IMPROVING CANCER SCREENING IN THE EUROPEAN UNION

SAPEA
Science Advice for Policy by European Academies

Evidence Review Report No. 10

This Evidence Review Report has been produced under the auspices of the SAPEA consortium, as a deliverable under Grant Agreement 737432 "Science Advice for Policy by European Academies" that was signed by the consortium and the European Commission on 22 November 2016.

In accordance with Article 35, paragraph 1 of the aforementioned Grant Agreement, the consortium identified all relevant interests of the experts requested to contribute to this Evidence Review Report, assessed whether an interest constituted a conflict of interests, and took — where relevant — measures to exclude that an interest could compromise or be reasonably perceived as compromising the impartiality or objectivity of the report. Further information about SAPEA's quality guidelines and working processes is available at www.sapea.info.

- ISBN 978-3-9823562-0-4
- DOI 10.26356/cancerscreening
- Downloadable from www.sapea.info/cancerscreening

Publisher

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SAPEA, Science Advice for Policy by European Academies. (2022). *Improving cancer screening in the European Union*. Berlin: SAPEA. https://doi.org/10.26356/cancerscreening

Version history

Version	Date	Summary of changes
1.0	2 March 2022	First published version

SAPEA

Science Advice for Policy by European Academies

Improving cancer screening in the European Union

Informs the Scientific Opinion
of the European Commission Group of Chief Scientific Advisors

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This Evidence Review Report was produced on an accelerated timetable due to the requirement to update the Council Recommendation on cancer screening in the first quarter of 2022, as stated in the scoping paper.

The evidence gathering process was overseen by two project chairs. Three expert workshops were organised and three corresponding rapid literature reviews were undertaken by Cardiff University.

For a detailed description of the process, please see Annex 1, p.142.

About SAPEA

SAPEA brings together outstanding expertise from natural sciences, engineering and technology, medical, health, agricultural and social sciences, and the humanities. We draw on over a hundred academies, young academies and learned societies in more than 40 countries across Europe.

SAPEA is part of the European Commission's Scientific Advice Mechanism. Together with the Group of Chief Scientific Advisors, we provide independent scientific advice to European Commissioners to support their decision-making.

We also work to strengthen connections between Europe's academies and Academy Networks, and to stimulate debate in Europe about the role of evidence in policymaking.

Europe's academies draw on the best scientific expertise to provide independent, balanced and authoritative scientific advice. This approach makes SAPEA a critical source of evidence for policymakers and the wider public.

Our five Academy Networks collectively represent over a hundred academies, young academies and learned societies across Europe. SAPEA works to strengthen these academies and provides a means for close collaboration in a unique and interdisciplinary way.

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Foreword

The field of cancer screening is rapidly evolving, and in 2022 the European Commission will make a proposal to update the Council Recommendation on cancer screening to ensure it reflects the latest available scientific evidence.

In support of this, the Commission's Group of Chief Scientific Advisors requested the Scientific Advice Mechanism to provide evidence to answer the following questions:

- How can existing cancer screening programmes targeting breast, cervical and colorectal cancers be improved throughout the EU?
- What is the scientific basis of extending screening programmes to other cancers and ensuring their feasibility throughout the EU?
- Which are the main scientific elements to consider, and best practices to promote, for optimising risk-based cancer screening and early diagnosis throughout the EU?

The Federation of European Academies of Medicine conducted initial scoping and exploratory work on behalf of SAPEA and was delighted when a request was made by the European Commission to the Group of Chief Scientific Advisors in May 2021 for SAPEA to produce a new Evidence Review Report on this topic, with FEAM acting as the lead academy network. This is the tenth report to be published by the SAPEA consortium, an integral part of the European Commission's Scientific Advice Mechanism. It informs the Scientific Opinion of the Group of Chief Scientific Advisors, and both the SAPEA and GCSA reports inform the European Commission and other policymakers.

We warmly thank all the experts for their valuable contributions, in addition to everyone involved in assembling this report. A special thanks goes to the two project chairs, Professors Rebecca Fitzgerald and Harry de Koning, alongside the scientific writer, Dr Kat Arney, who have worked incredibly hard to make this possible.

Professor Stefan Constantinescu
FEAM president

Professor George Griffin
FEAM past president

Professor Antonio Loprieno
Chair of the SAPEA board

Preface

In 2020, 2.7 million people in the European Union (EU) were diagnosed with cancer and another 1.3 million people lost their lives to it.[1] The EU has acknowledged the great significance of the cancer burden on the population, and the launch of the *Beating Cancer Plan* in 2021 demonstrated its strong commitment to tackling this challenge. The plan highlights that the responsibility for health lies predominantly with the governments of individual EU member states, and focuses on actions to support and coordinate member states' efforts at each stage of the disease.

One of the key stages is early detection, and screening offers the best chance of beating cancer and saving lives. Europe's *Beating Cancer Plan* aims to ensure that 90% of the eligible EU population are offered screening for breast, cervical and colorectal cancer by 2025.[2] Furthermore, there could be significant public health benefits to be gained through the introduction of screening for other types of cancer and the use of novel technologies such as blood-based biomarker testing.

The evidence cited in this report is based on a series of three expert workshops that took place in the autumn of 2021, designed by the chair and co-chair, in which a total of 45 leading experts from Europe and beyond were invited to give presentations and join roundtable debates. Additionally, Cardiff University's Specialist Unit for Review Evidence has conducted rapid literature reviews to accompany each of the questions listed above. For further details of this process, see the Annexes to this report (p.142). Full reports from each workshop and the rapid reviews can be found online at sapea.info/cancerscreening. The experts had the opportunity to comment on the workshop reports and rapid reviews, and we also sought independent peer review for this report.

We are grateful for all the constructive feedback we have received, and we have taken it into account in the production of the final documents.

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1 Most recent estimates from the European Cancer Information System (ECIS) for the EU-27 countries.

2 https://ec.europa.eu/health/sites/default/files/non_communicable_diseases/docs/eu_cancer-plan_en.pdf

Notes

- This report discusses cancer screening for the general population or those at increased risk due to lifestyle factors such as smoking. It does not cover screening for individuals at high risk of certain cancers due to specific inherited gene faults or hereditary cancer syndromes such as BRCA1/2 mutations or Lynch Syndrome (Garber & Offit, 2005; Rahner & Steinke, 2008).
- We acknowledge that there are several modifiable risk factors that contribute to a range of cancers, such as smoking, physical activity, bodyweight, alcohol consumption and certain infections. A full discussion of primary prevention is out of scope of this report, although we have highlighted the prevention opportunities in cancers where there is a particularly strong single modifiable risk factor, namely smoking cessation in lung cancer, HPV vaccination to protect against cervical cancer, and *H. pylori* 'screen and treat' strategies for preventing gastric cancer.
- Throughout this report, the terms 'woman'/'women' and 'man'/'men' are used to refer to people born female or male, respectively. However, we recognise that gender identity may not always match birth sex, which can have implications for sex-specific cancer screening (Haviland et al., 2020).
- The case studies highlighted in the report have been taken from presentations given at the expert workshops and are designed to provide real-world illustrations of some of the points in the main text.

Executive summary

Cancer is a leading cause of suffering and death across the European Union, with 2.7 million people diagnosed with cancer and 1.3 million people losing their lives to it every year. Not only does cancer carry great personal cost for individuals and their loved ones, but it also represents a significant financial and social burden on society.

The earlier cancer is diagnosed and treated, the greater the chances of survival. Early detection of cancer through population-based screening therefore offers a significant opportunity to save lives and reduce the personal and societal burden of the disease across the EU.

This report explores the underlying principles, governance and feasibility of organised cancer screening programmes, and how existing programmes for breast, colorectal and cervical cancer could be improved throughout the EU. It also covers the evidence for extending organised, population-based screening to other cancer types, notably lung and prostate, along with recent advances in targeting the type and frequency of testing according to the level of individual risk. We also consider emerging technologies that can be applied to cancer screening, including molecular biomarkers, liquid biopsy and artificial intelligence.

Evidence-based policy options have been highlighted at the end of each chapter to support decision-making for the European Commission and member states, as well as areas where further research is required.

Delivering effective cancer screening programmes in the EU

Cancer screening programmes can deliver, and already have delivered, significant health benefits for European citizens. However, any proposed cancer screening test must be thoroughly evaluated in order to demonstrate its effectiveness and an acceptable balance of benefits and harms, as well as cost-effectiveness. This balance can be altered, and thus improved, by using different types of tests and employing screening strategies based on individual risk factors such as age, sex, ethnicity, family history and lifestyle.

However, screening is not simply a test. It is an entire pathway from the initial identification of target populations through to invitation, risk assessment, delivery of screening, notification of results, and either follow-up and possible treatment or reminders for further screening rounds if appropriate. All of this should be underpinned by appropriate

governance, solid infrastructure, and independent systems for evaluation and quality control.

Delivering high-quality national or regionally organised cancer screening is a financial and logistical challenge, even for the wealthiest countries of the EU. Decisions about existing or proposed cancer screening programmes require multiple stakeholders and high-quality evidence.

The COVID-19 pandemic has had a major impact on organised cancer screening programmes across the world, resulting in many thousands of cancers being diagnosed later than they otherwise might have been and highlighting the benefits of cancer screening programmes. There are important lessons to be learned and shared between EU nations about how screening services in different member states responded to the pandemic, to help build resilience for the future.

Improving existing screening programmes

The majority of EU member states currently have one or more screening programmes for breast, cervical or colorectal (bowel) cancer. However, there are still significant inequalities in access to these three types of screening between and within member states, with wide variations in the quantity and quality of data that is gathered about them. Review of the current evidence suggests that:

- **Breast mammography screening** could be extended to younger women in their mid to late 40s. Furthermore, MRI screening could be considered for women categorised as having particularly dense breasts, due to the lower effectiveness of mammography in this group.
- Faecal immunochemical testing is recommended as the optimal **colorectal cancer screening** test and can be further optimised by altering the positivity threshold and frequency of screening according to age, sex and previous test results.
- Conventional cytology screening (smear tests) could be replaced by HPV testing as the primary method of **cervical cancer screening**, along with adding the possibility for at-home self-sampling to increase uptake. The combination of widespread HPV testing and vaccination offers a unique opportunity to ultimately eradicate cervical cancer in Europe.

More could also be done to coordinate and share information and data about how best to deliver cancer screening programmes between member states in order to provide equitable, high-quality screening for all EU citizens.

Extending screening to other cancer types

Any potential new cancer screening programme must be able to detect undiagnosed cancers or precancerous conditions that, if treated effectively, would reduce cancer deaths and improve quality of life and patient outcomes with an acceptable balance of benefits and harms. Screening programmes must also be cost-effective.

In addition to exploring improvements to the three existing screening programmes, this report summarises the scientific evidence for introducing population-based screening for other cancers, taking into consideration the disease prevalence, the burden of evidence and the emerging technologies. We specifically focused on five additional cancer types: lung, prostate, gastric (stomach), ovarian and oesophageal cancers which have a relatively large disease burden and evidence from large-scale randomised controlled trials. However, there are shared insights from this review that can be applied in the future when considering the introduction of screening programmes for other cancer types.

- There is strong scientific evidence for adding **low-dose CT lung cancer screening** for current and ex-smokers to the repertoire of population-wide organised screening programmes across the EU, particularly in light of the high number of deaths caused by the disease every year. This should go hand-in-hand with smoking cessation interventions to maximise benefits and increase cost-effectiveness.
- There is also good scientific evidence for the benefit of organised, population-based **PSA-based prostate cancer screening** (prostate-specific antigen, a protein produced by the prostate gland), particularly in combination with additional MRI scanning as a follow-up test and the use of active surveillance rather than immediate treatment. Further research and ongoing monitoring are needed to identify the groups that will most benefit from screening and ensure that an appropriate balance of benefits and harms is maintained. Offering ad hoc PSA testing for men without symptoms should be discouraged in order to reduce the risk of overdiagnosis and overtreatment, especially in older men.
- There is insufficient evidence on the benefits of introducing screening for gastric cancer. However, the introduction of well-designed screen and treat strategies for reducing *H. pylori* infection (a major cause of gastric cancer) could be considered for countries with high rates of the disease.
- There is insufficient evidence for ovarian cancer screening, based on recent large-scale trial results. But, with emergence of more risk-stratified screening, this should be kept under review.
- There is new evidence emerging for oesophageal cancer screening, including non-endoscopic, less invasive sampling devices. But targeted approaches are needed based on disease prevalence, and further evidence is awaited.
- Screening for other cancer types should be kept under review as risk-based approaches become more mainstream and as more data becomes available.

Novel screening technologies

There are significant opportunities arising from rapid advances in technologies — such as blood testing, improved imaging techniques and artificial intelligence — for early detection and screening for a broad range of cancer types. The EU is well placed to take advantage of these innovations as more evidence is generated.

Liquid biopsy (screening using blood, urine or breath) is emerging as a minimally invasive, highly specific technology for multiple cancers. Of these, blood-based cancer screening is the most advanced, with large-scale trials underway. Although such tests are not yet ready for adoption in national or regional screening programmes, a close eye should be kept on the emerging evidence base and consensus framework to ensure that promising innovations can be moved forward into implementation studies in a timely way across the EU.

Artificial intelligence algorithms can also help to streamline screening logistics and reduce pathology and radiology bottlenecks in the future.

There is also a need to develop strategies for comparing between different screening approaches, together with the establishment of validated EU biobanks to support biomarker-based cancer screening research.

Implementation of cancer screening programmes in the EU

Screening is a powerful tool that can save lives and reduce the burden of cancer across the European Union. But any population-wide cancer screening programme — whether current or future — must be effective, equitable and cost-effective to maintain an optimal balance of benefits and harms.

Clinical trials of cancer screening interventions cannot tell us exactly what will happen when a screening programme is adopted in the real world. Implementation of new screening tests and strategies should be done through small-scale, local pilot trials — taking account of local factors such as demographics, risk factors, health service capacity and more — before rolling out on a national or regional level. Continuous evaluation and assessment of benefits, harms and cost-effectiveness, along with ongoing programme optimisation, is essential.

The disparities in regulatory frameworks and procedures covering cancer screening across member states highlights the need for permanent formal organisational structures dedicated to the assessment and implementation of cancer screening programmes at

the EU level. 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. Living guidelines that can be rapidly amended and adopted would help minimise delays in improvements.

There is also a need to formally coordinate cancer screening and prevention programmes across the EU, to ensure continuity of knowledge and experience, rational use of resources, operational readiness and optimal integration with the existing healthcare system.

Alongside this, there is an ongoing need for greater widespread public engagement and communication about cancer in general and screening more specifically, in order to improve awareness of prevention and screening opportunities that are available at every stage of life. The uptake and perception of harm-to-benefit of screening tests is highly variable across EU member states.

It is proposed that there should be an upper age limit on cancer screening at population level, to address the issue that the number of cancers that will be found with no or marginal net benefit for the individual increases with age. Further research is needed to determine the age at which cancer screening should stop, and whether this should be the same for all individuals and cancer types. Research is also needed to determine whether there is a minimum level of individual risk for a given type of cancer that is required to take part in a screening programme in the first place, and how this should be measured and implemented in practice.

Summary

This expert evidence review shows there are a small number of crucial opportunities available to the European Commission and member states to optimise existing breast, cervical and colorectal cancer screening programmes, along with a sound scientific basis for introducing lung and prostate cancer screening programmes. Promising emerging tests and novel multi-cancer screening technologies are not yet ready for primetime, but research is moving fast. Adding all this together has the potential to make a real impact in ensuring uniformity, quality and equity in cancer screening across the EU, minimising harms and maximising the health benefits for all.

Chapter 1. The purpose and principles of cancer screening

1.1. The importance of early diagnosis and cancer screening

> 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 the disease.[2] Today, Europe accounts for a tenth of the world's population, but a quarter of the world's cancer cases. Cancer is set to overtake cardiovascular disease as the leading cause of death in the region, with cancer deaths in the EU set to increase by more than 24% by 2035.[3] Not only does cancer carry great personal cost for individuals and their loved ones, but it represents a significant burden on society. The total cost of cancer in Europe was €199 billion in 2018, and this figure is expected to rise in future (Hofmarcher et al., 2020).

Aside from prevention, early detection offers the best chance of beating cancer and saving lives. In general, the earlier a cancer is diagnosed, the greater the chances of more straightforward and successful treatment, leading to longer survival (Minicozzi et al., 2017). In addition to encouraging people to go to the doctor when they notice abnormal symptoms, screening of appropriate groups within the general population also has an important part to play in detecting and treating undiagnosed cancers and precancerous conditions at an early stage.

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. https://ecis.jrc.ec.europa.eu/

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

Screening for cervical, breast and, more recently, colorectal cancer has been in use in the EU for many years, and the majority of member states currently have one or more screening programmes in operation. Published in February 2021, Europe's Beating Cancer Plan: A new EU approach to prevention advocates for improving the early detection of cancer in part by ensuring that 90% of the EU population who qualify for breast, cervical and colorectal cancer screenings are offered screening by 2025.[4]

However, there are still significant variations in access to these three types of screening between and within member states, limiting its effectiveness and leading to inequalities for European citizens. There is plenty of room for improvements and efficiencies by more effectively stratifying screening programmes to ensure that those most at risk are able to benefit, while reducing harms such as overdiagnosis and false positives (see Chapter 2, p.37).

More broadly, there are potential gains to be made from expanding organised, population-based screening into other cancer types (see Chapter 3, p.59), and opportunities arising from rapid advances in technologies such as blood-based screening tests for a wide range of cancers, improved imaging techniques and artificial intelligence (see Chapter 4, p.84).

1.2. Principles of cancer screening

> Screening is a rough sorting process. It operates like a sieve, separating the people who probably do have the condition from those who probably do not. A screening test is never 100% accurate; it does not provide certainty but only a probability that a person is at risk (or risk-free) from the condition of interest.
>
> *Screening programmes: a short guide, World Health Organization*[5]

At the heart of any medical intervention lies an individual human being. Underpinning 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 1968 work *Principles and Practice of Screening For Disease*, Wilson and Jungner outlined ten principles of screening (Wilson et al., 1968):

- the condition being screened for should be an important health problem

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

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

- the natural history of the condition, from its early stages to diagnosed disease, should be adequately understood
- there should be a recognisable early stage
- there should be a suitable test that can detect the condition
- the test should be acceptable to people who have to undertake it
- there should be an agreed policy on who should be treated for the condition
- there should be an accepted treatment for patients who are diagnosed with the disease
- facilities for diagnosing and treating people with the disease should be available
- the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be balanced against overall healthcare spending
- screening should be an ongoing process and not 'one and done'

After considering 367 unique principles listed across the literature and undertaking a Delphi consensus process with international experts, Dobrow and colleagues have modernised, revised, defined more explicitly and expanded this list to include systemic, operational and implementation issues that were not captured earlier (Dobrow et al., 2018). These provide a useful and up-to-date starting point for discussions of the benefits, risks and implementation of screening in today's healthcare systems:

Box 1. Principles of screening

Disease/condition principles

- **Epidemiology of the 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 causes 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 is 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 able to be reached.

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 program) 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 the 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-on 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) that indicates 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 program, using a health system or societal perspective, should be conducted (or a clear plan to conduct an economic 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 economic and societal conditions. The context in which decisions about national or regional cancer screening programmes take place has also shifted to become ever more 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 are needed to inform programmatic and system-level screening decisions, including health service programme managers, policy analysts, information system specialists, health economists, ethicists, patients, high-risk populations and the wider public.

In the light of emerging evidence around new technologies and a move towards more fine-tuning of screening for 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 Chapter 5, p.98, 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 existing programmes to ensure efficacy and value in the real world.

1.3. Balancing the benefits and harms of cancer screening

Every cancer screening programme has a balance of benefits and harms, some of which are common across all types of screening while others are specific to certain types of tests. The balance of benefits and harms can be altered by modifying the strategies and protocols used based on individual factors such as age, sex, ethnicity, family history and lifestyle (see "Selecting who to screen", p.25). The benefits and harms relevant to specific types of cancer screening will be discussed further in Chapter 2 (p.37) and Chapter 3 (p.59), but the general benefits of cancer screening are:

- earlier stage detection of cancer or precancerous conditions and timely delivery of treatment that is more likely to be successful, and will be simpler and less arduous than for late-stage disease in many cases
- reduction in the number of cancer-specific deaths and increased overall survival
- increased likelihood that treatment is offered to those who will benefit from it
- social and economic benefits from a reduced burden of late-stage cancer and cancer deaths

The potential general harms of cancer screening include:

- false positives, where someone is referred for further investigation when they do not have cancer (the level of harm will vary according to the intensity and invasiveness of follow-up)
- overdiagnosis, where a slow-growing, harmless tumour is detected that would not cause a problem during an individual's lifetime, leading to unnecessary investigations and treatment
- risk of direct harms from the screening procedure and follow-up investigations (for example, radiation risk from X-ray imaging or bowel perforation from colonoscopy)
- the psychological impact of the screening process and subsequent actions resulting from it

There is also the risk of a false negative result, where a screening test fails to detect a cancer that is present but not causing symptoms. This is not a direct harm of screening per se, but may be a missed opportunity to detect a cancer at an early, more easily treated stage.

The sensitivity and specificity of cancer screening programmes can also be affected by the quality of screening services and triage or follow-up testing. For example, in the case of cervical cancer, the effectiveness of screening in a given country depends on the quality of HPV testing or cytology analysis laboratories and follow-up colposcopy.

Similarly, maximising the benefits FIT-based colorectal cancer screening relies on high-quality colonoscopy services to follow up positive test results.

Furthermore, more research needs to be done to understand the benefits and harms of screening when offered to people with underlying health conditions (comorbidities) that are likely to severely limit their life expectancy even in the absence of cancer, especially as risk models are not definitive personal predictors. Is it ethical to offer someone screening when they may only have a few years to live, if the risk of overdiagnosis and harm from treatment is high? Such decisions are to be weighed individually but must be decided at a group level when implementing population-based screening.

Any cancer screening test must be thoroughly evaluated in order to demonstrate its effectiveness and an acceptable balance of benefits and harms, with randomised controlled trials currently remaining the gold standard of scientific evidence. Large-scale trials of screening either aim to demonstrate a reduction in cancer-specific mortality resulting from a shift in the stage at which cancers are diagnosed, with a greater proportion of cancers being diagnosed in earlier stages (1 and 2) compared with a similar unscreened population, or an increase in the cancer detection rate for one type of screening compared with another.

One notable challenge in evaluating the effectiveness of cancer screening interventions is a phenomenon known as lead time bias. This happens when a screening intervention appears to increase survival but in fact the disease has progressed at the same speed that it would have anyway, had it been detected at a later stage (i.e. the diagnosis is made sooner, but this does not actually change the date at which someone will die of their disease).[6]

It should be noted that the experience of implementing population-wide screening programmes may differ from randomised controlled trials, making it difficult to fully evaluate the effectiveness of screening in any given country until it is rolled out into the real world (discussed in more detail in Chapter 5, p.98).

1.4. Cost-effectiveness, and how often to screen

We live in societies where needs are infinite, but resources are limited. If inefficient screening approaches are paid for through the public purse, fewer resources are available for more effective interventions, and population health will not be maximised. We must therefore adopt a principle of saving the most lives or gaining the greatest number of healthy life-years with the available resources.

6 https://www.cancer.gov/about-cancer/screening/research/what-screening-statistics-mean

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 assessing cancer screening (Sanders et al., 2016). An appropriate cost-effectiveness analysis should estimate the benefits of a given screening intervention, and factor in the cost of harms by adjusting for the quality of life-years gained and/or disability adjusted years of life lost (Davidović et al., 2021), as well as the overall costs of delivering the screening programme and subsequent follow-up tests and treatments.

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. Estimates of cost-effectiveness of screening may not fully account for the costs of cancer treatment, which are often much higher for later stage metastatic cancers than those diagnosed at an early stage, or the high price tag for innovative treatments such as immunotherapy. See Sanders et al. (2016) and the recent EUneTHA guidelines for further discussion of cost-effectiveness analyses.[7]

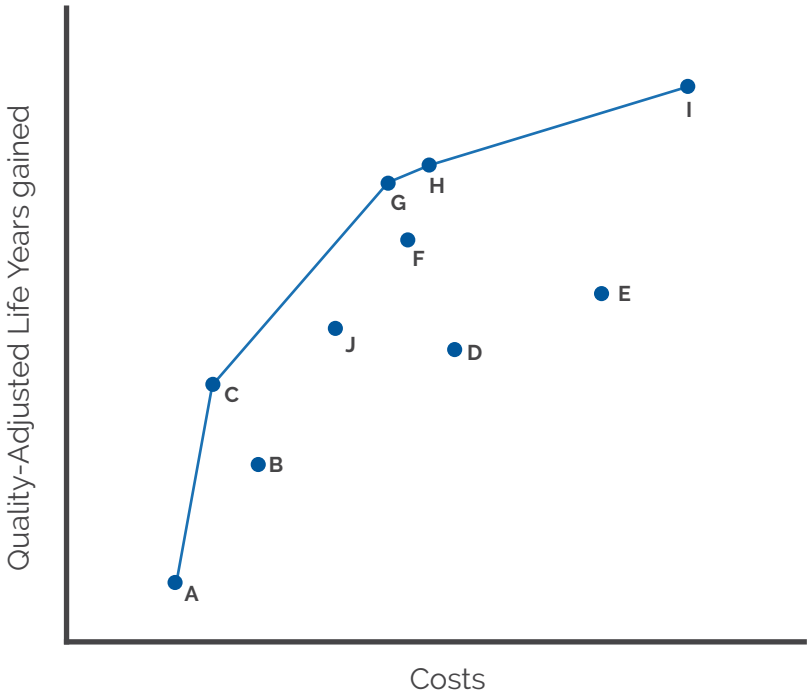

Figure 1. The comparative cost-effectiveness of healthcare interventions (based on Mark, 2002)

7 EUnetHTA WP6B2-5 Guideline Team. Practical considerations when critically assessing economic evaluations. Methodological Guidelines. Diemen (The Netherlands): EUnetHTA (2018). Available from https://www.eunethta.eu/

Any given intervention can be plotted on this graph according to its benefits in terms of quality-adjusted life years (QALYs) gained against cost (for example, per 1000 individuals screened). The strategies that provide best value for money are the ones lying on the line connecting the most efficient strategies, referred to as the Efficient Frontier. Any intervention lying below this line (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 between the strategies that do lie on the Efficient Frontier (A, C, G, H and I) depends on the budget available and the acceptable ratio between cost and quality-adjusted QALYs saved, which varies widely between EU member states (Kovács et al., 2020).

Estimating the costs and QALYs gained by screening is a significant 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.

The European EU-TOPIA project (Gini, van Ravesteyn, et al., 2021)[8] has been developing computer models that simulate the natural history of disease (for example, based on evidence from randomised controlled trials) and enable extrapolation from the outcomes of large-scale screening trials to the populations of different countries as a way of optimising screening interventions and estimating their effectiveness across the EU. 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. For example, EU-TOPIA models and analyses are available for colorectal cancer screening (Gini, Buskermolen, et al., 2021; Gini et al., 2020), breast cancer screening (Zielonke et al., 2020, 2021) and cervical cancer screening (Jansen et al., 2020).

8 https://eu-topia.org/

1.5. Selecting who to screen

Box 2. Screening strategies

Population-based cancer screening is offered to a group of people identified from the whole population as defined by age and sex — for example, offering colorectal cancer screening to all males and females aged 50–74.

Targeted screening relates to the eligibility for screening. It aims to improve health outcomes among groups of people identified as being at elevated risk of a specific condition due to lifestyle factors, genetic variants or having another health condition. For example, individuals who smoke may be offered screening as they are at a higher risk of developing lung cancer regardless of their age or sex.

Risk-stratified screening relates to the delivery of screening within an established screening programme, where the type of screening, the intensity or the modality can be varied according to the level of individual risk in order to achieve a more favourable balance of benefits and harms at the individual as well as population level. For example, cervical screening intervals may be lengthened for women who are HPV-negative.

The most important factor affecting an individual's cancer risk is age, with the chances of developing cancer increasing significantly after the age of 60 (Laconi et al., 2020). Cancer risk also varies widely between people according to their genetics, lifestyle and environment. For example, a woman aged 30 has a 1 in 228 chance of developing breast cancer within the next ten years, while her 60-year-old mother has a 1 in 29 risk.[9] By contrast, the lifetime risk of breast cancer in men is around 1 in 833.[10] It would not be feasible or cost-effective to offer breast screening to every adult in order to detect the very rare cancers in younger women or males, and such an approach would likely result in a significant number of over-diagnoses and false positives. Indeed, beyond age and sex, screening can be targeted further by considering factors such as family history of breast cancer and the inheritance of specific high-risk genetic variants (see Chapter 2, p.37).

Organised population-level cancer screening programmes aimed at specific groups of asymptomatic individuals at average risk of cancer help to reduce the likelihood of poor quality screening and follow-up, and minimise complications resulting from screening and subsequent investigations in very low-risk individuals (Miles et al., 2004). Given that

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

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

every country's screening capacity is limited to a greater or lesser extent, it makes sense to identify and screen those who are most likely to benefit while reducing screening for those at lowest risk.

According to the principles laid out by Dobrow et al. (see "Principles of cancer screening", p.17), the target population for cancer screening should be clearly defined, identifiable and able to be reached. The appropriate age group to invite for screening — and the age at which to stop screening — can only be determined by analysing the balance of benefits and harms for each age group, preferably based on data from large-scale trials.

Risk stratification

Within the selected target screening population who are invited (for example, according to age, sex, or smoking status), more sophisticated stratification approaches involve grouping individuals according to their specific risk profile (such as breast density or inherited genetic makeup) and then offering tailored screening and risk management strategies. In the example of breast cancer, future risk stratification strategies could involve reduced intensity or no screening for those at least risk, through to intensified screening with MRI or even prophylactic medical or surgical interventions for those in the highest risk categories (Pashayan et al., 2020).

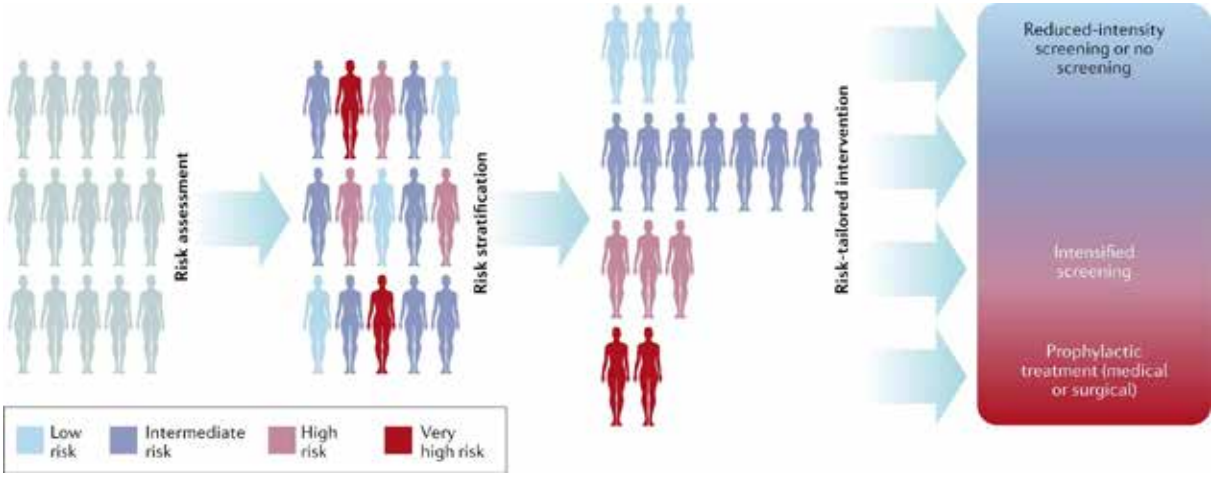

Figure 2. Risk stratification strategies for breast cancer (Pashayan et al., 2020)

Implementing such an approach raises a number of questions at each stage. Which risk factors should be assessed, at what point and how often? And how should this process be organised and delivered? How many risk groups should be identified, based on which metrics and thresholds? And finally, what screening or prevention strategy should be used for each of these groups, which outcomes should be optimised for (e.g. maximising benefits, minimising harms, reducing costs or increasing equity of access) and how will such a programme be organised?

We should also consider the type of evidence required to demonstrate these outcomes that will balance scientific robustness with speed and efficiency, such as randomised controlled trials, randomised studies within the health service, hybrid implementation-effectiveness studies or modelling studies. In addition, there are other factors to consider including the resources available, the existing healthcare system, the values, preferences and social norms of the population in question, and the evidence (or lack of evidence) to support risk-stratified screening approaches.

There are innovations being developed to reduce complexity around delivering risk-stratified screening and management for healthcare providers, such as smartphone risk assessment apps.[11] A healthcare professional can enter data about an individual and be given a recommendation for next steps (for example, repeat the test in one year, recommend for further investigation etc.) based on existing risk tables and thresholds.

These concepts of risk and risk-stratified screening are complex to understand and explain to the public and health professionals. There will be a need for social science research and the development of clear communications about these new approaches as they are brought in. This could also include supporting the wider use of risk counsellors, analogous to genetic counsellors, that can inform people about their personal risk of cancer and help them make informed choices about their health.

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

It is a challenge to continuously deliver high-quality systematic, uniform, organised, population screening programmes for cancer, even in the wealthiest countries of the EU. Although cancer screening can deliver significant health benefits in terms of cancer deaths prevented and healthy life-years gained, population-wide programmes are expensive and involve millions of citizens, whether delivered on a national or regional level. Furthermore, the costs of failures in the system can be significant, not only in terms of lives lost but also loss of public confidence and wasted money. Small backlogs can snowball, particularly in the face of unexpected disruptions such as COVID-19, which has significantly impacted all screening programmes across Europe (see “The impact of the COVID-19 pandemic on cancer screening”, p.35).

A cancer screening programme should be viewed as a major investment in infrastructure and workforce. Screening protocols involve a complex pathway from defining the appropriate target group up to agreed treating protocols for screen-detected cases,

11 For example, https://www.asccp.org/mobile-app

and it is not enough merely to have sufficient resources to roll out a particular screening test. According to a study involving people who research and manage cancer screening programmes, the most important elements of a successful screening programme are having up-to-date and evidence-based guidelines, followed by suitable systematic processes for ensuring uptake, and a comprehensive population registry enabling the monitoring of long-term outcomes (Priaulx et al., 2019). Screening must be supported by careful design of the whole programme, especially evidence-based management of people testing positive, along with the administrative and IT infrastructure required to deliver and monitor it to ensure ongoing quality, and access to appropriate diagnostic tests and cancer treatments.

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

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

Quality assurance is also vital, ensuring that screening programmes operate within agreed parameters so that they can deliver the expected population benefits. Failure to operate a screening programme within these accepted parameters means that expected benefits aren't achieved, harms may be unnecessarily high, and the programme is no longer cost-effective.

1.7. Barriers to success of existing screening programmes

The international EU-TOPIA project consortium identified and assessed barriers hindering the implementation of optimal cancer screening programmes in Europe, primarily focusing on barriers of effectiveness and barriers of equity/access (for example, see

Priaulx et al., 2018, 2020; Turnbull et al., 2018). This work formed the basis of roadmaps for improving screening programmes across individual member states.[12]

Barriers to screening identified by the project fall into three broad categories (Priaulx et al., 2020):

- **health system barriers** including availability, affordability and acceptability of screening
- **capability barriers** including workforce, resources and infrastructure
- **intention barriers** including public motivation and priorities, communication and social influence, and health beliefs and behaviours

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

1.8. Addressing the data gap in cancer screening

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

Despite the increasing use of common indicators and data standards, it is still challenging to compare screening programmes across the EU due to factors such as differences in invitation strategies, healthcare systems, referral and diagnostic processes, and more. For example, out of 22 member states with cervical cancer screening programmes, 19 gathered data on the performance of the programme, and only 15 collected data about participation rate. Meanwhile, a number of member states have no information available at all about outcomes for individuals who are referred for further investigation following breast screening.[13]

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

13 https://ec.europa.eu/health/system/files/2017-05/2017_cancerscreening_2ndreportimplementation_en_0.pdf

There are a number of changes happening in healthcare that bring opportunities as well as challenges for the delivery of cancer screening. For example, the introduction of new IT approaches such as electronic health records could bring significant opportunities to save time and streamline processes, while also offering the potential for data linkage, real-time monitoring and machine learning or AI analysis of health data.

Compiled data on population-based cancer screening programmes across the EU is available from IARC's CanScreen5 web portal[14] programme, enabling comparisons between member states. The European Cancer Information System (ECIS) portal, which currently gathers data from European cancer registries, will soon be upgraded to include data on screening across the EU.[15] However, the underlying data may not be in a standardised comparable format for direct submission to ECIS, and work will need to be done to ensure that cancer screening data is harmonised across member states.

1.9. Addressing inequalities in cancer screening

There is substantial variation in cancer prevention policies and organisation of screening across Europe, which contributes to variation in the participation rate and the persistence of inequalities. These variations exist at the level of policies about and organisation of screening programmes across member states, differing participations rate within and between countries, and underlying differences in healthcare systems. Meeting the ambitious target to offer 90% of people in eligible groups the opportunity to participate in cancer screening in Europe over the coming years will therefore require an expansion in access to screening across society.

There is still a significant need for a comprehensive review of the regulatory frameworks, governance, and financing (governmental and personal) of cancer screening programmes in order to more fully identify, understand and address these issues, some of which are summarised below. However, care should be taken to ensure that such comparisons do not end up focusing on relatively small differences within countries at the expense of much larger variations that exist between the various EU member states.

Cancer screening organisation and service delivery

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

14 https://canscreen5.iarc.fr/

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

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

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

More accessible methods of screening can also help to increase uptake among under-served groups such as at-home faecal immunochemical testing (FIT) (see "Colorectal cancer screening", p.46) and self-sampling for HPV testing (see "Cervical cancer screening", p.51).

Healthcare funding

Cancer screening is part of the healthcare system and is subject to the same kinds of limitations, inequalities and biases as other healthcare services, which are highly variable between European countries.[16] The affordability of and unequal access to new medical and computing technologies for cancer screening risks perpetuating or deepening inequalities within and between countries.

Another potential source of inequality is the financial model of healthcare within each individual member state. Cancer screening is not always offered for free, creating a barrier to uptake. In other places, while screening may be free, the subsequent costs of follow up and treatment may not necessarily be fully covered. The fear of incurring additional costs resulting from a positive test may put off people from attending screening, combined with logistical and other financial issues such as being able to take time off work for screening appointments or subsequent follow-up.

Reaching underscreened groups

People with higher socioeconomic status are generally more likely to participate in screening for cervical, breast and colorectal cancer (De Prez et al., 2020; Pallesen et al., 2021; Smith et al., 2019). While systematic organised screening programmes help to reduce strongly the impact of social inequalities in access to screening, they do not completely eradicate them (Gianino et al., 2018).

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

There may also be social, cultural and personal barriers to taking part in screening, for example for immigrants to the EU (Møen et al., 2017) and ethnic minorities (Marlow et al., 2015) which need exploring in order to fully address them. Additionally, it should be recognised that barriers to accessing healthcare including cancer screening exist for transgender and gender non-conforming individuals (Haviland et al., 2020), and more research is needed to understand how best to meet their needs to deliver equitable healthcare for all.

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

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

More carefully tailoring the language and channels used in screening invitations and other informational materials according to individual levels of understanding might also help to address inequalities and improve uptake, as well as the use of innovative communication channels such as social media (Plackett et al., 2020).

Cancer screening is only one of many healthcare interventions that people experience as they go through life. We should be looking for opportunities to make screening as convenient as possible, particularly for people undergoing multiple health examinations. More broadly, there is work to be done to promote cancer screening as part of general healthy behaviour, embedding in the population the idea that 'this is something proactive you can do to look after your health'.

1.10. Shared decision-making and public communication

Effective public communication is an important part of delivering organised cancer screening programmes, in order to ensure informed consent to take part in screening in a way that protects individual autonomy and dignity. This should go hand-in-hand with efforts to improve public health literacy within member states, as well as more general communication of information about cancer risks and prevention, including screening, to improve health outcomes across the EU (Oldach & Katz, 2014; Samoil et al., 2021; van der Heide et al., 2015).

A systematic review has shown that the general public tends to overestimate the benefits of cancer screening while underestimating the harms (Hoffmann & Del Mar, 2015) — something that should be borne in mind when communicating about population-wide screening programmes.

In the case of breast cancer screening, the public conversation has moved in recent years to a more nuanced discussion that recognises the benefits in terms of lives saved as well as the potential harms of screening such as false positives, overdiagnosis and unnecessary biopsies. The adoption of more tailored risk-stratification strategies can shift the balance of harms and benefits, requiring more sophisticated discussions and shared decision-making for individuals (Keating & Pace, 2018).

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

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

Sociological research such as discrete-choice experiments can help to tease out the factors that are more or less important when considering the decision to attend screening, as well as the trade-offs between harms and benefits that they are prepared to make. For example, Sicsic et al. (2018) found that less than half of women would be willing to accept 10 overdiagnoses to avoid one breast cancer related death, with screening acceptance rates higher among women from higher socioeconomic groups and lower among women in poorer health.

When considering individual risk of developing cancer, people are more driven by emotions and feelings — including intuitions, beliefs, values and social/cultural identity — than by rational cognitive processes (Klein et al., 2020). This is also highlighted by the observation that most adults do not change their behaviour after being told that they are at increased risk of breast or colorectal cancer due to their genetic makeup (Gray et al., 2017). People may therefore be particularly responsive to messages around cancer risk and screening that highlight social comparisons and identities, and acknowledge the existence of negative emotions and concerns. As well as considering the provision of public information about cancer screening to support decision-making, the views and attitudes of the healthcare professionals who are responsible for delivering it should also be explored (Rainey et al., 2018).

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

Decision aids such as pamphlets, videos and online tools can help people make informed choices about their health, including whether or not to take up the invitation for cancer screening. People who use decision aids when making a choice about treatment or screening feel more knowledgeable, better informed and clearer about their values (Trikalinos et al., 2014). There are no adverse effects on health outcomes or satisfaction, nor a significant increase in consultation time (Stacey et al., 2017). The use of decision aids can also help people make decisions that are congruent with their values (Munro et al., 2016).

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

When developing aids for shared decision-making, information should be simply presented and compatible with low literacy, ideally using easy-to-grasp graphics. However, it should be borne in mind that the production of such resources is influenced by the view and choices of both the creator and the person delivering the information. For example, decisions may be made to include or leave out certain pieces of information. The use of certain colours such as red or green can also be perceived as conveying information (for example, red=stop/dangerous, green=go/safe). Currently, there is no

consistent way in which information about the effectiveness, harms and benefits of cancer screening is conveyed across EU member states.

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

1.11. The impact of the COVID-19 pandemic on cancer screening

The COVID-19 pandemic has had a major impact on organised cancer screening programmes across the EU. Safety restrictions and lack of staff or capacity, together with public reticence at engaging with screening during this time, led to a significant reduction in cancer screening, testing and diagnosis. The backlog resulting from missed or cancelled appointments during each wave of infections then put further pressure on screening services as they restarted. This disruption has contributed to a dramatic drop in the number of cancer diagnoses, representing many thousands of cancers being missed or diagnosed later than they otherwise might have been (Kregting et al., 2021; Richards et al., 2020).

A microsimulation modelling study based on data from the Netherlands compared five different strategies for resuming breast, cervical and colorectal screening in the wake of the pandemic:

- no catchup
- catchup afterwards but everyone's screening is delayed
- no delays in catchup only for first round screening
- continue screening for all after usual stopping age
- catch-up after stopping for those due for screening during the disruption

The researchers found that catching up on screening after the disruption would have the smallest impact on cancer incidence and mortality, but would require a very high screening capacity to be available over a short catch-up period. An alternative strategy, where all screening is delayed but the age at which screening is stopped is extended, put less pressure on catch-up capacity with minimal impact on cancer incidence and mortality (Kregting et al., 2021).

Generally, countries with centralised screening registries and comprehensive IT systems for monitoring screening were able to recommence screening more quickly after the first wave of the pandemic, highlighting the importance of robust national or regional infrastructure for delivering screening programmes that can cope with unexpected disruption.

1.12. Evidence-based policy options

- Ongoing quantification of the harms and benefits of different types of screening and comparison between member states is crucial for establishing priorities for resourcing and funding cancer screening across the EU.
- Learnings could be shared between EU member states about effective delivery of cancer screening programmes, including national responses to the COVID-19 pandemic, in order to ensure effective and resilient screening for all EU citizens, now and in the future.
- Health technology assessments should be used to ensure optimal decision making and steering of cancer screening programmes so as not to over — or under-screen EU citizens.
- The data gathered about cancer screening programmes from across the EU should be used to support coordinated efforts to deliver equitable high-quality screening across member states, along with continuous monitoring and evaluation for quality assurance.
- Research aimed at addressing the underlying causes of inequalities in access to and uptake of cancer screening, both within and between member states, is essential in order to realise the lifetime health benefits of screening.
- The EU could consider investing in public engagement and communication to improve awareness of cancer prevention and screening, including research exploring communication and shared decision-making in the context of risk-stratified screening, to ensure that everyone can make fully informed decisions about their health.
- There is a need to work towards developing standardised, interoperable IT systems and data schemas for delivering, monitoring and evaluating cancer screening that can be used across all member states.

Chapter 2. Improving existing cancer screening programmes

2.1. Overview of organised cancer screening programmes in the EU

In 2003, the Council of the European Union issued recommendations calling on all member states to implement national or regional population-based screening programmes for breast, cervical and colorectal cancer. The first EU cancer screening report, published in 2008, showed that although there had been some progress, member states collectively fell short of the target for minimum number of examinations by more than 50%.[17]

A second report prepared in 2017 looked in detail at the status and performance of cervical, breast and colorectal screening programmes across 28 member states, using a set of common, harmonised process and outcome indicators to enable comparison between countries (Armaroli et al., 2020; Basu et al., 2018; Senore et al., 2019).[18] These indicators include:

- information and invitation of the target population
- performing the screening test
- assessment or follow-up of abnormalities detected
- referral for diagnostic confirmation and treatment
- treatment, if applicable

These indicators are assessed according to:

- rate of coverage by invitation
- rate of coverage by examination
- participation rates

17 https://ec.europa.eu/jrc/sites/default/files/cancer_screening.pdf

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

- rates of referral to and participation in further assessment
- detection rates of cancer and other clinical outcomes specific to the three types of screening programmes (e.g. in situ breast cancers, cervical intraepithelial neoplasias, or colorectal adenomas)

The process for the preparation of a third report is expected to start in early 2022. The next report will be linked to data held within the European Cancer Information System.[19]

Despite the EU-wide commitment to cancer screening, significant inequalities in access to these three types of screening still exist between individual member states, as well unequal coverage within countries.

Box 3. Screening provision in EU member states

Breast cancer screening

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

Colorectal cancer screening

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

Cervical cancer screening

Although cervical cancer screening is the oldest screening programme, first starting in Europe in the 1970s, EU-wide levels of screening seem more disappointing. By 2016, 22 of 28 member states have population-based screening, with 72% eligible EU residents aged 30–59 years having access to population-based screening. Full rollout was completed in just 12 member states, with significant variability across the EU. However, opportunistic screening is more common for this cancer site.

Source: *Against Cancer: Cancer Screening in the European Union, International Agency for Research on Cancer (2017)*[17]

19 https://ecis.jrc.ec.europa.eu/

2.2. Breast cancer screening

Breast cancer is the most common cancer in women in Europe, accounting for 355 500 cases and causing more than 91 000 deaths every year across the 27 EU member states.[20] Around one in 11 women in the EU will develop breast cancer before the age of 74.[21]

The earlier breast cancer is detected, the greater the chances of survival. Almost all women diagnosed with cancer at the earliest stage (stage 1) will survive for five years or more, with 90% survival for those diagnosed at stage 2. However, this figure drops to 72% for women diagnosed at stage 3, and just 26% for those with stage 4 disease.[22]

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

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

The greatest potential to improve the balance of benefits and harms is to improve the quality of screening by increasing the sensitivity while maintaining its specificity, reducing unnecessary recalls after screening (false positives) and improving communication and prompt evaluation among women recalled, together with the development of more effective screening tools and technologies.

Extending breast cancer screening under the age of 50

The risk of breast cancer increases with age. US SEER data presented at the workshop by Robert Smith shows that 45 per 100 000 women at age 35 will be diagnosed with breast cancer, compared with 79 per 100 000 women at age 39, 106 per 100 000 at age 40, and 165 per 100 000 by the age of 45. Looking more broadly, women aged 40-44 account for 6% of all invasive breast cancer deaths, while those aged 45-49 and 50-54 account for 10% and 12% of breast cancer deaths, respectively (Surveillance, Epidemiology and End Results (SEER) Program, 2015; Centers for Disease Control and Prevention, 2014).

20 https://ecis.jrc.ec.europa.eu/factsheets.php

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

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

Improving existing cancer screening programmes

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

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

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

The Swedish two-county study showed that the number of interval cancers (cancers diagnosed in between screening invitations) is significantly higher in women aged 40–49 compared with those over the age of 50, suggesting that these tumours maybe more aggressive and fast growing in younger women (Tabár et al., 1987), which could be more difficult to detect by conventional screening methods.

Meta-analysis of randomised controlled trials of breast screening in women aged 39–49 commonly showed a 15% reduction in breast cancer mortality associated with an invitation to screening in this age group (de Koning et al., 1995). Furthermore, there is a wide range of outcomes in these trials, which ranged from a 30% breast cancer mortality reduction to 47% excess mortality (Nelson et al., 2009). More favourable results have been seen in recent studies that screened younger women at more frequent intervals, with the Gothenburg trial showing 30% fewer breast cancer deaths in women aged 39–59 and 40% fewer deaths in women aged 39–49, including 39% fewer deaths due to grade 3 cancers, after 25 years of follow up (Bjurstam et al., 2016).

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

Miglioretti and colleagues showed that women who were premenopausal were more likely to be diagnosed with a breast cancer with a less favourable outcome if they underwent biennial versus annual mammograms, suggesting that cancers occurring in younger, premenopausal women are more aggressive (Miglioretti et al., 2015). Annual screening is also more effective for younger and premenopausal women in order to detect more dangerous fast-growing tumours. Overdiagnosis across screening methods may not be a significant problem for younger European women (Duffy et al., 2020; Gunsoy et al., 2012). Furthermore, women diagnosed with an early breast cancer in their forties benefit from considerable life-years gained from avoiding a premature death (Oeffinger et al., 2015).

Although the expert workshop and literature review focused on extending the lower age limit for breast cancer screening, it should be noted that there is also active discussion about upper age limit for screening, with the current European guidelines recommending screening up to the age of 74.[23] Further data gathering and analysis of the risks and benefits of breast screening in older women is proposed to ensure that the ongoing gathering and analysis of data about the risks and benefits of breast screening in older women, to ensure that potential public health gains are realised (see also "Age cut-off and eligibility", p.106). There are also moves towards assessing cancer risk in terms of underlying physiological age, as judged by biomarkers such as DNA methylation rather than chronological age (for example, see Kresovich et al., 2019), although more research is needed to ensure these metrics are robust.

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

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

Similarly, the pan-Canadian study of mammography screening showed a 44% reduction in breast cancer deaths in women aged 40–49 compared with 40% fewer deaths in women aged 50–59 (Coldman et al., 2014).

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

Risk stratification approaches in breast cancer

While age is the most significant risk factor for breast cancer, other things can also influence an individual woman's risk of developing the disease, including genetic makeup, mammographic breast density (see "MRI screening for women with dense breasts", p.43), age of first period, age at menopause, age of first child, family history of breast cancer, alcohol intake, smoking status, body mass index, and hormone replacement therapy use.

Increasing screening intensity for women at the highest risk of breast cancer while reducing it for those at lowest risk could therefore help to improve the balance of benefits and harms of screening (Pal Choudhury et al., 2020). As an example, the use of genetic information in the form of polygenic risk scores (PRS) has been demonstrated to have good predictive power for identifying women at highest and lowest risk of breast cancer, and could be used to improve breast screening programmes (Mavaddat et al., 2019). The UK PROCAS study has also shown that adding PRS and breast density to the widely used Tyrer-Cuzick breast cancer risk model is likely to be useful for risk stratification for more personalised screening and prevention (van Veen et al., 2018).

Box 4. What is a polygenic risk score?

A polygenic risk score (PRS) is an estimate of the likelihood of an individual getting a particular disease, based on their underlying genetic makeup. Calculating a PRS first requires a DNA test to discover the particular genetic variations that a person carries at many different places within their DNA, which have previously been linked to a small increase or decrease in the risk of the disease. All this data is then combined together to generate a personalised PRS.

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

Another recent modelling study based on US data incorporated PRS and family history to define 47 different risk groups with tailored screening start ages and intervals. The results showed that risk-based screening based on PRS had greater benefits than family history alone, compared with standard age-stratified screening, and that the combination of the two was even better. Furthermore, given a fixed number of screening appointments that can be delivered within a national or regional programme, allocating these resources based on risk reduces overdiagnosis and results in greater benefits across the whole population than age-based screening alone (van den Broek et al., 2021). Further modelling studies suggest that risk-adapted strategies can improve the benefit-harm

ratio with reasonable cost-effectiveness in the European setting (Canelo et al., 2018; Khan et al., 2021; Mühlberger et al., 2021).

These conclusions apply to breast screening in the context of the general population at average risk, and not strategies for women with an inherited predisposition to breast cancer, such as those with germline mutations in BRCA1/2 (see Dullens et al., 2020 for an overview of the current guidelines in various countries). It should also be noted that individual risk factors can change over time — most obviously age — so risk assessments will need to be repeated and risk thresholds adjusted in order to maintain accuracy (Pashayan et al., 2021). Importantly, such risk calculations are based on probabilities, not certainties. It is impossible to say on an individual basis who will and who will not develop breast cancer, and even women in the lowest risk categories will still have some level of overall lifetime risk of breast cancer.

Risk-stratified screening approaches for breast cancer are being investigated in a number of studies that are expected to report initial or further results in the next few years including: PROCAS in the UK (van Veen et al., 2018); the international MyPeBS randomised controlled trial;[24] the WISDOM study (Esserman, 2017); and the PERSPECTIVE Integration & Implementation project (Brooks et al., 2021).

MRI screening for women with dense breasts

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

Supplemental MRI screening has been proposed as a way to improve the sensitivity of breast screening in women with dense breasts. To date, there have been three large clinical trials investigating the value of supplemental MRI screening in women with dense or extremely dense breasts at average risk of breast cancer. The addition of MRI screening increased the number of cancers detected compared with mammography alone, and supplemental MRI screening also led to a significant reduction in interval cancers, therefore detecting more aggressive cancers at an earlier stage (Bakker et al., 2019; Comstock et al., 2020; Kuhl et al., 2017). However, it is not yet clear whether this leads to better outcomes or lower breast cancer mortality.

24 https://www.mypebs.eu/

In the DENSE trial in the Netherlands, women who were identified as having extremely dense breasts upon their initial screening mammogram were invited to have an additional MRI scan following a negative mammography result, of which 59% participated. Overall, the interval cancer rate was 0.83/1000 women in those receiving an MRI scan, compared with 4.88/1000 in those who declined. For comparison, the interval cancer rate in women in the control arm who underwent standard mammography screening was 4.98/1000 (Bakker et al., 2019).

Following a second round of screening, two studies also showed a reduction in breast cancer incidence as well as fewer false positives (Kuhl et al., 2017; Veenhuizen et al., 2021), meaning that the screening is effective at picking up early stage cancers also in second rounds. Overdiagnosis did not seem to be a significant problem (Veenhuizen et al., 2021).

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

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

MRI screening is more expensive than standard digital mammograms and cannot be delivered in the kind of mobile scanning units that are used to deliver standard mammography screening. However, switching to four-yearly MRI screening alone for women with the most dense breasts had the same benefits in terms of cancers detected and risk of overdiagnosis than standard mammography plus MRI, but fewer false positives. Modelling studies (Canelo et al., 2018; Khan et al., 2021; Mühlberger et al., 2021) and evidence from the DENSE trial suggest that risk-based strategies are likely to be reasonably cost-effective for high-risk groups. MRI at a four-year interval was most cost-effective (€15 620 per QALY) for women with extremely dense breasts (Geuzinge et al., 2021).

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

scans may also provide additional information about the biological behaviour and likely prognosis of any tumours detected, although this needs to be researched further.

Breast screening with digital breast tomosynthesis

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

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

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

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

One measure of the effectiveness of a screening programme is the interval cancer rate — the number of cancers that are diagnosed in between screening invitations (Zackrisson, 2019). A high number of interval cancers suggests that the screening programme is failing to pick up cancers at an early stage, while a proportionally low interval cancer rate is indicative of a more effective programme. To date, the trials comparing DBT with

mammography have not been sufficiently powered to show a difference in interval cancer rate. It is estimated that a randomised controlled trial would require at least 100 000 participants in order to show a significant difference in interval cancer rate.[25] However, recent meta-analyses of data from smaller trials showed that there was no difference in the interval cancer rate between DBT and mammography (Houssami, Hofvind, et al., 2021; Houssami, Zackrisson, et al., 2021). A small study in Sweden did suggest a significant decrease in interval cancer rate (Johnson et al., 2021), while another small Norwegian found no significant difference (Hofvind et al., 2021).

The most recent systematic review and meta-analysis of the data comparing conventional digital mammography and synthesised mammograms/DBT concludes that DBT together with synthetic mammography has a similar detection rate for breast cancer as standard digital mammography and could help to reduce overall radiation dose from breast screening, although there was no significant improvement in interval cancer rate (B. Zeng et al., 2021).

The European Commission Initiative on Breast Cancer currently recommends screening asymptomatic women at average risk aged 50–69 with either standard digital mammography or with DBT but not both, although this is a conditional recommendation with very low certainty of evidence.[26,27]

2.3. Colorectal cancer screening

Colorectal cancer is the third most common cancer diagnosed in men and the second most common in women in EU member states. More than 341 000 new cases are diagnosed every year in EU27 and 156 000 people die from the disease, representing 12.7% of all cancer cases and 12.4% of all cancer deaths in the member states and costing around €19 billion every year across Europe.[28,29]

The stage of diagnosis has a significant impact on outcome, with 90% of individuals diagnosed at the earliest stage (stage 1) surviving for at least five years compared with 10% survival for those diagnosed at the latest stage (stage 4). The costs of treatment for early-stage cancer are also ten-fold lower than for cancers diagnosed at stage 4.

25 Data presented at expert workshop 2 by Professor Solveig Hofvind.

26 https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-tests

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

28 https://ecis.jrc.ec.europa.eu/factsheets.php

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

However, without screening, only around 13% of cases are diagnosed at the earliest stage, while almost a quarter are diagnosed at stage 4.

Improving the effectiveness and cost-effectiveness of colorectal cancer screening, as well as increasing awareness and participation, therefore represents a significant opportunity to save lives across Europe.

Comparing colorectal cancer screening methods

Colorectal cancer screening usually either involves analysing stool samples for traces of blood, or colonoscopy/sigmoidoscopy to look for the presence of adenomas or malignant tumours. Other techniques include CT colonography, tiny swallowable cameras ('Pillcams'), and stool testing for genetic and DNA methylation markers, as well as liquid biopsy blood tests (see Chapter 4, p.84).

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

While stool testing itself carries virtually no risk, there can be harms caused by follow-up colonoscopy and psychological harms from false positives. It should be noted that there are also non-cancer conditions that can result in blood in the stool, including haemorrhoids and colitis. Furthermore, gFOBT detects the presence of any kind of blood, including animal blood eaten in food, and is therefore more susceptible to false positives than FIT, which only detects human haemoglobin (Hb). There are several different brands of FIT testing available with varying performance in direct comparison studies and clinical trials (for example, see Gies et al., 2018; Grobbee, Vlugt, et al., 2017), which should be considered before selection for a population-wide screening programme (Allison & Fraser, 2018).

FIT is more acceptable than gFOBT to participants, because it only requires one stool sample rather than three for gFOBT. FIT is also more effective than gFOBT, although this varies depending on the sex and age of participants (see "Personalised strategies for colorectal cancer screening", p.50). A Dutch randomised controlled trial comparing FIT and gFOBT showed that FIT was superior in terms of participation and detection of advanced adenomas and cancers (van Rossum et al., 2008). The Hb threshold value used to refer individuals for further investigation also has an impact on the efficacy of FIT-based screening. A meta-analysis pooling 46 trials and other studies revealed that the sensitivity of FIT for colorectal cancer detection could increase from 69% to 80% when lowering the positivity threshold from >10-20µg/g to ≤ 10µg/g at the expense of slightly decreased specificity (Selby et al., 2019).

Any positive results from gFOBT or FIT stool testing are usually referred for colonoscopy, which can become a limiting factor if there is insufficient capacity to cope with the demand. Care should be taken to avoid overwhelming colonoscopy capacity, for example by adjusting Hb threshold levels or implementing tailored screening strategies (see "Personalised strategies for colorectal cancer screening", p.50), while still screening those who are most at risk.

The majority of EU member states have rolled out population screening for colorectal cancer using gFOBT or FIT.[30] Furthermore, many countries that originally started with gFOBT are now switching or have switched to FIT (Cardoso et al., 2021). Further best practices to improve access to colorectal cancer screening include an advance notification followed by sending a FIT test kit to individuals together with the invitation to screening rather than sending them separately or having to go and collect a test, along with follow-up reminders.

A number of studies have investigated how to increase uptake of colorectal cancer screening, including using social norm-based motivational tools and worksheets aimed at aiding participants to make a plan to get screened (Wilding et al., 2020), as well as the use of decision aids (Schwartz et al., 2019), although neither approach had a significant impact on overall uptake. Involving general practitioners (family doctors) in inviting individuals and sending reminders can also increase participation in screening (Rat et al., 2018). A study from California showed that inviting people to take part in colorectal cancer screening by mailing a postcard and phoning them, followed by a postal FIT kit and a reminder phone call if the kit was not returned, led to significantly increased uptake and was also cost-effective within that healthcare system (Somsouk et al., 2020). Risk stratification using the Genetic and Environmental Risk Assessment (GERA) did not improve the uptake of colorectal cancer screening, although providing people with GERA feedback might improve screening adherence (Myers et al., 2011, 2015; Weinberg et al., 2014).

Some countries in the EU have introduced colorectal cancer screening with flexible sigmoidoscopy, in which a trained health professional uses an endoscope to look inside the rectum and lower bowel. The effectiveness of flexible sigmoidoscopy has been demonstrated in a number of randomised controlled trials in a European setting (Atkin et al., 2010; Holme et al., 2014, 2017; Schoen et al., 2012; Senore et al., 2022), and it also offers the opportunity to remove precancerous polyps directly during the procedure. However, this is a more invasive screening method that is less acceptable to participants than at-home stool sampling and requires costly equipment and highly trained staff to deliver.

While sigmoidoscopy has higher sensitivity and specificity than a single FIT or gFOBT test, a recent Norwegian study showed that repeated FIT tests result in higher participation

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

rates and detection of cancers and advanced adenomas than screening with flexible sigmoidoscopy (Randel et al., 2021). Modelling studies have shown that repeated FIT is almost as effective as colonoscopy (Buskermolen et al., 2019; Knudsen et al., 2016; Zauber et al., 2015). Combining the two approaches, interim results from a Chinese randomised controlled trial show that using a risk-based screening strategy — where individuals at higher risk of colorectal cancer are invited for colonoscopy while those at lower risk are offered FIT — has a high participation rate and a higher cancer detection rate than FIT alone. However, the limitations of colonoscopy and flexible sigmoidoscopy in terms of ease of participation, workforce requirements and effectiveness therefore make them less likely to be suitable or cost-effective for population-based screening across EU member states than repeated FIT stool testing.

Case study: Moving from gFOBT to FIT in Finland

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

In the light of promising data about FIT screening coming from other countries, Finland started a new pilot programme by inviting 60–66-year-old men and women for biennial FIT testing and gradually extending to a wider age group. Due to the known sex differences in test performance (see "Personalised strategies for colorectal cancer screening", p.50), the FIT cut-offs were set at 25µg/g for women and 70µg/g for men, to improve the sensitivity of the test in females and to minimise the gap in effectiveness by sex.

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

Based on the results of the pilot studies and cost-effectiveness modelling, a national FIT screening programme in Finland was recommended with the same legal basis as the existing breast and cervical screening programmes. Gradual rollout will start in 2022, with defined target ages and screening intervals but without specified Hb thresholds, to allow for further evidence-based changes in the future.

Personalised strategies for colorectal cancer screening

There is evidence that adopting more tailored strategies for FIT testing might influence the effectiveness and cost-effectiveness of colorectal cancer screening.

Age and sex

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

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

Using sex-specific and age-specific cut-off values for FIT testing can adjust test sensitivity for different groups and help to narrow the gap in test performance by sex and age. Setting threshold values should also be considered in the context of the overall health service, particularly the capacity for delivering colonoscopy services to follow up positive referrals. The use of sex-specific FIT cut-offs in colorectal screening has been investigated in a number of countries including Sweden, Finland and the Netherlands (Blom et al., 2019; Kortlever et al., 2021; Sarkeala et al., 2021).

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

Prior FIT test results

Another opportunity for delivering more personalised strategies and improving the effectiveness of colorectal cancer screening is by taking an individual's prior FIT test results into account when considering screening interval and age of stopping screening. Studies from Taiwan and Scotland show that having a higher level of haemoglobin (Hb)

in a first FIT screening test is associated with an increased risk of being diagnosed with colorectal cancer later on (L.-S. Chen et al., 2011; Digby et al., 2017).

Further studies in the Netherlands, Italy and Spain show that having low faecal Hb level on consecutive tests is associated with a much lower risk of colorectal cancer than individuals having a higher Hb level upon repeated testing (Buron et al., 2019; Grobbee, Schreuders, et al., 2017; Senore et al., 2020). Modelling analysis shows that taking age, sex and the results of two consecutive FIT tests into account is a highly predictive and clinically superior strategy compared with age and sex, or age, sex and a single test result.[31]

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

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

In summary, while most FIT-based colorectal cancer screening programmes currently use a single threshold value for all participants, it is clear that one size may not fit all. However, more research is needed to establish exactly which FIT thresholds are appropriate according to personal risk factors such as age and sex, and how to take account of serial test results, along with research into the consequences of adopting such an approach and how it is perceived by participants.

2.4. Cervical cancer screening

Cancer of the cervix uteri (the neck of the womb) is the ninth most common in women in Europe, with nearly 60 000 women diagnosed and more than 25 000 dying from the disease every year.[32] Virtually all cervical cancers are caused by infection with the human

31 Meester et al., unpublished results presented at WEO Colorectal Steering Committee meeting, 2021.

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

papillomavirus (HPV; Walboomers et al., 1999), with the majority of cancers being caused by HPV types 16 and 18. However, given that an estimated 80% of the sexually active population will be infected with HPV by the age of 45, and given that the cumulative incidence of developing cervical cancer varies from 0.5–2% (Arbyn, Weiderpass, et al., 2020), there must be other factors that determine whether a cancer will develop in an HPV-infected woman (Chesson et al., 2014).

Conventional cervical screening (smear test, cytology) involves scraping of cells from the cervix and analysing them under the microscope for presence of abnormal cells. Screening therefore prevents cervical cancer by picking up mostly pre-cancerous lesions and treating them before they develop into an invasive cancer. While significant inequalities exist in access to cervical screening across Europe,[18] a systematic review of ten observational studies of organised cervical screening programmes in Northern and Western Europe showed a 41–92% reduction in mortality from cervical cancer due to screening, with a lack of data from Eastern and Southern member states (Jansen et al., 2020).

The role of HPV testing in cervical cancer screening

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

Follow-up of four major European randomised controlled trials of HPV testing demonstrated that HPV-based screening is a more sensitive screening test, providing 60–70% greater protection against invasive cervical cancer compared with conventional cytology testing. The results suggest that screening intervals could be safely lengthened from three years to at least five years if using HPV testing rather than cytology (Ronco et al., 2014). Furthermore, 100% of women with persistent HPV infection in a Swedish randomised controlled trial of HPV screening went on to cervical precancer. However, women who cleared the infection and became HPV negative had no incidence of precancer (Elfgren et al., 2017).

HPV testing offers a more effective and long-lasting protection against cervical cancer than cytology testing, with fewer screening visits required. Sample testing can be carried out using automated equipment rather than requiring microscopic analysis, and at a lower cost than conventional cervical smear tests. Furthermore, self-sampling for HPV testing, either at home or in a healthcare facility, is an efficient and cost-effective way of gathering

samples and could improve access for under screened populations. Widespread adoption of HPV testing across Europe could therefore result in faster elimination of cervical cancer from the population. In support of this, a Swedish randomised healthcare policy trial of nearly 400 000 women aged 30–64 found that using HPV testing as the primary cervical screening method was acceptable and effective compared with cytology-based screening, and had comparable participation, referral and detection rates (Elfström et al., 2021).

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

HPV testing as the first line of cervical cancer screening, with follow-up cytology or colposcopy for those testing positive, was recommended by the World Health Organization in 2014 and by the European Union in 2015. However, HPV testing is not in use in all EU member states at the current time, representing a missed opportunity to save lives from cervical cancer.

Case study: Cervical screening in Sweden

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

The researchers discovered that there was a steady and significant increase in the proportion of smears that had been reported as normal but actually contained pre-cancerous cells (false negatives) of around 2% every year, suggesting that there was a significant issue with the quality assurance of cytology testing in the country (Edvardsson et al., 2021). This kind of problem could be avoided by switching to HPV testing with automated viral detection, removing the need for subjective human evaluation of cytology samples.

Self-sampling for HPV testing

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

Eleven commercially-available HPV tests have now been validated as being suitable for use in primary cervical screening on cervical specimens (Arbyn et al., 2021). A number of studies have compared the accuracy of self-sampling for HPV testing with clinician-collected samples, with a meta-analysis of 33 studies showing that self-sampling increases screening uptake, especially for under-screened women (Yeh et al., 2019). Work is also underway to validate HPV testing in vaginal self-samples and urine (Arbyn, Peeters, et al., 2018). The results of this work should contribute to the development of consistent protocols and lists of validated self-collection devices and tests for use in cervical screening programmes.

Offering self-sampling to under-screened populations may be more effective than inviting women to attend for conventional clinical sample collection. There are several different strategies that can be employed to offer self-sampling HPV testing kits to women. For example, they can be sent in the mail to all screening invitees; alternatively, women can opt in to receive a kit, or they can be offered directly to the woman by a health professional.

A meta-analysis of these different strategies showed that mail-to-all strategies were effective at encouraging participation (around 20% participation) while opt-in strategies had 8% participation (Arbyn, Smith, et al., 2018). On average, only about one fifth of self-sampling kits are actually used when posted to women's homes, resulting in considerable waste and plastic in the environment, which may limit the cost-effectiveness of this strategy.

Up to 95% participation was achieved through direct delivery of self-sampling devices to women (door-to-door kit or during a visit at a clinic), although these latter trials were conducted in South America and Africa and may therefore not be applicable to European populations (Arbyn, Smith, et al., 2018). Nevertheless, a small Belgian trial confirmed high response rates (78%) when general practitioners (family doctors) offer a self-sampling kit to eligible women coming for an unrelated consultation (Peeters et al., 2020).

Further research is needed to confirm that the quality obtained from self-testing is consistently high with a low proportion of failed tests or insufficient material for testing. There is also a need to develop standardised procedures and protocols for how best to handle and analyse samples from different self-sampling devices.

Self-sampling is well accepted by women, although they tend to prefer urine collection methods rather than vaginal self-sampling (De Pauw et al., 2021). It is also cost-effective compared to the standard cytology testing (Malone et al., 2020; Sroczynski et al., 2018). Self-sampling could also be considered as a first line procedure for contacting women for HPV testing in the general population after suitable pilot testing prior to national or regional roll out. Home-based testing is also a safe procedure during situations such as the COVID-19 pandemic when conventional screening appointments may not be possible (Arbyn, Bruni, et al., 2020).

However, the uptake of self-screening is highly variable across populations and may depend on the local setting. Pilot studies are needed to assess local responses before general roll out of a strategy for self-sampling. Furthermore, self-sampling should only be done in an organised setting with ongoing monitoring and quality control, and where follow up of women testing positive for HPV through self-sampling can be assured.

The impact of HPV vaccination on cervical cancer incidence and screening

Vaccines against the most dangerous strains of HPV have been available since the mid-2000s. HPV vaccination is currently offered in almost all EU member states, covering a range of ages, vaccine types and catch-up programmes (summarised in Nguyen-Huu et al., 2020). The sole exception is Romania, where the vaccination programme was discontinued due to poor uptake (Penţa & Băban, 2014). There are three HPV vaccines currently approved for use in Europe, currently given as two or three doses, with 6–12 months between the first and last doses:

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

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

A comparison of birth cohorts in England demonstrated a major impact of the national HPV vaccination programme on cervical cancer incidence. More than 17 000 cases of

abnormal CIN3 lesions and 563 cases of cervical cancer were diagnosed in women born prior to the vaccine rollout in 1990, compared with just 49 cases of CIN3 and 7 cancers in the cohort born five years later, 85% of whom had been fully vaccinated at age 12 or 13 — an 87% reduction. There was less of a protective effect in women who were vaccinated at ages 14–16 or 16–18, representing a 62% and 34% reduction in cervical cancers, respectively. This is likely due to the fact that some of these older girls would have already been exposed to HPV through sexual activity (Falcaro et al., 2021).

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

No new variants of HPV have been discovered over the past 30 years and there is no evidence to date of waning vaccination effectiveness, suggesting that protection is long-lived. It should be noted that there are a number of social and cultural determinants affecting HPV vaccination uptake, including religious beliefs and vaccine hesitancy. More research should be done to understand these determinants and develop strategies to address them in order to deliver better healthcare for all (for example, Rey et al., 2018).

Eliminating cervical cancer through vaccination and screening

In 2020, the World Health Organization launched a global strategy to accelerate the elimination of cervical cancer through the combination of vaccination, screening and treatment, which could prevent 50 million deaths worldwide by 2050.[33]

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

A previous analysis showed that four lifetime screens could be optimal and cost-effective for cohorts offered the Gardasil 9 vaccine in developed countries (Simms et al., 2016). However, this strategy does not take into account the development of herd immunity, which might make it safer to screen unvaccinated women less often, or the needs of

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

adult women immigrating into Europe who have not been vaccinated. The prevalence of HPV16/18 should also be monitored on an ongoing basis to check whether the effectiveness of the vaccine is waning or new variants of the virus are emerging.

The FASTER concept for the rapid control and ultimate elimination of cervical cancer proposes that women between the ages of 23 and 26 undergo simultaneous vaccination and HPV testing, with those who are HPV negative (approximately 90–95% of the population) expected to have an 83–90% efficacy of the vaccine in preventing cervical cancer. If testing positive, they will either be followed up with HPV testing until they test negative, at which point they are unlikely to develop invasive cervical cancer; or, in the case of women with persistent HPV infection, they should be monitored for the development of abnormal cells through cytology and given appropriate treatment and follow-up. In total, this approach could lead to more than 90% protection against invasive cervical cancer (Bosch et al., 2016).

In summary, we have an unprecedented opportunity to eliminate cervical cancer in the EU through a combination of HPV testing and vaccination. Given the tight link between HPV and cervical cancer and the effectiveness of vaccines in preventing HPV infection it may therefore become necessary to consider how to ramp down and cease organised cervical screening programmes as HPV and cervical cancer is eliminated through the combination of vaccination and screening.

2.5. Evidence-based policy options

Breast cancer:

- There is now compelling evidence that starting mammography breast screening in mid to late 40s will maintain an acceptable balance of harms and benefits for younger women, similar to those for older women. Introducing this change to national or regional breast screening programmes will help to reduce inequities for women in EU member states.
- MRI screening should be considered for women with particularly dense breasts.
- There should be ongoing consideration of the use of digital breast tomosynthesis (DBT) for breast cancer screening as evidence continues to emerge from large-scale trials.

Colorectal cancer:

- FIT is recommended as the optimal primary colorectal cancer screening test across the EU, in preference to gFOBT or colonoscopy.

Improving existing cancer screening programmes

- Uptake of colorectal cancer screening can be improved by awareness campaigns and making at-home stool testing highly convenient, for example by direct mailing as well as making them available on demand to eligible unscreened people.
- More research is needed to establish exactly which FIT thresholds are optimal based on factors including age, sex, testing interval and outcome of previous tests. This research can be conducted alongside the implementation of national or regional FIT-based colorectal screening programmes.

Cervical cancer:

- HPV testing can replace cytology testing as the primary method of cervical screening in all EU member states, with traditional cytology testing reserved for individuals with persistent HPV infection.
- Self-sampling for HPV testing should be considered to increase uptake among under-screened women.
- There is a need for research to elucidate the social and cultural determinants affecting HPV vaccination uptake, including economic constraints, religious beliefs and vaccine hesitancy, and develop strategies to address them. There may be lessons that can be learned from efforts to tackle COVID-19 vaccine hesitancy across the EU.

Chapter 3. Expanding screening to other cancer types

Any potential new cancer screening programme must demonstrate its effectiveness in terms of reducing the occurrence of cancer (in the case of screening for precancerous conditions), shifting the stage of diagnosis earlier, reducing cancer mortality and improving quality of life and patient outcomes, and that the benefits outweigh the harms. It must also be a cost-effective strategy.

This chapter summarises the scientific evidence for extending population-based 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 overall mortality or disability-adjusted life-years, and where screening test performance has been investigated in large-scale trials. Consideration of other cancer types where more targeted screening of high-risk individuals may be beneficial, such as liver or pancreatic cancer, is out of scope for this report.

3.1. Lung cancer screening

When considering men and women together, lung cancer is the biggest cancer killer in Europe, accounting for approximately 257 300 deaths every year across the EU27 — one in five cancer deaths[1] — and the loss of 3.2 million disability-adjusted life-years annually in the EU. Around seven out of eight lung cancer patients currently die within five years of diagnosis. Currently, average survival following a diagnosis of lung cancer is around 200 days, extended by a few hundred days by recent advances in immunotherapy.[34,35,36]

Smoking causes the majority of lung cancer cases in both men and women (O'Keeffe et al., 2018), so screening efforts are currently targeted at current and ex-smokers. There is growing awareness of air pollution as a leading cause of lung cancer, potentially warranting screening for individuals living in the most polluted areas (Khanna et al., 2021).

34 https://ecis.jrc.ec.europa.eu/factsheets.php

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

36 https://www.lungcancereurope.eu/lung-cancer/

This is particularly relevant for places such as China and India but may become more significant for the most polluted cities of Europe in the future.

Evidence of effectiveness of lung cancer screening

The effectiveness of low-dose computed tomography (LDCT) lung cancer screening has been explored in a number of randomised clinical trials, of which the largest are the US National Lung Screening Trial (NLST), which compared LDCT with chest X-ray, and the Dutch/Belgian NEderlands Leuvens Screening ONderzoek (NELSON) study (discussed on p.61). Other notable CT lung screening 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 Box 5 for further details).

The potential benefits of early diagnosis of lung cancer through 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 benefit of lung cancer screening was also 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).

Box 5. Evidence overview: Lung cancer screening

- Data from 13 published trials found higher lung cancer incidence as well as early-stage disease in the screening arm, compared to control. A review of pooled data from nine randomised controlled trials found that the overall lung cancer incidence was higher in the LDCT screening group compared to the control group (RR 1.26; 95%CI 1.10–1.45; Hunger et al., 2021).
- Reduced lung cancer mortality but not overall mortality was observed in the screening arm, compared to control with sex variation: 29% reduction in women and 13% reduction in men. A meta-analysis pooling data from eight randomised controlled trials calculated a relative risk of 0.88 (95%CI 0.79–0.97), suggesting a 12% reduction of lung cancer mortality in the screening versus control arm (Hunger et al., 2021).
- The harms due to false-positive screening results may be minimal, with some invasive investigations for benign disease but low complication rates (Balata et al., 2021; Hunger et al., 2021).
- There are short-term psychosocial harms observed, due to involvement or suspicious results of screening, but these may resolve in the long run (Bergh et al., 2011; Field et al., 2016; Hunger et al., 2021; Jonas et al., 2021; Pinsky, 2014).

Results from the NELSON and NLST lung cancer screening trials

The NELSON trial of lung cancer screening recruited nearly 16 000 men and women aged 50–75 years, who had at least 15 cigarettes per day for 25 years or more, or at least 10 cigarettes per day for 30 or more years, as well as former smokers who had quit less than 10 years ago. The trial 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, with 24% in males and 33–59% in women 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 (de Koning et al., 2020).

Similarly, the NLST, which recruited nearly 53 500 males and females aged 55–74, who had smoked more than 30 pack years and quit fewer than 15 years ago, also showed an increase in the number of lung cancers detected with LDCT compared with chest radiography. It also reported a significant reduction in both cancer-specific and overall mortality, particularly from five years post-randomisation (National Lung Screening Trial Research Team et al., 2011).

While the NLST did demonstrate a reduction in all-cause mortality, neither the NLST nor NELSON was formally powered to reveal overall mortality effects — a known challenge in clinical trials of screening interventions. Analysis by Heijnsdijk et al. (2019) showed that a minimum sample of 40 000 participants per arm (i.e. 80 000 participants in a two-arm randomised controlled trial) is required to show a statistically significant effect in a screening trial with the same magnitude effect on cancer-specific mortality as NELSON.

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. By contrast, the NELSON study analysed nodules by volume on CT and also called some participants for a confirmatory follow-up scan after three months, although this added additional cost to the screening process (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 (National Lung Screening Trial Research Team, 2019), while the NELSON trial reported only a small surplus of cases at year 11 (de Koning et al., 2020).

Expanding screening to other cancer types

Analysis of tumour subtypes in the US NLST and PLCO trials suggests that screening may detect adenocarcinoma (the most common form of lung cancer) up to four or 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.

Benefits and harms of lung cancer screening

On top of the more general advantages and risks discussed in Chapter 1 and quantified in section 3.1.1 above, there are additional benefits and harms specific to LDCT lung cancer screening, which have been quantified in randomised controlled trials.

Possible additional benefits:

- potential for earlier detection and treatment of other diseases on a thoracic CT scan (for example, coronary artery calcification, emphysema)
- opportunities for delivering smoking cessation advice and interventions

Additional small harms:

- small radiation risk from CT scans, equivalent to around 6 months of natural background radiation (Smith-Bindman et al., 2009)
- incidental non-life threatening findings, potentially leading to over-investigation and overdiagnosis (Tsai et al., 2018)
- false reassurance and 'licence to smoke' if screening test result is negative (see "Smoking cessation", p.65)

Benefits and harms can be managed and balanced by adherence to evidence-based guidelines around eligibility (see "Who should be screened for lung cancer?", p.63), 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 randomised UK Lung Screening trial (Balata H et al. in press, Lung Cancer 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).

Further detail on the potential risks from radiation and overdiagnosis from lung cancer as determined from controlled trials, as well as findings relating to psychosocial harms and smoking behaviours, are provided in Box 5, p.60.

Who should be screened for lung cancer?

Based on the balance of benefits and harms, and in the context of finite healthcare 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, set against the financial resources available. 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, an 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. In 2013, the US Preventive Services Task Force (USPSTF) 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 fewer than 15 years ago. 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 those who have 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 lung cancer surgery (US Preventive Services Task Force, 2021).

More sophisticated risk-screening models have now been developed to determine which individuals in the population should be invited for screening. One of the most commonly used is the $PLCO_{M2012}$ model, which incorporates information about age, level of education, body-mass index, family history of lung cancer, chronic obstructive pulmonary disease, chest X-rays in the previous three years, smoking status, history of cigarette smoking in pack-years, duration of smoking, and number of years since quitting smoking (Tammemägi et al., 2013).

When applied at a population level, these models tend to select slightly different populations from simpler strategies such as the USPSTF criteria. 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). Simple categorical criteria such as the USPSTF also appear to miss a significant number of women who would benefit from screening, which is improved by the use of the $PLCO_{M2012}$ model (Tammemägi et al., 2013).

Expanding screening to other cancer types

While risk stratification 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. (2021) showed that risk-based selection strategies were estimated to be associated with more benefits and fewer radiation-related deaths but more over-diagnosed cases than simple criteria.

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, Iraq and Europe, such as the 12 100 participant German HANSE study, are also exploring the feasibility of implementing personalised lung cancer screening (detailed in Box 5, p.60).[37]

Finally, it should be noted that 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.

Cost-effectiveness of lung cancer screening

The reported cost-effectiveness of lung screening varies widely. Two trial-data based studies estimated costs per quality-adjusted life year (QALY) as £8466 (95%CI £5516 to £12 634; Field et al., 2016) and $81 000 (95%CI $52 000 to $186 000; Black et al., 2014). Two systematic reviews have analysed the cost-effectiveness of lung cancer screening, covering twelve and nine studies respectively (Raymakers et al., 2016; Puggina et al., 2016). Most studies showed that lung screening was cost-effective, based on the suggested US QALY of either $50 000 or $100 000. See Box 5, p.60, for further evidence on the cost-effectiveness of lung cancer screening.

The cost-effectiveness of LDCT lung cancer screening is strongly influenced by the impact of smoking cessation services (see the next section). 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, although trials to date have shown this not to be the case.

An increase in the number of people quitting smoking as a result of the introduction of lung screening significantly improves the cost-effectiveness of the procedure (Goffin et al.,

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

2015). Cost-effectiveness analyses of lung cancer screening in Europe are still scarce, as many countries have been waiting for the results of the European NELSON trial. However, a cost-effectiveness analysis for Switzerland (a country with a relatively high smoking prevalence) based on the performance of the NLST showed ratios below €40 000 per QALY (Tomonaga et al., 2018).

Smoking cessation

Smoking is a major cause of lung cancer and the leading preventable cause of death in Europe, not only from cancer but other serious health conditions such as cardiovascular disease and lung disease (Janssen et al., 2021). Engaging with lung cancer screening offers a timely opportunity to promote smoking cessation for people 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%.

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), while a recent systematic review examined studies across four randomised controlled trials (DLCST, LSS, NELSON and NLST) and three cohort studies (not included in this current rapid review) found no obvious smoking cessation or abstinence between screening and control groups (Jonas et al., 2021).

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 (Hunger et al., 2021).

There are several 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).

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 four-week intervention (Murray et al., 2020, Crosbie et al., 2020).

Conclusion: Lung cancer screening

In conclusion, there is evidence from at least two large-scale randomised controlled trials that LDCT lung cancer screening is highly effective in reducing the burden of lung cancer mortality when offered to smokers or ex-smokers of both sexes in the age range 50–80. The amount of overdiagnosis, overtreatment and other harms are limited and, depending on selection criteria used, cost-effective screening scenarios can be designed.

Screening should include high-risk current and ex-smokers, with eligibility based on age and pack-years smoked and/or the $PLCO_{M2012}$ risk model (Tammemägi et al., 2013). Pilots in UK and several European countries show high acceptance rates, and these programmes can also be instrumental in reducing smoking in a population that is relatively resistant to quitting.

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. We consider that there is a strong scientific basis for extending screening programmes to lung cancer screening by low-dose CT scanning based on effectiveness and mortality burden.

3.2. Prostate cancer screening

Prostate cancer is the most commonly diagnosed cancer and the third leading cause of cancer death in European men, with more than 335 000 new cases and 70 000 deaths in 2020 within the EU.[1] The chances of developing prostate cancer are strongly linked to age, and one in 11 men will develop the disease by the age of 74.[38]

Cancers diagnosed at a metastatic stage (stage 4) have a significant impact on survival and quality of life, as well as high treatment costs. Detecting prostate cancer at an early stage, when treatment is less invasive and more likely to be effective, could therefore make a significant difference to cancer mortality and the burden of disease among European men.

38 https://ecis.jrc.ec.europa.eu/factsheets.php

However, prostate cancer is a highly heterogeneous disease. Around a third of prostate tumours grow aggressively and will benefit from early detection, while the rest will grow more slowly, in many cases never causing a problem within a man's natural lifetime. Autopsy studies show that many more men die with prostate cancer than of prostate cancer (Bell et al., 2015), posing a potential challenge for effective screening for the disease.

Evidence of effectiveness of prostate cancer screening

Testing blood levels of prostate-specific antigen (PSA, a protein produced by the prostate gland) has been proposed as a screening test for prostate cancer. However, due to the fact that PSA testing detects low volume, low grade cancers as well as dangerous high grade tumours, there is a significant risk of overdiagnosis and overtreatment, along with additional healthcare costs and impacts on quality of life. As a result, it was previously advised that systematic population-based PSA screening should not be undertaken — for example, see the European Association of Urology 2015 guidelines.[39]

Recommendations against systematic PSA testing are now being revised in the light of new data, including an observed increase in the number of metastatic prostate cancers diagnosed in men over the age of 75 following the US Preventive Services Task Force recommendation to stop PSA screening (Butler et al., 2020; Hu et al., 2017; Jemal et al., 2021), along with advances in screening technology such as MRI scanning (see "Additional testing to reduce unnecessary biopsy and overdiagnosis", p.71).

However, there are many unanswered questions surrounding the utility and cost-effectiveness of prostate cancer screening, particularly when balancing the risks of over- and under-diagnosis. PSA testing is still being prescribed for men over 50 and also older men over 70 as an unorganised or on-request PSA testing service in the majority of countries in the EU. Based on Dutch data, it was roughly estimated that these ad hoc screening efforts in relatively older men cost about €1 million per life-year gained (Heijnsdijk et al., 2015).

Experiencing typical symptoms of prostate cancer, such as problems with urination, are not necessarily a significant early indicator of prostate cancer (Frånlund et al., 2012). This has reinforced the message that if prostate cancer is to be diagnosed while it is still curable, it is preferable to offer PSA testing rather than wait for men to report symptoms. 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).

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

Box 6. Evidence overview: Prostate cancer screening

- Screening via low-threshold PSA test results in a small absolute reduction in deaths from prostate cancer, equating to one fewer prostate cancer death per 1000 men screened over 10 years.
- Any mortality benefit tends to be balanced against overdiagnosis and overtreatment of low-risk disease. One study estimated that, for every prostate cancer death saved by screening 1000 men over 10 years, approximately 1, 3, and 25 more men would experience biopsy- and treatment-related sepsis, urinary incontinence, and erectile dysfunction, respectively (Ilic et al., 2018).
- One trial suggests that using MRI scanning to indicate biopsy may reduce the risk of overdiagnosis in men with abnormal PSA (Nordström et al., 2021). Other studies are ongoing to look at risk-adapted prostate screening with MRI.
- Longer follow-up is required to fully evaluate real-world costs. Two trial-based studies modelled costs of €54 918 (Karlsson et al., 2021) and $73 000 (Heijnsdijk et al., 2015) per QALY gained.

Questions remain about the optimal eligibility criteria and strategies for population-based prostate cancer screening. Data from the 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). A one-time PSA test is therefore 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 large-scale ERSPC found a 21% reduction in prostate cancer mortality between the arms after 14 years of follow-up and 52% reduction after 19 years in an uncontaminated cohort. This is likely to represent a true effect of PSA screening of around 30–40% in an optimal situation (de Koning et al., 2018; Hugosson et al., 2019; Osses et al., 2019; Schröder et al., 2014).

The randomised controlled US Prostate, Lung, Colorectal and Ovarian (PLCO) trial of PSA-based screening failed to show a significant impact on prostate cancer mortality, due to the high rate of opportunistic PSA testing in the control arm being studied, together with a low biopsy rate of around 37% in screen-positive men (Pinsky et al., 2017). This finding illustrates 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 ERSPC, where similar contamination in the control group led to no observable effect of PSA screening on prostate cancer mortality at nine 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 prostate cancer mortality after 10 years (Martin et al., 2018).

Van Poppel and colleagues 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, Hogenhout, et al., 2021a, 2021b; Van Poppel, Roobol, et al., 2021). See Box 5, p.60, for further discussion of the evidence around prostate cancer screening.

Benefits and harms of prostate cancer screening

Although prostate cancer screening can reduce cancer-specific mortality, it comes with a risk of overdiagnosis and overtreatment. A systematic review and meta-analysis of the evidence to date shows that for every single prostate cancer death saved by screening 1000 men over 10 years, approximately 1, 3, and 25 more men will experience biopsy- and treatment-related sepsis, urinary incontinence, and erectile dysfunction, respectively (Ilic et al., 2018).

Reanalysis of the ERSPC and PLCO prostate screening trials demonstrates that the risk of overdiagnosis drops following additional years of follow-up. Cancer screening trials like ERSPC tend to initially over-estimate the harm-to-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 a future beneficial effect) but generally there is only a relatively short follow-up time in which to prove the benefit of screening 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, but this could be improved by introducing additional post-screening tests such as MRI (see section 3.2.4, Gulati et al., 2011).

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 3 000 online survey responses across 25 countries (Venderbos et al., 2020). Available in 19 languages, the study used validated quality-of-life questionnaires 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 surgical removal of the prostate (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 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.

Who should be screened for prostate cancer?

Another area where the balance of benefits and harms of prostate cancer screening can be adjusted 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 3.0 ng/ml screening with two-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. It is therefore important to have further strategies such as additional post-screening tests (see the next section) 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.

Risk-stratification approaches have been proposed as a way of refining prostate cancer screening to reduce potential harms. Heijnsdijk 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 two years until the age of 69, with a similar number of cancers detected and lives saved, together with a moderate reduction in overdiagnosis.

The use of risk stratification algorithms that include characteristics such as historical PSA results, family history (a proxy for genetic risk), and polygenic risk scores (PRS) can also

help to reduce the number of false positives from prostate cancer screening and the impact and harms of overdiagnosis (Poppel et al., 2021).

Callender et al. (2019) compared three different screening strategies:

- no screening
- age-based screening with four-yearly PSA testing between 55 and 69
- risk-stratified screening based on polygenic risk score, with men above a given risk threshold receiving four-yearly PSA testing from the age they reach the risk threshold to age 69

Based on their model, the researchers showed that employing risk stratification based on PRS is likely to be more cost-effective than age-based or no screening, improve the benefit-harm balance of the screening programme, and reduce overdiagnosis while maintaining the mortality benefits of age-based screening.

However, deciding the exact risk threshold at which screening should start, as determined by percentage chance of developing prostate cancer in the next 10 years based on age and PRS, is not simple and will depend on judging the trade-off between the benefits and harms of screening, as well as careful public communication about such approaches.

Additional testing to reduce unnecessary biopsy and overdiagnosis

A number of additional post-screening testing strategies (also known as reflex testing) can be offered to men with moderately elevated PSA levels, in order to help reduce overdiagnosis.

Importantly, low grade, low volume 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-wide organised screening setting.

The Swedish STHLM3-MRI randomised controlled trial has investigated the effectiveness of additional MRI scanning and biomarker testing following PSA-based prostate cancer screening. 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 Nordström et al. (2021) found that combining the Stockholm3 biomarker test with an

Expanding screening to other cancer types

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 et al. (2021), whereas post-PSA ultrasound scanning was not effective. Combining age-plus-PRS risk-stratified screening with additional MRI scanning for men with a positive PSA test further improve the benefit-harm ratio and the cost-effectiveness of the screening programme compared to age-based screening alone (Callender 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 Stockholm3 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.

MRI can also help doctors to select cases that are most likely to benefit from active surveillance ('watch and wait') rather than immediate intervention, reducing overtreatment. In addition, MRI allows the selection of cases for partial gland thermo-ablation — an emerging alternative therapy for significant unilateral prostate cancers visible at MRI, which has fewer side effects than conventional treatment (Fainberg et al., 2021).

Although MRI can significantly reduce the harms of prostate cancer screening through overdiagnosis and overtreatment, securing enough scanning resources and quality of reading will be challenging in many EU member states. 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 falls within acceptable limits for many healthcare systems and compares favourably against the costs of later prostate surgery, radiotherapy or drug treatment for metastatic disease (Getaneh et al., 2021). Introducing these scans on a national or regional level will require quality assurance, training and accreditation in order to maintain standards, similar to the current situation with mammography for breast cancer.

Research is ongoing to evaluate the use of additional molecular tests (biomarkers) for men with moderately elevated PSA levels between 4–10ng/ml as another way to reduce overdiagnosis. Most of these tests are based on looking for certain genes or molecules shed into urine — such as the presence of TMPTSS2:ERG, PCA3 messenger RNA or other panel-based molecular tests — offering a potentially useful non-invasive second line test to reduce overdiagnosis (Chang et al., 2021). Initial analysis shows that such tests can offer a moderate reduction in overdiagnosis with a slight reduction in lives saved by screening (Gulati et al., 2020), and further research in this area would be informative.

Cost-effectiveness of prostate cancer screening

Limited published evidence is available on the impact of organised prostate cancer screening on healthcare costs. Longer follow-up is required to fully evaluate cumulative real-world costs.

An analysis of eight prostate cancer screening trials by Sanghera et al. (2018) found that fewer than half of studies showed that screening came under the $100 000 per QALY threshold. 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 that, for prostate cancer screening to be cost-effective, screening and biopsy would have to be quite conservative particularly at older ages, with older men with low-risk disease would have to be treated with active surveillance rather than immediate treatment.

A simulation of PSA testing screening every four years in men aged 55–69 based on data from the ESPRC trial estimates an increase of 652 life-years and 366 QALYs per 10 000 men screened at a cost of €54 918 cost per QALY gained (Karlsson et al., 2021). Further modelling of ESPRC data evaluated the optimal parameters to be biennial screening within the age range 55–59 years, which generated an incremental cost-effectiveness ratio of $73 000 per QALY gained (Heijnsdijk et al., 2015). A Canadian modelling study showed that prostate cancer screening with PSA testing may be cost-effective, but that individual preferences for quality of life versus quantity of life left should also be considered (Pataky et al., 2014).

An individual registry-based analysis found little difference in healthcare costs between the Finnish arms of ERSPC, with slightly lower mean overall costs and slightly higher prostate cancer-specific costs in the screened group, although this study had low statistical power and opportunistic screening contamination of the control group (Booth et al., 2018). An analysis of hypothetical reflex tests in the US showed that follow-up MRI was not cost-effective (Jiao et al., 2021), although this is principally due to the high cost of conventional MRI scanning in the US setting rather than the cheaper biparametric MRI 'manogram' approach discussed on p.71.

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 — will have a further impact on the cost-effectiveness of prostate cancer screening. 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, which will also affect costs.

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. 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).

More recent evaluations that include limited testing to a certain upper age limit and reduced amounts of overdiagnosis and overtreatment due to better selection of patients for biopsy with MRI suggest that there are cost-effective strategies for population-based prostate cancer screening (Getaneh et al., 2020, 2021).

Conclusion: Prostate cancer screening

We consider there to be good evidence that prostate cancer screening with PSA testing can reduce deaths from prostate cancer. Overdiagnosis and overtreatment are major harms in prostate cancer screening, due to the high sensitivity of PSA testing, which detects a large number of slow-growing low grade cancers. Imposing an upper age limit on screening (possibly around 65–69), and/or a high-quality MRI scan or other accurate additional testing for PSA-positive men, will reduce overdiagnosis and improve the harm-to-benefit ratio. At the current time, limited PSA testing with the addition of biparametric MRI for PSA-positive men is likely to be cost-effective for many EU member states.

Opportunistic, unorganised PSA testing currently 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, and should be halted.

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 further research and monitor the effectiveness of approaches such as risk stratification, additional testing and active surveillance to ensure that a favourable balance of harms and benefits is maintained, reducing overdiagnosis and overtreatment of low grade slow-growing tumours while effectively diagnosing and treating life-threatening cancers in a timely way.

3.3. Gastric cancer screening

Although rates of gastric (stomach) cancer are relatively low in most European countries and have declined over recent years, there were around 75 400 cases and 52 100 deaths from the disease in 2020 (Dyba et al., 2021).

Rates of the disease are highest in Asia, Eastern Europe (Baltic and the neighbouring states), Portugal, and some parts of South America (Etemadi et al., 2020). Gastric cancer is strongly linked to infection with the bacteria *Helicobacter pylori*, which affects up to 84% of the population in some European countries (Venneman et al., 2018).

Evidence of effectiveness of screening for gastric cancer

There are four main ways of screening for gastric cancer or associated factors:

- endoscopy
- detection of the stomach protein pepsinogen in the blood, followed by endoscopy
- detection and treatment of *H. pylori* infection ('screen and treat' strategy)
- detection of biomarkers in breath or blood

Evidence for the effectiveness of gastric cancer screening in European populations is lacking, as research has tended to focus on high-incidence areas in Asia. A systematic review and meta-analysis of observational studies 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). Two other Chinese trials have looked at endoscopic screening for gastric cancer (Xiao et al., 2020; Zeng et al., 2020). Both found that detection rates for gastric cancers were low, and adherence rates were approximately 45%. Overall, the benefits, cost-effectiveness acceptability of endoscopy screening for gastric cancer is not evident in lower-risk countries outside Asia.

Due to the relative invasiveness of endoscopy, there is interest in using molecular testing as a triage tool to identify those individuals who are most likely to benefit from endoscopic screening. For example, testing for the presence of the stomach protein pepsinogen in the blood (Trivanovic et al., 2018) or volatile organic compounds (VOCs) in breath (Haddad et al., 2020; Krilaviciute et al., 2018; Wang et al., 2021) are showing promise as triage tools for gastric cancer screening.

Limited data from two trials included in a recent systematic review suggest a 79–80% sensitivity and specificity for cancer detection by breath analysis (Haddad et al., 2020). There may also 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), or other biomarkers such as circulating tumour DNA or cells (see Chapter 4). However, more data on all these technologies is required in the targeted screening populations.

The H. pylori screen and treat strategy

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. *H. pylori* infection is relatively easy to detect through blood, stool or breath testing, and can be treated with antibiotics. Estimates suggest that around 35–40% of gastric cancer 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.[40]

The benefits of this testing and treating approach have been demonstrated in a number of studies in Asia (Ford et al., 2015). For example, Chiang et al. 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 (Chiang et al., 2021). A large randomised controlled trial of nearly 185 000 residents of Linqu County in China is expected to unblind the data during 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 adherence 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).

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 GISTAR multi-centre randomised controlled trial of *H. pylori* eradication and pepsinogen testing is currently underway in a number of European countries with high rates of gastric cancer, notably the Baltic States and Eastern Europe, and the results will help to inform future recommendations (Leja et al., 2017).

As a note of caution, the screen and treat strategy for *H. pylori* eradication does require relatively high use of antibiotics by large numbers of people, which runs counter 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).

40 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

Cost-effectiveness of gastric cancer screening

Data about the cost-effectiveness of gastric cancer screening are currently lacking. The low adherence and gastric cancer detection rates suggest that endoscopy is unlikely to be a cost-effective mass screening tool. More targeted screening approaches or the use of novel technologies such as breath testing may prove to be cost-effective in the future, although this needs to be demonstrated in large-scale randomised controlled trials.

While there is a strong rationale for *H. pylori* test-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 nine 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).

Conclusion: Gastric cancer screening

While there is insufficient evidence to recommend endoscopic screening of gastric cancer in Europe, the screen and treat strategy for reducing *H. pylori* infection provides an opportunity to prevent gastric cancer in EU member countries with intermediate to high gastric cancer incidence.

3.4. Oesophageal cancer screening

Around 30 300 people are diagnosed with oesophageal cancer across the EU member states, with men being three times more likely than women to develop the disease, and around 25 600 die from it every year (Dyba et al., 2021). 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 (SCC). 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 local 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-stage 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 morbidity associated with treatment for advanced disease.

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, which 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 established link between Barrett's oesophagus and cancer, the majority of cases of Barrett's are currently 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 from low- or high-grade dysplasia to cancer are around 10–30% (Bhat et al., 2011).

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 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 transnasal endoscopy for screening and the results are encouraging (Sami et al., 2015).

A 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 currently rely on the discretion of family practitioners, since there is no population level, organised screening programme.

Data on the cost-effectiveness of endoscopic oesophageal cancer screening is limited. A single trial estimated the healthcare costs to detect one cancer/one early-stage cancer at $26 347 and $37 687 respectively (Li et al., 2019), but no estimates are available on the number of QALYs gained.

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 (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). Attention is now turning to non-endoscopic cell sampling techniques coupled with biomarkers as a simple, more cost-effective technique for screening (see Chapter 4).

Screening for oesophageal squamous cell carcinoma

The rates of SCC vary significantly around the world. The low incidence of oesophageal SCC in Europe compared with other areas, such as China, Iran and East Africa, does not warrant population-wide screening, but it 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)

Expanding screening to other cancer types

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 weighted carefully since regular surveillance may lead to overdiagnosis even for this group (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. Similar to 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 (see Chapter 4, p.84). Novel image-enhanced endoscopy technologies could also improve the early detection of gastric and oesophageal cancers in high-risk populations.

Conclusion: Oesophageal cancer screening

Oesophageal cancer is a lethal disease that urgently 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 present in that country (squamous or adenocarcinoma).

We do not find scientific grounds to recommend population-wide endoscopic 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 and effective endoscopic treatment.

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 and evaluation of accessible, affordable and acceptable testing strategies that do not rely on endoscopy would be valuable (see Chapter 4, p.84).

3.5. Ovarian cancer screening

In 2020, around 39 400 women were diagnosed with ovarian cancer across EU member states, more than half of which are diagnosed at a late stage (3 or 4), and around 27 100 died from the disease, making it the fourth most common cause of cancer death in European women. Although survival has doubled since the 1970s, it still remains relatively low, with fewer than half of all women surviving five years or more after diagnosis (Dyba et al., 2021).[41]

41 https://eurohealth.ie/policy-brief-women-and-ovarian-cancer-in-the-eu-2018/

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 (Reade et al., 2014). As a result, ovarian and tubal cancers now include the majority of the cancers that were previously assigned as arising from the peritoneum. Various ovarian cancer screening trials have used different definitions of the disease, making true like-for-like comparisons difficult.

To date, screening for ovarian cancer has been done using either transvaginal ultrasound (TVS) or a blood test for CA125, a glycoprotein that fluctuates naturally during the menstrual cycle and is often raised in ovarian cancer.

The randomised controlled Prostate, Lung, Colorectal and Ovarian (PLCO) 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).

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 and/or fallopian tubes, along with the potential for major surgical complications (Henderson et al., 2018). The risk of overdiagnosis was evaluated in both the UKCTOCS and PLCO trials, showing that there might be a possible risk of overdiagnosis (19th International Meeting of the European Society of Gynaecological Oncology, 2015; Prorok et al., 2018). The UKCTOCS 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).

Expanding screening to other cancer types

Although the UKCTOCS trial 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). A further nested case-control study drawn from the UKCTOCS cohort showed that incorporating genetic information in the form of polygenic risk scores (PRS) into a risk prediction model could effectively identify women at the highest risk of developing ovarian cancer, who could possibly be more likely to benefit from screening or other preventative interventions than those at average risk in the general population (Yang et al., 2018).

The lack of positive findings to date in randomised controlled trials of 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 that will make it 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, which may have contributed to the disappointing mortality results in UKCTOCS.

Conclusion: Ovarian cancer screening

In conclusion, two large randomised controlled trials on screening for ovarian cancer have failed to show a beneficial effect. We do not find 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, such as blood-based biomarker testing (see Chapter 4, p.84). Risk-stratification algorithms based on characteristics such as family history and PRS could identify women who are most likely to benefit from screening, although the best testing method and strategy is yet to be determined.

3.6. Evidence-based policy options

Lung cancer screening:

- There is a strong scientific basis for adding low-dose CT lung cancer screening to the current repertoire of population-wide organised screening programmes across the EU, based on effectiveness and mortality burden.
- Screening should include high-risk current and ex-smokers of both sexes around ages 50-80, with eligibility based on a minimum number of pack-years smoked and/or a personalised risk score.

- Pilot projects and regular, timely monitoring and evaluation of quality indicators, process indicators and intermediate outcomes should be mandatory for all new lung cancer screening programmes.
- Lung cancer screening programmes should go hand-in-hand with smoking cessation interventions to maximise benefits and increase cost-effectiveness.

Prostate cancer screening:

- There is good scientific evidence for the benefit of organised PSA-based prostate cancer screening, particularly in combination with additional MRI scanning and active surveillance for PSA-positive men. A limited number of tests in the age range 55-69 seems appropriate and cost-effective as a population-based screening approach.
- Opportunistic prostate cancer screening, especially in older men, should be discouraged in member states in favour of organised screening programmes with built-in quality assurance and monitoring, in order to reduce the risk of overdiagnosis and overtreatment.
- The effectiveness of approaches such as risk stratification and additional testing, such as MRI, should be monitored to ensure that a favourable balance of harms and benefits is maintained.

Gastric cancer screening:

- Well-designed 'screen and treat' strategies for reducing *H. pylori* infection provide a key opportunity to prevent gastric cancer in EU member countries with intermediate to high incidence of the disease and could be considered on a regional or national basis alongside thorough monitoring and outcome data collection.

Other cancer types:

- Further research is needed into more effective approaches for early detection of other types of cancer, such as blood-based biomarkers for ovarian cancer or non-endoscopic technologies for oesophageal cancer (see Chapter 4). Novel technologies may also prove fruitful in screening for other types of cancer not considered in this report, such as liver and pancreatic cancers.

Chapter 4. Novel cancer screening technologies

There is rapid progress in novel screening technologies for detecting cancer at an early stage. For example, there is growing interest in the use of 'liquid biopsy' blood tests to detect multiple different types of cancer from the same sample based on the presence of cells, proteins or other molecules, or genetic alterations. Similar principles can be applied to other samples such as urine, sputum and exhaled breath, but the technology generally lags behind applications in blood.

Alternatively, improved detection of biomarkers including DNA, RNA and proteins can be applied to tissue samples (for example, scrapings from cervix, nose or oesophagus) either to improve the accuracy of cytology-based screening or as a triage test.

4.1. Blood-based biomarkers for cancer screening

Blood is an easily accessible fluid that provides a window on the biological processes at work inside the body and can be easily collected in a minimally invasive way. There are several different blood-borne molecular markers that can reveal the presence of cancer in the body, including the presence of DNA or RNA, proteins, exosomes, metabolites and even the cancer cells themselves (Alix-Panabières & Pantel, 2021).

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

Despite this exciting potential, blood-based biomarkers are not necessarily specific for particular tumour types and most tests are not currently able to reveal exactly where in the body the cancer is located. Blood tests would therefore usually be followed up by subsequent investigation and imaging to confirm the tissue of origin, which requires sufficient healthcare resources and capacity. There is also the potential for causing uncertainty and anxiety in cases where a positive blood test result is followed

by a negative scan. Was the result a false positive? Or is there a cancer present that is currently undetectable with the imaging technique that has been used? And what should happen next?

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

In the context of such a fast-moving field, it is important that all these different liquid biopsy methods are standardised and validated, to support harmonisation of protocols within and between countries and quality assurance. The European Liquid Biopsy Society[42] and International Liquid Biopsy Standardization Alliance (Connors et al., 2020) are playing key roles in this respect.

Circulating tumour DNA

Many tumours release DNA into the bloodstream, known as circulating tumour DNA (ctDNA) (Wan et al., 2017). This DNA contains genomic changes that are the hallmarks of cancer, including mutations, copy number alterations, chromosomal rearrangements, and changes in DNA methylation (see “DNA methylation”, p.88) or other epigenetic marks. Blood can also reveal the presence of infectious agents known to be linked to cancer, such as Epstein-Barr virus, which is associated with nasopharyngeal cancer and other tumour types (Chan et al., 2017).

Importantly, the amount of ctDNA shed into the bloodstream varies according to the stage of disease, the type of cancer and the individual patient. In patients with advanced cancer, the amount of ctDNA in the blood is relatively high and can potentially be detected in a simple finger-prick blood spot test, opening up the possibility of future home-testing (Heider et al., 2020). While intense analysis methods can detect ctDNA sequences from very small tumours (<1cm^3) in patients known to have cancer (Heider et al., 2021), it is a much more challenging task to translate this into a screening test for the general population where the cancer type and mutations are unknown.

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

Furthermore, the proportion of mutant alleles ranges from 0.1% or less in stage 1 disease to around 10% or more in metastatic stage 4 cancer (Bettegowda et al., 2014). Furthermore, each patient's cancer is unique and only a handful of mutations recur across many different cancers, meaning that any multi-cancer blood-based screening test will have to look at multiple genes and mutations (Newman et al., 2014).

Other informative genomic biomarkers can be detected in ctDNA from a range of cancers in an unbiased fashion without needing pre-knowledge about the mutational profile of a certain tumour, such as copy number aberrations, which are seen in around 90% of solid tumours and 50% of blood cancers (Heitzer et al., 2016), or DNA methylation changes (see "DNA methylation", p.88). A blood test must also be able to distinguish between mutant DNA shed from a tumour and clonal haematopoiesis — a natural process of ageing in which mutated cells accumulate in the blood (Jaiswal & Ebert, 2019).

Although ctDNA technology is improving all the time, the utility of blood tests based solely on ctDNA for cancer screening to detect early-stage disease is currently limited due to the challenge of accurately detecting unknown mutated sequences amongst all the other DNA present in a typical blood sample. Some blood-based screening approaches have attempted to overcome this limitation by combining ctDNA analysis for multiple genes with other biomarkers, such as proteins or DNA methylation (for example, the CancerSEEK and GRAIL Galleri tests, see below). Others have developed sensitive assays for early stage cancers based on detecting abnormal fragments of DNA, such as the DELFI assay (Cristiano et al., 2019). Current blood-based ctDNA technologies used on their own will need to improve around ten-fold in order to effectively detect stage 1 cancers.[43]

Case study: CancerSEEK

CancerSEEK is a multi-analyte blood test for the detection of multi-cancer types. One version of the test analyses a panel of specific mutations in ctDNA and protein biomarkers that can reveal the presence of a number of different types of cancer. A retrospective case-control study of the test was carried out in 1,005 stage 1 or 2 cancer patients with eight different tumour types (breast, colorectal, oesophageal, liver, lung, ovarian, pancreatic and stomach) and 812 healthy controls (J. D. Cohen et al., 2018).

The test was able to correctly identify 62.2% of the cancers with a specificity greater than 99%. However, the sensitivity varied with tumour type, depending on the amount of ctDNA and/or protein shed into the blood. For example, more than 99% of ovarian and liver cancers were detected, while fewer than half of breast tumours did. Similarly, sensitivity varied with stage. Although a positive cancer signal could be detected from

43 Data presented at expert workshop 3 by Dr Nitzan Rosenfeld.

around 70% of stage 2 and 80% of stage 3 cancers, this fell to around 40% for early stage 1 tumours (J. D. Cohen et al., 2018).

The feasibility of CancerSEEK to detect cancers that would not otherwise be found at an early stage when successfully treatment is more likely is currently being tested in the prospective DETECT-A study.[44] 10 000 women aged 65–75 were recruited through the US Geisinger Health System, with every positive result being followed up with PET-CT scanning to confirm the diagnosis and location of the tumour.

Preliminary results show that of 96 cancers detected in women participating in the trial, 26 were found using CancerSEEK alone. There were 100 false positives, of which PET-CT scanning identified 63 people with no sign of cancer who did not undergo any additional follow-up (Lennon et al., 2020).[45]

There was a high degree of participant satisfaction (95% overall) and taking part in the trial did not prevent people from undergoing routine standard-of-care screening. Further refinements to the CancerSEEK technology are being developed, such as strand-specific PCR (Cohen et al., 2021), aneuploidy detection (Douville et al., 2020) and machine learning algorithms, with randomised controlled trials being planned.

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

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

Following on from these observations, Lenaerts and colleagues carried out a retrospective analysis of the results of more than 88 000 routine NIPT tests carried out at University Hospital Leuven in Belgium from 2013 to 2020. They discovered 15 cases for whom the NIPT results suggested the presence of an undiagnosed maternal cancer (Lenaerts et al., 2021). Further follow-up revealed the presence of cancer in 11 of these women, with two thirds being blood cancers and the remainder breast, ovarian and bone tumours. Of the remaining four, one was found to have no detectable cancer

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

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

or other health condition while three had clonal mosaicism in the blood, a potential precursor of leukaemia, and were offered regular monitoring. In one further case, a woman whose NIPT revealed a potentially cancer-related chromosomal abnormality but did not meet the threshold for onward investigation was found to have non-Hodgkin lymphoma nearly four years later.

The potential use of NIPT for cancer screening in the wider population has been investigated in a cohort of 1002 elderly individuals, of whom 30 had an abnormal NIPT result suggestive of an underlying cancer. After further investigation, six were found to have blood cancer or a pre-cancerous blood condition and nine had clonal mosaicism in the blood, while fifteen had no obvious origin for the abnormalities (false positives). Four cases of cancer (prostate, lung, colorectal and multiple myeloma) were also diagnosed during the study period in individuals with a normal NIPT result (false negatives) (Lenaerts et al., 2019).

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

DNA methylation

Methylation is a chemical modification of DNA that is involved in controlling patterns of gene activity. Different cell types express specific repertoires of genes, so DNA from a given tissue or cell-type will have a distinctive methylation profile. DNA methylation patterns can also be altered in cancer, with these changes usually occurring in the earliest stages of tumour growth. Analysing DNA methylation profiles can therefore reveal the presence of cancer and likely tissue of origin, and help to distinguish cancer from other conditions (Moss et al., 2018).

Blood-based ctDNA methylation analysis for early detection of cancer has been explored in a number of studies, both for specific cancers and in multi- or pan-cancer assays. This technology is already starting to come to market — for example, the Epi proColon blood test for colorectal cancer screening, and the GRAIL Galleri test. Some assays use PCR-based testing of methylation status at a limited number of genetic markers, while others use whole-genome or large-scale bisulphite sequencing (M. C. Liu et al., 2020) or immunoprecipitation and sequencing of cell-free methylated DNA to get a deeper view

of methylation patterns (Shen et al., 2018). While the specificity of methylation testing is usually high, the sensitivity is often relatively low, especially for early-stage disease.

The GRAIL Galleri multi-cancer blood test is designed to detect around 50 different cancer types by examining ctDNA methylation status at more than 100 000 sites throughout the genome. It has a specificity of around 99.3%, with an average sensitivity of around 25% for stage 1 cancers and 50–70% for stage 2. The early stage sensitivity is significantly higher for some cancers, such as colorectal, head and neck and pancreatic (M. C. Liu et al., 2020).[46] The Galleri assay is currently being tested in a randomised controlled trial of 140 000 adults aged 50–77 in England, in partnership with the National Health Service.[47] Results from the initial phase are expected in 2023, with testing extended to a further one million people in 2024–2025 if successful.[48]

Other DNA methylation-based blood tests for cancer screening include the PanSeer test (Chen et al., 2020), a four gene methylation test for colorectal cancer developed by Zhang et al. (2021), and the Danish 'TriMeth' test (Jensen et al., 2019). The Lunar-2 colorectal cancer screening test from Guardant also relies on methylation profiling, together with ctDNA mutation detection and fragment analysis,[49] while the company Freenome has also developed a multi-omic blood test that is showing promising results in a prospective study for detecting advanced bowel cancers.[50]

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

A Canadian randomised controlled trial with more than 15 000 participants showed that S5 methylation testing of baseline cervical screening samples was able to identify women at increased risk of having cervical cancer with a lead time of months to years (Cook et al., 2019), with high sensitivity for CIN3. A smaller study in Finland showed that S5

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

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

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

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

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

methylation status predicted the presence of progressive precancer (CIN2), suggesting it could be a useful tool for identifying women at the highest risk of going on to develop cervical cancer and would therefore benefit from prompt treatment (Louvanto et al., 2020).

Overall, DNA methylation biomarkers in tissue and body fluids such as urine and sputum are robust with very good performance for detecting some cancers and precancers. However, while results from case-control studies of blood-based methylation testing are promising, the sensitivity is low for early-stage cancers compared with later stage disease, and the most convincing studies have used relatively large volumes of blood (around 30ml).

In addition to blood, researchers are investigating the potential of DNA methylation detection in other sample types. For example, there is considerable interest in the use of DNA methylation biomarkers in stool samples for colorectal cancer detection, particularly methylation at the SDC-2 gene (reviewed in (Gachabayov et al., 2021). Urinary DNA methylation markers are being investigated for staging of prostate cancer (Bakavicius et al., 2019), while research is ongoing to detect lung cancer through the presence of methylated DNA in urine (B. Liu et al., 2020) and sputum (Hulbert et al., 2017).

There are currently no published randomised controlled trials demonstrating that ctDNA methylation analysis is an effective screening test for early-stage cancer. However, large prospective trials are underway that will provide significantly more information in the near future. Questions remain as to whether randomised controlled trials are the most effective way of evaluating these kinds of approaches, particularly if they are likely to take many years to reach mortality endpoints, or whether an approach based ongoing evaluation during implementation trials will be appropriate, acceptable, safe and more efficient (see “Assessing and comparing novel cancer screening technologies”, p.95).

Circulating tumour cells

In addition to ctDNA, entire tumour cells can be shed into the bloodstream, known as circulating tumour cells (CTCs). Advances in single cell detection and analysis technologies means that it is now possible to detect CTCs in the blood (Keller & Pantel, 2019), raising the suggestion that this could be used as a way of screening for cancer. Tumour cells can also be detected in other body fluids, such as cerebrospinal fluid, urine, cyst fluid, saliva and bone marrow (Alix-Panabières & Pantel, 2021). Other types of tumour-related cells in the blood, such as endothelial cells, may also be informative about the presence of cancer within the body (Bertolini et al., 2006).

CTCs are rare, even in advanced cancer, typically occurring at a concentration of around 1 tumour cell per million blood cells. Despite the growing interest in detecting and analysing CTCs for molecular profiling of tumours and prognostic prediction (Alix-Panabières & Pantel, 2021; Pantel & Alix-Panabières, 2019), their low abundance limits their

usefulness in detecting early stage cancers unless more sensitive technologies become available.

Several techniques have been developed to enhance the sensitivity of CTC assays, such as the use of novel markers to improve enrichment. Other approaches aim to increase the number of CTCs in a sample by using larger volumes of blood (e.g. 50ml) or even whole blood analysis (leukapheresis), or through the use of *in vivo* 'sieves' to capture CTCs directly within blood vessels (Keller & Pantel, 2019). The feasibility of *in vivo* capture devices has been demonstrated in both lung and prostate cancer (Gorges et al., 2016; Kuske et al., 2016). The use of CTCs for early detection of cancer is being investigated in a number of studies in Europe, such as the Hamburg City Health Study — a biobank containing blood and other biological samples from 45 000 inhabitants of the city aged 45–74 (Jagodzinski et al., 2020).

A range of protein biomarkers in blood is also being explored for cancer screening. For example, the Cysteine-rich Angiogenic Inducer 61 (Cyr61) protein has been shown to be a potential blood biomarker for early stage breast and lung cancers (Ac Kar et al., 2021; Bartkowiak, Heidrich, et al., 2021), as well as asbestos-related diseases (Bartkowiak, Casjens, et al., 2021). Another promising biomarker is CD24, which is elevated in a range of different cancer types and could serve as a universal blood test for detecting cancer (Shapira et al., 2021).

4.2. Tissue biomarkers for cancer screening

In addition to blood-based tests, there is growing interest in the detection of biomarkers in other sample types as a cancer screening tool. Most of these are still at an experimental stage, although some have been tested in prospective studies and are already in clinical use in some countries. Biomarker panels tend to show better specificity in cancer detection than single markers. Because biomarker-based tests can be applied to samples from the relevant at-risk group based on age, sex and other risk factors such as smoking, they could be used to identify individuals with cancer or precancerous lesions that need further investigation.

For example, as discussed in section 2.3, faecal immunochemical stool testing (FIT) is widely used for bowel cancer screening. Addition of mutation and methylation markers to the detection of haemoglobin (Hb) in FIT can enhance the performance. One multi-target stool test (Cologuard) includes quantitative molecular assays for KRAS mutation, aberrant NDRG4 and BMP3 methylation, and ß-actin, plus the same Hb immunoassay used in FIT. In asymptomatic people at average risk for colorectal cancer, the Cologuard test has been shown to detected significantly more cancers than FIT but at the expense of

more false positive results and increased cost (Imperiale et al., 2014). Of all cancer types, biomarker-based detection of colorectal cancer is the most intensively studied, including genomic, epigenetic and protein markers detected in blood, stool, urine and tissue (Anghel et al., 2021).

The upper aero-digestive tract (mouth, nose, throat, oesophagus and windpipe) are highly accessible sites for direct or indirect tissue sampling for biomarker testing. For example, Mazzone et al. (2021) have shown that applying artificial intelligence analysis to whole transcriptome RNA sequencing of samples obtained from nasal brushings in current or ex-smokers can help to distinguish people with benign lung nodules from those with cancer, helping to reduce over-investigation of harmless growths.

In the oesophagus, novel non-endoscopic devices have recently been developed as an alternative to endoscopy for collecting samples that can be tested for evidence of the premalignant condition Barrett's oesophagus using immunohistochemical biomarkers and machine learning-assisted analysis (Fitzgerald et al., 2020; Gehrung et al., 2021). Another example of the use of biomarkers for detecting pre-cancerous changes is testing for cytokines in saliva for the early detection of oral cancer (Chiamulera et al., 2021) and the detection of volatile organic compounds (VOCs) in breath (Amor et al., 2019) — most notably as a sign of gastric cancer (see "Gastric cancer screening", p.74, and Haddad et al., 2020) and lung cancer (Jia et al., 2019).

Case study: Cytosponge for non-endoscopic oesophageal cancer screening

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

Initial studies reported on promising safety, acceptability and accuracy of the technology (Kadri et al., 2010; Ross-Innes, Becq, et al., 2015; Ross-Innes, Debiram-Beecham, et al., 2015; Ross-Innes et al., 2017). The randomised controlled BEST3 trial of the Cytosponge recruited more than 13 000 people over the age of 50 who were on current medication for heartburn and had not had an endoscopy for five years. These were ascertained from GP prescribing databases. Half received standard care, including antacid medications and endoscopy at their doctor's discretion, while the other half were offered the opportunity for Cytosponge-TFF3 screening.

Ten times more cases of Barrett's were identified in the Cytosponge arm compared with standard care in a per protocol analysis, including dysplasia and stage 1 carcinoma (Fitzgerald et al., 2020). The trial also showed that the test was highly acceptable, with 97% rating it as five or higher on a scale of 1–10 (worst to very enjoyable experience), comparing favourably against unsedated or sedated endoscopy. In order to support scale-up of Cytosponge pathology reporting, an AI-assisted tool has been developed and validated (Gehrung et al., 2021).

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

There is currently no data to show whether or not Cytosponge-TFF3 testing would reduce mortality from oesophageal adenocarcinoma, but such a trial (BEST4) will take place in the UK starting in 2023. Other non-endoscopic technologies are also emerging in this space, such as the Esochek balloon and the Mayo sponge on a string device, coupled with DNA methylation biomarker assays (Iyer et al., 2020; Moinova et al., 2018), although evidence is yet to come from randomised clinical trials in the screening setting.

4.3. Applications of AI in cancer screening

Advances in artificial intelligence (AI), machine learning (ML) and deep learning (DL) can contribute to cancer screening in many different ways, including molecular and genetic data analysis, imaging, risk assessment and stratification, identifying novel biomarkers and more (Iqbal et al., 2021; Savage, 2020). Computer-assisted screening technologies have huge potential for increasing the efficiency, accessibility and effectiveness of cancer screening while reducing the costs, as well as helping to relieve the pressure on screening services due to the COVID-19 pandemic (see "The impact of the COVID-19 pandemic on cancer screening", p.35).

However, any algorithm is only as good as the data it is trained on. There is significant potential for introducing bias and inequalities if training data is not sufficiently unbiased and diverse, and AI/ML tools are not independently validated in the population in which they are ultimately being used (Vokinger et al., 2021). The general consensus in the field is that these technologies are not quite ready for primetime, and must be robustly validated in the populations to be screened — and then adopted by screening services — in order to deliver impact (Venkatesan, 2021).

The application of AI/ML in cancer screening is a vast and rapidly growing field that cannot be captured within the scope of this report, so we have focused here on image analysis, one of the most mature applications relevant to screening.

Image analysis

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

Using AI/ML algorithms to analyse screening images could help to ease this backlog, with the aim of supporting clinicians and speeding up the diagnostic process rather than replacing them altogether. For example, because AI-based image analysis tools can assess an image in a matter of seconds, they could be used as an initial triage step to rule out scans that are very unlikely to have signs of cancer. AI could also be used to compare between multiple scans from the same person over time, in order to identify subtle changes that could potentially be early signs of cancer. AI/ML image analysis tools can also be hosted on cloud computing servers, making them accessible from anywhere in the world with an internet connection and the capacity to securely and legally transfer sufficient data.

However, there are currently a number of limitations and challenges to the use of AI/ML for image analysis in cancer diagnosis and screening (Bi et al., 2019). Any algorithm is only as good as the datasets it is trained on, which should be as large and unbiased as possible, and there is likely to be a need for ongoing training and validation.

There are also questions around how best to develop the regulatory frameworks and quality assurance of such new technologies that are inherently adaptable and change over time. AI-based systems must also be able to integrate with and 'talk to' existing healthcare IT infrastructure which varies widely between hospitals and healthcare systems and may often be outdated. They also need to be able to cope with all the different types of imaging machines and systems that are available.

In addition, image analysis algorithms are built for one purpose at a time, meaning an algorithm trained to identify the likely presence (or not) of lung cancer on a CT scan cannot identify any other important health issues that might be spotted by an expert radiologist, such as clogging of the heart arteries (coronary calcification) or pneumonia.

Research is ongoing to test the effectiveness of AI-based cancer screening tools and explore how best to embed them into routine screening and clinical care. For example, an algorithm trained on 42 290 lung CT scans performed at least as well as human

radiologists, with 11% fewer false positives and 5% fewer false negatives (Ardila et al., 2019). An international evaluation of an AI-based system for breast screening, trained on 121 455 images, also performed as well as humans, with 5.7% fewer false positives and 9.4% fewer false negatives (McKinney et al., 2020).

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

Progress is also being made in applying digital imaging tools and AI/ML to molecular and genetic biomarker analysis in a range of samples including tissue and blood (Lancellotti et al., 2021; Lau et al., 2021), as well as clinical images such as CT scans (Forghani et al., 2019). Another area where AI/ML-assisted image analysis technology may be useful is in screening for melanoma skin cancer — a disease that is highly curable if detected in its earliest stages as an abnormal mole but often fatal once it has spread through the body (Forsea, 2020). Combining novel imaging modalities with deep learning could support the early detection of abnormal skin lesions, while mobile technology offers the opportunity for remote screening and diagnosis (Young et al., 2021).

AI/ML is an area that is evolving fast and likely to be implemented for a range of clinical applications in the near future, including cancer screening. Ongoing dialogue is also needed with radiologists, technology companies and healthcare infrastructure providers to develop user-focused solutions that can be effectively validated and will work in practice to deliver more effective screening solutions that improve outcomes and reduce costs. Care should be taken when developing regulatory frameworks governing the use of AI/ML in medical technologies to ensure that they are sufficient to protect privacy and reduce the risk of harm, while not so restrictive that they prevent the realisation of benefits for public health and cost-effectiveness.

4.4. Assessing and comparing novel cancer screening technologies

There is a finite amount of money and resources available for the introduction of cancer screening programmes. Any potential new cancer screening test must therefore compete with existing healthcare practices and demonstrate equivalent or greater effectiveness, harm-to-benefit balance, equity and/or cost-effectiveness than current diagnosis and treatment pathways. Some screening technologies may be complementary and could be used in combination with existing or new technologies to improve the overall

effectiveness of a screening programme or tailor screening strategies for individuals depending on their personal risk profile.

Research into biomarker discovery and validation for cancer screening should draw on established roadmaps, such as the framework developed by the Early Detection Research Network, established by the US National Cancer Institute in 2000 to improve biomarker-based risk stratification and detection of early-stage cancers (Bast & Srivastava, 2020; Feng & Pepe, 2020; Srivastava & Wagner, 2020).

High quality prospective trials are still necessary to ensure quality and effectiveness, reduce false positives and harms, and demonstrate that a screening test is capable of detecting early-stage cancer at a point where intervention will lead to improved outcomes. The cost-effectiveness and practical implementation of any novel screening test should also be considered.

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

The fast-changing evidence landscape around cancer screening requires innovative thinking in terms of governance and guidelines, to ensure that populations can quickly benefit from the latest advances in research while avoiding possible harms caused by the premature introduction of procedures that have not been sufficiently tested. As well as innovations in screening technologies, there is also a need to design novel implementation research in such a way that robust real-world evidence can be collected in a timely fashion (see “Clinical trials for cancer screening”, p.106).

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

It is also important to engage screening technology companies as early as possible in the process developing and introducing trials of novel approaches to help ensure availability, cost-effectiveness, regulatory approval and quality assurance (for example, the GRAIL Galleri multi-cancer blood test screening trial being carried out in partnership with the National Health Service in England — see Chapter 4, p.84).

The establishment of appropriate and validated biobanks within the EU would be beneficial for creating large, well-characterised cohorts to support cancer screening research, particularly for investigating blood-based biomarkers and testing the effectiveness of new technologies.

More could also be done to ensure that appropriate consent is obtained from participants in cancer screening trials for novel technologies to ensure that biological samples are available for future research to enable more effective comparison between technologies. It should be ensured that potential biomarkers for cancer screening are validated across the whole population in which they will be used, including by age, sex and ethnic/genetic background.

4.5. Evidence-based policy options

- The development and clinical testing of blood-based cancer screening is progressing rapidly, and a close eye should be kept on the emerging evidence base and consensus framework to ensure that promising innovations can be moved forward into implementation studies in a timely way.
- Developing strategies to enable fair comparisons between the wide range of innovative screening approaches coming down the pipeline would benefit from further work and discussion, supported by EU funding.
- The establishment of appropriate and validated biobanks within the EU would be beneficial for cancer screening research, and any potential biomarkers for cancer screening should be validated by age, sex and ethnic/genetic background. These sample collections could also facilitate research into the causes and early steps of cancer development to inform evidence-based methods to diagnose life-threatening cancers at an early stage and avoid over-diagnosis.
- Ongoing discussion is needed around how to secure appropriate consent from participants in cancer screening trials for novel technologies to ensure that biological samples are available for future research within the constraints of data privacy legislation such as the General Data Protection Regulation.

Chapter 5. Implementation and governance of population-based screening programmes

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

5.1. Implementing new cancer screening programmes in the EU

The results of randomised clinical trials for a given cancer screening intervention are just the beginning of a long process that may or may not lead to its implementation. Clinical trials of cancer screening interventions cannot tell us exactly what will happen when a screening programme is adopted in the real world. There is therefore a need for further pilot implementation testing and quantified modelling to adjust for factors such as local demographics and risk distribution, participant uptake, test specificity under real world conditions, quality, the capacity of local and national health services and more.

When considering developing recommendations for implementing cancer screening across Europe, the varying demographic and economic situations of different countries must be taken into account. In addition to cost-effectiveness, the World Health

Organization recommends the following criteria for assessing the feasibility of adopting cancer screening programmes:[51]

- **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 healthcare 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

Furthermore, the changing evidence landscape around cancer screening requires innovative thinking in terms of governance and guidelines, to ensure that populations can quickly benefit from the latest advances in research while avoiding possible harms caused by the premature introduction of procedures that have not been sufficiently tested. For example, it is possible to design implementation research of new technologies in such a way that robust evidence can be collected. One way of doing this is through cluster randomised trials, where certain regions or municipalities trial the new approach while others do not. Another option is stepped wedge cluster randomised trials, which increases the number of clusters exposed to the new intervention over time (Hemming et al., 2015), or randomisation by birth cohort. In any such studies, the number of clusters should be high and the size kept small to minimise selection bias. Other types of studies such as sequential randomised trials may also be helpful.

There is a need to develop a set of principles for targeted and risk-stratified screening to help address these questions and move these innovations through to implementation. Building on this, we propose that countries should start rolling out screening innovations on a local level to gather real-world evidence that goes beyond the confines of a randomised controlled trial before scaling up to the whole population.

Effective, large-scale randomised controlled trials 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 expert teams are able to match the results from the large-scale trials in less tightly controlled settings.

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

Implementation and governance

Finally comes the full national or regional rollout, 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. Importantly, it should always be remembered that cancer screening programmes are not set in stone: they can be stopped or changed if real-world quality assurance and cost-effectiveness data shows that they are not performing as expected.

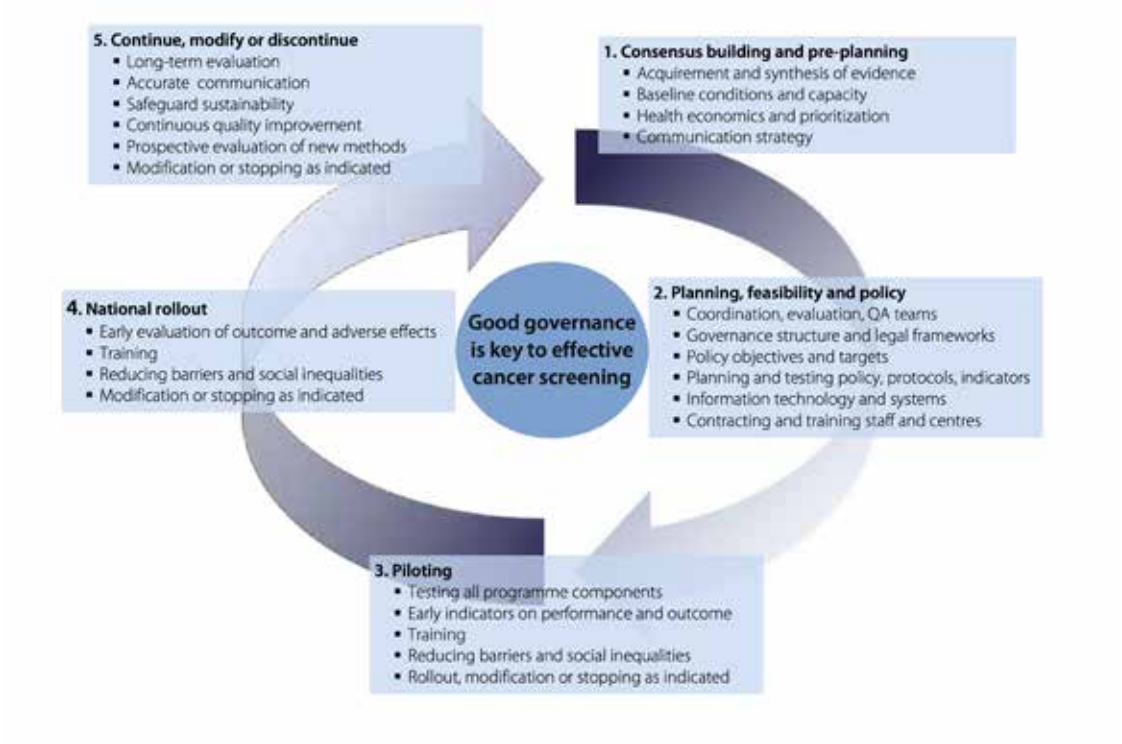

Figure 3. Steps required for the successful implementation of a population-based cancer screening programme (https://cancercontrol.eu/archived/guide-landing-page.html, reproduced with permission)

Screening programmes should also be integrated with other cancer prevention interventions, such as smoking cessation for lung cancer and HPV vaccination for cervical screening. Further exploration of 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.[52]

Alongside this, there is an ongoing need for greater widespread public engagement and communication about cancer in general and screening more specifically, in order to improve awareness of prevention and screening opportunities that are available at every stage of life.

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

Case study: Implementing lung cancer screening in England

Launched in 2019, one of the goals of the UK NHS Long Term Plan is to increase the proportion of cancers diagnosed early at stage 1 or 2 to 75%, with 55 000 more people surviving cancer for at least five years by 2028.[53] *As the most common cause of cancer death in the UK,*[54] *lung cancer is an obvious target for this aim.*

The large-scale randomised UK Lung Screening Trial (UKLS) of single LDCT screening in nearly 4 000 participants showed a 2.1% cancer detection rate. 86% of cancers were detected in stage 1 or 2, with an estimated incremental cost-effectiveness ratio, based on limited follow up period (ICER, the ratio of additional costs to additional health benefits) of around £8466 — an acceptable figure for a health intervention in the UK (Field et al., 2016, Field et al., 2021).

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 (Baldwin D. et al. in press).

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 for ex- and current smokers across England,[55] *along with a quality assurance standard framework covering skills and training, information and communication, and clinical delivery.*[56] *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 £71million was secured from NHS England to roll out targeted lung health checks over four years to people aged 55-74 who have ever smoked, with LDCT scanning being offered to those with a significant risk of lung cancer (Lebrett et al., 2020).*

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

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

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

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

5.2. Governance of national or regional cancer screening programmes

The European Guide on Quality Improvement in Comprehensive Cancer Control has produced a number of recommendations of the successful governance and implementation of national or regional cancer screening programmes (*European guide on quality improvement in comprehensive cancer control*, Albreht, Kiasuwa & Van den Bulcke, 2017):[57]

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

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 require ongoing political will and appropriate governance structures. Prioritisation of new cancer prevention interventions should be 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 one another 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 that are run within a given country should come under the umbrella of this screening board, sitting within the

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

ministry of health, in order to provide coherent oversight and funding, and to maintain close connections to health services.

5.3. Harmonising access, protocols and quality assurance for screening across the EU

Regulatory frameworks and procedures covering cancer screening differ widely across the EU member states — a lack of unification that may be a hindrance to public health. The disparities in cancer screening across Europe highlight the need for organisational structures dedicated to the assessment and implementation of cancer screening programmes at the EU level. 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 ongoing data-gathering to monitor and evaluate the quality, 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 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, van Ravesteyn, et al., 2021).[58] 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 in order to promote standardised, high-quality procedures (Sturdy et al., 2020).

58 https://eu-topia.org/

Reducing opportunistic cancer screening

A number of countries in Europe are offering opportunistic screening for diseases such as prostate and lung cancer (see Chapter 3, p.59), while screening for cancers that are covered by organised programmes in some EU member states may be offered on an ad hoc basis in those that do not have population-wide screening programmes in place.

These unorganised programmes represent a missed opportunity to gather data on the outcomes of screening and may not have sufficient monitoring and quality assurance in place to maximise benefits and minimise harms. Furthermore, ad hoc adoption of new screening 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.

We propose that cancer screening should only be carried out as part of an organised programme and that such opportunistic screening should either be stopped or only carried out with a commitment to gather such data and follow the existing guidelines.

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

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

Clinical and policy guidelines are typically updated infrequently (7–10 years), and are often outdated shortly after publication (Martínez García et al., 2014). Interim guidelines can address important developments, such as the replacement of cytology with HPV testing as the primary cervical cancer screening tool.

A longer-lasting alternative is the use of enduring or 'living' guidelines (see case study below), which can be updated more frequently and flexibly as the need arises. The process of updating these guidelines could be implemented by appointing expert scientific reviewers to continually assess and update the scientific evidence on screening as it emerges and make proposals to the European Commission as to whether or not specific guidelines should be modified. By having such an agreed framework in place for assessing innovative technologies, clinical and policy guidelines can be quickly updated to make the most of new opportunities to improve screening access and equity in a

timely manner while maintaining quality and avoiding harms such as the spontaneous adoption of unvalidated screening strategies.

Case study: Developing consensus 'living guidelines' for cervical screening in the US

The work leading to the development of the US Enduring Consensus Cervical Cancer Screening and Management Guidelines[59] *aimed to:*

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

Once a new technology is approved by the US FDA, it then goes to a risk assessment to see how it fits within the current clinical action thresholds, which have been previously determined by a consensus process. Next, the quality of studies supporting a new technology and certainty of risk estimates generated by it will be assessed, and if these thresholds are met then a vote will be taken about whether or not to adopt it. This data could come from clinical trials, high quality observational studies, medical record data and clinical consensus.

Different parts of this process are handled by separate groups — for example, the evidence around a particular technology and the validity of the risk estimates emerging from it are assessed by the NCI Technology and Risk Assessment Group, while a 20+ organisation Consensus Stakeholder Group comprising clinical societies, government/ regulatory and patient groups is responsible for prioritising and ratifying guidelines.

59 https://dceg.cancer.gov/research/cancer-types/cervix/enduring-guidelines

5.5. Further research required

There are a number of key themes in the field of cancer screening that would benefit from further research carried out within and supported by the EU.

Clinical trials for cancer screening

Questions remain about what the pathway should be from publication of the results of RCTs or other studies through to implementation and what kinds of evidence should be deemed sufficient to justify rollout on a regional or national scale (possibly including when or whether randomised controlled trials are always necessary).

There also needs to be consideration of appropriate intermediate outcome measures for screening studies, which can be lengthy and expensive, such as a reduction in the rate of cancers diagnosed at an advanced stage versus cancer-specific mortality. There is also an opportunity to move away from conventional two-arm trials and experiment with more adaptive multi-arm, multi-stage trial designs (Millen & Yap, 2020).

Age cut-off and eligibility

Cancer risk increases with age, so screening is more likely to detect cancer in older individuals. However, this must be balanced against the risks of treating the disease in very old people who are nearing the end of their lives or have other serious health conditions.

It is proposed that there should be an upper age limit on cancer screening at population level, because the number of cancers that will be found with no benefit for the individual will increase with age, yet this is currently an arbitrary cut-off. For example, the current age at which breast screening is stopped is 69 in some countries and 74 in others. Further research is needed to determine the age at which cancer screening should stop, and whether this should be the same for all individuals and cancer types.

More research is also needed to determine how individual risk profiles could be used to determine when to start or stop a particular type of screening, how this should be implemented and monitored in practice, and how this should be communicated to the public.

Cancer development and treatment

Finally, there is a need for research into the underlying biology and natural history of cancer to understand more about how the disease starts, grows and spreads, in order to develop more effective screening technologies and strategies, including risk stratification

approaches. While this process is well documented for some tumour types, such as cervical cancer, there are many gaps in our knowledge about other forms of the disease.

Continuing to fund fundamental biological research into cancer should be a priority for the EU, to help us discover more about the progression of cancer from its earliest stages to metastatic disease, in order to develop more effective screening methods that can detect cancer at an earlier, more treatable stage. There is also an urgent need for research aimed at distinguishing between slow growing, less dangerous tumours and aggressive, life-threatening cancers. At the same time, research is also needed into more effective, kinder treatments so that the full benefits of early diagnosis can be realised in terms of survival and quality of life.

5.6. Evidence-based policy options and conclusions

- Recommendations at EU level on the implementation of new cancer screening programmes could strongly influence decisions of individual EU Member States to ensure uniformity, quality, and equity for all citizens.
- Formal coordination of different cancer screening/prevention programmes in all phases across the EU could ensure continuity of knowledge and experience, rational use of resources, operational readiness and optimal integration with the existing healthcare system.
- Implementing new screening tests and strategies could be done through small scale local pilot trials, potentially as randomised cluster trials, sequential randomised trials or with well-defined data registry in screened and unscreened areas, before rolling out on a national or regional level.
- There is a need for cancer screening to be carried out as part of an organised programme. It is preferable for opportunistic screening to be stopped or only carried out with a commitment to gather data on quality and effectiveness.
- More research is needed to ascertain the appropriate age at which to stop each type of cancer screening in order to maximise benefits and minimise harms.
- There is a need at the EU level for permanent structures and guidelines dedicated to the assessment and implementation of cancer screening programmes, including continuous evidence review and updating of screening criteria, recommendations and standards to take advantage of new advances, and a move towards living guidelines to ensure ongoing implementation of optimal screening strategies.
- There needs to be a commitment to ongoing data-gathering to monitor and evaluate the performance and quality cancer screening (including ad hoc unorganised screening), with Europe-wide reporting and information sharing, to ensure that benefits are maximised and harms minimised.

Implementation and governance

- A lack of clear understanding persists regarding how cancer screening is organised and governed in different countries, and more work could be done in order to facilitate formal and informal sharing and learning around the social, as well as the technical aspects of screening governance.
- The EU could consider continuing to fund and participate in research aimed at understanding how cancer starts, grows and spreads, and how best to treat it, in order to develop more effective cancer screening technologies and strategies.
- The EU could consider continuing to fund and participate in research to evaluate promising, new screening technologies so that it can help to address EU-specific issues and be at the forefront of adoption when the time is right.

References

19th International Meeting of the European Society of Gynecological Oncology (ESGO 2015). (2015). International Journal of Gynecologic Cancer, 25(Supp 2), 1. https://doi.org/10.1097/01.IGC.0000473498.85773.6e

Ac Kar, L., Casjens, S., Andreas, A., Raiko, I., Brüning, T., Geffken, M., Peine, S., Kollmeier, J., Johnen, G., Bartkowiak, K., Weber, D. G., & Pantel, K. (2021). Blood-based detection of lung cancer using cysteine-rich angiogenic inducer 61 (CYR61) as a circulating protein biomarker: A pilot study. Molecular Oncology, 15(11), 2877–2890. https://doi.org/10.1002/1878-0261.13099

Alix-Panabières, C., & Pantel, K. (2021). Liquid Biopsy: From Discovery to Clinical Application. Cancer Discovery, 11(4), 858–873. https://doi.org/10.1158/2159-8290.CD-20-1311

Allison, J. E., & Fraser, C. G. (2018). The importance of comparing quantitative faecal immunochemical tests (FIT) before selecting one for a population-based colorectal cancer screening programme. Journal of Laboratory and Precision Medicine, 3(1), Article 1. https://jlpm.amegroups.com/article/view/3984

Amant, F., Verheecke, M., Wlodarska, I., Dehaspe, L., Brady, P., Brison, N., Van Den Bogaert, K., Dierickx, D., Vandecaveye, V., Tousseyn, T., Moerman, P., Vanderstichele, A., Vergote, I., Neven, P., Berteloot, P., Putseys, K., Danneels, L., Vandenberghe, P., Legius, E., & Vermeesch, J. R. (2015). Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing. JAMA Oncology, 1(6), 814–819. https://doi.org/10.1001/jamaoncol.2015.1883

Amor, R. E., Nakhleh, M. K., Barash, O., & Haick, H. (2019). Breath analysis of cancer in the present and the future. European Respiratory Review, 28(152). https://doi.org/10.1183/16000617.0002-2019

Anghel, S. A., Ioniță-Mîndrican, C.-B., Luca, I., & Pop, A. L. (2021). Promising Epigenetic Biomarkers for the Early Detection of Colorectal Cancer: A Systematic Review. Cancers, 13(19), 4965. https://doi.org/10.3390/cancers13194965

Arbyn, M., Bruni, L., Kelly, D., Basu, P., Poljak, M., Gultekin, M., Bergeron, C., Ritchie, D., & Weiderpass, E. (2020). Tackling cervical cancer in Europe amidst the COVID-19 pandemic. The Lancet Public Health, 5(8), e425. https://doi.org/10.1016/S2468-2667(20)30122-5

Arbyn, M., Peeters, E., Benoy, I., Vanden Broeck, D., Bogers, J., De Sutter, P., Donders, G., Tjalma, W., Weyers, S., Cuschieri, K., Poljak, M., Bonde, J., Cocuzza, C., Zhao, F. H., Van Keer, S., & Vorsters, A. (2018). VALHUDES: A protocol for validation of human papillomavirus assays and collection devices for HPV testing on self-samples and urine samples. Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology, 107, 52–56. https://doi.org/10.1016/j.jcv.2018.08.006

Arbyn, M., Ronco, G., Anttila, A., Meijer, C. J. L. M., Poljak, M., Ogilvie, G., Koliopoulos, G., Naucler, P., Sankaranarayanan, R., & Peto, J. (2012). Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine, 30 Suppl 5, F88-99. https://doi.org/10.1016/j.vaccine.2012.06.095

Arbyn, M., Simon, M., Peeters, E., Xu, L., Meijer, C. J. L. M., Berkhof, J., Cuschieri, K., Bonde, J., Vanlencak, A. O., Zhao, F.-H., Rezhake, R., Gultekin, M., Dillner, J., Sanjosé, S. de, Canfell, K., Hillemanns, P., Almonte, M., Wentzensen, N., & Poljak, M. (2021). 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. Clinical Microbiology and Infection, 27(8), 1083–1095. https://doi.org/10.1016/j.cmi.2021.04.031

Arbyn, M., Smith, S. B., Temin, S., Sultana, F., & Castle, P. (2018). Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: Updated meta-analyses. BMJ, 363, k4823. https://doi.org/10.1136/bmj.k4823

Arbyn, M., Weiderpass, E., Bruni, L., Sanjosé, S. de, Saraiya, M., Ferlay, J., & Bray, F. (2020). Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. The Lancet Global Health, 8(2),

e191–e203. https://doi.org/10.1016/S2214-109X(19)30482-6

Ardila, D., Kiraly, A. P., Bharadwaj, S., Choi, B., Reicher, J. J., Peng, L., Tse, D., Etemadi, M., Ye, W., Corrado, G., Naidich, D. P., & Shetty, S. (2019). End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nature Medicine, 25(6), 954–961. https://doi.org/10.1038/s41591-019-0447-x

Armaroli, P., Riggi, E., Basu, P., Anttila, A., Ponti, A., Carvalho, A. L., Dillner, J., Elfström, M. K., Giordano, L., Lönnberg, S., Ronco, G., Senore, C., Soerjomataram, I., Tomatis, M., Vale, D. B., Jarm, K., Sankaranarayanan, R., & Segnan, N. (2020). Performance indicators in breast cancer screening in the European Union: A comparison across countries of screen positivity and detection rates. International Journal of Cancer, 147(7), 1855–1863. https://doi.org/10.1002/ijc.32968

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

Atkin, W. S., Edwards, R., Kralj-Hans, I., Wooldrage, K., Hart, A. R., Northover, J. M., Parkin, D. M., Wardle, J., Duffy, S. W., & Cuzick, J. (2010). Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: A multicentre randomised controlled trial. The Lancet, 375(9726), 1624–1633. https://doi.org/10.1016/S0140-6736(10)60551-X

Bakavicius, A., Daniunaite, K., Zukauskaite, K., Barisiene, M., Jarmalaite, S., & Jankevicius, F. (2019). Urinary DNA methylation biomarkers for prediction of prostate cancer upgrading and upstaging. Clinical Epigenetics, 11(1), 115. https://doi.org/10.1186/s13148-019-0716-z

Bakker, M. F., de Lange, S. V., Pijnappel, R. M., Mann, R. M., Peeters, P. H. M., Monninkhof, E. M., Emaus, M. J., Loo, C. E., Bisschops, R. H. C., Lobbes, M. B. I., de Jong, M. D. F., Duvivier, K. M., Veltman, J., Karssemeijer, N., de Koning, H. J., van Diest, P. J., Mali, W. P. T. M., van den Bosch, M. A. A. J., Veldhuis, W. B., & van Gils, C. H. (2019). Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. New England Journal of Medicine, 381(22), 2091–2102. https://doi.org/10.1056/NEJMoa1903986

Balata, H., Ruparel, M., O'Dowd, E., Ledson, M., Janes, S., Booton, R., Baldwin, D., & Crosbie, P. (2021). MA05.06 Lung Cancer Screening – Cumulative Results from Five UK-Based Programmes. Journal of Thoracic Oncology, 16(3), S149. https://doi.org/10.1016/j.jtho.2021.01.169

Banila, C., Lorincz, A. T., Scibior-Bentkowska, D., Clifford, G. M., Kumbi, B., Beyene, D., Wheeler, C. M., Cuschieri, K., Cuzick, J., & Nedjai, B. (n.d.). Clinical performance of methylation as a biomarker for cervical carcinoma in situ and cancer diagnosis: A worldwide study. International Journal of Cancer, n/a(n/a). https://doi.org/10.1002/ijc.33815

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

Bartkowiak, K., Casjens, S., Andreas, A., Ačkar, L., Joosse, S. A., Raiko, I., Brüning, T., Geffken, M., Peine, S., Johnen, G., Weber, D. G., & Pantel, K. (2021). Sensitive Blood-Based Detection of Asbestos-Associated Diseases Using Cysteine-Rich Angiogenic Inducer 61 as Circulating Protein Biomarker. Clinical Chemistry, 67(2), 363–373. https://doi.org/10.1093/clinchem/hvaa232

Bartkowiak, K., Heidrich, I., Kwiatkowski, M., Banys-Paluchowski, M., Andreas, A.,

Wurlitzer, M., Geffken, M., Voß, H., Zeller, T., Blankenberg, S., Peine, S., Joosse, S. A., Müller, V., Schlüter, H., Oliveira-Ferrer, L., & Pantel, K. (2021). Circulating Cellular Communication Network Factor 1 Protein as a Sensitive Liquid Biopsy Marker for Early Detection of Breast Cancer. Clinical Chemistry, hvab153. https://doi.org/10.1093/clinchem/hvab153

Bast, R. C., & Srivastava, S. (2020). The National Cancer Institute Early Detection Research Network: Two Decades of Progress. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 29(12), 2396–2400. https://doi.org/10.1158/1055-9965.EPI-20-1158

Basu, P., Ponti, A., Anttila, A., Ronco, G., Senore, C., Vale, D. B., Segnan, N., Tomatis, M., Soerjomataram, I., Primic Žakelj, M., Dillner, J., Elfström, K. M., Lönnberg, S., & Sankaranarayanan, R. (2018). Status of implementation and organization of cancer screening in The European Union Member States—Summary results from the second European screening report. International Journal of Cancer, 142(1), 44–56. https://doi.org/10.1002/ijc.31043

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

Benaglia, T., Sharples, L. D., Fitzgerald, R. C., & Lyratzopoulos, G. (2013). Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. Gastroenterology, 144(1), 62-73.e6. https://doi.org/10.1053/j.gastro.2012.09.060

Bergh, K. A. M. van den, Essink-Bot, M. L., Borsboom, G. J. J. M., Scholten, E. T., Klaveren, R. J. van, & Koning, H. J. de. (2011). Long-term effects of lung cancer computed tomography screening on health-related quality of life: The NELSON trial. European Respiratory Journal, 38(1), 154–161. https://doi.org/10.1183/09031936.00123410

Bertolini, F., Shaked, Y., Mancuso, P., & Kerbel, R. S. (2006). The multifaceted circulating endothelial cell in cancer: Towards marker and target identification. Nature Reviews Cancer, 6(11), 835–845. https://doi.org/10.1038/nrc1971

Bettegowda, C., Sausen, M., Leary, R. J., Kinde, I., Wang, Y., Agrawal, N., Bartlett, B. R., Wang, H., Luber, B., Alani, R. M., Antonarakis, E. S., Azad, N. S., Bardelli, A., Brem, H., Cameron, J. L., Lee, C. C., Fecher, L. A., Gallia, G. L., Gibbs, P., … Diaz, L. A. (2014). Detection of circulating tumor DNA in early- and late-stage human malignancies. Science Translational Medicine, 6(224), 224ra24. https://doi.org/10.1126/scitranslmed.3007094

Bhat, S., Coleman, H. G., Yousef, F., Johnston, B. T., McManus, D. T., Gavin, A. T., & Murray, L. J. (2011). Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study. JNCI: Journal of the National Cancer Institute, 103(13), 1049–1057. https://doi.org/10.1093/jnci/djr203

Bi, W. L., Hosny, A., Schabath, M. B., Giger, M. L., Birkbak, N. J., Mehrtash, A., Allison, T., Arnaout, O., Abbosh, C., Dunn, I. F., Mak, R. H., Tamimi, R. M., Tempany, C. M., Swanton, C., Hoffmann, U., Schwartz, L. H., Gillies, R. J., Huang, R. Y., & Aerts, H. J. W. L. (2019). Artificial intelligence in cancer imaging: Clinical challenges and applications. CA: A Cancer Journal for Clinicians, 69(2), 127–157. https://doi.org/10.3322/caac.21552

Bianchi, D. W., Chudova, D., Sehnert, A. J., Bhatt, S., Murray, K., Prosen, T. L., Garber, J. E., Wilkins-Haug, L., Vora, N. L., Warsof, S., Goldberg, J., Ziainia, T., & Halks-Miller, M. (2015). Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies. JAMA, 314(2), 162–169. https://doi.org/10.1001/jama.2015.7120

Bjurstam, N. G., Björneld, L. M., & Duffy, S. W. (2016). Updated results of the Gothenburg Trial of Mammographic Screening. Cancer, 122(12), 1832–1835. https://doi.org/10.1002/cncr.29975

Black, W. C., Gareen, I. F., Soneji, S. S., Sicks, J. D., Keeler, E. B., Aberle, D. R., Naeim, A., Church, T. R., Silvestri, G. A., Gorelick, J., & Gatsonis, C. (2014, November 5). Cost-Effectiveness of CT Screening in the National Lung Screening Trial (world) [Research-article]. Http://Dx.Doi.Org/10.1056/NEJMoa1312547; Massachusetts Medical Society. https://doi.org/10.1056/NEJMoa1312547

Blom, J., Löwbeer, C., Elfström, K. M., Sventelius, M., Öhman, D., Saraste, D., & Törnberg, S. (2019). Gender-specific cut-offs in colorectal cancer screening with FIT: Increased compliance and equal positivity rate. Journal of Medical Screening, 26(2), 92–97. https://doi.org/10.1177/0969141318804843

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

Booth, N., Rissanen, P., Tammela, T. L. J., Taari, K., Talala, K., & Auvinen, A. (2018). Costs of screening for prostate cancer: Evidence from the Finnish Randomised Study of Screening for Prostate Cancer after 20-year follow-up using register data. European Journal of Cancer, 93, 108–118. https://doi.org/10.1016/j.ejca.2018.01.111

Bosch, F. X., Robles, C., Díaz, M., Arbyn, M., Baussano, I., Clavel, C., Ronco, G., Dillner, J., Lehtinen, M., Petry, K.-U., Poljak, M., Kjaer, S. K., Meijer, C. J. L. M., Garland, S. M., Salmerón, J., Castellsagué, X., Bruni, L., de Sanjosé, S., & Cuzick, J. (2016). HPV-FASTER: Broadening the scope for prevention of HPV-related cancer. Nature Reviews Clinical Oncology, 13(2), 119–132. https://doi.org/10.1038/nrclinonc.2015.146

Bourmaud, A., Soler-Michel, P., Oriol, M., Regnier, V., Tinquaut, F., Nourissat, A., Bremond, A., Moumjid, N., & Chauvin, F. (2016). Decision aid on breast cancer screening reduces attendance rate: Results of a large-scale, randomized, controlled study by the DECIDEO group. Oncotarget, 7(11), 12885–12892. https://doi.org/10.18632/oncotarget.7332

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

Brenner, H., Haug, U., & Hundt, S. (2010). Sex differences in performance of fecal occult blood testing. The American Journal of Gastroenterology, 105(11), 2457–2464. https://doi.org/10.1038/ajg.2010.301

Brenner, H., Kloor, M., & Pox, C. P. (2014). Colorectal cancer. Lancet (London, England), 383(9927), 1490–1502. https://doi.org/10.1016/S0140-6736(13)61649-9

Brooks, J. D., Nabi, H. H., Andrulis, I. L., Antoniou, A. C., Chiquette, J., Després, P., Devilee, P., Dorval, M., Droit, A., Easton, D. F., Eisen, A., Eloy, L., Fienberg, S., Goldgar, D., Hahnen, E., Joly, Y., Knoppers, B. M., Lofters, A., Masson, J.-Y., … Simard, J. (2021). Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I). Journal of Personalized Medicine, 11(6), 511. https://doi.org/10.3390/jpm11060511

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

Buron, A., Román, M., Augé, J. M., Macià, F., Grau, J., Sala, M., Louro, J., Martinez-Alonso, M., Alvarez-Urturi, C., Andreu, M., Bessa, X., Zaffalon, D., Castells, A., Pellisé, M., Aldea, M., Rivero, L., Hernández, C., Torá-Rocamora, I., & Castells, X. (2019). Changes in FIT values below the threshold of positivity and short-term risk of advanced colorectal neoplasia: Results from a population-based cancer screening program. European Journal of Cancer, 107, 53–59. https://doi.org/10.1016/j.ejca.2018.11.004

Buskermolen, M., Cenin, D. R., Helsingen, L. M., Guyatt, G., Vandvik, P. O., Haug, U., Bretthauer, M., & Lansdorp-Vogelaar, I. (2019). Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: A microsimulation modelling study. BMJ, 367, l5383. https://doi.org/10.1136/bmj.l5383

Butler, S. S., Muralidhar, V., Zhao, S. G., Sanford, N. N., Franco, I., Fullerton, Z. H., Chavez, J., D'Amico, A. V., Feng, F. Y., Rebbeck, T. R., Nguyen, P. L., & Mahal, B. A. (2020). Prostate cancer incidence across stage,

NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate-specific antigen screening in 2012. Cancer, 126(4), 717–724. https://doi.org/10.1002/cncr.32604

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

Callender, T., Emberton, M., Morris, S., Eeles, R., Kote-Jarai, Z., Pharoah, P. D. P., & Pashayan, N. (2019). Polygenic risk-tailored screening for prostate cancer: A benefit–harm and cost-effectiveness modelling study. PLOS Medicine, 16(12), e1002998. https://doi.org/10.1371/journal.pmed.1002998

Callender, T., Emberton, M., Morris, S., Pharoah, P. D. P., & Pashayan, N. (2021). Benefit, Harm, and Cost-effectiveness Associated With Magnetic Resonance Imaging Before Biopsy in Age-based and Risk-stratified Screening for Prostate Cancer. JAMA Network Open, 4(3), e2037657. https://doi.org/10.1001/jamanetworkopen.2020.37657

Canelo, C., Posso, M., Pacheco, K., Tapia, E., & Alonso-Coello, P. (2018). PRM129 - DECISION ANALYTIC MODELS TO INFORM ABOUT THE OPTIMAL MAMMOGRAPHY SCREENING INTERVALS: A SYSTEMATIC REVIEW. Value in Health, 21, S378. https://doi.org/10.1016/j.jval.2018.09.2249

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

Cardoso, R., Guo, F., Heisser, T., Hackl, M., Ihle, P., De Schutter, H., Van Damme, N., Valerianova, Z., Atanasov, T., Májek, O., Mužík, J., Nilbert, M. C., Tybjerg, A. J., Innos, K., Mägi, M., Malila, N., Bouvier, A.-M., Bouvier, V., Launoy, G., … Brenner, H. (2021). Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: An international population-based study. The Lancet. Oncology, 22(7), 1002–1013. https://doi.org/10.1016/S1470-2045(21)00199-6

Carethers, J. M. (2020). Fecal DNA Testing for Colorectal Cancer Screening. Annual Review of Medicine, 71, 59–69. https://doi.org/10.1146/annurev-med-103018-123125

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

Caumo, F., Zorzi, M., Brunelli, S., Romanucci, G., Rella, R., Cugola, L., Bricolo, P., Fedato, C., Montemezzi, S., & Houssami, N. (2018). Digital Breast Tomosynthesis with Synthesized Two-Dimensional Images versus Full-Field Digital Mammography for Population Screening: Outcomes from the Verona Screening Program. Radiology, 287(1), 37–46. https://doi.org/10.1148/radiol.2017170745

Centers for Disease Control and Prevention (2014). Deaths: Final data for 2011. Vol 63. Hyattsville, MD: National Center for Health Statistics.

Chan, K. C. A., Woo, J. K. S., King, A., Zee, B. C. Y., Lam, W. K. J., Chan, S. L., Chu, S. W. I., Mak, C., Tse, I. O. L., Leung, S. Y. M., Chan, G., Hui, E. P., Ma, B. B. Y., Chiu, R. W. K., Leung, S.-F., van Hasselt, A. C., Chan, A. T. C., & Lo, Y. M. D. (2017). Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer. New England Journal of Medicine, 377(6), 513–522. https://doi.org/10.1056/NEJMoa1701717

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

Chen, L.-S., Yen, A. M.-F., Chiu, S. Y.-H., Liao, C.-S., & Chen, H.-H. (2011). Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: Longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. The Lancet Oncology,

12(6), 551–558. https://doi.org/10.1016/S1470-2045(11)70101-2

Chen, X., Gole, J., Gore, A., He, Q., Lu, M., Min, J., Yuan, Z., Yang, X., Jiang, Y., Zhang, T., Suo, C., Li, X., Cheng, L., Zhang, Z., Niu, H., Li, Z., Xie, Z., Shi, H., Zhang, X., … Jin, L. (2020). Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. Nature Communications, 11(1), 3475. https://doi.org/10.1038/s41467-020-17316-z

Chesson, H. W., Dunne, E. F., Hariri, S., & Markowitz, L. E. (2014). The Estimated Lifetime Probability of Acquiring Human Papillomavirus in the United States. Sexually Transmitted Diseases, 41(11), 660–664. https://doi.org/10.1097/OLQ.0000000000000193

Chiamulera, M. M. A., Zancan, C. B., Remor, A. P., Cordeiro, M. F., Gleber-Netto, F. O., & Baptistella, A. R. (2021). Salivary cytokines as biomarkers of oral cancer: A systematic review and meta-analysis. BMC Cancer, 21(1), 205. https://doi.org/10.1186/s12885-021-07932-3

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

Cohen, E. O., Tso, H. H., Phalak, K. A., Mayo, R. C., & Leung, J. W. T. (2018). Screening Mammography Findings From One Standard Projection Only in the Era of Full-Field Digital Mammography and Digital Breast Tomosynthesis. AJR. American Journal of Roentgenology, 211(2), 445–451. https://doi.org/10.2214/AJR.17.19023

Cohen, J. D., Douville, C., Dudley, J. C., Mog, B. J., Popoli, M., Ptak, J., Dobbyn, L., Silliman, N., Schaefer, J., Tie, J., Gibbs, P., Tomasetti, C., Papadopoulos, N., Kinzler, K. W., & Vogelstein, B. (2021). Detection of low-frequency DNA variants by targeted sequencing of the Watson and Crick strands. Nature Biotechnology, 39(10), 1220–1227. https://doi.org/10.1038/s41587-021-00900-z

Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., Douville, C., Javed, A. A., Wong, F., Mattox, A., Hruban, Ralph. H., Wolfgang, C. L., Goggins, M. G., Molin, M. D., Wang, T.-L., Roden, R., Klein, A. P., Ptak, J., Dobbyn, L., … Papadopoulos, N. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science (New York, N.Y.), 359(6378), 926–930. https://doi.org/10.1126/science.aar3247

Coldman, A., Phillips, N., Wilson, C., Decker, K., Chiarelli, A. M., Brisson, J., Zhang, B., Payne, J., Doyle, G., & Ahmad, R. (2014). Pan-Canadian study of mammography screening and mortality from breast cancer. Journal of the National Cancer Institute, 106(11), dju261. https://doi.org/10.1093/jnci/dju261

Comstock, C. E., Gatsonis, C., Newstead, G. M., Snyder, B. S., Gareen, I. F., Bergin, J. T., Rahbar, H., Sung, J. S., Jacobs, C., Harvey, J. A., Nicholson, M. H., Ward, R. C., Holt, J., Prather, A., Miller, K. D., Schnall, M. D., & Kuhl, C. K. (2020). Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women With Dense Breasts Undergoing Screening. JAMA, 323(8), 746–756. https://doi.org/10.1001/jama.2020.0572

Connors, D., Allen, J., Alvarez, J. D., Boyle, J., Cristofanilli, M., Hiller, C., Keating, S., Kelloff, G., Leiman, L., McCormack, R., Merino, D., Morgan, E., Pantel, K., Rolfo, C., Serrano, M. J., Pia Sanzone, A., Schlange, T., Sigman, C., & Stewart, M. (2020). International liquid biopsy standardization alliance white paper. Critical Reviews in Oncology/Hematology, 156, 103112. https://doi.org/10.1016/j.critrevonc.2020.103112

Cook, D. A., Krajden, M., Brentnall, A. R., Gondara, L., Chan, T., Law, J. H., Smith, L. W., van Niekerk, D. J., Ogilvie, G. S., Coldman, A. J., Warman, R., Reuter, C., Cuzick, J., & Lorincz, A. T. (2019). Evaluation of a validated methylation triage signature for human papillomavirus positive women in the HPV FOCAL cervical cancer screening trial. International Journal of Cancer, 144(10), 2587–2595. https://doi.org/10.1002/ijc.31976

Cristiano, S., Leal, A., Phallen, J., Fiksel, J., Adleff, V., Bruhm, D. C., Jensen, S. Ø., Medina, J. E., Hruban, C., White, J. R., Palsgrove, D. N., Niknafs, N., Anagnostou, V.,

Forde, P., Naidoo, J., Marrone, K., Brahmer, J., Woodward, B. D., Husain, H., … Velculescu, V. E. (2019). Genome-wide cell-free DNA fragmentation in patients with cancer. Nature, 570(7761), 385–389. https://doi.org/10.1038/s41586-019-1272-6

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

Davidović, M., Zielonke, N., Lansdorp-Vogelaar, I., Segnan, N., de Koning, H. J., & Heijnsdijk, E. A. (2021). Disability-Adjusted Life Years Averted Versus Quality-Adjusted Life Years Gained: A Model Analysis for Breast Cancer Screening. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 24(3), 353–360. https://doi.org/10.1016/j.jval.2020.10.018

de Koning, H. J., Boer, R., Warmerdam, P. G., Beemsterboer, P. M., & van der Maas, P. J. (1995). Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials. Journal of the National Cancer Institute, 87(16), 1217–1223. https://doi.org/10.1093/jnci/87.16.1217

de Koning, H. J., Gulati, R., Moss, S. M., Hugosson, J., Pinsky, P. F., Berg, C. D., Auvinen, A., Andriole, G. L., Roobol, M. J., Crawford, E. D., Nelen, V., Kwiatkowski, M., Zappa, M., Luján, M., Villers, A., de Carvalho, T. M., Feuer, E. J., Tsodikov, A., Mariotto, A. B., … Etzioni, R. (2018). The efficacy of prostate-specific antigen screening: Impact of key components in the ERSPC and PLCO trials. Cancer, 124(6), 1197–1206. https://doi.org/10.1002/cncr.31178

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

De Pauw, H., Donders, G., Weyers, S., De Sutter, P., Doyen, J., Tjalma, W. A. A., Vanden Broeck, D., Peeters, E., Van Keer, S., Vorsters, A., & Arbyn, M. (2021). Cervical cancer screening using HPV tests on self-samples: Attitudes and preferences of women participating in the VALHUDES study. Archives of Public Health, 79(1), 155. https://doi.org/10.1186/s13690-021-00667-4

De Prez, V., Jolidon, V., Willems, B., Cullati, S., Burton-Jeangros, C., & Bracke, P. (2020). Cervical cancer (over)screening in Belgium and Switzerland: Trends and social inequalities. European Journal of Public Health, 30(3), 552–557. https://doi.org/10.1093/eurpub/ckaa041

de Wijkerslooth, T. R., Stoop, E. M., Bossuyt, P. M., Meijer, G. A., van Ballegooijen, M., van Roon, A. H. C., Stegeman, I., Kraaijenhagen, R. A., Fockens, P., van Leerdam, M. E., Dekker, E., & Kuipers, E. J. (2012). Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. The American Journal of Gastroenterology, 107(10), 1570–1578. https://doi.org/10.1038/ajg.2012.249

den Dekker, B. M., Bakker, M. F., de Lange, S. V., Veldhuis, W. B., van Diest, P. J., Duvivier, K. M., Lobbes, M. B. I., Loo, C. E., Mann, R. M., Monninkhof, E. M., Veltman, J., Pijnappel, R. M., van Gils, C. H., van Gils, C. H., Bakker, M. F., de Lange, S. V., Veenhuizen, S. G. A., Veldhuis, W. B., Pijnappel, R. M., … de Koning, H. J. (2021). Reducing False-Positive Screening MRI Rate in Women with Extremely Dense Breasts

Using Prediction Models Based on Data from the DENSE Trial. Radiology, 301(2), 283–292. https://doi.org/10.1148/radiol.2021210325

Digby, J., Fraser, C. G., Carey, F. A., Diament, R. H., Balsitis, M., & Steele, R. J. (2017). Faecal haemoglobin concentration is related to detection of advanced colorectal neoplasia in the next screening round. Journal of Medical Screening, 24(2), 62–68. https://doi.org/10.1177/0969141316653983

Dillner, J., Rebolj, M., Birembaut, P., Petry, K.-U., Szarewski, A., Munk, C., Sanjose, S. de, Naucler, P., Lloveras, B., Kjaer, S., Cuzick, J., Ballegooijen, M. van, Clavel, C., & Iftner, T. (2008). Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study. BMJ, 337, a1754. https://doi.org/10.1136/bmj.a1754

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

Douville, C., Cohen, J. D., Ptak, J., Popoli, M., Schaefer, J., Silliman, N., Dobbyn, L., Schoen, R. E., Tie, J., Gibbs, P., Goggins, M., Wolfgang, C. L., Wang, T.-L., Shih, I.-M., Karchin, R., Lennon, A. M., Hruban, R. H., Tomasetti, C., Bettegowda, C., … Vogelstein, B. (2020). Assessing aneuploidy with repetitive element sequencing. Proceedings of the National Academy of Sciences of the United States of America, 117(9), 4858–4863. https://doi.org/10.1073/pnas.1910041117

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

Duffy, S. W., Vulkan, D., Cuckle, H., Parmar, D., Sheikh, S., Smith, R. A., Evans, A., Blyuss, O., Johns, L., Ellis, I. O., Myles, J., Sasieni, P. D., & Moss, S. M. (2020). Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): Final results of a randomised, controlled trial. The Lancet Oncology, 21(9), 1165–1172. https://doi.org/10.1016/S1470-2045(20)30398-3

Dullens, B., de Putter, R., Lambertini, M., Toss, A., Han, S., Van Nieuwenhuysen, E., Van Gorp, T., Vanderstichele, A., Van Ongeval, C., Keupers, M., Prevos, R., Celis, V., Dekervel, J., Everaerts, W., Wildiers, H., Nevelsteen, I., Neven, P., Timmerman, D., Smeets, A., … Punie, K. (2020). Cancer Surveillance in Healthy Carriers of Germline Pathogenic Variants in BRCA1/2: A Review of Secondary Prevention Guidelines. Journal of Oncology, 2020, 9873954. https://doi.org/10.1155/2020/9873954

Dyba, T., Randi, G., Bray, F., Martos, C., Giusti, F., Nicholson, N., Gavin, A., Flego, M., Neamtiu, L., Dimitrova, N., Negrão Carvalho, R., Ferlay, J., & Bettio, M. (2021). The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. European Journal of Cancer, 157, 308–347. https://doi.org/10.1016/j.ejca.2021.07.039

Edvardsson, H., Wang, J., Andrae, B., Sparén, P., Strander, B., & Dillner, J. (2021). Nationwide Rereview of Normal Cervical Cytologies before High-Grade Cervical Lesions or before Invasive Cervical Cancer. Acta Cytologica, 65(5), 377–384. https://doi.org/10.1159/000515912

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

Elfgren, K., Elfström, K. M., Naucler, P., Arnheim-Dahlström, L., & Dillner, J. (2017). Management of women with human papillomavirus persistence: Long-term follow-up of a randomized clinical trial. American Journal of Obstetrics and Gynecology, 216(3), 264.e1-264.e7. https://doi.org/10.1016/j.ajog.2016.10.042

Elfström, K. M., Eklund, C., Lamin, H., Öhman, D., Hortlund, M., Elfgren, K., Sundström, K., & Dillner, J. (2021). Organized primary human papillomavirus-based cervical screening: A randomized healthcare policy trial. PLoS Medicine, 18(8), e1003748. https://doi.org/10.1371/journal.pmed.1003748

Esserman, L. J. (2017). The WISDOM Study: Breaking the deadlock in the breast cancer screening debate. Npj Breast Cancer, 3(1), 1–7. https://doi.org/10.1038/s41523-017-0035-5

Etemadi, A., Safiri, S., Sepanlou, S. G., Ikuta, K., Bisignano, C., Shakeri, R., Amani, M., Fitzmaurice, C., Nixon, M., Abbasi, N., Abolhassani, H., Advani, S. M., Afarideh, M., Akinyemiju, T., Alam, T., Alikhani, M., Alipour, V., Allen, C. A., Almasi-Hashiani, A., … Malekzadeh, R. (2020). The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: A systematic analysis for the Global Burden of Disease study 2017. The Lancet Gastroenterology & Hepatology, 5(1), 42–54. https://doi.org/10.1016/S2468-1253(19)30328-0

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

Fainberg, J. S., Al Awamlh, B. A. H., DeRosa, A. P., Chesnut, G. T., Coleman, J. A., Lee, T., & Ehdaie, B. (2021). A systematic review of outcomes after thermal and nonthermal partial prostate ablation. Prostate International. https://doi.org/10.1016/j.prnil.2021.04.001

Falcaro, M., Castañon, A., Ndlela, B., Checchi, M., Soldan, K., Lopez-Bernal, J., Elliss-Brookes, L., & Sasieni, P. (2021). The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: A register-based observational study. The Lancet, 0(0). https://doi.org/10.1016/S0140-6736(21)02178-4

Feng, Z., & Pepe, M. S. (2020). Adding Rigor to Biomarker Evaluations – EDRN Experience. Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 29(12), 2575–2582. https://doi.org/10.1158/1055-9965.EPI-20-0240

Field, J. K., Duffy, S. W., Baldwin, D. R., Brain, K. E., Devaraj, A., Eisen, T., 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., Rintoul, R. C., Screaton, N., Wald, N. J., … Hansell, D. M. (2016). The UK Lung Cancer Screening Trial: A pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technology Assessment, 20(40), 1–146. https://doi.org/10.3310/hta20400

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

Fitzgerald, R. C., Pietro, M. di, O'Donovan, M., Maroni, R., Muldrew, B., Debiram-Beecham, I., Gehrung, M., Offman, J., Tripathi, M., Smith, S. G., Aigret, B., Walter, F. M., Rubin, G., Bagewadi, A., Patrick, A., Shenoy, A., Redmond, A., Muddu, A., Northrop, A., … Sasieni, P. (2020). Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: A multicentre, pragmatic, randomised controlled trial. The Lancet, 396(10247), 333–344. https://doi.org/10.1016/S0140-6736(20)31099-0

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

Forghani, R., Savadjiev, P., Chatterjee, A., Muthukrishnan, N., Reinhold, C., & Forghani, B. (2019). Radiomics and Artificial Intelligence for Biomarker and Prediction Model Development in Oncology. Computational and Structural Biotechnology Journal, 17, 995–1008. https://doi.org/10.1016/j.csbj.2019.07.001

Forsea, A.-M. (2020). Melanoma Epidemiology and Early Detection in Europe: Diversity and Disparities. Dermatology Practical & Conceptual, 10(3), e2020033. https://doi.org/10.5826/dpc.1003a33

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

Freeman, K., Geppert, J., Stinton, C., Todkill, D., Johnson, S., Clarke, A., & Taylor-Phillips, S. (2021). Use of artificial intelligence for image analysis in breast cancer screening programmes: Systematic review of test accuracy. BMJ, 374, n1872. https://doi.org/10.1136/bmj.n1872

Gachabayov, M., Lebovics, E., Rojas, A., Felsenreich, D. M., Latifi, R., & Bergamaschi, R. (2021). Performance evaluation of stool DNA methylation tests in colorectal cancer screening: A systematic review and meta-analysis. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland, 23(5), 1030–1042. https://doi.org/10.1111/codi.15521

Garber, J. E., & Offit, K. (2005). Hereditary Cancer Predisposition Syndromes. Journal of Clinical Oncology, 23(2), 276–292. https://doi.org/10.1200/JCO.2005.10.042

Gehrung, M., Crispin-Ortuzar, M., Berman, A. G., O'Donovan, M., Fitzgerald, R. C., & Markowetz, F. (2021). Triage-driven diagnosis of Barrett's esophagus for early detection of esophageal adenocarcinoma using deep learning. Nature Medicine, 27(5), 833–841. https://doi.org/10.1038/s41591-021-01287-9

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

Getaneh, A. M., Heijnsdijk, E. A. M., Roobol, M. J., & de Koning, H. J. (2020). Assessment of harms, benefits, and cost-effectiveness of prostate cancer screening: A micro-simulation study of 230 scenarios. Cancer Medicine, 9(20), 7742–7750. https://doi.org/10.1002/cam4.3395

Geuzinge, H. A., Bakker, M. F., Heijnsdijk, E. A. M., van Ravesteyn, N. T., Veldhuis, W. B., Pijnappel, R. M., de Lange, S. V., Emaus, M. J., Mann, R. M., Monninkhof, E. M., de Koekkoek-Doll, P. K., van Gils, C. H., de Koning, H. J., & on behalf of the DENSE trial study group. (2021). Cost-Effectiveness of Magnetic Resonance Imaging Screening for Women With Extremely Dense Breast Tissue. JNCI: Journal of the National Cancer Institute, djab119. https://doi.org/10.1093/jnci/djab119

Gianino, M. M., Lenzi, J., Bonaudo, M., Fantini, M. P., Siliquini, R., Ricciardi, W., & Damiani, G. (2018). Organized screening programmes for breast and cervical cancer in 17 EU countries: Trajectories of attendance rates. BMC Public Health, 18(1), 1236. https://doi.org/10.1186/s12889-018-6155-5

Gies, A., Cuk, K., Schrotz-King, P., & Brenner, H. (2018). Direct Comparison of Diagnostic Performance of 9 Quantitative Fecal Immunochemical Tests for Colorectal

Cancer Screening. Gastroenterology, 154(1), 93–104. https://doi.org/10.1053/j.gastro.2017.09.018

Gini, A., Buskermolen, M., Senore, C., Anttila, A., Novak Mlakar, D., Veerus, P., Csanádi, M., Jansen, E. E. L., Zielonke, N., Heinävaara, S., Széles, G., Segnan, N., de Koning, H. J., & Lansdorp-Vogelaar, I. (2021). Development and Validation of Three Regional Microsimulation Models for Predicting Colorectal Cancer Screening Benefits in Europe. MDM Policy & Practice, 6(1), 2381468320984974. https://doi.org/10.1177/2381468320984974

Gini, A., Jansen, E. E. L., Zielonke, N., Meester, R. G. S., Senore, C., Anttila, A., Segnan, N., Mlakar, D. N., de Koning, H. J., Lansdorp-Vogelaar, I., & EU-TOPIA consortium. (2020). Impact of colorectal cancer screening on cancer-specific mortality in Europe: A systematic review. European Journal of Cancer (Oxford, England: 1990), 127, 224–235. https://doi.org/10.1016/j.ejca.2019.12.014

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

Gorges, T. M., Penkalla, N., Schalk, T., Joosse, S. A., Riethdorf, S., Tucholski, J., Lücke, K., Wikman, H., Jackson, S., Brychta, N., von Ahsen, O., Schumann, C., Krahn, T., & Pantel, K. (2016). Enumeration and Molecular Characterization of Tumor Cells in Lung Cancer Patients Using a Novel In Vivo Device for Capturing Circulating Tumor Cells. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 22(9), 2197–2206. https://doi.org/10.1158/1078-0432.CCR-15-1416

Gray, S. W., Gollust, S. E., Carere, D. A., Chen, C. A., Cronin, A., Kalia, S. S., Rana, H. Q., Ruffin, M. T., Wang, C., Roberts, J. S., & Green, R. C. (2017). Personal Genomic Testing for Cancer Risk: Results From the Impact of Personal Genomics Study. Journal of Clinical Oncology, 35(6), 636–644. https://doi.org/10.1200/JCO.2016.67.1503

Grobbee, E. J., Schreuders, E. H., Hansen, B. E., Bruno, M. J., Lansdorp-Vogelaar, I., Spaander, M. C. W., & Kuipers, E. J. (2017). Association Between Concentrations of Hemoglobin Determined by Fecal Immunochemical Tests and Long-term Development of Advanced Colorectal Neoplasia. Gastroenterology, 153(5), 1251-1259.e2. https://doi.org/10.1053/j.gastro.2017.07.034

Grobbee, E. J., Vlugt, M. van der, Vuuren, A. J. van, Stroobants, A. K., Mundt, M. W., Spijker, W. J., Bongers, E. J. C., Kuipers, E. J., Lansdorp-Vogelaar, I., Bossuyt, P. M., Dekker, E., & Spaander, M. C. W. (2017). A randomised comparison of two faecal immunochemical tests in population-based colorectal cancer screening. Gut, 66(11), 1975–1982. https://doi.org/10.1136/gutjnl-2016-311819

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

Gunsoy, N. B., Garcia-Closas, M., & Moss, S. M. (2012). Modelling the overdiagnosis of breast cancer due to mammography screening in womenaged 40 to 49 in the United Kingdom. Breast Cancer Research, 14(6), R152. https://doi.org/10.1186/bcr3365

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

Haviland, K. S., Swette, S., Kelechi, T., & Mueller, M. (2020). Barriers and Facilitators to Cancer Screening Among LGBTQ Individuals With Cancer. Oncology Nursing Forum, 47(1), 44–55. https://doi.org/10.1188/20.ONF.44-55

Heberle, C. R., Omidvari, A.-H., Ali, A., Kroep, S., Kong, C. Y., Inadomi, J. M., Rubenstein, J. H., Tramontano, A. C., Dowling, E. C., Hazelton, W. D., Luebeck, E. G., Lansdorp-Vogelaar, I., & Hur, C. (2017). Cost Effectiveness of Screening Patients With Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device. Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association, 15(9), 1397-1404.e7. https://doi.org/10.1016/j.cgh.2017.02.017

Heider, K., Wan, J. C. M., Gale, D., Ruiz-Valdepenas, A., Mouliere, F., Morris, J., Qureshi, N. R., Qian, W., Knock, H., Wulff, J., Howarth, K., Green, E., Castedo, J., Rundell, V., Cooper, W. N., Eisen, T., Smith, C. G., Massie, C., Gilligan, D., … Rosenfeld, N. (2021). CtDNA detection by personalised assays in early-stage NSCLC. MedRxiv, 2021.06.01.21258171. https://doi.org/10.1101/2021.06.01.21258171

Heider, K., Wan, J. C. M., Hall, J., Belic, J., Boyle, S., Hudecova, I., Gale, D., Cooper, W. N., Corrie, P. G., Brenton, J. D., Smith, C. G., & Rosenfeld, N. (2020). Detection of ctDNA from Dried Blood Spots after DNA Size Selection. Clinical Chemistry, 66(5), 697–705. https://doi.org/10.1093/clinchem/hvaa050

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

Heitzer, E., Ulz, P., Geigl, J. B., & Speicher, M. R. (2016). Non-invasive detection of genome-wide somatic copy number alterations by liquid biopsies. Molecular Oncology, 10(3), 494–502. https://doi.org/10.1016/j.molonc.2015.12.004

Hellquist, B. N., Duffy, S. W., Abdsaleh, S., Björneld, L., Bordás, P., Tabár, L., Viták, B., Zackrisson, S., Nyström, L., & Jonsson, H. (2011). Effectiveness of population-based service screening with mammography for women ages 40 to 49 years. Cancer, 117(4), 714–722. https://doi.org/10.1002/cncr.25650

Hemming, K., Haines, T. P., Chilton, P. J., Girling, A. J., & Lilford, R. J. (2015). The stepped wedge cluster randomised trial: Rationale, design, analysis, and reporting. BMJ, 350, h391. https://doi.org/10.1136/bmj.h391

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/

Hoffmann, T. C., & Del Mar, C. (2015). Patients' expectations of the benefits and harms of treatments, screening, and tests: A systematic review. JAMA Internal Medicine, 175(2), 274–286. https://doi.org/10.1001/jamainternmed.2014.6016

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

Hofvind, S., Holen, Å. S., Aase, H. S., Houssami, N., Sebuødegård, S., Moger, T. A., Haldorsen, I. S., & Akslen, L. A. (2019). Two-view digital breast tomosynthesis versus digital mammography in a population-based breast cancer screening programme (To-Be): A randomised, controlled trial. The Lancet Oncology, 20(6), 795–805. https://doi.org/10.1016/S1470-2045(19)30161-5

Hofvind, S., Moshina, N., Holen, Å. S., Danielsen, A. S., Lee, C. I., Houssami, N., Aase, H. S., Akslen, L. A., & Haldorsen, I. S. (2021). Interval and Subsequent Round Breast Cancer in a Randomized Controlled Trial Comparing Digital Breast Tomosynthesis and Digital Mammography Screening. Radiology, 300(1), 66–76. https://doi.org/10.1148/radiol.2021203936

Holme, Ø., Løberg, M., Kalager, M., Bretthauer, M., Hernán, M. A., Aas, E., Eide, T. J., Skovlund, E., Schneede, J., Tveit, K. M., & Hoff, G. (2014). Effect of Flexible Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality: A Randomized Clinical Trial. JAMA, 312(6), 606–615. https://doi.org/10.1001/jama.2014.8266

Holme, Ø., Schoen, R. E., Senore, C., Segnan, N., Hoff, G., Løberg, M., Bretthauer, M., Adami, H.-O., & Kalager, M. (2017). Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: Pooled analysis of randomised trials. BMJ, 356, i6673. https://doi.org/10.1136/bmj.i6673

Houssami, N., Hofvind, S., Soerensen, A. L., Robledo, K. P., Hunter, K., Bernardi, D., Lång, K., Johnson, K., Aglen, C. F., & Zackrisson, S. (2021). Interval breast cancer rates for digital breast tomosynthesis versus digital mammography population screening: An individual participant data meta-analysis. EClinicalMedicine, 34, 100804. https://doi.org/10.1016/j.eclinm.2021.100804

Houssami, N., Zackrisson, S., Blazek, K., Hunter, K., Bernardi, D., Lång, K., & Hofvind, S. (2021). Meta-analysis of prospective studies evaluating breast cancer detection and interval cancer rates for digital breast tomosynthesis versus mammography population screening. European Journal of Cancer (Oxford, England: 1990), 148, 14–23. https://doi.org/10.1016/j.ejca.2021.01.035

Hu, J. C., Nguyen, P., Mao, J., Halpern, J., Shoag, J., Wright, J. D., & Sedrakyan, A. (2017). Increase in Prostate Cancer Distant Metastases at Diagnosis in the United States. JAMA Oncology, 3(5), 705–707. https://doi.org/10.1001/jamaoncol.2016.5465

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

Hulbert, A., Jusue-Torres, I., Stark, A., Chen, C., Rodgers, K., Lee, B., Griffin, C., Yang, A., Huang, P., Wrangle, J., Belinsky, S. A., Wang, T.-H., Yang, S. C., Baylin, S. B., Brock, M. V., & Herman, J. G. (2017). Early Detection of Lung Cancer Using DNA Promoter Hypermethylation in Plasma and Sputum. Clinical Cancer Research, 23(8), 1998–2005. https://doi.org/10.1158/1078-0432.CCR-16-1371

Hunger, T., Wanka-Pail, E., Brix, G., & Griebel, J. (2021). Lung Cancer Screening with Low-Dose CT in Smokers: A Systematic Review and Meta-Analysis. Diagnostics, 11(6), 1040. https://doi.org/10.3390/diagnostics11061040

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

Ilic, D., Djulbegovic, M., Jung, J. H., Hwang, E. C., Zhou, Q., Cleves, A., Agoritsas, T., & Dahm, P. (2018). Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. BMJ, 362, k3519. https://doi.org/10.1136/bmj.k3519

Imperiale, T. F., Ransohoff, D. F., Itzkowitz, S. H., Levin, T. R., Lavin, P., Lidgard, G. P., Ahlquist, D. A., & Berger, B. M. (2014). Multitarget Stool DNA Testing for Colorectal-Cancer Screening. New England Journal of Medicine, 370(14), 1287–1297. https://doi.org/10.1056/NEJMoa1311194

Iqbal, M. J., Javed, Z., Sadia, H., Qureshi, I. A., Irshad, A., Ahmed, R., Malik, K., Raza, S., Abbas, A., Pezzani, R., & Sharifi-Rad, J. (2021). Clinical applications of artificial intelligence and machine learning in cancer diagnosis: Looking into the future. Cancer Cell International, 21(1), 270. https://doi.org/10.1186/s12935-021-01981-1

Iyer, P. G., Taylor, W. R., Johnson, M. L., Lansing, R. L., Maixner, K. A., Hemminger, L. L., Cayer, F. K., Yab, T. C., Devens, M. E., Slettedahl, S. W., Broderick, B. T., Mahoney, D. W., McGlinch, M. C., Berger, C. K., Foote, P. H., Giakomopoulos, M., Allawi, H., Smyrk, T. C., Wang, K. K., … Kisiel, J. B. (2020). Accurate Nonendoscopic Detection of Barrett's Esophagus by Methylated DNA Markers: A Multisite Case Control Study. The American Journal of Gastroenterology, 115(8), 1201–1209. https://doi.org/10.14309/ajg.0000000000000656

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

Jagodzinski, A., Johansen, C., Koch-Gromus, U., Aarabi, G., Adam, G., Anders, S., Augustin, M., der Kellen, R. B., Beikler, T., Behrendt, C.-A., Betz, C. S., Bokemeyer, C., Borof, K., Briken, P., Busch, C.-J., Büchel, C., Brassen, S., Debus, E. S., Eggers, L., … Blankenberg, S. (2020). Rationale and Design of the Hamburg City Health Study. European Journal of Epidemiology, 35(2), 169–181. https://doi.org/10.1007/s10654-019-00577-4

Jaiswal, S., & Ebert, B. L. (2019). Clonal hematopoiesis in human aging and disease. Science (New York, N.Y.), 366(6465), eaan4673. https://doi.org/10.1126/science.aan4673

Jansen, E. E. L., Zielonke, N., Gini, A., Anttila, A., Segnan, N., Vokó, Z., Ivanuš, U., McKee, M., Koning, H. J. de, Kok, I. M. C. M. de, Veerus, P., Anttila, A., Heinävaara, S., Sarkeala, T., Csanádi, M., Pitter, J., Széles, G., Vokó, Z., Minozzi, S., … Priaulx, J. (2020). Effect of organised cervical cancer screening on cervical cancer mortality in Europe: A systematic review. European Journal of Cancer, 127, 207–223. https://doi.org/10.1016/j.ejca.2019.12.013

Janssen, F., Gewily, S. E., & Bardoutsos, A. (2021). Smoking epidemic in Europe in the 21st century. Tobacco Control, 30(5), 523–529. https://doi.org/10.1136/tobaccocontrol-2020-055658

Jemal, A., Culp, M. B., Ma, J., Islami, F., & Fedewa, S. A. (2021). Prostate Cancer Incidence 5 Years After US Preventive Services Task Force Recommendations Against Screening. JNCI: Journal of the National Cancer Institute, 113(1), 64–71. https://doi.org/10.1093/jnci/djaa068

Jensen, S. Ø., Øgaard, N., Ørntoft, M.-B. W., Rasmussen, M. H., Bramsen, J. B., Kristensen, H., Mouritzen, P., Madsen, M. R., Madsen, A. H., Sunesen, K. G., Iversen, L. H., Laurberg, S., Christensen, I. J., Nielsen, H. J., & Andersen, C. L. (2019). Novel DNA methylation biomarkers show high sensitivity and specificity for blood-based detection of colorectal cancer—A clinical biomarker discovery and validation study. Clinical Epigenetics, 11(1), 158. https://doi.org/10.1186/s13148-019-0757-3

Ji, X., Li, J., Huang, Y., Sung, P.-L., Yuan, Y., Liu, Q., Chen, Y., Ju, J., Zhou, Y., Huang, S., Chen, F., Han, Y., Yuan, W., Fan, C., Zhao, Q., Wu, H., Feng, S., Liu, W., Li, Z., … Mao, M. (2019). Identifying occult maternal malignancies from 1.93 million pregnant women undergoing noninvasive prenatal screening tests. Genetics in Medicine: Official Journal of the American College of Medical Genetics, 21(10), 2293–2302. https://doi.org/10.1038/s41436-019-0510-5

Jia, Z., Patra, A., Kutty, V. K., & Venkatesan, T. (2019). Critical Review of Volatile Organic Compound Analysis in Breath and In Vitro Cell Culture for Detection of Lung Cancer. Metabolites, 9(3), 52. https://doi.org/10.3390/metabo9030052

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

Johnson, K., Lång, K., Ikeda, D. M., Åkesson, A., Andersson, I., & Zackrisson, S. (2021). Interval Breast Cancer Rates and Tumor Characteristics in the Prospective Population-based Malmö Breast Tomosynthesis Screening Trial. Radiology, 299(3), 559–567. https://doi.org/10.1148/radiol.2021204106

Jonas, D. E., Reuland, D. S., Reddy, S. M., Nagle, M., Clark, S. D., Weber, R. P., Enyioha, C., Malo, T. L., Brenner, A. T., Armstrong, C., Coker-Schwimmer, M., Middleton, J. C., Voisin, C., & Harris, R. P. (2021). Screening for Lung Cancer With Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA, 325(10), 971–987. https://doi.org/10.1001/jama.2021.0377

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

Kadri, S. R., Lao-Sirieix, P., O'Donovan, M., Debiram, I., Das, M., Blazeby, J. M., Emery, J., Boussioutas, A., Morris, H., Walter, F. M., Pharoah, P., Hardwick, R. H., & Fitzgerald, R. C. (2010). Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: Cohort study. BMJ (Clinical Research Ed.), 341, c4372. https://doi.org/10.1136/bmj.c4372

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

Kann, H., Hortlund, M., Eklund, C., Dillner, J., & Faust, H. (2020). Human papillomavirus types in cervical dysplasia among young HPV-vaccinated women: Population-based nested case-control study. International Journal of Cancer, 146(9), 2539–2546. https://doi.org/10.1002/ijc.32848

Karlsson, A. A., Hao, S., Jauhiainen, A., Elfström, K. M., Egevad, L., Nordström, T., Heintz, E., & Clements, M. S. (2021). The cost-effectiveness of prostate cancer screening using the Stockholm3 test. PloS One, 16(2), e0246674. https://doi.org/10.1371/journal.pone.0246674

Keating, N. L., & Pace, L. E. (2018). Breast Cancer Screening in 2018: Time for Shared Decision Making. JAMA, 319(17), 1814–1815. https://doi.org/10.1001/jama.2018.3388

Keller, L., & Pantel, K. (2019). Unravelling tumour heterogeneity by single-cell profiling of circulating tumour cells. Nature Reviews Cancer, 19(10), 553–567. https://doi.org/10.1038/s41568-019-0180-2

Khan, S. A., Hernandez-Villafuerte, K. V., Muchadeyi, M. T., & Schlander, M. (2021). Cost-effectiveness of risk-based breast cancer screening: A systematic review. International Journal of Cancer, 149(4), 790–810. https://doi.org/10.1002/ijc.33593

Khanna, V. K., Ghosh, S., MacMahon, H., & Mehta, A. C. (2021). Criteria for Low-Dose

CT Lung Cancer Screening in the Setting of Air Pollution: A Discussion That Is Long Overdue. CHEST, 159(1), 42–45. https://doi.org/10.1016/j.chest.2020.08.2091

Klein, W. M. P., Ferrer, R. A., & Kaufman, A. R. (2020). How (or Do) People "Think" About Cancer Risk, and Why That Matters. JAMA Oncology, 6(7), 983–984. https://doi.org/10.1001/jamaoncol.2020.0170

Knudsen, A. B., Zauber, A. G., Rutter, C. M., Naber, S. K., Doria-Rose, V. P., Pabiniak, C., Johanson, C., Fischer, S. E., Lansdorp-Vogelaar, I., & Kuntz, K. M. (2016). Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA, 315(23), 2595–2609. https://doi.org/10.1001/jama.2016.6828

Kortlever, T. L., van der Vlugt, M., Dekker, E., & Bossuyt, P. M. M. (2021). Individualized faecal immunochemical test cut-off based on age and sex in colorectal cancer screening. Preventive Medicine Reports, 23, 101447. https://doi.org/10.1016/j.pmedr.2021.101447

Koskenvuo, L., Malila, N., Pitkäniemi, J., Miettinen, J., Heikkinen, S., & Sallinen, V. (2019). Sex differences in faecal occult blood test screening for colorectal cancer. British Journal of Surgery, 106(4), 436–447. https://doi.org/10.1002/bjs.11011

Kovács, S., Erdősi, D., Németh, B., & Zemplényi, A. (2020). PNS25 MULTI-LEVEL Cost-Effectiveness Thresholds in Europe—Results of a Systematic Literature Review and Supplementary Research. Value in Health, 23, S648. https://doi.org/10.1016/j.jval.2020.08.1469

Kregting, L. M., Kaljouw, S., de Jonge, L., Jansen, E. E. L., Peterse, E. F. P., Heijnsdijk, E. A. M., van Ravesteyn, N. T., Lansdorp-Vogelaar, I., & de Kok, I. M. C. M. (2021). Effects of cancer screening restart strategies after COVID-19 disruption. British Journal of Cancer, 124(9), 1516–1523. https://doi.org/10.1038/s41416-021-01261-9

Kresovich, J. K., Xu, Z., O'Brien, K. M., Weinberg, C. R., Sandler, D. P., & Taylor, J. A. (2019). Methylation-Based Biological Age and Breast Cancer Risk. JNCI Journal of the National Cancer Institute, 111(10), 1051–1058. https://doi.org/10.1093/jnci/djz020

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

Kuhl, C. K., Strobel, K., Bieling, H., Leutner, C., Schild, H. H., & Schrading, S. (2017). Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer. Radiology, 283(2), 361–370. https://doi.org/10.1148/radiol.2016161444

Kuske, A., Gorges, T. M., Tennstedt, P., Tiebel, A.-K., Pompe, R., Preißer, F., Prues, S., Mazel, M., Markou, A., Lianidou, E., Peine, S., Alix-Panabières, C., Riethdorf, S., Beyer, B., Schlomm, T., & Pantel, K. (2016). Improved detection of circulating tumor cells in non-metastatic high-risk prostate cancer patients. Scientific Reports, 6, 39736. https://doi.org/10.1038/srep39736

Laconi, E., Marongiu, F., & DeGregori, J. (2020). Cancer as a disease of old age: Changing mutational and microenvironmental landscapes. British Journal of Cancer, 122(7), 943–952. https://doi.org/10.1038/s41416-019-0721-1

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

Lancellotti, C., Cancian, P., Savevski, V., Kotha, S. R. R., Fraggetta, F., Graziano, P., & Di Tommaso, L. (2021). Artificial Intelligence & Tissue Biomarkers: Advantages, Risks and Perspectives for Pathology. Cells, 10(4), 787. https://doi.org/10.3390/cells10040787

Landy, R., Windridge, P., Gillman, M. S., & Sasieni, P. D. (2018). What cervical screening is appropriate for women who have been vaccinated against high risk HPV? A simulation study. International Journal of Cancer, 142(4), 709–718. https://doi.org/10.1002/ijc.31094

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

Lau, R. P., Kim, T. H., & Rao, J. (2021). Advances in Imaging Modalities, Artificial Intelligence, and Single Cell Biomarker Analysis, and Their Applications in Cytopathology. Frontiers in Medicine, 8, 1014. https://doi.org/10.3389/fmed.2021.689954

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

Lei, J., Ploner, A., Lehtinen, M., Sparén, P., Dillner, J., & Elfström, K. M. (2020). Impact of HPV vaccination on cervical screening performance: A population-based cohort study. British Journal of Cancer, 123(1), 155–160. https://doi.org/10.1038/s41416-020-0850-6

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

Lenaerts, L., Brison, N., Maggen, C., Vancoillie, L., Che, H., Vandenberghe, P., Dierickx, D., Michaux, L., Dewaele, B., Neven, P., Floris, G., Tousseyn, T., Lannoo, L., Jatsenko, T., Bempt, I. V., Calsteren, K. V., Vandecaveye, V., Dehaspe, L., Devriendt, K., … Amant, F. (2021). Comprehensive genome-wide analysis of routine non-invasive test data allows cancer prediction: A single-center retrospective analysis of over 85,000 pregnancies. EClinicalMedicine, 35. https://doi.org/10.1016/j.eclinm.2021.100856

Lenaerts, L., Che, H., Brison, N., Neofytou, M., Jatsenko, T., Lefrère, H., Maggen, C., Villela, D., Verheecke, M., Dehaspe, L., Croitor, A., Hatse, S., Wildiers, H., Neven, P., Vandecaveye, V., Floris, G., Vermeesch, J. R., & Amant, F. (2020). Breast Cancer Detection and Treatment Monitoring Using a Noninvasive Prenatal Testing Platform: Utility in Pregnant and Nonpregnant Populations. Clinical Chemistry, 66(11), 1414–1423. https://doi.org/10.1093/clinchem/hvaa196

Lenaerts, L., Vandenberghe, P., Brison, N., Che, H., Neofytou, M., Verheecke, M., Leemans, L., Maggen, C., Dewaele, B., Dehaspe, L., Vanderschueren, S., Dierickx, D., Vandecaveye, V., Amant, F., & Vermeesch, J. R. (2019). Genomewide copy number alteration screening of circulating plasma DNA: Potential for the detection of incipient tumors. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 30(1), 85–95. https://doi.org/10.1093/annonc/mdy476

Lennon, A. M., Buchanan, A. H., Kinde, I., Warren, A., Honushefsky, A., Cohain, A. T., Ledbetter, D. H., Sanfilippo, F., Sheridan, K., Rosica, D., Adonizio, C. S., Hwang, H. J., Lahouel, K., Cohen, J. D., Douville, C., Patel, A. A., Hagmann, L. N., Rolston, D. D., Malani, N., … Papadopoulos, N. (2020). Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science (New York, N.Y.), 369(6499), eabb9601. https://doi.org/10.1126/science.abb9601

Li, F., Li, X., Guo, C., Xu, R., Li, F., Pan, Y., Liu, M., Liu, Z., Shi, C., Wang, H., Wang, M., Tian, H., Liu, F., Liu, Y., Li, J., Cai, H., Yang, L., He, Z., & Ke, Y. (2019). Estimation of Cost for Endoscopic Screening for Esophageal Cancer in a High-Risk Population in Rural China: Results from a Population-Level Randomized

Controlled Trial. PharmacoEconomics, 37(6), 819–827. https://doi.org/10.1007/s40273-019-00766-9

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

Liu, B., Ricarte Filho, J., Mallisetty, A., Villani, C., Kottorou, A., Rodgers, K., Chen, C., Ito, T., Holmes, K., Gastala, N., Valyi-Nagy, K., David, O., Gaba, R. C., Ascoli, C., Pasquinelli, M., Feldman, L. E., Massad, M. G., Wang, T.-H., Jusue-Torres, I., … Hulbert, A. (2020). Detection of Promoter DNA Methylation in Urine and Plasma Aids the Detection of Non-Small Cell Lung Cancer. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 26(16), 4339–4348. https://doi.org/10.1158/1078-0432.CCR-19-2896

Liu, M. C., Oxnard, G. R., Klein, E. A., Swanton, C., Seiden, M. V., Liu, M. C., Oxnard, G. R., Klein, E. A., Smith, D., Richards, D., Yeatman, T. J., Cohn, A. L., Lapham, R., Clement, J., Parker, A. S., Tummala, M. K., McIntyre, K., Sekeres, M. A., Bryce, A. H., … Berry, D. A. (2020). Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Annals of Oncology, 31(6), 745–759. https://doi.org/10.1016/j.annonc.2020.02.011

Lorincz, A. T., Brentnall, A. R., Scibior Bentkowska, D., Reuter, C., Banwait, R., Cadman, L., Austin, J., Cuzick, J., & Vasiljević, N. (2016). Validation of a DNA methylation HPV triage classifier in a screening sample. International Journal of Cancer, 138(11), 2745–2751. https://doi.org/10.1002/ijc.30008

Louvanto, K., Aro, K., Nedjai, B., Bützow, R., Jakobsson, M., Kalliala, I., Dillner, J., Nieminen, P., & Lorincz, A. (2020). Methylation in Predicting Progression of Untreated High-grade Cervical Intraepithelial Neoplasia. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 70(12), 2582–2590. https://doi.org/10.1093/cid/ciz677

Maes-Carballo, M., Moreno-Asencio, T., Martín-Díaz, M., Mignini, L., Bueno-Cavanillas, A., & Khan, K. S. (2021). Shared decision making in breast cancer screening guidelines: A systematic review of their quality and reporting. European Journal of Public Health, 31(4), 873–883. https://doi.org/10.1093/eurpub/ckab084

Malone, C., Barnabas, R. V., Buist, D. S. M., Tiro, J. A., & Winer, R. L. (2020). Cost-effectiveness studies of HPV self-sampling: A systematic review. Preventive Medicine, 132, 105953. https://doi.org/10.1016/j.ypmed.2019.105953

Marinovich, M. L., Hunter, K. E., Macaskill, P., & Houssami, N. (2018). Breast Cancer Screening Using Tomosynthesis or Mammography: A Meta-analysis of Cancer Detection and Recall. Journal of the National Cancer Institute, 110(9), 942–949. https://doi.org/10.1093/jnci/djy121

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

Marlow, L. A. V., Waller, J., & Wardle, J. (2015). Barriers to cervical cancer screening among ethnic minority women: A qualitative study. Journal of Family Planning and Reproductive Health Care, 41(4), 248–254. https://doi.org/10.1136/jfprhc-2014-101082

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

Martínez García, L., Sanabria, A. J., García Alvarez, E., Trujillo-Martín, M. M.,

Etxeandia-Ikobaltzeta, I., Kotzeva, A., Rigau, D., Louro-González, A., Barajas-Nava, L., Díaz Del Campo, P., Estrada, M.-D., Solà, I., Gracia, J., Salcedo-Fernandez, F., Lawson, J., Haynes, R. B., Alonso-Coello, P., & Updating Guidelines Working Group. (2014). The validity of recommendations from clinical guidelines: A survival analysis. CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne, 186(16), 1211–1219. https://doi.org/10.1503/cmaj.140547

Martínez-Alonso, M., Carles-Lavila, M., Pérez-Lacasta, M. J., Pons-Rodríguez, A., Garcia, M., Rué, M., & InforMa Group. (2017). Assessment of the effects of decision aids about breast cancer screening: A systematic review and meta-analysis. BMJ Open, 7(10), e016894. https://doi.org/10.1136/bmjopen-2017-016894

Mavaddat, N., Michailidou, K., Dennis, J., Lush, M., Fachal, L., Lee, A., Tyrer, J. P., Chen, T.-H., Wang, Q., Bolla, M. K., Yang, X., Adank, M. A., Ahearn, T., Aittomäki, K., Allen, J., Andrulis, I. L., Anton-Culver, H., Antonenkova, N. N., Arndt, V., … Easton, D. F. (2019). Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. American Journal of Human Genetics, 104(1), 21–34. https://doi.org/10.1016/j.ajhg.2018.11.002

Mazzone, P. J., Lamb, C., Rieger-Christ, K. M., Reddy, C. B., Qu, J., Wu, S., Ding, J., Whitney, D., Pankratz, D. G., Babiarz, J., Lofaro, L., Walsh, P. S., Wilde, J., Bhorade, S. M., Huang, J., Kennedy, G., & Spira, A. (2021). Early candidate nasal swab classifiers developed using machine learning and whole transcriptome sequencing may improve early lung cancer detection. Journal of Clinical Oncology, 39(15_suppl), 8551–8551. https://doi.org/10.1200/JCO.2021.39.15_suppl.8551

McKinney, S. M., Sieniek, M., Godbole, V., Godwin, J., Antropova, N., Ashrafian, H., Back, T., Chesus, M., Corrado, G. S., Darzi, A., Etemadi, M., Garcia-Vicente, F., Gilbert, F. J., Halling-Brown, M., Hassabis, D., Jansen, S., Karthikesalingam, A., Kelly, C. J., King, D., … Shetty, S. (2020). International evaluation of an AI system for breast cancer screening. Nature, 577(7788), 89–94. https://doi.org/10.1038/s41586-019-1799-6

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

Mesher, D., Panwar, K., Thomas, S. L., Edmundson, C., Choi, Y. H., Beddows, S., & Soldan, K. (2018). The Impact of the National HPV Vaccination Program in England Using the Bivalent HPV Vaccine: Surveillance of Type-Specific HPV in Young Females, 2010–2016. The Journal of Infectious Diseases, 218(6), 911–921. https://doi.org/10.1093/infdis/jiy249

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

Miglioretti, D. L., Zhu, W., Kerlikowske, K., Sprague, B. L., Onega, T., Buist, D. S., Henderson, L. M., & Smith, R. A. (2015). Risk of less-favorable breast tumor characteristics with biennial versus annual mammography by age and menopausal status. JAMA Oncology, 1(8), 1069–1077. https://doi.org/10.1001/jamaoncol.2015.3084

Miles, A., Cockburn, J., Smith, R. A., & Wardle, J. (2004). A perspective from countries using organized screening programs.

Cancer, 101(5 Suppl), 1201–1213. https://doi.org/10.1002/cncr.20505

Millen, G. C., & Yap, C. (2020). Adaptive trial designs: What are multiarm, multistage trials? Archives of Disease in Childhood - Education and Practice, 105(6), 376–378. https://doi.org/10.1136/archdischild-2019-317826

Minicozzi, P., Innos, K., Sánchez, M.-J., Trama, A., Walsh, P. M., Marcos-Gragera, R., Dimitrova, N., Botta, L., Visser, O., Rossi, S., Tavilla, A., Sant, M., Hackl, M., Zielonke, N., Eycken, E. V., Henau, K., Valerianova, Z., Dimitrova, N., Sekerija, M., … White, C. (2017). Quality analysis of population-based information on cancer stage at diagnosis across Europe, with presentation of stage-specific cancer survival estimates: A EUROCARE-5 study. European Journal of Cancer, 84, 335–353. https://doi.org/10.1016/j.ejca.2017.07.015

Møen, K. A., Kumar, B., Qureshi, S., & Diaz, E. (2017). Differences in cervical cancer screening between immigrants and nonimmigrants in Norway: A primary healthcare register-based study. European Journal of Cancer Prevention, 26(6), 521–527. https://doi.org/10.1097/CEJ.0000000000000311

Moinova, H. R., LaFramboise, T., Lutterbaugh, J. D., Chandar, A. K., Dumot, J., Faulx, A., Brock, W., De la Cruz Cabrera, O., Guda, K., Barnholtz-Sloan, J. S., Iyer, P. G., Canto, M. I., Wang, J. S., Shaheen, N. J., Thota, P. N., Willis, J. E., Chak, A., & Markowitz, S. D. (2018). Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus. Science Translational Medicine, 10(424), eaao5848. https://doi.org/10.1126/scitranslmed.aao5848

Moss, J., Magenheim, J., Neiman, D., Zemmour, H., Loyfer, N., Korach, A., Samet, Y., Maoz, M., Druid, H., Arner, P., Fu, K.-Y., Kiss, E., Spalding, K. L., Landesberg, G., Zick, A., Grinshpun, A., Shapiro, A. M. J., Grompe, M., Wittenberg, A. D., … Dor, Y. (2018). Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. Nature Communications, 9(1), 5068. https://doi.org/10.1038/s41467-018-07466-6

Mühlberger, N., Sroczynski, G., Gogollari, A., Jahn, B., Pashayan, N., Steyerberg, E., Widschwendter, M., & Siebert, U. (2021). Cost effectiveness of breast cancer screening and prevention: A systematic review with a focus on risk-adapted strategies. The European Journal of Health Economics, 22(8), 1311–1344. https://doi.org/10.1007/s10198-021-01338-5

Munro, S., Stacey, D., Lewis, K. B., & Bansback, N. (2016). Choosing treatment and screening options congruent with values: Do decision aids help? Sub-analysis of a systematic review. Patient Education and Counseling, 99(4), 491–500. https://doi.org/10.1016/j.pec.2015.10.026

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

Myers, R. E., Manne, S. L., Wilfond, B., Sifri, R., Ziring, B., Wolf, T. A., Cocroft, J., Ueland, A., Petrich, A., Swan, H., DiCarlo, M., & Weinberg, D. S. (2011). A randomized trial of genetic and environmental risk assessment (GERA) for colorectal cancer risk in primary care: Trial design and baseline findings. Contemporary Clinical Trials, 32(1), 25–31. https://doi.org/10.1016/j.cct.2010.08.013

Myers, R. E., Ruth, K., Manne, S. L., Cocroft, J., Sifri, R., Ziring, B., Burgh, D., Ross, E., & Weinberg, D. S. (2015). Effects of genetic and environmental risk assessment feedback on colorectal cancer screening adherence. Journal of Behavioral Medicine, 38(5), 777–786. https://doi.org/10.1007/s10865-015-9626-5

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

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

Nelson, H. D., Tyne, K., Naik, A., Bougatsos, C., Chan, B. K., Humphrey, L., & U.S. Preventive Services Task Force. (2009). Screening for breast cancer: An update for the U.S. Preventive Services Task Force. Annals of Internal Medicine, 151(10), 727–737, W237-242. https://doi.org/10.7326/0003-4819-151-10-200911170-00009

Newman, A. M., Bratman, S. V., To, J., Wynne, J. F., Eclov, N. C. W., Modlin, L. A., Liu, C. L., Neal, J. W., Wakelee, H. A., Merritt, R. E., Shrager, J. B., Loo, B. W., Alizadeh, A. A., & Diehn, M. (2014). An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. Nature Medicine, 20(5), 548–554. https://doi.org/10.1038/nm.3519

Nguyen-Huu, N.-H., Thilly, N., Derrough, T., Sdona, E., Claudot, F., Pulcini, C., Agrinier, N., & HPV Policy working group. (2020). Human papillomavirus vaccination coverage, policies, and practical implementation across Europe. Vaccine, 38(6), 1315–1331. https://doi.org/10.1016/j.vaccine.2019.11.081

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

Oeffinger, K. C., Fontham, E. T. H., Etzioni, R., Herzig, A., Michaelson, J. S., Shih, Y.-C. T., Walter, L. C., Church, T. R., Flowers, C. R., LaMonte, S. J., Wolf, A. M. D., DeSantis, C., Lortet-Tieulent, J., Andrews, K., Manassaram-Baptiste, D., Saslow, D., Smith, R. A., Brawley, O. W., & Wender, R. (2015). Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. JAMA, 314(15), 1599–1614. https://doi.org/10.1001/jama.2015.12783

O'Keeffe, L. M., Taylor, G., Huxley, R. R., Mitchell, P., Woodward, M., & Peters, S. A. E. (2018). Smoking as a risk factor for lung cancer in women and men: A systematic review and meta-analysis. BMJ Open, 8(10), e021611. https://doi.org/10.1136/bmjopen-2018-021611

Oldach, B. R., & Katz, M. L. (2014). Health Literacy and Cancer Screening: A Systematic Review. Patient Education and Counseling, 94(2), 149–157. https://doi.org/10.1016/j.pec.2013.10.001

Osses, D. F., Remmers, S., Schröder, F. H., van der Kwast, T., & Roobol, M. J. (2019). Results of Prostate Cancer Screening in a Unique Cohort at 19yr of Follow-up. European Urology, 75(3), 374–377. https://doi.org/10.1016/j.eururo.2018.10.053

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

Pal Choudhury, P., Wilcox, A. N., Brook, M. N., Zhang, Y., Ahearn, T., Orr, N., Coulson, P., Schoemaker, M. J., Jones, M. E., Gail, M. H., Swerdlow, A. J., Chatterjee, N., & Garcia-Closas, M. (2020). Comparative Validation of Breast Cancer Risk Prediction Models and Projections for Future Risk Stratification. Journal of the National Cancer Institute, 112(3), 278–285. https://doi.org/10.1093/jnci/djz113

Pallesen, A. V. J., Herrstedt, J., Westendorp, R. G. J., Mortensen, L. H., & Kristiansen, M. (2021). Differential effects of colorectal cancer screening across sociodemographic groups in Denmark: A register-based study. Acta Oncologica (Stockholm, Sweden), 60(3), 323–332. https://doi.org/10.1080/0284186X.2020.1869829

Palmer, T., Wallace, L., Pollock, K. G., Cuschieri, K., Robertson, C., Kavanagh, K., & Cruickshank, M. (2019). Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: Retrospective population study. BMJ (Clinical Research

Ed.), 365, l1161. https://doi.org/10.1136/bmj.l1161

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

Pantel, K., & Alix-Panabières, C. (2019). Liquid biopsy and minimal residual disease—Latest advances and implications for cure. Nature Reviews. Clinical Oncology, 16(7), 409–424. https://doi.org/10.1038/s41571-019-0187-3

Pashayan, N., Antoniou, A. C., Ivanus, U., Esserman, L. J., Easton, D. F., French, D., Sroczynski, G., Hall, P., Cuzick, J., Evans, D. G., Simard, J., Garcia-Closas, M., Schmutzler, R., Wegwarth, O., Pharoah, P., Moorthie, S., De Montgolfier, S., Baron, C., Herceg, Z., … Widschwendter, M. (2020). Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nature Reviews. Clinical Oncology, 17(11), 687–705. https://doi.org/10.1038/s41571-020-0388-9

Pashayan, N., Antoniou, A. C., Lee, A., Wolfson, M., Chiquette, J., Eloy, L., Eisen, A., Stockley, T. L., Nabi, H., Brooks, J. D., Dorval, M., Easton, D. F., Knoppers, B. M., Chiarelli, A. M., & Simard, J. (2021). Should Age-Dependent Absolute Risk Thresholds Be Used for Risk Stratification in Risk-Stratified Breast Cancer Screening? Journal of Personalized Medicine, 11(9), 916. https://doi.org/10.3390/jpm11090916

Pashayan, N., Morris, S., Gilbert, F. J., & Pharoah, P. D. P. (2018). Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. JAMA Oncology, 4(11), 1504–1510. https://doi.org/10.1001/jamaoncol.2018.1901

Pataky, R., Gulati, R., Etzioni, R., Black, P., Chi, K. N., Coldman, A. J., Pickles, T., Tyldesley, S., & Peacock, S. (2014). Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada. International Journal of Cancer, 135(4), 939–947. https://doi.org/10.1002/ijc.28732

Pattacini, P., Nitrosi, A., Giorgi Rossi, P., Iotti, V., Ginocchi, V., Ravaioli, S., Vacondio, R., Braglia, L., Cavuto, S., Campari, C., & RETomo Working Group. (2018). Digital Mammography versus Digital Mammography Plus Tomosynthesis for Breast Cancer Screening: The Reggio Emilia Tomosynthesis Randomized Trial. Radiology, 288(2), 375–385. https://doi.org/10.1148/radiol.2018172119

Peeters, E., Cornet, K., Cammu, H., Verhoeven, V., Devroey, D., & Arbyn, M. (2020). Efficacy of strategies to increase participation in cervical cancer screening: GPs offering self-sampling kits for HPV testing versus recommendations to have a pap smear taken - A randomised controlled trial. Papillomavirus Research (Amsterdam, Netherlands), 9, 100194. https://doi.org/10.1016/j.pvr.2020.100194

Penţa, M. A., & Băban, A. (2014). Mass media coverage of HPV vaccination in Romania: A content analysis. Health Education Research, 29(6), 977–992. https://doi.org/10.1093/her/cyu027

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. (2014). Assessing the benefits and harms of low-dose computed tomography screening for lung cancer. Lung Cancer Management, 3(6), 491–498. https://doi.org/10.2217/lmt.14.41

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

Pitkäniemi, J., Seppä, K., Hakama, M., Malminiemi, O., Palva, T., Vuoristo, M.-S., Järvinen, H., Paimela, H., Pikkarainen, P., Anttila, A., Elovainio, L., Hakulinen, T., Karjalainen, S., Pylkkänen, L., Rautalahti, M., Sarkeala, T., Vertio, H., & Malila, N. (2015). Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterology, 2(1), e000034. https://doi.org/10.1136/bmjgast-2015-000034

Plackett, R., Kaushal, A., Kassianos, A. P., Cross, A., Lewins, D., Sheringham, J., Waller, J., & Wagner, C. von. (2020). Use of Social Media to Promote Cancer Screening and Early Diagnosis: Scoping Review. Journal of Medical Internet Research, 22(11), e21582. https://doi.org/10.2196/21582

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

Priaulx, J., Csanádi, M., de Koning, H. J., & McKee, M. (2019). A choice experiment to identify the most important elements of a successful cancer screening program according to those who research and manage such programs. The International Journal of Health Planning and Management, 34(1), e34–e45. https://doi.org/10.1002/hpm.2697

Priaulx, J., de Koning, H. J., de Kok, I. M. C. M., Széles, G., & McKee, M. (2018). Identifying the barriers to effective breast, cervical and colorectal cancer screening in thirty one European countries using the Barriers to Effective Screening Tool (BEST). Health Policy (Amsterdam, Netherlands), 122(11), 1190–1197. https://doi.org/10.1016/j.healthpol.2018.08.004

Priaulx, J., Turnbull, E., Heijnsdijk, E., Csanádi, M., Senore, C., de Koning, H. J., & McKee, M. (2020). The influence of health systems on breast, cervical and colorectal cancer screening: An overview of systematic reviews using health systems and implementation research frameworks. Journal of Health Services Research & Policy, 25(1), 49–58. https://doi.org/10.1177/1355819619842314

Prorok, P. C., Patrick, W., Thomas, R. R., Barnett, S. K., Christine, D. B., & John, K. G. (2018). Overall and Multiphasic Findings of the Prostate, Lung, Colorectal and Ovarian (PLCO) Randomized Cancer Screening Trial. Reviews on Recent Clinical Trials, 13(4), 257–273.

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

Rahner, N., & Steinke, V. (2008). Hereditary cancer syndromes. Deutsches Arzteblatt International, 105(41), 706–714. https://doi.org/10.3238/arztebl.2008.0706

Rainey, L., Waal, D. van der, Donnelly, L. S., Evans, D. G., Wengström, Y., & Broeders, M. (2018). Women's decision-making regarding risk-stratified breast cancer screening and prevention from the perspective of international healthcare professionals. PLOS ONE, 13(6), e0197772. https://doi.org/10.1371/journal.pone.0197772

Randel, K. R., Schult, A. L., Botteri, E., Hoff, G., Bretthauer, M., Ursin, G., Natvig, E., Berstad, P., Jørgensen, A., Sandvei, P. K., Olsen, M. E., Frigstad, S. O., Darre-Næss, O., Norvard, E. R., Bolstad, N., Kørner, H., Wibe, A., Wensaas, K.-A., de Lange, T., & Holme, Ø. (2021). Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. Gastroenterology, 160(4), 1085-1096.e5. https://doi.org/10.1053/j.gastro.2020.11.037

Rat, C., Latour, C., Rousseau, R., Gaultier, A., Pogu, C., Edwards, A., & Nguyen, J.-M. (2018). Interventions to increase uptake of faecal tests for colorectal cancer screening: A systematic review. European

Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP), 27(3), 227–236. https://doi.org/10.1097/CEJ.0000000000000344

Raut, J. R., Guan, Z., Schrotz-King, P., & Brenner, H. (2020). Fecal DNA methylation markers for detecting stages of colorectal cancer and its precursors: A systematic review. Clinical Epigenetics, 12(1), 122. https://doi.org/10.1186/s13148-020-00904-7

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

Reade, C. J., McVey, R. M., Tone, A. A., Finlayson, S. J., McAlpine, J. N., Fung-Kee-Fung, M., & Ferguson, S. E. (2014). The Fallopian Tube as the Origin of High Grade Serous Ovarian Cancer: Review of a Paradigm Shift. Journal of Obstetrics and Gynaecology Canada, 36(2), 133–140. https://doi.org/10.1016/S1701-2163(15)30659-9

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

Rey, D., Fressard, L., Cortaredona, S., Bocquier, A., Gautier, A., Peretti-Watel, P., & Verger, P. (2018). Vaccine hesitancy in the French population in 2016, and its association with vaccine uptake and perceived vaccine risk–benefit balance. Eurosurveillance, 23(17), 17–00816. https://doi.org/10.2807/1560-7917.ES.2018.23.17.17-00816

Ribbing Wilén, H., Blom, J., Höijer, J., Andersson, G., Löwbeer, C., & Hultcrantz, R. (2019). Fecal immunochemical test in cancer screening—Colonoscopy outcome in FIT positives and negatives. Scandinavian Journal of Gastroenterology, 54(3), 303–310. https://doi.org/10.1080/00365521.2019.1585569

Richards, M., Anderson, M., Carter, P., Ebert, B. L., & Mossialos, E. (2020). The impact of the COVID-19 pandemic on cancer care. Nature Cancer, 1–3. https://doi.org/10.1038/s43018-020-0074-y

Ronco, G., Dillner, J., Elfström, K. M., Tunesi, S., Snijders, P. J. F., Arbyn, M., Kitchener, H., Segnan, N., Gilham, C., Giorgi-Rossi, P., Berkhof, J., Peto, J., & Meijer, C. J. L. M. (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: Follow-up of four European randomised controlled trials. The Lancet, 383(9916), 524–532. https://doi.org/10.1016/S0140-6736(13)62218-7

Ross-Innes, C. S., Becq, J., Warren, A., Cheetham, R. K., Northen, H., O'Donovan, M., Malhotra, S., di Pietro, M., Ivakhno, S., He, M., Weaver, J. M. J., Lynch, A. G., Kingsbury, Z., Ross, M., Humphray, S., Bentley, D., & Fitzgerald, R. C. (2015). Whole-genome sequencing provides new insights into the clonal architecture of Barrett's esophagus and esophageal adenocarcinoma. Nature Genetics, 47(9), 1038–1046. https://doi.org/10.1038/ng.3357

Ross-Innes, C. S., Chettouh, H., Achilleos, A., Galeano-Dalmau, N., Debiram-Beecham, I., MacRae, S., Fessas, P., Walker, E., Varghese, S., Evan, T., Lao-Sirieix, P. S., O'Donovan, M., Malhotra, S., Novelli, M., Disep, B., Kaye, P. V., Lovat, L. B., Haidry, R., Griffin, M., … Fitzgerald, R. C. (2017). Risk stratification of Barrett's oesophagus using a non-endoscopic sampling method coupled with a biomarker panel: A cohort study. The Lancet Gastroenterology & Hepatology, 2(1), 23–31. https://doi.org/10.1016/S2468-1253(16)30118-2

Ross-Innes, C. S., Debiram-Beecham, I., O'Donovan, M., Walker, E., Varghese, S., Lao-Sirieix, P., Lovat, L., Griffin, M., Ragunath, K., Haidry, R., Sami, S. S., Kaye, P., Novelli, M., Disep, B., Ostler, R., Aigret, B., North, B. V., Bhandari, P., Haycock, A., … BEST2 Study Group. (2015). Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: A multi-center case-control study. PLoS Medicine, 12(1), e1001780. https://doi.org/10.1371/journal.pmed.1001780

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

Samoil, D., Kim, J., Fox, C., & Papadakos, J. K. (2021). The importance of health literacy on clinical cancer outcomes: A scoping review. Annals of Cancer Epidemiology, 5(0), Article 0. https://doi.org/10.21037/ace-20-30

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

Sarkeala, T., Färkkilä, M., Anttila, A., Hyöty, M., Kairaluoma, M., Rautio, T., Voutilainen, M., Helander, S., Jäntti, M., Lehtinen, M., Patrikka, L., Malila, N., & Heinävaara, S. (2021). Piloting gender-oriented colorectal cancer screening with a faecal immunochemical test: Population-based registry study from Finland. BMJ Open, 11(2), e046667. https://doi.org/10.1136/bmjopen-2020-046667

Savage, N. (2020). How AI is improving cancer diagnostics. Nature, 579(7800), S14–S16. https://doi.org/10.1038/d41586-020-00847-2

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

Schoen, R. E., Pinsky, P. F., Weissfeld, J. L., Yokochi, L. A., Church, T., Laiyemo, A. O., Bresalier, R., Andriole, G. L., Buys, S. S., Crawford, E. D., Fouad, M. N., Isaacs, C., Johnson, C. C., Reding, D. J., O'Brien, B., Carrick, D. M., Wright, P., Riley, T. L., Purdue, M. P., … Berg, C. D. (2012). Colorectal-Cancer Incidence and Mortality with Screening Flexible Sigmoidoscopy. New England Journal of Medicine, 366(25), 2345–2357. https://doi.org/10.1056/NEJMoa1114635

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

Schwartz, P. H., Imperiale, T. F., Perkins, S. M., Schmidt, K. K., Althouse, S., & Rawl, S. M. (2019). Impact of including quantitative information in a decision aid for colorectal cancer screening: A randomized controlled trial. Patient Education and Counseling, 102(4), 726–734. https://doi.org/10.1016/j.pec.2018.11.010

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

Selby, K., Levine, E. H., Doan, C., Gies, A., Brenner, H., Quesenberry, C., Lee, J. K., & Corley, D. A. (2019). Effect of Sex, Age, and Positivity Threshold on Fecal Immunochemical Test Accuracy: A Systematic Review and Meta-analysis. Gastroenterology, 157(6), 1494–1505. https://doi.org/10.1053/j.gastro.2019.08.023

Senore, C., Basu, P., Anttila, A., Ponti, A., Tomatis, M., Vale, D. B., Ronco, G., Soerjomataram, I., Primic-Žakelj, M., Riggi, E., Dillner, J., Elfström, M. K., Lönnberg, S., Sankaranarayanan, R., & Segnan, N. (2019). Performance of colorectal cancer screening in the European Union Member States: Data from the second European screening report. Gut, 68(7), 1232–1244. https://doi.org/10.1136/gutjnl-2018-317293

Senore, C., Riggi, E., Armaroli, P., Bonelli, L., Sciallero, S., Zappa, M., Arrigoni, A., Casella, C., Crosta, C., Falcini, F., Ferrero, F., Fracchia, M., Giuliani, O., Risio, M., Russo, A. G., Visioli, C. B., Rosso, S., Segnan, N., & SCORE Working Group. (2022). Long-Term Follow-up of the Italian Flexible Sigmoidoscopy Screening Trial. Annals of Internal Medicine, 175(1), 36–45. https://doi.org/10.7326/M21-0977

Senore, C., Zappa, M., Campari, C., Crotta, S., Armaroli, P., Arrigoni, A., Cassoni, P., Colla, R., Fracchia, M., Gili, F., Grazzini, G., Lolli, R., Menozzi, P., Orione, L., Polizzi, S., Rapi, S., Riggi, E., Rubeca, T., Sassatelli, R., … Segnan, N. (2020). Faecal haemoglobin concentration among subjects with negative FIT results is associated with the detection rate of neoplasia at subsequent rounds: A prospective study in the context of population based screening programmes in Italy. Gut, 69(3), 523–530. https://doi.org/10.1136/gutjnl-2018-318198

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

Shapira, S., Aiger, G., Ohayon, A., Kazanov, D., Mdah, F., Shimon, M. B., Hay-Levy, M., Banon, L., Laskov, I., Mashiah, J., Lev-Ari, S., & Arber, N. (2021). Predictors of the CD24/CD11b Biomarker among Healthy Subjects. Journal of Personalized Medicine, 11(9), 939. https://doi.org/10.3390/jpm11090939

Shen, S. Y., Singhania, R., Fehringer, G., Chakravarthy, A., Roehrl, M. H. A., Chadwick, D., Zuzarte, P. C., Borgida, A., Wang, T. T., Li, T., Kis, O., Zhao, Z., Spreafico, A., Medina, T. da S., Wang, Y., Roulois, D., Ettayebi, I., Chen, Z., Chow, S., … De Carvalho, D. D. (2018). Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature, 563(7732), 579–583. https://doi.org/10.1038/s41586-018-0703-0

Sicsic, J., Pelletier-Fleury, N., & Moumjid, N. (2018). Women's Benefits and Harms Trade-Offs in Breast Cancer Screening: Results from a Discrete-Choice Experiment. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 21(1), 78–88. https://doi.org/10.1016/j.jval.2017.07.003

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

Simms, K. T., Laprise, J.-F., Smith, M. A., Lew, J.-B., Caruana, M., Brisson, M., & Canfell, K. (2016). Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: A comparative modelling analysis. The Lancet Public Health, 1(2), e66–e75. https://doi.org/10.1016/S2468-2667(16)30019-6

Skaane, P., Bandos, A. I., Eben, E. B., Jebsen, I. N., Krager, M., Haakenaasen, U., Ekseth, U., Izadi, M., Hofvind, S., & Gullien, R. (2014). Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: Comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology, 271(3), 655–663. https://doi.org/10.1148/radiol.13131391

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

Smith, D., Thomson, K., Bambra, C., & Todd, A. (2019). The breast cancer paradox: A systematic review of the association between area-level deprivation and breast cancer screening uptake in Europe. Cancer Epidemiology, 60, 77–85. https://doi.org/10.1016/j.canep.2019.03.008

Smith-Bindman, R., Lipson, J., Marcus, R., Kim, K.-P., Mahesh, M., Gould, R., Berrington de González, A., & Miglioretti, D. L. (2009). Radiation dose associated with common computed tomography examinations

and the associated lifetime attributable risk of cancer. Archives of Internal Medicine, 169(22), 2078–2086. https://doi.org/10.1001/archinternmed.2009.427

Somsouk, M., Rachocki, C., Mannalithara, A., Garcia, D., Laleau, V., Grimes, B., Issaka, R. B., Chen, E., Vittinghoff, E., Shapiro, J. A., & Ladabaum, U. (2020). Effectiveness and Cost of Organized Outreach for Colorectal Cancer Screening: A Randomized, Controlled Trial. JNCI: Journal of the National Cancer Institute, 112(3), 305–313. https://doi.org/10.1093/jnci/djz110

Srivastava, S., & Wagner, P. D. (2020). The Early Detection Research Network: A National Infrastructure to Support the Discovery, Development, and Validation of Cancer Biomarkers. Cancer Epidemiology and Prevention Biomarkers, 29(12), 2401–2410. https://doi.org/10.1158/1055-9965.EPI-20-0237

Sroczynski, G., Gogollari, A., Naslazi, E., Pashayan, N., Widschwendter, M., & Siebert, U. (2018). PMD83—CERVICAL CANCER SCREENING IN EUROPE - A SYSTEMATIC REVIEW ON COST EFFECTIVENESS STUDIES WITH SPECIFIC INTEREST ON RISK-ADAPTED STRATEGIES. Value in Health, 21, S257. https://doi.org/10.1016/j.jval.2018.09.1532

Stacey, D., Légaré, F., Lewis, K., Barry, M. J., Bennett, C. L., Eden, K. B., Holmes-Rovner, M., Llewellyn-Thomas, H., Lyddiatt, A., Thomson, R., & Trevena, L. (2017). Decision aids for people facing health treatment or screening decisions. The Cochrane Database of Systematic Reviews, 4, CD001431. https://doi.org/10.1002/14651858.CD001431.pub5

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

Surveillance, Epidemiology and End Results (SEER) Program (2015). SEER 18 registries, 2010–2012. National Cancer Institute.

Swart, N., Maroni, R., Muldrew, B., Sasieni, P., Fitzgerald, R. C., & Morris, S. (2021). Economic evaluation of Cytosponge®-trefoil factor 3 for Barrett esophagus: A cost-utility analysis of randomised controlled trial data. EClinicalMedicine, 37. https://doi.org/10.1016/j.eclinm.2021.100969

Tabár, L., Chen, H.-H., Fagerberg, G., Duffy, S. W., & Smith, T. C. (1997). Recent Results From the Swedish Two-County Trial: The Effects of Age, Histologic Type, and Mode of Detection on the Efficacy of Breast Cancer Screening. JNCI Monographs, 1997(22), 43–47. https://doi.org/10.1093/jncimono/1997.22.43

Tabár, L., Faberberg, G., Day, N. E., & Holmberg, L. (1987). What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. British Journal of Cancer, 55(5), 547–551.

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

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

Tomonaga, Y., Ten Haaf, K., Frauenfelder, T., Kohler, M., Kouyos, R. D., Shilaih, M., Lorez, M., de Koning, H. J., Schwenkglenks, M., & Puhan, M. A. (2018). Cost-effectiveness of low-dose CT screening for lung cancer in a European country with high prevalence of smoking-A modelling study. Lung Cancer (Amsterdam, Netherlands), 121, 61–69. https://doi.org/10.1016/j.lungcan.2018.05.008

Trikalinos, T. A., Wieland, L. S., Adam, G. P., Zgodic, A., & Ntzani, E. E. (2014). Decision Aids for Cancer Screening and Treatment. Agency for Healthcare Research and Quality (US). http://www.ncbi.nlm.nih.gov/books/NBK269405/

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

Turnbull, E., Priaulx, J., van Ravesteyn, N. T., Heinävaara, S., Siljander, I., Senore, C., Segnan, N., Vokó, Z., Hagymásy, J., Jarm, K., Veerus, P., de Koning, H. J., & McKee, M. (2018). A health systems approach to identifying barriers to breast cancer screening programmes. Methodology and application in six European countries. Health Policy (Amsterdam, Netherlands), 122(11), 1198–1205. https://doi.org/10.1016/j.healthpol.2018.08.003

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 den Broek, J. J., Schechter, C. B., van Ravesteyn, N. T., Janssens, A. C. J. W., Wolfson, M. C., Trentham-Dietz, A., Simard, J., Easton, D. F., Mandelblatt, J. S., Kraft, P., & de Koning, H. J. (2021). Personalizing Breast Cancer Screening Based on Polygenic Risk and Family History. JNCI: Journal of the National Cancer Institute, 113(4), 434–442. https://doi.org/10.1093/jnci/djaa127

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 der Heide, I., Uiters, E., Jantine Schuit, A., Rademakers, J., & Fransen, M. (2015). Health literacy and informed decision making regarding colorectal cancer screening: A systematic review. European Journal of

Public Health, 25(4), 575–582. https://doi.org/10.1093/eurpub/ckv005

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. (2021a). 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

Van Poppel, H., Hogenhout, R., Albers, P., van den Bergh, R. C. N., Barentsz, J. O., & Roobol, M. J. (2021b). A European Model for an Organised Risk-stratified Early Detection Programme for Prostate Cancer. European Urology Oncology, 4(5), 731–739. https://doi.org/10.1016/j.euo.2021.06.006

Van Poppel, H., 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, 80(6), 703–711. https://doi.org/10.1016/j.eururo.2021.07.024

van Rossum, L. G., van Rijn, A. F., Laheij, R. J., van Oijen, M. G., Fockens, P., van Krieken, H. H., Verbeek, A. L., Jansen, J. B., & Dekker, E. (2008). Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology, 135(1), 82–90. https://doi.org/10.1053/j.gastro.2008.03.040

van Veen, E. M., Brentnall, A. R., Byers, H., Harkness, E. F., Astley, S. M., Sampson, S., Howell, A., Newman, W. G., Cuzick, J., & Evans, D. G. R. (2018). Use of Single-Nucleotide Polymorphisms and Mammographic Density Plus Classic Risk Factors for Breast Cancer Risk Prediction. JAMA Oncology, 4(4), 476–482. https://doi.org/10.1001/jamaoncol.2017.4881

Vandenberghe, P., Wlodarska, I., Tousseyn, T., Dehaspe, L., Dierickx, D., Verheecke, M., Uyttebroeck, A., Bechter, O., Delforge, M., Vandecaveye, V., Brison, N., Verhoef, G. E. G., Legius, E., Amant, F., & Vermeesch, J. R. (2015). Non-invasive detection of genomic imbalances in Hodgkin/Reed-Sternberg cells in early and advanced stage Hodgkin's lymphoma by sequencing of circulating cell-free DNA: A technical proof-of-principle study. The Lancet. Haematology, 2(2), e55-65. https://doi.org/10.1016/S2352-3026(14)00039-8

Veenhuizen, S. G. A., de Lange, S. V., Bakker, M. F., Pijnappel, R. M., Mann, R. M., Monninkhof, E. M., Emaus, M. J., de Koekkoek-Doll, P. K., Bisschops, R. H. C., Lobbes, M. B. I., de Jong, M. D. F., Duvivier, K. M., Veltman, J., Karssemeijer, N., de Koning, H. J., van Diest, P. J., Mali, W. P. T. M., van den Bosch, M. A. A. J., van Gils, C. H., … DENSE Trial Study Group. (2021). Supplemental Breast MRI for Women with Extremely Dense Breasts: Results of the Second Screening Round of the DENSE Trial. Radiology, 299(2), 278–286. https://doi.org/10.1148/radiol.2021203633

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

Venkatesan, P. (2021). Artificial intelligence and cancer diagnosis: Caution needed. The Lancet Oncology, 22(10), 1364. https://doi.org/10.1016/S1470-2045(21)00533-7

Venneman, K., Huybrechts, I., Gunter, M. J., Vandendaele, L., Herrero, R., & Van Herck, K. (2018). The epidemiology of *Helicobacter pylori* infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: A systematic review. Helicobacter, 23(3), e12483. https://doi.org/10.1111/hel.12483

Verburg, E., van Gils, C. H., van der Velden, B. H. M., Bakker, M. F., Pijnappel, R. M., Veldhuis, W. B., & Gilhuijs, K. G. A. (2021). Deep Learning for Automated Triaging of 4581 Breast MRI Examinations from the DENSE Trial. Radiology, 203960. https://doi.org/10.1148/radiol.2021203960

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

Vokinger, K. N., Feuerriegel, S., & Kesselheim, A. S. (2021). Mitigating bias in machine learning for medicine. Communications Medicine, 1(1), 1–3. https://doi.org/10.1038/s43856-021-00028-w

Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J., Peto, J., Meijer, C. J., & Muñoz, N. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of Pathology, 189(1), 12–19. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

Wan, J. C. M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J. D., Caldas, C., Pacey, S., Baird, R., & Rosenfeld, N. (2017). Liquid biopsies come of age: Towards implementation of circulating tumour DNA. Nature Reviews Cancer, 17(4), 223–238. https://doi.org/10.1038/nrc.2017.7

Wanders, J. O. P., Holland, K., Veldhuis, W. B., Mann, R. M., Pijnappel, R. M., Peeters, P. H. M., van Gils, C. H., & Karssemeijer, N. (2017). Volumetric breast density affects performance of digital screening mammography. Breast Cancer Research and Treatment, 162(1), 95–103. https://doi.org/10.1007/s10549-016-4090-7

Wang, L., Li, J., Xiong, X., Hao, T., Zhang, C., Gao, Z., Zhong, L., & Zhao, Y. (2021). Volatile organic compounds as a potential screening tool for neoplasm of the digestive system: A meta-analysis. Scientific Reports, 11(1), 23716. https://doi.org/10.1038/s41598-021-02906-8

Weinberg, D. S., Myers, R. E., Keenan, E., Ruth, K., Sifri, R., Ziring, B., Ross, E., & Manne, S. L. (2014). Genetic and Environmental Risk Assessment and Colorectal Cancer Screening in an Average-Risk Population. Annals of Internal Medicine, 161(8), 537–545. https://doi.org/10.7326/M14-0765

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

Wilding, S., Tsipa, A., Branley-Bell, D., Greenwood, D. C., Vargas-Palacios, A., Yaziji, N., Addison, C., Kelly, P., Day, F., Horsfall, K., Conner, M., & O'Connor, D. B. (2020). Cluster randomized controlled trial of volitional and motivational interventions to improve bowel cancer screening uptake: A population-level study. Social Science & Medicine, 265, 113496. https://doi.org/10.1016/j.socscimed.2020.113496

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

Xiao, H.-F., Yan, S.-P., Chen, Y., Shi, Z., Zou, Y.-H., Zhu, S., Xu, K.-K., Song, T., & Liao, X.-Z. (2020). Community-Based Upper Gastrointestinal Cancer Screening in a Randomized Controlled Trial: Baseline Results in a Non-high-incidence Area. Cancer Prevention Research, 13(3), 317–328. https://doi.org/10.1158/1940-6207.CAPR-19-0422

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

Yang, X., Leslie, G., Gentry-Maharaj, A., Ryan, A., Intermaggio, M., Lee, A., Kalsi, J. K., Tyrer, J., Gaba, F., Manchanda, R., Pharoah, P. D. P., Gayther, S. A., Ramus, S. J., Jacobs, I., Menon, U., & Antoniou, A. C. (2018). Evaluation of polygenic risk scores for ovarian cancer risk prediction in a prospective cohort study. Journal of Medical Genetics, 55(8), 546–554. https://doi.org/10.1136/jmedgenet-2018-105313

Yeh, P. T., Kennedy, C. E., Vuyst, H. de, & Narasimhan, M. (2019). Self-sampling for human papillomavirus (HPV) testing: A systematic review and meta-analysis. BMJ Global Health, 4(3), e001351. https://doi.org/10.1136/bmjgh-2018-001351

Young, A. T., Vora, N. B., Cortez, J., Tam, A., Yeniay, Y., Afifi, L., Yan, D., Nosrati, A., Wong, A., Johal, A., & Wei, M. L. (2021). The role of technology in melanoma screening and diagnosis. Pigment Cell & Melanoma Research, 34(2), 288–300. https://doi.org/10.1111/pcmr.12907

Zackrisson, S. (2019). Tomosynthesis in breast screening: Great expectations? The Lancet Oncology, 20(6), 745–746. https://doi.org/10.1016/S1470-2045(19)30287-6

Zauber, A., Knudsen, A., Rutter, C., Naber, S., Doria-Rose, P., Pabiniak, C., Johanson, C., Fischer, S., Lansdorp-Vogelaar, I., & Kuntz, K. (2015). Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach.

Zeng, B., Yu, K., Gao, L., Zeng, X., & Zhou, Q. (2021). Breast cancer screening using synthesized two-dimensional mammography: A systematic review and meta-analysis. Breast (Edinburgh, Scotland), 59, 270–278. https://doi.org/10.1016/j.breast.2021.07.016

Zeng, H., Sun, K., Cao, M., Zheng, R., Sun, X., Liu, S., Zhang, Z., Liu, Y., Guo, G., Song, G., Zhu, Y., Wu, X., Song, B., Liao, X., Chen, Y., Song, M., Giovannucci, E., Zhuang, G., Wei, W., … He, J. (2020). Initial results from a multi-center population-based cluster randomized trial of esophageal and gastric cancer screening in China. BMC Gastroenterology, 20(1), 398. https://doi.org/10.1186/s12876-020-01517-3

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

Zhang, Y., Wu, Q., Xu, L., Wang, H., Liu, X., Li, S., Hu, T., Liu, Y., Peng, Q., Chen, Z., Wu, X., & Fan, J.-B. (2021). Sensitive detection of colorectal cancer in peripheral blood by a novel methylation assay. Clinical Epigenetics, 13(1), 90. https://doi.org/10.1186/s13148-021-01076-8

Zielonke, N., Gini, A., Jansen, E. E. L., Anttila, A., Segnan, N., Ponti, A., Veerus, P., de Koning, H. J., van Ravesteyn, N. T., Heijnsdijk, E. A. M., & EU-TOPIA consortium. (2020). Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. European Journal of Cancer (Oxford, England: 1990), 127, 191–206. https://doi.org/10.1016/j.ejca.2019.12.010

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

Annex 1. Background and methodology

Scoping phase

The lead network for the cancer screening topic, the Federation of European Academies of Medicine (FEAM), was responsible for conducting initial scoping and exploratory work on behalf of SAPEA in 2020 and 2021. In May 2021, the Group of Chief Scientific Advisors was requested by the European Commission to write a Scientific Opinion and SAPEA was requested to write a new Evidence Review Report on cancer screening in the European Union. The scoping paper was published online[1] and set out the issue at stake, background information and the three core questions that should be answered. The questions are:

- How can cancer screening programmes targeting breast, cervical and colorectal cancers, be improved throughout the EU?
- What is the scientific basis extending such screening programmes to other cancers e.g., lung, prostate and gastric cancers, and ensuring their feasibility throughout the EU?
- Which are the main scientific elements to consider, and best practices to promote, for optimising risk-based cancer screening and early diagnosis throughout the EU?

The scoping paper highlighted that the European Commission will make a proposal in 2022 to update the 2003 Council Recommendation on cancer screening[2] to ensure that it reflects the latest available scientific evidence. One of the objectives will be to consider the extension of cancer screening beyond breast, colorectal and cervical cancer to include prostate, lung and gastric cancer, and other cancers if supported by scientific evidence.

Responsibilities and working structure within the SAM

Four members of the Group of Chief Scientific Advisors were involved with the project: Éva Kondorosl, Nicole Grobert (Chair of the group), Eva Zažímalová and Alberto Melloni. Éva Kondorosl was appointed as Lead Scientific Advisor for the cancer screening topic and was responsible for chairing the SAM Coordination Group meetings. The representatives for SAPEA were Stefan Constantinescu (FEAM President) and George Griffin (FEAM Past President) supported by Hannah Whittle (SAPEA Scientific Policy Officer for FEAM). The two Project Chairs, Rebecca Fitzgerald (Professor of Cancer Prevention at the University of Cambridge, UK and Interim Director of the MRC Cancer Unit, United Kingdom) and Harry de Koning (Deputy Head and Professor of Public Health and Screening Evaluation, Erasmus MC University Medical Center, Rotterdam, Netherlands) and the Scientific Writer, Kat Arney, also joined Coordination Group meetings, alongside Louise Edwards (SAPEA Scientific Policy Officer for Academia

1 https://ec.europa.eu/info/sites/default/files/research_and_innovation/groups/sam/scoping_paper-cancer_screening-april_2021.pdf

2 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003H0878&from=EN

Europaea). Alison Weightman (Director of the Specialist Unit for Review Evidence at Cardiff University) also joined meetings to provide an update on the rapid literature reviews.

Ingrid Zegers, Matina Halkia and Vladia Monsurro coordinated the project from the Science Policy, Advice and Ethics unit at DG RTD. They were responsible for preparing the Coordination Group meetings, the stakeholder and sounding board meetings of the Advisors and the handover of the final Evidence Review Report and Scientific Opinion.

FEAM was responsible for organising several planning meetings, Working Group meetings and the three expert workshops, which were chaired by Rebecca Fitzgerald and Harry de Koning.

Expert workshops

Three expert workshops took place in September, October and November 2021. Each workshop focused on one of the three key questions listed in the scoping paper. The Project Chairs were responsible for selecting the expert speakers in accordance with their expertise and careful consideration was also given to gender and geographical balance. In total 33 experts from Europe, five from the USA, four from Canada and one from Israel, each delivered a 15-minute presentation at the workshops. This was followed by 10 minutes of discussion time with the Chairs and other participants. All expert speakers were also invited to participate in round-table debates during the workshops.

Prior to the workshops, the experts who accepted the invitation to participate were informed about the proposed title of their presentation and were given a specific subtopic of expertise to address. They were sent a copy of the relevant rapid literature review, conducted by Cardiff University, and the draft agenda. They were also asked to inform SAPEA if they did or did not have any conflicts of interest relating to the cancer screening project. These responses were assessed by the Project Chairs. Additionally, desk research on all speakers was undertaken to gather more information about interests. The Project Chairs and the scientific writer completed full declaration of interests forms and these are available on the SAPEA website for a duration of six months following the publication of this report.

The workshops were chaired by Rebecca Fitzgerald and Harry de Koning and each featured a presentation of the relevant rapid literature review. These presentations were delivered by staff from the Specialist Unit for Review Evidence at Cardiff University. Expert speakers were invited to provide feedback on the rapid literature reviews. Furthermore, after the workshops the Scientific Writer prepared workshop summary reports. All experts were sent a copy of the section that related to their presentation and were invited review it and to provide written feedback.

The workshops took place in a hybrid format, with some speakers based at a venue in Rotterdam and most attending online. The technical elements were overseen by technicians from MEB Rotterdam. Several experts from European Academies were invited to act as workshop observers.

Rapid literature reviews

Cardiff University's Specialist Unit for Review Evidence was responsible for the literature review, overseen by Academia Europaea. Three rapid reviews were undertaken, one for each of the main scoping questions. These are a lighter form of a full systematic review that take account of time constraints.

For every rapid review, a protocol was produced. This set out the search strategy, with a focus on controlled trials. Each protocol was approved by the Chairs prior to running the search. The initial results set was screened against the inclusion/exclusion criteria, then the final set of results was summarised by subject experts. The Review Team was led by Dr Alison Weightman, the Director of SURE, together with Dr Nick Courtier (Cardiff University), Dr Hui-Ling Ou (University of Cambridge) and Louise Edwards (Cardiff University/Academia Europaea).

The rapid review draft was provided to the workshop attendees, with a summary presented at the workshop and feedback invited. The draft reviews subsequently underwent rounds of revision, in response to feedback. The final drafts of the rapid reviews were peer-reviewed by senior subject experts, three at Cardiff University and one nominated by Academia Europaea.

These rapid reviews summarise a valuable subset of the evidence base. They emphasise the findings from recent randomised and other controlled clinical trials, providing evidence with the least potential for bias. To meet deadlines, a pragmatic and precise search strategy was employed. It is possible that further controlled trials would have been identified if there had been time for a detailed and sensitive systematic search. The timeline also precluded any statistical or meta-analysis of findings unless these were available from published systematic reviews. No formal critical appraisal was carried out, although information is provided on whether the trial included a power calculation. Data extraction and summary were undertaken by different reviewers and, although reviewed by another author, these have not been independently checked for accuracy and consistency.

The three rapid reviews are published separately on the SAPEA website. They provide comprehensive detail of methods employed, as well as the findings. The top-line results are included in the main SAPEA Evidence Review Report, with cross-referencing between the documents.

Peer review

In accordance with the SAPEA Quality Assurance Guidelines, a minimum of three peer reviewers were required to undertake a double-blind peer review process (i.e. peer reviewers do not know the identity of the Project Chairs, and vice versa, during the process). The peer reviewers were identified and chosen by the different SAPEA networks and consideration was given to gender and geographical balance. Following these directions, four peer reviewers were identified and three responded in the required format. The selection of the peer reviewers was done by EASAC and the peer review process was overseen by Louise Edwards from Academia Europaea.

Publication

The main evidence review report is accompanied by several parallel documents: three expert workshop summary reports and three rapid literature reviews. All documents can be accessed on the SAPEA website: www.sapea.info/cancerscreening/.

Plagiarism check

A plagiarism check on the main report and workshop summary reports was run by Cardiff University using Turnitin software.

Annex 2. Expert workshop attendees

The following pages summarise the attendees and agenda for each of the expert workshops that took place during the preparation of this report.

For further details of all the workshops, please refer to the workshop summary reports: https://www.sapea.info/cancerscreening/

Workshop 1 (21 September 2021)

- **Chairs:**
  - Professor Rebecca Fitzgerald (Professor of Cancer Prevention at the University of Cambridge, UK and Interim Director of the MRC Cancer Unit, United Kingdom)
  - Professor Harry de Koning (Deputy Head and Professor of Public Health and Screening Evaluation-Erasmus MC University Medical Center, Rotterdam, Netherlands)
- **For SAPEA:**
  - Professor Stefan Constantinescu (FEAM president)
  - Professor George Griffin (FEAM past president)
- **For the Specialist Unit for Review Evidence at Cardiff University, Wales:**
  - Dr Alison Weightman (Director)
- Professor David Baldwin (Consultant Respiratory Physician and Honorary Professor of Medicine, Respiratory Medicine Unit, Nottingham University Hospitals and University of Nottingham, United Kingdom)
- Professor Jelle Barentsz (Professor of Radiology and Chair of the Prostate MR Expert Centre, Radboudumc, Netherlands)
- Professor Matthew Callister (Consultant Respiratory Physician, Leeds Teaching Hospitals NHS Trust, United Kingdom)
- André Deschamps (Chairman, EUROPA UOMO-The Voice of Men with Prostate Cancer in Europe, Antwerp, Belgium)
- Professor Mark Dobrow (Associate Professor, Institute of Health Policy, Management and Evaluation, University of Toronto, Canada)
- Professor Ruth Etzioni (Public Health Sciences Division-Fred Hutchinson Cancer Research Centre, Seattle, USA)
- Professor/ Chief Physician Jonas Hugosson (Department of Urology, University of Gothenburg, Sweden)
- Dr Urska Ivanus (Assistant Professor, Head of Screening Department, Institute of Oncology Ljubljana and Head on National Cancer Screening Committee, Slovenia)
- Professor Rudolf Kaaks (Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany)
- Professor Michal Kaminski (Head of Department of Cancer Prevention and Head of Endoscopy Unit, Department of Gastroenterological Oncology at the Maria-Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland)
- Dr Iris Lansdorp-Vogelaar (Associate Professor-Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands)
- Professor Mārcis Leja (Professor, Faculty of Medicine, University of Latvia, Latvia)
- Professor Usha Menon (Professor of Gynaecological Cancer, MRC Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, United Kingdom)
- Professor Linda Rabeneck (Vice President, Prevention and Cancer Control, Ontario Health and Professor of Medicine, University of Toronto, Canada)
- Professor Martin Tammemagi (Senior Scientist- Prevention and Cancer Control, Faculty of Health Sciences, Brock University, Canada)
- Dr Carmen Ungurean (Cancer screening coordinator, 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

Workshop 2 (10 October 2021)

- **Chairs:**
  - Professor Rebecca Fitzgerald (Professor of Cancer Prevention at the University of Cambridge, UK and Interim Director of the MRC Cancer Unit, United Kingdom)
  - Professor Harry de Koning (Deputy Head and Professor of Public Health and Screening Evaluation-Erasmus MC University Medical Center, Rotterdam, Netherlands)
- **For SAPEA:**
  - Professor Stefan Constantinescu (FEAM president)
  - Professor George Griffin (FEAM past president)
- **For the Specialist Unit for Review Evidence at Cardiff University, Wales:**
  - Louise Edwards (SAPEA Scientific Policy Officer at Academia Europaea)
  - Dr Hui-Ling Ou (Postdoctoral Research Associate at University of Cambridge, UK; seconded)
- Professor Marc Arbyn (Coordinator of the Unit of Cancer Epidemiology, Belgian Cancer Centre, Belgium)
- Dr Mirza Balaj (CHAIN Research Coordinator, Norwegian University of Science and Technology, Trondheim, Norway)
- Dr Partha Basu (Deputy Head of Early Detection, Prevention and Infection Branch, International Agency for Research on Cancer, World Health Organisation, France)
- Professor Patrick M Bossuyt (Professor of Clinical Epidemiology, University of Amsterdam, Netherlands)
- Professor Joakim Dillner (Professor in infectious disease epidemiology at Karolinska Instituet, Sweden)
- Dr Sirpa Heinävaara (Senior Researcher at Finnish Cancer Registry, Finland)
- Professor Solveig Hofvind (Cancer Registry of Norway and Department of Health and Care Sciences, Faculty of Health Sciences, The Arctic University of Norway, Tromsø, Norway)
- Dr Iris Lansdorp-Vogelaar (Associate Professor-Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands)
- Professor Anne Mackie (Director of Screening at Public Health England, United Kingdom)
- Zorana Maravic (CEO at Digestive Cancers Europe, Brussels, Belgium)
- Professor Peter Sasieni (Academic Director of King's Clinical Trials Unit and Professor of Cancer Prevention, King's College London, United Kingdom)
- Professor Robert Smith (Cancer Epidemiologist and Senior Director, Cancer Control at the National Office of the American Cancer Society in Atlanta, Georgia, USA)
- Professor Carla H. van Gils (Professor of Clinical Epidemiology of Cancer, UMC Utrecht, Netherlands)
- Professor Zoltán Voko (Director and Professor of Epidemiology at Centre for Health Technology Assessment, Semmelweis University, Budapest and Medical Director at Syreon Research Institute, Hungary)

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

Workshop 3 (8 November 2021)

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

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

Annex 3. Glossary of key terms

Term	Explanation
Achalasia	A rare motility disorder that makes it difficult for food and liquid to pass from the oesophagus into the stomach. It can be associated with cancer.
Adenocarcinoma	A malignant tumour originating in glandular epithelium.
Adenoma	Benign tumour of glandular tissue in which tumour cells form glands or gland-like structures.
Artificial Intelligence (AI)	The ability of a computer or computer-controlled robot to perform tasks commonly associated with intelligent beings.
Barrett's dysplasia	A pre-cancerous stage in Barrett's oesophagus, where the cells develop more abnormal features.
Barrett's oesophagus	A condition in which the tissue lining the oesophagus is replaced by tissue similar to that of the intestinal lining. This occurs at the lower end of the oesophagus, usually in response to chronic damage from bile and acid reflux.
Biomarker	An objective measure, such as the presence of a particular protein or other molecule, that captures what is happening in a cell or an organism at a given moment.
Biparametric magnetic resonance imaging (bpMRI)	A type of MRI scanning used in prostate cancer screening.
Capability barriers	Barriers including workforce, resources and infrastructure.
Carcinoma in situ	A cancer that is only present in the place where it started and is superficial and has not spread to any tissues nearby.
Cervical intraepithelial neoplasia (CIN)	The abnormal growth of cells on the surface of the cervix that could potentially lead to cervical cancer.
Circulating tumour cell (CTC)	A cell that has been shed into the bloodstream or lymphatic system from a primary tumour and is carried around the body.
Circulating tumour DNA (ctDNA)	DNA found in the bloodstream that comes from cancerous cells and tumours.
Clonal haematopoiesis	A process of normal ageing that occurs when a stem cell starts making a population of blood cells with the same genetic alteration.
Clonal proliferation	Multiplication or reproduction by cell division of a population of identical cells descended from a single progenitor.
Colonoscopy	A type of endoscopy examination used to detect changes or abnormalities in the large intestine (colon) and rectum.
Colorectal adenoma	A benign glandular tumour of the colon or rectum that is a precursor to colorectal cancer.
Comorbidities	The state of having multiple medical conditions at the same time, especially when they interact with each other in some way.
Computed tomography (CT)	A type of scan that uses X-rays to generate images of the tissues inside the body.

Term	Explanation
Cytology	Involves examining cells from bodily tissues or fluids to determine a diagnosis.
Deep Learning	A machine learning technique that constructs artificial neural networks to mimic the structure and function of the human brain.
Dense breasts	Women with a lower proportion of fat and more fibrous/glandular tissue in their breasts are said to have 'dense' breasts.
Digital Breast Tomosynthesis (DBT)	Also referred to as 3D mammography. It is an imaging test that uses X-rays to take multiple pictures of the breast.
DNA methylation	A chemical modification of DNA that is involved in controlling patterns of gene activity.
Ductal carcinoma in situ (DCIS)	The presence of abnormal cells inside a milk duct in the breast, considered to be the earliest, non-invasive form of breast cancer.
Dysplasia	Localised abnormal pre-cancerous growth of cells or tissues. If these cells continue to grow, they can create tumours.
Endothelial cells	Cells that form a barrier between vessels and tissues. They control the flow of substances and fluid into and out of a tissue.
Epigenetics	The study of how alterations in proteins and chemicals around the DNA can cause changes that affect the way genes work.
Exosomes	Small biological 'packets' released from cells that can shuttle genetic information and proteins to other cells in the body.
Faecal immunochemical test (FIT)	An antibody-based test for the presence of hidden blood in the stool, which can be an early sign of colorectal cancer.
Flexible sigmoidoscopy	A type of endoscopy examination used to detect changes or abnormalities in the rectum and lower part of the colon.
Gastro-oesophageal junction	The part of the gastrointestinal tract where the oesophagus and stomach join.
Genome sequencing	Technology used to read the information in a DNA molecule.
Germline mutations	Also called hereditary mutations. They are passed on from parents to offspring. Inherited germline mutations play an important role in cancer risk and susceptibility.
Guaiac faecal occult blood test (gFOBT)	A chemical test for the presence of hidden blood in the stool, which can be an early sign of colorectal cancer.
Health system barriers	Barriers including availability, affordability and acceptability of screening.
Helicobacter pylori (*H. pylori*)	A bacterium that is commonly found in the stomach and is a cause of stomach cancer.
Human papillomavirus (HPV)	A common virus from the Papillomaviridae family. Some strains are associated with certain types of cancer, most notably cervical cancer.
Immunotherapy	Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process.
Intention barriers	Barriers including public motivation and priorities, communication and social influence, and health beliefs and behaviours.

Glossary of key terms

Term	Explanation
Interval cancers	Cancers that are diagnosed in between routine screening appointments.
Lead time bias	When a screening intervention appears to increase survival but in fact the disease has progressed at the same speed that it would have anyway, had it been detected at a later stage.
Liquid biopsy	Sampling and analysis of non-solid biological tissue, often blood but can also be breath, urine or other biofluids.
Low-dose CT scan (LDCT)	A type of CT scan that produces high-resolution three-dimensional images while limiting the radiation exposure to the patient.
Magnetic resonance imaging (MRI)	A type of scan that uses magnetic fields to generate images of the tissues inside the body.
Melanoma	A type of skin cancer that develops from the pigment-producing cells known as melanocytes. Melanomas typically occur in the skin, but can occur in internal organs as well.
Metastatic	The process of cancer spreading from the site where it first starts to neighbouring tissues or other parts of the body.
Mosaicism	A condition where one or more groups of cells in the body can have a different genetic makeup from others.
Multiomics	An approach where the data from different types of molecular analysis, DNA, RNA and methylation, are combined.
Multiparametric magnetic resonance imaging (mpMRI)	The combination of multiple magnetic resonance techniques to achieve an image that will allow for better identification of tumour size and location.
Non-invasive prenatal testing (NIPT)	A blood test taken from the mother in pregnancy, which uses DNA analysis to evaluate whether a baby is likely to have certain genetic conditions.
Pepsinogen	A substance which is secreted by the stomach wall and converted into the enzyme pepsin by gastric acid.
Positron emission tomography (PET)	A type of scan that uses a safe radioactive drug to show areas of the body where cells are more active than normal.
PET-CT	A type of medical imaging combining a CT scan and a PET scan. The CT scan takes a series of x-rays and combines them to create a 3-dimensional picture.
Polygenic risk score (PRS)	An estimate of the likelihood of an individual getting a particular disease, based on their underlying genetic makeup.
Prophylactic	Medication or treatment designed and used to prevent a disease from occurring.
Prostatectomy	The surgical removal of all or part of the prostate gland.
Prostate-specific antigen (PSA)	PSA is secreted by the epithelial cells of the prostate gland and can be detected in a sample of blood.
Quality- Adjusted Life Year (QALY)	A standardised measure of disease burden which combines both survival and health-related quality of life into a single index, primarily used to analyse the cost-effectiveness analyses of different healthcare interventions.
Squamous cell carcinomas (SCCs)	A term referring to a number of different types of cancer that arise from squamous cells. These cells form on the surface of the skin, on the lining of some hollow organs in the body, including parts of the respiratory and digestive tracts (oesophagus and anus).
Transnasal endoscopy (TNE)	An upper endoscopy method which is performed by the nasal route (rather than the mouth) using a thin endoscope less than 6 mm in diameter.

Annex 4. Acknowledgements

SAPEA wishes to thank the following people for their valued contributions and support in the production of this report.

Project Chairs

- Professor Rebecca Fitzgerald, Professor of Cancer Prevention at the University of Cambridge, UK and Interim Director of the MRC Cancer Unit, United Kingdom
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Plagiarism check

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- MEB Rotterdam Event Professionals

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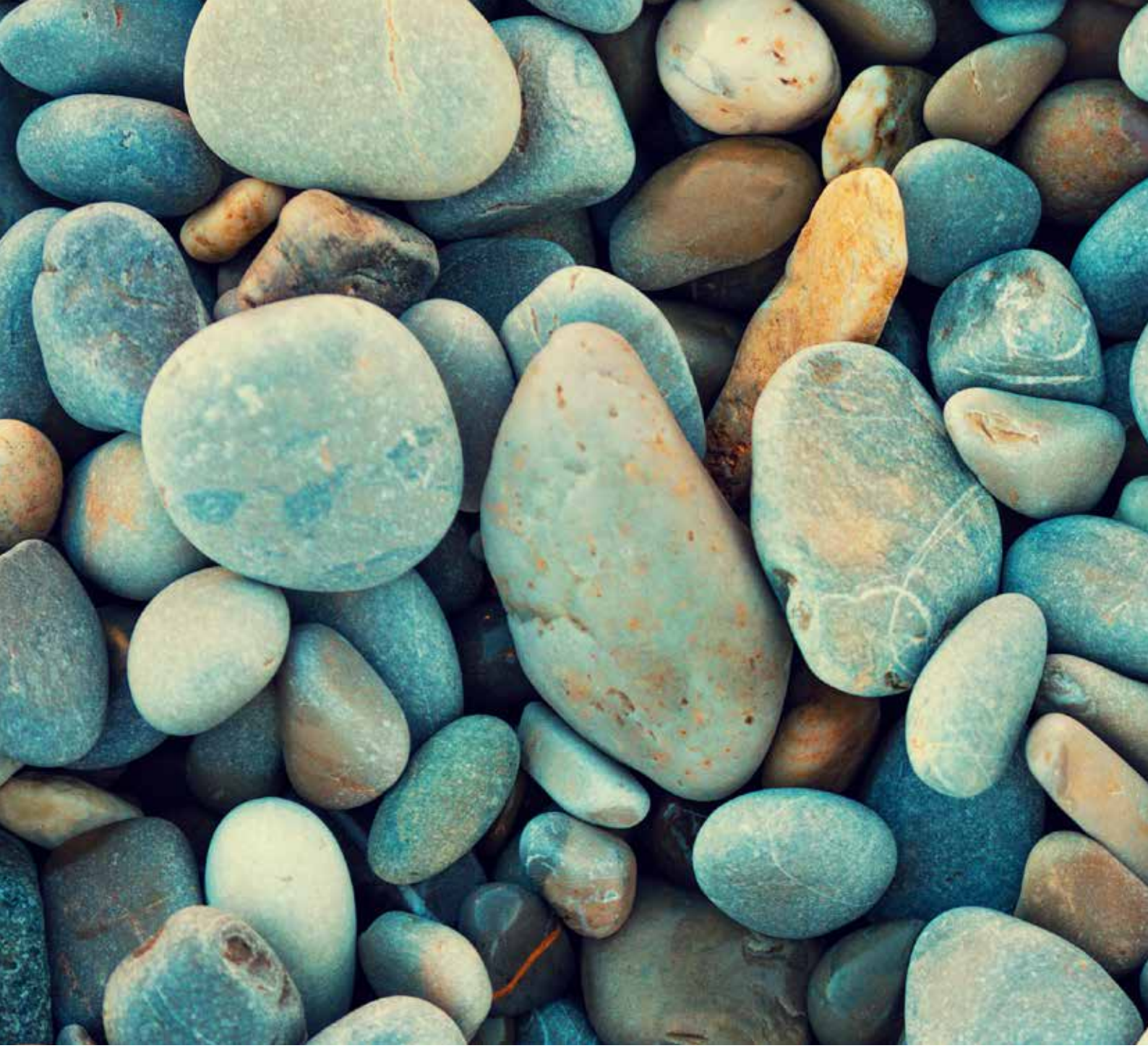

SAPEA is part of the European Commission's Scientific Advice Mechanism, which provides independent, interdisciplinary, and evidence-based scientific advice on policy issues to the European Commission.

This Evidence Review Report informs the Group of Chief Scientific Advisors' Scientific Opinion on the topic.

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