National Institute for Health and Care Excellence

Draft for consultation

Addendum to Clinical Guideline 164, Familial breast cancer

Genetic testing for women with triple negative breast cancer and no family history

Clinical Guideline Addendum 164.2

Methods, evidence and recommendations

November 2016

Draft for consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the NICE surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the committee are joined by up to 6 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the committee' is referred to, this means the entire committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the committee.

Details of the committee membership and the NICE team can be found in appendix A. The committee members' declarations of interest can be found via appendix B.

1 Summary section

1.1 Update information

The NICE guideline on familial breast cancer (NICE clinical guideline CG164) was reviewed in November 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The original guideline did not have a review question on referral criteria. The aim of this update was to review the evidence in this area.

The review question that the committee considered was:

1) What clinical features (eg age, tumour subtype, etc) in women presenting with triple negative breast cancer and no family history are associated with at least a 10% probability that they carry a BRCA1/2 mutation?

The original guideline can be found here.

The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendations in this update. These are marked as **[new 2017].**

1.2 Recommendations

1. **Offer genetic testing for *BRCA1* and *BRCA2* mutations to women under 50 years with triple negative breast cancer, but no family history of breast or ovarian cancer. [new 2017]**

1.3 Patient-centred care

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.4 Methods

This update was developed based on the process and methods described in Developing NICE guidelines: the manual.

2 Evidence review and recommendations

2.1 Review question

What clinical features (e.g. age, tumour subtype, etc) in women presenting with triple negative breast cancer and no family history are associated with at least a 10% probability that they carry a BRCA1/2 mutation?

2.2 Introduction

The NICE guideline on familial breast cancer was reviewed in 2015 by the surveillance team and new evidence from a cohort study shows that a small proportion of cases of triple-negative breast cancer (TNBC) are related to mutations in the BRCA 1/2 genes, and that the average age of diagnosis of TNBC was under 50 years in women with a BRCA1/2 mutation and no family history, compared to 52 years for those with no mutations. This new evidence may provide reasonable evidence that genetic testing should be extended to those under 50 with TNBC regardless of family history.

2.3 Clinical evidence review

A systematic search was conducted (see appendix D) which identified 806 articles. The titles and abstracts were double screened and 38 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 28 were excluded as they did not meet the criteria and 10 met the criteria and were included.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.3.1 Methods

Summary of review protocols

The population included people with triple negative breast cancer and no family history.

Clinical features specified by the topic experts were:

a) Age less than 50 years
b) Tumour phenotype including grade of tumour

The positive predictive value of detecting a BRCA1 or BRCA2 mutation in those with the above clinical features was the outcome of interest. This question was specifically restricted to triple negative breast cancer and the BRCA1/2 mutations to reflect the new evidence identified by surveillance; other breast cancer associated genes were not prioritised by the topic experts for this update.

Quality assessment - risk of bias

Modified GRADE methodology as described below was used for quality assessment for this particular question.

- **Risk of bias:**

The quality of individual studies was assessed using the QUADAS-2 checklist for diagnostic studies as guided in Developng NICE guidelines: the manual. This checklist addresses 4 main domains including 1) patient selection 2) execution and interpretation of the index test

3) execution and interpretation of the reference standard and 4) patient flow and timing (see appendix J for quality assessment of individual studies). The domain on index test was not assessed for this particular question and marked as not applicable as the index test i.e. age or tumour phenotype were assessed independently of the reference standard i.e mutation status.

The overall risk of bias for all studies examining a particular test was then assessed as follows:

  - if a study did not satisfy 1 of the 3 criteria (patient selection, reference standard, flow and timing) – downgrade 1 level
  - if a study did not satisfy 2 or more of the 3 criteria (patient selection, reference standard, flow and timing) – downgrade 2 levels

- **Indirectness:**
  - details from the PICOs in the review protocol (see appendix C) were used to assess the directness of the included studies. Based on the first 2 areas of the QUADAS-2 checklist (patient selection and reference standard), the applicability of the study in terms of how well it matches the predefined review protocol was assessed for each study (see appendix J for quality assessment of individual studies).

  The overall level of indirectness for all studies examining a particular test was then assessed as follows:

  - if a study did not satisfy 1 of the 2 criteria (applicability of patient selection and reference standard) – downgrade 1 level
  - if a study did not satisfy both criteria (applicability of patient selection and reference standard) – downgrade 2 levels

- **Inconsistency**
  - The assessment of inconsistency was not relevant to this review question given the data was not pooled (see statistical analysis section for more information)
- **Imprecision**
  - All studies in which the confidence interval crossed the pre-specified 10% probability threshold were marked down once for serious imprecision.
- **Overall quality**
  - As only prospective observational studies were included for this review, the quality rating began at ‘high’ and was further downgraded one level for each ‘serious’ source of uncertainty and two levels for each ‘very serious’ source of uncertainty.

Statistical analysis

Conventional meta-analyses were not conducted as the main outcome of interest was positive predictive value which is dependent due varying underlying prevalence of BRCA1/2 mutations in the studies. The data is therefore presented on a per study prevalence basis.

Positive predictive values and 95% confidence intervals were calculated using 2x2 data reported in the studies and presented in the evidence summary.

Overall summary of evidence

For a summary of included studies please see below Table 7 onwards (for the full evidence tables and GRADE profiles, please see appendices H and I). For the full details on quality assessment of the individual included studies please see appendix J.

All studies were cross-sectional and assessed the prevalence of BRCA1/2 or both mutations in a cohort of triple negative breast cancer patients – in studies which included both subjects

with and without family history, only the data for those without family history of breast or related cancers has been extracted.

There are 10 included studies in total for this particular review question (Evans 2011; Fostira 2012; Couch 2015; Andres 2014; Young 2009; Qang 2015; Robertson 2012; Hartman 2012; Meyer 2012; Phuah 2012). All studies reported on age <50 years as a clinical feature for detecting BRCA1/2 mutations; none of the studies reported on tumour grade in those without a family history.

Overall, the quality of the evidence ranged from low to high. Typical reasons for downgrading included exclusion criteria not reported therefore applicability unclear and imprecision in the effect estimates.

1 **Table 1: Summary of included studies**

2

Study reference (including study design)	Study population	Clinical features	Mutations assessed	Comments
Evans 2011 Cross-sectional study	Two population based patient cohorts of young onset triple negative breast cancer with documented absence of any family history of breast or ovarian cancer N=63	• Age <50years vs >50 years	• BRCA1	• Although BRCA2 mutations were tested for, all mutations identified were in BRCA1.
Fostira 2012 Cross-sectional study	Women with triple negative receptor status N=298	• Age <50 years vs >51 years	• BRCA1	• Authors indicate that parts of the BRCA1 coding region are left out by the screening strategy employed and so the true frequency of BRCA1 mutations is underestimated by 6%. • Only outcome for those without family history has been extracted given study included both those with and without family history. • Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.

Study reference (including study design)	Study population	Clinical features	Mutations assessed	Comments
Couch 2015 Cross-sectional study	Patients with triple negative independent of family history of breast or ovarian cancer and age at diagnosis N=969	• Age <50 years vs >50 years	• BRCA1/2	• Only outcome for those without family history has been extracted given study included both those with and without family history. • Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.
Andres 2014 Cross-sectional study	Patients diagnosed with triple negative breast cancer without family history and younger than 50 years N=92	• Age <50 years vs >50 years	• BRCA1	• None
Young 2009 Cross-sectional study	Women diagnosed with breast cancer at age 40 years and younger without significant family history, negative for ER, PR and HER2 with grade III breast carcinoma. N=54	• Age <50 years vs >50 years	• BRCA1/2	• Significant family history as defined by the American Society of clinical oncology. • 4 results not analysed as samples were of poor quality therefore total n was 54 instead of 58 which makes a difference in PPV from 11.1 to 10.3
Wang 2015 Cross-sectional study	Patients with triple negative breast cancer unselected for	• Age <50 years vs >50 years	• BRCA1	• Only outcome for those without family history has been extracted.

Study reference (including study design)	Study population	Clinical features	Mutations assessed	Comments
	age at diagnosis or family history of breast cancer. N=847			• Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.
Robertson 2012 Cross-sectional study	Subjects with triple negative breast cancer (oestrogen receptor, progesterone receptor and HER2 status confirmed either in a histopathology report and/or a clinician's referral letter). N=103	• Age <50 years vs >50 years	• BRCA1	• Only outcome for those without family history has been extracted. • Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.
Hartman 2012 Cross-sectional study	Patients presenting with triple negative breast cancer in a community oncology network from 2005 to 2010 N=153	• Age <50 years vs >50 years	• BRCA1/2	• Only outcome for those without significant family history has been extracted - significant family history defined as breast cancer before the age of 50 years or ovarian cancer at any age in any first degree or second degree relative. • Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the

Study reference (including study design)	Study population	Clinical features	Mutations assessed	Comments
				whole study group as opposed to only those without family history.
Meyer 2012 Cross-sectional study	Newly diagnosed cases of individuals with TNBC diagnosed between 2005 and 2010 were selected from the Pathology Unit N=12	• Age <50 years vs >50 years	• BRCA1/2	• Only outcome for those without family history has been extracted. • Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.
Phuah 2012 Cross-sectional study	Women with isolated triple-negative breast cancer diagnosed at between 36 and 50 years old in the absence of family history N= 47	• Age <50 years vs >50 years	• BRCA1/2	• Although study reports outcomes of interest for the group without family history; baseline characteristics such as age are reported for the whole study group as opposed to only those without family history.

1

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist:

- undertook a systematic review of the published economic literature

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to familial breast cancer in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 15th June 2016. The health economic search strategies are detailed in appendix P.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014*.

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.20 Results of the economic literature review

The search returned 103 articles, all of which were excluded based on title and abstract. The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix L.

2.5 Evidence statements

2.5.1 Clinical evidence statement

Ten cross sectional studies in women with triple negative breast cancer and no family history examined the association between age less than 50 years and probability of carrying a BRCA1/2 mutation.

Five studies examined the probability of carrying a BRCA1/2 mutation. Two of these studies, which were of moderate and high quality, reported overall prevalence of BRCA1/2 mutation of 8.6% and 33% respectively. They found age less than 50 years to have a positive predictive value of BRCA1/2 mutation of greater than 10%; 13.1 (10.3 to 16.6) in one study and 60% (23.1 to 88.2) in the second study. The remaining 3 studies of low to moderate quality reporting a range in prevalence from 5.2% to 11.1% found positive predictive values less than 10%. The upper confidence limit however in all of these studies exceeded the 10% threshold.

The other 5 studies of mainly low quality examined the probability of carrying a BRCA1 mutation only. All 5 studies reporting a range in prevalence from 5% to 12.7% found positive predictive values less than 10% however the upper confidence limit in all of these exceeded the 10% threshold.

2.5.2 Health economic evidence statements

No economic evidence was identified via the health economic literature review. An estimate of £950 for genetic testing of an individual affected by breast cancer was available from the 2013 update to the guideline. This figure consists of a cost of £700 for laboratory testing and £250 for two hours of genetic counselling from a band 7 to band 8 counsellor in primary medical care.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The aim of this review was to investigate what clinical features (age <50 years and tumour phenotype including grade of tumour) in women presenting with triple negative breast cancer and no family history are associated with a 10% probability that they carry a BRCA1/2 mutation. The committee therefore prioritised positive predictive value of at least 10% as the outcome of interest. The 10% threshold was selected for consistency with the existing threshold for referral to a genetic specialist.
Quality of evidence	As this was a diagnostic review, the QUADAS-2 checklist was used to assess the quality of the evidence, which indicated that the overall quality of the evidence ranged from low to high. The main reasons for downgrading was the exclusion criteria not being reported and hence concerns regarding applicability and also serious imprecision in the effect estimates. Evidence was limited to studies examining age <50 years; no evidence assessing tumour grade as a clinical feature was identified. The data was not meta-analysed as the main outcome of interest was positive predictive values which are dependent on the varying underlying prevalence of BRCA1/2 mutations in the studies. The committee noted that the age distribution varied across studies which could explain the variation in prevalence but concluded that there could be considerable unexplained variation in which case pooling the data would not be appropriate.

	Committee discussions
	The committee considered separating the results for studies including those <40 years versus >40 years into 2 separate tables however the evidence did not allow for this as in 7/10 studies, age was not reported at all or not reported for the population of interest (i.e. for those without family history) and instead for the total study group. To take into account the fact that some studies examined BRCA1/2 mutations versus BRCA1 mutations only, a separate table of results was constructed for each of the following groups: 1) Studies examining both BRCA1/2 mutations 2) Studies examining BRCA1 mutations only
Trade-off between benefits and harms	10 cross sectional studies in women with triple negative breast cancer and no family history examined the association between age less than 50 years and the probability of carrying a BRCA1/2 mutation. 5 studies examined the probability of carrying a BRCA1/2 mutation. The committee noted that two of these studies of moderate and high quality reporting population prevalence of 8.6% and 33% respectively found positive predictive values greater than 10%; 13.1 (10.3 to 16.6) in one study and 60% (23.1 to 88.2) in the second study. The remaining 3 studies of low to moderate quality reporting a range in prevalence from 5.2% to 11.1% found positive predictive values less than 10% however the upper confidence limit in all of these studies exceeded the 10% threshold. The other 5 studies of mainly low quality examined the probability of carrying a BRCA1 mutation only. All 5 studies reporting a range in prevalence from 5% to 12.7% found positive predictive values less than 10% however the upper confidence limit in all of these exceeded the 10% threshold and hence somewhat supported the remaining evidence indicating that BRCA1/2 genetic testing should be extended to those <50 years with triple negative breast cancer and no family history.
Trade-off between net health benefits and resource use	As this review question addresses the clinical risk factors associated with a 10% probability of a BRCA1/2 mutation, rather than considering the threshold at which genetic testing should be offered, the committee determined that the question was not suitable for economic analysis. Due to the number of patients involved, the committee expressed the view that extending testing to women with triple negative breast cancer and no family history under the age of 50 would be unlikely to have a significant impact on resource usage. Moreover, the committee noted that, in their experience, a significant proportion of centres are currently offering testing to women under the age of 50, meaning that the resource impact of a recommendation of offering testing to women under 50 would be smaller than anticipated. Furthermore, while increasing the age at which women are offered genetic testing may increase costs in the short term (from testing and offering preventive surgeries), it is likely that considerable cost savings will be achieved in the long term from reducing breast cancer incidence.
Other considerations	None.

2.7 Recommendations

2. Offer genetic testing for *BRCA1* and *BRCA2* mutations to women under 50 years with triple negative breast cancer, but no family history of breast or ovarian cancer. [new 2017]

2.8 Research recommendations

1. What is the prevalence of *BRCA1* mutations in unselected basal phenotype breast cancer compared with unselected triple negative breast cancer? [new 2017]

Why is this important?

The association of breast cancer with *BRCA1* mutations was originally with the basal phenotype. Although triple negative breast cancer has been used as a proxy for the basal phenotype, they do not fully overlap. Badve et al (2010) found that 71% of triple negative breast cancers were basal-like and 77% of basal-like cancers were triple negative. Triple negative breast cancer has been adopted as a proxy for the basal phenotype because most pathology laboratories test for triple negative cancer as a standard. Rakha et al. (2009) found that the basal phenotype has a high positive predictive value for the *BRCA1* mutation. A study of the prevalence of *BRCA1* mutations would be useful because we may be missing these in basal phenotype breast cancers that are not tested as standard. This information would indicate whether *BRCA1* testing is helpful for basal phenotype cancers.

Table 2: Criteria for selecting high-priority research recommendations

PICO	**Population:** Women with basal phenotype breast cancer compared with those with triple negative breast cancer. **Intervention:** Prevalence of BRCA1 mutations in unselected basal phenotype breast cancer **Comparison:** Prevalence of BRCA1 mutations in triple negative breast cancer **Outcomes:** • Risk ratios
Current evidence base	None
Study design	Cross sectional, cohort studies
Other comments	None

3 References

Andres R, Pajares I, Balmana J, et al. (2014). Association of BRCA1 germline mutations in young onset triple-negative breast cancer (TNBC). Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico, 16(3), 280-4.

Couch FJ, Hart SN, Sharma P, et al. (2015). Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of Clinical Oncology, 33(4), 304-11.

Evans DG, Howell A, Ward D, et al. (2011). Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. Journal of Medical Genetics, 48(8), 520-2.

Fostira F, Tsitlaidou M, Papadimitriou C, et al. (2012). Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Research & Treatment, 134(1), 353-62.

Hartman AR, Kaldate RR, Sailer LM, et al. (2012). Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer, 118(11), 2787-95.

Meyer P, Landgraf K, Hogel B, et al. (2012). BRCA2 mutations and triple-negative breast cancer. PLoS ONE [Electronic Resource], 7(5),.e38361.

Phuah SY, Looi LM, Hassan N, et al. (2012). Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast Cancer Research, 14(6), R142.

Robertson L, Hanson H, Seal S, et al . (2012). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. British Journal of Cancer, 106(6), 1234-8.

Wang C, Zhang J, Wang Y, et al. (2015). Prevalence of BRCA1 mutations and responses to neoadjuvant chemotherapy among BRCA1 carriers and non-carriers with triple-negative breast cancer. Annals of Oncology, 26(3), pp.523-8.

Young SR, Pilarski RT, Donenberg T, et al. (2009). The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer, 9, 86.

4 Glossary

Please refer to the NICE glossary.

Additional terms used in this document are listed below:

Breast cancer risk category

	Breast cancer risk category		
	Near population risk	**Moderate risk**	**High risk[1]**
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%

[1]This group includes known *BRCA1*, *BRCA2* and *TP53* mutations and rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (*STK11*), Cowden (*PTEN*) and familial diffuse gastric cancer (E-Cadherin).

First-degree relatives

Mother, father, daughter, son, sister, brother.

Second-degree relatives

Grandparent, grandchild, aunt, uncle, niece, nephew, half-sister, half-brother.

Third-degree relatives

Great grandparent, great aunt, great uncle, first cousin, great grandchild, grand nephew, grand niece.

Triple negative breast cancer

Oestrogen receptor, progesterone receptor, HER2 negative breast cancer.

1 Appendices

2 Appendix A: Standing Committee 3 members and NICE teams

A.1 4 Core members

Name	Role
Susan Bewley	Chair
Gita Bhutani	Associate Director for Psychological Professions
Simon Corbett	Cardiologist
Rachel Churchill	Professor of Evidence Synthesis
Gail Fortes Mayer	Commissioner
John Graham	Consultant Oncologist (Vice Chair)
Nathan Griffiths	Consultant Nurse - Paediatric Emergency and Ambulatory Medicine
Manoj Mistry	Lay member
Mark Rodgers	Research Fellow – Methodologist
Sietse Wieringa	General Practitioner

A.2 5 Topic expert Committee members

Name	Role
Gareth Evans	Professor of Medical Genetics and Cancer Epidemiology
Sacha Howell	Medical Oncologist
Paul Pharoah	Professor of Cancer Epidemiology
Judith Reeves	Lead Breast Care Nurse
Amy Taylor	Genetic counsellor
Ursula van Mann	Lay member

A.3 6 NICE project team

Name	Role
Jessica Fielding	Public Involvement Adviser
Bhash Naidoo	Technical Lead (Health Economics)
Rupert Franklin	Guideline Commissioning Manager
Louise Picton	Senior medicines adviser
Sharon Summers-Ma	Guideline Lead
Nichole Taske	Technical Lead
Jeremy Wight	Clinical Adviser
Trudie Willingham	Guideline Co-ordinator

7

A.41 Clinical guidelines update team

Name	Role
Martin Allaby	Clinical Adviser
Emma Banks	Co-ordinator
Elizabeth Barrett	Information Specialist
Nicole Elliott	Associate Director (from July 2016)
Ben Johnson	Health Economist
Hugh McGuire	Technical Adviser
Susannah Moon	Programme Manager
Nitara Prasannan	Technical Analyst
Lorraine Taylor	Associate Director (Until July 2016)

2

Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available in a separate document.

Appendix C: Review protocol

Components	Details
Review question 2	What clinical features (eg age, tumour subtype, etc) in women presenting with triple negative breast cancer and no family history are associated with at least a 10% probability that they carry a BRCA1/2 mutation?
Background/ objectives	The NICE guideline on familial breast cancer was reviewed in 2015 by the surveillance team and new evidence from a cohort study shows that a small proportion of cases of triple-negative breast cancer (TNBC) are related to mutations in the BRCA 1/2 genes, and that the average age of diagnosis of TNBC was under 50 years in women with a BRCA1/2 mutation and no family history, compared to 52 years for those with no mutations. This new evidence may provide reasonable evidence that genetic testing should potentially be extended to those under 50 with TNBC regardless of family history.
Type of review question	Diagnostic accuracy review
Types of study to be included	Cohort studies, cross-sectional studies
Language	English language only
Status	Published papers (full text only) – searches to be run from the start of database to present
Population	People with triple negative breast cancer and no family history
Clinical features/factors	• Age less than 50 years • Tumour phenotype including grade of tumour
Outcomes	PPV* of 10%; (for consistency with existing CG164 threshold for referal to a genetic specialist) *Estimates will be sensitive to the underlying prevalence (pooled if appropriate) of BRCA1/2 mutations in this cohort. Data will be presented on a per study prevalence basis.
Any other information or criteria for inclusion/exclusion	• The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches. • The topic experts also advised to only include papers with mixed populations of women with no family history and with family history (such as Couch 2015) if we can dis-aggregate the data for women with no family history to analyse this separately. • This question will be specifically restricted to triple negative breast cancer and the BRCA1/2 mutations to reflect the new evidence identified by surveillance; other breast cancer associated genes were not prioritised by the topic experts for this update.

Analysis of subgroups or subsets	-
Data extraction and quality assessment	Sifting Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered to be not relevant to the topic will be excluded. i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will be conducted due to the anticipated complexity in determining relevant study designs for this review question. In cases of uncertainty, the lead technical analyst will discuss with the support technical analyst; if a decision cannot be reached by the lead and support analyst then a third referee will be asked to assess the study. ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will also be conducted - see above. Other mechanisms will be in place for QA: The Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which haven't been picked up by the searches. Data extraction Information from included studies will be extracted into standardised evidence tables. Critical appraisal The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual for intervention/observational studies identified. Quality assessment GRADE methodology will be used to assess the quality of evidence on an outcome basis: • Risk of bias will be assessed using critical appraisal checklist • Inconsistency will be assessed using I2 • Indirectness will be assessed after considering population, intervention and outcomes of included studies, relative to the target population; • Imprecision will be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available Topic experts will be asked to provide MID's. Quality Assurance: The following quality assurance mechanisms will be in place:

	• Internal QA by CGUT technical adviser (10%) on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. • The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	• If possible a meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A fixed effects model will be used as it is expected that the studies will be homogenous in terms of population and we can assume a similar effect size across studies. A random effects model will be used if this assumption is not correct. • An evidence summary outlining key issues such as volume, applicability and quality of evidence and presenting the key findings from the evidence will be produced.
Searches	<u>Sources to be searched</u> • Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. • Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. <u>Supplementary search techniques</u> • None identified <u>Limits</u> • Studies reported in English • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • No date limit will be set
Key papers	<u>Studies identified by surveillance process</u> • Couch FJ, Hart SN, Sharma P et al. (2015) Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of Clinical Oncology 33:304-311.

1

2

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in table 9. The Medline search strategy is shown in table 10. The same strategy was translated for the other databases listed.

Table 3: Clinical search summary

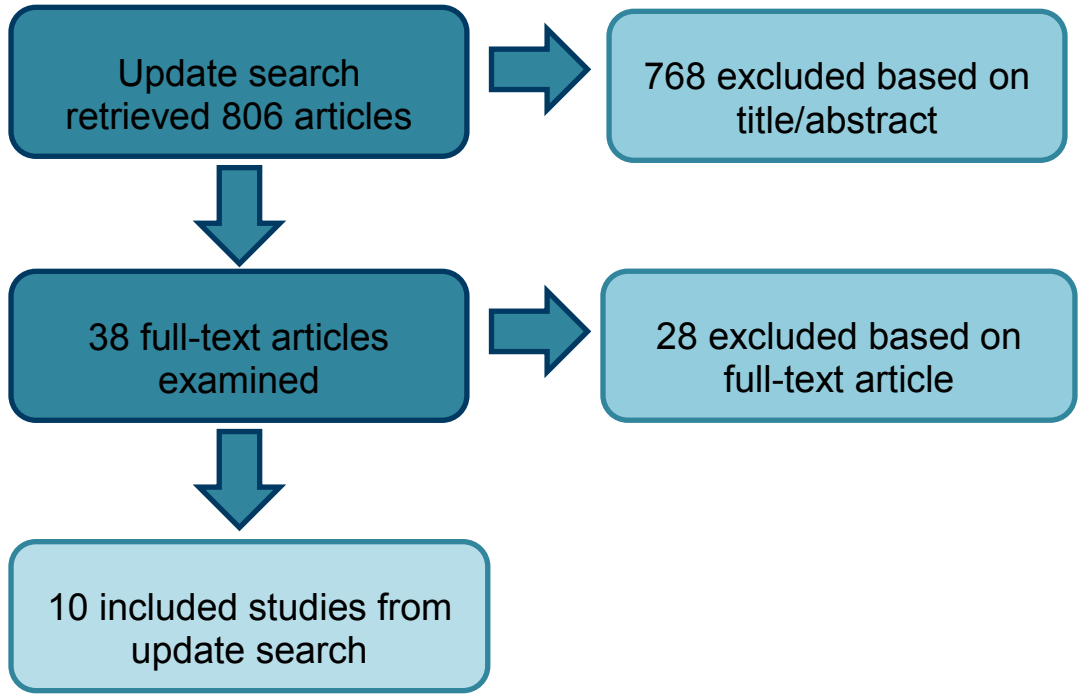
Databases	Date searched	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	08/06/2016	34
Cochrane Database of Systematic Reviews (CDSR)	08/06/2016	0
Database of Abstracts of Reviews of Effect (DARE)	08/06/2016	0
Embase (Ovid)	08/06/2016	662
MEDLINE (Ovid)	08/06/2016	397
MEDLINE In-Process (Ovid)	08/06/2016	92
PubMed	08/06/2016	27
Health Technology Assessment (HTA Database)	08/06/2016	0

Table 4: Clinical search terms (Medline)

Database: Medline
Strategy used: Database: Ovid MEDLINE(R) <1946 to May Week 4 2016> Search Strategy: --- 1 Triple negative breast neoplasms/ (1399) 2 (((triple or her2) adj4 negative) and breast).tw. (5288) 3 1 or 2 (5433) 4 brca1 protein/ or brca2 protein/ (5669) 5 (brca1 or brca2 or "breast cancer 1" or "breast cancer 2" or fancd1 or fanconi anemia or fanconi anaemia).tw. (13800) 6 4 or 5 (14607) 7 3 and 6 (422) 8 animals/ not humans/ (4226276) 9 7 not 8 (412)

Database: Medline	
10	limit 9 to english language (397)

Appendix E: Review flowchart



1 Appendix F:Excluded studies

2

Reference	Reason for exclusion
Asleh-Aburaya K, and Fried G. (2015). Clinical and molecular characteristics of triple-negative breast cancer patients in Northern Israel: single center experience. Springerplus, 4, pp.132.	No relevant results for subgroup without family history and for those less than 50 years.
Atchley D P, Albarracin C T, Lopez A, Valero V, Amos C I, Gonzalez-Angulo A M, Hortobagyi G N, and Arun B K. (2008). Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. Journal of Clinical Oncology, 26(26), pp.4282-8.	Unclear whether subjects had family history or not as details not reported.
Comen E, Davids M, Kirchhoff T, Hudis C, Offit K, and Robson M. (2011). Relative contributions of BRCA1 and BRCA2 mutations to "triple-negative" breast cancer in Ashkenazi Women. Breast Cancer Research & Treatment, 129(1), pp.185-90.	Family history information available for 43 of 64 women with TNBC of which the majority (65%) had positive family history. No relevant results for those without family history and less than 50 years.
Cragun D, Bonner D, Kim J, Akbari M R, Narod S A, Gomez-Fuego A, Garcia J D, Vadaparampil S T, and Pal T. (2015). Factors associated with genetic counseling and BRCA testing in a population-based sample of young Black women with breast cancer. Breast Cancer Research & Treatment, 151(1), pp.169-76.	Majority of study population (61%) had family history; no relevant results reported for the subgroup without family history.
Gonzalez-Angulo A M, Timms K M, Liu S, Chen H, Litton J K, Potter J, Lanchbury J S, Stemke-Hale K, Hennessy B T, Arun B K, Hortobagyi G N, Do K A, Mills G B, and Meric-Bernstam F. (2011). Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clinical Cancer Research, 17(5), pp.1082-9.	No relevant results for those aged <50 years.
Gonzalez-Rivera M, Lobo M, Lopez-Tarruella S, Jerez Y, Del Monte-Millan , M , Massarrah T, Ramos-Medina R, Ocana I, Picornell A, Garzon S S, Perez-Carbornero L, Garcia-Saenz J A, Gomez H, Moreno F, Marquez-Rodas I, Fuentes H, and Martin M. (2016). Frequency of germline DNA genetic findings in an unselected prospective cohort of triple-negative breast cancer patients participating in a platinum-based neoadjuvant chemotherapy trial. Breast Cancer Research & Treatment, 156(3), pp.507-15.	No relevant results for those without family history.
Greenup R, Buchanan A, Lorizio W, Rhoads K, Chan S, Leedom T, King R, McLennan J, Crawford B, Kelly Marcom, P , Shelley Hwang, and E . (2013). Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. Annals of Surgical Oncology, 20(10), pp.3254-8.	No relevant results for those without family history.
Lee E, McKean-Cowdin R, Ma H, Spicer D V, Van Den Berg , D , Bernstein L, and Ursin G. (2011). Characteristics of triple-negative breast cancer in patients with a BRCA1 mutation: results from a population-based study of young women. Journal of Clinical Oncology, 29(33), pp.4373-80.	No relevant results.
Lee L J, Alexander B, Schnitt S J, Comander A, Gallagher B, Garber J E, and Tung N. (2011). Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. Cancer, 117(14), pp.3093-100.	No relevant data and family history not reported.

Reference	Reason for exclusion
Li Y T, Ni D, Yang L, Zhao Q, and Ou J H. (2014). The prevalence of BRCA1/2 mutations of triple-negative breast cancer patients in Xinjiang multiple ethnic region of China. European Journal of Medical Research, 19, pp.35.	No relevant data for those without family history and less than 50 years.
Lips E H, Mulder L, Oonk A, van der Kolk , L E, Hogervorst F B, Imholz A L, Wesseling J, Rodenhuis S, and Nederlof P M. (2013). Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. British Journal of Cancer, 108(10), pp.2172-7.	No relevant results.
Maksimenko J, Irmejs A, Nakazawa-Miklasevica M, Melbarde-Gorkusa I, Trofimovics G, Gardovskis J, and Miklasevics E. (2014). Prognostic role of BRCA1 mutation in patients with triple-negative breast cancer. Oncology Letters, 7(1), pp.278-284.	No relevant results and family history not reported.
Mavaddat N, Barrowdale D, Andrulis I L, Domchek S M, Eccles D, Nevanlinna H, Ramus S J, Spurdle A, Robson M, Sherman M, Mulligan A M, Couch F J, Engel C, McGuffog L, Healey S, Sinilnikova O M, Southey M C, Terry M B, Goldgar D, O'Malley F, John E M, Janavicius R, Tihomirova L, Hansen T V, Nielsen F C, Osorio A, Stavropoulou A, Benitez J, Manoukian S, Peissel B, Barile M, Volorio S, Pasini B, Dolcetti R, Putignano A L, Ottini L, Radice P, Hamann U, Rashid M U, Hogervorst F B, Kriege M, van der Luijt , R B, Hebon , Peock S, Frost D, Evans D G, Brewer C, Walker L, Rogers M T, Side L E, Houghton C, Embrace , Weaver J, Godwin A K, Schmutzler R K, Wappenschmidt B, Meindl A, Kast K, Arnold N, Niederacher D, Sutter C, Deissler H, Gadzicki D, Preisler-Adams S, Varon-Mateeva R, Schonbuchner I, Gevensleben H, Stoppa-Lyonnet D, Belotti M, Barjhoux L, Collaborators Gemo Study, Isaacs C, Peshkin B N, Caldes T, de la Hoya , M , Canadas C, Heikkinen T, Heikkila P, Aittomaki K, Blanco I, Lazaro C, Brunet J, Agnarsson B A, Arason A, Barkardottir R B, Dumont M, Simard J, Montagna M, Agata S, D'Andrea E, Yan M, Fox S, kConFab Investigators, Rebbeck T R, Rubinstein W, Tung N, Garber J E, Wang X, Fredericksen Z, Pankratz V S, Lindor N M, Szabo C, Offit K, Sakr R, Gaudet M M, Singer C F, Tea M K, Rappaport C, Mai P L, Greene M H, Sokolenko A, Imyanitov E, Toland A E, Senter L, Sweet K, Thomassen M, Gerdes A M, Kruse T, Caligo M, Aretini P, Rantala J, von Wachenfeld , A , Henriksson K, Collaborators Swe-Brca, Steele L, Neuhausen S L, Nussbaum R, Beattie M, Odunsi K, Sucheston L, Gayther S A, Nathanson K, Gross J, Walsh C, Karlan B, Chenevix-Trench G, Easton D F, Antoniou A C, Consortium of Investigators of Modifiers of, and Brca . (2012). Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiology, and Biomarkers & Prevention, 21(1), pp.134-47.	No relevant data.
Muendlein A, Rohde B H, Gasser K, Haid A, Rauch S, Kinz E, Drexel H, Hofmann W, Schindler V, Kapoor R, Decker T, and Lang A H. (2015). Evaluation of BRCA1/2 mutational status among German and Austrian women with triple-negative breast cancer. Journal of Cancer Research & Clinical Oncology, 141(11), pp.2005-12.	No relevant data.
Oonk A M, van Rijn , C , Smits M M, Mulder L, Laddach N, Savola S P, Wesseling J, Rodenhuis S, Imholz A L, and Lips E H. (2012). Clinical correlates of 'BRCAness' in triple-negative breast cancer of patients receiving adjuvant chemotherapy. Annals of Oncology, 23(9), pp.2301-5.	No relevant results and no mention of family history.
Podo F, Santoro F, Di Leo , G , Manoukian S, de Giacomi , C , Corcione S, Cortesi L, Carbonaro L A, Trimboli R M, Cilotti A, Preda L, Bonanni B, Pensabene M, Martincich L, Savarese A,	No relevant results

Reference	Reason for exclusion
Contegiacomo A, and Sardanelli F. (2016). Triple-Negative versus Non-Triple-Negative Breast Cancers in High-Risk Women: Phenotype Features and Survival from the HIBCRIT-1 MRI-Including Screening Study. Clinical Cancer Research, 22(4), pp.895-904.	
Rummel S, Varner E, Shriver C D, and Ellsworth R E. (2013). Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer. Breast Cancer Research & Treatment, 137(1), pp.119-25.	No relevant results for those less than 50 years and data on tumour grade not split by those without family history.
Sharma P, Klemp J R, Kimler B F, Mahnken J D, Geier L J, Khan Q J, Elia M, Connor C S, McGinness M K, Mammen J M, Wagner J L, Ward C, Ranallo L, Knight C J, Stecklein S R, Jensen R A, Fabian C J, and Godwin A K. (2014). Germline BRCA mutation evaluation in a prospective triple-negative breast cancer registry: implications for hereditary breast and/or ovarian cancer syndrome testing. Breast Cancer Research & Treatment, 145(3), pp.707-14.	No relevant results for those <50 years without family history – 62% had family history.
Spurdle A B, Couch F J, Parsons M T, McGuffog L, Barrowdale D, Bolla M K, Wang Q, Healey S, Schmutzler R, Wappenschmidt B, Rhiem K, Hahnen E, Engel C, Meindl A, Ditsch N, Arnold N, Plendl H, Niederacher D, Sutter C, Wang-Gohrke S, Steinemann D, Preisler-Adams S, Kast K, Varon-Mateeva R, Ellis S, Frost D, Platte R, Perkins J, Evans D G, Izatt L, Eeles R, Adlard J, Davidson R, Cole T, Scuvera G, Manoukian S, Bonanni B, Mariette F, Fortuzzi S, Viel A, Pasini B, Papi L, Varesco L, Balleine R, Nathanson K L, Domchek S M, Offitt K, Jakubowska A, Lindor N, Thomassen M, Jensen U B, Rantala J, Borg A, Andrulis I L, Miron A, Hansen T V, Caldes T, Neuhausen S L, Toland A E, Nevanlinna H, Montagna M, Garber J, Godwin A K, Osorio A, Factor R E, Terry M B, Rebbeck T R, Karlan B Y, Southey M, Rashid M U, Tung N, Pharoah P D, Blows F M, Dunning A M, Provenzano E, Hall P, Czene K, Schmidt M K, Broeks A, Cornelissen S, Verhoef S, Fasching P A, Beckmann M W, Ekici A B, Slamon D J, Bojesen S E, Nordestgaard B G, Nielsen S F, Flyger H, Chang-Claude J, Flesch-Janys D, Rudolph A, Seibold P, Aittomaki K, Muranen T A, Heikkila P, Blomqvist C, Figueroa J, Chanock S J, Brinton L, Lissowska J, Olson J E, Pankratz V S, John E M, Whittemore A S, West D W, Hamann U, Torres D, Ulmer H U, Rudiger T, Devilee P, Tollenaar R A, Seynaeve C, Van Asperen , C J, Eccles D M, Tapper W J, Durcan L, Jones L, Peto J, dos-Santos-Silva I, Fletcher O, Johnson N, Dwek M, Swann R, Bane A L, Glendon G, Mulligan A M, Giles G G, Milne R L, Baglietto L, McLean C, Carpenter J, Clarke C, Scott R, Brauch H, Bruning T, Ko Y D, Cox A, Cross S S, Reed M W, Lubinski J, Jaworska-Bieniek K, Durda K, Gronwald J, Dork T, Bogdanova N, Park-Simon T W, Hillemanns P, Haiman C A, Henderson B E, Schumacher F, Le Marchand , L , Burwinkel B, Marme F, Surovy H, Yang R, Anton-Culver H, Ziogas A, Hooning M J, Collee J M, Martens J W, Tilanus-Linthorst M M, Brenner H, Dieffenbach A K, Arndt V, Stegmaier C, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Lindblom A, Margolin S, Joseph V, Robson M, Rau-Murthy R, Gonzalez-Neira A, Arias J I, Zamora P, Benitez J, Mannermaa A, Kataja V, Kosma V M, Hartikainen J M, Peterlongo P, Zaffaroni D, Barile M, Capra F, Radice P, Teo S H, Easton D F, Antoniou A C, Chenevix-Trench G, Goldgar D E, Investigators Abctb, Group Embrace, Network Genica, Group Hebon, and kConFab Investigators. (2014). Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast Cancer Research, 16(6), pp.3419.	No relevant data.

Reference	Reason for exclusion
Tun N M, Villani G, Ong K, Yoe L, and Bo Z M. (2014). Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis. Clinical Genetics, 85(1), pp.43-8.	Systematic review but no mention of family history criteria. Relevant references checked for inclusion.
Tung N, Gaughan E, Hacker M R, Lee L J, Alexander B, Poles E, Schnitt S J, and Garber J E. (2014). Outcome of triple negative breast cancer: comparison of sporadic and BRCA1-associated cancers. Breast Cancer Research & Treatment, 146(1), pp.175-82.	No relevant results.
Tung N, Garber J E, Lincoln A, and Domchek S M. (2012). Frequency of triple-negative breast cancer in BRCA1 mutation carriers: comparison between common Ashkenazi Jewish and other mutations. Journal of Clinical Oncology, 30(35), pp.4447-8.	Letter to the editor
Villarreal-Garza C, Alvarez-Gomez R M, Perez-Plasencia C, Herrera L A, Herzog J, Castillo D, Mohar A, Castro C, Gallardo L N, Gallardo D, Santibanez M, Blazer K R, and Weitzel J N. (2015). Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexico. Cancer, 121(3), pp.372-8.	No relevant results.
Villarreal-Garza C, Weitzel J N, Llacuachaqui M, Sifuentes E, Magallanes-Hoyos M C, Gallardo L, Alvarez-Gomez R M, Herzog J, Castillo D, Royer R, Akbari M, Lara-Medina F, Herrera L A, Mohar A, and Narod S A. (2015). The prevalence of BRCA1 and BRCA2 mutations among young Mexican women with triple-negative breast cancer. Breast Cancer Research & Treatment, 150(2), pp.389-94.	No relevant data and family history not reported.
Wong-Brown M W, Meldrum C J, Carpenter J E, Clarke C L, Narod S A, Jakubowska A, Rudnicka H, Lubinski J, and Scott R J. (2015). Prevalence of BRCA1 and BRCA2 germline mutations in patients with triple-negative breast cancer. Breast Cancer Research & Treatment, 150(1), pp.71-80.	No relevant data for those without family history.
Wong E S, Shekar S, Chan C H, Hong L Z, Poon S Y, Silla T, Lin C, Kumar V, Davila S, Voorhoeve M, Thike A A, Ho G H, Yap Y S, Tan P H, Tan M H, Ang P, and Lee A S. (2015). Predictive Factors for BRCA1 and BRCA2 Genetic Testing in an Asian Clinic-Based Population. PLoS ONE [Electronic Resource], 10(7), pp.e0134408.	No relevant data for those without family history.
Yip C H, Taib N A, Choo W Y, Rampal S, Thong M K, and Teo S H. (2009). Clinical and pathologic differences between BRCA1-, BRCA2-, and non-BRCA-associated breast cancers in a multiracial developing country. World Journal of Surgery, 33(10), pp.2077-81.	No relevant results and all subjects had family history.
Yu J H, Lee J W, Son B H, Kim S W, Park S K, Lee M H, Kim L S, Noh W C, Kim E K, Yoon D S, Lee J, Jung J H, Jung S S, Gong G, and Ahn S H. (2014). Characteristics of BRCA1/2 Mutation-Positive Breast Cancers in Korea: A Comparison Study Based on Multicenter Data and the Korean Breast Cancer Registry. Journal of Breast Cancer, 17(2), pp.129-35.	Population of BRCA mutations not triple negative breast cancer.

1

1 Appendix G: Evidence tables

G.12 Andres 2014

Bibliographic reference	**Andres R, Pajares I, Balmana J, Llort G, Ramon Y Cajal T, Chirivella I, Aguirre E, Robles L, Lastra E, Perez-Segura P, Bosch N, Yague C, Lerma E, Godino J, Miramar M D, Moros M, Astier P, Saez B, Vidal M J, Arcusa A, Ramon y Cajal, S , Calvo M T, and Tres A. (2014). Association of BRCA1 germline mutations in young onset triple-negative breast cancer (TNBC). Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico, 16(3), pp.280-4.A**
Study type	Cross sectional
Aim	To determine the prevalence of BRCA1 germline mutations in patients with no breast and ovarian cancer family history and diagnosed with triple negative breast cancer before age 50 based upon the informativeness of their family history.
Patient characteristics	**Inclusion criteria** • Patients diagnosed with triple negative breast cancer defined by a lack of expression by immunohistochemistry of ER, PR and HER2. Fluorescent in situ hybridisation for Her-2 was performed for Her-2 IHC score of ++/+++. • Younger than 50 years and no family history of breast and ovarian cancer among second degree relatives. **Exclusion criteria** • Not reported **Baseline characteristics** • Age younger than 35 years at diagnosis, n (%): 16 (17.39) • Age 35 or older but less than 50 at diagnosis, n (%): 76 (82.61)
Number of patients	N=92
Index test	• Age < 50 years vs > 50 years
Mutation status	• BRCA1 carrier vs non-carrier • Genomic DNA was isolated from blood using standard procedures. Mutation analysis was performed using PCR, denaturing high performance liquid chromatography and sequencing all exons as well as intron boundaries of the BRCA1 genes.

<table>
<tr><td>Bibliographic reference</td><td>Andres R, Pajares I, Balmana J, Llort G, Ramon Y Cajal T, Chirivella I, Aguirre E, Robles L, Lastra E, Perez-Segura P, Bosch N, Yague C, Lerma E, Godino J, Miramar M D, Moros M, Astier P, Saez B, Vidal M J, Arcusa A, Ramon y Cajal, S , Calvo M T, and Tres A. (2014). Association of BRCA1 germline mutations in young onset triple-negative breast cancer (TNBC). Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico, 16(3), pp.280-4.A</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1 positive</th><th>BRCA1 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>7 (TP)</td><td>85 (FP)</td><td>92</td></tr>
<tr><td>Age >50 years</td><td>0 (FN)</td><td>0 (TN)</td><td>0</td></tr>
<tr><td>Totals</td><td>7</td><td>85</td><td>92</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 7/92 = 7.6 (3.7 to 14.9)
BRCA1 Prevalence = 7/92 = 7.6%

*Calculated by analyst based on data reported in the article
TP: true positives
FP: false positives
FN: false negatives
TN: true negatives
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>• Exclusion criteria not reported</td></tr>
</table>

G.21 Couch 2015

Bibliographic reference	**Couch F J, Hart S N, Sharma P, Toland A E, Wang X, Miron P, Olson J E, Godwin A K, Pankratz V S, Olswold C, Slettedahl S, Hallberg E, Guidugli L, Davila J I, Beckmann M W, Janni W, Rack B, Ekici A B, Slamon D J, Konstantopoulou I, Fostira F, Vratimos A, Fountzilas G, Pelttari L M, Tapper W J, Durcan L, Cross S S, Pilarski R, Shapiro C L, Klemp J, Yao S, Garber J, Cox A, Brauch H, Ambrosone C, Nevanlinna H, Yannoukakos D, Slager S L, Vachon C M, Eccles D M, and Fasching P A. (2015). Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of Clinical Oncology, 33(4), pp.304-11.**
Study type	Cross sectional
Aim	To assess the frequency of mutations in 17 predisposition genes, including BRCA1 and BRCA2 in a large cohort of patients with triple negative breast cancer unselected for family history of breast or ovarian cancer to determine the utility of germline genetic testing for those with TNBC.
Patient characteristics	**Inclusion criteria** • Patients with triple negative independent of family history of breast or ovarian cancer and age at diagnosis **Exclusion criteria** • Not reported **Baseline characteristics*** • Ethnicity: white, n= 1761; Hispanic, n=10; African, n= 34; Asian, n=10; Mixed, n=2; unknown, n=7. • Grade: 1, n=20; 2, n=215; 3, n= 1119 • Family history: of the 1510 patients with available family history information, 514 (34%) had at least one first or second degree relative with breast cancer and 4% had a relative with ovarian cancer. • Average age at diagnosis in years, (range): 51 (22 to 93) *These are however for the whole study group as opposed to those without family history only
Number of patients	N=1824 of 969 had no family history
Index test	• Age <50 years vs > 50 years
Mutation status	• BRCA1/2 carrier vs non-carrier • Germline DNA samples from patients with TNBC underwent custom capture of all coding sequences and intron/exon boundaries of coding exons from 122 DNA repair genes. Products from each capture reaction were sequenced on a HiSeq 2000 and all likely deleterious mutations were validated by Sanger sequencing.

Bibliographic reference	**Couch F J, Hart S N, Sharma P, Toland A E, Wang X, Miron P, Olson J E, Godwin A K, Pankratz V S, Olswold C, Slettedahl S, Hallberg E, Guidugli L, Davila J I, Beckmann M W, Janni W, Rack B, Ekici A B, Slamon D J, Konstantopoulou I, Fostira F, Vratimos A, Fountzilas G, Pelttari L M, Tapper W J, Durcan L, Cross S S, Pilarski R, Shapiro C L, Klemp J, Yao S, Garber J, Cox A, Brauch H, Ambrosone C, Nevanlinna H, Yannoukakos D, Slager S L, Vachon C M, Eccles D M, and Fasching P A. (2015). Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. Journal of Clinical Oncology, 33(4), pp.304-11.**
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	Various – Germany, Greece, US, Finland and UK
Diagnostic accuracy measures (2 x 2 table)	<table><tr><th></th><th>BRCA1/2 positive</th><th>BRCA1/2 negative</th><th>Totals</th></tr><tr><td>Age <50 years</td><td>59 (TP)</td><td>390 (FP)</td><td>449</td></tr><tr><td>Age >50 years</td><td>24 (FN)</td><td>496 (TN)</td><td>520</td></tr><tr><td>Totals</td><td>83</td><td>886</td><td>969</td></tr></table> **PPV (95%CI)* = TP/TP+FP = 59/449 = 13.1 (10.3 to 16.6)** **BRCA1/2 Prevalence = 83/969= 8.6%** *Calculated by analyst based on data reported in the article TP: true positives FP: false positives FN: false negatives TN: true negatives
Source of funding	Supported by national institutes of Health Grant, Breast cancer research foundation and Grohne family foundation
Comments	• Only results for those without family history has been extracted. • Exclusion criteria not reported.

G.31 Evans 2011

Bibliographic reference	**Evans D G, Howell A, Ward D, Lalloo F, Jones J L, and Eccles D M. (2011). Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. Journal of Medical Genetics, 48(8), pp.520-2.**
Study type	Cross sectional

Bibliographic reference	**Evans D G, Howell A, Ward D, Lalloo F, Jones J L, and Eccles D M. (2011). Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. Journal of Medical Genetics, 48(8), pp.520-2.**
Aim	To undertake a study in the UK population to clarify the probability that an isolated young onset TNBC patient presenting with her first breast cancer at <41 years might carry a BRCA1 or BRCA2 mutation.
Patient characteristics	**Inclusion criteria** • Two population based patient cohorts of young onset breast cancer with documented absence of any family history of breast or ovarian cancer • Group 1 was a population based sample of all TNBCs ascertained in the Manchester <31 study and group 2 were patients with isolated TNBCs ascertained through the POSH study which recruited breast cancer cases aged <41 years through oncology clinics nationally **Exclusion criteria** • Not reported **Baseline characteristics** • **POSH study** – age and selection: <41 years, sporadic • **Manchester study** – age and selection: <31 years, unselected
Number of patients	Manchester study: n= 24 POSH study: n=39 Total n of all isolated TNBC therefore = 63
Index test	• Age <50 years vs age >50 years • Tumour grade not reported
Mutation status	• BRCA1 carrier vs non BRCA 1 carrier - BRCA2 mutations not identified although subjects were tested for this. • Patients were tested for an underlying BRCA1/2 mutation with a full mutation screen of both genes including a dosage test for exon deletions/duplications in either the National Genetics Reference Laboratory, Wessex or the National Genetics Reference Laboratory in Manchester.
Time between testing & treatment	n/a
Length of follow-up	n/a
Location	UK

Bibliographic reference	**Evans D G, Howell A, Ward D, Lalloo F, Jones J L, and Eccles D M. (2011). Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. Journal of Medical Genetics, 48(8), pp.520-2.**
Diagnostic accuracy measures (2 x 2 table)	<table><tr><th></th><th>BRCA1 positive</th><th>BRCA1 negative</th><th>Totals</th></tr><tr><td>**Age <50 years**</td><td>8 (TP)</td><td>55 (FP)</td><td>63</td></tr><tr><td>**Age >50 years**</td><td>0 (FN)</td><td>0 (TN)</td><td>0</td></tr><tr><td>**Totals**</td><td>8</td><td>55</td><td>63</td></tr></table> **PPV (95%CI)* = TP/TP+FP = 8/63 = 12.7 (6.6 to 23.1)** **BRCA1 Prevalence: 8/63 =12.7%** *Calculated by analyst based on data reported in the article TP: true positives FP: false positives FN: false negatives TN: true negatives
Source of funding	The Manchester studies were supported by the Genesis Breast Cancer Prevention Appeal. The POSH study receives funding from Cancer Research UK and Breast Cancer Campaign
Comments	• All mutations were in BRCA1; BRCA2 mutations not identified although subjects were tested for this. • Patient selection: exclusion criteria not reported

G.41 Fostira 2012

Bibliographic reference	**Fostira F, Tsitlaidou M, Papadimitriou C, Pertesi M, Timotheadou E, Stavropoulou A V, Glentis S, Bournakis E, Bobos M, Pectasides D, Papakostas P, Pentheroudakis G, Gogas H, Skarlos P, Samantas E, Bafaloukos D, Kosmidis P A, Koutras A, Yannoukakos D, Konstantopoulou I, and Fountzilas G. (2012). Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Research & Treatment, 134(1), pp.353-62.**
Study type	Cross sectional
Aim	To screen a large sample of 403 women diagnosed with triple negative invasive breast cancer, independently of their age or family history, for germline BRCA1 mutations
Patient characteristics	**Inclusion criteria**

<table>
<tr><td>Bibliographic reference</td><td>Fostira F, Tsitlaidou M, Papadimitriou C, Pertesi M, Timotheadou E, Stavropoulou A V, Glentis S, Bournakis E, Bobos M, Pectasides D, Papakostas P, Pentheroudakis G, Gogas H, Skarlos P, Samantas E, Bafaloukos D, Kosmidis P A, Koutras A, Yannoukakos D, Konstantopoulou I, and Fountzilas G. (2012). Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Research & Treatment, 134(1), pp.353-62.</td></tr>
<tr><td></td><td>• Women with triple negative receptor status (ER-negative, PR-negative, and HER2-negative; for ER and PR, a tumour tissue sample was classified as negative based on a 1% or less count of positive nuclei by immunohistochemistry; for HER2, IHC scores of 0 and +1 were classified as negative as well as +2 scores with a following negative FISH/CISH result).

Exclusion criteria
• Medical records regarding ER, PR and HER2 status were incomplete or inconclusive, or if biological samples were unavailable.

Baseline characteristics
• Median age at diagnosis (range): 50 years (20-83)*
*This is however for the total study group as opposed to those without family history only</td></tr>
<tr><td>Number of patients</td><td>N=403 of which 298 had no family history</td></tr>
<tr><td>Index test</td><td>• Age < 50 vs >51</td></tr>
<tr><td>Mutation status</td><td>• BRCA1 carrier vs non-carrier
• BRCA1 was screened by direct DNA sequencing in all patients, including all exons where a mutation was previously found, including diagnostic PCRs to detect the three Greek founder large genomic rearrangements.</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>Greece</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1 positive</th><th>BRCA1 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>11 (TP)</td><td>111 (FP)</td><td>122</td></tr>
<tr><td>Age >50 years</td><td>4 (FN)</td><td>172 (TN)</td><td>176</td></tr>
<tr><td>Totals</td><td>15</td><td>283</td><td>298</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 11/122 = 9.0 (5.1 to 15.4)
</td></tr>
</table>

Bibliographic reference	**Fostira F, Tsitlaidou M, Papadimitriou C, Pertesi M, Timotheadou E, Stavropoulou A V, Glentis S, Bournakis E, Bobos M, Pectasides D, Papakostas P, Pentheroudakis G, Gogas H, Skarlos P, Samantas E, Bafaloukos D, Kosmidis P A, Koutras A, Yannoukakos D, Konstantopoulou I, and Fountzilas G. (2012). Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Research & Treatment, 134(1), pp.353-62.**
	BRCA1 Prevalence = 15/298 = 5% *Calculated by analyst based on data reported in the article TP: true positives FP: false positives FN: false negatives TN: true negatives
Source of funding	Study partly supported by the Greek General Secretary for Research and Technology Program, funded by 75% from the European Union and the Operational Program.
Comments	• Authors indicate that parts of the BRCA1 coding region are left out by the screening strategy employed and so the true frequency of BRCA1 mutations is underestimated by 6%.

G.51 Hartman 2012

Bibliographic reference	**Hartman A R, Kaldate R R, Sailer L M, Painter L, Grier C E, Endsley R R, Griffin M, Hamilton S A, Frye C A, Silberman M A, Wenstrup R J, and Sandbach J F. (2012). Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer, 118(11), pp.2787-95.**
Study type	Cross sectional
Aim	To assess BRCA1 and BRCA2 mutation prevalence in an unselected cohort of patients with triple negative breast cancer.
Patient characteristics	**Inclusion criteria** • Patients presenting with triple negative breast cancer in a community oncology network from 2005 to 2010 • Alive • ≥18 years • Consent to genetic testing for BRCA1 and BRCA2 if testing has not occurred previously **Exclusion criteria** • Patients diagnosed before 2005 to minimise mortality ascertainment bias

<table>
<tr><td>Bibliographic reference</td><td>Hartman A R, Kaldate R R, Sailer L M, Painter L, Grier C E, Endsley R R, Griffin M, Hamilton S A, Frye C A, Silberman M A, Wenstrup R J, and Sandbach J F. (2012). Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer, 118(11), pp.2787-95.</td></tr>
<tr><td></td><td>Baseline characteristics*
Median age in years (range): 52 (23 to 79)
Menopausal status, n (%): Premenopausal – 63 (36.8); perimenopausal – 20 (11.7); postmenopausal – 88 (51.5); missing – 28
Ethnicity, n (%): Black – 27 (13.6); Native American – 1 (0.5); Hispanic – 31 (15.7); Asian – 3 (1.5); Caucasian – 131 (66.2); Unknown – 1 (0.5); Other: 4 (2), Missing – 1
Without significant** family history, n (%): 153 (76.9)
*These are however for the total study group as opposed to those without family history only
**Defined as breast cancer before the age of 50 years or ovarian cancer at any age in any first degree or second degree relative.</td></tr>
<tr><td>Number of patients</td><td>N= 199 of which 153 had no significant family history</td></tr>
<tr><td>Index test</td><td>Age < 50 years vs > 50 years
Tumour grade not reported</td></tr>
<tr><td>Mutation status</td><td>BRCA1/2 carrier vs non-carrier
Full sequencing and large genomic rearrangement analysis performed by Myriad Genetic Laboratories
Large rearrangement testing was performed for patients who had only sequencing testing previously</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a (retrospective cohort)</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1/2 positive</th><th>BRCA1/2 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>6 (TP)</td><td>60 (FP)</td><td>66</td></tr>
<tr><td>Age >50 years</td><td>2 (FN)</td><td>85 (TN)</td><td>87</td></tr>
<tr><td>Totals</td><td>8</td><td>145</td><td>153</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 6/66 = 9.1 (4.2 to 18.4)
BRCA1/2 Prevalence: 8/153 = 5.2%

*Calculated by analyst based on data reported in the article</td></tr>
</table>

Bibliographic reference	**Hartman A R, Kaldate R R, Sailer L M, Painter L, Grier C E, Endsley R R, Griffin M, Hamilton S A, Frye C A, Silberman M A, Wenstrup R J, and Sandbach J F. (2012). Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer, 118(11), pp.2787-95.**
	TP: true positives FP: false positives FN: false negatives TN: true negatives
Source of funding	Myriad Genetic Laboratories
Comments	• Results shown are for those without significant family history - significant family history defined as breast cancer before the age of 50 years or ovarian cancer at any age in any first degree or second degree relative.

G.61 Meyer 2012

Bibliographic reference	**Meyer P, Landgraf K, Hogel B, Eiermann W, and Ataseven B. (2012). BRCA2 mutations and triple-negative breast cancer. PLoS ONE [Electronic Resource], 7(5), pp.e38361.**
Study type	Cross sectional
Aim	To investigate the role of BRCA2 germline mutations in triple negative breast cancer
Patient characteristics	**Inclusion criteria** • Newly diagnosed cases of individuals with TNBC diagnosed between 2005 and 2010 were selected from the Pathology Unit (Histological samples were classified as TNBC when the following criteria were met: less than 1% of cells demonstrated nuclear staining for estrogen and progesterone receptors, and immuno-histochemical staining for HER2 showing a 0, 1-fold, or a 2-fold positive score and a FISH ratio (HER2 gene signals to chromosome 17 signals) of less than 1.8 according to the relevant ASCO and CAP guidelines. **Exclusion criteria** • No further selection criteria was applied **Baseline characteristics** • Median age at diagnosis: 58 years* *This is however for the whole study group as opposed to those without family history only

<table>
<tr><td>Bibliographic reference</td><td>Meyer P, Landgraf K, Hogel B, Eiermann W, and Ataseven B. (2012). BRCA2 mutations and triple-negative breast cancer. PLoS ONE [Electronic Resource], 7(5), pp.e38361.</td></tr>
<tr><td>Number of patients</td><td>N=30 of which 12 no had family history</td></tr>
<tr><td>Index test</td><td>• Age < 50 years vs > 50 years</td></tr>
<tr><td>Mutation status</td><td>• BRCA1/2 carrier vs non-carrier
• DNA extraction from whole blood samples (EDTA) was performed according to standard protocols. To amplify exons and exon-intron boundaries of BRCA1 and BRCA2, primer pairs and polymerase chain reaction (PCR) was used.
• To exclude deletions and duplications of one or more exons, Multiplex Ligation-dependent Probe Amplification (MLPA) of both genes was performed.</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>Germany</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1/2 positive</th><th>BRCA1/2 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>3 (TP)</td><td>2 (FP)</td><td>5</td></tr>
<tr><td>Age >50 years</td><td>1 (FN)</td><td>6 (TN)</td><td>7</td></tr>
<tr><td>Totals</td><td>4</td><td>8</td><td>12</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 3/5 = 60 (23.1 to 88.2)
Prevalence of BRCA1/2: 4/12 = 33%
</td></tr>
<tr><td>Source of funding</td><td>Supported by the Human Genetics Foundation Munich</td></tr>
<tr><td>Comments</td><td>• Family history status only reported for 28/30 patients – unclear if status was unknown for remaining 2 patients as details not reported</td></tr>
</table>

G.71 Phuah 2012

Bibliographic reference	**Phuah S Y, Looi L M, Hassan N, Rhodes A, Dean S, Taib N A, Yip C H, and Teo S H. (2012). Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast Cancer Research, 14(6), pp.R142.**
Study type	Cross sectional
Aim	To determine whether TNBC is a predictor of germline BRCA1 mutations, in the context of multiple predictive factors.

Bibliographic reference	**Phuah S Y, Looi L M, Hassan N, Rhodes A, Dean S, Taib N A, Yip C H, and Teo S H. (2012). Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast Cancer Research, 14(6), pp.R142.**
Patient characteristics	**Inclusion criteria** • Breast cancer patients recruited into the MyBrCa study • All women with (a) early-onset breast cancer (≤35 years of age, 35 with and 96 without family history of breast and ovarian cancer); (b) family history of breast or ovarian cancer in first- and second-degree relatives (193 women); or (c) isolated triple-negative breast cancer diagnosed at between 36 and 50 years old in the absence of family history (47 women) **Exclusion criteria** Not reported **Baseline characteristics*** • Age at diagnosis in years, n (%): ≤30: 50 (11.6); 31-40: 164 (38.1); 41-50: 144 (33.4); >50: 73 (16.9) • Ethnicity, n (%): Malay: 115 (26.7); Chinese: 248 (57.5); Indian: 59 (13.7); Others: 9 (2.1) • Early onset ≤35 years, regardless of family history , n (%): 131 (30.4) • Two cases of breast cancer, one <50 years, n (%):126 (29.2) • Three cases of breast or ovarian cancer, n (%):76 (17.6) • One case of bilateral breast cancer <50 years, in index or first- and second-degree relative, n (%): 39 (9.0) • One case of breast and ovarian cancer in same individual in index or first and second-degree relative, n (%): 8 (1.9) • Triple-negative breast cancer, ≤50 years, n (%):98 (22.7) • Triple-negative breast cancer, ≤50 years, n (%): 47 (10.9) *These are however for the whole study group not those without family history only
Number of patients	N= 64 with no family history of which 47 were screened for mutations.
Index test	• Age < 50 years vs > 50 years
Mutation status	• BRCA1/2 carrier vs non-carrier • Mutation detection for germline BRCA1 and BRCA2 mutations was conducted by using direct DNA sequencing and multiple ligation-dependent probe amplification (MLPA)

<table>
<tr><td>Bibliographic reference</td><td>Phuah S Y, Looi L M, Hassan N, Rhodes A, Dean S, Taib N A, Yip C H, and Teo S H. (2012). Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast Cancer Research, 14(6), pp.R142.</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>Malaysia</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1/2 positive</th><th>BRCA1/2 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>4 (TP)</td><td>43 (FP)</td><td>47</td></tr>
<tr><td>Age >50 years</td><td>0 (FN)</td><td>0 (TN)</td><td>0</td></tr>
<tr><td>Totals</td><td>4</td><td>43</td><td>47</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 4/47 =8.5 (3.4 to 19.9)
Prevalence of BRCA1/2: 4/47 =8.5%
</td></tr>
<tr><td>Source of funding</td><td>Research grants from the Malaysian Ministry of Science</td></tr>
<tr><td>Comments</td><td>• Exclusion criteria not reported</td></tr>
</table>

G.81 Robertson 2012

<table>
<tr><td>Bibliographic reference</td><td>Robertson L, Hanson H, Seal S, Warren-Perry M, Hughes D, Howell I, Turnbull C, Houlston R, Shanley S, Butler S, Evans D G, Ross G, Eccles D, Tutt A, Rahman N, TMG T N. T. Trial, and Bcsc . (2012). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. British Journal of Cancer, 106(6), pp.1234-8.</td></tr>
<tr><td>Study type</td><td>Cross sectional</td></tr>
<tr><td>Aim</td><td>To evaluate the BRCA1 mutation frequency and the implications for clinical practice of undertaking genetic testing in women with triple negative breast cancer.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
• Subjects with triple negative breast cancer (oestrogen receptor, progesterone receptor and HER2 status confirmed either in a histopathology report and/or a clinician’s referral letter. When not explicitly stated, ER and PR status were scored as negative when there was absent expression. HER2 was regarded as negative when scored as 0 or 1 + for HER2 by immunohistochemistry and/or when there was non-amplification of HER2 by fluorescent in situ hybridisation).</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Robertson L, Hanson H, Seal S, Warren-Perry M, Hughes D, Howell I, Turnbull C, Houlston R, Shanley S, Butler S, Evans D G, Ross G, Eccles D, Tutt A, Rahman N, TMG T N. T. Trial, and Bcsc . (2012). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. British Journal of Cancer, 106(6), pp.1234-8.</td></tr>
<tr><td></td><td>Exclusion criteria
Not reported
Baseline characteristics
Not reported</td></tr>
<tr><td>Number of patients</td><td>N= 308 of which 103 had no family history</td></tr>
<tr><td>Index test</td><td>Age <50 years vs > 50 years</td></tr>
<tr><td>Mutation status</td><td>BRCA1 carrier vs non carrier
Mutation analysis included multiplex ligation-dependent probe amplification analysis for large deletions/duplications performed in DNA from all cases. This was either performed through a clinical BRCA test by the local centre or was undertaken by ourselves by sequencing genomic DNA through the 24 coding exons and intron-exon boundaries of BRCA1 and undertaking MLPA using probe mix P002.
All mutations were confirmed by separate bi-directional sequencing in a second sample.</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1 positive</th><th>BRCA1 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>8 (TP)</td><td>95 (FP)</td><td>103</td></tr>
<tr><td>Age >50 years</td><td>0 (FN)</td><td>0 (TN)</td><td>0</td></tr>
<tr><td>Totals</td><td>8</td><td>95</td><td>103</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 8/103 = 7.8 (4 to 14.6)
BRCA1 Prevalence: 8/103 = 7.8%

*Calculated by analyst based on data reported in the article
TP: true positives
FP: false positives
</td></tr>
</table>

Bibliographic reference	**Robertson L, Hanson H, Seal S, Warren-Perry M, Hughes D, Howell I, Turnbull C, Houlston R, Shanley S, Butler S, Evans D G, Ross G, Eccles D, Tutt A, Rahman N, TMG T N. T. Trial, and Bcsc . (2012). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. British Journal of Cancer, 106(6), pp.1234-8.**
	FN: false negatives TN: true negatives
Source of funding	Cancer Research UK, US Military Acquisition, Era of Hope Award and Institute of Cancer Research.
Comments	• Exclusion criteria not reported

G.91 Wang 2015

Bibliographic reference	**Wang C, Zhang J, Wang Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, and Xie Y. (2015). Prevalence of BRCA1 mutations and responses to neoadjuvant chemotherapy among BRCA1 carriers and non-carriers with triple-negative breast cancer. Annals of Oncology, 26(3), pp.523-8.**
Study type	Cross sectional
Aim	To examine the prevalence of the BRCA1/2 germline mutations among 956 triple negative breast cancer patients who were selected without regards to age or family history; further investigated the association between BRCA1 mutation status and response to neoadjuvant chemotherapy among the patients (n = 652) who received neoadjuvant chemotherapy; finally, we compared the survival of the BRCA1 carriers and non-carriers in terms of 5-year recurrence-free survival (RFS) and distant recurrence-free survival (DRFS) in the study population (n = 947).
Patient characteristics	**Inclusion criteria** • Patients with triple negative breast cancer unselected for age at diagnosis or family history of breast cancer (ER, PR and HER2 status determined using the breast cancer tissues obtained from the core-needle biopsy taken before the initiation of neoadjuvant chemotherapy or tumour tissues procured following operation. ER or PR immunostaining was considered positive when >1% of the tumour cells showed positive nuclear staining. HER2 status determined via fluorescence in situ hybridisation). • Triple negative defined as ER and PR <1% of cells staining and HER negativity according to the guidelines. **Exclusion criteria** • Not reported **Baseline characteristics*** • Median age in years (range): 51 (24 to 90)

<table>
<tr><td>Bibliographic reference</td><td>Wang C, Zhang J, Wang Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, and Xie Y. (2015). Prevalence of BRCA1 mutations and responses to neoadjuvant chemotherapy among BRCA1 carriers and non-carriers with triple-negative breast cancer. Annals of Oncology, 26(3), pp.523-8.</td></tr>
<tr><td></td><td>• No family history, n (%): 847 (89)
• Tumour grade I, n (%): 62 (6.5)
• Tumour grade II, n (%): 500 (52)
• Tumour grade III, n (%): 307 (32)
• Tumour grade unknown, n (%): 87 (9)

*These are however for the whole study group as opposed to those without family history only</td></tr>
<tr><td>Number of patients</td><td>N=956 of which 847 had no family history</td></tr>
<tr><td>Index test</td><td>• Age <50 years vs >50 years</td></tr>
<tr><td>Mutation status</td><td>• BRCA1 carrier vs non-carrier
• Genomic DNA was extracted from peripheral mononuclear blood cells; the complete coding regions and exon-intron boundaries of the BRCA1/2 gene were screened</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>China</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1 positive</th><th>BRCA1 negative</th><th>Totals</th></tr>
<tr><td>Age ≤50 years</td><td>34 (TP)</td><td>373 (FP)</td><td>407</td></tr>
<tr><td>Age >50 years</td><td>12 (FN)</td><td>428 (TN)</td><td>440</td></tr>
<tr><td>Totals</td><td>46</td><td>801</td><td>847</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 34/407 = 8.4 (6 to 11.4)
BRCA1 Prevalence: 46/847 = 5.4%

*Calculated by analyst based on data reported in the article
TP: true positives
FP: false positives</td></tr>
</table>

Bibliographic reference	**Wang C, Zhang J, Wang Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, and Xie Y. (2015). Prevalence of BRCA1 mutations and responses to neoadjuvant chemotherapy among BRCA1 carriers and non-carriers with triple-negative breast cancer. Annals of Oncology, 26(3), pp.523-8.**
	FN: false negatives TN: true negatives
Source of funding	National Key Technology Research and Development Program of the Ministry of Science and Technology of China; program for Breast Cancer Tissue Bank of Beijing, and grants from the National Natural Science Foundation of China .
Comments	• Exclusion criteria not reported

G.101 Young 2009

Bibliographic reference	**Young S R, Pilarski R T, Donenberg T, Shapiro C, Hammond L S, Miller J, Brooks K A, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, and Narod S A. (2009). The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer, 9, pp.86.**
Study type	Cross sectional
Aim	To estimate the proportion of BRCA1 mutation carriers among women diagnosed at age 40 or younger with triple-negative breast cancer, without a significant family history of cancer.
Patient characteristics	**Inclusion criteria** • Women with a cancer diagnosis within three years of study initiation were invited to participate • Women diagnosed with breast cancer at age 40 years and younger and who did not have a significant family history of breast or ovarian cancer (significant family history as defined by the American Society of clinical oncology). • Eligible if medical records indicated that breast carcinoma was grade III and was negative for ER, PR and HER2; HER2 overexpression was defined as moderate to strong staining that totally encircles the cell membrane (2+ or 3+) **Exclusion criteria** • Patients of Ashkenazi Jewish heritage because they would be eligible for routine genetic testing (founder mutations) in any cancer centre and because the authors did not expect to find non-founder mutations in this population. • Insufficient documentation of triple negative status to include them in the study • Positive family history of cancer • Age of diagnosis missing **Baseline characteristics**

<table>
<tr><td>Bibliographic reference</td><td>Young S R, Pilarski R T, Donenberg T, Shapiro C, Hammond L S, Miller J, Brooks K A, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, and Narod S A. (2009). The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer, 9, pp.86.</td></tr>
<tr><td></td><td>• Mean age of cancer diagnosis was 34.7 years (range 24 to 40 years)</td></tr>
<tr><td>Number of patients</td><td>N=58 however 4 samples were of poor quality and excluded, n therefore = 54.</td></tr>
<tr><td>Index test</td><td>• Age < 50 years vs >50 years</td></tr>
<tr><td>Mutation status</td><td>• BRCA1/2 carrier vs non-carrier
• DNA was extracted from whole blood lymphocytes using standard methodology. The entire coding sequence of BRCA1 and the large exons 10 and 11 of BRCA2 was evaluated for mutations.
• DNA was screened for two common BRCA1 alterations (185delAG and 5382insC) and one BRCA2 alteration (6174delT) by rapid fluorescent multiplexed-PCR analysis.
• All patients were screened for the BRCA1 exon-13 6 kb duplication. BRCA1 exon 11, and BRCA2 exons 10 and 11 were screened using protein truncation test (PTT).
• All other BRCA1exons, with the exception of exons 1a/b and 4, were also scanned by fluorescent multiplexed denaturing gradient gel electrophoresis (DGGE).
• All variants identified by either PTT or DGGE were confirmed by direct sequencing.</td></tr>
<tr><td>Time between testing & treatment</td><td>n/a</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<table>
<tr><th></th><th>BRCA1/2 positive</th><th>BRCA1/2 negative</th><th>Totals</th></tr>
<tr><td>Age <50 years</td><td>6 (TP)</td><td>48 (FP)</td><td>54</td></tr>
<tr><td>Age >50 years</td><td>0 (FN)</td><td>0 (TN)</td><td>0</td></tr>
<tr><td>Totals</td><td>6</td><td>48</td><td>54</td></tr>
</table>
PPV (95%CI)* = TP/TP+FP = 6/54 = 11.1 (5.2 to 22.2)
BRCA1/2 Prevalence: 6/54 = 11.1%

*Calculated by analyst based on data reported in the article
TP: true positives
FP: false positives
</td></tr>
</table>

Bibliographic reference	**Young S R, Pilarski R T, Donenberg T, Shapiro C, Hammond L S, Miller J, Brooks K A, Cohen S, Tenenholz B, Desai D, Zandvakili I, Royer R, Li S, and Narod S A. (2009). The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer, 9, pp.86.**
	FN: false negatives TN: true negatives
Source of funding	Not reported
Comments	• 4 results not analysed as samples were of poor quality therefore total n was 54 instead of 58 which makes a difference in PPV from 11.1 to 10.3

Appendix H: GRADE profiles

H.1 Studies reporting BRCA1/2 prevalence

Quality assessment							No of patients	Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**True positive/test positive/N**	**Positive predictive value (95%CI)**	
Outcome: Positive predictive value of age <50 years vs >50 years in detecting BRCA1/2 mutation									
BRCA1/2 positive prevalence of 5.2% (8/153)									
1 (Hartman 2012)	Cross sectional	No serious[1]	No serious[2]	N/A	Serious[3]	None	6/66	9.1% (4.2 to 18.4)	Moderate
BRCA1/2 positive prevalence of 8.5% (4/47)									
1 (Phuah 2012)	Cross sectional	Serious[4]	No serious[5]	N/A	Serious[3]	None	3/47	8.5% (3.4 to 19.9)	Low
BRCA1/2 positive prevalence of 8.6% (8/969)									
1 (Couch 2015)	Cross sectional	Serious[4]	No serious[5]	N/A	No serious[6]	None	59/449	13.1% (10.3 to 16.6)	Moderate
BRCA1/2 positive prevalence of 11.1% (6/54)									

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	True positive/test positive/N	Positive predictive value (95%CI)	
1 (Young 2009)	Cross sectional	Serious[7]	No serious[2]	N/A	Serious[3]	None	6/54	11.1% (5.2 to 22.2)	Low
BRCA1/2 positive prevalence of 33% (4/12)									
1 (Meyer 2012)	Cross sectional	No serious[1]	No serious[2]	N/A	No serious[6]	None	3/5	60% (23.1 to 88.2)	High

[1] No serious risk of bias
[2] No serious indirectness
[3] Serious imprecision as confidence interval of PPV crosses 10% threshold
[4] Serious risk of bias as exclusion criteria not reported therefore applicability unclear
[5] Though there are concerns in the applicability of the patient population (as exclusion criteria not reported), this has not been downgraded twice as already taken account of in the risk of bias assessment.
[6] No serious imprecision
[7] 4 results not analysed as samples were of poor quality therefore total n was 54 instead of 58 which makes a difference in PPV from 11.1 to 10.3

H.29 Studies reporting BRCA1 prevalence only

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	True positive/test positive/N	Positive predictive value (95%CI)	
Outcome: Positive predictive value of age <50 years vs >50 years in detecting BRCA1/2 mutation									
BRCA1 positive prevalence of 5.4% (46/847)									
1 (Wang 2015)	Cross sectional	Serious[1]	No serious[2]	N/A	Serious[3]	None	34/407	8.4% (6 to 11.4)	Low
BRCA1 positive prevalence of 7.6% (7/92)									
1 (Andres 2014)	Cross sectional	Serious[1]	No serious[2]	N/A	Serious[3]	None	7/92	7.6% (3.7 to 14.9)	Low
BRCA1 positive prevalence of 7.8% (8/103)									

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	True positive/test positive/N	Positive predictive value (95%CI)	
1 (Robertson 2012)	Cross sectional	Serious[1]	No serious[2]	N/A	Serious[3]	None	8/103	7.8% (4 to 14.6)	Low
BRCA1 positive prevalence of 12.7% (8/63)									
1 (Evans 2011)	Cross sectional	Serious[1]	No serious[2]	N/A	Serious[3]	None	8/63	12.7% (6.6 to 23.1)	Low
Outcome: Positive predictive value of age <50 years vs >51 years in detecting BRCA1 mutation									
BRCA1 positive prevalence of 5% (15/298)									
1 (Fostira 2012)	Cross sectional	Serious[4]	No serious[5]	N/A	No serious[6]	None	11/122	9.0% (5.1 to 15.4)	Moderate

[1] No serious risk of bias
[2] No serious indirectness
[1] Serious risk of bias as exclusion criteria not reported therefore applicability unclear
[2] Though there are concerns in the applicability of the patient population (as exclusion criteria not reported), this has not been downgraded twice as already taken account of in the risk of bias assessment.
[3] Serious imprecision as confidence interval of PPV crosses 10% threshold
[4] Authors indicate that parts of the BRCA1 coding region are left out by the screening strategy employed and so the true frequency of BRCA1 mutations is underestimated by 6%; applicability of reference standard therefore questionable.
[5] Though there are concerns in the applicability of the reference standard used, this has not been downgraded for indirectness as already accounted for in risk of bias.
[6] No serious imprecision

Appendix I: Forest plots

No forest plots

Appendix J: Quality assessment

	Risk of bias					Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Overall risk of bias	Patient selection	Index test	Referenc standard
Evans 2011	?	n/a	√	√	Serious	√	n/a	√
Fostira 2012	√	n/a	?	√	Serious	√	n/a	√
Couch 2015	?	n/a	√	√	Serious	√	n/a	√
Andres 2014	?	n/a	√	√	Serious	√	n/a	√
Young 2009	√	n/a	√	?	Serious	√	n/a	√
Wang 2015	?	n/a	√	√	serious	√	n/a	√
Robertson 2012	?	n/a	√	√	Serious	√	n/a	√
Hartman 2012	√	n/a	√	√	No serious	√	n/a	√
Meyer 2012	√	n/a	√	√	No serious	√	n/a	√
Phuah 2012	?	n/a	√	√	Serious	√	n/a	√

√ Low risk

× High risk

? Unclear risk

n/a not applicable

Appendix K: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 5. The search strategy is shown in Table 6. The same strategy was translated for the other databases listed.

Table 5: Economic search summary

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	15/06/2016	1946 to June wk 1 2016	19
MEDLINE in Process (Ovid)	15/06/2016	June 14 2016	10
Embase (Ovid)	15/06/2016	1974 to 2016 June 14	47
NHS Economic Evaluation Database (NHS EED) (legacy database)	15/06/2016	Issue 2 of 4 April 2015	0
Health Technology Assessment (HTA Database)	15/06/2016	2 of 4 April 2016	0
Pubmed	15/06/2016	N/A	27

Table 6: Economic search strategies

Database: Medline
Database: Ovid MEDLINE(R) <1946 to June Week 1 2016> Search Strategy: --- 1 Triple negative breast neoplasms/ (1413) 2 (((triple or her2) adj4 negative) and breast).tw. (5314) 3 1 or 2 (5459) 4 brca1 protein/ or brca2 protein/ (5678) 5 (brca1 or brca2 or "breast cancer 1" or "breast cancer 2" or fancd1 or fanconi anemia or fanconi anaemia).tw. (13830) 6 4 or 5 (14637) 7 3 and 6 (426) 8 limit 7 to english language (411) 9 Economics/ (26727) 10 exp "Costs and Cost Analysis"/ (198983)

Database: Medline

11	Economics, Dental/ (1880)
12	exp Economics, Hospital/ (21569)
13	exp Economics, Medical/ (13890)
14	Economics, Nursing/ (3937)
15	Economics, Pharmaceutical/ (2623)
16	Budgets/ (10477)
17	exp Models, Economic/ (11765)
18	Markov Chains/ (11309)
19	Monte Carlo Method/ (22735)
20	Decision Trees/ (9544)
21	econom$.tw. (177820)
22	cba.tw. (9088)
23	cea.tw. (17715)
24	cua.tw. (837)
25	markov$.tw. (13456)
26	(monte adj carlo).tw. (23586)
27	(decision adj3 (tree$ or analys$)).tw. (9549)
28	(cost or costs or costing$ or costly or costed).tw. (347974)
29	(price$ or pricing$).tw. (25800)
30	budget$.tw. (19097)
31	expenditure$.tw. (38909)
32	(value adj3 (money or monetary)).tw. (1527)
33	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2991)
34	or/9-33 (729270)
35	"Quality of Life"/ (138766)
36	Quality Adjusted Life Year/ (8503)

Database: Medline

37 Quality of Life Index/ (0)

38 Short Form 36/ (0)

39 Health Status/ (66648)

40 quality of life.tw. (161679)

41 quality adjusted life.tw. (7258)

42 (qaly$ or qald$ or qale$ or qtime$).tw. (5934)

43 disability adjusted life.tw. (1558)

44 daly$.tw. (1488)

45 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (17510)

46 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1077)

47 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3287)

48 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)

49 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (346)

50 (euroqol or euro qol or eq5d or eq 5d).tw. (4939)

51 (qol or hql or hqol or hrqol).tw. (29473)

52 (hye or hyes).tw. (54)

53 health$ year$ equivalent$.tw. (38)

54 utilit$.tw. (128167)

55 (hui or hui1 or hui2 or hui3).tw. (975)

56 disutili$.tw. (256)

57 rosser.tw. (72)

58 quality of wellbeing.tw. (6)

59 quality of well-being.tw. (346)

Database: Medline

60 qwb.tw. (184)

61 willingness to pay.tw. (2709)

62 standard gamble$.tw. (691)

63 time trade off.tw. (821)

64 time tradeoff.tw. (216)

65 tto.tw. (669)

66 or/35-65 (395516)

67 34 or 66 (1071448)

68 8 and 67 (19)

1

Database: MiP

atabase: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 14, 2016>
Search Strategy:
---

1 Triple negative breast neoplasms/ (0)

2 (((triple or her2) adj4 negative) and breast).tw. (1426)

3 1 or 2 (1426)

4 brca1 protein/ or brca2 protein/ (0)

5 (brca1 or brca2 or "breast cancer 1" or "breast cancer 2" or fancd1 or fanconi anemia or fanconi anaemia).tw. (1270)

6 4 or 5 (1270)

7 3 and 6 (92)

8 limit 7 to english language (90)

9 Economics/ (0)

10 exp "Costs and Cost Analysis"/ (0)

11 Economics, Dental/ (0)

12 exp Economics, Hospital/ (0)

13 exp Economics, Medical/ (0)

Database: MiP

14	Economics, Nursing/ (0)
15	Economics, Pharmaceutical/ (0)
16	Budgets/ (0)
17	exp Models, Economic/ (0)
18	Markov Chains/ (0)
19	Monte Carlo Method/ (0)
20	Decision Trees/ (0)
21	econom$.tw. (24971)
22	cba.tw. (250)
23	cea.tw. (1165)
24	cua.tw. (99)
25	markov$.tw. (3304)
26	(monte adj carlo).tw. (10951)
27	(decision adj3 (tree$ or analys$)).tw. (1149)
28	(cost or costs or costing$ or costly or costed).tw. (53200)
29	(price$ or pricing$).tw. (3468)
30	budget$.tw. (2992)
31	expenditure$.tw. (3939)
32	(value adj3 (money or monetary)).tw. (209)
33	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (423)
34	or/9-33 (94063)
35	"Quality of Life"/ (0)
36	Quality Adjusted Life Year/ (0)
37	Quality of Life Index/ (0)
38	Short Form 36/ (0)
39	Health Status/ (0)

Database: MiP

40 quality of life.tw. (23158)

41 quality adjusted life.tw. (978)

42 (qaly$ or qald$ or qale$ or qtime$).tw. (829)

43 disability adjusted life.tw. (290)

44 daly$.tw. (256)

45 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (1876)

46 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (489)

47 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (468)

48 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (3)

49 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (15)

50 (euroqol or euro qol or eq5d or eq 5d).tw. (928)

51 (qol or hql or hqol or hrqol).tw. (4426)

52 (hye or hyes).tw. (4)

53 health$ year$ equivalent$.tw. (2)

54 utilit$.tw. (17920)

55 (hui or hui1 or hui2 or hui3).tw. (123)

56 disutili$.tw. (41)

57 rosser.tw. (3)

58 quality of wellbeing.tw. (5)

59 quality of well-being.tw. (17)

60 qwb.tw. (9)

61 willingness to pay.tw. (486)

62 standard gamble$.tw. (44)

Database: MiP

63 time trade off.tw. (82)

64 time tradeoff.tw. (9)

65 tto.tw. (76)

66 or/35-65 (42541)

67 34 or 66 (130993)

68 8 and 67 (10)

1

Database: Embase

Database: Embase <1974 to 2016 June 14>
Search Strategy:
---

1 triple negative breast cancer/ (7813)

2 (((triple or her2) adj4 negative) and breast).tw. (15210)

3 1 or 2 (16484)

4 brca1 protein/ or brca2 protein/ (13061)

5 (brca1 or brca2 or "breast cancer 1" or "breast cancer 2" or fancd1 or fanconi anemia or fanconi anaemia).tw. (21312)

6 4 or 5 (26308)

7 3 and 6 (1415)

8 nonhuman/ not human/ (3735656)

9 7 not 8 (1398)

10 limit 9 to embase (1349)

11 limit 10 to (conference abstract or conference paper or conference proceeding or "conference review") (659)

12 10 not 11 (690)

13 limit 12 to english language (663)

14 exp Health Economics/ (694531)

Database: Embase	
15	exp "Health Care Cost"/ (234633)
16	exp Pharmacoeconomics/ (179203)
17	Monte Carlo Method/ (27136)
18	Decision Tree/ (7612)
19	econom$.tw. (259495)
20	cba.tw. (11157)
21	cea.tw. (26707)
22	cua.tw. (1035)
23	markov$.tw. (20202)
24	(monte adj carlo).tw. (33020)
25	(decision adj3 (tree$ or analys$)).tw. (14577)
26	(cost or costs or costing$ or costly or costed).tw. (528977)
27	(price$ or pricing$).tw. (40435)
28	budget$.tw. (28493)
29	expenditure$.tw. (54735)
30	(value adj3 (money or monetary)).tw. (2384)
31	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (7036)
32	or/14-31 (1315613)
33	"Quality of Life"/ (320173)
34	Quality Adjusted Life Year/ (16258)
35	Quality of Life Index/ (2080)
36	Short Form 36/ (16025)
37	Health Status/ (98981)
38	quality of life.tw. (280469)
39	quality adjusted life.tw. (11911)
40	(qaly$ or qald$ or qale$ or qtime$).tw. (12132)

Database: Embase

41 disability adjusted life.tw. (2229)

42 daly$.tw. (2297)

43 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (29341)

44 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1738)

45 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (5936)

46 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (41)

47 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (375)

48 (euroqol or euro qol or eq5d or eq 5d).tw. (10527)

49 (qol or hql or hqol or hrqol).tw. (59227)

50 (hye or hyes).tw. (101)

51 health$ year$ equivalent$.tw. (40)

52 utilit$.tw. (195149)

53 (hui or hui1 or hui2 or hui3).tw. (1552)

54 disutili$.tw. (526)

55 rosser.tw. (90)

56 quality of wellbeing.tw. (22)

57 quality of well-being.tw. (402)

58 qwb.tw. (214)

59 willingness to pay.tw. (4877)

60 standard gamble$.tw. (884)

61 time trade off.tw. (1218)

62 time tradeoff.tw. (236)

63 tto.tw. (1139)

Database: Embase

64 or/33-63 (670039)

65 32 or 64 (1878517)

66 13 and 65 (47)

1

Database: Cochrane

Strategy used:
Search Name: FBC Q2
Date Run: 08/06/16 14:02:09.579
Description:

ID	Search	Hits
#1	MeSH descriptor: [Triple Negative Breast Neoplasms] this term only	33
#2	(triple or her2) near/4 negative and breast:ti,ab,kw (Word variations have been searched)	682
#3	#1 or #2	682
#4	MeSH descriptor: [BRCA1 Protein] this term only	46
#5	MeSH descriptor: [BRCA2 Protein] this term only	41
#6	brca1 or brca2 or "breast cancer 1" or "breast cancer 2" or fancd1 or fanconi anemia or fanconi anaemia:ti,ab,kw (Word variations have been searched)	371
#7	#4 or #5 or #6	371
#8	#3 and #7	34

2

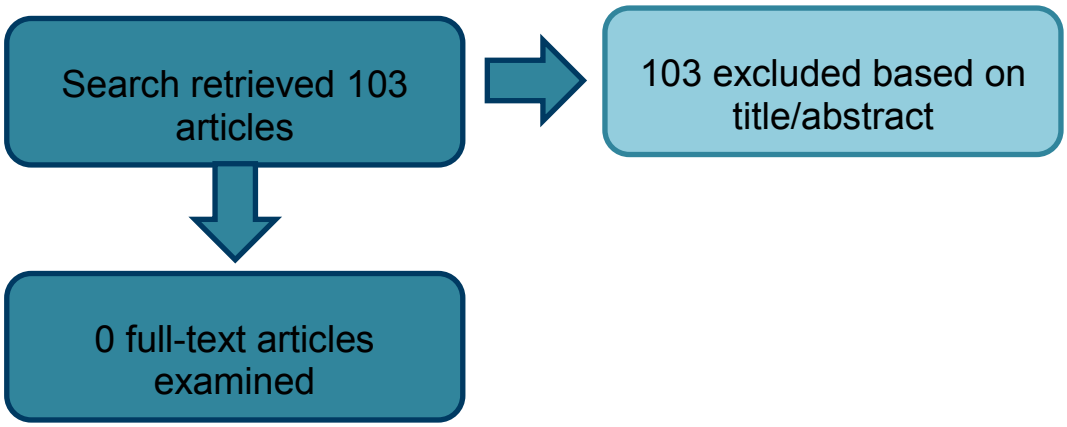
Database: Pubmed

HistoryDownload historyClear history
Recent queries

Search	Add to builder	Query	Items found	Time
#7	Add	Search (#3 and #6)	0	05:11:54
#6	Add	Search ("2016/06/13"[Date - Entrez] : "3000"[Date - Entrez])	9397	05:11:28
#5	Add	Search (#3 and #4)	27	05:10:56
#4	Add	Search publisher[sb]	497225	05:10:44
#3	Add	Search (#1 and #2)	538	05:10:24
#2	Add	Search (brca1[Title/Abstract] OR brca2[Title/Abstract] OR breast cancer 1[Title/Abstract] OR breast cancer 2[Title/Abstract] OR fancd1[Title/Abstract] OR fanconi anemia[Title/Abstract] OR fanconi anaemia[Title/Abstract])	15115	05:10:11
#1	Add	Search (((triple[Title/Abstract] OR her2[Title/Abstract])) AND negative[Title/Abstract]) AND breast[Title/Abstract]	8330	05:09:01

3

Appendix L:Economic review flowchart



Appendix M: Definitions of categories for risk of developing breast cancer (NICE, 2004)

	Definitions of categories for risk of developing breast cancer		
	Near population risk	Moderate risk	High risk [1]
Lifetime risk from age 20	Less than 17%	Greater than 17% but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3–8%	Greater than 8%

[1]This group includes people with known BRCA1, BRCA2 and TP53 mutations and those with rare conditions that carry an increased risk of breast cancer such as Peutz-Jegher syndrome (STK11), Cowden (PTEN) and familial diffuse gastric cancer (E-Cadherin).