2-year surveillance 2015 – Familial breast cancer (2013) NICE guideline CG164

Appendix A: decision matrix

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
The clinical significance of a family history of breast cancer		
164 – 01 Accuracy of family history [2004] (1.1.1–1.1.7, 1.1.9– 1.1.11, 1.1.13–1.1.18) • **How should family history taking and initial assessment be carried out for women who may be at risk of familial breast cancer?**		
One RCT was identified which tested a breast cancer risk assessment and education intervention in women (n=1235). The study found that the intervention resulted in increased discussion about family cancer history, high-risk clinics and genetic counselling/testing compared to control[1].	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The new evidence found that a risk assessment and educational intervention improved communication between patients and doctors regarding family history and breast cancer risk. This evidence is consistent with the existing guideline which recommends taking a family history in primary care to assess breast cancer risk, and that tools should be made available to enable an accurate collection of family history information. **Surveillance decision** This review question should not be updated.
164 – 02 Risk assessment tools [2004] (1.1.8, 1.1.12) • **Which risk assessment tools should be used for predicting individual risk of developing breast cancer in women with a family history of breast cancer?**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
		Surveillance decision This review question should not be updated.
164 – 03 What are the optimal methods for assessing the carrier probability of people (whether or not they have a personal history of breast cancer) at different thresholds for genetic testing in women and men at risk of familial breast cancer? (1.1.19–1.1.21)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 04 Communicating cancer risks and carrier probabilities [2004] (1.1.22–1.1.24) • **How should risk be communicated to women who may be at risk of familial breast cancer?**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Information and support		
164 – 05 Patient information and support [2004] (1.2.1-1.2.5)		
A RCT assessing the effectiveness of a telephone-based peer-delivered intervention for women (n=207) with a BRCA1/2 mutation was identified. The study found that telephone intervention reduced distress and unmet information needs compared to usual care[2].	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. The new evidence suggests that peer-delivered information and support for women at risk of breast cancer was beneficial in reducing associated distress. This evidence is unlikely to impact on current recommendations which recommend offering patients

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
		individually tailored information, including information about sources of support. **Surveillance decision** This review question should not be updated.
Care of people in primary care		
164 – 06 Care and management of approach in primary care [2004] (1.3.1-1.3.6) • **What is the best management approach of women with a family history of breast cancer in primary care?**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 07 Patient education and information [2004] (1.3.7-1.3.9)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Care of people in secondary care and specialist genetic clinics		
164 – 08 Care and management [2004] (1.4.1-1.4.8)		
No relevant evidence identified.	A study was highlighted by the topic experts which assessed the frequency of genetic mutations in individuals with triple-negative breast cancer (TNBC) unselected for family history of breast or ovarian cancer (n=1824). The study found that 11.2% of participants had mutations in the BRCA1 and BRCA2 genes. It was	New evidence was identified that may change current recommendations. The new evidence shows that a small proportion of cases of TNBC are related to mutations in the BRCA1/2 genes, and that the average age of diagnosis of TNBC

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
	also reported that individuals with TNBC with BRCA 1/2 mutations were diagnosed at an earlier age, with an average age at diagnosis of 44 and 47 years for patients with BRCA1 and BRCA2 mutations respectively, compared to 52 years for those with no mutations. However, age at diagnosis of TNBC ranged from 25-80 years for those with a BRCA1 mutation, and from 25-79 years for those with a BRCA2 mutation[3].	was under 50 years in women with a BRCA1/2 mutation, compared to 52 years for those with no mutations. The implications of this study may suggest that at the 10% threshold probability for detecting a germline mutation, even without a family history, patients with TNBC under 50 were close to the currently recommended threshold and, as such, may provide reasonable evidence that testing should potentially be extended to those under 50 with TNBC regardless of family history. **Surveillance decision** This review question should be updated.
164 – 09 Genetic counselling for people with no personal history of breast cancer [2004] (1.4.9-1.4.11) • **What is the impact of genetic counselling in women with a family history of breast cancer?**		
One RCT was identified which assessed the effect of a website providing computer-tailored information and a question prompt sheet to individuals prior to receiving breast cancer genetic counselling (n=192). Compared to usual care, those receiving the intervention more often shared their agenda, directed the communication and paraphrased the counsellors' words[4]. The results of a RCT showed that uptake of BRCA1/2 testing was lower following telephone genetic counselling than in-person counselling for women at risk for BRCA1/2 mutations (n=988), although telephone counselling was non-inferior in terms of psychosocial	None identified relevant to this question.	No evidence was identified that may change current recommendations. Among the evidence identified were 2 studies which found that telephone counselling appeared to be non-inferior to in-person counselling, although uptake of genetic testing was lower following counselling in the telephone counselling groups. Overall, the evidence suggests that genetic counselling is associated with improved outcomes including increased knowledge and reduced stress. Currently the guideline recommends that all women

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
outcomes[5]. Another RCT of participants without newly diagnosed or metastatic cancer (n=669) also found that BRCA1/2 test uptake was lower following telephone genetic counselling compared to in-person counselling. However, telephone counselling was non-inferior to in-person counselling in terms of knowledge, perceived stress and satisfaction[6].		referred to a specialist genetic clinic should be offered a referral for genetic counselling and that prior to genetic counselling women should receive standardised information describing the process, the range of topics to be covered and brief educational material. The guideline makes no recommendations about methods of delivering counselling. Further consistent evidence on the benefits of different delivery methods is needed before telephone genetic counselling can be considered for inclusion in the guideline. **Surveillance decision** This review question should not be updated.
Genetic testing		
164 – 10 Genetic testing for people with a family history but no personal history of breast cancer [2004] (1.5.1-1.5.7) • **What is the predictive ability of different genetic testing techniques for women who may be at increased risk of developing breast cancer?** • **What is the psychological impact of genetic testing in women who may be at increased risk of developing breast cancer?** • **What are the information and support needs of women under genetic testing?**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 11 What is the carrier probability at which genetic testing should be offered to people who are (a) unaffected but with a family history of breast/ovarian/related cancer and an affected relative willing to have a test; (b) unaffected with a family history and no living relative and (c) affected people? (1.5.8-1.5.13)		
No relevant evidence identified.	Feedback from topic experts highlighted that there is now more evidence on testing for triple negative breast	New evidence is unlikely to impact on guideline recommendations.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
	cancer cases with no family history. A study was identified which assessed the frequency of genetic mutations in individuals with triple-negative breast cancer (TNBC) unselected for family history of breast or ovarian cancer (n=1824). The study found that the frequency of BRCA1/2 mutations with no family history of breast or ovarian cancer was 8.6% in patients aged 40-49, 7.5% in patients aged 50-59 and 1.4% in those over 60[3]. Topic expert feedback suggested that there is variation in the implementation of the recommendation for genetic testing at the 10% risk threshold.	The new evidence found that the probability of a mutation in the BRCA1 or BRCA2 genes is lower than 10% in those diagnosed with TNBC over 40 years with no family history of cancer. Currently the guideline recommends genetic testing for individuals with a 10% carrier probability. This new evidence is therefore unlikely to impact on this recommendation. Topic expert feedback indicated that there may be an issue regarding the implementation of the guideline recommendation for genetic testing at the 10% risk. NICE collects publications that measure uptake of our guidance. No uptake data on this recommendation in CG164 are currently available to highlight the extent of this problem. We will examine this area further at the next surveillance review of the guideline to determine if there is an impact on the current guideline recommendations. **Surveillance decision** This review question should not be updated.
164 – 12 Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options and/or does it usefully inform immediate decisions about risk-reducing options? (1.5.14-1.5.16) (See RR-02)		
A RCT assessing the impact of rapid genetic counselling and testing on newly diagnosed breast cancer patients' (n=265) choice of surgery was identified. The study found no difference between rapid testing and usual care in uptake of direct bilateral mastectomy (BLM) and delayed contralateral prophylactic mastectomy.	None identified relevant to this question.	New evidence is unlikely to impact on guideline recommendations. There is limited evidence from one study which suggests that rapid genetic counselling and testing influences

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
However, only a minority of patients in the intervention group received DNA test results prior to surgery. Per-protocol analysis indicated that patients who received test results before surgery opted for direct BLM more often than those who received usual care[7].		decisions about risk-reducing surgery. During development of the guideline the committee agreed that there was insufficient evidence to say whether knowledge of mutation status before making decisions about risk-reducing mastectomy influenced outcome. There was also no evidence that a delay in genetic testing at diagnosis of breast cancer affected overall survival. As such, no recommendations were made for fast track genetic testing outside the context of a clinical trial. A recommendation for further research in this area was made in order to determine the benefits and harms of creating rapid access to genetic testing, in particular the optimum model for service delivery, clinical and cost effectiveness, uptake and patient experience. Whilst the new evidence suggests genetic testing may usefully inform treatment decisions, further consistent evidence is needed to demonstrate that fast track testing is beneficial before it can be considered for inclusion within CG164. **Surveillance decision** This review question should not be updated.
164 – 13 Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur? (1.5.17)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
Surveillance and strategies for early detection of breast cancer		
164 – 14 Breast awareness [2004] (1.6.1) • **What is the accuracy of either clinical or self-breast examination as the sole screening modality in women with a family history of breast cancer and/or BRCA1/2 mutations?**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 15 What are the specific surveillance needs of women with a family history who have no personal history of breast cancer? (1.6.2–1.6.9, 1.6.17-1.6.26)		
CG164 noted inconsistencies in the recommendations for the surveillance of women identified as being at high risk of developing breast cancer between CG164 and the NHS Cancer Screening Programme 'Guidelines on organising the surveillance of women at higher risk of developing breast cancer in an NHS Breast Screening programme' (March 2013). Following publication of CG164, the NHSBSP's protocols for screening women with TP53 mutations were modified to bring them into line with CG164 (The NHS Breast Screening Programme (NHSBSP) Protocols for the surveillance of women at higher risk of developing breast cancer version 4 (June 2013)).	It was highlighted by the topic expert that some patient organisations have reported an ongoing issue with screening of people at moderate risk of breast cancer, with ongoing confusion about what should be happening in this area. In particular, there were concerns about the differences between the recommendations in CG164 and those of NHSBSP. There was also concern about the strength of the evidence relating to moderate risk women. It was suggested that this could mean that the recommendations for this group will not be implemented resulting in inequitable service provision.	New evidence is unlikely to impact on guideline recommendations. The NHSBSP recommendations for the surveillance of women at high risk of developing breast cancer have been updated to bring them into line with the recommendations for high risk women presented in the guideline. Clinical feedback indicated that there they may be issues regarding the implementation of the recommendations for surveillance of moderate risk women. However, no further evidence was provided which would impact on the current recommendations for women at moderate risk of breast cancer which state: offer annual mammographic surveillance to women aged 40-49 years; consider annual mammographic surveillance for women aged 50-59 years; and offer

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
		mammographic surveillance as part of the population screening programme to women aged 60 years and over. **Surveillance decision** This review question should not be updated.
164 – 16 What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk-reducing bi-lateral-mastectomy? (1.6.10-1.6.16, 1.6.17-1.6.26)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Risk reduction and treatment strategies		
164 – 17 Risk factors [2004] (1.7.1-1.7.19) **Do the following factors increase/decrease the risk of breast cancer in women with a family history of breast or ovarian cancer?** • **Risks associated with family history** • **Menstrual and reproductive factors** • **Reproductive and fertility issues** • **Sub-fertility and induced ovulation** • **Hormonal contraceptives** • **Breast feeding** • **Hormone replacement therapy (HRT)** • **Alcohol consumption** • **Smoking** • **Weight and physical activity**		

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 18 What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer? (1.7.20-1.7.29) (See RR – 06)		
No relevant evidence identified.	Two studies on chemoprevention were highlighted by topic experts. These studies were not identified through the literature search for the 2-year surveillance review because both studies include postmenopausal women and so would not have been picked up through the terms used in the search. One RCT reporting the long-term follow-up of the IBIS-I trial of pre- and post-menopausal women at increased risk of breast cancer based on a family history of breast cancer or abnormal benign breast disease (n=7154) was identified. The study reported that after a median follow up of 16 years, tamoxifen was more effective in preventing breast cancer compared to placebo, with a significant reduction in ductal carcinoma in situ (DCIS) breast cancer in the first 10 years of follow-up, but no significant effect on invasive oestrogen receptor-negative breast cancer. The study also reported that there was no significant difference in mortality between tamoxifen and placebo[8]. Topic expert feedback indicated that the reduction in breast cancer risk reported in the study was not associated with a reduction in breast cancer mortality, with no difference	New evidence was identified that may change current recommendations. The topic experts highlighted new evidence which suggests that tamoxifen is effective in the long term at reducing the risk of breast cancer in high risk women. However, the results also show that the reduction in breast cancer risk is not linked to a reduction in breast cancer mortality. During the development of the guideline, the guideline committee considered outcomes including development of cancer, adverse events, health related quality of life and overall survival to be the most important to this clinical question. However, all outcomes except overall survival were reported in the evidence. Whilst the new evidence suggests that tamoxifen is effective in the long term at preventing breast cancer, the impact of tamoxifen on long term survival may potentially impact on the current guideline recommendation to offer women tamoxifen or raloxifene for 5 years.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
	between placebo and tamoxifen, which is likely to impact on the current recommendation to offer tamoxifen to high risk women. The topic experts also highlighted the following study on the use of anastrazole, an aromatase inhibitor, and suggested that the evidence for using aromatase inhibitors is similar to that for using the tamoxifen: A RCT was identified which assessed the efficacy of anastrozole for the prevention of breast cancer in post-menopausal women at high risk of the disease (n=3864). The study found that after a median follow-up of 5 years, anastrozole was significantly more effective in preventing breast cancer compared to placebo. The study also reported that no specific cause of death was more common in either the anastrozole or placebo group[9]. Topic expert feedback indicated that there have been some reports to patient organisations that as the drugs currently recommended for chemoprevention are not licensed for this indication, this may represent a barrier for those clinicians that would prescribe them.	A further study was identified which found that the aromatase inhibitor, anastrozole, reduced the risk of breast cancer compared to placebo. Anastrozole is licensed in the UK, however, as with tamoxifen and raloxifene, it is not licensed for chemoprevention. Aromatase inhibitors were included as an intervention in the guideline, however, the guideline committee were unable to recommend the use of a particular drug because the evidence did not differentiate between the different aromatase inhibitors. The new evidence for anastrozole may therefore impact on the current recommendations for chemoprevention. **Surveillance decision** The topic experts agreed that the recommendations on tamoxifen for chemoprevention need to be reviewed in an update to enable consideration of the new trial evidence in this area. The topic experts also agreed that an update should also include consideration of raloxifene as some recommendations include both tamoxifen and raloxifene as options for chemoprevention. The topic experts felt that the use of aromatase inhibitors may also need to be considered for chemoprevention although opinion was divided. The IBIS-2[9] results published in 2014 were early results, in that median follow up was 5 years in a trial where treatment is for 5 years. The number of events (new cancers) was fairly low and the panel was concerned about whether it would be possible to be certain of the benefits. In addition to the IBIS-2 trial, a recent report:

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
		'Achieving world class cancer outcomes: a strategy for England 2015–2020' from the Independent Cancer Taskforce was identified. This report included a recommendation indicating that updated NICE guidelines should consider the use of aromatase inhibitors for untreated post-menopausal women at high risk. In light of the output of the Independent Cancer Taskforce report and the availability of data from the IBIS-2 trial, it was felt than an update of chemoprevention in the guideline should include consideration of aromatase inhibitors in addition to tamoxifen and raloxifene. This review question should be updated.
164 – 19 Risk reducing mastectomy for women with no personal history of breast cancer [2004] (1.7.30-1.7.40) • **What is the effectiveness of mastectomy (bilateral) as risk reducing measure in women at increased risk of breast cancer due to their family history?**		
No relevant evidence identified.	The following study was highlighted by topic experts: A study was identified which found that there was a reduced risk of death from breast cancer following contralateral mastectomy compared with unilateral mastectomy in women with a BRCA1 or 2 mutation and a family history of breast cancer (n=390)[10].	New evidence is unlikely to impact on guideline recommendations. The new evidence is unlikely to impact on the guideline which currently recommends bilateral mastectomy as a risk-reducing strategy option for all women at high risk of breast cancer. **Surveillance decision** This review question should not be updated.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
164 – 20 Risk-reducing oophorectomy for women with no personal history of breast cancer [2004] (1.7.41-1.7.52) • **What is the effectiveness of oophorectomy as risk reducing measure in women at increased risk of breast cancer due to their family history?**		
No relevant evidence identified.	The following study was highlighted by topic experts: A prospective study was identified which found that prophylactic oophorectomy reduced the risk of ovarian, fallopian tube or peritoneal cancer in women with a BRCA1 or BRCA2 mutation (n=5783)[11].	New evidence is unlikely to impact on guideline recommendations. The new evidence is consistent with the current guideline recommendations for bilateral oophorectomy as a potential risk-reducing strategy for women who are classified as high risk. **Surveillance decision** This review question should not be updated.
164 – 21 What are the risks and benefits of HRT for women under the age of 50, with a BRCA1 or BRCA2 mutation who have undergone a bilateral salpingo-oophorectomy? (1.7.53-1.7.54)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 22 What level of risk indicates that risk reducing surgery is a viable option? (1.7.55-1.7.62)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
164 – 23 What are the factors that indicate that offering risk reducing surgery is not appropriate? (1.7.63-1.7.64)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
		recommendations. **Surveillance decision** This review question should not be updated.
164 – 24 What is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ (DCIS) with a TP53 mutation or at high risk of TP53 mutation? (1.7.65-1.7.66)		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
Research recommendations		
RR – 01 Further research is recommended into developing and validating models for calculating carrier probability, which incorporate additional data, such as the molecular pathology of tumours and the prevalence of mutations in different ethnic groups.		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 02 Research is recommended to determine the benefits and harms of creating rapid access to genetic testing for people with newly diagnosed breast cancer. This research should address the optimum model for service delivery and organisation, the clinical and cost effectiveness of such a change, uptake outcomes and patients' experience.		
See 164–12	None identified relevant to this question.	See 164–12 **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
RR – 03 Research is recommended as part of a trial of fast track genetic testing to determine: • **which members of the multidisciplinary team should/could discuss fast track testing with people with newly diagnosed breast cancer** • **the best way of providing information about fast track genetic testing to people with newly diagnosed breast cancer** • **the psychosocial impact of receiving information about genetic testing within 4 weeks of a diagnosis of breast cancer** • **the short, medium and long-term psychosocial impact of undergoing fast track genetic testing.**		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 04 Research is recommended to establish the risk and benefits of MRI surveillance compared with mammography in women over 50 years with a personal history of breast cancer. Studies should include sub-analysis for breast density.		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 05 Research is recommended to assess the benefit of MRI surveillance in terms of mortality of all ages for people with a personal history of breast cancer.		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

Summary of new evidence from 2-year surveillance	Summary of new intelligence from 2-year surveillance	Impact
RR – 06 A randomised controlled trial is recommended to compare the clinical and cost effectiveness of aromatase inhibitors and tamoxifen for reducing the incidence of breast cancer in women with a family history of breast or ovarian cancer.		
See 164 - 18	None identified relevant to this question.	See 164 - 18 **Surveillance decision** The decision was an update of the effectiveness of chemoprevention for the reduction of the incidence of breast cancer therefore; this research recommendation will be considered as part of that process.
RR – 07 Further research is recommended to compare psychosocial and clinical outcomes in women who chose and women who do not choose to have risk-reducing surgery.		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 08 Prospective and retrospective international collaborative studies are recommended to assess the risks and benefits of radiotherapy and chemotherapy for people with a TP53 mutation.		
No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

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