Population-based screening for cancer: hope and hype

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Abstract | Several important lessons have been learnt from our experiences in screening for various cancers. Screening programmes for cervical and colorectal cancers have had the greatest success, probably because these cancers are relatively homogenous, slow-growing, and have identifiable precursors that can be detected and removed; however, identifying the true obligate precursors of invasive disease remains a challenge. With regard to screening for breast cancer and for prostate cancer, which focus on early detection of invasive cancer, preferential detection of slower-growing, localized cancers has occurred, which has led to concerns about overdiagnosis and overtreatment; programmes for early detection of invasive lung cancers are emerging, and have faced similar challenges. A crucial consideration in screening for breast, prostate, and lung cancers is their remarkable phenotypic heterogeneity, ranging from indolent to highly aggressive. Efforts have been made to address the limitations of cancer-screening programmes, providing an opportunity for cross-disciplinary learning and further advancement of the science. Current innovations are aimed at identifying the individuals who are most likely to benefit from screening, increasing the yield of consequential cancers on screening and biopsy, and using molecular tests to improve our understanding of disease biology and to tailor treatment. We discuss each of these concepts and outline a dynamic framework for continuous improvements in the field of cancer screening.

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The proximate goal of cancer screening is the identification of early stage cancer, or precancerous lesions, before a person develops symptoms and at a point in the disease trajectory when treatment is likely to result in cure. This concept is simple, but practicing effective screening on a population level is a complex endeavour. In 1968, Wilson and Jungner[1] of the WHO proposed criteria that should be met before a screening test should be implemented (BOX 1); these principles continue to guide policy in countries where implementation of organized screening programmes is being considered. For a number of common cancers, some of these criteria have been met; however, many continue to present challenges and remain incompletely addressed (BOX 1). Wilson and Jungner's suggestion that "the natural history of the condition, including development from latent to declared disease, should be adequately understood" (REF. 1) seems particularly prophetic. At the time of the WHO report, and for decades after, the prevailing model of carcinogenesis was that of a linear progression from precursor disease to early stage (localized) cancer and, subsequently, to advanced-stage (disseminated) cancer. Indeed, the models of colorectal cancer (CRC) tumorigenesis proposed by Vogelstein *et al.*[2] in the late1980s suggested a relatively slow, stereotyped evolution from colonic polyp to cancer, commensurate with the acquisition of certain mutations over time. A similar paradigm has become established for the natural history of cervical cancer, and health-care organizations in a number of countries, including the USA, introduced screening for breast and prostate cancers, presuming that these diseases also followed this classic developmental framework.

With mass implementation of screening for cancer, our experiences on the population level have deepened our understanding of cancer biology. Screening efforts have revealed a previously unappreciated reservoir of precancerous lesions and indolent cancers that would not have otherwise come to clinical attention. By contrast, other cancers have been recognized to grow so fast that screening assessments performed at predetermined intervals do not enable detection before their spread to local or distant organs. Indeed, we now understand that 'cancer' comprises a heterogeneous collection of diseases, both across and within organ sites. The advent of

Key points

- Tumours within any organ site can have a spectrum of biological phenotypes, ranging from indolent to highly aggressive
- Screening for cancer is most likely to be beneficial when the target tumour type has a relatively uniform biology and a slower rate of progression
- Not all precursor lesions are on an obligate pathway towards invasive-cancer development
- Strategies for early detection of cancer must balance the benefits of mortality reduction (and reduction in invasive-disease incidence with screening for precancers) with the heterogeneity of the target disease and the consequent risk of overdiagnosis
- Screening can be viewed as a 'cascade' involving multiple steps, such as selection of individuals to be screened, administration of the screening test, workup of positive findings, and, ultimately, treatment
- Efforts are underway to individualize decision-making surrounding risk stratification, the modality and frequency of screening, and diagnostic and therapeutic interventions tailored to the biology of the detected tumour

gene-expression profiling and other molecular diagnostic methodologies has advanced our understanding of cancer biology beyond the original model proposed by Vogelstein and colleagues. In fact, treatment decisions are increasingly being guided by gene-expression profiling, rather than by traditional factors, such as disease stage or histopathological features[3].

The challenge in screening for and prevention of disease relates to the concept that it is difficult to make healthy people better off than they already are, but not as difficult to make them worse off. Screening, by virtue of increasing the likelihood of performing a biopsy, will potentially uncover a reservoir of biologically more-indolent cancers, some of which might lack the potential to progress to metastatic disease (the ultimate cause of most cancer-related deaths). Detection of indolent lesions is not intrinsically harmful, but can lead to downstream diagnostic and therapeutic interventions that cause serious adverse effects to patients. Nevertheless, screening can be of benefit when diagnosis and treatment of a precancerous lesion or an early stage tumour will avert progression of disease to metastasis and/or death. This hope continues to form the basis for population screening for cancer, but also fuels the hype that surrounds cancer screening.

Going forward, lessons learned from the careful distillation of several decades of experience in cancer screening can guide practice and drive improvements in cancer screening. Four key lessons and their corollaries form the foundations for this Review of screening for breast, prostate, cervical, colorectal, and lung cancers (BOX 2). These concepts serve to refine — rather than replace — the Wilson and Jungner criteria, by highlighting the corresponding action points that must be considered to continue improving the delivery of screening assessments. We present a framework for improving cancer screening, based on a stepwise examination of the decisions that must be made before, during, and after deployment of a screening test. Owing to the scope of this topic, emerging technological advancements in screening tests are discussed where relevant, but are not otherwise comprehensively covered.

Screening: a population-based view

Cancer screening can contribute to decreasing cancer morbidity and mortality through two mechanisms: the detection of a precursor lesion, or the early detection of invasive cancer. The benefits of screening are greater when the detection of disease at an earlier (or precancerous) stage improves outcomes; therefore, the available treatment should be safe, acceptable, and more effective when implemented earlier in the disease course.

The identification of true precursor lesions through population screening should result in a decrease in the incidence rates of invasive cancer over time. Colonoscopy and colposcopy (following cervical cytology) enable direct visualization of the target organs (rectum and colon, and cervix, respectively), and concurrent or subsequent removal of at-risk tissue. The use of these approaches depletes the reservoir of precancerous lesions, namely colonic polyps and cervical intraepithelial neoplasia (CIN), which has led to a decrease in the overall incidence of the respective invasive cancers[4] (FIG. 1). The success of population-based screening programmes using cervical cytology in reducing the incidence and mortality rates of invasive cervical cancer fuelled enthusiasm surrounding screening for other (pre)cancers. The detection and removal of all suspected precursor lesions, however, does not lead to the same result in all screening programmes. As is discussed herein, widespread use of mammography screening has increased the frequency of intervention to remove *in situ* breast lesions, but has not resulted in a decline in the incidence of invasive breast cancer[5,6]. The underlying biology and heterogeneity of cancers largely determine the tradeoff between the benefits and the harms of screening.

Differences in disease biology between cancers of the same organ site are of particular importance for tests aimed at the early detection of invasive cancer. Such tests rely on either radiographic imaging of a target organ (for example, mammography for breast cancer and low-dose computed tomography (LDCT) for lung cancer), or measurement of a circulating biomarker associated with presence of the disease (for instance, PSA testing for prostate cancer). These tests are beneficial when they detect invasive cancer at an early, localized stage. The desired effect is a 'stage shift', whereby the proportion of patients diagnosed with early stage disease increases over time, accompanied by a decline in incidence of advanced-stage disease — reflecting averted progression of cancers via early detection and treatment. Importantly, the absolute decrease in the incidence rate of advanced-stage disease should be considered, rather than the change in the relative proportions of these cancers versus early-stage disease, as the latter comparison can be falsely reassuring if an excess of early stage cancers that would not otherwise progress to advanced stages is detected through screening[7]. Additionally, one must consider whether the stage shift is associated with an improvement in disease-related mortality, or because this measure is also affected by the efficacy of treatment, the incidence of metastatic cancers[8].

Box 1 | **Cancer screening in 2016: meeting the Wilson and Jungner[1] criteria?**

1. The condition sought should be an important health problem
   - Criterion met
2. There should be an accepted treatment for patients with recognized disease
   - Criterion met
3. Facilities for diagnosis and treatment should be available
   - Criterion met
4. There should be a recognizable latent or early symptomatic stage
   - Criterion not fully met. Owing to the spectrum of disease heterogeneity, more often true for some cancer types (cervical and colorectal), but less often true for other types (breast, prostate, and lung)
5. There should be a suitable test or examination
   - Criterion met
6. The test should be acceptable to the population
   - Criterion met
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
   - Criterion not fully met. Focus for improvement: cervical intraepithelial neoplasia, ductal carcinoma *in situ*, colonic polyps, lung nodules, and indolent invasive cancers (for example, Gleason 6 prostate cancers)
8. There should be an agreed policy on whom to treat as patients
   - Criterion not fully met. Focus for improvement: management of disease entities listed in above
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
   - Criterion not fully met. Focus for improvement: refining targets of screening and biopsy to improve yield and focus on precursor or early stage forms of potentially morbid disease
10. Case-finding should be a continuing process and not a "once and for all" project
    - Criterion not fully met. Focus for improvement: screening registries should be established to facilitate quality improvement

The focusing of screening programmes on the early detection of invasive cancer arose from an incomplete understanding of the heterogeneity in cancer biology. Cancers can have a spectrum of clinical behaviours, ranging from indolent to aggressive. At one end of this spectrum lies a subset of cancers so aggressive that screening will not, ultimately, be of benefit. This subset comprises cancers that are prone to early systemic spread and, therefore, have a poor prognosis[8]. Despite routine screening, patients with these cancers will already have distant metastatic disease at the time of detection. The term 'interval cancer' is commonly applied to symptomatic tumours that arise in between screening intervals. These cancers tend to be more aggressive and are diagnosed at more-advanced stages than screen-detected lesions[9]. Representing more of a limitation of screening, rather than a harm, patients with interval cancers present with clinical symptoms, and at the same disease stages, regardless of screening. Moreover, in clinical studies, these clinically detected cancers are associated with a worse prognosis than those detected as a result of screening[10], thus challenging the paradigm that screening is effective at improving patient outcomes for all tumour phenotypes.

Screening predominantly detects lesions other than interval cancers, which necessarily include tumours with slow and moderate growth velocities. A difficult challenge, therefore, is to avoid preferential detection of indolent (slow-growing) cancers that might not otherwise come to clinical attention; detection of these cancers might increase the incidence of early stage cancers, but is unlikely to substantially reduce the incidence of advanced-stage cancers because they would probably never progress to such a stage during the patient's lifetime. Herein lies a potential harm of screening: in addition to the intrinsic risk of false-negative and false-positive results owing to the imperfect sensitivity and specificity of the screening tests, screening incurs 'overdiagnosis', defined as the detection of cancerous lesions that would not have caused morbidity or mortality. A closely related concept is 'overdetection' — the detection of premalignant lesions that are not destined to progress to malignancy. Patients with premalignant lesions and indolent cancers can be subjected to invasive tests and treatments, or toxic therapies; therefore, the theoretical risks of overdetection can be similar to those of overdiagnosis: 'overtreatment'. Overtreatment refers to therapy that is inappropriately invasive or extensive in relation to the biology of disease and can occur with a variety of diseases.

Overdiagnosis has been observed on the population level since the 1990s, when screening of children for neuroblastoma was associated with this effect[11]; however, a particularly illustrative example is that of thyroid-cancer screening in the Republic of Korea (South Korea). Widespread government-sponsored screening in South Korea led to a fivefold increase in the incidence of papillary thyroid cancers without a concomitant decrease in disease-specific mortality[12]. Organized population-screening for thyroid cancer does not exist in the USA, although the incidence rate of thyroid cancer is increasing most rapidly of all cancers, owing largely to opportunistic ultrasonography screening[13,14].

The uncovering of a large reservoir of indolent thyroid cancers illustrates the potential for overdiagnosis when screening is targeted at cancer types with a large reservoir of nonprogressive disease (BOX 2: Lesson 1). Similarly, not all precancerous lesions are obligate precursors of invasive disease (BOX 2: Lesson 2). As will be explained in the following sections, population-wide trends, such as those seen for thyroid cancer in the Republic of Korea, can provide valuable clues as to whether screening is having unintended consequences (BOX 2: Lesson 3). In these instances, screening exposes a large population of healthy people to unnecessary harms (BOX 2: Lesson 4). Specifically, overdiagnosis leads to subsequent diagnostic and therapeutic interventions that carry risks, but are ultimately of limited or no benefit (overtreatment).

Thus, screening is likely to be of limited benefit at either extreme of cancer aggressiveness. The challenge is to leverage the experience with screening on the population level gained to date, to continue advancing our understanding of cancer biology, in order to avoid overdiagnosis and overtreatment. In the following sections, we review the two major population-based screening strategies, detection of precursor lesions and early detection of invasive cancer, to further illustrate the lessons and corollaries outlined in BOX 2.

Box 2 | **Key lessons surrounding cancer screening and their corollaries**

Lesson 1: The biology of invasive cancers ranges from indolent to aggressive
Corollary: Screening will be of greatest benefit if targeted at detecting progressive, potentially morbid disease while avoiding identification, and/or reflexive treatment, of indolent disease

Lesson 2: Not all precancerous lesions are obligate precursors of invasive cancers; in fact, most are not
Corollary: Treatment of precancerous lesions is of greatest benefit when it prevents potentially morbid disease, or otherwise removes precursors of less-aggressive disease in an effective, nontoxic way

Lesson 3a: Effective screening and removal of early stage cancers should cause a concomitant decline in the incidence of advanced-stage cancers
Lesson 3b: Effective screening and removal of precursor lesions should cause a concomitant decline in the incidence of invasive cancers
Corollary: Population-level trends can be analysed to identify unintended consequences of screening, such as overdiagnosis, and drive efforts aimed at improving outcomes

Lesson 4: Not all individuals will benefit equally from screening
Corollary: Screening should be offered to a carefully defined target population after consideration of risk factors and overall prognosis

Detection of precursor lesions

Cervical-cancer screening was adopted based largely on the results of early observational studies that showed a decrease in incidence of the disease coincident with widespread screening[15,16]. Randomized clinical trials (RCTs) performed in India subsequently revealed a mortality benefit of cervical-cancer-screening programmes[17–19]. Moreover, high usage of cytology-based screening in US women has been accompanied by a decline in cervical-cancer incidence and mortality (FIG. 1). The causal link between screening and reduced cervical-cancer mortality is also supported by the observation that over half of the incident cervical cancer cases reported each year in the USA and other countries occur in the relatively small subpopulation of unscreened women[20,21]. Of note, cervical-cancer risk can be entirely eliminated among women who undergo total hysterectomy; the high prevalence of hysterectomy by the age of 65 years among women in the USA — up to 50% — has contributed heavily to the observed low rates of cervical cancer in this population[22].

The benefits of screening colonoscopy have largely been extrapolated from the results of RCTs of sigmoidoscopy, and from findings of observational studies that demonstrated a reduction in CRC incidence and mortality rates in participants who received colonoscopy[23–25]. The data from RCTs of sigmoidoscopy-based screening, although differing in the number and frequency of assessments, endoscopic equipment used, and trial design, indicate that this approach is associated with reductions in CRC incidence rate by 18–23% and in disease-specific mortality by 22–31%[26]. Of note, the reductions in the incidence rate and mortality were only statistically significant for distal cancers[25], leading to the hypothesis that regular screening with colonoscopy would enable detection of as many distal cancers and more proximal cancers than screening with sigmoidoscopy, given the ability of colonoscopy to enable visualization of the colon proximal to the splenic flexure. Indeed, findings of two early multicentre trials on one-time colonoscopy screening for asymptomatic individuals indicated that sigmoidoscopy alone might result in a substantial burden of high-risk lesions being missed, as approximately 50% of these advanced-stage neoplasms occurred in the proximal colon and were not associated with distal adenomas[27,28]. To date, no completed trial has directly compared the efficacy of sigmoidoscopy and colonoscopy, but pooled analyses of data from cohort studies on colonoscopy have revealed decreases in CRC incidence and mortality related to proximal and distal cancers[25]. These findings mirror the population decline in CRC incidence and mortality since the 1980s (FIG. 1); the sharpest decline in incidence rates occurs after 2000, when data from the above multicentre colonoscopy trials spurred increased uptake of colonoscopy screening. Colonoscopy every 10 years is considered by some experts to be the most-favourable screening strategy, given its sensitivity, ability to detect serrated polyps, and long-lasting protection against future CRC[29]; however, other CRC screening strategies have also been shown to be effective, including sigmoidoscopy every 5 years and/or yearly stool-based testing with faecal immunohistochemical or faecal occult blood tests[30]. Simulation models have estimated that the cumulative effect of the various CRC screening strategies is responsible for 50% of the observed decline in incidence and mortality rates of this disease in the USA[31].

Screening for cervical cancer and CRC capitalizes on the typically slow, stereotyped progression that lesions comprising atypical cervical cells and colonic polyps undergo during their transformation into malignant neoplasms. The discovery of human papillomavirus (HPV) as the aetiological driver of most cervical cancers prompted further change in the approach to screening for this disease to incorporate consideration of HPV-infection status and adjust future interventions accordingly[32]. Cervical cells infected by oncogenic strains of HPV can sometimes develop into CIN, which can progress to cervical cancer if left untreated[33]. Similarly, some colonic polyps progress to malignancy after acquiring genetic mutations, which differ based on the histological type of the polyp; for example, investigators have demonstrated that hyperplastic polyps and tubulovillous polyps have distinct mutagenesis pathways[34]. The lead-time for such transitions spans several years, allowing adequate time for detection and treatment of the polyp before it becomes malignant. The findings regarding the biology of these diseases, and the experience in screening for them demonstrated that screening is most likely to be beneficial when the targeted cancer has a relatively uniform biology and a slower rate of progression (BOX 2: Lesson 1, corollary).

Another important lesson learned is that not all precancerous lesions are obligate precursors to invasive cancers; in fact, most are not (BOX 2: Lesson 2). Even in the absence of screening and removal, many cases of CIN do not progress to cervical cancer — the immune system often clears HPV infections associated with CIN grade 1, and 40% of CIN grade 2 lesions spontaneously regress[32,35]. Similarly, most colonic polyps will not transform into invasive neoplasms, and a substantial

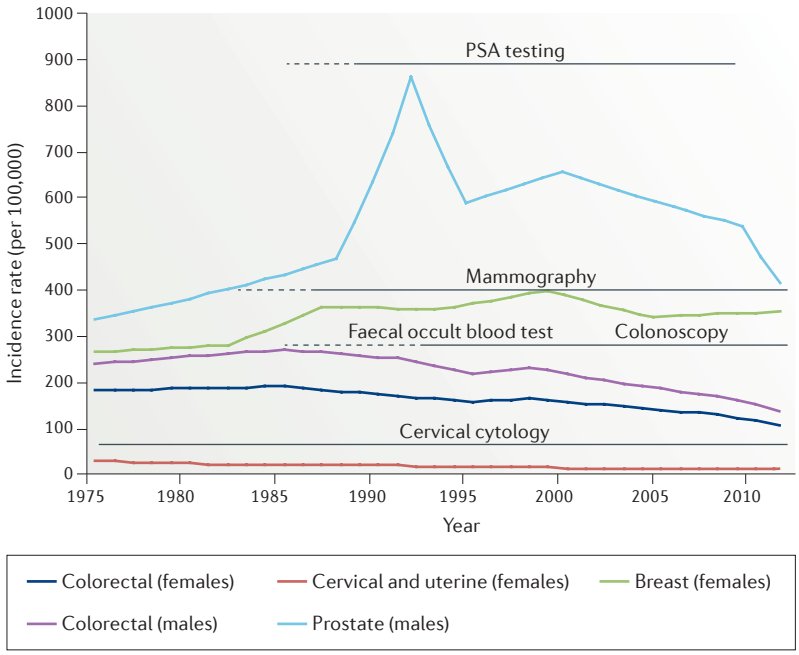

Figure 1 | **Age-adjusted incidence rates of invasive cancers for which population-based screening is practiced in the USA.** Annual incidence rates in men (for prostate and colorectal cancers) and women (for cervical and uterine, breast and colorectal cancers) over the age of 50 years are shown for a 37-year period (1975–2012), based on data from the Surveillance, Epidemiology, and End Results (SEER) registry[4]. Approximate eras of widespread use of the respective screening tests are represented by black lines, with dotted regions representing initial periods of increasing dissemination of the tests following their introduction. The incidence rates of cervical cancer in women and colorectal cancers in both men and women have declined since the early-to-mid 1980s, probably owing to the screening-based detection and subsequent removal of cervical intraepithelial neoplasia and colonic polyps, respectively. On the other hand, the incidence rates of prostate cancer and breast cancer have increased over the same timeframe, probably owing to increased detection of localized cancers as a result of the widespread use of prostate-specific antigen (PSA)-based and mammography screening, respectively.

proportion — perhaps 30% — of small (<6–9 mm) polyps will regress, as suggested by findings of CT-colonography surveillance of unresected polyps[36]. Thus, many resected CIN lesions and colonic polyps would not have otherwise caused morbidity or death. Identification and removal of such lesions represents overdetection and overtreatment, respectively. Treatments for both of these lesion types are generally considered minimally invasive; nevertheless, they have inherent risks. Polypectomy to remove colonic polyps can rarely be complicated by bleeding or colonic perforation[37], and colonoscopy can commonly lead to abdominal pain and bloating[38]. Excisional treatments for cervical lesions, such as loop excision and cone biopsy, carry risks, including bleeding and infection, and have been linked to adverse obstetrical outcomes, such as preterm birth[39]. Treatment harms are difficult to prove with certainty, and the increased risk of preterm birth among women who undergo the most-common cervical excisional technique (loop excision) has been called into question[40]. Nonetheless, current management guidelines recommend restraint in using excisional procedures for the treatment of cervical neoplasia in young women to avoid potential long-term health consequences associated with preterm birth.

Such risks, although not trivial, are generally tolerated because excisional treatments for CIN and colonic polyps are considered effective at preventing the development of invasive cancers, and are less toxic than the treatments that would otherwise be required if the diseases progressed to this stage (BOX 2: Lesson 2, corollary). Additionally, this practice is probably the predominant reason for the observed decline in the incidence of CRC and cervical cancers in the countries where screening is widespread (BOX 2: Lesson 3b). Tailoring the frequency of screening and limiting intervention for lesions that are not believed to be precursors to morbid disease, however, have been key challenges in screening aimed at prevention of these cancers. In guidelines published in 2012, the United States Preventive Services Task Force (USPSTF) recommend increasing the age of initiation of cervical screening cytology from 18 to 21 years, extending screening intervals, and implementing an upper age limit of 65 years for screening of women with prior negative test results[32], reflective of a deeper understanding of the underlying biology of cervical neoplasia (BOX 2: Lesson 4).

On the other hand, the management of ductal carcinoma *in situ* (DCIS) of the breast has been the subject of heavy scrutiny precisely because current treatment strategies are not satisfying the corollary of Lesson 2 (BOX 2): treatment itself is associated with some risks, especially considering that the risk of progression and death for certain types of DCIS and invasive disease is quite low. The incidence of DCIS in the USA increased more than 500% between the early 1980s and late 1990s, largely paralleling the advent of screening mammography, and has stayed relatively constant since then[41,42]. That many cases of DCIS do not progress to invasive breast cancer is widely acknowledged; nevertheless, the standard therapy over the past 25 years or more has been surgical resection (mastectomy, or lumpectomy plus adjuvant radiotherapy) and hormonal therapy[6,43]. Despite treatment of >60,000 DCIS cases per year in the USA, the incidence of invasive breast cancer has not fallen[42]; moreover, breast-cancer mortality has been unaffected by widespread treatment of DCIS (BOX 2: Lesson 3a)[44]. The natural history of DCIS is largely unknown, as most DCIS lesions are surgically resected. According to the available data, the prevalence of invasive cancer in the setting of DCIS might range from 0–50%[45,46]. Notably, the biology of the lesion dictates the risk of associated invasive cancer, with high-grade comedo-type DCIS having a higher likelihood of co-incident invasive cancer[47].

High-grade comedo and low-grade non-comedo DCIS are increasingly recognized to represent distinct disease entities, with the latter probably constituting overdiagnosis. Low-grade DCIS, even if untreated, is unlikely to cause breast-cancer-specific mortality: a recent study reported 10-year survival of 98.8% for women with untreated low-grade DCIS, and 98.6% for those in whom low-grade DCIS was surgically excised[48]. For low-grade DCIS, the risk might be spread over the woman's lifetime, whereas for high-grade DCIS, it might be concentrated within 5 years[46]. Indeed, high-grade DCIS is more-commonly associated

with local recurrence after treatment, distant metastasis, and mortality, and could be considered a true precursor lesion[49,50]. Consideration of DCIS grade alone, however, is unlikely to be sufficient in determining the risk of invasive cancer, and could potentially continue to result in overdiagnosis. In the past 3 years, a gene-expression-profiling test has been introduced as a tool to delineate DCIS biology[45]. In addition, profiling of the tumour immune microenvironment might provide insights into the aetiology of, and inform treatment approaches for, the highest risk DCIS lesions[51].

Early detection/stage shift

Screening approaches aimed at early detection of invasive cancer have been shown to reduce cancer-related mortality rates in some large RCTs with long-term follow up; however, considerable controversy remains over optimal use of the screening tests, and regarding how to balance the benefits and the harms of overdiagnosis and subsequent overtreatment, especially in settings outside of closely monitored clinical trials. For example, mammography-based screening was shown to reduce breast-cancer-related mortality in early RCTs[52–54], although more-recently available long-term follow-up data from completed trials have provided conflicting information on whether mammography decreases breast-cancer mortality[55,56]. Of note, mammography trials have varied in key aspects, such as screening frequency and technique, randomization scheme, and attribution of outcome[57]. In meta-analyses of screening trials, investigators have reported a decrease in disease-specific mortality associated with screening for breast cancer of approximately 20%, although the mortality reduction varies by age[57,58]: the absolute mortality reduction at 10 years is greatest in women aged 60–69 years (21 deaths per 10,000 women), and lowest in those aged 40–49 years (3 deaths per 10,000 women)[59].

At the population level, breast-cancer mortality in the USA has declined since 1990 (REF. 13). Despite some uncertainty, this decline is probably attributable to the combined effects of screening and therapy, and might be dominated by the unquestioned improvements in systemic therapy for locally-advanced and node-positive breast tumours over the past two decades[60]. Microsimulations have yielded a very broad range of estimates for the contribution of screening to the decline in mortality observed in the USA (28–65%)[61]. The magnitudes of these estimates vary dramatically because simulations are influenced by the assumptions and inputs on which each model is based. In fact, even the lower bound estimate might be optimistic. As systemic treatments improve, the mortality reduction attributable to screening diminishes, and accurate modelling of the dissemination of new therapies, or the magnitude of their effects, can be difficult[60]. Likewise, accounting for overdiagnosis and length-time bias in models is challenging, leading to overestimation of the benefits of screening[62]. This consideration is important because 22–31% of breast cancers detected on mammography are estimated to represent overdiagnosis[63].

Thus, two points relevant to screening can be made with the example of breast cancer. First, the mortality reduction attributable to screening diminishes as systemic treatments improve. Notably, most of the screening mammography trials were conducted before the advent of modern adjuvant treatment for breast cancer. Second, a reservoir of indolent disease exists that is detected with screening. After the widespread implementation of mammographic screening in the USA in the mid-to-late 1980s, the overall incidence of invasive breast cancer increased substantially, and remains substantially higher than rates before screening[7] (FIG. 1). This increased incidence largely reflects detection of a greater number of localized (early stage) tumours, accompanied by a disproportionately small decrease in late-stage cancers[7], and whether this trend translates to lowering of disease-related mortality is controversial. Interestingly, an ecological study showed no reduction in breast-cancer-specific mortality in regions of the USA with the highest uptake of mammographic screening[64].

In the face of such complexity, the differing interpretation of the evidence by several guideline-issuing professional bodies around the world is perhaps unsurprising (TABLE 1). In updated guidelines published in February 2016, the USPSTF continued to recommend screening mammography every 2 years for women aged 50–74 years, and that women aged 40–49 years should only be offered screening based on individual circumstances related to patient preferences[65]. These recommendations were based, in part, on a decision analysis[66] and systematic reviews[59,67] commissioned by the USPSTF. In 2015, the American Cancer Society (ACS) modified their guidelines for breast-cancer screening, based on a separate systematic review[58], and their recommendations now more closely resemble the USPSTF guidelines, with the exception of recommended annual screening for women between the ages of 45 and 54 years[68]. American breast-imaging societies and the American College of Obstetrics and Gynecology (ACOG) continue to recommend annual screening beginning at the age of 40 years[69,70], whereas European countries recommend screening every 2–3 years, with starting ages that range between 40 and 50 years[71–73].

A similar picture is seen with screening for prostate cancer. Death from prostate cancer has also declined since the 1990s[13], and this reduction is probably at least partially attributable to screening[74]. In the USA, the incidence of prostate cancer presenting initially as metastatic disease has decreased since the advent of PSA-based screening, indicating that screening and subsequent intervention does avert the progression of some localized tumours[8]. Nevertheless, two major RCTs of PSA-based screening produced discrepant findings related to prostate-cancer-specific mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO)-study investigators reported no benefit[75], whereas the European Randomized Study of Screening for Prostate Cancer (ERSPC) investigators reported a 21% reduction in the relative risk of prostate-cancer-specific mortality[76]. Differences in the study designs and populations, as well as the relatively high proportions of men in the control

groups who underwent PSA-based screening, might explain these conflicting results[77]. Regardless, the potential for overdiagnosis, with subsequent overtreatment, is widely recognized as a major downside of PSA-based screening. Indeed, a substantial increase in the incidence of prostate cancer has been observed following the dissemination of PSA-based screening (FIG. 1), mostly driven by early stage tumours with a low Gleason score[7]. Many low-grade prostate cancers will not invade beyond the prostatic capsule during the man's lifetime[78], and thus subsequent biopsies, resections, and/or radiation therapy expose the patient to unnecessary harms. Additionally, a normal serum PSA level (typically below 4 ng/ml) does not exclude the possibility of prostate cancer: in the Prostate Cancer Prevention Trial[79], 42.4% of all cancers with Gleason score ≥7 occurred in men with PSA values of ≤3 ng/ml. In the face of an unfavourable risk-to-benefit ratio, the USPSTF has now recommended against the routine use of PSA-based screening, and to date, no country has introduced a national PSA-based screening programme[80,81]. Other major professional societies, however, urge shared decision-making regarding PSA-based screening. For example, the ACS recommends that this discussion should begin at the age of 50 years for men at average risk[82], whereas the American Urological Association (AUA) recommends consideration of screening in men aged 55–69 years[83]. Similarly to the ACS, the European Association of Urology (EAU) recommends that PSA testing should be offered to men over 50 years of age (or earlier in certain risk groups, such as men with a family history of prostate cancer), and can continue until the individual's life expectancy is less than 15 years[84].

Lung cancer screening with LDCT has garnered increased attention based on results of the National Lung Screening Trial (NLST)[85,86]. In this study, 53,454 adults deemed to be at high risk of lung cancer on the basis of age and smoking history were randomly assigned to undergo three annual screenings with either LDCT or chest radiography[85,86]. After a median follow-up duration of 6.5 years, the LDCT arm had three fewer deaths per 1,000 individuals screened than the radiography arm — a 16% reduction in the relative risk of lung-cancer-specific mortality[86,87]. An excess of 120 lung cancers was detected by LDCT versus radiography,

Table 1 | **Summary of mammography guidelines from selected nations**

Country and organisation	Start screening at age (years)	Terminate screening at age (year)	Frequency of assessment	Comments
USA				
United States Preventive Services Task Force (USPSTF)[65]	50	74	Every 2 years (for women at average-risk of breast cancer)	Screening for women aged 40–49 years is a 'grade C' recommendation ('offer or provide this service for selected patients depending on individual circumstances')
American Cancer Society (ACS)[68]	45	As appropriate based on life expectancy	Annually then biennially at 55 years of age and older	Recommend continuing screening as long as the individual is in good health and has a life expectancy exceeding 10 years
American College of Obstetricians and Gynecologists (ACOG)[69]	40	As appropriate based on life expectancy	Annually	Suggest discussing cessation of screening with physician starting at age 75
American College of Radiology (ACR)/Society of Breast Imaging (SBI)[70]	40	As appropriate based on life expectancy	Annually	Suggest continued screening as long as life expectancy exceeds 5–7 years
Canada				
Canadian Task Force on Preventive Health Care[146]	50	74	Every 2–3 years	Not applicable
Sweden				
Socialstyrelsen[73]	40	74	Every 18–24 months	Not applicable
UK				
National Health Service[71]	50	70	Triennially	Expanding the age range of invited women to 47–73 years is being considered
Netherlands				
National Breast Screening Programme[72]	50	75	Biennially	Not applicable
Australia				
Royal Australian College of General Practitioners[147]	50	74	Biennially	Not applicable

however. With the use of modelling to account for lifetime follow up, the overdiagnosis rate for screening with LDCT was estimated to be 11% overall, but was nearly 50% for bronchioloalveolar-cell carcinoma and only 3% for other cell types[88]. The use of LDCT was also associated a cumulative false-positive rate of 37% owing to the detection of benign pulmonary nodules that share imaging characteristics with lung cancer[85]. Results of a retrospective analysis of the NLST data, however, indicate that application of the Lung-RADS reporting system, developed by the American College of Radiology, could potentially reduce the false-positive rate and overdiagnosis[89]. Findings of the Dutch–Belgian NELSON trial[90] of screening for lung cancer with LDCT at 2-year intervals after the initial screen indicated improved specificity compared with annual screening in the NLST[85] (98.6% versus 73.4%), with the tradeoff of lower sensitivity (84.6% versus 93.8%). Nevertheless, a similar percentage of lung cancers were detected at stage 1 in the NELSON trial and the NLST[85,90]. Interval cancers comprised 35 out of 187 diagnosed lung cancers in the NELSON trial, although only 12 of these interval cancers (35%) were not visible on the prior screening scan[90].

A concern is that the efficacy of LDCT seen in the clinical-trial setting will not translate into effectiveness in community practice; some of the success in the NLST might be due to the high level of expertise in LDCT interpretation and patient management at the participating medical centres, 76% of which were National Cancer Institute (NCI)-designated cancer centres[91]. Nevertheless, in the USA, screening for lung cancer is currently recommended for former or current smokers with a 30 pack-year history of tobacco use (and a quit date within 15 years for former smokers) by the USPSTF and other professional societies[92–94]. Beginning screening at the age 55 years is generally advocated, but the recommended age at which to end screening varies between the guidelines[94].

The careful delineation of the candidates for LDCT-based screening illustrates an understanding that not all individuals benefit equally from screening (BOX 2: Lesson 4). The prevailing lesson learned from current experience in screening of lung, breast, and prostate cancers, however, is that these cancers are truly heterogeneous in terms of their biological phenotype (BOX 2: Lesson 1). If the corollary of this lesson is not heeded, screening will disproportionately detect slower growing cancers and has the potential to reveal a reservoir of more-indolent disease. Given the clear excess of early stage cancers detected with population-level screening for breast and prostate cancers, room for improvement of these programmes clearly exists (BOX 2: Lesson 3a). Screening can lead to overdiagnosis and overtreatment if the potential for the detection of indolent cancers is not recognized and treatment decision-making does not account for disease biology. Gene-expression profiling of breast tumours, for example, has revealed a wide array of phenotypic features associated with differences in aggressiveness, and has begun to highlight the important interaction between biological phenotype and approaches to treatment[95–97].

Tempering hype: an eye on improvement

The perception and message surrounding screening for cancer has evolved to acknowledge the complex interplay of risks and benefits inherent to its practice. Hype around screening initially centred around the sound bite that 'early detection saves lives' — an intuitive, powerful message, attractive to practitioners and patients alike. Early campaigns promoting the use of screening tests, such as mammography and colonoscopy, prominently featured (and in some cases, inflated) the purported benefits, while neglecting the potential harms[98]. Wide-reaching population screening was initiated at a time when the linear model of cancer progression prevailed. Reports from cancer registries showed that patients with early stage cancers had good-to-excellent outcomes, and those with advanced-stage disease had much higher mortality rates. This observation led to the belief that detecting cancer at an early stage would uniformly reduce cancer-related mortality; however, this framework did not account for the extensive biological complexity and heterogeneity in cancer, which we are increasingly recognizing, or the associated variability in disease progression. Thus, the nearly uniform enthusiasm for screening contributed to a low-value, or 'more is better', approach to screening[99]. Admittedly, conceptualizing the rewards from less screening is difficult, and the lay public, based on decades of public-health messaging, tend to overestimate the benefits and underestimate the harms of screening[100]. Findings suggest that the concept of overdiagnosis, a clear harm that can be incurred in healthy, asymptomatic people, is discussed relatively infrequently between patients and health-care providers[101].

A guiding principle of cancer prevention and screening is that making healthy people better off than they already are is difficult. Prasad *et al.*[102] have argued that no clear evidence indicates that any of the current cancer screening protocols convincingly reduce all-cause mortality, except LDCT-based screening for lung cancer — and even then, raise the possibility that the reduction in all-cause mortality in the NLST might be smaller than reported. The downstream harms of overdiagnosis and overtreatment probably dilute or even nullify disease-related benefits of cancer screening in general, and exposure to such harms is more difficult to justify in the healthy population than in the management of patients with symptomatic disease. The frequency of screening should, therefore, be optimized based on detection of the tumour types for which beneficial outcomes of intervention are most likely. Those patients with tumours that progress too fast will not benefit from more-intensive screening, which would, however, increase the rates of false-positive findings and overdiagnosis on the population level.

In Europe, such harms are ameliorated, to some extent, by the centralized approach to screening; programmes are organized with fixed budgets, and with formal consideration of the tradeoffs, as opposed to the opportunistic approach used in the USA. In each setting, the same data are viewed and interpreted through different metaphorical lenses — relating to,

for example, the financing and organization of health care, malpractice litigation and cultural attitudes toward risk, interventions, and the politics behind the 'war on cancer'. In Europe, such considerations have led to the generally more-conservative approach to the dissemination of screening. Consider breast-cancer screening, for example: each European nation follows one guideline, and screening of women is usually recommended to begin at 50 years of age, occur every other year, and end at the age of 65–70 years (TABLE 1). Currently, no organized population-screening programmes for lung or prostate cancer are active in Europe. Moreover, government-based screening in European nations affords several additional benefits. Firstly, comprehensive registries of screening outcomes are assembled. Secondly, quality measures can be better implemented, which probably explains the lower recall rates and higher cancer-to-biopsy ratios reported in Europe compared with the USA. Factors relevant to the latter advantage include the minimum requirement for mammogram reads (960 every 2 years in the USA compared with 5,000 per year in Denmark and the UK); double reading (having two radiologists review each image); and the centralization of reading, possibly making mammograms easier to compare, with an emphasis on high specificity[103–105].

Nevertheless, important efforts are emerging in the USA to acknowledge the limitations and tackle the knowledge gaps with regard to cancer screening. These efforts have brought about renewed hope that screening programmes will meet the hype that initially accompanied them. First of all, increased awareness of overdiagnosis has prompted major professional groups to revise their guidelines[68,106]. Furthermore, the NCI convened a working group on overdiagnosis, which made several key recommendations to guide practice and research[107]. The American College of Physicians has also focused attention on high-value care in cancer screening[99,108]. Moreover, increased coverage in the press and other lay-publications in response to these actions has helped disseminate the screening debate among the general public.

Taking the key lessons learned from past experience and their corollaries (BOX 2), we can formulate corresponding action points to improve cancer-screening efforts. In the face of a heterogeneous disease biology (BOX 2: Lesson 1), efforts should be made to identify the true 'targets' of screening — namely, better defining a positive test result based on molecular phenotyping of lesions. Given the uncertainty regarding whether all precursor lesions are predecessors to clinically consequential disease (BOX 2: Lesson 2), a prevention or risk-reduction strategy, rather than treatment intervention, should be considered as the initial approach for some of these lesions. Considering the heterogeneity of risk in the population (BOX 2: Lesson 3), risk stratification might better identify the individuals who are most likely to benefit from screening. Population-based data on screening outcomes should be compiled into registries to provide continued feedback and thus enable quality improvement (BOX 2: Lesson 4). Lastly, similarly to treatment, screening should be based on both prognostic and predictive diagnostics, informed by a better understanding of disease phenotype, with a goal of characterizing and correlating screening abnormalities with the specific type of cancer biology using emerging prognostic and predictive tools. We posit that progress is being made across all five of these goals, with evidence of application and progress across all of the five cancers that are key targets for screening (that is, those of the breast, prostate, lung, cervix, and colon/rectum).

We have integrated the lessons learned with the screening 'cascade' proposed by Harris *et al.*[109] to illustrate how tailored innovations are being incorporated at each step of the screening process (FIG. 2). We believe that such innovations set the stage for 'precision screening', which incorporates individualized risk-prediction, based on clinical factors and biomarkers integrated with molecular characterization of the cancers detected. This approach should improve elucidation of the targets for cancer screening and prevention. Individualized data and patient values should be taken into account when making key decisions on whom to screen, when to initiate and cease screening, how often to screen, and what action to take for patients with abnormal findings. Efforts are already well underway to generate the information that will enable us to harness this knowledge to improve screening. The 'output' generated at each step of the screening cascade is linked with valuable opportunities for continued improvement. We have summarized the tools that will facilitate improvements in screening practices (BOX 3).

Precision along the screening cascade

Persons who are screened

Initiation of screening has to be undertaken acknowledging that "overdiagnosis exists and is common," which is one of five recommendations made by an NCI-sponsored think-tank working group on overdiagnosis[107]. The decision to screen should factor in an individual's pretest probability of cancer, a threshold risk level at which testing is most likely to have a net benefit, and patient values and attitudes towards risk tolerance. Risk stratification has been practiced in a rudimentary form since the advent of screening, as the cumulative risk of nearly all cancers increases with age; therefore, minimum ages at which to begin screening in individuals at low-to-average risk have been recommended — be it faecal occult blood testing, sigmoidoscopy, or colonoscopy at the age of 50 years, or cervical cytology at 21 years of age. Differences in interpretation of the available evidence, however, continue to spur disagreement over these age thresholds[110]. Additionally, the presence of familial risk syndromes or a concurrent disease state associated with an elevated cancer risk places an individual in a high-risk group, warranting consideration of earlier and more-frequent screening. Examples include hereditary nonpolyposis colorectal syndromes[111] or inflammatory bowel disease[112,113] and CRC risk.

Beyond age and conditions associated with an increased risk of malignancy, exposure history is increasingly considered in risk-stratification. For example,

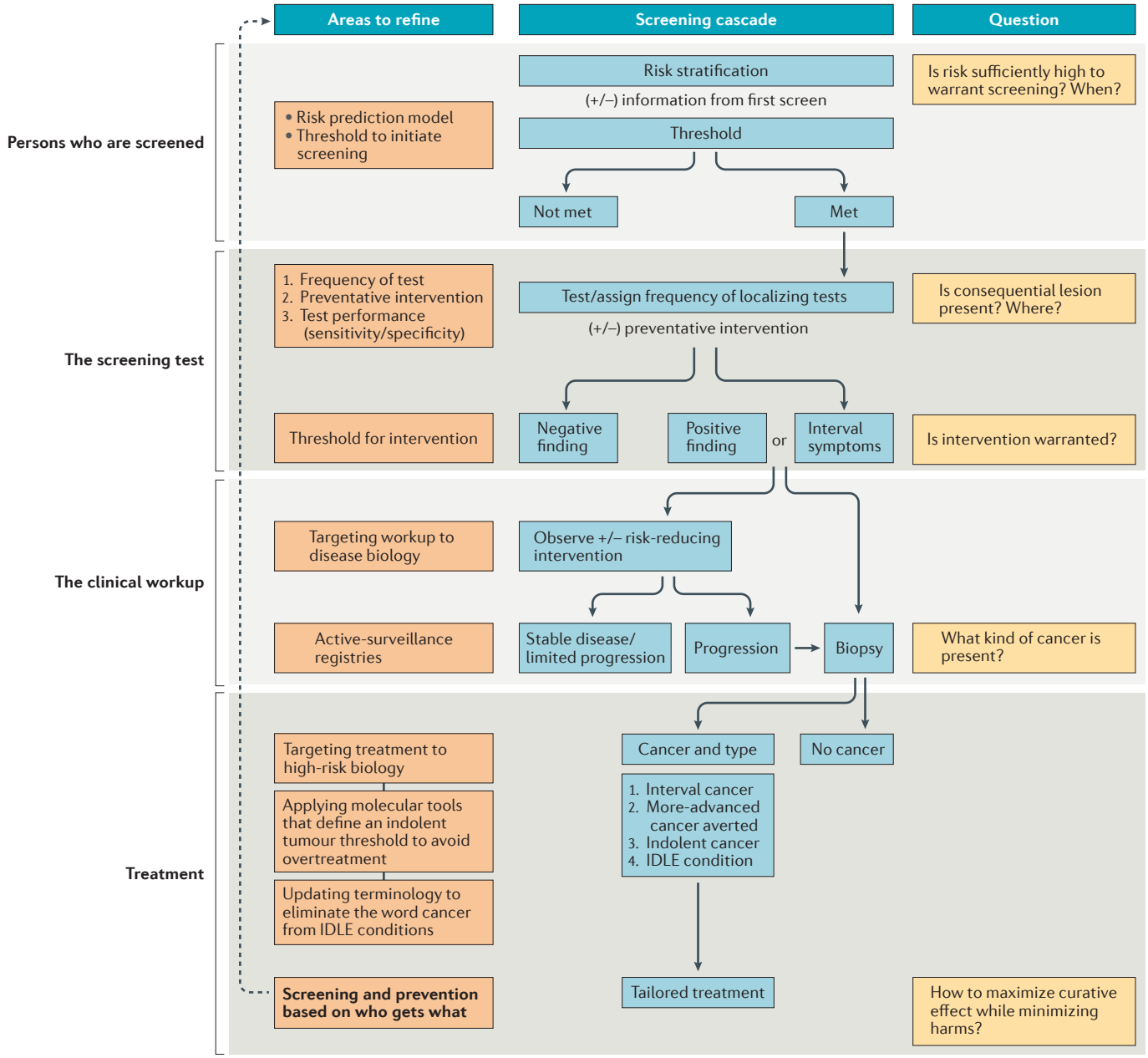

Figure 2 | **A framework for ongoing improvement of cancer-screening programmes.** We present a modified version of the screening cascade proposed by the High-Value Care Task Force of American College of Physicians[109]. Our recommendations for cancer-screening programmes focus on incorporation of key clinical questions at each step of the cascade, as well as components of the 'feedback loop' (areas to refine) — aspects of screening decision-making that can be actively improved using outcomes from the corresponding step on the cascade. IDLE, indolent lesions of epithelial origin.

given the robust, dose-dependent association between cigarette smoking and lung cancer, the NLST investigators selectively enrolled participants who met a minimum of 30 pack-years of smoking history and, if former smokers, had quit less than 15 years before study entry[85]. Most screening guidelines and reimbursement criteria for lung-cancer screening reflect the participant demographics of the NLST, namely limiting use of LDCT to people with a minimum smoking history of 30 pack-years[92,114]. Similar risk-stratification tools have been developed for CRC screening[115] and lung-cancer screening[116], and their clinical utility is currently being studied. Newer proposed algorithms for cervical-cancer screening suggest that HPV testing alone can identify a low-risk population (those with a negative test result), or that type-specific testing of HPV types 16 and/or 18 might help to further refine risk-stratification, such that women with evidence of oncogenic HPV types should have more-diligent evaluation[117,118].

Risk-prediction models are increasingly being used for risk-stratification. The Breast Cancer Risk Assessment Tool, one of the earliest risk prediction

tools, was developed to identify women for inclusion in trials of preventive interventions for breast cancer, and considers exposure to endogenous hormones, in addition to other clinical risk factors[119]. Other risk-prediction models are targeted at individuals suspected of having familial breast cancer[120,121]. The Breast Cancer Surveillance Consortium (BCSC) risk-prediction tool incorporates age, race, family history, mammographic breast density, history of prior breast biopsy (and type of benign breast disease, if present) to calculate a woman's 5-year and 10-year risks of developing breast cancer[122,123]. Beyond risk factors commonly incorporated in prediction models, some specific exposures clearly identify women at risk (for example, history of mantle radiation), and these women are recommended to undergo annual screening with MRI and mammography[124]. In addition, biomarkers have been combined with risk-prediction tools in the hope of improving their performance. A polygenic risk score based on 76 single nucleotide polymorphisms (SNPs) has been shown to independently predict breast-cancer risk, and improved risk-prediction when incorporated into the existing BCSC model[125]. To date, more than 90 SNPs have been associated with breast-cancer risk[126], and incorporation of additional SNPs might further enhance the predictive value of the polygenic risk score. In the upcoming WISDOM trial[127], investigators will use the BCSC model, genetic mutation analysis, and a SNP panel to estimate the 5-year breast-cancer risk score of the women enrolled and, ultimately, assign them a tailored plan, personalizing the starting age, stopping age, and frequency of screening — all within the bounds of the USPSTF guidelines at study initiation. Over time, the risk model will be refined, as will screening-test assignment[127].

The screening test

Screening should follow another of the goals raised at the NCI-sponsored think-tank: to "mitigate overdiagnosis by testing strategies that lower the chance of detecting unimportant lesions" (REF. 107). One can pursue this within three domains, as discussed in the following sections.

Choice of screening test. Imaging tests serve to localize lesions and provide visual clues about the likelihood of malignancy and aggressiveness. With regard to prostate-cancer screening, following up detection of an elevated PSA level with prostate MRI can help to rule out a false-positive result, and if a lesion is present, to improve the yield of tumour tissue upon biopsy[128]. Women at very high risk of breast cancer, such as *BRCA*-mutation carriers, first-degree relatives of *BRCA*-mutation carriers, or those with a 20–25% lifetime risk according to prediction models, should be screened annually with MRI, as an adjunct to mammography, given the superior sensitivity of MRI in this population[124,129–131]. Conversely, use of less invasive or costly strategies is a possibility for individuals on the other end of the risk spectrum. For example, less-frequent screening might be appropriate for individuals considered to be at 'very low' to 'low' risk of CRC according to the prediction model discussed in the previous section[115]. Of note, all current cervical screening guidelines by the ACS, USPSTF, and ACOG incorporate HPV testing as an alternative to cytology-only strategies[108].

Box 3 | **Toolkit for improving screening**

Site-specific tools

- Risk-prediction models
- Molecular-based tests to inform risk-stratification and treatment decisions
- Feedback-based modification of screening interval and modality, and thresholds for initiating and stopping screening
- Registry of outcomes as a resource for continued quality improvement
- Standardization of test delivery and interpretation
- Shared decision-making tools
- Continued study of the biology, natural history, and treatment response of precancerous and cancerous lesions

Generalized strategies (applicable across all organ sites)

- Integration of comorbidity assessment into decisions about screening, workup, and treatment
- Common molecular classification of indolent tumours, for example, 'IDLE' (indolent lesions of epithelial origin) conditions — that is, redefinition of the term 'cancer'
- Screening systems that includes invitation to screen, recall, and outcomes tracking: 'registry 2.0'

Frequency of screening. The frequency of testing is a question that has long been central to quality-improvement efforts in cervical-cancer and CRC screening. In both scenarios, results of the first test or previous tests are used to inform decisions about how and when to repeat screening. In cervical-cancer screening, a combination of a normal cytology-test result and a test result showing no evidence of infection with high-risk (oncogenic) HPV types among women aged ≥30 years predicts a particularly low risk of CIN and invasive cancer[33]; a 5-year screening interval is currently recommended for these women[32]. Women with evidence of infection with oncogenic HPV types can have more-diligent evaluation, whereas those with non-oncogenic HPV infections can be followed less intensively[117,118].

Likewise, the absence of colonic polyps on colonoscopy (and even the presence of small polyps that lack concerning histological features) is associated with a low risk of CRC development over the next decade, and the next screen can, therefore, occur in 10 years[132]. Breast-density measurements obtained from initial mammograms (breast imaging-reporting and data system (BI-RADS) density) has been strongly linked to breast-cancer risk; for example, extremely dense breasts in the setting of elevated risk, such as a family history of breast cancer, or in a woman aged 40–49 years support annual (rather than biennial) screening with mammography[133]. In the Stockholm-3 (STHLM3 trial)[134],

a baseline PSA threshold of 1 ng/ml informed the frequency of prostate cancer screening: if a participant had a PSA level <1 ng/ml, he was not recommended to undergo screening during the following 6 years.

Definition of a positive test result. Experience with precursor lesions has shown that not every 'positive' result warrants further immediate investigation or a biopsy. Historically, the standard of care for young women with abnormal cytology was follow-up colposcopy; however, newer screening approaches integrate watchful waiting (active surveillance). The 2012 management guidelines of the American Society for Colposcopy and Cervical Pathology[135], for example, recommend that women aged 21–24 years with minimally abnormal cytological findings be followed with annual cytology testing, as many such lesions regress spontaneously. Incorporating strict criteria for embarking on a clinical workup into the screening cascade is important. Active surveillance, which will be covered in detail in the next section, can be used for individuals with indeterminate lesions, or those that probably represent indolent disease or its precursors. Additionally, according to the Lung-RADS reporting criteria, pulmonary nodules <6 mm in diameter detected on an initial LDCT screen do not constitute a 'positive' result given they do not require intervention, or necessitate changes to the screening frequency or modality[136]. This example illustrates an important concept, and one that is applicable to any screening study: a 'finding' does not necessarily constitute a 'positive' result. Lastly, results from the STHLM3 trial[134] indicate that combining information on PSA levels, SNP genotype, circulating protein markers, and clinical variables can improve the accuracy of detection for prostate cancers with a Gleason score of ≥7. This demonstration that the STHLM3 model outperformed PSA testing alone for detection of these high-risk prostate cancers might usher in an era in which screening tests have more-narrowly-defined targets related to clinically consequential cancers[134].

The clinical workup

The aim of a clinical workup in an individual with a positive screening-test result is to establish a pathological diagnosis of cancer or high-risk neoplasia, and gather the data necessary for precision treatment. In many cases, a positive result will trigger an invasive diagnostic test, for example, an image-guided biopsy for a suspicious breast mass detected on mammography. In addition to standard pathological review for histology, extent of disease, and tumour markers, increasing options are available for molecular characterization of tumours. Gene-expression-profiling tests have been developed to enable prediction of recurrence risk after treatment for invasive cancers and to support treatment decisions. Notable examples are the Oncotype DX® and MammaPrint® assays for gene-expression profiling of breast cancers[95,96]. Further refinements to these tests, such as establishment of an 'indolent threshold' for the MammaPrint® 70-gene signature[137], have enabled identification of a particularly indolent form of the disease. These advances have enabled gene-expression profiling to be performed on biopsy samples of screen-detected tumours to facilitate risk-stratification and thus prevent overtreatment.

Molecular profiling has changed the view that a standard treatment is uniformly beneficial for all invasive cancers. Approximately one-third of breast cancers detected using modern screening modalities are defined as 'ultra-low risk' based on gene-expression profiling[138]. These cancers are associated with no risk of breast-cancer-related death in the first 15 years after surgical treatment and a <5% risk of late breast-cancer-related death (17–20 years after surgical treatment) with a short course of tamoxifen[137]. Certainly, identification of a precursor of this kind of indolent cancer has no rationale. Low-histological-grade DCIS, as defined by pathologists, is probably a risk factor for the development of such indolent cancers, and this disease entity closely matches the definition of indolent lesions of epithelial origin, or 'IDLE' conditions, that was proposed by the working group convened by the NCI[107]. Other candidate IDLE conditions include the subset of indolent lung cancers identified within the NLST and Gleason 3 + 3 prostate cancers[107]. Setting up observational registries for IDLE conditions will enrich our understanding of the natural history of these tumours and provide guidance on how to incorporate information on disease dynamics (that is, whether the tumours progress, remain stable, or regress) into individualized management approaches. These efforts would parallel the NCI working group's recommendation of creating observational registries for IDLE conditions[107].

This approach has already been shown to hold promise with regard to lung-cancer screening. The rollout of LDCT occurred in an era when the risks associated with screening and subsequent diagnostic testing were recognized, and as such, quality measures were formulated to standardize the clinical workup. For example, the Lung-RADS tool can be used to guide the management of nodules detected on LDCT[136]: on the basis of size, appearance, and growth rate, nodules are assigned a probability of malignancy using this tool, as well as a recommended timeframe and modality for surveillance. This strategy limits unnecessary imaging (only nodules larger than 6 mm, or 4 mm if new, require follow-up assessment) and tissue sampling, which is reserved for 'Category 4B and 4X' lesions, such as >1.5 cm solid nodules[136]. Likewise, the investigators of the NELSON study used strictly defined criteria for a 'positive' test result based on nodule volume or volume-doubling time, which probably improved the positive predictive value of LDCT (40.4%, 95% CI 35.9–44.7%), compared with the performance of this modality reported in other studies, such as the NLST (3.8%, 95% CI 3.4–4.3%)[85,90].

The observation that CIN grade 2 lesions have a high spontaneous regression rate has led to recommendations that these lesions be followed, rather than treated, especially in young women in whom treatments might lead to adverse reproductive outcomes[135]. Repeating colposcopy with cytology at 6-month intervals is specifically recommended for women aged 21–24 years, but

can be offered to women of any age with CIN grade 2 in whom the harms of treatment are believed to outweigh the benefits[135].

Treatment

A comprehensive discussion of cancer therapy is outside the scope of this Review, but tailored therapy is discussed briefly, in the context of limiting overtreatment of indolent tumours. Gene-expression profiling has deepened our understanding of the range of disease entities that are currently classified as 'cancer' based on the classic criteria of histological appearance. In the cases with diagnostic test results that suggest indolent disease, less-aggressive therapies should be pursued. For instance, low-grade DCIS is more likely to be an indicator for an increased risk of future invasive cancer, similarly to its closely related pathological entity atypical ductal hyperplasia[46], rather than an indication for immediate surgery and radiation therapy; a potentially better alternative is to consider these lesions as an opportunity for prevention, using selective oestrogen-receptor modulators or aromatase inhibitors. Thus, for certain women with breast lesions, endocrine therapy alone might be sufficient[96,137].

Moreover, if the workup reveals an IDLE tumour, consideration should be given to active surveillance. When appropriate, changing the nomenclature of IDLE lesions, to reflect their typically benign clinical course, will help frame the decision between patients and providers. The NCI-sponsored think-tank members recommended removing terms related to 'cancer' — as has been instituted for some CIN grade 3 lesions, formerly known as carcinoma *in situ* [107]. A consortium of seven centres (funded by grants from the NCI) are working together to identify common biological criteria for indolent cancers and IDLE conditions, to help redefine 'cancer' in the era of modern molecular medicine[139].

Systems-level improvements

Across the entire screening cascade, several advancements have the potential to improve screening programmes. For example, outcomes registries can support continued improvement by providing real-time feedback. National cancer registries have long been a mainstay in Europe, and have provided an opportunity for detailed cohort studies on screening outcomes[140,141]. In the USA, more-limited registries, such as the Breast Cancer Screening Consortium[142], have linked data from regional mammography registries to form a representative sample of the country. The American College of Radiology's lung-cancer-screening registry represents a burgeoning attempt to form a national screening registry with an aim towards quality improvement[143]. The ultimate goals of this and similar ventures are to promote evidence-based practices (such as management of incidental findings) and improve reporting in order to enable continued assessment of screening practices. Participation in this registry enables screening centres to meet the quality-reporting requirements mandated by the Centers for Medicare and Medicaid Services[143].

One key knowledge gap is centred on screening in the elderly and particularly those with considerable comorbidities — demographics in which few clinical trials of screening interventions have been conducted. Screening should proceed cautiously in the elderly, frail population; for example, many smokers aged within the 55–74 year range who represent the target for LDCT screening for lung cancer, based on the NLST results[85,87], have concurrent cardiac or pulmonary disease that will limit their lifespan. Across the screening cascade, ideally, the individual's underlying comorbidities and frailty should be incorporated into decision-making on the risk–benefit tradeoff. One such example of this approach is provided by e-Prognosis, a prediction tool that is available online (http://eprognosis.ucsf.edu/) and as a smartphone application, and can be used to guide cancer screening in the elderly. The tool juxtaposes the predicted mortality benefit from screening with competing risks, based on a synthesis of published geriatric risk indices[144]. Integration of such tools into screening decisions is a promising area of future research, and the development of a tool that could be applied widely across all screening indications should be a research priority.

Finally, engaging individuals through shared decision-making and the routine offer of participation in studies should be major goals. Many decision tools have been created to facilitate discussions around screening, and tackle the complex interplay between risks, benefits, and each individual's preferences[145]. Patient-oriented studies, such as the WISDOM trial[127], are probing the feasibility and acceptability of precision screening, and should provide critically needed data and key insights. Moreover, the Centers for Medicare and Medicaid Services has mandated that a "lung cancer screening counselling and shared decision making visit" must occur before a LDCT scan being ordered, and is a requirement for reimbursement, emphasizing the need to consider patient preferences[143].

Patient preference could have an important role at the points in the screening cascade at which a biopsy or treatment is recommended. If potentially morbid disease is unlikely to be present, or the suspected lesion is thought to be associated with low mortality, then such uncertainties should be communicated to the patient. Patients' values and levels of risk tolerance can help direct decision-making: those intolerant of the risks of a potential malignancy might favour an aggressive approach and, therefore, intervention, whereas others might favour a watchful-waiting approach. Those in the latter group should be cautioned of the potential need for more-frequent diagnostic testing, and the associated risks and benefits.

Conclusions

We now recognize that cancer encompasses a heterogeneous collection of conditions, and approaches to screening are changing accordingly. Opportunities for improvement are demonstrated by advancements in each of the screening programmes for lung, breast, prostate, colorectal, and cervical cancers, and can inform efforts to further advance the state of the art of screening. Learning who is at risk of which cancers, in terms of both site and

biology, will be a critical underpinning for improvements in screening. The tools required to conduct studies to elucidate these data are coming online, owing to our increasing understanding of the genetic and biological basis of cancer risk, as well as the immunotypes, genotypes, and phenotypes of the tumours that arise. Herein, we have assembled the lessons learned from screening for five major cancers (breast, lung, prostate, cervical, and colorectal cancers; BOX 2) into a quality framework to accelerate our ability to introduce precision screening (FIG. 2), tailored to biology, patient preference, and clinical performance status.

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All authors researched the data for article, contributed substantially to discussions of content and reviewed/edited the manuscript before submission. Y.S. and L.J.E. wrote the manuscript.

Competing interests statement
M.E. is named on four patents applications for prostate-cancer diagnostics. G.F.S. is Principal Investigator of an NCI-funded grant that aims to identify the range of reasonable options for cervical-cancer screening from a patient-centred and economic perspective (R01CA169093). Y.S., W.C.B., B.S.K., and L.J.E. declare no competing interests.

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