Cancer screening in Europe

Expert workshop 2

19 October 2021

How can cancer screening programmes targeting breast, cervical and colorectal cancers be improved throughout the EU?

SAPEA
Science Advice for Policy by European Academies

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1. Introduction

Screening of the general population (asymptomatic individuals) for breast, colorectal and cervical cancer has been in use in the EU for many years, and the majority of member states have one or more screening programmes operational.

Published in February 2021, Europe's Beating Cancer Plan: A new EU approach to prevention advocates for improving the early detection of cancer in part by ensuring that 90% of the EU population who qualify for breast, cervical and colorectal cancer screenings are offered screening by 2025.[1]

However, there are still significant inequalities in access to these three types of screening between and within individual countries. And there are opportunities for improvements and efficiencies by more effectively stratifying screening programmes to ensure that those most at risk are able to benefit, while reducing harms such as overdiagnosis. Any screening test has a balance of benefits and harms, which can be altered by modifying the strategies and protocols used based on individual factors such as age, sex, ethnicity and family history.

Furthermore, there is the concept of stratifying individuals for cancer screening according to their personal risk, which was first proposed more than a decade ago (Lieberman, 2008) but has yet to be implemented in national screening programmes due to the high level of data collection required, the resources needed (e.g. in IT and management) and the possibly modest additional benefits to be gained when applying such strategies at a population level. It is also unknown whether employing risk stratification strategies impacts on participation by introducing the potential for misunderstanding and stigmatisation.

This report summarises the presentations and discussion of the expert workshop convened on 19 October 2021 to discuss how the existing cancer screening programmes for colorectal, breast and cervical cancer could be improved throughout the EU.

This expert workshop is supported by an associated Rapid Review of the scientific literature conducted by the Specialist Unit for Review Evidence (SURE) at Cardiff University exploring to what extent more stratified approaches to breast, cervical and colorectal cancer screening programmes impact on uptake, efficacy, harm-benefit and cost-effectiveness. A full list of contributors to the workshop can be found in Appendix 1 on page 40.

1 https://ec.europa.eu/commission/presscorner/detail/en/ip_21_342

Introduction

Note: throughout this report, the terms 'woman'/'women' and 'man'/'men' are used to describe people born female or male, respectively. We recognise that gender identity may not always match birth sex, and that barriers to accessing healthcare including cancer screening exist for transgender and gender non-conforming individuals (Haviland et al., 2020). However, in-depth consideration of this issue is out of scope for this report and it was not discussed at the workshop.

2. The current state of existing cancer screening programmes in the EU

In 2003, the Council of the European Union issued recommendations calling on all EU countries to implement national, population-based screening programmes for breast, cervical and colorectal cancer. The first EU cancer screening report, published in 2008, showed that although there had been some progress, member states fell short of the target for minimum number of examinations by more than 50%.

A second report, prepared by IARC in 2017, looked in detail at the status and performance of cervical, breast and colorectal screening programmes across 28 member states, using a set of common, harmonised process and outcome indicators to enable comparison between countries.[2] These indicators include:

- coverage by invitation or examination
- participation rate
- further assessment rates
- further assessment compliance rates
- treatment referral rates
- detection rates
- positive predictive values
- proportion of DCIS among all cancers (breast only)
- benign surgical biopsy rate (breast only)
- colonoscopy completion rates (CRC only)

The process for the preparation of a third report is expected to start in early 2022. The next report will be linked to the European Cancer Information System.

Breast cancer screening

By 2016, 25 of 28 member states had some kind of population-based breast screening programme, with 95% of eligible EU resident women aged 50–69 having access to screening. Full roll-out of the programme (defined as 90% of the target population receiving at least one invitation for screening) was achieved in 21 EU member states.

2 https://ec.europa.eu/health/sites/default/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf

Colorectal cancer screening

By 2016, 20 member states had some level of population-based colorectal screening and three more were contemplating introducing it shortly, encompassing 72% of eligible EU residents aged 50–74 years. Due to the relative recency of colorectal screening technology, full roll-out was only achieved in 11 states.

Cervical cancer screening

Although cervical cancer screening is the oldest screening programme, first starting in Europe in the 1970s, EU-wide levels of screening seem more disappointing. 22 of 28 member states have population-based screening, with 72% eligible EU residents aged 30–59 years having access to population-based screening. Full roll-out completed in just 12, with significant variability across the EU. However, opportunistic screening is more common for this cancer site.

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2.1. Challenges of delivering organised cancer screening programmes in the EU

It is a significant challenge to deliver systematic, organised population screening programmes for cancer, even in the wealthiest countries of the EU. Although they can deliver significant health benefits in terms of cancer deaths prevented and healthy life-years gained, screening programmes are expensive and involve millions of citizens. Furthermore, the costs of failures in the system can be significant, not only in terms of lives lost but also loss of public confidence and wasted money. Small backlogs can quickly snowball, particularly in the face of unexpected disruptions such as COVID-19, which has significantly impacted all screening programmes across Europe.

A national screening programme should be viewed as a major investment in infrastructure and workforce. Screening protocols are complex and it is not enough to have sufficient resources to roll out a particular screening test. Screening must be supported by careful design of the whole programme, especially evidence-based management of people testing positive, along with the administrative and IT infrastructure required to deliver and monitor it to ensure ongoing quality, and continuous (independent) evaluation.

It is important to ensure that everyone who is eligible for a particular type of screening according to the agreed protocol and has not yet undergone testing is invited to attend, to avoid missing out individuals or groups. Uptake of screening can be variable throughout a country, and implementation research is needed to understand individual barriers to screening and how these can be overcome (for example, lack of information, inconvenient appointments, personal discomfort).

Furthermore, it is important to remember that screening is a pathway, not just a test. The end-to-end care pathway should be fully joined up, from the moment that someone is invited for screening, through to a positive result, further follow-up investigation and treatment, to ensure that nobody falls through the gaps. This pathway should ideally be the same in all parts of the country, to avoid creating regional inequalities.

Quality assurance is also vital, ensuring that screening programmes operate within agreed parameters so that they can deliver the expected population benefits. Failure to operate a screening programme within these accepted parameters means that expected benefits are not achieved and the programme is no longer cost effective.

Targeting groups for screening based on risk can help to deliver more cost-effective screening and improve the ratio of benefits to harms, such as lung cancer screening for heavy smokers, bowel cancer screening in younger individuals with Lynch syndrome, a genetic condition that increases the risk of the disease, or breast cancer screening for women with an inherited BRCA gene fault. However, targeting specific groups and introducing elements of risk stratification (see the report from the third workshop) adds additional complexity to screening protocols and must be done carefully in order to realise the potential benefits while not inadvertently causing harms, such as stigmatising individuals at higher risk, and introducing inequalities.

Novel technologies such as artificial intelligence and smartphone apps can help to improve the effectiveness and efficiency of cancer screening, but care must be taken to ensure they are a help rather than a hindrance.

2.2. Addressing the data gap in cancer screening

Despite the use of common indicators and standards, it is still challenging to compare screening programmes across the EU due to factors such as differences in invitation strategies, healthcare systems, referral and diagnostic processes, and more. Out of 22 member states with cervical cancer screening programmes, 19 gathered data on the performance of the programme, and 15 collected data about participation rate. A number of member states have no information available about outcomes for individuals who are referred for further investigation following breast screening.

The current state of existing cancer screening programmes in the EU

Compiled data on population-based cancer screening programmes across the EU is available from IARC's CanScreen5 web portal programme,[3] enabling comparisons between member states. The European Cancer Information System (ECIS) portal, which currently gathers data from European cancer registries, will soon be upgraded to include data on screening across the EU.[4] However, the underlying data may not be in a standardised comparable format for direct submission to ECIS, and work will need to be done to ensure that cancer screening data is harmonised across member states.

The EU-topia project,[5] funded by the Horizon 2020 programme, has been systematically evaluating and quantifying the harms and benefits of screening programmes for breast, cervical, and colorectal cancer in all European countries to identify ways to improve health outcomes and increase equity. The project has identified a number of criteria for effective performance and outcome indicators for population-based screening programmes that should be applied across the EU in order to generate comparable data to improve standards and access to screening.

These indicators should:

- be optimised to make screening settings comparable
- be able to include settings with opportunistic ('wild') screening
- be able to capture inequities
- be adapted to be used in settings with risk-stratified screening protocols
- identify barriers to optimal screening
- enable impact assessment including the harms of screening
- be categorised by importance and/or priority
- be able to include new cancer sites under consideration
- accommodate monitoring and evaluation of new screening approaches
- act as red flags for policy and clinical guideline changes

The data gathered about screening programmes from across the EU should be used to support coordinated efforts to roll out equitable screening across member states, along with staff training and continuous monitoring and evaluation for quality assurance.

There is an open question about the potential for developing standardised IT systems for delivering and monitoring screening that could be used across all members states, which would help to address this data challenge.

3 https://canscreen5.iarc.fr/

4 https://ecis.jrc.ec.europa.eu/explorer.php

5 https://eu-topia.org/

2.3. Barriers to success of existing screening programmes

The international EU-topia project consortium identified and assessed barriers hindering the implementation of optimal cancer screening programmes in Europe, primarily focusing on barriers of effectiveness and barriers of equity/access. This work formed the basis of roadmaps for improving screening programmes across individual member states.[6]

The identified barriers fell into three broad categories (Priaulx et al., 2020):

- **health system barriers:** including availability, affordability and acceptability of screening
- **capability barriers:** including knowledge and skills
- **intention barriers:** including public motivation and priorities, communication and social influence, and health beliefs and behaviours

Engagement with screening programme stakeholders across member states identified six general domains of potential barriers to screening (Priaulx et al., 2019):

Category	Attribute
Identification of population at risk	Register used to identify population eligible for screening includes all people who require screening. Register used to identify population eligible for screening is regularly updated with changes of address, death and other criteria.
Generation of knowledge and effectiveness	There is a well-defined national screening organisation responsible for assessing needs, evaluating the evidence and system design. Guidelines for cancer screening are up-to-date and evidence-based.
Maximisation of uptake	The rate of informed participation is monitored and evaluated systematically, including monitoring equity of access to ensure everyone has the same opportunity to attend.
Operation of the programme	A system is in place to assure the quality of screening. Parallel opportunistic screening outside of the population-based screening programme is not allowed to take place. Guidelines are adhered to.
Maximisation of follow-up and treatment	There is a procedure and process for the systematic follow-up of screen-detected lesions. Monitoring of long-term outcomes is established through a link between screening records and cancer registries.

Next, screening programme stakeholders within EU member states were asked to rank 23 predefined barriers within these six domains on a scale of 1 to 5, to see which ones

6 See https://eu-topia.org/downloads/ for country-specific roadmaps.

were having the biggest impact on the successful implementation of breast, bowel and cervical screening in their countries (Barriers to Effective Screening Tool; Priaulx et al., 2018).

The results reveal a number of barriers to effective implementation of organised screening programmes that are shared across all three types of screening (Turnbull et al., 2018a; Turnbull, 2018b).

Overall, the main barriers are mostly either related to maximising uptake of screening (public information and promotion by health professionals) or successful operation (resources, protocols and IT support). The most common specific barriers were:

- beliefs and values that lead to non-participation in screening
- insufficient human, physical or financial resources to operate a screening programme, for example limited capacity organisational or logistical issues
- inadequate adherence by providers to screening guidelines and protocols, including opportunistic screening occurring outside the organised screening programme
- inadequate public promotion of screening programmes, for example primary care doctors not sharing information or promoting screening
- inadequate response to low levels of uptake and patterns of screening participation including inequalities among some subgroups
- issues with establishing protocols processes and legal frameworks including inadequate national governance structures and professionals with relevant knowledge
- inadequate information technology systems and disjointed systems
- for some people, practical issues lead to non-participation in screening such as inconvenient appointments and inadequate health insurance

Barriers also vary by country depending on the availability of resources required to set up, roll out and monitor/evaluate screening programmes on an ongoing basis, particularly in Eastern and Central Europe, as well as governance (regional versus nationally implemented programmes). However, the challenge of a lack of public information and communication about the benefits and risks of screening is widespread across member states. It should be remembered that patients and the public are also important stakeholders in screening programmes and must always be consulted when trying to understand barriers and make improvements.

2.4. Inequalities in cancer screening

There is an ambitious aim of offering 90% of people in eligible groups the opportunity to participate in cancer screening in Europe over the coming years. However, targets for

cervical screening have yet to be met in any EU member states, while targets for breast and colorectal cancer have only been met in a handful of countries. More should also be done to monitor, map and compare inequalities in cancer screening between countries, and to carry out research into interventions aimed at addressing the underlying causes of these inequalities. However, care should be taken to ensure that such comparisons do not end up focusing on relatively small differences within countries at the expense of much larger variations that exist across the EU member states.

Cancer screening is part of the healthcare system and is therefore subject to the same kinds of limitations, inequalities and biases as other healthcare services, which are highly variable between European countries.[7] People with higher socio-economic status are generally more likely to participate in screening for cervical, breast and colorectal cancer (De Prez et al., 2020; Pallesen et al., 2021; Smith et al., 2019). While systematic organised national screening programmes help to reduce the impact of social inequalities in access to screening strongly, they do not completely eradicate them (Gianino et al., 2018).

There is substantial variation in cancer prevention policies and organisation of screening across Europe, which also contributes to variation in the participation rate and the persistence of inequalities. These variations exist at the level of policies about and organisation of screening programmes across member states, differing participations rate within and between countries, and underlying differences in healthcare systems.

However, there is still a significant need for a comprehensive review of the regulatory frameworks, governance, financing (governmental and personal) of cancer screening programmes in order to more fully identify, understand and address these issues, some of which are summarised below.

Cancer screening organisation and service delivery

Attention to the regulatory framework and governance for cancer screening can influence participation, helping to reduce or avoid introducing inequalities. This should involve the development of a long-term strategy for cancer screening which includes clear targets for equity and inclusion, including deciding on the population to be invited.

The geographical distribution of cancer screening centres should also be regulated to avoid regional inequalities, and stakeholders from the public and patient groups should be involved in developing cancer screening that works for all. And there can be issues with the provision of screening in terms of access to services and trained workforce that can result in inequalities of access within and between countries.

7 European Commission: Inequalities in access to healthcare: a study of national policies https://ec.europa.eu/social/main.jsp?catId=738&langId=en&pubId=8152&furtherPubs=yes

A lack of integration between screening programmes and healthcare services, principally a lack of integration within primary care or a clear end-to-end care pathway from screening through to treatment, can also lead to individuals falling through the gaps and experiencing poorer outcomes.

Delivering equity: proportional universalism

Delivering equity in cancer screening does not necessarily mean 'one size fits all' or treating every individual exactly the same. Instead, it should involve making an extra effort to identify and reach individuals who are currently under-served and experiencing barriers to healthcare, to understand their needs and challenges, and develop strategies that enable them to have an equal opportunity to participate in screening.

Another potential source of inequality is the financing of healthcare. While countries may offer cancer screening for free, the subsequent costs of follow-up and treatment are not necessarily covered in countries that do not have a national health service free at the point of use. This may put off people from attending screening, combined with logistical and other financial issues such as being able to take time off work for screening appointments or subsequent follow-up.

Understanding personal choices

While there are systemic and organisational barriers to screening, participation in underserved groups can be improved by:

- engaging healthcare providers that are trusted by these individuals and communities, such as GPs and community health workers
- minimising the costs of participation (for example, transport or taking time off work), and highlighting the benefits and positive aspects of screening using a story-led approach
- understanding social and cultural norms among different groups, and making screening feel like 'this is something that people like you do'
- providing feedback to individuals about how they're taking care of their health

Addressing inequalities in access to and participation in cancer screening will likely require a more tailored approach to reach specific groups. However national screening programmes are already huge complex organisations that contact millions of people every year. Some interventions aimed at reducing inequalities, such as phone calls in an individual's native language, may not be feasible or affordable at a national level, but there is an opportunity to think smarter about how outreach and follow-ups for screening invitations could be delivered through local GPs and communities, building coalitions across the health service to reach out with messaging about cancer screening.

More accessible methods of screening can also help to increase uptake among under-served groups, such as at-home FIT testing for colorectal cancer and self-sampling for HPV testing in cervical cancer screening. More carefully tailoring the language and channels used in screening invitations and other informational materials according to individual levels of understanding might also help to address inequalities and improve uptake, as well as the use of channels such as social media (Plackett et al., 2020).

3. Improving colorectal cancer screening

Colorectal cancer is the third most common cancer in men and the second most common in women in Europe. More than 540 000 new cases are diagnosed every year and 259 000 people die from the disease, representing 12.9% of all cancer cases and 12.6% of all cancer deaths across Europe and costing around €19 billion every year.[8]

The stage of diagnosis has a significant impact on outcome, with 90% of individuals diagnosed at the earliest stage (stage 1) surviving for at least 5 years compared with 10% survival for those diagnosed at the latest stage (stage 4). The costs of treatment for early-stage cancer are also ten-fold lower than for cancers diagnosed at stage 4. However, without screening, only around 13% of cases are diagnosed at the earliest stage, while almost a quarter are diagnosed at stage 4.7 Improving the effectiveness and cost-effectiveness of colorectal cancer screening, as well as increasing awareness and participation, therefore represents a significant opportunity to save lives across Europe.

3.1. Colorectal cancer screening methods

Colorectal cancer screening usually either involves analysing stool samples for traces of blood, or colonoscopy/sigmoidoscopy to look for the presence of adenomas and/or malignant tumours. Other techniques, such as CT colonography, 'Pillcams' (tiny swallowed cameras), stool testing for DNA or methylation markers are being developed, as well as 'liquid biopsy' blood tests (see the report for workshop 3), but are less well established.

There are two different types of test for detecting blood in stool: the older guaiac faecal occult blood test (gFOBT) and the more recent faecal immunochemical test for haemoglobin (FIT). Both tests involve participants taking stool samples at home, which are then sent to a laboratory for analysis. Individuals with a positive result for blood in their stool will be referred for further investigation through colonoscopy.

It should be noted that there are also non-cancer conditions that can result in blood in the stool, including haemorrhoids and colitis. Furthermore, gFOBT detects the presence of any kind of blood, including animal blood eaten in food, and is therefore more susceptible to false positives than FIT, which only detects human haemoglobin. There are several different brands of FIT testing available with varying performance (Gies et al.,

8 https://digestivecancers.eu/wp-content/uploads/2021/01/DICE_Roadmap_Colorectal_Cancer_Europe_FINAL.pdf

2018), which should be considered before selection for a national screening programme (Allison & Fraser, 2018).

FIT is more acceptable than gFOBT to participants, because it only requires one stool sample rather than the three needed for gFOBT. FIT is also more accurate than gFOBT, although this varies depending on the sex and age of participants and the threshold value used to refer individuals for further investigation, discussed in more detail in section 3.2 (Selby et al., 2019).

The majority of EU member states have rolled out population screening for colorectal cancer using gFOBT or FIT.[9] Furthermore, many countries that originally started with gFOBT are now switching or have switched to FIT (Cardoso et al., 2021). While stool testing itself carries virtually no risk, there can be harms caused by follow-up colonoscopy and psychological harms from false positives.

While a single colonoscopy-based screening test has higher sensitivity and specificity than a single FIT or gFOBT test, it is much less acceptable to participants than at-home stool sampling and requires costly equipment and highly trained staff to deliver. Furthermore, stool testing is easily regularly repeated, and modelling studies have shown that repeated FIT is almost as effective as colonoscopy (Buskermolen et al., 2019). This makes colonoscopy less suitable, effective and cost-effective for population-based screening across EU member states than stool testing, and it will not be considered further in this report.

Case study: Moving from gFOBT to FIT in Finland

Finland first began a randomised trial of gFOBT screening for colorectal cancer in 2004, inviting 60–69-year-olds in volunteering municipalities to be screened every two years or not. By 2014, only 40% of the target population had been involved in the study, partly due to a lack of financial incentives for municipalities to take part in the study. However, of those who were invited for screening, 62% of men and 76% of women took part (69% overall). Although being a relatively short FU period, after a median 4.5 years of follow-up there was no evidence of effectiveness but an indication for a difference by sex (Pitkäniemi et al., 2015). The programme was put on hold in 2016.

In the light of promising data about FIT screening coming from other countries, Finland started a pilot programme by inviting 60–66-year -old men and women for biennial FIT testing and gradually extending to a wider age group. Due to the known sex differences in test performance (see section 3.1), the FIT cut-offs were set

9 https://ueg.eu/files/779/67d96d458abdef21792e6d8e590244e7.pdf

at 25 µg/g for women and 70 µg/g for men, to improve the sensitivity of the test in females and to minimize the gap in effectiveness by sex.

First round participation was 79% (75% in men, 83% in women), with 90% attendance for follow-up colonoscopy. However, positivity rates were still lower than expected in both sexes, suggesting that the threshold cut-off haemoglobin values were too high. As a result, thresholds were decreased to 50 µg/g for men and 15 µg/g in 2020. Other indicators were comparable with other screening programmes in EU member states.

The Finnish National Screening Board was established in 2018 to support governance, steering and policymaking around cancer screening. Based on the results of the pilot studies and cost-effectiveness modelling, in 2019 the Board recommended the roll-out of a national FIT screening programme in Finland with the same legal basis as the existing breast and cervical screening programmes. Gradual roll-out will start in 2022, with defined target ages and screening intervals but without specified haemoglobin thresholds, to allow for further evidence-based changes in the future.

3.2. Personalised strategies for colorectal cancer screening

Age and sex

The performance of gFOBT and FIT colorectal cancer screening tests differs by birth sex. Positivity rates are generally higher in men than in women, and the likelihood of a positive test result indicating cancer is also higher in men than in women (Brenner et al., 2010; de Wijkerslooth et al., 2012; Koskenvuo et al., 2019; Ribbing Wilén et al., 2019; Selby et al., 2019). Risk of having colorectal cancer also increases with age (Brenner et al., 2014), as does the chance of having cancer that is detected through a positive FIT test (de Wijkerslooth et al., 2012).

Because FIT testing is quantitative, measuring absolute amount of haemoglobin present per gram of stool in µg/g, changing the threshold value at which a sample is declared positive has a significant impact on test sensitivity. A low threshold (e.g. 5 µg/g) will result in a high number of positive tests requiring follow-up, as well as a higher number of false positives, while a high cut-off (e.g. 50 µg/g) will result in fewer positive tests and referrals but might mean that people who actually have cancer are missed (lower sensitivity).

Using sex- and age-specific cut-off values for FIT testing can adjust test sensitivity for different groups and help to narrow the gap in test performance by sex and age. Setting threshold values should also be considered in the context of the overall health service, particularly the capacity for delivering colonoscopy services to follow up positive referrals.

The use of using sex-specific FIT cut-offs in colorectal screening has been investigated in a number of countries including Sweden, Finland and the Netherlands (Blom et al., 2019; Kortlever et al., 2021; Sarkeala et al., 2021).

However, although using different thresholds can help to equalise test sensitivity by sex and age, it can exacerbate the difference in positive predictive value of the test, due to the fact that men with a positive test are more likely to have cancer than women testing positive. A lower threshold for women could also therefore result in a higher number of false positives, increasing potential physical and psychological harms.

Prior FIT test results

Another opportunity for delivering more personalised strategies and improving the effectiveness of colorectal cancer screening is by taking an individual's prior FIT test results into account when considering screening interval and age of stopping screening. Studies from Taiwan and Scotland show that having a higher level of haemoglobin in a first FIT screening test is associated with an increased risk of being diagnosed with colorectal cancer later on (Chen et al., 2011; Digby et al., 2017).

Further studies in the Netherlands, Italy and Spain show that having low faecal haemoglobin level on consecutive tests is associated with a much lower risk of colorectal cancer than individuals having a higher haemoglobin level upon repeated testing (Buron et al., 2019; Grobbee et al., 2017; Senore et al., 2020). Modelling analysis shows that taking age, sex and the results of two consecutive FIT tests into account is a highly predictive and clinically superior strategy compared with age and sex or age, sex and a single test result (Meester, 2021).

Prior faecal haemoglobin concentration is a promising means for introducing risk stratified colorectal cancer screening with good predictive performance that is anticipated to get better with additional screening rounds. Furthermore, there is no need for additional data collection as FIT scores are recorded with every test, making this a relatively cost effective and simple intervention to apply to improve the effectiveness of screening.

It could also be beneficial to use different FIT cut-offs for people who have missed previous screening opportunities, although research needs to be done to discover whether this improves effectiveness and which threshold(s) might be appropriate. Furthermore, given the common occurrence of other conditions that can cause colorectal bleeding, there is the potential to increase the specificity and sensitivity of colorectal cancer screening by combining or replacing FIT-based screening with additional tests such as DNA testing of stool samples to reveal genetic mutations and/or alterations in DNA methylation (reviewed in Carethers, 2020; Raut et al., 2020).

In summary, while most FIT-based programmes currently use a single threshold value for all participants, it is clear that one size may not fit all. However, more research is needed to establish exactly which FIT thresholds are appropriate, the consequence of adopting such an approach, and whether it is also acceptable to participants.

3.3. Improving access to colorectal cancer screening

There is generally a lack of awareness about colorectal cancer symptoms and screening across Europe.[10] This suggests that much more could be done in terms of public information and awareness campaigns to explain the purpose of screening, as well as the risks and benefits. Such campaigns and materials should be developed together with patients and the public to ensure that they hit the mark and are effective.

Further best practices to improve access to screening include using FIT testing rather than colonoscopy, sending an advance notification followed by sending a FIT test kit to individuals together with the invitation to screening rather than sending them separately or having to go and collect a test, along with follow-up reminders. Involving GPs in inviting individuals and sending reminders can also increase participation in screening.[11]

The COVID-19 pandemic has had a significant impact on colorectal cancer screening. However, countries with centralised screening registries and comprehensive IT systems for monitoring screening were able to recommence screening more quickly after the first wave, highlighting the importance of robust national infrastructure for delivering robust programmes that can cope with unexpected disruption. Learnings should be shared between EU member states to help those which have performed less well during the pandemic to be better prepared for the future.

Digestive Cancers Europe, an EU-wide umbrella organisation of national organisations representing patients with colorectal and other digestive cancers, recently issued a joint statement[12] recommending that individual member states should develop national implementation plans to achieve the committed goals of 65% participation rates among citizens aged 50–74 in colorectal cancer screening, investing in infrastructure, technology and human resources that enable successful roll-out and ongoing monitoring of the programme. At an EU institutional level, the statement recommends that institutions should ensure that all member states apply best practices in colorectal screening, and that all EU colorectal cancer screening agencies join a common platform to exchange best practices.

10 https://digestivecancers.eu/publication/understanding-the-experience-and-needs-of-patients-with-metastatic-colorectal-cancer-results-of-a-european-patient-survey/

11 https://digestivecancers.eu/wp-content/uploads/2021/03/ScreeningBestPractice_NE_IrisLansdorp.pdf

12 https://ec.europa.eu/health/sites/default/files/policies/docs/2021_js_dice_en.pdf

3.4. Conclusion: colorectal cancer screening

FIT is the optimum triage test for referring individuals on for follow-up colonoscopy, based on accuracy and public preferences. The uptake of and compliance of colorectal cancer screening needs to be improved and can be promoted via awareness campaigns and making at-home stool testing highly convenient.

While most FIT-based programmes currently use a single threshold value for all participants, it is clear that one size does not fit all. More research is needed to establish exactly which FIT thresholds are appropriate based on factors including age, sex, testing interval and outcome of previous tests. This research can be conducted in parallel to the implementation of national programmes.

4. Improving breast cancer screening

Breast cancer is the most common cancer in women in Europe, accounting for 355 500 cases and causing more than 91 000 deaths every year across the 27 EU member states. Around one in 11 women in the EU will develop breast cancer before the age of 74.[13]

The earlier breast cancer is detected, the greater the chances of survival. Almost all women diagnosed with cancer at the earliest stage (stage 1) will survive for five years or more, with 90% survival for those diagnosed at stage 2. However, five-year survival drops to 72% for women diagnosed at stage 3, and just 26% for those with stage 4 disease.[14]

Breast screening by mammography has been in use since the 1960s, originally starting with x-ray films produced with general purpose x-ray devices, then evolving to dedicated film-screen equipment, and eventually moving to digital imaging in the 2000s. Population-based mammography screening can detect cancers at an earlier stage, often before they can be seen or felt, when treatment is more likely to be successful.

As with any cancer screening programme, there is a balance of benefits and harms to be struck when considering organised population-level breast screening. While screening does save lives from breast cancer, there is a small risk of overdiagnosis, with women ending up being treated for tumours that might never have caused them a problem in their lifetime. There is also the anxiety of being recalled if an abnormality is found through screening.

The greatest potential to improve the balance of benefits and harms is to improve the quality of screening, reduce the avoidable recall rate, and improve communication and prompt evaluation among women recalled, together with the development of more effective screening tools and technologies. By focusing on women most at risk, the ratio of recalls to cancers detected improves, but among women screened less frequently, the likelihood of being diagnosed with an advanced cancer increases. It should be noted that risk calculations are based on probabilities, not certainties. It is impossible to say on an individual basis who will and who won't develop breast cancer, and even lower risk women have a significant lifetime risk of breast cancer.

13 https://www.europadonna.org/breast-cancer-facs/

14 https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Three

This expert workshop considered the age at which screening should start and appropriate interval between screens, the use of new technologies such as digital breast tomosynthesis, and addressing the challenge of screening in women with dense breasts.

4.1. Breast screening under the age of 50

The risk of breast cancer increases with age. US SEER data presented at the workshop by Robert Smith shows that around 45 per 100 000 women at age 35, 79 per 100 000 women at age 39, going to 106 per 100 000 at age 40, and up to 165 per 100 000 by the age of 45 will be diagnosed with breast cancer (National Cancer Institute, 2015). Looking more broadly, women aged 45-49 only have a slightly lower risk than those aged 50-54, accounting for 10% and 12% of all breast cancer deaths, respectively. However, the risk is around a third lower in those aged 40 to 44, accounting for just 6% of all invasive breast cancer deaths in the US (Murphy et al., 2015).

The benefits of breast screening by mammography have been demonstrated in women over the age of 50, but there is ongoing debate about the benefits of extending breast screening to younger age groups, particularly women aged 40 to 49. It is also more challenging to detect breast cancers in younger and premenopausal women due to the higher breast density in these groups, which makes it more difficult to spot potential tumours on mammograms.

Current European Commission Initiative on Breast Cancer guidelines recommend organised mammography screening for different ages groups as follows:[15]

- women aged 40-44: no screening
- women aged 45-49: screening every 2 or 3 years
- women aged 50-69: screening every 2 years
- women aged 70-74: screening every 3 years

The Swedish 2 county study showed that the number of interval cancers (cancers diagnosed in between screening invitations) is significantly higher in women aged 40 to 49 compared with those over the age of 50, suggesting that these tumours maybe more aggressive and fast growing in younger women (Tabár et al., 1987). Further analysis of the Swedish data concluded that early detection of breast cancer is likely to be more difficult in younger women, especially with a two-year screening interval (Tabár et al., 1997).

Meta-analysis of randomised controlled trials of breast screening in women aged 39–49 commonly showed a 15% reduction in breast cancer mortality associated with an invitation to screening in this age group. However, there is a wide range of outcomes in

15 https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies

these trials, which ranged from a 30% mortality reduction to 47% excess mortality (Nelson et al., 2009). More favourable results have been seen in recent studies that screened younger women at more frequent intervals, with the Gothenburg trial showing 30% fewer breast cancer deaths in women aged 39–59 and 40% fewer deaths in women aged 39–49, including 39% fewer deaths due to grade 3 cancers, after 25 years of follow-up (Bjurstam et al., 2016).

Importantly, trials that achieved a reduction in advanced stage disease of 20% or more observed an average breast cancer mortality reduction of 28%, while trials that achieved a reduction in advanced stage disease of less than 10% observed no reduction in breast cancer mortality (Tabár et al., 2015).

In 2015, the International Agency for Research on Cancer updated their breast cancer screening handbook and concluded that that there was sufficient evidence that women aged 50–69 years who attend mammography screening have an average of 40% reduced risk of mortality from breast cancer. By contrast, IARC concluded that the evidence supporting the value of mammography screening in women aged 40–49 was limited, although they noted mammography screening in this age group has been associated with about a 20% reduction in the risk of dying from breast cancer, and that the benefits may be greater in women aged 45 to 49 years compared with those aged 40–44.[16] The Swedish natural experiment (see case study) is one of the most recent sources of evidence for younger women showing benefits.

Miglioretti et al. (2015) showed that women who were premenopausal were more likely to be diagnosed with a breast cancer with a less favourable outcome if they underwent biennial versus annual mammograms, suggesting that cancers occurring in younger, premenopausal women are more aggressive.

In conclusion, the risk of being diagnosed with breast cancer aged 40–44 is low but increases with every passing year. During the 10-year period between the age of 45 and 54, the risk also increases but is broadly similar throughout this time. Therefore, the logic for starting screening at the age of 50 also extends to the age of 45. Annual screening is also more effective for younger and premenopausal women in order to detect more dangerous fast-growing tumours. Women under the age of 45 may benefit from more personalised screening strategies based on individual risk including genetic information and family history. It should also be noted that women diagnosed with an early breast cancer in their forties benefit from considerable life years gained from avoiding a premature death (Oeffinger et al., 2015).

16 https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Breast-Cancer-Screening-2016

Case study: The impact of breast screening in younger women in Sweden

A natural experiment into the impact of screening for breast cancer at different ages has been carried out in Sweden where half of the counties began screening at the age of 50, while the rest started screening at the age of 40, with a screening interval of 18 months for women under 55 and 24 months for those older. They observed a 26% reduction in mortality in counties that offered screening to women in their 40s compared to those who did not, with women aged 40–44 having an 18% reduction in breast cancer mortality and those aged 45–49 having a 32% reduction (Hellquist et al., 2011). Similarly the pan-Canadian study of mammography screening showed a 44% reduction in breast cancer deaths in women aged 40 to 49 compared with 40% fewer deaths in women aged 50–59 (Coldman et al., 2014).

4.2. Breast screening with digital breast tomosynthesis (DBT)

Most breast screening programmes now use two view digital mammography, where two-dimensional x-ray images are taken from two different angles. In digital breast tomosynthesis, the x-ray tube moves through an angle creating multiple image slices through the breast that can be used to create a more three-dimensional view of the breast tissue, although it is not a fully three-dimensional reconstruction of the entire breast.

DBT was initially used in addition to standard digital mammography images. However, this resulted in a higher radiation dose, increasing the risk of harm. This then progressed to using DBT for generating one view of the breast, and standard digital mammography for the second view. Recent advances in DBT technology mean that it is now possible to generate synthetic 2-D mammography images from DBT data in order to compare with previous mammograms and detect calcifications in the breast. This has an advantage over the combined use of DBT and standard mammography by not requiring additional radiation dose or time spent on positioning the machinery for the second view.

Recent studies have shown that these synthetic two-dimensional images are as good as conventional mammograms for the detection of breast cancer (Caumo et al., 2018; Cohen et al., 2018; Skaane et al., 2014). There have been a number of unpaired, paired, retrospective and prospective studies comparing DBT with standard mammography, although varying methodologies makes it difficult to compare between them. To date, there have been two reported randomised controlled trials of the use of DBT in breast cancer screening (Hofvind et al., 2019; Pattacini et al., 2018), with several more studies ongoing.

A 2018 meta-analysis of studies comparing DBT and standard 2-D digital mammography showed that, in Europe, the use of DBT increased the recall rate (the number of women referred for further investigation after screening). However, studies in the US, where more women tend to be referred following screening, showed that DBT could significantly reduce the recall rate. Furthermore, the use of DBT detected more cancers than standard mammography, and the more detailed data available from DBT is more appealing to radiologists than standard mammography (Marinovich et al., 2018).

One measure of the effectiveness of a screening programme is the interval cancer rate — the number of cancers that are diagnosed between screening invitations (Zackrisson, 2019). A high number of interval cancers suggests that the screening programme is failing to pick up cancers at an early stage, while a low interval cancer rate is indicative of a more effective programme. To date, the trials comparing DBT with mammography have not been sufficiently powered to show a difference in interval cancer rate.

As reported by Professor Solveig Hofvind at the workshop, it is estimated that a randomised controlled trial would require at least 100 000 participants in order to show a significant difference in interval cancer rate. However, recent meta-analyses of data from smaller trials showed that there was no difference in the interval cancer rate between DBT and mammography (Houssami, Hofvind, et al., 2021; Houssami, Zackrisson, et al., 2021). A small study in Sweden did suggest a significant decrease in interval cancer rate (Johnson et al., 2021), while another small Norwegian found no significant difference (Hofvind et al., 2021).

The European Commission Initiative on Breast Cancer currently recommends screening with either standard digital mammography or with DBT but not both, although this is a conditional recommendation with low certainty of evidence.[17],[18] The most recent systematic review and meta-analysis of the data comparing conventional digital mammography and synthesised mammograms/DBT concludes that DBT together with synthetic mammography has a similar detection rate for breast cancer as standard digital mammography and could help to reduce overall radiation dose from breast screening, although there was no significant improvement in interval cancer rate (Zeng et al., 2021).

There are a few further issues to take into account when considering switching to DBT from conventional digital mammography:

- There is variability between DBT machines and manufacturers, highlighting a need to develop standards for technology, image quality and data transfer.
- There is a higher data storage requirement for DBT compared with standard digital mammography, which will bring additional infrastructure needs and costs.

17 https://healthcare-quality.jrc.ec.europa.eu/

18 https://healthcare-quality.jrc.ec.europa.eu/sites/default/files/Guidelines/EtDs/Updated/2020/ECIBC_GLs_EtD_DBT_vs_DM.pdf

- Further data needs to be gathered on the cost-effectiveness of DBT compared with standard digital mammography, especially over multiple screening rounds.
- More research needs to be done into the histopathology of tumours detected with DBT versus digital mammography, to ensure that it is not detecting small slow-growing tumours that are unlikely to cause a problem (overdiagnosis). One study underway to explore this question is the US TMIST study.[19]
- It will be important to be able to distinguish tests performed with DBT and standard digital mammography in order to effectively monitor and evaluate screening programmes as methods switch.
- Radiologists will require additional training in the interpretation of DBT images, and they can be slower to process at least at first, which could cause further backlogs in already overloaded screening systems.
- Artificial intelligence tools for scoring mammograms could help to support breast screening, but more research is needed to see how effective they are when applied to DBT.

On balance, the current evidence slightly favours the use of DBT in breast screening over standard digital mammography. However, further evidence on efficacy and cost-effectiveness is continuing to emerge from ongoing trials, which will help to shape future recommendations on the use of DBT in population-level breast screening programmes in the EU.

4.3. Improving screening for women with high breast density

The composition of the breast differs between women with varying proportions of fibrous, glandular and fatty tissues, which affects the transmission of x-rays through the breast. Women with a lower proportion of fat and more fibrous/glandular tissue in their breasts are said to have 'dense' breasts. Not only is this known to be a risk factor for breast cancer, this fibrous/glandular tissue shows up as white masses in standard mammograms, making it difficult to distinguish small tumours. As a result, screening by mammography is less sensitive in women with denser breasts. For example, the Dutch breast screening programme has 61% sensitivity in women with the densest breasts compared with 86% for women with least dense (Wanders et al., 2017).

Supplemental MRI screening has been proposed as a way to improve the sensitivity of breast screening in women with dense breasts. To date, there have been three large clinical trials investigating the value of supplemental MRI screening in women with dense breasts at average risk of breast cancer. The addition of MRI screening increased the

19 https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/tmist

number of cancers detected compared with mammography alone, and supplemental MRI screening also led to a significant reduction in interval cancers, therefore detecting more aggressive cancers at an earlier stage (Bakker et al., 2019; Comstock et al., 2020; Kuhl et al., 2017).

In the DENSE trial in the Netherlands, women who were identified as having extremely dense breasts upon their initial screening mammogram were invited to have an additional MRI scan following a negative mammography result, of which 59% participated. Overall, the interval cancer rate was 0.83/1000 women in those receiving an MRI scan, compare with 4.88/1000 in those who declined (for comparison, the interval cancer rate in women who did not have dense breasts and underwent standard mammography screening was 4.98/1000). Following a second round of screening, two studies also showed a reduction in breast cancer incidence as well as false positives (Kuhl et al., 2017; Veenhuizen et al., 2021), meaning that the screening is effective at picking up early-stage cancers also in second rounds.

More research could be done to investigate the reasons for why some women do not respond to the offer of MRI screening and how they could be addressed, in order to ensure that women are not inadvertently missing out on the benefits to be gained from supplemental MRI screening (Geuzinge et al., 2021).

Microsimulation modelling of the harms and benefits of biennial mammography combined with MRI imaging for women with the densest breasts shows that there would be nearly 30 additional cancers detected for every 1000 women screened compared with biennial mammography alone, with 330 false positives per 1000 women undergoing supplemental MRI compared with 141 with standard mammography. There would also be 19 fewer BC deaths per 1000 women compared with an unscreened population – 8 more than with mammography alone. However, there would be an additional 5 over diagnosed cases per 1000 women undergoing mammography plus MRI compared with standard mammography alone (Geuzinge et al., 2021).

MRI screening is more expensive than standard digital mammograms and cannot be delivered in the kind of mobile scanning units that are used to deliver standard mammography screening. However, switching to 4-yearly MRI screening alone for women with the most dense breasts had the same benefits in terms of cancers detected and risk of overdiagnosis than standard mammography plus MRI, but fewer false positives and was also cost-effective given the relatively small size of the population at risk (Geuzinge et al., 2021).

Additional innovations such as abbreviated MRI, which is quicker and less costly than standard breast MRI, as well as the use of machine learning and artificial intelligence algorithms for automated initial triaging of MRI images could help to improve cost-effectiveness and reduce workload (den Dekker et al., 2021; Verburg et al., 2021). MRI

scans may also provide additional information about the biological behaviour and likely prognosis of any tumours detected.

Out of a range of novel alternative and supplemental breast screening modalities, including DBT, ultrasound, molecular breast imaging and contrast-enhanced mammography, only MRI has so far demonstrated a statistically significant reduction in the interval cancer rate as well the incidence of late-stage disease (Berg et al., 2021).

It should be noted that this workshop only considered breast screening in the context of the general population at average risk. The experts did not consider screening strategies for women with an inherited predisposition to breast cancer, such as those with germline mutations in BRCA1/2 (see Dullens et al., 2020 for an overview of the current guidelines in various countries).

4.4. Conclusion: breast cancer screening

Breast cancer can occur in younger women than the age at which screening currently starts, and often grows more rapidly. There is now compelling new evidence that reducing the age of the first screen to 47 or 44 will maintain an acceptable balance of harms and benefits for women offered breast mammography screening.

Of the various novel alternative and supplemental breast screening modalities, including DBT, ultrasound, molecular breast imaging and contrast-enhanced mammography, only MRI has so far demonstrated a reduction in the interval cancer rate as well the incidence of late-stage disease. MRI should be considered for premenopausal women with dense breasts.

5. Improving cervical cancer screening

Cancer of the cervix uteri (the neck of the womb) is the ninth most common in women in Europe, with nearly 60 000 women diagnosed and more than 25 000 dying from the disease every year.[20] Virtually all cervical cancers are caused by infection with the human papillomavirus (HPV) (Walboomers et al., 1999), with the majority of cancers being caused by HPV types 16 and 18. However, given that an estimated 80% of the sexually active population will be infected with HPV by the age of 45, and given that the cumulative incidence of developing cervical cancer varies between 0.5 and 2% (Arbyn, Weiderpass, et al., 2020), there must be other factors that determine whether a cancer will develop in an HPV infected woman (Chesson et al., 2014).

Cervical screening (smear test/cytology) involves scraping of cells from the cervix and analysing them under the microscope for presence of abnormal cells. Screening therefore prevents cervical cancer by picking up pre-cancerous lesions and treating them before they develop into an invasive cancer. While significant inequalities exist in access to cervical screening and HPV vaccination across Europe, a systematic review of ten observational studies of organised cervical screening programmes in Northern and Western Europe showed a 41% to 92% reduction in mortality from cervical cancer due to screening, with a lack of data from Eastern and Southern member states (Jansen et al., 2020).

5.1. HPV testing

The first commercial HPV test was approved by the US FDA in 1988, and the technology has been continued to develop over the past two decades. Results from the joint European cohort study of more than 24 000 women showed that having a negative HPV test is protective against developing cervical carcinoma in situ (early-stage cancer or CIN3) for 6 years, compared to 3 years for a negative cytology test. Furthermore, there is no additional benefit in continuing regular cytology testing for women testing negative for HPV (Arbyn et al., 2012; Dillner et al., 2008)

Follow-up of four major European randomised controlled trials of HPV testing demonstrated that HPV-based screening provides 60–70% greater protection against invasive cervical cancer compared with cytology testing, and also suggested that screening intervals could be lengthened from three years to at least five years if using

20 https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf

HPV testing rather than cytology (Ronco et al., 2014). Furthermore, 100% of women with persistent HPV infection in a Swedish randomised controlled trial of HPV screening went on to cervical precancer. However, women who cleared the infection and became HPV negative had no incidence of precancer (Elfgren et al., 2017).

HPV testing offers a more effective and long-lasting protection against cervical cancer than cytology testing, with fewer screening visits required. Sample testing can be carried out using automated equipment rather than requiring microscopic analysis, and at a lower cost than conventional cervical smear tests. Furthermore, self-sampling for HPV testing, either at home or in a healthcare facility, is an efficient and cost-effective way of gathering samples and can improve access for under screened populations. Widespread adoption of HPV testing across Europe could therefore result in a (somewhat) faster elimination of cervical cancer from the population.

Incorporating HPV typing as part of testing also offers the opportunity for risk-stratification, by identifying women with the most dangerous strains of the virus that are responsible for the majority of cases (HPV16/18). However, it should be noted that evidence from Sweden suggests that continuing cervical screening in populations with a high level of HPV vaccination still picks up cervical abnormalities, but there are associated with strains of the virus that are extremely unlikely to cause cancer. Continuing the same protocol for population-level cervical screening in highly vaccinated populations should therefore be avoided as it is most likely to be overdiagnosis (Kann et al., 2020).

Cervical screening with HPV testing is the recommended cervical screening strategy, being recommended by the WHO in 2014 and by the European Union in 2015. Which guideline However, it is not in use in all EU member states at the current time, representing a missed opportunity to save lives from cervical cancer.

Case study: cervical screening in Sweden

In 2015, the Swedish government screening agency recommended the use of HPV testing as the primary cervical cancer screening method. However, about half the country continued using cytology testing. Following this switch, a concerning increase of more than 30% in the incidence of cervical cancers in women receiving normal cytology results was noticed. To understand the cause of this rise, researchers retrieved all screening histories and archived smear tests from the entire country dating back ten years for review.

The researchers discovered that there was a steady and significant increase in the proportion of smears that had been reported as normal but actually contained pre-cancerous cells (false negatives) of around 2% every year, suggesting that there was a significant issue with the quality assurance of cytology testing in the

country (Edvardsson et al., 2021). This kind of performance drift could be avoided by switching to HPV testing, because cytology testing relies on subjective evaluation by a trained pathologist as opposed to automated viral detection used for HPV testing.

5.2. Self-sampling for HPV testing

There are many reasons why women are unable or unwilling to attend cytology-based cervical screening, ranging from inconvenience and embarrassment to cultural beliefs, disability, previous trauma or experiencing severe discomfort or pain from the procedure (for example, see Marlow et al., 2015). However, HPV testing can be carried out using a vaginal swab that can be easily collected by a woman herself in the comfort of her own home or in private in a healthcare setting. This kind of self-sampling has significant potential to expand access to HPV testing in women who are currently under-screened and offers a significant opportunity to reduce the incidence of cervical cancer in these populations.

Eleven commercially-available HPV tests have now been validated as being suitable for use in primary cervical screening on cervical specimens (Arbyn et al., 2021). A number of studies have compared the accuracy of self-sampling for HPV testing with clinician-collected samples. Signal-amplification based HPV tests have worse performance on self-collected samples compared with clinician-collected samples, while target-amplification (clinically validated PCR) tests have similar sensitivity and a slightly lower specificity in both types of sample (Arbyn et al., 2014; Arbyn, Smith, et al., 2018; Arbyn & Castle, 2015). Work is also underway to validate HPV testing in vaginal self-samples and urine (Arbyn, Peeters, et al., 2018). The results of this work should contribute to the development of consistent protocols and lists of validated self-collection devices and tests for use in national cervical screening programmes.

Offering self-sampling to under-screened populations may be more effective than invitation letters to go for clinical sample collection. There are a number of different strategies that can be employed to offer self-sampling HPV testing kits to women. For example, they can be sent in the mail to all screening invitees, alternatively women can opt in to receive a kit, they can be offered directly to the woman by a health professional. A meta-analysis of these different strategies showed that mail-to-all strategies were effective at encouraging participation (25% participation) while opt-in strategies had 18% participation. However, much higher levels of participation (95%) were gained through direct delivery of a self-sampling devices to women (door-to-door kit or during a visit at a clinic), although these latter trials were conducted in Latin America and Africa and may therefore not be applicable to European populations (Arbyn, Smith, et al., 2018). Nevertheless, a small Belgian trial confirmed high response rates (78%) when GPs offer a

self-sampling kit to eligible women coming for an unrelated consultation (Peeters et al., 2020)

In general, sending self-samplers to women in the mail is more effective than routine invitations to screening, and may encourage uptake of HPV screening in currently under-screened populations. Self-sampling is generally well accepted by women, although they tend to prefer urine collection methods rather than vaginal self-sampling (De Pauw et al., 2021). Self-sampling is also a safe procedure during situations such as the COVID-19 pandemic when conventional screening appointments may not be possible (Arbyn, Bruni, et al., 2020).

Generally, the quality of samples from self-testing is high, with a low proportion of failed tests or insufficient material for testing. However, there is a need to standardise procedures for handling samples and standardised protocols for how best to handle and analyse samples from different self-sampling devices. Self-sampling could also be considered as a first-line procedure for contacting women for HPV testing in the general population after suitable pilot testing prior to national roll-out.

However, the response to self-screening is highly variable and may depend on the local setting. Pilot studies are needed to assess local responses before general roll-out of a strategy for self-sampling. Furthermore, self-sampling should only be done in an organised setting with ongoing monitoring and quality control, and where follow-up of women testing positive for HPV through self-sampling can be assured. On average, only about one fifth of self-sampling kits are actually used when posted to women's homes, resulting in considerable waste plastic in the environment, which may limit the cost-effectiveness of the strategy. The experience of Professor Peter Sasieni in the UK suggests that offering self-sampling kits through GPs can result in very high uptake, while sending study kits in the post was less effective, confirming the findings of the Belgian GP trial.

5.3. The impact of HPV vaccination

Vaccines against the most dangerous strains of HPV have been available since the mid-2000s. There are three HPV vaccines currently approved for use in Europe, currently given as two or three doses, with 6–12 months between the first and last doses:

- 9-valent HPV vaccine (Gardasil® 9, 9vHPV), protective against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
- quadrivalent HPV vaccine (Gardasil®, 4vHPV, protective against HPV types 6, 11, 16 and 18
- bivalent HPV vaccine (Cervarix®, 2vHPV), protective against HPV 16 and 18

HPV vaccination is currently offered in almost all EU member states, covering a range of ages, vaccine types and catch-up programmes (summarised in Nguyen-Huu et al., 2020). The sole exception is Romania, where the vaccination programme discontinued due to poor uptake (Penţa & Băban, 2014).

HPV vaccines are highly effective, providing more than 97% protection against type-specific infection in women who are not currently infected with HPV. No new variants of HPV have been discovered over the past 30 year and there is no evidence to date of waning vaccination effectiveness, suggesting that protection is long-lived.

HPV vaccination made a significant impact on the prevalence of HPV infections in vaccinated groups, leading to a steep decline in the prevalence of HPV infections in vaccinated cohorts (Mesher et al., 2018), along with a similar fall in the incidence of precancerous CIN2+ cells in the cervix (Palmer et al., 2019).

Results from a linkage study joining HPV vaccination data with the cancer registry in Sweden show that protection against cervical cancer is seen rapidly after HPV vaccination with girls who are vaccinated below 17 years of age having virtually zero risk of cervical cancer over the coming decade. However women who were vaccinated between the ages of 17 and 30 still had some risk of cervical cancer, which is likely due to the fact that they were already infected with HPV before their vaccination (Lei et al., 2020).

Should vaccinated populations be screened differently for cervical cancer?

Given the tight link between HPV and cervical cancer and the effectiveness of vaccines in preventing HPV infection, there is an open question about what kind of cervical screening is appropriate for populations with widespread vaccination and vaccinated individuals.

Modelling by Landy and colleagues show that in the absence of vaccination, 3-5 yearly cytology screening would prevent around 64% of cervical cancers, and that 69% of cancers would be prevented with 6–10-yearly HPV testing. However, vaccination alone would prevent around 70% of cervical cancers. Vaccination plus two rounds of HPV screening at age 30 and 45 would protect against 86% of cervical cancers, while vaccination and three rounds of screening at 30, 40 and 55 protected against 88% of cancers (Landy et al., 2018).

A previous analysis showed that four lifetime screens could be optimal and cost-effective for cohorts offered the Gardasil 9 vaccine in developed countries (Simms et al., 2016). However, this strategy does not take into account the development of herd immunity, which might make it safer to screen unvaccinated women less often, or the needs of adult women immigrating into Europe who have not been vaccinated. The prevalence of HPV16/18 should also be monitored on an ongoing basis to check whether the effectiveness of the vaccine is waning or new variants of the virus are emerging.

A comparison of birth cohorts in England demonstrated a major impact of the national HPV vaccination programme on cervical cancer incidence. More than 17 000 cases of abnormal CIN3 lesions and 563 cases of cervical cancer were diagnosed in women born prior to the vaccine roll-out in 1990, compared with just 49 cases of CIN3 and 7 cancers in the cohort born five years later, 85% of whom had been fully vaccinated at age 12–13 — an 87% reduction. There was less of a protective effect in women who were vaccinated at age 14–16 or 16–18 — 62% and 34% reduction in cervical cancers, respectively — likely due to the fact that some of them would have already been exposed to HPV through sexual activity (Falcaro et al., 2021).

Presenting to the expert workshop, Professor Peter Sasieni suggest a stratified cervical screening programme, depending on the type of vaccines that have been given:

- **unvaccinated women:** six rounds of HPV screening at ages 25, 31, 37, 43, 53 and 63
- **vaccinated women (Cervarix or Gardasil 4):** two screens at ages 30, 45
- **vaccinated women (Gardasil 9):** one HPV screen at age 35
- **vaccination status unknown:** test for HPV antibodies in saliva (Louie et al., 2018) or screen according to birth cohort (women born before 1990 were not offered vaccination)
  - HPV positive with normal cervical examination: screen every three years
  - not screened: invite for screening every 5 years

It should be noted that there are a number of social and cultural determinants affecting HPV vaccination uptake, including religious beliefs and vaccine hesitancy. More research should be done to understand these determinants and develop strategies to address them in order to deliver better healthcare for all (for example, Rey et al., 2018).

Eliminating cervical cancer: the FASTER concept

In 2020, the World Health Organisation launched a global strategy to accelerate the elimination of cervical cancer through the combination of vaccination, screening and treatment, which could prevent 50 million deaths worldwide by 2050.[21]

Simpler than the schema outlines above, the FASTER concept for the rapid control and ultimate elimination of cervical cancer proposes that women between the ages of 23 and 26 undergo simultaneous vaccination and HPV testing with those who are HPV negative (approximately 90–95% of the population) expected to have an 83–90% efficacy of the vaccine in preventing cervical cancer. If testing positive, they will either be followed up with HPV testing until they test negative, at which point they are unlikely to develop invasive cervical cancer, or in the case of women with persistent HPV infection

21 https://www.who.int/news/item/17-11-2020-a-cervical-cancer-free-future-first-ever-global-commitment-to-eliminate-a-cancer

they should be monitored for the development of abnormal cells and given appropriate treatment and follow-up.

In total, this approach could lead to more than 90% protection against invasive cervical cancer (Bosch et al., 2016). This approach could not only be highly beneficial for European women but would save many thousands of lives worldwide in countries with less access to cervical screening and cancer treatment. At some point, it may therefore become necessary to consider how to ramp down and cease organised cervical screening programmes as HPV and cervical cancer is eliminated through the combination of vaccination and screening.

5.4. Conclusion: cervical cancer screening

We have an unprecedented opportunity to eliminate cervical cancer in the EU through a combination of HPV testing and vaccination. To achieve this, HPV testing should be rolled-out to replace cytology testing in all EU member states, with traditional cytology testing reserved for individuals with persistent HPV infection. Self-sampling for HPV testing may increase uptake among under-screened women.

Widespread HPV vaccination is likely to have a significant impact on the incidence of infection with the most dangerous strains of HPV, as well as the incidence of cervical cancer. This is likely to require a change to cervical cancer screening strategies in the future. Research should be done to elucidate the social and cultural determinants affecting HPV vaccination uptake, including religious beliefs and vaccine hesitancy, and develop strategies to address them.

Appendix 1: Programme and contributors

- **Chairs:**
  - Professor Rebecca Fitzgerald (Professor of Cancer Prevention at the University of Cambridge, UK and Interim Director of the MRC Cancer Unit, United Kingdom)
  - Professor Harry de Koning (Deputy Head and Professor of Public Health and Screening Evaluation-Erasmus MC University Medical Center, Rotterdam, Netherlands)
- **For SAPEA:**
  - Professor Stefan Constantinescu (FEAM president)
  - Professor George Griffin (FEAM past president)
- **For the Specialist Unit for Review Evidence at Cardiff University, Wales:**
  - Louise Edwards (SAPEA Scientific Policy Officer at Academia Europaea)
  - Dr Hui-Ling Ou (Postdoctoral Research Associate at University of Cambridge, UK; seconded)

- Professor Marc Arbyn (Coordinator of the Unit of Cancer Epidemiology, Belgian Cancer Centre, Belgium)
- Dr Mirza Balaj (CHAIN Research Coordinator, Norwegian University of Science and Technology, Trondheim, Norway)
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- Professor Joakim Dillner (Professor in infectious disease epidemiology at Karolinska Instituet, Sweden)
- Dr Sirpa Heinävaara (Senior Researcher at Finnish Cancer Registry, Finland)
- Professor Solveig Hofvind (Cancer Registry of Norway and Department of Health and Care Sciences, Faculty of Health Sciences, The Arctic University of Norway, Tromsø, Norway)
- Dr Iris Lansdorp-Vogelaar (Associate Professor-Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands)
- Professor Anne Mackie (Director of Screening at Public Health England, United Kingdom)
- Zorana Maravic (CEO at Digestive Cancers Europe, Brussels, Belgium)
- Professor Peter Sasieni (Academic Director of King's Clinical Trials Unit and Professor of Cancer Prevention, King's College London, United Kingdom)
- Professor Robert Smith (Cancer Epidemiologist and Senior Director, Cancer Control at the National Office of the American Cancer Society in Atlanta, Georgia, USA)
- Professor Carla H. van Gils (Professor of Clinical Epidemiology of Cancer, UMC Utrecht, Netherlands)
- Professor Zoltán Voko (Director and Professor of Epidemiology at Centre for Health Technology Assessment, Semmelweis University, Budapest and Medical Director at Syreon Research Institute, Hungary)

10:00	Welcome	Rebecca Fitzgerald Harry de Koning Stefan Constantinescu George Griffin
10:10	Rapid review of the published evidence	Hui-Ling Ou Louise Edwards
Section 1: Overarching considerations for improving existing screening programmes		
10:20	State of affairs: existing cancer screening programmes in the EU	Partha Basu
10:45	Main barriers: Existing programmes in the EU	Zoltán Voko
11:10	Difficulties in management of screening programmes	Anne Mackie
11:35	Inequity in cancer screening	Mirza Balaj
Section 2: Specific colorectal cancer screening improvements		
12:00	From gTOBT to FIT pilot Finland	Sirpa Heinävaara
12:25	Gender-specific strategies	Patrick Bossuyt
12:50	Personalising screening based on Faecal Haemoglobin concentration: the logical next step for CRC screening?	Iris Lansdorp-Vogelaar
13:15	Patient voice	Zorana Maravic
13:40	Break	
Section 3: Specific breast cancer screening improvements		
14:20	Screening under the age of 50	Robert Smith
14:45	Tomosynthesis	Solveig Hofvind
15:10	Dense breasts and screening	Carla H. van Gils
15:35	Break	
Section 4: Specific cervical cancer screening improvements		
16:00	HPV testing	Joakim Dillner
16:25	Self-sampling	Marc Arbyn
16:50	Vaccination consequences	Peter Sasieni
Section 5: Discussion		
17:15	Discussion Increasing benefits: Coverage, age extensions, opportunistic & equity More personalised programmes - Mix of imaging/test modalities and intervals, use of algorithms Informed (non-)participation Labour force issues Reducing harms and inequalities	All
17:50	Wrap-up and conclusions	Rebecca Fitzgerald Harry de Koning

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