Cancer screening in Europe

Rapid review 2

To what extent do more risk-stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?

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Science Advice for Policy by European Academies

- DOI: ~forthcoming
- Downloadable from https://www.sapea.info/cancer-screening/

Version history

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

Publisher

SAPEA
c/o acatech
Pariser Platz 4a
10117 Berlin, Germany

Contact

SAPEA Communications Office
Rue d'Egmont 13
1000 Brussels, Belgium
contact@sapea.info

SAPEA, Science Advice for Policy by European Academies. (2022). *Cancer screening in Europe: Rapid review 2*. Berlin: SAPEA.

Rapid Review 2

To what extent do more risk-stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?

Rapid Review Details

Review conducted by:
A team led by the Specialist Unit for Review Evidence (SURE) for SAPEA (Science Advice for Policy by European Academies)

Review Team:
- Dr Hui-Ling Ou, Research Associate, Cambridge Centre Lung Cancer Early Detection Group, Cambridge University UK
- Dr Nicholas Courtier, Senior Lecturer Radiography, School of Healthcare Sciences, Cardiff University UK
- Dr Alison Weightman, Director Specialist Unit for Review Evidence, Cardiff University UK
- Louise Edwards, Hub Manager, Academia Europaea, Cardiff University UK

Acknowledgements:
The advisory group for the review team, comprising the Chairs of the Expert Workshop, Professor Ole Petersen (Academia Europaea), members of SAPEA, the Group of Chief Scientific Advisors (Advisors) and the SAM Unit. Dr Sunil Dolwani (Cancer Theme Lead, School of Medicine, Cardiff University) and Professor Jacek Jassem (Head, Department of Oncology & Radiotherapy, Medical University of Gdańsk) for reviewing and commenting on the draft pre-publication.

Method:
This is one of three rapid reviews - a lighter form of a full systematic review that takes account of time constraints. The top-line results are included in the main SAPEA Evidence Review Report, with cross-referencing between the documents.

The review summarises a valuable subset of the evidence base, emphasising the findings from recent randomised and other controlled clinical trials, and modelling studies based on trial data. To meet deadlines, a pragmatic and precise search strategy was employed; it is possible that further controlled trials would have been identified if there had been time for a detailed and sensitive systematic search. The timeline also precluded any statistical or meta-analysis of findings unless these were available from published systematic reviews. No formal critical appraisal was carried out although information is provided on whether the trial included a power calculation. Data extraction and summary were undertaken by different reviewers and, although reviewed by another author, these have not been independently checked for accuracy and consistency.

Disclaimer: The authors of this work declare that they have no conflicts of interest.

To what extent do more risk-stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?

TOPLINE SUMMARY

Who is this summary for?

To support the work of SAPEA in providing evidence to the European Commission's Group of Chief Scientific Advisers on cancer screening in Europe.

Background

This review is one of three rapid reviews conducted on the topic of cancer screening in Europe. It was produced specifically for the expert workshop convened to discuss how cancer screening programmes targeting breast, cervical and colorectal cancers can be improved throughout the EU. This final version has been revised to address feedback received on earlier drafts and supplements the workshop report (available on the SAPEA website).

Aim

To examine the published evidence base for the question: *'To what extent do more risk-stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?*'

Rapid review method

A literature search was conducted in September 2021 for controlled trials published since 2007, supplemented with studies from published systematic reviews and modelling studies based on trial data. Trials were included if they examined screening for first diagnosis of breast, cervical or colorectal cancer and included data on efficacy, harm-benefit or cost-effectiveness in relation to targeting screening uptake and screening methods.

Key findings

Breast cancer [16 trials]:

- Modelling data suggest risk-stratified and adapted strategies can improve benefit-harm ratio with reasonable cost-effectiveness in the European setting
- Annual mammography ± ultrasound ± digital breast tomosynthesis ± MRI is likely to be feasible, acceptable and effective in higher risk 40–49 year-old European women. Supplemental MRI screening increases sensitivity for younger women with dense breasts
- Overdiagnosis is unlikely to be a significant problem where screening is targeted at younger European women

Cervical cancer [11 trials]:

- Screening with HPV self-sampling increases the screening uptake, especially for under-screened women, and is most cost-effective compared to standard cytology testing
- Screening intervals may be extended for women with negative HPV results and older age

- Increased sensitivity of HPV testing may reflect early detection of lesions rather than overdiagnosis

Colorectal cancer [13 trials]:

- The majority of the population prefers FIT to colonoscopy in terms of CRC screening uptake although the latter has a higher sensitivity and specificity in detecting advanced neoplasms
- The uptake and compliance with screening can be promoted via pro-active interventions
- Risk-stratification by age or family history remain the most used inclusion criteria

Strength of evidence

No formal critical appraisal was carried out within this rapid review but the included evidence is from randomised and other controlled clinical trials, with the least theoretical potential for bias.

Full report

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1. Background

This Rapid Review is one of three reviews conducted to support the work of Expert Groups convened to assist the European Commission Scientific Advice Mechanism (SAM) in developing policy guidance in relation to cancer screening. As described in the Scoping Paper[1], this review supported the second of the Expert Group workshops being convened to discuss the question **"How can cancer screening programmes targeting breast, cervical and colorectal cancers, be improved throughout the EU?"**

An advisory group was formed to provide guidance to the review team, comprising the Chairs, Professor Ole Petersen (Academia Europaea), members of SAPEA, the Group of Chief Scientific Advisors and the SAM Unit.

1.1 Purpose of this review

Following detailed discussions with the co-chairs, the question for the rapid review to inform the second workshop was:

"To what extent do more stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?"

Post-review this was clarified to:

"To what extent do more risk-stratified approaches to screening programmes for breast, cervical and colorectal cancers impact on uptake, efficacy, harm-benefit and cost-effectiveness?"

1.2 Research question

Rapid Review Question
Based on findings from controlled trials on efficacy, harm-benefit and cost-effectiveness, and modelling studies based on those controlled trials, what is the current evidence related to the risk-stratification of screening programmes for breast, cervical and colorectal cancers?

As defined in 'Cancer Screening in the EU' SAPEA Evidence Review Report, **Risk-stratified screening** relates to the delivery of screening within an established screening programme, where the type of screening, the intensity or the modality can be varied according to the level of individual risk in order to achieve a more favourable balance of benefits and harms at the individual as well as population level.

It was agreed at review protocol stage that a broad approach to risk-stratification would be adopted to include targeting specific populations by risk factors (including age, gender, ethnicity/race, other socio-demographic differences), interval and interval by age comparisons, and stratified screening method comparisons (see Section 7.1).

[1] Scientific Advice Mechanism. European Commission's Group of Chief Scientific Advisors. Scoping Paper: Cancer Screening. 22 April 2021

2. Results

2.1 Summary of the evidence base

In all, 67 reports have been summarised. We provide a narrative overview of the identified evidence below. A summary of each included trial is provided in Section 2.2.

Breast cancer

16 trials (in 24 reports), two systematic reviews and seven simulation modelling papers were identified.

Modelling data included three systematic reviews of risk-based screening simulations (Canelo et al. 2018; Khan et al. 2021; Mühlberger et al. 2021) and one analysis of modelling techniques (Arnold 2017). Review data are neither based on, nor confirmed by controlled trials; a summary of harm-benefit balance has been included because of limitations in RCTs of complex stratified screening. Five European risk-adapted screening studies predict superior efficacy (BCa specific mortality, increased life expectancy, reduced overdiagnosis) and cost-effectiveness (increased QALYs and/or incremental cost-utility/cost-effectiveness) compared to conventional age-based/non-risk adapted screening (Mühlberger et al. 2021).

Modelling studies of risk-based screening (Canelo et al. 2018; Khan et al. 2021) from Europe, US and China indicate annual mammography in high-risk women and the age group 40-49 years was cost-effective compared to no screening or non-risk adapted screening, and compared with a longer screen interval – yielding higher mortality rate reduction and QALYs at expense of higher absolute cost and false positives. However, the modelling studies generated inconsistent results regarding the cost effectiveness of supplementary MRI use to minimise false positives and overdiagnosis in dense-breasted women.

Modelling of UK RCT data favoured annual over biennial or triennial screening when targeted at women aged 40 to 49 (Gunsoy et al. 2012). Overdiagnosis, based on invasive and in-situ disease, was predicted to be approximately 0.8% (range 0.5-2.9) due to 'short cancer sojourn times'. Quality of modelling studies was difficult to establish, with heterogeneous methods, approaches to risk stratification and underlying assumptions.

RCT data was extracted from 16 trials; eight including European data. The primary rationales were to test screen method, invitation age or frequency. Four tested risk-adapted screening in a higher risk population e.g. supplemental screening for dense breast parenchyma and four tested risk-stratified screening in the general population (by an individualised risk model encompassing previous biopsies, family history, breast density and genetic markers.)

Cost-effectiveness

Trial data were limited. Modelling data (above) indicate that risk-stratified screening is likely to be reasonably cost-effective. Microsimulations of the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial data suggests that additional MRI at a four-year interval was most cost effective (€15,620 per QALY) for women with extremely dense breasts (Geuzinge et al. 2021). Supplemental annual MRI screening may reduce cost-effectiveness in risk-stratified populations: for

example, a Netherlands cohort study found annual mammography plus MRI to be expensive for women with an estimated cumulative lifetime breast cancer risk of 15−50% (Saadatmand et al. 2012). More recent preliminary US trial data indicated biennial, supplemental MRI and personalised risk-based screening could be delivered at lower cost versus annual screening; (14.1 v 22.1 million US$ per 100,000 women) (Shieh 2019). Individualisation of a US intervention to increase screening compliance was more costly and less effective than a generic version (Lairson et al. 2011).

Compliance and uptake

Consistent evidence across stratification and screen methods showed uptake of risk-based screening was typically between 50 and 70%. Relative uptake of and compliance with ultrasound or MRI (Bakker et al. 2019; Berg et al. 2012; Constock et al. 2020; Huang et al. 2010; Veenhuizen et al. 2021) suggest that they are broadly acceptable breast screening modalities. When given a choice, individualised risk-based screening was preferred by over 80%, with no discernible elevation of anxiety levels (Naeim 2018). The compliance rate for 47–49 years group was only slightly lower than for 71–73 years (24% v 29%) with a significantly greater proportion of older women requesting screening after allocation to no screening (Moser et al. 2011). Almost 90% of women below 50 years with a false positive attended their next routine screening (Duffy et al B, 2020).

Mortality

RCT data is limited to the effect of targeting annual mammographic screening in women 40–49 years. A large UK trial demonstrated a relative reduction in breast cancer mortality of 25% at 10 years follow up, which was attenuated thereafter (Duffy et al. a 2020). An older Canadian trial found only a 1% (-12 to 12) relative risk reduction in BCa mortality at 22 years (Miller et al. 2014)[2] and a slight increase in risk of BCa-specific death for women 40–49 years (Narod et al. 2014). Results are methodlogically controversial and unlikely to reflect developments in adjuvant therapies. However, a Swedish trial reported a 40% reduction in breast mortality after 25 years (Bjurstam et al. 2016). Modelling based on almost 50,000 screened, estimated a relative risk of BCa mortality of 0.83 for annual versus triennial mammography in UK (Van Ravesteyn et al. 2011).

Cancer incidence and detection efficacy

Target Screening population level data is largely from North America: A simulated target screening population of 100,000 US women predicted no significant difference in proportion of ≥ stage IIB BCa for personalised risk-based screening (Shieh et al. 2019).

For younger women 40–49 years: Incidence was approximately 6–7x more in the 50–59 years group versus 40-49 years across 25 years follow up (Shieh 2019). BCa incidence in UK was 0.5% versus 1.1% in a 71–73 age group (Moser et al. 2011). Incidence was slightly higher in screened versus unscreened women aged 40-49 years in Canada (Miller et al. 2014) and equivalent after 23 years follow up in the UK (Duffy et al. b 2020). The addition of ultrasound demonstrated a 3-4 x increased detection rate versus mammography alone in Taiwanese women aged 40-49 years (Huang et al. 2010).

Dense breast tissue: The supplemental yield of BCa events from MRI screening was between 7 and 16.5 per 1000 women with dense breasts. (Bakker et al. 2019, Berg et al. 2014, Comstock et al. 2020). MRI was associated with 'significantly fewer interval cancers' than mammography alone

[2] The methodology employed by this study was criticised post-publication. See commentary associated with the publication at http://dx.doi.org/10.7326/0003-4819-160-10-201405200-02007

(Bakker et al. 2019). As expected, the MRI cancer detection rate decreases significantly at subsequent MRI screening rounds (Veenhuizen et al. 2021). Digital breast tomosynthesis plus synthetic mammography demonstrated a significant positive association between relative risk of BCa and stratified breast density in a Norwegian trial (Moshina et al. 2020).

Harm-benefit

Evidence of high rates of overdiagnosis from North American trials e.g. 22% of all screen-detected cancer (excluding DCIS) with no overall survival benefit (Miller et al. 2014) is not borne out by 20 years follow up for younger women in the UK setting (Dufffy et al. a 2020; Gunsoy et al. 2012). Furthermore, rates of false-positive recall were comparable with routine screening (Johns et al. 2010). The recall rate from digital breast tomosynthesis + synthetic mammography appeared to be sensitive to breast density, with fewer recalls for lower density and higher rates for higher density (Moshina et al. 2020). Concerns that digital breast tomosynthesis may increase overdiagnosis were not born out from a repeated round of screening (Hofvind 2021). A false-positive rate for women with dense breasts was almost 80 per 1000 at the first round of MRI screening, but this reduced to 26.3 per 1000 at a second round (Veenhuizen et al. 2021).

Cervical cancer

11 trials and 4 systematic reviews were included and the information across the 11 RCTs was extracted and summarised in the Table. The sample size per RCT ranged from 975 to 94,370 participants. Most trials took place in Europe (9 RCTs), one in the US and one in Australia. Across RCTs with various trial designs, HPV self-sampling and Pap-smear (by midwife or clinician) were used as screening methods.

Compliance and uptake

The screening uptake was higher when HPV self-sampling was offered as a screening option than Pap-smear among women due or overdue for CC screening. The compliance rate was generally high irrespective of the testing type, although slightly descended over rounds of screening. Consistent with other RCTs reviewed (Elfström et al., 2019; Gök et al., 2012; Sancho-Garnier et al., 2013; Tranberg et al., 2018), a meta-analysis pooling data across 33 studies (29 RCTs and 4 observational studies) reported that HPV self-sampling promoted the screening uptake substantially (RR 2.13; 95% CI 1.89-2.40) compared to the standard care control. Among different dissemination methods studied, directly mailing the HPV self-sampling kit (RR 2.27; 95% CI 1.89-2.71) as well as door-to-door offering (RR 2.37; 95% CI 1.12-5.03) increased the participation rate of cervical cancer screening, but not the opt-in intervention (requested on demand; RR 1.28; 95% CI 0.90-1.82) (Yeh et al. 2019).

Cancer incidence and detection efficiency

In general, incidence of CC or CIN2+ was higher in women screened with HPV self-sampling than cytology, probably owing to the higher sensitivity of HPV testing. Among women with HPV positive results, the CC incidence was much higher than those with HPV negative results (Dijkstra et al., 2016), suggesting that HPV testing may be a potential risk-stratification tool for targeting women of higher cancer risk. A meta-analysis pooling data across 4 RCTs (176,464 women in total) also suggested that HPV-based screening may provide better protection against cervical cancer compared to conventional cytology testing (Ronco et al. 2014). The incidence of high-grade lesions (CIN3) did not vary with the screening frequency (Louvanto et al., 2020) and thereby some studies (including the largest RCT in Netherlands) suggested that an extended screening interval (> 5 years)

may be implemented, especially for women with HPV-negative results in former screening rounds for optimised harm/benefit balance (Dijkstra et al., 2016; Gilham et al., 2019).

The detection rate of CIN2+ varied among RCTs as a result of different screening methods and triages. The Compass trial (Canfell et al., 2017), for instance, reported CIN2+ detection rates ranging from 0.1% to 1.2% when liquid-based cytology (LBC) was utilised alone or when HPV screening was first used to identify those with higher risk (positive for HPV16/18) before referring to colposcopy and LBC (Canfell et al., 2017). One study reported a CIN2+ detection rate of 18.2% among HPV-positive responders while the other reported a detection rate of 9.5% (Elfström et al., 2019; Gök et al., 2012; Sancho-Garnier et al., 2013).

Altogether the evidence of CC/CIN2+ incidence and detection efficiency is inconsistent because of variations across RCTs providing relevant data.

Survival, cancer and all-cause mortality

There were no studies reporting data in terms of CC survival and mortality.

Cost-effectiveness

Among RCTs reviewed, no study provided a cost-effectiveness analysis. However, comprehensive data on cost-effectiveness were reported in two systematic reviews pooling data across different continents from modelling studies (Malone et al., 2020; Sroczynski et al., 2018).

Most (14 of 16) studies in Malone et al. (2020) reported that HPV-based self-sampling screening was more effective than a cytology-based screening strategy in terms of patient-relevant outcomes. The lifetime cost-effectiveness outcomes were mostly provided in forms of willingness to pay threshold for cost-effectiveness, ranging from $756 USD/LYG in Uganda to $103,531 USD/QALY in Norway (Malone et al., 2020). Another systematic review looked at 14 modelling studies comparing HPV with cytology screening (Sroczynski et al., 2018). In scenarios where women were screened with at least a 3-year (non-vaccinated) or 5-year (vaccinated) interval, HPV-based screening versus cytology alone would be considered cost-effective at a willingness-to-pay threshold of €50,000/LYG (Sroczynski et al., 2018).

Colorectal cancer

13 RCTs and two systematic reviews were included and the information across 13 trials was extracted and summarised in the Table. The size of RCTs ranged from 230 to 37,311 participants with most trials taking place in the US (8 RCTs), one in China, one in Australia, two in Europe and one unspecified. Whilst different types of screening methods were used across all RCTs, FIT and colonoscopy were the most dominant among RCTs examined.

Risk-prediction Models for CRC

Across RCTs reviewed, many used age and family histories for evaluating the CRC risk and thereby the eligibility for CRC screening (Kinney et al., 2014; Lowery et al., 2014; Carey et al., 2016; Ingrand et al., 2016; Ingrand et al., 2019 Reeves et al., 2019; Paskett et al., 2020). One systematic review analysed data across 29 risk models that incorporate common genetic variants for estimating future incidence of CRC in the general population. Results showed that involvement of genetic variants, e.g., single-nucleotide polymorphisms, alongside other factors, e.g., age and family histories,

increased the discrimination power, which would substantially change the risk stratification in the population, leading to an earlier (up to 23 years) screening invitation to whom of the top 20% for risk (McGeoch et al., 2019).

Compliance and uptake

The uptake of CRC screening test varied across different RCTss with types of screening offered, with or without active intervention, ranging from 7.6% to 83.5%. The compliance/adherence rate in general was between 50-60%, which can be improved by several pro-active interventions (Carey et al., 2016; Ingrand et al., 2016; Ingrand et al., 2019; Kinney et al., 2014;Lairson et al., 2008; Liang et al., 2021; Lowery et al., 2014; Paskett et al., 2020; Percac-Lima et al., 2016; Reeves et al., 2019; Skinner et al., 2015; Yen et al., 2021).

The largest RCT in Europe showed that general population with average risk were more prone to accept biennial FIT than one-time colonoscopy in terms of CRC screening (34.25% vs 25.38%; $P < 0.001$) (Salas et al., 2014; Urturi et al., 2012).

Risk-stratification using GERA did not improve the uptake of CRC screening; however, the GERA feedback might improve screening adherence (Myers et al., 2011; Myers et al., 2015; Weinberg et al., 2014). Another study used a blood test of methylated SEPT9 DNA for risk evaluation and found an increased uptake as well as compliance rates of CRC screening (Liang et al., 2021).

Cancer incidence and detection efficiency

Among RCTs reviewed in this report, few studies provided data on cancer incidence and detection efficiency. The incidence of CRC and AA was 0.23-0.6% and 2.4-6.9%, respectively, using colonoscopy as the screening approach for high-risk populations, either with family history or evaluated via a scoring system (Chen et al., 2019; H. Chen et al., 2020; H. D. Chen et al., 2020; Ingrand et al., 2016; Ingrand et al., 2019), which demonstrated the highest sensitivity across different approaches.

As FIT may be more preferred among populations due for CRC screening, and could be an option for risk-stratification prior to colonoscopy, the COLONPREV trial in Spain (the largest RCT included) provided analysis on how different positivity cutoffs of FIT may affect the detection efficiency in men: the sensitivity of advanced adenoma and neoplasm detection declined 7-11% when the positivity cutoffs were increased from 75 ng/ml to 125 ng/ml (Urturi et al., 2012).

A meta-analysis pooling 46 studies revealed that the specificity of FIT for CRC detection could increase from 69% to 80% when lowering the positivity threshold from >10-20 μg/g to ≤ 10 μg/g at the expense of slightly decreased specificity (-3%). Likewise, the FIT sensitivity for detecting advanced adenoma may increase from 21% to 31% when lowering the threshold. The authors performed modelling for accessing the changes of FIT sensitivity and specificity on a theoretical cohort of 100,000 participants and found the number of CRC and advanced adenoma detected increased by 16% and 43%, respectively, when lowering the positivity threshold from >10-20 μg/g to ≤ 10 μg/g (Selby et al., 2019).

In general, the CRC detection rate was higher by means of colonoscopy compared to other screening types (Chen et al., 2019; H. Chen et al., 2020; H. D. Chen et al., 2020; Liang et al., 2021; Salas et al., 2014; Urturi et al., 2012). The largest RCT in Europe showed that the detection rate of any neoplasms using colonoscopy was much higher compared to FIT (OR 12.06; 95%CI 10.73-13.55) (Salas et al., 2014; Urturi et al., 2012). Similar results were reported in the largest RCT in Asia where

detection rate of CRC or advanced neoplasms was better utilising colonoscopy than FIT. Yet using FIT or risk-adapted screening strategy as primary care options could reduce the number of colonoscopies thus the resource load required for detecting one advanced colorectal neoplasm (Chen et al., 2019; H. Chen et al., 2020; H. D. Chen et al., 2020).

Survival, cancer and all-cause mortality

No study provided data on CRC survival or mortality.

Cost-effectiveness

The cost-effectiveness analysis was only reported in two RCTs. One study reported comparable QALYs between subjects receiving risk-level tailored advice and general information for CRC screening uptake were found comparable. The ICER amounted to 258 AUD per person properly screened from the health care perspective whilst 275 AUD from the societal perspective (Reeves et al., 2019). The other study compared the promoting efficiency of CRC screening uptake among three groups: SI, TI, TIP and a control group with usual care. The ICER was estimated at 319 USD in SI compared to usual care and was more effective and dominated TI (Lairson et al., 2008).

2.1 Summary of the evidence base [table]

Breast cancer

Citation	Study Details	Participants	Outcomes	Results	Notes
MyPeBS **MyPeBS 2017**	RCT Belgium, France, Israel, Italy, United Kingdom and Spain 2018-present Standard M vs. M ± US ± MRI stratified by 4 risk groups*	**Total # screened:** Target N ~ 85,000 **Population:** Target screening population, women 40–70 yrs	1. Proportion of > stage IIB tumours 2. Reduction in recall rate Number of biopsies	Protocol: No results available	Power calculation: Y *5-yr risk of BCa defined by Breast Cancer Surveillance Consortium individualised breast cancer risk prediction model: *Low risk* (<1%): M every 4 years. *Medium risk* (1–1.66%): biennial M (if high density, US every 2 years) *High risk* (1.67–6%): annual M (if high density US every year) *Very high risk* (> = 6%): annual M + MRI

EA1141
Comstock 2020
	Study with randomised screening modality order
	US & Germany
	2006-2007
	One time screening with abbreviated MRI vs DBT
		Total # screened:
		N = 1444*
		Population:
		Women 40–75 yrs with dense or extremely dense breast tissue
		12 yrs FU
			1.Invasive BCa detection rate
			2.
			Sensitivity
			Specificity
			Additional imaging recommendation rate (callback plus recommendation for short-term follow-up)
			PPV of biopsy for invasive BCa & DCIS
				Uptake: NR
				Compliance:*all 1444 women received both imaging modalities with randomised temporal order
				Outcomes
				Incidence/stage: At ~12 years, MRI detected 17/17 invasive BCa and 5/6 DCIS vs 7/17 and 2/6 women for DBT
				BCa detection rate was 11.8 (95%CI 7.4–18.8) per 1000 women for MRI vs 4.8 (95%CI 2.4-10.0) per 1000 women for DBT; a difference of 7 (95%CI 2.2-11.6) per 1000 women (P = .002)
				Harms-benefits: For detection of BCa and DCIS: *sensitivity* = 95.7% (95%CI 79.0–99.2) for MRI vs. 39.1% (95%CI 22.2-59.2) for DBT (P = .001);
					Power calculation: Y

				specificity = 86.7% (95% CI, 84.8%-88.4%) vs. 97.4% (95% CI, 96.5%-98.1%), respectively (P < .001). The additional imaging recommendation rate was 7.5% (95%CI 6.2%–9.0%) for MRI vs 10.1% (95%CI 8.7%–11.8%) with DBT (P = .02); PPV = 19.6% (95%CI 13.2%–28.2%) vs. 31.0% (95%CI 17.0%-49.7%), respectively (P = .15) **Mortality:** NR	
WISDOM **Naeim et al. 2018** **Shieh et al. 2019** **Acerbi et al. 2021**	Pragmatic preference-tolerant RCT US 2016 - present Annual M vs RBS of M ± MRI stratified by 4 risk groups* [validation of risk thresholds in Shieh 2017)	N~ 100,000 target 28706 consented as of July 2020 *(Acerbi 2021)* **Total # screened:** NR **Population:** Target screening population Women 40–74 yrs	1. Rate of ≥ stage IIB tumours Reduced rate of recall and breast biopsy between arms 2. Rate of stage IIB and interval cancers Rate of DCIS Recall rates and follow-up procedures Proportion of women enrolling in randomised vs. self-assigned cohort Within self-assigned cohort, % choosing risk-based screening vs. standard annual screening PROMIS anxiety score Breast cancer risk worry	**Uptake:** NR **Compliance:** Interim analysis of N = 1643/1817 (90.4%) completing baseline questionnaires. 1071/1643 (65.1%) willing to be randomised to a study arm. Risk perception not significantly different between random vs observational arms. 474/572 (82.9%) of those who joined the observational cohort selected the personalised risk arm. Anxiety levels low and similar across arms. Mean (SD) *anxiety* scores at baseline = 14.0 (4.6). Mean (SD) Breast Cancer Risk Worry scores = 5.7 (1.05). (Naeim et al 2018) **Outcomes** **Incidence:** A study population simulated cohort of 100,000 women modelled no statistically significant difference in % of ≥ stage IIB BCa between personalised vs standard screening, RR = 1.01 (95%CI 0.89-1.12). The average 5-year BCa risk of annual screening under the personalised strategy was higher than the hybrid strategy (M+MRI), 1.7% vs. 1.2%. The average 5-year risk of biennial screening was lower under the personalised strategy, 1.1% vs. 1.9%. **Mortality: NR**	Power calculation: Y Both a randomised cohort and observational cohort - intervention assignment self-selected - integrated into WISDOM. High-risk of bias in the observational cohort. *5-yr risk of BCa defined by Breast Cancer Surveillance Consortium individualised breast cancer risk prediction model: *Low risk* (40–49 years and <1.3%): start M at age 50 years. *Medium risk* (50–74 years, or 40-49 years with risk≥ 1.3%): biennial M. *High risk* (extremely dense breasts, risk ≥ 0.75% of ER- tumour): annual M. *Very high-risk* (genetic mutations): annual M + MRI

				Harm-benefit: Biennial, hybrid (M+MRI), and personalised strategies resulted in fewer FP, RR = 0.55 (95%CI 0.46-0.65) and biopsies RR = 0.56 (0.47-0.65) compared to annual screening. (Shieh et al 2019) **Cost effectiveness:** Modelling indicated biennial, hybrid and personalised strategies delivered at lower cost vs annual screening; 14.1 v 22.1 million US$ per 100,000 women. (Shieh et al 2019)	

ACRIN 6666
 	
Berg et al. 2012
	RCT sub study
	
	USA
	
	2004-2006
	
	3 annual rounds of M+US ± one-time MRI after 24-month M
		Total # screened:
		N = 2809 underwent 7473 M and US
		
		Population:
		Women with ≥ 1 other BCa risk factor* AND heterogeneously dense or extremely dense breast tissue
			1. Supplemental cancer detection rate with 1 MRI
			
			2.
			Sensitivity
			Specificity
			
			PPV of biopsies performed and interval cancer rate
				Uptake: Of a total 7473 M and US screenings: 2659 completed the first annual M + US (35.6%)
				Compliance:; 2493/2659 completed the second (93.8%); 2321 the third (87.3%). 703 chose to undergo MRI (612 with complete data)
				Outcomes
				Incidence/stage: 111 BCa events detected: 89 invasive BCa and 22 DCIS. 33 detected by M only, 32 by US only, 26 by both, and 9 by MRI (after M + US); 11 not detected by any modality.
				
				For M alone: *sensitivity* was 0.52 (95%CI, 0.40-0.64); *specificity*, 0.91 (95%CI, 0.90-0.92); PPV, 0.38 (95%CI, 0.28-0.49; P.001 all comparisons. *Supplemental yield of US screening* was 3.7 cancers per 1000 screens (95%CI, 2.1-5.8). *Sensitivity* for M + US was 0.76 (95%CI, 0.65-0.85); *specificity*, 0.84 (95%CI, 0.83-0.85); PPV, 0.16 (95%CI, 0.12-0.21). 16 of 612 MRI participants (2.6%) had breast cancer diagnosed. S*upplemental yield of MRI* was 14.7 per 1000 (95%CI, 3.5-25.9). *Sensitivity* for MRI +M + US was 1.00 (95%CI, 0.79-1.00); S*pecificity*, 0.65 (95% CI, 0.61-0.69); *PPV*, 0.19 (95% CI, 0.11-0.29).
				Mortality: NR
					Power calculation: NR
					
					*Risk factors
					Mutation in BRCA1 or BRCA2
					History of prior chest, mediastinal, or axillary irradiation
					Personal history of breast cancer
					Lifetime risk, Gail/Claus model ≥25%
					-Year risk, Gail model ≥2.5%
					5-Year risk, Gail model ≥1.7% and extremely dense breasts
					ADH/ALH/LCIS or atypical papilloma
					ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ

				Harm-benefit: NND 1 cancer was 127 (95%CI, 99-167) for M; 234 (95%CI, 173-345) for supplemental US; and 68 (95% CI, 39-286) for MRI after -ve MRI + US.	

DENSE
 	
Bakker et al. 2019 Geuzinge et al 2021 Veenhuizen et al. 2021
	RCT
	
	Netherlands
	
	2011-2015
	
	3 rounds of biennial screening with
	M + MRI vs M alone
		N = 40,373
		I = 8061
		Total # screened = 4783
		C = 32,312
		
		Population:
		Women 50–75 yrs with extremely dense breast tissue*
		
		2-year FU
			1. Incidence of interval cancer (proxy for reduction in morbidity and mortality)
			2.
			Recall rate
			MRI screening Detected cancer
			FP rate
			PPV
			Tumour characteristics
			QoL
			Cost effectiveness
				Uptake: 4783/8061 accepted MRI invite (59%).
				Compliance:. 3436/4783 (72%) underwent a second MRI round
				Incidence/stage: Interval-cancer rate/1000 screenings = 2.5 in I group vs 5.0 in C group [difference of 2.5 per 1000 screenings (95%CI 1.0-3.7; P<0.001). Of 20 interval cancers detected in I group, 4 cases underwent MRI (0.8/1000 screenings) and 16 did not accept the invitation (4.9/1000 screenings). MRI cancer-detection rate = 16.5/1000 screenings (95%CI, 13.3-20.5). PPV = 17.4% (95%CI, 3.8-9.0) for recall for additional testing and 26.3% (95%CI, 21.7-31.6) for biopsy.
				At screening round 2, MRI cancer-detection rate = 5.8/1000 screenings (95%CI, 13.3-20.5). PPV = 18% (95%CI, 12.1.2-26.4) for recall for additional testing and 24.0% (95%CI, 16.0-33.9) for biopsy.
				Mortality: NR
				Harm-benefit: FP rate was 79.8 /1000 screenings at round 1 and 26.3/1000 at round 2 screenings. 0.1% who underwent MRI had an adverse/serious adverse event during or immediately after screening.
				Cost effectiveness: MRI alone very 4 years dominated both trial arms at €15,620/QALY. A 3-year interval resulted in an ICER of €15,620/QALY. Geuzinge et al 2021
					Power calculation: Y
					
					*grade 4 as measured on Volpara imaging software

UK Age trial	RCT UK	N = 160,921 I = 53,883 **Total # screened** ~37,179	1. Mortality from BCa diagnosed in intervention period	**Uptake:** Uptake was 36,622/53,801 invitations (68·1%) at round 1and 176,746/255,618 (69·1%) across subsequent rounds ~ 31% average non-compliance rate (Johns 2010.)	Power calculation: Y

Duffy et al. a 2020 **Duffy et al. b 2020** **Johns et al. 2010** **Gunsoy et al. 2012**	1990-1997 Annual M till 48 yrs vs usual care of no screening via UK NHSBSP	C = 106,953 **Population:** Women 39-41 yrs i.e. below eligible age for screening via UK NHSBSP 23 yr FU	2. Mortality from BCa diagnosed after randomisation All-cause mortality Mortality from causes other than breast cancer (in the entire trial population and in the subgroup of women with breast cancer), incidence of breast cancer	**Compliance:** 89% of women who had a FP recall at their previous screen attended their next invitation to routine screening. (Duffy et al. b 2020) **Incidence/stage:** RR of BCa incidence just before the first NHSBSP screen = 1.09 (95%CI 1.00-1.19; p = 0.03). RR up to and including first NHSBSP screen = 0.99 (95%CI 0.92-1.07; p = 0.7). At the end of 23 yr FU, RR = 0.99 (95%CI 0.94-1.04; p = 0.6). i.e. no excess in I group in addition to cancers diagnosed in the NHSBSP from the age of 50 years onwards. **BCa mortality**: 83 BCa deaths in I group vs. 219 in C group (RR = 0·75 (95%CI 0·58–0·97; p=0·029) represents ~ 25% reduction in BCa mortality at 10 years FU. No significant reduction was observed thereafter: 126 deaths in I group vs 255 deaths in C group after more than 10 years FU (RR=0·98 [0·79–1·22]; p=0·86). (Duffy et al. b 2020) Absolute benefit of screening ~ 1 death prevented per 1000 women screened (Duffy et al. a 2020) **All-cause mortality:** No significant difference in all-cause mortality: 3507 deaths in I group vs 6932 in C group (RR = 1·01, 95%CI 0·96–1·05; p=0·66), or mortality from causes other than BCa (RR = 1·02 (0·97–1·07; p=0·43). (Duffy et al. b 2020) **Harms-benefits:** 14.6% (7,893) of I group experienced ≥1 FP. Rates of FP rate at first and subsequent routine screens were 4.9% and 3.2%, respectively. Cumulative FP rate over 7 screens = 20.5%. PPV of recall was 2% at first screen and 3%–5% at subsequent screens, increasing with age. [comparison NHSBSP PPV of 8% at first screens and 16% at subsequent screens] (Johns 2010)	

				Total # of expected screen-detected cancers was 164 vs 244 observed. This suggests 80 (8.5%) of screen-detected cancers diagnosed in the intervention phase were *overdiagnosis*. This equates to 32.8% of screen-detected cancers, and an absolute rate of 0.2% over 8 years of screening in women 40-49. Markov modelling estimate overdiagnosis as 0.7% of screen-detected cancers (range 0.5% to 2.9%). Simulated screen-detectable mean duration of pre-clinical cancer states (mean sojourn time) of non-progressive and progressive in situ cancers was 1.3 (95%CI 0.4-3.4) and 0.11 (95%CI 0.05-0.19) years, respectively, and 0.8 years (95%CI 0.6-1.2) for preclinical invasive breast cancer. The sensitivity of M for invasive and in situ breast cancers was 90% (95%CI 72-99) and 82% (43-99), respectively. (Gunsoy et al. 2012)	

UK Breast Screening Frequency Trial
 	
Van Ravesteyn et al. 2011
	RCT
	
	UK
	
	1989-1996
	
	Standard triennial M vs. 3 annual M screens
		N = 99 389
		Total # screened:
		I = 49 173
		C = 50 216
		
		Population:
		Target screening population, women aged 50–62 yrs
			Predicted BCa mortality	**Uptake:** NR
				Compliance: The attendance rate in the control group among women who had attended the prevalence screen was 85%. In the study group, attendance rates at the three yearly sreens were 78%, 78% and 81% resepectively.
				BCa mortality: MISCAN modelling estimated RR = 0.83 for BCa mortality in I group vs C group (point statistic within reported trial 95%CI). Increasing the simulated FU to lifetime had no effect on predicted RR. A simulated increase of screening sensitivity and attendance rate both reduced predicted RR to 0.81
					Power calculation: Y

Breast Cancer Screening with Alternate Mammography and Ultrasound **Huang et al. 2010**	RCT Taiwan 2003–2008 Cross-over design with M and US on alternate years until 2008	N = 79,691 **Total # screened** I_M = 20,040 first assigned to M I_{US} = 20,088 first assigned to US* C = 39,563 **Population**: Women aged 40–49 yrs	Detection rate and annual incidence rate of interval cancer as a percentage of the control group (I/E ratio) compared between M vs US.	**Uptake:** Attendance rate at round 1 was 11921/20040 (59%) for M and 11249/20088 (56%) for US. **Compliance:** Attendance rates of both groups was 85% and 91% in rounds 2 and 3, respectively. **Incidence:** At round 1, the BCa detection rates were 0.34% for I_M group and 0.22% for I_{US} group. The additional detection rate was 0.16% from a subsequent US screen and 0.36% from a subsequent M. M + US was 3-4x more likely to detect BCa compared with C group (annual incidence rate was 0.17%). The detection rate of interval cancer as a % of the C group was lower after M vs. after US screening.	Power calculation: Y *Cross-over design with mammography and US on alternate years until 2008 Limited data reporting from conference abstract

J-START
 	
Ishida et al. 2014
	RCT
	Japan
	
	2006-2012
	M + US v M alone
	
	2 rounds biennially
		N = 76,196
		Total # screened
		I = 38,313
		C = 37,883
		
		Population:
		Women aged 40–49 yrs
			1.
			sensitivity, specificity and the rate of detection of cancer
			2. cumulative rate of advanced breast cancer
				Uptake: NR
				Compliance: 74.1% of participants at round 1 were screened at round 2
				Outcomes - Only preliminary data reported after round 2 of screening complete
				Incidence/stage/mortality: NR
					Power calculation: Y

Project HOME
 	
Lairson et al. 2011
	RCT
	
	US
	
	Dates NR
	
	Interventions to increase compliance with BCa screening (i) generic messages
		N = 5500
		Total # screened =3660
		I1 = 1857 generic intervention
		I2 = 1803 tailored intervention
		C = 1840 control (survey only)
		
		Population:
		Female, veterans, 52 years of age or older
			Prevalence of at least 1 self-reported post-intervention M and 2 post-intervention Ms 6-15 months apart.
			
			ICERs per additional person screened
				Uptake: 44.7%, 46.9% and 46% in C group, I1 group and I2 group reported undergoing at least one M
				Compliance: Not applicable
				Incidence/stage/mortality: NR
				Cost effectiveness: At 2008 US$ values, the societal costs for generic intervention were $25 per person vs. $52 per person for tailored intervention. ~ 27% of total costs were identifying and recruiting eligible population. Eligibility costs were a higher proportion of total cost (40%) for I1 vs. I2 (20%). The ICER was $1,116 comparing I1 vs. C groups (95%CI = $493 to dominated). The I2 (tailored) intervention was
					Power calculation: NR

	(ii) tailored to individual responses to questionnaire			dominated by the I1 (generic) intervention, i.e., I2 more costly and less effective than I1.	

Canadian NBSS National Breast Screening Study
 	
Miller et al. 2014
Narod et al. 2014
	RCT
	
	Canada
	
	1980-1985
	
	4 to 5 annual M + breast exam for I group till age 60
		N =89,835
		Total # screened I = 44,925
		C = 44, 910
		
		Population:
		Women 40 to 49 yrs, no history of breast cancer, no M in past 12 months
		
		Mean 22 yr, max 25 yrs FU
			1. BCa mortality
			2.
			BCa incidence
			overdiagnosis
				Uptake: NR
				Compliance: NR
				Outcomes
				Incidence/ mortality: BCa detected in 1.5% (40-49 yrs) and 7.2% (50-59) of I group vs. 1.2% and 7.0% of the C group across the 25-yr FU period. At a mean 22 yrs FU, BCa mortality rate / 10,000 women was 108 vs 100 in I and C groups RRR = 1% (95%CI -12 to 12). (Miller et al. 2014)
				A cohort of n = 50,436 age 40–49 years were FU until age 60. (Narod et al. 2014) Of 256 deaths from BCa recorded in the study cohort, 134 occurred in I group, and 122 in C group. The cumulative risk of death from BCa to age 60 was 0.53% and 0.48% for I and C groups, respectively The hazard ratio for BCa–specific death associated with 1 or more screening mammograms before age 50 was 1.10 (95%CI 0.86-1.40).
				Harms-benefits: For the whole study population at 22 years, 22% of screen-detected invasive Bca cases and 50% of nonpalpable cancer were overdiagnosis (Miller et al. 2014)
					Power calculation: Y
					
					DCIS excluded from analysis would likely increase overdiagnosis estimate

Extension of the invited age range in NHSBSP **Moser et al. 2011**	Cluster RCT UK 2009–2010 Invitation v no invitation for	N = 60,708 **Total # screened** = 31,069 [*47–49 yrs* I = 20,596 C = 19,409; *71 – 73yrs* I = 10,473 C = 10,230]	Workload from randomisation screening uptake among women invited self-referrals among women not invited and screening outcomes among women invited	**Uptake:** 63% accepted screening (63% aged 47–49, 62% aged 71–73). A higher proportion of the younger group DNA (29% vs. 24%). **Compliance:** Over the 12 month study, 31 women (0.2%) aged 47–49 who had been randomised to C group requested M screening. For women aged 71–73 697 (6.8%) requested M screening. **Outcomes**	Power calculation: Y

	standard NHSBSP triennial M screening	**Population:** Women aged 47– 49 & 71–73 yrs		**Incidence:** BCa incidence rate was 0.5% and 1.1% in the 47–49 vs 71–73 age groups. **Harms-benefits:** Recall rate was 7.5% and 3.0% in the 47–49 vs 71–73 age group. Among the women recalled for assessment 7% (65/966) of those recalled aged 47–49 were found to have BCa vs 36% (70/192) of recalled women aged 71–73. The percentage of women 2.8% vs. 1.8% of those screened had a needle biopsy in the 47–49 vs 71–73 age group. **Mortality:** NR	

To-Be 1 Trial Moshina et al. 2020
 	
To-Be 2 Trial Hofvind et al. 2021
	RCT
	
	Norway
	
	2016-2017
	SM + DBT vs. DM
		N = 28,749
		Total # screened
		I = 14,380 (DBT+ SM)
		C = 14,369 (DM)
		
		Population: Target screening population stratified by breast tissue density*
			To-Be 1
			Rates of recall
			FP rate
			Biopsy
			cancer detection rate, PPV of recalls & biopsies
			Tumour histopathology
			To-Be 2
			Cancer detection rates and tumor characteristics of interval cancers
				Uptake: Of 44,266 women invited for screening, 32,976 (74.5%) attended screening and 29,453 (66.5%) consented to participate in the trial.
				Compliance: Of the 28,749 women screened in To-Be1 22,306 (77.6%) returned for a second screening round in to-BE2 (11,105 from C group and 11,201 from I group)
				Outcomes
				Incidence: For DBT+SM, RR of screen-detected breast cancer (VDG 2: 2.4; *P* = .004; VDG 3: 2.8; *P* = .01; VDG 4: 2.8; *P* = .05) increased with VDG, whereas no differences in RR were observed for DM (VDG 2: 1.7; P = .13; VDG 3: 2.1; P = .06; VDG 4: 2.2; P = .15).
				At round 2 (To-Be 2 trial), 20 interval cancers were detected (rate of 1.4 per 1000 screens) in I group vs 29 (2.0 per 1000 screens) in C group.
				Tumor characteristics were similar between groups
				The
				RR of interval cancer was 0.69 (95%CI: 0.39–1.22; P = .20) for DBT versus DM,
					Power calculation: Y
					
					*Volpara Density Grade (VDG) 1–4
					To-BE 1 particiapnts were screened and followed for 2 years, then invited to To-BE 2 (if met eligibility)

				Harms-benefits: The recall rate for I group vs. C group for VDG: 1 = (2.1% [81 of 3929] vs 3.3% [106 of 3212]; P = .001 2 = (3.2% [200 of 6216] vs 4.3% [267 of 6280]; P = .002). For DBT+SM, RR of recall (VDG 2: 1.8; P < .001; VDG 3: 2.4; P < .001; VDG 4: 1.8; P = .02) increased with VDG, whereas no differences were observed for DM (relative risk of recall for VDG 2: 1.3; P = .06; VDG 3: 1.1; P = .41; VDG 4: 1.1; P = .71)	
Patient Navigation for Comprehensive Cancer Screening **Percac-Lima et al. 2016**	RCT US 2014 IT -enabled patient navigation for routine cancer screening	Among 1612 patients (673 men and 975 women) N = 1612* I = 7927 C = 829 **Population:** Target screening population* -women 50-74 yrs for BCa in in low income & ethnic/racial minority populations.	1. Mean cancer screening test completion rate over 8-month trial 2. proportion of patients completing overdue cancer screening test(s)	**Uptake:** Not applicable. **Compliance:** Of patients at high risk for non-compliance 605/797 (75.9%) allocated to intervention received the intervention and 764/829 (92.1%) of patients allocated to control. For the I group, patient navigators were unable to reach 151 (19%), deferred 246 (38%) (patient declined, competing comorbidity), and navigated to 202 (32%). **Outcomes** The mean proportion up to date with screening among all overdue screening examinations for I group vs C group was 14.7% vs 11.0% (95%CI 0.2%-7.3%; P = .04) for breast cancer screening. The proportion of I group vs C groupcompleting breast screening was 23.4% vs 16.6% (95%CI 1.8%-12.0%; P = .009). **Incidence/stage/mortality:** NR	Power calculation: NR *Study of combined breast, cervical and colorectal cancers.

Pasynkov et al. 2021	RCT
	
	Russia
	
	Dates NR
		Total # screened
		N = 2078
		Random allocation NR
		I = UX + CAD
		C = US alone
		Population:
		Women 40-72 yrs
			Number and size of lesions detected with and without the CAD results	**Uptake:** All 2078 women meeting criteria were screened with randomly allocated modality
				Compliance: Not applicable.
				Incidence/stage: 16 vs 22 BCa detected in the C I group (US +CAD).
					Power calculation: NR
					
					Superficial reporting of trial methods and results

	US ± Computer aided detection (CAD) system during screening	with dense breast tissue after negative M 3 yr FU		3 /16 BCs (18.8%) in C group vs 11 /22 (50.0%) BCa in I group were <1cm dia (p< 0.05). During 3-year FU, 9 more BCa in C group and 2 more BCa in I group were detected **Harm-benefit:** The rate of benign lesions requiring biopsy was 76 /1039 (7.31%) in C group and 68 /1039 (6.54%) in I group. **Mortality:** NR	

Gothenburg Trial
 	
Bjurstam et al. 2016
	RCT
	
	Sweden
	
	Dates 1982-2007
	
	Mammographic screening vs usual care for women 39-49 vs 50-59
		Total # screened
		N = 21,904
		Age 39-49 11,792
		Age 50-50 10,112
		
		I = Offer of mammography every 18 months (N= 21,904)
		C = Usual care (N= 30,318)
		
		25 yr FU
			Cumulative mortality	**Uptake:** NR
				Compliance: NR
				Incidence/stage: The reduction in the incidence rate of node-positive cancers was significant in the 39- to 49-year age group (RR, 0.65; 95% CI, 0.43-0.97; *P* = .03) but not in the 50- to 59-year group (RR, 0.98; 95% CI, 0.67-1.43; *P* = .9).
				Harm-benefit: NR
				Mortality: In women aged 39 to 49 years, there was a significant 40% reduction in breast cancer mortality (RR, 0.60; 95% CI, 0.43-0.85; *P* = .003). In the 50- to 59-year age group, there was a nonsignificant 18% breast cancer mortality reduction (RR, 0.82; 95% CI, 0.54-1.26; *P* = .4).
					Power calculation: NR

Abbreviations and Acronyms	
	N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened *Uptake:* Percentage of invited population agreeing to participate in the trial *Compliance:* Percentage of trial population completing the baseline screening
BCa	Breast cancer
BMI	body mass index
C [group]	Control/non-screened group

CI	confidence interval
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
DENSE	Dense Tissue and Early Breast Neoplasm Screening Trial
DM	Digital mammography
DNA	Did not attend
FP(R)	False positive (rate)
FU	Follow up
HR	Hazard ratio
HRQOL	Health-related quality of life
I [group]	Intervention/screened group
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
J-START	Japan Strategic Anti-cancer Randomised Trial
M	Mammography/mammographic screening
MISCAN	Microsimulation of Screening Analysis
MLT	Mean lead time [average time by which diagnosis is advanced by screening relative to without screening]
MyPeBS	My Personal Breast Screening
MRI	Magnetic resonance imaging
NBSS	National Breast Screening Study
NHSBSP	National Health Service Breast Screening Programme
NND	Number needed to invite to diagnose to prevent one cancer death
NNI	Number needed to invite to screening to prevent one cancer death
NPV	Negative predictive value
NR	Not reported
PPV	Positive predictive value
ProjectHOME	Project Healthy Outlook on the Mammography Experience
QALY	Quality-adjusted life-years
RCT	Randomised controlled trial
RETomo	Reggio Emilia Tomosynthesis trial
RBS	Risk-based screening
RR	Relative risk
SM	Synthetic mammography
I [group]	Intervention group
VDG	Volpara Density Grade

WISDOM	Women Informed to Screen Depending On Measures of Risk Study

Cervical cancer

Trial	Trial Details	Participants	Outcomes/Results	Notes
ARTISTIC **(Gilham et al., 2019)**	UK 2001-2003 NA	N = 24,510 I = NR C = NR S = 23,888 Mean age NR (20-69 y) 12 y follow-up post randomisation **Population:** general population eligible for routine cervical cytology screening	**Uptake:** NR **Compliance:** Among 24,510 women, 24,496 (ca 100%) participated at round 1 and 13,591 (55%) women remained for analysis at round 2. **Outcomes:** - **CC/CIN incidence:** In total, 505 CIN3+ cases were identified with 22 being invasive cancers. - **Detection rate:** Among 331 women with double positive of high-risk HPV tests, 115 (35%) were positive with a new HPV type at round 2 and 216 (65%) showed persistent infection of specific genotype. - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **CC Risk:** The 10-year cumulative CIN3+ risk in women with HC2-negative at entry was higher in those aged 25-39 years (0.40%; 95%CI 0.28-0.56%) compared to those aged > 40 years (0.11%; 95%CI 0.06-0.20%) (*P* < 0.001). Higher cumulative CIN3+ risk was observed in women with HPV 16 infection than those with infections of any other genotype. HPV16 infection also showed the highest 10-year cumulative CIN3+ risk following a new infection at round 2. Persistent infection of any genotype was associated with higher risk (20.4%; 95%CI 15.6-26.4%).	Power calculation: Y This trial was aimed to compare the HPV testing with routine cytology regarding the risk and corresponding screening intervals of women. Cytology was performed using LBC technology at the trial entry (baseline), 3 and 6 years after entry, which were subjected to HPV test. After trial ended in 2009, women returned to routine cytological screening with recall every 3 years (aged < 50 years) or 5 years (aged 50-64 years).

CHOiCE **(Tranberg et al., 2018)**	Denmark 2016-2017 1) A self-sampling kit directly mailed to home (directly mailed group; I_1) 2) An invitation sent for ordering kit (opt-in group; I_2) 3) A standard 2nd reminder mailed for regular cytology screening (control group; C)	N = 9791 I_1 = 3265 I_2 = 3264 C = 3262 S = NR Mean age NR (30-64 y) 1 y follow-up **Population:** general population due for the 2nd reminder of routine cervical cytology screening	**Uptake:** The trial examined differential uptake amongst all women (34-64) due to receive a second reminder from the Central Denmark region. **Compliance/Uptake:** Higher participation rate was observed in the directly mailed group compared to the control for women of Western immigrants (PD 18.1%; 95%CI 10.2-26.0%) and social welfare recipients (PD 15.2%; 95%CI 9.7-20.6%). Compared to the control group, the largest effects of opt-in strategy were found for women receiving social welfare (PD 7.8%; 95%CI 2.6-13.1%) and women with middle level of education (PD 7.3%; 95%CI 4.5-10.1%). In general, mailing the kit directly led to higher participation than the opt-in strategy, particularly in Western immigrants, which resulted in two times higher participation rate (34.3% vs 16.0%; RR 2.14; 95%CI 1.51-3.04). **Compliance:** Not applicable **Outcomes:** - **CC/CIN incidence:** NR. - **Detection rate:** NR - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	*Power calculation: Y* *This trial was designed to compare the invitation strategy, kit directly mailed versus invitation for opt-in, for screening uptake by women across various socioeconomic groups.*
Compass **(Canfell et al., 2017)**	Australia 2013-2014 1) LBC with HPV triage of low-grade cytology (LBC screening group; I_1)	N = 5006 I_1 = 998 I_2 = 1996 I_3 = 2012 C = NA S = 4995 Mean age NR (25-64 y) 18 m follow-up	**Uptake:** 5,303 participants were recruited from 8,595 eligible women approached (62%). **Compliance:** The compliance rate was 99.8% across all groups. **Outcomes:** - **CC/CIN incidence:** The overall CIN2+ incidence rates were 0.1%, 1.0% and 1.2% in the LBC screening, HPV+LBC triage and HPV+DS triage groups,	Power calculation: Y This trial was designed to evaluate the influence of implementation of HPV vaccination on the CC screening and detection efficiency.

	2) HPV screening with those positive for HPV16/18 referred to colposcopy and with LBC triage for OHR (HPV+LBC triage group; I_2) 3) HPV screening with those positive for HPV16/18 referred to colposcopy and with dual-stained cytology triage for OHR (HPV+DS triage; I_3)	**Population:** general population	respectively, whilst the corresponding CIN3+ rates were 0.1%, 0.7% and 0.8%. - **Detection rate:** NR - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** The overall PPVs for CIN2+ and CIN3+ were 3.7% and 3.7% for the LBC screening; 26.7% and 17.3% for HPV+LBC triage; 30.4% and 21.5% for HPV+DS triage, provided primary and triage referral mechanisms and 12-m follow-up were considered.	All women aged ≤ 33 years at the time of trial enrolment (2014) were offered HPV vaccination (22% of participants).
HPV self-sampling vs Pap-smear **(Sancho-Garnier et al., 2013)**	France 2011 1) HPV self-sampling (I_1) 2) Pap-smear (I_2)	N = 18,730 I_1 = 8829 I_2 = 9901 C = NA S = 1811 Mean age NR (35-69 y) Time follow-up NR **Population:** nonattenders of CC screening from lower socioeconomic groups	**Uptake:** Trial examined differential uptake from all non responders to invitation for a Pap-smear who had not had a Pap-smear in ≥ 2 years. The uptake rate was 0.2% in the Pap-smear group compared to 18.3% in the HPV self-sampling group ($P \leq 0.001$). The completion rate of Pap-smear increased with age ($P < 0.001$) while no age-associated trend was observed in the HPV self-sampling group. **Compliance:** The compliance of follow-up recommendations was around 55% in the Pap-smear group and 41% in the HPV self-sampling group. **Outcomes:**	Power calculation: NR Sample quality was generally good with only 0.5% of Pap-smear classified as unsatisfactory and 0.56% of HPV self-sampling unanalysed due to technical issues.

			- **CC/CIN incidence:** Two CIN3 were diagnosed in the Pap-smear group while 6 CIN2, 3 CIN3 and 2 invasive cancers were diagnosed in the HPV self-sampling group, rendering the prevalence of CIN2+ lesions 9.5% in the latter. - **Detection rate:** Around 4.5% (9 of 198) women of Pap-smear group had abnormal results whilst the positive rate of HPV was 17.6% (283 of 1604). The prevalence of HPV type was 3.24% HPV16, 1.4% HPV18 and 13% non-HPV16/18. The detection rate of CIN2+ was 0.2 per 1000 for the Pap-smear group compared to 1.25 per 1000 for the HPV self-sampling group (*P* = 0.01). - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
HPV vaccines vs screening frequency **(Louvanto et al., 2020)**	Finland 2014-2017 1) Frequent screening at age of 22/25/28 (Arm 1; I_1) 2) Infrequent screening at the age of 28 (Arm 2; I_2) 3) Safety control who had HPV16/18	N = 4273 I_1 = 2073 I_2 = 2200 C = 1329* S = NR Mean age 22 y > 4 y follow-up **Population:** females who received HPV16/18 vaccination in 2007-2009 at age of 13-15 *Safety control for risk assessment	**Uptake:** Of 13,354 eligible 22 year olds 4,273 (32%) were randomised to infrequent vs frequent screening. **Compliance:** The compliance rate of the 1st screening visit was 97% across three arms. **Outcomes:** - **CC/CIN incidence:** The incidence rates of CIN3 were comparable between infrequently screened, cross-vaccinated Arm 3 and frequently screened Arm 1 (0.4% for both). - **Detection rate:** The positive rates of HPV16/18 and other high-risk genotype were 0.5% and 25% in Arm 1; 0.2% and 24% in Arm 2; 3.1% and 23% in Arm 3. - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: NR For all consented participants, Pap-smear and a cervicovaginal self-sample for HPV and Chlamydia trachomatis DNA-testing were obtained at the 1st and 2nd screening visits at ages of 22 and 25.

	vaccination at age 18 (Arm 3; C)			
NCT02553538 **(Percac-Lima et al., 2016)**	US 2014 1) PN intervention (I) 2) Usual care (UC; C)	N = 975 I = 479 C = 496 S = NR Mean age NR (21-64 y) 8 m follow-up **Population:** general population due or overdue for CC screening	**Uptake:** The trial examined differential uptake amongst all patients overdue for at least one cancer screening The mean cervical cancer screening completion rate was 11.1% in the PN arm compared to 5.7% in the UC arm (*P* = 0.002) in the intention-to-treat analysis. In as-treated analysis, the completion rate was 14.1% in the PN arm compared to 6.2% in the UC arm (*P* < 0.001). Among participants overdue for cervical screening during follow up, the completion rate was higher in the PN group than UC group in both intent-to-treat analysis (14.4% vs 8.6%; 95%CI 1.6-10.5%; *P* = 0.007) and as-treated analysis (18.0% vs 9.3%; 95%CI 3.3-13.7%; *P* = 0.001). **Compliance:** Not applicable **Outcomes:** - **CC/CIN incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: Y Participants randomized to the PN intervention group were referred to navigators via IT system to track, contact and provide help for screening completion. The type of cervical screening was Papanicolaou and HPV testing.
NTCC **(Ronco et al., 2010)**	Italy 2002-2004 1) HPV testing with or without thin-layer cytology (I) 2) Conventional cytology (C)	N = 94,370 I = 47,369 (22,708 in Phase 1 and 24,661 in Phase 2) C = 47,001 (22,466 in Phase 1 and 24,535 in Phase 2) S = 92,829* Mean age NR (25-60 y) Median follow-up 5.1 y **Population:** eneral population	**Uptake:** 94,370 (74%) of 128,026 eligible women were randomised. **Compliance:** At the baseline, 46,680 women in the intervention arm (99%) and 46,149 women in the control arm (98%) completed the test. The compliance rate between 2-5 years after recruitment was comparable between intervention and control arms (73% vs 70%). **Outcomes:** - **CC/CIN incidence:** After 2 rounds of screening, eighteen invasive cancer cases were detected in the conventional cytology group compared to 7 cases in	Power calculation: NR The screening was composed of 2 phases: the intervention group received thin-layer cytology and HPV test in Phase 1 whereas the same group received HPV test alone in Phase 2. The control group received conventional cytology in both Phases.

		*Baseline testing	the HPV group (*P* = 0.028). At the end of follow-up, a total of 24 and 7 invasive cell carcinomas were confirmed in the control group and intervention group, respectively. - **Detection rate:** The relative detection rate of invasive cervical carcinoma was RR 0.37 (95%CI 0.17-0.80) in the intervention group compared to control group. - **Stage:** Among 24 cases confirmed in the conventional cytology, 11 were > Stage 1A whereas only 1 in 9 cases in the HPV testing was > Stage 1A. - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Women with positive HPV results were referred to colposcopy or cytological triage (women aged 25-34 years in Phase 1).
POBASCAM **(Dijkstra et al., 2016)**	Netherland 1999-2002 1) HPV+cytology co-testing (I) 2) Cytology testing only (C)	N = 44,938 I = 22,420 C = 22,518 S = 43,339 Mean age 42.8 y (29-61 y) 14 y follow-up **Population:** general population eligible for 5-yearly screening	**Uptake:** NR **Compliance:** During the 14-y follow-up, the compliance rate of women who were eligible for both 2nd and 3rd screening rounds was 90.7% in the intervention arm and 90.3% in the control arm. The compliance rate for the 3rd screening round was 84.3% and 84.5% in the intervention and control group, respectively. **Outcomes:** - **CC/CIN incidence:** Among women with positive HPV and negative cytology results, the CC incidence was lower in the intervention arm compared to control arm (RR 0.29; 95%CI 0.10-0.87; *P* = 0.02). The CC incidence after 2nd and 3rd screening round was 0.01% and 0.07% among double-negative women in the intervention arm whilst 0.09% and 0.19% among cytology-negative women in the control arm. The CIN3+ incidence after 2nd and 3rd screening round was 0.27% and 0.52% among double-negative women in the intervention arm whilst 0.69% and 1.20% among cytology-negative women in the control arm. The CC incidence after the 3rd screening round was similar among HPV negative and double-negative women in the intervention arm	Power calculation: NR Women in the intervention arm were informed of their HPV and cytology results while women in the control arm only received the cytology result.

			compared with cytology-negative women from the control arm (RR 0.97; 95%CI 0.41-2.31; *P* = 0.95; RR 0.83; 95%CI 0.32-2.15; *P* = 0.69). Higher CC (64.2% higher; *P* = 0.32) yet lower CIN3+ (72.1% lower; *P* < 0.001) incidence was observed among double-negative women aged ≥ 40 years than younger women. Likewise, higher CC (62.0% higher; *P* = 0.29) yet lower CIN3+ (72.2% lower; *P* < 0.001) incidence was observed among HPV negative women aged ≥ 40 years than younger women. There was 11.9 times higher CC incidence among HPV positive women with negative cytology triage compared to HPV negative women (95%CI 3.7-38.1; *P* < 0.001). - **Detection rate:** NR - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
PROHTECT-2 **(Gök et al., 2012)**	Netherland 2007-2008 1) HPV self-sampling group (I) 2) Control group re-invited for regular cytology-based screening (C)	N = 26,409 I = 26,145 C = 264 S = 7887 Mean age NR (29-63 y) 18 m follow-up **Population:** general population eligible but not attending the CC screening programme	**Uptake:** Not applicable. All non-attendees to the regular screening programme were included. **Compliance:** Among participants of HPV self-sampling group, 30.8% returned a self-sampled specimen while only 6.5% of control group responded for the recall of cervical cytology test (chi-square = 71.77; *P* < 0.01). Most women (99.7%) returned specimen valid for HPV test. Around 90% of women with HPV positive results adhered to further workups. **Outcomes:** - **CC/CIN incidence:** Among HPV-positive responders, the incidence of CC, CIN3 and CIN2 was 3.6%, 35.4% and 18.2%, respectively, at baseline. Among women underwent colposcopy after 1 year, the incidence of CC, CIN3 and CIN2 was 3.8%, 18.5% and 11.1%, respectively. The cumulative incidence of CIN3+ and CIN2+ within 18-m follow-up of HPV-positive women	Power calculation: Y

			were 1.0% and 1.5%, respectively. Among the same population, higher incidence of CIN2+/CIN3+ was observed in younger women compared to older women (CIN2+: 2.9% vs 0.8%; *P* < 0.01; CIN3+: 2.0% vs 0.8%; *P* < 0.01). - **Detection rate:** Among women returned a valid sample for HPV test, the positive rate of high-risk HPV was 8.3%. The positive rate decreased with age: 15.6% in women aged 29-33 years whilst 4.6% in women aged 59-63 years (chi-square for linear trend = 113.14; *P* < 0.01). - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Concordance of physician-taken cervical scrapes vs self-sampling:** The concordance between two samplings was high (68.8%; 95%CI 64.7-73.0%). In women diagnosed with CIN2+/CIN3+, the concordance was over 90%.	
Swedescreen **(Elfström et al., 2014)**	Sweden 1997-2000 1) HPV & cytology double testing (I) 2) Cytology only, with samples frozen for future HPV testing (C)	N = 12,527 I = 6257 C = 6270 S = 12,091 Mean age NR (32-38 y) 13 y follow-up **Population:** general population attending organised screening programme	**Uptake:** NR **Compliance:** Among enrolled participants, 12,091 women completed the baseline cytology and at least one-follow-up test (96.5%). No uptake rate was provided specifically in the intervention group or control group. **Outcomes:** - **CC/CIN incidence:** In total, 387 women were confirmed with CIN2+ while 230 women were diagnosed with CIN3+ during the 13-year follow-up. The number of CIN2+ cases in the intervention and control arms was 198 and 189, respectively. The CIN3+ cases were 119 in the intervention group compared with 111 in the control group.	Power calculation: NR With long-term follow-up, the accumulated cases of CIN2+ became similar between HPV testing and cytology screening, for which the authors suggested that the increased sencitivity of HPV testing might reflect early detection instead of overdiagnosis.

			- **Detection rate:** NR - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** The sensitivity of cytology in detection CIN2+ was 85.94% in the control group at 3 years while the sensitivity of HPV testing was 86.40% in the intervention group at 5 years. The longitudinal sensitivity of cytology in detecting CIN3+ was 92.02% in the control group at 3 years while HPV showed a sensitivity of 89.34% at 5 years in the intervention group. Higher NPV was observed for HPV testing compared to cytology in terms of CIN2+ and CIN3+ detection.	
Intervention targeting long-term nonattenders of cervical screening **(Elfström et al., 2019)**	Sweden 2016 1) HPV self-sampling kit sent directly (Arm 1; I_3) 2) Invitation to order an HPV self-sampling kit using new web application (Arm 2; I_2) 3) Invitation to consulting a midwife for questions and concerns (Arm 3; I_3)	N = 8000 I_1 = 2000 I_2 = 2000 I_3 = 2000 C = 2000 S = 658 Mean age 47.6 (33-60 y) 7 m follow-up **Population:** general population eligible but not attending the CC screening programme in 10 years	**Uptake:** The total uptake rate was 8.2% (658 of 8000). The uptake rate by arm was 18.7% in Arm 1; 10.7% in Arm 2; 1.9% in Arm 3; 1.7% in the routine practice arm as control. **Compliance:** Not applicable **Outcomes:** - **CC/CIN incidence:** Among women tested positive at screening 39.1% were diagnosed with CIN2+ lesions, of which 72% were CIN3+ lesions. - **Detection rate:** Among women returning HPV self-sampling specimen, 12.2% were positive for high-risk HPV. The corresponding detection rate of CIN2+ per arm was: 4.5% in Arm 1; 2.3% in Arm 2; 5.4% in Arm 3; 2.9% in routine practice control arm. The overall detection rate of CIN2+ was 3.8%. - **Stage:** NR - **CC and all-cause mortality:** NR - **Sensitivity/Specificity:** The PPV for CIN2+ per arm was: 47.2% in Arm 1; 22.7% in Arm 2; 50.0% in Arm 3; 100%	*Power calculation: Y*

	4) Standard annual renewed invitation with pre-booked appointment (routine practice; C)		in routine practice arm, leading to an overall PPV of 39.1%.	

Abbreviations and Acronyms	
	N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened *Uptake:* Percentage of invited population agreeing to participate in the trial *Compliance:* Percentage of trial population completing the baseline screening
CC	Cervical cancer
CIN	Cervical intraepithelial neoplasia
CHOiCE	Cervical HOme-based CancEr screening
CRIS	Cancer Risk Intake System
FDR	First-degree relatives
HC	Hybrid capture
HR	Hazard ratio
HPV	Human papillomavirus
ICER	Incremental cost-effectiveness ratio
IT	Information technology
LBC	Liquid-based cytology
LYG	Life-years gained
m	Month
NA	Not applicable
NR	Not reported
NTCC	New Technologies for Cervial Cancer Screening
OHR	Other high risk (HPV genotypes)
OR	Odds ratio
Pap-smear	Papanicolaou cytology
PD	Absolute difference in participation rate
PN	Patient navigation

POBASCAM	Population-based screening study Amsterdam
PPV	Positive predictive value
PROHTECT	PRotection by Offering Hpv Testing on Cervicovaginal specimens Trial
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Rate ratio
y	Year

Colorectal cancer

Trial	Trial Details	Participants	Outcomes/Results	Notes
ACCS **(Paskett et al., 2020)**	US 2013-2017 1) Website intervention plus PN (I) 2) Website intervention control (C)	N = 1043 I = 515 C = 528 S = NA Mean age 51.7 y (25-75 y) 49.6% Male 5 y follow-up **Population:** adult FDRs of CRC patients	**Uptake:** A total of 1225 and 1178 eligible FDRs randomised to control and intervention group, respectively, among which 528 (43%) and 515 (44%) were finally enrolled for analysis. **Compliance:** An overall of 78.6% participants were adherent to the CRC screening recommendation received from the website survey. The ratio was similar between PN and control group (OR 1.27; 95%CI 0.92-1.75; *P* = 0.14). Yet among those receiving recommendation for a colonoscopy, higher adherence was observed in the PN group compared to the control group (52.8% vs 29.8%), leading to an OR of 2.98 (95%CI 1.68-5.28; *P* = 0.0002). **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Barriers to screening:** Most participants in the PN group reported no barrier to following the screening adherence (77.7%). The most common barriers reported included: not a priority/too much bother/unwillingness (45.1%); other priorities or health issues (33.3%); not enough time (32.4%); no or controversial recommendation from doctor (24.5%) and not at risk or not necessary (23.5%).	Power calculation: Y This trial was designed to evaluate whether PN intervention would improve the adherence of FDRs of CRC patients to recommended CRC screening. The 1043 FDRs were enrolled across 513 families. The website survey for personal CRC screening recommendation was based on the National Comprehensive Cancer Network guidelines version 2.2012. PN was accessed via telephone to address any individual barriers to adhering to the personal CRC screening recommendation.

ACTRN12609000628246 **(Carey et al., 2016; Reeves et al., 2019)**	Australia 2009-2011 1) Risk-level tailored advice (I) 2) General information control (C)	N = 574 I = 322 C = 252 S = NA Mean age 51 y (> 18 y) 43.3% Male 12 m follow-up **Population:** adult FDRs of CRC patients	**Uptake:** Among eligible index cases and FDRs, 752 (25%) and 574 (34%), respectively, consented to participate the trial and completed the baseline interviews. **Compliance:** The adherence rate to CRC screening guidelines was 61% in the intervention arm compared to 58% in the control arm (mixed effects logistic regression group by time interaction effect = 2.7; 95%CI 1.2-5.9; *P* = 0.013). Another study with extended follow-up revealed the adherence rate of 59% and 52% in the intervention and control arm, respectively, resulting an incremental of 6.6%. **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Cost-effectiveness:** The QALYs was comparable between two groups (0.82 for intervention; 0.83 for control). From the health care perspective, the ICER was 258 AUD per person appropriately screened while the ICER amounted 275 AUD from the societal perspective. That was about 13% more of cost per person screened for every 15 people receiving screening message.	Power calculation: Y This trial was designed to evaluate whether the intervention with advice tailored to risk-level would improve the adherence of FDRs of CRC patients to colorectal cancer screening. Screening adherence was assessed at baseline and at 12 months through self-report. The cost-effectiveness was estimated based on the Standard Australian unit cost for 2016/2017.
Blood test of methylated SEPT9 DNA and CRC testing uptake **(Liang et al., 2021)**	NR NR 1) Informed of over-due screening with an additional option of a blood test provided	N = 359 I = 181 C = 178 S = NA Mean age NR (50- 75 y) % Male NR	**Uptake:** The uptake rate of CRC screening was 18.2% in the intervention arm (33 of 181; 5 colonoscopy; 17 FIT; 11 blood test) compared to 10.7% in the control arm (19 of 178; 2 colonoscopy; 17 FIT) (*P* = 0.04). **Compliance:** Taking COVID into consideration for the screening completion rate, 19.9% of intervention participants completed screening compared to 9.6% in the control group (*P* = 0.01). **Outcomes:**	Power calculation: NR This trial was designed to evaluate whether an additional option of blood test, where positive results obtained,would

	colonoscopy or FIT was not preferred (I) 2) Informed of over-due screening with colonoscopy or FIT (C)	6 m follow-up **Population:** screen-eligible Veterans who refused colonoscopy or FIT with the previous 6 m	- **CRC/advanced neoplasm incidence:** NR - **Detection rate:** FIT positivity was 8.8% while blood-test positivity was 18.2%. - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	improve the uptake of CRC screening.
COLONPREV **(Salas et al., 2014; Urturi et al., 2012)**	Spain 2009-2011 1) One-time colonoscopy (I_1) 2) Biennial FIT (I_2)	N = 37,311 I_1 = 19,868 I_2 = 17,443 C = NA S = 14,100 Mean age NR (50-69 y) 47.9% Male 10 y follow-up **Population:** general	**Uptake:**Uptake was higher in participants of the FIT arm (34.25%) than the colonoscopy arm (25.38%; *P* < 0.001). In terms of sex, women were more prone to screening uptake than men regardless of the screening type (25.89% vs 24.81% in colonoscopy, *P* = 0.045; 35.31% vs 33.06% in FIT, *P* < 0.001). In terms of age, participants aged 50-59 years were more likely to take up screening than those aged 60-69 years, which was 25.86% vs 24.76% in colonoscopy, *P* = 0.042 and 34.89% vs 33.43% in FIT, *P* = 0.013). The multivariate analysis with two models reported a lower participation rate when invited to colonoscopy than FIT with OR ranging 0.43-0.64. **Compliance:** Not applicable **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** The CRC detection rate was 0.52% with colonoscopy and 0.36% with FIT (*P* = 0.002). The detection rate of advanced adenoma was 9.90% with colonoscopy compared to 2.41% with FIT (*P* < 0.001). Overall, the OR of detecting any neoplasm was 12.06 (95%CI 10.73-13.55) using colonoscopy than FIT. Yet it was less likely to detect any lesion in women aged 50-59 years than men aged 60-69 years (OR 0.33; 95%CI 0.29-0.39). - **Stage:** NR	Power calculation: NR This trial compared two strategies of CRC screening. The crossover between two strategies was allowed. The crossover was mainly from the colonoscopy arm to FIT arm (24.17% vs 1.2%).

			- **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** The accuracy of FIT was evaluated using different positivity cutoff levels (75, 100, or 125 ng/ml). Whilst the detection rates were similar among 3 different cutoffs in general, the sensitivity of detection in men > 60 years decreased 8.1% in cutoff levels of 100 and 125 ng/ml compared to 75 ng/ml. The sensitivity of detecting advanced adenoma and advanced neoplasms also dropped 7-11% in men of all age with an incremental in the positive cutoff levels.	
CRIS **(Skinner et al., 2015)**	US NR 1) CRIS + tailored printouts (I_1) 2) CRIS + standard information (I_2) 3) No contact control (C)	N = 1012 I_1 = 329 I_2 = 322 C = 361 S = NA Mean age 59.0 y (25-75 y) 37.1% Male 12 m follow-up post-randomisation **Population:** general; potentially eligible for CRC screening due to family history or personal history of inflammatory bowel disease or adenomatous polyp	**Uptake:** The uptake rate of CRC testing was higher in the CRIS-implemented groups compared to no-contact control (47% vs 16%; *P* < 0.0001). Between the CRIS-implemented groups, higher participation of CRC testing was observed in patients aged > 50 years old with tailored printouts than those receiving standard information (53% vs 44%; *P* < 0.023). **Compliance:** Not applicable **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: NR This trial was designed to evaluate the impact of CRIS for patient risk-stratification and tailored communication of information on the participation of any type of colorectal cancer screening.

GERA and CRC screening adherence **(Myers et al., 2011; Myers et al., 2015; Weinberg et al., 2014)**	US NR 1) Usual care (UC; C) 2) Intervention with GERA feedback (GERA; I)	N = 562 I = 369 C = 193 S = NA Mean age NR (50-79 y) 42% Male 6 m follow-up **Population:** general population eligible for CRC screening yet not taken	**Uptake:** The uptake of FIT was comparable between UC (35.7%) and GERA (33.1%) group. **Compliance:** The adjusted OR for screening completion was 0.88 (95%CI 0.64-1.22). No statistically significant was found between GERA participants with various risk levels (OR 0.75 for elevated-risk vs average-risk; 95%CI 0.39-1.42). Multivariate analyses revealed an interaction between race and GERA feedback status in terms of screening adherence (*P* = 0.043), specifically among those at elevated risk where adherence was higher in whites (66.7%) compared to non-whites (33.3%). **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: Y This trial was designed to evaluate the impact of GERA feedback on the uptake and adherence of CRC screening (FIT). The GERA was based on a blood test for polymorphic variants of methylene tetrahydrofolate reductase (MTHFR) and serum folate level.
NCT02553538 **(Percac-Lima et al., 2016)**	US 2014 1) PN intervention (I) 2) Usual care (UC; C)	N = 1612 I = 792 C = 820 S = NA Mean age 57 y (50-75 y) 39.5% Male 8 m follow-up **Population:** general population due or overdue for CRC screening	**Uptake:** The trial examined differential uptake amongst all patients overdue for at least one cancer screening The mean CRC screening completion rate was 7.6% in the PN arm compared to 4.6% in the UC arm (*P* = 0.01) in the intention-to-treat analysis. In as-treated analysis, the completion rate was 9.9% in the PN arm compared to 4.9% in the UC arm (*P* < 0.001). Among participants overdue for CRC screening during follow up, the completion rate was found higher in the PN group than UC group in both intent-to-treat analysis ((13.7% vs 7.0%; 95%CI 3.2-10.4%; *P* < 0.001)) and as-treated analysis (18.1% vs 7.6%; 95%CI 6.3-14.9%; *P* < 0.001). **Compliance:** Not applicable **Outcomes:** - **CRC/advanced neoplasm incidence:** NR	Power calculation: Y Participants randomized to the PN intervention group were referred to navigators via IT system to track, contact and provide help for screening completion. The type of CRC screening was not specified.

			- **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
NCT03819920 **(Yen et al., 2021)**	US 2015-2018 1) Tailored risk assessment using CCRAT (I) 2) Control with standard education (C)	N = 230 I = 114 C = 116 S = NA Mean age 59.1 y (50-75 y) 41.3% Male 360 days follow-up **Population:** general population due for CRC screening	**Uptake:** The behavioural change was assessed using the transtheoretical model. In terms of screening intent, the respective proportion of participants in the pre-contemplative, contemplative and preparation stages were 36.9%, 56.9% and 6.2% in the CCRAT arm compared to 54.0%, 33.3% and 12.7% in the control arm at 12 months (*P* = 0.021). **Compliance:** In terms of screening completion, the completion rate was 38.6% in the CCRAT arm compared to 44.0% in the control arm (OR 0.80; 95%CI 0.47-1.37; *P* = 0.41). The proportion of test chosen was comparable between two arms: half-half between FIT and colonoscopy in the CCRAT groups while 52.9% and 47.1% of control participants chose FIT and colonoscopy, respectively. **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: Y This trial was designed to evaluate the impact of CCRAT on CRC screening uptake and completion.
Nurse-led tailored intervention and colonoscopy uptake **(Ingrand et al., 2016; Ingrand et al., 2019)**	France 2010-2013 1) Tailored leaflets and telephone interview (I)	N = 304 I = 160 C = 144 S = NA Mean age 53.5 y (17-75 y)	**Uptake:** The uptake rate of colonoscopy was 56.3% in the intervention arm compared to 35.4% in the control arm (*P* = 0.0027). **Compliance:** After adjustment for those refusing to participate, the rates were 69.2% and 37.0%, respectively (*P* < 0.0001). **Outcomes:** - **CRC/advanced neoplasm incidence:** Among those accepted colonoscopy, one was diagnosed with invasive carcinoma	Power calculation: Y This trial was designed to evaluate the impact of nurse-led tailored information on the colonoscopy uptake of FDRs of CRC/CAR patients.

	2) Control with standard information (C)	52% Male 1 y follow-up post diagnosis of the index patients **Population:** adult FDRs of CRC or CAR patients	(0.6%) in the intervention group while none in the control group. Higher proportion of advanced adenoma was found in the intervention group than control group (6.9% vs 3.5%; *P* = 0.022). - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
TARGET-C **(Chen et al., 2019; H. Chen et al., 2020; H. D. Chen et al., 2020)**	China 2018-2019 1) One-time colonoscopy (I_1) 2) Annual FIT for consecutive 4 years (I_2) 3) Annual risk-adapted screening strategy for consecutive 4 years (I_3)	N = 19,582 I_1 = 3937 I_2 = 7858 I_3 = 7787 C = NA S = 19,546 Mean age 60.5 y (50-74 y) 41.7% Male 10 y follow-up **Population:** general	**Uptake:** The uptake rates were 42.5% for colonoscopy screening, 94.0% for FIT and 85.2% for risk-adapted screening. Among those assessed to be high-risk of CRC in the risk-adapted group (18.9%, 1472 of 7776), 49.2% accepted colonoscopy screening (*P* < 0.05 compared to 42.5% of colonoscopy group). The uptake was lower in men then in women (48.5% vs 61.0%; OR 0.57; *P* = 0.023). No difference was observed between FIT group and low-risk subjects in the risk-adapted group in terms of FIT uptake (both 94.0%). **Compliance:** The overall positivity rate of FIT was 14.3%, among which over 85% accepted further diagnostic colonoscopy. **Outcomes:** - **CRC/advanced neoplasm incidence:** The incidence of CRC was 0.23%, 0.09% and 0.17% in colonoscopy, FIT and risk-adapted screening groups, respectively. The diagnostic yield of advanced neoplasms was 2.40% in colonoscopy, 1.13% in FIT and 1.66% in the risk-adapted screening arm, resulting in ORs of 2.16 (Colonoscopy vs FIT; 95%CI 1.61-2.90; *P* < 0.0001), 1.45 (Colonoscopy vs risk-adapted screening; 95%CI 1.10-1.90; *P* = 0.001), and 1.49 (risk-adapted screening vs FIT; 95%CI 1.13-1.97; *P* = 0.004). - **Detection rate:** The detection rate of CRC was better in colonoscopy than FIT (0.54% vs 0.10%; OR 5.11; 95%CI 1.88-	Power calculation: Y The risk-adapted screening strategy used the Asian-Pacific Colorectal Screening Score where high-risk participants were referred for colonoscopy whilst low-risk participants were referred for FIT. Those with positive FIT results were further referred for diagnostic colonoscopy.

			14.44; *P* = 0.001). The detection rate of advanced neoplasms was 5.68% in colonoscopy, 1.25% in FIT and 2.00% in the risk-adapted screening arm, resulting in ORs of 4.19 (Colonoscopy vs FIT; 95%CI 3.10-5.66; *P* < 0.0001), 2.38 (Colonoscopy vs risk-adapted screening; 95%CI 1.79-3.14; *P* < 0.0001), and 1.83 (risk-adapted screening vs FIT; 95%CI 1.39-2.42; *P* < 0.0001). - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** Fewer colonoscopies were required to detect one advanced colorectal neoplasm in the FIT (10) and risk-adapted screening (11) compared to the colonoscopy arm (18). - **Resource load:** For detecting one advanced colorectal neoplasm, 18 subjects need to be screened in the colonoscopy arm; 81 in the FIT arm; 50 in the risk-adapted screening arm.	
Targeted or tailored intervention on the CRC screening **(Lairson et al., 2008)**	US NR 1) Usual care control (C)	N = 1546 I_1 = 387 I_2 = 386 I_3 = 386 C = 387 S = NR	**Uptake:** **Compliance:** Around 33% participants were screened in the usual care group compared with 46% in the standard intervention group, 44% in the tailored intervention group and 48% in the tailored plus telephone call group. **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	*Power calculation: Y* *This trial was designed to evaluate the cost-effectiveness of various interventions for promoting CRC screening.* *Costs were shown in $USD.*

			Cost-effectiveness: The cost of SI was $42 per individual while $150 for TI. An additional $50 per individual was incurred in the TIP group, making the total cost of $200. The ICER was amounted $319 in SI compared to usual care, which was more effective and dominated TI. The ICER was amounted $5843 in TIP when compared to SI.	
TeleCARE **(Kinney et al., 2014)**	US 2009-2011 1) TeleCARE (I) 2) Low-intensity control (C)	N = 481 I = 232 C = 249 S = NA Mean age 50.3 y (30-74 y) 42.6% Male 9 m follow-up post randomisation **Population:** eligible for CRC screening due to family history	**Uptake:** In total 79.8% participants completed the risk assessments. The uptake rate of colonoscopy was 35.4% in the TeleCARE group while 15.7% in the control group. The intent-to-treat analysis revealed that TeleCARE participants were more likely to accept screening than the control group (OR 2.83; 95%CI 1.87-4.28; *P* < 0.001). **Compliance:** **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR - **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Power calculation: Y This trial was designed to evaluate whether intensive, personalised remote intervention (TeleCARE) would influence the uptake of medically verified colonoscopy.
Telephone counseling and colonoscopy adherence **(Lowery et al., 2014)**	US 2005-2006 1) Tailored telephone counseling intervention (I) 2) Mailed intervention control (C)	N = 632 I = 322 C = 310 S = NA Mean age NR (25-80 y) 41.3% Male 24 m follow-up **Population:** Adult FDRs of CRC patients due for colonoscopy within 24 m	**Uptake:** In total 328 participants had a colonoscopy during follow-up. The uptake rate of colonoscopy dropped slightly from 52.1% to 49.8% in the mailed group after 24 months. The uptake rate of colonoscopy increased from 43.2% to 54% after 24 months in the group receiving tailored telephone intervention. **Compliance:** The intent-to-treat analysis revealed that telephone intervention was associated with 24% (unadjusted bivariate analysis; HR 1.24; *P* = 0.04) to 32% (adjusted multivariate analysis; HR 1.32; *P* = 0.01) increase of colonoscopy adherence. **Outcomes:** - **CRC/advanced neoplasm incidence:** NR - **Detection rate:** NR	Power calculation: Y This trial was designed to evaluate whether tailored telephone intervention would improve the adherence of high-risk patients to colonoscopy (24 m vs baseline).

			- **Stage:** NR - **CRC and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	

Abbreviations and Acronyms	
	N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened *Uptake:* Percentage of invited population agreeing to participate in the trial *Compliance:* Percentage of trial population completing the baseline screening
ACCS	The Adherence to Colorectal Cancer Screening study
ACRTN	Australian and New Zealand Clinical Trials Registry
CAR	Colorectal adenomatous polyps
CARES	Colorectal Cancer Awareness, Research, Education and Screening
CCRAT	National Cancer Institute's CRC Risk Assessment Tool
CRC	Colorectal cancer
CRIS	Cancer Risk Intake System
FDR	First-degree relatives
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
GERA	Genetic and environmental risk assessment
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IT	Information technology
m	Month
NA	Not applicable
NR	Not reported
OR	Odds ratio
PN	Patient navigation
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Rate ratio

SI	Standard intervention
TeleCARE	Tele-Cancer Risk Assessment and Evaluation
TI	Tailored intervention
TIP	Tailored intervention plus telephone
y	Year

2.2 Bottom line results

Based on data from the 67 papers included in the rapid review (including many randomised controlled trials) some key findings relating to the evidence on efficacy, harm-benefit and cost-effectiveness may be summarised as follows.

Breast cancer:

Modelling data suggest that risk-adapted strategies can improve benefit-harm ratio with reasonable cost-effectiveness in the European setting (Canelo et al. 2018; Khan et al. 2021; Mühlberger et al. 2021).

Consistent evidence across risk stratification and screen methods showed uptake was typically between 50 and 70%. Compliance/uptake of ultrasound and/or MRI suggests that they are feasible supplementary screening modalities (Bakker et al. 2019; Berg et al. 2012; Constock et al. 2020; Huang et al. 2010; Veenhuizen et al. 2021).

Long-term follow up supports annual mammographic screening in terms of mortality reduction (Bjurstam et al. 2016; Duffy et al. 2020; Miller et al. 2014) with one (controversial) trial noting a slight increase in risk of breast cancer-specific death for women 40–49 years (Narod et al. 2014). Overdiagnosis across screening and risk methods may not be a significant problem for younger European women (Duffy et al. 2020; Gunsoy et al. 2012; Hofvind et al. 2021; Johns et al. 2010; Veenhuizen et al. 2021), particularly women in their mid to late 40s.

Trial data are limited to cancer detection for other screening methods: Annual standard digital mammography ± ultrasound (Huang et al. 2010; Taiwan) ± digital breast tomosynthesis (Pattacini et al 2018) ± MRI (Acerbi et al. 2021, Bakker et al. 2019) is likely to be feasible, acceptable and effective in high risk 40–49 year-old European women; the age group most studied within randomised controlled trials. The European MyPeBS trial should provide further evidence of the role of MRI and ultrasound in the risk-stratified detection of advanced disease of a whole screening population.

The supplemental value for MRI over mammographic screening alone is between 7 and 16.5 per 1000 women in women with dense breasts (Bakker et al. 2019, Berg et al. 2014, Comstock et al. 2020). MRI was associated with 'significantly fewer interval cancers' than mammography alone (Bakker et al. 2019). Modelling studies (Canelo et al. 2018; Khan et al. 2021; Mühlberger et al. 2021) and evidence from the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial suggest that risk-based strategies are likely to be reasonably cost-effective for high-risk groups. MRI at a four-year interval was most cost effective (€15,620 per QALY) for women with extremely dense breasts (Geuzinge et al. 2021).

Cervical cancer:

Screening with HPV self-sampling increases the screening uptake, especially for under-screened women. Consistent with other RCTs reviewed (Gök et al., 2012; Sancho-Garnier et al., 2013; Tranberg et al., 2018), a meta-analysis pooling data across 33 studies (29 RCTs and 4 observational studies) reported that HPV self-sampling promoted the screening uptake substantially (RR 2.13; 95% CI 1.89-2.40) compared to the standard care control (Yeh et al. 2019).

In terms of HPV testing as a risk-stratification approach, the long-term follow-up data from Swedescreen trial showed a similar number of CIN2+ cases between HPV testing and conventional cytology screening, which may reflect an early detection function of HPV testing (Elfstrom 2014). A meta-analysis pooling data across 4 RCTs (176,464 women in total) also suggested that HPV-based screening may provide better protection against cervical cancer compared to conventional cytology testing (Ronco et al. 2014).

Screening intervals may be extended for women with negative HPV results and older age (Dijkstra et al., 2016; Gilham et al., 2019).

HPV self-sampling is cost-effective compared to the standard cytology testing (Malone et al., 2020; Sroczynski et al., 2018).

Colorectal cancer:

The majority of the population prefers FIT to colonoscopy in terms of CRC screening uptake, in spite of the higher risk of undiagnosed CRC. The largest RCT in Europe showed that the general population with average risk were more prone to accept biennial FIT than one-time colonoscopy in terms of CRC screening (34.25% vs 25.38%; $P < 0.001$) (Salas et al., 2014; Urturi et al., 2012).

The uptake and compliance across screening methods in general was between 50-60%, which can be improved by several pro-active interventions (Carey et al., 2016; Ingrand et al., 2016; Ingrand et al., 2019;; Kinney et al., 2014; Lairson et al., 2008; Liang et al., 2021; Lowery et al., 2014; Paskett et al., 2020; Percac-Lima et al., 2016; Reeves et al., 2019; Skinner et al., 2015; Yen et al., 2021). Risk-stratification using the Genetic and Environmental Risk Assessment (GERA) did not improve the uptake of CRC screening; however, the GERA feedback might improve screening adherence (Myers et al., 2011; Myers et al., 2015; Weinberg et al., 2014).

In general, the CRC detection rate was higher by means of colonoscopy compared to other screening types (Chen et al., 2019; H. Chen et al., 2020; H. D. Chen et al., 2020; Liang et al., 2021; Salas et al., 2014; Urturi et al., 2012). The largest RCT in Europe showed that the detection rate of any neoplasms using colonoscopy was much higher compared to FIT (OR 12.06; 95%CI 10.73-13.55) (Salas et al., 2014; Urturi et al., 2012). However, a meta-analysis pooling 46 trials and other studies revealed that the specificity of FIT for CRC detection could increase from 69% to 80% when lowering the positivity threshold from >10-20 μg/gto ≤ 10 μg/gat the expense of slightly decreased specificity (-3%) (Selby et al., 2019), implying the potential of this more inclusive screening approach.

Two trials undertook a cost-effectiveness analysis but both were outside Europe, and exploring different methods for promoting screening uptake rather than the cost of screening itself (Lairson et al., 2008; Reeves et al., 2019).

3. Discussion

3.1 Summary

This rapid review provides evidence for the efficacy of a number of screening regimens, based on the findings of controlled trials.

Although not within the remit of this review, since the topic relates to vaccination rather than screening, it is noted that HPV vaccination as a strategy is being adopted in almost all EU states (see workshop report, available on SAPEA website).

A key issue in relation to the overall reach and impact of screening programmes in the general population is the overall measure of those willing to participate based on the screening offer. Within this rapid review, data giving the reported uptake (the % of the invited population agreeing to participate in the trial) and compliance rates (the % of the trial population screened and/or adherence to multiple screening rounds) are provided within the Evidence Tables (Section 2.1). Information on compliance only may over-estimate the true proportion likely to take up the screening offer in a real-life situation.

3.2 Strengths and limitations of this Rapid Review

3.2.1 Strengths

This review summarises a valuable sub-set of the evidence base. This review emphasises the findings from recent randomised and other controlled clinical trials, providing the evidence with the least potential for bias. Despite the very short time period available for the review, a very large number of trial reports, and modelling studies based on trials, have been included in the summary.

3.2.2 Limitations

In order to complete the review in a timely fashion a pragmatic and precise search strategy was employed. It is possible that further studies would have been identified should there have been time for a detailed and sensitive systematic search. It is acknowledged that other types of non-trial evidence are relevant to the topic, notably 'real life' screening populations and modelling studies derived from screening cohorts.

The timeline also precluded any statistical or meta-analysis of findings unless these were available from published systematic reviews. No formal critical appraisal was carried out although information is provided on whether the trial included a power calculation. Data extraction and summary were undertaken by different reviewers and, although reviewed by another author, these have not been independently checked for accuracy and consistency.

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7. Rapid review method

7.1 Eligibility criteria

- Randomised controlled trial (RCT), controlled clinical trial[3], or modelling study based on trial data
- All interventions including: targeting specific populations (by risk factors including age, gender, ethnicity/race and other socio-demographic differences); interval & interval by age comparisons; screening method comparisons
- Published during or after 2007
- Screening for first diagnosis of breast, cervical or colorectal cancer
- Inclusion of data on efficacy, harm-benefit or cost-effectiveness relating to targeting screening uptake and screening methods
- All locations, all languages but to emphasise the findings from EU studies within the narrative write up

7.2 Literature search strategy

Searches were carried out for publications from 2016 onwards using title and Medical Subject Heading (MeSH) searches of the Cochrane Central Register of Controlled Trials (CCTR). This includes trial data from Medline, Embase and the International Clinical Trials Registry Platform (ICTRP). Supplementary searching of Medline, Embase and the ICTRP was carried out for publications in 2021 that may not yet have been included in the CCTR.

To ensure coverage of trial reports back to 2007, Cochrane Reviews, Health Technology Assessment and the US Preventive Services Taskforce (USPSTF) was searched for systematic reviews on the topics. These were then examined for relevant trial reports.

Text word terms: [breast OR cervi* OR colorectal OR colon OR bowel] *in Record Title* AND [cancer* OR neoplasm*] *in Record Title* AND [screen* OR "early detection"] *in Record Title*
OR
MeSH terms: (exp[4] breast neoplasms OR uterine cervical neoplasms OR exp colorectal neoplasms) AND (early detection of cancer)
AND
(stratif* OR target* OR pre-select* OR risk assess* OR risk based OR risk adapted OR genetic* OR age OR gender OR socio* OR demographic* OR race OR ethnic* OR interval OR subsequent round OR inform* OR personali*) in *Record Title*

In Medline using above terms [AND randomized controlled trial.pt OR controlled clinical trial.pt OR pragmatic clinical trial.pt OR systematic review.m+titl]; In Embase using above terms [AND exp controlled clinical trial/ OR systematic review.m+titl].

[3] Quasi-randomised and other controlled trials where randomisation is not explicit, but cannot be ruled out
[4] The exp (explode) function directs the selection of all papers tagged with this heading and any more specific sub-headings.

Additional search methods: Relevant systematic reviews published since 2016 were examined for additional trials. Some studies identified in early scoping searches for the topic and as suggested by the scientific writers were added that met the review inclusion criteria. The screened results were provided to the co-chairs of the Expert Workshop who were asked to liaise with workshop attendees and the workshop report was scrutinised to note any additional studies meeting the inclusion criteria.

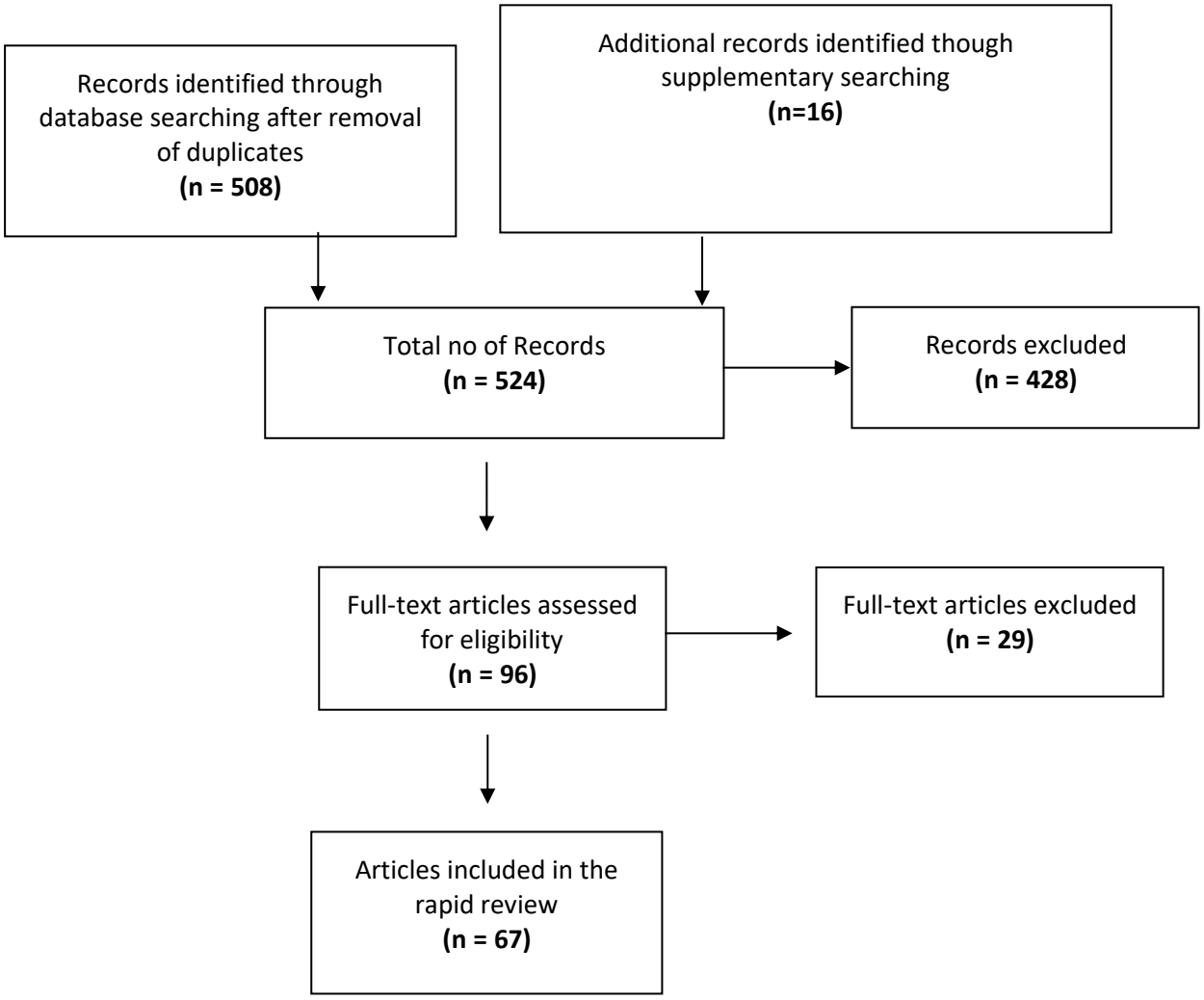
7.3 Resources list

Clinical trials.gov
Cochrane Library [Cochrane Reviews/Cochrane Central Register of Controlled trials]
Health Technology Assessment
Embase
International Clinical Trials Registry Platform (ICTRP)
Medline
US Preventive Services Taskforce (USPSTF)

7.4 Study selection process

Results from the literature searches were imported into EndNote 20, where duplicates were removed. Titles and abstracts were screened for inclusion followed by full text screening. Both screening stages were undertaken by a team of reviewers according to the eligibility criteria in Section 5.1. Identified systematic reviews were examined for trials dating back to 2007.

7.5 Study selection flow chart



7.6 Data extraction

Data from main trial report(s) on efficacy, harm-benefit or cost effectiveness were extracted into a summary table for each cancer by a single reviewer (Section 2.1).

7.7 Quality appraisal

Each included study was identified as RCT or controlled clinical trial (CCT) according to the study design as provided in the database(s) within the evidence table (Section 2.1) along with a note as to whether a power calculation was included as part of the trial. No other formal critical appraisal was carried out.

7.8 Synthesis

The findings are summarised in a narrative report, drawing from the summary tables with brief findings based on the consensus from the included studies.

8. Additional information

8.1 Conflicts of interest

None

8.2 Acknowledgements

This template is based, with permission, on the rapid review template used within the Palliative Care Evidence Review Service (PaCERS) and the Welsh Covid 19 Evidence Centre.

9. About the review team

The Specialist Unit for Review Evidence (SURE) is a team of experienced systematic reviewers and information specialists at Cardiff University who conduct all forms of systematic and other evidence reviews, and teach evidence review methods. The team work across all topic areas and also specialise in health and social care. Staff have carried out a number of reviews for SAPEA, working closely with Academia Europaea and experienced reviewers within the University's Library Service. Reviews are carried out in close collaboration with subject specialists for each review topic. For these rapid reviews the subject specialists are Dr Hui-Ling Ou (Cambridge University) and Dr Nicholas Courtier (Cardiff University).

SAPEA is part of the European Commission's Scientific Advice Mechanism, which provides independent, interdisciplinary, and evidence-based scientific advice on policy issues to the European Commission.

SAPEA has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 737432.

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