Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment (HTA) of surveillance of women aged less than 50 years at elevated risk of breast cancer

Executive Summary

19 March 2013

Safer Better Care

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive continuous improvement in Ireland's health and personal social care services, monitor the safety and quality of these services and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.

- **Social Services Inspectorate** – Registering and inspecting residential centres for dependent people and inspecting children detention schools, foster care services and child protection services.

- **Monitoring Healthcare Quality and Safety** – Monitoring the quality and safety of health and personal social care services and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health Technology Assessment** – Ensuring the best outcome for people who use our health services and best use of resources by evaluating the clinical and cost effectiveness of drugs, equipment, diagnostic techniques and health promotion activities.

- **Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

Foreword

Breast cancer is the most common invasive cancer diagnosed in women in Ireland and the second most common cause of cancer death in women. Although the majority of breast cancers are sporadic, it is estimated that 25% of cases relate to a familial risk with 5% to 10% of all cases specifically relating to a genetic predisposition. Cancers relating to genetic predisposition have a median age of onset more than 20 years earlier than the general population. The lifetime risk of developing breast cancer is 10% to 11% for the general population; for female carriers of mutations of the *BRCA1* and *BRCA2* genes, average lifetime rates of up to 60% to 80% are reported.

Screening and surveillance are secondary preventive measures that aim to detect breast cancer at the earliest possible stage in order to reduce the rate of breast cancer death. Screening refers to monitoring those at average risk of a disease; surveillance refers to the monitoring of those known to be an increased risk of the disease. Internationally recommended surveillance imaging options include digital mammography, magnetic resonance imaging (MRI) or a combination of the two. However, there is currently no consensus as to the optimal design of a surveillance programme.

The Director of the National Cancer Control Programme (NCCP) in the Health Service Executive (HSE) requested that the Health Information and Quality Authority (the Authority or HIQA) undertake a health technology assessment (HTA) in relation to a potential national surveillance programme for women aged less than 50 years at elevated risk of breast cancer due to a familial or genetic predisposition. The purpose of this HTA is to examine the safety, effectiveness, cost-effectiveness, budget impact, and resource implications of a surveillance programme based on digital mammography, magnetic resonance imaging (MRI) or a combination thereof.

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate of the Authority. A multidisciplinary Expert Advisory Group (EAG) was convened to advise the Authority during the conduct of this assessment.

The Authority would like to thank its Evaluation Team, the members of the EAG and all who contributed to the preparation of this report.

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Acknowledgements

The Authority would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment (HTA).

Particular thanks are due to the Expert Advisory Group (EAG), Dr David Gallagher (Mater Misericordiae University Hospital, Dublin), Dr Andrew Green (National Centre for Medical Genetics in Our Lady's Children's Hospital, Crumlin, Dublin), James O'Mahony (PhD fellow, Trinity College, Dublin), Dr Niall Sheehy (St James's Hospital, Dublin) and the individuals within the organisations listed below who provided advice.

The membership of the EAG was as follows:

Professor Peter Daly, Consultant Medical Oncologist, nominated by the Royal College of Physicians of Ireland

Dr Barbara Dunne, Consultant Pathologist, St James's Hospital, Dublin, nominated by the Faculty of Pathology, Royal College of Physicians of Ireland

Ms Naomi Fitzgibbon, Public representative, nominated by the Irish Cancer Society*

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* Martin Flattery left the Authority in February 2012; Ms Mairead Lyons was replaced by Ms Naomi Fitzgibbon in September 2012; Dr Deirdre Mulholland was replaced by Dr Máirín Ryan in September 2012

Organisations that assisted the Authority in providing information, in writing or through meetings, included:

Beaumont Hospital

Cork University Hospital

Health Service Executive (HSE)

Mayo General Hospital

National Cancer Registry Ireland

National Cancer Screening Service

National Centre for Medical Genetics

Mater Misericordiae University Hospital

Mid-Western Regional Hospital Limerick

St James's Hospital

University Hospital Galway

Waterford Regional Hospital

Original model adapted for this HTA:

The model used in this HTA was adapted from a model kindly provided by the National Clinical Guideline Centre in London (Familial breast cancer (CG41). London: National Clinical Guideline Centre, 2006).

Members of the Evaluation Team:

Members of the Authority's Evaluation Team included: Martin Flattery,^ Dr Patricia Harrington, Patrick Moran, Dr Linda Murphy, Michelle O'Neill, Dr Conor Teljeur and Dr Máirín Ryan.

^ Martin Flattery left the Authority in February 2012

Conflicts of Interest

None reported.

Executive Summary

I. Background

On 28 July 2011, the Director of the National Cancer Control Programme (NCCP) in the Health Service Executive (HSE), Dr Susan O'Reilly, requested that the Health Information and Quality Authority (the Authority or HIQA) undertake a health technology assessment (HTA) in relation to a potential national surveillance programme (using digital mammography or magnetic resonance imaging [MRI], or a combination thereof) for women aged less than 50 years at elevated risk of breast cancer because of either a genetic predisposition or a strong family history.

II. Objectives

The terms of reference for this HTA were to:

- Describe the epidemiology of breast cancer for those under the age of 50 at high and moderate risk of hereditary breast cancer (due to genetic predisposition or strong family history).
- Review the evidence of the effectiveness and safety of mammography, MRI surveillance and a combination of the two in the specified population(s) including both different surveillance frequencies and age groups.
- Examine the cost-effectiveness of these surveillance options compared to the current practice of no organised surveillance and relative to each other.
- Estimate the budget impact of the introduction of a surveillance programme for the selected population(s).
- Identify the key additional resources necessary in order to implement a surveillance programme as effectively and efficiently as possible.
- Consider any additional impact that a surveillance programme is likely to have including wider ethical or societal implications for the healthcare system or for affected families.

III. Methodology

This HTA was conducted using the general principles of HTA and employing the processes and practices used by the Authority in such projects.

In summary:

- The Terms of Reference of the HTA and the specific questions to be addressed were agreed between the Authority and the National Cancer Control Programme.
- An Expert Advisory Group (EAG) – comprising representatives from relevant stakeholders and patients' organisations, clinicians with specialist expertise, and a HTA expert – was established, and an Evaluation Team was appointed comprising internal Authority staff.
- Irish epidemiological data was reviewed along with relevant international literature reporting the prevalence of familial and genetic risk. A review of relevant scientific literature was performed to summarise the available clinical evidence on the safety and effectiveness of digital mammography and MRI in women aged less than 50 years at elevated risk of breast cancer.
- The likely costs, cost-effectiveness and budget impact over five years for the Irish healthcare system were assessed. Surveillance strategies using digital mammography, MRI, or a combination thereof were compared to the current practice of no organised surveillance (ad hoc surveillance), to a strategy of no surveillance and compared to each other in the specified populations and using different surveillance frequencies and age groups. Data to support the economic evaluation were obtained from a literature review, Irish databases and expert opinion. Endorsement of all inputs was sought from the EAG.
- The key additional resources necessary to implement a surveillance programme were identified.
- A review of the ethical implications of a national surveillance programme was also undertaken.

IV. Burden of disease

Breast cancer is the most common invasive cancer in women in Ireland; there are over 2,600 new cases each year, accounting for 32% of all cases of invasive cancer. Twenty-five percent of diagnoses are in women aged less than 50 years, with 10% of deaths, an average of 88 deaths per annum, occurring in this age group. Regardless of age, prognosis is strongly linked to stage of diagnosis, with five-year

survival probability of 98.9% for those diagnosed at Stage I compared to 27.7% when diagnosed at Stage IV.

Although breast cancer is predominantly a sporadic disease, it is estimated that 25% of cases relate to a familial risk with 5% to 10% of all cases specifically relating to a genetic predisposition. Mutation carriers of identified high penetrance genes such as *BRCA1* and *BRCA2* have a lifetime risk of breast cancer as high as 60% to 80%, with much of this risk occurring between ages 30 and 50 years. Using the NICE (National Institute for Health and Care Excellence in the UK) risk classification that has been recommended for adoption in Ireland, women may be classified as average, moderate or high risk based on a 10-year risk of breast cancer between age 40-50 years of less than 3%, between 3% and 8%, and greater than 8%, respectively. Average, moderate and high risk can also be defined based on a lifetime risk of breast cancer of less than 17%, between 17% and 30%, and greater than 30%, respectively. Estimating the number of women aged less than 50 years in each group in Ireland is complicated by limited prevalence data. Based on international evidence, the percentage population in the average, moderate and high risk groups is estimated to be 92.4%, 5.7% and 1.9%, respectively. However, the known population in the moderate and high risk groups is small. The true population of women aged less than 50 at high and moderate risk of developing breast cancer is approximately 18,000 and 55,500, respectively. The estimated known population of women aged less than 50 at high and moderate risk is approximately 2,000 and 2,500, respectively. Women at high risk of breast cancer contribute disproportionately to the incidence of early breast cancer. Although comprising less than 2% of the population, women at high risk are estimated to contribute 10% of incidence of breast cancer in women aged less than 50 years.

V. Technology description

A number of imaging techniques can be used as part of a surveillance programme to monitor individuals known to be at elevated risk of breast cancer. This HTA specifically investigated the efficacy and safety of two of these technologies: digital mammography and MRI. Both technologies are widely used as diagnostic tests in the healthcare system. Although breast MRI is more resource intensive than digital mammography, it has a number of advantages including that it does not entail exposure to ionising radiation. Although uncommon, frequent exposure through a mammography-based surveillance programme from a young age may induce breast cancers. The sensitivity of mammography is lower for women with dense breast tissue, which is commonly found in pre-menopausal women. Tissue density is less of a factor in MRI surveillance, although diagnostic accuracy is impacted by hormonal

factors and it is recommended that testing be performed in week two of the menstrual cycle.

The surveillance process was reviewed, including the subsequent management of women who have an abnormal test result. A review of international practices and guidelines in relation to breast cancer surveillance was also undertaken. Internationally, there is no consensus in terms of the optimal design of a surveillance programme, with variation in the age, frequency and type of surveillance offered by risk category. The evidence underpinning these surveillance recommendations is noted to be limited in a number of these guidelines with recommendations based on non-randomised screening trials and observational studies or expert consensus opinion. Most surveillance programmes limit use of mammography to those aged 30 years and older, because of an unfavourable risk-benefit profile in younger women. The use of MRI is discussed as an adjunct to mammography to address the potential limitations of mammography surveillance in younger women (reduced test sensitivity in dense breasts and exposure to ionising radiation) with none of these guidelines addressing the potential use of MRI as a sole surveillance strategy.

A wide range of possible surveillance strategies for a national programme were identified and subsequently refined to a list of feasible options in discussion with the Expert Advisory Group.

VI. Summary of clinical effectiveness

A systematic review of the literature was undertaken to examine the diagnostic accuracy of mammography, MRI, and a combination thereof, in women at elevated risk of breast cancer. Relevant studies were identified, assessed and described and a meta-analysis conducted of the pooled data. The finding of this review was that there is limited evidence directly comparing surveillance MRI, film mammography and digital mammography in women aged less than 50 years at an elevated risk of breast cancer. Based on the available data, the estimated sensitivity and specificity[¥] of MRI for the target population were 0.80 and 0.92, respectively. The estimated sensitivity and specificity of digital mammography for the target population were 0.38 and 0.97, respectively. These estimates were predominantly based on film mammography data due to the lack of studies comparing digital mammography and MRI in women at elevated risk of breast cancer. The estimated sensitivity and specificity of combined MRI and digital mammography for the target population were

[¥] Sensitivity is the proportion of people who have the illness and who return a positive test result. Specificity is the proportion of those who do not have the illness and who return a negative test result.

0.88 and 0.88, respectively. These findings were consistent with other published reviews concerning surveillance of women at elevated risk of breast cancer, showing MRI to have the greatest sensitivity of any single test, with a combination of MRI and mammography producing an increase in sensitivity over MRI alone, along with a slight decrease in specificity.

To provide context, a brief summary of the reported effectiveness of surveillance in women at elevated risk of breast cancer was provided. The goal of surveillance is a reduction in breast cancer mortality due to earlier detection and treatment. There is currently a lack of evidence of a mortality reduction in women aged less than 50 at elevated risk of breast cancer, although there is data to support a reduction in mortality with mammographic screening in an average risk population. No published evidence of a reduction in mortality with MRI screening was identified. It was noted that not all risk subgroups may benefit equally from surveillance. Due to aggressive intrinsic characteristics of cancers in *BRCA1* and *BRCA2* mutation carriers, earlier detection may not translate into improved survival benefit. Surveillance has non-mortality effects that are both positive (e.g., early detection leading to less toxic treatment) and negative (e.g., radiation-induced carcinoma, overdiagnosis and unnecessary biopsies). The ratio of benefits to harms depends on the target population. Frequent exposure of breast tissue to radiation doses below the age of 30 years (such as in a surveillance programme) may carry a risk of breast cancer induction, with suggestions that *BRCA1* and *BRCA2* mutation carriers might have increased radiosensitivity.

VII. Economic evaluation

Economic evaluation in HTA involves the comparative analysis of alternative courses of action. In this case, the additional costs and health benefits associated with a prospective national surveillance programme were compared with the current scenario of ad hoc surveillance and to a scenario of no surveillance. The results of the evaluation indicate that for all risk subgroups, MRI offers the most effective approach to surveillance in terms of increased quality-adjusted life years (QALYs) per person and reductions in breast cancer mortality, but at an increased cost. With the exception of a strategy of no surveillance, digital mammography alone results in the fewest QALYs per person, and the highest breast cancer mortality. The limited effect of digital mammography is due to a combination of poor test sensitivity in women aged less than 50 years and the increased incidence of cancer induced by radiation exposure. Of note, the cancer risk varies within subgroups such that a strategy that is not, on average, cost-effective for a subgroup, may be cost-effective for some

women within that subgroup. (This may be reflected in the current approach to surveillance.)

For women aged less than 50 years with identified high penetrance genetic mutations, surveillance offers a significant opportunity to reduce mortality. Some surveillance strategies are cost-effective compared to no surveillance. The superior sensitivity and lack of radiation exposure associated with MRI make it the most effective imaging modality for this cohort. Annual MRI from age 30 is the recommended strategy for those with *BRCA1* and *BRCA2* mutations (i.e. it is both more effective and less costly than the current practice of offering annual MRI from age 30 plus digital mammography in combination from age 30 or 35). Annual MRI from age 30 plus digital mammography from age 40 as implemented in the current UK NHS breast cancer surveillance programme is also a reasonable option for these women. In individual cases where there may be a family history of early onset breast cancer, it may be appropriate to offer annual MRI surveillance from an earlier age. For women with *TP53* mutations, annual MRI surveillance from age 20 is the recommended strategy.

For women at high familial risk with no identified genetic mutations, surveillance before the age of 40 is not recommended on the basis of cost or clinical effectiveness. Although not cost-effective by traditional standards compared to no surveillance, providing annual MRI-based surveillance from 40 to 49 is less costly than existing ad hoc surveillance and offers the potential of a minor mortality reduction. If considered impractical to offer MRI-based surveillance to such a large cohort, then annual digital mammography from age 40 to 49 would be less costly and more effective than the existing system of no organised, or ad hoc, surveillance.

For women at moderate risk, surveillance before the age of 40 is not recommended on the basis of cost or clinical effectiveness. Similar to women with high familial risk, surveillance is not cost-effective from ages 40 to 49 compared to no surveillance. However, providing annual MRI-based surveillance is less costly than existing ad hoc surveillance and offers the potential of a minor mortality reduction. If it is considered impractical to offer MRI-based surveillance to such a large cohort, but offering some form of standardised surveillance is considered desirable, then annual digital mammography from age 40 to 49 would be less costly and more effective than existing surveillance.

The known population of women aged less than 50 who are carriers of high penetrance genetic mutations is relatively small. As a consequence, the incremental budget impact of different surveillance strategies for this cohort tends to be small. However, the small size of the cohort means that potential mortality reductions are small in absolute terms. Compared to current ad hoc surveillance, the recommended

surveillance strategies will result in a modest reduction in budget impact, a reduction in digital mammography requirements, and no substantive change in the number of MRIs and MR-guided biopsies per annum. The budget impact estimates are directly proportional to the identified population. A 10% increase in the identified population will lead to a 10% increase in the budget impact.

The uncertainty in the results of the model was primarily driven by uncertainty in the probability of developing cancer, the cost of imaging, and the diagnostic test accuracy. The probability of developing cancer was estimated from international studies. Very limited data are available on diagnostic test accuracy specific to women aged less than 50 at elevated risk of developing breast cancer. Sensitivity and scenario analyses were used to test the impact of assumptions and found that interpretation of the results is unchanged.

VIII. Ethical considerations

Potential ethical issues arising from a decision to introduce or not introduce a nationally organised surveillance programme for those at elevated risk of breast cancer were considered in this HTA. The main ethical issues associated with the provision of such a programme include informed consent (particularly on the benefits versus risks of surveillance), equity of access and allocation of resources. It was noted that women should be fully informed about the benefits and risks of surveillance. An organised surveillance programme will improve equity of access; it should have quality key performance indicators (KPIs) to measure performance against targets or expectations. Reallocation of healthcare resources in order to establish a surveillance programme could impact the existing healthcare system as it may divert resources from other effective treatments for the same condition or from the overall healthcare fund. Although ethical issues associated with identifying individuals as being at elevated risk of breast cancer were beyond the remit of this HTA, it was noted that these issues (including the right to know and not know, and the duty to disclose and warn others) may also arise in the delivery of a surveillance programme.

IX. Discussion

Although the definitions of the risk subgroups are clear, the population is poorly identified, and understanding of disease pathology and progression in these cohorts is ill-defined. The benefits of surveillance are based on assumptions of early detection leading to improved outcomes. Disease progression and pathology in

women with high penetrance genetic mutations may be different from older women at average risk, which may impact on the benefits of surveillance. Where possible, the model used in this study availed of data specific to the target population. However, data were limited and data relevant to an average risk population were used for some parameters potentially over- or underestimating the benefits of surveillance.

X. Conclusions

Health technology assessment supports evidence-based decision making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions may be drawn. For women aged less than 50 years with identified high penetrance genetic mutations other than *TP53*, surveillance with annual MRI from ages 30 to 49 is cost-effective compared to no surveillance. In accordance with current international practice, surveillance may be combined with annual digital mammography from ages 40 to 49. For the subgroup with a *TP53* mutation, annual MRI surveillance from age 20 is the recommended strategy. For women at high familial risk with no identified genetic mutations and those at moderate risk, surveillance is not cost-effective by traditional standards compared to no surveillance. However, if the goal is to maximise health gain using existing resources and taking account of current international practice, then annual surveillance with digital mammography from ages 40 to 49 is preferable to existing ad hoc surveillance.

The establishment of an organised surveillance programme would necessitate detailed service planning to ensure that it could meet the requisite internationally accepted quality standards. This includes the development of quality key performance indicators (KPIs) to measure performance against targets or expectations.

Published by the Health Information and Quality Authority.

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