commentaries

Leveraging Molecular Diagnostic Technologies to Close the Global Cancer Pathology Gap

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Background

Low- and middle-income countries (LMICs) now have increasing access to cancer medicines, which are being integrated into national cancer control programs. This development is, in part, due to the WHO's expansion of the list of essential medicines (EMLs), and the growth of multisectoral partnerships that have made cancer medicines more affordable in emerging markets.[1] However, limited access to cancer diagnostics remains a critical bottleneck to efficiently tailoring available medicines. There have been increased calls to couple investments in cancer diagnostics to those in cancer medicines—including harmonization of the EML with the List of Essential In Vitro Diagnostics (EDL) and List of Priority Medical Devices for Cancer Management (PMDL).[2-4]

To date, the limited efforts toward advancing cancer diagnostics in LMICs have focused on basic pathology services. Molecular diagnostics—now a standard part of cancer management in high-income countries—remain underutilized. This lag in uptake has been primarily due to concerns regarding affordability, technical capacity, and limited diagnostic and clinical infrastructure. However, the landscape of molecular diagnostics is rapidly evolving in health care, with development and deployment of smaller and more efficient point-of care instruments, as well as a greater appreciation for molecular technologies in the context of the COVID-19 pandemic. In this article, we draw on lessons from global infectious disease control and our experience with the GeneXpert (GX) platform to argue that innovations in molecular diagnostics can be used to narrow the global cancer pathology gap. We provide a framework for how stakeholders can leverage molecular diagnostics to advance cancer care in LMICs moving forward—including in-country health technology assessments, context-appropriate endorsement of relevant technologies by international governing bodies, and sustained, multisectoral investments (Fig 1).

Molecular Diagnostics in Infectious Disease

In the past 2 decades, progress in global infectious disease control has partially been from strategic deployment of molecular diagnostics. In the case of tuberculosis (TB), utilization of the GX platform—a fully automated cartridge-based reverse transcriptase polymerase chain reaction (PCR) system from Cepheid that requires minimal hands-on sample preparation and produces results in < 2 hours—was a game changer. The GX platform and the Xpert assay for detection of Mycobacterium tuberculosis and rifampin resistance (Xpert MTB/RIF) simplified TB diagnosis in people living with HIV and those with multidrug-resistant TB; critical results that previously took several weeks to obtain were now available within a single clinic visit. After multicountry assessments of the assay's effectiveness, the WHO endorsed the technology in 2010, and the assay continues to be included in the EDL.[3,5,6] Although the cost of GX and Xpert MTB/RIF assay initially raised concerns regarding its scalability and feasibility in LMICs, multisectoral investments made its widespread impact possible. In 2011, Cepheid launched the High-Burden Developing Country access program to make GX machines and cartridges available to certain LMICs at a reduced price. And in 2012, a prepurchasing collaboration between the Bill and Melinda Gates Foundation, United States President's Emergency Plan for AIDS Relief, United States Agency for International Development, and Unitaid helped reduce the cost of the MTB/RIF assay by 40% from approximately $17 US dollars (USD) to $10 USD in 145 countries.[7]

Before the severe acute respiratory syndrome coronavirus 2 pandemic, more than 10,000 GX machines and tens of millions of TB cartridges were procured by LMICs through the High-Burden Developing Country access program.[8] The platform's widespread deployment helped improve global TB outcomes—especially in rural clinical settings, where historically, patients were not started on appropriate TB treatment because of long turn-around-times for diagnosis and the need for patients to return to clinic.[9-12] Similar advances in HIV, Hepatitis C, Chlamydia trachomatis, and Neisseria gonorrhoeae control have been accomplished globally through utilization of GX and other molecular diagnostic technologies; between 2014 and 2016, of

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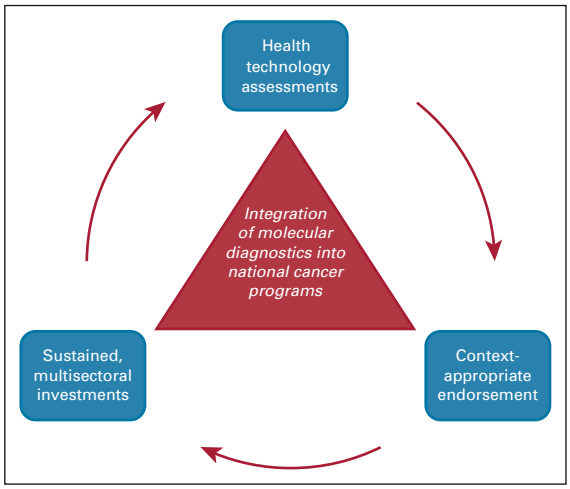

FIG 1. Framework to integrate context-appropriate molecular diagnostic technologies into national cancer programs.

21 high-TB-burden countries, 37% were using the GX platform for diseases beyond TB.[13]

Molecular Diagnostics in Cancer: The Case of Chronic Myelogenous Leukemia

Similar to their impact in infectious disease control, novel molecular diagnostics can also be leveraged to strengthen cancer programs in LMICs. We share the example of an innovative cancer medicine access program through The Max Foundation to highlight the potential impact of molecular diagnostics in cancer care. CMLPath to Care, a collaboration between Novartis and The Max Foundation (previously named Glivec International Patient Assistance Program) has helped make imatinib for chronic myelogenous leukemia (CML), GI stromal tumor, and other select cancers available at no cost to patients in many LMICs.[14,15] Since 2001, The Max Foundation has provided tyrosine kinase inhibitor treatment to over 90,000 patients, with 30,267 patients with CML on treatment as of December 31, 2021 (source The Max Foundation database). Patients enrolled in the program have had a 5-year survival rate of 89%, which compares favorably with survival in high-income countries.[14]

At the onset of the imatinib access program, BCR-ABL1 testing for CML diagnosis and management (which involves PCR or fluorescence in situ hybridization) was not available in many LMICs. Testing was performed by shipping blood or bone marrow samples to other countries—an approach that was costly, time-consuming, and difficult to scale.[16] In 2006, the first version of a semiautomated Xpert BCR-ABL cartridge-based reverse transcriptase PCR assay designed for CML monitoring became commercially available. A more sensitive version, Xpert BCR-ABL Ultra, followed several years later. The Max Foundation partnered with Cepheid to make GX technologies available at a preferential price in more than 60 LMICs and facilitate in-country BCR-ABL monitoring.[16,17] The expansion of on-site point-of-care BCR-ABL testing has streamlined appropriate tyrosine kinase inhibitor selection for patients in the Max Access Solutions program.[16]

Despite investments and efforts to scale GX technology for CML management, BCR-ABL testing continues to be a primary barrier for optimal CML outcomes in many LMICs. Logistical challenges of importation and shelf life, limited access to technical support, and lack of local registration of the test have contributed to persistent gaps in molecular testing for CML. Moreover, the test's price and maintenance costs have also limited its adoption. A recent study estimated that over a 5-year period, the gap in PCR monitoring capacity for patients with CML in countries covered by the Max Access Solutions program was approximately $29 million USD, 86% of which was driven by cartridge costs.[16] Although the Xpert BCR-ABL Ultra cartridge is approved for CML monitoring, there remains a lack of accessible molecular technologies for primary CML diagnosis. Overcoming the PCR gap for CML diagnosis and monitoring will require large investments but doing so could improve survival for thousands of patients and potentially reduce treatment costs through treatment optimization and discontinuation for select patients.

Ultimately, investments in molecular monitoring with GX may have health dividends for cancers beyond CML. GX is a cross-cutting platform that can be leveraged for molecular diagnostics across several cancers, such as human papillomavirus (HPV) testing for cervical cancer (Xpert HPV) and biomarker classification for breast cancer (Xpert Breast Cancer STRAT4).[18,19] Both Xpert HPV and Xpert Breast Cancer STRAT4 tests are CE-IVD In Vitro Diagnostic Medical Devices but are not available in the United States. Similarly, there are other molecular diagnostic technologies proving to have value for management of other cancers in LMICs, including the diagnosis and classification of lymphoma.[20-23]

The Path Forward for Molecular Diagnostics and Global Oncology

Our experience with on-site diagnostics for the management of CML has shown that molecular technologies can be leveraged to advance cancer care in LMICs. The question that remains is how and to what extent. Leaning on the lessons learned in infectious disease, we present a three-pronged approach to leverage molecular diagnostics in global oncology: implementation evaluation, context-appropriate endorsement, and multisectoral investment in relevant technologies (Fig 1).

First, implementation of molecular diagnostics should be rigorously evaluated in-country beyond their clinical validation. Stakeholders can use existing implementation science paradigms, such as the Implementation Outcomes Framework, to study how contextual factors influence technology effectiveness.[24,25] For example, the Implementation Outcomes Framework focuses on evaluation of eight implementation outcomes, including (1) acceptability,

(2) adoption, (3) appropriateness, (4) cost, (5) feasibility, (6) fidelity, (7) penetration, and (8) sustainability. Evaluation of these outcomes in one country can promote the systematic uptake of evidence-based practices that improve effectiveness of technologies across similar contexts. For example, the sample handling and preparation requirements for certain Xpert assays may be a challenge in some settings; the Xpert STRAT4 assay for breast cancer biomarker classification currently requires formalin-fixed, paraffin-embedded tissue, which requires functioning histology laboratory procedures. In pursuing clinical validation of the assay and ensuring production of high-quality tissue samples, laboratories will likely face implementation barriers. As they design solutions to overcome these barriers, their implementation knowledge should be shared widely to guide adoption across similar contexts. In 2014, the National Cancer Institute's Center for Global Health launched the Affordable Cancer Technologies program to support the adaptation, application, and validation of cancer technologies in LMICs, including molecular diagnostics.[26] We need similar, multilateral funding initiatives to support the implementation and evaluation of cancer technologies across LMICs.

Second, the WHO should consider endorsement of novel cancer molecular diagnostic technologies, especially as diagnostic and implementation studies continue to underscore their value.[27] The affordability of cancer molecular diagnostics may be a barrier to WHO endorsement in LMICs. However, endorsements and inclusion of relevant technologies in the EDL or PMDL can catalyze differential pricing programs and multisectoral partnerships that make these technologies more affordable, as was the case for Xpert MTB/RIF.[3] There are currently several cancer-related diagnostic tests—such as immunohistochemical testing for relevant markers of solid and liquid tumors and BCR-ABL transcript, HPV, and epidermal growth factor receptor testing—included in the EDL. However, no molecular diagnostic technologies are recommended in either the EDL or PMDL to operationalize these tests.[3,4] Several molecular diagnostic technologies for HPV testing (including Xpert HPV) have been included on the WHO list of prequalified in vitro diagnostics, but none are yet included as recommended assays.[28] As the evidence behind the value of molecular diagnostic technologies in LMICs grows, WHO endorsement of validated technologies should be heavily considered. Alongside endorsements, governing bodies should recommend prioritization of these technologies to guide public procurement by LMICs. Prioritization of cancer diagnostic technologies can be based on their influence on treatment selection, degree of clinical benefit, and estimated prevalence of the relevant cancer types—factors similar to those considered for selection of medicines for EML.[29]

Third, multisectoral, sustained investments will be vital to maximizing the impact of cancer molecular diagnostics in LMICs. A buy-down approach including up-front, high-volume prepurchases of endorsed diagnostic technologies can be used to reduce prices and expand access. Organizations such as the Foundation of Innovative New Diagnostics can work with industry partners (through initiatives such as Access Accelerated) to negotiate purchasing strategies for molecular diagnostics.[30,31] Although Foundation of Innovative New Diagnostics has previously focused on infectious disease diagnostics, the organization has more recently entered the global oncology space.[32]

Although investments in molecular diagnostics are necessary, they will only influence patient outcomes if matched molecular therapeutics are available and affordable. Similarly, administration of molecularly targeted therapies without confirmation of the specific molecular aberration is not responsible and possibly dangerous. Therefore, investments in molecular diagnostics must be coupled with those in therapeutics. Access initiatives, such as the Cancer Access Partnership—a collaboration between African Cancer Coalition, Clinton Health Access Initiative, and the American Cancer Society—could match their investments and negotiating leverage for cancer diagnostics to those for molecular therapeutics.[33] To date, this potential has been largely unrealized. Moreover, to sustain financing for cancer diagnostics, these investments from nonprofit organizations should be matched with long-term commitments from biotechnology companies, government agencies, and regional and international governing bodies such as the African Union, African Development Bank, and World Bank. Investments should also prioritize building of local research and development capacities in LMICs.

In the coming decades, as cancer incidence rates rise in LMICs, improving cancer care delivery will be an increasing public health priority. To narrow the existing global cancer outcomes gap, efforts to expand access to cancer therapeutics should be coupled with those to strengthen health care infrastructure, including the ability to diagnose and monitor cancers. Although innovations in cancer molecular technologies can facilitate this process, they have been an underutilized tool. Moving forward, robust implementation research, context-appropriate technology endorsements, and sustained multisectoral investments in cancer molecular diagnostics will be key to achieving universal health coverage and equity in cancer care.

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