NHS England

Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations

Reference: NHS England xxx/x/x

Information Reader Box (IRB) to be inserted on inside front cover for documents of 6 pages and over, with Publications Gateway Reference number assigned after it has been cleared by the Publications Gateway Team. Publications Gateway guidance and the IRB can be found on the Intranet.

Clinical Commissioning Policy: Genetic Testing for *BRCA1* and *BRCA2* Mutations

First published:

Prepared by NHS England Specialised Services Clinical Reference Group for Medical Genetics

Published by NHS England, in electronic format only.

Contents

Policy Statement

NHS England will commission genetic testing for (Breast Cancer genes 1 and 2) *BRCA1* and *BRCA2* in those that have a pre-test *BRCA1* and *BRCA2* carrier probability risk of 10% or more as recommended in NICE CG 164 in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed the clinical indications for this test (*BRCA1* and *BRCA2* related breast and ovarian cancers) and the options for treatment. It has considered the place of genetic testing in current clinical practice, whether scientific research has shown the test to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for the commissioning and funding of this genetic testing service for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Specific inherited changes in the known breast cancer predisposition genes, *BRCA1* and *BRCA2*, are associated with an increased risk of developing breast and/or ovarian cancer. These genes normally repair DNA, however when these *BRCA1/2* genes contain a harmful mutation, they are no longer able to function in their normal way to prevent cancer developing. For those individuals who carry a harmful mutation in either of the BRCA genes they will have a much higher risk of developing breast and/or ovarian cancer compared with the general population.

Genetic testing for harmful *BRCA1* and *BRCA2* mutations gives people the chance to learn if their personal and/or family history of breast cancer and/or ovarian cancer is due to an inherited gene mutation. This allows them to make a choice about options that could potentially reduce their risk of developing breast and/or ovarian cancer and also their treatment options if they do develop a cancer.

This commissioning policy has been produced in order to provide and ensure equity, consistency and clarity on who should be offered genetic testing for *BRCA1* and *BRCA2* and how NHS England would commission the service.

1. Introduction

Genetic testing for *BRCA1* and *BRCA2* aims to identify harmful mutations in the genes that predispose individuals, or their relatives, to cancer. It gives people the chance to learn if their personal and/or family history of breast and /or ovarian cancer is due to an inherited gene mutation.

Having a mutation in the *BRCA1* or *BRCA2* genes can increase a woman's risk of developing breast cancer, by the age of 70, to between 65 and 85 per cent for *BRCA1* mutations and between 40 and 85 per cent for *BRCA2*. This compares with the 12.5 per cent lifetime risk for the average woman in the UK. The likelihood of breast cancer being genetic is between 1 in 20 (5 per cent) and 1 in 10 (10 per cent). Approximately 1 in 400 individuals carry a *BRCA1* or *BRCA2* mutation.

The statistics for ovarian cancer are similar. Having a harmful mutation in *BRCA1* or *BRCA2* genes can increase a woman's risk of developing ovarian cancer by the age of 70 to between 30 to 50 per cent for *BRCA1* mutations and between 10 and 20 per cent for BRCA2. This compares with the 1.5 to 2 per cent lifetime risk for ovarian cancer for the average woman in the UK.

Up to 1 in 6 (15 per cent) of people diagnosed with ovarian cancers may have inherited a harmful BRCA mutation. This accounts for 1020 of the 6800 cases of ovarian cancer diagnosed every year in the UK. (Peto J et al.,1999, Anglian Breast Cancer Study Group 2000, Walsh T et al., 1995, Ford D et al., 1995 Cancer Research, 2014).

When a woman is found to have a harmful mutation in *BRCA1* and or *BRCA2* genes interventions to reduce the risk of cancer are offered. These include earlier, more frequent and intensive cancer screening, risk-reducing medication and risk-reducing surgery. If they do get cancer, their choice of treatment options may be different from those of individuals who do not have the harmful mutation.

Genetic testing for *BRCA1* and *BRCA2* is currently commissioned by NHS England as per the Medical Genetics Service Specification. (NHS England E/01/S/a, 2013). The currently commissioned clinical practice is based on a pre-test probability of having a BRCA mutation of at least 20% as per the NICE Guideline CG41 published in 2006– the existing guideline at the time the service specification was written (NICE CG41, 2006). Since the publication of the service specification in 2013, NICE has reviewed the evidence base for the threshold of testing and published new guidance in 2013 with the threshold for testing reduced to a pre-test probability of having a BRCA mutation of 10% (NICE CG164, 2013). Whilst awaiting the updating of the relevant service specification, clinical practice has changed in some places to reflect the new recommended threshold. This has

resulted in significant variation across England of the threshold risk and therefore the eligible individuals being offered access to genetic testing for B*RCA1* and *BRCA2*. (Solomons, 2013)

In line with the most recent NICE guideline, this policy recommends that the standard for commissioning the genetic testing service should be the new NICE guideline CG164 with a lower pre-test carrier probability threshold of offering genetic testing for *BRCA1* and *BRCA2* at 10%.

The gap in the current services offered and therefore the potential resource implications of implementing testing at this threshold are highlighted.

2. Definitions

Affected relatives – A relative who currently has, or has had, malignant breast or ovarian cancer.

Bilateral breast (or ovarian) cancer – Cancer that appears in both breasts (or ovaries)

BRCA1* and *BRCA2 are human genes that produce proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material. When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. Carriers of these altered genes have been shown to be at an increased risk of developing breast, ovarian and other cancers.

Carrier – An individual who has inherited a genetic trait or mutation but does not display that trait or show symptoms of the disease. Carriers are, however, able to pass the gene onto their offspring, who may then express the gene

Pre-test Carrier probability – The probability that an individual carries a genetic mutation in one of the genes known to make individuals susceptible to developing specific cancers.

Family history – A family history of a disease of an individual is the occurrence of the disease in a blood relative of that individual.

Gene – Segments of DNA that appear on a chromosome. Genes are responsible for controlling physical and inheritable characteristics of individuals. They also specify the structure of particular proteins for normal body functions.

Pathogenic/deleterious Genetic mutation – A permanent change in the DNA

sequence that makes up a gene affecting its function. Inherited genetic mutations can be passed on from a parent to a child.

Lifetime risk – Based on a new born baby, this is an estimate of the risk of being diagnosed with cancer at some point within their lifetime.

Relatives: First degree – Closest blood relatives (being related by marriage does not count); these include: father, mother, son, daughter, brother, sister. They are on both the mothers and father's side of the family

Relatives: Second degree – These are blood related grandparents, grandchildren, uncle, aunt, first cousin, nephew, and niece. They are on both the mothers and father's side of the family.

Relatives: Third degree – These are blood related great grandparents, great grandchildren, great uncle, great aunt, children of great uncle or great aunt, second first cousin, children of first cousin, grand-nephew and grand-niece. They are on both the mother and father's side of the family.

Risk –A person who inherits a faulty gene is more likely to develop cancer than the average person, i.e. be at greater risk, however it does not mean that they will definitely develop disease.

Risk factor – A clearly defined occurrence or characteristic that, in research studies of similar people, has been associated with the increased rate of a subsequently occurring disease or health problem. Risk factors include aspects of personal behavior, lifestyle, environmental exposure, or inborn or inherited characteristics, which are known to be associated with the disease.

3. Aim and objectives

This policy aims to :
Specify the conditions under which genetic testing for *BRCA1* and *BRCA2* will be routinely commissioned by NHS England as a means of identifying people who are at a significantly higher risk of developing breast, ovarian or other linked cancers.

The objectives are to:

- Ensure that all those with 10% or greater carrier probability risk of having a genetic mutation in the *BRCA1* and/or *BRCA2* gene are offered a genetic test to identify definitively if they are carriers.
- To reduce the current unacceptable variation in access to genetic testing for

BRCA1 and *BRCA2*.

- To reduce the incidence of BRCA related breast and ovarian cancers in the English population

4. Epidemiology and needs assessment

Understanding the epidemiology of harmful *BRCA1* and *BRCA2* mutations is important as it helps define the characteristics of individuals and families who are likely to be at a high risk of having a harmful mutation of the BRCA genes and therefore might benefit from a referral for genetic counselling and testing.

The impact of *BRCA1* and *BRCA2* on Breast and Ovarian Cancer Risk

In the general population, 12.3% of women will develop breast cancer during their lifetime and 2.74% will die of the disease, whereas 1.5% - 2% of women will develop ovarian cancer and 1.0% will die of the disease (Nelson, 2013). As previously stated, various international studies have shown that these risks are significantly increased when an individual has a harmful mutation of *BRCA1* and or *BRCA2* (Walsh T et al., 1995, Ford D et al., 1995, Peto J et al.,1999, Anglian Breast Cancer Study Group 2000, Antoniou et al, 2000, Antoniou et al, 2003, Chen et al, 2007). The most recent findings from a prospective follow up of patients in the UK are shown in table 1 below[1] (Mavaddat et al, 2013).

Table 1: The Impact of *BRCA1*and *BRCA 2* mutations on Breast and Ovarian Cancer Risks (Mavaddat et al, 2013)

Disease	Risk if you do not have mutation in *BRCA 1 or 2*	Risk of Developing Disease if you have a mutation in	
		BRCA1	***BRCA2***
Breast cancer, in unaffected women (up to age 70)	12%	60%	55%
Ovarian cancer, risk (up to age 70)	2%	59%	16.5%
Male breast cancer, lifetime risk	0.1%	0.1–1%	5–10%

[1] Lifetime risk was calculated using 2010 data for females and 2008-2010 data for males by the Statistical Information Team at Cancer Research UK, 2012.

Additional Cancer risks for *BRCA 1* and *BRCA2*

Harmful mutations in *BRCA1* and *BRCA2* increase the risk of several cancers in addition to breast and ovarian cancer – which have been widely studied. Harmful *BRCA 1* mutations have been shown to increase a woman's risk of developing fallopian tube cancer and primary peritoneal cancer (Brose et al, 2002; Finch et al, 2006). Men with *BRCA2* mutations, and to a lesser extent *BRCA1* mutations, are also at increased risk of breast cancer (Tai et al, 2007). Men with harmful *BRCA1* or *BRCA2* mutations have a higher risk of prostate cancer (Levy et al, 2007). Men and women with *BRCA2* mutations may be at increased risk of pancreatic cancer (Ferrone et al, 2009).

Population Prevalence of BRCA 1 and BRCA 2

Harmful *BRCA 1* and *BRCA2* gene mutations are relatively rare in the general population with studies in the United States (Ford 1995, Whittemore 2004) reporting prevalence rates of 0.25 – 0.5% (between one in 400 to 800). Other studies have also reported a prevalence of 3 per cent in women with breast cancer, 6 per cent in women with breast cancer onset before the age of 40 years, 10 per cent in women with ovarian cancer and 20 per cent in high-risk families (Howlader et al, 2013) Sattery 1993, Johnson et al, 1995).

Variation among Racial and Ethnic groups

Prevalence of *BRCA1* and *BRCA2* has been found to vary by ethnic group. Among unselected Ashkenazi Jewish men and women, about 2.5% (one in 40) have a *BRCA1/2* mutation whilst prevalences of 10% have been reported in high-risk families. Table 2 below shows how the prevalence of *BRCA1* and *BRCA2* mutations varies among breast cancer survivors from different ethnic groups in the US.

Table 2: Prevalence of *BRCA1* and *BRCA2* mutations among women with breast cancer by ethnic group (U.S.)

Racial/Ethnic Group	BRCA1	BRCA2
Asian American	0.5%	Data not available
African American	1.3-1.4%	2.6%
Caucasian (non-Ashkenazi Jewish)	2.2-2.9%	2.2%
Hispanic	3.5%	Data not available
Ashkenazi Jewish	8.3-10.2%	1.1%

Variation among the different age groups

Sporadic breast cancer is strongly age related with only 5% of all breast cancers occurring in women under 40 years old. However studies have shown that the harmful BRCA genes have been reported in about 6% of breast cancers occurring in women under the age of 40.

Variation among the Sexes:

Breast cancer is generally more common in women; the incidence in men is low.

In summary, the epidemiology of the harmful *BRCA1* and *BRCA2* genes indicates that whilst these genes significantly increase the risk of developing breast and or ovarian cancer, the prevalence in the general population is not at a level to warrant a population screening programme. A targeted screening programme at specific populations would be useful to enable these high risk groups to adopt strategies to reduce the risk of malignancy and to improve the outcomes if they develop cancer.

Genetic testing for *BRCA 1* and *2* – A summary of the Eligibility and Anticipated Need for *BRCA1* and *BRCA2* Testing

NICE estimates that, based on the population in England, the proportion of cancers caused by *BRCA1* and *BRCA2* and the incidence of breast and ovarian cancer in England, an assessment of the need for *BRCA1* and *BRCA2* testing based on a 10% pre-test carrier probability of carrying a cancer causing mutation indicates an estimated 11,589 individuals would be eligible for the genetic test in England as shown below in table 3.

Table 3: England population eligible for *BRCA1* and *BRCA2* testing at 10% pre-test probability of a mutation threshold

Population Group	No. eligible for *BRCA1* and *BRCA2* testing
Affected people (men and women) with a family history	3863
Unaffected relatives	7726
Total no eligible for genetic testing	11,589

There is however evidence from the published literature that indicates that not all eligible patients would accept the offer for genetic testing. Current practice in England indicates about 86% of affected patients and about 50% of unaffected relatives accept the offer for *BRCA1* and *BRCA2* testing. Bennett et al 2008, Bowen et al, 2006, Helmes et al 2006)

Thus if current rates of acceptance are extrapolated to the English population, it is anticipated the need for BRCA testing will be as shown in table 4.

Table 4: England population eligible for and accepting *BRCA1* and *BRCA2* testing at 10% pre-test probability of a harmful mutation threshold

Population Group	No eligible for *BRCA1* & *BRCA2* testing
Number of women offered and who take up genetic testing (at carrier probability of 10%) – affected women	3,307
Unaffected relatives	3,845
Number of men offered and who take up genetic testing (at carrier probability of 10%) – affected men	16
Unaffected relatives	18
Total no. likely to NEED genetic testing at a pre-test probability threshold of 10%	**7,186**

Current Genetic Testing Practice

Expert opinion suggests that implementation of NICE clinical guideline 41 with a pre-test risk threshold of 20% is currently inconsistent. A survey conducted by the NICE guideline development group (GDG) of cancer geneticists and gynaecological oncologists in 2012 (prior to the development and publication of the new NICE guideline) showed that genetic testing for *BRCA1* and *BRCA2* were being offered to women with a pre-test probability of mutation of between 10% and 30%. About 46% were using a lower threshold of 10% or greater (Solomons 2013)

Based on the findings from the survey, NICE estimates that in England 34% (3,930) of eligible individuals are currently accessing genetic testing for *BRCA1* and *BRCA2*.

Gap analysis for *BRCA1* and *BRCA2* testing

Based on the numbers who have a clinical need of *BRCA1* and *BRCA2* testing at the 10% recommended pre-test threshold in this policy and current testing levels, there is a gap of 3,256 eligible patients who need to be offered the test every year.

Commissioners would therefore need to ensure adequate specialised genetic laboratory resources and resources for clinical genetics services to undertake risk assessment and counsel those individuals with mutations are available for the service to be delivered.

In addition to the increase in numbers eligible for and accepting genetic testing as a result of the decreased threshold for testing, there will be an increase and therefore an impact on a number of clinical services outside the scope of this policy document:

i. **The breast screening service** –due to an increase in the number of individuals requiring surveillance (MRI scan and mammogram)
ii. **Clinical Services** – due to an increase in the number requiring chemoprophylaxis (drug costs and 6 monthly GP checks for prescription)

iii. **Surgical services** - due to an increase in the numbers requiring prophylactic mastectomies and bilateral salpingo-oophrectoromies**.**

5. Evidence base

The evidence review presented in this section is a summary of the review underpinning NICE CG 164.

Summary of Evidence Review

In the original NICE guidance (CG14) the threshold of carrier probability risk to offer genetic testing for *BRCA1* and *BRCA2* mutation identification was set at 20%. This recommendation was set to address and reduce the known variation in clinical practice. Since 2004, the cost of genetic testing and the reporting timeframe for results has significantly decreased, due to this, a proportion of genetic centres have lowered their threshold for offering testing and by doing so, further variation in clinical practice has been introduced.

In the 2004 and 2006 guidelines (CG14 & CG41 respectively), there was no clinical evidence to compare different carrier probability risk thresholds for genetic testing. For the 2013 guidelines (CG164), the literature review was undertaken again. As before, no clinical evidence was found comparing different carrier probability thresholds for genetic testing for any of these population groups.

An important consideration of varying the genetic threshold level is the impact on the number of people that can be identified with a gene mutation and the impact of identifying these additional individuals on both cost and patient outcomes such as increased life expectancy. In the first instance an economic evaluation of the literature was undertaken and four papers were identified.

The four studies that were identified in the economic evaluation were of limited quality and robustness due to limited discussion around methodologies used to undertake literature reviews and light reporting of patient characteristics.

Balmana et al (2004) did not provide explicit population criteria, stating only those with a family history and breast cancer risk assessed by the Claus Model were included. Only an average age of 47 years was reported. Holland et al 2009 examined a 35 year old woman who had an associated family risk of breast and/or ovarian cancer. Kwon et al 2010a included women with ovarian cancer with a population including those with a family history of breast and/or ovarian cancer. Kwon et al 2010b included women in the general population with a previous 30 history of breast cancer aged 50 years and younger.

Of the interventions studied, Balmana et al looked at genetic testing with/without annual mammography with no screening. Holland et al compared genetic testing followed by preventative surgery (if applicable) with no testing but with on-going surveillance. Kwon et al 2010 (a & b) compared genetic testing with no testing. In all studies, the interventions and comparator were only briefly described.

The health outcomes were quantified in terms of Quality Adjusted Life Years (QALYs) by Holland et al (2009), with both the Kwon et all (2010a & 2010b) looking at incremental cost per life year gained (ICER).

Balmana, *et al.,* (2004) showed that the cost-effectiveness ratio of their genetic counselling and screening program was £5267.17 per life-year gained. The model was sensitive to the prevalence of mutation carriers, the lifetime risk of breast cancer and the effectiveness of the screening, suggesting that testing for breast cancer in a high risk population may be cost-effective. Holland, *et al.,* (2009) suggested that at a 10% probability of mutation, undertaking a genetic test generated 22.9 QALYs over a lifetime and cost £87,575.42, while the no genetic testing strategy generated 22.7 QALYs and cost £86,833.26. The incremental cost-effectiveness ratio of the test strategy was £6679.48 and the differences between costs and effects were not substantial.

These results were sensitive to the frequency of inconclusive test results and utility gains from a negative test result. In a cohort of women with a personal history of ovarian cancer, Kwon, *et al.,* (2010a) showed that BRCA testing based on personal/family history and ancestry could prevent future cases in first-degree relatives with an ICER of £22,589.58 per year of life (LY) gained compared with the reference strategy. In a cohort of women with a personal history of breast cancer, Kwon, *et al.,* (2010b) showed that whilst BRCA mutation testing for all women with breast cancer who were younger than 50 years could prevent the highest number of breast and ovarian cancer cases, this was not cost-effective. Testing women with triple negative breast cancers who were younger than 40 years was cost-effective with an ICER of £4,796.64 per year of life gained (£5,495.06 per QALY) and could reduce subsequent breast and ovarian cancer risks.

Based on these findings, no reliable conclusions could be drawn from these papers and therefore an economic cost-effectiveness model was built. The model outputs were used instead to formulate a conclusion on what risk level to change the offer of a genetic test to. Inputs into the model included relevant clinical evidence, health-related preferences (utilities), healthcare resource use and costs. All ages were considered in the model, which was split by 10 year age group in order to assess whether genetic testing requirements would differ according to a person's age.

The economic analysis demonstrated that for individuals with no personal history but with a living affected family member available to test genetic testing would be cost-effective at both 5% and 10% carrier probability up to the age of 60. The results also indicated that genetic testing was only likely to be cost-effective at a £20,000/QALY threshold for individuals 60 years and over at higher carrier probabilities. To avoid any inequity of provision of genetic tests, no upper age limit was recommended on who could access genetic testing, although it is recognised that the majority of people are likely to be under 60 years of age.

The economic analysis also demonstrated cost-effectiveness at both the 5% and 10% carrier probabilities across all age groups for those individuals with no personal history and without a living affected family member available to test.

Cost effectiveness was also demonstrated at the 5% and 10% carrier probability level up to the age of 60, for an individual with a personal history of breast or

ovarian cancer. There were no incidence data available for those aged under 40 included within the model, however as genetic testing was cost effective for the 40-49 age group and the incidence of new breast cancer has been shown to be higher the younger the affected person at first diagnosis, it could be assumed that genetic testing would be cost-effective for the younger age groups too.

The economic analysis supports a level of genetic testing at both 5% and 10% carrier probability. Consideration has been given whether to recommend the lower level of genetic testing (5%) as this was cost-effective for some age groups and populations, and would substantially increase the number of people being eligible for testing. However this increase in numbers being able to access the test may not only cause an overload onto the existing infrastructure and services but is also out of line with the threshold offered by most other countries (10%).

Therefore a level of 10% has been recommended as benefits at this level are perceived to be reduced morbidity and mortality, reduced variation in practice, increased patient choice, improvement in informed decision making and a reduction in unnecessary surgery/treatment. Potential harms resulting from the 10% threshold include more families and individuals experiencing uncertainty/anxiety (due to increased number of variants of unknown significance) and the potential increased waiting times for testing. However it was felt that the agreed benefits outweighed the harms.

6. Rationale behind the policy statement

Genetic risk assessment and the testing of individuals deemed to be at a high risk of a clinically significant *BRCA1* and *BRCA2* mutation would lead to increased awareness of cancer risk and the effective use of interventions to reduce *BRCA1* and *BRCA2* related cancer incidence and mortality in the England.

The existing NHS England Medical Genetics Service Specification (NHS England E0/S/1a) acknowledges this evidence and commissions genetic testing for *BRCA1* and *BRCA2* based on NICE clinical guideline 41 which states the threshold for offering predictive testing is a pre-test carrier probability of 20% or more. This policy statement is in line with updated evidence published by NICE which shows there is still an overall benefit when the threshold of testing is decreased to a 10% carrier probability risk

7. Criteria for commissioning

Genetic testing for *BRCA1* and *BRCA 2* will be routinely commissioned by NHS England for the following groups of people as stated in NICE clinical guideline 164 NICE CG164, 2013):

Persons with no personal history of breast and/or ovarian cancer but with an available affected relative

- Genetic testing will be offered in a specialist genetic clinic to the relative with a personal history of breast and/or ovarian cancer if that relative has a combined *BRCA1*and *BRCA2* mutation carrier probability of 10% or more.

Persons with no personal history of breast and/or ovarian cancer and no available affected relative to test

- Genetic testing will be offered in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing.

Persons with breast or ovarian cancer

- Genetic testing will be offered in specialist genetic clinics to a person with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more.

Genetic testing for *BRCA1/2* mutations within 4 weeks of diagnosis of breast cancer –

- Offer those people that are eligible for referral to a specialist genetic clinic (based on their risk) a choice of accessing genetic testing during initial management or at any time thereafter.
- For patients having fast-track genetic testing (within 4 weeks of a diagnosis of breast cancer) offer recruitment to a clinical trial, if one is available.
- Offer detailed consultation with a clinical geneticist or genetics counsellor to all those with breast cancer who are offered genetic testing, regardless of the timeframe for testing.

Exclusions:

i. Patients whose pre-test carrier probability risk is assessed to be less than 10%
ii. As per Medical Genetics service specification (NHS England E0/01/S/1a), *BRCA1* and *BRCA2* genetic tests requested outside the specialised services care pathway.

8. Patient pathway

Using personal and family history of cancers as well as with the help of one of the models that have been developed to estimate the probability of finding a *BRCA1* or *BRCA2* mutation such as BOADICEA (Antoniou et al, 2008) and the Manchester score (Evans et al., 2005) a patient pathway for access to genetic tests for *BRCA1* and *BRCA2* is via specialist clinical genetic services. This pathway is currently commissioned as per the Medical Genetics Service Specification based on the NICE guideline CG 41.

This policy based on NICE CG 164 is not proposing any amendments to this currently commissioned pathway

9. Governance arrangements

This service is governed by the NHS England Medical Genetics Service Specification (E01). The specification outlines the conditions under which NHS England Specialised Services will fund laboratory activities carried out by Regional Genetic Centres in addition to the clinical genetics services it commissions.

10. Mechanism for funding

NHS England Specialised Services commissions Specialised Clinical Genetics Services and Specialised Laboratory Genetics Services from specified Providers via the relevant area teams.

Specialised Services Area teams will only pay for clinical genetics or laboratory genetics where the service is provided by a commissioned provider of these services.

The service specification states that genetic laboratories will also provide tests outside the NHS England Specialised Services contracts. These may include tests for services commissioned by Clinical Commissioning Groups (CCGs) and non-clinical genetics referrers both within and outside the NHS

Funding requests for *BRCA1* and *BRCA2* genetic testing are NOT to go via Individual Funding Request processes.

11. Audit requirements

- Each Genetics Centre should maintain a computerised family-based record system, incorporating disease-specific records

- Auditable Information should be collected to allow for an audit of the implementation of the clinical threshold for genetic testing of *BRCA1* and *BRCA2* as outlined in this policy document. .

- All laboratories should participate in the UK GTN audits of laboratory activity.

12. Documents which have informed this policy

NHS England Manual for Prescribed Specialised Services 2013/14 (NHS England PSS, 2013)

NICE CG 164 - Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (NICE CG 164,2013)

NICE CG164 – Costing report and template (NICE CG 164, 2013)

Familial Breast Cancer: Full needs assessment report, (Solomons, 2013)

NHS England Medical Genetics Service Specification (E01)

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in March 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *British Journal of Cancer* 2000;83(10):1301-8.

Antoniou AC, Gayther SA, Stratton JF, et al. Risk models for familial ovarian and breast cancer. *Genetic Epidemiology*. 2000;18(2):173-90.

Antoniou A, Pharoah P, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *American Journal of Human Genetics* 2003;72(5):1117-30.

Antoniou AC, Cunningham AP, et al., (2008) The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions', British Journal of Cancer 98,pp 1457 - 66

Balmana J, Sanz J, Bonfill X, Casado A, Rue M, Gich I, Diez O, Sabate JM, Baiget M & Alonso MC 2 (2004) Genetic counseling program in familial breast cancer: analysis of its effectiveness, cost and 3 cost-effectiveness ratio. International Journal of Cancer, 112: 647-652.

Bennett P, Wilkinson C, Turner J, et al. Psychological factors associated with emotional responses to receiving genetic risk information. *J Genet Couns*. 2008;17(3):234-41.

Bowen DJ, Burke W, Culver JO, et al. Effects of counseling Ashkenazi Jewish women about breast cancer risk. *Cultur Divers Ethni Minor Psychol*. 2006;12(1):45-56.

Brose MS, Rebbeck TR, Calzone KA, et al. (2002) Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *Journal of the National Cancer Institute*; 94(18):1365–1372.

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *Journal of Clinical Oncology* 2007;25(11):1329-33.

Evans DG, Lalloo F et al, (2005). Update on the Manchester Scoring System for BRCA 1 and BRCA2 testing. Journal of Medical Genetics, 42, e39

Ferrone CR, Levine DA, Tang LH, et al. (2009) BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *Journal of Clinical Oncology*; 27(3):433–438.

Finch A, Beiner M, Lubinski J, et al. (2006) Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. *JAMA*; 296(2):185–192.

Ford D, Easton DF, Peto J (1995): Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57 (6): 1457-62

Helmes AW, Culver JO, Bowen DJ. Results of a randomized study of telephone versus in-person breast cancer risk counseling. *Patient Educ Couns*. 2006;64(1-3):96-103

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute; 2013. Accessed at http://seer.cancer.gov/csr/1975_2010/ on 25 November 2013.

Johnson N, Lancaster T, Fuller A. The prevalence of a family history of cancer in general practice. *Fam Pract*. 1995;12(3):287-9.
Kwon JS, Daniels MS, Sun CC & Lu KH (2010a) Preventing future cancers by testing women with 7 ovarian cancer for BRCA mutations. Journal of Clinical Oncology, 28: 675-682.

Kwon JS, Gutierrez-Barrera AM, Young D, Sun CC, Daniels MS, Lu KH & Arun B (2010b) Expanding 9 the criteria for BRCA mutation testing in breast cancer survivors. Journal of Clinical Oncology, 28: 10 4214-4220

Levy-Lahad E, Friedman E. (2007) Cancer risks among BRCA1 and BRCA2 mutation carriers. *British Journal of Cancer*; 96(1):11–15.

Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E et al on behalf of EMBRACE. (2013) Cancer Risks for *BRCA1* and *BRCA2* Mutation Carriers: Results From Prospective Analysis of EMBRACE *Journal of the National Cancer Institute*;105:812–822

McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, Easton D, Emery J, Gray J, Halpin J, Hopwood P, McKay J, Sheppard C, Sibbering M, Watson W, Wailoo A, Hutchinson A (2004) *Clinical Guidelines and Evidence Review for The Classification and Care of Women at Risk of Familial Breast Cancer*, London: National Collaborating Centre for Primary Care/University of Sheffield

Nelson HD, Fu R, Goddard K, Mitchell JP, Okinaka-Hu L, Pappas M, Zakher B (2013). Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: Systematic Review to Update the U.S. Preventive Services Task

Force Recommendation. Evidence Synthesis No. 101. AHRQ Publication No. 12-05164-EF-1. Rockville, MD: Agency for Healthcare Research and Quality.
NHS England E/01/S/a, 2013).

NHS England PGD policy 2013 - http://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2014/04/e01-med-gen.pdf

(NHS England PSS, 2013 Manual for prescribed Specialised Services http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

National Collaborating Cancer for Primary Care (2006). Familial Breast Cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care .Avaialble at: www.nice.org.uk/CG041

National Collaborating Centre for Cancer (2013). Clinical Guideline: Familial Breast Cancer: Classification and care of women at risk of familial breast cancer and management of breast cancer and associated risks in people with a family history of breast cancer. Available at:
https://www.nice.org.uk/guidance/cg164/resources/guidance-familial-breast-cancer-pdf

National Collaborating Centre for Cancer (2013). Cost Effectiveness Evidence Review: Familial Breast Cancer: Classification and care of women at risk of familial breast cancer and management of breast cancer and associated risks in people with a family history of breast cancer. Available at: www.nice.org.uk

National Collaborating Centre for Cancer (2012). Familial Breast Cancer – Search Strategies. Available at: www.nice.org.uk

Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. *JAMA.* 1993;270(13):1563-8. PMID: 8371466

Solomons J. 2013 Familial Breast Cancer: Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. An assessment of need.

Tai YC, Domchek S, Parmigiani G, Chen S. (2007) Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *Journal of the National Cancer Institute*; 99(23):1811–1814.

Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J, Roach KC, Mandell J, Lee MK, Ciernikova S, Foretova L, Soucek P, King MC. Spectrum of mutations in

BRCA1, *BRCA2*, CHEK2, and *TP53* in families at high risk of breast cancer. JAMA. 2006 Mar 22;295(12):1379-88.

Whittemore AS, Gong G, John EM, et al. (2004).: Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiology Biomarkers Prev 13 (12): 2078-83