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The role of in vitro diagnostics in early detection and treatment of cancer

ASCP American Society for Clinical Pathology

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Executive Summary

Cancer is the second leading cause of mortality globally. Early detection of cancer and access to effective anti-cancer treatment can result in higher rates of survival and a better quality of life. However, patients in low-and middle-income countries (LMIC) are often diagnosed at a late disease stage, which contributes to higher cancer mortality.

In vitro diagnostics (IVDs) are a subset of tests or medical devices that examine specimens taken from the human body which provide essential data for screening, diagnosis and treatment. Access to IVDs is vital for the early detection of cancer, however in many LMICs, access to quality assured medical diagnostics is not a given.

Between 30% - 50% of human cancers are preventable[1] and several can be screened for, using IVDs. Even though prevention and screening are important measures to undertake in order to reduce the global cancer burden, access to these services, especially in LMICs is fragmented. Therefore, even preventable and screenable cancers often present as invasive disease, requiring a diagnosis with IVDs prior to treatment.

Major challenges to the availability of IVDs include patient access, regulatory aspects, quality, supply chain, physical and personnel infrastructure, and costs. However, solutions are available depending on local context, political will, and resource allocation. Furthermore, the most common IVDs for cancer include aging technologies that are ripe for innovation to improve quality, accuracy, and access. Evidence-based innovation connecting patients to increasingly available treatments is key to achieving global decreases in morbidity and mortality from cancer.

In this context, the Union for International Cancer Control (UICC) in collaboration with the Foundation for Innovative New Diagnostics (FIND) and the American Society for Clinical Pathology (ASCP) has developed this report through the support of CUBEBIO to highlight the role of IVDs in early detection, explore the barriers in access to IVDs and outline ways to address them and discuss the future of IVDs in early detection and their potential for use in point-of-care settings.

Importance of in vitro diagnostics in early detection

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Cancer is the second leading cause of death worldwide, with both incidence and mortality growing each year[2]. However, with robust prevention, screening, and early detection measures followed by access to quality-assured diagnostics and prompt and effective treatment and care, a significant number of deaths could be avoided[3]. Generally, when cancers are detected early, they are easier to treat which results not only in better outcomes but also in a reduction in the cost of treatment with substantial savings to health systems[4].

For example, a 2014 study by Cancer Research UK found that late diagnosis is a major driver of the UK's National Health Service (NHS) cancer treatment costs. Treatment for stage III and IV colon, rectal, lung, and ovarian cancer costs the NHS nearly 2.5 times the amount spent treating stage I and II cancers[5]. For breast cancer, a 2013 analysis of the total economic savings from an effective prevention, early detection, and treatment strategy, versus a treatment-only approach, was estimated at roughly 60% across all world regions[6].

Cancer patients, particularly those in low-and middle-income countries, are often diagnosed at a late disease stage. Access to affordable and quality-assured medical diagnostics in LMICs is either fragmented or impossible and most LMICs do not have organised cancer screening programmes due to a lack of resources to sustain them[7][8][9]. The high cost of implementation and execution of quality screening programmes is prohibitive primarily due to the cost of diagnostic tests, personnel/training needs and infrastructure requirements[10][11]. Additionally, many LMICs do not have specific guidelines for the management of cancer[12], which is associated with lower screening rates for cancer, one example is cervical cancer[13].

In vitro diagnostics in early detection

In vitro diagnostics play a critical role in driving clinical decision-making for cancer screening, diagnosis and treatment.

IVDs specific for cancer screening include diagnostic pathology techniques such as cytology, surgical pathology, flow cytometry and molecular testing (see Annex 1 for more details). In addition, fluid biomarkers for cancer are proteins or other substances that are made in higher amounts by cancer cells than normal cells. These can be found in the blood, urine, stool, or other bodily fluids of some patients with cancer. Alpha-fetoprotein (AFP) is an example of a screening biomarker that helps with the diagnosis of hepatocellular carcinoma[14]. Another example is the faecal immunochemical test (FIT) for colorectal cancer screening. The FIT detects human haemoglobin which could indicate bleeding in the gastrointestinal tract[15]. Increasingly, genomic markers such as tumour gene mutations, patterns of tumour gene expression, and nongenetic changes in tumour DNA, are also being used as tumour markers as either part of diagnostic pathology or as blood or other fluid testing[16].

In addition, IVD testing can answer crucial questions about a patient's health status, including the risk or predisposition for developing a certain cancer; the stage of disease, and the prognosis for progression/remission after therapy[17]. Examples of IVD testing include screening for human papillomavirus (HPV) which has a causal link to cervical cancer[18] and the presence of a bcr-abl fusion gene for determining whether to use imatinib to treat chronic myeloid leukaemia (CML)[19]. In this way, IVDs serve to guide the appropriate treatment decisions following diagnosis.

Major advances in technology and immunochemistry have led to the development of accurate and inexpensive IVDs including point-of-care (POC) testing and self-testing. The growing inclusion of cancer IVDs in the second World Health Organization (WHO) Model list of Essential In Vitro Diagnostics for use in clinical laboratories (WHO EDL)[20], illustrates their increasingly important role in cancer prevention, treatment, and care. There is an opportunity for LMICs to embrace these innovations and move towards more precise techniques such as the use of IVDs to diagnose infection with cancer-causing pathogens such as HPV and hepatitis C virus (HCV), and genetic and biomarker tests for other cancer types[21 22 23].

IVDs play a vital role throughout the cancer care pathway and should not be described in isolation. Considering the entire continuum of care, access does not only need to be ensured for adequate diagnostic testing but also for quality assured treatment. For example, breast cancer patients need access to tamoxifen therapy pre- or post-surgery for improved outcomes. Advances in new and innovative targeted therapies have revolutionised the treatment of many cancers. Examples are monoclonal antibodies (e.g., pembrolizumab and others) for a variety of tumours as well as BRAF inhibitors for cancers such as metastatic melanoma for which there was no prior effective treatment. However, these targeted therapies only work when the companion diagnostics are also available. Companion diagnostics are used to determine whether targeted therapy is the appropriate treatment option for an individual. For example, imatinib is effective in the treatment of CML, however, it should only be administered to patients whose leukaemia cells contain the bcr-abl fusion protein, and for this to be determined, access to cytogenetic or molecular testing is required[24]. Similar companion diagnostics are needed for tamoxifen (oestrogen receptor testing), pembrolizumab (PD-L1 and/or microsatellite instability testing), and BRAF inhibitors (BRAF testing of tumour cells).

Access, availability, and affordability across the pathway of detection, diagnosis and treatment as an integrated approach towards care should be a critical consideration in National Cancer Control Plans (NCCPs). WHO guidance supports this approach, where diagnostic and treatment capacities are introduced hand in hand. An example illustrating the importance of access to IVDs in targeted therapy was a proposal to add the tyrosine kinase inhibitors (erlotinib, gefitinib, afatinib and crizotinib) for the treatment of non-small cell lung cancer to the WHO Model list of Essential Medicines in 2017. The application was rejected despite evidence in favour of the treatment benefit itself. The decision to reject the application cited the lack of global access to affordable and quality assured IVDs for this cancer[25]. This highlights the important need for coherence of clinical guidelines with those of national lists of essential diagnostics and essential medicines.

The importance of an evidence-based approach to increasing access

Access to diagnostics is challenging, both in terms of supply of the tests and sustainable implementation of diagnostic services. Most tests involve the purchase and stock management of multiple different components, from instrumentation to various reagents and controls. Service and maintenance of test platforms are crucial for functionality, and staff must be trained to both perform the test and interpret the result correctly for appropriate clinical intervention[26]. Testing platforms can be geographically distributed (e.g., at point-of-care) or central labs (e.g., pathology laboratories) based on the cost, complexity, and direct impact on patient's needs. Therefore, planning must be paralleled by strong specimen transport mechanisms and referral networks for patients.

It is essential that the availability of IVDs reflects national need. For example, cervical cancer is responsible for the deaths of more than 311,000 women every year, 85% of whom are in LMICs[27].

The HPV DNA test was included in the 1st WHO EDL[28] and coincides with the global commitment for the elimination of cervical cancer, one of the aims being to scale up national screening programmes. In this regard, the WHO EDL is a tool to help countries prioritise IVDs for public procurement. The 2nd WHO EDL was revised in 2019 and includes IVDs specific to certain cancers. Examples include the AFP immunoassay for liver cancer and a panel of immunohistochemical (IHC) markers for diagnosis of solid tumours. It is important to note that IHC can only be performed if traditional diagnostic pathology is in place. This is severely lacking in many LMICs (see Annex 1).

According to the WHO, countries should consider a variety of factors to select IVDs for public procurement. These factors include:

- local demographics and pattern of diseases
- treatment facilities and scope of testing services
- the training and experience of personnel to collect and transport specimens, to perform diagnostics tests, to interpret test results and to manage diagnostics laboratories
- specimen referral/transport networks
- local testing gaps
- reliable supply chain management and quality assurance capacity
- local availability of treatment
- financial resources
- available infrastructure and environmental factors[29].

Therefore, given that early detection is key to achieving optimal outcomes for cancer patients, IVDs have the potential to have a substantial impact on cancer care. However, IVD products frequently fail to reach target populations in low-resource settings[30][31], thus their potential is not often fully realised. Detecting cancer early requires an accurate understanding of current barriers to and delays in care. Once known, effective programmes can be prioritised, and resources allocated in a cost-sensitive manner[32].

The next chapter will explore the barriers in access to IVDs and outline some ways to address these barriers.

Ensuring access to IVDs

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Introduction

A number of overarching barriers contribute to limited access to IVDs in LMICs, including accessing health services, regulatory capacity, quality and supply factors, workforce and equipment shortages, economic concerns, cultural beliefs, transportation constraints, and lack of organised screening programmes[33 34 35]. This chapter discusses some of the key aspects relating to access to cancer IVDs in LMICs.

Accessing health services

Access to primary care is the first step along the cancer care pathway – without this, patients cannot be referred for biopsy and laboratory services and will not receive subsequent treatment and care. However, there are several factors that can prevent patients from seeking care. As there are limited facilities providing cancer services in LMICs and these are often in capitals or large cities, travel to health clinics can be difficult due to the distances and time commitments involved, and the lack of transport options[36 37 38 39]. For this reason, people may delay seeking diagnosis until they experience severe illness. Given the importance of early diagnosis and treatment in cancer management, this is likely to substantially worsen outcomes. Cost can also be a barrier to access when expenses are borne by the user. In interviews with cancer support groups and advocacy group leaders in Kenya, most cited screening and diagnostic costs as the leading barrier to timely testing and treatment[40]. There is also a tendency for both patients and physicians to save limited financial resources for treatment and conduct fewer or less complex diagnostic tests[41].

Furthermore, embarrassment, fear of screening procedures or test outcomes are all factors that can present barriers to accessing services, as found in studies of women eligible for cervical cancer screening in Uganda[42]. Innovative technologies, such as self-sampling HPV testing devices, can play an important role in overcoming some of these barriers, as well as in facilitating logistics for cancer screening.

Program ROSE is an initiative to improve uptake of screening for cervical cancer in Malaysia that utilises a self-sampling method to avoid the need for pelvic examination by a healthcare professional. This is followed by HPV testing at the central laboratories and prompt and secure delivery of results straight to the patient's mobile phone (all within 3 weeks). Upon a positive test result, the patient is requested to contact the Program ROSE team for follow-up care[43 44]. The program has already received excellent feedback from participants, demonstrating the feasibility of this approach. The results showed that from women who screened positive, 89% engaged in follow- up care and 97% would recommend the process to their friends.

Studies have found that the acceptability of self-sampling for HPV testing is generally high among women, including those who do not tend to access services due to fear or embarrassment of the procedure[45 46]. Self-sampling may also increase the uptake of screening as a recent meta-analysis found that mailing self-sampling kits was more effective in reaching women for screening, compared to sending screening invitations for facility-based sampling[47].

Regulatory pathways

Regulatory pathways for diagnostics in LMIC markets can be complex and are much weaker than those for other medical products such as medicines and vaccines[48 49 50]. In order to access these markets, IVD developers are increasingly required to register their products locally[51]. However, standards and processes differ from country to country, legal and policy frameworks are still evolving, and there is a shortage of people with sufficient technical and regulatory expertise to review submissions, leading to long delays. This makes it extremely challenging to manufacturers wishing to achieve product registration and thereby enter markets in many LMICs[52 53].

The lack of established criteria or guidelines for registration can lead to suboptimal and poor-quality tests reaching LMICs[54 55]. For cancer IVDs, which represent a relatively new area for many LMICs and may be considered a lower priority compared to IVDs specific for infectious diseases, this could represent a substantial barrier. Even frameworks developed by international global health bodies to support national regulatory authorities in LMICs, such as the WHO prequalification (PQ) programme (the process by which the capacity of manufacturers to make medical products in accordance to international and WHO/UNFPA standards is assessed), tends to focus heavily on infectious diseases[56]. For cancer, the WHO PQ currently only evaluates IVDs for the detection of high-risk HPV types. This leaves countries with the challenge of setting up their own frameworks for registration and performing local evaluations for cancer IVDs to understand performance in their intended use population. Widening the scope of WHO PQ to include further cancer IVD tests, particularly those which can be used on the same diagnostic device as infectious diseases tests (such as molecular point-of-care machines), has the potential to alleviate the burden of additional in-country test evaluation.

The first step to achieving local registration of an IVD is to generate clinical validation data[57]. Validation studies for local registration are often required to be conducted at in-country clinical trial sites[58], in particular, the point-of-care tests. One draw-back to this approach is that in-country clinical trial sites may not have the benefit of access to laboratories or expertise[59]. In addition, poor knowledge and awareness of cancer in the general population in LMICs has been shown to lead to reduced trial participation[60], making recruitment for clinical trials for cancer-related products particularly challenging. The International Agency for Research on Cancer (IARC) has been working to address research gaps in LMICs and has successfully implemented a range of research projects, such as the HPV-AHEAD study[61] , and presents an ideal opportunity to build research capacity as well as generate local data[62].

Quality standards

Once an IVD has been approved for use, effective national quality assurance (QA) programmes are essential to ensure that they are used correctly and to monitor long-term reliability. QA programmes have several functions, including method validation, error identification, performance comparison across laboratories, and addressing accuracy and reproducibility of tests. Furthermore, they are essential in the context of laboratory quality management systems, to plan, control and improve laboratory services and obtain accreditations[63].

There are several international accreditation bodies used by laboratories in LMICs[64] and the WHO has issued guidelines for improvement and evaluation checklists to support laboratories in Africa that are working towards achieving accreditation. These include SLIPTA (Stepwise Laboratory Improvement Process Toward Accreditation) which is a checklist and explains key elements essential for laboratory quality improvement and SLMTA (Strengthening Laboratory Management Toward Accreditation) which teaches the implication of practical quality management systems in resource limited settings[65] [66].

While these guidelines can be challenging for laboratories to implement[67], a dedicated mentorship program for SLIPTA implementation introduced in hospital laboratories in Lesotho has proven to be an effective way to work towards laboratory accreditation[68].

However, accreditation is not necessarily synonymous with quality. Ultimately, effective QA requires real-time data collection, sampling, and testing of the system, supported by robust QA standards. Furthermore, accreditation does not specifically address anatomic pathology, the mainstay of cancer diagnosis, and most accreditations for LMICs are designed for African countries, and thus may not be appropriate for non-African LMICs. Unfortunately, most LMICs lack in-country regulations to make participation in QA programmes mandatory, and as such, many laboratories have no QA programme in place. Although the WHO has developed a guideline on Laboratory Quality Standards and their Implementation[69], which is based on the internationally recognised ISO standards and adapted to the circumstances in LMICs, a large proportion of laboratories do not meet these standards. An analysis of 954 clinical laboratories in Kampala, Uganda showed that only 45 (5%) laboratories met or surpassed minimal standards for quality as defined by the WHO Regional Office for Africa[70].

Opportunities exist to greatly improve access to quality cancer diagnostics by encouraging wider adoption of QA programmes across laboratories in LMICs. In particular, the development and implementation of cancer-focussed QA programmes is required to better ensure quality of cancer diagnostics in LMICs. In the United States, the American Society for Clinical Pathology (ASCP) has developed the National Pathology Quality Register (NPQR), a quality and benchmarking programme that captures data to measure adherence to clinical practice guideline recommendations, quality and performance standards, and appropriate utilization of laboratory testing[71]. Programmes such as the NPQR may serve as a basis for adaptation to LMIC settings.

Supply chains

A reliable supply of reagents is of paramount importance to ensure continuous provision of services, however, interruptions in the supply of IVDs and associated reagents and materials is known to impede patient care in LMICs[72]. Stock-outs of IVDs are known to occur frequently, affecting not only cancer services but other disease areas as well. For example, an irregular supply of disposable speculums in rural areas of low-income countries has been highlighted as a barrier to clinic-based cytology for cervical cancer detection[73]. Common reasons for supply chain issues include poor quantification, inadequate forecasting and inventory management, inadequate or lack of supervision during implementation leading to wastage, inaccurate documentation, poor distribution systems, costly importation processes and delays in customs clearance[74]. Limited shelf life of reagents can also provide challenges in countries, as poor stock management has been found to result in expiration of products[75] and lengthy importation processes may reduce product shelf-life unnecessarily. These issues impact supply of all IVDs, however IVDs that are required in lower volumes, such as cancer IVDs, are likely to be disproportionally affected. It has been suggested that lessons learned from HIV on how to tackle supply chain challenges could be transferred to noncommunicable diseases[76]. However, it remains to be determined how implementation of electronic logistics management information systems and the development of laboratory forecasting tools for high volume products can be applied to low-volume cancer IVDs.

Laboratory services and infrastructure

Many LMICs have inadequate laboratory infrastructure to support the use of IVDs[77]. Typically, only a small number of centralised laboratories have the instruments and supplies, stable electrical power, water supply, technical support, storage facilities and information technology that are common to laboratories in high-resource countries[78].

As a result, many patients are unable to access quality testing services or experience long wait times to receive test results.

Moving towards integrated laboratory services, specimen transport/referral networks and linked systems is a key factor to increase access to and availability of diagnostic services for different diseases, avoiding duplication of investments in infrastructure, equipment and laboratory support systems. The integration of POC HPV screening into existing HIV early-infant-diagnosis testing schemes proved successful in Lesotho, where the team concluded that multi-disease integration on the same testing platforms is feasible and improved cervical cancer screening in the community[79]. At the global level, stakeholders have taken an active approach in laboratory strengthening and integrated testing, as exemplified by the implementation of the WHO European Laboratory Initiative on TB, HIV and Viral Hepatitis[80], and the Global Fund's drive to foster the strengthening of laboratory systems in countries receiving support[81].

Laboratory network initiatives also have the potential to support optimisation of laboratory services, such as the WHO HPV LabNET initiative, which aims to ensure the availability of competent laboratory services worldwide for HPV testing for surveillance and monitoring of vaccination. Driving harmonized and standardized laboratory testing procedures and capacity building are key objectives of this initiative[82].

Given the importance of early diagnosis in cancer treatment and care, laboratory strengthening and integration of services is likely to have a significant impact on patient outcomes by enabling existing laboratories to provide cancer testing thereby giving more patients access to a diagnosis.

Training and retention of the workforce

Most IVDs require trained healthcare professionals or technicians to perform and interpret the tests. The lack of trained staff has been identified as an obstacle to successful implementation of cervical cancer screening programmes in LMICs[83][84].

However, the provision of training facilities is not necessarily a quick solution to this issue.
To guarantee the success of a cancer screening programme in LMICs, training and continuing education are essential. Interviews with healthcare workers in oncology services in LMICs have identified the need for continuing medical education, access to relevant medical literature, expert opinions on challenging cases, and specialty training as major deficiencies[85]. Additionally, LMICs often lose a high fraction of their trained healthcare workers to migration, due to improved working conditions or salaries elsewhere[86], making retention of knowledge and skills challenging.

Moreover, in many LMICs, there is a shortage of physicians and pathologists specialising in cancer diagnosis (e.g. in cytopathology, colposcopy, or pathology). In some countries, regulation of pathology and availability of suitably trained physicians and pathologists is so weak that many diagnoses are carried out by unqualified individuals[87][88][89]. A survey across 26 sub-Saharan African countries found that the number of pathologists per population ranged from one pathologist per 84,133 persons in Mauritius to one pathologist per 9.26 million persons in Niger contrasting with countries like the UK or the US with one pathologist per 15-20,000[90]. Organized task shifting from physicians or pathologists to non-physician health workers can play an important role in overcoming some of these shortages. Cervical cancer screening programs in Ghana and Tanzania have demonstrated task shifting through the use of a smartphone-enhanced visual inspection with acetic acid (SEVIA) screening approaches[91][92]. After performing traditional visual inspection with acetic acid (VIA), nurses perform cervicography with a smartphone camera and send photos, together with a proposed diagnosis and treatment plan to a qualified expert reviewer. Once feedback is received, the nurses implement appropriate care. The method was found to be feasible and effective in increasing nurses' skills and accuracy, as well as being highly acceptable by the clients.

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Cost

Financial and economic constraints are barriers to accessing healthcare across LMICs and disease areas. Striving for universal health coverage (UHC) worldwide, to ensure that all people obtain the health services they need without suffering financial hardship, will play an important role in making cancer care more accessible. WHO progress in monitoring for UHC currently includes cervical cancer screening[93], but other services delivered in primary healthcare settings under the UHC umbrella can also be used to integrate cancer screening and prevention, e.g. for breast cancer during antenatal care or through HBV and HPV vaccination programmes during childhood immunization[94].

Increased investment in cancer screening and prevention has been globally recognised as a way to achieve a long-term health and economic benefit[95]. The essential package of cancer control interventions in LMICs, as outlined in the Diseases Control Priorities, highlights a set of interventions that could be cost-effective, affordable and feasible in many LMICs[96]. These include HBV vaccination, screening and treatment for cervical cancer, HPV vaccination, diagnosis and early treatment for breast cancer and highly curable childhood cancers. The first two interventions are also among the WHO-identified "Best-Buys" for reducing economic impact of noncommunicable diseases in LMICs[97].

Improving access to cancer IVDs

Fortunately, several initiatives are ongoing that aim to tackle some of the overarching issues affecting access to IVDs. For example, substantial global investments in health programmes over recent years have begun to improve the laboratory infrastructure in LMICs. For Pathology and Laboratory Medicine (PALM) a delivery package has been proposed, which, integrated within a nationally tiered laboratory system, could form part of an overarching national laboratory strategic plan[98]. For product registration, the WHO is piloting a collaborative registration procedure for IVDs in five African countries, using an HIV IVD as the test product, which could potentially be rolled out to cancer IVDs in the future to address regulatory complexities[99].

To improve access to high-risk populations, a number of programmes have begun integrating cervical cancer prevention services into existing service delivery platforms[100]. For example, the cervical cancer programme in Zambia, supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR), is integrated with public clinics offering HIV/AIDS care and treatment[101], and the Cervical Cancer Screening and Preventive Therapy (CCS&PT) initiative in Kenya, Nigeria, Tanzania, and Uganda provides cervical cancer screening through reproductive health networks[102]. These initiatives have reported increased uptake and promoted increased efficiencies through health personnel and infrastructure sharing[103][104], and are now being built upon to provide screening services for other cancers[105].

Some of the barriers to accessing cancer diagnostics may be addressed through innovative IVD design. Tests that can be used near the patient, i.e. at the point-of-care, would have the potential to reach a greater number of people as they can be used outside of the traditional laboratory setting, and are likely to have fewer training requirements for users, removing barriers related to infrastructure and workforce. Point-of-care tests for cancer are effective in high-resource settings, but translation to the LMIC setting has so far proven challenging due to resource constraints[106].

A low cost, simple to use, point-of-care cancer IVD could have a significant impact on test uptake. Some initiatives, such as the National Institutes of Health Affordable Cancer Technologies (ACTs) programme, are seeking to adapt existing technologies to LMIC settings to bring HPV molecular testing closer to the point-of-care[107].

Tests or sampling that can be performed by the patient or at the community level may also help to address social, educational and logistical barriers to access by providing more privacy and reducing time commitments[108], leading to improved uptake[109]. In alignment with this, the WHO's recently released global strategy towards the elimination of cervical cancer as a public health problem encourages the development of high-performance HPV self-testing and digital health options[110].

The collective learnings from ongoing initiatives of laboratory service strengthening, quality improvement, care integration as well as innovative testing solutions, can pave the way for broad improvement in access to cancer IVDs in LMICs.

The future of IVDs

Introduction

A thorough understanding of the traditional and current IVD methods is vital to imagining a 'desirable future' for cancer diagnostics, where future forms of IVDs are integrated into global, regional, national, or local plans to combat cancer. Specifically, recognizing the significant cost savings and increases in coverage and impact of innovative IVDs in LMICs is paramount for the necessary leapfrogs needed to reduce the cancer burden through facilitating access to prompt and effective treatment and realizing the potential of reducing cancer mortality. The current landscape of IVDs and their value, use, and relative cost within cancer care is detailed in Annex 1.

Active disruptive innovations in cancer IVDs: infrastructure challenges

Across the landscape of cancer care, multiple new approaches to IVDs are emerging or becoming standards of care. However, these are at different levels of readiness for deployment in LMICs.

The visual examination of cells (cytology) and tissues (histology) as detailed in Annex 1 is undergoing transformative innovation (see inset) through advances in artificial intelligence (AI) to increase volume throughput for a given laboratory. Artificial intelligence is the theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages. Such AI approaches are actively being developed by a multitude of companies. For example, for a lab that has a small number (10,000 per year) of histology samples but moves to a larger number (50,000 per year) of samples, traditional histology examination would require the addition of more pathologists at a high cost per physician; however, artificial intelligence could increase the output of a single pathologist 10- or 20-fold in theory, resulting in a conservation of costs for personnel without sacrificing quality for the patient.

Another example of transformative innovation of immunohistochemistry (i.e., visualization of tumour markers in tissue, see Annex 1) is the new range of treatment-related markers (e.g., BRAF, ALK, EGFR, PDL-1, and MSI/MSH) that are not used to identify the tumour but rather specifically used to determine the treatment for a given patient (similar to traditional markers such as ER, PR, HER2 and CD20). Assessing tamoxifen susceptibility for breast cancer treatment through ER and/or PR testing is standard of care and access to tamoxifen is almost universal due to its lower costs and inclusion on national essential medicines lists (NEMLs). ER and PR testing can be easily performed with immunohistochemistry. Targeted treatment decisions can then be made by the care team, based on the presence or absence of these markers. This evolution is exciting but not without challenges for the newer treatments, including access to specific medicines and markers. However, unlike tamoxifen, trastuzumab for HER2 positive breast cancer and rituximab for CD20 positive lymphomas are very expensive for health systems and patients. For both HER2 and CD20, a specific test using histology and immunohistochemistry (IHC) is required which is also expensive but required for appropriate use. As mentioned in Chapter 1, with the advent of immune-oncology agents (i.e., tumour treatments that work through the human immune system), specific testing by either immunohistochemistry or molecular methods is rapidly evolving in the timing of treatment protocols from late-stage to first-line therapies; however, the cost of these therapeutics as well as the need for intense monitoring and treatment of adverse reactions creates huge barriers to LMIC deployment. The immunohistochemistry or molecular methods testing is also costly but is required before treatment can begin. Efforts are underway to introduce these agents as proof of concept for use in healthcare systems in LMICs. Barriers to their use include cost, adverse event management and, one of the largest barriers identified, access to these required tests.

A true example of disruptive innovation (see inset) in this space is the Cepheid GeneXpert BreastStrat4 cartridge which provides quantitative Reverse transcription polymerase chain reaction (RT-PCR) for RNA signatures of the genes whose expression levels are traditionally evaluated at the protein level by IHC as ER, PR, HER2, and Ki-67[111]. This assay was designed by Cepheid for LMICs as a point-of-care test and is being field tested and validated in more than a dozen sites in Africa for immediate future deployment. Traditional IHC for breast cancer costs ~$60 USD for the reagents for one patient (not including the costs for surgery, primary histology, etc.) whereas the BreastStrat4 cartridge, which can be run from FNA/B material directly from the patient with cytological confirmation of malignancy, will cost less than $50 USD[112]. With such a tool and cytology services deployed broadly, women with breast masses can be seen, diagnosed, and started on treatment within a few hours in their own village. Although this innovation could be transformative, it is currently only applicable to breast cancer. Other cancers could benefit from such point-of-care approaches if there was proper market motivation to develop them.

Transformative innovation is a new tool or process that creates such cost savings in the current system that all participants in the system adopt the tool or process to continue to compete optimally. An example is online purchase/payment systems. Disruptive innovation is a new tool or process that shifts a current system dramatically, resulting in the adoption of a completely new system and, eventually, loss or abandonment of the old system. An example is cellular telephone use in Africa.

Multi cancer screening (MCS) tests are another example of disruptive innovation—a tool that would be ground-breaking and a paradigm shift for the identification of cancer (especially for rare cancers) or at-risk patients in a population using a simple sample such as blood, urine or stool. The cost of the technologies and individual testing is very high relative to the population benefit for LMICs due to competing health priorities, limited health budgets, and lack of infrastructure to support the patient treatment journey after diagnosis. In addition, MCS tests are largely in development and have not yet been deployed nationally in high-income countries. These molecular platforms, however, can detect 20 to 50 cancers across all stages (albeit, more sensitive with later stages) and, with reductions in cost and simplification of platforms, could be both multi cancer screening as well as multi cancer diagnostic tests (replacing the need for initial cytology/FNA/B or histology)[113][114]. The current platforms can detect tumour signatures and localise the tumour to origin with high accuracy. A major technical hurdle for both high income countries (HICs) and LMICs is that the detection of the signature is so sensitive that patients may have a positive MCS test at a point in care when there is no confirmatory test yet available (i.e., no radiologically detected image or localized lesion). An ethical challenge with such multiplex platforms is the need for existing corollary treatments for every possible diagnosis. In HICs, some cancers still do not have good treatment available (for example, stomach, pancreatic and ovarian cancers), raising the question as to whether early detection of these cancers would result in decreased mortality. For LMICs, access to available treatment for cancer continues to pose a major ethical challenge when introducing screening tests. Despite these challenges, investments in MCS testing in a population that has previously been unscreened—common in LMICs—will be an innovative leap at a much lower cost than trying to introduce and implement four to five major traditional single cancer screening programmes.

For LMICs faced with choosing when and how to screen, the economy of scope and scale offered by an MCS test must be considered along with test performance, costs, and available treatments when planning cancer budgets.

Feasible future states of IVDs for cancer: disruptive innovations

The infrastructure and training of personnel built by expanding cytology and histology access across a population (see Annex 1) lays the foundation for the impact of POC cancer diagnostics. For example, access to the BreastStrat4 in a location where cytology can be performed massively increases capabilities to rapidly diagnose and start treatment for patients. Additional POC tests for the major cancers as well as the common paediatric tumours could shift both the population average stage and mortality; however, individual POCs of increasing number by cancer type will eventually be cost prohibitive because of individual test aggregate costs in a population. Multi cancer screening/diagnostic approaches therefore show promise for large scale implementation where the costs for these test platforms can be reduced. Similarly, the use of self-sampling kits that can be easily transported, centrally processed, and results reported via electronic messaging to both a patient and a clinical team is a valuable innovative approach to increasing access to patient cancer services, as was discussed with Program ROSE. Such self-sampling programs are being evaluated for cervical cancer screening and prevention through HPV testing. The design of other such tests must include an actionable result with minimal interpretation and, therefore would have the largest value if they provide treatment options as a result. In the case of cervical self-sampling, a positive test requires an actual visit to a care centre; thus, the current high value of this approach is for patients with negative results. Self-sampling for multi cancer screening (i.e., home collection of a blood spot on filter paper) would similarly have extremely high value for patients with negative results; however, positive results require follow up to a functioning cancer referral system.

Such systems are often lacking in LMICs as previously detailed in Chapter 2.

Currently, the need for a pathological diagnosis in cancer care is because cancer protocols are written based on pathological diagnosis by body location (i.e., established links). Multiple new types of data about cancer have been developed over the past two decades including genomics, proteomics, transcriptomics, metabolomics, etc. As routine clinical, pathological, radiological, and other data continue to accumulate across patients, they produce datasets for a given cancer. By integrating the new types of data with traditional data, AI can scour and produce a mean set of cancer markers (of any data type) that create a shorter, more efficient pathway from tumour sampling to treatment through a minimal number of coordinated point-of-care assays or a multiplexed assay. The integration of these data using complex bioinformatic pipelines is critical to create datasets that are valuable for the development of individual point-of-care tests or a multiplex (i.e., multi-cancer) test in the future.

To benefit from this integration of data, multimodality testing (i.e., the ability to detect different types of markers such as RNA, DNA, protein, etc) on a single platform is required. Several firms and/or academic laboratories have developed technical integration for multimodality testing but have not yet commercialized these for use. For example, microchips can be printed with hundreds of copies of different molecules to produce disposable diagnostics at very low cost —the question is what molecules and in what combinations make a cancer diagnosis?[115] Another example is the ORIEN platform from the Ohio State University (and other large data collection platforms) that gathers all data available from patients. Digital profiles are created that can match individual patients to treatments and clinical trials. These platforms include dozens of diagnostic results per patient. Therefore, applying AI to these datasets could produce useful multimodality test models in the future.

The challenge for an innovative diagnostic is breadth. For the main cancers (i.e., breast, cervix, lung, prostate, colon, lymphoma/leukaemia and paediatric), creating 10 to 15 point-of-care diagnostics that can dictate treatment may be a reality and eventually can be combined together in a single test platform (i.e., multiplexed). But what about the rare cancers that would still rely on other traditional methods for diagnosis? At some point in the technical spectrum, a universal platform that can screen and/or diagnose all known cancer types becomes significantly less expensive and more efficient than trying to manage 15 or more POC tests along with a traditional diagnostic platform like cytology, histology, or flow cytometry. Therefore, we are at a critical stage in cancer globally where very forward thinking and nimble firms that develop diagnostics have an opportunity to create a set of POC tests which will be of great value to patients and the health system while we await the inevitable development of low-cost universal diagnostic tests on the horizon.

Overview of anatomical and clinical pathology methods, sample types and target detection

	Key methods	Sampling method	Detection of what and how
Anatomical pathology	**Cytology**	Fine needle Aspiration Biopsy (FNAB) (and cell block preparation), vaginal swabs	Abnormal cellular morphology under the microscope (after staining)
	Histology	FNAB, surgical tissue sampling	Abnormal morphology under the microscope (after staining)
Clinical pathology	**Flow Cytometry**	Venous blood collection	Abnormal number of cells or proteins on or within cells through staining and automated cell sorting (haematology)
	Biomarker testing through immunochemical, serological methods, and mass spectrometry	Venous blood collection, stool sampling, vaginal swabs, oral/throat swabs	Presence of quantity of specific proteins through
Molecular testing	**PCR, RT-PCR, sequencing**	Venous blood collection, stool sampling, vaginal swabs, oral/throat swabs, cell blocks from FNAB, samples from surgical procedures	DNA/RNA can be circulating in the blood from tumours, or abnormalities in cells from body fluids or tissue or even from pathogens that cause cancer (such as HPV)

Consider the scenario of a 38-year-old woman who has a 3-centimetre mass in her left breast, with no obvious lymph nodes in her chest or arm. She has travelled 10 hours to a hospital seeking help with the removal of a lesion, which she is scared to leave in her breast due to the death of her aunt, who died of breast cancer last year. She has limited financial resources and no family nearby the hospital. Available to the hospital clinical team is a Fine needle Aspiration Biopsy (FNA/B) of the lesion with access to a cell block and IHC or invasive surgery which will produce a sample for complete surgical pathology. Based on this patient in this situation, what will her options be?

Based on her clinical scenario, the best treatment is likely a surgery to remove the lesion with margins followed by chemotherapy, if this is a cancer. If it is benign, the patient has expressed a strong desire to have it removed. Are her options an FNA/B and wait for interpretation of the lesion including IHC on the cell block (2 to 3 days) or getting the surgery and sending the sample to pathology for histology evaluation (2 to 3 days)? From a resource point of view, the surgery will happen regardless, so cytology is not needed, as it would decrease the time-value for this patient, and she will have the same outcome.

If this situation occurred in her home village or at a hospital that she lived only a few kilometres from, FNA/B would be a much better choice because follow-up is simpler for the patient and a more informed decision can be made about the surgery with the cytology information. It should be clear that the choice of diagnostic test is specific to each patient and a "universal" test for cancer is difficult to achieve.

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One major corollary to this is the actual diagnosis. It is true that the differential diagnosis by probability in this patient example is invasive ductal carcinoma, followed by benign, followed by other rare breast cancer, followed by other diseases. However, in the other diseases category there is also lymphoma, tuberculosis, and mastitis—all of which have non-surgical treatments. The epidemiology, clinical signs and symptoms, patient history, and acumen of the evaluating clinician all must be considered.

Furthermore, this case study serves to illustrate the value of some types of diagnostics at the POC. As in the future, this woman could benefit from POC testing by FNAB in her village which would give more data on whether the surgery is necessary which would save costs and needless stress for the patient.

Conclusion

The lack of or delay in diagnosis has a significantly adverse impact on the delivery of quality cancer care. Leveraging screening and/or early detection programmes is a key driver for prevention and diagnosis of cancers at a stage with potential for cure and/or a good quality of life. IVDs play a key and growing role in early detection and diagnosis, but we see inequities in access to IVDs for cancer across and within countries. To achieve comprehensiv e cancer control, it is essential to improve diagnostic capabilities by addressing the challenges to access in those resource- constrained settings, where cancer mortality is highest.

Governments need to act now to address barriers to access and to also prioritise selection of relevant and appropriate tools to ensure accurate diagnosis, especially in resource-constrained settings.

Early detection drives success in cancer care and treatment, but only works if it is connected to timely and appropriate treatment. It is therefore essential that selection and procurement of IVDs and essential medicines are aligned.

Access to services for early detection is key to achieving the targets set out in the Global Action Plan for the Prevention and Control of NCDs 2013–2020 and the Sustainable Development Goals. It is also an essential component towards universal health care.

Advances in technology is enabling decentralisation of services and ensuring access to diagnostics at primary care level and also a health workforce that need less training – therefore increasing feasibility for lower income settings. Furthermore, the promise of future innovative diagnostics would be potentially transformative in resource limited settings at the right cost. This is a step in the right direction with potential positive public health impact on the global burden of cancer.

The role of in vitro diagnostics in
early detection and treatment of cancer

Key messages

1 Implementation of prevention strategies, screening and early detection programmes play a critical role in reducing cancer-related illness and death, but only when access to quality assured treatment is also ensured.

2 To ensure maximum use of resources, governments need to select essential IVDs based on national needs and capacity for treatment and must be aligned with national essential medicines lists (NEMLs).

3 Governments should consider emerging technologies, especially when these can address the barriers to access, and ensure that paths for registering them are not overly complex and bureaucratic.

4 Investment in appropriate evidence based in-vitro diagnostics is vital, not only for better treatment outcomes but also for savings to health systems but must be accompanied by accessible high-quality treatment options.
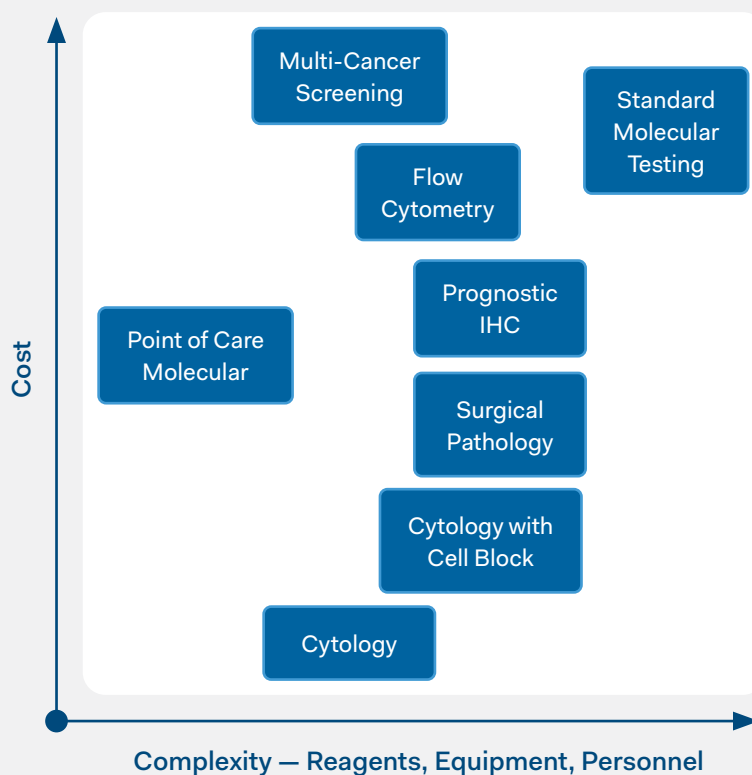
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Annex 1

Traditional IVDs for Cancer: Room for Improvement

IVDs that are currently available warrant a brief discussion to understand where these techniques are today, their impact per investment, what evolutions are forthcoming for these tools, and which future IVDs may replace or circumvent them in the immediate or near future. The current IVDs for cancer diagnosis centre around four disciplines. These are cytology (fine needle aspiration/biopsy (FNA/B), exfoliative), surgical pathology (tissue biopsy and resection), flow cytometry and molecular testing and can be used alone or in any combination with each other to achieve a final diagnosis for a given patient.

Figure 1.

Comparisons of current and developing diagnostics by complexity and cost. Note that complexity may include the complexity of the reagents or supply chain, types of equipment and training to operate them, and level of education and training needed by personnel as well as number of personnel. Costs are presented as relative.

Cost

Multi-Cancer Screening

Standard Molecular Testing

Flow Cytometry

Prognostic IHC

Point of Care Molecular

Surgical Pathology

Cytology with Cell Block

Cytology

Complexity — Reagents, Equipment, Personnel

The role of in vitro diagnostics in early detection and treatment of cancer

Cytology is the discipline of examining individual cells for their morphological appearance using a microscope. Cytology samples are obtained by fine needle aspiration/biopsy (FNA/B) or exfoliation and can be examined either directly or as a "cell block" material. A cell block is made by taking the material from a fine needle aspirate, mixing it with a solidifying agent, centrifuging to a pellet, and then processing the pellet per routine histology for sectioning and staining.

Cytology is highly effective in any setting because of the extremely low costs, ease of procedure for healthcare provider and patient, and high-value information provided[116]. A challenge in cytology is the technique of obtaining samples (i.e. FNAB): limitations of FNA/B include difficult access to and identification of certain tissues without radiological tools (to identify exact positions or even detect lumps/masses that cannot be felt), limited information without dedicated histology services and trained personnel (for cell blocks and IHC), and time-value of patient given their circumstances (especially in LMICs).

Health systems can improve the value of cytology by increasing access to various radiological tools such as ultrasound, computed tomography (CT)-guided procedures, and fluoroscopy using. This will allow clinicians to identify and accurately access a wider range of patient lesions and reduce the need for surgery.

Cytology as a discipline outside of central hospitals, especially for screening, is paramount to achieving high-volume screening of common diseases and proper triage of patients for more complex care and, therefore forms an important tool in any screening programme that aims for universal coverage. Body sites that are particularly amenable include any surface/visible lesion (skin, oropharyngeal, rectal, vagina/cervical, etc) and palpable lesions (lymph nodes, breast masses, abdominal masses, soft tissue masses). Because of its ease of use and access to fresh material for molecular and other future IVDs, cytology should be foundational to cancer screening and diagnostic programs and evolve with increasingly powerful imaging tools to aid in sample collection.

An example of common cytology use is the traditional or liquid-based cervical examination using the Papanicolaou stain (Pap).

Cytology is greatly enhanced when access to cell block creation and subsequent histology is available, as it provides very limited information without the use of cell blocks. Moreover, the samples are much smaller and the processing time is faster which creates time-value for the patient (i.e., the specific benefit to the patient's cancer journey that is attributed to rapid, accurate, high quality services which shorten or reduce the cancer journey to an optimal level). The time-value for the patient overall when choosing between performing a FNA/B or performing a tissue biopsy requires thinking about the downstream treatments available in the local setting, the presumed clinical stage of the patient, and the resources of the patient (see inset for patient case).

Histology serves to analyse the anatomy of tissue. Samples can be obtained by FNAB with cell block formation as mentioned, which allows the microscopic evaluation of the tissue sample after centrifugation.

Surgical pathology, the cornerstone of pathological cancer diagnosis, also results in samples for histology (or histopathology, the evaluation of fixed tissue on frozen or permanent sections), which includes standard, special histochemical, and immunohistochemical (IHC) stains for diagnosis. In addition, surgical pathology includes gross examination of the evaluation of tumour size, margins, and involvement of tissues. These two techniques are the primary partner of surgical interventions ranging from biopsies to large resections as a plethora of information related to diagnosis, prognosis, and staging is determined. It should also be noted that histology of small biopsies (e.g., breast needle cores or incisional biopsies, cervical biopsies, biopsies of head and neck lesions, examination of polyps or other colon lesions) is a crucial part of the cancer screening paradigm at both the population and individual patient level.

The capital investment for histology services in total is such that a minimum number of samples per year (at least 10,000) from a given population should be evaluated before the placement of a pathology laboratory to achieve both economies of scope and scale as well as justify the investment in IHC supplies and reagents. Given the estimate that there are approximately 5000 cancers per million people and, thus, 10,000 samples per million assuming a 50% rate of clinical acumen for malignancy, a population catchment area of 1 million people should be served by at least one pathology laboratory[117]. The capacity of histology, once installed, is much higher, with a single system for tissue processing and slide production being capable of producing nearly 50,000 samples for evaluation per year with only twice the cost of reagents and supplies (Lejeune et al, in preparation).

The limitations of histology are related to overall costs, complex reagent and supply chain requirements, time required for processing, staining, and interpretation, and inherent risks of misdiagnosis when there is inappropriate clinical information or poorly trained clinical partners. The supply chain for histology is complicated because of the need for several hazardous, difficult to import chemicals in large volumes (i.e., formalin, xylene, alcohol) but this can be augmented by investments in reagent recycling systems—such systems are also better environmentally and save costs. In addition to these three main reagents, multiple reagents for staining, special stains, IHC, and processing are required, and stock outs can bring services to a complete stop. Unlike cytology which can produce an answer in minutes (e.g., a patient with a 4 cm breast mass and palpable lymphadenopathy can be diagnosed and staged by a cytologist with two FNAs, one of the lesion and one of the lymph node, and started on treatment immediately), histology requires 24 to 48 hours from the time of collection to the time of a reportable diagnosis in the most efficient system— there are much higher costs for systems that can produce reportable slides for biopsies within 4 to 8 hours but these are impractical unless volumes are near 100,000 samples per year.

If there is poor clinical communication with the laboratory, uninformed pathologists trying to interpret histology samples leads to errors, but these can be corrected with constant communication and electronic medical records. For large medical centres that have surgical services and serve more than 1 million people, a histology laboratory is required. However, with specimen transport networks and biopsy/small surgery services at regional or district hospitals, large central pathology laboratories can serve upwards of 5 to 10 million people with appropriate personnel.

The risks for histology with regards to primary diagnosis of cancer with the advent of new IVDs include circumventing the process altogether with data from broad spectrum molecular testing on blood, FNA/B, or fresh tissue samples. However, surgical centres will require pathology examination of surgical resections for the foreseeable future due to the interdependence of oncology on many data points from pathology that are not simply the histological diagnosis (e.g., size, grade, mitoses, invasion, lymphovascular invasion, lymph node status).

Other image-based techniques include fluorescent in situ hybridization (FISH), chromogenic in situ hybridization, extreme high magnification confocal microscopy, and digital and laser-based automated imaging techniques. These approaches all require access to tissue and, thus, have similar limitations to standard histology (including increased cost over histology) although provide higher resolution and/or more specific diagnostic information.

Flow cytometry is a specialized technique of the haematology laboratory, which many are familiar with from the HIV/AIDs era for the quantification of CD4 cells to determine treatment and prognosis. Flow cytometry combines cytology (individual cell evaluation) and immunophenotyping (e.g., IHC) in a liquid phase using quantitative methods for a multitude of markers. Although initial flow cytometry assays (e.g., as with CD4) used only a few colours (excited by lasers and detected by optics) and were thus limited in scope, modern flow cytometry can use dozens of lasers and analyse many dozens of colours.

This advancement means that with a single tube of blood and a pre-mixed kit of antibodies (in one to two separate sample runs), a patient with a suspected leukaemia or lymphoma can be efficiently and effectively diagnosed. The increased number of markers per assays means a reduction in cost, turnaround time, and personnel training needed. Although a limitation is the initial capital investment required to set up the system, reagent and supply chain are vastly improving with room temperature reagents, as opposed to traditional cold-chain requirements. The major limitation of flow cytometry is that it is only applicable to a limited number of diseases (i.e., leukaemia, lymphoma, etc.); however, it forms the cornerstone of diagnosis for these diseases, especially in paediatric tumours.

Molecular testing is a broad term which encompasses any IVD for cancer that is not one of the traditional methods (cytology, histology, flow cytometry) and analyses molecular signatures (i.e., DNA, RNA, protein) qualitatively or quantitatively. Common techniques include (but are not limited to) polymerase chain reaction (PCR), real-time PCR (quantitative), reverse-transcriptase real-time PCR (quantitative RNA), sequencing, and mass spectroscopy. Current human papillomavirus (HPV) testing and typing is a common molecular test that can be used as a primary screening tool or in conjunction with cytology Pap testing for optimal results (i.e, co-testing)[118]. Sequencing of DNA or RNA is growing rapidly in value as costs are reduced and the wealth of information produced can be rapidly analysed by standard bioinformatic techniques; thus, sequencing stands to largely replace traditional single gene or gene panels done by PCR approaches.

The challenges of molecular techniques currently are the requirement of expensive capital equipment, supply chain of reagents and supplies, requirement for bioinformatic pipelines, and limited relationship to current treatment protocols. In addition to the costs and supply chain (similar to histology and flow cytometry), interpretation of molecular techniques can require the use of a bioinformatics system and/or experts to both interpret the results in the context of the patient for reporting as well as with the treating clinician

to understand treatment options. There is great excitement regarding new therapeutic agents available which can be ascribed by the presence of a molecular signal. However, this must be tempered with the fact that less than 5% of all cancers benefit from these tests currently and the therapeutics are very costly. Thus, further refinement, cost reduction, and increased breadth for the diagnostic-therapeutic axes are needed. In consideration of when and where to bring on molecular techniques, the cancer treatment system should tie these specific tests to the reliable availability of the therapeutics that can be used once the tests are available.

Definitions

Pathology and Laboratory Medicine (PALM): the field of medical practice which covers any form of diagnostic testing excluding radiology and includes all in vitro diagnostic tests (IVDs)

Traditional IVDs: the full spectrum of current testing modalities for cancer found in any branch of PALM with established links to cancer treatment protocols including cytology, surgical pathology, flow cytometry, and molecular pathology

Future IVDs: any testing modality that is in use, design, development, or production that does not currently have an established link to a cancer treatment protocol; requires data to demonstrate effectiveness in the cancer care value-chain; may be currently inhibited by cost

Anatomic Pathology: the branch of PALM (also known as, "Pathology") that is concerned with the examination of cells and tissues for morphology and staining characteristics including cytology, surgical pathology, and autopsy; includes the principle tools for the diagnosis of cancer.

Clinical Pathology: the branch of PALM (also known as, "laboratory medicine") that is concerned with the analysis of blood and body fluids to measure biomarkers including chemistry, haematology, microbiology, immunology, and transfusion medicine; includes flow cytometry for the diagnosis of cancer.

Molecular Pathology: the branch of PALM (also known as, "molecular diagnostics") that is concerned with the analysis of DNA, RNA, protein, or other subcellular signals by specialized techniques; includes sample types from both anatomic and clinical pathology and may be independent or part of either branch logistically

Cytology: the examination of individual cells for diagnostic criteria that are obtained from fine needle aspirates/biopsies, exfoliation (e.g., scrapping, smears, or brushing), or fluid centrifugation; includes rapid on site evaluation (ROSE) and minimal processing; may include the creation of "cell blocks" which require histology processing

Cell block: a pellet of cells produced from centrifugation of a cytology sample that can be fixed and processed using various methods to produce histological sections for special stains and immunohistochemistry

Surgical pathology: the examination of tissue samples, ranging from small incised biopsy to large resections, for diagnosis of lesions; includes both oncological and non-oncological diagnoses; requires histology processing

Autopsy: the examination of the human body after death to determine the mechanistic processes and exact cause of the patient's demise

Flow cytometry: the examination of blood and body fluids for the quantification of cells including benign and malignant cells; includes the diagnosis of leukaemia and lymphoma

Molecular Testing: any testing modality employing molecular techniques to detect or quantify biomarkers used for the diagnosis and treatment of disease including cancer; includes all variations of polymerase chain reaction (PCR), sequencing, and mass spectrometry

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