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IMPLICATIONS FOR ONCOGENETICS PRACTICE.**

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THE CARRIER CLINIC: AN EVALUATION OF A NOVEL CLINIC DEDICATED TO THE FOLLOW UP OF BRCA1 AND BRCA2 CARRIERS; IMPLICATIONS FOR ONCOGENETICS PRACTICE.

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ABSTRACT

BACKGROUND

A novel oncogenetic clinic was established in 2002 at the Royal Marsden NHS Foundation Trust offering advice and specialist follow-up for families with a germline mutation in *BRCA1* or *BRCA2*. The remit of this multidisciplinary clinic, staffed by individuals in both oncology and genetics, is to provide individualised screening recommendations, support in decision-making, risk-reducing strategies, cascade testing, and an extensive research portfolio.

METHODS

A retrospective analysis was performed to evaluate uptake of genetic testing, risk-reducing surgery and cancer prevalence in 346 *BRCA1/BRCA2* families seen between January 1996 and December 2006.

RESULTS

661 individuals attended the clinic and 406 mutation carriers were identified; 85.8% mutation carriers have chosen to attend for annual follow-up. 70% of mutation carriers elected for risk-reducing bilateral salpingo-oophorectomy (RRBSO). 32% of unaffected women chose risk-reducing bilateral mastectomy; 32% of women with breast cancer chose contralateral risk-reducing mastectomy at time of diagnosis. Some women took over eight years to decide to have surgery. 91% of individuals approached agreed to participate in research programmes.

INTERPRETATION

A novel specialist clinic for *BRCA1/2* mutation carriers has been successfully established. The number of mutation positive families is increasing. This and high demand for RRBSO in women over 40 is inevitably going to place an increasing demand on existing health resources. Our clinic model has subsequently been adopted in other centres and this will greatly facilitate translational studies and provide a healthcare structure for management and follow up of such people who are at a high cancer risk.

INTRODUCTION

Clinical testing for *BRCA1* and *BRCA2* germline mutations through the National Health Service (NHS) became available in the United Kingdom (UK) in 1995-6. Whilst the population frequency of *BRCA1* and *BRCA2* mutations is not high, collectively they account for approximately five percent of breast and ovarian cancer, moreover the risks of these cancers are high in mutation carriers; with lifetime risks of an estimated 44–75% for breast cancer and 20–45% for ovarian cancer in *BRCA1* and 10–20% in *BRCA2* mutation carriers.[1,2]

An increased cancer risk is also recognised in men with *BRCA2* mutations, conferring a six percent lifetime risk of breast cancer and a three to seven fold increased risk of developing prostate cancer.[3,4]

Increasing demand for *BRCA1/2* gene mutation testing from individuals with a family history of breast and/or ovarian cancer, coupled with advances in molecular diagnostics, has led to a rapid rise in the number of *BRCA* gene mutation carriers identified. However, there are no national or international guidelines for the long-term clinical management of carriers. For mutation carriers, there are a number of recommendations focussing on medical management, including surveillance programmes and risk-reducing surgery, but there are currently no national guidelines regarding the best means of maintaining contact with families. Ongoing contact is important for providing up-to-date information about changes in management, supporting decision-making, and disseminating information through the family.

Research is changing the way in which these patients are managed with the development of new modalities for early detection, an increased understanding of the impact of environmental and reproductive factors on modification of risk and with advances in chemoprevention and treatment options.[5-8] The best means of updating families and their health professionals on screening and prevention recommendations in a field that is constantly changing remains uncertain.[9] Different models of ongoing follow-up have been evaluated reporting mixed results.[10-12] These studies indicate that there is a need for ongoing follow-up and contact with families with *BRCA* mutations, but have focused largely on supportive aspects of care rather than information provision and guiding decision-making. This is where a specialist multi-disciplinary follow-up clinic may be effective.

The aim of this study is to present our experience of a novel model for the follow-up of *BRCA1/2* mutation carriers and perform a retrospective analysis of clinic attendance, uptake of risk-reducing surgery, research participation, pattern of genetic testing, and cancer occurrence in families who have attended the clinic over a ten year period.

METHODS

At the Royal Marsden NHS Foundation Trust (RMH), families harbouring a mutation in *BRCA1* or *BRCA2* have been offered annual clinical follow-up since the introduction of clinical testing in 1995. In 2002, as the number of families increased, follow-up was formalised into a novel oncogenetic clinic specifically for *BRCA1* and *BRCA2* families, called the Carrier Clinic.

The remit of this multidisciplinary clinic is to provide individualised screening recommendations and clinical management, ongoing psychological support, advice about cascade testing, and facilitate family communication. In addition it offers an opportunity for those at risk to engage in ongoing research programmes. The clinic is staffed by individuals with training in oncology and genetics, including medical practitioners, genetic/nurse counsellors and research staff. Clinic appointments are

offered annually and for those individuals who find it difficult to attend the clinic a telephone consultation with a Clinical Nurse Specialist or Genetic Counsellor is offered. [13] This virtual clinic enables patients to have a point of contact in between appointments for ongoing help and support and provides a point of rapid access.

Bilateral risk-reducing mastectomy (RRM) or contralateral RRM with simultaneous reconstruction is an option discussed with all women with a known *BRCA* mutation without evidence of metastatic disease. A psychologist is involved in the assessment of unaffected women considering bilateral RRM. Risk-reducing salpingo-oophorectomy (RRBSO) is recommended on completion of child-bearing, usually from age 40 although women wishing to pursue this at an earlier age are referred to a gynaecologist for assessment. The use of hormone replacement therapy (HRT) in unaffected women who have ovarian surgery prior to the natural menopause is recommended up to 50 years to help maintain bone health and to avoid vasomotor symptoms in this group.

All families identified between July 1996 and December 2006 with a pathogenic germline mutation in *BRCA1* or *BRCA2* seen at RMH have been included in this study. A total of 346 families were seen (201 with *BRCA1* mutations and 145 with *BRCA2* mutations). Mutations in these families were identified either through the UK National Health Service (NHS) (n = 275), through the commercial vendor Myriad (www.myriad.com, n = 25) or through research testing which was subsequently confirmed in the diagnostic setting (n = 46).

All mutation carriers and untested family members were offered annual follow-up in the clinic with. At each follow-up visit, data on mutation status, cancer occurrence, surveillance and risk-reducing surgery were collected.

Statistical Analysis

Descriptive statistics were obtained using SPSS statistical software (version 15.0).

RESULTS

A total of 661 individuals from 346 families were eligible for inclusion in this analysis (406 mutation carriers: 239 *BRCA1*, 165 *BRCA2*, two both *BRCA1* and *BRCA2*; 193 individuals with a negative predictive test, and 62 untested family members) constituting the entire patient group that came forward for a consultation between 1996 and 2006.

Of the 406 mutation carriers 33 were male (16 *BRCA1*, 17 *BRCA2*) and 373 female (223 *BRCA1*, 148 *BRCA2*, 2 *BRCA1* & *BRCA2*). At time of mutation detection 4 men and 172 women had not had a cancer diagnosis. The mean length of follow-up from the date of mutation detection was 48 months (range 0.5-127 months).

Genetic Testing

Between July 1996 and December 2006 406 individuals were identified with a pathogenic mutation in *BRCA1* and/or *BRCA2*. Out of 188 mutations identified through direct mutation analysis, 35 were identified in the research setting. Four hundred and thirty individuals eligible for predictive testing have attended the clinic and 368 of these [308 women (84%) and 60 men (16%)] proceeded to testing. Median age at testing was 44 years (range 21–79 years). Figure 1 summarises the method of mutation detection in the 406 carriers and how this has changed over time.

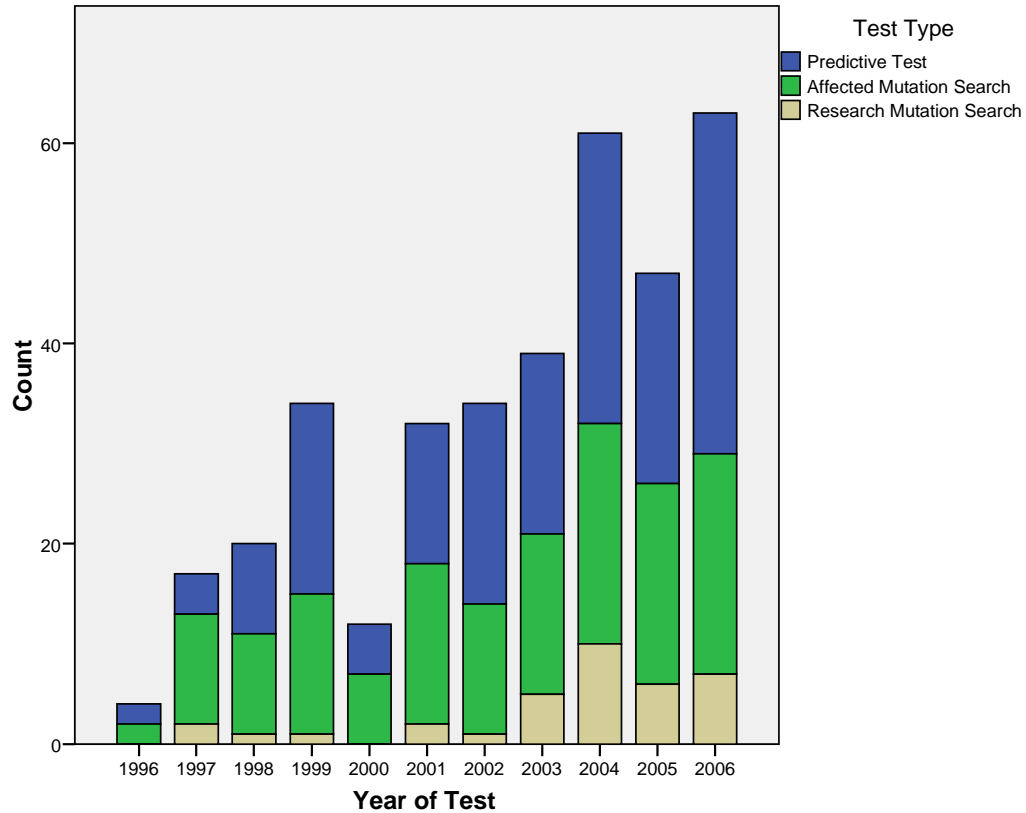


Figure 1: Pattern of genetic testing from 1996-2006

Time to predictive testing was calculated using the date the mutation was first identified in the family and the test result date [data on individuals referred from other centres for follow-up have been excluded ($n=43$)]. Median time to predictive testing was five months (mean 14.5 months; SD = 20.9; Range 1-121 months). Fifty of 368 individuals (13.6%) waited three years or more before proceeding to predictive genetic testing.

Of the 373 female *BRCA1/2* mutation carriers, 85.8% chose to have regular follow-up either through the carrier clinic or by telephone. Table 1 summarises the follow up in tested and untested individuals. Table 2 describes the uptake into research programmes. Of the 661 members of families with a known *BRCA* gene mutation, invited to take part in research programmes the uptake was high with 91% of mutation carriers, 72% non-carriers and 74% untested individuals enrolled.

Choice of Follow Up	Gene carriers (n = 373)	Untested (n = 62)
Attends carrier clinic	296 (79.4%)	47 (75.8%)
Annual telephone follow-up	24 (6.4%)	2 (3.2%)
Local follow-up (moved out of area)	36 (9.7%)	1 (1.6%)
Elderly / unwell	10 (2.7%)	0
No follow-up	7 (1.9%)	12 (19.4%)

Table 1. Choice of follow-up

	Mutation Carriers (n = 406)	Non-carriers (n = 193)	Untested individuals (n=62)
Number invited	361 (89%)	152 (79%)	43 (69%)
Number enrolled	330 (81%)	109 (56%)	32 (52%)
Number declined	14 (3%)	8 (4%)	2 (3%)
Number of non-responders	17 (4%)	35 (18%)	9 (15%)

Table 2. Participation in research

Cancer Prevalence

Of 406 male and female *BRCA1/2* mutation carriers, a total of 322 cancers were diagnosed in 245 individuals. The cancer spectrum is described in Table 3. In total 254 breast cancers were observed in 202 individuals. Thirty one of 115 (20.5%) *BRCA1* and 14/88 (15.9%) *BRCA2* carriers have had more than one primary breast cancer with median time to a second primary of five and six years respectively. Thirty-three individuals (all female) have died during follow-up: 14 (11 *BRCA1*; 3 *BRCA2*) died from metastatic breast cancer; 15 (11 *BRCA1*, 4 *BRCA2*) from metastatic ovarian cancer and four from other cancers.

	Number of individuals	<i>BRCA1</i>	Mean age at first diagnosis	<i>BRCA2</i>	Mean age at first diagnosis
No cancer	161	95	na	66	na
Breast Cancer	202*	115	39.4 yrs (25-67)	88 ⁺	43.6 yrs (21-71)
Ovarian / Fallopian Tube Cancer	50	36	49.8 yrs (32-64)	14	56.2 yrs (46-74)
Primary Peritoneal Cancer	3	2	46.0 yrs	1	52.0 yrs
Prostate Cancer	4	1	48.0 yrs	3	50.7 yrs
Other cancer	11	4	na	7	na

* Includes 1 woman with *BRCA1* and *BRCA2* mutations.

⁺ One individual was male.

na: not applicable

Table 3: Observed cancers in clinic cohort (includes all individuals diagnosed with cancer pre and post testing).

Forty-nine cancers developed in 45 individuals post mutation detection: 15 were detected through routine screening (13 breast cancers, one ovarian cancer, one prostate cancer) 19 were self-detected / symptomatic (nine breast cancers, six ovarian cancers, one prostate cancer, three other cancers) and seven were detected at time of risk-reducing surgery (four breast cancers and three ovarian cancers). Of the self-detected / symptomatic breast cancers, six were interval cancers and three were outside of screening. Of the self-detected / symptomatic ovarian cancers four were interval cancers and two were outside of screening.

An additional eight cancers were detected as a direct result of attendance at the Carrier Clinic. Four cancers (two breast cancers and two prostate cancers) were detected through research screening tests, three (two breast cancers, one primary

peritoneal cancer) were detected through investigation of symptoms elicited in clinic and one breast cancer was detected by initiation of an overdue screening test. This equates to 31 breast cancers being detected in 933 women years.

Risk-reducing surgery

Fifty-three of the 373 female *BRCA1/2* mutation carriers had already undergone bilateral mastectomy at time of mutation detection (24 for bilateral breast cancer, 24 had contralateral RRM and five had bilateral RRM based on family history criteria). Of the 320 women with remaining breast tissue post mutation detection, bilateral RRM was chosen by 89 (27.8%) and 9 of 28 (32.1%) women who subsequently developed breast cancer chose contralateral RRM at time of treatment. Post mutation detection, unaffected women chose to have bilateral RRM at a mean age of 37.4 years (range 23-62yrs). The median interval from mutation detection to surgery was nine months (range 2-64 months). A mean of 2.8 (range 1-8) appointments in the Carrier Clinic were attended prior to surgery. Four out of 98 women were found to have an incidental cancer at RRM (4.1%). All had previously had breast cancer. The histopathology of these cancers is detailed in Table 4.

Age at surgery	Mutation	Risk-reducing surgery	Previous cancer history	Previous treatment	Tumour identified at risk-reducing surgery
42	<i>BRCA1</i> 185delAG	Right RRM at time of L mastectomy for newly diagnosed DCIS	1. Right Medullary cancer age 34; ER- 2. Right IDC age 39	1. Right wide local excision (WLE) 2. Right WLE	Right Invasive Ductal Carcinoma ; Grade III, ER-
42	<i>BRCA1</i> 185delAG	Bilateral RRM	Left Invasive Ductal Carcinoma; Grade III, ER- age 40	Left WLE	Right Invasive Ductal Carcinoma and DCIS; Grade III, ER-
33	<i>BRCA2</i> 2157delG	Bilateral RRM	Right Invasive Ductal Carcinoma ; Grade III, ER+ age 30	Right WLE	Left Invasive Ductal Carcinoma; Grade III, ER+
52	<i>BRCA1</i> 4184del4	Bilateral RRM	Right Invasive Ductal Carcinoma age 36	Right WLE	Right Lobular carcinoma; Grade II, ER+
48	<i>BRCA1</i> 2594delC	RRBSO	None	None	Stage 1a, Grade III serous carcinoma of the R ovary.
53	<i>BRCA1</i> 2313G>T	RRBSO	None	None	Stage 3 ovarian serous carcinoma (bilateral)
47	<i>BRCA1</i> 185delAG	RRBSO	Bilateral breast cancer, age 40.	Bilateral mastectomy	Stage 1c serous carcinoma of the right ovary

Table 4: Incidental cancers detected at risk-reducing surgery post-mutation detection (insignificant details amended to maintain anonymity)

Out of 373 female *BRCA1/2* carriers 296 had ovarian tissue at the time of mutation detection. Seventy-seven had previously had their ovaries removed: 40 as treatment for ovarian cancer, three as treatment for breast cancer, three for benign gynaecological conditions and 31 had chosen RRBSO prior to knowledge of genetic status.

Post mutation detection, RRBSO was chosen by 131/186 (70.4%) women aged over 40 and 142/239 (59.4%) women aged 35 and over (women with advanced metastatic breast cancer were excluded unless they had survived beyond two years). There was no significant difference in the mean ages of surgery for *BRCA1* (46 years, SD = 7.5) and *BRCA2* (48 years, SD = 7.7) carriers. Post mutation detection, the median time to surgery was 9 months (mean 16.7, range 0-104 months). A mean of 2.4 (range 1-

8) appointments in the carrier clinic were attended prior to surgery. Twenty-one women had a simultaneous hysterectomy.

Three incidental cancers were detected at RRBSO (see Table 4). In all cases no abnormalities had been detected on transvaginal ultrasound pre-operatively and CA125 levels had been within normal range.

DISCUSSION

The population frequency of *BRCA1* and *BRCA2* mutations in the UK are estimated at 0.12% and 0.20% respectively, with higher frequencies in certain ethnic groups such as the Ashkenazim.[14] We found our clinic population to consist of approximately two-thirds *BRCA1* and one third *BRCA2* mutation carriers which is likely to be explained by the chronology of the introduction of *BRCA1* and *BRCA2* mutation testing into clinical practice.

The number of gene carriers identified has rapidly increased in recent years in our clinic. This increase may in part be explained by the introduction of full sequencing of coding regions plus Multiplex Ligation-dependent Probe Amplification (MLPA) from early 2006 onwards and the availability of research testing, particularly for families that do not meet the criteria for NHS testing. This together with an increasing awareness of genetic testing for cancer predisposition is having an impact on demand for genetics services across the world. A large proportion of gene carriers was identified through predictive testing. We found the median time interval to predictive testing from the time the family were informed was five months, which is a shorter time to predictive testing than previously reported by other UK groups.[15,16]. However, a significant minority of subjects were found to defer testing by several years, which is in line with these reports, and may reflect more distant relatives waiting for a result in a closer relative before deciding to undergo testing or the decision to wait until an age is reached where screening or risk-reducing surgery become influencing factors [15,16,17].

The results of this study show that there is a high demand for follow up within a formal clinic setting with over 85% of individuals choosing to either attend the clinic or have an annual telephone appointment. A high level of uptake of research programmes was observed, with over 90% of those people invited subsequently enrolled in a study. This may be facilitated by the face-to-face contact of the clinic as poorer response rates have been reported when comparing postal invitations with face-to-face recruitment.

Bilateral RRM reduces the risk of breast cancer by an estimated 90% and provides a significant reduction in mortality.[18-20] Twenty eight percent of unaffected women in our cohort elected to have bilateral RRM and, to date, no breast cancers have been reported post-surgery. Uptake levels in other single centre studies vary from 15-51%.[20-23] A large international study combined data from 9 centres and found an overall uptake of RRM of 18% in unaffected women, but this varied between 36.3% in the United States (US) and 2.7% in Poland.[24] Therefore the variation reported is likely to reflect local practice and cultural differences. The median interval of nine months from genetic testing to bilateral RRM is longer than that reported in two studies, one from Europe and one from the US, and may reflect differing local surgical protocols or health system processes.[21,22] A recent evaluation of a large UK series reported similar findings to this analysis, with the majority of women choosing bilateral RRM within 2 years of receiving their genetic test result.[18] We found that women attended an average of three appointments in the Carrier Clinic before proceeding to surgery, suggesting the importance of the multidisciplinary team

in supporting decision making. Studies have demonstrated the absence of long-term psychological impact on body image or sexuality providing the decision has been made in the context of careful counselling.[25,26]

Contralateral breast cancer risk in carriers has been estimated at 50-60% by age 70.[3,27] Contralateral RRM has been found to reduce the risk of a second primary by 90-95%, however further data are required to establish whether it reduces breast cancer-specific mortality.[28,29,30] One third of confirmed *BRCA* mutation carriers attending the Carrier Clinic chose to have contralateral RRM as a preventative measure as a part of their breast cancer treatment which is a similar proportion to that reported in a large international study (27.3%).[31] In our cohort approximately one fifth of women affected by breast cancer have had more than one primary breast cancer, with a small subset having multiple primary cancers. There is therefore a strong case for considering contralateral RRM at initial diagnosis for those in good prognostic groups from their primary disease, in this population. In particular, this may be an important consideration for women diagnosed under the age of 50 years as the residual breast cancer risk is thought to plateau over the age of 50.[1,32,33]

Women who have completed their family are informed about the significant benefits of having RRBSO prior to the natural menopause both to reduce ovarian cancer risk by 90% and breast cancer risk by approximately 50%.[32,33] RRBSO has been reported to reduce mortality in this high-risk population.[34] A high proportion of women attending the Carrier Clinic chose RRBSO; 49% of women over 35 years and 70% of women over 40 years. Meijers-Heijboer et al. (2003) report similar results in a Dutch cohort with 49% of mutation carriers over the age of 35 choosing surgery.[23] Kauff et al. (2002) reported that 58% of women over the age of 35 proceeded to surgery in one centre in the US.[32] However, in the US RRBSO is recommended from age 35, whereas in the UK this is usually offered from age 40 based on the BCLC penetrance estimates,[34,35] which could explain the difference in these results. Neither study present data using a cut-off of 40 years for comparison. The high proportion of women over 40 choosing RRBSO observed in this cohort could be due to the recent validation of data about the risk-reduction offered by this approach and the lack of data supporting the efficacy of ovarian screening as an alternative.[30,37] Three occult cancers were detected at surgery, of which two were early stage. All three women had normal TVUS and CA125 results immediately prior to surgery, and were enrolled in ovarian screening programmes. These results support the increasing evidence that screening is not a safe alternative to surgery.[30,37,38].

The majority (61%) of women had RRBSO within a year of finding out their test results suggesting that this could be a strong motivation for testing. On average, two or three appointments in the carrier clinic were required to facilitate this decision, highlighting the role of this clinic in this decision-making process. Psychosocial research has shown that RRBSO is an emotionally significant procedure and that balanced information should be provided about the risk reducing benefits of surgery versus the potential physical and emotional consequences.[39]

It is universally accepted that the fallopian tubes should be removed during surgery but there is an ongoing debate about whether the uterus should also be removed, with practice varying between countries. The data about whether there is an increased risk of endometrial cancer in *BRCA* carriers are preliminary.[40] If hysterectomy is performed then HRT post-RRBSO can be easier to manage using oestrogen only preparations. An argument for retaining the uterus is that it reduces the risk of complications and thus morbidity. In the UK usual practice is to remove the ovaries

and fallopian tubes but not the uterus unless indicated by the individual's medical history. This practice would be supported by the opinions in the literature.[40,41]

The experience reported by some gene carriers is that the significance of their genetic status can get lost across specialities. The average General Practice will manage only a handful of gene carriers but for the majority of families, once seen by a genetics service, screening is organised locally. *BRCA1* and *BRCA2* account for an estimated five to ten percent of breast and ovarian cancer cases, constituting a small percentage of an oncologist's caseload (and arguably less than the estimated 5% as more women opt for preventative surgery). Genetic status is an important consideration when a cancer is diagnosed, for example the significant risk of a contralateral breast primary. In addition there is some suggestion that platinum agents are more effective in women with *BRCA1* and *BRCA2* mutations who are being treated for ovarian cancer than in sporadic ovarian cancer cases.[42,43] With the advent of new targeted drug therapies such as PARP inhibitors currently being trialled in the research arena, knowledge of genetic status is going to become an increasingly important consideration.[44]

It was found that structured follow up within the Carrier Clinic led to the earlier diagnosis of eight cancers. A high number of breast cancers were observed during follow-up, with 31 detected in 933 women years. In the NHS Breast Screening Programme the expected cancer detection rate over the same time period is 2.5 cancers.[45]

In conclusion, this novel clinic enables a team of professionals with a specialist interest in cancer genetics to coordinate the management of these families. It facilitates rapid communication of changes in practice recommendations to patients. A very high number of individuals choose follow up in this clinic and the number of families is increasing annually both through clinical and research testing. There is a higher demand for RRBSO reported amongst this cohort than previously reported and the clinic plays a significant role in facilitating decision-making. This clinic model has subsequently been adopted in two other centres in London, offering the opportunity to greatly facilitate translational studies in this group. There are currently no national or international recommendations about the best practice for following up of *BRCA1/2* gene carriers; such guidance could help to direct funding sources to support these specialist clinics.

Contributors

EK Bancroft had overall responsibility for the analyses and writing of the article. All authors contributed to the study design, provided data or contributed to data interpretation, writing, or editing of the report, and approved the final version. R. Eeles and A. Ardern-Jones developed the Carrier Clinic Model and R. Eeles had overall responsibility for the study.

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Conflict of interest

RE has received an educational grant from Vista Diagnostics and support from Astra Zeneca for a feasibility cancer prevention trial.

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Figure 1: Pattern of genetic testing from 1996-2006

