Cancer screening in Europe

Expert workshop 3

8 November 2021

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

SAPEA
Science Advice for Policy by European Academies

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1. Introduction

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

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

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

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

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

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

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

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

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

2. Risk-based screening for cancer

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

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

2.1. Principles of targeted and risk-stratified screening

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

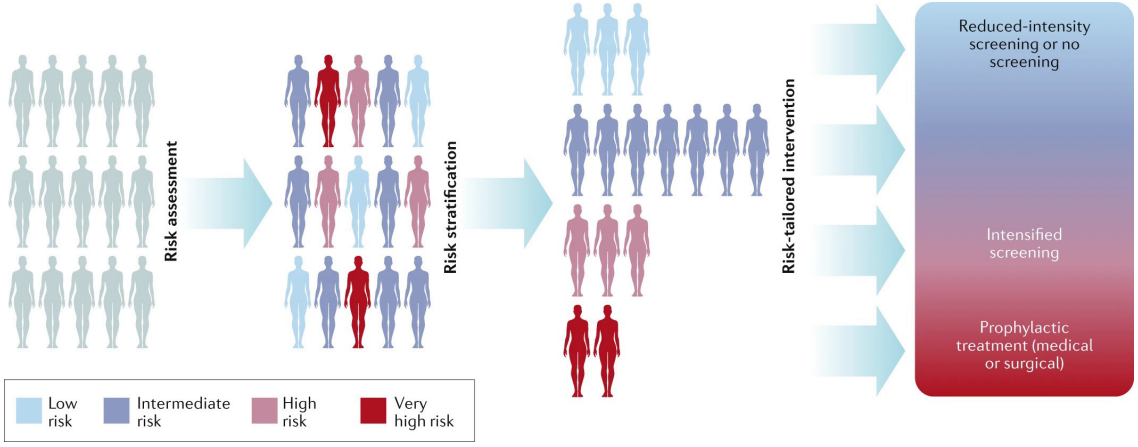

Figure 1. From Pashayan et al., 2020

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

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

2.2. Risk-stratified screening for breast cancer

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

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

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

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

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

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

2.3. Risk-stratified screening for prostate cancer

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

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

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

3 https://www.mypebs.eu/

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

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

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

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

2.4. Conclusions

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

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

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

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

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

3. Shared decision-making around cancer screening

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Emerging novel biomarker-based cancer screening technologies

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

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

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

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

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

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

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

Case study: Cytosponge for non-endoscopic oesophageal cancer screening

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

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

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

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

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

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

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

4.1. Circulating tumour DNA (ctDNA)

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

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

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

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

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

Case study: CancerSEEK

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

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

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

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

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

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

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

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

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

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

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

4.2. DNA methylation

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

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

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

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

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

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

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

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

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

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

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

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

4.3. Circulating tumour cells

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

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

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

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

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

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

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

4.4. Conclusion

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

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

Emerging novel biomarker-based cancer screening technologies

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

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

5. Principles for targeted cancer screening

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

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

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

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

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

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

- quality and performance management

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7. AI applied to radiology for cancer detection

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

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

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

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

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

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

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

8. Discussion

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

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

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

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

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

Appendix 1: Programme and contributors

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

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

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