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Advances in the criteria for cancer screening

Work Package 5, task 5.2. Cancer Screening: Background Paper

Authors:	Ahti Anttila, Satu Lipponen, Deependra Singh, Stefan Lönnberg, Clarissa Bingham, Ana Molina Barceló, Paolo Giorgi Rossi, Marco Zappa - A.A., Sa.L., St.L, D.S., C.B. from the Cancer Society of Finland, Helsinki; A.M.B. from the Fundació per al Foment de la Investigació Sanitaria i Biomédica de la Comunitat Valenciana, FISABIO, Valencia; P.G.R. from the Inter-institutional Epidemiology Service in Reggio Emilia, Italy; M.Z. from the Istituto per lo studio, la prevenzione e la rete oncologica (ISPRO), Florence
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Abbreviations

EU	European Union
iPAAC	Innovative Partnership for Action Against Cancer
EPAAC	European Partnership for Action Against Cancer
CANCON	Cancer Control Joint Action
EFTA	European Free Trade Association
ECL	Association of European Cancer Leagues
IARC	International Agency for Research on Cancer
WP	Work Package
WHO	World Health Organization
HPV	Human Papillomavirus
BC	Breast cancer
BCRA	Breast cancer gene
US	United States
HIV	Human immune-deficiency virus
PPV	Positive predictive value
RCT	Randomized controlled trial
LDCT	Low-dose computed tomography
PSA	Prostate-specific antigen
NLST	National Lung Cancer Screening Trial
NELSON	Nederlands Leuven Longkanker Screenings Onderzoek
PCa	Prostate cancer
PLCO	Prostate, Lung, Colorectal and Ovarian
ERSPC	European Randomized Study of Screening for Prostate Cancer
MISCAN	Microsimulation Screening Analysis
CHAFEA	Consumers, Health, Agriculture and Food Executive Agency
CIN 3	Cervical Intraepithelial neoplasia grade 3
CT	Computed tomography
FIT	Faecal immunochemical test
QA	Quality assurance
QALY	Quality-adjusted life-year(s)

Executive summary

There have been considerable developments during the last 15 years in the implementation of population-based screening programmes for cancer within the European Union Member States. Still many of the Member States lack systematic, comprehensive policy-making protocols and structures for well-functioning cancer screening programmes. Developed in previous Joint Actions, WP5 is looking for social innovations and tools for implementation in three EU council recommended screening programmes. One key area is reducing inequality through cancer screening programmes. This report highlights the current concepts and criteria for population-based cancer screening. Quality assurance and good governance are important themes of effective programmes. The topical issues of the report include principles of risk-adjusted screening within the population-based screening programmes, based on information on high risk groups or genetic susceptibility data. Information and suggestions on potential new programmes (lung, prostate) are also briefly updated in this report. Topics presented in this report will be further discussed in the Conference on cancer screening, to be held in Helsinki on the 5th of December 2019; and further discussions and conclusions will be modified accordingly. The report will also be utilized in developing the Roadmap on Implementation and Sustainability of Cancer Control Actions.

1. Introduction

1.1. Work Package 5 and its tasks

The aim of the iPAAC Work Package is to foster cancer prevention and health promotion and to reduce social and health inequalities. Specific tasks include addressing current barriers to early detection, strengthening implementation of population-based cancer screening programmes, strengthening implementation of the European Code Against Cancer as well as developing health aspects in all policies within the Member States. In the current task 5.2. on Cancer Screening, the main objective is to quality assurance and quality improvement aspects of population-based cancer screening programmes by developing decision-making tools; and by investigating the possibilities and barriers of risk-stratified protocols, in all their facets, within the frameworks of population-based cancer screening programmes. Possible new evidence from the evolving field of genomics will also be examined in this respect.

The task 5.2. deals with aspects related to means and opportunities to optimize the balances of harms and benefits of population-based cancer screening. The work on the population-based cancer screening programmes will be largely built upon the EU Council recommendation on cancer screening (12/2003), respective European quality assurance guidelines, and other such documents defining the concepts, elements and implementation criteria for cancer screening programmes (Perry et al., eds., 2006 & 2013; Arbyn et al., eds., 2008; Anttila et al., eds., 2015; Segnan et al., eds., 2010; JRC ECIBC). Recommendations for policy-making and governance for cancer screening programmes (Lönnberg et al., 2017), as well as on how to reduce health inequalities in cancer control (Peiro et al. 2017) as laid down in the earlier EU-wide Joint Actions on cancer, EPAAC and CANCON, are also of key importance for the task.

Many of the Member States lack still such basic policy-making protocols and structures recommended by the CANCON. The Work Package 5 will produce a chapter on cancer prevention to the final deliverable of this Joint Action, called the Roadmap on Implementation and Sustainability of Cancer Control Actions. It will encompass both early diagnosis and early detection, population-based cancer screening programmes, health promotion and cancer prevention. Priority target group is decision-makers in member states.

1.2. Innovation and co-creation

We will in this draft provide some preliminary thoughts of how innovation could enhance performance of cancer screening programmes. There is room for improvement in many parts of the screening process.

The European Union maps innovative member states, regions and products regularly. Innovation implies newness but this definition brings in questions: what is new, how new and to whom? (Johannessen et al, 2001). Similarly broad is the definition from Eurostat glossary: the use of new ideas, products or methods where they have not been used before (https://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Innovation).

Quality improvement in cancer screening requires innovation and new openings. There are at least three different levels in innovations:

- goods, equipment, tests or services
- process innovation
- applicability according to specific criteria of the process.

We will, with keeping in mind the complex process of health systems and screening sub-systems, define innovation here political, social and everyday inventions (Taipale 2013).

Based on work done in Joint Action CANCON, quality improvement in cancer screening requires action in Europe and better policy guidance, maybe locally done innovation and new openings regionally. As an innovative partnership, we will briefly explore new ideas, mainly social innovations in the task 5.2. when reporting the screening conference outcomes.

What topics are included in practice? Innovations in the area of cancer screening may include actions like, for instance the following:

- increasing the coverage of the programme through research and novel interventions in the local conditions and better invitational practices
- introducing new technologies and methods in population-based screening programmes in an evidence-based manner
- researching what is happening between screening intervals in the use of health services
- mapping profound changes in the legal frameworks necessary for such activities for quality improvement in cancer screening

Cancer screening should also have support from population to succeed. Truthful information on benefits and harms of screening is crucial to obtain this. Still there is lack of evaluation in many programmes, affecting suboptimal awareness and lack of adherence also of the service providers to the population-based approaches.

Some changes imply potentially better technologies. All screening programmes have undergone technology changes: in cervical cancer from pap smears to HPV DNA-testing and HPV vaccinations; in colorectal cancer from FOBT test to FIT or sigmoidoscopy or colonoscopy; and in breast cancer screening from film to digital mammography. From the effectiveness point of view there are numerous ways to improve screening programmes step by step, including, for example, risk stratification and potential modifications of screening policies based on the risk. Thus, one indicator of innovation could then be the frequency of academic research around population-based screening programmes. Scientific activity is an important indicator in innovation because any new idea needs to be put into practice and improvement clearly demonstrated in comparison to the present practice. Also, the European quality-assurance guidelines for cancer screening programmes define scientific-level evaluation as one important component of screening.

As many innovations in health are technologically and digitally driven, using machine learning and big data, genomics will bring new ways to study risks (Warnke, 2019) There is a link to iPAAC WP6 Genomics. But because screening programmes vary much in their performance in Europe, we chose innovations improving performance, solutions advancing implementation and quality assurance as our priority areas.

Concept of social innovation is very well suited with cancer screening. Need for innovations can be originating from social demand, such as reducing existing inequalities. There might be societal challenges or systemic change that are drivers for social innovation (EU Guide to social innovation 2013).

Public acceptance of screening programmes is important. To increase engagement and outreach, new ways of creating ideas together are involving stakeholders more broadly than before. Living labs, deliberative consultations and co-designing services are examples of these actions. To foster innovation, the three major WP5 meetings are organized in co-creational way. Co-creation aims at facilitating discussion and dialogue, thus increasing engagement across participants (Mazzucato 2019). This will also enable involvement of stakeholders outside the consortium by attending the meetings. The outcomes of the Joint Action and the WP will be strengthened through the associate and collaborative partners and with Association of European Cancer Leagues (ECL) and international Agency for Research on Cancer (IARC). The partnerships are unique because they bring together the rich variety of cultural interpretations of health and cancer.

1.3. Implementation of cancer screening in Europe

The EU Council has recommended screening for breast, cervical and colorectal cancer through systematic population-based approach with quality assurance at all levels (EU Council, 2003). The second report on status of cancer screening in European Union published in 2017 documented population-based screening (in rolling-out, piloting or planning phases) for breast, cervical and colorectal cancers in 25, 22 and 23 out of 28 Member States (Ponti et al., 2017; Basu et al., 2018, Senore et al. 2019). This report indicates a considerable increase in the extension of population-based screening. There were still remarkable problems in many programmes, such as sub-optimal attendance and coverage compared with the European benchmarks, lack of clinical quality assurance and lack of systematic monitoring and evaluation. There are barriers, respectively, in reducing social and health inequalities with cancer screening that is potentially at stake.

Among the estimated 32 million female annual population for breast cancer screening in the age group of 50-69 years in the EU, nearly 25 million have been invited to mammography screening in the population-based programmes in the index year (coverage by invitation 79%) and 16 million have been screened (coverage by examination 49%) (*ibid.*). Among the women invited in this age, on average 60% participated in screening though the participation rates among the Member States varied remarkably, between 6.2% and 84%. The mean treatment referral rate in this age group was 7.1/1000 women screened (range 2.3 – 12) and the mean detection rate of any malignancies was 6.2 (range 2.3 - 10) per 1000 women screened.

The quantitative information available from 19 of the countries on population-based cervical cancer screening programme showed that 59% (range 7.3 – 100.0) of the annual target women aged 30-59 years (the minimum age group targeted in the EU countries) were invited for screening and 53.2% (range 23.9 – 86.7) were tested in the index years. The mean participation rate to screening in the 30-59 years age group in the countries providing data was 51% (range 12 – 68). The mean colposcopy referral rate was 2.1% (range 0.9 - 3.8) and the overall detection rate of CIN 2 or worse lesions was 4.4/1000 (range 2.0 - 10).

The estimated coverage by invitation and by examination of the annualized EU population aged 50 to 74 years for colorectal cancer screening were 33% (range 1.4 – 112) and (as low as) 14% (range 0.5 - 65), respectively. The values of the other performance indicators differed with the target age, screening tests used and also the threshold of positivity used by the programmes.

In another survey it was demonstrated that there are shortcomings in the appropriate governance structures and legal frameworks in many EU Member States and EFTA countries, preventing effective implementation and qulaity assurance of cancer screening (Lönnberg et al., 2017; Majek et al., 2018). Only about half of the EU and EFTA countries with population-based cervical cancer screening programmes have successfully performed record linkage studies to evaluate key performance indicators, such as interval cancers, and early outcomes measures and eventually long-term outcomes, which are nevertheless a key recommendation for quality assurance of the entire screening process (Majek et al., 2018). The current European legislation is open to the possibility of using health data for this purpose. However, member states themselves must recognize the public interest to create a legal basis which would enable all the necessary functions for appropriate quality assurance for cancer screening programmes. Many Member States have not yet recognized the interest.

1.4. Outcome of the task 5.2.

This drafted report is a background paper for the task 5.2. and a dedicated conference on the 5th December 2019 in Helsinki, entitled *New Openings in Cancer Screening in Europe*. The conference will be co-creational and the group work will be reported in a conference report. The main work of the task will be based on this document and the document will be updated based on the results of the conference. The final conference report will also be available for developing the European roadmap and for other tasks of the WP.

The expected outcome will be reinforcing cancer prevention and early detection through a review of current recommendations for cancer screening and a sound assessment of the potential that might exist for the introduction of possible new screening programmes. One important question is how to modify the existing programmes based on new technologies or risk information. Key issues involve how novel solutions and modifications can be implemented within the large-scale, population-based programmes – what information is required and which are research priorities for implementing effective cancer screening. There will be also critical assessments based on the population-based approaches in the field of genomics, with linkage to WP6 Genomics. WP5 will also assess the implementation and potential modifications of the European Code Against Cancer, where cancer screening is one of the 12 strategies to reduce cancer risk.

2. Definitions and criteria for cancer screening

Screening refers to the use of relatively simple tests across an apparently healthy population in order to identify individuals who have risk factors or an unrecognized disease or defect. A screening test is not intended to be diagnostic, and persons with a positive or suspicious finding must be referred for a confirming diagnosis, if necessary, to treatment (Wilson & Jungner, 1968). By definition, unrecognized symptomatic disease is included, as well as pre-symptomatic disease (*ibid.*) and the majority of the persons to be screened are asymptomatic and disease-free. These first WHO criteria for screening date from 1968 and have since been refined to highlight the importance of evidence of an acceptable balance between benefit and

harm, integrated monitoring and evaluation, improved equity, and informed choices based on available evidence (EU Council 2003; Andermann et al., 2008; Lönnberg et al., 2017; Peiro et al., 2017; Dobrow et al., 2018;). Based on the criteria by WHO and others (Wilson & Jungner, 1968; EU Council 2003; Andermann et al., 2008; Lönnberg et al. 2017; Peiro et al., 2017; Dobrow et al., 2018; WHO, 2019), three key conditions largely determine the relevance of a *population-based cancer screening programme* (from Lönnberg et al., 2017):

(1) There has to be appropriate evidence for the effectiveness of screening, and that

(2) the benefits of screening outweigh the harms and

(3) screening is cost-effective.

Additional aspects relate e.g. to acceptability and ethics, respect for autonomy, and informed choice. The same requirements are important also for genetic testing for cancer screening purpose (Andermann et al., 2008 & 2011).

“Unselected target population” includes population groups with higher or lower disease risk than the average; and a small number of persons who have signs or symptoms consistent with cancer. These signs or symptoms may be unspecific, with a smaller clinical potential to indicate the disease than more severe signs that had led to clinical diagnosis outside screening (i.e. symptomatic cases of cancer). Also genetic predisposition can alter cancer risks. Risk-stratified screening, i.e., *selective screening in a population-based approach* (Wilson & Jungner, 1968) aims to improve the screening programme by modifying screening policies within a population-based programme based on individual-level disease risk. For example, for breast cancer the risk after certain mutations or genetic alterations can become unusually high or low (Mavaddat et al. 2013 & 2018). Colorectal cancer screening has been proposed to be stratified by risk of the disease assessed with help of family history, lifestyle, environmental and genetic factors (Kuipers & Spaanders, 2018). For cervical cancer, individual risk assessment has been proposed to guide the screening policy (Castle et al., 2007).

Vaccination status against HPV viruses is an example which can alter cervical cancer risk in high magnitudes and in many countries the HPV vaccinated birth cohorts have already entered (or will soon enter) to the lowest age groups of cervical cancer screening programmes. In some countries, including Italy, guidelines of cervical cancer screening policy among vaccinated birth cohorts has already been developed (Giorgi-Rossi et al., 2017). Coverage of HPV-vaccination programmes is variable between Member States, posing challenges also in formulating future screening policies (Anttila et al., eds. 2015). Of note, continued cervical cancer screening has also been proposed e.g. among those who did not regularly attend or among women with abnormal screening results also after the general stopping age. The continued screening may be considered due to high risk and potential to benefit (IARC, 2005; Wang et al., 2017).

It is stated in the EU Council recommendation on cancer screening that “due account should be taken of specific needs of persons who may be at higher cancer risk for particular reasons (e.g. biological, genetic, lifestyle and environmental, including occupational reasons)”. No further advice is provided on this topic. Risk-stratified screening is an example of development on this area. There may also be population groups for which the general recommendations on cancer screening may not be valid at all due to very high risk. Lynch syndrome or e.g. BRCA mutations are examples of determinants for such high-risk groups (Canadian Task Force on Preventive Health Care, 2011 & 2016; IARC, 2019). Various surveillance modalities exist in many Member States for them, arranged usually in addition to population-based cancer screening.

Conceptually, testing in ***a surveillance programme*** is separated from screening itself, even though the word 'screening' is sometimes used as a synonym for surveillance (as repeat tests are used for early detection purpose; Wilson and Jungner 1968; FH01 Collaborative teams, 2010; Evans et al., 2019; IARC, 2019). **Surveillance is defined throughout this document as close and continuous observation of high-risk patient groups identified largely from the clinical environment or their close relatives; e.g. patients positive for a given syndrome, clinical finding or genetic test indicating very high risk**. Noteworthy, the criteria and principles of cancer screening (see above) may not apply for surveillance. Usually no similar monitoring and evaluation is available than for the population-based screening, and there is not much information about the benefits and harms of such activities prior management. For the sake of clarity, we prefer to distinct the two terms (surveillance, and population-based cancer screening) in this document, and surveillance programmes are further dealt within the task 6.2. of the IPAAC.

Table 1 Example of screening vs surveillance

Colorectal cancer: Examples of cancer screening, vs some surveillance strategies of high-risk groups (IARC, 2019)

Testing modality and indication	Test method	Target age	Interval	Evaluation of information on benefits outweigh the harm
SCREENING STRATEGIES				
	Faecal blood	50–70	1 or 2 years	Sufficient
	FS	50–70	Single screen	Sufficient
	Colonoscopy	50–70	Single screen	Sufficient/limited
	Computed tomography colonography	50–70	Single screen	Limited/inadequate
SURVEILLANCE STRATEGIES				
Lynch syndrome*	Colonoscopy	Age 20–25 onwards	1–2 years	Not available
Classic familial adenomatous polyposis*	Sigmoidoscopy or colonoscopy	Age 11 onwards	1 year	Not available
Attenuated familial adenomatous polyposis*	Colonoscopy	Age 20 onwards	2 years	Not available
Family history of colorectal neoplasia	Colonoscopy	Variable	Variable	Not available
Personal history of colorectal neoplasia	Colonoscopy	Variable	Variable	Not available (trials on-going)
Medical conditions	Colonoscopy	Variable	Variable	Not available

* Examples of high-risk groups by genetic predisposition

Potentially relevant for the current work on cancer screening will be still to consider whether availability of surveillance programmes should be taken into account when responding to screenees e.g. after a negative test; and whether it is feasible to try to integrate surveillance activities into the monitoring and evaluation structures of cancer screening programmes. For instance, the recommended interval for testing by the screening programme may not be valid for the population under surveillance. Considering the latter, it is worthwhile considering whether testing also outside the screening programme, and related management, should be included into the register-based evaluations of the screening programmes and then also testing due to surveillance purposes should be included. There is no further advice, however, what items should be included about surveillance in such monitoring and evaluation.

2.1. Main benefits and harms for cancer screening policies

Main benefits of cancer screening include decrease in the disease specific mortality and, in some cases, incidence; and improved quality of life in cancer patients due to less aggressive treatments. Even though with demonstrated impact on cause-specific mortality – that is the critical outcome – screening often does not associate with a demonstrated decrease in the overall mortality, because the cause-specific mortality targeted by screening may affect just to a small proportion of all deaths (Grade-handbook) or timing of a RCT may not provide good opportunities for it. There are, however, some examples where also overall mortality has been significantly affected (Nyström et al. 2001; NLST 2011). Changes in other causes than the screened disease itself may also have affected the overall mortality in these studies. Impact on overall mortality would be highly essential for cancer control. Overall mortality can associate strongly e.g. with lifestyle and risk-taking behavior, use of health services and other such factors related to health inequities and social inequalities in health.

The main harms of cancer screening include adverse effects of treatments, even potential increase in mortality due to very severe complications, overdiagnosis of cancers, detection of non-progressive precancerous lesions, over-treatment (due to overdiagnosis, or unnecessarily aggressive treatments), more lifetime with a cancer diagnosis due to earlier diagnosis, psychosocial impacts, false positives or negatives, adverse effects due to screening or diagnostic test itself (discomfort, anxiety, also complications if an aggressive test such as colonoscopy), incidental findings e.g. of clinically irrelevant signs, and additional costs.

The benefits and harms need to be measured in observational studies, and for potential new cancer screening programmes from long-lasting randomized trials. Addition assessments on the absolute probabilities of the above benefits and harms, and e.g. life-years and quality-adjusted life-years, must be produced for a lifetime and possibly for the overall programme span or other such age groups; and evaluation of cost-effectiveness performed with favourable results.

In addition, for ethical reasons it is important to take into account whether there are other, alternative or complementary control strategies available. If effective measures are available, primary prevention is usually more beneficial for the benefit/harm -ratio and cost-effectiveness than cancer screening, due to its non-invasiveness and capability to affect a wide range of diseases (Advisory Committee on Cancer Prevention, 2000). Effective cancer screening may be needed also after the complementary primary prevention, if the disease risk remains still higher than desirable (see the WHO Global strategy on the elimination of cervical cancer, https://www.who.int/cancer/cervical-cancer/cervical-cancer-elimination-strategy/).

Other ethical principles include improved equity, respect for dignity and autonomy (see Andermann et al., 2008; Dobrow et al., 2018), appropriate information-based decision to attend, acceptability to population and medical service producers, non-maleficence and beneficence (e.g. adherence to guidelines and QA protocols), and precaution. Primary prevention in connection with cancer screening can be an important tool to improve equity, because it can affect a wide range of diseases known to correlate with social conditions.

Important for policy decisions, the requirements in the resource needs and cost-effectiveness need also to be satisfied. Results of cost-effectiveness studies are highly variable, depending upon assumptions in the simulations and types of costs included. Critical threshold values in cost-effectiveness evaluations have been developed but only in few Member States (Lönnberg et al., 2017).

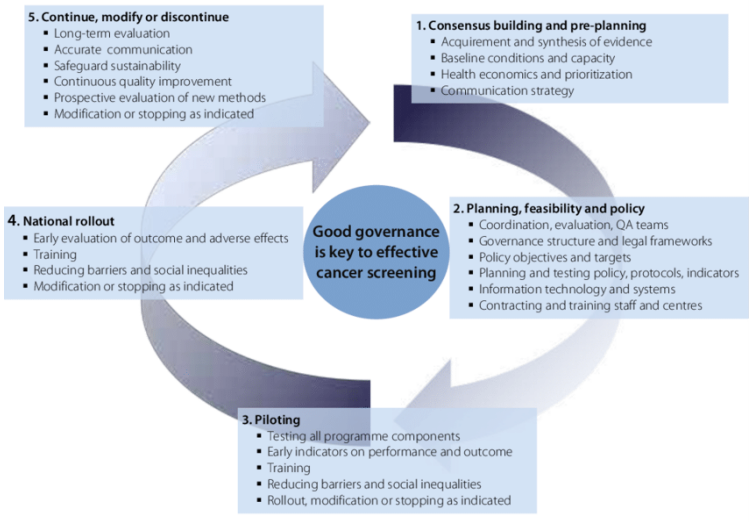
3. Key recommendations for effective and innovative implementation of population-based cancer screening

According to the CANCON guide, the quality-assured implementation of cancer screening for breast, cervical and colorectal cancers involves careful planning and piloting, and scaling up from pilot to sustainable full-scale national rollout. *Modifications of existing programmes* are also needed to reflect developments in screening, diagnostic and treatment methods, or because of developments in complementary primary prevention (e.g. HPV vaccination).

According to key recommendations for on-going programmes (Lönnberg et al., 2017), successful evidence-based cancer screening needs:

- a competent, multidisciplinary and transparent governance structure with political, financial and stakeholder support
- the legal code in a country should be developed, providing a specific framework for population-based cancer screening, enabling e.g. personal invitation, mandatory notification and central registration of complete screening and outcome data, and individual linkage to cancer and cause of death registries for appropriate quality assurance and audits.
- Deficiencies in the governance structures for population-based screening may severely impede the full implementation of effective population-based cancer screening programmes.

Figure 2 Examples of tasks of organization, evaluation and governance in different phases of implementation and quality improvement of a cancer screening programme. (CANCON)



Effective cancer screening programmes require significant resources for quality assurance. **Implementation should be a carefully managed multistep process through the phases of coordinated planning, piloting, roll-out and continuous improvement**. The mandate and resources for screening coordination and training, and for the electronic information systems necessary for quality assurance and incremental improvement, must be secured before starting the population-based screening service.

Whenever relevant, evaluation and regular monitoring of cancer screening should also detect social inequalities and trigger research and interventions on improved equity in health. Research collaboration has an added value to develop interventions and solutions in the local settings where social barriers and social inequalities in cancer have prevailed.

Benefits and harms of screening need to be clearly communicated to the public, as the appropriate balance may be judged differently by individuals. Truthful communication strategies need to be developed at every phase of implementing cancer screening. The cost-effectiveness of a programme or a specific modification of it should also be evaluated prior to deciding on its full implementation; Member States should define a threshold value relevant for decisions on cancer screening, considering affordability and available resources.

3.1.1. Potential new programmes

Potential new screening programmes (for example, for lung or prostate cancers) require stepwise decision-making which includes the establishment of evidence base on effectiveness, benefits that outweigh the harms and cost-effectiveness. New trials need to be financed to investigate optimal strategies for cancer screening. Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice.

3.1.2. How to modify or launch programmes with risk-stratified screening?

The CANCON guide did not specifically deal with ‘risk-stratified screening’. Still, it was recommended to modify the programme, when indicated; and that the stepwise process should be structured and defined based on clear, evidence-based criteria to ensure that a proposed new or modified screening programme is able to reach an optimal balance between benefit, harm and costs (such as cost per QALY gained).

3.2. Recommendations on reducing social inequalities in cancer screening

Specific recommendations to improve equitable access and compliance with cancer screening programmes were developed in the context of the previous Joint Action on Cancer Control, CANCON (https://cancercontrol.eu/).

Provide screening processes that address the whole population, with additional emphasis among socially vulnerable groups, is one of the suggestions included in the Policy Paper on Tackling Social Inequalities in Cancer Prevention and Control for the European Population (Peiró et al, 2017). This recommendation aims to assure equitable access based on universal actions but with a scale and intensity that are proportionate to the level of disadvantage, which is to say, to work from a proportionate universalism approach (Marmot, 2010).

Some strategies have been shown to enhance access to screening among socially vulnerable groups. These strategies include elimination of geographical barriers to access (Guillaume et al, 2017), greater involvement of primary care physicians (Senore et al, 2010), and communication strategies tailored to specific groups of the population (Escribà-Agüir et al, 2016).

An example of this kind of strategies is an intervention lead by the Reference Centre for Epidemiology and Cancer Prevention in Piedmont (Italy) to promote participation in cervical cancer screening of immigrant women. The aim was to improve the quality of communication strategies. A multi-disciplinary team was created including medical doctors, community health workers, members of associations working in the field of immigration and cultural mediators. Leaflets and posters in eight languages were produced and disseminated in clinics, pharmacies, medical offices, cultural centres and associations and were included in a wider mass campaign (http://www.cpo.it/en/articles/show/prevenzione-serena-integration-also-in-prevention/).

Another recommendation from CANCON Policy Paper is to promote the exchange of good practices and support development of professional expertise in social inequalities in cancer in all European Union Member States. Following this recommendation the current Joint Action on Innovative Partnership for Action Against Cancer (https://www.ipaac.eu/) has launched, within the Work Package 5 (WP5) on Cancer Prevention, a Contest on Best Practice tackling social inequalities in cancer prevention (https://www.ipaac.eu/news-detail/en/23-contest-of-best-practices-tackling-social-inequalities-in-cancer-prevention-extended-deadline/). The Contest aims at identifying and compiling relevant European experiences, then disseminating them among European countries in order to promote and facilitate their implementation; and contributing to the exchange and replication of best practices on equity in cancer prevention. The first results will be available in the next WP5 meeting in Helsinki (5th December 2019).

Finally, following the CANCON recommendations (Peiro et al, 2017), equity must be considered as a crucial quality criterion to be included in the guidelines for quality assurance in cancer screening. As an example, the European Commission Initiative on Breast Cancer has included specific recommendations to cover the special needs of vulnerable women, including socially disadvantage women, women with intellectually disability, and non-native speaking women (https://ecibc.jrc.ec.europa.eu/recommendations/list/Professional).

4. Innovations on risk-stratified screening

4.1. Further definitions of risk-stratified screening

In principle the screening test divides the population undergoing screening in two groups: a group (positive to the test) with a higher prevalence of a cancer and/or a precursor of the target cancer and the group (negative to the test) with a lower prevalence (see the section on definitions). So far the screening tests in breast, colorectal and cervical cancer were aimed to find a sign potentially correlated with the presence of the cancer or of its precursor. **We can speak *of risk-stratified screening*** (sometimes referred also as personalized screening; for other synonyms see section 3) **when different protocols of screening are scheduled for**

different groups of individuals of the same target population according to characteristics conditioning the specific risk. A specific condition (family history, a genetic predisposition, a specific biomarker, i.e. density of the breast, vaccination against HPV, smoking habits for example) should characterize such groups of individuals for having a different risk of disease (higher or lower than the general population) may justify modification of the screening programme by variable protocols. (Lönnberg et al., 2017)

The screening for lung cancer with low dose CT Scan is a risk-stratified screening being proposed only to heavy smokers or ex-smokers is an example of stratifying screening policy. There the screening decision is based on a specific and high individual disease risk. (https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening)

Generally speaking, age and gender are main determinants identifying the target population for the population-based screening approach. Screening policy (test or interval) can be variable in different age groups, depending on age-specific variability of disease risk and of screening validity. This is not considered yet 'personalized' or risk-stratified screening. On the other hand, varying the target age of screening in different groups according to risk-stratification, or changing colorectal cancer screening protocols by gender, can be considered elements of risk-stratified screening.

There can be presence of symptoms that may shift an individual from a screening programme directly to a diagnostic pathway. Or there can a previous examination determining the exclusion from the invitation to the screening programme (e.g., a recent colonoscopy if used as an exclusion criteria). These are not a criteria for risk-stratified primary screening.

Other situations may be more challenging to be classified. For example, in the new cervical cancer screening based on HPV testing the test is aimed to identify a situation of higher risk (the infection with high risk HPV virus), making cervical cancer screening actually a risk-stratified protocol, even if HPV test is still considered to be a standard first level test. Furthermore, the screening algorithm is based on the risk of having a CIN3 immediately or in the next future, stratifying women according to the results of previous tests: for example, according to European and US Guidelines management of HPV positive women changes if this is the first HPV positive result or if it is a second positive test.

For colorectal cancer screening, it has been suggested that the cumulative value of fecal haemoglobin in the previous negative test is a strong predictor of the risk of detecting advanced adenomas or cancer or interval cancer in the subsequent test (Auge et al., 2014; Buron et al., 2018). Defining different screening intervals according to the previous level of haemoglobin in fecal blood could be considered an element of risk-stratification.

4.1.1. General remarks

In stratified screening, harms (including complications of tests or treatments, overdiagnosis and psychological harms; see section on benefits and harms of cancer screening) need to be considered co-equally with benefits. Genetic tests should be offered only in the case of evidenced better risk /benefit ratio. To be aware of an increased risk is not good *per se*. This leads to anxiety as well as possibly incidental findings. In particular, this is true in the case of genetic tests as anxiety can also involve one's relatives. Professional and clinical advice and support is necessary in interpreting the risk on individual level and for deciding the evidence-based options possible for further individual management.

The criteria for risk-stratified screening should be defined in advance. All the subjects in the target population should be alerted in advance of the criteria of risk-stratified screening.

4.1.2. In which situations a shift from generalized screening to risk-stratified screening could be proposed?

In general terms two are such situations

1) There are factors influencing the accuracy of primary test (in particular sensitivity)
2) There are factors influencing the prevalence and mortality risk of disease (the risk for the subject).

Nevertheless, these conditions are not sufficient yet to guarantee that the risk-stratified screening approach would be better than the generalized one and that the risk-stratified screening approach would satisfy the targets on disease prevention and avoid potential harm.

As an example of the first case, breast density affects the accuracy of mammography (Puliti et al., 2018), but not that of ultrasound (Ohuchi et al., 2016). A test that is less effective in the general population can become more promising in a subgroup with a particular condition. In the Puliti et al. (2018) study, almost one third of breast cancers (screen-detected or interval cancer) of women who participated at age 49–54 at their first screening mammography were found in those having a high volumetric breast density measured with fully automated software. The highest breast density category, compared with the other groups together, had double the invasive BC risk (RR = 2.0; 95% CI 1.5–2.8) and almost fourfold risk of advanced breast cancer (RR = 3.8; 95% CI 1.8–8.0). However, it is not evident yet with which testing methods and procedures would correct for such problems.

Another example could be cervical cancer screening in HIV positive women, where the progression of the disease from HPV infection to cancer seems to be faster than in the general population, suggesting the adoption of shorter screening intervals in these women (WHO recommendations: https://apps.who.int/iris/bitstream/handle/10665/94830/9789241548694_eng.pdf;jsessionid=E3B21A515C8BC4522E532C61F225BAEB?sequence=1). In such cases there could be the rationale for changing the screening test or the interval, not because of the risk, but because a different screening protocol could be more effective and safe.

It is assumed that the presence of a higher level of risk should deserve a more intensive protocol. This is partially correct. From one side it is true that in presence of a higher prevalence screening tends to be more efficient. In fact, in most cases, the positive predictive value (PPV) depends largely on the prevalence of the disease: with higher prevalence of the disease we will have a lower proportion of false positive and, consequently, the number of persons referred to assessment to find a diseased person will be lower, i.e. the process is more efficient, reducing the assessment costs, and less harming reducing the undesirable effects of the ascertainment tests, that in some cases can be invasive, with direct consequences, and almost always induce anxiety in healthy individuals.

On the other hand, risk-stratified screening should also assess possibilities to reduce the intensity of screening in people with lower risk. Majority of people participating in screening will never have the target disease, but many will experience some (even transient) adverse effects.

The aim of risk-stratified screening is to achieve a better balance between harms and benefit. In other terms in a risk-stratified screening a more extensive and aggressive protocol will be provided to people at high level of risk but at the same time a less aggressive protocol should

be offered to subjects in a lower risk stratum. The goal from a public health point of view is to achieve:

1) a better balance between benefits ad harms

2) a better cost/outcome ratio (more cancers detected per exam, less advanced cancer).

It must be considered that individual risk usually does not influence the relative efficacy in terms of desirable effects of screening, but influences the absolute amount of desirable effects since the benefits can only occur in people who have or would have (in the case of screening targeting pre-cancerous lesions) the disease in absence of screening, while most of the undesirable effects occur in the general population (direct consequence of the test) or in a quite stable proportion of it (consequences of the ascertainment occur in those positive to the test). Changes in the ratio between benefits and harms can therefore be the rationale for the following types of changes in the screening algorithm:

1) The age at which we start or stop screening could be different (usually higher in people with lower risk, since most epithelial cancers have an increasing incidence with age)
2) We can change the screening interval (more frequent screening in people at higher risk);
3) Identify a group at so low risk that screening is not beneficial at any age
4) Identify a group with a sufficiently high risk for which a test that is too invasive for the general population, reaches a beneficial balance of benefits and harms.

Conditions 1 and 3 do not need a new proof of efficacy of the intervention, but are based on the application of criteria for deciding if implementing a screening on the general population to a subgroup for which we know the balance of benefits and harms, at invariant conditions of screening efficacy, are different. Conditions 2 and 4 need that we have proof of effectiveness of a different interval or of a different test. In particular, effectiveness of screening, under certain conditions, i.e. when the time to develop the disease since the onset of its precursors is much longer than the actual screening interval, may be almost independent of the interval. Thus increasing screening frequency in high risk group could be ineffective.

4.2. Is it useful to tailor screening based on personal risk?

The answer depends on the point of view. A more intensive screening protocol is supposed to provide a more sensitive approach but also higher level of side effects.

With personalized screening two or more groups will be created:

One at higher cancer risk screened more frequently and/or more intensively;

One at lower cancer risk screened less intensively or not screened at all.

We must consider different point of views:

1) The point of view of the **individual**:

If a subject is stratified in a Low Risk Group **she** will experience:

- A lower number of tests;
- A lower lifetime probability of a false positive result;

- Less side effects (e.g., lower irradiation);
- A lower probability of surgically treated benign lesions
- A higher probability of delayed diagnosis of cancer, that could result in more invasive treatments and worse prognosis.

The contrary if the subject is stratified in the high risk group.

2) The point of view of the **society**

- With a risk-stratified screening a more cost-effective result may be obtained:

➔ With the same amount of resources, a higher number of saved lives may be obtained, or the same number of saved lives can be obtained with lower amount of resources.

➔ If the criteria for offering different screening are only based on the ratio between benefits and harms, this should be independent of the costs and stratification of screening will optimize the intervention also from the individual point of view. If, as usual, tailoring is also used for a better allocation of resources, societal and individual point of view may conflict in the case of individuals in low risk groups.

Moreover, more equity can be reached if the gap in mortality from breast cancer between high risk group and low risk group can be reduced. Even if introducing expensive tests for risk assessment and complex algorithms may reduce access of the most deprived women or the sustainability of the public program, exiting in increased inequalities.

A risk-stratified screening approach is more complex to organize and it also causes additional organizational and communication costs. Specific aspects should be taken into consideration:

- would a woman classified at low risk agree to have a lower protection from breast cancer?
- there is need for a proper communication strategy.

4.3. On what basis can we decide to modify a screening programme with a risk-stratified approach?

A risk-based screening can be adopted at a population level only with valid evidence of better risk/benefit ratio. In theory RCTs with breast cancer mortality as primary endpoint should be carried out. Practically it is difficult, if not impossible, if condition is very rare, because large sample size and long period of observation would be needed. To adopt validated early indicators of effectiveness, as rate of advanced cancers, should be considered. This can enable gradual, well-controlled introduction of the *modifications to the screening policy* with profound evaluation of effectiveness of the programme in long term. Another issue in making such trials is if we should pretend the superiority of a tailored/risk-stratified approach compared to a standard screening strategy or if we can accept a non-inferiority comparison in the case an overall decreasing intensity of screening and consequently decreasing harms are obvious.

The sustainability (cost, resources, organizational aspects) should be deeply evaluated.

The communication and the psychological impact of such an approach should be monitored and evaluated. See box 1 for a good example of an RCT for testing the efficacy and effectiveness of a risk-stratified screening approach.

It is possible to adopt risk-stratified screening in case of a very high risk. Some possible harms of screening, in particular overdiagnosis and false positive rate, may not be relevant anymore. Evaluating the efficacy of screening in these cases can be theoretically easier, even if low numbers and ethical considerations make the conduction of trial as well challenging. Depending on screening methods, risk may remain high even in women testing negative. Therefore, evaluation of alternative methods for prophylaxis is important.

4.4. The case of breast cancer

4.4.1. How to evaluate the introduction of a risk-stratified screening?

Excluding the cases in which the stratification leads only to identify different age to start or stop screening, for risk-stratification implying differential intensity of the screening protocol we should apply the same criteria we use in the evaluation of the introduction of a new screening:

a. A strong evidence that a risk-stratified screening overall assure a better balance between harms and benefit as compared to a not personalized screening.

b. Such a comparison should be based on specific randomized clinical trials (RCTs) and evidence synthesis drawn from them.

c. For evaluating an effect on mortality a very large RCT should be carried out and followed for a very long time

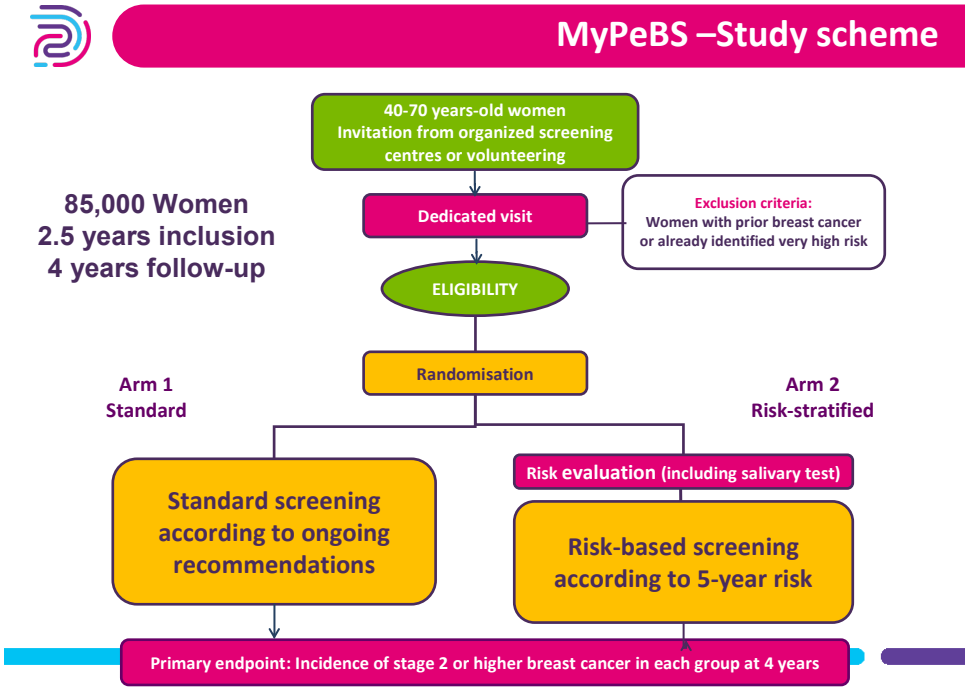
d. Comparison trials based on proxy indicators (as rate of advanced cancers) preferably also with their management histories should be considered.

The trial MyPEBS is a good example of study scheme to assess if a stratified risk screening is better than a traditional one, see box 1 and Figure 2.

Box 1. My Personalized Breast Screening (MYPeBS) trial

- *MyPEBS compares two models of organised breast cancer screening*
  1. *Standard (as organised in the 5 participating countries)*
  2. *Based on each women's individual risk of BC*
- *Bases of comparison*
  1. *The primary objective is to show non-inferiority of the stratified screening strategy in terms of incidence of BC of stage II and higher*
  2. *The key secondary is to show superiority of such screening (80% power to detect a 30% relative decrease of stage II+ BC incidence in the risk-based arm)*
  3. *Other major endpoints are ethical and psycho-social impact of both strategies*
  4. *Medico-economic evaluation*
- *MyPEBS prepares recommendations for the future of breast cancer screening in Europe*

Figure 2 Example of breast cancer MyPeBS



MY Pebs

1. The Primary objective of MyPeBS is to show a non-inferiority of the stratified screening strategy in terms of incidence of BC of stage 2 and higher.
2. If non-inferiority is shown, then superiority of the risk-based screening arm for reduction of stage 2+ BC will be tested (key secondary) against the control arm (closed testing procedure).

Secondary objectives

1. To compare the rates of false positive imaging findings and benign biopsies between arms
2. Psycho-social impact of each strategy
3. Costs and cost-effectiveness of each strategy
4. Incidence of any stage breast cancer in each arm
5. Estimate overdiagnosis and overtreatment rates in risk-based screening and standard screening arms
6. Compare the rate of false negative mammograms and interval cancers between arms
7. Breast cancer-specific mortality at 10 years and 15 years in MyPeBS and in a combined analysis of the Wisdom and My-PEBS studies
8. Added value of tomosynthesis (TS) in the detection of stage 2+ breast cancers
9. Incidence of all stage and stage 2 and higher breast cancers at 10 and 15 years follow-up
10. Incidence of stage 2+ breast cancer in risk-based screening in women aged 40-50 as compared to standard screening
11. Rate of cancers discovered at second reading in each arm
12. False positive imaging findings and benign breast biopsy rates in women classified in the low risk category.

4.4.2. What are the positions in Europe for risk-adjusted screening?

At the moment for breast cancer screening, except for very high-risk conditions, age is currently the sole criterion to enter breast cancer screening programs, See Fig. 3, https://ecibc.jrc.ec.europa.eu/. One size fits almost all. Screening for breast cancer is recommended at age 50-69. Starting breast cancer screening already at age 45 is conditionally recommended, with very low certainty of the evidence. Screening is suggested to be continued also at age 70-74 (conditional recommendation, moderate certainty of the evidence). Research on optimal strategies e.g. on women with dense breasts is a key (Box 2).

Figure 3. ECIBC recommendations are available for patients, professionals and policy makers.

BOX 2. What are the current recommendation for personalized screening in Breast cancer screening for breast density? European Commission Initiative for Breast Cancer recommendation https://ecibc.jrc.ec.europa.eu/

- Should tailored screening with automated breast ultrasound system (ABUS) based on high mammographic breast density, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?
  Conditional recommendation against the intervention, very low certainty of the evidence.
- Should tailored screening with digital breast tomosynthesis (DBT) based on high mammographic breast density, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?
  Conditional recommation for either the intervention or the comparison, low certainty in the evidence.
- Should tailored screening with hand-held ultrasound (HHUS) based on high mammographic breast density, in addition to mammography, vs. mammography alone be used for early detection of breast cancer in asymptomatic women?
  Conditional recommendation against the intervention, low certainty of the evidence.
- Should tailored screening with magnetic resonance imaging (MRI) based on high mammographic breast density, in addition to mammography, vs. Mammography alone be used for early detection of breast cancer in asymptomatic women?
  Conditional recommendation against the intervention, very low certainty of the evidence.

5. Potential of new cancer screening programmes: updated evidence on lung and prostate cancer screening

The CANCON project provided brief evidence updates on several potential new cancer screening programmes. Below further updates are presented on prostate and lung cancer screening research. More details are presented in an Annex. The EU Council (2003) or the WHO (2019) do not recommend screening programmes for these cancer sites. According to the WHO (2019) many authorities discourage screening for prostate cancer; and lung cancer screening is controversial, advocated by some and discouraged by others.

Of note, lung cancer is an exceptional cancer site for cancer screening research, compared with most other cancer sites, because there is strong evidence on primary prevention of its main causal agent, tobacco smoking (IARC 2007 & 2009). Quitting smoking is beneficial at any age (Doll et al., 2004; Jha et al., 2013; Jha & Peto, 2014). Still, when quitting smoking takes place at a younger age – below age 45 – the subsequent risk of lung cancer and of overall mortality becomes very close to those of lifetime non-smokers (ibid.). After stopping smoking at age 55-64, the risk of lung cancer has been reported to remain very high, about 8-fold compared with lifetime non-smokers and continued excess in the overall mortality, too. It is still of relevance for the task 5.2. to consider whether screening experiments for lung cancer could complement the implementation of tobacco-free policies. This makes a link also to the task 5.3. on primary prevention.

5.1. Prostate cancer screening

To date, five randomized controlled trials, enrolling 721 718 men, have been conducted on PSA screening for prostate cancer. Studies have varied with respect to screening frequency and intervals, PSA thresholds for biopsy, and risk of bias. Systematic information on the common use of PSA tests outside the trial, mainly for opportunistic testing and for clinical testing purposes in men with unspecific urinating symptoms, have not been included in the trials. Screening probably did not affect to all-cause mortality and when considering the whole body of evidence did not affect clearly the prostate-specific mortality. Analysis of studies at lower risk of bias demonstrated a 21% decrease in prostate-specific mortality. This corresponded to one less death from prostate cancer per 1000 men screened over 10 years. Direct comparative data on biopsy and treatment related complications from the included trials were limited. Using modelling, it was estimated that for every 1000 men screened, approximately 1, 3, and 25 more men would be hospitalized for sepsis, require pads for urinary incontinence, and report erectile dysfunction. Screening increased the detection of prostate cancer of any stage by 57%. (Ilic et al., 2018). Also cost-effectiveness of PSA-based screening is of concern.

Based on results of the randomized trials, a weak recommendation against systematic PSA screening has been suggested (Tikkinen et al., 2018). On the other hand, PSA testing based on clinical indication is common (discussed in the iPAAC task 5.1. Conference report). Efforts are underway also in form of new trials trying to find screening strategies to detect particularly high-grade prostate cancers and avoid detection of low-grade cancers (Brawley et al., 2016; Auvinen et al., 2017). The increasing use of multi-parametric magnetic resonance imaging

before biopsy is improving diagnosis and may reduce the number of men needing biopsy (Kasivisvanathan et al., 2017).

5.2. Lung cancer screening

In a RCT on lung cancer screening in the US with low-dose computed tomography compared with chest X-ray radiography, annual screening was associated with a 15–20% decrease in lung cancer mortality and about a 7% reduction in overall mortality (NLST, 2011; Pinsky et al, 2013). As a drawback, the proportion of false positive test results leading to diagnostic confirmation was very high, particularly in the first two screenings. The study population consisted of current tobacco smokers or ex-smokers. There are several trials being reported or under follow-up in European countries, with variation in the lung nodule management protocols and of the definition of the high-risk population and also with variable results (see the Annex). The largest European trial, the "Nederlands Leuven Longkanker Screenings Onderzoek" (NELSON), has examined the impact of low-dose computed tomography screening in association with active intervention to quit tobacco smoking (Ru Zhao et al. 2011; van der Aalst et al., 2011). Based on a conference abstract, an effect of 26% in decreasing lung cancer mortality in men and 39% in women has been reported (De Koning et al., 2018). Publication of peer-reviewed reports are awaited to take place soon.

The harms of lung cancer screening include false-positive results, complications from invasive follow-up and overdiagnosis with associated overtreatment. Performance characteristics of screening tools, particularly specificity and false positives, are largely associated with the algorithms and protocols. High referral rates as seen in the first trial in the United States do not seem feasible in Europe. There are also concerns of availability of technologies and resources for adopting the novel technologies used in the NELSON trial where the surveillance and referral rates were reasonably lower.

There is an emphasis on integrating interventions to quit tobacco smoking with lung cancer screening also in the US (Steliga & Young, 2019). However, the integration of cessation resources in screening is not done uniformly, and there is only limited information on effectiveness of the various components in the overall intervention. Mortality results as well as assessments of benefits and harms, cost-effectiveness and alternative or complementary prevention strategies are needed based on the European trials.

Noteworthy, even though lung cancer screening is not generally recommended in Europe, there are implementation studies to assess aspects potentially relevant for public health and clinical uses of the methods (Field et al., 2016; Hinde et al., 2018; Crosbie et al., 2019; Ghimire et al., 2019; Rzyman et al., 2019). Key aspects in the implementation studies have included:

- Availability of CT scanners and the pressure on radiological and nodule management services
- Clinical validation, training and accreditation of the novel diagnostic and management services -- potentially relevant also for other services than screening research
- How to select target population
- How to reach the potential target population and achieve substantial participation among them
- How to integrate interventions on smoking cessation with screening optimally

- To understand aspects related to other findings than on lung cancer mortality, reported by some trials.

6. Discussion and conclusions

Topics presented in this draft report will be further discussed in the Conference on cancer screening. Therefore, we will not yet try to identify key conclusions here at this stage prior the conference. The final deliverable on the Joint Action iPAAC will be A Roadmap on Implementation and Sustainability of Cancer Control Actions. This Roadmap will be solution-oriented and developed together with partnership of participating Member States. What does the task 5.2. offer to the development of cancer screening?

1. WP5 has a cross-cutting theme on inequality. One priority will be looking solutions to disparities between member states, regions in cancer screening and have focus on specific vulnerable groups. Inequalities and health inequities are an important focus area for also the so-called risk-stratified screening concepts.

2. Another priority is explained in chapter 4: what is needed that population-based screening programmes function well. There are now three cancer screening programmes recommended in the European Union: breast, cervical and colorectal cancers. How can we increase their effectiveness and optimize the benefits and harms of the activity? Support for implementation of the quality assurance step by step, as recommended by the European guidelines, was introduced in CANCON. It will be developed further as an online tool. We need to focus on finding solutions for better coverage, legal frameworks, governance and data. Continuous monitoring, as well as research collaboration for evaluation of cancer screening are required. Also the Cancer Mission of the EU may become one important channel for these collaborations in the future.

3. Risk-stratification within the population-based screening programmes has apparently started already. This is the case especially in cervical cancer screening. There are risk-stratified approached under development also in other programmes.

4. Looking into the future, what is the role of genomics? How do we inform about surveillance programmes for high risk individuals as genetic data becomes more common? Truthful communication of both harms and benefits is one area of discussion.

5. Already now we can conclude that planning open meetings and having multiple voices in the process enriches our work. IPAAC consortium is based on expertise and support. Partnerships with International Agency for Research on Cancer (IARC) and Association of European Cancer Leagues is providing its strong network of civil society in policy-making arenas. An inclusive, multi-disciplinary and multi-stakeholder voice which is needed for finding social advances and innovations in cancer screening.

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Annex

1. Pubmed search strategy for literature on lung cancer

"Lung" [Mesh]

"Neoplasms"[Mesh]

"Lung Neoplasms"[Mesh]

"lung cancer"[tiab]

1)

"Lung" AND (Neoplasms [MESH] OR "lung cancer"[tiab] OR "Lung Neoplasms"[Mesh])

trial [tiab]

"randomized controlled trial" [tiab]

"controlled clinical trial" [tiab]

random* [tiab]

2) trial[tiab] OR "randomized controlled trial" [tiab] OR "controlled clinical trial" [tiab] OR random* [tiab]

"Clinical Trial" [tiab]

"screening trial" [tiab]

"lung screening trial" [tiab]

3) "Clinical Trial" [tiab] OR "screening trial" [tiab] OR "lung screening trial" [tiab]

4) 2 AND 3

(trial[tiab] OR "randomized controlled trial" [tiab] OR "controlled clinical trial" [tiab] OR random* [tiab]) AND ("Clinical Trial" [tiab] OR "screening trial" [tiab] OR "lung screening trial" [tiab])

5) = 1 AND 4

("Lung" AND (Neoplasms [MESH] OR "lung cancer"[tiab] OR "Lung Neoplasms"[Mesh])) AND (trial[tiab] OR "randomized controlled trial" [tiab] OR "controlled clinical trial" [tiab] OR random* [tiab]) AND ("Clinical Trial" [tiab] OR "screening trial" [tiab] OR "lung screening trial" [tiab])

#Mortality

7)

("mortality" [tiab] OR "lung cancer mortality" [tiab] OR "death*" [tiab] OR "lung cancer death*" [tiab] OR "survival" [tiab] OR "effectiveness" [tiab] OR "screening effectiveness" [tiab])

8) == 7 AND 8

("Lung" AND (Neoplasms [MESH] OR "lung cancer"[tiab] OR "Lung Neoplasms"[Mesh])) AND (trial[tiab] OR "randomized controlled trial" [tiab] OR "controlled clinical trial" [tiab] OR random* [tiab]) AND ("Clinical Trial" [tiab] OR "screening trial" [tiab] OR "lung screening trial" [tiab])) AND ("mortality" [tiab] OR "lung cancer mortality" [tiab] OR "death*" [tiab] OR "lung cancer death*" [tiab] OR "survival" [tiab] OR "effectiveness" [tiab] OR "screening effectiveness" [tiab]) AND ("2009/09/20"[PDat] : "2019/10/02"[PDat] AND "humans"[MeSH Terms] AND English[lang])

#Smoking cessation

9)

"smoking cease*" [tiab]

10) == 5 and 9

("Lung" AND (Neoplasms [MESH] OR "lung cancer"[tiab] OR "Lung Neoplasms"[Mesh])) AND (trial[tiab] OR "randomized controlled trial" [tiab] OR "controlled clinical trial" [tiab] OR random* [tiab]) AND ("Clinical Trial" [tiab] OR "screening trial" [tiab] OR "lung screening trial" [tiab]) AND ("smoking cessation" [tiab])

2. Summary results of randomized lung cancer screening studies using low-dose spiral tomography (LDCT)

Study and country of study	Recruitment period	Selection criteria (age)	Selection criteria (pack years)	Screening methods	Smoking cessation intervention	Sample size	Follow up time	Cancer detection rate	Mortality hazard ratio and 95% CI between study arms
NLST (National Lung Screening Trial team et al., 2011), US	2002-2004	55-74 years	≥30 pack-years; quit smoking <15 years earlier	Annual LDCT vs CXR for 3 years	No	53454	median= 6.5 years, maximum= 7.4	1.0%	LCM= 0.80 (0.73 - 0.93); ACM= 0.93(0.86 - 0.99)
MILD (Pastorino et al., 2019), Italy	2005-2011	>49 years	≥20 pack-years; quit <10 years earlier	Three groups: no screen vs annual LDCT vs biennial LDCT for 5 years	Yes	4099	10 years	0.7%	LCM= 0.61 (0.39 - 0.95); ACM= 0.80 (0.62 - 1.02)
ITALUNG (Paci et al., 2017), Italy	2004-2006	55-69 years	≥20 pack-years	Annual LDCT for 4 years vs no screen	No	3206	maximum 10 years	1.4%	LCM= 0.70 (0.47 - 1.03); ACM= 0.83 (0.67 - 1.03)
DANTE (Infante et al., 2015), Italy	2001-2006	60-74	≥20 pack-years; quit <10 years earlier	Annual LDCT for 4 years vs no screen	No	2811	maximum 12 years	2.2%*	LCM= 0.99 (0.69 - 1.43); ACM= 0.95 (0.77 - 1.17)
LUSI (Becker et al., 2019), Germany	2007-2011	50-69 years	heavy smoking history	Annual LDCT and smoking cessation for 5 years vs smoking cessation alone	Yes	4052	average 8.8 years	1.1% initial (half in later screens)*	LCM= 0.74 (0.46-1.19); ACM= 0.99 (0.79-1.25)

DLCST (Wille et al., 2016), Denmark	2004-2006	50-70 years	≥20 pack-years; quit <10 years earlier	Annual LDCT vs usual care for 5 years	No	4104	at least 5 years since last screening	0.8%	LCM= 1.03 (0.66 to 1.6); ACM= 1.02 (0.82 to 1.27)
DEPISCAN **(Blanchon et al., 2007), France	2002-2004	50-75 years	≥15 pack-years	Annual LDCT vs CXR for 2 years	No	765	baseline results	2.4%	Not available
LSS** (Gohagan et al., 2005), US	2000-2001	55-74 years	≥30 pack-years; quit smoking <10 years earlier	Annual LDCT vs chest X-ray	No	3318	median= 5.2 years	NA	LCM= 1.24 (0.74 to 2.08); ACM= 1.2 (0.94 to 1.54)
UKLS**(Field et al., 2016), UK	2011-2012	50-75 years	high risk groups, ≥5% over 5 years	Single LDCT screen vs no screen	No	4055	NR	2.1%	Not reported
NELSON (Horeweg et al., 2013, 2014), The Netherlands and Belgium	2003-2006	50-75 years	≥15 pack-years	LDCT screen at 0, 1, 3, and 5.5 years vs no screen	Yes	15822	10 years	0.8-1.0%	Not reported

**feasibility randomized trial / pilot study

LCM= lung cancer mortality; ACM= all-cause mortality; PLCOm2012= 6-year lung cancer risk calculation ; CI= confidence interval

Summary of findings

Using annual low dose computed tomography (LDCT) has demonstrated a 20% reduction in lung cancer mortality in the US National Lung Screening Trial (NLST) (NLST Research Team, 2011). In Europe, multiple screening studies/trials are currently ongoing and few published studies have reported somewhat variable findings (both significant and non-significant reduction) on lung cancer mortality (Field et al., 2016; Horeweg et al., 2014, 2013; Infante et al., 2015; Blanchon et al., 2007; Wille et al., 2016; Paci et al., 2017; Spiro et al., 2016; Becker et al., 2019; Pastorino et al., 2019) with substantial clinical heterogeneity in the trials. A summary table on the findings from the published studies and the literature search strategy are presented in the Table above. The heterogeneity between trials is due to lack of uniform screening methods applied (between the intervention and control arms population), which in turn make findings difficult to compare across countries; and lack of sufficient statistical power, different comparison groups and heterogeneity as to interventions on smoking cessation. The lung cancer mortality effect has been suggested to be more beneficial among female participants than in males (Becker et al., 2019, Field et al., 2019). The implication for possibly larger mortality gain in women compared with men is poorly understood and also requires further investigation. It has been proposed that the heterogeneity is the result of different relative proportions of lung tumor subtypes by gender (Becker et al., 2019). On the other hand, the trials have not yet reported in detail possible differences between genders in the lifetime cumulative smoking histories and frequencies in stopping smoking after the accrual time of the trial (during randomization period, or follow-up).

A pooled analysis results showed a significant increase in the stage shift towards earlier stage while comparing LDCT to no screening groups (Snowsill et al., 2018). Most of the studies reported a significant increase in lung cancer detection rate using LDCT screening method (Snowsill et al., 2018). Also, the comparison of LDCT to no screening showed a non-significant reduction in the risk of late-stage lung cancer compared with controls. This implied the possibility of overdiagnosis and then leading to overtreatment. Similarly, the false-positive (LDCT) screening test ranged between 7% and 23% and of those positives, 91% to 96% were diagnosed without cancer (Coureau et al., 2016). This may be associated with more complication attributable to follow-up invasive investigation as well as huge additional cost of further assessment and rise in psychological distress and consequences.

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4. Evidence on PSA-based screening

Altogether, five prostate cancer screening trials conducted in Europe and North America reported the results, of which three trials has substantive methodological weakness posing a high risk of bias (Heijnsdijk et al., 2018; Ilic et al., 2013; Pinsky et al., 2017). A recent review study summarizes the findings of all five trials (Ilic et al., 2018) and long term follow up results of ERSPC trial are summarized in a recent study by Hugosson et al. (2019). Except the European Randomised study of Screening for Prostate Cancer (ERSPC) trial, all other studies and meta-analysis reported no statistically significant reduction in prostate cancer-specific mortality (Hugosson et al., 2019; Ilic et al., 2011; Heijnsdijk et al., 2018; Ilic et al., 2018). The US Prostate, Lung, Colorectal and Ovarian (PLCO) trial showed no benefit of screening on PCa mortality and high degree of contamination because of pre-trial and control arm screening (Grubb et al., 2008; Gulati et al., 2012). The ongoing UK CAP/ProtecT trial is already subjected to low participation with a single PSA test (Lane et al., 2010), thus will be less likely to answer the controversy.

The ERSPC trial is the largest with sufficient statistical power that demonstrated a significant reduction in PCa mortality at a longer follow up time at 9, 11, 13 and 16 years (Schröder et al., 2009, 2012, 2014; Hugosson et al., 2019). The latest study from the ERSPC trial reported a 20% (11% to 28%) reduction in PCa mortality at 16 years follow up (Hugosson et al., 2019). A pilot study conducted in Rotterdam within the ERSPC trial follow up cohort (without previous screening contamination) found a substantial reduction (though not statistically significant) in PCa mortality and risk of metastatic disease than previously reported (Osses et al., 2019). The IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer) study interim results after 3 years of screening demonstrated that PSA detected more serious prostate cancer in men with BACA2 mutations and clinically significant tumors as compared to men with BRCA2 non-carriers (Page et al., 2019).

In contrast, the review study by Ilic et al. (2018) showed that PSA screening has no effect on all-cause mortality, increases detection of lower stage (I and II) prostate cancer and slightly decreases the detection of higher stage (III and IV) cancer. On the other hand, published studies on harms reported more than 75% negative biopsy results in positive PSA tests (Andriole et al., 2009; Loeb et al., 2012), overdiagnosis ranged between 27% and 56% of all screen detected cancers (Draisma et al., 2003, 2009) and several serious side-effects of prostate cancer treatment (Carlsson et al., 2011; Korfage et al., 2005; Punnen et al., 2015; Resnick et al., 2013; Sanda et al., 2008). The evidence on cost-effectiveness estimates are mainly based on modeling (using MISCAN model) (Heijnsdijk et al., 2014). A Finnish cost-effectiveness (17-years) follow-up study that linked ERSPC trial cohort with register data found minor difference in overall health-care costs or in overall mortality, and suggested the need for longer follow up including multiple cohort (or trials) studies (Booth et al., 2019).

In conclusion PSA screening can yield a small benefit on prostate cancer mortality, which should be weighed against the potential harms of screening.

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