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Cancer overdiagnosis: a biological challenge and clinical dilemma

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Abstract

For cancer screening to be successful, it should primarily detect cancers with lethal potential or their precursors early, leading to therapy that reduces mortality and morbidity. Screening programmes have been successful for colon and cervical cancers, where subsequent surgical removal of precursor lesions has resulted in a reduction in cancer incidence and mortality. However, many types of cancer exhibit a range of heterogeneous behaviours and variable likelihoods of progression and death. Consequently, screening for some cancers may have minimal impact on mortality and may do more harm than good. Since the implementation of screening tests for certain cancers (for example, breast and prostate cancers), a spike in incidence of in situ and early-stage cancers has been observed, but a link to reduction in cancer-specific mortality has not been as clear. It is difficult to determine how many of these mortality reductions are due to screening and how many are due to improved treatments of tumours. In cancers with lower incidence but high mortality (for example, pancreatic cancer), screening has focused on high-risk populations, but challenges similar to those for general population screening remain, particularly with regard to finding lesions with difficult-to-characterize malignant potential (for example, intraductal papillary mucinous neoplasms). More sensitive screening methods are detecting smaller and smaller lesions, but this has not been accompanied by a comparable reduction in the incidence of invasive cancers. In this Opinion article, we focus on the contribution of screening in general and high-risk populations to overdiagnosis, the effects of overdiagnosis on patients and emerging strategies to reduce overdiagnosis of indolent cancers through an understanding of tumour heterogeneity, the biology of how cancers evolve and progress, the molecular and

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Author contributions

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cellular features of early neoplasia and the dynamics of the interactions of early lesions with their surrounding tissue microenvironment.

The goal of cancer screening is to detect either a preneoplastic lesion or a cancer at an early stage where treatment will change the outcome and prolong survival. Two cancers for which screening has been shown to reduce cancer-specific mortality are colorectal cancer[1] (for example, a UK trial that enrolled 170,000 patients and a US trial that enrolled 155,000 patients found that screening with flexible sigmoidoscopy reduced colorectal cancer mortality by 31% and 26%, respectively[2,3]) and cervical cancer (for example, a screening study in England in which 11,619 women were diagnosed with cervical cancer reported that screening resulted in a 70% reduction in cervical cancer deaths[4]). These reductions in mortality are largely due to the removal of preneoplastic lesions: colon polyps and cervical intraepithelial neoplasia. However, these major clinical and public health benefits come at a cost of detection of many lesions with little or no lethal potential or even risk of progression to invasive cancers. A review of US Medicare claims that, of 1.8 million colonoscopies performed, approximately 30% of the patients had polyps[5]. Most of these polyps will not develop into cancer, but they are surgically removed during colonoscopy. It is estimated that only approximately 5% of adenomas if not removed would progress to cancer. A polyp surveillance study in the USA reported that only 22% of 306 small polyps grew, 28% shrank (10% completely regressed) and 50% remained stable[6]. While colonoscopy is a relatively safe procedure, there are adverse events, including approximately 4 perforations and 8 instances of major bleeding per 10,000 colonoscopies[7]. However, on the basis of randomized controlled trials in both the USA and Europe, the United States Preventive Services Task Force (USPSTF) has concluded that, for asymptomatic adults aged 50–75 years, the benefits of screening outweigh the potential harms[7]. For other cancers, the benefits of screening, especially on the extent of mortality reduction, are less clear, and the harms of screening may outweigh the benefits. A major potential harm of screening is overdiagnosis.

Overdiagnosis is generally defined as the diagnosis of disease that would never cause symptoms or death during a given patient’s lifetime. Overdiagnosis is distinct from misdiagnosis. Overdiagnosis is primarily driven by screening asymptomatic patients. Screening can detect not only asymptomatic cancers that are destined to cause harm but also indolent or benign forms of the disease that will never harm the patient (FIG. 1). In fact, most available screening tests are better at detecting slow-growing tumours than detecting rapidly progressing ones, a phenomenon known as length-biased sampling (FIG. 2). Overdiagnosis should also not be confused with a false positive result: a positive test in an individual who does not have cancer. For example, a false positive occurs when a patient has a positive faecal immunochemical test but is found not to have cancer or polyps on a subsequent colonoscopy exam. By contrast, an overdiagnosed patient has a tumour that fulfils the histopathological criteria for cancer.

USPSTF identified overdiagnosis as an important consideration for breast cancer (November 2009) when it recommended screening based on an individualized, informed decision rather than across the board[8]. Over the past 10 years, there has been an increasing awareness of

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the extent and clinical importance of overdiagnosis and related overtreatment and of the need to develop tests that better distinguish indolent or very-slow-growing cancers from aggressive ones[9–13]. Overdiagnosis occurs either when the detected cancer is never going to progress and cause symptoms or when the cancer will not progress rapidly enough to cause symptoms in a person with limited life expectancy. Using these criteria and the amalgamation of several studies, it can be estimated that approximately 25% of breast cancers detected by mammography, 50% of lung cancers detected by chest radiography and/or sputum examination, 13–25% of lung cancers detected by low-dose computed tomography (LDCT), and 50–60% of prostate cancers detected by prostate-specific antigen (PSA) are overdiagnosed[8,9,14]. Observational studies and population-based cancer statistics suggest that overdiagnosis also occurs for paediatric neuroblastoma, thyroid cancer, melanoma and kidney cancer[9,14–16] (TABLE 1). Indeed, some degree of overdiagnosis may be the rule, rather than the exception, when commonly available screening tests are involved.

In this Opinion article, we focus on several organ types for which a common screening test is available for the general population and there is supporting evidence of the magnitude of overdiagnosis through meta-analysis and/or randomized trials (for example, breast, prostate and lung cancers). We also discuss the use of screening in high-risk populations for cancers with relatively low incidence but high mortality, such as pancreatic cancer.

Factors influencing overdiagnosis

Challenges in estimating overdiagnosis.

Because most people who are diagnosed with a pre-malignant lesion or a preinvasive cancer are also treated, it is difficult to directly assess the unperturbed natural history of a given lesion and therefore to determine whether overdiagnosis has occurred in an individual patient. Thus, most inferences about overdiagnosis come from the study of populations, in which screening-associated disparities between tumour incidence and mortality are more obvious. A systematic review of methods to measure the extent of overdiagnosis grouped these studies into four categories[17]: (1) extended follow-up of well-designed randomized controlled trials, (2) imaging or pathological (including autopsy) studies, (3) statistical modelling studies and (4) ecological studies and cohort studies. The authors of that review identified strengths and weaknesses of each of these methodological approaches and concluded that, in the general population, well-conducted ecological and cohort studies in multiple settings are the most appropriate approach for quantifying and monitoring overdiagnosis in cancer screening programmes. However, the extent of overdiagnosis was found to vary widely even among studies that used similar methodological approaches. For example, 18 ecological and cohort studies reported widely different results for the proportion of breast cancers that were overdiagnosed, from as low as 5% to as high as 50%[17]. Even limiting these studies to those with moderate risk of bias and long-term follow-up, the extent of overdiagnosis varied from about 20% to 50% (for example, the extent of overdiagnosis was estimated to be 20% in the Norwegian Cancer Screening Program that studied 702,000 women[18] and 45% in a Swedish study of approximately 750,000 women[19]). By contrast, the USPSTF concluded in their systematic review of breast cancer screening[6] that three well-designed randomized controlled trials (two Canadian studies and one Swedish study

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that together enrolled approximately 130,000 women[20]) were the least biased estimates of overdiagnosis. In this case, the trials estimated 11–22% overdiagnosis in the screened population. This high degree of variation makes it difficult for clinicians to advise patients on the likelihood of their cancer being indolent or progressive and on which course of action to take — treatment or active surveillance.

Reservoir of indolent lesions.

The major contributory factor to overdiagnosis is slow-growing or indolent tumours that create a large reservoir of silent and non-lethal cancers that may be detected upon screening asymptomatic patients. Indeed, screening tests are more effective in detecting slow-growing tumours than ones that grow faster because of a longer preclinical asymptomatic period, and the number of indolent lesions in the reservoir may exceed the number of rapidly growing tumours with lethal potential. Autopsies of older men in the USA who died of causes other than prostate cancer showed that, among men aged 70–79 years, prostate cancer was found in 36% of white men and 51% of black men, which is an indication of the size of the reservoir of indolent cancer that could be detected by screening[21,22]. Developing more sensitive tests that can detect additional prostate cancers in this reservoir but do not distinguish indolent from aggressive cancer will likely do more harm than good by putting a larger number of patients through unnecessary intervention. Hence, the clinical dilemma of overdiagnosis exists — an increase in detection of cancer incidence without a comparable reduction in late-stage disease or mortality.

Extent and harms of overdiagnosis

Harms associated with overdiagnosis include the burden of unnecessary diagnostic procedures, surgeries, chemotherapy, adjuvant therapy, morbidities and in rare cases mortality associated with these treatments. Overdiagnosed individuals also often experience physical (for example, an unnecessary mastectomy or adverse effects of chemotherapy or radiation) and psychological harms (for example, stress and anxiety). There are also economic harms to both individual patients and health-care systems. Patients are often not educated about the harms and benefits of screening procedures, and it may also be difficult for clinicians to effectively communicate the concept of overdiagnosis to their patients.

Prostate cancer.

Prostate cancer is a heterogeneous disease with a wide spectrum of clinical behaviours ranging from prolonged latency during adult life to rapid spread and lethality[23,24]. The ideal screening method for prostate cancer, as with most cancers, would be one in which clinically relevant cancers that have substantial potential to cause morbidity or mortality are detected at a time when they are curable. Screening of asymptomatic men for prostate cancer with PSA is controversial primarily because of the very high rates of false positives and overdiagnosis[25]. The USPSTF analysis of multiple trials reported that two-thirds to three-quarters of men with elevated PSA (above 3–4 ng ml^{-1}) do not have cancer detected by biopsy[25]. For example, the European Randomized Study of Screening for Prostate Cancer, which screened 61,404 men, reported that 76% of the prostate biopsies performed for an elevated PSA identified no cancer[26]. Of those with a positive biopsy, an estimated

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20–50% represent overdiagnosis[25] (for example, 50.4% in the European Randomized Study of Screening for Prostate Cancer, which enrolled 61,404 men[26], and 20.7% in the US Prostate, Lung, Colorectal and Ovarian cancer Screening Trial (PLCO), which enrolled 148,000 men[25]). In addition, the false negative rate is approximately 15% (for example, in the Prostate Cancer Prevention Trial in the USA, 449 of the 2,950 men who never had PSA above 4 ng ml^{-1} were later diagnosed with prostate cancer[27]). Tumours with Gleason score 6 (Grade Group 1 tumour) (GS6/GG1) have a low capacity for metastasis and death[28–30]. It is estimated that approximately 20–30% of the 150,000 prostate cancers diagnosed each year in the USA are GS6/GG1. Even if 60–70% of these men select active surveillance, between 9,000 and 18,000 men with a Gleason score 6 will still be unnecessarily treated each year with radical surgery or radiotherapy.

In 2012, the USPSTF recommended against PSA screening, as the potential benefits did not outweigh the potential harms, including false positive results, complications from transrectal prostate biopsies and the harms of treatment (urinary incontinence and erectile dysfunction)[31]. In 2018, the USPSTF changed their recommendation: for men aged 55–69 years, the decision to undergo periodic PSA screening should be a personal one based on a discussion with their clinician about potential benefits and harms; they recommended against screening for men aged >70 years[25]. This change in recommendation was primarily based on additional evidence that screening reduces the risk of metastatic disease in some men who have sufficient remaining life expectancy to benefit. Public Health England's 2016 guidance for prostate cancer risk concluded that the PSA test was not accurate enough to meet the requirements of a national screening programme (Public Health England prostate cancer risk management programme). This recommendation was based in large part on the conclusion that PSA detects slow-growing cancers that may never cause symptoms or shorten life, resulting in unnecessary treatments with side effects that can affect daily life. A recent meta-analysis of five randomized controlled trials concluded that PSA screening results in at best a small reduction in disease-specific mortality (less than 1 death avoided for 1,000 men screened over 10 years), but it has no effect on overall mortality[32].

Although an increasing number of men with low-grade prostate cancer are electing to undergo more conservative management[33,34], such as active surveillance, overdiagnosis is still common, and active surveillance can itself have serious side effects related to multiple prostate biopsies and can be costly over time to both individual patients and the health-care system. However, the increased awareness of overdiagnosis of prostate cancer has resulted in a decrease in radical prostatectomies for low-grade cancers[33–35].

Breast cancer.

With the advent of screening mammography, the detection of ductal carcinoma in situ (DCIS) in the USA has increased from 10 per 100,000 (1975–1979) to 79 per 100,000 (2008–2012), but there has not been a commensurate decrease in invasive cancer[36]. If one assumes that half of the cases of DCIS progress to invasive carcinoma, this increase in DCIS detection should have resulted in a decrease of approximately 35 cases of invasive cancer per 100,000. However, rather than decreasing, the incidence of invasive cancer increased from 217 per 100,000 (1975–1979) to 281 per 100,000 (2008–2012)[36], indicating

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that mammography detects a large number of DCIS cases that never progress to invasive cancer. Mammography also detects some cases of invasive stage 1 cancers that are not destined to progress, and their detection contributes to overdiagnosis. Statistical modelling and population trends suggest that much, or most, of the observed reduction in breast cancer mortality is attributable to improvements in treatment for stage 2 and stage 3 diseases[37]. Yet, recent data from Sweden found that women who participated in an organized mammography screening programme had a 60% reduction in the risk of dying from breast cancer 10 years after diagnosis and a 47% reduction in risk 20 years after diagnosis[38]. Interval cancers missed by screening mammography are usually more aggressive and faster growing and more likely to be diagnosed at an advanced stage[39] and be oestrogen receptor (ER)-negative[40–42] than screen-detected breast cancers. On the other end of the spectrum are invasive cancers that are indolent and will not progress (sometimes referred to as indolent lesions of epithelial origin (IDLE)[43,44]) and DCIS, which is considered noninvasive and unlikely to become invasive; these may account for at least half of the in situ and invasive cancers diagnosed today. These two extremes represent the conditions in which screening faces its biggest challenges.

Lung cancer.

The results from the US National Lung Screening Trial (NLST) of 53,453 high-risk current and former smokers found that screening by LDCT decreased lung cancer mortality by approximately 15–20%. However, 25% of the subjects in the LDCT arm of the NLST had abnormalities, and 95% of those lesions were determined to be false positives, and as many as 30% were overdiagnosed[45,46]. A recent analysis of the Danish Lung Cancer Screening Trial (2,050 subjects in the screened group and 2,050 subjects in the control group) estimated that 67% of the cancers detected by LDCT were due to overdiagnosis[47]. By contrast, the Italian Lung Screening Trial (1,613 subjects in the screened group and 1,593 subjects in the control group) found no evidence for overdiagnosis but did note nonsignificant reductions of 17% in overall mortality and 30% in lung cancer-specific mortality[48]. There are currently no organized lung screening programmes with LDCT either in North America or Europe[49].

In the NLST[45,46], most of the false positives were followed up only by additional imaging; however, 2.5% required an invasive procedure such as a needle biopsy. Lesions thought to be malignant on imaging often require additional diagnostic procedures resulting in increased radiation exposure, needle biopsy or other invasive procedures such as thoracotomy. Thoracotomy carries risk, especially in people with underlying cardiac or lung disease from years of tobacco smoking. Potentially serious complications can result from these procedures and delay appropriate treatment. A retrospective study of 174,702 patients in the USA who had an invasive diagnostic procedure (cytology, biopsy, bronchoscopy or surgery) to examine abnormalities found with lung cancer screening reported that 23% resulted in complications (19% after needle biopsies and 52% after surgery). In addition, the mean costs were approximately US$6,300 for minor complications and $57,000 for major complications[50]. Importantly, these patients did not have a diagnosis of lung cancer 1 year before or after the diagnostic procedure.

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Pancreatic cancer.

Screening in the general population is not feasible for pancreatic ductal adenocarcinoma (PDAC) owing to its relatively low incidence and prevalence, but screening studies have been performed on asymptomatic individuals at high risk of PDAC, be it because of a strong family history or a predisposing germline mutation[51,52]. The benefits and risks of screening of high-risk individuals for PDAC have been highlighted in recently published studies, showing that while pancreatic cancer can be identified at early stages, other pancreatic lesions with variable malignant potential are also found[51,53–56]. For example, mucinous pancreatic cysts are commonly found in patients who participate in these high-risk screening protocols, and these mucinous cysts have the potential to become PDAC. In fact, these cysts present a broader problem for health-care providers beyond overdiagnosis owing to screening. Pancreatic cysts have increased in prevalence owing to increased use of cross-sectional abdominal imaging in the general population owing to reasons unrelated to the pancreas such as chronic abdominal pain, gastrointestinal discomfort or accidents[57–59]. Much may be gleaned from incidentalomas, despite the biology and clinical conundrums caused by incidental lesions perhaps being different than those related to screen-detected lesions. For example, a recent multi-institutional study found that 44% of pancreatectomies (141 out of 320) for pancreatic cysts were found to be either low-grade or intermediate-grade dysplasia, which is not considered to be life-threatening[60]. These results in the general population should give caution to the design and interpretation of screening protocols for individuals at high risk of pancreatic cancer: overdiagnosis as well as overtreatment may occur owing to incidental findings or discovery of indeterminate lesions within the pancreas or outside of it.

The finding of a pancreatic cyst can be worrisome for both physicians and patients owing to the fear of having PDAC[61]. The fundamental diagnostic uncertainty associated with whether pancreatic cysts are indolent or likely to progress to adenocarcinoma often triggers overtreatment, which would be surgical resection of the cyst and a portion of the pancreas. Although it is known that certain mucinous cysts, such as mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs), can progress to adenocarcinoma[62,63], there are currently no diagnostic tests with sufficient specificity to identify the lesions that harbour cancer or are likely to undergo malignant transformation[64]. Work up of these potential precursors of cancer is invasive and can lead to major surgery with substantial postoperative morbidity and even a small risk of mortality. For example, current guidelines for management of IPMNs have relatively high sensitivity for detecting high-risk lesions[65] but have low specificity, capturing a high proportion of nonprogressive lesions. Despite improved perioperative outcomes, pancreatic resections for pancreatic cysts have 2–4% operative mortality and 30–40% morbidity (these are estimations based on the amalgamation of several different studies)[66–70]. Furthermore, these surgeries are costly and require substantial recovery time, both of which can be potentially avoided through development of accurate diagnostic tests for low-risk and high-risk lesions.

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The biology of overdiagnosis

There is an urgent need to improve the ability to identify overdiagnosis at the individual patient level and to accurately determine whether the cancer will progress. To date, discussions of overdiagnosis have largely been based on epidemiological findings rather than on the underlying biology. The identification of biological mechanism(s) that determine tumour aggressiveness could help identify biomarkers of aggressiveness and guide clinical decisions with respect to both extent and type of treatment and frequency of follow-up. The biological mechanisms that drive the development of aggressive tumours can be organized according to the 'Hallmarks of Cancer', as proposed by Hanahan and Weinberg[71]. What conceivably may distinguish indolent cancers from aggressive ones are the mechanisms that influence the activation of invasion and metastasis, as well as sustained proliferation. Indeed, recent work has revealed that gene expression signatures may predict indolent or aggressive biology (for example, for breast[72] and prostate cancers[73]). Gene panels of aggressive cancers are enriched for genes related to proliferation and metastasis, and gene panels of indolent cancers are enriched for genes related to ageing and senescence[73]. The fundamental gap in knowledge is the underlying mechanisms that lead to these molecular signatures. Here, we do not attempt to review all aspects of the biological underpinnings of overdiagnosis for each tumour type but rather provide a few examples of different aspects: tumour evolution, tumour heterogeneity and the tumour microenvironment.

Tumour evolution.

The course of growth and development of a normal single cell (or a few cells) into a heterogeneous tumour mass is propelled by gene mutations or other molecular changes in the cell in concert with selection pressure from the microenvironment[74]. To develop a better understanding of tumour evolution, there is a need to understand the process of initiation and the causal intrinsic and extrinsic factors. To date, application of the principles of natural selection in breast cancer[75], pancreatic cancer[76], prostate cancer[77] and lung cancer[78] has revealed insights into the molecular events that make these diseases highly lethal. However, the selective pressures that lead to indolent lesions in these organs remain poorly understood. For example, pathologists have proposed a continuum of morphological features to describe the transition from DCIS to invasive breast cancer[79], but comparative analysis of gene expression between DCIS and invasive cancer[79–81] found no common or consistent genetic changes associated with this transition. Some protein differences were observed (for example, an increase in insulin-like growth factor binding protein 2 (IGFBP2)), but this is likely more a consequence of transition than a cause. Similarly, the step-wise model from pancreatic intraepithelial neoplasia transitioning to invasive carcinoma has also been challenged recently. The authors reported that a single neoplasm can give rise to multiple independent lesions that diverge spatially and genetically overtime[82]. These studies highlight the ways in which applications of evolutionary concepts can reveal new insights into these diseases and may help us better understand how to identify indolent and aggressive cancers using molecular methods.

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Tumour heterogeneity.

Even for the same cancer type, tumours have distinct morphological and phenotypic profiles, including differences in gene expression, proliferation and metastatic potential. Intratumour heterogeneity is closely related to cancer progression, resistance to therapy and recurrence[83]. Deep sequencing and single cell sequencing have contributed greatly to our understanding of the extent of tumour genetic heterogeneity and are beginning to provide information that can be used to determine the likelihood a tumour will progress. For example, large-scale sequencing studies of both primary and metastatic cancers have shown that prostate cancer consists of different molecular subtypes[24,84–87], with 74% falling into 7 categories: 59% with gene fusions (46% involving *ERG*, 8% involving ETS variant 1 (*ETV1*), 4% involving *ETV4* and 1% involving friend leukaemia integration 1 transcription factor (*FLI1*)), 11% with speckle-type POZ protein (SPOP) mutations, 3% with FOXA1 (also known as HNF3α) mutations and 1% with isocitrate dehydrogenase 1 (IDH1) mutations[24]. The precise relationship between these molecular subgroups and the aggressiveness of the cancer is not currently known, but transmembrane protease serine 2–ERG (*TMPRSS2–ERG*) fusions appear to mediate invasion[88]. Other alterations occur in a non-mutually exclusive manner across many of the subtypes. Some alterations, such as *PTEN* loss, 8q24 gain and *TP53* mutations, have been shown to be prognostic for poor outcome[89–91].

One approach to develop biomarkers to distinguish indolent from aggressive cancers is to compare the genomic, transcriptomic, proteomic and/or immune profiles of what are thought to be indolent and aggressive cancers or more commonly to compare screen-detected (less aggressive) and interval or incidental cancers (more aggressive). This approach has been fruitful for prostate cancer[24,84–87], and applications of omics approaches to breast cancers may also appear to help distinguish aggressive lesions from less aggressive or indolent ones. Specific findings from these studies have shown that there are molecular characteristics of tumours, such as germline DNA repair defects in prostate cancer that are associated with disease aggressiveness[92] and *TP53*, protein phosphatase 1 regulatory subunit 3A (*PPP1R3A*) and histone-lysine *N*-methyltransferase 2B (*KMT2B*) mutations that occur more frequently in interval breast cancers than in screen-detected breast cancers[93].

Tumour microenvironment.

There is evidence of the profound influence of stroma on growth and progression of tumours[94]. The main stromal components of the tumour microenvironment are angiogenic vascular cells, infiltrating immune cells and non-immune cells (for example, cancer-associated fibroblasts). The immune infiltrates of high-grade DCIS with a history of recurrence contain higher percentages of forkhead box P3 $(FOXP3)^+$ cells, $CD68^+$ and $CD68^+$ proliferating cell nuclear antigen $(PCNA)^+$ macrophages, human leukocyte antigen-DR isotype $(HLA\text{-}DR)^+$ cells, $CD4^+$ T cells, $CD20^+$ B cells and total tumour-infiltrating lymphocytes than non-high-grade DCIS[95]. Tumours with similar molecular profiles may have very different growth trajectories dependent upon differences in stromal influence. For example, the lung microenvironment is thought to play a role in determining tumour progression[96–99]. Similarly, a hallmark feature of PDAC, including those that arise from mucinous cysts[100], is an extensive desmoplastic reaction, and subtypes of PDAC may be defined based on stromal gene expression signatures[101]. An emerging area of interest related

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to the tumour microenvironment is the microbiome, which has been studied in the context of cancers of the lung, prostate, pancreas and other organs[102]. Further research on the influence of the microbiotic flora of an individual on cancer risk is expected to advance our understanding of the biology of overdiagnosis.

Research needs

One of the greatest needs is to develop biomarkers and/or imaging methods that can more accurately detect early-stage cancers or precancerous lesions and determine which are likely to progress and to determine how best to inform the patient. The biology and molecular pathways that lead to overdiagnosis are just beginning to be understood, and more research is needed to fully understand the mechanisms and to use this information to accurately determine whether a cancer is indolent or aggressive. Some of the resources needed to refine the characterization of overdiagnosis at the patient level are labour intensive, particularly those that require prospective, longitudinal collections of samples (BOX 1). The US National Cancer Institute (NCI) has developed two research consortia, the Early Detection Research Network (EDRN) and the Molecular and Cellular Characterization of Screen-Detected Lesions (MCL), whose missions include developing assays to better distinguish indolent from aggressive cancers (BOX 2). The two general research approaches in this area are to determine the molecular profiles of indolent versus aggressive cancers that can be used to develop biomarkers or panels of biomarkers and to understand the molecular and signalling pathways for cancer development that can be used to develop biomarkers or be targeted for preventive interventions. It is unclear which approach will be most productive in any given situation. Given the clinical importance of overdiagnosis and the level of research in this area, it seems likely that more accurate tests will be developed and deployed in the future. In the following section, we outline some of the needs, with attention to those that are tumour type-specific, However, some needs are common to multiple cancer types, including more accurately determining the extent of overdiagnosis in different patient populations, understanding tumour evolution, the role of the microenvironment and additional longitudinal studies.

Prostate cancer.

An important issue is whether a Gleason 6 cancer will progress to Gleason 7 or higher. A number of studies have shown that Gleason pattern 3 (GP3) cancers often harbour the same somatic DNA alterations as an adjacent Gleason pattern 4 (GP4) cancer, which may be indicative of either a common clonal origin or disease progression[103–106]. A single longitudinal study of the clonality of GS6/GG1 and higher-grade subsequent lesions in men on active surveillance supports a common clonal origin of GP3 and GP4 tumours in some cases, which suggests the potential for GP3 to progress to GP4 (REF.[107]). Improved molecular interrogation of prostate cancer needle biopsy samples is needed to determine whether samples with only GP3 represent adequate sampling of an indolent lesion or are part of a larger tumour already containing GP4 with more malignant potential. There is also a need for improvements in imaging technology, such that if a man is diagnosed with GS6/GG1 prostate cancer, clinicians can have sufficiently high confidence that the patient does not harbour any Gleason 7 disease. While imaging by itself may not be able to fully

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rule out high-grade cancer, magnetic resonance imaging (MRI)–ultrasound fusion-directed biopsies of suspicious lesions can lead to more accurate determinations of Gleason scores. This would make active surveillance more appealing for men with GS6/GG1 disease. However, further refinements in MRI will be necessary if it is to be accurate enough to detect high-grade cancer[108].

Several tests have been reported to improve the detection of clinically important prostate cancer and to distinguish low-grade cancer from high-grade cancer. A meta-analysis of the diagnostic accuracy of the prostate health index (PHI)[109] (a combination of total PSA (tPSA), free PSA (fPSA) and [−2]proPSA (p2PSA)) and a panel of four kallikreins (4 K-panel) reported that the PHI had a pooled sensitivity of 93% for high-grade prostate cancer (Gleason score 7 and above) at a specificity of 34% and that the 4 K-panel had a pooled sensitivity of 87% for high-grade prostate cancer at a specificity of 61%[110]. Combining PSA with prostate cancer antigen 3 (*PCA3*) and *TMPRSS2-ERG* urinary RNAs improves the specificity for aggressive prostate cancer (Gleason score 7 and above) to 39% compared with 18% for PSA alone while maintaining a sensitivity of 95%[111]. Furthermore, OncotypeDx Genomic Prostate Score (GPS), a 17-gene expression array, has been reported to be associated with increased risk of biopsy upgrading in men undergoing active surveillance and could be useful in managing these men[112]. Additional research is needed to determine whether these or other tests can result in a significant decrease in overdiagnosis.

Breast cancer.

To date, most attempts to discover biomarkers for aggressiveness have looked for molecular differences between noncancerous tissues and cancers with different degrees of aggressiveness. Many of the detected alterations are consistent with what is known about the biology of tumour development and progression[113]. Evidence suggests that breast cancer progression is influenced by signalling between cancer cells and non-malignant cells, such as macrophages, T lymphocytes and mast cells[95],[114], and profiling the microenvironment is another approach to develop assays to distinguish indolent from aggressive cancers.

Modelling can be applied to gene expression and sequence data to begin to answer questions about progression. One such exercise demonstrated a high probability that most cases of DCIS and accompanying or subsequent invasive carcinoma arise simultaneously from a common progenitor and evolve in parallel[115]. This would seem to contradict the concept of evolutionary selection pressure, which is assumed to be different between in situ versus invasive cancers, and an intrinsic cancer genomic instability and/or mutator phenotype. However, a better conceptual model might involve mutations (or other epigenetic and/or heritable changes) leading up to a point of in situ transformation and initiation followed by minimal ongoing instability. This has been shown in one context to be the result of shortening telomeres contributing to increased instability, followed by a re-stabilization of the telomere (survival of telomere-based crisis)[116]. Subsequent progression, latency, metastasis, plasticity and treatment sensitivity and so on may then be relatively fixed, with only a slow or rare additional selection of genetic changes[117]. In a recent single cell sequence approach, even the clonal heterogeneity of the invasive cancer was also seen in the

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DCIS[118]. If the malignant potential and rate of progression are relatively fixed at the time of initiation, several important questions remain. How is malignant progression programmed, or what biological properties at initiation lead to faster, slower or indolent progression rates? Can these properties be used to better stratify DCIS and localized invasive carcinomas? Finally, what are the likely biological properties, if they are not directly related to gene expression or mutation — is this the proof of concept for control of progression by the microenvironment, tumour and/or stroma cell metabolism or host factors including immune recognition?

Lung cancer.

As with other cancers, next-generation sequencing has been used to determine the mutational landscape of lung cancers[119–122]. While differences between cancer and normal lung tissues have been described[123], the mutations that accurately distinguish aggressive from indolent cancers have not been determined. Dissecting the molecular pathways from preneoplasia to carcinoma in situ and a comparison of interval with screen-detected lung cancers at the genetic level will be critical for identifying biomarkers related to rapidly progressing and aggressive tumour phenotypes. As with other cancers, investigators are examining the role of the microenvironment in lung cancer progression[94,124]. There must also be a concerted effort to improve imaging analysis to better classify these tumours and an emphasis on molecular profiling to determine which computed tomography (CT)-detected lung nodules represent aggressive lung cancer. Current imaging methods have high sensitivity for lung cancer but low specificity and consequently very high false positive rates (approximately 95%)[45,46]. A number of investigators are exploring the use of radiomics to better classify LDCT images of lung nodules[125,126]. Radiomics is the process of converting standard of care digital medical images into quantitative image-based feature data that can be subsequently analysed using conventional biostatistics and machine learning methods. This will facilitate early treatment and thereby improve lung cancer outcomes. As over 70% of lung cancers in the USA occur in individuals who fall outside NLST criteria (persons aged 55–74 years who have a ≥30 packs a year smoking history and currently smoke or have quit in the past 15 years), there is also a need for research to develop molecular biomarkers to identify additional individuals who would benefit from LDCT screening[127].

The recently announced SUMMIT study in the UK, a lung cancer screening project, plans to enrol 50,000 participants, half of which will be people who meet certain criteria based on whether they currently smoke or have smoked regularly in the past (equivalent to the current criteria for LDCT screening) and half who do not have a significant smoking history or will have never smoked. All participants will provide a blood sample annually for 2 years. The blood samples will be used to develop and evaluate a blood test for early lung cancer detection. Another aim is to determine the feasibility of implementing a lung cancer screening programme to help more at-risk people in the UK.

Pancreatic cysts.

Efforts have focused on using genetic-based, blood-based, microbiome-based and immune-based associations to develop biomarkers to help stratify indolent and aggressive mucinous cysts[62,128,129]. Studies are currently at the preclinical and translational stage[64]. Research

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is needed to determine how genetic drivers of pancreatic cyst formation interact with the surrounding tumour microenvironment to fuel malignant progression and to understand the interactions between the biology and physical attributes of cystic lesions of the pancreas. Although guidelines exist for the management of cystic lesions, they are increasingly being detected because of increased use and sensitivity of abdominal imaging modalities. It is challenging using current imaging techniques to determine which cysts are cancerous or are likely to become cancerous. Investigators are working to determine whether radiomic features on diagnostic imaging can be used to more accurately classify these lesions[130,131]. For effective management of the disease and to avoid putting patients through unnecessary resection, it will be useful if a correlation can be deciphered between imaging features and molecular predictors of malignancy.

Perspective

Screening tests can incur both benefits and harms. Benefits include the detection of an early-stage cancer or even a precursor lesion and the possibility of a better treatment outcome. Harms include overdiagnosis, negative side effects of unnecessary treatment and adverse events associated with the screening test itself and subsequent diagnostics, such as biopsies that can result in perforation or infection. Screening tests miss some aggressive life-threatening cancers that become symptomatic between scheduled screening tests. One possible approach to decrease the extent of overdiagnosis is to develop an initial screening test that detects fewer indolent cancers. For example, the PHI and 4K-panel tests are reported to be as sensitive as PSA for aggressive prostate cancer (Gleason 7 and above) but detect fewer low Gleason grade cancers. An alternate approach is to use a broad sensitive initial screen followed by a test that distinguishes indolent from aggressive cancers (FIG. 3). For example, LDCT for lung cancer, which is very sensitive, followed by a molecular test that would be very specific for aggressive cancer. Indeed, both approaches are being actively pursued.

The estimates of overdiagnosis for specific types of cancer vary widely, depending on population, study design and statistical methods used, but whatever the frequency, overdiagnosis presents a potentially substantial harm to the patient and a clinical dilemma. How does one who is told that their cancer has a given chance of progressing to metastatic disease decide what to do? Do they undergo surgery, radiation, and/or chemotherapy or active surveillance? It is clear that tests, either imaging or molecular, that can accurately distinguish aggressive from indolent disease are needed, but there is also a need to improve decision sharing and decision aids. Although guidelines frequently recommend that the physician discuss the potential benefits and harms of screening with the patients, evidence indicates that more effort is needed to ensure that physicians spend more time discussing potential harms and benefits with their patients and that decision aids are effectively employed[132–134].

Glossary

Active surveillance

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A treatment plan that involves closely watching a patient's condition but not giving treatment unless there are changes in the test results that show the condition is worsening.

Cohort studies
Research studies that compare a particular outcome (such as breast cancer) in groups of individuals who are alike in many ways but differ in certain characteristics (for example, women who are screened for breast cancer compared with those who are not).

Decision aids
Evidence-based educational tools that facilitate shared decision making, improve knowledge of treatment options, may increase satisfaction with treatment choice and likely facilitate long-term quality of life. They include educational literature, videos and website interactive programmes.

Ecological studies
Observational studies that focus on the comparison of groups rather than individuals. Data are analysed at the population or group level rather than at the individual level.

Gleason pattern
In terms of microscopic appearance of prostatic carcinoma, there are a number of different recognizable patterns that range in number from 1 to 5, with pattern 1 most resembling normal glands and pattern 5 least resembling normal glands.

Gleason score
Prostate cancer is often heterogeneous, with often more than one pattern being present in a given tumour nodule. Gleason score is the sum of the most common and second most common patterns (for example, 3 + 4 = 7) in prostatectomy specimens and the most common and highest pattern in needle biopsy samples. Gleason scores range from 2 to 10.

Grade Group
With modern grading, it was found that almost all prostate cancers range from Gleason score 6 to 10. It is often assumed by many that a Gleason 6 out of 10 is quite aggressive, when in fact this is essentially the lowest grade one can have. Grade groups take this into account by referring to Gleason score 6 tumours as Grade Group 1 (GG1). It also forced a separation of Gleason 7 tumours (which could be either Gleason 3 + 4 = 7 or Gleason 4 + 3 = 7) into two groups because these are known to have a substantially different prognosis.

Incidentalomas
Unanticipated findings that are not related to the original diagnostic inquiry.

Interval cancers
Cancers missed during routine screening but diagnosed between scheduled screening tests.

Overdiagnosis
A condition that fulfils standard diagnostic criteria but would not go on to cause symptoms or death. Cancer overdiagnosis occurs most frequently when a tumour is identified by a screening test but may also be detected as an incidentaloma on images of unrelated target organs.

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Reservoir of silent and non-lethal cancers

The existence of a substantial number of subclinical cancers that can be found through routine screening or imaging.

Sigmoidoscopy

A procedure in which a flexible, narrow tube with a light and tiny camera on one end, called a sigmoidoscope or scope, is used to look inside a patient's rectum and lower colon. During sigmoidoscopy, abnormal growths in the rectum and sigmoid colon can be removed for biopsy.

SPOP

The *SPOP* gene encodes speckle-type POZ protein, which is thought to modulate the transcriptional repression activities of death-associated protein 6 (DAXX) and is part of an E3 ubiquitin ligase complex that is involved in controlling protein stability of the androgen receptor and some of its transcriptional co-activators.

Thoracotomy

A surgical procedure in which a cut is made between the ribs to see and reach the lungs or other organs in the chest or thorax.

TMPRSS2–ERG

Fusion of the genes *ERG* and transmembrane protease serine 2 (*TMPRSS2*) is the most frequent genomic alteration in prostate cancer. *ERG* is an oncogene that encodes a member of the family of ETS transcription factors. *TMPRSS2* is an androgen-regulated gene that is preferentially expressed in the prostate.

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Box 1 |

Resources needed to support research on cancer overdiagnosis

- Registries, such as Surveillance, Epidemiology, and End Results (SEER), National Health and Nutrition Examination Survey (NHANES), that can provide data on the incidence and outcomes of screen-detected, interval-detected and symptom-detected cancers.
- Collections of clinically annotated normal, neoplastic and tumour tissues from both screen-detected and symptom-detected cancers that can be used to study the natural history of cancers. These specimens may come from longitudinal screening or surveillance programmes.
- Specimens collected from cohorts and control arms of randomized screening and treatment trials with long-term follow-ups.
- Precancerous and indolent lesions collected from surgical and autopsy specimens.
- Specimens and imaging data from immunologically susceptible individuals to understand the selective forces shaping the evolution of cancer in its earliest stages.
- Imaging and biological specimens obtained from animal models with strain-specific behaviours.

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Box 2 |

Research focus of NCI's MCL Consortium

- Examination of genomic and microenvironmental determinants that distinguish indolent tumours from aggressive cancers.
- Evaluation of host and environmental factors that affect tumour development and progression, including the roles of the cells of origin, obesity, the microbiome, chronic infection, inflammation, immune response, ageing and DNA repair enzyme polymorphisms.
- DNA sequencing and proteomic analysis of precursor lesions, circulating tumour cells and host niches to clarify the selection pressures that influence the phenotypic trajectory of a tumour.
- Determination of molecular and genomic predictors of aggressive lesions using longitudinal data, as natural history studies must examine tumour dynamics over time and not at a single time point.
- Collection of cross-sectional data (observing many subjects at the same point of time) with annotated samples from unique human cohorts, animal models with strain-specific behaviours and immunologically susceptible individuals to study the selective forces shaping the evolution of cancer in its earliest stages.
- Collection of longitudinal data (for example, annotated biological specimens, annual imaging and medical records) from cohorts of patients who do not undergo treatment to understand tumour dynamics and trajectory.
- Functional imaging and imaging of spatiotemporal modelling of tissues.
- Modelling to merge various data sets and to consider the characteristics of tumour cells in a holistic way.
- Construction of a Precancer Imaging Atlas to serve as a reference on indolent lesions.

MCL, Molecular and Cellular Characterization of Screen-Detected Lesions; NCI, National Cancer Institute.

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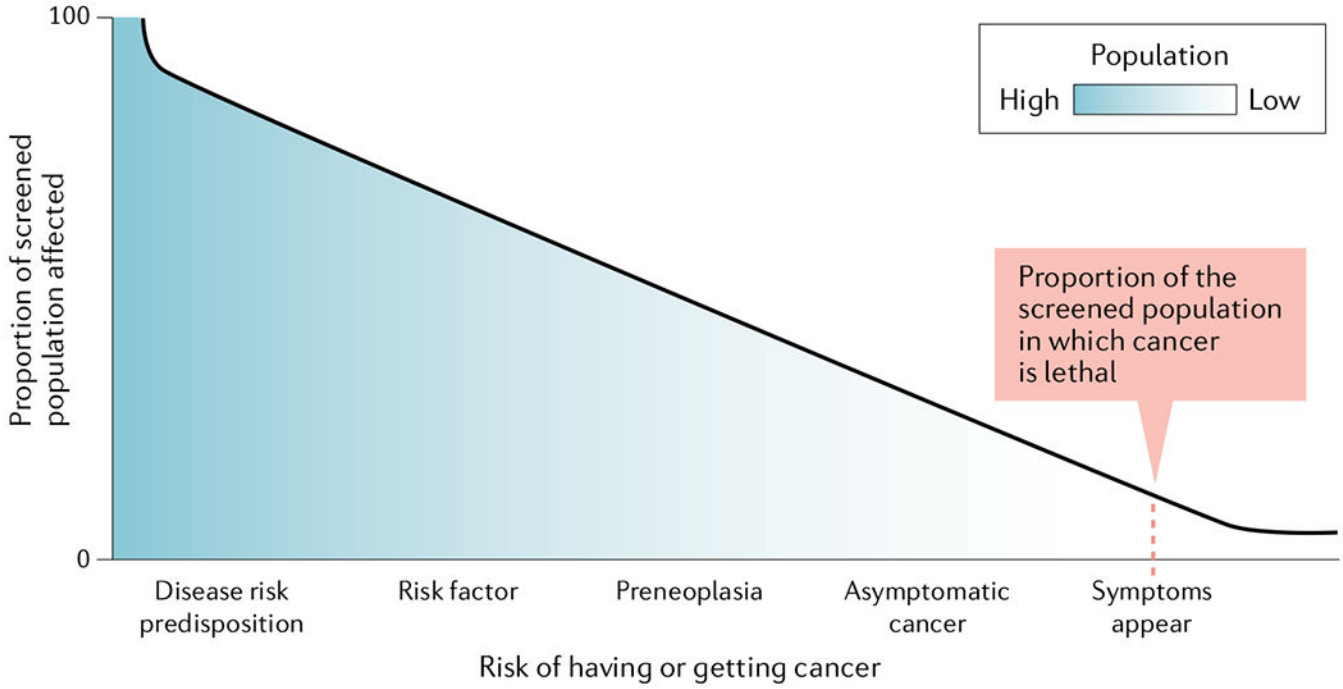

Fig. 1 |. Magnitude of the problem of overdiagnosis owing to screening.

This schematic illustrates that only a small proportion of a screened population will have cancer that is lethal. However, screening for asymptomatic cancers, preneoplastic lesions or risk factors has the potential to label very large numbers of people as at risk , including those who were not destined to develop life-threatening disease.

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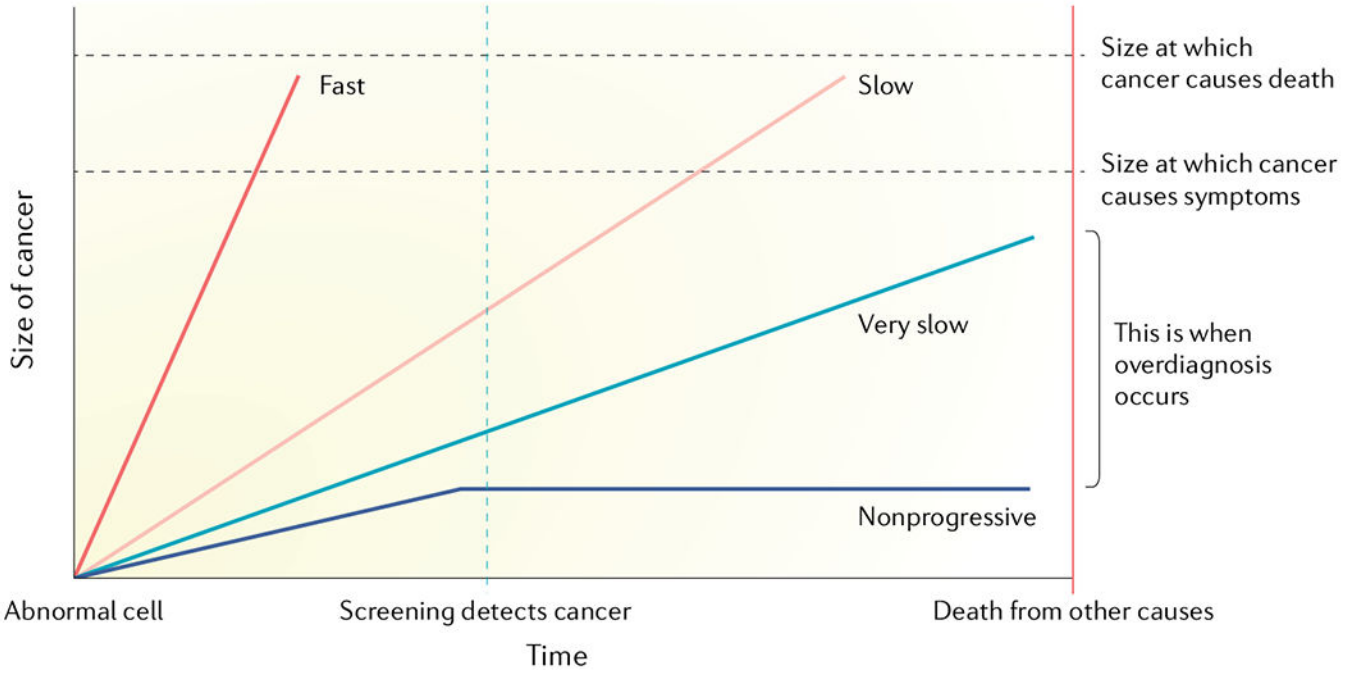

Fig. 2 |. Slow versus rapid progressors — unpredictable tumour growth trajectory.
This schematic illustrates the large variability in growth rates and lethal potential of malignant cells. Overdiagnosis occurs when screen-detected cancers are either non-growing or so slow- growing that they would never cause medical problems before death from other causes. Therefore, the prerequisites of overdiagnosis are a reservoir of silent disease and a screening or detection activity that leads to detection of subclinical disease within the reservoir. Adapted with permission from REF.[9], Oxford University Press.

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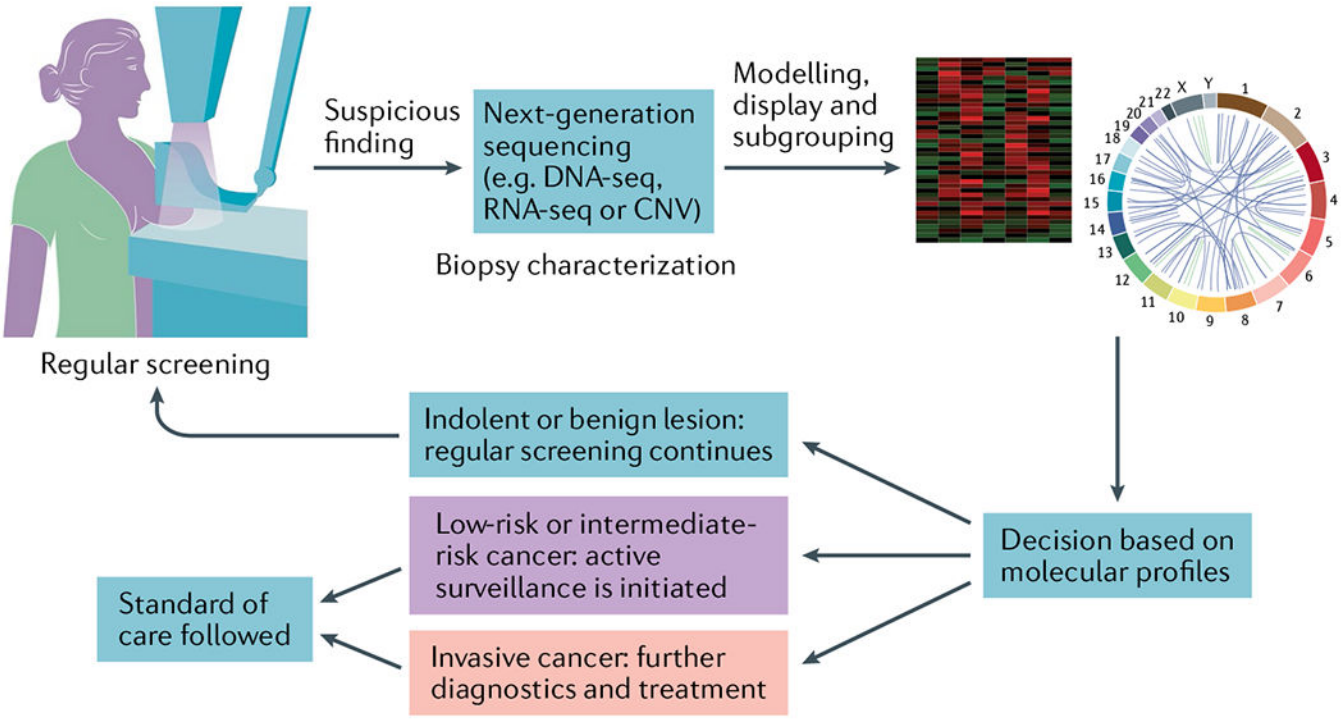

Fig. 3 |. Molecular profiling to distinguish indolent from aggressive cancers.

The schematic illustrates the use of validated molecular aberrations, including cellular and phenotypic changes, that could help develop decision criteria for clinical management. This hypothetical workflow assumes that there is a screening process in place, overdiagnosis occurs and validated molecular assays exist to stratify screen-detected lesions as low-risk , intermediate-risk or invasive cancer. The schematic is not intended to be the only possible workflow , and other clinical scenarios may require additional diagnostic work-ups at any stage of this workflow. CNV, copy number variation; seq, sequencing.

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Table 1 |

Overdiagnosed cancers

Cancer type	Estimated amount of overdiagnosis	Screening modality
Breast	25%[9]	Mammography
Prostate	50–60%[9]	PSA
Lung	13–25%[14]	CT
Melanoma	Approximately 50–60%[9,15]	Crude estimate based on population trend
Kidney	Twofold increase in incidence but no increase in deaths[9]	Incidental detection on abdominal CT
Thyroid	Twofold increase in incidence but no increase in deaths[9,16]	Incidental detection by imaging performed for other reasons including sinus symptoms and headaches or by palpitation of the neck

CT, computed tomography; PSA, prostate-specific antigen.

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