NICE National Institute for Health and Care Excellence

2023 surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101) and advanced breast cancer: diagnosis and treatment (NICE guideline CG81)

Surveillance report

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Surveillance decision

We will update the NICE guidelines on early and locally advanced breast cancer: diagnosis and management and advanced breast cancer: diagnosis and treatment.

Early and locally advanced breast cancer

We plan to update the following areas:

- Genetic testing for people with early and locally advanced breast cancer
- Further surgery after breast-conserving surgery based on tissue margins (early and locally advanced breast cancer)
- Neoadjuvant chemotherapy for people with HER2-positive invasive breast cancer and triple-negative invasive breast cancer (early and locally advanced breast cancer)
- Platinum-based neoadjuvant chemotherapy regimens for people with triple-negative invasive early and locally advanced breast cancer

Advanced breast cancer

We plan to update the following areas:

- Chemotherapy for advanced breast cancer
- Biological therapy for advanced breast cancer

All stages of breast cancer

We plan to update the following areas:

- Ovarian function suppression for premenopausal and perimenopausal women with oestrogen receptor-positive early, locally advanced and advanced breast cancer
- Psychological support for all people with breast cancer

- Lymphoedema in all people with breast cancer
- Menopausal symptoms in all people with breast cancer

Changes without an evidence review

We will also amend the guidelines in the areas of:

- Providing information and support (amalgamate and align recommendation content for early, locally advanced and advanced breast cancer).
- Decision aids (amend current recommendation wording across the breast cancer guidelines to highlight importance of shared decision making and use of decision aids for all people with breast cancer, with links added to the section on patient decision aids in NICE's guideline on shared decision making).
- Endocrine therapy for advanced breast cancer (content alignment with NICE technology appraisal guidance on CDK4/6 inhibitors and ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer).
- Managing metastatic breast cancer in the brain (content alignment with recommendations on management of confirmed brain metastases in NICE's guideline on brain tumours (primary) and brain metastases in over 16s).

Content alignment means amending recommendations to be consistent with more up to date NICE guidance, without the need for an evidence review. This differs from decisions to add cross-references within the NICE guidelines on breast cancer to related recommendations published in other NICE guidance such as technology appraisals. These cross-references are considered as additional/complementary recommendations to existing recommendations within the NICE guidelines on breast cancer.

Areas that will not be updated

Topic areas that we do not plan to update, but for which we are monitoring the evidence base, are described under ongoing research.

Reasons for the decision

This section provides a summary of the areas that will be updated and the reasons for the decision to update. See appendix A for further details and a summary of all evidence identified in surveillance.

Genetic testing for people with early and locally advanced breast cancer

Recommendation 1.1.4 in NICE's guideline on early and locally advanced breast cancer, recommends offering genetic testing for BRCA1 and BRCA2 mutations to women under 50 years with triple-negative breast cancer, including those with no family history of breast or ovarian cancer. This was based on recommendations on genetic testing in NICE's guideline on familial breast cancer. As there was no evidence review question on genetic testing for NICE's guideline on early and locally advanced breast cancer, evidence on this was not searched for as part of this surveillance review; however, we received feedback from a patient group and topic expert that the recommendation differs from newer guidance from NHS England in 2022 on genetic testing (see NHS England's National genomic test directory). We also identified a 2022 NIHR evidence alert on genetic risk scores for breast cancer not being accurate in some ethnic groups, which found that while genetic tests accurately predict the risk of breast cancer in White Europeans, these risk scores are inaccurate and exaggerate risk in Black, Asian, mixed-race and Ashkenazi Jewish women, so need adapting for use in women from these groups. As recommendation 1.1.4 on genetic testing is out-of-date with the latest guidance from NHS England, an update is required to consider whether the recommendation should be changed. Consideration should also be given to the finding that established genetic risk scores may be overestimating the breast cancer risk of women from Black, Asian, mixed-race and Ashkenazi Jewish backgrounds.

Further surgery after breast-conserving surgery based on tissue margins, invasive cancer (early and locally advanced breast cancer)

Evidence from 1 systematic review indicates that there is a benefit in terms of reducing local and distant recurrence from having further surgery where invasive cancer is present within 2 mm of the radial margins (greater than 0 mm and less than 2 mm). This may change the wording of recommendation 1.3.2 in NICE's guideline on early and locally

advanced breast cancer, which says to discuss the benefits and risks of further surgery (re-excision or mastectomy) to minimise the risk of local recurrence, but does not provide specific information on the benefits of further surgery. The current wording of recommendation 1.3.2 was based on no evidence of a clear and consistent benefit of having tumour-free tissue margins between >0 mm and 2 mm for invasive disease. Because there was not enough evidence to clearly define an optimum margin width between 0 mm and 2 mm to minimise local recurrence rates and minimise further surgery, the committee agreed that this was an important topic for further research, and made a recommendation for research on the optimum tumour-free margin width after surgery to the breast. There appears to now be evidence that could address this recommendation for research.

Two related ongoing trials are being tracked by NICE:

- Wide margin versus narrow margin in post-neoadjuvant lumpectomy
- Identifying factors that predict the need for increased tissue removal during breast-conserving surgery for breast cancer, in order to reduce the need for a second surgery

Neoadjuvant chemotherapy for people with HER2-positive invasive breast cancer and triple-negative invasive breast cancer (early and locally advanced breast cancer)

New evidence from 2 systematic reviews that undertook network meta-analyses comparing neoadjuvant treatment regimens for HER2-positive early and locally advanced breast cancer found that as well as NICE's technology appraisal guidance on pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer, (see recommendation 1.11.2 in NICE's guideline on early and locally advanced breast cancer), neoadjuvant regimes containing trastuzumab emtansine or carboplatin (a platinum-based chemotherapy drug) are also effective in achieving a pathological complete response in patients with HER2-positive breast cancer. As there are no existing NICE technology appraisals for trastuzumab emtansine or carboplatin-containing regimens as a neoadjuvant treatment in HER2-positive early and locally advanced breast cancer, we are proposing that evidence on this should be considered in an update.

New evidence from 4 systematic reviews that assessed the efficacy and safety of immune checkpoint inhibitors plus neoadjuvant chemotherapy compared with neoadjuvant chemotherapy in people with early-stage triple-negative breast cancer, found that

compared with neoadjuvant chemotherapy alone, a combination of immune checkpoint inhibitors plus neoadjuvant chemotherapy resulted in a significant improvement in pathological complete response. However, the randomised control trial (RCT) evidence within the systematic reviews does not meet the inclusion criteria for the evidence review question on the effectiveness of neoadjuvant chemotherapy on which recommendations in NICE's guideline on early and locally advanced breast cancer were made (see evidence review J: neoadjuvant treatment). To be included an RCT had to assess neoadjuvant chemotherapy ± biological therapy compared with no neoadjuvant chemotherapy ± biological therapy, whereas all the evidence in the above systematic reviews had neoadjuvant chemotherapy as the comparator. However as neoadjuvant chemotherapy is now accepted as standard treatment, we think that neoadjuvant chemotherapy should be included as a comparator when assessing evidence on the effectiveness of the addition of immune checkpoint inhibitors to neoadjuvant chemotherapy on outcomes in people with early-stage triple-negative breast cancer.

One ongoing study is being tracked by NICE:

- Response to optimal selection of neo-adjuvant chemotherapy in operable breast cancer

Platinum-based neoadjuvant chemotherapy regimens for people with triple-negative invasive early and locally advanced breast cancer

New evidence from 2 systematic reviews is consistent with the content of recommendation 1.11.4 in NICE's guideline on early and locally advanced breast cancer to consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline for people with triple-negative invasive breast cancer as it provides further evidence that, compared with anthracycline ± taxanes-based neoadjuvant chemotherapy, platinum-containing neoadjuvant chemotherapy regimens improve pathological complete response rate in people with triple-negative breast cancer. As this represents further supportive evidence, the committee may want to assess whether the strength of the recommendation wording should change from a consider to offer recommendation (see section 9.2 wording the recommendations in developing NICE guidelines: the manual for further information on wording reflecting the strength of evidence).

The evidence from 2 systematic reviews also indicates that the addition of platinum to anthracycline ± taxanes-based neoadjuvant chemotherapy is associated with a significant

increase in disease-free survival, and possibly overall survival, at least for carboplatin-based neoadjuvant chemotherapy, in people with invasive triple-negative cancer. Recommendation 1.11.5 in NICE's guideline on early and locally advanced breast cancer says to discuss the benefits and risks (listed in table 6) of adding a platinum to an anthracycline-containing neoadjuvant chemotherapy regimen. Table 6 says that there is no increase in overall survival with platinum-based chemotherapy, however new evidence indicates that there may be a survival benefit. It is therefore proposed that evidence on survival outcomes is considered in an update.

There are currently no recommendations in NICE's guideline on early and locally advanced breast cancer on neoadjuvant chemotherapy regimens for people with the BRCA germ line mutation subgroup as no evidence was available. We identified a systematic review which indicates that there is available RCT data for this subgroup. An update should therefore also include a check for new evidence on the relationship between BRCA status in people with triple-negative breast cancer and pathological complete response rates with platinum-based neoadjuvant chemotherapy compared with neoadjuvant chemotherapy alone.

Evidence on homologous recombination deficiency (HRD) has not been reported in this surveillance review as this was not considered within evidence review J. For information, homologous recombination 'is a multistep DNA repair process involving several mediators, most notably BRCA1 and BRCA2. Alteration in HR genes is prevalent among many cancer types (13% to 17%), especially breast, ovarian, and pancreatic cancers. BRCA1 and BRCA2 are the most altered HR genes, with germline pathogenic variants (PVs) found in 2% to 3% of unselected tumours in several pan-cancer analyses' (Toh and Ngeow 2021). We are aware, from our literature search, of a small body of evidence which indicates that HRD status may play a role in mediating the effectiveness of platinum-based neoadjuvant chemotherapy in people with triple-negative cancer (Chai et al. 2022 and Zhang et al. 2022). As part of the evidence review development process for the update on platinum-based neoadjuvant chemotherapy regimens for people with triple-negative invasive early and locally advanced breast cancer, whether a review of the evidence on whether HRD impact the efficacy of platinum-based neoadjuvant chemotherapy is currently appropriate should be considered (see breast cancer committee feedback).

A Cochrane review on platinum-based chemotherapy for early-stage triple-negative breast cancer is expected in 2022/2023; and 6 ongoing studies are being tracked by NICE:

- Carboplatin in early triple negative breast cancer trial

- Adjuvant treatment of EC followed by taxane +/- carboplatin in triple-negative breast cancer
- Platinum and polyadenosine 5 diphosphoribose polymerisation inhibitor for neoadjuvant treatment of triple negative breast cancer and/or germline BRCA positive breast cancer
- Doxorubicin hydrochloride and cyclophosphamide followed by paclitaxel with or without carboplatin in treating patients with triple-negative breast cancer
- Platinum in treating patients with residual triple-negative breast cancer following neoadjuvant chemotherapy
- Addition of cisplatin to adjuvant chemotherapy for early stage breast cancer in high-risk Women

Chemotherapy for advanced breast cancer

Recommendations on chemotherapy for people with advanced breast cancer have not been updated since 2009. Topic experts highlighted that chemotherapy for advanced breast cancer recommendations require an update and cumulative evidence from surveillance indicates that this should now be undertaken. There are also several relevant NICE technology appraisals that should be cross-referenced.

The 2018 surveillance review found various studies on platinum-based chemotherapy for people with advanced breast cancer, but reported that results on efficacy were inconclusive and did not have an impact on the generic recommendations 1.3.8 and 1.3.9 in NICE's guideline on advanced breast cancer, which state on disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy, and consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. We identified new evidence from a Cochrane review and 2 systematic reviews which indicate that a platinum containing chemotherapy regime for women with triple-negative metastatic breast cancer leads to significant improvements in progression free survival, but not for overall survival.

Evidence was also identified from 1 Cochrane review and 2 systematic reviews which indicate that capecitabine combination chemotherapy could improve the survival rate of

patients with advanced breast cancer, whereas recommendation 1.3.10 in NICE's guideline on advanced breast cancer only recommends capecitabine monotherapy as either a second- or third-line chemotherapy treatment. We propose that an update is conducted in this area to assess whether capecitabine combination therapy is preferential to the currently recommended monotherapies.

New evidence, from a Cochrane review and systematic review was identified which indicates that taxanes could be considered as a first line treatment.

Nineteen ongoing trials are being tracked by NICE looking at chemotherapy in combination with biological and/or endocrine therapy.

Biological therapy for advanced breast cancer

Topic experts and a patient group said that an update needs to be made in the area of recommendation 1.3.12 in NICE's guideline on advanced breast cancer as it is the only recommendation on the use of trastuzumab for advanced breast cancer. However, there are a number of biological therapeutic agents, beyond trastuzumab, which are now available on the NHS, for which there are relevant NICE technology appraisals, including on immune checkpoint inhibitor drugs; bevacizumab; trastuzumab emtansine; pertuzumab with trastuzumab and docetaxel; tucatinib with trastuzumab and capecitabine.

It is planned that the future guideline will be organised to ensure that the relevant NICE technology appraisals are within the recommendation section on biological therapy for advanced breast cancer.

New evidence from 4 systematic reviews was also identified that found survival benefits from anti-HER2 antibody treatment regimens and second-line therapies, following trastuzumab based treatments for women with HER2 positive metastatic breast cancer, which may be considered in an update if they add additional treatment options/regimes beyond those recommended within current and planned NICE technology appraisals.

There is a large volume of ongoing research looking at biological therapy in combination with chemotherapy and/or endocrine therapy, however much of this is for treatments covered by existing NICE technology appraisals.

Ovarian function suppression for premenopausal and

perimenopausal women with oestrogen receptor-positive early, locally advanced and advanced breast cancer

The findings from a Cochrane review and 2 systematic reviews are consistent with recommendation 1.7.4 in NICE's guideline on early and locally advanced breast cancer to consider ovarian function suppression in addition to endocrine therapy for premenopausal women with oestrogen receptor-positive early and locally advanced invasive breast cancer.

Evidence from 3 systematic reviews indicated that ovarian function suppression with an aromatase inhibitor is a suitable, or potentially better, alternative to ovarian function suppression with tamoxifen in premenopausal women with oestrogen receptor-positive early and locally advanced invasive breast cancer, due to better outcomes for local and distant disease recurrence in those on ovarian function suppression with an aromatase inhibitor compared with ovarian function suppression with tamoxifen. Tamoxifen is recommended as the first-line choice for endocrine therapy for this population (see recommendation 1.7.2 in NICE's guideline on early and locally advanced breast cancer), whereas an aromatase inhibitor is only recommended for postmenopausal women with oestrogen receptor-positive invasive breast cancer (see recommendation 1.7.3 in NICE's guideline on early and locally advanced breast cancer).

While recommendation 1.7.4 does not name tamoxifen as the endocrine therapy of choice, the rationale and impact section on ovarian function suppression only discusses tamoxifen, as only evidence on tamoxifen was assessed. An update should therefore consider evidence on the comparative effectiveness of ovarian function suppression with tamoxifen and ovarian function suppression with an aromatase inhibitor (also see breast cancer committee feedback).

No evidence was identified that was relevant to recommendations 1.3.5 and 1.3.6 in NICE's guideline on advanced breast cancer on offering tamoxifen and ovarian function suppression to premenopausal and perimenopausal women with oestrogen receptor-positive advanced breast cancer. However system intelligence indicates that these recommendations are out-of-date. It is therefore proposed that the update also considers whether there is any relevant RCT evidence for this population that can inform recommendations.

Three ongoing studies are being tracked by NICE:

- Neoadjuvant aromatase inhibitor with ovarian suppression versus chemotherapy in premenopausal breast cancer patients
- Adjuvant ovarian suppression plus aromatase inhibitor or tamoxifen in young women
- A study to evaluate exemestane tablets combined with ovarian function suppression/ablation in treatment of premenopausal breast cancer patients with CYP2D6*10 mutations

Psychological support for all people with breast cancer

Looking at recommendation 1.2.3 in NICE's guideline on early and locally advanced breast cancer, recommends offering all people with breast cancer prompt access to specialist psychological support and, where appropriate, psychiatric services. While this recommendation remains valid, a large body of evidence from Cochrane reviews and systematic reviews was identified which supports the development of recommendations on effective strategies to prevent and manage psychological distress in patients with early-stage breast cancer. The evidence is also potentially relevant to patients with locally advanced or advanced breast cancer as the abstracts of most systematic reviews have not specified the breast cancer stage within study samples.

The evidence supports the use of specific interventions to prevent and manage psychological distress in patients with breast cancer. This included evidence from 2 Cochrane reviews and 9 systematic reviews on the beneficial effects of psychological interventions based on cognitive behavioural therapy, mindfulness and/or acceptance strategies and/or supportive-expressive group psychotherapy. There was also evidence from 1 Cochrane review and 11 systematic reviews that physical activity and/or mind-body interventions may lead to reductions in anxiety and depression and improve other outcomes related to positive mental health. There was a small body of evidence identified in 1 systematic review on appearance care interventions, which indicated that these may lead to improvements in anxiety and depression in breast cancer patients; and there was mixed evidence from 2 systematic reviews concerning the effectiveness of acupuncture on depression in patients with breast cancer. There was also evidence from 2 Cochrane reviews and 6 systematic reviews on mode of delivery of interventions that aim to support the psychological needs of patients with breast cancer and breast cancer survivors, which could be considered as part of an update.

The review question on which recommendation 1.2.3 was developed in 2009 was what are the effective strategies to prevent and manage psychological distress in patients with

early-stage breast cancer? The inclusion criteria for this review question were broad: any strategy to treat psychological distress was included; and included outcomes were alleviation of psychological distress. It is proposed that clarification of outcomes of interest are needed, including consideration of outcomes indirectly related to psychological distress such as fatigue, which was reported in a large number of identified studies that also reported on anxiety, depression and quality of life outcomes. While there is no existing review question on strategies to prevent and manage psychological distress in patients with advanced cancer, nor any recommendations within NICE's guideline on advanced breast cancer for psychological support, it is proposed that consideration of psychological support needs for all people with breast cancer should be made in an update given the importance of mental wellbeing for all, and the existing evidence base. However, it is recognised that breast cancer stage and prognosis will have an impact on psychological needs, concerns, timing and potentially mode of delivery, so differences according to whether a person has early, locally advanced or advanced breast cancer will need to be considered during recommendation development.

A Cochrane review update on psychological interventions for women with non-metastatic breast cancer is expected in 2022/2023 and 2 related ongoing trials are being tracked by NICE (for example the impact of findings from these will be considered as soon as possible following publication):

- 12-week exercise intervention program versus observation in early stage breast cancer patients on the impact on mental health, quality of life and immune markers
- A pilot study of a mindfulness intervention among women in recovery from breast cancer

Lymphoedema in all people with breast cancer

Two systematic reviews indicated that a combination of surveillance for breast cancer-related lymphoedema plus early intervention in breast cancer survivors reduces the risk of chronic breast cancer-related lymphoedema. There was also evidence from 2 systematic reviews that vascularised lymph node transfer is an effective intervention for managing breast cancer-related lymphoedema. NICE's guideline on early and locally advanced breast cancer currently only includes recommendations for the prevention of breast cancer-related lymphoedema; and while NICE's guideline on advanced breast cancer has recommendations on managing lymphoedema, it does not make any recommendations concerning surveillance and early intervention or vascularised lymph node transfer.

Given that lymphoedema is known to result in limited physical function and/or adverse psychological and social effects, means by which lymphoedema can be identified and managed as early as possible, would benefit all people with breast cancer who have undergone axillary intervention. It is therefore proposed that the evidence review question for NICE's guideline on early and locally advanced breast cancer is expanded to include management of lymphoedema; and that the prevention and management of lymphoedema is an area for update in both of NICE's guidelines on breast cancer.

Evidence was also identified that indicates the effectiveness of management of lymphoedema by laser therapy (1 systematic review), extracorporeal shockwave therapy (1 systematic review) or manual lymphatic drainage (4 systematic reviews) remains uncertain. There was also evidence from 2 systematic reviews that exercise may decrease breast cancer-related lymphoedema, but this was not sufficient to indicate that exercise should be considered as a strategy for preventing or managing breast cancer-related lymphoedema. The evidence base for these interventions will be monitored.

A Cochrane review on physical therapies for reducing and controlling lymphoedema of the limbs is expected in 2022/2023; and 3 ongoing studies are being tracked by NICE:

- Impact of a surgical sealing patch on lymphatic drainage after ALND for breast cancer
- Does immediate lymphatic reconstruction decrease the risk of lymphedema after axillary lymph node dissection
- Lymph node transfer for breast cancer related lymphoedema

Menopausal symptoms in all people with breast cancer

Topic experts provided feedback that the management of menopausal symptoms in breast cancer patients is considered a high priority area. New evidence from 4 systematic reviews indicated that acupuncture may improve menopausal symptoms in women with breast cancer. Although the evidence on effectiveness was mixed there is sufficient evidence to indicate that the use of acupuncture to reduce menopausal symptoms in people with breast cancer should be considered as an area for update. It should be noted that there is an ongoing update considering evidence on the effectiveness of cognitive behavioural therapy in the management of menopausal symptoms in people with breast cancer as part of an update of NICE's guideline on menopause: diagnosis and management. It will therefore be important to ensure that the future breast cancer guidelines link to any new recommendations in NICE's guideline on menopause and that

there is consistency between the content in all. There are currently no recommendations within NICE's guideline on advanced breast cancer on managing or preventing menopausal symptoms in women with advanced breast cancer, the needs of this population should also be considered within an update.

Evidence was also identified from a Cochrane review and systematic review which was consistent with recommendations 1.12.9 and 1.12.10 in NICE's guideline on early and locally advanced breast cancer to stop systemic hormone replacement therapy (HRT) in women who are diagnosed with breast cancer, and to not routinely offer HRT to women with menopausal symptoms and a history of breast cancer, and to only offer HRT in exceptional circumstances to women with severe menopausal symptoms and with whom the associated risks have been discussed.

A Cochrane review on non-hormonal pharmacological interventions for hot flushes in women with a history of breast cancer and a Cochrane review on Chinese medicinal herbs to treat the side effects of chemotherapy in women with breast cancer are expected in 2022/2023. No ongoing studies have been identified for monitoring.

Overview of 2023 surveillance methods

NICE's surveillance team checked whether recommendations in the following guidelines remain up-to-date:

- early and locally advanced breast cancer (NICE guideline NG101)
- advanced breast cancer (NICE guideline CG81).

The surveillance process consisted of:

- Feedback from topic experts and patient groups via a questionnaire and from an external reference group for breast cancer.
- Assessment of health inequalities.
- Consideration of evidence from previous surveillance.
- Examining related NICE guidance.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for new or updated Cochrane reviews, national policy and NIHR signals.
- A search for ongoing research.
- System intelligence.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline.
- Feedback from the breast cancer living guideline committee on proposed surveillance decisions.

For further details about the process and the possible update proposals that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

The surveillance review decisions are the first step in ensuring breast cancer

recommendations are up-to-date, integrating the latest evidence, practice and technologies. Further work is being undertaken, in line with the NICE strategy 2021 to 2026, to provide dynamic, living guideline recommendations. This includes identifying and focusing on topic areas within breast cancer that represent key priority areas that are continuously monitored, with timely course of actions or decisions taken.

Evidence considered in surveillance

Search strategy

We searched for new evidence related to the whole of both guidelines; however the following areas were not considered within this surveillance review as they were the subject of recent exceptional surveillance reviews for NICE's guideline on early and locally advanced breast cancer:

- Adjuvant bisphosphonates, (see the August 2022 exceptional surveillance)
- Radiotherapy, dose fractionation (see the July 2022 exceptional surveillance)
- Arm mobility (see the May 2022 exceptional surveillance)

We found 5,706 studies in a search for systematic review evidence published between 1 January 2020 and 25 August 2022 and Cochrane reviews published between 1 January 2015 and 26 June 2022.

Eighty-one systematic reviews were included for NICE's guideline on early and locally advanced breast cancer and 29 systematic reviews for NICE's guideline on advanced breast cancer.

We also included:

- Twelve Cochrane reviews for NICE's guideline on early and locally advanced breast cancer.
- Three Cochrane reviews for NICE's guideline on advanced breast cancer.

- Four relevant RCTs, 2 NIHR alerts, 4 reports, 1 policy document (NHS long term plan) and 2 external guidelines identified from initial intelligence; 1 RCT and 1 systematic review that post-dated the systematic review search dates identified from system intelligence.

From all sources, we considered 131 studies to be relevant to the guidelines.

See appendix A for details of all evidence considered.

Selecting relevant studies

Studies were considered for inclusion using criteria defined by the guideline review protocols contained in the evidence reviews for NICE's guideline on early and locally advanced breast cancer (see evidence reviews – July 2018) and the evidence review – February 2009 for 2009 recommendations not updated in 2018. For NICE's guideline on advanced breast cancer, see full guideline, evidence review.

In certain circumstances evidence was included if it answered a review question but differed slightly from inclusion criteria (for example, a different comparator was used than originally included). Where this was done, a full explanation has been given for why it was included (see appendix A).

Some 2009 recommendations within NICE's guideline on advanced breast cancer were not clearly linked to a review question, so evidence was considered relevant if it addressed a recommendation, even when there was no linked review question (see appendix A for explanations).

Ongoing research

We checked for relevant ongoing research registered on ClinicalTrials.gov and on ISRCTN registry. A large number of studies (approximately 90) were assessed as having the potential to change recommendations. There will be a regular check for the published results of these studies. The impact of the results on current recommendations will be evaluated as quickly as possible. In addition to ongoing research in the areas being updated (see reasons for the decision), ongoing studies covering the following areas are being monitored:

- imaging assessment for advanced breast cancer

- preoperative staging of the breast and axilla in early and locally advanced breast cancer
- radiotherapy for early and locally advanced breast cancer (deep inspiratory breath-hold radiotherapy techniques, whole compared with partial breast radiotherapy, after neoadjuvant chemotherapy, and dose fractionation)
- adjuvant chemotherapy for early and locally advanced breast cancer
- endocrine therapy for advanced breast cancer
- endocrine therapy for ductal carcinoma in situ
- extended endocrine therapy for early and locally advanced breast cancer
- neoadjuvant endocrine therapy for early and locally advanced breast cancer
- biological therapy for early, locally advanced and advanced breast cancer
- adjuvant bisphosphonate therapy for early and locally advanced breast cancer
- managing complications:
  - arm mobility
  - bone metastases
  - brain metastases
- follow-up imaging for early and locally advanced breast cancer.

Intelligence gathered during surveillance

A summary of intelligence received that led to update decisions is provided above; and detailed information on all intelligence received, and decisions made are provided in appendix A.

Topic experts

We considered the views of topic experts who had been members of the committees that developed either or both of NICE's guidelines on breast cancer and topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their

specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy, practice, and services related to the guidelines.

We received 6 questionnaire responses from topic experts: 2 consultant clinical oncologists, a consultant histopathologist, a specialist breast cancer pharmacist, an advanced nurse practitioner and a GP principle and associate medical director with special interest in primary care oncology and palliative care.

Patient groups

Six patient groups were contacted for their views on developments in evidence, policy, practice, and services related to the guidelines and the need to update recommendations. We received a response from 1 patient group. The patient group highlighted a number of relevant NICE technology appraisals and other NICE guidance that is of direct relevance to breast cancer. It is planned that this guidance be presented alongside the relevant recommendations from both NICE guidelines on breast cancer as part of NICE's digital living guidelines ambition. See appendix A for all other feedback and its impact.

External reference group for breast cancer

We received feedback on the implementation of recommendations within the NICE guidelines on breast cancer from an external reference group who were established to advise on the key sources of, and support the interpretation, of system intelligence affecting implementation in the context of digital living guidelines. Membership includes policy, clinical, quality improvement and patient representatives alongside the chair of the guideline development group and NICE clinical adviser.

System intelligence

This describes feedback received from NICE internal teams. We received feedback from a NICE clinical expert, publishing team, field team, and medicines prescribing team at various stages of the surveillance process.

Other sources of information

We considered all other external correspondence received since the guideline was published.

Breast cancer committee feedback

Surveillance proposal, areas for update

The 20 members of the breast cancer standing committee were asked to provide feedback on the proposed surveillance decisions which were provided as a draft report and the details provided in appendix A. This was done by an electronic survey, with findings discussed at a breast cancer committee meeting on 25 November 2022. Seventeen responses to the survey were received, these were from 9 lay members, 3 breast surgeons, 2 radiologists, 1 therapeutic radiographer, 1 physiotherapist and 1 clinical oncologist.

There was agreement for all areas proposed for update, with only 1 person expressing disagreement with the proposal to update recommendations on the prevention and management of lymphoedema. They disagreed with the update proposal based on their experience that treatments are not available, and that there are difficulties with accessing lymphoedema specialists. They thought that people need to learn how to manage after node removal and have quicker access to clinics. They also said that GPs need more training on lymphoedema prevention and management. Implementation issues with current recommendations are not considered a reason for not undertaking an update on areas that may improve outcomes.

Additional questions

The breast cancer committee were also asked some additional questions on areas proposed for update to gather detailed information specific to the proposed updates and to inform potential future work. This information will be shared with the NICE breast cancer digital living guideline team for consideration.

The breast cancer committee were asked whether the current evidence review question for ovarian function suppression: what is the effectiveness of ovarian suppression in addition to endocrine therapy in premenopausal women with oestrogen-positive breast cancer? and protocol (see evidence review D: endocrine therapy for invasive disease) should be amended to include progesterone receptor-positive breast cancer that is considered oestrogen receptor-negative (this would also involve considering the threshold score to define a cancer as oestrogen receptor-positive). This was asked in response to topic expert feedback that data from the Suppression of ovarian function trial suggested a

broader population of premenopausal patients benefit from ovarian suppression, for example, not just those who have oestrogen-positive invasive breast cancer as the trial included oestrogen receptor and/or progesterone receptor positive-breast cancer. It is known that there are a small group of people with oestrogen receptor-negative and progesterone receptor positive-breast cancer, and benefits from endocrine therapies are less certain for this population.

Five committee members said they were not able to provide feedback, but 9 did agree with amending the review question and protocol to include evidence on the effectiveness of ovarian suppression in addition to endocrine therapy in premenopausal women with progesterone receptor-positive breast cancer that is considered oestrogen receptor-negative. Feedback highlighted that patients often ask about the implications of progesterone receptor-positive breast cancer, but that there is only limited information that can be provided to them. Other committee members agreed in principle if oncologists agreed with the proposal. The clinical oncologist agreed with including evidence on progesterone receptor status in an update. Of the 3 who disagreed, 1 questioned whether there would be sufficient evidence on progesterone receptor-positive breast cancer that is considered oestrogen receptor-negative; and another said that progesterone receptor status has no impact on the efficacy of hormonal therapy. In support of their statement, they cited Early Breast Cancer Trialists' Collaborative Group 2011, which reported that 5 years of adjuvant tamoxifen safely reduced the 15-year risk of breast cancer recurrence and death, with oestrogen receptor status the only recorded factor importantly predictive of the proportional reductions; and that in oestrogen receptor-positive disease, relative risk was approximately independent of progesterone receptor status (or level).

The breast cancer committee were also asked whether the evidence review question for ovarian function suppression and protocol should be amended to include aromatase inhibitors as an intervention and comparator (for example, as well as endocrine therapy without ovarian suppression, include endocrine therapy with an alternative ovarian suppression as comparator). This was asked because studies included in evidence review D only compared ovarian function suppression plus endocrine therapy with endocrine therapy alone (and did not include evidence on aromatase inhibitors); whereas we identified evidence comparing the efficacy of ovarian function suppression with different endocrine therapy regimes against one another (for example, ovarian function suppression plus an aromatase inhibitor compared with ovarian function suppression plus tamoxifen). Results of the latter comparisons indicated that ovarian function suppression with an aromatase inhibitor may result in better outcomes for local and distant disease recurrence when compared with ovarian function suppression plus tamoxifen in premenopausal

women with hormone receptor-positive breast cancer.

Five committee members said they were not able to provide feedback, 11 agreed with amending the protocol and there was only 1 disagreement. The committee member who disagreed said that aromatase inhibitors should be included, but not as a comparator and said that most women get ovarian suppression and aromatase inhibitor, not tamoxifen. As recommendations 1.7.4 and 1.7.5 in NICE's guideline on early and locally advanced breast cancer do not explicitly name aromatase inhibitor as an option, it is considered important to include evidence on ovarian function suppression plus an aromatase inhibitor, and consider its relative efficacy compared with ovarian function suppression plus tamoxifen so that recommendations can be made about both options.

The breast cancer committee were also asked whether the update on platinum-based neoadjuvant chemotherapy regimens for people with triple-negative early and locally advanced breast cancer should include how HRD may impact the efficacy of platinum-based neoadjuvant chemotherapy. Three committee members said they were not able to provide feedback on this question, 12 agreed based on evidence provided, but highlighted this was an area requiring specialist input; and 2 disagreed. One committee member disagreed on the basis that they were unsure whether there is currently sufficient evidence to support conclusions in this area; and another said that HRD should only be considered if there is a plan/clinical capacity/consensus and quality assurance to determine and report HRD status in routine clinical histopathology labs - that histopathology input and advice is required to see if it is feasible and possible to test for HRD in the UK setting.

The breast cancer committee were also asked about potentially updating recommendations 1.8.1 to 1.8.3 in NICE's guideline on early and locally advanced breast cancer on adjuvant chemotherapy for invasive breast cancer in order to provide recommendations on:

- dose-dense anthracycline and taxane-based chemotherapy because evidence (from intelligence, see appendix A) supports scheduling and use of dose-dense chemotherapy given every 2 weeks or sometimes weekly, rather than every 3 weeks
- the use (or not) of 5-fluorouracil as, while not discussed in recommendations because it is not generally given with anthracycline, 5-fluorouracil is reportedly mentioned in some NHS guidance and by the European Society for Medical Oncology

- de-escalation of chemotherapy (including omission of anthracyclines) in lower risk disease as this was highlighted by a topic expert as an area needing update (Customising local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021, was provided as supporting information).

Half of the committee did not feel able to respond to these questions.

In response to needing recommendations on dose-dense anthracycline and taxane-based chemotherapy, 1 committee member said this was not needed as they considered it to be accommodated by the existing recommendations. Two of 7 who responded that recommendations were needed, said that dose-dense anthracycline and taxane-based chemotherapy is increasingly being offered to patients, so it would be good to have clarification on this within recommendations, while others were more circumspect and felt that oncology input on the decision would be needed – clinical oncologist feedback was that a medical oncologist or clinical oncologist whose practice includes systemic treatment is needed to provide feedback on this.

Three committee members thought it was not necessary to have recommendations on 5-fluorouracil as it is not used, which was also said by some of the 7 who agreed with adding information, but they thought it would be useful to provide clarity in order to reduce variation in practice.

With regards to de-escalation of chemotherapy in lower risk disease, 8 committee members thought this should be an area for update as it is important to consider de-escalation where evidence suggests it is safe to do so, as this can avoid unnecessary additional toxicity. One committee member did not think recommendations were needed as individual clinicians can choose to alter traditional regimens if necessary, depending on patient comorbidities and other relevant factors.

The NICE breast cancer digital living guideline team should consider the above committee feedback as part of the continual update process for breast cancer guidance.

Surveillance proposal, withdrawing recommendations

We also proposed withdrawing recommendation 1.13.4 in NICE's guideline on early and locally advanced breast cancer on clinical follow-up for people with early and locally advanced breast cancer as there is an expectation that since 2019 all trusts have a follow-

up pathway after breast cancer treatment that suits the needs of patients, and ensures they can get rapid access to clinical support where they are worried that their cancer may have recurred (see NHS long term plan). And in NICE's strategic pillar 2 to develop dynamic, living guideline recommendations, the focus is on topic areas that represent key priorities and where NICE is uniquely and best placed to use our skills to add value, ensuring we maintain the right portfolio with the greatest impact on health and on reducing health inequalities (see the NICE strategy 2021 to 2026). As part of the work to meet the strategy ambitions, we are considering standing down recommendations that are service model and good practice recommendations that duplicate and/or overlap with other national policy or guidance. It was therefore proposed that the recommendation on clinical follow-up be withdrawn.

All 9 lay members and 2 other committee members disagreed with the proposal to withdraw the recommendation on clinical follow-up. Some said that they strongly disagreed, with reasons being that the recommendation provides useful information for patients as it identifies what follow-up to expect; and means that they can challenge services if they are not receiving the expected follow-up care. Concerns were also raised that recommended practice is not being followed, with some saying that there is geographical variation in the follow-up patients receive. There were also concerns that if NICE completely removes mention of clinical follow-up that this may be interpreted by users as meaning this is not considered important. Some who disagreed with withdrawing the recommendation, and others who agreed with the proposal, thought that if the recommendation is withdrawn, that there should remain some mention of clinical follow-up, which could include cross-referencing to relevant guidance such as the NHS long term plan. Of the 5 committee members who agreed with withdrawing recommendation 1.13.4 on clinical follow-up, 2 said that all centres provide follow-up and 2 said that they agreed with the rationale for withdrawing the recommendation.

Additional areas for update

The committee members were also asked whether they thought there were any other areas relevant to early, locally advanced and advanced breast cancer that should be updated now or in the future.

Several committee members raised concerns about the accuracy of mammography in detecting breast cancer in dense breasts. While screening options after a negative mammography in women with dense breasts was raised as an area for update, the content of the national breast cancer screening programme is not within NICE's remit as this is the

responsibility of the Breast Cancer UK National Screening Committee. Imaging during preoperative assessment and follow-up is within the scope of the breast cancer guidelines, and recommendation 1.1.2 in NICE's guideline on early and locally advanced breast cancer does say to offer MRI of the breast to people with invasive breast cancer, if breast density precludes accurate mammographic assessment. However, the recommendations on follow-up imaging do not mention imaging options for dense breasts. We have proposed that there is a cross-reference to recommendations on surveillance and strategies for early detection of breast cancer in NICE's guideline on familial breast cancer, which do highlight the possibility that mammography might miss a cancer in dense breasts, and that having dense breasts will increase the likelihood of further investigations, with the option of having an MRI (see appendix A). However, these recommendations are only for people with or without a personal history of breast cancer who also have a family history of breast, ovarian or another related (prostate or pancreatic) cancer. There is therefore a potential gap in recommendations on imaging follow-up for those with early or locally advanced breast cancer who have dense breasts and no family history of cancer. It is also important to note that younger women naturally have more dense breast tissue (see equalities). The breast cancer committee said that breast cancer patients with dense breasts do express concerns about only having mammography follow-up; and decisions around whether or not MRI is offered come down to clinician choice, with no consensus on when alternative imaging techniques to mammography should be offered to those with dense breasts. The committee also highlighted that other countries such as America and Germany recommend MRI follow-up in people with dense breasts and a history of breast cancer. We did not find any evidence that supports the use of MRI for dense breasts (see appendix A), and it is our understanding that while it is recognised that mammography is less accurate for detecting cancer within dense compared with normal breast tissue, that there is not currently sufficient evidence on the diagnostic accuracy of alternative imaging procedures in this population. Given the uncertainties in imaging follow-up for people with a history of breast cancer and dense breasts, and patient concerns about receiving appropriate follow-up, it is recommended that this is an area for which evidence is monitored and considered for a future update.

Some committee members also said that screening for lobular carcinoma in situ (LCIS) should be included in the breast cancer guidelines, however the content of the NHS breast screening (BSP) programme is not within NICE's remit; and LCIS is not cancer, even though it does indicate an increased risk of developing breast cancer (LCIS was excluded from NICE's guideline on early and locally advanced breast cancer).

Feedback was also received that invasive lobular breast cancer should have separate

recommendations on preoperative assessment, follow-up imaging and treatment options. Invasive lobular breast cancer is included within NICE's guideline on early and locally advanced breast cancer, and if relevant evidence identified, separate recommendations would be made. Recommendation 1.1.2 in NICE's guideline on early and locally advanced breast cancer does say to offer MRI of the breast to people with invasive breast cancer, to assess the tumour size if breast-conserving surgery is being considered for invasive lobular cancer but invasive lobular breast cancer is not mentioned in recommendations on follow-up. During the surveillance review, no systematic review evidence was identified specific to invasive lobular breast cancer.

The breast cancer committee also raised concerns around geographical differences in the provision of immediate breast reconstruction and the applicability of recommendations to male breast cancer patients. These are discussed in the equalities section.

Feedback was also received on lack of information (due to evidence gaps) on appropriate surgical and treatment options for people with specific genetic profiles. The issue of how care can keep up with the rapidly evolving field of breast cancer genetics/genomics was identified as a gap and future area for update. Other areas where there are gaps in recommendations: imaging modalities such as use of contrast mammography instead of MRI; radiotherapy techniques such as irradiating the internal mammary chain for high-risk disease; liquid biopsy; prehabilitation (a programme of support and advice to support getting ready for cancer treatment before it starts); and prevention and management of breast and chest wall lymphoedema in breast cancer patients. All feedback will be shared with the NICE breast cancer digital living guideline team for consideration.

Equalities

The equalities and health inequalities assessment in appendix B provides details of equality and health inequalities issues that have been identified during this surveillance review, which should be considered during the proposed updates of the NICE breast cancer guidelines, and as part of the initial and ongoing development of the breast cancer digital living guideline.

Feedback was received from topic experts, patient group and breast cancer committee members on regional differences in the provision of immediate breast reconstruction. It was described as a postcode lottery, with huge discrepancies between trusts in advice around the risks and benefits of delayed as opposed to immediate reconstruction, with many women being told reconstruction is not possible before radiotherapy despite NICE

recommendations that say it should be discussed as a possibility, with the risk and benefits explained. Offers of breast reconstruction were also found to be less often provided to older women (NICE breast cancer health inequalities briefing), even though they may want to have breast reconstruction; and rates of surgery in older women have been shown to vary considerably across breast units in the UK even though research suggests that breast cancer surgery is a safe option for women over 70 years old. Concerns about older people not being offered active treatments solely based on age were also raised by breast cancer committee members.

Inequalities in access to services based on geography, in particular immediate breast reconstruction and lymphoedema specialist care were identified. Inequalities in access to services based on geography are considered implementation issues and will be shared with relevant teams within NICE, however commissioning and funding decisions are beyond the remit of NICE.

The NICE breast cancer health inequalities briefing also reported that deprived groups, people from minority ethnic family backgrounds and people with a disability may have delays in diagnosis of breast cancer due to lower levels of screening attendance. There are currently no recommendations on measures that may improve access to/attendance at national breast cancer screening programme appointments for these populations. Consideration should be made as to whether this gap could be addressed through new recommendations within the breast cancer guideline or via other NICE products or teams, such as NICE implementation.

The issue of breast density being a problem in follow-up monitoring is of direct relevance to younger women who naturally have more dense breast tissue, and for whom mammograms alone may not be the ideal diagnostic tool. Breast cancer committee members also said that women are not advised of their breast density status during routine scans or after diagnosis, but there is patient interest in having access to this information in order to discuss the risks with clinicians. Due to a lack of evidence of the increased accuracy of detecting cancer recurrence using alternative imaging such as MRI for dense breasts an update has not been proposed, but this has been highlighted as a gap within current recommendations that may be considered in the future work of the breast cancer digital living guideline.

Experts also said that women from ethnic minority backgrounds experience differences in the stage and age of diagnosis, survival outcomes, and experiences of care and treatment, which was also identified within the NICE breast cancer health inequalities briefing. Some

of this may result from lower breast screening uptake, possibly due to cultural and language barriers; but there is also a relationship between ethnicity and tumour characteristics, with ethnic minorities more likely to have cancers with less favourable tumour characteristics. For example, it is known that people from Black African or Caribbean family backgrounds have elevated rates of triple-negative breast cancer. Neoadjuvant chemotherapy and platinum-based neoadjuvant chemotherapy regimens for people with triple-negative invasive breast cancer are areas for update, which may therefore lead to improvements in outcome for people from Black African or Caribbean family backgrounds who have triple-negative breast cancer.

The applicability of recommendations to male, trans and non-binary people with breast cancer was identified as a concern with the current recommendations in both NICE guidelines on breast cancer, some of which date back to 2009. The NICE publishing team will be working with the breast cancer committee to identify which recommendations are applicable to whom and to use appropriate language to describe populations, in line with the NICE style guide on gender.

All subsequent updates should ensure that the applicability of recommendations according to gender, age and ethnicity is considered, and where appropriate, recommendations specify to whom they are and are not applicable.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we decided that an update is necessary for a number of topic areas in NICE's guidelines on early and locally advanced breast cancer: diagnosis and management and advanced breast cancer diagnosis and treatment, and to align content with other NICE guidance.

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