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Optical imaging for screening and early cancer diagnosis in low-resource settings

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Abstract

Low-cost optical imaging technologies have the potential to reduce inequalities in healthcare by improving the detection of pre-cancer or early cancer and enabling more effective and less invasive treatment. In this Review, we summarise technologies for in vivo widefield, multi-spectral, endoscopic, and high-resolution optical imaging that could offer affordable approaches to improve cancer screening and early detection at the point-of-care. Additionally, we discuss approaches to slide-free microscopy, including confocal imaging, lightsheet microscopy, and phase modulation techniques that can reduce the infrastructure and expertise needed for definitive cancer diagnosis. We also evaluate how machine learning-based algorithms can improve the accuracy and accessibility of optical imaging systems and provide real-time image analysis. To achieve the potential of optical technologies, developers must ensure that devices are easy to use; the optical technologies must be evaluated in multi-institutional, prospective clinical tests in the intended setting; and the barriers to commercial scale-up in under-resourced markets must be overcome.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

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Therefore, test developers should view the production of simple and effective diagnostic tools that are accessible and affordable for all countries and settings as a central goal of their profession.

Short Summary:

The ability to detect precancer at the point-of-care is important to reduce global inequities in cancer outcomes. This Review outlines how low-cost optical imaging technologies, slide-free microscopy and machine learning can improve imaging performance and provide real-time interpretation in settings with limited resources.

Introduction

Cancer is the first or second leading cause of premature death in 134 countries, and it is estimated that the global incidence of cancer will increase by 50% from 2018 to 2040 ref.[1]. The number of cancer cases is especially high in low- and middle-income countries (LMICs) [2], which have the least resources and infrastructure to care for people with cancer. It is projected that by 2030 75% of global cancer deaths will occur in LMICs [3]. Disparities also exist within high-income countries such as the USA, where there are substantial disparities in cancer outcomes [2,4] in minority racial and ethnic groups and other medically underserved populations[4]. The term ‘low-resource settings’ refers to settings where outcomes are limited due to human resource limitations, underdeveloped infrastructure, financial shortages, restricted social resources, suboptimal healthcare service delivery, geographic and environmental factors, lack of knowledge, research challenges, or influences of beliefs and practices [5]. In this Review, we adopt this approach and use the term to refer to settings in which healthcare systems do not meet standards recommended by the WHO or other national norms due to a lack of resources.

Sustainable Development Goal 3.4 calls for all countries to reduce preventable mortality due to cancer by one-third by 2030 ref.[6]. In support of this goal, the Global Action Plan on Non-Communicable Diseases (NCDs) produced by the World Health Organisation (WHO) has proposed a target of 80% availability of affordable services for prevention, early detection and timely treatment of cancer together with palliative care[7]. Meeting these goals requires the development and delivery of affordable, accurate and accessible technologies for screening and early detection of cancer.

Cancers that arise in epithelial tissue account for 80–90% of all cancer cases and could be prevented or cured if detected in the pre-cancerous or early stages[8]. Most epithelial cancers occur in sites that can be imaged directly including the uterine cervix, oral cavity, oesophagus, colon and rectum[8]. These cancers follow a similar path of progression, evolving from hyperplasia, through increasing grades of dysplasia and eventually invasive cancer [9] (Fig. 1a). Optical imaging technologies[10-22] can detect and quantify early morphological and molecular changes associated with neoplastic cells and the supporting vasculature. Despite the promising clinical performance and potential low-cost of optical imaging technologies, only a few examples have been successfully translated and commercialized for use in low-resource settings[23].

Cancer screening programmes that test asymptomatic individuals can improve the detection of precancers and early cancers. Screening programmes usually target at-risk groups to minimize the potential harms of screening, including false-positive or false-negative test results, and overdiagnosis of cancers that would not have caused symptoms and did not need treatment. When coupled with timely diagnosis and treatment, screening programmes can reduce cancer incidence rates and improve survival. In low resource settings, screening is generally recommended less frequently and for a smaller population of individuals at increased risk because fewer screening tests are available (Box 1). Tests available in low-resource settings are often less accurate than those available in high-resource settings; for example, screening for cervical cancer using visual inspection with acetic acid, which is mostly used in low-resource settings, is less effective than screening with human papillomavirus (HPV) DNA testing, which is widely used in high-resource settings[24]. All individuals who screen positive require confirmatory diagnostic testing, which usually involves image-guided biopsy. In low-resource settings, the availability of many imaging modalities is limited to urban centers, and resources for histopathology are limited. As a result, individuals who screen positive can experience delays in receiving a cancer diagnosis and therefore delays in initiating treatment[25,26].

In this Review, we outline high priority needs to enable screening and early detection of cancer in low-resource settings. We review advances in low-cost optical imaging techniques with two important use cases in low-resource settings (Fig. 1b), including, first, the use of, in vivo optical imaging to improve early detection of cervical, oral, anal and oesophageal cancer and, second, the use of in vitro, slide-free optical microscopy to improve accessibility to histopathological diagnosis to guide and monitor effective cancer treatment. We also consider ways in which machine learning could increase the diagnostic speed and accuracy as well as reduce the need for clinical expertise at the point-of-care. We conclude by discussing strategies to accelerate the development and equitable translation of technologies to medically underserved settings.

Optical imaging for cancer detection

Imaging techniques are used to help physicians see whether a tumour is present. Common imaging modalities include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) scans and optical imaging technologies such as colposcopy and endoscopy. To make a definitive diagnosis, biopsy samples can be obtained with a needle or a biopsy forceps. Biopsies are often obtained by an expert specialist physician during an imaging procedure (for example, endoscopy or ultrasound) or at the time of surgery. Biopsied tissue is fixed, sectioned, stained and examined under a light microscope by a pathologist. Below we outline some of the key optical techniques that are promising for improving early detection of epithelial pre-cancers in low- and high-resource settings and could be integrated into the workflow described above.

Widefield imaging

Advances in low-cost, quantitative widefield and high-resolution optical imaging systems have shown great promise to improve early detection of epithelial pre-cancers (Fig. 1). For accessible epithelial surfaces, visual inspection or digital white light imaging with a low-power microscope or endoscope can reveal potentially precancerous lesions [23]. For example, changes in the colour or texture of the epithelial surface observed under visual examination with white light illumination can help to identify precancerous oral lesions [27]. Low-power magnification can increase the accuracy of the identification of precancerous lesions; for example, a colposcope is a microscope used to examine the uterine cervix with 6× to 14× optical magnification to reveal changes in the epithelial surface that indicate a possible precancerous lesion or early cancer [28]. Fiber optic endoscopes can be used to image epithelial surfaces within the gastrointestinal (GI) tract. High-definition endoscopes can achieve optical magnification of 35× and endoscopes with variable digital and optical magnification ranging from 60× to 150× are available [29-31].

Illumination with green light enhances contrast for small blood vessels near the surface of the epithelium and can help identify vascular atypia that accompanies the development of precancerous lesions [32] (Fig. 1a). Topical contrast agents can be applied to increase the contrast between healthy and precancerous tissue to localize lesions. For example, acetic acid increases light scattering within precancerous tissue making lesions appear white and Lugol's iodine stains glycogen containing cells dark brown but does not stain precancerous lesions [32]. Illumination with (narrow-band) blue light, which is strongly absorbed by haemoglobin, can also reveal vascular atypia [10] and can increase the accuracy of precancer detection. Alternatively, blue–green illumination can excite endogenous tissue fluorescence, which can be viewed by eye or captured with a low-cost digital camera [20,33]. Precancerous lesions are associated with decreased blue–green collagen fluorescence and increased red fluorescence owing to the presence of endogenous porphyrins. Autofluorescence imaging of oral tissue can be used to detect precancerous lesions with higher sensitivity than examination under white light[34-36].

High-resolution imaging

High-resolution imaging techniques have been developed to reveal cellular and sub-cellular changes within the epithelium [19,37-39]. For example, confocal microscopy uses a pinhole aperture to reject multiply scattered photons and can image changes in the size, shape and spacing of cellular nuclei throughout the entire epithelium that are characteristic of precancerous lesions [40-43]. Topical contrast agents such as acetic acid can also enhance nuclear scattering and contrast in reflectance mode confocal imaging [44], and fluorescent dyes such as 2-NBDG (2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxyglucose) can be used to measure glucose uptake and changes in metabolic rate and nuclear morphology [45]. Multi-photon fluorescence microscopy uses a focused, short pulse duration, near-infrared (NIR) excitation beam to limit the volume of tissue in which fluorescence is excited, providing high spatial resolution images within the epithelium [19,46]. Confocal and multi-photon microscopes can produce images with sub-cellular resolution; however, the depth of penetration is typically less than the thickness of the epithelium.

Optical coherence tomography (OCT) uses a coherence gate to provide high spatial resolution. Typically, OCT systems can image up to 2 mm deep in scattering tissue; therefore, OCT can image beneath the epithelial surface and identify microinvasive cancers, although sub-cellular resolution is not typically achieved [39]. Photoacoustic imaging uses a pulsed laser to deliver focused, high-intensity illumination, which is absorbed by chromophores such as haemoglobin causing them to undergo thermoelastic expansion producing an acoustic wave that is detected using an ultrasound transducer [38]. Photoacoustic images of microvasculature can be produced at depths of up to several hundreds of microns with sub-micron resolution or at depths of several centimetres with reduced acoustic-resolution [47]; this extended depth of imaging is useful for the early identification of skin cancers and breast cancer.

Increasing access to optical imaging

Major improvements in the quality of portable, sophisticated optical imaging systems have led to a substantial decrease in the cost of many high-performance optical components. Driven by a revolution in consumer grade imaging devices (such as, cell phone cameras), there are now various inexpensive, bright, low-power light emitting diodes (LEDs) for illumination; sensitive and high-resolution charged-coupled device (CCD) and complementary metal oxide semiconductor (CMOS) cameras for detection; high-performance plastic optical imaging components; and low-power, high-performance computers to store and process images. These components are being used to design low-cost optical imaging systems that meet the unique needs of low-resource settings (Box 2). Many of these optical systems use endogenous contrast and do not require consumables such as contrast agents, which might be expensive or difficult to stock in low-resource settings.

In addition to requiring suitable instrumentation, many optical imaging techniques currently require clinical personnel with the expertise to interpret images at the point-of-care. Access to such experts can be limited in some low-resource settings. For example, in sub-Saharan Africa, which is comprised of LMICs, there is on average only one pathologist per 1 million patients, a ratio that is nearly 50 times lower than that in high-income countries [48]. Machine learning strategies can be used to address this problem by automating image analysis [22,49]. Additionally, machine learning could be used to improve image quality, reducing the device requirements needed to obtain images with sufficient quality to detect cancer.

In vivo optical imaging

There is potential for imaging technologies to improve early detection of cancer. However, despite this potential, many optical imaging technologies are still too complex and expensive for use in low-resource settings. Substantial effort is needed to develop and translate devices that are simple, robust , and affordable for effective clinical use. The following sections outline how optical imaging could facilitate early diagnosis of cervical, oral, anal and oesophageal cancer, particularly in low resource settings.

Helping to eliminate cervical cancer

In May 2018, the Director-General of the WHO announced a global call to action to eliminate cervical cancer [50]. The goals of this initiative include 90% of girls worldwide should receive the HPV vaccine by the age of 15; 70% coverage of screening should be achieved using a high-performance test at the ages of 35 and 45 years; and 90% of women with pre-invasive or invasive cervical disease should receive treatment. The focus of the WHO initiative is on LMICs, where >90% of cervical cancer cases occur [51]. A Cervical Precancer Planning Tool is available to help decision makers in LMICs compare the accuracy of existing screening strategies and to deploy the equipment needed for treatment [52]. However, existing screening and diagnostic technologies will be insufficient to meet the WHO goals. Therefore, there is an urgent need for novel, low-cost and technologically feasible approaches to achieve cervical screening, diagnosis, and treatment in a single visit [53-55].

In high-resource settings, the standard of care includes cervical screening with cytology (Papanicolaou test) and/or HPV testing. Colposcopy and biopsy are then used to diagnose individuals who screen positive. Finally, precancerous lesions (cervical intraepithelial neoplasia grade 2 (CIN 2) or more severe grades [CIN2+]) are treated with a loop electrosurgical excision procedure (LEEP) [56]. This process requires three visits and both pathology services and skilled clinicians are required at each step. As a result, many women are lost to follow-up and are incompletely treated, especially in LMICs [57,58]. The 2021 WHO guidelines include the use of a ‘Screen & Treat’ approach, in which women are screened with HPV testing and, if positive, directly undergo treatment with ablation (cryotherapy or thermal ablation) or excision with a LEEP, avoiding the need for a cervical biopsy and histological diagnosis [59]. This single-visit approach decreases loss to follow-up and removes the need for gynaecology and pathology services. A major limitation of this approach is that it results in overtreatment, as the majority (50–70%) of women infected with HPV do not, and will not, have high-grade cervical disease.

The preferred approach in the WHO guidelines is therefore ‘Screen, Triage & Treat’, in which the decision of whether to perform treatment is based on a positive primary screening test followed by a positive second triage test with or without a histologically confirmed diagnosis [59]. The WHO suggests HPV genotyping, colposcopy, visual inspection with acetic acid (VIA) or cytology as possible triage tests, with the choice depending on feasibility, training, programme quality assurance and local resources [59]. Unfortunately, these triage tests are not widely available in many LMICs [60] owing to cost (HPV genotyping), lack of trained personnel and infrastructure (cytology and colposcopy) and patient inability to access care owing to transportation or financial barriers. Moreover, some of these strategies (such as, VIA) have limited reproducibility and accuracy.

Optical technologies have the potential to offer immediate and accurate triage tests, and many approaches are currently being developed and evaluated, including low-cost, handheld colposcopes, high resolution optical imaging systems, and multi-modal optical imaging systems that integrate widefield and high-resolution imaging devices. These optical imaging approaches can combine high-quality image capture with the potential for online data

management, allowing healthcare providers to visualize the cervix, document exams, and perform a consultation.

Low-cost colposcopes—Low-cost colposcopes have been developed for screening and triage [61], including improvised mobile phone-based systems, commercially available mobile phone-based systems [62-65], and low-cost digital colposcopes [66]. For example, the AV Magnivisualizer is a low-cost ($160), battery-powered, hand-held magnifying device that uses a halogen light to illuminate and visualize the cervix with 2× to 5× magnification [67]. In a study of 100 women who screened positive by VIA, the performance of the AV Magnivisualizer was compared to that of colposcopy performed with the COLpro222DX, a $4,000 high-definition video colposcope, using histopathology as the gold standard. Assessment using the AV Magnivisualizer was followed by colposcopy and was performed by the same person at the same sitting for each participant. Diagnostic accuracy was assessed by computing the area under the receiver operator characteristic (ROC) curve, a metric that characterizes the tradeoff between sensitivity and specificity as the test cutoff is varied; the area under the ROC curve can range from 0.5 (test accuracy equivalent to chance) to 1 (perfect test accuracy). In this study, the area under the ROC curve for the AV Magnivisualizer (0.80) was comparable to that of the colposcope (0.86) [67].

Similarly, the Gynocular is a commercially available, portable, relatively low-cost colposcope (~$3,500) with LED illumination and 5× to 12× magnification. A study of 123 women in Sweden who screened positive owing to an abnormal cervical cytology result found that there were no statistically significant differences in the sensitivity or specificity for the detection of biopsy-proven high grade cervical precancer using a low-cost portable Gynocular colposcope or a standard colposcope [68]. Additionally, a study of 528 VIA-positive and 404 unscreened women in Bangladesh found that there were no statistically significant differences in the accuracy of the detection of cervical lesions with the Gynocular when performed by VIA trained nurses compared with those performed by physicians, although specificity for nurses was found to improve after the first 50 cases [69]. These studies show that trained nurses and physicians can use low-cost colposcopes to provide cervical cancer screening and triage without compromising diagnostic accuracy compared to the standard of care in high-resource settings.

Mobile detection devices—The use of mobile phone-based cameras to acquire digital images for cervical cancer screening or triage, with visual [70] or automated image interpretation [64,65] has also been explored. Such cameras, either used alone or with simple attachments, can consistently obtain digital images of sufficient quality for diagnostic evaluation [71,64]. Additionally, the results of histological diagnosis were found to agree with findings obtained using a mobile phone-based device with 5× magnification and colposcopic findings [70]. The ability to record digital images and videos enables changes in the appearance of precancerous cervical lesions to be measured as a function of time after application of acetic acid and digital images can be used for training purposes [72]. Additionally, smartphone apps can be integrated with the device to provide decision support job aids, document clinical decisions, track outcomes of prevention programmes [62], and provide expert mentorship [73]. Mobile phone-based VIA was used by nurses to screen 4,247

women in rural Eswatini; trained nurses performed VIA with a mobile phone camera, offering same-day treatment where indicated, and a remote expert reviewed a subset of the images to provide regular support and feedback to nurses [73]. This mobile-VIA approach with expert mentoring improved the reliability and reproducibility of VIA, with false positive rates decreasing further with the provision of training and mentoring, decreasing the burden on downstream provision of diagnostic and treatment services.

Despite these advances, only two mobile digital colposcopes are currently commercially available. They include the Mobile ODT Enhanced Visual Assessment system [74] and the Point of Care Tampon (Pocket) digital Colposcope (Box 3) [75]. The Mobile ODT enhanced visual assessment system uses an optical adaptor that connects to a mobile phone camera to provide colposcopy grade images, integrated with digital tools that allow clinicians to document examinations, share results with patients in ways that could encourage participation in screening, and access a reference library to assist with decision making [74]. In a screening study of 3,600 women in the Yunan province in China, who had not previously been screened for cervical cancer, the mobile ODT enhanced visual assessment system was used to perform same-day digital colposcopy for 168 participants who screened positive for high-risk HPV. The digital colposcope identified 15 out of 16 women with CIN2+ lesions detected using standard colposcopy and biopsy [63]. The Pocket colposcope is a digital colposcope designed for vaginal insertion and imaging is performed with the distal tip positioned 30–40 mm from the uterine cervix [75]. The device is powered and controlled by plugging it into a mobile phone, tablet, or computer [76], and incorporates consumer grade light sources and cameras used in smart phones to provide colposcopy quality white-light and green-light images without the need for high magnification optics [66]. The Pocket colposcope has comparable resolving power and colour reproduction accuracy to existing, high-cost fixed colposcopes . In a study of 129 women in Peru, 83% of the physician interpretations of digital images acquired with the Pocket colposcope agreed with the diagnosis obtained with a standard colposcope. The sensitivity and specificity for the detection of cervical precancer were similar for the Pocket colposcope (sensitivity = 71.2%, specificity = 57.5%) and a standard colposcope (sensitivity = 79.8%, specificity = 56.6%) compared to the gold standard of histopathology [23].

Deep learning-based approaches—Although high quality optical images can be captured using low-cost systems, experienced providers are still needed to interpret the images and ensure that the images are satisfactory for diagnosis. This requirement is a major challenge in low-resource settings, where there can be a shortage of human resources for healthcare. As an alternative, deep learning-based approaches have shown promise to provide objective and accurate interpretation of digital images of the cervix [77 78]. For example, Automated Visual Evaluation (AVE) is a deep learning algorithm that differentiates precancerous lesions and identifies patterns of precancer from colposcopic images [49,79]. AVE was developed by training a classifier on large datasets of images of the cervix collected from a population-based longitudinal clinical trial in which confirmatory biopsies were taken. The algorithm detected high-grade cervical precancer (CIN 2+) and advanced cancer with an area under the ROC curve over 0.9 ref. [80,81]. However, there are risks of overtraining and performance drop when deep-learning based algorithms are used

prospectively or to classify images acquired with different colposcopes [82,83]. For example, the performance of the best deep-learning models developed and optimized using a large, multi-institutional dataset of cervical images acquired from five studies using different devices only achieved an area under the ROC curve ranging from 0.73–0.79 ref.[82], which is much lower than earlier estimates of 0.9 ref.[80,81]. Similarly, a study in Nigeria included images acquired with three different systems: a common smartphone, the MobileODT digital colposcope, and a traditional fixed colposcope. The deep learning-based clustering approach could differentiate images acquired with the three systems with 97% accuracy [83]. Thus, to develop robust machine learning classifiers for precancer detection that can be used with any system, there is an urgent need for a large curated set of training images acquired with different sources and with validated diagnoses, such as, that compiled by the Medical Imaging and Data Resource Center (MIDRC) [83].

High-resolution imaging—As an alternative to widefield imaging, several low-cost, high-resolution imaging strategies have been developed for imaging the cervical epithelium. A low-cost, high-resolution fluorescence microendoscope (HRME) can provide in situ diagnosis without the need for biopsy and pathology services. The HRME is a fiber-optic fluorescence microscope, which relays images of tissue in contact with the distal tip of the coherent fiber bundle to a camera. HRME systems, with reported costs as low as $1,200 have been developed including laptop-, tablet-, mobile phone-, and single board computer-based systems [84-86]. This approach displays images of nuclei stained with proflavine (a topical fluorescent dye) on a tablet computer in real time and the software automatically reports whether or not a precancerous lesion is present based on changes in nuclear morphology.

HRME imaging in a mobile van in Brazil was used to facilitate a single-visit, point-of-care Screen, Triage & Treat approach [87]. There was a 37% relative increase in diagnostic follow-up completion rates for people referred to the mobile van (87%) compared with those referred to the central hospital (64%). In vivo HRME imaging in the mobile van provided automated diagnosis with sensitivity and specificity similar to that of colposcopy without the need for biopsy. No significant differences in rates of neoplastic progression were noted between patients exposed to proflavine and those in a matched control group ($p = 0.21$) [88]. The diagnostic performance of HRME to detect CIN 2+ (moderate grade) and CIN 3+ (severe grade) was prospectively evaluated in 1,468 women with abnormal cervical screening results in Brazil [89] and compared to that of colposcopy using histopathologic diagnosis as the gold standard. HRME with morphological image analysis for the detection of CIN 3+ had a similar sensitivity (95.6% vs. 96.2%, $p = 0.81$) and specificity (56.6% vs. 58.7%, $p = 0.18$) to that of colposcopy. Machine learning approaches can further increase the accuracy of HRME. A multi-task convolutional neural network-based algorithm showed no significant differences in the sensitivity and specificity of HRME with neural network analysis for detecting CIN 2+ (sensitivity = 94%, specificity = 58%) compared with that of colposcopy (sensitivity = 95% (p=0,3), specificity = 62% ($p = 1.0$))[22], suggesting HRME could provide a low-cost, point-of-care alternative to colposcopy and biopsy in the prevention of cervical cancer [89].

Confocal imaging systems provide better stray light rejection than the bare coherent fiber bundle of the HRME. Confocal fluorescence imaging of fresh cervical biopsies stained with acriflavine can visualize nuclear morphology at the epithelial surface and at depths of 15–30 μm beneath the surface. The presence of high-grade precancer could be detected from these measurements with high sensitivity using algorithms based on nuclear morphology [90]. Low-cost confocal fluorescence microscopes have been developed to image cervical tissue in vivo. For example, a low-cost (<$5,000), portable confocal microendoscope that employs digital apertures on a digital light projector and a CMOS sensor to implement line-scanning confocal imaging was used to image cervical tissue in vivo [91] (Fig. 1g). The measurements made with the portable confocal microendoscope offered better visualization of nuclear morphology than those obtained with the HRME, contributing to significantly improved recognition of clinically important features for the detection of cervical precancer. For example, observers segmented up to three times as many nuclei per unit area in confocal images of cervical sites with high scattering than in HRME images with less inter-observer variation ($p = 0.002$). However, commercially available confocal microscopes remain too costly and complex for use in most low-resource settings. Efforts to reduce cost and complexity, together with the development and evaluation of simple contrast agents are needed.

Optical coherence microscopy, which combines the spatial gate of confocal microscopy with the coherence gate of OCT could improve the detection of cervical precancer [92]. A study of 159 ex vivo samples with support vector machine-based classification yielded an area under the ROC curve of 0.959 with ten-fold cross validation [93]. Another high-resolution imaging approach, based on two photon excited fluorescence imaging of endogenous NAD(P)H (the reduced form of nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide), was used to characterize the structural and functional metabolic status of freshly excised cervical samples [94]. Diagnostic algorithms for high-grade precancer based on the combination of structural and functional markers had a higher area under the ROC curve (0.949) than algorithms based on structural (0.754) or functional markers (0.850) alone. However, existing multiphoton microscopes are complex and expensive. Additionally, it is difficult to reduce the cost of these devices whilst retaining the ability to detect weak levels of endogenous autofluorescence.

Multi-modal imaging—Multi-modal imaging strategies, combining low-cost widefield and high-resolution imaging have been developed to further improve diagnostic performance. For example, a system that combined OCT with a microscope produced images of specimens resected during a LEEP procedure with good diagnostic accuracy (sensitivity = 88%, specificity = 69%) for identifying high-grade precancer. These results suggest that combining OCT with a colposcope could improve the detection of high-grade squamous intraepithelial lesions [95]. A multi-modal colposcope, consisting of a Pocket Colposcope combined with a high-speed, HRME was used to rapidly image epithelial cell nuclei as it was moved across large areas of tissue to identify precancerous lesions in situ with real time image classification [96].

Achieving early oral cancer diagnosis

Like cervical cancer, oral cancer disproportionately affects people in low-resource settings. An estimated 377,000 people develop cancers of the lip and oral cavity each year and 178,000 deaths are attributable to oral cancer [51]; approximately two-thirds of cases of oral cancer occur in LMICs [1]. Early diagnosis of oral cancer can reduce treatment-related morbidity and improve long-term survival [27]. Unfortunately, oral cancer mortality is higher in LMICs [51] because the cancer is often diagnosed at a more advanced stage than in high-income countries. A retrospective analysis of people living with HIV in Botswana, showed that if the cancer originates in a hidden primary site (tongue, floor of mouth, buccal mucosa, palate, maxilla, and gingiva) or the person resides in a low socioeconomic area with little access to care [97] the risk of presenting with advanced oral cancer is increased [97]. Globally, fewer years of education and/or lower income are associated with an increased risk of developing oral cancer [98]. However, in the USA, people with fewer years of education, no insurance, and/or lower incomes are less likely to receive oral cancer screening exams, even after recent dental visits, which can be effectively integrated with oral cancer screening[99]. In the USA, African American patients with head and neck cancer are more likely to be diagnosed with a high tumour burden and have higher mortality than non-African American patients [100]. The increased incidence and mortality of oral cancer in low-resource settings and marginalised and underserved communities highlights the need to develop approaches to improve access to screening and early detection of oral cancer and its precursors, especially in groups with a high risk of developing oral cancer. It is important to develop approaches that are feasible to implement in low-resource settings, because incidence is high and these settings lack capacity to treat patients with invasive oral cancer.

The standard of care for oral cancer detection is conventional oral examination with palpation followed by biopsy. Although the screening of high-risk groups is cost-effective, most national organizations in the USA do not recommend population-based oral cancer screening because there is no evidence showing that screening asymptomatic individuals reduces oral cancer mortality[27]. In areas with good access to health care resources, opportunistic screening by dentists is recommended [27]; in LMICs , screening by community health care workers is feasible [101,102] and has proven beneficialin countries such as India [21]. However, visual examination with white light illumination is subjective and has poor diagnostic accuracy in distinguishing potentially malignant oral lesions with dysplasia and cancer from benign lesions. Despite the challenges associated with existing screening methods, oral cancer screening has great potential to save lives. The largest oral cancer screening study was a cluster-randomized trial involving 191,873 people in India [103,104]. This study tested the efficacy of three rounds of oral cancer screening performed at three-year intervals based on visual inspection by trained community health workers provided with job aids that included photos of oral lesions. Initial findings indicated that visual inspection led to a significant increase in early-stage diagnosis (72.3% in the intervention group compared with 12.5% in the unscreened control group, $p < 0.05$) and a decrease in 3-year mortality rates from oral cancer (14.9% in the intervention group compared with 56.3% in the control group) [103]. A 15-year follow-up study confirmed that this oral cancer screening programme led to a sustained, cost-effective 12% reduction in oral cancer mortality [104]. Additionally, there was an even larger reduction in mortality of participants

who adhered to repeated screening rounds. Oral cancer screening was most beneficial when performed in people with an increased risk of developing oral cancer such as users of tobacco and/or alcohol; there was a 38% reduction in oral cancer incidence and 81% reduction in oral cancer mortality in tobacco and/or alcohol users who adhered to four rounds of screening [105]. Therefore, opportunistic oral cancer screening could improve the early detection of oral cancer and its precursors, reducing oral cancer related morbidity and mortality.

Autofluorescence imaging—Several non-invasive, adjunctive imaging techniques have been developed to help improve the early diagnosis of oral cancer and its precursors [35,36], including autofluorescence imaging [106], confocal imaging [107], OCT [108], and perfusion imaging [16]. Many studies have suggested that autofluorescence imaging can improve sensitivity for early detection of oral cancer and its precursors. There are several low-cost commercial autofluorescence imaging systems available [109,110]. For example, the VElScope is a $2,000 battery powered, handheld system that uses blue LED illumination to excite autofluorescence, which is viewed by eye through a longpass filter; an adapter can be connected to the device so that digital images can be acquired with a mobile phone. Precancerous lesions are associated with decreased blue–green fluorescence relative to healthy tissue [111,112]. The clinical value of autofluorescence imaging is debated in the literature; some studies conclude that autofluorescence has high sensitivity for the identification of precancerous lesions but lacks specificity to distinguish between benign inflammation and precancer [20,112-114]. However, other studies suggest that quantitative analysis of digital images can increase the specificity of autofluorescence imaging for the detection of precancerous lesions [113,114]. A meta-analysis of 27 clinical studies of autofluorescence found a pooled sensitivity of 82% with a pooled specificity of 62% ref.[20]. A pooled subset of seven studies, indicated that autofluorescence imaging has a higher sensitivity (78%) than conventional oral examination (50.1%) ref.[20]. The improved sensitivity is attributed to the increased contrast and more distinct borders between precancerous lesions (regions with reduced autofluorescence) and the surrounding healthy tissue[20].

Combined white light and autofluorescence imaging—Combining digital white light and autofluorescence imaging could enable early detection of oral cancer and precancer. A low-cost device was developed that combines white light and autofluorescence imaging in a single mobile phone-based platform [106]. This device uses an external 405 nm blue LED to provide illumination for autofluorescence imaging through a longpass filter and data are uploaded to the cloud for off-site quality control and diagnosis by a remote expert. Images that passed quality control, which was based on a specialist assessment of whether the image was in focus and had minimal motion blur, were classified as normal or suspicious using an algorithm based on a convolutional neural network (CNN). This device was tested in a field evaluation in India involving 99 people with clinically suspicious oral lesions, a history of previously treated oral cancer, or recently diagnosed, untreated oral cancer or precancerous lesions. The device showed good sensitivity and specificity for oral cancer diagnosis by a remote specialist (sensitivity of 93% and specificity of 87%) and for a CNN-based algorithm (sensitivity of 85% and specificity of 89%) compared to the diagnosis

provided by an on-site specialist. However, only 47% of image pairs passed quality control; better integration of the remote specialist in the clinical environment could potentially help provide feedback to improve the image quality. A large field evaluation was performed to assess the accuracy of the dual imaging technology combined with a simple phone-based CNN for automated diagnosis [15]. In this study, frontline health workers used the device with an onsite specialist for 752 patients and all the results were evaluated by a remote specialist. Telediagnosis by the remote specialist showed high accuracy compared with diagnosis performed by an onsite specialist (sensitivity of 95% and specificity of 84%). The phone-integrated CNN identified lesions with 82% sensitivity compared to telediagnosis.

Confocal microscopy—Confocal microscopy, in either fluorescence [42] or reflectance mode [43], is a promising technique for in vivo histological visualization of the oral epithelium and diagnosis of oral cancer and precancer. Confocal images of oral cancer show features such as pleomorphism, increased nuclear-to-cytoplasmic ratios, and architectural disarray relative to images of healthy tissue. However, the confocal microscopes required to obtain such images are too complex and expensive for use in most low-resource settings. Other limitations of confocal microscopy include poor penetration depth and strong light scattering in highly keratinized tissue or dense inflammatory infiltrates [43]. Combining autofluorescence imaging with low-cost, high resolution fluorescence microendoscopy could improve specificity compared to autofluorescence imaging alone [115]. For example, an algorithm based on the combination of autofluorescence and high resolution imaging correctly classified 98% of sites as normal or neoplastic in a study of 100 clinically normal and abnormal sites in 30 patients scheduled for surgical resection of clinically visible oral lesions [115]. Meanwhile, only 76% of sites were classified correctly using a simple algorithm based on autofluorescence alone. [115]

In vivo imaging for global anal cancer screening

In the USA, anal cancer is over 30 times more common in people living with HIV than people who are HIV-negative[116]. A compromised immune system makes people living with HIV susceptible to coinfection with HPV in the anal canal, which is linked to 90% of anal cancer cases [117]. Treatment of anal cancer precursor lesions can reduce the risk of people living with HIV developing anal cancer [118]; therefore, clinical experts recommend the use of anal cytology and/or HPV testing to screen for anal precancer [119]. Participants who screen positive are asked to return for a second visit in which high-resolution anoscopy (HRA) is used to identify suspicious regions, which are then biopsied and evaluated by a pathologist[120]. HRA-guided biopsy requires a high degree of expertise with new HRA practitioners needing to perform around 200 procedures to begin to consistently identify all precancerous lesions or anal intraepithelial neoplasia (AIN) as grade 2 or more severe (AIN 2+) [121]. Participants diagnosed with AIN 2+ are asked to return for a third visit to receive treatment. Although treatment of anal precancer can substantially reduce the risk of progression to cancer[118], this multiple visit approach can lead to high loss-to-follow-up rates outside of clinical trial settings. A study on the outcomes of an anal cancer-screening programme during 2009–2019 found that only 58% of people diagnosed with AIN 2+ returned for treatment [122].

Optical methods could be used to simplify early detection of AIN 2+ by facilitating in vivo diagnosis during HRA to enable more selective biopsies. Additionally, the ability of optical techniques such as high resolution or multimodal imaging to delineate normal mucosa from neoplastic mucosa in real-time could facilitate 'Screen & Treat' and 'Screen, Triage & Treat' approaches, reducing the number of people lost to follow-up.

Despite the clinical need, efforts to develop optical imaging strategies for early detection of anal cancer have been limited [123]. A low-cost $150 device capable of imaging the entire anal canal (with a field of view of 100 x 120 mm) within 10 seconds was developed using the contact image sensor technology used in commercial flatbed scanners(Fig. 1f) [123]. An in-human study using the device successfully obtained images of the entire anal canal in 10 of the 14 participants enrolled in the study [124]. The anal mucosal findings from the low-cost device were qualitatively similar to those obtained with HRA; however, the spatial resolution of the low-cost imaging device was lower than that of HRA as the resolution was limited by the pixel density of the image sensor. A low-cost HRME was used under HRA guidance to image lesions in 77 people living with HIV. The images obtained were analysed with a machine-learning based classifier and an area under the ROC curve of 0.84 was achieved for the detection of AIN 2+. The microendoscope achieved a comparable specificity and sensitivity for AIN2+ detection to expert HRA when using histopathology as the gold standard [125].

Low cost endoscopy for early oesophageal cancer detection

Oesophageal cancer is the 6th most common cancer worldwide [1]; globally, 604,000 people are diagnosed with oesophageal cancer each year and the disease results in 544,000 deaths annually [126]. Despite advances in chemoradiation therapy, the 5-year survival remains <20% in the USA and <5% in many LMICs, because it is often diagnosed at an advanced, incurable stage [1]. Indeed, the survival rate decreases, once the tumour has breached the mucosal layer, reinforcing the importance of early detection. Although the disease has a substantial impact worldwide, certain geographic areas (such as, South America, Iran, China) have particularly high incidence rates [1] . Endoscopic screening and surveillance protocols have been implemented with limited success and the mortality-to-incidence ratio still remains near 1:1 ref.[1].

Endoscopy is the gold standard for screening individuals with an increased risk of oesophageal cancer for Barrett's oesophagus-associated adenocarcinoma or oesophageal squamous cell carcinoma; however, it is invasive and expensive [127] (Fig. 1c). China accounts for 50% of the global burden of oesophageal squamous cell carcinoma; organized endoscopic screening programmes have helped to improve the early diagnosis rate to over 70% although the cost-effectiveness of this approach remains uncertain [128]. High-definition endoscopes offer 35× magnification and have been used since 2005. More recently, magnification endoscopy (up to 150× magnification) has been developed by adding optical extension accessories to high-definition endoscopes, allowing endoscopic characterization of anatomic micro-structures [29] (Fig. 1d). Prospective studies show that when magnification endoscopy is used together with image enhancement strategies (such as, narrow band imaging), an accuracy of >90% can be achieved for the characterization of malignant

tumours [29]. Narrow band imaging uses blue–green illumination to enhance the contrast of superficial microvessels to improve the detection of Barrett's oesophagus (pre-cursor lesion) during endoscopy [30]. Several other strategies to improve endoscopic diagnosis have been developed, including high magnification endoscopes offering several hundred-fold magnification, confocal laser endomicroscopy, and flexible spectral imaging colour enhancement; however, these techniques remain expensive and require provider expertise, limiting their accessibility and adoption in low-resource settings [30].

Endoscopy-based screening programmes have been difficult to implement in many LMICs owing to shortages of endoscopy resources and trained healthcare providers [129]. The cost of conventional GI endoscopes has been reported in the range from $20,000 to $120,000 USD [130]. This cost is a substantial barrier for many low-income countries; for example, a study of endoscopic capacity in healthcare facilities in Ethiopia, Kenya, Malawi and Zambia found that endoscopic capacity was between 1–10% that of resource-rich countries [131]. Ultra-thin nasal endoscopy is a more cost-effective and well-tolerated alternative that does not require sedation, with comparable sensitivity and specificity to conventional GI endoscopy for the diagnosis of Barrett's oesophagus [14,127,132] (Fig. 1e). Capsule-based endoscopes, consisting of an illuminator, camera, and transmitter encased in a pill-sized capsule, have been developed to image the oesophagus [133]; however, many current versions are expensive and have a low accuracy for detecting Barrett's oesophagus with a sensitivity of 60 %–67 % and specificity of 84 %–100 % ref.[127]. A smartphone-based endoscope with LED illumination; a low-cost CMOS sensor that approaches the resolution of high definition scopes; and an articulating tip, which is operated with a joystick-based interface, has been demonstrated in anatomically relevant phantoms. The projected cost of the total system is $700–$1,500 USD [130]. A small pilot study of a similar smartphone-based laryngoscope demonstrated that the device was able to identify people with vocal pathologies [134].

Advances in lensless imaging also have potential to reduce the size and cost of traditional endoscopes (Fig. 1h) [13,135,136]. Traditional fiber optic endoscopes use each fiber core to act as a single pixel in the image. Alternatively, a lens-free computational microendoscope replaces lenses at the distal tip of the bundle with a random binary spatial mask that modulates the intensity of the light traveling from each point on the target to the surface of the fiber bundle [136]. Each fiber core measures a pseudorandom linear combination of light from various points within the scene. The system is calibrated by scanning a point source through the sample plane and images are reconstructed using a minimization algorithm. The resulting reconstructed images are free from pixilation artifacts. Unlike conventional endoscopes, lensless systems can computationally refocus at different depths and do not require additional elements to adjust for chromatic aberration; however, the reported field of view in current devices is less than 1 mm ref.[136].

Challenges and potential of optical imaging

These studies demonstrate the potential of low-cost optical imaging technologies to improve the screening and early detection of cervical pre-cancer, oral cancer, anal cancer and GI cancers. Therefore, developing and translating proven technologies that meet the clinical need should be a priority for the biomedical optics community. Table 1 summarizes the

status, limitations and future directions of optical imaging technologies for early cancer detection in low-resource settings. Low-cost digital widefield imaging with automated algorithms to ensure image adequacy and provide automated diagnosis are particularly promising for cervical cancer screening owing to their ease of use and high reported accuracy in initial clinical evaluations. Additionally, low-cost high-resolution and multi-modal imaging approaches for cervical cancer screening could offer improved specificity for single visit approaches that combine screening, diagnosis and treatment. Handheld, affordable, rugged instruments are already available for the early detection of oral cancer such as the VELscope and other mobile phone-based imaging systems. However, the clinical performance of these devices must be evaluated in large, multi-center studies and compared with the results of histological diagnosis (rather than clinical impression alone). Although endoscopy techniques for improving early detection and prevention of GI cancers have been developed, existing endoscopy equipment is not affordable and is difficult to maintain in most low-resource settings. Additionally, expensive processing equipment is required to clean and disinfect endoscopes. Efforts to reduce the cost of endoscopic hardware and to develop reusable alternatives that can be used without the need for sedation could improve early cancer detection.

It is essential to ensure that new imaging tools can be effectively integrated into clinical workflows in low-resource settings; that they are validated in large, prospective clinical studies in low-resource settings; and that tools are commercially available at affordable prices. Technology transfer is particularly challenging in low-resource settings, where clinical need is high but financial resources are limited (Box 3). When designing devices it is important to also consider the differences in the resources and clinical infrastructure available across LMICs. For example, according to the WHO Global Health Expenditure Database the annual health expenditures per capita varies by more than fifty-fold across low-income countries (for example, USD$16 in Burundi and USD$33 in Malawi), lower-middle income countries (for example, USD$83 in Kenya) and upper-middle income countries (for example, USD$363 in Botswana and USD$701 in Brazil).

Microscopes for point-of-care pathology

Histopathology has a crucial role in the early detection and treatment of cancer and precancer. Microscopic examination of cells and tissues is a routine way to confirm a cancer diagnosis, and it can help to assess disease severity, determine and manage treatment plans, and monitor response to therapy. Despite the widespread availability of microscopes, access to diagnostic pathology is limited in many settings, including community hospitals in rural parts of the USA and in large portions of LMICs, because of the high cost of equipment (such as, microtomes and slide stainers) and the need for trained personnel (for example, histotechnologists and expert pathologists) [137 48]. Barriers to expanding access to pathology services in low-resource settings include insufficient workforce capacity, inadequate infrastructure, inadequate training programmes [138], and insufficient standards and accreditation programmes [48]. One study performed in Pakistan reported that the average cost of performing five frozen margins for an individual is US$75 ref.[139], a cost that exceeds the per capita health expenditures of more than 40 countries, including Pakistan. These bottlenecks limit or delay clinical decision-making and eventually treatment, resulting in

worse patient outcomes. Given its critical importance, it has been recommended that Level 2 pathology labs with histopathology services should be established at all district hospitals in LMICs [137]. Therefore, affordable tools to support quality histopathology programmes are urgently needed. Techniques that improve the performance of microscopy without the need for complicated sample processing and staining have the potential to fill this gap.

The integration of smartphones with standard microscopes to capture high quality digital images of slides has helped to expand access to pathology in low-resource settings by making it possible to send the images to experts for review in telepathology programmes. One study of the diagnosis of thyroid disease from fine needle aspiration in Brazil observed >80% agreement between the remote diagnosis approach described above and a conventional diagnosis approach involving an on-site cytopathologist [140]. In another study, a low-cost (<$3,000), portable slide scanner based on a smart phone coupled to imaging and slide control modules was used to scan standard cervical cytology slides with 0.7 um spatial resolution in <20 minutes [141]. A set of 209 cervical cytology slides were scanned with both this smartphone-based system and a traditional, more expensive digital pathology scanner. The digital images were examined by three experts who achieved consensus diagnosis and the results were compared to a gold standard consensus clinical review based on direct visual examination of the slides. The classification accuracy was excellent for images acquired with both the low-cost and traditional scanner (kappa values for diagnostic concordance were 0.81 and 0.80, respectively). Additionally, low-cost adapters have been developed to enable the use of smart phones to collect LED-illuminated high-resolution images from slides or liquid samples. A community-based schistosomiasis screening programme in Côte d'Ivoire achieved high sensitivity (85.7%) and specificity (93.3%) for the detection of *Schistosoma haematobium* in urine samples using mobile phone microscopy [142]. Algorithms have been developed to enable automated classification of curated images, for example, to measure steatosis in liver biopsies [143] or diagnose precancer in cervical biopsies [144,145]. The algorithms used in these examples achieved good agreement with diagnosis performed by expert pathologists.

Although microscopes are widely available, including in LMICs, conventional microscopy has several important limitations such as a narrow depth-of-field (DOF) <30 μm, and limited endogenous optical contrast in tissue samples. The narrow DOF means that tissue samples must be thinly sliced with a microtome before imaging, because typical variations in tissue surface topography can extend to ~200 μm ref.[18,21]. The limited endogenous optical contrast of tissue means that sliced samples must be stained with optically absorbing dyes, a complicated process with numerous wash steps that require both substantial time and the presence of a trained expert.

UV surface excitation

Rapid advances in ultraviolet (UV) LEDs, new optical fabrication technologies, and artificial intelligence are driving the design of a new class of microscopes for slide-free pathology, that address the challenges of conventional microscopy [146] (Fig.2a). For example, because of its limited penetration depth of just a few microns, the use of UV excitation in a standard fluorescence microscope can restrict the excitation of conventional fluorescent stains to

the tissue surface, eliminating the need for physical sectioning of samples [147]. Microscopy with UV surface excitation (MUSE) can produce high-resolution diagnostic images from slide-free samples within minutes using inexpensive topically applied fluorescent dyes such as Rhodamine B, which stains cytoplasm and extracellular matrix, and DAPI (4′,6-diamidino-2-phenylindole), which stains nuclei (Fig. 2b, **left**). The images obtained with MUSE resemble those obtained from samples prepared with conventional, labour- and resource-intensive haematoxylin-and-eosin (H&E) histology techniques. A comparison of MUSE images and standard H&E dermatopathology slides showed that MUSE can identify most normal skin structures seen on routine H&E pathology but was rated as inferior for the depiction of cytoplasmic details (for example, inflammatory cells); however, MUSE could identify diagnostic features associated with basal cell carcinoma [148]. MUSE has also been implemented in the Pocket MUSE system: a compact smartphone-based microscope fabricated with parts from consumer electronics (Fig. 2b, **right**). This system provides high-quality multichannel fluorescence microscopy for slide free histology with submicron resolution over a 10× equivalent field of view [17]. A smartphone camera adapted to record high magnification fluorescence images achieved a lateral resolution of 0.57 μm with high quality images of fresh pancreatic tissue over a 500 μm field of view [149]. Microscopes equipped with MUSE are affordable and sufficiently rugged to be used in low-resource settings, but large scale end-to-end studies are needed to validate the efficacy of the staining procedures and diagnostic adequacy for early cancer detection.

Optical sectioning

Light-sheet microscopy is an alternative approach for slide-free pathology and can be used to rapidly collect images with comparable resolution to histological images from large clinical samples [18]. Optical sectioning is achieved by illuminating the sample with a thin sheet of light and collecting fluorescence in an orthogonal direction. This technique can achieve high spatial resolution and extended DOF by using a low numerical aperture to illuminate the sample and a high numerical aperture to collect the fluorescence. An open-top light sheet microscope for slide-free imaging of tissue samples has been developed in which the samples are placed on a flat glass plate and imaged from beneath using a solid immersion lens to deliver a weakly converging cylindrically focused illumination beam and collect light from a strongly converging spherically focused beam at a large angle of incidence (Fig. 2c). The sample is moved in one direction to image a strip, and the process is repeated in the other direction to obtain two dimensional images. Images of fresh prostate tissue [18,150] and fresh core needle biopsies of breast tissue obtained with this technique demonstrate diagnostic features of invasive cancer, high-grade pre-cancer and inflammation [18]. Open-top light-sheet images of resected breast tumours have comparable quality to that of gold-standard histology images of formalin fixed paraffin embedded tissues and surpass the quality of gold standard histology images of frozen sections used for intraoperative decision making [151]. Additionally, in a pilot study of 12 samples light-sheet microscopy achieved a sensitivity and specificity >90% ref.[152]. A light-sheet microscopy technique with variable imaging resolution was demonstrated by incorporating a solid immersion meniscus lens with interchangeable low- and high-magnification air-based objective lenses [153]. OpenSPIM, an open source hardware and software platform for selective-plane illumination microscopy (SPIM) with more than 20,000 users, is designed to increase access to lightsheet

microscopes by providing detailed, easy-to-follow instructions to build devices using off-the-shelf components and 3D-printed parts [154]. Additionally, a miniature, low-cost (<$200) lightsheet microscope (miniSPIM) has been developed that enables the use of mobile camera devices to perform imaging with optical sectioning [155]. However, further work is needed to develop low-cost rugged platforms for use in low-resource settings, validate sample staining protocols and assess diagnostic accuracy.

Other types of optical sectioning microscope have also shown promise to reduce the infrastructure required and reduce the turnaround time for diagnostic pathology services including confocal microscopy of fresh tissue specimens stained with fluorescent dyes [156] or multiphoton fluorescence microscopy of fixed, cleared, and fluorescently stained tissue specimens [157]. One study used clearing histology with multiphoton microscopy (CHiMP) to process 20 clinical prostate biopsy specimens and compared the results with those obtained using standard histological techniques (H&E staining) [157]. Comparing the pathologist interpretation of the physical slides and digital CHiMP images to a gold standard reference diagnosis from H&E stained slides revealed that 89% of diagnoses by physical slides and 95% of diagnoses by multiphoton microscopy agreed with the reference diagnosis. Additionally, the digital slides took only 2.8 hours to process on average, which is faster than the typical 16–24 hours required to process physical slides. However, there are substantial barriers to the use of these approaches in low-resource settings, including the cost of commercially available confocal and multiphoton microscopes, which can exceed $100,000, and the long, multi-step processing required for optical clearing.

Wavefront encoding

In contrast to optical sectioning-based approaches, wavefront encoding has been used to break the dependence between DOF and resolution, enabling high resolution imaging of fresh tissue. In a conventional microscope with standard objective lenses, achieving subcellular lateral resolution (~2–3 μm) restricts the DOF to ~30 μm. However, variations in surface topography of freshly resected tissue surfaces can extend to depths of 200 μm. In the DeepDOF microscope an inexpensive (less than $10) phase mask is inserted in the pupil plane of a conventional fluorescence microscope to encode the light field and enhance the depth-invariance of the point-spread function, making it possible to overcome this DOF limitation [21] (Fig. 2d). When used with a jointly optimized image-reconstruction algorithm, the ability to resolve subcellular features can be maintained while extending the DOF to 200 μm. When used to image resected oral surgical specimens the DeepDOF microscope was able to consistently visualize nuclear morphology and other important diagnostic features across highly irregular resected tissue surfaces without requiring serial refocusing. Existing microscopes in low-resource settings can be easily adapted to incorporate wavefront encoding strategies.

Low-cost strategies for slide-free microscopy, such as MUSE or wavefront encoding-based approaches could expand access to histopathology services, particularly when coupled with machine-learning based image analysis algorithms. Therefore, large studies to optimize staining protocols and validate the performance of these techniques in low-resource settings should be prioritized.

Outlook

Cancer is a major challenge for all countries, but cancer incidence and mortality are increasing most rapidly in LMICs. Unless action is taken, the already major gaps in global cancer equity will continue to widen. Improving early detection of cancer through cost-effective screening and diagnosis programmes could close these cancer-related equity gaps. The benefits of early detection are unquestionable; when detected early, outcomes for cancer patients improve, the costs of early treatment are lower, and patients who receive early treatment experience fewer life-altering side effects. In low-resource settings, infrastructure to provide treatment to patients diagnosed with late stage disease is often not available, making it even more important to shift cancer diagnoses to earlier stages when treatment is more widely available.

Many of the emerging optical technologies for early cancer detection remain prohibitively expensive for application in low-income regions. Further investment and research is needed to make these devices affordable, more durable, easier for non-experts to use, and safe for reuse with simple disinfection protocols (Table 1). Advances in the quality of cameras and image processors, coupled with the falling prices of optical components, offers the opportunity to further reduce the cost of these optical technologies.

Although the clinical need is great in low-resource settings, most studies to develop and evaluate low-cost imaging tools have been conducted in high-resource settings using prototype devices that are not sufficiently rugged for use in settings with limited infrastructure and technical support and are not yet commercially available. Most evaluations of clinical performance are based on relatively small pilot studies or larger, retrospective studies that use the same dataset for both algorithm development and assessment, which can lead to an over-estimation of the accuracy of the techniques. Definitive, prospective studies are needed to assess the sensitivity, specificity and treatment outcomes in relevant populations compared to a high-quality gold standard. Systematic efforts are needed to directly compare the potential of the various modalities to improve early detection of particular types of cancers in relevant at-risk populations and locations.

Given the limited access to and growing need for surgical pathology in low-resource settings, the potential impact of advancing optical imaging tools for slide-free histology is high. It is important to standardize tissue staining protocols, improve the ease-of-use and further reduce the cost of slide-free microscopes. Larger studies are then needed to assess performance compared to standard H&E histology. These studies should also include workflow considerations, linking screening and diagnosis efforts wherever possible to enable same-day screening, diagnosis, and treatment of patients with precancerous lesions.

Machine learning algorithms could enable providers with less clinical experience interpreting images to identify precancerous lesions (such as, nurses and community health workers) to use imaging tools to perform high-accuracy field-based screening; ensure that high quality images that are adequate for diagnosis are obtained and automate the interpretation of endoscopic and pathological images. Therefore, machine learning could make cancer screening and diagnosis possible even in settings with human resource

shortages. Technological advances can also help users to obtain high-quality images that can be shared virtually with remote experts. Large-scale datasets with validated endpoints are needed from various multi-institutional settings to train algorithms and ensure that they are generalizable and portable from one imaging system to another.

Improving early cancer diagnosis with optical techniques could also lead to promising optical approaches to treat early cancers. For example, combining photodynamic therapy with sonodynamic therapy [158,159] could be used to treat early stages of several types of cancerous and precancerous lesions in the cervix, head, neck, and skin [160-164]. Linking the development of optical technologies for diagnosis and treatment can help ensure that improved capacity for early cancer diagnosis is matched with improved treatment capacity.

Most low-cost optical imaging systems targeted for use in low-resource settings are not available for commercial purchase. There are major differences in the availability of infrastructure and resources between and within countries. Therefore, it is important that technology developers understand and address the needs of each individual low-resource setting, from both an infrastructural and clinical perspective. Commercial markets in low-resource settings are uncertain and hard to access and this is a barrier to the commercialization of appropriate cancer screening and diagnosis technologies [165]. Strategies are needed to support the development, translation, and scale of innovative technologies [166,167]. For example, health system managers should develop cancer control plans that highlight the role that new technologies could have in their settings; professional societies could outline target product profiles that new imaging technologies should meet to add the most value [168,169]; and funders should consider offering market guarantees to purchase products that meet these target product profiles [170].

Finally, universities in low- and high-resource settings should adopt curricular reforms that emphasize invention and help students to become successful practitioners of frugal design [171]. For example, the Invention Education Toolkit is a resource for faculty at African universities working to transform engineering education to solve local and global challenges. Additionally, governments of low- and high-income countries should recognize that simpler devices could eventually be produced partially or totally in the countries that use them, which would also contribute to economic growth.

Citation diversity statement

We acknowledge that papers authored by scholars from historically excluded groups are systematically under-cited. Here, we have made every attempt to reference relevant papers in a manner that is equitable in terms of racial, ethnic, gender and geographical representation.

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Key points

- Global equity gaps for cancer are growing. Early diagnosis improves patient outcomes, but screening and diagnosis programmes are scarce in low-resource settings, where limitations in infrastructure, human resources, financial resources, and/or social resources limit the ability to deliver healthcare.
- Advances in consumer grade imaging tools (such as, light emitting diodes (LEDs), digital cameras, plastic lenses) have enabled the use of high-performance, low-cost, portable optical imaging systems to visualize cellular, vascular, and architectural hallmarks of pre-cancers and early cancers.
- In vivo optical imaging can improve early detection of cervical, oral, oesophageal, anal, and other epithelial cancers but large studies with commercially available, low-cost devices are needed.
- To facilitate the adoption of optical imaging techniques in understaffed low-resource settings, technologies to improve cancer screening and early diagnosis must be simple to operate and easy to maintain; therefore, technology developers should emphasize usability throughout the design process.
- High quality, slide-free histology can be achieved with low-cost microscopes to improve diagnosis and guide treatments, but large-scale validation of these techniques with standardized staining protocols and commercially available systems is needed.
- Machine learning can improve imaging performance and reduce the need for human resources by automating image interpretation; however, large, curated image databases from relevant populations are needed for the development and validation of portable algorithms.

Box 1:

Global recommendations and limitations for cancer screening and early diagnosis

WHO guidelines for cancer screening

The WHO Guide to Early Cancer Diagnosis stresses the importance of early diagnosis to improve outcomes by increasing the likelihood of successful treatment, at reduced cost and requiring less complex interventions [175]. The WHO recommends the implementation of cancer prevention and early detection programmes at a primary care level [1] including vaccination against the human papillomavirus (HPV) for girls aged 9–13 to prevent cervical cancer; hepatitis B immunization to prevent liver cancer; and programmes to screen targeted groups of asymptomatic individuals for cervical cancer, breast cancer, colorectal cancer, oral cancer, and associated precancerous lesions [176]. To be effective, positive screening tests must be followed by timely tests to confirm the diagnosis alongside treatment of detected precancers and cancers. However, many existing tests for cancer screening and early cancer diagnosis are too complex and/or expensive to implement in primary care settings, particularly in medically underserved areas. For example, the list of essential diagnostic techniques produced by the WHO in 2020 lists essential diagnostics for clinical labs, but does not recommend any cancer-related tests for use in community settings or health facilities without labs [177], underscoring the need to develop affordable, accurate tests that can be used by local providers, particularly in clinics or other outpatient settings [178]. The variations in the screening tests recommended in the USA and WHO [176] recommended screening tests suitable for LMICs are outlined below.

Cancer screening tests in the USA

Breast cancer:

mammography generally recommended beginning at age 40–50 for women at average risk.

Cervical cancer:

Human papillomavirus (HPV) DNA test and/or Papanicolaou test generally recommended for women aged 21–65 years.

Colorectal cancer:

colonoscopy, sigmoidoscopy, and/or stool tests (high-sensitivity fecal occult blood tests and stool DNA tests) are generally recommended for people at average risk for colorectal cancer at aged 45 or 50–75 years).

Cancer screening tests that are considered cost-effective and feasible for use in LMICs

Breast cancer:

mammography recommended for women aged 50–69 years.

Cervical cancer:

visual inspection with acetic acid or HPV DNA test or Papanicolaou test recommended for women aged 30–49 years.

Colorectal cancer:

fecal occult blood test recommended starting at age 50.

Oral cancer:

visual examination and palpation is recommended for people with an increased risk of developing oral cancer (for example, people who use tobacco or chew betel-nuts).

Box 2:

Technology development for low-resource settings

Most medical technologies are designed for use in high-resource settings [171,179]; owing to financial and infrastructure limitations, many of these technologies are not available in low-resource settings. For example, pathology laboratories in high-resource settings use automated equipment to process tissue pathology samples whereas many labs in low-resource settings rely on manual processes with less stringent quality control. To illustrate this difference the figure shows pathology labs at a central hospital in the USA with automated equipment (left), a central hospital in Mozambique with manual equipment (middle) and a district hospital in Mozambique with only a slide staining station (right).

Medical devices designed for use in high-resource settings often fail when used in the harsh environmental conditions found in some low-resource hospitals, including wide fluctuations in temperature and humidity, high levels of dust, frequent power outages, and poor electrical power quality [180]. When devices fail, spare parts are often not accessible and, as a result, many broken devices remain in equipment graveyards [171,179].

Therefore, rigorous strategies are needed to enable the development and validation of medical devices that are effective, affordable, rugged, and easy to use in low-resource settings. Diagnostic developers should follow the revised ReASSURED criteria as a target for the required performance of point-of-care technologies [181]:

- Real-time connectivity: a reader or mobile phone is used to power the test and/or read test results to provide data to decision makers.
- Ease of sample collection: tests are designed for use with specimens that can be acquired non-invasively.
- Affordable: tests are affordable to end-users and health systems.
- Specific: avoid false positives.
- Sensitive: avoid false negatives.
- User-Friendly: test can be performed in few steps with little training.
- Rapid and robust: results available to ensure treatment of patient at 1st visit (within 15 minutes to 2 hours); tests do not require special transport and storage conditions (such as, refrigerators).
- Environmentally friendly and simple equipment: test does not require special equipment or can be performed with simple devices that use solar or battery power; completed tests are easy to dispose of and made from reusable or recyclable materials.
- Deliverable to end users: accessible to those who need the tests the most.

Consideration should also be given to the impact on the environment when developing and implementing screening and diagnostic tests [182]. Many tests require reagents

and have disposables such as plastic cartridges and other waste that could harm the environment. Careful planning is needed to ensure that any waste can be disposed of correctly and staff should be trained on the correct handling and disposal techniques.

Left image courtesy of Preetha Ramalingam. Middle image courtesy of Cesaltina Ferreira.

Box 3:

Technology transfer considerations

The traditional staged pipeline for moving innovations from prototype to efficacy and effectiveness testing to real-world implementation generally results in slow dissemination and uptake of effective interventions and technologies [183,184]. A review of evidence gaps in point-of-care (POC) diagnostic test evaluation [185] showed that most new diagnostic technologies underwent clinical performance assessment (71.2%); however, very few progressed to comparative clinical effectiveness (10.0%) or cost-effectiveness evaluation (8.6%). Although it was not reported, it can be assumed that an even smaller proportion were adopted and integrated into real-world healthcare settings. To accelerate efficient and effective translation and adoption of POC technologies for equitable cancer screening and early detection, developers must understand how introducing a new test will impact the clinical care pathway; the workflow and workload of any staff involved in the care pathway; and the perspectives of stakeholders involved in the decision-making to adopt and pay for a new technology [186].

Although there are a number of promising prototype optical imaging technologies that could improve cancer screening in low-resource settings, few devices are commercially available; these include three low-cost colposcopes for early detection of cervical cancer (Mobile ODT Enhanced Visual Assessment system, figure **a;** the Pocket Colposcope, figure **b;** and Gynocular, figure **c**) and the VELScope (figure **d)** for early detection of oral cancer. Part a is reprinted with permission from ref. [63]. Part b is reprinted with permission from ref. [66]. Part c is reprinted with permission from ref.[69]. Part d is reprinted from ref. [112], CC BY 4.0.

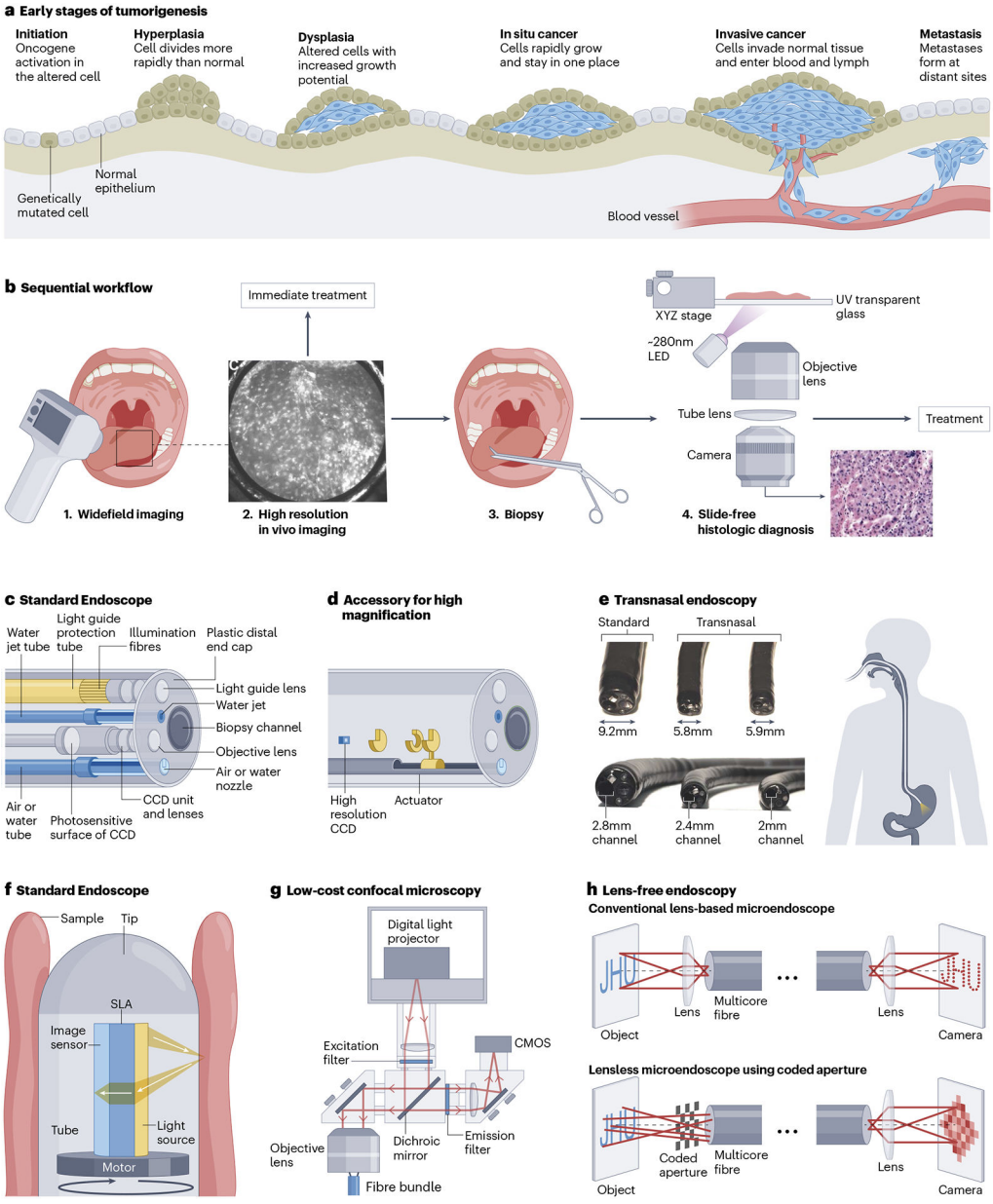

Figure 1: Widefield and high resolution imaging systems to improve early detection of precancerous epithelial lesions.

a | Epithelial cancers follow a similar progression beginning with initiation and hyperplasia, evolving through grades of dysplasia, and invasive cancer. Optical imaging tools can improve the detection of precancer and early cancer by visualizing architectural and morphological biomarkers in precancerous epithelial cells, stromal angiogenesis, and microinvasion of epithelial cells beneath the basement membrane. **b** | A proposed clinical workflow for how widefield imaging, high-resolution imaging, biopsy, and slide-free histological diagnosis could be integrated into current screening and diagnosis workflows. (1) Widefield imaging modalities, including white light and autofluorescence imaging systems, can be used to visualize suspicious lesions; (2) high resolution imaging tools can delineate regions of precancer with high enough specificity to enable immediate treatment

or (3) biopsy can be performed to confirm the diagnosis using (4) slide-free histology methods. LED, light emitting diode; UV, ultraviolet. **c** | Standard endoscope which uses a charge-coupled device (CCD) and an objective lens to acquire optical images of the region of interest. **dl** An optical extension accessory for high-definition endoscopes in which the optical lens can be moved to achieve high magnification (up to 150×) [172]. **e**| Ultrathin transnasal endoscope for upper gastrointestinal endoscopy in unsedated patients. **f**| Low-cost scanning endoscope based on commercial contact image sensor technology with a self-focusing lens array (SLA). **g**| The design of a low cost, line scanning confocal microendoscope for imaging cervical tissue in vivo. This device uses a digital light projector with a synchronized rolling shutter complementary metal-oxide semiconductor (CMOS) camera. Both widefield and confocal images can be acquired by changing the projected aperture. **h**| Lens-free microendoscope, that allows simultaneous miniaturization and wide field of view, achieved by replacing distal lenses (top) with a coded aperture together with computational image recovery (bottom). Part a is adapted from ref. [173], Springer Nature Limited. Part b (second step) is reprinted with permission from ref. [34]. Part b (fourth step) is adapted from ref. [147], Springer Nature Limited. Part c is adapted with permission from ref. [174]. Part e, image courtesy of Scott Inglis. Part f is adapted with permission from ref. [123]. Part g is adapted with permission from ref. [91]. Part h is adapted with permission from ref. [136].

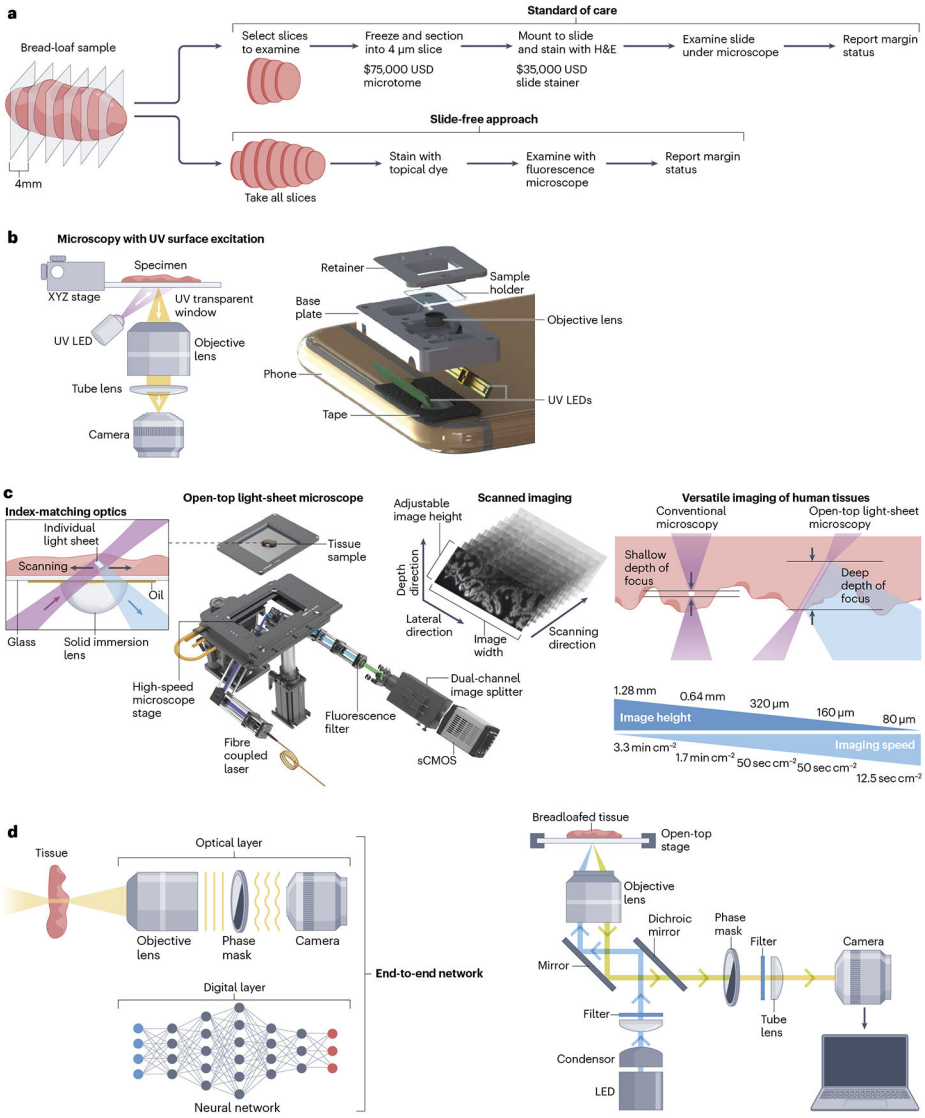

Figure 2: Microscopy approaches to enable rapid, low-cost, slide-free histology.

a | Workflow for standard of care histology compared to slide-free approaches. The standard of care requires expensive instrumentation, trained staff, multiple steps, and results are not available for at least 30 minutes. Slide-free approaches can be performed with inexpensive instrumentation and obtain results in minutes. **b** | Left, schematic diagram of microscopy with UV surface excitation (MUSE) in which the sample is illuminated by an ultraviolet (UV) light emitting diode (LED). The stage moves so the entire sample can be scanned. Right, the components of a pocket MUSE device, which uses a mobile phone camera to capture UV-excited fluorescence images. **c** | Left, schematic diagram of an open-top light-sheet microscope in which the light sheet (purple) enters the sample and produces fluorescent emission (cyan), which is then transmitted through an emission filter (green) and detected by a high speed scientific complementary metal-oxide semiconductor (sCMOS) camera. Left inset, a solid immersion lens and oil layer are used for refractive index matching of the incoming and outgoing beams. Middle, the sample is mounted

on a moveable stage to enable the reconstruction of a 2D image. Right, open-top light sheet microscopy can achieve both rapid scanning and deep depth of field (DOF) unlike conventional microscopy. **d** | DeepDOF microscope uses a $10 phase mask to encode the light field and enhance the depth-invariance of the point-spread function. Left, schematic illustrating the simultaneous optimization of the phase mask and image reconstruction algorithm to extend the DOF. Right, DeepDOF uses a conventional fluorescence microscope equipped with a LED (blue) to excite fluorescence (green) and a phase mask to extend the DOF. Part b (left) is adapted from ref. [147], Springer Nature Limited. Part b (right) is reprinted from ref. [17]. Part c is adapted from ref. [18], Springer Nature limited. Part d is adapted with permission from ref. [21].

Table 1:

Optical imaging technologies for early cancer detection in low-resource settings.

Modality	Commercial availability	Approximate cost[a] ($USD)	Status, limitations, and future directions
Widefield imaging technologies for accessible organ sites (oral cavity, uterine cervix, anal canal)			
Widefield white light imaging	Many devices available	800–9,600	Status: simple devices can capture, transmit, and interpret digital images acquired with white-light illumination; low-cost, narrow-band and/or polarized illumination can enhance contrast of precancer and early cancer. Future work: incorporate digital image processing to improve performance.
Widefield autofluorescence imaging	Several affordable models available	900–40,000	Status: simple, low-cost devices with optical filters are available; low-cost instrumentation can provide spectral analysis of images. Future work: incorporate digital image processing to improve performance.
Endoscopic imaging technologies for hollow organs (oesophagus, stomach, colon)			
Endoscopy, including high definition, narrow band imaging and magnification	Wide array of models available from many manufacturers in different countries	3,500–37,0000	Status: digital filters and processing can reduce cost and simplify devices to enhance the contrast of precancer and early cancer. Limitations: challenging to maintain; devices for processing and decontaminating endoscopes following clinical use are costly. Future work: automate movement control to simplify use, reduce cost and improve durability; explore the development of affordable topography based on endoscopy images.
Low cost, transnasal, smartphone-based or lensless endoscopes	Limited commercial availability but many devices in development	1,800–5,000	Status: easy to use, and must be re-usable for use in low-income countries. Further work: achieve digital magnification and effective coupling to smartphones; simplify motion control to improve usability and reduce cost and maintenance.
High resolution imaging technologies for accessible and hollow organs			
Confocal microscopy and multi-photon fluorescence microscopy	Several models available	10,000–100,000	Status: can be used alone or in combination with widefield imaging to improve specificity. Limitations: too expensive for clinical use in low-resource settings. Future work: reduce costs and simplify operation and maintenance; artificial intelligence could enhance the spatial resolution.
OCT and microscopy	Many models available, with a range of technical complexities	10,500–28,000	Limitations: operation requires special training and cost remains high. Future work: reduce the complexity of scanning mechanisms; full fiber operation could reduce cost.
Photoacoustic imaging	Many models with a range of resolutions available; portable devices are nearing commercial availability	13,500–120,000	Future work: absorbing dyes (such as, ICG) could increase sensitivity and reduce price; low-cost detectors might simplify current versions.
Microscope technologies for pathology			
Smartphone-based microscope for digital pathology	Many available	400–2,100	Future work: increase optical resolution; develop software to improve image quality and provide automated image interpretation; identify simple stains and staining protocols to improve image contrast.
Microscopes for slide-free histology	Limited commercial availability but many devices in development	200–18,000	Future work: develop low-cost, rugged options with sufficient resolution for histological diagnosis.

MUSE, Microscopy with UV surface excitation; UV, ultraviolet; ICG, Indocyanine green; OCT, optical coherence tomography.

[a]Estimated cost of commercially available devices based on publicly available vendor pricing; costs of prototype devices based on publicly available cost of goods and estimated assembly costs.