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).

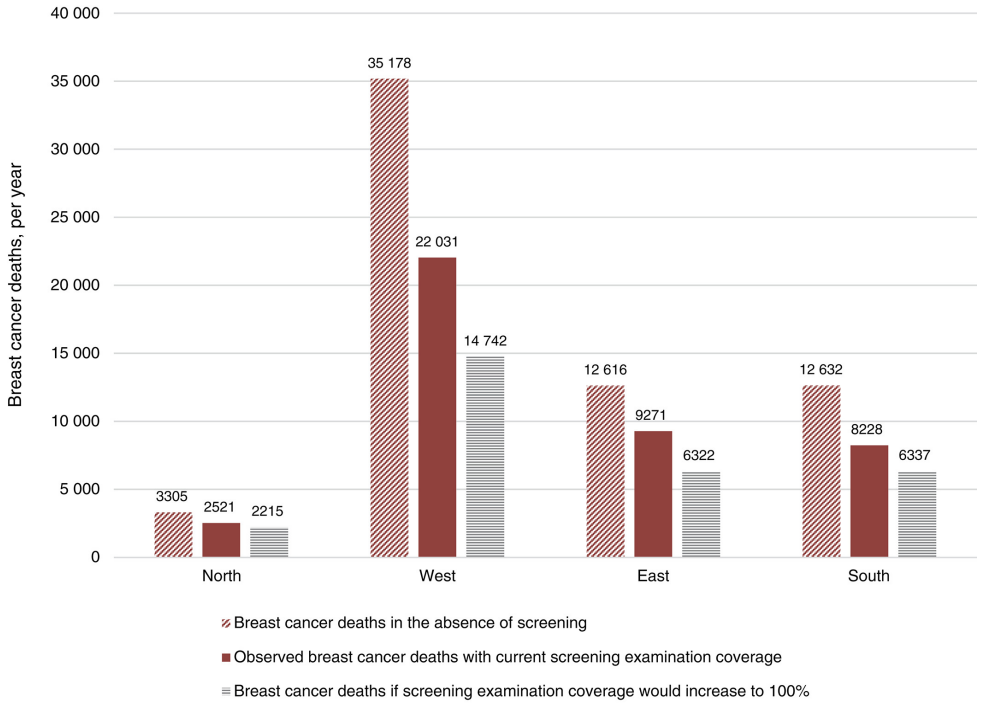
1 https://www.england.nhs.uk/wp-content/uploads/2019/02/report-of-the-independent-review-of-adult-screening-programme-in-england.pdf

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).

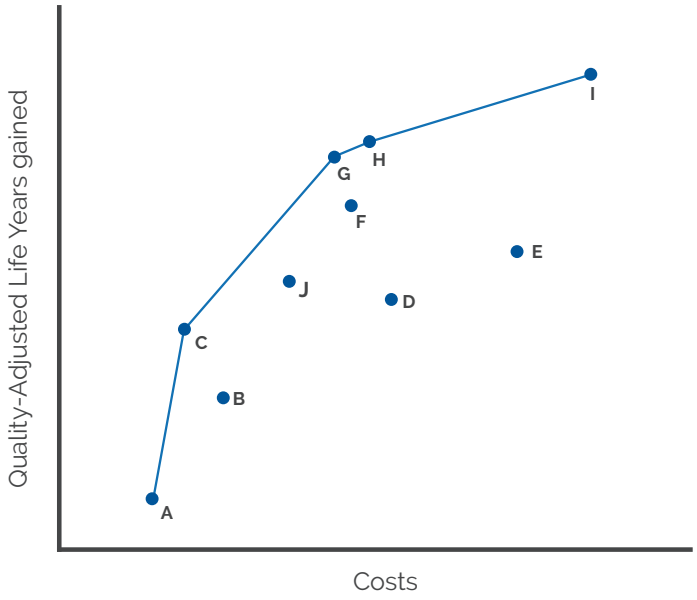


Figure 2. The comparative cost-effectiveness of healthcare interventions (based on Mark, 2002)

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

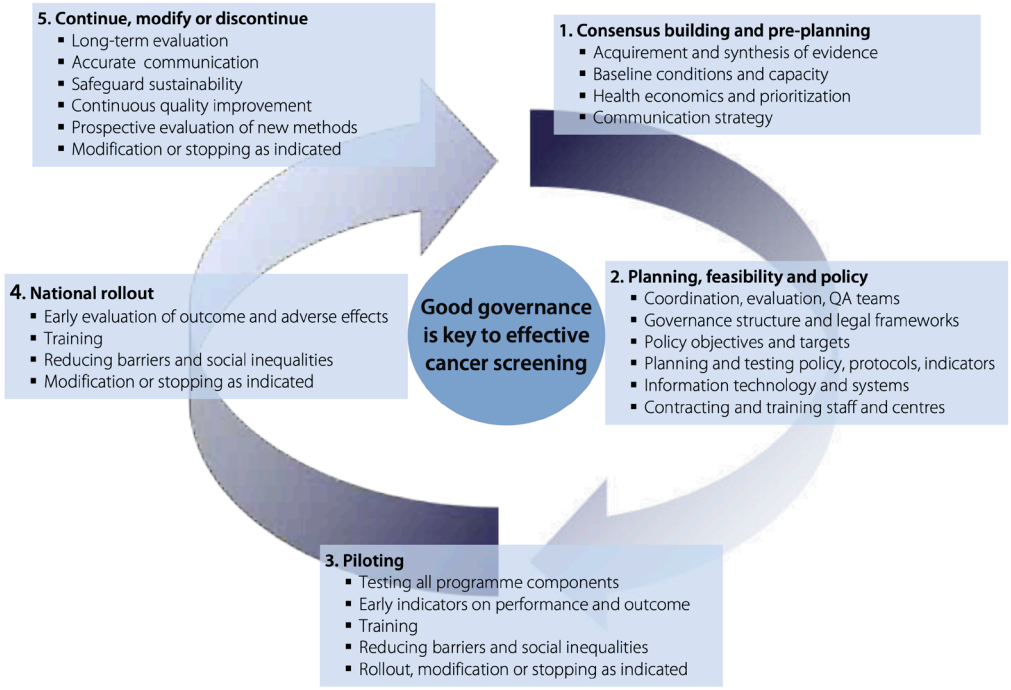


Figure 3. [24]

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 (Expert-National Institute of Public Health, 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

Appendix 2: References

Arnold, M., Rutherford, M. J., Bardot, A., Ferlay, J., Andersson, T. M.-L., Myklebust, T. Å., Tervonen, H., Thursfield, V., Ransom, D., Shack, L., Woods, R. R., Turner, D., Leonfellner, S., Ryan, S., Saint-Jacques, N., De, P., McClure, C., Ramanakumar, A. V., Stuart-Panko, H., … Bray, F. (2019). Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): A population-based study. The Lancet. Oncology, 20(11), 1493–1505. https://doi.org/10.1016/S1470-2045(19)30456-5

Ashraf, H., Saghir, Z., Dirksen, A., Pedersen, J. H., Thomsen, L. H., Døssing, M., & Tønnesen, P. (2014). Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: Final results after a 5-year screening programme. Thorax, 69(6), 574–579. https://doi.org/10.1136/thoraxjnl-2013-203849

Bach, P. B., Kattan, M. W., Thornquist, M. D., Kris, M. G., Tate, R. C., Barnett, M. J., Hsieh, L. J., & Begg, C. B. (2003). Variations in lung cancer risk among smokers. Journal of the National Cancer Institute, 95(6), 470–478. https://doi.org/10.1093/jnci/95.6.470

Balata, H., Ruparel, M., O'Dowd, E., Ledson, M., Field, J. K., Duffy, S. W., Quaife, S. L., Sharman, A., Janes, S., Baldwin, D., Booton, R., & Crosbie, P. A. J. (2021). Analysis of the baseline performance of five UK lung cancer screening programmes. Lung Cancer (Amsterdam, Netherlands), 161, 136–140. https://doi.org/10.1016/j.lungcan.2021.09.012

Barrett, J., Jenkins, V., Farewell, V., Menon, U., Jacobs, I., Kilkerr, J., Ryan, A., Langridge, C., Fallowfield, L., & UKCTOCS trialists. (2014). Psychological morbidity associated with ovarian cancer screening: Results from more than 23,000 women in the randomised trial of ovarian cancer screening (UKCTOCS). BJOG: An International Journal of Obstetrics and Gynaecology, 121(9), 1071–1079. https://doi.org/10.1111/1471-0528.12870

Bell, K. J. L., Del Mar, C., Wright, G., Dickinson, J., & Glasziou, P. (2015). Prevalence of incidental prostate cancer: A systematic review of autopsy studies. International Journal of Cancer, 137(7), 1749–1757. https://doi.org/10.1002/ijc.29538

Blyuss, O., Burnell, M., Ryan, A., Gentry-Maharaj, A., Mariño, I. P., Kalsi, J., Manchanda, R., Timms, J. F., Parmar, M., Skates, S. J., Jacobs, I., Zaikin, A., & Menon, U. (2018). Comparison of Longitudinal CA125 Algorithms as a First-Line Screen for Ovarian Cancer in the General Population. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 24(19), 4726–4733. https://doi.org/10.1158/1078-0432.CCR-18-0208

Brain, K., Carter, B., Lifford, K. J., Burke, O., Devaraj, A., Baldwin, D. R., Duffy, S., & Field, J. K. (2017). Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial. Thorax, 72(10), 912–918. https://doi.org/10.1136/thoraxjnl-2016-209690

Buisset, J., Norris, J. M., Puech, P., Leroy, X., Ramdane, N., Drumez, E., Villers, A., & Olivier, J. (2021). Negative Prebiopsy Magnetic Resonance Imaging and Risk of Significant Prostate Cancer: Baseline and Long-Term Followup Results. The Journal of Urology, 205(3), 725–731. https://doi.org/10.1097/JU.0000000000001414

Buys, S. S., Partridge, E., Black, A., Johnson, C. C., Lamerato, L., Isaacs, C., Reding, D. J., Greenlee, R. T., Yokochi, L. A., Kessel, B., Crawford, E. D., Church, T. R., Andriole, G. L., Weissfeld, J. L., Fouad, M. N., Chia, D., O'Brien, B., Ragard, L. R., Clapp, J. D., … PLCO Project Team. (2011). Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA, 305(22), 2295–2303. https://doi.org/10.1001/jama.2011.766

Cao, P., Jeon, J., Levy, D. T., Jayasekera, J. C., Cadham, C. J., Mandelblatt, J. S., Taylor, K. L., & Meza, R. (2020). Potential Impact of Cessation Interventions at the Point of Lung Cancer Screening on Lung Cancer and Overall Mortality in the United States. Journal of Thoracic Oncology, 15(7), 1160–1169. https://doi.org/10.1016/j.jtho.2020.02.008

Cassidy, A., Myles, J. P., van Tongeren, M., Page, R. D., Liloglou, T., Duffy, S. W., & Field, J. K. (2008). The LLP risk model: An individual risk prediction model for lung cancer. British Journal of Cancer, 98(2), 270–276. https://doi.org/10.1038/sj.bjc.6604158

Castro, C., Bosetti, C., Malvezzi, M., Bertuccio, P., Levi, F., Negri, E., Vecchia, C. L., & Lunet, N. (2014). Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015. Annals of Oncology, 25(1), 283–290. https://doi.org/10.1093/annonc/mdt486

Chang, E. K., Gadzinski, A. J., & Nyame, Y. A. (2021). Blood and urine biomarkers in prostate cancer: Are we ready for reflex testing in men with an elevated prostate-specific antigen? Asian Journal of Urology. https://doi.org/10.1016/j.ajur.2021.06.003

Chiang, T.-H., Chang, W.-J., Chen, S. L.-S., Yen, A. M.-F., Fann, J. C.-Y., Chiu, S. Y.-H., Chen, Y.-R., Chuang, S.-L., Shieh, C.-F., Liu, C.-Y., Chiu, H.-M., Chiang, H., Shun, C.-T., Lin, M.-W., Wu, M.-S., Lin, J.-T., Chan, C.-C., Graham, D. Y., Chen, H.-H., & Lee, Y.-C. (2021). Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: A long-term cohort study on Matsu Islands. Gut, 70(2), 243–250. https://doi.org/10.1136/gutjnl-2020-322200

Crosbie, P. A., Gabe, R., Simmonds, I., Kennedy, M., Rogerson, S., Ahmed, N., Baldwin, D. R., Booton, R., Cochrane, A., Darby, M., Franks, K., Hinde, S., Janes, S. M., Macleod, U., Messenger, M., Moller, H., Murray, R. L., Neal, R. D., Quaife, S. L., … Callister, M. E. (2020). Yorkshire Lung Screening Trial (YLST): Protocol for a randomised controlled trial to evaluate invitation to community-based low-dose CT screening for lung cancer versus usual care in a targeted population at risk. BMJ Open, 10(9), e037075. https://doi.org/10.1136/bmjopen-2020-037075

de Koning, H. J., Meza, R., Plevritis, S. K., ten Haaf, K., Munshi, V. N., Jeon, J., Erdogan, S. A., Kong, C. Y., Han, S. S., van Rosmalen, J., Choi, S. E., Pinsky, P. F., Berrington de Gonzalez, A., Berg, C. D., Black, W. C., Tammemägi, M. C., Hazelton, W. D., Feuer, E. J., & McMahon, P. M. (2014). Benefits and harms of computed tomography lung cancer screening strategies: A comparative modeling study for the U.S. Preventive Services Task Force. Annals of Internal Medicine, 160(5), 311–320. https://doi.org/10.7326/M13-2316

de Koning, H. J., van der Aalst, C. M., de Jong, P. A., Scholten, E. T., Nackaerts, K., Heuvelmans, M. A., Lammers, J.-W. J., Weenink, C., Yousaf-Khan, U., Horeweg, N., van 't Westeinde, S., Prokop, M., Mali, W. P., Mohamed Hoesein, F. A. A., van Ooijen, P. M. A., Aerts, J. G. J. V., den Bakker, M. A., Thunnissen, E., Verschakelen, J., … Oudkerk, M. (2020). Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. New England Journal of Medicine, 382(6), 503–513. https://doi.org/10.1056/NEJMoa1911793

Dobrow, M. J., Hagens, V., Chafe, R., Sullivan, T., & Rabeneck, L. (2018). Consolidated principles for screening based on a systematic review and consensus process. CMAJ, 190(14), E422–E429. https://doi.org/10.1503/cmaj.171154

Drost, F.-J. H., Osses, D. F., Nieboer, D., Steyerberg, E. W., Bangma, C. H., Roobol, M. J., & Schoots, I. G. (2019). Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. The Cochrane Database of Systematic Reviews, 4, CD012663. https://doi.org/10.1002/14651858.CD012663.pub2

Dubuc, J., Legoux, J.-L., Winnock, M., Seyrig, J.-A., Barbier, J.-P., Barrioz, T., Laugier, R., Boulay, G., Grasset, D., Sautereau, D., Grigoresco, D., Butel, J., Scoazec, J.-Y., Ponchon, T., & Société Française d'Endoscopie Digestive. (2006). Endoscopic screening for esophageal squamous-cell carcinoma in high-risk patients: A prospective study conducted in 62 French endoscopy centers. Endoscopy, 38(7), 690–695. https://doi.org/10.1055/s-2006-925255

References

Eklund, M., Jäderling, F., Discacciati, A., Bergman, M., Annerstedt, M., Aly, M., Glaessgen, A., Carlsson, S., Grönberg, H., & Nordström, T. (2021). MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. New England Journal of Medicine, 385(10), 908–920. https://doi.org/10.1056/NEJMoa2100852

Eldred-Evans, D., Burak, P., Connor, M. J., Day, E., Evans, M., Fiorentino, F., Gammon, M., Hosking-Jervis, F., Klimowska-Nassar, N., McGuire, W., Padhani, A. R., Prevost, A. T., Price, D., Sokhi, H., Tam, H., Winkler, M., & Ahmed, H. U. (2021). Population-Based Prostate Cancer Screening With Magnetic Resonance Imaging or Ultrasonography: The IP1-PROSTAGRAM Study. JAMA Oncology, 7(3), 395–402. https://doi.org/10.1001/jamaoncol.2020.7456

Eyestone, E., Williams, R. M., Luta, G., Kim, E., Toll, B. A., Rojewski, A., Neil, J., Cinciripini, P. M., Cordon, M., Foley, K., Haas, J. S., Joseph, A. M., Minnix, J. A., Ostroff, J. S., Park, E., Rigotti, N., Sorgen, L., Taylor, K. L., & SCALE Collaboration. (2021). Predictors of Enrollment of Older Smokers in Six Smoking Cessation Trials in the Lung Cancer Screening Setting: The Smoking Cessation at Lung Examination (SCALE) Collaboration. Nicotine & Tobacco Research, ntab110. https://doi.org/10.1093/ntr/ntab110

Field, J. K., Duffy, S. W., Baldwin, D. R., Whynes, D. K., Devaraj, A., Brain, K. E., Eisen, T., Gosney, J., Green, B. A., Holemans, J. A., Kavanagh, T., Kerr, K. M., Ledson, M., Lifford, K. J., McRonald, F. E., Nair, A., Page, R. D., Parmar, M. K. B., Rassl, D. M., … Hansell, D. M. (2016). UK Lung Cancer RCT Pilot Screening Trial: Baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax, 71(2), 161–170. https://doi.org/10.1136/thoraxjnl-2015-207140

Field, J. K., Vulkan, D., Davies, M. P. A., Baldwin, D. R., Brain, K. E., Devaraj, A., Eisen, T., Gosney, J., Green, B. A., Holemans, J. A., Kavanagh, T., Kerr, K. M., Ledson, M., Lifford, K. J., McRonald, F. E., Nair, A., Page, R. D., Parmar, M. K. B., Rassl, D. M., … Duffy, S. W. (2021). Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. The Lancet Regional Health – Europe, 0(0). https://doi.org/10.1016/j.lanepe.2021.100179

Ford, A. C., Forman, D., Hunt, R., Yuan, Y., & Moayyedi, P. (2015). Helicobacter pylori eradication for the prevention of gastric neoplasia. The Cochrane Database of Systematic Reviews, 7, CD005583. https://doi.org/10.1002/14651858.CD005583.pub2

Frånlund, M., Carlsson, S., Stranne, J., Aus, G., & Hugosson, J. (2012). The absence of voiding symptoms in men with a prostate-specific antigen (PSA) concentration of ≥3.0 ng/mL is an independent risk factor for prostate cancer: Results from the Gothenburg Randomized Screening Trial. BJU International, 110(5), 638–643. https://doi.org/10.1111/j.1464-410X.2012.10962.x

Getaneh, A. M., Heijnsdijk, E. A., & de Koning, H. J. (2021). Cost-effectiveness of multiparametric magnetic resonance imaging and MRI-guided biopsy in a population-based prostate cancer screening setting using a micro-simulation model. Cancer Medicine, 10(12), 4046–4053. https://doi.org/10.1002/cam4.3932

Gini, A., van Ravesteyn, N. T., Jansen, E. E. L., Heijnsdijk, E. A. M., Senore, C., Anttila, A., Novak Mlakar, D., Veerus, P., Csanádi, M., Zielonke, N., Heinävaara, S., Széles, G., Segnan, N., de Koning, H. J., & Lansdorp-Vogelaar, I. (2021). The EU-TOPIA evaluation tool: An online modelling-based tool for informing breast, cervical, and colorectal cancer screening decisions in Europe. Preventive Medicine Reports, 22, 101392. https://doi.org/10.1016/j.pmedr.2021.101392

Goffin, J. R., Flanagan, W. M., Miller, A. B., Fitzgerald, N. R., Memon, S., Wolfson, M. C., & Evans, W. K. (2015). Cost-effectiveness of Lung Cancer Screening in Canada. JAMA Oncology, 1(6), 807–813. https://doi.org/10.1001/jamaoncol.2015.2472

Grönberg, H., Eklund, M., Picker, W., Aly, M., Jäderling, F., Adolfsson, J., Landquist, M., Haug, E. S., Ström, P., Carlsson, S., & Nordström, T. (2018). Prostate Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric Magnetic Resonance Imaging. European Urology, 74(6), 722–728. https://doi.org/10.1016/j.eururo.2018.06.022

Gulati, R., Cheng, H. H., Lange, P. H., Nelson, P. S., & Etzioni, R. (2017). Screening Men at Increased Risk for Prostate Cancer Diagnosis: Model Estimates of Benefits and Harms. Cancer Epidemiology and Prevention Biomarkers, 26(2), 222–227. https://doi.org/10.1158/1055-9965.EPI-16-0434

Gulati, R., Inoue, L. Y. T., Gore, J. L., Katcher, J., & Etzioni, R. (2014). Individualized Estimates of Overdiagnosis in Screen-Detected Prostate Cancer. JNCI: Journal of the National Cancer Institute, 106(2). https://doi.org/10.1093/jnci/djt367

Gulati, R., Mariotto, A. B., Chen, S., Gore, J. L., & Etzioni, R. (2011). Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. Journal of Clinical Epidemiology, 64(12), 1412–1417. https://doi.org/10.1016/j.jclinepi.2011.06.011

Gulati, R., Morgan, T. M., A'mar, T., Psutka, S. P., Tosoian, J. J., & Etzioni, R. (2020). Overdiagnosis and Lives Saved by Reflex Testing Men With Intermediate Prostate-Specific Antigen Levels. Journal of the National Cancer Institute, 112(4), 384–390. https://doi.org/10.1093/jnci/djz127

Haddad, G., Schouwenburg, S., Altesha, A., Xu, W., & Liu, G. (2020). Using breath analysis as a screening tool to detect gastric cancer: A systematic review. Journal of Breath Research. https://doi.org/10.1088/1752-7163/abc4d5

Heijnsdijk, E. A. M., Csanádi, M., Gini, A., ten Haaf, K., Bendes, R., Anttila, A., Senore, C., & de Koning, H. J. (2019). All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: A review and modeling study. Cancer Medicine, 8(13), 6127–6138. https://doi.org/10.1002/cam4.2476

Heijnsdijk, E. a. M., de Carvalho, T. M., Auvinen, A., Zappa, M., Nelen, V., Kwiatkowski, M., Villers, A., Páez, A., Moss, S. M., Tammela, T. L. J., Recker, F., Denis, L., Carlsson, S. V., Wever, E. M., Bangma, C. H., Schröder, F. H., Roobol, M. J., Hugosson, J., & de Koning, H. J. (2015). Cost-effectiveness of prostate cancer screening: A simulation study based on ERSPC data. Journal of the National Cancer Institute, 107(1), 366. https://doi.org/10.1093/jnci/dju366

Heijnsdijk, E. A. M., Gulati, R., Tsodikov, A., Lange, J. M., Mariotto, A. B., Vickers, A. J., Carlsson, S. V., & Etzioni, R. (2020). Lifetime Benefits and Harms of Prostate-Specific Antigen–Based Risk-Stratified Screening for Prostate Cancer. JNCI: Journal of the National Cancer Institute, 112(10), 1013–1020. https://doi.org/10.1093/jnci/djaa001

Henderson, J. T., Webber, E. M., & Sawaya, G. F. (2018). Screening for Ovarian Cancer: An Updated Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US). http://www.ncbi.nlm.nih.gov/books/NBK493399/

Hofmarcher, T., Lindgren, P., Wilking, N., & Jönsson, B. (2020). The cost of cancer in Europe 2018. European Journal of Cancer, 129, 41–49. https://doi.org/10.1016/j.ejca.2020.01.011

Huang, S., Guo, Y., Li, Z.-W., Shui, G., Tian, H., Li, B.-W., Kadeerhan, G., Li, Z.-X., Li, X., Zhang, Y., Zhou, T., You, W.-C., Pan, K.-F., & Li, W.-Q. (2021). Identification and Validation of Plasma Metabolomic Signatures in Precancerous Gastric Lesions That Progress to Cancer. JAMA Network Open, 4(6), e2114186. https://doi.org/10.1001/jamanetworkopen.2021.14186

Hugosson, J. (2018). Stopping screening, when and how? Translational Andrology and Urology, 7(1), 463–453.

Hugosson, J., Roobol, M. J., Månsson, M., Tammela, T. L. J., Zappa, M., Nelen, V., Kwiatkowski, M., Lujan, M., Carlsson, S. V., Talala, K. M., Lilja, H., Denis, L. J., Recker, F., Paez, A., Puliti, D., Villers, A., Rebillard, X., Kilpeläinen, T. P., Stenman, U. H., … ERSPC investigators. (2019). A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. European Urology, 76(1), 43–51. https://doi.org/10.1016/j.eururo.2019.02.009

Hüsing, A., & Kaaks, R. (2020). Risk prediction models versus simplified selection criteria to determine eligibility for lung cancer screening: An analysis of German federal-wide survey and incidence data. European Journal of Epidemiology, 35(10), 899–912. https://doi.org/10.1007/s10654-020-00657-w

References

Jacobs, I. J., Menon, U., Ryan, A., Gentry-Maharaj, A., Burnell, M., Kalsi, J. K., Amso, N. N., Apostolidou, S., Benjamin, E., Cruickshank, D., Crump, D. N., Davies, S. K., Dawnay, A., Dobbs, S., Fletcher, G., Ford, J., Godfrey, K., Gunu, R., Habib, M., … Skates, S. J. (2016). Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. The Lancet, 387(10022), 945–956. https://doi.org/10.1016/S0140-6736(15)01224-6

Jiao, B., Gulati, R., Hendrix, N., Gore, J. L., Rais-Bahrami, S., Morgan, T. M., & Etzioni, R. (2021). Economic Evaluation of Urine-Based or Magnetic Resonance Imaging Reflex Tests in Men With Intermediate Prostate-Specific Antigen Levels in the United States. Value in Health, 24(8), 1111–1117. https://doi.org/10.1016/j.jval.2021.02.009

Joseph, A. M., Rothman, A. J., Almirall, D., Begnaud, A., Chiles, C., Cinciripini, P. M., Fu, S. S., Graham, A. L., Lindgren, B. R., Melzer, A. C., Ostroff, J. S., Seaman, E. L., Taylor, K. L., Toll, B. A., Zeliadt, S. B., & Vock, D. M. (2018). Lung Cancer Screening and Smoking Cessation Clinical Trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration. American Journal of Respiratory and Critical Care Medicine, 197(2), 172–182. https://doi.org/10.1164/rccm.201705-0909CI

Kamangar, F., Nasrollahzadeh, D., Safiri, S., Sepanlou, S. G., Fitzmaurice, C., Ikuta, K. S., Bisignano, C., Islami, F., Roshandel, G., Lim, S. S., Abolhassani, H., Abu-Gharbieh, E., Adedoyin, R. A., Advani, S. M., Ahmed, M. B., Aichour, M. T. E., Akinyemiju, T., Akunna, C. J., Alahdab, F., … Naghavi, M. (2020). The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology, 5(6), 582–597. https://doi.org/10.1016/S2468-1253(20)30007-8

Katki, H. A., Kovalchik, S. A., Berg, C. D., Cheung, L. C., & Chaturvedi, A. K. (2016). Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. JAMA, 315(21), 2300–2311. https://doi.org/10.1001/jama.2016.6255

Krilaviciute, A., Stock, C., Leja, M., & Brenner, H. (2018). Potential of non-invasive breath tests for preselecting individuals for invasive gastric cancer screening endoscopy. Journal of Breath Research, 12(3), 036009. https://doi.org/10.1088/1752-7163/aab5be

Lagergren, J., Bergström, R., Lindgren, A., & Nyrén, O. (1999). Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. The New England Journal of Medicine, 340(11), 825–831. https://doi.org/10.1056/NEJM199903183401101

Lansdorp-Vogelaar, I., Meester, R. G. S., Laszkowska, M., Escudero, F. A., Ward, Z. J., & Yeh, J. M. (2021). Cost-effectiveness of prevention and early detection of gastric cancer in Western countries. Best Practice & Research. Clinical Gastroenterology, 50–51, 101735. https://doi.org/10.1016/j.bpg.2021.101735

Lebrett, M. B., Balata, H., Evison, M., Colligan, D., Duerden, R., Elton, P., Greaves, M., Howells, J., Irion, K., Karunaratne, D., Lyons, J., Mellor, S., Myerscough, A., Newton, T., Sharman, A., Smith, E., Taylor, B., Taylor, S., Walsham, A., … Crosbie, P. A. J. (2020). Analysis of lung cancer risk model (PLCOM2012 and LLPv2) performance in a community-based lung cancer screening programme. Thorax, 75(8), 661–668. https://doi.org/10.1136/thoraxjnl-2020-214626

Leja, M., Cine, E., Poļaka, I., Daugule, I., Murillo, R., Parshutin, S., Ražuka-Ebela, D., Rotberga, L., Anarkulova, L., Kriķe, P., Šantare, D., Tzivian, L., Herrero, R., & Park, J. Y. (2021). Factors influencing participation in preventive interventions for gastric cancer: The results from the GISTAR study. European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP). https://doi.org/10.1097/CEJ.0000000000000682

Leja, M., & Dumpis, U. (2020). What Would the Screen-and-Treat Strategy for Helicobacter pylori Mean in Terms of Antibiotic Consumption? Digestive Diseases and Sciences, 65(6), 1632–1642. https://doi.org/10.1007/s10620-019-05893-z

Leja, M., Park, J. Y., Murillo, R., Liepniece-Karele, I., Isajevs, S., Kikuste, I., Rudzite, D., Krike, P., Parshutin, S., Polaka, I., Kirsners, A., Santare, D., Folkmanis, V., Daugule, I., Plummer, M., & Herrero, R. (2017). Multicentric randomised study of Helicobacter pylori eradication and pepsinogen testing for prevention of gastric cancer mortality: The GISTAR study. BMJ Open, 7(8), e016999. https://doi.org/10.1136/bmjopen-2017-016999

Liou, J.-M., Malfertheiner, P., Lee, Y.-C., Sheu, B.-S., Sugano, K., Cheng, H.-C., Yeoh, K.-G., Hsu, P.-I., Goh, K.-L., Mahachai, V., Gotoda, T., Chang, W.-L., Chen, M.-J., Chiang, T.-H., Chen, C.-C., Wu, C.-Y., Leow, A. H.-R., Wu, J.-Y., Wu, D.-C., … Asian Pacific Alliance on Helicobacter and Microbiota (APAHAM). (2020). Screening and eradication of Helicobacter pylori for gastric cancer prevention: The Taipei global consensus. Gut, 69(12), 2093–2112. https://doi.org/10.1136/gutjnl-2020-322368

Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. (2019). Journal of Thoracic Oncology, 14(10), 1732–1742. https://doi.org/10.1016/j.jtho.2019.05.044

Mark, D. H. (2002). Visualizing cost-effectiveness analysis. JAMA, 287(18), 2428–2429. https://doi.org/10.1001/jama.287.18.2428

Marques de Sá, I., Marcos, P., Sharma, P., & Dinis-Ribeiro, M. (2020). The global prevalence of Barrett's esophagus: A systematic review of the published literature. United European Gastroenterology Journal, 8(9), 1086–1105. https://doi.org/10.1177/2050640620939376

Martin, R. M., Donovan, J. L., Turner, E. L., Metcalfe, C., Young, G. J., Walsh, E. I., Lane, J. A., Noble, S., Oliver, S. E., Evans, S., Sterne, J. A. C., Holding, P., Ben-Shlomo, Y., Brindle, P., Williams, N. J., Hill, E. M., Ng, S. Y., Toole, J., Tazewell, M. K., … for the CAP Trial Group. (2018). Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA, 319(9), 883–895. https://doi.org/10.1001/jama.2018.0154

McMahon, P. M., Kong, C. Y., Bouzan, C., Weinstein, M. C., Cipriano, L. E., Tramontano, A. C., Johnson, B. E., Weeks, J. C., & Gazelle, G. S. (2011). Cost-effectiveness of computed tomography screening for lung cancer in the United States. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer, 6(11), 1841–1848. https://doi.org/10.1097/JTO.0b013e31822e59b3

Menon, U., Gentry-Maharaj, A., Burnell, M., Singh, N., Ryan, A., Karpinskyj, C., Carlino, G., Taylor, J., Massingham, S. K., Raikou, M., Kalsi, J. K., Woolas, R., Manchanda, R., Arora, R., Casey, L., Dawnay, A., Dobbs, S., Leeson, S., Mould, T., … Parmar, M. (2021). Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. The Lancet, 397(10290), 2182–2193. https://doi.org/10.1016/S0140-6736(21)00731-5

Menon, U., Ryan, A., Kalsi, J., Gentry-Maharaj, A., Dawnay, A., Habib, M., Apostolidou, S., Singh, N., Benjamin, E., Burnell, M., Davies, S., Sharma, A., Gunu, R., Godfrey, K., Lopes, A., Oram, D., Herod, J., Williamson, K., Seif, M. W., … Jacobs, I. (2015). Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 33(18), 2062–2071. https://doi.org/10.1200/JCO.2014.59.4945

Meza, R., Jeon, J., Toumazis, I., ten Haaf, K., Cao, P., Bastani, M., Han, S. S., Blom, E. F., Jonas, D. E., Feuer, E. J., Plevritis, S. K., de Koning, H. J., & Kong, C. Y. (2021). Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: Modeling Study for the US Preventive Services Task Force. JAMA, 325(10), 988–997. https://doi.org/10.1001/jama.2021.1077

References

Murray, R. L., Brain, K., Britton, J., Quinn-Scoggins, H. D., Lewis, S., McCutchan, G. M., Quaife, S. L., Wu, Q., Ashurst, A., Baldwin, D., Crosbie, P. A. J., Neal, R. D., Parrott, S., Rogerson, S., Thorley, R., & Callister, M. E. (2020). Yorkshire Enhanced Stop Smoking (YESS) study: A protocol for a randomised controlled trial to evaluate the effect of adding a personalised smoking cessation intervention to a lung cancer screening programme. BMJ Open, 10(9), e037086. https://doi.org/10.1136/bmjopen-2020-037086

National Lung Screening Trial Research Team, Aberle, D. R., Adams, A. M., Berg, C. D., Black, W. C., Clapp, J. D., Fagerstrom, R. M., Gareen, I. F., Gatsonis, C., Marcus, P. M., & Sicks, J. D. (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. The New England Journal of Medicine, 365(5), 395–409. https://doi.org/10.1056/NEJMoa1102873

Neumann, P. J., Cohen, J. T., & Weinstein, M. C. (2014, August 27). Updating Cost-Effectiveness—The Curious Resilience of the $50,000-per-QALY Threshold (world) [N-perspective]. Http://Dx.Doi.Org/10.1056/NEJMp1405158; Massachusetts Medical Society. https://doi.org/10.1056/NEJMp1405158

Nordström, T., Discacciati, A., Bergman, M., Clements, M., Aly, M., Annerstedt, M., Glaessgen, A., Carlsson, S., Jäderling, F., Eklund, M., Grönberg, H., Cavalli-Björkman, C., Björklund, A., Hune, B.-M., Clements, M., Hao, S., Discacciati, A., Grönberg, H., Eklund, M., … Annerstedt, M. (2021). Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): A prospective, population-based, randomised, open-label, non-inferiority trial. The Lancet Oncology, 22(9), 1240–1249. https://doi.org/10.1016/S1470-2045(21)00348-X

Pakarainen, T., Nevalainen, J., Talala, K., Taari, K., Raitanen, J., Kujala, P., Stenman, U.-H., Tammela, T. L. J., & Auvinen, A. (2019). The Number of Screening Cycles Needed to Reduce Prostate Cancer Mortality in the Finnish Section of the European Randomized Study of Prostate Cancer (ERSPC). Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 25(2), 839–843. https://doi.org/10.1158/1078-0432.CCR-18-1807

Pan, K., Zhang, L., Gerhard, M., Ma, J., Liu, W., Ulm, K., Wang, J., Zhang, L., Zhang, Y., Bajbouj, M., Zhang, L., Li, M., Vieth, M., Liu, R., Quante, M., Wang, L., Suchanek, S., Zhou, T., Guan, W., … You, W. (2016). A large randomised controlled intervention trial to prevent gastric cancer by eradication of Helicobacter pylori in Linqu County, China: Baseline results and factors affecting the eradication. Gut, 65(1), 9–18. https://doi.org/10.1136/gutjnl-2015-309197

Paulden, M. (2017). Recent amendments to NICE's value-based assessment of health technologies: Implicitly inequitable? Expert Review of Pharmacoeconomics & Outcomes Research, 17(3), 239–242. https://doi.org/10.1080/14737167.2017.1330152

Phoa, K. N., van Vilsteren, F. G. I., Weusten, B. L. A. M., Bisschops, R., Schoon, E. J., Ragunath, K., Fullarton, G., Di Pietro, M., Ravi, N., Visser, M., Offerhaus, G. J., Seldenrijk, C. A., Meijer, S. L., ten Kate, F. J. W., Tijssen, J. G. P., & Bergman, J. J. G. H. M. (2014). Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia: A Randomized Clinical Trial. JAMA, 311(12), 1209–1217. https://doi.org/10.1001/jama.2014.2511

Pinsky, P. F., Prorok, P. C., Yu, K., Kramer, B. S., Black, A., Gohagan, J., Crawford, E. D., Grubb, R., & Andriole, G. (2017). Extended Mortality Results for Prostate Cancer Screening in the PLCO Trial with Median 15 Years Follow-up. Cancer, 123(4), 592–599. https://doi.org/10.1002/cncr.30474

Pinsky, P. F., Yu, K., Kramer, B. S., Black, A., Buys, S. S., Partridge, E., Gohagan, J., Berg, C. D., & Prorok, P. C. (2016). Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecologic Oncology, 143(2), 270–275. https://doi.org/10.1016/j.ygyno.2016.08.334

Poppel, H. V., Roobol, M. J., Chapple, C. R., Catto, J. W. F., N'Dow, J., Sønksen, J., Stenzl, A., & Wirth, M. (2021). Prostate-specific Antigen Testing as Part of a Risk-Adapted Early Detection Strategy for Prostate Cancer: European Association of Urology Position and Recommendations for 2021. European Urology, 0(0). https://doi.org/10.1016/j.eururo.2021.07.024

Puggina, A., Broumas, A., Ricciardi, W., & Boccia, S. (2016). Cost-effectiveness of screening for lung cancer with low-dose computed tomography: A systematic literature review. European Journal of Public Health, 26(1), 168–175. https://doi.org/10.1093/eurpub/ckv158

Qumseya, B. J., Bukannan, A., Gendy, S., Ahemd, Y., Sultan, S., Bain, P., Gross, S. A., Iyer, P., & Wani, S. (2019). Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. Gastrointestinal Endoscopy, 90(5), 707-717.e1. https://doi.org/10.1016/j.gie.2019.05.030

Raymakers, A. J. N., Mayo, J., Lam, S., FitzGerald, J. M., Whitehurst, D. G. T., & Lynd, L. D. (2016). Cost-Effectiveness Analyses of Lung Cancer Screening Strategies Using Low-Dose Computed Tomography: A Systematic Review. Applied Health Economics and Health Policy, 14(4), 409–418. https://doi.org/10.1007/s40258-016-0226-5

Reiter, M. J., Nemesure, A., Madu, E., Reagan, L., & Plank, A. (2018). Frequency and distribution of incidental findings deemed appropriate for S modifier designation on low-dose CT in a lung cancer screening program. Lung Cancer (Amsterdam, Netherlands), 120, 1–6. https://doi.org/10.1016/j.lungcan.2018.03.017

Roth, J. A., Gulati, R., Gore, J. L., Cooperberg, M. R., & Etzioni, R. (2016). Economic Analysis of Prostate-Specific Antigen Screening and Selective Treatment Strategies. JAMA Oncology, 2(7), 890–898. https://doi.org/10.1001/jamaoncol.2015.6275

Rubenstein, J. H., Raghunathan, T., Doan, C., Schneider, J., Zhao, W., Metko, V., Nofz, K., Khodadost, M., & Corley, D. A. (2021). Validation of Tools for Predicting Incident Adenocarcinoma of the Esophagus or Esophagogastric Junction. The American Journal of Gastroenterology, 116(5), 949–957. https://doi.org/10.14309/ajg.0000000000001255

Sanders, G. D., Neumann, P. J., Basu, A., Brock, D. W., Feeny, D., Krahn, M., Kuntz, K. M., Meltzer, D. O., Owens, D. K., Prosser, L. A., Salomon, J. A., Sculpher, M. J., Trikalinos, T. A., Russell, L. B., Siegel, J. E., & Ganiats, T. G. (2016). Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA, 316(10), 1093–1103. https://doi.org/10.1001/jama.2016.12195

Sanghera, S., Coast, J., Martin, R. M., Donovan, J. L., & Mohiuddin, S. (2018). Cost-effectiveness of prostate cancer screening: A systematic review of decision-analytical models. BMC Cancer, 18(1), 84. https://doi.org/10.1186/s12885-017-3974-1

Scherübl, H., Lampe, B. von, Faiss, S., Däubler, P., Bohlmann, P., Plath, T., Foss, H.-D., Scherer, H., Strunz, A., Hoffmeister, B., Stein, H., Zeitz, M., & Riecken, E.-O. (2002). Screening for oesophageal neoplasia in patients with head and neck cancer. British Journal of Cancer, 86(2), 239–243. https://doi.org/10.1038/sj.bjc.6600018

Schröder, F. H., Hugosson, J., Roobol, M. J., Tammela, T. L. J., Zappa, M., Nelen, V., Kwiatkowski, M., Lujan, M., Määttänen, L., Lilja, H., Denis, L. J., Recker, F., Paez, A., Bangma, C. H., Carlsson, S., Puliti, D., Villers, A., Rebillard, X., Hakama, M., … Auvinen, A. (2014). The European Randomized Study of Screening for Prostate Cancer – Prostate Cancer Mortality at 13 Years of Follow-up. Lancet, 384(9959), 2027–2035. https://doi.org/10.1016/S0140-6736(14)60525-0

Scialpi, M., D'Andrea, A., Martorana, E., Malaspina, C. M., Aisa, M. C., Napoletano, M., Orlandi, E., Rondoni, V., Scialpi, P., Pacchiarini, D., Palladino, D., Dragone, M., Di Renzo, G., Simeone, A., Bianchi, G., & Brunese, L. (2017). Biparametric MRI of the prostate. Turkish Journal of Urology, 43(4), 401–409. https://doi.org/10.5152/tud.2017.06978

References

Shaheen, N. J., Sharma, P., Overholt, B. F., Wolfsen, H. C., Sampliner, R. E., Wang, K. K., Galanko, J. A., Bronner, M. P., Goldblum, J. R., Bennett, A. E., Jobe, B. A., Eisen, G. M., Fennerty, M. B., Hunter, J. G., Fleischer, D. E., Sharma, V. K., Hawes, R. H., Hoffman, B. J., Rothstein, R. I., … Lightdale, C. J. (2009). Radiofrequency Ablation in Barrett's Esophagus with Dysplasia. New England Journal of Medicine, 360(22), 2277–2288. https://doi.org/10.1056/NEJMoa0808145

Silva, M., Milanese, G., Sestini, S., Sabia, F., Jacobs, C., van Ginneken, B., Prokop, M., Schaefer-Prokop, C. M., Marchianò, A., Sverzellati, N., & Pastorino, U. (2021). Lung cancer screening by nodule volume in Lung-RADS v1.1: Negative baseline CT yields potential for increased screening interval. European Radiology, 31(4), 1956–1968. https://doi.org/10.1007/s00330-020-07275-w

Slatore, C. G., Baumann, C., Pappas, M., & Humphrey, L. L. (2014). Smoking behaviors among patients receiving computed tomography for lung cancer screening. Systematic review in support of the U.S. preventive services task force. Annals of the American Thoracic Society, 11(4), 619–627. https://doi.org/10.1513/AnnalsATS.201312-460OC

Sturdy, S., Miller, F., Hogarth, S., Armstrong, N., Chakraborty, P., Cressman, C., Dobrow, M., Flitcroft, K., Grossman, D., Harris, R., Hoebee, B., Holloway, K., Kinsinger, L., Krag, M., Löblová, O., Löwy, I., Mackie, A., Marshall, J., O'Hallahan, J., … Zappa, M. (2020). Half a Century of Wilson & Jungner: Reflections on the Governance of Population Screening (5:158). Wellcome Open Research. https://doi.org/10.12688/wellcomeopenres.16057.2

Su, Y.-Y., Chen, W.-C., Chuang, H.-C., Guo, C.-S., Lin, Y.-T., Luo, S.-D., Fang, F.-M., & Chien, C.-Y. (2013). Effect of routine esophageal screening in patients with head and neck cancer. JAMA Otolaryngology-- Head & Neck Surgery, 139(4), 350–354. https://doi.org/10.1001/jamaoto.2013.46

Tammemägi, M. C., Darling, G. E., Schmidt, H., Llovet, D., Buchanan, D. N., Leung, Y., Miller, B., & Rabeneck, L. (2021). Selection of individuals for lung cancer screening based on risk prediction model performance and economic factors—The Ontario experience. Lung Cancer (Amsterdam, Netherlands), 156, 31–40. https://doi.org/10.1016/j.lungcan.2021.04.005

Tammemägi, M. C., Katki, H. A., Hocking, W. G., Church, T. R., Caporaso, N., Kvale, P. A., Chaturvedi, A. K., Silvestri, G. A., Riley, T. L., Commins, J., & Berg, C. D. (2013). Selection Criteria for Lung-Cancer Screening. New England Journal of Medicine, 368(8), 728–736. https://doi.org/10.1056/NEJMoa1211776

Tammemägi, M. C., Ruparel, M., Tremblay, A., Myers, R., Mayo, J., Yee, J., Atkar-Khattra, S., Yuan, R., Cressman, S., English, J., Bedard, E., MacEachern, P., Burrowes, P., Quaife, S. L., Marshall, H., Yang, I., Bowman, R., Passmore, L., McWilliams, A., … Lam, S. (2022). USPSTF2013 versus PLCOm2012 lung cancer screening eligibility criteria (International Lung Screening Trial): Interim analysis of a prospective cohort study. The Lancet Oncology, 23(1), 138–148. https://doi.org/10.1016/S1470-2045(21)00590-8

Tanner, N. T., Kanodra, N. M., Gebregziabher, M., Payne, E., Halbert, C. H., Warren, G. W., Egede, L. E., & Silvestri, G. A. (2016). The Association between Smoking Abstinence and Mortality in the National Lung Screening Trial. American Journal of Respiratory and Critical Care Medicine, 193(5), 534–541. https://doi.org/10.1164/rccm.201507-1420OC

ten Haaf, K., Bastani, M., Cao, P., Jeon, J., Toumazis, I., Han, S. S., Plevritis, S. K., Blom, E. F., Kong, C. Y., Tammemägi, M. C., Feuer, E. J., Meza, R., & de Koning, H. J. (2020). A Comparative Modeling Analysis of Risk-Based Lung Cancer Screening Strategies. JNCI: Journal of the National Cancer Institute, 112(5), 466–479. https://doi.org/10.1093/jnci/djz164

Ten Haaf, K., van Rosmalen, J., & de Koning, H. J. (2015). Lung cancer detectability by test, histology, stage, and gender: Estimates from the NLST and the PLCO trials. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 24(1), 154–161. https://doi.org/10.1158/1055-9965.EPI-14-0745

Tepes, B., Kastelic, M., Vujasinovic, M., Lampic, P., Seruga, M., Jurecic, N. B., Nyssen, O. P., Donday, M. G., O'Morain, C., Megraud, F., McNicholl, A. G., & Gisbert, J. P. (2018). Helicobacter pylori treatment results in Slovenia in the period 2013-2015 as a part of European Registry on Helicobacter pylori Management. Radiology and Oncology, 52(1), 1–6. https://doi.org/10.1515/raon-2017-0055

Tinmouth, J., Vella, E. T., Baxter, N. N., Dubé, C., Gould, M., Hey, A., Ismaila, N., McCurdy, B. R., & Paszat, L. (2016). Colorectal Cancer Screening in Average Risk Populations: Evidence Summary. Canadian Journal of Gastroenterology & Hepatology, 2016, 2878149. https://doi.org/10.1155/2016/2878149

Trivanovic, D., Honovic, L., Dembic, M., Matosevic, K., & Buic Grzeta, M. (2018). Gastric cancer detection using the serum pepsinogen test method in Croatian patients. Journal of Clinical Oncology, 36(15_suppl), e24055–e24055. https://doi.org/10.1200/JCO.2018.36.15_suppl.e24055

Tsai, E. B., Chiles, C., Carter, B. W., Godoy, M. C. B., Shroff, G. S., Munden, R. F., Truong, M. T., & Wu, C. C. (2018). Incidental Findings on Lung Cancer Screening: Significance and Management. Seminars in Ultrasound, CT, and MR, 39(3), 273–281. https://doi.org/10.1053/j.sult.2018.02.005

Tsodikov, A., Gulati, R., Heijnsdijk, E. A. M., Pinsky, P. F., Moss, S. M., Qiu, S., de Carvalho, T. M., Hugosson, J., Berg, C. D., Auvinen, A., Andriole, G. L., Roobol, M. J., Crawford, E. D., Nelen, V., Kwiatkowski, M., Zappa, M., Luján, M., Villers, A., Feuer, E. J., … Etzioni, R. (2017). Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials. Annals of Internal Medicine, 167(7), 449–455. https://doi.org/10.7326/M16-2586

US Preventive Services Task Force. (2021). Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA, 325(10), 962–970. https://doi.org/10.1001/jama.2021.1117

van de Wiel, J. C. M., Wang, Y., Xu, D. M., van der Zaag-Loonen, H. J., van der Jagt, E. J., van Klaveren, R. J., Oudkerk, M., & NELSON study group. (2007). Neglectable benefit of searching for incidental findings in the Dutch-Belgian lung cancer screening trial (NELSON) using low-dose multidetector CT. European Radiology, 17(6), 1474–1482. https://doi.org/10.1007/s00330-006-0532-7

van der Aalst, C. M., van den Bergh, K. A. M., Willemsen, M. C., de Koning, H. J., & van Klaveren, R. J. (2010). Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. Thorax, 65(7), 600–605. https://doi.org/10.1136/thx.2009.133751

van der Aalst, C., Oudkerk, M., Haaf, K. T., Baldwin, D., Murray, R., O'Dowd, E., Kaaks, R., Katzke, V., Becker, N., Espinàs, J., Borras, J., Aigner, C., Balleyguier, C., Planchard, D., Janes, S., Sozzi, G., Pastorino, U., & Koning, H. D. (2020). Towards personalized lung cancer CT screening in Europe. European Respiratory Journal, 56(suppl 64). https://doi.org/10.1183/13993003.congress-2020.4171

Van Haren, R. M., Delman, A. M., Turner, K. M., Waits, B., Hemingway, M., Shah, S. A., & Starnes, S. L. (2021). Impact of the COVID-19 Pandemic on Lung Cancer Screening Program and Subsequent Lung Cancer. Journal of the American College of Surgeons, 232(4), 600–605. https://doi.org/10.1016/j.jamcollsurg.2020.12.002

Van Poppel, H., Hogenhout, R., Albers, P., van den Bergh, R. C. N., Barentsz, J. O., & Roobol, M. J. (2021). Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission. European Urology, 79(3), 327–329. https://doi.org/10.1016/j.eururo.2020.12.010

References

Venderbos, L. D. F., Deschamps, A., Dowling, J., Carl, E.-G., Remmers, S., van Poppel, H., & Roobol, M. J. (2020). Europa Uomo Patient Reported Outcome Study (EUPROMS): Descriptive Statistics of a Prostate Cancer Survey from Patients for Patients. European Urology Focus, S2405-4569(20)30297-2. https://doi.org/10.1016/j.euf.2020.11.002

Villers, A., Bessaoud, F., Trétarre, B., Grosclaude, P., Malavaud, B., Rebillard, X., Iborra, F., Daubisse, L., Malavaud, S., Roobol, M., Heijnsdijk, E. A., de Koning, H. J., Hugosson, J., Rischmann, P., & Soulié, M. (2020). Contamination in control group led to no effect of PSA-based screening on prostate cancer mortality at 9 years follow-up: Results of the French section of European Randomized Study of Screening for Prostate Cancer (ERSPC). Progrès En Urologie, 30(5), 252–260. https://doi.org/10.1016/j.purol.2020.02.011

Weusten, B., Bisschops, R., Coron, E., Dinis-Ribeiro, M., Dumonceau, J.-M., Esteban, J.-M., Hassan, C., Pech, O., Repici, A., Bergman, J., & di Pietro, M. (2017). Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy, 49(2), 191–198. https://doi.org/10.1055/s-0042-122140

Wilschut, J. A., Hol, L., Dekker, E., Jansen, J. B., Van Leerdam, M. E., Lansdorp-Vogelaar, I., Kuipers, E. J., Habbema, J. D. F., & Van Ballegooijen, M. (2011). Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Gastroenterology, 141(5), 1648-1655.e1. https://doi.org/10.1053/j.gastro.2011.07.020

Wilson, J. M. G., Jungner, G., & World Health Organization (1968). Principles and practice of screening for disease. World Health Organization. https://apps.who.int/iris/handle/10665/37650

Xu, D. M., Gietema, H., de Koning, H., Vernhout, R., Nackaerts, K., Prokop, M., Weenink, C., Lammers, J.-W., Groen, H., Oudkerk, M., & van Klaveren, R. (2006). Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer (Amsterdam, Netherlands), 54(2), 177–184. https://doi.org/10.1016/j.lungcan.2006.08.006

Zhang, X., Li, M., Chen, S., Hu, J., Guo, Q., Liu, R., Zheng, H., Jin, Z., Yuan, Y., Xi, Y., & Hua, B. (2018). Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review. Gastroenterology, 155(2), 347-354.e9. https://doi.org/10.1053/j.gastro.2018.04.026

Zielonke, N., Kregting, L. M., Heijnsdijk, E. A. M., Veerus, P., Heinävaara, S., McKee, M., de Kok, I. M. C. M., de Koning, H. J., van Ravesteyn, N. T., & Collaborators, the E.-T. (2021). The potential of breast cancer screening in Europe. International Journal of Cancer, 148(2), 406–418. https://doi.org/10.1002/ijc.33204

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