Molecular tests represent a powerful strategy for screening, early detection, tumor classification, and monitoring efficacy of intervention. Emerging technologies marry advanced biochemical methods with innovative fluidics and electronics to address the need for robust, automated test systems. These technologies are poised to facilitate a quantum leap forward in cancer diagnostics in low- and middle-income countries.

In parallel with improved communication technology are advances in biochemical sensors that make feasible measurements of multiple DNA, RNA, or microRNA targets. Heightened capital investment in devices, often referred to as Lab on a Chip, is streamlining specimen processing, biochemical analysis, and data manipulation.1 Before a new device can be implemented, performance data must demonstrate that the test system is analytically sound and clinically useful in the hands of the professionals who use it.2 The bar for success might be lessened by innovative internal quality control, automation from input to reporting, and other engineering feats that promote good outcomes when implemented by minimally trained personnel.

Cancer prevalence and mortality are high in developing nations, where resources for cancer control are inadequate. Nearly one-quarter of cancers in resource-limited nations are infection related, and molecular assays can capitalize on this relationship by detecting pertinent pathogen genomes and human gene variants to identify those at highest risk for progression to cancer, to classify lesions, to predict effective therapy, and to monitor tumor burden over time. Prime examples are human papillomavirus in cervical neoplasia, Helicobacter pylori and Epstein-Barr virus in gastric adenocarcinoma and lymphoma, and hepatitis B or C virus in hepatocellular cancer. Research is underway to engineer devices that overcome social, economic, and technical barriers limiting effective laboratory support. Additional challenges include an educated workforce, infrastructure for quality metrics and record keeping, and funds to sustain molecular test services. The combination of well-designed interfaces, novel and robust electrochemical technology, and telemedicine tools will promote adoption by frontline providers. Fast turnaround is crucial for surmounting loss to follow-up, although increased use of cell phones, even in rural areas, enhances options for patient education and engagement. Links to a broadband network facilitate consultation and centralized storage of medical data. Molecular technology shows promise to address gaps in health care through rapid, user-friendly, and cost-effective devices reflecting clinical priorities in resource-poor areas. (J Mol Diagn 2014, 16: 601–611; http://dx.doi.org/10.1016/j.jmoldx.2014.07.002)

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workers or patients. Thus, modern technology shows promise to address gaps in health care through rapid, inexpensive, automated test systems that identify and monitor the types of neoplasia prevalent in resource-poor areas.

**Cancer Burden in Resource-Limited Nations**

Noncommunicable diseases are projected to become the major global health burden in the near term, with cancer accounting for approximately one-quarter of this burden, of which at least one-third is preventable. The annual global incidence of cancer is projected to increase from 12.7 to 22.2 million by 2030, with 13.1 million expected deaths. More than two-thirds of the burden will occur in low- and middle-income countries, wherein seven cancer types (lung, colon, breast, stomach, liver, cervical, and esophageal) account for nearly two-thirds of incident cases (GLOBOCAN 2012, http://globocan.iarc.fr, last accessed September 8, 2014). In the world’s poorest countries, women are more than twice as likely to die of their breast cancer, and children are up to ninefold less likely to be cured of acute lymphoblastic leukemia.

**Cancer Linked to Infectious Disease**

In developing nations, nearly one-quarter of cancers are infection related, and four infectious agents account for >80% of the burden: human papillomavirus (HPV), *Helicobacter pylori*, hepatitis B virus (HBV), and hepatitis C virus (HCV). Epstein-Barr virus (EBV) adds a significant burden in several areas of the world (Figure 1).

Approximately 30% of infection-associated cancers occur in people <50 years. Compared to more developed regions, less developed nations have more cancers of the stomach, uterine cervix, and liver, all three of which are infection related (GLOBOCAN 2012, http://globocan.iarc.fr, last accessed September 8, 2014). *Helicobacter pylori* and EBV infection are linked to gastric adenocarcinoma and lymphoma, whereas HPV is uniformly found in cervical neoplasia. HBV or HCV infections often predate hepatocellular carcinoma.

Research into the link between infection and cancer sheds light on the mechanisms of oncogenesis. Interestingly, the aforementioned infection-related cancers that are prevalent in the developing world are the same three cancer types with the most complex genomic signatures as elucidated by mutation analysis. Mutations in infection-related cancer have been attributed to the following: i) pathogen-induced effects, such as heightened oxidation that damages DNA, ii) viral integration events disrupting human genes or their regulatory factors, iii) viral properties that prolong cell survival and resist apoptosis or immune destruction, and iv) suppression of DNA repair.

There is an unmet need for affordable devices to detect cancer-related infections. Such devices could capitalize on the link between infection and cancer to assist in screening and early diagnosis, tumor classification, pathogen-targeted therapy, and monitoring tumor burden over time.

**Figure 1** Infection-related cancers comprise 23% of all cancers worldwide. Oncogenic pathogens (A) are linked to higher cancer burden in less developed regions of the world (B). Data are from de Martel et al. HTLV1, human T-cell lymphotropic virus 1.

**HPV**

The HPV genome is present in virtually all cervical carcinomas. Because infection precedes malignancy, tests for the relevant high-risk strains of HPV add value in cervical neoplasia screening programs. Interestingly, the spectrum of HPV strains in high-grade cervical lesions differs somewhat by geographic region and by HIV status. These population-specific differences emphasize the need to validate genomic assays for each target population.

Rapid, low-cost devices are being developed to test for HPV DNA and RNA. The careHPV test system (Qiagen, Hilden, Germany) was devised specifically for resource-poor areas, and published data suggest that its performance is similar to the US Food and Drug Administration–approved HC2 test. The battery-powered bench-top instrument requires neither electricity nor running water to perform hybrid capture of RNA probes bound to high-risk HPV DNA genomes. The manufacturer states that the reagents are tolerant of temperature swings that may characterize a rural laboratory having spotty electricity for refrigeration. The careHPV test can be performed by minimally trained technologists at
threefold less cost and sixfold less time than the HC2 assay, potentially permitting same-day intervention for HPV-positive patients.\textsuperscript{15} HPV tests may complement or replace the visual inspection strategy that is currently favored over cytology and over laboratory tests for cervical neoplasia detection in many low-resource settings.\textsuperscript{14,16}

High-risk HPV testing of a self-collected specimen, with or without additional molecular tests of human genes, shows promise to improve cost-effectiveness of screening programs in low-resource settings.\textsuperscript{17–20} High levels of HPV 16 DNA in mouthwash or tonsil swab samples likewise show promise for identifying patients with infection-associated oropharyngeal carcinoma.\textsuperscript{21}

*Helicobacter pylori*

Gastric adenocarcinoma is the leading global cause of infection-related cancer mortality and overall is the second leading cause of cancer death, projected to increase to eighth in all-cause mortality in the near term (GLOBOCAN 2012, [http://globocan.iarc.fr, last accessed September 8, 2014]). *Helicobacter pylori* infection is the strongest known risk factor for gastric carcinogenesis. Risk depends not only on bacterial genetics (eg, *cagA* and *vasAs1m1* virulence factors) but also on host genotypes [cytokine variants (eg, *IL1B* 511T)] and coinfections, which lend themselves to molecular testing.\textsuperscript{22–25} Molecular test panels are being developed to examine germline and somatic variants that, along with molecular evidence of *H. pylori*, EBV, and other infections, could improve prediction of gastric cancer progression.\textsuperscript{24,26,27}

*Helicobacter pylori* is also associated with gastric mucosa-associated lymphoid tissue lymphoma (MALT), and eradicating the bacteria via antibiotic therapy is curative in some patients with lymphoma.\textsuperscript{28} Antibiotic drug selection is improved by molecular testing of bacterial DNA.\textsuperscript{29} Clinical trials examining efficacy of antibiotics may benefit from molecular tests of bacterial DNA in biopsy, stool, or body fluids, including saliva.\textsuperscript{30–32} A creative strategy for specimen collection from the upper gastrointestinal tract involves swallowing a capsule attached to a fixed string that is then retrieved through the mouth for nucleic acid analysis.\textsuperscript{33}

**HBV and HCV**

HBV and HCV infections are common and predispose to hepatocellular carcinoma.\textsuperscript{34} Transfusion-mediated infection remains a concerning means of spread for these and other pathogens in countries lacking a centralized system for blood collection and laboratory testing for transmissible agents. Perinatal infection accounts for approximately half of the burden among the 350 million people with chronic HBV infection.\textsuperscript{35} Vaccination is recommended for HBV-related cancer prevention, whereas treatment of HCV is associated with reduced cancer risk.\textsuperscript{36} Viral genomes can be detected, characterized, and monitored using molecular tests, such as real-time quantitative PCR (qPCR).\textsuperscript{37,38} Proof of principle for a point-of-care device for HBV DNA was recently reported.\textsuperscript{39} In this test system, an inexpensive microfluidic chip moves DNA and wash/detection buffers through channels containing immobilized probe. Interestingly, the reporter probe was designed to enzymatically convert sucrose into glucose so that probe hybridization signals were measurable on the type of personal glucometer that is commonly used at point of care.

**EBV**

EBV is deemed a group 1 carcinogen because of its putative role in pathogenesis of endemic Burkitt’s lymphoma (BL), extranodal natural killer/T-cell lymphoma (nasal type), angioimmunoblastic T-cell lymphoma, aggressive natural killer cell leukemia, immunodeficiency-related lymphoid neoplasia including AIDS lymphoma, nasopharyngeal carcinoma, gastric adenocarcinoma, and Hodgkin lymphoma. In each type of neoplasm, the viral genome is localized within malignant cells, providing a convincing link between infection and neoplasia that forms the basis for quantifying tumor burden by blood EBV qPCR.\textsuperscript{9} Affected patients with cancer tend to have high circulating EBV DNA loads that predate clinical diagnosis of malignancy. Serial viral load measurements reflect efficacy of therapy.\textsuperscript{9}

BL is an example of a cancer that is prevalent in resource-limited areas of tropical Africa and for which molecular tests can support a diagnosis. MYC translocation, clonal *IGH* gene rearrangement, and EBV viral load tests have been applied to blood, aspirate, or biopsy specimens suspected to represent BL.\textsuperscript{40–43} Results of testing support a clinical diagnosis of cancer pending definitive cytologic or histological diagnosis that may be delayed because of limited access to histopathology services.

**HHV8**

Another member of the human herpesvirus family, human herpesvirus 8 (HHV8; alias Kaposi’s sarcoma–associated herpesvirus), is a group 1 carcinogen by virtue of its putative role in causing primary effusion lymphoma and Kaposi’s sarcoma. Endemic and HIV-associated Kaposi’s sarcoma are prevalent in sub-Saharan Africa. Differentiation of Kaposi’s sarcoma from clinical look-alikes, bacillary angiomatosis (caused by *Bartonella* species) and pyogenic granuloma, was recently achieved using a novel colorimetric nanoparticle aggregation method targeting the DNA of each pathogen.\textsuperscript{14} In another advance, solar energy was used as the heat source for a thermocycler that assisted, by a smartphone-based camera, to detect fluorescence, and an accompanying app to analyze data was capable of detecting HHV8 DNA in skin biopsy specimens of patients with Kaposi’s sarcoma.\textsuperscript{45}

**Tuberculosis**

Tuberculosis is responsible for 1.7 million deaths per year. Risk of lung cancer (especially adenocarcinoma) is increased
11-fold among patients with tuberculosis. Proposed mechanisms of mycobacteria-related carcinogenesis include long-term immune stimulation (eg, tumor necrosis factor effect on anti-apoptotic NF-κB signaling), neoangiogenesis, and DNA damage from reactive oxygen species. Molecular tests can detect and speciate mycobacteria and predict drug resistance to assist clinicians in selecting rifampin, isoniazid, or second-line medications. Cepheid was among first device manufacturers to develop a PCR test system specifically designed to be rapid and user friendly in low-volume testing laboratories. The performance of Cepheid’s Xpert MTB/RIF test has been shown in tuberculosis-endemic regions to help guide appropriate therapy of affected patients and also to promote infection control in the larger community, leading to reduced transmission rates and fewer drug-resistant organisms.

HIV and Malaria

Immunodeficiency (eg, HIV infection or malaria-related immune dysregulation) is a well-established predisposing factor for selected forms of cancer, some of which, in turn, harbor other viral genomes. HIV and malaria appear to act indirectly to diminish T-cell defenses against viruses and against tumor cells. Progressive HIV infection increases risk of cancer up to 200-fold, whereas recent malaria infection reportedly increases risk of BL by 21-fold. Patients with HIV or malaria remain at increased risk of cancer, even with appropriate access to medical care.

The HIV epidemic markedly accelerated development of molecular technologies and associated laboratory services. The need for rapid HIV testing continues to drive improvements to laboratory infrastructure that is then applied to diagnose other infectious diseases, cancer, or heritable disease, and to provide pharmacogenetic predictions.

Recently, microfluidic chips were reported to detect HIV and associated opportunistic infections (mycobacteria and pneumocystis) by PCR or by isothermal loop-mediated nucleic acid amplification. A promising handheld device can detect and speciate malaria by isothermal rRNA amplification of 2 μL of blood without the need for extraction. An optimized molecular method claims to be 2500-fold more sensitive than conventional microscopy for malaria parasites. Cost savings accrue with proper diagnosis and treatment versus unnecessary spending associated with misdiagnosis.

Multigene Test Panels Targeting Human and Pathogen Nucleic Acid

The Cancer Genome Atlas project is a major step forward in cataloging mutation patterns and gene expression profiles in concert with traditional diagnostic histopathological analysis. Results to date confirm known cancer-related infections and provide new insights into the genetic underpinnings of neoplasia. Most tumors harbor many somatic changes that, along with transcriptome and methylome data, reveal potential druggable pathways that can be explored in clinical trials.

Multigene test panels can characterize signaling pathways driving tumor growth. A proof-of-principle study showed that genotyping is achievable on fresh, frozen, or fixed tissue in just 70 minutes using an instrument platform that performs automated extraction, followed by Invader chemistry, to query 13 mutations in KRAS, BRAF, and PIK3CA genes. Another study detected heritable variants in cytochrome p450 coding sequences to facilitate bedside clopidogrel dosing. Although these technologic advances are exciting, the particular somatic and heritable variants targeted may be off target for the needs of resource-poor facilities, where downstream interventions are limited. A more practical test panel in hospitals lacking on-site pathology services might examine fine-needle aspirate material from a mass lesion to help distinguish infection from tumor, pending send out for a pathologist’s definitive diagnosis days to weeks later.

Most of the technologies described herein are not yet implemented because of an insufficient evidence base and/or inadequacy for particular local needs. Investment is required to devise suitable genomic assays that answer pertinent biological and medical questions in clinical trials and ultimately in routine patient care. When applied in resource-limited areas, one must consider the unique logistic, cultural, and technologic features that promote success. As with all clinical research, multidisciplinary collaboration is required to optimize assay design and to ensure the study plan is ethical when offered to patients with few alternatives for care. Judicious use of precious resources is critical. Batch testing in a reference laboratory is generally less expensive and more effective than is point-of-care testing, although suitably designed test systems could alter this equation. Even central laboratories will adopt one-off test systems when rapid turnaround is required.

Cancer Screening

There are marked global disparities in access to cancer screening tests and programs. For cervical neoplasia, screening programs are well established in many resource-poor areas. Recent studies suggest that HPV DNA testing is cost effective as a primary screening method on self-collected specimens or on samplings gathered by health care personnel. Nasopharyngeal carcinoma screening by qPCR of EBV DNA in saliva or in nasopharyngeal brushings shows promise as a means to identify tumor in high-risk individuals. Screening for other cancers that are prevalent in the developing world (lung, stomach, breast, liver, colon, and esophagus) is in early stages of investigation to find genomic signatures distinguishing precursor lesions likely to act benign from those that are at risk of progressing and, thus, require intervention (GLOBOCON...
Community-based mobile unit. Endoscopic imaging technologies showed feasibility of biometric screening and education in a preventive health initiative in New Mexico in 2014. A recent preventive health initiative in New Mexico has been adapted for biometric screening and education in a community-based mobile unit.82 Endoscopic imaging technologies are advancing in parallel with molecular devices, and the two strategies may synergize to better visualize lesions to collect by biopsy or brushing.

Design of Molecular Devices for Resource-Limited Settings

Government-sponsored research has devised test systems for military and aerospace use, and some of these advances have been adapted for benefit of civilian health care facilities. For example, in the 1990s, the US government funded Idaho Technologies (now BioFire Defense, Salt Lake City, UT) to develop a briefcase-bound version of a thermocycler that was later redesigned for clinical laboratory use (Figure 2). A modern Biofire FilmArray System is being developed to test 27 nucleic acid targets in 1 hour with only 2 minutes of hands-on time.75 Even smaller portable devices were designed for deployment by first responders in emergency situations.76 These devices tend to operate without electricity and have flexible test options with barcode readers to ensure proper selection reagents for each protocol. Reagents are freeze dried, which makes them light weight to transport, and stable at room temperature for 6 months. Software includes analysis and archiving functions.77 Integrated test systems include pre-analytic and postanalytic steps that are as important as the hybridization phase for ensuring good outcomes.78

Although repurposing devices for resource-poor areas may be helpful, the optimal device is built from the ground up to meet the unique requirements of the locale and the intended use. Although most of the world’s countries have at least one state-of-the-art medical complex, some tests must be performed in more remote facilities served by a meager workforce, perhaps with limited access to refrigeration, electricity, and potable water. Universally appealing device characteristics include low-cost, robust, and sustainable systems that are medically fit for purpose. Table 1 lists features promoting adoption of laboratory test devices, recognizing that various medical providers have differing priorities.

Competition among vendors is a major driver of low cost and innovation, as is trade policy improving access to commercial products in the developing world. The recent US Supreme Court ruling that isolated DNA does not infringe on gene patents opens the door for molecular device design on the basis of medical and public health needs above costly legal quagmires.

Rapid, Inexpensive Molecular Technology

PCR is the mainstay of hybridization assays worldwide, but emerging molecular technologies may be less expensive and equally effective. A recent study of patients with hemorrhagic fever in Sudan showed that isothermal loop-mediated amplification (LAMP) was more rapid, less expensive, and performed as well as RT-PCR for detecting viral RNA in serum samples of patients with acute infection. The reaction is performed in a 63°C water bath rather than the more expensive thermocycler needed for PCR.

Another isothermal nucleic acid sequence-based amplification (NASBA) technology is being adapted to quantify HIV RNA and to predict drug resistance.79 NASBA is well suited for RNA profiling because it skips the need for reverse transcriptase used in RT-PCR. Expressed RNAs are naturally more abundant than DNA, although RNA is also more labile, thus generating the potential for specimen degradation unless the test is done promptly or preservatives are used.

Isothermal amplification eliminates the need for costly heating and cooling steps that characterize PCR. Instead, enzymes achieve strand separation, and these enzymes (eg, helicase) may be more tolerant of inhibitors than is the polymerase used in PCR, potentially reducing the need to purify analytes in crude specimens before hybridization.80,81 LAMP technology typically relies on six primers, two of which form stem loops that self-prime, and a strand-displacing polymerase then amplifies concatenated products. The assay yields an insoluble end product that can be quantified visually or in real time using a turbimetric detector, potentially saving cost by eliminating expensive fluorescent dyes. An option for fluorescence detection permits multiplexing of LAMP assays in one reaction vessel.

LAMP assays have been developed to detect tumor-specific RNA and also a range of microorganisms (bacteria, mycobacteria, viruses, parasites, amoeba, and protozoa) using handheld, battery-operated devices with disposable fli

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**Table 1** Features promoting adoption of laboratory test devices

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<th>Feature</th>
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<td>Accessibility</td>
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<td>Robustness</td>
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<td>Sustainability</td>
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<td>Medical fit</td>
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**Figure 2** Devices initially developed for military or aerospace use can be re-appropriated for laboratory medicine. A portable thermocycler with laptop computer interface, initially developed for military field work, was later adapted for health care settings. The military version, dubbed the ruggedized advanced pathogen identification device (RAPID), was designed, in part, to examine environmental samples for biowarfare agents. The device requires limited space and technologist expertise, while still providing reliable real-time molecular results. Image used with permission of BioFire Defense.
Table 1 Desirable Characteristics of Laboratory Test Systems

<table>
<thead>
<tr>
<th>Medical performance</th>
<th>Administrative qualities</th>
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<tr>
<td>Reliable results (suitably sensitive, specific, linear, and reproducible)</td>
<td>Low cost to establish and to maintain the test system</td>
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<td>Informative for actionable medical decision making</td>
<td>Straightforward training of staff and supervisory personnel</td>
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<td>Same-day turnaround time to minimize loss to follow-up</td>
<td>User-friendly interface</td>
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<td>Intact supply chain for supplies and reagents</td>
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<td>Option to use expired reagents with documented explanation (eg, for training)</td>
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<td>Simple equipment maintenance with reminders and record keeping</td>
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<td>Available service and repairs</td>
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<td>Safe for patients and for testing personnel</td>
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<td>Accessible where medically necessary</td>
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<th>Quality assurance</th>
<th>Environmental factors</th>
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<tr>
<td>Document and report provider’s ID, patient ID (option for barcoding), specimen type, date/time collected and reported, raw data, reportable result, interpretation, and comments</td>
<td>Minimal requirements for continuous electricity, Wi-Fi access, sterility, and clean water</td>
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<tr>
<td>Automation to reduce risk of human error</td>
<td>Long shelf life under extreme conditions of transport and storage</td>
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<td>Built-in quality checks with recorded results, such as endogenous control</td>
<td>Disposal of toxic chemicals, biohazards, cartridges, and sharps</td>
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<td>Contamination alert (eg, statistically unlikely series of results)</td>
<td>Durable hardware, and in some cases waterproof or portable</td>
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<td>Flags to alert for malfunction, abercancies, and suggested corrective action</td>
<td>Lockable in a physical way and from a patient privacy perspective</td>
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<td>Barcoded supplies and reagent lot numbers recorded; alerts for expiration dates</td>
<td>Prociency survey availability</td>
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<td>Proficiency survey availability</td>
<td>Educational materials for clinicians and for testing personnel</td>
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<th>Educational materials for clinicians and for testing personnel</th>
<th>Preservation of Nucleic Acid before Analysis</th>
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| Microfluidic cartridges.81–85 Open-source hardware, software, and protocols are intended to spur further innovation.82 Technical reviews of LAMP and other isothermal amplification technologies were recently published.88,89,90 Thus far, intellectual property concerns have hindered combining these promising chemistries with specimen collection tools, fluidics, and informatics modules required for a functional test system. Next-generation sequencing is exceptionally powerful in its ability to identify genetic variants, although user-friendly sequencing devices remain to be commercialized. The technical costs of sequencing continue to plummet, but implementation in health care remains in its infancy due to the labor-intensive processes of preparing specimens and interpreting sequence variants. As with all cancer genetic tests, interpretation is done in the context of the clinical question being posed and the input material on which each test is performed (eg, tumor type, proportion of neoplastic cells, and fresh versus fixed tissue). Patient data are examined alongside multiple quality checks that reflect performance of the test system and adequacy of patient material.86 Research is ongoing to construct databases linking sequence variants to evidence of clinical actionability and improved patient outcome.

Chips, Assay Miniaturization, and Automation

Electronic sensors can detect DNA hybridization by its effect on current flowing through an electrode on a circuit board (Figure 3). This technology, combined with miniaturization (nanotechnology) and fluidics, could provide cost savings by using fewer and less expensive reagents, faster thermocycling, and less labor when compared with traditional plate-based hybridization.87 On-chip fluidics can accommodate multistep processing, including cell separation, cell lysis, and nucleic acid purification, before analysis. Automation promotes standardization and reproducibility. Several commercial test systems are capable of accommodating small input volume for multiwell analysis using disposable components.88,89 Interfaced barcode readers and laboratory information systems promote specimen identification and data analysis for interpretation and reporting.

Preservation of Nucleic Acid before Analysis

Abundant data confirm that dried blood spots are amenable for genotyping.41,43,90–93 Dried specimens stored or transported at ambient temperature represent a cost-effective means of amassing specimens for batch testing. DNA, RNA, and microRNA targets are reportedly recoverable from filter paper on which blood or other body fluids have been dessicated. Alternative stabilizers have been described.
to promote specimen integrity between collection and analysis. 94–97

Human Resources

The single most important aspect of high-quality laboratory service is competent personnel. This includes all personnel in the chain from test order through collection, transport, analysis, interpretation, reporting, and downstream action. A recent white paper from COLA highlights problems surrounding tests done in poorly regulated health care environments. 98 Waived testing sites (ie, point-of-care sites) in the United States indicated that 35% of personnel did not properly record quality control data, and 31% did not maintain a log of tests performed. Poor preventive maintenance of equipment can result in a variety of problems, including contamination that may adversely affect sensitive molecular tests. The findings highlight the potential gap between a well-trained, well-supervised laboratory technologist and the reality when other (well-meaning) health care providers perform laboratory tests. It is, thus, recommended that testing be done in a centralized laboratory, except when there is medical need for rapid turnaround, to prevent loss to follow-up, or when transport would compromise specimen integrity.

When less-experienced personnel are expected to perform tests, it is important that test systems are engineered accordingly to address likely errors in technique, interpretation, or documentation. A supervisor should periodically oversee the work of testing personnel (trust but verify) and nurture those serving on the front lines who may otherwise feel isolated. Continuing medical education motivates workers to persist in and take pride in their specialized work. Poor-quality test results not only harm patients but ultimately undermine clinician’s confidence in the utility of laboratory tools, making it even more difficult to establish and maintain laboratory services. Software is available to facilitate oversight of point-of-care testing.

It is difficult to recruit and retain pathologists and technologists in developing countries. For example, in Honduras there are only nine certified histotechnologists, none of whom are positioned in rural areas. Staffing is likely to get worse in the coming decades due to a workforce shortage of both pathologists and technologists. The looming crisis must be addressed through training programs in developed nations and in the developing world. A non-profit organization, Pathologists Overseas, has a 25-year track record of providing, advising, and promoting self-sustaining pathology and laboratory services. 99 Many other noteworthy programs exist, such as those coordinated by the African Society for Laboratory Medicine, the Pan American Health Organization, the World Health Organization, the American Society for Clinical Pathology, the American Society of Cytopathology, the US and Canadian Academy of Pathology, The Diagnostic Microbiology Development Program, the Royal College of Pathologists, The International Network for Cancer Treatment and Research, and the College of American Pathologists Foundation. The programs are aimed at building local laboratory capacity. 100–102 It is important to coordinate with in-country leaders, particularly with the Minister of Health, to ensure that effort is appropriate for local needs and that resources are strategically allocated.

To promote capacity building, ideally local practitioners are empowered for independence within the framework of multinational regional networks (eg, Central America). 102–105 The American Association for Clinical Chemistry offers an online training program for point-of-care specialists. The Association for Molecular Pathology helps arrange regional chapters of molecular laboratory professionals. Much effort of the aforementioned organizations is focused on educating personnel working in central laboratories and academic centers, who, in turn, train others in the region. The College of American Pathologists offers proficiency surveys that form one component of quality assurance.

Telepathology

Telepathology encompasses the practice of pathology at a distance. Remote interpretation of qualitative or quantitative laboratory results is feasible, such as visualizing peaks on an electropherogram or analyzing BAM files generated by sequencing DNA of patients and associated controls. Guidance from the Canadian Association of Pathologists provides a framework for telepathology implementation and validation. 106

Telepathology assumes that an infrastructure exists to perform the technical component of testing near the point of care, and that technical components should be overseen by a physician responsible for ensuring quality of transmitted data or images. Broadband connection is available to only one-third of the world’s population, although efforts are underway to render access universal (eg, http://internet.org). A large bandwidth is required for image transmission.

Telepathology is a mechanism for second opinion consultation and for sharing case workload, reviewing unusual cases for continuing medical education, and promoting quality assurance. One concern about remote consultation is the lack of consultant familiarity with local medical practices and with regional diseases, such as pertussis (whooping cough), tropical enteropathy, or nutrient deficiencies. Video-conferencing is helpful for two-way learning, devising and updating work plans, and facilitating train the trainer programs.

Gopal et al 107 recently described their experience establishing a histopathology laboratory in Malawi, including digital image transmission of scanned slides to a consulting pathologist at the University of North Carolina who reviews findings with the primary pathologist in Malawi. The establishment of new laboratory services is expensive and requires multidisciplinary coordination (eg, with clinicians and a wide range of staff). Medical equipment or supply donations can be arranged by agencies such as Project

Information Systems

Same-day turnaround is often crucial for surmounting loss to follow-up, although increasing availability of cell phones, even in rural areas, provides better opportunity for patient engagement. Text messaging is ubiquitous worldwide. Smartphones are much more expensive but offer added benefits of global positioning system geotagging and interfaced biometric sensors with optional data upload to a central databank.108,109 Patients and their providers can then view serial data and receive customized notifications or educational materials. An application for testing personnel (eg, Radiometer America’s Avoid Errors application) contains instructional videos on specimen collection, a competency test, and tips to interpret findings or to troubleshoot problems. Connectivity to fiberoptic or mobile broadband service not only offers a way to deliver health care but also to facilitate epidemiological monitoring of emerging disease, and to access consultants.75 Transmission errors are reduced when data are automatically transferred.

The Computing For Good (http://limswiki.org/index.php/C4G_BLIS, last accessed September 8, 2014) program at Georgia Institute of Technology recently teamed with the Centers for Disease Control and Prevention to field-test an open-source basic laboratory information system for computer data entry and retrieval in laboratory settings.

Conclusion

Advances in molecular technology show promise to improve cancer control in resource-limited nations through rapid, informative, reliable, user-friendly, and cost-effective laboratory tests. Much of the focus in developing nations is on infection-related cancers because of their prevalence and potential for cost-efficient prevention, as well as the unique opportunity to use the pathogen as a tumor marker promoting diagnosis, monitoring, and targeted therapy. Encouraging progress has been made in engineering devices to overcome the economic and social barriers that often limit effective laboratory support. Recent advances in technology are yielding small, but powerful, instruments that, along with accessible reagents, make feasible the types of molecular diagnostic systems that are suited to frontline providers.

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