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New openings of cancer screening in Europe

Work Package 5, task 5.2. Cancer Screening: Conference report

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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
BRCA	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)
Hb	Hemoglobin
BD	Breast density
IT	Information Technology
mpMRI	Multiparametric Magnetic Resonance Imaging

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, the iPAAC 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. The background documentation for the WP5 task on cancer screening highlighted 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 background document included also 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) were also briefly updated.

The above topics were discussed further in the Technical meeting and Conference on cancer screening, held in Helsinki on the 4th and 5th of December 2019. Results, discussions and conclusions have been summarized in this report and below, accordingly.

One future key priority in cancer screening monitoring and evaluation will be looking solutions to disparities between Member States and regions, between various population groups within the Member States and have more focus on specific vulnerable groups. These topics need new investments and support both at the Member State and pan-European levels to find effective solutions to tackle inequities.

Another key priority is to solve inadequacies with respect to what is needed for 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, strengthen their evaluation and quality assurance components and optimize the balance between benefits and harms of the activity? We need to furthermore focus on finding binding solutions for better coverage, legal frameworks, governance structures and standardized data at the pan-European level.

Risk-stratification within the population-based screening programmes has apparently started already. This is the case especially in cervical cancer screening where HPV vaccination status changes the screening needs and algorithms in female populations remarkably. The HPV vaccination coverage as well as cervical cancer screening policy and coverage vary remarkably between the Member States, however; readiness to develop their synergies and optimal cervical cancer control policies is also highly variable.

Risk-stratified approaches are under development also in breast and colorectal cancer screening programmes. To adopt validated surrogate/early indicators of effectiveness, as rate of advanced cancers, survival and quality of life after treatment should be considered. This can enable gradual, well-controlled modifications to the screening policy with profound evaluation of effectiveness of the programme in long term. Still, even if evidence-base will become available from such studies and from efficacy trials, there will be challenges on how to reliably assess the lifetime benefits and harms of the various options. Feasibility due to demanding logistics and organizational requirements has also to be taken into account.

The EU Council recommendation on cancer screening has been an important cornerstone for the improvements in implementation of cancer screening. The document needs updates, however, and suggestions were made on aspects that need to be taken into account in the update. Quality improvement through regular measurement of screening performance using standardized data collection tools, protocols and outputs at the European level is needed on a continuous basis. This includes developing acceptable standards for the core indicators. Better integration between primary and secondary preventive strategies through comprehensive approaches should also be put on the European agenda. Furthermore, updating evidence raised for the potential of new cancer screening programmes is permanently needed.

Updating evidence raised for the potential of new cancer screening programmes is also permanently needed. There are particular challenges to develop appropriate health economic assessments across Member States for potential new cancer screening programmes, taking into account the huge variation in resources, affordability, and alternative or complementary prevention strategies. In the health-economic assessments on lung cancer screening it is a challenge to assess the alternative primary prevention scenarios or complementary interventions with screening and primary prevention. For prostate cancer, early diagnosis of prostate cancers based on unspecific symptoms is an important issue and, as concluded by the iPAAC WP5 task 5.1. on early diagnosis, its evidence-base is not yet developed well enough.

Even though cancer screening has been demonstrated to work effectively in large number of Member States, there is suboptimal implementation in many countries. It is therefore proposed to reactivate autonomous networks of cancer screening coordinators and evaluators to share experiences and develop effective solutions in settings that have not yet a well-functioning programme. This network could also develop training and capacity-building, suggest novel data collection structures, and assist and collaborate in assessing evidence on cancer screening to be continuously updated for the Europe-wide recommendations. It is also necessary to build up good collaboration and links between such a network and other groups in cancer information domain to develop the European cancer information system for adequate evaluation and monitoring of cancer screening and early diagnosis.

Planning open meetings and having multiple voices in the process has enriched 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 is needed for finding social advances and innovations in cancer screening.

The report will be utilized in developing the final deliverable of the iPAAC Joint Action, the Roadmap on Implementation and Sustainability of Cancer Control Actions. The meeting experts and participants brought novel contributions to the European cancer control agenda on cancer screening. The results and ideas developed will be transferred and shared for further planning and development of the European cancer control agenda – such as the Europe's Beating Cancer Plan, the Cancer Mission, and development of the European Health Programme.

1 Introduction

1.1 Work Package 5.2 tasks and the outcome

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 address 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 introducing 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, IARC Handbooks on breast and CRC Screening). 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 of cancer, population-based cancer screening programmes, health promotion and cancer prevention. Priority target group is decision-makers in member states. In this report we will provide some preliminary thoughts on 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 calls for both technological and social innovations. There are at least three different levels in innovations:

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

1.2 Innovation and co-creation

We will define, keeping in mind the complex process of health systems and screening sub-systems, social innovation as 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? Technological and social innovations in the area of cancer screening may include actions like, for instance the following:

- increasing coverage of the programme through research and improved invitational practices contextualized to the local conditions
- introducing new technologies and methods in population-based screening programmes in an evidence-based manner
- evaluation of use of services within and outside the screening programme; in asymptomatic as well as symptomatic populations
- 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 gFOBT 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 adequately investigated

before being put into practice. Research should clearly demonstrate the benefits of new interventions in comparison to the present standard of care practice. Also, the European quality-assurance guidelines for cancer screening programmes define scientific-level evaluation as an 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.

This conference report is based on 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 used co-creational methods and group work is described in this conference report. The main work of the task will be based on this document and the WP5 Milestone 5.2. *Report of innovations, including harms and benefits from risk-stratified screening* (2019) The conference report will also be available for developing the European roadmap and for other tasks of the WP5.

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 respectively 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 participation 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 are potentially at stake. (Deandrea et al.; 2016).

Among the estimated 32 million annual female population for breast cancer screening in the age group of 50-69 years (the minimum age group targeted in the EU countries) 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%) (Ponti et al., 2017). Among the women invited in this age, on an 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 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 women screened (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 quality 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.

WP5 task 5.2. will consist of two documents: Milestone 5.2. Report of innovations, including harms and benefits from risk-stratified screening from September 2019 and the conference report based on co-creational meeting *New Openings in Cancer Screening in Europe,* which was held in Helsinki 5 December 2019 as a side event of Finland's Presidency of the Council of the European Union. Both documents were prepared in technical meetings were iPAAC consortium partners played an important role in total of 4 technical meetings. One of them was held 4 December at the Cancer Society of Finland offices. Others were online meetings.

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, and 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 criteria for screening, published by the WHO Bulletin, date back to 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, feasibility and sustainability ensuring that the programme achieves the goals, 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; WHO Regional Office for Europe, 2020). 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 Regional Office for Europe 2019 and 2020), 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).

2.1 Further definitions

“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 nonspecific, 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; Helsingen et al., 2019).

For cervical cancer, individual risk assessment has been proposed to guide the screening policy (Castle et al., 2007).

Vaccination status against HPV is an example which can substantially alter cervical cancer risk 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 not regularly attended or women with abnormal screening results also after the general stopping age due to high risk and potential 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. The evaluation of the information on benefits outweighing the harm indicates that it is sufficient for the recommended screening strategies and mostly not available for the surveillance strategies (Table 1). Usually no similar monitoring and evaluation is available for surveillance than for the population-based screening. For the sake of clarity, we prefer to distinguish 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. Colorectal cancer: Examples of screening vs some surveillance strategies of high-risk groups (modified from 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 informing screenees after a negative test result; and whether it is feasible to try to integrate surveillance activities into the monitoring and evaluation structures of cancer screening programmes. The recommended testing interval by the screening programme may not be valid for the population under surveillance and this could be taken into account in the response to the screenee. 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 in current European quality assurance guidelines, however, what items should be included about surveillance in such monitoring and evaluation.

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 (Schünemann et al., eds., 2013) 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., 2002; NLST 2011). In these studies changes in other causes than the screened disease itself may also have affected the overall mortality. Impact on overall mortality would be highly essential for cancer control. It 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.

2.2 Main benefits and harms for cancer screening policies

The main harms 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, for potential new cancer screening programmes from long-lasting randomized trials. Additional 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 must also 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

3.1 Governance

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 and clear delegation of responsibilities
- the development of the country legal code, 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.
- actions to avoid deficiencies in the governance structures for population-based screening that may severely impede the full implementation of effective population-based cancer screening programmes.

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.

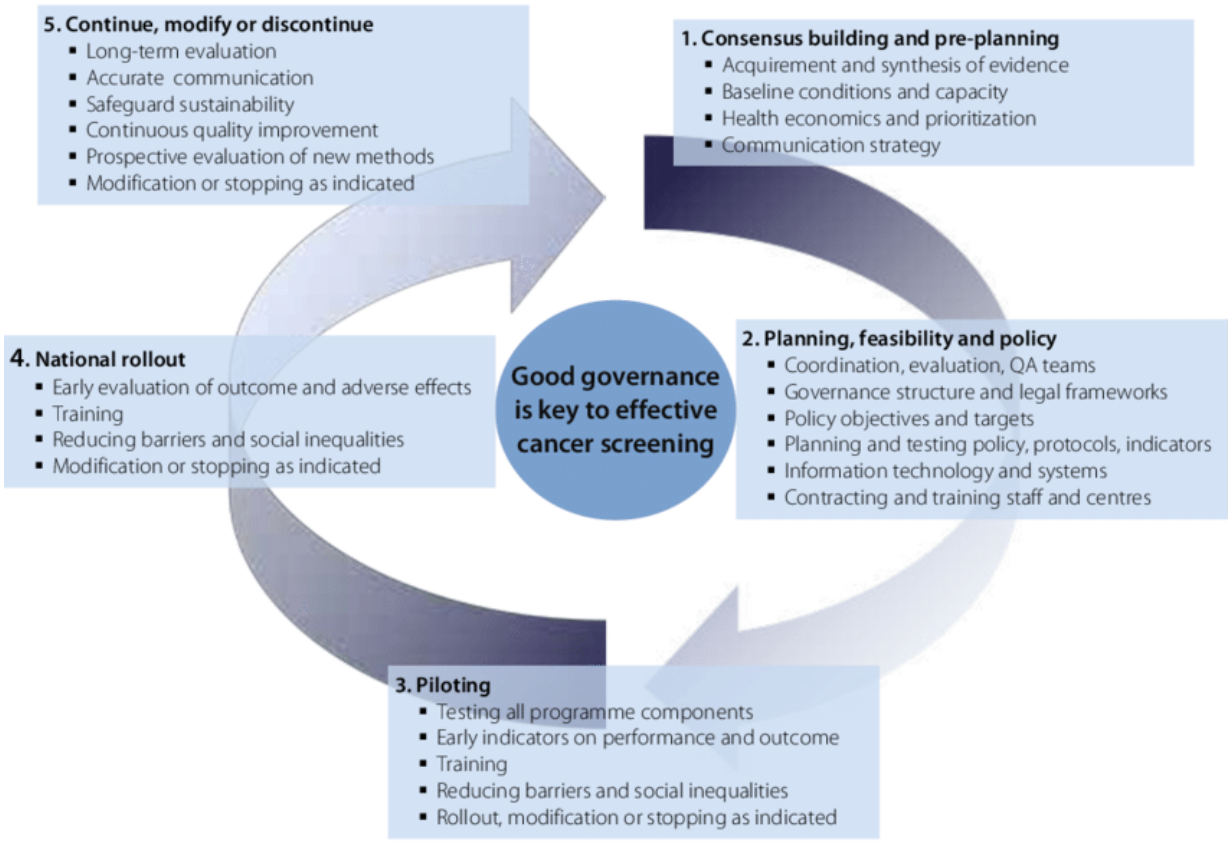

Figure 1. Examples of tasks of organization, evaluation and governance in different phases of implementation and quality improvement of a cancer screening programme. (CANCON)

3.1.1 Potential new programmes

Assessments of 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. Priorities to investments to alternative, complementary or competing strategies need also to be taken into account carefully in these assessments. This entails assessments e.g. of scenarios and investments to primary prevention for lung cancer, and possibilities for develop improved early diagnosis and evidence-based treatment strategies for prostate cancer.

In order to acquire the appropriate evidence-base, new trials need to be financed to investigate optimal strategies for cancer screening. Once evidence exists to support these criteria, the planning phase to be launched would entail further assessments of the policy

targets in relation to screening, existing capacities and readiness of the country to have a new programme; and the requirements of additional human, technical and financial resources (see section Lönnberg et al., 2017; and section 3.1.). Implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice. A new programme will require stepwise implementation (see Fig. 1.).

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).

4 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 led 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 (Peiró et al, 2017) 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 Practices tackling social inequalities in cancer prevention The Contest aimed at identifying and compiling relevant European experiences, 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. All the documents associated with the Call and the results of the Contest are available at: https://www.ipaac.eu/en/contest-best-practices/.

Finally, following the CANCON recommendations (Peiró 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 determine the best way to invite women covering the special needs of vulnerable women, including socially disadvantaged women, women with intellectual disability, and non-native speaking women (https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/Invitation-to-screening-and-decision-aid).

5 Risk-stratified screening: criteria and innovations

5.1 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 being proposed only to include heavy smokers or ex-smokers within a specified age, is an example of risk stratified 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.

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

Other situations may be more challenging to be classified. In the new cervical cancer screening based on Human papilloma virus (HPV) testing, the test is aimed to identify a situation of higher risk (the infection with high risk HPV virus). This makes 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. If these protocols are adopted similarly to all women, then HPV screening is not yet risk-stratified screening. However, if the screening protocol would vary individually based e.g. on risk scores (Castle et al., 2007), then it can be risk-stratified screening.

For colorectal cancer screening, it has been suggested that the cumulative value of fecal Hb 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 Hb could be considered an element of risk-stratification. The risk stratification based on multiple parameters is also a good example of potential risk-stratified screening strategies for colorectal cancer (Kuipers & Spaanders 2018; Helsingen et al., 2019).

5.1.1 General remarks

Also 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 benefit/risk 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 descendants. 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.

5.1.2 Proposed situations for a shift from generalized screening to risk-stratified screening

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 (BD) affects the accuracy of mammography (Puliti et al., 2018), but not that of ultrasound (Ohuchi et al., 2016). So 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 BD 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 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 - as in 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.

Regarding the second case, 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 of the targeted disease (precancer and cancer) 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 benefits. 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 starting later in people with lower risk, since most epithelial cancers have an increasing incidence with age)
2) The screening interval can be different (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 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.

5.1.3 Is it useful to tailor screening based on personal risk?

A more intensive screening protocol in a selected risk group is supposed to provide a more sensitive approach but also a 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/he** will experience:

- A lower number of tests;
- A lower lifetime probability of a false positive result and consequential physical and psychological harms;
- Less side effects (e.g., lower irradiation);
- A lower probability of surgically treated benign lesions
- Though the number would be less, it is possible that the cancers will be diagnosed late which 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:

- Less burden on the health system
- Better compliance of the high risk group to participate
- Identifying the 'high-risk' group itself may be a challenge

➔ 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 protocols 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 the targeted cancer between high risk group and low risk group can be reduced. Nonetheless, 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.

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

- would an individual classified at low risk agree to have a less intensive management, or would she feel to have a lower protection from cancer?
- there is need for a proper communication strategy, explaining the concept of risk-based approach but equal protection.

6 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 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 surrogate/early indicators of effectiveness, as rate of advanced cancers, survival and QoL after treatment 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 logistic issues and higher level of complexities of risk based screening should be taken into account, and feasibility and sustainability are also important elements for the decision possibly to modify the programme.

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 challenging as well. Depending on screening methods, risk may remain high even in women testing negative. Therefore, evaluation of alternative methods for prophylaxis is important.

6.1 Case of breast cancer

6.1.1 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 assures a better balance between harms and benefits as compared to ´standard of care´ 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 with a very long follow-up should be carried out

d. Comparison trials based on proxy indicators (as rate of advanced cancers) preferably including also 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 woman'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*

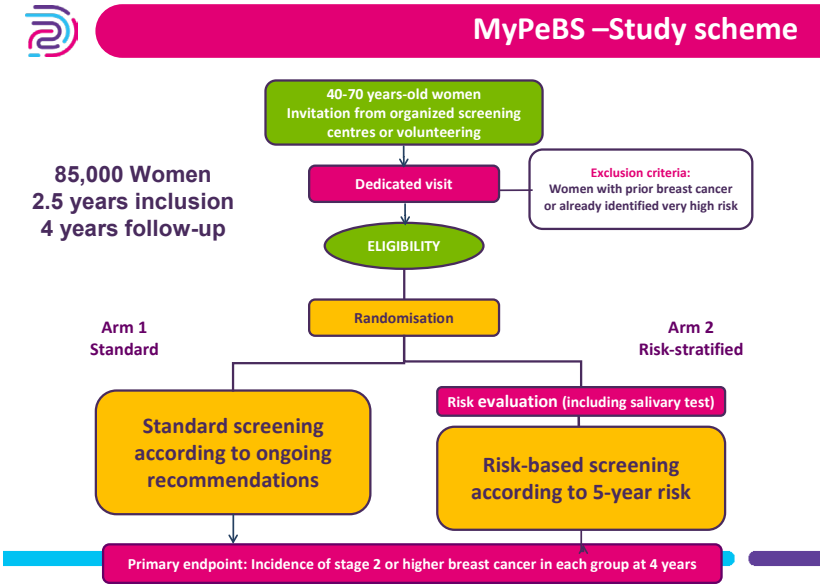

Figure 2 Example of breast cancer screening MyPeBS

MyPeBS

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.

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).

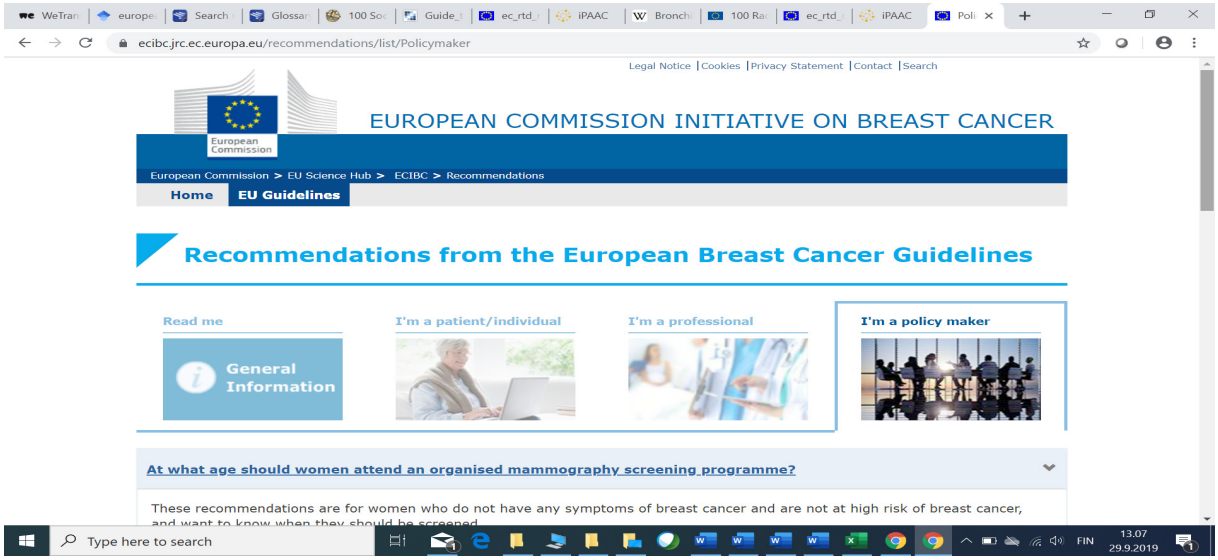

Figure 3. ECIBC recommendations are available for patients, professionals and policy makers.

BOX 2. What are the current recommendations for personalized screening in breast cancer screening for breast density?

In the context of an organised screening programme for asymptomatic women with high mammographic breast density, the European Commission Initiative for Breast Cancer Guidelines Development Group suggests

https://ecibc.jrc.ec.europa.eu/;

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

- **screening with either digital breast tomosynthesis (DBT) or digital mammography**
  (conditional recommendation, very low certainty of the evidence)
- **not implementing tailored screening with both DBT and digital mammography**
  (conditional recommendation, very low certainty of the evidence)
- **not implementing tailored screening with magnetic resonance imaging (MRI)**
  (conditional recommendation, very low certainty of the evidence)
- **not implementing tailored screening with automated breast ultrasound system (ABUS)**
  (conditional recommendation, very low certainty of the evidence)
- **not implementing tailored screening with hand-held ultrasound (HHUS)**
  (conditional recommendation, low certainty of the evidence)

7 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; U.S. Department of Health and Human Services, 2020). Importantly, when quitting smoking takes place at a relatively young age – below age 40 or 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. Stopping smoking at an older age, or not stopping smoking, is associated, respectively, with a much higher lung cancer and all-cause mortality risks (*ibid.*). Due to large impact of tobacco on the risk of lung cnacer and many other chronic diseases, the priority in governmental tobacco control policy is in primary prevention of tobacco and nicotine products. It is still important to consider whether lung cancer screening can be integrated in the future into optimal tobacco control policies. It is 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.

7.1 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 the 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. There are contradictory findings from studies on this topic.

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).

7.2 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 screening rounds. The study population consisted of current tobacco smokers or ex-smokers within specified age groups. There are several trials being reported or under follow-up in European countries, with variation in the lung nodule management protocols and 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). The peer-reviewed report of the NELSON trial, published in 2020, has reported 24% decrease in lung cancer mortality in men and 33% decrease in women and no decrease in overall mortality (de Koning et al., 2020). A meta-analysis on lung cancer screening trials using low-dose computed tomography has demonstrated an average impact of 17% on reducing lung cancer mortality and of 4% on reducing all-cause mortality in the screening group compared with the control group during the follow-up period of the trial protocols (Sadate et al., 2020).

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 most

sophisticated trials where the surveillance and referral rates were reasonably lower and there are needs also to clinical validation of novel methods in this respect.

There is an emphasis on integrating interventions to quit tobacco smoking with lung cancer screening also in the US (Steliga & Yang, 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 nor by the WHO, there are implementation studies to assess aspects potentially relevant for public health and clinical uses of the methods (Field et al., 2016, 2019; Crosbie et al., 2019; Ghimire et al., 2019; Rzyman et al., 2019; Pinsky et al., 2013; Becker et al., 2019; WHO 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 best integrate interventions on smoking cessation with screening
- To understand aspects related to other findings than on lung cancer mortality, reported by some trials.
- To further investigate the mortality benefits by gender, which is shown to be more beneficial among female participants than males as apparent to the difference in histological tumor subtypes.

8 Technical meeting in Helsinki – what 40 WP partners and experts have to say?

8.1 Agenda and introduction

The iPAAC WP5.2 technical meeting of the associated partners and invited experts was organized by the Cancer Society of Finland on December 4, 2019, in Helsinki. The main agenda of the meeting was to provide an overview of the iPAAC Work Package WP5 and to discuss definitions and criteria for cancer screening and priorities ahead. Also the final deliverable of the joint action, the roadmap, was discussed among WP5 partners and experts. The first part of the meeting focused on expert's opinions and presentations on key priorities ahead on cancer screening and the roadmap. The second part involved participants to discuss screening criteria and recommendations, and suggestions for the roadmap.

8.2 Key priorities ahead on cancer screening

Invited partners and experts from professional and scientific organizations presented on the criteria and priorities ahead on cancer screening. The presentations of the technical meeting are annexed in this report. The meeting reinforced the fact that screening is the key for successful cancer control and highlighted that collaboration and partnership between the EU member states is fundamental. To start with, the EU Council recommendation on cancer screening has been an important cornerstone for the improvements in implementation of cancer screening. The document is however already rather old and needs updates, discussed in detail in the open conference (see Chapter 7).Thus, the priority ahead is to develop consensus on screening across Member States.

Social inequalities in cancer screening is an important continuum for cancer incidence and mortality. It is important to address essential aspects in tackling inequities using best practice methodologies and criteria. Recent systematic review on cancer screening criteria generated 12 consolidated principles with a focus on shifting principles (such as infrastructure requirement, coordination, acceptability of screening programmes and performance management principles) and shift in decision-making. However, the principles could not address the gaps in some important issues of cancer screening in today's world such as risk-based screening, issues on inequity and changes in the societal principles. Another important priority ahead on cancer screening is identifying everyone in target population especially the high-risk groups while implementing the risk-stratified screening approach. Population based screening programmes are not possible if there is no registration mechanism. In addition, the priorities for cancer screening should be identified based on assessment of the balance of harms and benefits, quality assurance mechanism, life expectancy of the population and poverty.

8.2.1 Essential points to be included to the Roadmap on cancer screening

- Implementation and sustainability of cancer screening programmes
- Focus on social innovation and the importance of appropriate implementation
    - One pager reporting, the WP Leader and Partners will have a decisive role in developing topics and contents for One pager
- Keeping the iPAAC work in progress also after the current activity period
- For information: new steering body for cancer research mission, EU action plan on cancer.

8.3 Group work results

Participants in the technical meeting were divided into five groups. The group work was conducted in two rounds. In the first round, all group members introduced themselves and nominated a facilitator and discussed/brainstormed on the important criteria for cancer screening for the existing programmes as well as potential new programmes in the future. The second round mainly focused on suggestions for the roadmap on implementation and sustainability of cancer control actions. The facilitator of each group presented the results from individual groups, which was then followed by questions/answer round. Many of the questions and answers were noted by the organizing committee and are mentioned below as well.

Group work 1 (Breast cancer):
The group discussion started with a focus on communication strategy on benefits and harms of breast cancer screening. The participants identified the need to address women with low health literacy about breast cancer screening and all treatment strategies/options available. There should be a standardized data collection system and follow up of women. The group suggested strategies breast cancer control actions including risk stratified screening, role of artificial intelligence in imaging, new modalities such as clinical trials for new multiparametric MRI, and evidence-based implementation of screening programmes.

Group work 2 (Cervical cancer):
The group started the discussion with the challenges and opportunities on shifting from cytology to HPV based screening. Participants highlighted the importance of harmonizing protocols at program level when introducing HPV test – selection of correct technology and appropriate protocol and triage & follow up strategies, and addressing screening inequities such as coverage, access and quality. Some important issues for implementation were discussed, such as focusing on equity and universal coverage – resource mobilization, setting up laboratory services, training of health professionals and integrated health services.

Group work 3 (Colorectal cancer):
The discussion about the criteria of colorectal cancer screening started with the difficulty to carry out risk stratification-based screening. There is lack of evidence and appropriate

register-based information. To reduce inequalities and barriers within the programmes, participants suggested focusing on uptake of screening in high-risk or underserved population groups, (such as men, high and low income groups, tobacco smokers, obese population), and shared data (e.g., link on individual level at national and international level). Role of artificial intelligence, and sustainability (reduce plastic while sending for FIT test) were also discussed. Strategies to develop primary prevention are needed also for colorectal cancer screening programmes participants.

Group work 4 (Inequalities):
The discussion about inequalities mainly focused on empowerment and peer-education on cancer prevention (primary and secondary) by community health agents particularly in socially vulnerable settings; evidence-based targeted actions in order to improve equity in access (by gender, immigration, socio-economic factors); and citizen's involvement in the design of cancer screening programmes. Participants suggested identifying and sharing good practices that have proven to be effective to reduce social inequalities in cancer screening and to monitor potential inequalities in cancer screening indicators (uptake and follow-up) more systematically than done thus far in European monitoring data and on a regular basis.

Group work 5 (New potential programmes):
The group focused on lung cancer screening as a new potential programme with a primary issue of identifying the high-risk population using population-based questionnaires, primary care records and self-referrals, and how best to reach the socially disadvantaged population. Participants also highlighted the potential use of big data mainly to identify the high-risk population based on recorded characteristics such as age, gender, place of residence, and to make implementation strategies within the legal framework of the member states.

8.4 Concluding remarks

In the roundtable reports there were three areas that would need more in-depth discussions. First, it is clear that there is a lack of register-based information (colorectal cancer group). The screening programmes could be advanced with systematic follow-up (breast cancer group). Shifting from cytology to HPV tests makes harmonizing protocols important at programme-level (cervical cancer group).

Second, new technologies require flexibility to adopt new measures in implementation of the programmes but with step-wise procedures. Technology itself is not enough. In breast cancer screening artificial intelligence and imaging development could bring advancement. Third, high risk concepts are gaining ground in population-based programmes. This is a challenge especially in cervical cancer screening when HPV vaccinated cohorts come into screening age. High risk or underserved population groups need more attention and tailored communication strategies.

9 Conference in Helsinki – December 5, 2019

9.1 Agenda and introduction

The iPAAC WP5.2 Conference on 'New Openings of Cancer Screening in Europe' was jointly organized by Finnish Institute for Health and Welfare (THL) and the Cancer Society of Finland on December 5, 2019, in Helsinki. The conference was organized as a side event of Finland's Presidency of the Council of the European Union. The main agenda of the conference was to discuss and find new strategies for cancer screening in Europe with the primary focus on risk-stratified screening and possible new screening programmes. The first part of the conference focused on experts' presentations on the agenda. The latter part involved participants to discuss different dimensions of cancer screening and cancer types, and to find shared understanding on the issues among group participants based on the idea of co-creation.

9.2 Current status of cancer screening in EU and need to update the recommendation by the Council of the European Union

Implementation of cancer screening programmes to reduce the burden of the common cancers is a priority for the EU member states. The EU council recommendation on cancer screening, in 2003, urged member states to offer evidence-based screening for breast, cervical and colorectal cancer using a population-based approach with quality assurance at all levels. The recommendation directed member states to ensure availability of resources, monitor process and outcomes, evaluate screening data and report the progress to the council on a regular basis. The progress report on cancer screening was published in 2008 and 2017. During the time, a lot of progress have been made on the implementation of cancer screening programmes, including shifting from non-population-based to population-based screening programmes.

Out of 28 member states, 25 countries have population-based breast cancer screening programmes, 22 countries have either national or regional population-based cervical cancer screening programmes, and colorectal cancer screening programme has been implemented in 20 countries with majority of them having completed the rollout (Second report on the implementation of cancer screening in EU, 2017). Despite of the progress, several barriers, such as access to screening services and delivery of quality assured services exists, leading to serious inequities across programmes and significant heterogeneity across member states.

At the same time, several new screening tests and protocols have been developed and validated in the Member States, and recommended in recent European quality assurance guidelines, but have not been updated in the EU Council recommendation on cancer screening. There is a need to review the evidence on benefits and harms of screening for

different screening strategies (for example, methods of screening, screening age range, screening intervals, risk-stratified screening) and review available evidences on new cancer sites (such as prostate and lung cancers). The EU council should also develop or update recommendation on the integration of primary and secondary preventive strategies through comprehensive approaches, which is necessary to reduce the cancer burden and to control the rising trend of other non-communicable diseases.

The proposed new health initiative, the EU4Health Programme will set out key action areas in fighting cancer in Europe. Cancer screening should be on its agenda to ensure that early detection functions well. Screening programmes reduce, if implemented effectively, inequalities across countries, regions, groups and individuals. (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020PC0405)

For the update of Council Recommendation (2003) and an expert network to support this work, specific resources should be secured with adequate follow-up measures.

9.3 New strategies for cancer screening

9.3.1 Risk-stratified screening

Risk-stratified screening in a population-based approach means selective personalized screening with aims to improve the screening programme by modifying screening policies based on individual-level disease risk (see section 2.1. on definitions above). The aim of risk-stratified screening is to achieve a better balance between harms and benefit (section 3.1.). Experts suggested certain favourable situations when risk-stratified screening could be proposed, such as presence of factors influencing the accuracy of primary test and presence of factors influencing the risk of developing a cancer, for example, density of the breast. The screening protocols for risk-based screening can be more intensive in certain groups of population to almost no screening for lower risk groups. The risk-stratified screening in population-based approach can be cost effective as, theoretically, the higher number of lives can be saved with same amount of resources, or with lower amount of resources, the same number of lives can be saved.

Within the EU recommended population-based organized screening programmes that currently exist in many countries, certain high-risk groups have been already identified, for example, in case of breast or colorectal cancers. Women with highest density breast have higher risk of breast cancer as compared to low dense breast. In case of colorectal cancer, high-risk groups based on family history, genetic markers or faecal haemoglobin value could be identified. Studies are undergoing about effectiveness of potential lung cancer screening in high-risk groups, such as heavy smokers. However, to find the solution on how to screen the high-risk groups, either by offering frequent screening or by changing screening techniques, is the actual difficulty. In any case, the sustainability (in terms of cost, resources,

and organizational aspects) of implementing such risk-based strategies should be deeply evaluated and communicated well with the screening target population.

9.3.2 New potential screening programmes

The current recommendation of WHO is screening for cervical, colorectal and breast cancer, and does not recommend screening for other types of cancer. Lung and prostate cancers are considered as the possible future cancer screening programmes. The main criteria for potential new cancer screening programmes are sufficient evidence on efficacy and effectiveness from clinical trials, balance of benefit outweigh harms and cost effectiveness. Evidence on the effectiveness on screening for lung and prostate cancer from randomized trials and implementation studies are already mentioned as background material in chapter 5 of this report.

An important question raised for new potential programmes to start implementing is the value of the evidence of improved balance of benefit and harms for policy-making. Another important agenda could be whether to launch new programme to the whole target population or only for the high-risk groups. For example, in case of lung cancer, there is evidence that LDCT prevents death from lung cancer in high-risk population who are screened but evidence on benefits of whole population targeted for screening is lacking. For prostate cancer screening by PSA, the improved balance of benefit outweighing harms is unclear and opinions are shared on whether or not to start implementing screening. Experts argue that evidence on ovarian cancer is not sufficient, thus, needs longer term follow up. While evidence to start implementing these potential screening programmes is greatly sought, experts make aware of the possibility that new screening programme might introduce more challenges such as increasing social inequalities, incomplete coverage, low feasibility and low participation in the programme. Combining new screening programme with primary prevention strategy will be the key for the long-term success of cancer prevention.

9.3.3 Group work results

Group work 1 (Breast cancer): Theme – Risk adjusted strategy
In breast cancer screening, still we need more evidence before planning a risk-adjusted screening strategy. One of the questions raised is to find out how many women would be classified as having high dense or low dense breast. Participants assumed that 20% could be considered as having high dense breast, but this parameter decreases with ageing. There is a need to develop an algorithm in order to classify and adjust the risk in every round based on breast density, age, menopausal status, hormonal treatments and other risk factors. At the same time, many registries do not collect information in these factors. There are uncertainties also on which screening methods and protocols would help (see section 4.4.2.) and it is possible that completely new screening methods or strategies, not yet available,

need to be developed. In addition, it is important to convince women about screening, professionals and scientists about the risk-adjusted strategy, which implies communicating the results via doctor appointments or other personalized means. Participants doubted that not all countries or regions would participate in the MyPeBS study because of limited budget, extra workload, difficulties to get grants, issues on recruitment and getting informed consent and other logistic issues.

Group work 2 (Breast cancer): Theme – Inequality, including issues how to improve coverage

The discussion started with screening inequalities in the most deprived population, in women with low education, low health literacy, physical disabilities (such as hearing loss, mental health problem), prisoners, immigrants, etc. It is important to involve citizens from the deprived communities to communicate the message about screening. Another important barrier is to screen working aged women who are eligible for screening. For example, in Hungary, working aged women are reached through occupational health system and marginalized groups are reached through mobile screening clinics. However, there is high possibility of loss to follow up of women screened in mobile clinics. In addition, social integration for immigrants is a challenge because of many social and cultural factors rather than just reaching them.
To overcome these challenges, participants proposed to have involvement of local level in execution of programme with central level focusing mainly on planning of programme. Moreover, there should be joint discussion of community representatives and service providers so that the screening message could be well delivered to the target population. The primary prevention message should be integrated while inviting women to the screening clinics. The programme should provide an option free call number so that women can use that service if she wants to know more about screening. At last, the participants highlighted the importance of sharing efforts and experiences across programmes or countries.

Group 3 (Lung cancer): Theme – Implementation research needs

The group focused on identifying the current implementation research needs and priorities on lung cancer screening. There should be an organized approach to recruit screening population, with a focus on quality assurance and use of necessary resources. There are countries that can identify smokers easily in the population, for example; there may be still population groups where it is not straightforward and that remain hard-to-reach. Resources use should focus on the new diagnostic methods and technologies needed for lung cancer screening; and e.g. on training of radiologists and other staff. Synergy with prevention also with quitting smoking, or ex-smokers, is important. Building up and developing registries is an essential task. Lung cancer screening being a potential new screening programme, there is a need to have pilot implementation projects across member countries. Policy and decision makers should be provided with clear and realistic proposals on implementation of lung cancer screening programme together with primary prevention strategies. More money and research is needed on feasibility of implementation on certainties of screening and on outcome research. This is a challenge also for the European Cancer Mission from proposed European Union´s Horizon Europe research and innovation programme 2021–2027.

Group 4 (Lung cancer): Theme – The synergy in cancer prevention: the optimal strategy to prevent lung cancers

Primary prevention strategies are in a very high priority for public health, irrespective of lung cancer screening plans. This concerns governmental tobacco control strategies, as well as need to develop evidence-based strategies and interventions for tobacco smoking cessation. Primary prevention can have still a very large impact to decrease lung cancer risk, also at ages younger than possibly targeted for screening. However, if a person has not quitted smoking at such a rather old age relevant for lung cancer screening, his/her lung cancer risk will remain very high, also even after stopping smoking. Therefore, screening can further prevent cause-specific mortality. Still, it is very important to integrate primary prevention strategies in any potential lung cancer screening activity and rigorously evaluate both the primary and secondary prevention components in the intervention. Counselling also for quitting smoking could be mandatory in lung cancer screening activity. An important challenge is to evaluate exposure to smoking environment other than cigarette because of the difficulty to define the target population that are at risk. So far the results on the best combined strategies are inconclusive and there is a need to rethink of the best strategy. In several LDCT trials there have been remarkable incidental findings, related to diseases other than lung cancer, and overall mortality has also been affected in several, but not all, trials. In particular, differences in management of coronary microcalcifications can have occurred, ~~and~~ but, unfortunately, such aspects have not been reported systematically in the trials. There is therefore a need for in-depth studies to clarify the best protocols for such incidental findings, too. Finding best screening strategy, either population-based only or also spontaneous screening, is a challenge. It is not yet completely clear whether only the population-based approach, or also spontaneous screening with integrated systematic quality assurance, would work best. Participants argued that without a population-based approach, it is not possible to accumulate evidence for the best way of screening.

Group 5 (Cervical cancer): Theme – How to improve coverage and participation?

Participants started the discussion with the importance of encouraging HPV vaccination of adolescent girls and screening of age-eligible women. It is important to continuously monitor and evaluate the existing programmes and recognize the strength of population-based screening. Participants highlighted the need for involvement of all health professionals involved in the different phases of the screening process, with annual meetings for sharing results and critical issues and plan together ways ahead to improve coverage participation and quality (example in Italy). The example of misinformation about screening in Ireland was shared, raising awareness for other programmes to prepare good evidence-based communication strategies. Participants discussed about the influence of HPV-based screening in countries with active population-based cytology screening and in countries where only opportunistic screening is in place: planning, piloting, improve information technology (IT) infrastructure, quality assurance and monitoring protocols. It is important to train health professionals involved in organized screening, at the beginning of the implementation and periodically thereafter.

Group 6 (Cervical cancer): Theme – How to improve screening
Participants of the group started the discussion about improving data collection and integration from different sources (legally and methodologically) for surveillance on cervical cancer screening with the aim to improve quality management and to generate evidence on established and novel screening schemes. Developing communication concepts for screening targeted at the public, at health care professionals and at policy makers addressing the chances and risk of cervical cancer screening and on the process of knowledge generation through scientific methods in general. The registration model in Slovenia was identified as a best practice model of organised cervical cancer screening with respect to data collection and integration. Cultural, legal and political frameworks of member states are quite different and should be shared among member states, which may determine the possibilities for countries with no population-based cervical cancer screening programmes.

Group 7 (Innovation): Theme – Data, Artificial Intelligence and Personalized screening potential
Participants of the group emphasized on unified, structured data delivery to ensure regular monitoring and evaluation of the programme. The “E-vite”, electronic platform for invitation, re-scheduling invitations, SMS reminders, providing responses and information on further assessment are vital. It will be useful to have uniform indicators for cancer screening programmes for policy makers to find out how countries are performing. Participants proposed to incorporate artificial intelligence into mammography screening and to find out how digital solutions can improve the quality of screening programmes, e.g., machine learning in mammography screening.

Group 8 (Innovation): Theme – Social innovations: services, health system, inequality
The discussion started with challenges that screening programmes are currently facing, such as cost effectiveness of cancer screening programmes and low participation because of cultural barriers, economic status, gender issues (masculinity), logistical issues, misconception about screening, inequalities in implementation status between countries and regions. Participants proposed more cost effective programmes, self-sampling for HPV test (as done in Finland and Norway) and use of local leaders to improve screening participation in socially vulnerable groups in screening and use of smart phone to improve invitation strategy in other programmes as is done in Spain already. More behavioural research on misconception about screening harm is needed in order to design innovative evidence-based interventions, to effectively overcome anti-screening campaigns and to combine population and targeted interventions to tailor screening messages and communication to specific subgroups. Research on risk stratification methods including the use of artificial intelligence and big data. In addition, research on economic evaluation of these innovative screening interventions is needed to show the return on the investment to policy makers (for example, taking the sample at home implies saving time to work, other than saving direct cost of the health system).

Group 9 (Colorectal cancer): Theme – Risk-adjusted possibilities, genomics, gender, risk profiles

The discussion focused on integrating prevention into colorectal cancer (CRC) screening programme. It is important to communicate to the population mainly on lifestyle changes and need to help people find ways to change lifestyle and encourage them for primary prevention and screening programme. As most of CRC screening programmes are new and thus without historical perspective, risk-stratified screening is not really on the agenda in most countries yet, except different threshold for different gender. Enabling networking, sharing of information (such as quality assurance, improving uptake and logistics) and learning from each other should be ideal to improve cancer screening. Most of the risk-stratified options are still in research phase, like genomics, risk profiling, except different test cut-offs by gender as started in screening programmes in Finland and Sweden. In addition, if a given risk-stratified screening is evidence-based and feasible, one needs to be able to communicate risk-stratified screening strategy also to the public. EU could provide guidelines to make sharing of data on a national and international level more easily.

Group 10 (Colorectal cancer): Theme – Inequality, how to improve coverage, tools for policy

Participants started the discussion with strategies on improving communication to reach the target population. It is important to send reminder letters for follow up of the target population and the follow up telephone calls to learn the reason why people do not participate, example in Scotland. In addition, to improve participation, central info line available for the public to answer any queries related to screening (example in Finland) and letter from the health institute organizing the screening and personal letter, for example in Hungary, from the major could play an important role. Especially, in lower socio-economic groups, providing education about screening including the good examples of screening is important to improve participation. Social media campaigns, for example, Digestive Cancers Europe campaign showed that it is important to have a focal person to answer incoming questions about screening arising because of campaign, helps to increase awareness and participation.

The group proposed several important topics to be considered in the action against cancer and the cancer mission. EU guidelines on colorectal cancer screening needs to be updated and simplified. Providing proof of concept on social media campaigns could be a successful way to promote screening. In addition, individual level data linkages are required for comprehensive evaluation. Finally, use of artificial intelligence in colonoscopy should be studied to assess whether it could help to identify lesions otherwise potentially missed.

Group 11 (Colorectal cancer): Theme – How to integrate primary prevention into the screening program

Primary prevention is an essential part for the screening programme to succeed. For example, lifestyle related factors account for about half of all colorectal cancer cases. The group reported that “screening is a missed opportunity for prevention”, “a great opportunity for prevention”, but also a “challenge” considering that people are sceptical, prefer medicine,

not so familiar with the concept of “health promoting health service” and hard to convince about behaviour change in vulnerable groups. Another important strategy is to include health promotion and healthy behaviour information when sending the FIT letter and kit, example in Scotland, and target the work site programme to increase uptake. For participants with negative results, it is a good opportunity to provide information on risk reduction and aware them to avoid a “health certificate effect”. More research is needed to identify most effective mechanism to deliver health promotion materials and support impact on awareness of cancer risk, intention to change behaviours and actual behaviour change. It is also important to balance between the health promotion message and the duty of care by the health care system. Studies have shown that patients are interested in receiving lifestyle advice if they know the relevance. Health promotion ambassadors, testimonials and patient voice for prevention should be encouraged for primary prevention also in colorectal cancer screening programmes.

Group 12 (Prostate cancer): Theme – Evidence-based methods to balance the benefits and harms

The current situation in the field of prostate cancer screening is confusing, for both healthcare workers and public. Including men aged 50 years or more who are exposed to contradictory messages and recommendations regarding the prostate cancer screening from media, peers, their clinicians, public health workers, scientists and governmental bodies. Men are currently engaging in the opportunistic cancer screening in many countries, based on the information that they have and believe in. The most important finding that the group agreed on was that all stakeholders need to align on main messages and recommendations regarding the prostate cancer screening. The alignment should be multidisciplinary with aim that all stakeholders (1) acknowledge, understand and interpret the available evidence in the same way and (2) that they convey same messages and recommendations to health workers, public on general and men at counselling. The group did not agree whether we do need or not additional evidence for the mortality reduction due to prostate cancer screening. Even if prostate cancer screening with PSA has a potential to reduce mortality, all other criteria for screening, as well as use of the PSA test by indication, must be taken into consideration. The group did not reach consensus regarding the benefits to harm ratio of prostate cancer screening strategies used in trials. Novel technology (mpMRI and other), not used in earlier trials, successfully lowers the need for biopsies and invasive treatment in men with low risk of aggressive prostate cancer; however, it does not return men to screening. Results from the trials show, that even if men are reassured that their prostate cancer is non-aggressive and are advised active surveillance, many of them opt-in for the invasive treatment; besides that there is some evidence that their quality of life is similar to those who were recommended treatment at the first place. Also, all/most of the diagnostic after the initial elevated screening PSA is done at specialists (urology, radiology), which increase costs and the need for the highly trained personnel and sophisticated infrastructure with high capacity due to the high recall-rates.

Group 13 (Guidelines): Theme – Guidelines for effective screening
The group proposed two levels of guidelines –guidelines underlying evidence-supporting screening and lower level guidelines on program/system level evidence. The guidelines should target different audiences (e.g., policymakers, clinicians, researchers and patients/ public) and the timeliness of the guidelines should be considered. Smaller member states that do not have mechanisms to conduct research, reviews, etc., to support decision-making could rely on European level guidelines. In addition, guidelines should be widely applicable and should provide both high-level guidance for specific cancers and generic systematic and clinical guidance (including standardization of data collection and key performance indicators). It is also important to have coordination of efforts of different organizations involved in cancer screening to have one set of guidelines, for example, by developing an international forum to share best practice and develop consensus in order to achieve recognition and acceptance of recommendations.

9.4 Evaluation of the conference

The programme of the conference included presentations to the main themes and co-creational group work. The main themes were cervical, breast and colorectal cancer screening in Europe, risk-stratified screening programmes, needs to update the EU Council recommendation on cancer screening, possibilities of new cancer screening programmes and the future of screening criteria for informing new screening programmes and co-creation: building a bridge from knowledge-production to change-making.

In co-creational group work the participants tried to identify examples on country or regional level and what concrete themes and questions should be included in the Europe´s Beating Cancer Plan and Cancer Mission.

65 participants received evaluation survey after the Conference, out of which 32 submitted it (49%). The questionnaire consisted of 6 closed-ended questions and one open-ended question. Answers are presented in Chart 1.

Participants were mostly satisfied with the meetings' quality, i.e. they agreed with statements regarding satisfaction with the usefulness and organization of the conference. Open-ended question was more focused on some specific comments that participants could have regarding the meeting (e.g., were the right people involved in the meeting, what was the quality of interaction between the participants, what did they particularly liked/not liked about the meeting, was there something missing from the meeting).

Only 14 out of 32 participants who filled out the survey answered to open-ended question (43,8%). The answers to this question varied and range from great satisfaction with the whole organization, topics and discussion to those in which attention is drawn to the problem of insufficient time, lack of structure and unclear objectives.

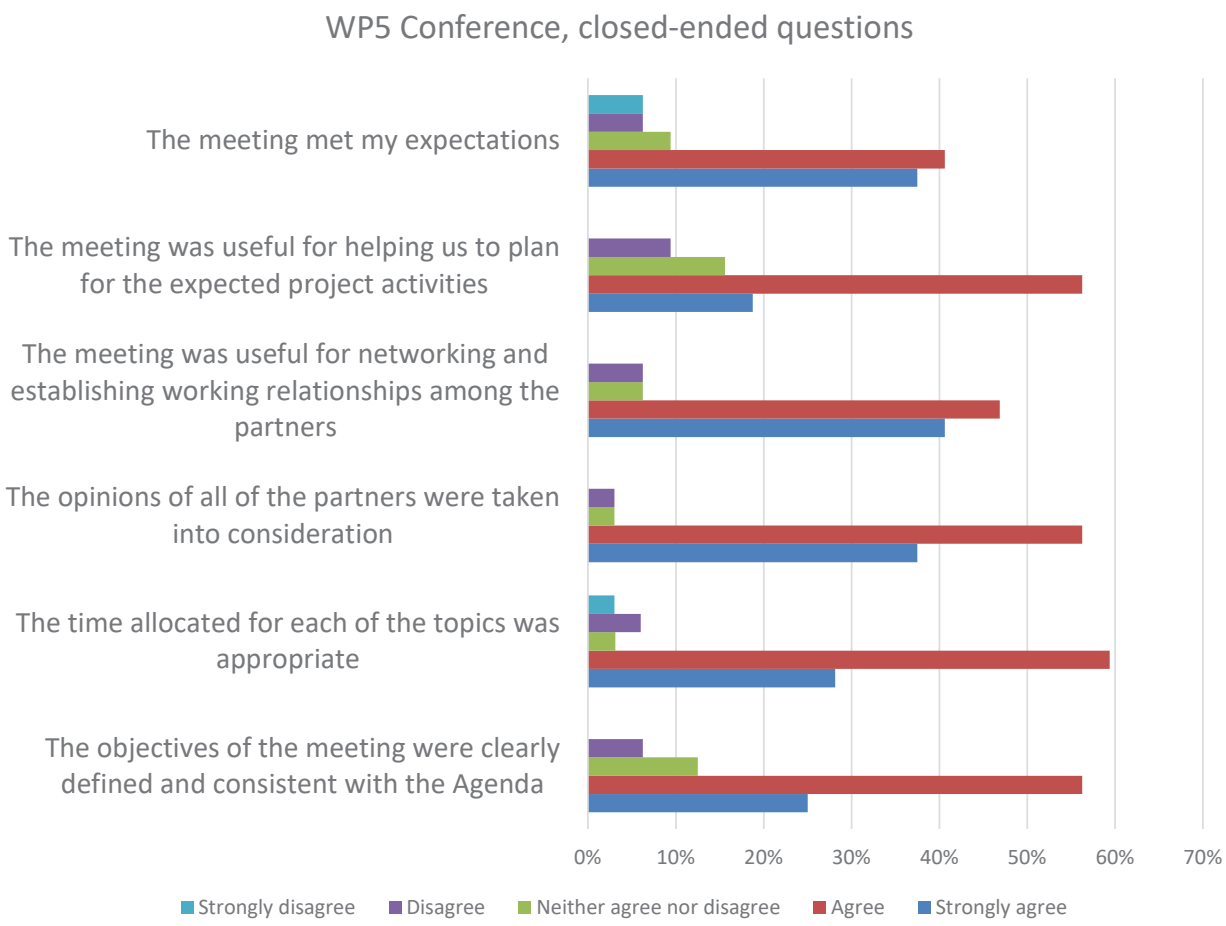

Chart 1. Survey results of WP5 Conference

9.5 Concluding remarks and what's next?

The meeting experts and participants brought novel contributions to the meeting and the European screening agenda. The discussions in the tables between the participants were very productive, and enjoyable, and brought many new insights for the future. The key results, suggestions and conclusions of the conference will be summarised in this report prepared together with the organisers, invited experts and group rapporteurs. The results and ideas will be transferred and shared for further planning and development of the European cancer control agenda – the European cancer control initiative Europe´s Beating Cancer Plan, the Cancer Mission from Horizon Europe research and innovation programme, development of the European Health Programme, and preparations in the European

Parliament, including its Special Committee on Cancer. This will be done already when the draft of the report will be available for commenting. The final report is expected by end of September 2020.

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. The conference report will be available also for the preparation of the Roadmap.

10 Discussion and conclusions

Based on the conference results, what does the task 5.2. offer to the development of cancer screening?

1) WP5 has a cross-cutting theme on inequality. One priority in cancer screening monitoring and evaluation will be to solve the disparities between Member States and regions, and between various population groups within the Member States, and have more focus on specific vulnerable groups. Social inequalities in access and use of services and distribution of risk factors lead to large inequities in health and these need new investments and support in order to find effective solutions to tackle inequities both at the Member State and pan-European levels. For instance, in rather low-resource settings with suboptimal screening coverage, research and novel interventions are needed in the local conditions. In the European setting, such research could be planned for and implemented jointly in collaborative networks involving screening coordinators and evaluators from different settings and countries. Cancer Mission of the EU may become one important channel for these collaborations in the future. The challenges with social inequalities in health are an important focus area also for the so-called risk-stratified screening concepts.

2) Another priority is to solve inadequacies with respect to what is needed for population-based screening programmes to 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, strengthen their evaluation and quality assurance components and optimize the benefits and harms of the activity? Requirements for good governance for implementing the quality assurance required step by step, as recommended by the European guidelines, was introduced in CANCON. The CANCON recommendation will be developed further as an online tool. We need to furthermore focus on finding solutions for better coverage, legal frameworks, governance structures and standardized data at the pan-European level. These may become important tasks also for the EU Cancer Control programme under development.

3) Risk-stratification within the population-based screening programmes has apparently started already. This is the case especially in cervical cancer screening where HPV vaccination status changes the screening needs and algorithms in female populations remarkably. Unfortunately, both the HPV vaccination coverage as well as cervical cancer screening policy and coverage vary highly significantly between the Member States, indicating that readiness to develop their synergies and optimal cervical cancer control policies is also highly variable. The feasible solutions may differ in the different settings. However, there is very little collaboration between research centers and screening coordinators and evaluators to solve the information and policy development needs on these issues.

4) A number of risk-stratified approaches are under development also in other on-going programmes for breast, cervix and colorectal cancer screening. Modifications to screening protocols have been proposed based on multiple factors, such as screening history, biological and risk factors, family risks, and genetic susceptibility affecting cancer risk or screening validity. However, the evidence-base for risk-stratified screening is not yet available, or weak, and further studies and results are still awaited. Often the conditions with proposed alternative screening and management strategies conform just a rather small proportion within the whole target population. Therefore, it may be impossible to produce full information on the benefits/harms ratio using mortality and other such critical outcomes for cancer screening programmes. To adopt validated early indicators of effectiveness, as rate of advanced cancers, survival and QoL after treatment 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. Still, if evidence-base will become available from such studies and from efficacy trials, there will be challenges on how to reliably assess the lifetime benefits and harms of the various options. Also feasibility due to demanding logistics and organizational requirements has to be taken into account.

5) Looking into the future, what is the role of genomics? How do we inform about surveillance programmes for high risk individuals if individual-level genetic data will become more common? Truthful communication of both harms and benefits is one area of discussion.

6) Several European lung cancer screening trials have reported their findings, and a meta-analysis has indicated average effect of about 17% in decreasing in lung cancer mortality and 4% in decreasing in all-cause mortality from the trials on low-dose computed tomography. The conference brought up several important questions that need to be addressed in further implementation research; for example, how to select the potential target population, how to reach the potential target population and achieve substantial participation among them and how to best integrate interventions on smoking cessation with screening. Protocols related in the trials to other findings than lung cancer need also to be understood better. Assessments of lifetime benefits and harms, as well as health-economic aspects, of lung cancer screening will also pose challenges in many Member States, respectively.

7) Prostate cancer screening based on currently studied PSA-test methods is still a controversial issue and even though the trials have indicated a small impact to decrease cause-specific mortality, the balance of benefit and harm is generally comprised not appropriate for screening due to overdiagnosis of prostate cancers. There are still contradictory messages from different stakeholders, and men are currently engaging in opportunistic testing in many countries. There are novel technologies (mpMRI and other) successfully lowering the need for biopsies and

invasive treatment in men with low risk of aggressive prostate cancer in clinical service; however, their validity and effectiveness have not been studied in screening trials. Even if prostate cancer screening with PSA has a potential to reduce mortality, all other criteria for screening, as well as use of the PSA test by indication, must be taken into consideration.

8) 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 providing strong network of civil society in policy-making arenas has been important. An inclusive, multi-disciplinary and multi-stakeholder voice is needed for finding social advances and innovations in cancer screening.

9) It is important to incorporate the proposals highlighted by the group reports considering how to improve participation through multi-disciplinary professional involvement, networks and improved screening organization into the roadmaps.

In conclusion

One future key priority in cancer screening monitoring and evaluation will be looking solutions to disparities between Member States and regions, between various population groups within the Member States and have more focus on specific vulnerable groups. These topics need new investments and support both at the Member State and pan-European levels in order to find effective solutions to tackle inequities.

Another key priority is to solve inadequacies with respect to what is needed for 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, strengthen their evaluation and quality assurance components and optimize the balance between benefits and harms of the activity? We need to furthermore focus on finding binding solutions for better coverage, legal frameworks, governance structures and standardized data at the pan-European level.

Risk-stratification within the population-based screening programmes has apparently started already. This is the case especially in cervical cancer screening where HPV vaccination status changes the screening needs and algorithms in female populations remarkably.The HPV vaccination coverage as well as cervical cancer screening policy and coverage vary remarkably between the Member States, however; indicating that readiness to develop their synergies and optimal cervical cancer control policies is also highly variable.

Risk-stratified approaches are under development also in breast and colorectal cancer screening programmes. To adopt validated surrogate/early indicators of effectiveness, as rate of advanced cancers, survival and quality of life after treatment should be considered. This can enable gradual, well-controlled modifications to the screening policy with profound evaluation of effectiveness of the programme in long term. Still, if evidence-base will become available from such studies and from efficacy trials, there will be challenges on how to reliably assess the lifetime benefits and harms of the various options. Also feasibility due to demanding logistics and organizational requirements has to be taken into account.

The EU Council recommendation on cancer screening has been an important cornerstone for the improvements in implementation of cancer screening. The document, however, needs updates. The more recent European quality assurance guidelines have already updated several of the recommendations on screening methods and policies. There is a need to add new agendas, such as social and health inequalities, and risk-stratified screening, in the European screening recommendations and quality assurance guidelines. Within many Member States with currently existing cancer screening programmes, problems have occurred in proper monitoring and evaluation, affecting suboptimal coverage/participation. There are defects also in quality assurance activities actually performed. One problem is that a proper legal framework enabling systematic quality assurance and evaluation of cancer screening is not yet in place everywhere. Due to these reasons the European-level binding recommendations and regulations should involve guidance on how to build up appropriate governance and legal framework enabling appropriate quality assurance, and effective and cost-effective implementation of screening.

Furthermore, quality improvement through regular measurement of screening performance using standardized data collection tools, protocols and outputs at the European level is needed on a continuous basis. This includes developing acceptable standards for the core indicators. Better integration between primary and secondary preventive strategies through comprehensive approaches should also be put on the European agenda.

Updating evidence raised for the potential of new cancer screening programmes is also permanently needed and the results need to be taken into account. There are particular challenges to develop appropriate health economic assessments across Member States for potential new cancer screening programmes, taking into account the huge variation in resources, affordability, and alternative or complementary primary or secondary prevention strategies. In the health-economic assessments on lung cancer screening it is a challenge to assess the alternative primary prevention scenarios (e.g., prevention of tobacco and nicotine products at a younger age than the potential screening target age), or complementary or combined interventions with screening and primary prevention. For prostate cancer, early diagnosis of prostate cancers based on unspecific symptoms is an important issue and, as concluded by the iPAAC WP5 task 5.1. on early diagnosis, it´s evidence-base is not yet developed well enough. There will be also novel testing and management algorithms that may improve the service. In order to assess the full picture, better registration of current

practices for early diagnosis of prostate cancers from electronic databases in health care has been suggested, along with appropriate trials for potential new methods.

Even though cancer screening has been demonstrated to work effectively in large number of Member States, there are examples of suboptimal implementation in many countries. It is therefore proposed to reactivate autonomous networks of cancer screening coordinators and evaluators, in order to share experiences and develop effective solutions in those settings that have not yet a well-functioning programme with appropriate quality assurance at all levels for the recommended cancer sites. This network could also develop training and capacity-building for cancer screening and early detection, suggest novel data collection structures required, as well as assist and collaborate in assessing evidence on cancer screening required to be continuously updated for the Europe-wide recommendations. It is also necessary to build up good collaboration and links between such a network and other related groups and networks in cancer information domain, in order to develop the European cancer information system in all of its components required for adequate evaluation and monitoring of cancer screening and early diagnosis

The report will be utilized in developing the final deliverable of the iPAAC Joint Action, the Roadmap on Implementation and Sustainability of Cancer Control Actions. The meeting experts and participants brought novel contributions to the European cancer control agenda on cancer screening. The results and ideas developed will be transferred and shared for further planning and development of the European cancer control agenda – such as the Europe's Beating Cancer Plan, the Cancer Mission, and development of the European Health Programme.

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Annexes

1. EU guidelines on cancer screening (breast, cervical and colorectal cancers)
2. Cancon Guide and Cancer screening chapter
3. EU council recommendation on cancer screening (2003) and
   Report on the Implementation (2017)
4. Pubmed search for lung cancer and prostate cancer screening
5. Summary of online meetings to prepare report on risk-stratification of
   cancer screening and this Conference report
6. Agenda and participants of the technical meeting in Helsinki on December 4, 2019
7. Agenda, presentations and group work template of the Conference,
   Helsinki 5th December, 2019
8. Opening speech 5th December, 2019, Dr. Sakari Karjalainen,
   Secretary General, Cancer Society of Finland, ECL president
9. List of participants New openings in Cancer Screening in Europe

1 EU guidelines on cancer screening (breast, cervical and colorectal cancers)

Guidelines on breast cancer screening and diagnosis
https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines
https://publications.jrc.ec.europa.eu/repository/bitstream/JRC106915/ecibc_plenary_2017_final_report.pdf

Guidelines on quality assurance in cervical cancer screening
http://screening.iarc.fr/doc/ND7007117ENC_002.pdf

Guidelines on quality assurance in colorectal cancer screening
https://op.europa.eu/en/publication-detail/-/publication/de2c911e-f207-4ab6-8bfc-992871d5a516/language-en

2 Cancon Guide and Cancer screening chapter

The Joint Action Cancon Guide, European Guide on Quality Improvement in Comprehensive Cancer Control
https://cancercontrol.eu/archived/guide-landing-page/index.html

Cancer screening: policy recommendations on governance, organization and evaluation of cancer screening, chapter 4, WP9
https://cancercontrol.eu/archived/uploads/images/Guide/042017/CanCon_Guide_4_Screening_LR.pdf

and in HTML form
https://cancercontrol.eu/archived/guide-landing-page/guide-cancer-screening.html

3 EU council recommendation on cancer screening (2003) and Report on the Implementation (2017)

COUNCIL RECOMMENDATION of 2 December 2003 on cancer screening (2003/878/EC)
https://ec.europa.eu/jrc/sites/jrcsh/files/2_December_2003%20cancer%20screening.pdf

Cancer Screening in the European Union, Report on the implementation of the Council Recommendation on cancer screening (2017)
https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf

4 Pubmed search for lung cancer and prostate cancer screening

4.1 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])

4.2 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, years**	**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	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),de Koning et al., 2020# 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%	LCM= 0.76 (0.61.0.94) in men LCM= 0.67(0.38-1.14) in women ACM= 1.01 (0.92-1.11) in men
Manchester** (Hinde et al., 2018), UK	2016-2018	55-74 years	PL-COm2012≥1.51% (high risk groups)	LDCT at baseline and 1 year	No	1384	NA	3% at baseline; 4.4% overall	Not reported

**feasibility randomized trial/pilot study # available shortly after the conference
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). The US Preventive Service Task Force (2004, 2013) and organizations such as the National Comprehensive Cancer Network (NCCN, 2014), and the International Association for the Study of Lung Cancer (IASLC, 2018) have recommended for implementation of annual LDCT screening. As a consequence, voluntary screening in high risk population has now been implemented (Ali et al., 2016). In Europe, multiple screening studies/trials are currently ongoing and few published studies have reported mixed 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; Beker et al., 2019; Pastorino et al., 2019) and the presence of substantial clinical heterogeneity in the trials. 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). A summary table on the findings from the published studies and the literature search strategy are presented in the annex (1 and 2) part. The table includes also results published on the large European NELSON trial short after the conference (de Koning et al., 2020). The considerable uncertainty in the results is due to lack of sufficient evidence on the potential benefits (mainly in terms of mortality), published by studies with insufficient power, and the lack of uniform screening methods applied (between the intervention and control arms population), which in turn make findings difficult to compare across countries.

On the other hand, 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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4.4 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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5 Summary of online meetings to prepare report on risk-stratification of cancer screening and this Conference report

Summary, 2 online meetings 12.9. 2019, 17.10.2019

The third meeting was in connection to the Screening conference 4.12.2019 and reported in this document (chapter 5)

12.9.2019
Discussion about the background paper, *Report of innovations, including harms and benefits from risk-stratified screening*, which is the Milestone 5.2.

- Aim is to provide key recommendations from the evidence on risk-based screening and socio-economic inequalities in cancer screening.
- EU council recommendation on population-based screening programmes (2003)
- Definitions used in the report, which is in line e.g. to Wilson and Jungner (1968). Separate the term 'surveillance ' arising mainly from clinical environments from 'risk-based screening', which are integrated with the population-based screening; need to define because now word 'screening' is sometimes used as synonym also about testing within surveillance. Population-based screening programmes have specific criteria and unselected target population, while surveillance programmes target very high risk groups are the criteria and requirements may not be the same as for cancer screening. In iPAAC surveillance outside screening programmes will be dealt is WP6 task 6.2
- Proposed two conditions for risk-stratified screening; firstly by factors influencing accuracy (sensitivity) and second by dividing the population according to the level of risk. - Judgement: Better cost-effectiveness with given resources
- We need to know more about the implementation of risk-based screening in the member states. Risk-based screening has not been covered e.g. in the screening implementation status reports.
- Improvement of the background paper for the conference still needs to continue after the Milestone is ready. Updates of literature still needed e.g. for lung cancer screening (incl. peer-reviewed papers probably coming soon from the NELSON trial), and prostate cancer screening. And conclusions and suggestions can be added also even after the conference.

17.10.2019
Discussion about the background paper

- The background paper will be incorporated into the conference report with practical examples from member states. In addition, in the task 5.2. quality criteria for screening, developed in the Joint Action CANCON, will be further modified into practical illustrations for member states and conference participants.

Discussion about the technical meeting 4th December

- The participants discussed (with examples from Italy and Germany) about modifying the screening criteria for colorectal cancer screening with a focus on high risk groups and modifications in the definitions and terminologies used in screening guidelines.
- The need for common quality criteria and finding a common platform or decision aids tool so that the generated evidence can be applied sustainably in member states
- The need to find a common ground to include scientific evidence into policy papers
- Coverage and participation play an important role in the effectiveness and cost-effectiveness issues.

Discussion about the conference 5th December

- An open conference working mode 'co-creation' in a group of 6-8 people and discuss the agendas.
- Discussion about the list of topics to be included for the group works.
- The participants discussed also the final deliverable, the Roadmap.

Associated partners, participants (21) from 12 countries of online meetings
Urska Ivanus , Institute of Oncology Ljubljana, Slovenia
Mirela Strandzheva, National Center for Public Health and Analyses, Bulgaria
Annarosa Del Mistro , Cancer Research and Prevention Institute, Italy
Stephanie Xuereb, Ministry of Health, Malta
Isabel Portillo , Osakidetza (Servicio Vasco de Salud/Basque Health System), Basque Country , Spain
Melina Vasic, Institute of Public Health of Serbia "Dr Milan Jovanović Batut", Serbia
Satu Lipponen, Ahti Anttila, Clarissa Bingham, Deependra Singh, Cancer Society of Finland (CSF), Finland
Ondrej Ngo, Ondrej Majek, Institute of Health Information and Statistics of the Czech Republic (UZIS), Czech Republic
Susanne Weg-Remers, German Cancer Research Center (DKFZ) under Federal Ministry of Health (BMG), Germany
Edit Marosi, National Institute of Oncology (OOI), Hungary
Mari Nygård , Margarethe Meo, Cancer Registry of Norway (OUS), Norway
Molina Anabar, Marta Hernandez, The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO), Spain
Carolina Espina Garcia, International Agency for Research on Cancer (IARC), France
Andre Carvalho, International Agency for Research on Cancer (IARC), France
Marco Zappa, Cancer Research and Prevention Institute (ISPRO), under National Institute of Public Health (ISS), Italy

6 Agenda and participants of the technical meeting in Helsinki on December 4, 2019

WP5 Technical Meeting, Helsinki on the 4th of December 2019

Invitation only: Technical meeting for iPAAC Associated Partners

Date and location

Start: the 4th of Dec. at 09:30 registration & coffee, 10:00 welcome & introductions

End: the 4th of Dec. at 16:30

Location: Cancer Society of Finland offices, Unioninkatu 22, 00130 Helsinki, Bank meeting room Flavour on the 2nd floor. Please register yourself at the reception desk and you will be guided to the 2nd floor.

You may travel easy from and to the airport by train or by taxi https://www.finavia.fi/en/airports/helsinki-airport/access/trains .

Agenda and Goal

Agenda: Overview of the WP5 work and discussions of priorities ahead, including the final deliverable of the Joint Action iPAAC, the Roadmap

Goal: To discuss WP5 -specific tasks and deliverables, to inform and prepare for the 5th December Conference, to take a look into new developments and screening criteria.

N.B.: 6th of December - Independence Day - is a public national holiday in Finland and there may be traffic jam in the city in the evening of Dec the 5th. Please, consider this if you are driving by taxi to the airport on that day.

Meeting Agenda

9.30	Registration at the reception and coffee, meeting room Flavour, 2nd floor
10:00	Welcome remarks, Cancer Society of Finland and the Finnish Cancer Registry, Nea Malila
10:15	Overview of the WP5 tasks and deliverables, including the Roadmap, associated partners and current status, Satu Lipponen, Cancer Society of Finland, WP5 leader
10:30	Task 5.2. Cancer screening, Ahti Anttila, Finnish Cancer Registry
10:45	Best practices on equity in cancer screening, Marta Hernández-García, FISABIO
11:00	Principles and criteria of cancer screening, Mark Dobrow, University of Toronto
11.30	Commentaries: Bob Steele, UK and Tytti Sarkeala, Finland
12:00	What is the Roadmap, expectations from today, Marc Van Den Bulcke, Sciensano, WP4 leader
12:15	Discussion + briefing for group work (practicalities)

12:30 – 13:30	Lunch, restaurant Bank
13:30	Group work 1 Screening criteria and recommendations, what next?
14:00	Discussion
14.30	Coffee break
15:00	Group work 2 What should be included in the Roadmap from WP5 cancer screening?
15:30	Discussion
16:00	Summary, Ahti Anttila
16:30	Meeting ends

Participants list 4.12. 2020

Ahti Anttila	Finland
Tytti Sarkeala	Finland
Kaarina Tamminiemi	Finland
Satu Lipponen	Finland
Deependra Singh	Finland
Nea Malila	Finland
Stephanie Xuereb	Malta
Urska Ivanus	Slovenia
Mark Dobrow	Canada
Frédéric De Bels	France
Annarosa del Mistro	Italy
Ondrej Ngo	Czech
Susanne Weg-Remers	Germany
Giske Ursin	Norway
Marco Zappa	Italy
Bob Steele	UK
David Ritchie	Belgium
Ana Molina	Spain
Tit Albreht	Slovenia
Marc Van Den Bulcke	Belgium

7 Agenda, presentations and group work template of the Conference, Helsinki 5th December, 2019

Agenda and presentations
https://www.ipaac.eu/news-detail/en/29-new-openings-of-cancer-screening-in-europe/

Group work template
Group Work, iPAAC WP5 Conference Helsinki, December 5, 2019

Reporting at the conference venue and after the conference you will be filling out a simple template (example below) introducing briefly 1–2 main findings sending the template to tuija.seppanen@cancer.fi contributing to the conference report (by June 2020) by adding other topics and sources.

It is recommended that you fill in the template at the meeting and share it with the group. Please add other topics discussed and any contacts or links that are useful for us in finding out further information.

TEMPLATE

Facilitator and topic:

Please add here if there were any name changes to the printed version of the group:

Case examples:

Main findings:

8 Opening speech 5th December, 2019, Dr. Sakari Karjalainen, Secretary General, Cancer Society of Finland, ECL president

Ladies and Gentlemen, Dear Friends,

Cancer control in Europe is at the crossroads. Europe has a lot of challenges but also plenty of new opportunities.

The first challenge is the cancer burden itself. With more than 3.7 million new cancer cases and 1.9 million deaths each year, Europe accounts for almost one fourth of cancer cases and one fifth of cancer deaths, globally. Still we have only 9 per cent of the global population.

Our most important goal is to reduce incidence of cancer and mortality from cancer.

What does this mean in practice? First, we must strengthen our efforts to prevent cancer. Cancer leagues – which I represent here – play in this work a major role. We can reach people and give evidence-based information how to reduce the risk of getting cancer by one's own choices. That is not enough, however. We can influence decision-makers and demand governments to reduce risk of cancer by legislative reforms and tax policies. Second, we must do our best to enhance early diagnosis and access to diagnostic services in health care. In Finland, the Cancer Society of Finland has, in fact, developed the organized screening of cancer. It started with screening of cervical cancer in 1960's and screening of breast cancer in 1980's. The Cancer Society has also initiated and supported very important screening trials in prostate cancer and colorectal cancer. And finally, in this year we succeeded in getting our government to decide to start colorectal cancer screening in Finland.

Thus, the most important role of cancer leagues in this area is to advocate for evidence-based screening.

The existing inequities between and within countries are the second major European challenge. The inequities are demonstrated by incidence and mortality differences between population groups. Generally, people with only basic education and lower social status have a higher risk of getting cancer and higher risk of dying after cancer diagnosis. One recent research finding from Finland is startling. Pediatric cancer patients whose parents have only basic education or whose mother tongue is not Finnish or Swedish have higher risk of dying than patients whose parents have higher education degree or are native Finns. Pediatric cancer patients are treated following very strict protocols which makes this finding especially alarming. However, we do not know enough about the causes of socioeconomic differences in cancer patient survival and more research is needed.

The third challenge in cancer control is the high cost of new innovative medicines and non-rational variation in their use in different countries and regions. A few years ago, ECL the Association of European Cancer Leagues started a task force on Access to Medicines. And a new European Fair Pricing Network has been established. And our own Cancer Society has also started a project where we try to find out why new cancer medicines come into use late in Finland. All these projects aim to

change the power balance between the big pharma and countries purchasing medicines. This work will be hard and complex, and we will fail in advocacy without strong evidence base. Obviously, we appreciate the role of big pharma in improving cancer treatments, but we also demand affordable prices and fair pricing.

I said in the beginning that we are at the crossroads in Europe. Everyone talks now about the Cancer Mission and the European Commission's Beating cancer plan. These two major initiatives will strengthen cancer research and cancer control in Europe in a historical way. The new health commissioner Ms Stella Kyriakides is very committed to create something new and great in cancer control. She is a cancer survivor and Past President of the Europa Donna. I had an opportunity to meet her in Cyprus in this Spring and became convinced both of her ability and will to make change.

I wish you a very successful meeting. I am glad that the best experts in cancer screening are gathered today in Helsinki.

9 List of participants New openings in Cancer Screening in Europe

List of participants in the conference

Ahti Anttila	CSF, Finland
Aisling Carton	Department of Health, Ireland
Alexandra Turkovicova	Ministry of Health, Slovak Republic
Ana Molina	FISABIO- Salud Publica
Annarosa Del Mistro	Istituto Oncologico Veneto IOV-IRCCS
Annika Auranen	Tampere University Hospital
Annie Scott Anderson	University of Dundee
Antonella Cardone	European Cancer Patient Coalition
Barbara Dorelli	Sapienza University of Rome
Blaz Podobnik	Institute of Oncology, Ljubljana
Carmen Ungurean	National Institute of Public Health
Cecilia Györgyi Müller	National Public Health Center
Clodagh Murphy	Department of Health
David Ritchie	Association of European Cancer Leagues (ECL)
Deependra Singh	Finnish Cancer Registry
Edit Marosi	National Institute of Oncology
Elena Ortiz de Solorzano	Vinces
Evette Wade	Department of Health
Frank Hernes	Norwegian Cancer Society
Frederic de Bels	French National Cancer Institute
Giske Ursin	Cancer Registry of Norway
Hein Van Poppel	European Association of Urology (EAU)
Hilary Coffey Farrell	National Screening Service
Inga Cechanoviciene	Ministry of Health of the Republic of Lithuania
Irena Debeljak	National institute of Public Health
Iris Seriese	RIVM (national health institution)
Isabel Portillo	The Basque Health Service – The Basque Ministry of Health
Jolanta Gore-Booth	Digestive Cancers Europe/ EuropeColon
Jon Kirknes	Norwegian Cancer Society
Jone Miren Altzibar	Osakidetza-Basque Health Service
Jörn Knöpnadel	National Associaton of Statutory Health Insurance Phycisians
Josep A Espinas	Catalonian Cancer Strategy, Department of Health, Catalonia, Spain
Kaarina Tamminiemi	CSF, Finland
Karmen Korda	Croatian Institute of Public Health
Katja Kovse	Institute of Oncology Ljubljana

Kimmo Järvinen	Propo Suomen Eurauhasyhdistys
Lars Rohwer	Siemens Healthineers
Luiza Purcaro	Filantropia Clinical Hospital
Magdakena Bielska-Lasota	NIPH-NIH
Marco Zappa	Ispro Florence, Italy
Marina Pollan	National Center fir Epidemiology, Carlos III Institute of Health
Martina Vrankar	Institute of Oncology Ljubljana
Miljana Stojanovska	Youth Ambassador, Association of European Cancer Leagues (ECL)
Nicole Denoy	Cocir
Olga Monteagudo Piqueras	Murcia Regional Health Council
Ondrej Ngo	Institute of Health Information and Statistics of the Czech Republic
Parha Basu	International Agency for Research on Cancer
Pekka Jousilahti	Finnish Institute for Health and Welfare (THL)
Pentti Tuohimaa	Europa Uomo
Peter Nagy	National Institute of Oncology
Robert JC Steele	University of Dundee
Sakari Karjalainen	CSF, Finland
Satu Lipponen	CSF, Finland
Sebastian Schmidt	Siemens Healthcare GmbH
Silva Mitro	Veneto Institute of Oncology
Sirpa Heinävaara	CSF/ Finnish Cancer Registry
Sonja Tomsic	Institute of Oncology, Ljubljana
Souad Belarbi	Hologic
Stanislav Spanic	Ministry of Health of the Slovak Republic
Stephanie Xuereb	Primary Healthcare, Ministry of Health
Susanne Weg-Remers	Deutsche Krebsforschungszentrum
Tit Albreht	National Institute of Public Health of Slovenia
Tomas Poskus	Vilnius University Hospital Santara Clinics
Tuija Seppänen	CSF, Finnish Cancer Registry
Tutta Kosonen	CSF, Finland
Tytti Sarkeala	Finnish Cancer Registry
Urska Ivanus	Institute of Oncology Ljubljana
Verica Jovanovic	Institute of Public Health, Serbia
Yordan Aleksandrov	RPP Group
Nea Malila	Finnish Cancer Registry
Wendy Yared	Association of European Cancer Leagues (ECL)
Kaisa Lähteenmäki-Smith	MDI Finland
Milla Lehtinen	CSF, Finland