

1 **Familial breast cancer:**

2 **Classification and care of women at risk of familial breast**
3 **cancer and management of breast cancer and related risks**
4 **in people with a family history of breast cancer.**

5 An assessment of need

6
7 Joyce Solomons
8
9

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1.1 Introduction

Breast cancer is by far the most common cancer diagnosed in women worldwide, with an estimated 1.38 million new female breast cancer cases diagnosed in 2008 (around 23% of all the cancers in women only, and around 11% of all the cancers in men and women together) (Ferlay J et al 2010). Breast cancer incidence rates are highest in Western Europe and North America, and the incidence of female breast cancer in the UK is estimated to be the 6th highest in Europe. In 2010, there were 49,961 new cases of breast cancer in the UK - 49,564 (99%) in women and 397 (less than 1%) in men. Female breast cancer incidence is strongly related to age, with the highest incidence rates overall being in older women. In the UK between 2008 and 2010, an average of 45% of cases were diagnosed in women aged 65 years and over, and 80% were diagnosed in the 50s and over (Office for National Statistics, 2012). The lifetime risk of developing breast cancer in the UK is estimated to be 1 in 8-10 for women and around 300,000 women are currently alive having been diagnosed with breast cancer in the past 10 years (National Cancer Intelligence Network 2010).

Breast cancer is a multifactorial disease, which may involve an interaction between environmental, lifestyle, hormonal and genetic factors. A family history of breast cancer is associated with an increased risk of the disease with the risk increasing with the number of relatives affected and with the age at diagnosis of the relative – the younger the age of diagnosis the greater the risk (Collaborative Group on Hormonal Factors in Breast Cancer 2001). Based on UK incidence data the probability of a woman aged 20 developing breast cancer by the age of 80 who has no affected relatives is 7.8%; with 1 affected relative, 13.3% and with 2 affected relatives, 21.1%. Also, the younger the relative was when she developed the disease, the greater the risk of developing breast cancer. (Collaborative Group on Hormonal Factors in Breast Cancer 2001). However, in the majority of affected women, the cause is unknown, rather than due to known high risk genetic or shared lifestyle factors.

The majority of cases of breast cancer arise in women with no apparent close family history. Between 6-19% of women with breast cancer will have a family history of the disease (Department of Health 2000, Hill et al 1997). Given that breast cancer is common, a family history of breast cancer does not inevitably point to a shared cause. Hereditary breast cancer is characterized by an unusually high number of family members affected with breast or related cancers, typically at a younger age than observed in the general population. If there have been more cases of breast cancers in families than would be expected by chance alone, it may be that genes transmitted between generations are sufficient to cause or, more likely, contribute to the development of breast cancer.

About 5% of all breast cancers are largely attributable to inherited mutations in specific genes including BRCA1, BRCA2 and TP53 (Peto J et al., 1999, Anglian Breast Cancer Study Group 2000, Walsh T et al., 1995, Ford D et al., 1995). The lifetime risk of breast cancer in women with a mutation in one of these genes is substantially increased compared to the general population (Antoniou A et al 2003). Such an inherited predisposition to breast cancer is usually characterized by early age of onset, a high incidence of bilateral disease and with a family history of other malignancies.

Breast cancer occurring in a woman with a family history of the disease is known as “familial breast cancer”. Sometimes the term “hereditary” breast cancer is used to describe breast cancer in families with an apparently dominant inheritance suggesting that a high penetrance breast cancer risk gene is segregating in that family. However, not all such familial clusters can be explained by known breast cancer susceptibility genes. Breast cancer occurring in a woman without a family history is often referred to as “sporadic”, but this should not be interpreted as non-genetic, as all breast cancer has a polygenic

1 component to its etiology. Furthermore, some cases of “sporadic” breast cancer occur in
2 women who carry a high-penetrance breast cancer susceptibility gene mutation but do not
3 have a family history of breast cancer.
4

5 This NICE guideline provides recommendations for the classification and care of women
6 who are at an increased risk of developing breast cancer because of a family history or they
7 have a high chance of carrying a high-penetrance breast cancer susceptibility allele. The
8 purpose of the needs assessment is to provide a context to the guideline, by providing an
9 overview on the burden of the disease and the current practices in managing individuals
10 affected and at risk of familial breast cancer. A detailed report on the needs assessment is
11 available as a supplement to the guideline.
12

13 **1.2 Methodology**

14
15 Routine data from England and Wales pertaining to familial breast cancer was actively
16 sought to inform about the extent of the disease and the current practices at different levels
17 of the health care system in UK. Information from published data and ongoing projects
18 informing the burden of familial breast cancer and ongoing management of patients and
19 families with the disease amongst professionals in the primary, secondary, specialist and
20 laboratory settings were identified.
21

22 The process of needs assessment revealed a lack of published data from cancer geneticists
23 and gynaecological oncologists, who play a vital role in the management of patients and
24 families with familial breast cancer. Hence dedicated surveys were carried out in these
25 groups of professionals to build the necessary dataset.
26

27 The questionnaire for the cancer geneticists was aimed at obtaining data on the burden of
28 familial breast cancer and current management practice pertaining to referrals, triaging
29 process, risk assessment, genetic testing, screening and advice on risk- reducing surgeries
30 in this group of patients. This group of professionals were also asked to comment on any
31 issues concerning provision of genetic services for familial breast cancer based on individual
32 experience.
33

34 The questionnaire for gynaecological oncologists was designed to gather information on the
35 demand familial breast cancer posed on gynaecological services and the practices
36 surrounding risk- reducing surgery, ovarian screening and hormone replacement therapy.
37

38 The questionnaires were generated with input from members of the guideline development
39 group (GDG) and then set up as a web based survey by the NICE- NCC team.
40

41 The respective web-based surveys were circulated by electronic mail with a cover letter to all
42 the consultant cancer geneticist members of cancer genetics group (CGG) and the
43 consultant gynaecological oncologist members of the British Gynaecological Cancer Society
44 (BGCS).
45

46 **1.3 Disease Burden**

47 **International cancer risk communication study (InCRisC) data**

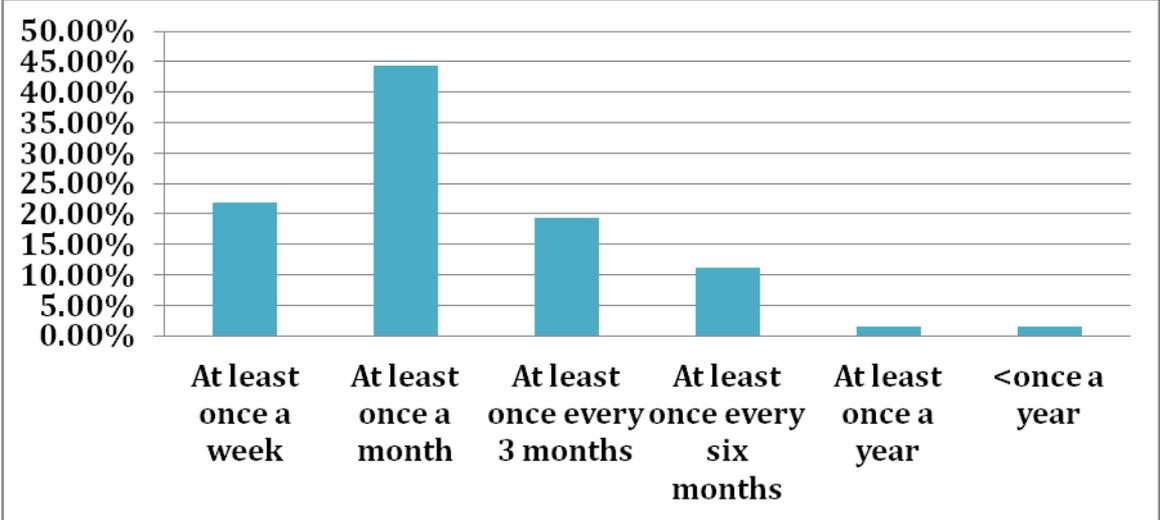
48
49
50
51 InCRisC (Harris H et al 2011) was a questionnaire-based multicentre European research
52 project on cancer risk communication, predictive testing and management of familial breast

1 cancer in primary care and by breast surgeons in the United Kingdom, France, Germany
2 and Netherlands.

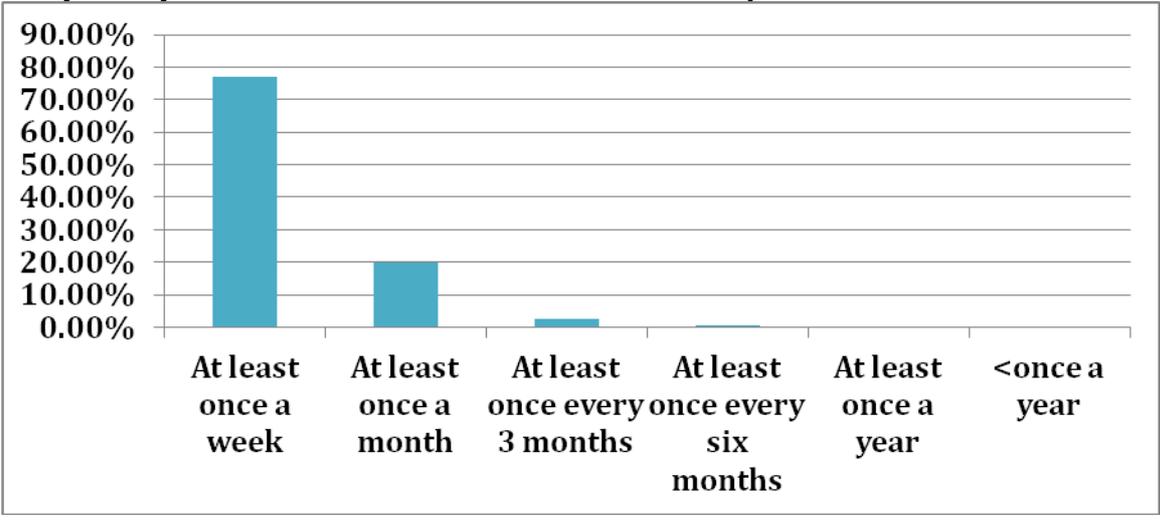
3
4 The data from the UK was included in this needs assessment. A total of 197 general
5 practitioners from all over UK representing GP practices located in the inner city, suburban
6 and rural areas with an average work experience of 16.77 ± 9.36 years participated in the
7 study. A total of 156 breast surgeons working in NHS district general hospitals, university
8 teaching hospitals and private practice with an average work experience in breast surgery
9 and oncology of 14.66 ± 8.88 years responded to the questionnaire.

10
11 The InCRisC data suggests that general practitioners in UK are engaged in consultation
12 involving family history of breast cancer ranging between once a week to once in 6 months,
13 while majority of the breast surgeons are engaged in such consultations once a week.
14 (Figure 1.1 and 1.2). This data informs on the demand posed by familial breast cancer on
15 primary and secondary health care.

16
17 **Figure 1.1: Frequency at which general practitioners in UK are engaged in a consultation**
18 **involving family history of breast cancers.** *Data Source: InCRisC study*



19
20
21 **Figure 1.2: Frequency at which breast surgeons in UK are engaged in a consultation involving**
22 **family history of breast cancers.** *Data Source: InCRisC study*

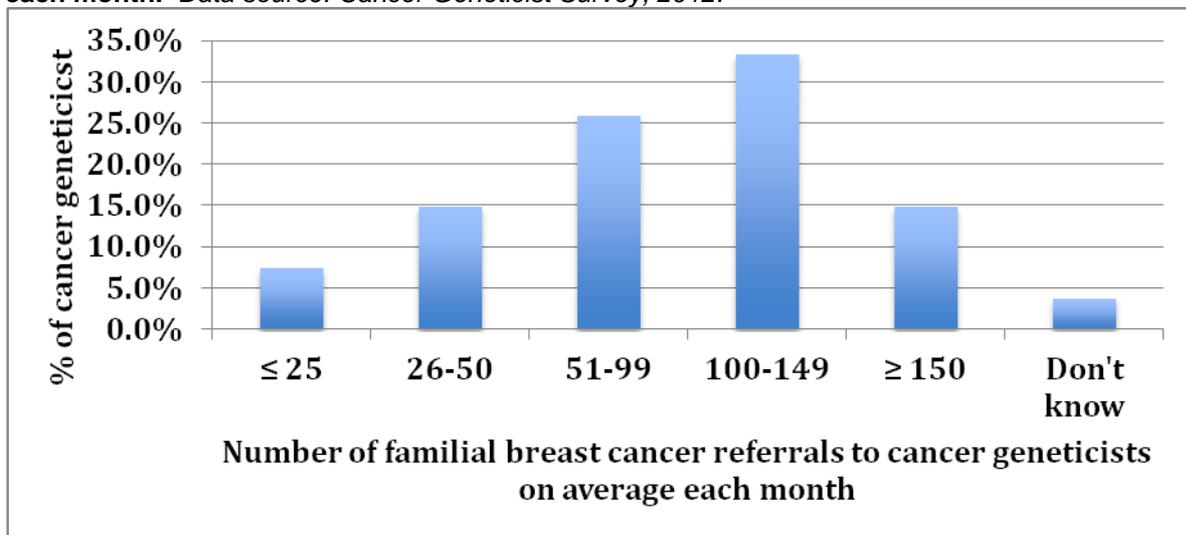


1 **Needs assessment Cancer Geneticist GDG survey data**

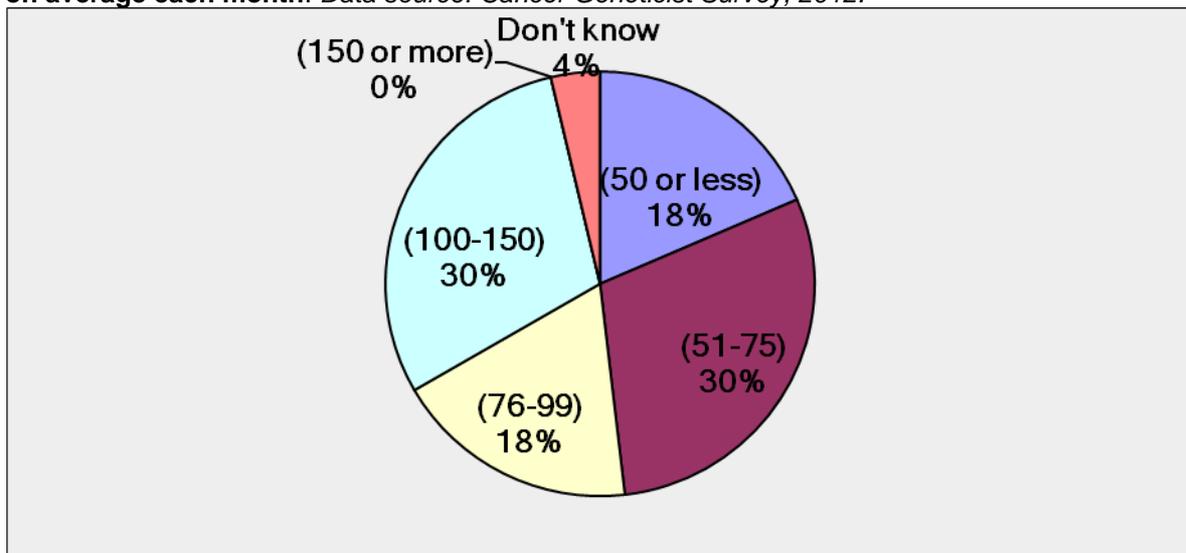
2
3 A total of 27 responses were obtained from the cancer geneticists. The survey responses
4 were representative of 17 major genetic centres in England, Wales and Northern Ireland.
5 The population covered by the cancer teams in these genetic centres varied from 300,000 to
6 5 million.

7
8 Usually affected individuals and other members of the family at-risk of familial breast cancer
9 are referred to cancer genetics team following initial risk assessment by primary or
10 secondary care professionals. 16 of the 27 (59.2%) cancer geneticists were referred
11 between 50-150 patients and a further 4 (14.8%) were referred more than 150 patients with
12 a family history of breast cancer on average each month (Figure 1.3). A majority of cancer
13 genetics teams reviewed between 50-150 breast cancer families each month (Figure 1.4).

14
15 **Figure 1.3: The number of familial breast cancer referrals to cancer geneticists on average**
16 **each month.** *Data source: Cancer Geneticist Survey, 2012.*



17
18
19 **Figure 1.4: The number of familial breast cancer families reviewed by to cancer genetics teams**
20 **on average each month.** *Data source: Cancer Geneticist Survey, 2012.*



21
22 (Values in bracket denote the number of referrals)

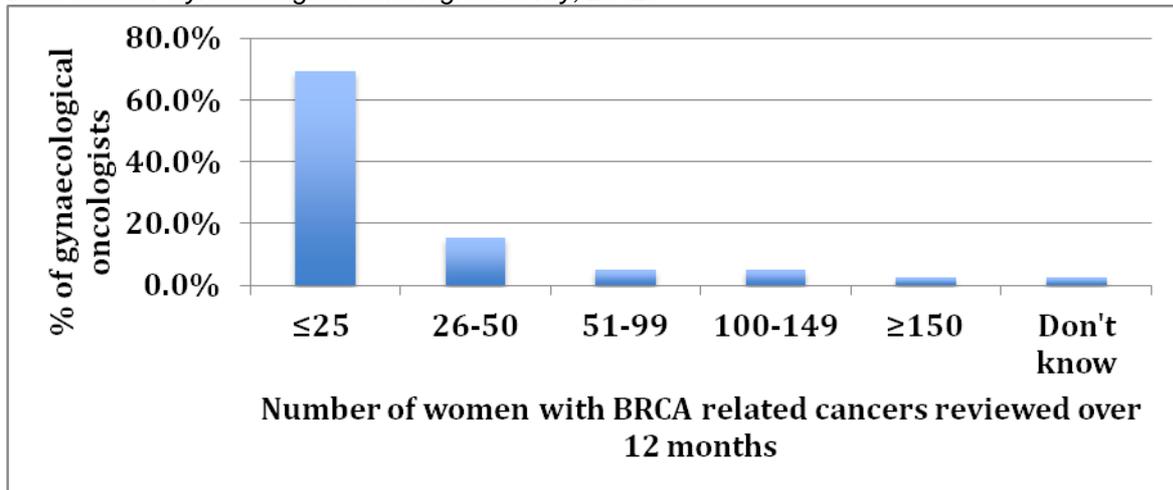
1 **Needs assessment Gynaecological Oncologist GDG Survey data**

2
3 Consultant gynaecological oncologists from all over UK responded to the GDG survey. A
4 total of 41 responses were obtained from this group of professionals catering to populations
5 ranging between 250,000 to 6 million. 28 (70%) of these gynaecological oncologists were
6 based in hospitals linked to clinical genetics services.

7
8 Women presenting to gynaecological oncologists with ovarian cancer could have a
9 significant family history of BRCA related cancers (breast, ovarian or related cancers).
10 Women at high risk of a BRCA gene mutation are usually referred to the gynaecological
11 oncologists to discuss options of ovarian screening or risk reducing oophorectomy. 35 of the
12 41 (89.7%) respondents reviewed less than a 100 patients with a family history of BRCA
13 related cancers (breast, ovarian or related cancers) over a year and a significant proportion
14 of them reviewed less than 25 with a family history of BRCA related cancer in this period
15 (Figure 1.5). The survey showed that the gynaecological oncologists in the UK generally
16 performed between 1 and 50 risk reducing oophorectomies in women with a family history of
17 BRCA related cancers over a one-year period (Figure 1.6).

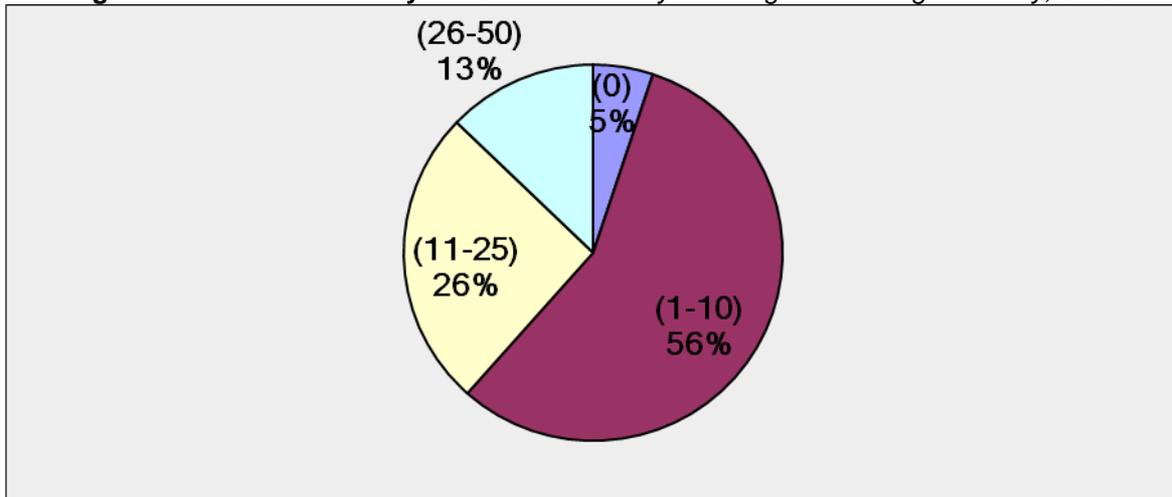
18
19 **Figure 1.5: The number of patients with family history of BRCA related cancers (breast,**
20 **ovarian and related cancers) reviewed by gynaecological oncologists in UK over one year.**

21 *Data source: Gynaecological Oncologist Survey, 2012.*



22
23

1 **Figure 1.6: Number of risk-reducing salpingo oophorectomies performed by gynaecological**
 2 **oncologists in the UK over one year.** *Data source: Gynaecological Oncologist Survey, 2012*



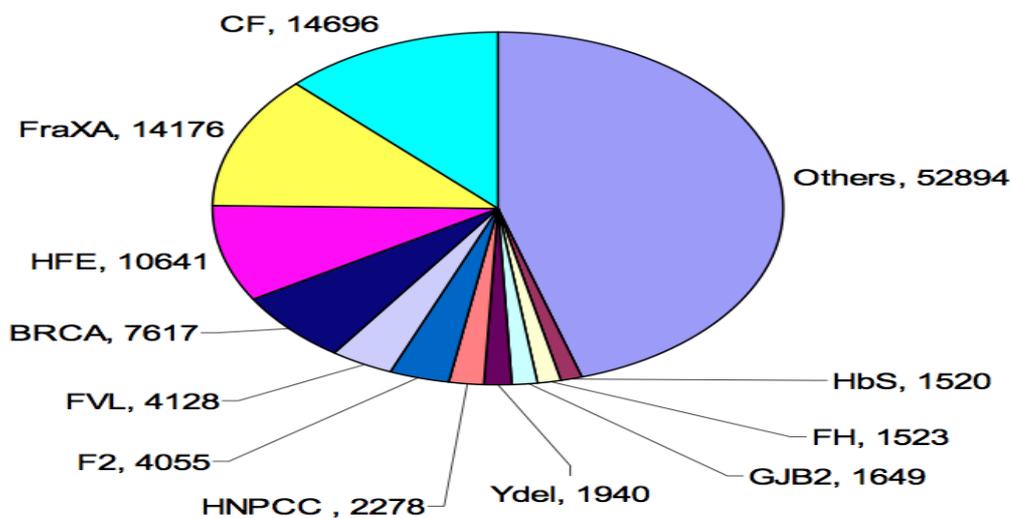
3
 4 *Values in bracket denote the number of patients.*

6 **Clinical Molecular Genetics Society (CMGS) audit**

7
 8 The Clinical Molecular Genetics Society (CMGS) produce an annual report based on an
 9 audit of the genetic testing activity undertaken by the member laboratories. The audit
 10 commenced in 1993 and the member laboratories represented in the CMGS audit comprise
 11 nearly all of the UK Regional Molecular Genetic Services and some specialist services. The
 12 audit data includes information on the number of samples received and extracted, the
 13 number of predictive and confirmatory tests carried out and reporting times. This data is a
 14 useful reference source for estimating the volume of activity and reporting times of BRCA
 15 genetic tests amongst the molecular genetics laboratories at a national level.

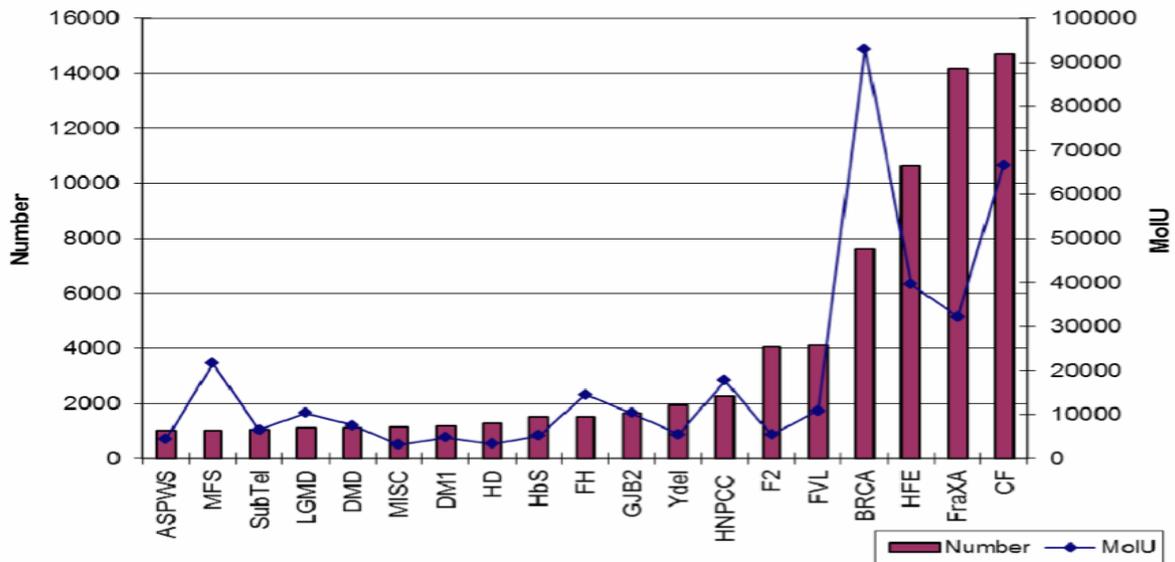
16
 17 The CMGS audit data showed that BRCA testing accounted for 6.5% (7617 of a total of
 18 117,117) of all the specialized test categories (with more than 1500 reports) (Figure 1.7) and
 19 the highest contributor of workload during 2010-2011 (Figure 1.8).

20
 21 **Figure 1.7: Depicts individual specialised genetic test categories that account for more than a**
 22 **total of 1500 reports.** *Data source: CMGS audit report, 2010-2011*



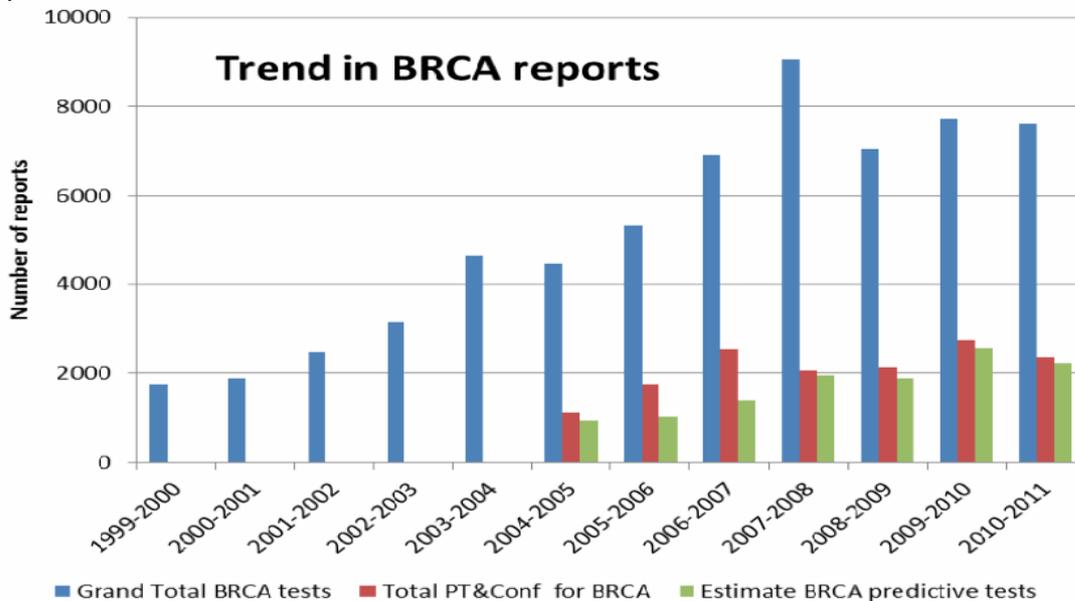
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 24

1 **Figure 1.8: Individual specialised genetic test categories (postnatal) that account for more**
 2 **than 1000 reports (number of reports) together with the associated workload (MoIU).** Data
 3 source: CMGS audit report, 2010-2011



4
 5
 6 The total numbers of BRCA tests have generally been following an increasing trend followed
 7 by a plateau, with a peak during 2007-2008 (Figure 1.9). This peak can be explained by
 8 backlog testing undertaken during this period in patients who had limited screening prior to
 9 2003. This followed publication of CG14 in 2004, which advised complete screening for
 10 BRCA1/2.

11
 12 **Figure 1.9: Trend in test activity for breast/ovarian cancer to show the grand total and**
 13 **component number of predictive (PT) and confirmatory (Conf) tests** Data source: CMGS audit
 14 report, 2010-2011



15
 16
 17 The most recent audit data (2010-2011) showed 70% and 74% compliance to target
 18 reporting times for routine complex (a full BRCA1 and BRCA2 gene screening within a 8
 19 week target) and routine simplex 2W (screening for specific familial BRCA gene mutation
 20 within 2 weeks target) BRCA tests respectively (Table 1.1). The target reporting times for
 21 routine complex and routine simplex BRCA tests for UK molecular genetic labs at the

1 present time is 8 weeks and 2 weeks respectively. The reporting times measured the interval
2 between the activation of the genetic test to when the results are reported, and because time
3 between taking the sample and activation was not measured, the data does not always
4 accurately reflect the waiting time for patients.

Table 1.1: Average reporting times for BRCA genetic test between labs. Routine complex indicates full screening for BRCA1 and BRCA2 genes, routine simplex indicates screening for a specific familial BRCA gene mutation. 2W and 4W indicate 2 weeks and 4 weeks reporting times.

Data source: CMGS audit report, 2010-2011

Gene(s)	Disease	Average																%																	
		Routine complex	Routine complex	Routine complex	Routine complex	Routine simple 2W	Routine simple 2W	Routine simple 2W	Routine simple 2W	Routine Simple 4W	Routine Simple 4W	Routine Simple 4W	Routine Simple 4W	Urgent	Urgent	Urgent	Urgent	Routine complex	Routine complex	Routine complex	Routine simple 2W	Routine simple 2W	Routine simple 2W	Routine Simple 4W	Routine Simple 4W	Routine Simple 4W	Urgent	Urgent	Urgent						
		Min	Max	Mean	count	Min	Max	Mean	count	Min	Max	Mean	count	Min	Max	Mean	count	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean						
2010-11	FAMILIAL BREAST & OVARIAN CANCER	22	237	55	11	7	10	8	8	7	19	13	4					27	98	70	28	98	74	78	100	89									
2009-10		22	617	110	10	7	26	12	12					2	2	2	1	1	100	51	1	94	66				100	100	100						
2008-9		20	356	89	10	6	13	11	10									7	100	61	1	95	63						62	62					
2007-8		23	381	107	9	6	62	15	12										100	39		100	62												
2006-7		24	357	105	10	8	17	12	10						1	19	7	3	9	100	42	29	87	62				100	100	100					
2005-6		76	575	256	11	7	63	24	13						5	10	7	2																	
2004-5					197	10			97	9																									

1 **Ethnic minority data**

2
3 "Ethnic Monitoring in Clinical Genetics" was a project funded by the department of
4 health and undertaken by Genetics Interest Group (GIG) in 2003. A multi-centre
5 prospective pilot study involving South -West Thames Regional Genetics Service,
6 North -West Thames Regional Genetics Service, and Leicestershire Clinical
7 Genetics Service was carried out as part of the project. The pilot study was carried
8 out in areas where minority ethnic groups made up approximately 10% of the
9 population. During the one-month study period 498 appointments were attended
10 across the three clinics. Ethnic data was gathered from a total of 459 patients, giving
11 an overall recording rate of 92%.

12
13 Chi – square analysis was used to evaluate whether the frequency of cancer
14 referrals across different ethnic groups was proportionate to the background
15 population frequency of each ethnic group. Data from the 'Mixed', 'Asian', 'Black' &
16 'Other Ethnic Group' categories was grouped together and compared with the White
17 ethnic background data. These analyses showed that there was a significant under-
18 representation of cancer referrals from minority ethnic groups. Less than 6% (6/110)
19 of all cancer referrals to clinical genetics services during the pilot period were for
20 members of minority ethnic communities (Table 1.2).

21

Table 1.2: The ethnic breakdown of all the cancer referrals seen during the study period.

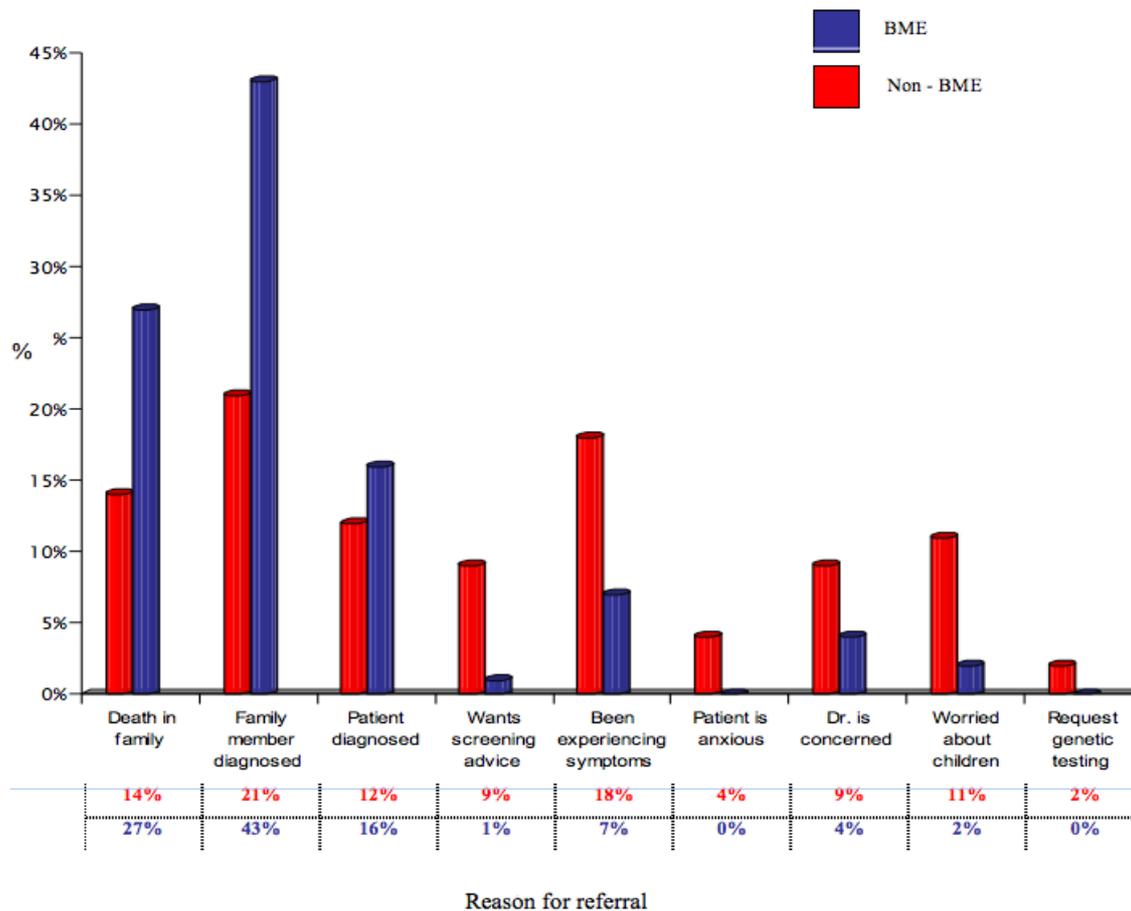
Data source: Ethnic minority in clinical genetics project report. GIG, July 2003

	North West Thames		South West Thames		Leicester		Total	
	Observed cancer referrals	Expected cancer referrals						
White	26	22	63	60	15	12.825	104	94.825
British	12		50		15			
Irish	2		1		0			
Any Other White background	12		12		0			
Mixed	1	0.754	0	1.056	0	0.18	1	1.99
White and Black Caribbean	1		0		0			
White and Black African	0		0		0			
White and Asian	0		0		0			
Any Other Mixed Background	0		0		0			
Asian or Asian British	0	3.77	0	2.44	0	1.725	0	7.935
Indian	0		0		0			
Pakistani	0		0		0			
Bangladeshi	0		0		0			
Any Other Asian Background	0		0		0			
Black or Black British	0	1.71	1	1.386	0	0.18	1	3.276
Caribbean	0		1		0			
African	0		0		0			
Any Other Black Background	0		0		0			
Other Ethnic Groups	2	0.754	2	0.924	0	0.09	4	1.768
Chinese	0		1		0			
Any Other Ethnic Background	2		1		0			
Total	29	29	66	66	15	15	110	110

1 “Tipping Points” is a study undertaken by Leicester cancer genetics services in
 2 collaboration with Genetics Alliance UK to identify the causes and quality of referrals
 3 to cancer genetics services, to promote earlier and appropriate referrals for genetic
 4 assessment. The study involved a retrospective case review of randomly allocated
 5 active files of 508 patients who were the first referred family members to a regional
 6 cancer genetics unit assessed for familial cancer risk in the preceding three years
 7 (2012-2011). Referring medical specialty, reasons for referral, family history at point
 8 of referral, and ethnicity were extracted from the family history questionnaires
 9 completed by patients on initial clinic appointments.

10
 11 The findings of the “Tipping points” project highlighted that individuals with significant
 12 family history of cancers from black and minority ethnic groups (BME) are more likely
 13 to be referred later to cancer genetics services in comparison to non-BME groups.
 14 There was a marked difference in the reason triggering referrals to cancer genetics
 15 services between the two groups. BME groups were more likely to be referred due to
 16 a recent diagnosis of cancer or death of a family member. BME groups were more
 17 than twice as likely to be referred due to a recent family member being diagnosed -
 18 at 43% for BME and 21% for non-BME. BME groups were also more likely to be
 19 referred because of a recent death of a family member at 27% versus non-BME at
 20 14% (Figure 1.10). Also of note was that non-BME groups were 9 times more likely
 21 to ask for referral because of screening advice compared to BME groups.
 22
 23

24 **Figure 1.10: Depicting the reasons for referrals from varying specialities between BME**
 25 **and Non BME groups.** *Data source: Tipping points project, 2009-2011*



1 “Access to assessment of Familial Cancer Risk by people from minority ethnic
2 backgrounds” is an ongoing research study being undertaken by Genetics Alliance
3 UK aiming to explore the reasons for under-representation of individuals from
4 minority ethnic groups with a significant family history of cancer in clinical genetics
5 services and to inform future intervention and service development. This study has
6 explored the views of health care professionals and the experiences of individuals
7 affected with or at-risk of familial cancer. The study involved in-depth interviews and
8 focus groups with a sample of 58 individuals including 15 patients with familial
9 cancers (breast, ovarian, prostate and bowel), 20 individuals at-risk of familial cancer
10 from African- Caribbean, South Asian and Irish communities and 23 health care
11 professionals. A workshop of 41 stakeholders including clinicians, service users, third
12 sector and academics was organized to discuss and analyze the qualitative data
13 obtained, to help develop findings and recommendations. Preliminary results from
14 this study has highlighted some important points that could contribute to under-
15 representation of individuals from ethnic minority groups with, or at-risk of familial
16 cancers to genetics services, such as language barrier, difficulties in providing
17 accurate information pertaining to family history, inconsistencies in following
18 guidelines for referrals and cultural influences on peoples attitude and expectations.
19 The study group has made recommendations for service and intervention
20 development based on their findings which includes, a drive towards raising
21 awareness in the minority ethnic communities, routine systematic enquiries about
22 family history of cancers in primary care, availability of simplified referral guidelines
23 and targeted education amongst clinicians involved in the care of patients with a
24 family history of cancers.

25
26 All the above projects have looked at familial cancers in general rather than familial
27 breast cancer in particular. However, individuals with and at-risk of familial breast
28 cancer form a significant part of these projects.

29 30 31 **1.4 Current practice on management of families with familial breast** 32 **cancer**

33
34 Patients with familial breast cancers and unaffected family members at-risk of familial
35 breast cancer could present to the general practitioners in primary care or to the
36 breast surgeons, breast screening team or gynaecological oncologists in a
37 secondary care setting. Following initial assessment of family history, appropriate
38 individuals are then referred to cancer genetics services. Management of affected
39 patients and individuals at risk of familial breast cancer includes risk assessment,
40 genetic testing, appropriate surveillance, potential risk reducing surgeries and
41 ongoing support, which usually involve multidisciplinary input.

42
43 As part of needs assessment, data informing the current practice amongst various
44 groups of professionals involved in the management of affected patients and family
45 members at risk of familial breast cancer was actively sought. The InCRisC data
46 informs about the current practice in primary care and amongst the breast surgeons.
47 The GDG surveys for the cancer geneticists and gynaecological oncologists included
48 specific questions to gather information on existing practice and assess any regional
49 variations in management of patients and families with familial breast cancer.

1 **Referral to local genetic services**

2

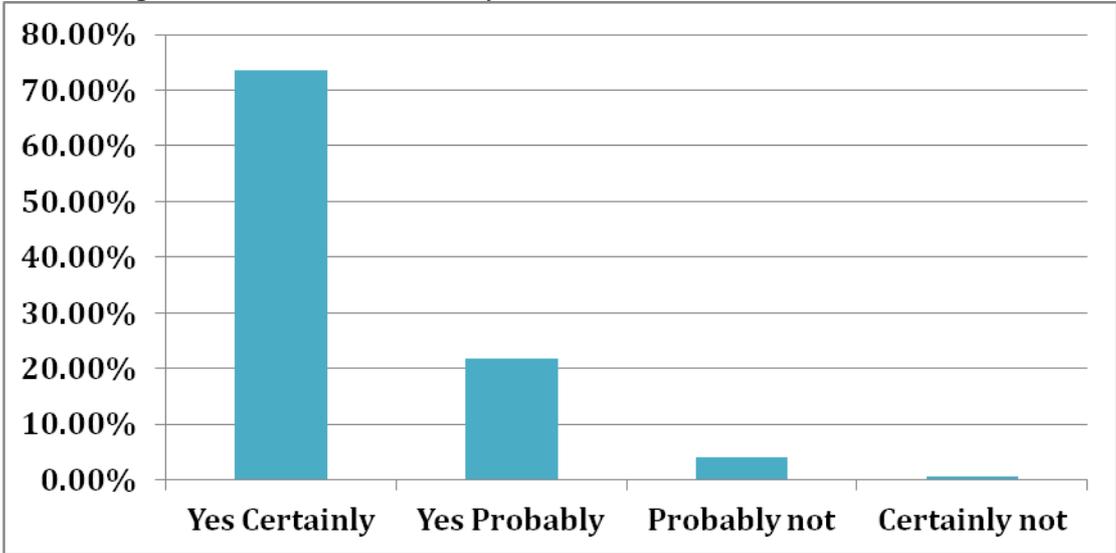
3 Most genetics centres represented on the GDG survey had specific guidelines to
4 direct primary/secondary care referrals of individuals with a family history of breast,
5 ovarian or related cancers. These guidelines were generally in keeping with the
6 NICE recommendations to ensure appropriate referrals and were made available on
7 the websites of respective genetics centres.

8

9 When presented with a specific scenario, a majority of the general practitioners and
10 breast surgeons on the InCRisC study agreed that they would refer an unaffected
11 woman with a family history of BRCA mutation for further genetic counseling (Figure
12 1.11 and 1.12)

13

14 **Figure 1.11: Responses of the general practitioners in UK on referring an unaffected**
15 **woman presenting with a family history of BRCA mutation for further genetic**
16 **counselling.** *Data source InCRisC Study*

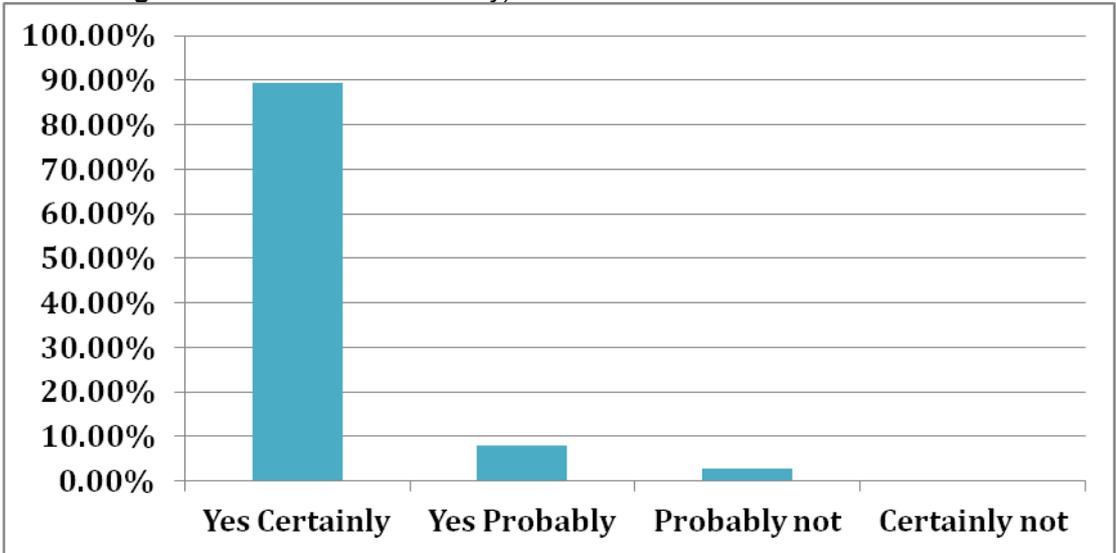


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20 **Figure 1.12: Responses of the breast surgeons in UK on referring an unaffected**
21 **woman presenting with a family history of BRCA mutation for further genetic**
22 **counselling.** *Data source: InCRisC study*



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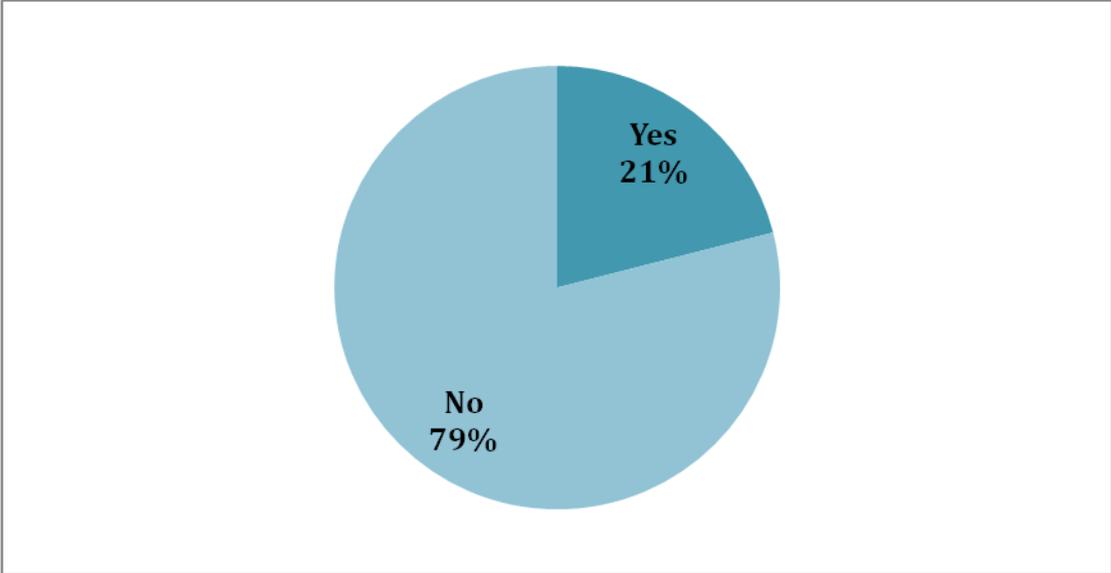
1 **Risk assessment and triaging process**

2

3 In general eligible patients and family members at risk of familial breast cancer are
4 referred to genetics services following an initial assessment of family history in a
5 primary or a secondary health care setting. Most of the breast surgeons on the
6 InCRiSC study agreed that the general practitioner should perform the initial risk
7 assessment in a healthy unaffected woman concerned about her family history of
8 breast cancer. A majority of the general practitioners replied that in everyday practice
9 they would not provide information by themselves on lifetime risk of developing
10 breast cancer or the risk of inheriting a familial BRCA mutation, to an unaffected
11 woman presenting with a significant family history of breast cancers. (Figure 1.13
12 and 1.14)

13

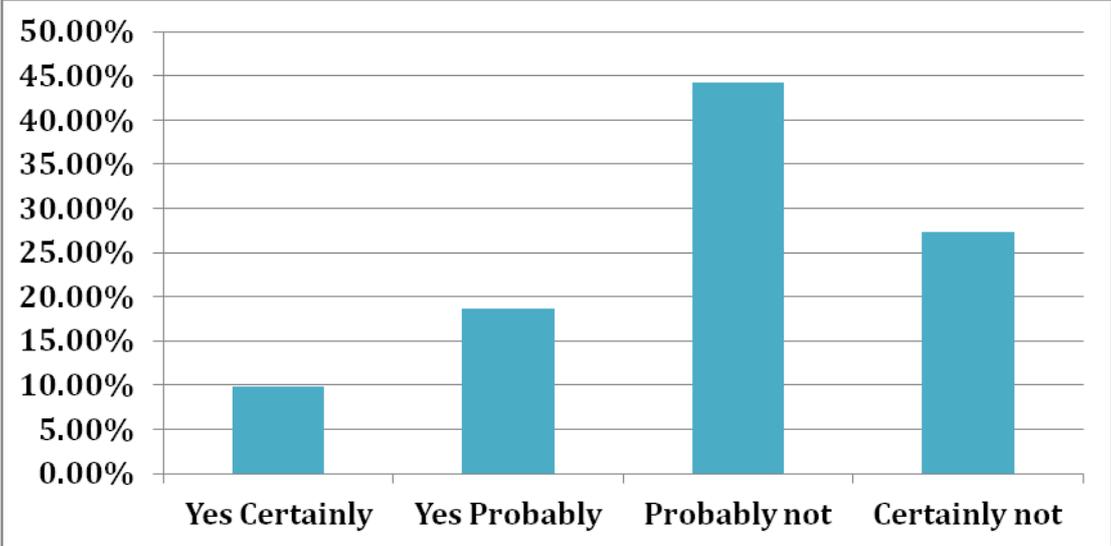
14 **Figure 1.13. Responses of general practitioners on providing information on lifetime**
15 **risk of developing breast cancer to an unaffected woman at-risk of familial breast**
16 **cancer**



17

18

19 **Figure 1.14: Responses of general practitioners on giving information on the likelihood**
20 **of carrying a BRCA mutation providing to an unaffected woman with a BRCA mutation**
21 **in the family. Data source: InCRiSC study**

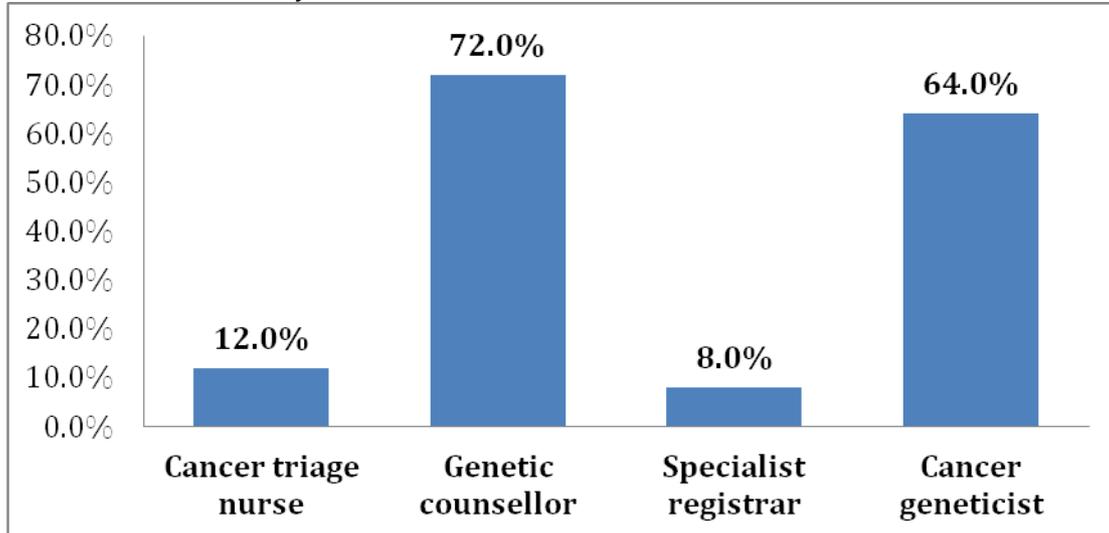


22

1 Referrals made by primary and secondary care to genetics services are triaged by
2 various members of the team including cancer geneticists, genetic counselors,
3 specialist registrars and cancer triage nurses (Figure 1.15).

4
5
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Figure 1.15: Depicting the triaging process in various genetic services. *Data source Cancer Geneticist Survey, 2012.*

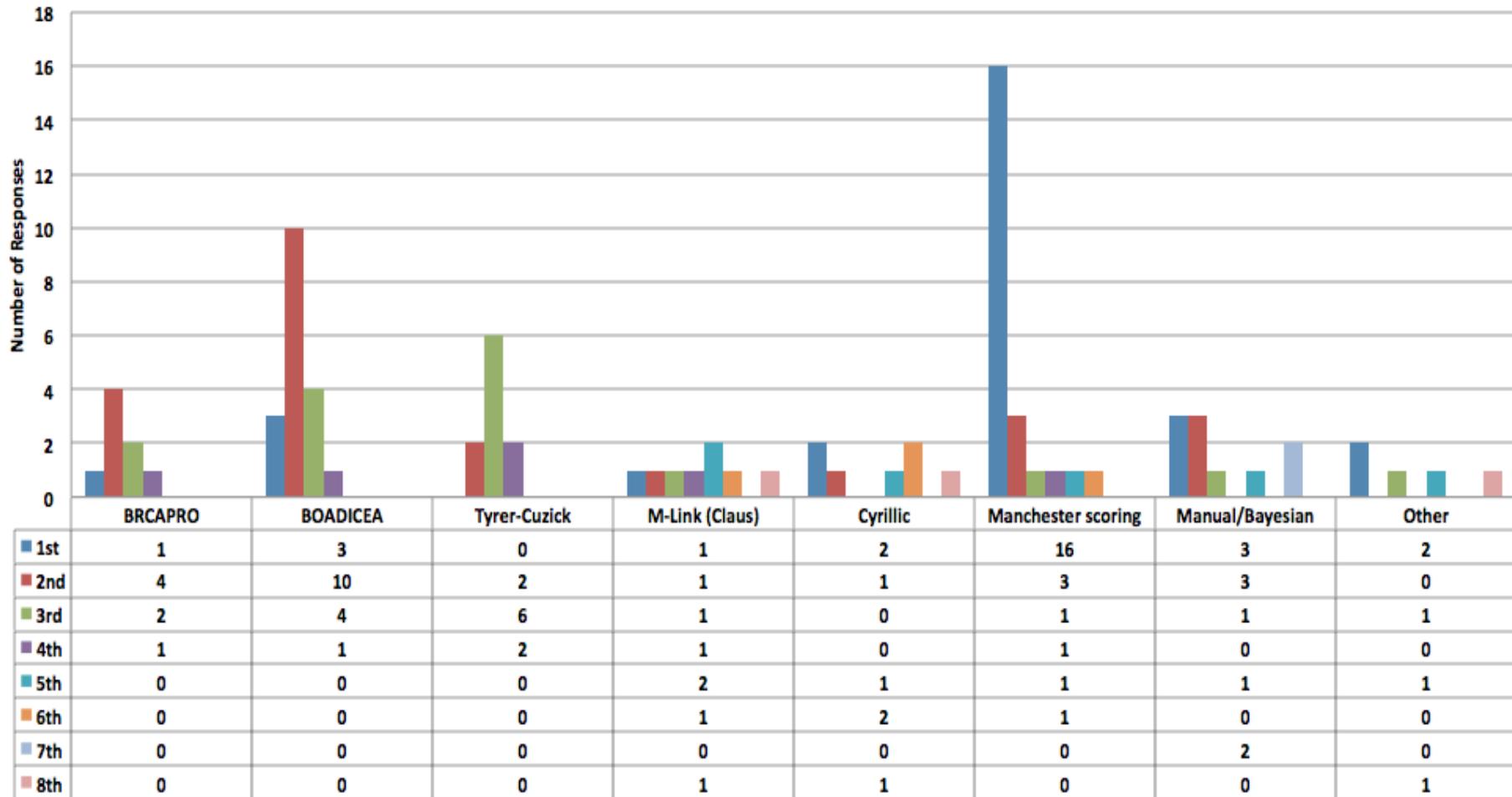


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8

9 Various risk assessment tools including the manual method, Manchester score and
10 computerized programmes are available to assess the probability of a gene mutation
11 in a family with BRCA related cancers. Most of the genetic centres use a
12 combination of these methods to aid risk assessment. Cancer geneticists were
13 asked on the GDG survey to rank the various risk assessment tools in the order of
14 the frequency used in their respective centres. The Manchester scoring system was
15 the most frequently used tool followed by BOADICEA. (Figure 1.16).

Figure 1.16: Various risk assessment tools as ranked by the cancer geneticists in the order of frequency used in their respective genetic centres.

Data source: Cancer Geneticist GDG Survey, 2012.



1 **Threshold for genetic testing**

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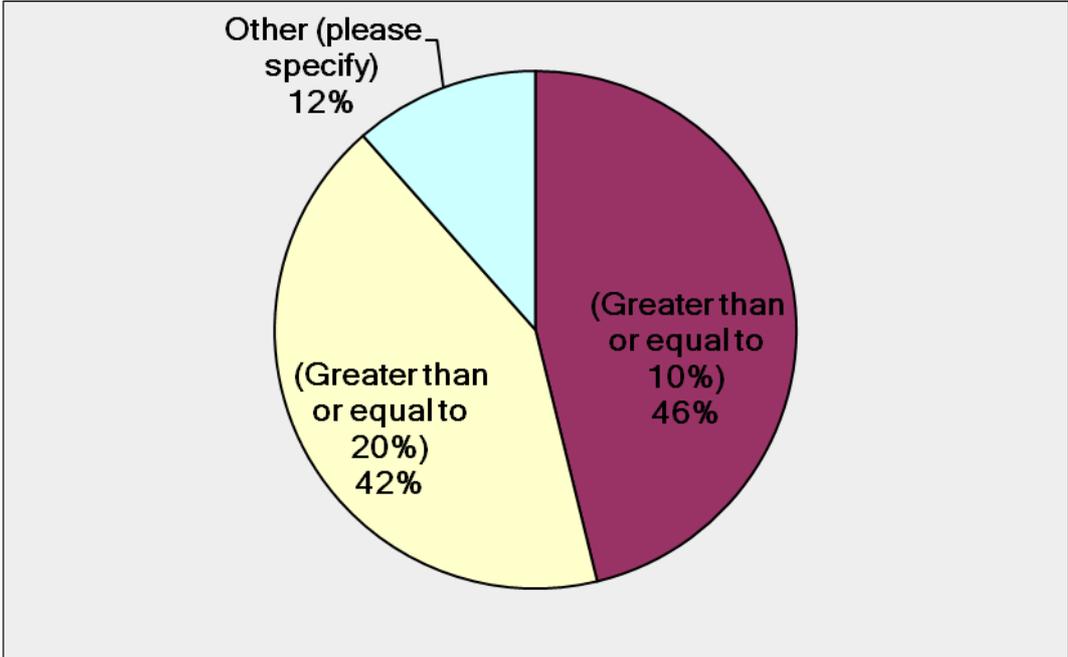
3 The familial breast cancer NICE guidance (CG14) recommends genetic testing in
4 affected women with a 20% or greater chance of carrying a mutation in a breast
5 cancer predisposing gene, based on their family history.

6

7 In practice, genetic testing is frequently offered to affected women with less than
8 20% probability of carrying a BRCA gene mutation. The GDG survey showed that
9 42% of cancer geneticists offered genetic testing to an affected woman with a
10 probability of 20% or greater of carrying a BRCA mutation. 46% of the cancer
11 geneticists used a lower threshold of 10% or greater to offer genetic testing in an
12 affected woman. (Figure 1.17). Some genetic centres offer genetic testing in
13 affected individuals where the Manchester score is 15 or above. In certain situations,
14 such as young onset “triple negative” breast cancers (estrogen receptor,
15 progesterone receptor and HER2 negative), young onset breast cancer in a small
16 family, or unknown family history, testing is often offered at a lower risk value. In
17 certain populations, such as those of Ashkenazi Jewish, Polish or Icelandic descent,
18 testing for the founder mutations is often offered before full screening of the genes.

19

20 **Figure 1.17; The threshold (probability of finding a BRCA mutation) for offering genetic**
21 **testing in affected women by cancer geneticists.** *Data source: Cancer Geneticist Survey,*
22 *2012.*



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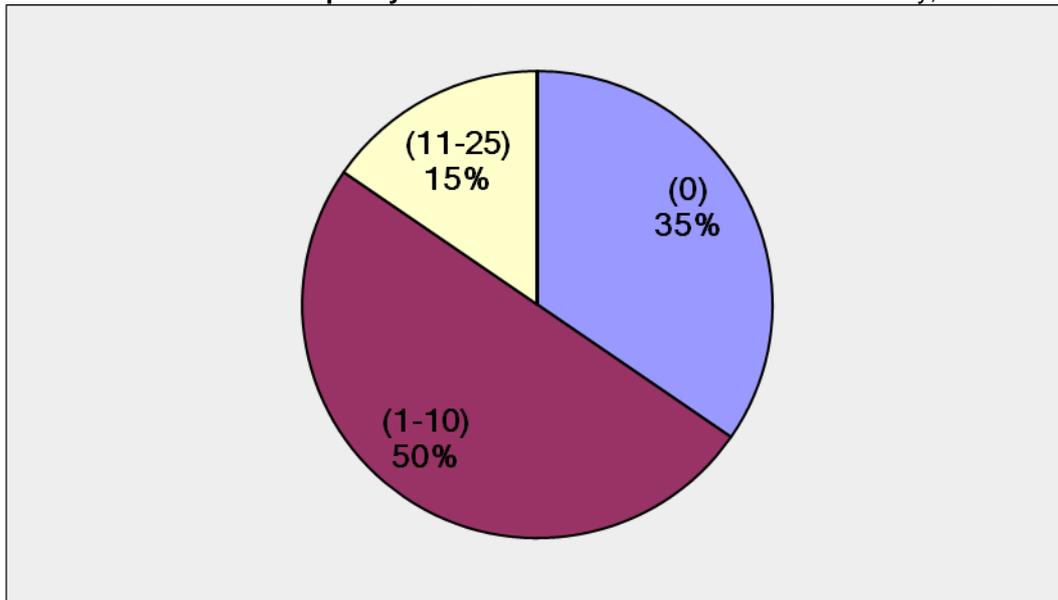
24 *Values in bracket denote the threshold used for testing.*

25

26 Generally a full BRCA1/2 genetic test to detect a familial mutation is offered in the
27 first instance to an affected individual. However, Over 65% of the cancer geneticists
28 had offered BRCA1/2 gene mutation testing to unaffected individuals who had a
29 family history of breast, ovarian or related cancers when a test could not first be done
30 in an affected relative. These situations were relatively rare with each geneticist citing
31 no more than 25 such examples per year to date. (Figure 1.18). The mutation carrier
32 probability threshold for offering testing in such instances were either greater than
33 20% or 30%.

34

1 **Figure 1.18: The frequency at which full BRCA1/2 gene mutation testing were offered in**
2 **unaffected women in the past year.** Data source: Cancer Geneticist Survey, 2012.



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4 *Values in bracket denote the number of unaffected women who were offered full BRCA1/2*
5 *genetic tests*

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8 **Surveillance**

10 Surveillance is a vital aspect of management of patients and family members at-risk
11 of familial breast cancer. Individuals at-risk of familial breast cancer are referred for
12 appropriate surveillance based on eligibility following risk assessment and/ or genetic
13 testing.

14

15 The familial breast cancer NICE guidance (2006) recommends that annual MRI
16 screening should be offered to women: i) From 30-39 years to women who have a
17 10-year risk greater than 8% ii) From 40-49 years to women who have a 10-year risk
18 greater than 20% or to women with a 10-year risk greater than 12%, where
19 mammography has shown a dense breast pattern. 17 of the 26 cancer geneticists
20 who answered the GDG survey (65.4%) reported that women under their care
21 eligible for annual MRI received the recommended surveillance. The GDG survey for
22 the cancer geneticists has highlighted marked regional variation in availability of MRI
23 surveillance for eligible high-risk women. These variations are not uncommon
24 between regions covered by the same genetics service. Frequently mentioned
25 reasons for inconsistency in availability of MRI for eligible high-risk women included
26 problems with lack of resources.

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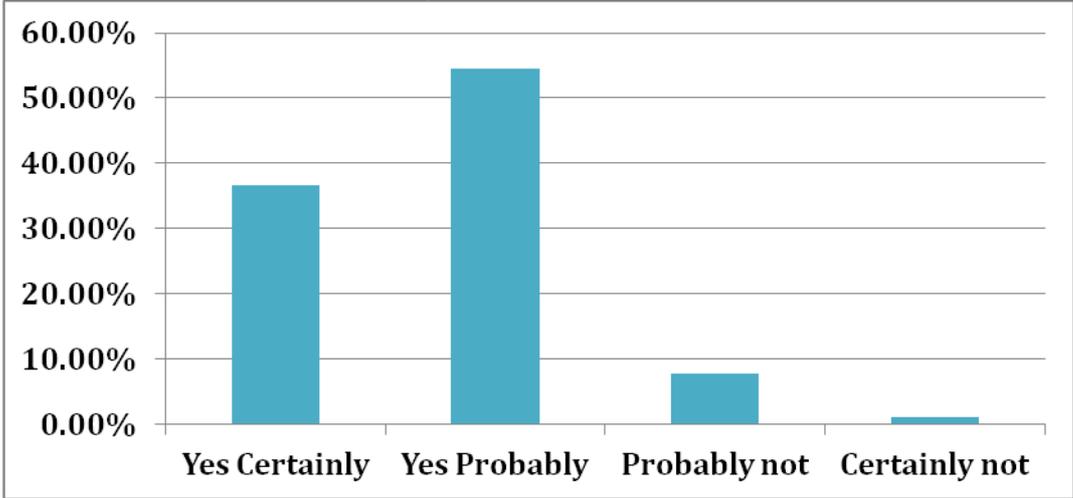
28 Ovarian screening for women who are at risk of ovarian cancers due to BRCA
29 mutation is not robust at the present time. In the past women at-risk of ovarian
30 cancers received screening as part of UK familial Ovarian Cancer Screening Study
31 (UK FOCSS), which stopped recruitment in 2010. Over 86% of the gynaecological
32 oncologists on the GDG survey offered ovarian screening as part of UK FOCSS for
33 high-risk unaffected women, who had not undergone risk reducing salpingo
34 oophorectomy. About half of the gynaecological oncologists on the survey have
35 continued offering ovarian screening outside the UK FOCSS. Ovarian screening,
36 when offered, is usually in the form of annual transvaginal ultrasound and CA125
37 levels.

1 **Risk-reducing surgeries**

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The InCRisC data suggests a wide variation in the view amongst the general practitioners about risk reducing surgeries as a management option for unaffected BRCA carrier women. About 1 in 3 general practitioners who took part in the study thought that risk-reducing mastectomy was ‘certainly’ an option for an unaffected BRCA carrier woman, while a small proportion of general practitioners on the study did not consider it as an option for the same group of individuals (Figure 1.19).

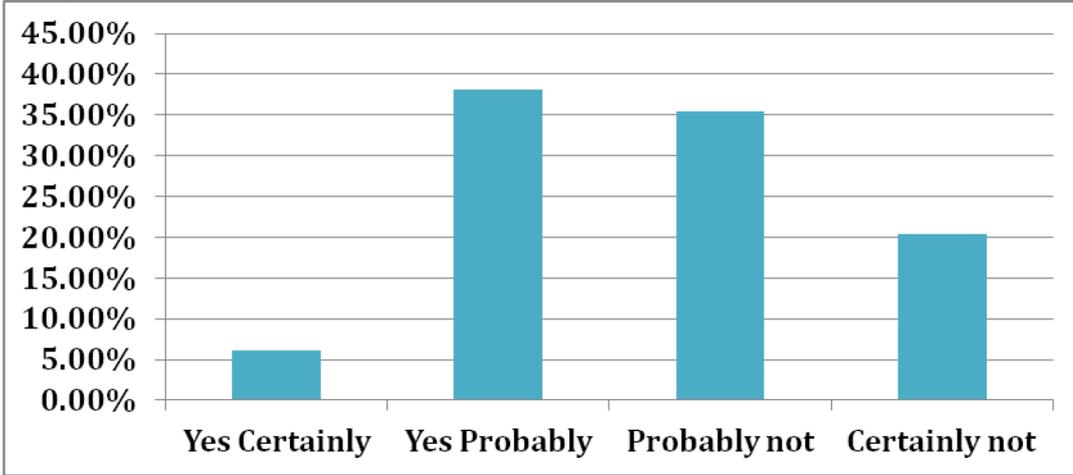
10 **Figure 1.19: The responses of general practitioners in UK on their belief about risk**
 11 **reducing mastectomy as a possible management option for unaffected BRCA carrier**
 12 **women: Data source: InCRisC study**



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The breast surgeons in general considered risk reducing mastectomy and risk reducing oophorectomy before the age of 40 as an option for an unaffected BRCA carrier woman. A proportion of the breast surgeons would consider discussing the option of risk reducing mastectomy with an unaffected woman with a significant family history of young onset breast cancers in the absence of a BRCA gene mutation detected in the family. (InCRisC study) (Figure 1.20)

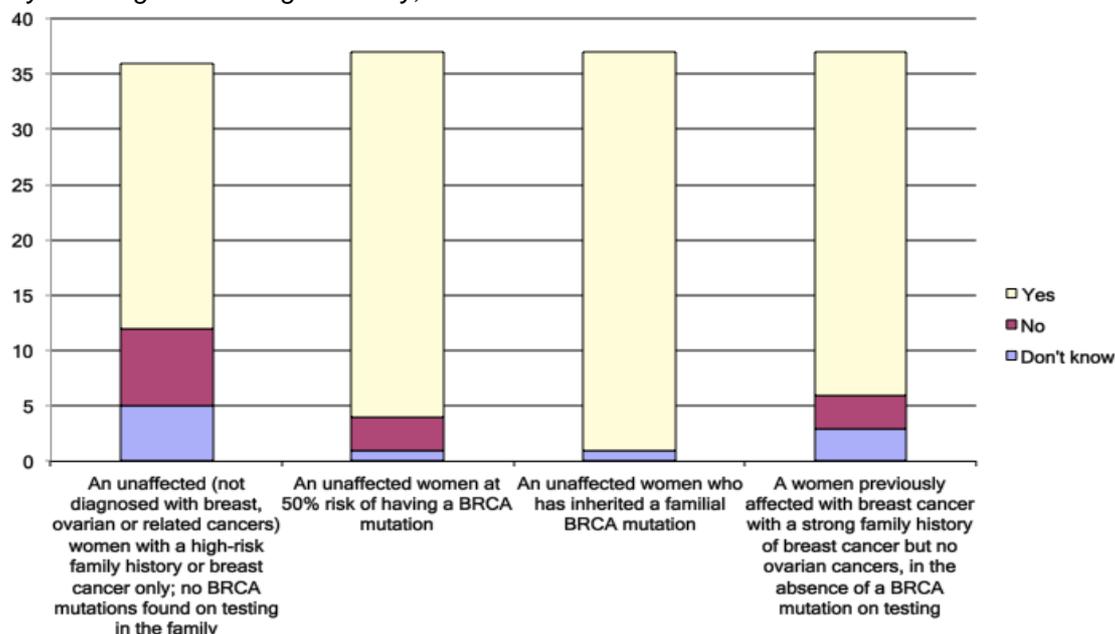
22 **Figure 1.20: Responses of the breast surgeons in UK on their practice of discussing**
 23 **the option of risk reducing mastectomy with an unaffected woman with a significant**
 24 **family history of young onset breast cancers in the absence of BRCA mutation in the**
 25 **family. Data source InCRisC study**



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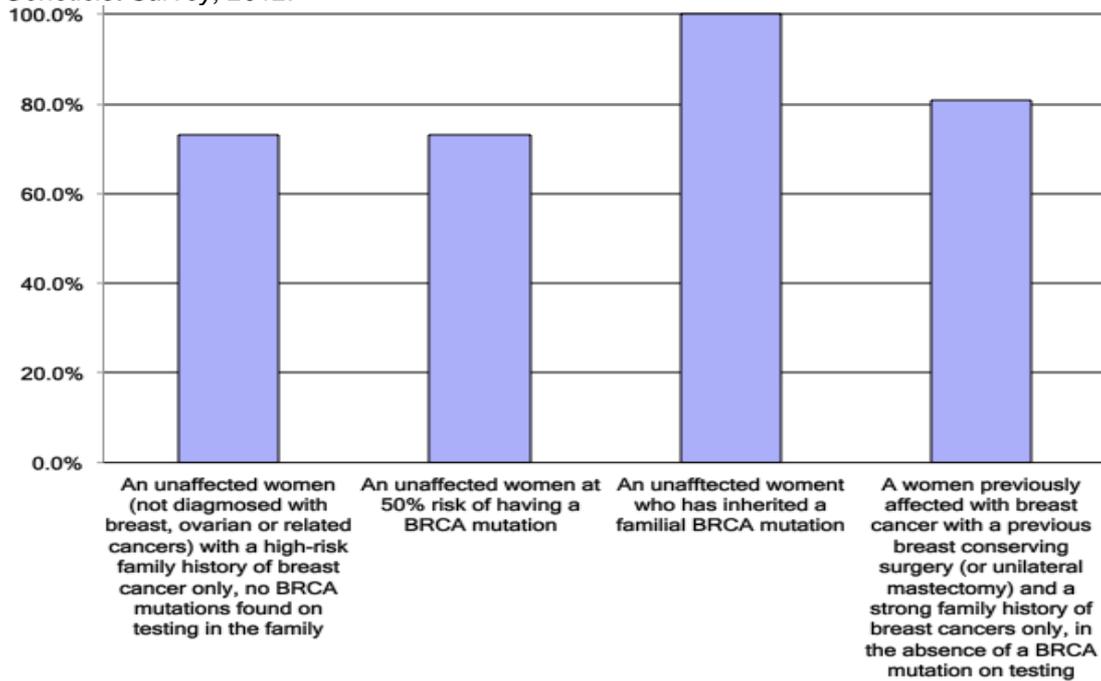
Specific scenarios were presented to the gynaecological oncologists as part of the GDG survey to gather information on clinical practice in management of high-risk women and BRCA carriers with respect to risk reducing oophorectomy. A majority (24 of the 36 respondents) of gynaecological oncologists agreed that they would discuss the option of risk reducing oophorectomy in an unaffected woman with a high-risk family history of breast cancers, with no BRCA mutations detected in the family on testing and more so (31 of the 37 respondents) in an affected woman with a past history of breast cancer in the same situation. A vast majority of the participants agreed that they would discuss the option of risk reducing oophorectomy in unaffected women at 50% risk of familial BRCA mutation and with known BRCA carriers (Figure 1.21).

Figure 1.21: The responses of gynaecological oncologists regarding advice on risk-reducing oophorectomy in high-risk women in various clinical scenarios. *Data source Gynaecological Oncologist Survey, 2012.*



A significant proportion (73.1%) of the cancer geneticists would discuss risk-reducing mastectomy in unaffected women with high-risk family history of only breast cancers, in the absence of a BRCA mutation on testing in the family, while a greater proportion (80.8%) of them would discuss this option with a woman in the same situation who was previously affected with breast cancer. All cancer geneticists agreed that they would discuss the option of risk reducing surgeries in an unaffected woman with a familial BRCA mutation (Figure 1.22).

1 **Figure 1.22: The percentage of cancer geneticists who would discuss risk-reducing**
 2 **mastectomy in various clinical scenarios to high-risk women.** *Data source: Cancer*
 3 *Geneticist Survey, 2012.*

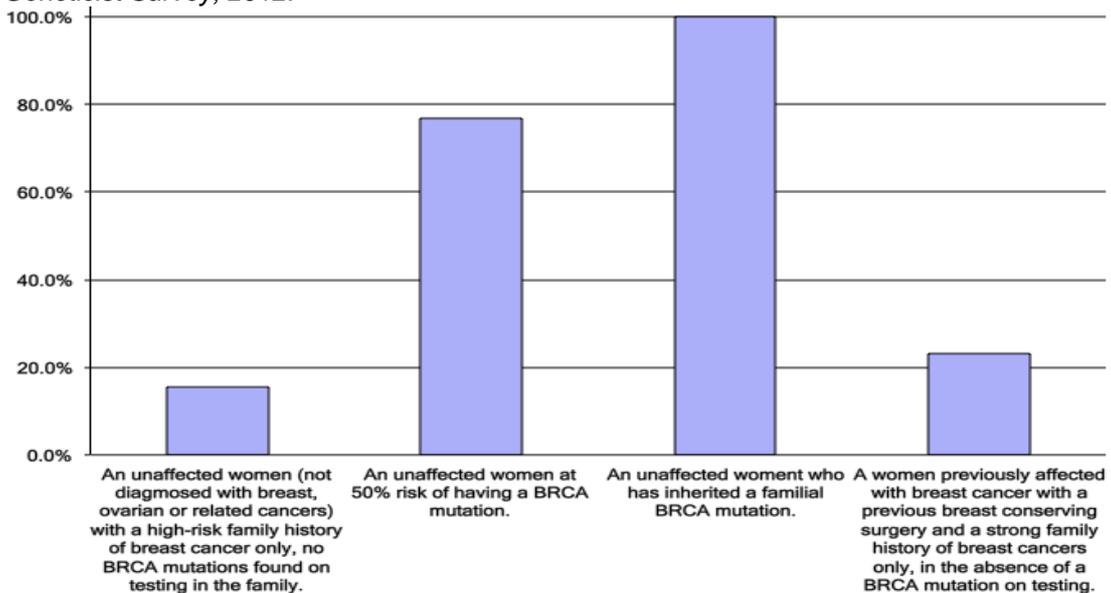


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6 In contrast to the gynaecological oncologists, a significantly smaller proportion
 7 (15.4% and 23.1% respectively) of the cancer geneticists would consider discussing
 8 risk reducing oophorectomy with unaffected women with a significant family history of
 9 breast cancers with no BRCA mutation detected on testing in the family and with
 10 affected women with a previous diagnosis of breast cancer in the same situation
 11 (Figure 1.23).

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Figure 1.23: The percentage of cancer geneticists who would discuss risk-reducing
mastectomy in various clinical scenarios to high-risk women. *Data source: Cancer*
Geneticist Survey, 2012.



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1 **Hormonal therapy**

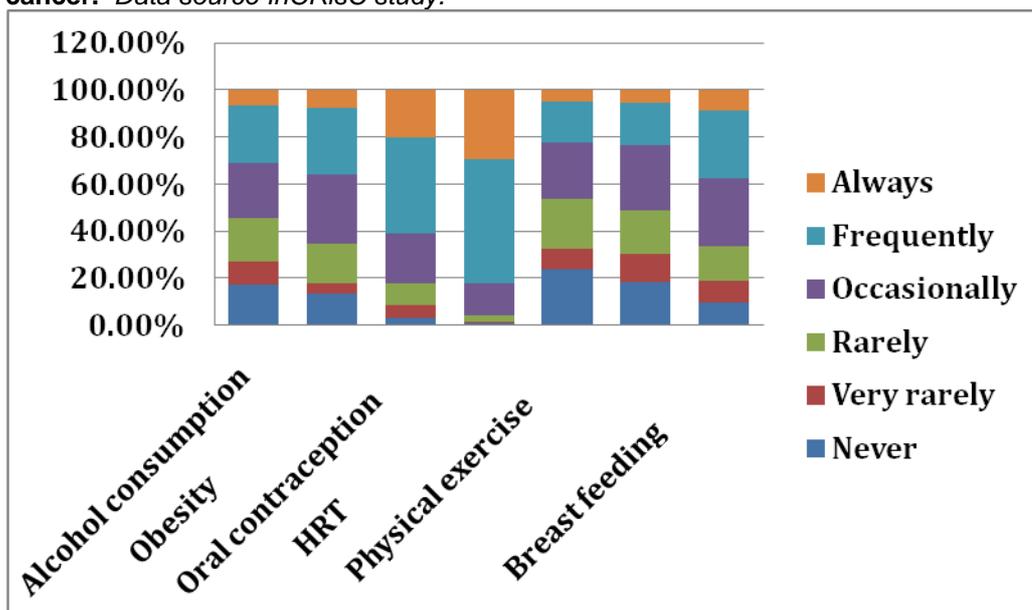
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3 All the gynaecological oncologists participating in the GDG survey agreed that they
4 would advise hormone replacement therapy (HRT) in unaffected women, who were
5 at high-risk, following a risk reducing oophorectomy before the age of 50 years. The
6 risks and benefits of HRT would be discussed. Factors that would influence advice
7 given include previous history of breast cancer, menopausal symptoms and the age
8 of the patient. The choice of HRT would depend on whether the woman still has her
9 uterus. A combined oestrogen and progesterone treatment is being offered for those
10 women who still have their uterus, while oestrogen only replacement is offered for
11 those without. HRT is usually continued till the age of 50, but other factors such as
12 risk of breast cancer, patient's decision and menopausal symptoms might modify
13 this. Gynaecological oncologists would consider HRT as a contraindication in women
14 with a previous diagnosis of ER/PR positive breast cancer, current diagnosis of any
15 type of breast cancer, or if there is a history of liver disease, deep vein thrombosis
16 and pulmonary embolism. Breast oncologists would be involved in discussions while
17 considering HRT in women with previous diagnosis of breast cancer.

18
19 88.5% cancer geneticists on the survey agreed that they would specifically discuss
20 the option of HRT, and if necessary refer unaffected high-risk women for specific
21 advice on HRT following risk reducing oophorectomy.

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23 **Life style advice**

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25 IncRisC data suggests that general practitioners sometimes offered advice on impact
26 of lifestyle on risk of breast cancers in unaffected women with family history of breast
27 cancers. Advice on the impact of alcohol consumption, obesity, oral contraception,
28 exercise, child bearing at younger age and breast-feeding were sometimes but not
29 routinely given to unaffected women at risk of familial breast cancer (Figure 1.24).
30 The breast surgeons followed a similar trend in their advice. (Figure 1.25 pertaining
31 to lifestyle factors in high-risk unaffected women)

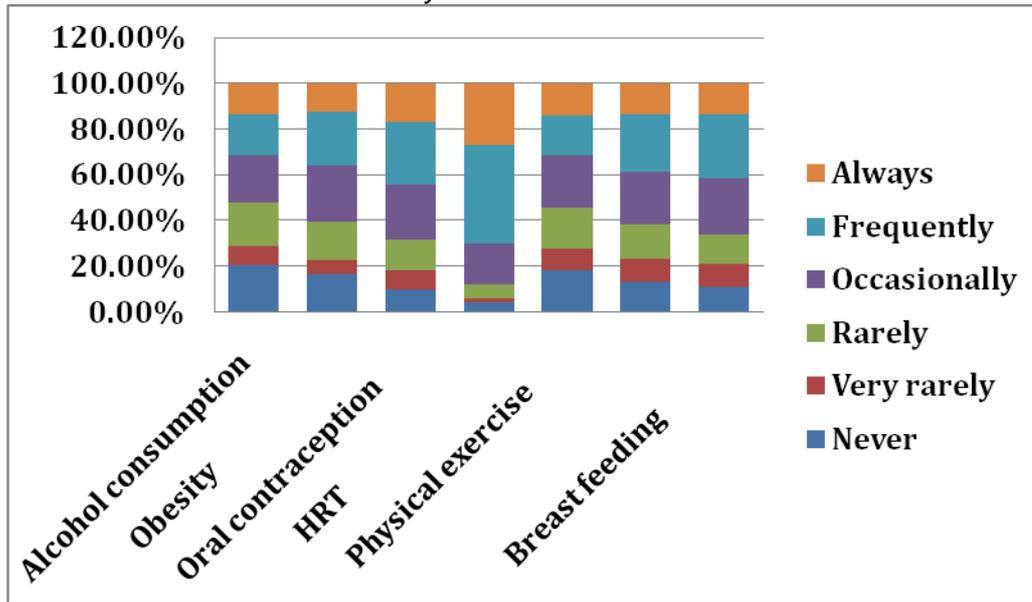
32
33 **Figure 1.24: The responses of general practitioners about their current practice on**
34 **discussing lifestyle factors with unaffected women at high-risk of familial breast**
35 **cancer. Data source InCRisC study.**



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Figure 1.25; The responses of breast surgeons about their current practice on discussing lifestyle factors with unaffected women at high-risk of familial breast cancer. *Data source InCRisC study.*



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Most cancer geneticists routinely discuss the importance of breast awareness and regular surveillance for unaffected women with a high-risk family history of breast cancer (GDG survey).

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1.5 Comments on genetic service provision

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In the GDG survey cancer geneticists raised some important issues for them about the provision of genetics services for patients and families with familial breast cancer. Frequently mentioned issues included considering lower thresholds to offer BRCA genetic testing, considering testing in unaffected individuals in the absence of a surviving affected relative, widening the gene testing profile to include other breast cancer predisposing genes and inconsistencies in screening in high-risk groups due to funding issues.

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1.6 Summary

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The process of needs assessment has highlighted the dearth of routine data informing the burden of the disease and current practice in primary, secondary and specialist care settings in management of individuals at high-risk of familial breast cancers.

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The InCRisC study and the GDG surveys have highlighted some important points pertaining to existing practice in management of women at risk of familial breast cancer.

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It is not uncommon for cancer geneticists to offer genetic testing in affected individuals with mutation probability lower than the NICE guidance (CG14) recommendation of 20%. Comments from cancer geneticists suggest a move towards increased genetic testing in clinical practice by considering testing at lower

1 threshold (lower than the 20% recommended threshold) and more frequent testing in
2 unaffected individuals than in the past.

3

4 Just over 65% of the cancer geneticists said that women with high-risk family history
5 eligible for MRI screening received recommended surveillance. Regional variations
6 in the availability of MRI surveillance for high-risk eligible women are not infrequent.
7 The stated reasons for these variations include problems with funding and lack of
8 resources.

9

10 Unaffected women with a family history of breast cancer presenting in a primary and
11 secondary care setting may not always receive advice on the impact of lifestyle
12 factors on breast cancer risks.

13

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