clinics and just as important for health professionals not working within such a specialized clinic. Considering the expected shortage in capacity in these specialized screening clinics in central Israel, combined with the paucity in dedicated clinics outside of the central Israel, it is likely that increasing numbers of *BRCA* mutation carriers will have to rely on screening possibilities outside of these specialized clinics. Physicians caring for *BRCA* mutation carriers in the community, most of whom were not specifically trained, needed clear guidelines regarding referrals for screening tests and ongoing updates to discuss available and possible novel risk-reducing strategies.

Multiple studies have shown that healthcare professionals who were not working within specialized screening clinics felt

Table 1. International guidelines on screening and risk reduction for BRCA deleterious mutation carriers vs. and the practice in Israeli high-risk clinics

	NCCN Guidelines version 1.22 [5]	ESMO Clinical Practice Guidelines 2016 [7]	Practice in Israel
Screening			
Breast clinical exam	Every 6–12 months starting at age 25	Every 6–12 months starting age 25, or 10 years before youngest diagnosis in the family	Every 6 months, varying ages to start (18–25)
Breast imaging	• Age 25–29: MRI annually, earlier if diagnosis < age 30 in a family member; mammogram if MRI cannot be performed • Age 30–75: MRI and mammogram annually, consider tomosynthesis • Individualize recommendations after age 75	• Age 25–29: MRI annually, if MRI cannot be performed avoid mammogram, consider ultrasound • Age ≥ 30: MRI and mammography annually from the age of 30; ultrasound may be considered as an adjunct to mammography	• MRI annually starting age 25 • Ultrasound annually age varying (18–30) • Mammogram annually age varying (25–40)
Ovarian screening	Consider annual transvaginal ultrasound and serum ca-125 from the age 30–35	Consider every 6 months transvaginal ultrasound and serum ca-125 from the age 30	Transvaginal ultrasound and serum ca-125, most starting age 25, varying 6–12 months
Risk reduction			
Breast risk reduction	• Discuss risk reducing agents: tamoxifen (pre-menopausal), or raloxifene/ aromatase inhibitors (post-menopausal) • Discuss RRM as risk reducing surgery	• Discuss lifestyle modifications: breastfeeding, exercise, healthy weight, limited alcohol consumption • Consider use of tamoxifen • Discuss RRM as risk reducing surgery • Consider MRI or ultrasound screening for residual breast tissue after nipple sparing RRM	• Only two clinics offer risk reducing agents • All clinics discuss bilateral RRM • Most clinics recommend alternating ultrasound and MRI every 6–12 months after RRM
Ovarian risk reduction	• Recommend rrBSO age 35–40 for *BRCA1*, age 40–45 for *BRCA2* • Discuss concurrent hysterectomy for *BRCA1* • Use caution when considering long-term combined hormone replacement therapy • No surveillance recommended after rrBSO	• Recommend rrBSO age 35–40 • Short-term use of hormone replacement therapy following rrBSO is safe among healthy mutation carriers • Oral contraceptives may be considered as risk reduction measure • No surveillance recommended after rrBSO	• All clinics recommend rrBSO age 35–40 • Most clinics recommend oral contraceptives as risk reduction • Most clinics continue annual transvaginal ultrasound and serum ca-125 after rrBSO
Screening for *BRCA*-associated malignancies	• General melanoma risk management: annual full body skin examination • Consider pancreatic screening by annual EUS/MRCP if there is family history of pancreatic cancer, starting age 50, or 10 years younger than youngest effected family member	• Consider annual skin and eye examination as screening for melanoma for *BRCA2* • Consider annual screening for pancreatic cancer with EUS or MRI/MRCP starting at age 50, or 10 years before the earliest diagnosed case in the family for *BRCA2*	• Half of the clinics refer to dermatology surveillance • All clinics refer patients with family history of pancreatic cancer for EUS/ MRI screening
Reproductive considerations	Discuss PGD or prenatal diagnosis	Discuss PGD or prenatal diagnosis	All clinics discuss PGD or prenatal diagnosis

NCCN = National Comprehensive Cancer Network, ESMO = European Society for Medical Oncology, RRM = risk reducing mastectomy, rrBSO = risk-reducing bilateral salpingo-oophorectomy, EUS = endoscopic ultrasound, MRCP = magnetic resonance cholangiopancreatography, PGD = preimplantation genetic diagnosis

Ages are shown in years

a lack of confidence in their ability to provide the proper care for carriers of deleterious mutations. They tended to recommend their personal interpretation of screening regimens and risk-reducing options, and often were unaware, of or did not implement, the correct management for high-risk cases [15-18]. National guidelines could provide accessible and current information for consistent screening practice even for patients not treated within specialized clinics for *BRCA* mutation carriers.

LIMITATIONS

The limitations of this study include the fact that no attempt was made to identify confounders such as socioeconomic class, type of mutations, and specific family history, which may have affected some of the locally developed recommendations. This observational study highlights some of the needs anticipated by the possible use of *BRCA* carriers that are expected within the next few years in Israel and cannot be extrapolated to countries where there are no population screenings implemented.

CONCLUSIONS

Considering the variability in practice in *BRCA* dedicated screening clinics in Israel and the expected rise in demand because of the newly implemented *BRCA* population testing, a nationally centralized system of clinic distribution and screening guidelines are urgently needed.

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Capsule

Mutations in SARS-CoV-2 spike protein impair epitope-specific CD4⁺ T cell recognition

CD4⁺ T cells are essential for protection against viruses, including SARS-CoV-2. The sensitivity of CD4⁺ T cells to mutations in SARS-CoV-2 variants of concern (VOCs) is poorly understood. **Tye** et al. isolated 159 SARS-CoV-2-specific CD4⁺ T cell clones from healthcare workers previously infected with wild-type SARS-CoV-2 (D614G) and defined 21 epitopes in spike, membrane, and nucleoprotein. Lack of CD4⁺ T cell cross-reactivity between SARS-CoV-2 and endemic beta-coronaviruses suggested these responses arose from naïve rather than pre-existing cross-reactive coronavirus-specific T cells. Of the 17 epitopes located in the spike protein, 10 were mutated in VOCs and CD4⁺ T cell clone recognition of 7 of them was impaired, including 3 of the 4 epitopes mutated in omicron. These results indicated that broad targeting of epitopes by CD4⁺ T cells likely limits evasion by current VOCs. However, continued genomic surveillance is vital to identify new mutations able to evade CD4⁺ T cell immunity.

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