Cancer screening in Europe

Expert workshop 1

21 September 2021

What is the scientific basis for extending screening programmes to other cancers — including lung, prostate, gastric, oesophageal and ovarian cancers — and ensuring their feasibility throughout the EU?

SAPEA
Science Advice for Policy by European Academies

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1. Introduction

> Every day of delay is a missed opportunity to catch a person's cancer or disease at an earlier point, and potentially save their life.
>
> *Professor Sir Mike Richards, Independent Review of Adult Screening Programmes in England, 2019*[1]

In 2020, 2.7 million people in the European Union were diagnosed with cancer, and 1.3 million people lost their lives to it.[2] Cancer is an individual diagnosis that has important impacts on patients, but it also severely affects the lives of their families and friends. Today, Europe accounts for a tenth of the world's population, but a quarter of the world's cancer cases, and lives lost to cancer in the EU are set to increase by more than 24% by 2035,[3] making it the leading cause of death in the EU. The total cost of cancer was €199 billion in Europe in 2018, and is only set to increase (Hofmarcher et al., 2020).

In many cases, the earlier a cancer is diagnosed, the greater the chances of successful early treatment and subsequent survival.[4],[5] Early detection therefore offers the best chance of beating cancer and saving lives, apart from primary prevention. Screening of non-symptomatic populations, such as the current programmes for breast, colorectal and cervical screening that are in place in the majority of EU nations, have a significant part to play in achieving this aim. As an example, a recent paper estimated that approximately 22 000 breast cancer deaths are prevented yearly due to mass screening (Zielonke et al., 2021).

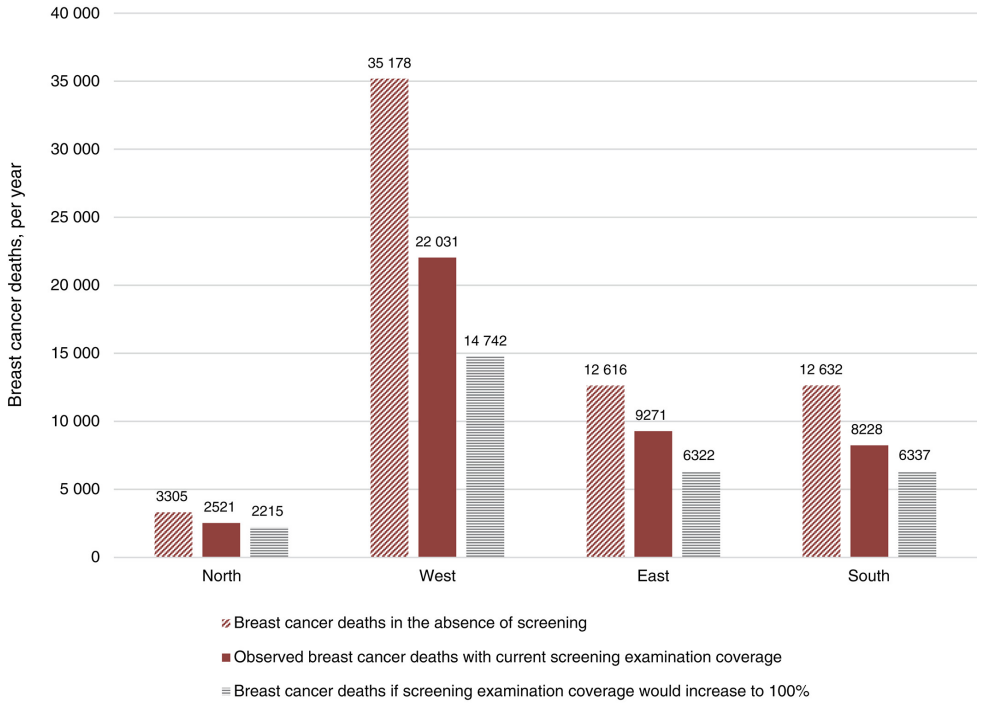
1 https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf

2 Most recent estimates from the European Cancer Information System (ECIS) for the EU-27 countries. New diagnoses cover all types of cancer, apart from non-melanoma skin cancer.

3 https://gco.iarc.fr/tomorrow/en/

4 O. f. N. Statistics, "Cancer survival in England — adults diagnosed," August 2019. [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

5 Public Health England, "Case-mix adjusted percentage cancers diagnosed at stages 1 and 2 by CCG in England," May 2020. [Online]. Available: https://www.gov.uk/government/statistics/case-mix-adjusted-percentage-cancers-diagnosed-at-stages-1-and-2-by-ccg-in-england



Northern Europe: Denmark, Estonia, Finland Iceland, Latvia, Lithuania, Norway and Sweden.
Western Europe: Austria, Belgium, France, Germany, Ireland, Luxembourg, The Netherlands, United Kingdom and Switzerland.
Eastern Europe: Bulgaria, Czech Republic, Croatia, Hungary, Poland, Romania, Slovakia and Slovenia.
Southern Europe: Cyprus, Gibraltar, Greece, Italy, Malta, Portugal and Spain

Figure 1. Annual number of observed and preventable breast cancer deaths, ages 50–74, per European region (Zielonke et al., 2021).

A number of other cancers have been proposed as being suitable for screening, including lung, prostate, gastric, ovarian and oesophageal. However, the decision-making process concerning the adoption of any potential new cancer screening programmes must establish the effectiveness of the testing process in terms of shifting the stage of diagnosis earlier, reducing cancer mortality and improving quality of life and patient outcomes; that the benefits outweigh the harms; and also that it is cost-effective.[6]

This report summarises the presentations and discussion of the first expert workshop convened on 21 September 2021 to discuss the scientific evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers and ensuring their feasibility throughout the EU. These cancers were selected based on disease burden, measured by mortality and/or disability-adjusted life-years.

This expert workshop is supported by an associated Rapid Review of the scientific literature conducted by the Specialist Unit for Review Evidence at Cardiff University. A full list of contributors to the workshop can be found in Appendix 1 on page 36.

6 https://cancercontrol.eu/archived/uploads/images/Guide/042017/CanCon_Guide_1_Introduction_LR.pdf

2. The principles of screening programmes

At the heart of any medical intervention lies an individual. Underlying any discussion of cancer screening should be solid ethical principles of *primum non nocere* (first do no harm); respecting personal dignity and autonomy; prudence and precaution; honesty and transparency; an emphasis on informed decision-making and consent based on benefits and harms; and the provision of appropriate patient support services.

In their seminal work *Principles and Practice of Screening For Disease*, Wilson and Jungner (1968) outline ten principles of screening:

- The condition sought should be an important health problem.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- There should be an agreed policy on whom to treat as patients.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for diagnosis and treatment should be available.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a 'once and for all' project.

Fifty years on, Dobrow and colleagues have revised and expanded this list to include systemic, operational and implementation issues that were not fully captured in Wilson and Jungner's original analysis. After considering 367 unique principles listed across the literature and undertaking a Delphi consensus process with international experts, 12 consolidated principles emerged (Dobrow et al., 2018). These now provide a useful and up-to-date starting point for discussions of the risks, benefits and implementation of screening in today's healthcare systems, and are listed in Box 1.

Box 1. Consolidated principles of screening

Disease/condition principles

- **Epidemiology of disease or condition:** The epidemiology of the disease or condition should be adequately understood, and the disease or condition should be an important health problem (e.g. high or increasing incidence or prevalence, or causing substantial morbidity or mortality).
- **Natural history of disease or condition:** The natural history of the disease or condition should be adequately understood, the disease or condition should be well-defined, and there should be a detectable preclinical phase.
- **Target population for screening:** The target population for screening should be clearly defined (e.g. with an appropriate target age range), identifiable and reachable.

Test/intervention principles

- **Screening test performance characteristics:** Screening test performance should be appropriate for the purpose, with all key components specific to the test (rather than the screening programme) being accurate (e.g. in terms of sensitivity, specificity and positive predictive value) and reliable or reproducible. The test should be acceptable to the target population and it should be possible to perform or administer it safely, affordably and efficiently.
- **Interpretation of screening test results:** Screening test results should be clearly interpretable and determinate (e.g. with known distribution of test values and well-defined and agreed cut-off points) to allow identification of screening participants who should and should not be offered diagnostic testing and other post-screening care.
- **Post-screening test options:** There should be an agreed course of action for screening participants with positive screening test results that involves diagnostic testing, treatment or intervention, and follow-up care that will modify the natural history and clinical pathway for the disease or condition; that is available, accessible and acceptable to those affected; and that results in improved outcomes (e.g. increased functioning or quality of life, decreased cause-specific mortality). The burden of testing on all participants should be understood and acceptable, and the effect of false-positive and false-negative tests should be minimal.

Programme/system principles

- **Screening programme infrastructure:** There should be adequate existing infrastructure (e.g. financial resources, health human resources, information technology, facilities, equipment and test technology), or a clear plan to develop

adequate infrastructure, that is appropriate to the setting to allow for timely access to all components of the screening programme.

- **Screening programme coordination and integration:** All components of the screening programme should be coordinated and, where possible, integrated with the broader health care system (including a formal system to inform, counsel, refer and manage the treatment of screening participants) to optimise care continuity and ensure no screening participant is neglected.
- **Screening programme acceptability and ethics:** All components of the screening programme should be clinically, socially and ethically acceptable to screening participants, health professionals and society, and there should be effective methods for providing screening participants with informed choice, promoting their autonomy and protecting their rights.
- **Screening programme benefits and harms:** The expected range and magnitude of benefits (e.g. increased functioning or quality of life, decreased cause-specific mortality) and harms (e.g. overdiagnosis and overtreatment) for screening participants and society should be clearly defined and acceptable, and supported by existing high-quality scientific evidence (or addressed by ongoing studies) indicating that the overall benefit of the screening programme outweighs its potential harms.
- **Economic evaluation of screening programme:** An economic evaluation (e.g. cost-effectiveness analysis, cost–benefit analysis and cost–utility analysis) of the screening programme, using a health system or societal perspective, should be conducted (or there should be a clear plan to conduct such an evaluation) to assess the full costs and effects of implementing, operating and sustaining the screening programme while clearly considering the opportunity costs and effect of allocating resources to other potential non-screening alternatives (e.g. primary prevention, improved treatments and other clinical services) for managing the disease or condition.
- **Screening programme quality and performance management:** The screening programme should have clear goals or objectives that are explicitly linked to programme planning, monitoring, evaluating and reporting activities, with dedicated information systems and funding, to ensure ongoing quality control and achievement of performance targets.

(Taken from Dobrow et al., 2018)

Importantly, these principles are not static, and will continue to evolve in the light of new scientific evidence and technological advancements as well as shifting and economic and societal conditions.

It is noted that the scientific methodology and evidence base around screening interventions is much better developed than that around programmes and systems, which will be more dependent on population and geographical context. It is therefore important to develop a broader and more sophisticated, but still scientifically rigorous, conception of evidence for screening programmes that takes all of this into account.

The context in which decisions about national cancer screening programmes take place has also shifted to become highly complex, involving multiple linked decisions that can run over several years. The expertise required to make these decisions is also diverse, involving multiple stakeholders with differing perspectives. For example, while assessing the information around a particular disease condition or screening intervention typically falls to clinical experts and epidemiologists, a broader range of stakeholders including health service programme managers, policy analysts, information system specialists, health economists, ethicists, patients, high-risk populations and the wider public are needed to inform programmematic and system level screening decisions.

In the light of emerging evidence around new technologies and screening of high-risk populations, it is important to ensure that adhering to these underlying principles remains at the heart of decisions about cancer screening programmes. As discussed in 9 on page 46, governance has a paramount role to play in clarifying ownership of these principles and responsibility for screening decisions, the stakeholders and evidence sources that should contribute to the discussion and how they should be combined and weighted, and the ongoing monitoring of extant programmes to ensure efficacy and value in the real world.

Case study: Colorectal cancer screening in Ontario

Examples of this approach in practice can be seen in the work done by Rabeneck et al.[7] in taking a phased approach to considering the harms and benefits of implementing various colorectal cancer screening methods in the Canadian province of Ontario (population 14.4 million):

1. Reviewing the evidence around the effectiveness of different screening methods with a small working group, compiled into a review by the Program in Evidence-based Care at McMaster University and Cancer Care Ontario (Tinmouth et al., 2016).
2. Convening an international multidisciplinary stakeholder panel with a broader range of backgrounds to provide input on evidence and wider considerations. In additional to the review of the scientific evidence around the efficacy of various testing methods, the panel also considered:

7 https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCCScreeningRecommendations.pdf

- the impact on participation of offering more than one test
- data modelling around the optimal age brackets for testing
- cost-effectiveness
- acceptability and impact on healthcare providers, particularly primary care and specialists
- acceptability by participants
- the feasibility of implementation within the context of the province

3. Combining these inputs together to inform the recommendations for the province, published in 2016, recommending screening with a faecal immunochemical test every two years for asymptomatic people aged 50–74 without a family history of colorectal cancer.

This three-phase approach had a significant positive impact on the final recommendations. Based on the evidence report from Phase 1 alone, the recommendation would have been to offer more than one screening test. However, following the Phase 2 discussion, although it was felt that more than one test might improve participation, this would be challenging to implement in practice in the province.

Going forward, the same approach will be used to develop recommendations for colorectal cancer screening for people at increased risk, as well as lung cancer screening in (ex-)smokers, cervical screening and colposcopy to account for the move from Pap smear tests to HPV testing, and screening for liver cancer in people with underlying chronic liver disease from viral hepatitis.

3. Modelling cost-effective health policies

In addition to considering the evidence for the effectiveness and feasibility of a given screening intervention and whether the benefits outweigh the harms, we must also consider the cost-effectiveness. We live in societies where needs are infinite but resources are limited. If inefficient interventions are paid for through the public purse, fewer resources are available for more effective approaches, and population health will not be maximised. We must therefore adopt a principle of saving the most lives with the available resources.

Cost-effectiveness analysis or economic evaluation is a way to compare alternative courses of action by identifying, measuring, comparing, and valuing their health effects and costs. There are various different types of economic evaluation available, but cost-utility analysis is currently considered to be the gold standard and is widely used in cancer screening (Sanders et al., 2016). It is good to note that an appropriate cost-effectiveness analysis tries to estimate the benefits (effectiveness) first, includes harms by adjusting life-years gained for positive and negative quality of life impacts for individuals, and finally relates all this to cost (e.g. resources and manpower).

When considering the costs of cancer screening, we should not only include the obvious costs such as the administrative burden of inviting individuals and the cost of the test itself, but indirect costs including the care costs for people living with the long-term health impacts of their disease who might otherwise have died, and healthcare costs that would not have been incurred without screening (for example, due to overdiagnosis).

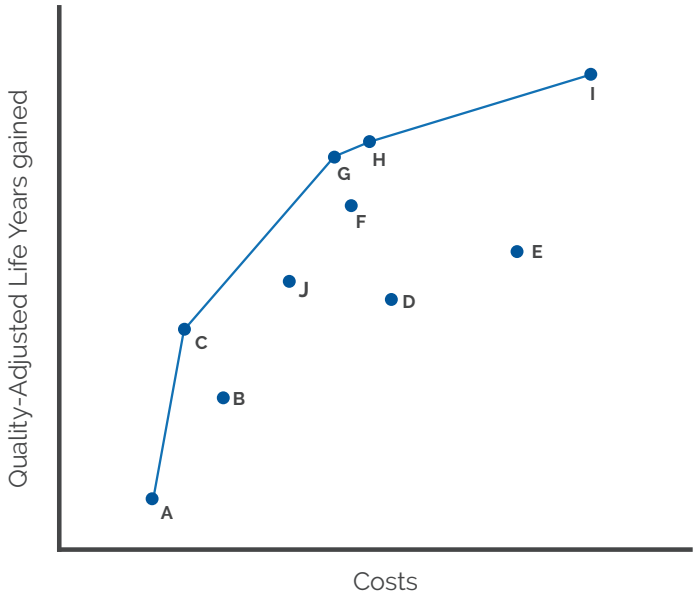


Figure 2. The comparative cost-effectiveness of healthcare interventions (based on Mark, 2002)

Any given intervention can be plotted on this graph according to its benefits in terms of Quality-Adjusted Life Years (QALYs) gained (y-axis) against cost (x-axis). The strategies that provide best value for money are therefore the ones lying in the upper-left corner of the graph. The line connecting the most efficient strategies is referred to as the Efficient Frontier. Any intervention lying below this line (e.g. strategies B, D, E, F and J) will provide less value for money than those that lie on it and should not be adopted. One important point to note is that the flattening curve represents diminishing returns in additional QALYs gained per expenditure. As an example, due to the natural history of disease, more frequent screening may not lead to a proportional increase in benefits after a certain point.

Picking among the strategies that do lie on the Efficient Frontier (e.g. A, C, G, H and I) depends on the budget available and the acceptable ratio between cost and lives or life-years saved, which differs between countries. For example, in the United States, an acceptable cost per QALY has been proposed of around $100 000 (Neumann et al., 2014), while in the United Kingdom it is generally set at around £30 000, rising to around £50 000 for end-of-life interventions and significantly higher exceptions of up to £300 000 for very rare diseases (Paulden, 2017).

Estimating the costs and QALYs gained by screening is a further challenge. Large-scale long-term randomised trials of screening can only compare one or sometimes two different screening strategies due to the high costs and practicalities involved. And although the typical follow-up period of such trials is usually around 10–15 years, this is still a relatively short amount of time in which to measure the benefits of screening.

Furthermore, volunteer trial participants may not be representative of the wider population(s) who will ultimately be the recipients of screening.

Several international groups have been developing computer models that simulate the natural history of disease (e.g. based on evidence from randomised controlled trials) and enable extrapolation from the outcomes of large-scale screening trials to the population of interest as a way of optimising screening interventions. These models incorporate adjustments for lower adherence to screening in the real world compared with a trial, as well as poorer health, higher disease risks and worse life-expectancy in the general population compared with trial participants. Notably, such models have been developed in close collaboration with EU member states (see the EU-Topia project).[8]

Taking the example of biennial colorectal cancer screening, Lansdorp-Vogelaar were able to model the impact of these factors upon different screening tests (gFOBT and FIT) across various starting/stopping age ranges and test positivity cut-off points (Wilschut et al., 2011).

Combining data from large-scale screening trials with real-world evidence from the Netherlands, including local demographics, life expectancy and healthcare capacity, an initial analysis revealed that FIT screening approaches with a relatively low cut-off for referral for further investigation of 10 µg/g would be the most cost-effective strategies (FIT-10). The graph shows the FIT-10 scenarios on top of all other considered strategies (most benefits for equal resources). However, the Netherlands did not have the colonoscopy capacity to follow-up all the cases that would be referred through such an approach. Taking this into account, a further analysis showed that with limiting colonoscopy capacity, a recommendation of biennial FIT screening between the ages of 55 and 75 with a test positivity cut-off of 15 µg/g for referral for colonoscopy would be the best strategy for the country.

8 https://eu-topia.org/

4. Lung cancer screening

Lung cancer is the biggest cancer killer in Europe, accounting for approximately 270 000 deaths every year — around 20% of all cancer deaths - and for the loss of 3.2 million disability-adjusted life-years annually in the region. Three quarters of lung cancer cases occur among the over-60s, and seven out of eight patients currently die within five years of diagnosis.[9]

4.1. Evidence of effectiveness of lung cancer screening

Currently, average survival following a diagnosis of lung cancer is around 200 days, extended by a few hundred days by recent advances in immunotherapy. The potential benefits of early diagnosis of lung cancer through low dose CT (LDCT) screening could be around 12.5 years of additional life, even in the presence of comorbidities, with possibly around 22 000 lung cancer deaths prevented in Europe every year even under the most stringent screening eligibility (de Koning et al., 2014).

The top line findings from the rapid literature review of 13 trials of lung cancer screening are:

- In all CT screening trials, more lung cancers as well as early-stage disease are found in the screening arm during CT screening rounds, compared to a control arm without CT scanning just offering usual care if symptoms are reported.
- Reduced lung cancer mortality is observed in the screening arm, compared to controls, being statistically significant in 2 large-scale trials, with some differences by sex.
- The harms due to false-positive screening results may be minimal.
- There are short-term psychosocial harms observed, due to involvement or suspicious results of screening, but this may resolve in the long run,

The potential impact of real world lung cancer screening was recently demonstrated in a paper by Van Haren et al., who showed that cessation of LDCT screening in the US due to the COVID-19 pandemic resulted in a significant increase in the number of people being diagnosed with the disease at a later stage (Van Haren et al., 2021).

In 2013, the US Preventive Services Task Force recommended annual LDCT screening for individuals over the age of 55 with at least 30 pack-years of smoking history, including current smokers and those who had quit less than 15 years ago.

9 https://www.erswhitebook.org/chapters/lung-cancer/ and https://www.lungcancereurope.eu/lung-cancer/

These guidelines were revised in 2021 to recommend annual LDCT screening for adults aged 50–80 with a 20 pack-year history, either current smokers or quit within 15 years, with screening to be stopped once a person has not smoked for 15 years or develops a health problem that substantially limits their life expectancy or their willingness or ability to have curative lung cancer surgery (US Preventive Services Task Force, 2021). This strategy was supported by a cost-effectiveness analysis of this strategy performed by 4 different modelling groups, based on US National Lung Screening Trial data (Meza et al., 2021).

4.2. The NELSON and NLST trials of lung cancer screening

The two largest randomised controlled trials of LDCT lung cancer screening are the US National Lung Screening Trial (NLST), which compared LDCT with chest X-ray, and the European Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON). Other notable CT-trials include the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) trial, the DANTE, DLCST, ITALUNG, LungSEARCH, LUSI, MILD and UKLS trials in Europe, and the Chinese ChiCTR-Shanghai trial (see Rapid Review for further details).

The NELSON trial of lung cancer screening demonstrated an impressive shift in the stage of diagnosis, with 60% of cancers detected in the screen arm being diagnosed in stage 1 (during screening period) compared with just 13% diagnosed at this stage in the control group. Furthermore, lung cancer mortality was significantly reduced (de Koning et al., 2020a & 2020b), with 24% in males and 33–59% in females during 7–10 years post-randomisation. Separating participants by birth sex, the reduction in lung cancer mortality shown in the NELSON study is around 24% for males and 59% for females after eight years following randomisation (both statistically significant), and around 33% by year 10, likely due to a dilution effect (de Koning et al., 2020a & 2020b).

Analysis of histology subtypes in the US NLST and PLCO trials suggests that screening may detect adenocarcinomas up to four to five years earlier in men and up to six years earlier in women (Ten Haaf et al., 2015). Scaling these findings up to the whole population, annual LDCT screening could prevent up to 87 lung cancer deaths per 1000 eligible screened women.

Similarly, the NLST also showed a slight increase in the number of cancers detected, compared with chest radiography, but a significant reduction in overall mortality, particularly from 5 years post-randomisation (National Lung Screening Trial Research Team et al., 2011). However, this study was not powered to reveal overall mortality effects, unlike NELSON and other trials (Heijnsdijk et al., 2019).

Due to differences in screening methodology, only around 2.1% of participants in the NELSON trial were referred for diagnostic workup with cancer detected in around half (0.9%), compared with around 20% referrals in the NLST with a similar cancer rate. The high false-positive and referral rate in the US NLST is due to the fact that referral was based solely on the diameter of suspicious nodules, whereas the NELSON study analysed nodules by volume on CT and also called participants for a confirmatory follow-up scan after 3 months (Xu et al., 2006).

After 12 years of follow-up in the NLST, the rates of lung cancer were similar in the LDCT screening group compared with the chest X-ray, suggesting that there is no significant overdiagnosis of slow-growing tumours and that cancers detected in the study were genuinely dangerous (The National Lung Screening Trial Research Team, 2019). Also, the NELSON trial reported a small difference at year 11.

While the NELSON trial did demonstrate a significant reduction in lung cancer mortality, it was not sufficiently powered to show a reduction in all-cause mortality. This is a known challenge in clinical trials of screening interventions, with analysis by Heijnsdijk et al. (2019) showing that a minimum sample of 40 000 participants per arm (i.e. 80 000 participants in a two-arm controlled trial) is required to show an effect on all-cause mortality.

Although large clinical trials have shown beyond doubt that annual LDCT screening can reduce lung cancer mortality, questions remain about the optimal strategy in terms of stratification by age, risk factors and screening intervals. For example, analysis by Silva et al. (2021) of the Lung-RADS v1.1 study shows that people with a negative LDCT scan have a 40-fold lower risk of lung cancer after two years compared with those having a positive scan.

Looking in further depth at this issue, the 4-IN-THE-LUNG-RUN trial is recruiting 26 000 participants across five European countries to find out whether a more personalised approach to screening based on individual risk and a negative baseline scan can reduce the costs and implementation challenges of introducing lung cancer screening within Europe (Van der Aalst et al., 2020). Other trials in the USA, UK, China and Europe, such as the 12 100 participant German HANSE, study have also explored the feasibility of implementing lung cancer screening (detailed further in the Rapid Review).[10]

4.3. Feasibility and cost-effectiveness of lung cancer screening

Demonstrating the feasibility of a potential cancer screening programme first requires large scale randomised controlled trials to demonstrate efficacy of the testing procedure.

10 https://clinicaltrials.gov/ct2/show/NCT04913155

However, this is just the beginning of a long process that may or may not lead to its implementation on a local or national level (see section 9 on page 46).

Effective large-scale RCTs should be followed by smaller local implementation projects to demonstrate the ability to recruit from relevant populations and other measures, along with additional trials aimed at improving efficiency and reducing costs.

The next step is to then roll out screening to a number of pilot sites, to show that enthusiastic expert teams are able to match the results from the large-scale trials in less tightly controlled settings. Finally comes the full national roll-out, which should be carefully monitored to ensure the quality and effectiveness of the test in a truly real world setting where it is competing with other health interventions.

4.4. Benefits and harms of lung cancer screening

There are benefits and harms of any cancer screening programme, which must be weighed against each other to establish feasibility. Some are generic, others are specific to the intervention. In the case of lung cancer screening, the main benefits and harms are as follows:

- Benefits
  - Earlier stage detection of disease and delivery of effective safe treatment
  - Avoidance of the need for palliative care where possible
  - Reduced cancer-specific mortality
  - Opportunities for smoking cessation
  - Avoidance of delays in diagnosis and treatment
  - Interventions such as treatment more likely to be offered to those who will benefit from it
  - Potential for detection of other diseases on thoracic CT (coronary artery calcification, emphysema)
- Harms
  - Radiation risk from CT scans
  - Psychological impact of the screening process and subsequent actions resulting from it
  - False positive referrals
  - Complications caused by additional diagnostic testing/biopsy and treatments for cancer
  - Overdiagnosis, where tumours are found that would not have subsequently been life-threatening
  - Incidental findings, such as lung nodules, potentially leading to over-investigation and overdiagnosis (Tsai et al., 2018)

- Possible false reassurance and 'licence to smoke'

The impacts of the benefits and harms of lung screening have been quantified from controlled trials and are summarised in the Rapid Review. Benefits and harms can be managed and balanced by adherence to evidence-based guidelines around eligibility, clinical work-up, smoking cessation and the management of incidental findings, along with regular monitoring and reporting.

For example, the development of standardised protocols in the lung cancer screening pilot studies of nearly 12 000 people in England led to a 5% benign resection rate (the percentage of people undergoing investigative surgery who subsequently turn out not to have cancer), with zero major complications or deaths as a result. This compares favourably with a benign resection rate of 21% in the US NLST, 23% in NELSON, and 10% in the initial randomised UK Lung Screening trial (Balata et al., 2021).

However, it should be noted that there is debate around how best to deal with incidental findings made through lung cancer screening, such as lung nodules (van de Wiel et al., 2007; Reiter et al., 2018). Furthermore, more work needs to be done to understand the benefits and harms of screening when offered to people with comorbidities that are likely to severely limit their life expectancy even in the absence of cancer, especially as risk models are not definitive individual predictors. Is it ethical to offer someone screening when the individual may only have a few years to live, when the risk of overdiagnosis and harm from treatment is high? Such decisions are to be weighed individually, but for implementation such quantifications are at least crucial at group level.

Case study: Lung cancer screening in England

Launched in 2019, one of the goals of the NHS Long Term Plan is to increase the proportion of cancers diagnosed at stage 1 or 2 to 75%, with 55 000 more people surviving cancer for at least five years by 2028.[11] As the most common cause of cancer death in the UK,[12] lung cancer is an obvious target for this aim.

The large-scale randomised UK Lung Screening Trial (UKLS) of single LDCT screening in nearly 4000 participants showed a 2.1% cancer detection rate and a substantial reduction in lung cancer deaths. 86% of cancers were detected in stage 1 or 2, with an estimated incremental cost-effectiveness ratio of around £8466, based on limited follow-up period (ICER, the ratio of additional costs to additional health benefits) — an acceptable figure for a health intervention in the UK (Field et al., 2016; Field et al., 2021).

11 https://www.longtermplan.nhs.uk/

12 https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer

In 2017, researchers launched the Accelerate Coordinate Evaluate study for lung cancer screening, running pilot studies of around 12 000 participants in expert respiratory centres in Liverpool, Manchester, Nottingham and University College London. Preliminary results showed a 2.1% cancer detection rate, similar to the UKLS trial. Additional trials continued to show similar results, whether in fixed site or mobile screening facilities, setting the stage for a national screening programme to be rolled out (Balata et al., 2021).

A standardised screening protocol was subsequently developed to ensure a consistent and equitable approach to the provision and monitoring of targeted screening for lung cancer across England,[13] along with a quality assurance standard framework covering skills and training, information and communication, and clinical delivery.[14] Finally, screening was implemented on a progressive local basis across the country, focusing initially on areas with the highest rates of lung cancer.

Funding of £71 million was secured from NHS England to roll out targeted lung health checks over 4 years to people aged 55-74 who have ever smoked, with LDCT scanning being offered to those with a significant risk of lung cancer ($PLCO_{m2012}$ of ≥1.51% risk of lung cancer over 6 years and/or LLPv2: ≥2.5% risk of lung cancer over 5 years; see below and Lebrett et al., 2020).

4.5. Eligibility criteria for lung cancer screening

Based on the balance of harms and benefits and in the context of limited resources, it is not appropriate to offer lung cancer screening to the entire adult population. Instead, selection criteria must be used to identify groups of people who are most likely to benefit and least likely to be harmed, balanced against the financial resources available. Over recent years these have widened eligibility, to include individuals who are younger and with lower cumulative smoking history. For example, as of 2021, the US Preventive Services Task Force (USPSTF) recommends LDCT lung cancer screening for people aged 50–80, who have smoked for a minimum of 20 pack-years during their lifetime and are either current smokers or quit less than 15 years ago.

There are a number of different eligibility criteria recommendations for LDCT lung cancer screening adopted by various organisations and countries. The benefits and harms of these various approaches can be compared through modelling (e.g. de Koning et al., 2014; US Preventive Services Task Force, 2021; Meza et al., 2021).

13 https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf

14 https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-screening-for-lung-cancer-quality-assurance-standard.pdf

Building on this, various models have been developed to predict an individual's risk of developing lung cancer within a certain period of time, which take into account a selection of factors including age, sex, ethnicity, body mass index, other health conditions, family history, asbestos exposure and smoking behaviour. These include Bach, LLP2008, $PLCO_{m2012}$ and LCRAT, which have been validated in numerous independent prospective cohorts worldwide (Cassidy et al., 2008; Bach et al., 2003; Tammemägi et al., 2013; Katki et al., 2016). Age, sex and smoking history are likely to be the most important components of these models, which will differ by population, and so must be calibrated by country or region.

Compared with simple eligibility criteria such as those set by USPSTF, which are derived from lung cancer screening trials, these prediction models can offer a more sophisticated way to select individuals who will benefit most from screening based on personalised risk. When applied at a population level, these models tend to select different populations than simple criteria-based rules. For example, an analysis of the German population showed that the $PLCO_{m2012}$ risk model selected individuals in higher age groups for screening, including ex-smokers with longer average quitting times, compared to USPSTF eligibility criteria (Hüsing & Kaaks, 2020).

Based on these findings, it has been suggested that risk models select individuals with a shorter life expectancy, who are actually less likely to benefit from screening. When this question was addressed through the International Lung Screening Trial led by Tammemägi and colleagues, they found that because there were so many more early lung cancers detected in the group selected by the PLCOm2021 model, this led to a significant gain in life years compared with the group selected by the USPTSF 2013 criteria.

While risk-based strategies for determining lung cancer screening eligibility have been shown to prevent more deaths from the disease than deterministic cut-off criteria, the increase in life expectancy is more modest and there is more overdiagnosis of cancers that would not have represented a clinical problem until later on (ten Haaf et al., 2020). Similarly, Meza et al. showed that Risk model-based selection strategies were estimated to be associated with more benefits and fewer radiation-related deaths but more over-diagnosed cases than simple criteria (Meza et al., 2021).

Simple categorical criteria such as the USPSTF also appear to miss out a significant number of women who would benefit from screening, which is improved by the use of the $PLCO_{m2012}$ model. It should be noted that the Bach and LCRAT models may end up exacerbating sex disparities by including a term that inappropriately downweights female sex.

It is argued that simple cut-off criteria such as the USPSTF (pack-years) are simpler for doctors to use than risk-based models when determining whether an individual should

be put forward for lung cancer screening. However, the experience of Tammemägi et al. (2021) in Ontario showed that the PLCOm2021 risk screening tool could be delivered by a trained navigator in an average of 13 minutes, which was preferred by both doctors and patients. Anecdotal expert evidence suggests that the PLCOm2021 risk questionnaire can be delivered over the phone in under 5 minutes, while others are investigating online tools to accelerate the process.

Finally, there is still some discussion around the appropriate upper age limit after which lung cancer screening should be stopped, which should be determined through further modelling and empirical testing. However, most recommendations include stopping ages between 75–80.

4.6. Cost-effectiveness of lung cancer screening

A number of factors feed into the cost-effectiveness of lung cancer screening, including:

- selection criteria for screening (i.e. size of invited population)
- invitation and administration costs
- costs of the LDCT scanning
- costs of clinical workup
- costs of treatment (especially reducing costs for immunotherapy)
- costs of management of incidental or indeterminate findings
- costs of smoking cessation services, along with the costs of smoking itself

These costs can be influenced by the use of standardised protocols and quality assurance standards, along with consistent implementation of smoking cessation services.

The reported cost-effectiveness of lung screening varies widely. Four studies reporting the cost-effectiveness of lung cancer screening (DANTE, DLCST, KLST and UKLS) gives a range of approximately €8500–€60 000 per QALY gained. Two systematic reviews have analysed the cost-effectiveness of lung cancer screening, covering 12 and 9 studies respectively (Raymakers et al., 2016; Puggina et al., 2016). The majority of studies analysed showed that lung screening was cost-effective, based on the suggested US QALY of either $50 000 or $100 000.

4.7. Smoking cessation

Smoking causes the majority of lung cancer cases in both men and women.[15] Lung cancer screening offers an opportunity to promote smoking cessation for those people engaging in screening who continue to smoke.

The evidence shows that encouraging people to quit smoking has a significant impact on mortality and public health. A retrospective analysis of the NLST data showed that people who have quit smoking for 15 years and undergo LDCT lung screening have a 38% reduction in lung cancer mortality (Tanner et al., 2016). Modelling by Cao et al. (2020) shows that for every 10% that the smoking quit rate goes up, lung cancer deaths drop by 14% and life years gained increase by 81%.

An invitation to attend lung screening can act as a 'teachable moment', where it is possible to reach people with smoking cessation messaging and encourage them to quit. Conversely, some people may consider a clear lung screening result as a 'licence to smoke' and continue the habit. These conflicting behaviours can have a significant impact on the cost-effectiveness of lung screening.

An increase in the number of people quitting smoking as a result of the introduction of lung screening ('teachable moment') significantly improves the cost-effectiveness of the procedure (Goffin et al., 2015). By contrast, if fewer people quit smoking (the 'permission to smoke' effect) then the costs of screening increase dramatically (McMahon et al., 2011).

To date, three studies have been carried out to investigate which of these behaviours dominates on a population level, with NELSON showing a reduction in quitting in the screening population compared with a control group (Van der Aalst et al., 2010), the Danish Lung Cancer Screening trial showing no difference (Ashraf et al., 2014), as did a 2014 systematic review by the USPSTF (Slatore et al., 2014). However, a later study from UKLS showed an increase in quitting in those invited for screening (Brain et al., 2017).

Looking more closely at participants who take part in screening, multiple studies show that those who receive an abnormal lung scan result are more likely to quit smoking compared with those who receive a clear (negative) result (for example (Ashraf et al., 2014; Slatore et al., 2014; Van der Aalst et al., 2010).

There are a number of alternative methods for encouraging people to quit smoking, including psychological and pharmaceutical methods as well as e-cigarettes, with varying degrees of success. The US-based SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration is researching the best approaches for encouraging smoking cessation within the screening setting (Joseph et al., 2018; Eyestone et al., 2021).

15 https://www.erswhitebook.org/chapters/lung-cancer/

The experience of Callister and colleagues in Yorkshire, UK, has shown that having a co-located smoking cessation service alongside lung screening can have success in encouraging people to quit, with 84% of current-smoking participants meeting with a smoking cessation practitioner and 75% accepting a 4-week intervention (Murray et al., 2020; Crosbie et al., 2020).

4.8. Conclusion: lung cancer screening

In conclusion, two large-scale RCTs (of which one in Europe) have shown CT scanning to be highly effective in reducing the extreme high burden of lung cancer mortality in Europe when applied to smokers or ex-smokers of both sexes in the age range 50–80. The amount of overdiagnosis and overtreatment (and other harms) are limited and, depending on selection criteria, cost-effective screening scenarios can be designed.

Screening should include high risk current and ex-smokers, with eligibility based on pack-years smoked and/or the $PLCO_{m2012}$ criteria.

Pilots in the UK and several European countries show high acceptance rate and these programmes can be instrumental in reducing smoking in a relatively persistent population.

High-quality CT-screening can significantly reduce the burden of lung cancer in the EU, possibly to a similar extent to that achieved by current breast screening programmes. The experts therefore find a strong scientific basis for extending screening programmes to lung cancer screening based on effectiveness and mortality burden.

5. Prostate cancer screening

Prostate cancer is the most commonly diagnosed cancer and the leading cause of cancer death in non-smoking European men, with more than 417 000 new cases and 92 000 deaths each year.[16] Around one in five prostate cancers are currently diagnosed at a metastatic stage (stage 4),[17] bringing significant impacts on survival and quality of life, as well as high treatment costs.

The chances of developing prostate cancer are strongly linked to age, with a lifetime risk of around one in seven. However, for a large proportion of men who develop a prostate tumour, it is slow growing (indolent/low volume, low grade) and may never cause a problem in their lifetime. Autopsy studies show that many more men die with prostate cancer rather than of prostate cancer (Bell et al., 2015), posing a challenge for effective screening for the disease.

5.1. Evidence of effectiveness of prostate cancer screening

Testing blood levels of prostate-specific antigen (PSA, a molecule produced by prostate cancer cells) has been proposed as a screening test for prostate cancer. Due to the high number of low volume, low grade cancers detected and risk of overtreatment, it was previously advised that systematic national PSA screening should not be undertaken (e.g. European Association of Urology 2015 guidelines).[18]

However, in the majority of countries in the EU, PSA testing is being prescribed for men over 50 and also older men over 70 as an unorganised or on-request PSA testing service. Based on Dutch data, it was roughly estimated that these screening efforts in relatively old men cost about €1 million per life-year gained (Heijnsdijk et al., 2015).

Importantly, experiencing typical symptoms of prostate cancer, such as problems with urination, are not a significant early indicator of prostate cancer, with the message that if you want to diagnose prostate cancer while it is still curable you cannot wait for men to report symptoms (Frånlund et al., 2012).

Recommendations against systematic PSA testing are now being revised in the light of new trial data and screening technology such as MRI scanning (Van Poppel et al., 2021). However, there are still many issues surrounding the utility and cost-effectiveness of

16 https://epad.uroweb.org/wp-content/uploads/EAU_policy-briefing_PSA.pdf

17 https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

18 https://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2015-v2.pdf

prostate cancer screening, particularly when balancing the risks of over- and under-diagnosis.

The top line findings from the rapid literature review of 7 controlled trials of prostate cancer screening, of which 4 are randomised and 1 cluster randomised, are:

- Screening via low-threshold prostate-specific antigen (PSA) results in a statistically significant reduction in prostate cancer/any cause mortality.
- Any mortality benefit tends to be balanced against overdiagnosis and overtreatment of low-risk disease.
- Longer follow-up is required to fully evaluate real-world costs.

Furthermore, real-world experience from Sweden shows that, while the rise of unorganised PSA testing in the population has led to an increase in prostate cancer incidence, this has gone hand-in-hand with a decrease in prostate cancer mortality in all age groups except the oldest men (Hugosson, 2018). While this data shows that PSA testing can be effective, questions remain about eligibility criteria (see) and screening regimens.

A large part of the challenge of screening for prostate cancer is that the disease is highly heterogeneous. Around a third grow aggressively and will benefit from early detection, while the rest will grow more slowly, in some cases never causing a problem within a lifetime. However, a mixture of these tumours might be detected by PSA testing, running the risk of overdiagnosis and overtreatment, which comes with significant effects on quality of life (see later).

Data from the large-scale European Randomised Study of Screening for Prostate Cancer (ERSPC) shows that the cancer mortality benefits of PSA screening only become apparent after multiple rounds of screening, rather than a single test (Hugosson et al., 2019; Pakarainen et al., 2019). Therefore, a single one-time PSA test is not advised for any prostate cancer screening programme. Furthermore, the longer the duration of the screening programme, the more effective it appears to be. The ERSPC found a 21% reduction in prostate cancer mortality between the arms, likely to represent a true effect of PSA screening of around 30–40% (Hugosson et al., 2019; Schröder et al., 2014).

The randomised controlled US Prostate, Lung, Colorectal and Ovarian trial of PSA-based screening failed to show a significant impact on prostate cancer mortality, due to the high rate of unorganised PSA testing in the control arm being studied, together with a low biopsy rate in screen-positive men (Pinsky et al., 2017). The authors note that this finding suggests that, in the US, organised PSA screening shows no benefit over opportunistic testing, illustrating how high rates of unorganised testing can interfere with the delivery of meaningful clinical trials in prostate cancer screening. Bearing this in mind, Tsodikov

et al. (2017) re-analysed the ERSPC and PLCO trials, finding around a 25-32% reduction in prostate cancer mortality in men who were screened compared with those who were not.

The same conclusions were reached in the French arm of the ERSPC, where contamination in the control group led to no observable effect of PSA screening on prostate cancer mortality at 9 years follow-up (Villers et al., 2020). The UK CAP randomised controlled trial of more than 415 000 participants also showed that, while a one-time PSA test detected more cancers than the unscreened control arm, there was no significant reduction in mortality after 10 years (Martin et al., 2018).

Van Poppel et al. argue that the increasing burden of prostate cancer in the EU and the uneven rollout of unorganised PSA testing calls for a contemporary, organised, risk-stratified programme for early detection of the disease. They suggest that not only will this reduce the harms of prostate cancer in terms of survival and quality of life, but it will also improve the harm-to-benefit ratio by reducing the likelihood of potential overdiagnosis and overtreatment while avoiding underdiagnosis (Van Poppel et al., 2021).

Much more could be done to gather meaningful data from the large number of men who are undergoing ad hoc unorganised/opportunistic PSA testing across Europe, including gathering data about participants, diagnostic workup and clinical outcomes. This will require political will and input to achieve, but could make a major contribution to our understanding of the harms and benefits of screening and improve the early diagnosis of life-threatening prostate cancers.

5.2. Benefits and harms of prostate cancer screening

The harm/benefit ratio of a cancer screening intervention can be expressed as the 'number needed to detect'. In relation to prostate cancer screening, this is the number of people who have been over-diagnosed relative to the number of deaths prevented.

Reanalysis of the ERSPC and PLCO prostate screening trials demonstrates that the number needed to detect drops following additional years of follow-up. Cancer screening trials like ERSPC tend to initially overestimate the harm/benefit ratio due to a relatively high number of cancers detected in the first years of the trial under optimal screening conditions (which may be both a source of potential harm as well as implying future beneficial effect) but generally there is only a relatively short follow-up time in which to prove the benefit of the intervention in terms of overall survival or reduction in cancer-mortality. As a result, the benefits of prostate screening only truly start to emerge around 7–10 years following randomisation (Gulati et al., 2011).

Prostate cancer screening

Another area where the harms and benefits of prostate cancer screening must be balanced is in the age at which men are invited for testing. Older men are at greater risk of prostate cancer, but also greater risk of overdiagnosis (Gulati et al., 2017; Gulati et al., 2014).

Based on economic analysis and modelling of data from the ERSPC, using a strategy of PSA threshold of 3.0ng/ml screening with 2-year intervals between ages 55–59 would result in a 13% drop in prostate cancer mortality, with a limited amount of overdiagnosis (33% of screen-detected cancers overdiagnosed) (Heijnsdijk et al., 2015). This analysis also showed that continuing PSA testing for older men would lead to reduced quality of life improvements for the group as a whole compared to stopping around age 59–64.

However, at an individual level it might seem unethical to cut screening off at a certain age. It is therefore important to have further strategies such as additional post-screening tests (see section 5.3 on page 31) and risk stratification, to determine whether it might be of value to continue screening at older ages and to reduce the risks of overdiagnosis if the upper age limit is extended.

As well as screening strategies, the treatment options offered to men with screening-detected cancers also influence the cost-effectiveness, harms and benefits of prostate screening, with current more aggressive treatments leading to higher costs and reduced quality of life compared with conservative approaches such as active surveillance (Roth et al., 2016).

Risk-stratification approaches have been proposed as a way of refining prostate cancer screening to reduce potential harms. Heijsdijk et al. (2020) showed that stopping screening for men at the age of 60 with a PSA level <1ng/ml had a significant impact on reducing the burden of screening compared with continuing to offer testing to all men every 2 years until the age of 69, with a similar number of cancers detected and lives saved. However, it did not significantly reduce overdiagnosis.

The use of risk stratification algorithms that include characteristics such as historical PSA results and family history (a proxy for genetic risk) can also help to reduce the number of false positives from prostate cancer screening and the impact and harms of overdiagnosis (see e.g. Poppel et al., 2021).

To date, most of the research in prostate screening has focused on reducing harms due to overdiagnosis. These efforts most likely inadvertently result in a small increase in the number of harmful cancers that are missed. Going forward, it will be important to monitor the effectiveness of approaches such as risk stratification and reflex testing to ensure that a favourable balance of harms and benefits is maintained.

5.3. Additional testing to reduce unnecessary biopsy and overdiagnosis

A number of additional post-screening testing strategies (sometimes known as reflex testing) have been put forward to further stratifying individuals with moderately elevated PSA levels to distinguish between the indolent (low grade, low volume) and the aggressive cancers and reduce overdiagnosis.

Low-risk (clinically insignificant) tumours, which are unlikely to lead to death from prostate cancer within 15 years, are defined as:

- small (volume of less than <0.5cc)
- low grade (Gleason grade 3 only, or Grade Group 1)
- slow growing (doubling time more than 2–4 years)
- very low risk of metastasis (<2%)

Importantly, such tumours mostly do not show up with MRI scanning, and never show up if the tumour volume is less than 0.2cm^3. A systematic review of 20 studies of MRI scanning, including more than 5200 participants, showed that prostate MRI could reduce the need for biopsy in men with an abnormal PSA result by around a third. Conversely, if the MRI did detect a tumour, this was likely to be cancerous in around 96% of cases (Drost et al., 2019). However, these studies were carried out in the context of self-referred unorganised PSA testing, rather than in a population screening setting.

Two randomised controlled trials have investigated the effectiveness of reflex MRI scanning following PSA screening programme. Eklund et al. (2021) showed that MRI scanning for men with abnormal PSA results showed a significant reduction in the need for biopsies and associated harms, while Nordstrom et al. (2021) found that combining the Stockholm 3 test with an MRI-targeted biopsy approach for prostate cancer screening decreases over-detection while maintaining the ability to detect clinically significant cancers. The effectiveness of MRI scanning was also demonstrated in a cohort study by Eldred-Evans, whereas post-PSA ultrasound scanning was not effective (Eldred-Evans et al., 2021).

The evidence shows that MRI and biopsy indication should only be used in the context of pre-testing with PSA as a standalone screening tool or replaced by another equivalent test such as the much more expensive Stockholm 3 blood test (Grönberg et al., 2018), or alongside measurements of PSA-density (PSA/prostate gland volume) (Buisset et al., 2021). It should be noted that MRI scanning has only been tested in the context of one-off PSA tests, rather than alongside repeated PSA testing every couple of years. The potential for the MRI diagnostic pathway to reduce unnecessary harms is also demonstrated by its key role in selecting cases for active surveillance to reduce overtreatment. In addition,

MRI allows the selection of cases for partial gland thermo-ablation — an experimental treatment for significant unilateral cancers visible at MRI, which can avoid most sexual and urinary side effects.

Although MRI can significantly reduce the harms of prostate cancer screening through overdiagnosis, securing enough scanning resources and quality of reading will be a challenge in many countries. One solution is to offer biparametric MRI scanning, or 'Manogram', which does not require expensive contrast agents, is relatively quick and costs less than €100 per scan (Scialpi et al., 2017). Cost-effectiveness analysis suggests that this approach will fall within acceptable limits for many healthcare systems and compare favourably against the costs of later prostate surgery, radiotherapy or drug treatment for metastatic disease (Getaneh et al., 2021). Introducing these scans widely will require quality assurance, training and accreditation in order to maintain standards, similar to the situation with mammography for breast cancer.

The use of additional tests (reflex biomarkers) for men with moderately elevated PSA levels between 4–10 ng/ml have been suggested as a way to reduce overdiagnosis. Most of these are based on looking for certain genes or molecules shed into urine — such as the presence of TMPTSS2:ERG gene fusions or PCA3 mRNA — offering a potentially useful non-invasive second line test to reduce overdiagnosis (Chang et al., 2021). These tests offer a moderate reduction in overdiagnosis with a slight reduction in lives saved by screening (Gulati et al., 2020).

A cost-effectiveness analysis of hypothetical reflex tests showed that MRI screening did not fall on the Efficient Frontier (Jiao et al., 2021). This was partially due to the high cost of MRI un the US setting. It should also be noted that most discussions of cost-effectiveness of prostate cancer screening fail to take into account the high costs of treatment for metastatic disease, the economic costs of life years lost, or the impact on quality of life for patients. More research is needed to develop cheaper reflex testing for prostate cancer screening.

5.4. Cost-effectiveness of prostate cancer screening

An analysis of eight prostate cancer screening trials by Sanghera and colleagues found that fewer than half of studies showed that screening came under the $100 000 per QALY threshold (Sanghera et al., 2018). However, this was highly dependent on treatment strategies and the age range and screening interval, with opportunities for cost-effectiveness through active surveillance and limiting screening to younger age groups. Roth et al. (2016) showed for prostate cancer screening to be cost-effective, screening and biopsy would have to be quite conservative particularly at older ages and men with low-risk disease would have to be treated conservatively with active surveillance.

Incorporating secondary testing and more stratified participant selection to determine whether and when to start prostate screening (and to determine the age at which to stop), and the continued development of risk predictors and algorithms that better select men who need a biopsy will be needed to decrease the high risk of over-diagnosis and over-treatment and have a further impact on cost-effectiveness.

Case study: Listening to the experiences of men with prostate cancer

Led by patients for patients, the Europa Uomo EUPROMS study was carried out in order to discover more about the impact of prostate cancer, gathering nearly 3000 online survey responses across 25 countries (Venderbos et al., 2020). Available in 19 languages, the study used validated quality-of-life questionnaires (EPIC-26, EORTC-QLQ and EQ-5D-5L) to show that men's sex lives were affected most by treatment, with nearly half of all men saying that it was a big or moderate problem and three in four men who have been treated for prostate cancer rating their current sexual function as poor or very poor.

The survey also showed that chemotherapy was most associated with tiredness, pain and discomfort, insomnia and poor mental health. Radiotherapy plus hormone therapy also had a notable impact on pain/discomfort, insomnia and poor mental health, while treatments involving prostatectomy had the greatest impact on continence.

The more advanced a prostate cancer is at diagnosis, the worse the effects of treatment on quality of life. Therefore, in the eyes of patients, diagnosing the disease at an early stage is of paramount importance. Furthermore, early diagnosis followed by active surveillance should be considered as the first line treatment where it can be safely applied, in order to ensure the best quality of life for men with prostate cancer and to reduce healthcare costs.

5.5. Conclusion: Prostate cancer screening

In conclusion, one large-scale RCT has shown PSA testing to be effective in reducing prostate cancer mortality and metastatic disease. It applied to the core age group 55–69. The US trial and French ERSPC trials have been underpowered due to substantial testing in the control arm, diluting the true effect, and a very low biopsy rate in screen-positive men. A re-analysis using all ERSPC and PLCO data showed that the PLCO trial was not in fact in dispute with the benefit of PSA testing found in the ERSPC trial, while the study of one-time PSA testing in the UK with low compliance rates is not informative.

Overdiagnosis and overtreatment are major harms in prostate cancer screening, due to the high prevalence of slow-growing low grade cancers in men. Imposing an upper age

limit on screening (possibly around 65-69), and/or a high-quality MRI or other accurate reflex testing pathway for PSA-positive men will likely reduce overdiagnosis and improve the harm-benefit ratio. Such scenarios are likely to be cost-effective for many EU member states. Opportunistic, unorganised PSA testing leads to insufficient use in younger men and overdiagnosis in older men, resulting in substantial amounts of unnecessary overtreatments for older men and preventing the realisation of benefits in younger men.

The experts find the scientific basis for organised prostate cancer screening strong provided that the age criteria are appropriate. It is likely that MRI will become part of prostate screening in the future. We strongly recommend that we need to address the high levels of opportunistic PSA testing in order to reduce overdiagnosis and harm.

6. Gastric cancer screening

Gastric (stomach) cancer is strongly linked to infection with the bacteria *Helicobacter pylori*, a common infection affecting around 50% of the global population. Rates of the disease are highest in Asia, Eastern Europe (Baltic and the neighbouring states), Portugal, and some parts of South America.

Although rates are lower in Europe and have declined over recent years, around 136 000 Europeans are diagnosed and 97 000 die from gastric cancer every year, projected to rise to around 169 000 cases and 124 000 deaths by 2040. Estimates suggest that around 35-40% of these deaths could be prevented by identification and treatment of *H. pylori* infection, which would add up to many tens of thousands of lives saved over the coming years.[19]

The top line findings from the rapid literature review of gastric cancer screening trials are:

- Endoscopy is able to identify individuals with precancerous lesions to be referred for further surveillance.
- The cost-effectiveness of endoscopic screening has not been justified outside East Asian countries.
- Compliance rates for endoscopic screening were approximately 45% based on studies in East Asia; lower compliance would be expected outside Asia.
- Pepsinogen detection in the circulation is the best studied non-invasive test to identify precancerous lesions, primarily gastric atrophy, although it has relatively low sensitivity for detecting atrophic gastritis.
- Limited data from two trials not identified within this rapid review, but included in a systematic review, suggest a 79–80% sensitivity and specificity for cancer identification by breath analysis; this technology is still evolving.

6.1. Effectiveness of screening for gastric cancer

Screening for gastric cancer falls into four areas:

- endoscopic screening
- detection of the protein pepsinogen in the blood
- detection and treatment of *H. pylori* infection ('screen-and-treat' strategy)
- breath analysis (detection of volatile organic compounds)

19 https://gco.iarc.fr/

A systematic review and meta-analysis of trials of endoscopy screening for gastric cancer in Korea, Japan and China involving more than 342 000 individuals showed a significant reduction in mortality from the disease (Zhang et al., 2018). However, the cost-effectiveness and acceptability of the procedure is not evident in lower-risk countries outside Asia.

There is insufficient evidence to support the use of pepsinogen detection as a screening method for gastric cancer, although it could potentially be useful as a pre-screening test to identify individuals who may benefit from further endoscopic investigation (for example, (Trivanovic et al., 2018).

There may be utility in using more sophisticated signatures of metabolic markers in the blood for early identification of precancerous gastric lesions that are likely to progress to cancer (Huang et al., 2021).

Breath tests could also potentially be used as a screening tool or to select individuals for gastroscopy, although more research needs to be done to validate this approach (Krilaviciute et al., 2018; Haddad et al., 2020).

6.2. H. pylori 'screen-and-treat'

The 'screen-and-treat' strategy for reducing H. pylori infection is emerging as a key opportunity to prevent gastric cancer and was highlight by IARC in 2014 as a global priority in reducing deaths from the disease.[20]

The benefits of this approach have been demonstrated in a number of studies in Asia (Ford et al., 2015). For example, Chiang et al. (2021) showed a 53% reduction in gastric cancer incidence and mortality on the Taiwanese island of Matsu through the use of a breath test to identify infected individuals followed by antibiotic treatment. A large randomised controlled trial of nearly 185 000 residents of Linqu County in China is expected to unblind the data some time in 2022 (Pan et al., 2016).

However, it is not clear how transferable these findings from Asia are to European populations. In Europe, the GISTAR study is recruiting individuals aged 40–64 in Latvia to investigate the efficacy of blood and breath-based screening for pepsinogen and other markers, as well as *H. pylori* screening and eradication, on reducing mortality from gastric cancer at 15 years (Leja et al., 2017). Initial findings on acceptability and compliance are positive, although there is a need to raise awareness of gastric cancer and its prevention among the population for such screening and treatment programmes to succeed (Leja et al., 2021).

20 https://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/-Em-Helicobacter-Pylori-Em-Eradication-As-A-Strategy-For-Preventing-Gastric-Cancer-2014

The 2020 Taipei global consensus concluded that there is sufficient evidence to support the testing of all high risk individuals for *H. pylori* infection and subsequent treatment, and that mass screening and eradication of *H. pylori* should be considered in populations at higher risk of gastric cancer (Liou et al., 2020).

The forthcoming EU Maastrict VI-Florence guideline is expected to suggest that population-based *H. pylori* screen-and-treat programmes should be integrated into healthcare priorities in regions with intermediate to high gastric cancer incidence, where such strategies are most cost-effective. Programmes should be targeted to requirements at a regional level, including the choice of screening tool, treatment options, and ongoing surveillance of high-risk individuals. However, so far Slovenia is one of the first countries to investigate the potential for screening and treating *H. pylori* infection on a population level (Tepes et al., 2018).

As a note of caution, the screen-and-treat strategy does require relatively high use of antibiotics by large numbers of people, which runs contrary to the principles of stewardship that are required to tackle the challenge of antimicrobial resistance. Solutions to this problem could be the use of antibiotics that are not required for treating life-threatening diseases, or a more narrow selection of individuals for *H. pylori* screening (Leja & Dumpis, 2020).

To summarise, according to the recommendations of the IARC expert group,[21] implementation research of screen-and-treat strategy should be facilitated in Europe.

6.3. Cost-effectiveness of gastric cancer screening

While there is a strong rationale for *H. pylori* screen-and-treat strategies in countries with high rates of gastric cancer, the balance between benefits, harms and costs of screening is less clear-cut in regions with low rates, including most European countries. A systematic review of 9 studies in Western countries showed that a strategy of screening and treating for *H. pylori* infection was cost-effective with the majority of studies coming in under $50 000 per QALY. By contrast, all three reviewed studies of endoscopic screening for premalignant gastric conditions in Western countries were over $100 000 per QALY and therefore not cost-effective (Lansdorp-Vogelaar et al., 2021).

6.4. Conclusion: Gastric cancer screening

Gastric cancer rates are falling with improvements in living conditions and reduction in *H. pylori* infection rates. However, prevention strategies are still required since the disease

21 https://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/-Em-Helicobacter-Pylori-Em-Eradication-As-A-Strategy-For-Preventing-Gastric-Cancer-2014

will not disappear by itself. There is insufficient evidence to recommend endoscopic screening of gastric cancer in Europe. The screen-and-treat strategy for reducing *H. pylori* infection provides a key opportunity to prevent gastric cancer in EU countries with intermediate to high gastric cancer incidence.

Research is needed to develop a holistic approach to screening and prevention strategies for oesophageal and gastric cancer since these are easily accessible, adjacent organs. Further research to find easier, affordable testing strategies that do not rely on endoscopy would be valuable.

Immediate, well-designed *H. pylori* screen-and-treat implementation strategies could be recommended on a regional or national basis alongside thorough monitoring and outcome data collection.

7. Oesophageal cancer screening

Around 53 000 people are diagnosed with oesophageal cancer in the EU every year, and around 45 500 will die from the disease. This disease is around three times more common in males than females.[22] It should be noted that cancers around the gastro-oesophageal junction are sometimes classified as gastric and so these rates may be an underestimate.

There are two distinct histological categories of oesophageal cancer: adenocarcinoma and squamous cell carcinoma. The two types generally have an inverse distribution, with countries with high rates of adenocarcinoma tending to have low rates of SCC and vice versa.

Rates of adenocarcinoma have risen rapidly in recent years in several European countries including Denmark, the Netherlands, UK and Switzerland (Castro et al., 2014), while SCC tends to be more common in Southern Europe. These geographical variations relate to the distinct risk factors for the two subtypes. Hence, any possible screening and primary prevention strategies would need to be tailored to the dominant subtype (Kamangar et al., 2020).

The majority of oesophageal cancers are diagnosed at a late stage, when the chances of survival are low. Overall, fewer than 20% of patients survive for at least five years — a figure that has changed little over the past 40 years (Arnold et al., 2019). Since early disease can be treated endoscopically with endoscopic resection and ablation, earlier diagnosis of both types of oesophageal cancer represents a significant opportunity to reduce cancer mortality and reduce the morbidity associated with the systemic therapy and oesophagectomy required for more advanced disease.

The trial data is limited for this cancer type but the top line findings from the rapid literature review of oesophageal cancer screening are:

- Studies from China, where the incidence rates are highest for squamous cell carcinoma, show that endoscopic screening can improve the detection rate of SCC, compared to the control group.
- Compliance rates were less than 50%.
- There are no data reported on cancer mortality outcomes.

22 https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf

7.1. Screening for oesophageal adenocarcinoma

The majority of oesophageal adenocarcinoma develops from a pre-cancerous condition called Barrett's oesophagus. Barrett's oesophagus is a change in the normal squamous lining of the oesophagus to a glandular phenotype that is more protective against acid and bile reflux coming up from the stomach. Reflux symptoms are the major risk factor for developing Barrett's oesophagus and oesophageal adenocarcinoma is estimated to occur in up to 10% with chronic heartburn and around 1 in 100 people globally (Lagergren et al., 1999), although the prevalence is highly varied geographically (Marques de Sá et al., 2020). Despite the link between Barrett's oesophagus and cancer, the majority of cases of Barrett's are undiagnosed, raising the question of whether screening for the pre-cancerous condition should be introduced.

Barrett's oesophagus is diagnosed with endoscopy, and patients identified as having the condition are then entered into monitoring or surveillance programmes to identify pathological changes termed dysplasia. While the majority of people with non-dysplastic Barrett's (90%) will not go on to develop further dysplasia or cancer in their lifetime the chances of progression to cancer from low- or high-grade dysplasia are substantial (10-30%). Endoscopic treatment is therefore recommended for Barrett's dysplasia. This comprises resection ablation techniques that can be done as an outpatient procedure, and randomised controlled trial data shows that the response is durable and curative in many cases (Phoa et al., 2014; Shaheen et al., 2009). Therefore, there is a strong rationale for identifying and monitoring people with Barrett's oesophagus so that treatment can be given for dysplasia and early cancer to prevent progression to advanced, incurable disease.

Endoscopy screening can be performed with standard white light oral endoscopy or as an office-based unsedated transnasal procedure. While transnasal endoscopy (TNE) is potentially more accessible, as it can be delivered either in a clinical setting or in a mobile unit, it still requires a skilled operator and investment in equipment, limiting its feasibility for widespread screening. The biopsy samples are smaller with trans-nasal endoscopy than with an oral procedure and are generally sufficient for diagnostic but not for monitoring purposes.

There is no population based, randomised controlled trial data on endoscopic screening for Barrett's oesophagus. However, there have been some studies comparing the yield between oral and trans-nasal endoscopy for screening and the results are encouraging (Sami et al., 2015). Attention is now turning to non-endoscopic cell sampling techniques as a simple, more cost-effective technique for screening, which will be discussed in the third expert workshop on novel screening technologies.

The current European consensus on screening for Barrett's oesophagus is that endoscopic screening is not recommended, except for people with long-standing gastroesophageal reflux disease (GERD, also manifesting as acid reflux or heartburn) together with other risk factors such as older age, white ethnicity, male sex, obesity and strong family history (Weusten et al., 2017).

Meta-analysis of 49 studies involving more than 300 000 individuals looking at the relationship between risk factors and Barrett's oesophagus suggests that any screening intervention will need to be targeted to the groups most at risk in order to identify Barrett's with a prevalence of 3% or more (Qumseya et al., 2019; Rubenstein et al., 2021). These recommendations rely on the discretion of family practitioners and there is no organised screening programme.

7.2. Early detection of oesophageal squamous cell carcinoma

The rates of squamous cell carcinoma (SCC) vary significantly around the world. Compared with China and Iran (e.g. Wei et al. 2015) the low incidence of oesophageal SCC in Europe does not warrant population-wide screening, but may be beneficial for individuals with known factors that put them at highest risk, including:

- previously having had surgery for oesophageal SCC
- recently having SCC elsewhere in the head or neck
- heat or mechanical damage to the oesophagus
- history of heavy tobacco and alcohol use
- achalasia (a rare condition that makes it difficult to swallow)

However, the available evidence shows that the population most likely to benefit from surveillance is those who have recently had SCC elsewhere in head and neck (Dubuc et al., 2006; Scherübl et al., 2002), and the pros and cons need to be weighed carefully since, even for this group, regular surveillance may lead to overdiagnosis (Su et al., 2013).

More research is needed to determine whether screening or targeted surveillance for oesophageal SCC is effective and reduces mortality from the disease. As for detection of Barrett's oesophagus, attention is now turning towards non-endoscopic cell sampling techniques which are being trialled in high incidence areas of China and which could improve the ease, accessibility and costs of screening in targeted groups.

7.3. Conclusion: oesophageal cancer screening

In conclusion, oesophageal cancer is a lethal disease that needs better approaches to screening and prevention. The particular approach taken will need to be tailored across EU member states according to the main subtype (squamous or adenocarcinoma).

Neither the experts nor the literature review finds scientific grounds to recommend population-wide oesophageal cancer screening for EU member states at the current time. However, more could be done to ensure that guidelines for endoscopy referral in at risk groups are followed to maximise opportunities for earlier diagnosis.

Further research is encouraged for novel approaches to targeted oesophageal screening that improve access, acceptability and affordability, such as the Cytosponge (presented in this workshop but to be discussed in the New Technologies section of the Evidence Review Report).

8. Ovarian cancer screening

Around 67 000 cases of ovarian cancer are diagnosed every year in Europe, at least half of which are diagnosed at a late stage (3 or 4). Although survival has doubled since the 1970s, it still remains relatively low, with fewer than half of all women surviving 5 years or more.

Screening for ovarian cancer has been done to date using either transvaginal ultrasound (TVS) and/or a blood test for CA125, a glycoprotein that fluctuates naturally during the menstrual cycle and is often raised in ovarian cancer. Large randomised control trials in average risk women using these screening tests did not result in a reduction in deaths from ovarian cancer, and screening for ovarian cancer is therefore not currently recommended for the general population at average risk in any country.

Recommendations for screening women at high genetic risk who have not undergone preventative surgery to remove their ovaries and fallopian tubes vary. European and US guidelines state that screening may be considered using 6-monthly TVS and CA125 testing, after discussion with the patient that there is currently no evidence to show that this is effective in reducing mortality from the disease.

The top line findings from the rapid literature review of ovarian cancer screening trials are that in the general population:

- Although screening with CA125 testing using a longitudinal algorithm led to a stage shift in ovarian cancer diagnosis, a large randomised controlled trial showed no improvement in cancer mortality using any of the screening strategies employed, compared with no screening.
- There were unnecessary operations as a result of screening in all trials.
- The psychosocial harms were minor for screening, unless high-level repeat screening was required.

8.1. Evidence of effectiveness of ovarian cancer screening

Ovarian cancer has been redefined in recent years to reflect the new evidence of the tubal origin of high-grade serous cancer. As a result, the new WHO 2014 classification of ovarian and tubal cancers includes the majority of the cancers that were previously assigned as arising from the peritoneum. Various trials have used different definitions of the disease, making like-for-like comparisons difficult.

Bearing this in mind, no trials of ovarian cancer screening to date have demonstrated a mortality benefit. However, the harms of ovarian cancer screening include surgery

following a false-positive test, often resulting in removal of one or both ovaries or fallopian tubes, along with the potential for major surgical complications (Henderson et al., 2018). The randomised controlled Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial of nearly 70 000 US women aged 55–74 evaluated annual screening using TVS and CA125 (interpreted using a cut-off). There was no benefit in terms of ovarian cancer incidence, stage at diagnosis or cancer mortality reduction after 15 years of follow-up. Unnecessary surgery as a result of a false-positive screen findings was associated with a 15% complication rate (Buys et al., 2011; Pinsky et al., 2016).

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) randomised more than 200 000 post-menopausal average risk women aged 50-74 to either annual multimodal screening using CA125 interpreted using a longitudinal algorithm followed by second line repeat CA125 testing and TVS screening (50 640 participants) or ultrasound with first- and second-line screening with TVS only (50 639) with an unscreened control group of 101 359 participants.

After a median 16.3 years of follow-up, the study showed no difference in incidence between either of the screened and unscreened groups. While there was a 10% decrease in advanced stage disease in the multimodal screening arm, there was no overall improvement in cancer-specific mortality from either screening approach (Menon et al., 2021). During the trial, in both arms women had unnecessary surgery (14 per 10 000 annual screens in multimodal and 50 per 10 000 annual screens in ultrasound arm) with a 3.1–3.5% major complication rate (Jacobs et al., 2016). The researchers also found that being asked to return for repeated screening following an elevated CA125 result did cause some anxiety for participants (Barrett et al., 2014).

Although the UKCTOCS did not show a positive result, it did suggest that there may be utility to using more personalised risk algorithms based on serial CA125 levels to interpret test results (Blyuss et al., 2018; Menon et al., 2015).

The lack of positive findings to date in ovarian cancer screening suggests that more work needs to be done to develop biomarkers and imaging techniques that are based on the advances in our understanding of the natural history of ovarian cancer and its histological subtypes. Only then will it be possible to detect the disease early enough to impact on mortality. There is also a need to explore better treatment options for screen-detected aggressive early-stage cancers.

8.2. Conclusion: Ovarian cancer screening

In conclusion, two large RCTs on screening for ovarian cancer did not find a beneficial effect. Neither the experts nor the literature found scientific grounds to recommend ovarian cancer screening for EU member states at the current time.

Further research is needed to identify improved technological approaches for this lethal cancer (to be discussed in the New Technologies section of the main report).

9. Feasibility and governance

A cancer screening test must demonstrably shift the stage of diagnosis earlier, reduce cancer-specific mortality and improve quality of life and patient outcomes, and the benefits must outweigh the harms in terms of avoiding overdiagnosis and treatment.

Although it may offer significant savings in terms of reducing treatment costs and economic life years lost, early diagnosis of cancer through screening is not always necessarily affordable to implement. Any proposed screening programme must also be cost-effective for the population in which it will be used, and there must be suitable oversight and expertise in order to deliver and monitor it effectively, along with the health service infrastructure required to follow up and treat cancers identified through screening.

9.1. Feasibility of introducing new cancer screening programmes

In addition to the principles of screening outlined in section 2 on page 9, the World Health Organisation recommends the following principles for assessing the feasibility of cancer screening programmes:[23]

- **Infrastructure:** adequate existing infrastructure (e.g. financial and human resources, information technology, facilities, equipment and test technology) to allow equal and equitable access
- **Coordination and integration:** coordinated components of the programme and, where possible, integrated with the broader health care system to optimise care continuity and ensure no screening participant is neglected
- **Quality and performance management:** clear goals or objectives that are explicitly linked to programme planning, monitoring, evaluating and reporting activities, with dedicated information systems and funding, to ensure ongoing quality control and achievement of performance targets

The results of randomised clinical trials for a given cancer screening intervention are therefore just the beginning of a long process that may or may not lead to its implementation. The diagram below shows the steps required for the successful implementation of a national screening programme (taken from the European Guide on Quality Improvement in Comprehensive Cancer Control).

23 https://www.euro.who.int/en/publications/abstracts/screening-programmes-a-short-guide.-increase-effectiveness,-maximize-benefits-and-minimize-harm-2020

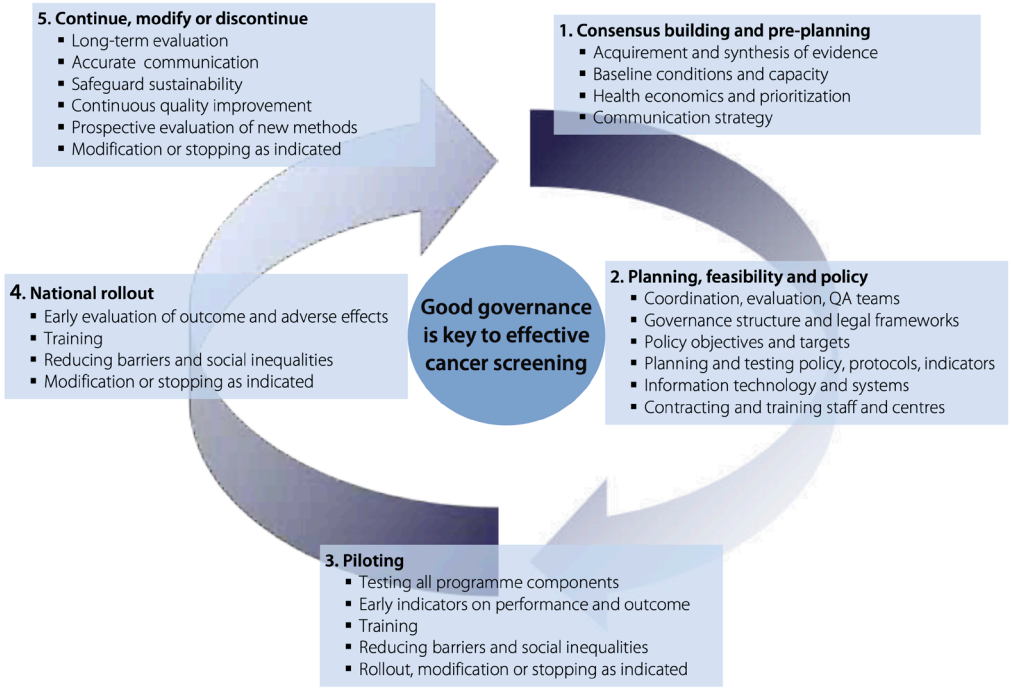


Figure 3. [24]

As highlighted in section 2 on page 9, cancer screening does not necessarily need to involve the whole population, and is likely to be more beneficial, less harmful and more cost-effective if steps are taken to stratify participants according to their risk, as in the case of lung cancer screening (see section 4 on page 17). However, this might be more time-consuming and costly than more straightforward categorical invitation for screening and requires a more sophisticated understanding of cancer risks by healthcare professionals and the public.

At the same time, care must be taken to ensure that everyone who is eligible for a screening test is able to take up the opportunity, to avoid perpetuating health inequalities. Screening programmes should also be integrated with other cancer prevention interventions, such as smoking cessation for lung cancer and HPV vaccination for cervical screening. Ways in which the European Code Against Cancer, which focuses on cancer prevention, can be embedded into cancer screening programmes have been explored in more detail by the Association of European Cancer Leagues, BPO Piedmonte and IARC.[25]

When considering developing recommendations for cancer screening in Europe, the varying demographic and economic situations of different countries must be taken into account. The implementation of the three current screening programmes that are available across Europe for breast, colorectal and cervical screening varies by

24 https://cancercontrol.eu/archived/guide-landing-page.html

25 https://www.europeancancerleagues.org/ecl-screening-actions/

country, and many thousands of people are still dying of preventable cancers. These discrepancies could be addressed through a greater focus on the implementation of recommendations geared towards providing screening programmes in real-life settings, together with an emphasis on the governance and investment required to deliver and monitor them.

There are a number of countries in Europe offering opportunistic ad hoc screening for diseases such as prostate and lung cancer. As mentioned in section 5 on prostate cancer screening, these unorganised programmes represent a missed opportunity to gather data on the benefits and harms of screening. It is the opinion of the expert group that cancer screening should only be carried out as part of an organised programme and that such 'wild' screening programmes should either be stopped or only carried out with a commitment to gather such data.

There are a number of changes happening in preventive healthcare that bring opportunities as well as challenges for the delivery of cancer screening. For example, new medical technologies such as biomarker tests or imaging techniques can improve the efficacy of screening, while the introduction of new IT approaches such as electronic health records brings significant opportunities to save time and streamline processes, while offering the potential for data linkage, real-time monitoring and machine learning/AI analysis of health data.

However, the unorganised adoption of new tests can skew the ratio of harms, benefits and cost-effectiveness of established screening interventions or clinical trials, especially if they have not been fully clinically validated. And the affordability of and unequal access to new medical and computing technologies also risks perpetuating or deepening inequalities within and between countries.

Finally, there is generally a need for greater widespread public engagement and communication about cancer in general and screening more specifically, in order to improve awareness of cancer, prevention and the screening opportunities that are available for them.

9.2. Governance of national cancer screening programmes

The European Guide on Quality Improvement in Comprehensive Cancer Control (CanCon) has produced a number of recommendations of the successful governance and implementation of national cancer screening programmes:[26]

- Successful evidence-based cancer screening needs a competent, multidisciplinary and transparent governance structure with political, financial and stakeholder support.

26 https://cancercontrol.eu/archived/guide-landing-page.html

- The legal code should provide a specific framework for population-based cancer screening, enabling as a minimum the following basic functions: personal invitation, mandatory notification and central registration of complete screening and outcome data and individual linkage to cancer and cause of death registries for appropriate quality assurance including audits.
- Successful implementation of effective cancer screening programmes requires significant resources for quality assurance, that is 10–20% of the estimated total expenditure of a full-scale programme.

In a presentation given at the first expert workshop, Dr Urska Ivanu, Head of Screening Department, Institute of Oncology, Ljubljana, Slovenia, noted that there is a need at the EU level for permanent structures dedicated to the assessment and implementation of cancer screening programmes. This should include continuous evidence review and updating of screening criteria, guidelines, recommendations and standards in order to take advantage of new advances and evidence in screening. This will help to avoid losing lives through late implementation of effective screening practices or doing inadvertent harms through incompletely tested interventions.

There needs to be a commitment to data-gathering to monitor and evaluate of the benefits and harms of cancer screening (including ad hoc unorganised screening), with Europe-wide reporting and information-sharing. Similarly, the exchange of knowledge and experience should be encouraged between the EU countries and projects to assess evidence and support decision-making processes around screening, the planning, implementation and delivery of screening services, and responses to changes in the environment (for example, infectious disease outbreaks) on a national and regional level. Such knowledge-sharing would also support the development, optimisation and uptake of validated screening processes.

This could be modelled on the process for road-map development and policy cycle developed by the EU-TOPIA project[27] on breast, cervical and colorectal cancer screening, along with the EU-TOPIA tools such as simulations of the natural history of these cancers, tailored to individual European countries, to inform screening decisions (Gini et al., 2021). More research should be done to understand how cancer screening is organised and governed in different countries in order to facilitate formal and informal sharing and learning around the social as well as the technical aspects of governance (Sturdy et al., 2020).

On a national level, the timely implementation, high coverage and quality of recommended organised screening programmes and their sustainability within the limitations of a country's economic and infrastructure resources requires permanent political structures. Prioritisation of new cancer prevention interventions should be

27 https://eu-topia.org/

made according to need, availability and affordability, and will not necessarily be exactly the same across all countries of the EU. This will help to prevent cancer screening programmes within a country having to compete between each other or other for funding.

Starting at the top, effective implementation of cancer screening requires shared vision and leadership, bringing all national, regional and local stakeholders on-board from the beginning to develop consensus. Decisions around the prioritisation and introduction of new screening programmes, changes to existing programmes, or stopping some types of screening altogether should be made by national screening boards or committees made up of relevant stakeholders, charged with making transparent and independent evidence-based decisions. All cancer screening programmes run within a given country should come under the umbrella of this national screening board, sitting within the ministry of health, in order to provide coherent oversight and funding, and to maintain close connections to health services.

There also needs to be formal coordination of different cancer screening and prevention programmes in all phases, from assessment and decision-making through to implementation and monitoring to ensure continuity of knowledge and experience, rational use of resources, operational readiness and optimal integration with the existing healthcare system.

9.3. Conclusion

The international experts are of the opinion that recommendations at EU level on possible new cancer screening programmes, such as for lung and prostate, should strongly influence decisions of EU member states to ensure uniformity, quality, and equity for EU citizens.

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:**
  - Dr Alison Weightman (Director)

- Professor David Baldwin (Consultant Respiratory Physician and Honorary Professor of Medicine, Respiratory Medicine Unit, Nottingham University Hospitals and University of Nottingham, United Kingdom)
- Professor Jelle Barentsz (Professor of Radiology and Chair of the Prostate MR Expert Centre, Radboudumc, Netherlands)
- Professor Matthew Callister (Consultant Respiratory Physician, Leeds Teaching Hospitals NHS Trust, United Kingdom)
- André Deschamps (Chairman, EUROPA UOMO-The Voice of Men with Prostate Cancer in Europe, Antwerp, Belgium)
- Professor Mark Dobrow (Associate Professor, Institute of Health Policy, Management and Evaluation, University of Toronto, Canada)
- Professor Ruth Etzioni (Public Health Sciences Division-Fred Hutchinson Cancer Research Centre, Seattle, USA)
- Professor/ Chief Physician Jonas Hugosson (Department of Urology, University of Gothenburg, Sweden)
- Dr Urska Ivanus (Assistant Professor, Head of Screening Department, Institute of Oncology Ljubljana and Head on National Cancer Screening Committee, Slovenia)
- Professor Rudolf Kaaks (Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany)
- Professor Michal Kaminski (Head of Department of Cancer Prevention and Head of Endoscopy Unit, Department of Gastroenterological Oncology at the Maria-Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland)
- Dr Iris Lansdorp-Vogelaar (Associate Professor-Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands)
- Professor Mārcis Leja (Professor, Faculty of Medicine, University of Latvia, Latvia)
- Professor Usha Menon (Professor of Gynaecological Cancer, MRC Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, United Kingdom)
- Professor Linda Rabeneck (Vice President, Prevention and Cancer Control, Ontario Health and Professor of Medicine, University of Toronto, Canada)
- Professor Martin Tammemagi (Senior Scientist- Prevention and Cancer Control, Faculty of Health Sciences, Brock University, Canada)
- Dr Carmen Ungurean (Cancer screening coordinator, NIPH, Romania)
- Professor Arnauld Villers (Urologist, Department of Urology, Centre Hospitalier Universitaire of Lille, Lille University, France)

10:00	Welcome	Rebecca Fitzgerald Harry de Koning Stefan Constantinescu George Griffin
10:10	Rapid review of the published evidence	Alison Weightman
Section 1: General introduction — scientific basis of screening programmes		
10:20	Revised framework criteria considering harms and benefits of screening	Mark Dobrow Linda Rabeneck
10:45	Modelling (cost-)effective health policies	Iris Lansdorp-Vogelaar
11:10	Patient voices	André Deschamps
Section 2: Extending to lung cancer screening		
11:35	Trial evidence effectiveness (evidence from NELSON, the largest European trial for low-dose CT screening)	Harry de Koning
12:00	Feasibility and consideration of potential harms vs benefits	David Baldwin
12:25	Eligibility criteria	Rudolf Kaaks Martin Tammemägi
12:50	Smoking cessation	Matthew Callister
13:15	Discussion: Personalised prevention	All Section 2 speakers
13:40	Break	
Section 3: Extending to prostate cancer screening		
14:20	Trial evidence effectiveness	Jonas Hugosson
14:45	Harm/benefit	Ruth Etzioni
15:10	MRI diagnostic pathway to reduce unnecessary harms	Jelle Barentsz Arnauld Villers
15:35	Discussion: Risks vs benefits of prostate cancer screening	All Section 3 speakers
16:00	Break	
Section 4: Trial evidence in other relevant cancers		
16:20	Oesophageal cancer: screening for pre-cancerous Barrett's Oesophagus	Rebecca Fitzgerald
16:35	Oesophageal squamous cell cancer screening	Michal Kaminski
16:50	Gastric cancer	Mārcis Leja
17:05	Ovarian cancer	Usha Menon
17:20	Discussion: Trials in common cancers	All Section 4 speakers
Section 5: Feasibility and governance		
17:35	Discussion	Urska Ivanus Carmen Ungurean
17:50	Wrap-up and conclusions	Rebecca Fitzgerald Harry de Koning

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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?

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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)
- Dr Partha Basu (Deputy Head of Early Detection, Prevention and Infection Branch, International Agency for Research on Cancer, World Health Organisation, France)
- Professor Patrick M Bossuyt (Professor of Clinical Epidemiology, University of Amsterdam, Netherlands)
- 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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Cancer screening in Europe

Expert workshop 3

8 November 2021

Which are the main scientific elements to consider, and best practices to promote, for optimising risk-based cancer screening and early diagnosis throughout the EU?

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1. Introduction

Cancer risk varies widely between people according to their genetics, lifestyle and environment. An individual's risk also changes throughout their lifetime, most significantly increasing with age. Taking a future-focused view, this expert workshop explored a number of questions related to optimising cancer screening, including more sophisticated risk stratification and the use of novel technologies such as blood testing and artificial intelligence.

Cancer screening is not a benign procedure, bringing both benefits and harms. Although effective screening programmes can save lives by identifying potentially life-threatening cancers at an early stage when treatment is more likely to be successful, they can also cause physical and psychological harm through false positives and over-diagnosis. Care must be taken to ensure that the individuals who undergo screening are the ones that are most likely to benefit, and that this outweighs the risk of harm.

For example, a woman aged 30 has a 1 in 228 chance of developing breast cancer within the next ten years, while her 60-year-old mother has a 1 in 29 risk.[1] By contrast, the lifetime risk of breast cancer in men is around 1 in 833.[2] It would not be feasible or cost effective to offer breast screening to every adult in order to detect the very rare cancers in younger age groups or males, and such an approach would likely result in a significant number of over-diagnoses and false positives. Given that every country's screening capacity is limited to a greater or lesser extent, it makes sense to identify and screen those who are most likely to benefit while reducing screening for those at lowest risk.

New technologies have the potential to improve the efficacy and cost effectiveness of screening, but their benefits must be demonstrated through robust scientific studies. Furthermore, the changing evidence landscape around cancer screening requires innovative thinking in terms of governance and guideli.e. to ensure that populations can quickly benefit from the latest advances in research while avoiding possible harms caused by the premature introduction of procedures that have not been sufficiently tested. For example, it is possible to design implementation research of new technologies in such a way that robust evidence can be collected for example through cluster randomised or step-wedge approaches.

This workshop is supported by an associated Rapid Review of the scientific literature conducted by the Specialist Unit for Review Evidence at Cardiff University asking which

1 https://www.breastcancer.org/symptoms/understand_bc/risk/understanding

2 https://www.cancer.org/cancer/breast-cancer-in-men/about/key-statistics.htm

are the main scientific elements to consi.e. and best practices to promote, for optimising risk-based cancer screening and early diagnosis throughout the EU?

A full list of contributors to the workshop can be found in “Appendix 1: Programme and contributors” on page 36.

2. Risk-based screening for cancer

One way of influencing the ratio of benefits to harms achieved by cancer screening programmes is by altering the population that is invited to participate.

According to the principles laid out by Dobrow et al. (2018) (see also Workshop 1), the target population for cancer screening should be clearly defined (e.g. with an appropriate target age range), identifiable and able to be reached. Existing cancer screening programmes use targeted selection of individuals for screening by general demographic characteristics, for example age or sex. However, more personally tailored risk-stratified screening regimens can help to shift towards a more favourable balance of risks and harms for the group of individuals as a whole. Risk stratification refers to selecting specific groups of people for cancer screening depending on their individual risk of the disease being screened for, going beyond age and sex.

2.1. Principles of targeted and risk-stratified screening

Current population-based cancer screening programmes are already targeted to some extent, as individuals are invited according to age and sex. Within the screening population, more sophisticated approaches involve grouping individuals according to their risk profile and then offering tailored screening and risk management strategies. This could involve reduced intensity or no screening for those at least risk, through to intensified screening or even prophylactic medical or surgical interventions for those in the highest risk categories (Pashayan et al., 2020).

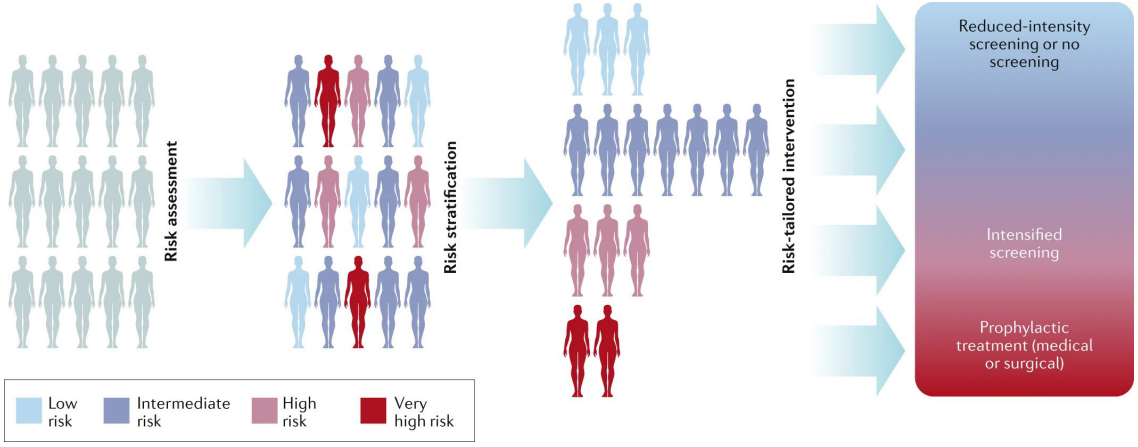

Figure 1. From Pashayan et al., 2020

Implementing such an approach raises a number of questions at each stage. Which risk factors should be assessed, at what point and how often? And how should this process be organised and delivered? Secondly, how many risk groups should be identified, based on which metrics and thresholds? And finally, what screening or prevention strategy should be used for each of these groups, which outcomes should be optimised for (e.g. maximising benefits, minimising harms, reducing costs or increasing equity of access) and how will such a programme be organised? We should also consider the type of evidence required to demonstrate these outcomes that will balance scientific robustness with speed and efficiency, such as randomised controlled trials, randomised studies within the health service, hybrid implementation-effectiveness studies or modelling studies.

In addition, there are other factors to consider, including the resources available, the existing healthcare system, the values, preferences and social norms of the population in question, and the evidence (or lack of evidence) to support risk-stratified screening approaches.

2.2. Risk-stratified screening for breast cancer

While age is the most significant risk factor for breast cancer, a number of other things can influence an individual woman's risk of developing the disease, including genetic makeup, mammographic breast density, age of first period, age at menopause, age of first child, family history of breast cancer, alcohol intake, smoking status, body mass index, and hormone replacement therapy use.

Increasing screening intensity for women at the highest risk of breast cancer while reducing it for those at lowest risk could therefore help to improve the balance of benefits and harms of screening (Pal Choudhury et al., 2020). As an example, the use of genetic information in the form of polygenic risk scores (PRS) has been demonstrated to have good predictive power for identifying women at highest and lowest risk of breast cancer, and could be used to improve breast screening programmes (Mavaddat et al., 2019). It should be noted that some individual risk factors can change over time, most obviously age, so risk assessments will therefore need to be repeated and risk thresholds adjusted in order to maintain accuracy (Pashayan et al., 2021).

A modelling study conducted by Pashayan et al. (2018) showed that risk-stratified screening was more cost-effective than purely age-based screening, and that the ratio of overdiagnosis to cancer deaths improved as the risk threshold increased (i.e. only women at the highest risk undergo screening).

Another recent modelling study based on US data incorporated PRS and family history to define 47 different risk groups with tailored screening start ages and intervals. The results showed that risk-based screening based on PRS had greater benefits than family history

alone, compared with standard age-stratified screening, and that the combination of the two was even better. Furthermore, given a fixed number of screening appointments that can be delivered within a national programme, allocating these resources based on risk reduces overdiagnosis and results in greater benefits across the whole population than age-based screening alone (van den Broek et al., 2021).

Risk-stratified screening approaches for breast cancer are being investigated in a number of studies that are expected to report results in the next few years including: PROCAS in the UK (see case study); the international MyPeBS randomised controlled trial;[3] the WISDOM study (Esserman, 2017); and the PERSPECTIVE Integration & Implementation project (Brooks et al., 2021).

2.3. Risk-stratified screening for prostate cancer

Applying a similar modelling approach to prostate cancer, for which there is currently no organised national screening programme in any EU member state, Callender et al compared three different screening strategies: no screening; age-based screening with four-yearly PSA testing between 55 and 69; risk-stratified screening based on polygenic risk score, with men above a given risk threshold receiving four-yearly PSA testing from the age they reach the risk threshold to age 69. Based on their model, the researchers showed that employing risk stratification based on PRS is likely to be more cost-effective than age-based or no screening, improve the benefit-harm balance of the screening programme, and reduce overdiagnosis while maintaining the mortality benefits of age-based screening (Callender et al., 2019).

Combining age-plus-PRS risk-stratified screening with additional MRI scanning for men with a positive PSA test further improved the benefit-harm ratio and the cost effectiveness of the screening programme compared to age-based screening alone (Callender et al., 2021). However, it is not simple to decide the exact risk threshold at which screening should start, as determined by percentage chance of developing prostate cancer in the next ten years based on age and PRS, and it will depend on judging the trade-off between the benefits and harms of screening, as well as careful public communication about such approaches.

Colorectal and ovarian cancer screening could also benefit from the application of risk stratification based on PRS but were not discussed in detail in this workshop.

3 https://www.mypebs.eu/

Case study: PROCAS — incorporating breast density and polygenic risk scores in breast screening

The Predicting Risk Of Cancer At Screening (PROCAS) study explored population breast cancer risk in a UK cohort based on polygenic risk scores, mammographic breast density and epidemiological risk factors (Tyrer-Cuzick model, see Himes et al., 2016). More than 50 000 women aged 46-73 were recrui.e. of whom 10 000 underwent genetic testing.

Combining mammographic density with the Tyrer-Cuzick model was able to identify a greater proportion of women who developed breast cancer than epidemiological risk factors alone. Adding in polygenic risk scores derived from 18 single nucleotide polymorphisms (SNPs, specific DNA variations known to be associated with either an increased or decreased risk of breast cancer) further increased the ability to stratify by risk, significantly increasing the proportion of women in the highest and lowest risk categories from 2.02% to 5.69% and 0.16% to 3.77%, respectively (van Veen et al., 2018).

Including 143 SNPs in the polygenic risk score calculation, together with breast density and epidemiological risk prediction, showed substantial improvement in risk stratification for both oestrogen receptor-positive and negative breast cancers (Brentnall et al., 2020). Furthermore, cancers occurring in the lowest risk group were more likely to be low grade (less aggressi.e. suggesting that risk-stratified screening is more likely to pick up life-threatening cancers in those at highest risk while reducing overdiagnosis in women at lower risk. Applying the SNP18 polygenic risk score to women with an existing family history of breast cancer but do not have a high risk version of BCRA1/2 also demonstrated utility for risk stratification (Evans et al., 2017).

2.4. Conclusions

Model-based estimates so far show that risk stratification using epidemiological factors, PRS and other factors (e.g. breast density) have the potential to improve existing screening programmes, and this approach could support the introduction of new screening programmes by improving the balance of benefits to harms and cost effectiveness.

The utility of PRS risk stratification in breast cancer screening has been demonstrated in a number of studies, and further trials that are due to report soon should help to confirm that such approaches work in the wider world. Implementation of risk-stratified screening will also be context-specific, depending on the populations and healthcare systems it is being applied to. Care must also be taken when setting risk thresholds, and that information about risk-stratified screening is clearly communicated to the public. It should

be remembered that some individuals may not wish to take part in risk stratification for cancer screening, so a generalised age-based option should always be retained.

It should be noted that current PRS calculations are mostly based on data from European ancestry populations and may not accurately reflect risk in other ethnic groups. Further research is needed to increase the diversity of populations in genetic research, in order to ensure equitable access to these tools (Evans et al., 2022). Data storage and privacy will also need to be considered as part of the implementation of any genetically stratified screening programmes.

There is good evidence to support the introduction of large national randomised implementation trials of risk-stratified screening in breast cancer. Careful ongoing analysis will be required to look at the impact of withdrawing screening for women at the lowest risk, and the proportion of overdiagnosis in those at increased risk. Analysis would need to be done to demonstrate cost effectiveness in terms of earlier diagnosis of breast cancer, but there could potentially be some healthcare cost savings through a reduction in breast cancers by offering the highest risk women preventative strategies such as chemoprevention with the drug anastrozole (Cuzick et al., 2020).

3. Shared decision-making around cancer screening

Any cancer screening procedure comes with potential benefits and harms. For example, in the case of breast cancer screening, the public conversation has moved in recent years to a more nuanced discussion that recognises the potential harms of screening such as false positi.e. overdiagnosis and unnecessary biopsies, as well as the benefits in terms of lives saved. As discussed in section 2 on page 9, the adoption of more tailored risk stratification strategies can shift the balance of harms and benefits, requiring more sophisticated discussions and shared decision-making for individuals (Keating & Pace, 2018).

The decision whether or not to take up an invitation for cancer screening rests with each individual. This is influenced by a wide range of factors:

- **demographics:** including age, gender, location, education, ethnicity/race, health knowledge and access to information, immigration status, and income/wealth
- **individual beliefs:** perceived susceptibility to a given disease and its severity, perceived benefits of and barriers to preventative action, and perceived self-efficacy
- **information and cultural context:** exposure to information and media campaigns, interactions with healthcare practitioners, experiences of friends and family, cultural norms, and previous personal experiences

Sociological research such as discrete-choice experiments can help to tease out the factors that are more or less important when considering the decision to attend screening, as well as the trade-offs between harms and benefits that they are prepared to make. For example, Sicsic et al. (2018) found that less than half of women would be willing to accept ten overdiagnoses to avoid one breast cancer-related death, with screening acceptance rates higher among women from higher socioeconomic groups and lower among women in poorer health.

When considering individual risk of developing cancer, people are more driven by emotions and feelings — including intuitions, beliefs, values and social/cultural identity — rather than rational cognitive processes (Klein et al., 2020). This is also highlighted by the observation that most adults do not change their behaviour after being told that they are at an increased risk of breast or colorectal cancer due to their genetic makeup (Gray et al., 2017). People may therefore be particularly responses to messages around cancer risk and screening that highlight social comparisons and identities, and acknowledge the existence of negative emotions and concerns.

As well as considering the provision of public information about cancer screening to support decision-making, the views and attitudes of the healthcare professionals who are responsible for delivering it should also be explored. A study of health professionals in Sweden, the Netherlands and the UK identified five themes that they believed may impact a woman's decision whether or not to undergo risk stratified breast screening (Rainey et al., 2018):

- anxiety/worry
- taking proactive control of one's own health
- feeling reassured by knowing about personal risk
- lack of knowledge
- organisation of risk assessment and feedback of results

3.1. The use of decision aids in shared decision-making around cancer screening

Decision aids (e.g. pamphlets, videos and online tools) can help people make informed choices about their health, including cancer screening. A systematic review showed that people exposed to decision aids when making a choice about treatment or screening feel more knowledgeable, better informed and clearer about their values. There are no adverse effects on health outcomes or satisfaction, or significant increase in consultation time. They also probably have a more active role in decision-making and more accurate risk perceptions, although this is not fully proven (Stacey et al., 2017).

A systematic review and meta-analysis of decision aids in breast cancer screening showed that the use of such aids led to a slight decrease in the proportion of women deciding to undergo screening, together with an increase in knowledge and feeling of making an informed choice (Martínez-Alonso et al., 2017). A similar result was found in a randomised controlled trial of a decision-making aid in the French DECIDEO study, which led to a reduced attendance at breast screening (Bourmaud et al., 2016) For prostate cancer PSA screening, a Cochrane review showed that the use of decision aids slightly reduced the proportion of men choosing to undergo screening, whereas for colorectal cancer there was a slight but non-significant increase in the desire to participate in screening (Stacey et al., 2017).

When developing aids for shared decision-making, information should be simply presented and compatible with low literacy, ideally using easy-to-grasp graphics. However, it should be borne in mind that the production of such resources is influenced by the view and choices of both the creator and the person delivering the information. For example, decisions may be made to include or leave out certain pieces of information. The use of certain colours such as red or green can also be perceived as conveying

information (for example, red=stop or dangerous, green=go or safe). Currently, there is no consistent way in which information about the effectiveness, harms and benefits of cancer screening is conveyed across EU member states.

A systematic review of international breast screening clinical practice guidelines and consensus statements revealed that reference to shared decision-making appeared in only half of them, mostly those issued more recently. Guidelines that did mention shared decision-making were judged as being of higher quality than those that did not (Maes-Carballo et al., 2021). It should be noted that these guidelines refer only to age-based screening rather than risk-stratified screening.

More research is needed to look at shared decision-making in the context of risk-stratified screening, as well as generating reliable data about the harms and benefits of screening in any given individual, to ensure that everyone can make fully informed decisions about their health.

4. Emerging novel biomarker-based cancer screening technologies

Existing cancer screening tests rely on tests that look for physical or molecular characteristics associated with a specific type of cancer. As genetic and molecular analytical techniques have improved, there is growing interest in the use of 'liquid biopsy' tests to detect multiple different types of cancer from the same sample based on the presence of certain cells, molecules or genes in blood or other body fluids, such as urine. Similar principles could be applied to other samples such as cervical smears or oesophageal samples (see the case study on the next page) and also to improve the accuracy of tissue-based screening tests.

Blood is an easily accessible fluid that provides a window on the biological processes at work inside the body and can be easily collected in a minimally invasive way. There are several different blood-borne molecular markers that can reveal the presence of cancer in the body, including the presence of DNA or RNA, proteins, exosomes, metabolites and even the cancer cells themselves (Alix-Panabières & Pantel, 2021). However, these biomarkers are not necessarily specific for particular tumour types and may not reveal exactly where in the body the cancer is. These tests would therefore usually be followed up by a scan of some sort, such as MRI or PET-CT, to localise the cancer.

There are also biological challenges presented by the potential use of blood testing to detect cancer. We know that the proliferation of non-cancerous mutated cells (clonal proliferation) and benign conditions increases with age, along with other health conditions that could confound the results and lead to false positives. The presence of some cancer types may also be less easily detected in blood. For example, Bettegowda and colleagues report detectable ctDNA in more than three-quarters of patients with advanced pancreatic, ovarian, colorectal, bladder, gastroesophageal, breast, melanoma, hepatocellular, and head and neck cancers, but in less than half of primary brain, renal, prostate, or thyroid cancers (Bettegowda et al., 2014).

Any blood test will also be subject to sensitivity limits depending on the technology used. A less sensitive test might miss genetic or molecular markers that are present at low abundance in the earliest stages of disease, while an overly sensitive test could pick up biomarkers resulting from rare non-clonal mutation events that will not lead to cancer. The specific cut-off values chosen for any given biomarker will also influence the sensitivity and specificity of such tests. A high cut-off will result in higher specificity (fewer

false positives) and lower sensitivity (some true positives are missed), while a low-cut off increases the sensitivity (fewer false negatives) at the expense of specificity (more false positives).

Blood testing as a means of screening for cancer could be simpler and more cost-effective than current screening methods, depending on the costs of the technology involved. It would also enable people to be screened for a larger number of cancers than is currently possible, covering multiple different cancers in the same test. However, like any other screening procedure, a blood test must also be effective at detecting cancers at an earlier, more treatable stage where lives can be saved, while minimising potential harms through overtreatment and invasive follow-up of false positives due to overdiagnosis.

In the context of such a fast-moving field, it is important that all these different liquid biopsy methods are standardised and validated, to support harmonisation of protocols within and between countries and quality assurance. The European Liquid Biopsy Society (ELBS) brings together more than 60 partners from academia and industry to foster the introduction of liquid biopsy into clinical practice by encouraging collaborations and partnerships, supporting implementation, developing guidelines and delivering training. Another key role is disseminating knowledge and increasing the visibility of the technology throughout Europe and the wider world.[4] The ELBS is a founding member of the International Liquid Biopsy Standardization Alliance (Connors et al., 2020).

Case study: Cytosponge for non-endoscopic oesophageal cancer screening

The Cytosponge-TFF3 test ('sponge on a string') can be safely delivered by a nurse in a community setting. The Cytosponge is a small pill-sized capsule on a string, which is swallowed. The capsule then dissolves in the stomach to reveal a small polyester sponge that is pulled back up through the oesophagus, capturing a small sample of cells along the way. The sponge is placed in a standard lab assay pot and the cells are analysed for the presence of Trefoil Factor 3 (TFF3), which indicates Barrett's oesophagus — a precursor condition that can occasionally progress to oesophageal cancer.

Initial studies reported on promising safety, acceptability and accuracy of the technology (Kadri et al., 2010; Ross-Innes, Becq, et al., 2015; Ross-Innes, Debiram-Beecham, et al., 2015; Ross-Innes et al., 2017). The randomised controlled BEST3 trial of the Cytosponge recruited more than 13 000 people over the age of 50 who were on current medication for heartburn and had not had an endoscopy for 5 years.

4 https://www.uke.de/english/departments-institutes/institutes/tumor-biology/european-liquid-biopsy-society-elbs/index.html

These were ascertained from GP prescribing databases. Half received standard care, including antacid medications and endoscopy at their doctor's discretion, while the other half were offered the opportunity for Cytosponge-TFF3 screening.

The uptake was 24% and 10-fold more cases of Barrett's were identified in the Cytosponge arm compared with standard care in a per protocol analysis, including dysplasia and stage 1 carcinoma (Fitzgerald et al., 2020). The trial also showed that the test was highly acceptable, with 97% rating it as 5 or higher on a scale of 1-10 (worst to very enjoyable experience), comparing favourably against unsedated or sedated endoscopy. However, there is currently no data to show whether or not Cytosponge-TFF3 testing would reduce mortality from oesophageal adenocarcinoma, but such a trial (BEST4) is in advanced stages of planning in the UK. In order to support scale-up of Cytosponge pathology reporting, an AI assisted tool has been developed and validated (Gehrung et al., 2021).

Health economic modelling suggests that Cytosponge-TFF3 is cost effective and affordable in real world settings, delivering more favourable cost effectiveness than endoscopy and saving money on costly late-stage therapies and life years lost through enabling earlier diagnosis and curative treatment (Benaglia et al., 2013; Heberle et al., 2017; Swart et al., 2021).

Other non-endoscopic technologies are also emerging in this space, such as the Esochek balloon and the Mayo sponge on a string device, coupled with biomarker assays such as DNA methylation (Iyer et al., 2020; Moinova et al., 2018).

4.1. Circulating tumour DNA (ctDNA)

Many tumours release DNA into the bloodstream, known as circulating tumour DNA (ctDNA) (Wan et al., 2017). This DNA contains genetic changes including mutations, copy number alterations, chromosomal rearrangements, and changes in DNA methylation or other epigenetic marks.

The use of blood tests to detect ctDNA has been proposed for a range of clinical applications in cancer. ctDNA testing is currently used in some countries for routine molecular profiling of some cancer patients to aid in treatment selection, for example in non-small cell lung cancer. Regular ctDNA testing can also be used to non-invasively monitor response to therapy, detect residual disease after treatment, and follow the subsequent evolution of resistance and relapse (Wan et al., 2017) In patients with advanced cancer, the amount of ctDNA in their blood is relatively high and can potentially be detected in a simple finger-prick blood spot test, opening up the possibility of future home-testing (Heider et al., 2020). Blood can also reveal the presence of infectious

agents known to be linked to cancer, such as Epstein-Barr virus, which is associated with nasopharyngeal cancer and other tumour types (Chan et al., 2017).

However, the amount of ctDNA shed into the bloodstream varies according to the stage of disease, the type of cancer and the individual patient. The proportion of mutant alleles ranges from 0.1% or less in stage 1 disease to around 10% or more in metastatic stage 4 cancer (Bettegowda et al., 2014). Furthermore, each patient's cancer is unique and only a handful of mutations recur across many different cancers, meaning that any multi-cancer blood-based screening test will have to look at multiple genes and mutations (Newman et al., 2014). However, other genetic biomarkers can be detected in ctDNA from a range of cancers in an unbiased fashion without needing pre-knowledge about the mutational profile of a certain tumour, such as copy number aberrations (seen in around 90% of solid tumours and 50% of blood cancers; Heitzer et al., 2016) or DNA methylation changes (see section 4.2 on page 22). A blood test also needs to distinguish between mutant DNA shed from a tumour and clonal haematopoiesis which is benign and increases with age (Jaiswal & Ebert, 2019). While intense analysis methods can detect ctDNA sequences from very small tumours (<1 cm^3) in patients known to have cancer (Heider et al., 2021), it is a much more challenging task to translate this into a screening test for the general population where the cancer type and mutations are unknown.

Although ctDNA technology is improving all the time, the utility of blood tests based solely on ctDNA for cancer screening to detect early-stage disease is currently limited due to the challenge of accurately detecting unknown mutated sequences amongst all the other DNA present in a typical blood sample. Some blood-based screening approaches have attempted overcome this limitation by combining ctDNA analysis for multiple genes with other biomarkers, such as proteins or DNA methylation (for example, the CancerSEEK and GRAIL Galleri tests, see below). Others have developed sensitive assays for early-stage cancers based on detecting abnormal fragments of DNA, such as the DELFI assay (Cristiano et al., 2019). According to Dr Nitzan Rosenfeld, presenting at the expert workshop, current blood-based ctDNA technologies used on their own will need to improve around 10-fold in order to effectively detect stage 1 cancers.

Case study: CancerSEEK

CancerSEEK is a multi-analyte blood test for the detection of multi-cancer types. One version of the test analyses a panel of specific mutations in ctDNA and protein biomarkers that can reveal the presence of a number of different types of cancer. A retrospective case-control study of the test was carried out in 1005 stage 1 and 2 cancer patients with 8 different tumour types (breast, colorectal, oesophageal, liver, lung, ovarian, pancreatic and stomach) and 812 healthy controls (Cohen et al., 2018). The test was able to correctly identify 62.2% of the cancers with a specificity greater than 99%. However, the sensitivity varied with tumour type, depending on the

amount of ctDNA and/or protein shed into the blood. For example, more than 99% of ovarian and liver cancers were detected, while fewer than half of breast tumours were detected. Similarly, sensitivity varied with stage. And although cancer signal could be detected from around 70% of stage 2 and 80% of stage 3 cancers, this figure is around 40% for early stage 1 tumours (Cohen et al., 2018).

The feasibility of CancerSEEK to detect cancers that would not otherwise be found at an early stage when successfully treatment is more likely is currently being tested in the prospective DETECT-A study.[5] 10 000 women aged 65–75 were recruited through the US Geisinger Health System, with every positive result being followed up with PET-CT scanning to confirm the diagnosis and location of the tumour. Preliminary results show that of 96 cancers detected in women participating in the trial, 26 were found using CancerSEEK alone. There were 100 false positi.e. of which PET-CT scanning identified 63 with no findings concerning for cancer and they did not undergo any additional follow-up procedure (Lennon et al., 2020).[6] There was a high degree of participant satisfaction (95% overall), and taking part in the trial did not prevent people from undergoing routine standard-of-care screening. Further improvements to the CancerSEEK technology are being developed, such as strand-specific PCR (Cohen et al., 2021), aneuploidy detection (Douville et al., 2020) and machine learning algorithms, with randomised controlled trials being planned.

Case study: Lessons from non-invasive prenatal tests as a tool to screen for cancer

Non-invasive prenatal testing (NIPT) is a type of blood test offered to pregnant women that can detect the presence of fetal aneuploidies by looking for chromosomal alterations in fetal DNA that has made its way into the mother's bloodstream. However, in case of an undiagnosed cancer in the mother, this test can also detect the presence of chromosomal copy number aberrations in ctDNA that is shed by the tumour into the maternal circulation. A number of papers have been published documenting the incidental detection of cancer in pregnant women undergoing NIPT (for example, (Amant et al., 2015; Bianchi et al., 2015; Ji et al., 2019; Vandenberghe et al., 2015).

Following on from these observations, Lenaerts and colleagues carried out a retrospective analysis of the results of more than 88 000 routine NIPT tests carried out at University Hospital Leuven in Belgium from 2013 to 2020. They discovered 15 cases for whom the NIPT results suggested the presence of a hidden maternal

5 https://www.geisinger.org/precision-health/detect-study

6 https://www.abstractsonline.com/pp8/#!/9045/presentation/10735

cancer (Lenaerts et al., 2021). Further follow-up revealed the presence of cancer in 11 of these women, with two thirds being blood cancers and the remainder breast, ovarian and bone tumours. Of the remaining four, one was found to have no detectable cancer or other health condition while three had clonal mosaicism in the blood, a potential precursor of cancer, and were offered regular monitoring. In one further case, a woman whose NIPT revealed a potentially cancer-related chromosomal abnormality but did not meet the threshold for onward investigation was found to develop non-Hodgkin lymphoma nearly 4 years later.

The potential utility of NIPT for screening in the wider population has been investigated in a cohort of 1002 elderly individuals without a known diagnosis of cancer, of whom 30 had an abnormal test result suggestive of an underlying cancer. After further investigation, 6 were found to have blood cancer or a pre-cancerous blood condition and 9 had clonal mosaicism in the blood, while 15 had no obvious origin for the abnormalities (false positives). 4 cases of cancer (prostate, lung, colorectal and multiple myeloma) were diagnosed during the study period in individuals with a normal NIPT result (false negatives) (Lenaerts et al., 2019).

Similar to other ctDNA methods, the sensitivity of NIPT depends on the type of cancer and the stage of disease (Lenaerts et al., 2020). However, NIPT is based on low-pass whole genome sequencing and as such is an unbiased method (i.e. does not rely on pre-existing knowledge of the tumour genome), and is relatively cheap compared with other more in-depth sequencing-based ctDNA analysis methods. Its accuracy could also be improved through the application of machine learning/ artificial intelligence.

4.2. DNA methylation

Methylation is a chemical modification of DNA that is involved in controlling patterns of gene activity. Different cell types express specific repertoires of genes, so DNA from a given tissue or cell-type will have a distinctive methylation profile. DNA methylation patterns can also be altered in cancer, with these changes usually occurring in the earliest stages of growth. Analysing methylation profiles in tissue, body fluid, stool or blood samples can therefore reveal the presence of cancer and tissue of origin, and help to distinguish cancer from other conditions (Moss et al., 2018). For example, urinary DNA methylation markers are being investigated for staging of prostate cancer (Bakavicius et al., 2019), while research is ongoing to detect lung cancer through urine (B. Liu et al., 2020) and sputum (Hulbert et al., 2017).

Blood-based ctDNA methylation analysis for early detection of cancer has been explored in a number of studies, both for specific cancers and in multi — or pan-cancer assays, and this technology is already starting to come to market — for example, the

Epi proColon blood test for colorectal cancer screening, and the GRAIL Galleri test, see below. Some assays use PCR-based testing of methylation status at a limited number of genetic markers, while others use whole-genome or large-scale bisulphite sequencing (Liu et al., 2020) or immunoprecipitation and sequencing of cell-free methylated DNA to get a deeper view of methylation patterns (Shen et al., 2018). While the specificity of methylation testing is usually high, the sensitivity is often relatively low, especially for early-stage disease.

The GRAIL Galleri™ multi-cancer blood test is designed to detect around 50 different cancer types by examining ctDNA methylation status at more than 100 000 sites throughout the genome. It has a specificity of around 99.3%, with an average sensitivity of around 25% for stage 1 cancers and 50–70% for stage 2. The early stage sensitivity is significantly higher for some cancers, such as colorectal, head and neck and pancreatic (M. C. Liu et al., 2020).[7] The Galleri™ assay is currently being tested in a randomised controlled trial of 140 000 adults aged 50–77 in England, in partnership with the UK National Health Service.[8] Results from the initial phase are expected in 2023, with testing extended to a further one million people in 2024–2025 if successful.[9]

Other DNA methylation-based blood tests for cancer screening include the PanSeer test (Chen et al., 2020), a four gene methylation test for colorectal cancer developed by Zhang and colleagues (Zhang et al., 2021), and the Danish 'TriMeth' test (Jensen et al., 2019). The Lunar-2 colorectal cancer screening test from Guardant also relies on methylation profiling, together with ctDNA mutation detection and fragmentomic analysis,[10] while the company Freenome has also developed a multiomic blood test that is showing promising results in a prospective study for detecting advanced bowel cancers.[11]

DNA methylation testing has also been explored in cervical cancer as a way of identifying abnormal cells that are at higher risk of developing into cancer. The S5 DNA methylation assay, developed by Lorincz and colleagues, examines methylation status at four viral genes in various strains of HPV and the human EPB41L3 gene (Lorincz et al., 2016), and the method has been explored in a number of studies for detecting the precursors of cervical cancer, including comparison with cytology and HPV testing, as well as detecting oropharyngeal and anal precancers. For example, a study of more than 500 cervical cancers from various countries around the world revealed low S5 methylation scores in normal or CIN1 cervical samples, intermediate scores in CIN2/3, and higher scores in invasive cancer (Banila et al., 2021).

7 https://grail.com/wp-content/uploads/2020/12/BOG_2019_Tumor_Fraction_Venn_Poster_Final-1.pdf

8 https://www.nhs-galleri.org/

9 https://www.england.nhs.uk/2021/09/nhs-launches-world-first-trial-for-new-cancer-test/

10 https://guardanthealth.com/solutions/#lunar-2

11 https://www.freenome.com/blood-based-detection-of-advanced-adenomas

A Canadian randomised controlled trial with more than 15 000 participants showed that S5 methylation testing of baseline cervical screening samples was able to identify women at increased risk of having cervical cancer with a lead time of months to years (Cook et al., 2019), with high sensitivity for CIN3. A smaller study in Finland showed that S5 methylation status predicted the presence of progressive precancer (CIN2), suggesting it could be a useful tool for identifying women at the highest risk of going on to develop cervical cancer and would therefore benefit from prompt treatment (Louvanto et al., 2020).

4.3. Circulating tumour cells

In addition to ctDNA, entire tumour cells can be shed into the bloodstream, known as circulating tumour cells (CTCs). Advances in single cell detection and analysis technologies means that it is now possible to detect CTCs in the blood (Keller & Pantel, 2019), raising the suggestion that this could be used as a way of screening for cancer. Travelling tumour cells can also be detected in other body fluids, such as cerebrospinal fluid (CSF), urine, cyst fluid, saliva and bone marrow (Alix-Panabières & Pantel, 2021). Other types of tumour-related cells in the blood, such as endothelial cells, may also be informative about the presence of cancer within the body (Bertolini et al., 2006). One advantage of CTC over ctDNA analysis is the assessment of intra-patient heterogeneity, which can reveal information about the potential for evolving resistance to treatment (Gorges, Kuske, et al., 2016).

A large number of studies in various cancers have shown that having a relatively high number of CTCs in the blood is associated with a worse outcome. For example, metastatic breast cancer patients with 5 or more CTCs per 7.5 ml of blood survived an average of 16 months, compared with three years for those with less 5 (Cristofanilli et al., 2019). Despite the growing interest in detecting and analysing CTCs for molecular profiling of tumours and prognostic prediction (Alix-Panabières & Pantel, 2021; Pantel & Alix-Panabières, 2019), their low abundance limits their usefulness in detecting early stage cancers unless more sensitive technologies become available.

CTCs are rare, even in advanced cancer, typically occurring at a concentration of around 1 tumour cell per million blood cells. Any blood sample must first be enriched for tumour cells, using methods based on physical properties such as size or density, or the presence or absence of certain cell surface markers. Next, the CTCs are identified using techniques such as immunocytology, molecular biology or functional assays, followed by molecular analysis and characterisation.

A range of techniques have been developed to enhance the sensitivity of CTC assays, such as the use of novel markers to improve enrichment. Other approaches aim to increase the number of CTCs in a sample by using larger volumes of blood (e.g. 50 ml) or

even whole blood analysis (leukapheresis), or through the use of in vivo 'sieves' to capture CTCs directly within blood vessels (Keller & Pantel, 2019).

The feasibility of in vivo capture devices has been demonstrated in both lung and prostate cancer (Gorges, Penkalla, et al., 2016; Kuske et al., 2016). The use of CTCs for early detection of cancer is being investigated in a number of studies in Europe, such as the Hamburg City Health Study — a biobank containing blood and other biological samples from 45 000 inhabitants of the city aged 45-74 (Jagodzinski et al., 2020).

Another opportunity for blood-based early detection of cancer is testing for specific cancer-associated proteins. For example, the Cysteine-rich Angiogenic Inducer 61 (Cyr61) protein has been shown to be a potential blood biomarker for early stage breast and lung cancers (Ac Kar et al., 2021; Bartkowiak, Heidrich, et al., 2021), as well as asbestos-related diseases (Bartkowiak, Casjens, et al., 2021). Curiously, there appear to be sex-specific differences in the abundance of this marker in lung cancer, with elevated levels of Cyr61 seen in males but not females (Ac Kar et al., 2021). Another promising biomarker is CD24, which is elevated in a range of different cancer types and could serve as a universal blood test for detecting cancer (Shapira et al., 2021).

4.4. Conclusion

Blood-based cancer screening technology is advancing rapidly and offers the potential for screening for a much larger range of cancers than is currently possible. There are many different liquid biopsy approaches being investigated, and it is difficult to directly compare between all of them to determine which is the most effective. There is currently a lack of evidence from prospective randomised controlled trials of liquid biopsy to demonstrate effective detection of early-stage cancers, and sensitivity varies widely depending on the type of cancer. The cost effectiveness and practical implementation of any novel screening test should also be considered.

Overall, DNA methylation biomarkers in tissue and body fluids such as urine and sputum are robust with very good performance for detecting some cancers and precancers. However, while results from case-control studies of blood-based methylation testing are promising, the sensitivity is low for early-stage cancers compared with later stage disease, and the most convincing studies have used relatively large volumes of blood (around 30ml). There are currently no published randomised controlled trials demonstrating that ctDNA methylation testing is an effective screening test for early-stage cancer. However, large prospective trials are underway that will provide significantly more information in the near future. Questions remain as to whether randomised controlled trials are the most effective way of evaluating these kinds of approaches, particularly if they are likely to take many years to reach mortality endpoints, or whether an approach based ongoing evaluation during implementation trials will be more efficient.

Emerging novel biomarker-based cancer screening technologies

It is important to note that current liquid biopsy screening tests for cancer may give an indication of the likely site of a tumour, but cannot confirm what type of cancer is present (although this may change in the future). Any positive test result would likely be followed by subsequent investigation and imaging to confirm the tissue of origin, which requires sufficient healthcare resources and capacity. There is also the potential for uncertainty and anxiety in cases where a positive blood test result is followed by a negative scan. Was the blood test result a false positive? Or is there a cancer present that is currently undetectable with the imaging technique that has been used? And what should happen next?

Finally, it is not enough just to identify cancers at an early stage through innovative screening approaches such as liquid biopsy, there must also be parallel development and integrated testing of suitable treatments that could improve outcomes for individuals with cancers identified through screening in terms of survival and quality of life.

5. Principles for targeted cancer screening

The International Agency for Research on Cancer currently defines a number of principles of organised screening programmes:

- Screening should be offered to a defined target population (usually delineated by age and sex, but also smoking status for lung screening).
- Every member of that target population should be invited (usually by postal letters, but increasingly moving towards electronic invitation).
- There should be timely access to screening tests.
- There should be quality assurance of the screening process.
- There should be tracking of outcomes, to ensure that screening is effective.

When compared to opportunistic or on-demand screening, organised population-level cancer screening programmes aimed at asymptomatic individuals at average risk of cancer help to protect against harms by avoiding over-screening, reducing the likelihood of poor quality screening and follow-up, and minimising complications resulting from screening and subsequent investigations (Miles et al., 2004; also discussed in more depth in Workshops 1 and 2).

Implementing organised population-level cancer screening is a major investment for any country, requiring substantial support from policymakers, healthcare providers and workforce, and the public. Screening is not simply a test. It is a pathway from the initial identification of target populations through to invitation, risk assessment, delivery of screening, notification of results, and either follow-up/investigation or recall/reminder for further screening rounds if appropriate. All of this should be underpinned by a solid IT infrastructure and independent systems/structures for evaluation and quality control.

Increasing attention is being paid to programmatic and system issues in the planning and delivery of national cancer screening programmes (see Dobrow et al., 2018 and Workshop 1), namely:

- infrastructure
- coordination and integration within existing national and local programmes, frameworks and services
- acceptability and ethics
- the balance of benefits and harms
- economic evaluation

- quality and performance management

Most discussions of cancer screening have centred on populations at average risk. However, there is a paradigm shift under way, with increasing focus on the opportunities for screening specific sub-populations or groups that are thought to be at increased risk from a given disease (known as risk stratified or precision screening). There are several major implications of such a move, including narrowing the eligibility for screening for some individuals (i.e. those deemed to be in lower risk categories), and whether screening should be extended to a wider range of cancers.

Any proposed novel screening test or stratification process needs evaluation, with randomised controlled trials (RCTs) currently remaining the 'gold standard' of evidence. Yet questions remain about what the pathway should be from publication of the results of RCTs or other studies through to implementation and what kinds of evidence should be deemed sufficient to justify roll-out on a local or national scale, including whether RCTs are always necessary. There also needs to be more consideration of appropriate surrogate endpoints for screening studies, which can be lengthy and expensive, such as a reduction in the proportion of cancers diagnosed at an advanced stage versus cancer-specific mortality.

Speaking at the expert workshop, Professor Linda Rabeneck pointed to the need to develop a set of principles for targeted screening to help address these questions and move screening innovations through to implementation. Governance is another issue to be discussed: who decides whether a new test or technology should be rolled out? And who decides where this decision sits? The development of such principles could be carried out through a Delphi consensus process (see Barrett & Heale, 2020, for further information). Also, it will be important to engage screening technology companies as early as possible in the process developing and introducing trials of novel approaches to help ensure availability, cost effectiveness, regulatory approval and quality assurance (for example, the GRAIL Galleri™ multi-cancer blood test screening trial being carried out in partnership with the NHS in England).

The expert consensus emerging from the workshop is that it is beneficial to enable countries to start rolling out screening innovations on a local level to gather real-world evidence that goes beyond the confines of a randomised controlled trial before scaling up to the whole population (See Workshop 1). There may also be lessons that can be learned from the introduction of lung cancer screening for people with a current or recent history of smoking, which is effectively a risk-stratified screening approach.

Case study: A 'one-stop shop' for cancer screening

Each one of us has a finite amount of time and resources to devote to our health, including taking part in cancer screening and tests for other conditions such as heart disease. As the number and type of tests expands in future, it may become increasingly burdensome to participate. Professor Nadir Arber, Director of the Integrated Cancer Prevention Centre in Tel Aviv, Israel, shared his experience of establishing a 'one-stop shop' for health, offering a range of tests that are completed in a matter of hours on the same day on an annual basis. This includes tests for the 12 most common cancers, including cancers of the skin, mouth, thyroid, breast, lung, ovary, cervix, prostate, testicles, colon/rectum and lymph nodes.

Some of the tests are offered on a risk-stratified basis through the use of risk scores or algorithms, such as the Tyrer-Cuzick model for assessing breast cancer risk (Himes et al., 2016). Attendees are also offered genetic testing to look for inherited gene variants that may impact on their health.

As reported by Centre Director Professor Nadir Arber at the expert workshop, more than 22 000 healthy individuals have attended since it was established in 2006, with an average age of 47. 288 cancers (1.3%) have been detected in otherwise healthy individuals, with 75% of cancers diagnosed at stage 0, 1 or 2.

6. A 'living guidelines' approach for delivering screening in a changing innovation landscape

New tests, biomarkers and risk stratification processes will likely only add more complexity to existing screening programmes. This fast-changing landscape presents a problem for clinical guidelines around cancer screening, such as how to correctly assess an individual person's risk and what steps should subsequently be followed depending on their outcome of their test.

Clinical guidelines are typically updated infrequently (every 7–10 years), and are often outdated shortly after publication (Martínez García et al., 2014). Interim guidelines can address important developments, such as the replacement of cytology with HPV testing as the primary cervical cancer screening tool. A longer-lasting alternative is the use of enduring or 'living' guidelines, which can be updated more frequently and flexibly as the need arises.

Professor Nicolas Wentzensen Head of the Clinical Epidemiology Unit and Deputy Chief of the Clinical Genetics Branch at the National Cancer Institute in Bethesda, USA, described the development of the consensus *Enduring Guidelines* for cervical screening in the US. This process aimed to:

- enable the constant evaluation of new technologies and approaches to cervical cancer screening, management, and surveillance
- improve cervical cancer prevention by both increasing targeted cancer prevention for high-risk individuals and decreasing unnecessary invasive procedures in low-risk individuals
- reduce health disparities
- prioritise the improvement of public health

Once a new technology is approved by the US Food and Drug Administration, it then goes into a risk assessment to see how it fits within the current clinical action thresholds, which have been previously determined by a consensus process. Next, the quality of studies supporting a new technology and certainty of risk estimates generated by it will be assessed, and if these thresholds are met then a vote will be taken about whether or

not to adopt it. This data could come from clinical trials, high quality observational studies, medical record data and clinical consensus.

Different parts of this process are handled by separate groups — for example, the evidence around a particular technology and the validity of the risk estimates emerging from it are assessed by the NCI Technology and Risk Assessment Group, while a 20+ organisation Consensus Stakeholder Group comprising clinical societies, government/ regulatory and patient groups is responsible for prioritising and ratifying guidelines. By having an agreed framework in place for assessing innovative technologies, clinical guidelines can be quickly updated to make the most of new opportunities to improve screening while maintaining quality and avoiding harms.

There are innovations being developed to reduce complexity around delivering risk-stratified screening and management for healthcare providers, such as a smartphone risk assessment app from the American Society for Colposcopy and Cervical Pathology (ASCCP), or the $PLCO_{m2012}$ lung cancer risk calculator. A healthcare professional can enter data about an individual and be given a recommendation for next steps (for example, 'repeat the test in one year' or 'recommend for further investigation') based on existing risk tables and thresholds.

These concepts of risk and risk-stratified screening and case management are complex to understand and explain to the public. There will be a need for clear communications about these new approaches as they are brought in, potentially alongside the increasing use of 'risk counsellors' that can inform people about their personal risk and help them make informed choices about their health.

7. AI applied to radiology for cancer detection

Some types of cancer screening, such as breast and lung screening, rely on the capture of digital images that are then analysed by one or two expert radiologists to look for signs of cancer. This need for highly trained human intervention is increasingly creating a bottleneck in the screening process, exacerbated by a shortage of radiologists in many EU member states and the increasing technical demands on the workforce.[12]

Using machine learning (ML) and artificial intelligence (AI) algorithms to analyse screening images could help to ease this backlog, for example as an initial triage step to rule out scans that are very unlikely to have signs of cancer, as AI-based image analysis tools can assess an image in a matter of seconds. AI could also be used to compare between multiple scans from the same person over time, to identify subtle changes that could potentially be early signs of cancer. Tools can also be hosted on cloud computing servers, making them accessible from anywhere in the world with an internet connection and the capacity to securely and legally transfer sufficient data.

However, any algorithm is only as good as the datasets it is trained on, which should be as large and unbiased as possible, and there is likely to be a need for ongoing training and revalidation. There are also questions around how best to develop the regulatory frameworks and quality assurance of such new technologies that are inherently adaptable and change over time. AI-based systems must also be able to integrate with and 'talk to' existing healthcare IT infrastructure which varies widely between hospitals and healthcare systems and may often be outdated. They also need to be able to cope with all the different types of imaging machines and systems that are available. In addition, these algorithms are built for one purpose at a time — so one algorithm can only identify the likely presence (or not) of lung cancer on a CT scan and cannot identify any other health issues that might be spotted by an expert radiologist. A different algorithm would be needed for pneumonia detection on the same CT scan, for example.

Research is ongoing to test the effectiveness of AI-based cancer screening tools and explore how best to embed them into routine screening and clinical care. For example, an algorithm trained on 42 290 lung CT scans performed at least as well as human radiologists, with 11% fewer false positives and 5% fewer false negatives (Ardila et al., 2019). An international evaluation of an AI-based system for breast screening, trained on 121 455 images, also performed as well as humans, with 5.7% fewer false positives and 9.4% fewer false negatives (McKinney et al., 2020). However, a recent systematic review

12 https://www.signifyresearch.net/digital-health/top-five-drivers-global-teleradiology-market/

of AI-based breast screening tools concluded that overall AI tools were not currently sufficiently specific to replace human assessment of scans, and that more research is needed to demonstrate effectiveness, particularly in prospective real-world trials (Freeman et al., 2021).

Ongoing dialogue is needed with radiologists, technology companies and healthcare infrastructure providers to develop user-focused solutions that will work in practice to deliver more effective screening solutions that improve outcomes and reduce costs.

8. Discussion

There is rapid progress in novel screening technologies and risk stratification approaches. However, any novel technology must compete with existing screening methods and demonstrate equivalent or greater effectiveness and/or cost effectiveness in order to be adopted. High quality prospective trials are still necessary to ensure quality and effectiveness, reduce false positives and harms, and demonstrate that the test is capable of detecting early-stage cancer at a point where intervention will lead to improved outcomes.

When considering how to translate innovations in screening from 'gold standard' randomised controlled trials through to implementation on a national scale the experts conclude that this should be done through small scale local pilot trials, potentially as randomised cluster trials, before rolling out on a national level.

The establishment of appropriate and validated biobanks within the EU would be beneficial for creating large phenotyped cohorts to support cancer screening research, particularly for investigating blood borne biomarkers and testing the effectiveness of new technologies. More could also be done to ensure that appropriate consent is obtained from participants in cancer screening trials for novel technologies to ensure that biological samples are available for future research to enable more effective comparison between technologies.

There is a finite amount of money and resources available for the introduction of cancer screening programmes, so decisions must be made about which programmes to implement on a national level, and within that which technologies and risk stratification processes should be applied and for whom. Some screening technologies may be complementary and could be used in combination to improve the overall effectiveness of a screening programme or allocated to different individuals depending on their personal risk profile.

Being able to directly compare between new screening innovations would be useful, but the wide range of different technologies coming down the pipeline makes this challenging. Developing strategies to enable fair comparisons between innovative screening approaches is an area that would benefit from further work and discussion, supported by EU funding.

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:**
  - Dr Alison Weightman (Director)
- Professor Nadir Arber (Director, Integrated Cancer Prevention Centre, Tel Aviv, Israel)
- Dr Suzette Delaloge (Medical Oncologist and Director of Interception Programme at Department of Cancer Medicine, Institut Gustave Roussy, France)
- Professor Mozziyar Etemadi (Medical Director, Advanced Technologies, Northwestern Medicine, Chicago, USA)
- Professor Gareth Evans (Professor in Medical Genetics and Cancer Epidemiology at University of Manchester, United Kingdom)
- Dr Liesbeth Lenaerts (Research Expert, Cancer in Pregnancy group, Department of Oncology, KU Leuven, Leuven, Belgium)
- Professor Attila Lorincz (Emeritus Professor of Molecular Epidemiology, Queen Mary University of London, United Kingdom)
- Professor Klaus Pantel (Chairman of Institute of Tumour Biology at the University Medical Centre, Hamburg, Eppendorf, Germany)
- Professor Nickolas Papadopoulos (Professor of Oncology and Pathology and Director of Translational Genetics at Ludwig Center for Cancer Genetics and Therapeutics, Sidney Kimmel Comprehensive Cancer Center, USA)
- Professor Nora Pashayan (Professor of Applied Cancer Research and Hon Consultant of Public Health Medicine at University College London, United Kingdom)
- Professor Linda Rabeneck (Vice President, Prevention and Cancer Control, Ontario Health and Professor of Medicine, University of Toronto, Canada)
- Dr Nitzan Rosenfeld (Group leader at the Cancer Research UK Cambridge Institute, University of Cambridge, United Kingdom)
- Dr Nicolas Wentzensen (Head of Clinical Epidemiology Unit, Deputy Chief, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics at National Cancer Institute, Bethesda, USA)

10:00	Welcome	Rebecca Fitzgerald Harry de Koning Stefan Constantinescu George Griffin
10:10	Rapid review of the published evidence	Alison Weightman
Section 1: Setting the scene		
10:20	Setting the scene for risk-based screening	Nora Pashayan
10:45	Risk-based screening in practice	Gareth Evans
11:10	Shared decision-making	Suzette Delaloge
Section 2: Emerging blood-based pan-cancer technologies		
11:35	Cancer SEEK technology	Nickolas Papadopoulos
12:00	ctDNA assays and blood spot technology	Nitzan Rosenfeld
12:25	Circulating tumour cells	Klaus Pantel
12:50	Lessons from non-invasive prenatal tests as a tool to screen for cancer	Liesbeth Lenaerts
13:15	DNA methylation	Attila Lorincz
13:40	Break	
Section 3: Practical approaches for next-generation screening methods		
14:20	Principles for targeted cancer screening: Is there a gap?	Linda Rabeneck
14:45	One-stop shop for cancer screening	Nadir Arber
15:10	Risk-based cervical cancer screening: A living guidelines approach to integrating new biomarkers into clinical practice	Nicolas Wentzensen
15:35	AI applied to radiology for cancer detection	Mozziyar Etemadi
15:35	Break	
16:20	Discussion Opportunities for blood-based biomarkers Challenges to be overcome Other liquid biopsy e.g. urine, breath Role of AI for digital imaging When will these technologies be ready for primetime?	All
17:30	Wrap-up and conclusions	Rebecca Fitzgerald Harry de Koning

Appendix 2: References

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