CONCLUSION

The Feasibility of Laboratory Diagnosis in African Settings

We have the research knowledge, but it is a question of getting it into the field and actually doing something about the problem.

—Tony Jordan, 2001

In May 2009, the *Annals of Tropical Medicine and Hygiene* published an audit of diagnostic services in the Tanga region of Tanzania. The audit was performed roughly five years after Tanzania had committed to an ambitious health care reform program, which commendably included a stated intention of ensuring access to high-quality and effective laboratory services whenever these were required for diagnosis. The findings were, as described by the report's Tanzanian authors, "depressing":[1] most of the labs failed to meet the Tanzanian national recommendations. As few as eighty-four personnel staffed thirty-seven health laboratories, most of whom lacked training in diagnostic laboratory services and were working without supervision. Essential protocols such as culture—for diagnosing life-threatening bacteremia and meningitis—could not be performed at any laboratory. HIV and tuberculosis testing was available at less than half of them, and although most reported that they performed blood smears for malaria, microscopes were often defective so that the quality of these tests, and many others, could not be assured. Whenever only limited testing is available, the priority should be highly prevalent diseases or those where a precise diagnosis would alter the course of treatment. Instead, the researchers observed that resources available at laboratory facilities in the Tanga region were not reflective of health care needs or the burden of disease.

The Tanzanian laboratory audit cited Ghana as a model of diagnostic development but even there, regional laboratories are often not equipped to respond to local health needs.[2] However, Ghana's first two teaching hospitals do have reasonably well-equipped and staffed laboratories. Laboratory capacity at one of these hospitals was formally assessed in 2005, revealing that blood, cerebrospinal

fluid, urine, and stool were routinely cultured for bacterial pathogens. Sputum smear microscopy was available for tuberculosis diagnosis, and malaria could be diagnosed by microscopy. Eleven of the twenty lab staff members had a bachelor's degree in medical laboratory sciences, and five others were qualified laboratory technicians. Four of the five laboratories in the twelve-hundred-bed institution used appropriate internal quality control methods. Even though problems with data management and physician attitudes were recorded, the laboratory was equipped for the task of diagnosing the most common endemic infections that can be cheaply identified with present-day technology.[3]

Ghanaian teaching hospital laboratories are attached to local tertiary-care hospitals. Although they do participate in international research projects and clinical trials, their primary function is to support patient care. They are answerable to the Ghanaian health system and in some cases oversee services at district laboratories. They demonstrate that integrated laboratory services can and do work. At a time when health care development on the continent is of global interest, the rarity of such establishments raises the question of why laboratory services in many more parts of Africa, as illustrated by the Tanga evaluation, are suboptimal or derelict. The failure to imagine a different mode of health care delivery for Africa is so widespread and of such long standing that many people inside as well as outside the health care sector, incognizant of or ignoring the important exceptions, assume the situation is intractable. Long-standing arguments against providing diagnostic laboratory services at all levels of medical practice in developing countries are repeatedly echoed, even in association with the most well-meaning health initiatives. These paralyzing arguments are grounded on unsupported presumptions that must be unpacked and critically examined.

Many adamantly argue that laboratory testing is not feasible under African conditions. This, in turn, is accompanied by the notion that diagnostic testing necessarily requires more time than clinical practice allows. Then there is the belief that the cost of microbiological diagnostics would simply be untenable given resource constraints. Finally, many presume that there is, and always will be, an insurmountable lack of the kind of expertise required to use appropriate diagnostics. All of this is amplified by the misconception that diagnostic testing is not really necessary. Justifying diagnostic development in Africa requires us to debunk the six most prevalent myths.

Diagnostic Mythology

Too Many Patients, Too Little Time

Government hospitals in developing countries are among the most crowded health facilities in the world and are staffed by woefully overworked health

professionals. The seemingly unending stream of patients makes it impossible for them to devote more than a few minutes to each one.[4] Even the most rapid laboratory tests take a few minutes, and often outpatients must come back for their results to be read. The idea that ordering, performing, reporting, and interpreting diagnostic tests could slow down long lines is a valid concern. Eliminating necessary diagnostic tests does not make patient care more efficient, however, because every misdiagnosis incurs costs in time and money for patients as well as for health care systems. Incorrectly treated outpatients return, or go elsewhere; they spread the disease to others, who must then seek care. Misdiagnosed outpatients often end up as inpatients, who more easily overwhelm resource-constrained health systems.

It is no coincidence that Sir Arthur Conan Doyle, author of the popular Sherlock Holmes detective tales, was a medical doctor. Medical diagnosis is a sophisticated and often time-consuming process of careful observation and deductive reasoning. Research has repeatedly shown that, even with diagnostic flowcharts and other aids, health workers, particularly when they are not qualified doctors or nurse practitioners, are imperfect clinical diagnosticians.[5] Incorporating objective information from laboratory tests increases diagnostic precision. Laboratory testing is especially important when health workers are overtaxed or semitrained, and when consulting time is short.

Today, rapid malaria tests can be performed during a single outpatient visit. Laboratory diagnosis of many other infections takes longer, but the technology to develop rapid tests for other common infections exists. In the most overcrowded health facilities, the time that outpatients spend sitting or standing in line is often used for prescreening by a nurse or aide who looks for clinical signs of disease. Rapid diagnostic tests for one or more highly prevalent diseases could be performed as part of the screening process so that results are available to the prescriber and no time is lost. Less rapid and more expensive tests, if required, could be ordered by the consulting health worker. It is unfortunate that patients must wait at all, or, when unavoidable, return for the interpretation of the results, but the gains in terms of diagnostic accuracy, appropriate prescription, and the avoidance of therapeutic failure far outweigh the inconvenience.

A critical examination of the "inconvenience" that routine testing might entail is worthwhile. In many parts of Africa, a culture of treating patients as aggregates is a legacy from colonial medicine, where the health of the individual African was not of interest and patients were processed in a conveyor belt mode.[6] It may be the baneful influence of this construct on medical practice, rather than the nature of biomedical science per se, that occasions the prevalent criticisms of biomedical neglect of the whole person and alienation of the patient.[7] Patients are less likely to be suspicious of a system that views them as individuals rather than as faceless members of an aggregate. Diagnostic development will force a

level of individualization in healthcare delivery that could also improve patients' attitudes toward health services.

Laboratory Facilities Are Too Expensive

The largest share of health expenditure in Africa, from colonial times until today, has gone to medicines. A long-standing misperception that is prevalent worldwide is that diagnostics are of lower value than drugs.[8] Diagnostics inform drug development and they are key to ensuring that existing drugs are appropriately used. Diagnostics are not cheap, but their direct costs should not be the primary factor in deciding their use and development; to authentically assess costs, the savings that diagnostics provide must be deducted from their price. Recent studies in resource-poor settings, as well as mathematical models, show that for malaria, sexually transmitted diseases, and other infections, diagnostic testing is almost always cost effective, even when testing is not optimal.[9] In some cases, the cost-effectiveness of diagnostic testing has been compromised by prescribers failing to utilize test results to inform care. But this points to the need for prescriber education rather than toward abolishing testing.

Add-ons to the real cost of materials inflate the cost of biomedical science, including testing in many parts of Africa. Converters and other supporting equipment must be purchased to utilize machines that are designed to operate in other countries. Present-day prohibitive maintenance costs arise because "gadgetry [is] simply too scarce to support a domestic service economy."[10] In the West, a substantial proportion of the cost of a test covers the time spent by technicians and consultants to perform and interpret it. As the absolute value of salaries in Africa is lower, this component of the cost will also be lower.

Another common miscalculation arises from the fact that diagnostic services are much more expensive on a case-by-case basis when used rarely than when used routinely. Because it often costs as much to run five samples through laboratory tests as it does two dozen, the cost of each test falls dramatically when more patients in need of testing are screened. Currently, where available at all, laboratory diagnostics in Africa are often reserved for complicated or refractory cases and available at tertiary care and research centers. Were they used routinely, economies of scale could sustain a market for equipment and reagents. Competition should encourage lower markups as well as local manufacture and distribution.[11]

A global economic crisis that became apparent in 2008 overlapped with health care crises of emerging infections and drug resistance. All of these threats must be addressed by careful investment of resources and in a manner that guarantees successes and minimizes waste. For infectious diseases, this includes

adequate preventive measures and the efficient diagnosis of common infections so that they are treated with the cheapest appropriate medicines before they are allowed to spread. Resource-poor health systems that are weighed down by the needless disease transmission that accompanies misdiagnosis have a greater need for diagnostic precision than their more affluent counterparts. It behooves us to be wary of naysayers who cite prohibitive cost as the excuse for avoiding any effective health intervention. Almost every time someone has bothered to check the figures, the indirect cost of doing nothing, or doing the improper, exceeds that of the direct cost of administering appropriate care. Still, cries of "cost-ineffectiveness" continue to undermine health care delivery in the poorest countries, very often masking less easily justified reasons for inaction.[12]

The Ideal Tests for Africa Have Not Been Invented Yet

Interest in diagnostics has increased in recent years. However, as clinical microbiologist Keith Klugman lamented in 2010, the revolution in diagnostics is a slow one. Some of the sluggishness arises because current resources are underutilized. A tuberculosis laboratory capacity building program in Lesotho has demonstrated that we do not need to wait for improvements before implementing currently available tests in African health clinics. However, it must be acknowledged that the age-old scourges of tuberculosis, typhoid fever, and other bacterial infections—and malaria until recently—are all diagnosed with tests that are approximately a century old. Many of these tests are too slow, too complex, or too expensive to be used at the point of care. By contrast, HIV, a "new" virus of global significance, has seen four cycles of diagnostic test development within a quarter of a century. Why is there such a small knowledge base for appropriate primary-care diagnostics for Africa? The answer is connected to profit motivation because most common infectious agents are known and can be detected, many of them simply and rapidly. For many tropical diseases where a useable test is yet to reach the clinical laboratory bench, we know development is possible because diagnostic tests are available for similar organisms that are prevalent in Western countries.[13]

Vaccine and drug development are driven by the needs of patients in the richest countries in the world. The same is true for diagnostics. Multiplex tests, which could detect more than one pathogen in a single specimen, would have inestimable value for many syndromes common in Africa, but they do not yet exist. However, veterinary diagnostics that can detect up to five different pathogens in a stool sample from a calf with diarrhea are routinely used in industrialized countries. One of these tests screens for two common viral, one protozoal, and two bacterial targets. The test is performed without any equipment, can be run

outdoors on a farm, and the results are ready in fifteen minutes.[14] An outbreak of calf diarrhea can have tremendous financial implications for a farm and even a national food program, which is what motivated the development and use of the test.

Until very recently, there were few financial incentives for developing vaccines or drugs specifically designed for people who cannot pay for them, and even fewer for developing diagnostic tests. But today, economists and policymakers are beginning to put forward ideas to incentivize innovation that could improve the health of the poor. These include public-private initiatives, such as the suggestion that donors offer to pay for drugs when they are developed.[15] Similar stimuli would apply to diagnostics so that the estimated one hundred million rapid diagnostic tests for TB required each year will be paid for when they become available.[16]

We have the technical expertise to develop tests de novo in areas of need. Diagnostic development has yet to receive the same attention or lobbying effort as medicines, but, with the right stimulus, the ongoing genomic and nanotechnology revolutions make it relatively simple to identify diagnostic candidates and make them the basis for point-of-care tests. Veterinarians performing molecular tests out in the field, under conditions that are much worse than in an African clinic, do not need to understand molecular biology to accurately perform and interpret the tests, nor do they need temperamental electronic equipment.[17] The chlamydial rapid test developed by Helen Lee's group is as sensitive as conventional nucleic acid amplification tests but lacks their technical complexity and instrumentation requirements. This thirty-minute test can be performed while a patient visits any health provider, and the test is so simple that a version has been developed for home use. Blood tests for estimating blood cell counts and hemoglobin levels traditionally required microscopes and skilled technicians. Today they can be performed with a portable instrument that provides a digital readout when blood collected from a pinprick is applied. This type of test has been used to assist diagnoses of very sick children in Tanzania.[18] Recently, an isothermal amplification test for drug-resistant tuberculosis was developed and tested in Peru, Bangladesh, and Tanzania. Although the test has a molecular basis, it is simple and safe to perform and is rapid and robust.[19]

WHO has suggested that diagnostic tests for use in resource-poor areas must be "ASSURED": affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to areas of need.[20] The aforementioned examples meet most or all of these important criteria. Incentives to develop, validate, and deploy diagnostic tests for Africa's infectious diseases exist primarily in Africa's health and research sectors. The tardy and slow entry of molecular biology and nanoscale chemistry into the underexploited local scientific community is

one of several factors limiting diagnostic development.[21] Africa's scientific community is small, but a relatively high proportion is studying endemic infectious diseases, with a handful of scientists focusing on diagnostics. Some are making good progress and beginning to generate global interest. A research group in Ghana has developed and field tested a point-of-care urine test for schistosomiasis. The test has greater sensitivity than microscopy, the currently advocated method of diagnosis, but is easier to perform. Similarly, researchers at the Kenya Medical Research Institute (KEMRI) have developed tests for hepatitis B and HIV, and a Nigerian working in South Africa is the innovator for a promising new tuberculosis diagnostic platform.[22] With the right support,[23] African scientists could drive the development of diagnostics, as well as control measures and treatments, and their innovations could improve health care delivery in their own countries.

New diagnostics offer great promise, but even currently available tests are underutilized across Africa. Lack of infrastructure is often cited as the reason for dispensing with even the most basic tests. But microscopy can be performed without electricity, using a mirror and sunlight, and even bacterial culture can be performed in laboratories equipped with sterilizers that use alternate fuels, kerosene-fueled refrigerators, and phase-change incubators.[24] Most existing tests are less complex than mobile phone technology, which was unheard of when bacteriology tests were developed, but which, unlike microbial diagnostics, has invaded the most remote African villages in the last twenty years. In short, tests that were developed a hundred years ago typically don't require expensive or sophisticated infrastructure, and newer rapid diagnostic tests can be used with no equipment at all. Even without new developments, it is possible to offer many effective tests in today's health clinics.

Local Technical Expertise Cannot Support Diagnostic Testing

From the late colonial era, African doctors, nurses, engineers, and teachers were produced in specially targeted training programs, modeled on European systems, with the specific goal of creating a professional cadre that could build Africa from independence and teach later generations. The real and the perceived shortage of technical expertise for diagnostic testing is as much the consequence as the cause of diagnostic insufficiency. Failure to prioritize the development of diagnostic capacity in the hospital and public health infrastructure has been coupled with the collapse of educational facilities for laboratory scientists and pathologists. Laboratory specialties were included in Africa's first medical schools, such as the University of Ibadan and University of Ghana Medical Schools but in 2004

ʻṢegun Ojo, a Nigerian professor of pathology, noted that many newer medical schools in his country did not have a pathologist on the faculty. Similarly, in Malawi, medical schools train too few students in laboratory medicine.[25]

Diagnostic laboratory services are best overseen by consultant pathologists and are appropriately staffed by clinical scientists who have received training and certification in biochemistry, microbiology, or related sciences. A college degree in the sciences or, at the very minimum, two years of postsecondary education with compensatory experience is optimal for reliably implementing all but point-of-care diagnostic tests. In developing countries, the shortage of people with higher education is felt intensely in the health sector. It would be a real challenge for several countries to staff fully functional diagnostic laboratories in every secondary and tertiary care health facility. However, highly skilled workers are not required for all tasks in a diagnostic laboratory, and diagnostic services can be structured to make the most of staff with less formal training. Moreover, technical training programs are less expensive and difficult to mount than programs to train clinical professionals. However, Nigeria, the African country with the most medical schools, trains more doctors and pharmacists than medical laboratory technologists.

Were every patient with relevant symptoms to gain access to as few as eight diagnostic tests, including point-of-care tests for malaria, sexually transmitted infections, and tuberculosis, as well as blood tests for endemic parasites and bacteria, medical care in Africa would be revolutionized. Modern point-of-care tests are often simpler than the highly technical tests of yesteryear and could be performed by trained semiskilled workers at the primary care level with local or regional supervision. Laboratory scientists at Zambia's University Teaching Hospital effectively supervise sputum smear microscopy for tuberculosis diagnosis at several health centers in and around Lusaka and the Lesotho national TB lab was recently equipped to perform a similar function. Ongoing boosts to information technology and communications across Africa offer attractive possibilities for even more remote supervision. For example, microscopy slide data can now be transmitted via the Internet or mobile phones.[26]

Currently, even in the face of a shortage of laboratory technologists, there are very few career opportunities for graduate biochemists, biologists, chemists, and microbiologists in much of Africa. A significant proportion of graduates working in the banking and insurance industries hold bachelor's degrees in scientific disciplines, and biomedical laboratories struggle to retain highly skilled staff.[27] Attrition of the potential laboratory workforce begins even earlier as concerns about poor employment prospects lead the strongest biology and chemistry students to enter undergraduate programs in medicine, pharmacy, or engineering, so that potential biomedical scientists are diverted to other professional fields.

Medical doctors who choose to specialize are unlikely to select pathology or laboratory medicine, as these specialties offer few opportunities to augment income through private practice. Adjustments in compensation and working conditions for laboratory technologists could address many of these problems.

Any diagnostic development initiative must seek to address the root causes of the laboratory workforce shortage but should also provide training for existing laboratory staff, many of whom have never performed some tests for the most prevalent diseases in their countries. In 2005, the American Society for Microbiology began its International Laboratory Capacity Building Program, or "LabCap," which solicits scientists from its forty-thousand-strong membership (five thousand of whom are certified clinical microbiologists) to assist in developing laboratory capacity in Africa. In less than three years, volunteers had built significant capacity for tuberculosis diagnosis in Namibia, Zambia, and Nigeria, training local personnel in sustainable methods. By 2009, programs in those countries had begun to have spillover effects on other laboratories in those countries while "LabCap" programs were also established in Tanzania, Botswana, Kenya, Cote D'Ivoire, Rwanda, Mozambique, and South Africa. The Society estimates that at least ten thousand technicians will need to be trained for about two thousand African laboratories. It is far from this goal, but the initial successes demonstrate that developing the necessary human resource is feasible.

Diagnostic Tests Are Superfluous

Many argue that if intensive use of laboratory diagnostics were best practice in medicine, this would be the norm in the developed countries. People who state this position do not take the African disease landscape and differences in resource availability and access to care into consideration. Sadly, both Western and African physicians and public health professionals are guilty of attempting, or at least wishing, to model health care delivery in Africa after that in Europe or North America. This misguided aspiration is due not only to the absence of other models but also to practitioners' efforts to make the practice of medicine more uniform around the globe.[28]

The differences in the need for laboratory diagnostics in these two settings can be easily explained. First, most outpatient visits in the West are for irritating but self-resolving infections, such as the common cold, ear infections, and benign food poisoning, or for conditions with noninfectious etiologies. If there is a chance that symptoms are masking a more serious infection, patients are given supporting therapy and told to "come back if things do not improve." In tropical Africa, most patients coming to an outpatient clinic have life-threatening infections such as malaria or pneumonia. A good number present for the first time

only days before they might be dead or disabled by the infection. Many cannot afford to return for a reevaluation if the first course of therapy fails. If they receive the correct diagnosis promptly, most patients can be given medicine that will cure them. The proportion of patients with relatively mild, self-resolving illnesses is smaller and less likely to reach the clinic. These differences in acuity and the prevalence of infectious diseases mean that initial microbiological diagnosis is more important and more cost effective in Africa than in the West.

Those who insist on applying Western standards of care in Africa seem unaware that patients in the West who present with symptoms of fever and a travel history to a malaria-endemic area are invariably tested.[29] So are patients who present with signs that suggest life-threatening infections, including medium-grade fevers. The idea that medical institutions in Africa can or should be less well equipped than those in the West that address diseases common or endemic in Africa is one piece of unpacked colonial baggage.

Even more important, the impression that diagnostic tests are rarely used in the West is erroneous and outdated. It is true that a 1975 British study reported that 85 percent of final diagnoses were based on information that the physician obtained during consultation in the course of taking a history and 7 percent on physical examination, while only 8 percent of diagnoses required a laboratory test or other diagnostic procedure such as an X-ray.[30] However, since that time, more, faster, and better diagnostic tests have become available. At the same time, diseases that present with macroscopical diagnostic features, such as measles, mumps, whooping cough, and chickenpox, have become less common. Importantly, the need to make diagnosis more precise in order to use antimicrobials prudently and avoid promoting resistance has recently been acknowledged. As a result, laboratory diagnosis has increased severalfold.

In the United States, 170,102 diagnostic laboratories were documented in 2000.[31] A tenth as many laboratories could solve the problems of TB diagnostic delay in Africa. Well over half of the U.S. labs (62%) were in physicians' offices, undertaking simple tests for conditions such as strep throat at the point of care. Other tests, often forgotten by the patient, are sent away to laboratories by the physician's office. In the Netherlands, a 2006 study recorded that 12 percent of patients with diarrheal disease were tested.[32] Testing is recommended when the patient has protracted diarrhea, bloody diarrhea, acute pain, or a history of foreign travel—particularly to Africa. In U.K. (2000) and U.S. (2004) studies, rates of testing were even higher (27% and 44%).[33] Outbreak identification for *Shigella* and O157 and other enterohemorrhagic *E. coli* in Western countries depends on analysis of specimens from patients visiting their primary care providers.[34] Testing and surveillance are routine in spite of the fact that diarrheal disease, a major but silent killer in Africa, kills or permanently disables relatively few Americans and Europeans.

The microbiology laboratory in a Nigerian teaching hospital that attends over two hundred thousand patients annually, over half of whom have an infectious disease, processes only fifteen thousand specimens each year. In a recent Swedish study, half of children presenting with symptoms suggestive of an infection, including the common cold, were referred for laboratory testing.[35] Authors of the report, who found that test results promoted rational drug use, advocated even more testing. This point underscores an important consideration. Although laboratory tests are regularly used in the West, their use is still insufficient to inform rational prescribing; in this sense, diagnostic insufficiency exists even there.

The response to the accusation that patients in Western countries do not get tested very often is that, compared with patients in sub-Saharan Africa, they need testing less, receive it more, and will be subjected to even more testing in a future of increasingly personalized care.[36] Diagnostic tests are not just nice to have, they are essential for health care delivery, and their deployment in resource-limited settings would have a significant and measurable impact on the major causes of death in developing countries.[37]

Laboratory Diagnostics Make No Contribution to Disease Prevention

Many preventive interventions can be implemented without laboratories. For example, barriers against biting insects, safe drinking water supplies, good sanitation, and improved nutrition do not require laboratory testing. Diagnostic development will have its greatest impact on curative medicine, but it will make important contributions to preventive medicine and public health such as supporting prioritization and assessment of costly but high impact interventions.

At the very least, diagnostic support for curative medicine contains infectious diseases. Safe water prevents cholera, which continues to plague African societies without access to potable water supplies. If rapidly and adequately rehydrated, cholera patients will recover from this dreaded and deadly disease without antimicrobial drugs. However, when appropriate antimicrobials are not used in a cholera outbreak, the disease spreads rapidly and the size of the outbreak is increased severalfold. Identifying a cholera outbreak early, and determining the susceptibility pattern of the causative strain, can prevent thousands of illnesses and deaths. In the last fifteen years, documented outbreaks that were amplified by diagnostic insufficiency have occurred almost exclusively in sub-Saharan Africa.[38] Similarly, as discussed in chapter 7, diagnostic delay is driving drug-resistant tuberculosis epidemics.

Disease-specific interventions, such as new vaccines against the causes of deadly pneumonia and diarrhea in children, would be helped by information

that a diagnostic infrastructure and surveillance systems could provide. Researchers developing vaccines for typhoid and tests for schistosomiasis all agree that preventive and curative interventions for both diseases are underimplemented because of epidemiological blindness arising from diagnostic insufficiency. Epidemiological data also assists scientists in developing life-saving vaccines and convincing countries to adopt new vaccines and donors to pay for them.[39]

Diagnostic facilities are essential to identify and contain new diseases and to disburse health assistance to the areas of greatest need. Emerging infectious diseases are carefully mapped in Europe, Oceania, and North America, less robustly documented in Asia and South America, and rarely documented in Africa.[40] As a consequence, interventions that could prevent or halt epidemics in Africa are often delayed.

The Real Roadblock: Lack of Sustained Commitment

In Lesotho, efforts to increase the speed of diagnosis and introduce diagnostic capacity for multidrug-resistant tuberculosis required the revolutionizing of the national laboratory. Authors of a technical paper describing the two-year initiative attributed its success to strong collaborations—between the national reference laboratory, WHO, and international foundations devoted to global health and diagnostic development—and to political commitment.[41] Diagnostic development lies within the realm of science, but diagnostic insufficiency is also a political and socioeconomic problem. More than funds, expertise, or knowledge, what is needed to spur diagnostic development is a long-term commitment from all stakeholders. This includes health workers and policymakers as well as those that bear the ultimate costs of diagnostic inadequacies—patients and others that pay for health care such as governments and donors.

Local initiative and partnering is as crucial as external support in developing lasting laboratory services because temporary diagnostic proficiency can be attained even without diagnostic development. An illustrative example is the deployment of military diagnostic personnel and resources during the post–September 11, 2001 war in Iraq. Following a report of severe acute pneumonitis as the cause of two deaths, the military recognized the need for on-site clinical diagnostic support and promptly set up microbiology laboratories in Iraq.[42] Although the U.S. military claimed that since ailing soldiers are often repatriated, the long-term beneficiaries of these services were Iraqis, that claim is questionable. The laboratories were rapidly stocked with highly specific and sensitive imported and kit-based test reagents. In most cases, although cheaper, more

rugged protocols were available, the army opted for those tests that could be performed with minimal on-site pre-preparation. Most of the selected reagents were more expensive than those that would be employed by diagnostic laboratories in the United States. Specimens for essential tests that could not be performed on-site were shipped by the Air Force to a reference laboratory in Germany.[43] The diagnostic facilities developed to serve the base during the war did help treat Iraqi civilians as well as military patients but are unlikely to assist in diagnostic development in postwar Iraq.

The purpose of the military diagnostic initiative was to serve U.S. interests while the country was at war, but it is an illustrative model of unsustainable diagnostic aid, which has been offered innumerable times in response to epidemics and other health needs in Africa. Upon exacerbation of mortality due to an outbreak that is amplified by misdiagnoses, a WHO, CDC, or other humanitarian fairy godmother brings a field laboratory or facilitates access to a reference lab to enable accurate diagnosis. The agent is rapidly named, its spread is halted, and the epidemic abates with the wave of a wand. When her task is done, the fairy godmother vanishes, taking with her essential resources for diagnosing and controlling the disease. In the more memorable cases, some disused equipment of ornamental rather than practical value remains as a glass slipper reminder of the efficacy of laboratory diagnostics.

To end the Cinderella cycle, infrastructure needs to be put in place so that diagnostic support can be obtained routinely, not just in visible crises. National and international health policymakers need to acknowledge that medicines should be prescribed for the specific diseases they are designed to treat. The cost of diagnosis must be acknowledged as a necessary component of care that can produce savings in other areas. Allopathic medical doctors must acknowledge that, just as they were taught in medical school, laboratory input is needed to resolve a differential diagnosis. They must view their access to laboratory services as an important and distinctive feature of their practice, and one that delineates them from the practitioners of other schools of medicine. They must then, of course, be granted this access. Finally, patients need to advocate for the best standard of care, including the right to know what is wrong with them at the time they are being treated.

A recent study cataloging emerging infectious disease events identified very few events in Africa, not because they did not occur but because the distribution of documented events mirrors the availability of diagnostic laboratory infrastructure. Like disease eradication, global diagnostic proficiency is a "Weakest Link Public Good,"[44] because all countries are at risk when a particular locality lacks the resources to identify and report dangerous pathogens. (This is true at the level of the individual as well as the collective.) Wealthy countries can gain

from assisting in the development of diagnostic capability in less affluent countries, even if they have lower infectious disease burdens, because it will increase the likelihood that a new disease, or a new version of an existing disease, will be contained before it is disseminated internationally.[45]

From the mid-2000s, some actors in richer countries began to recognize this and commenced model initiatives to improve laboratory capacity. For example, the U.S. Clinical Laboratory Standards Institute (CLSI), the WHO, the CDC, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the World Bank all have laboratory capacity-building programs and the Clinton Foundation now negotiates discounted diagnostics, as well as medicines, for HIV patients in Africa. The American Societies for Microbiology and Clinical Pathology are among professional societies that offer human resources to train laboratory personnel in-country. These and other types of international aid can result in maximal gains for primary health care only if they are an adjunct to local efforts. The best outcome would be diagnostic development that improves the management of endemic diseases in African countries and enhances capacity to detect pandemic diseases of global concern. Donors are becoming increasingly aware that the most effective aid is that awarded in response to locally articulated needs and toward measurable outcomes.[46] To achieve cost-effective, sustained, and accountable diagnostic sufficiency, Africa must drive her own diagnostic development.

A Road Map for Africa to Advocate Her Own Diagnosis

Although the benefits in averting high human costs and economic losses would be great, the infrastructural, educational, and financial investments required to attain diagnostic sufficiency in Africa are undeniably large and must be allocated in the face of competing demands such as governance, preventive health, elementary education, food security, general infrastructure, and the eradication of extreme poverty.[47] This must have been on the minds of the "representatives of governments, multilateral agencies, development partners, professional associations and academic institutions" who were signatories of the Maputo Declaration on the Strengthening of Laboratory Systems in January 2008.[48] An awareness of diagnostic needs emerged coincident with a global recession that made it necessary for individuals, countries, banks, and potential donors to tighten their belts. Diagnostic development will not come cheap and must quickly produce detectable results. Reassuringly, unlike many development objectives, diagnostic development increases the quality and precision of measurement, so that implementation enhances assessment.[49]

Ideally, every patient would have access to all the laboratory support necessary to confirm his or her diagnosis. This goal is neither feasible nor cost effective but it is certainly essential and possible to grant most patients lifesaving diagnostic support. High-burden diseases should be the most important targets for diagnostic test development and deployment, particularly when testing would contribute significantly to treatment and disease control.[50] Laboratory support that makes it possible to use inexpensive, first-line drugs instead of expensive, newer therapies, or that preserves the effective life of antimicrobial agents, could pay for itself and should be a priority for diagnostic development. For prevention, diagnostic support for eradication and elimination must be prioritized, as diagnostic precision is indispensable at the tail end of such programs. Finally, as many different diagnostics are needed, it makes sense to begin by developing those that can be easily and cheaply designed.

The case studies in this book have highlighted areas where diagnostic development would easily bring cost savings and significant improvements in the delivery of curative care. Fever management and diagnosis of infections caused by sexually transmitted pathogens and blood-borne viruses are crucial. Malaria diagnostics are reasonably well developed but inadequately deployed and are compromised by the absence of other diagnostics to support a differential diagnosis of fevers. It makes sense to use malaria tests in conjunction with diagnostics for a multitude of common infections, particularly treatable bacterial infections. Multiplexes, that is, single tests that return results for multiple diagnostic queries would be valuable for patients with fever, sexually transmitted diseases, respiratory infections, and persistent diarrhea.

Scientists in Africa need to play a central role in developing and validating diagnostics for endemic diseases. Not only do they have a real incentive to do so, they also have the most familiarity and best access to patients and health systems for which these tests will be used. It is not enough to develop or validate tests locally. They can and should be manufactured on the continent. This will bring production costs down, secure the supply chain, and make it easier to get diagnostics to primary health centers regularly. It also will ensure that diagnostic sufficiency is sustained when Africa weans itself off international aid.

Diagnostic facilities must be decentralized. As of 2006, 80 percent of the seven hundred hospitals and health centers in Tanzania had at least some laboratory facilities, most admittedly in need of development. However, a 2006 audit reported that most Tanzanians sought care at one of 4,679 dispensaries, almost all of which lacked any diagnostic capability.[51] The capacity to transport infectious specimens safely while retaining their diagnostic worth is lacking in most of tropical Africa. The more specimens that can be tested close to the patient's primary health care provider, the more useful information can be obtained in time

to influence treatment. In developing countries "primary health care" and "technology" have long been considered oxymorons. However, the 1978 Declaration of Alma-Ata, made at the end of a pivotal international conference on primary health care, requires primary care to have a practical and acceptable *scientific* basis, using accessible *methods and technology.*[52] Such a basis cannot but include diagnostics. When testing becomes a standard and visible part of primary care, patients will come to understand it as an integral part of the diagnostic process. In appreciating how diagnostic tests enhance their therapy, patients will be more inclined to use official rather than unsanctioned health care providers or to self-medicate. An increase in successful treatments at first presentation will engender confidence in allopathic medicine and the distinctions between allopathic and other forms of medicine will become less blurred.

Rapid diagnostic tests, with acceptable sensitivity and specificity, should be performed by nurses or aides at the point of care, or by technicians who have received specialized training. Diagnosis of up to 90 percent of the population 90 percent of the time could very well be performed at the primary care level. Point-of-care tests for malaria and other endemic parasites and common viruses such as HIV, culture and sensitivity testing of common bacteria and, in most cases, tuberculosis testing should be available at, or close to, the primary care level. Although existing technology does not permit $CD4^+$ counting for HIV patients at this level, special equipment that allows samples to be collected for this purpose and relayed to regional diagnostic centers has recently been developed. Remote testing is not sustainable for many infectious diseases, but it is useable for HIV because patients require continuous care and often lifelong drug therapy. Rapid diagnostic tests for some bacterial pathogens could be developed for point-of-care use and would enhance the diagnostic value of the other tests. General hospitals should be given the capacity to assess performance of point-of-care tests, perform expert microscopy for parasitic diseases, and carry out bacterial culture and antimicrobial susceptibility testing.

Regional laboratories with more sophisticated equipment, managed by infectious disease consultants and technicians with advanced training, could test for less prevalent pathogens and oversee local primary care centers.[53] These laboratories would be located at tertiary care centers, or located within secondary-level state hospitals. In this era when infectious disease can spread rapidly, every country requires the capacity to detect all known pathogens and to perform preliminary characterization of new agents. This means that every country needs at least one facility with Biosafety Level 3 or 4 laboratories, to detect the most dangerous pathogens. Although they require the most sophisticated personnel and infrastructure, this aspect of diagnostic development could be more easily established by taking advantage of existing research institutes. African health

ministries could work up collaborative agreements to set up national diagnostic laboratories attached to research centers of excellence, which could take advantage of such expensive resources as large equipment and reference libraries.

A real challenge for clinical laboratories is sourcing reagents and equipment. Laboratory equipment is produced by very few companies worldwide and is designed for use in industrialized country laboratories in temperate parts of the world, located in close proximity to manufacturers who provide servicing and technical support. Christoph H. Larsen, Gary M. Cohen, and C. N. "Param" Paramasivan and his colleagues have independently cataloged the challenges that laboratories face when they try to use such equipment in Africa and have proposed possible solutions.[54] Today, African laboratories invariably pay more for equipment but receive less service over a dramatically shortened life span. Service contracts, which are the norm in North American laboratories, are either too expensive or are not offered to African laboratories. When equipment fails, it can take over three weeks to secure what should be a one- or two-day repair job. Many of these challenges arise because there are too few laboratories running such equipment to make local servicing and repair attractive to manufacturers and their agents. Manufacturers should be encouraged to modify equipment so that it is less likely to be susceptible to electricity blackouts and brownouts, and to damage from heat and particulate matter. It is also possible to engineer system components to allow users to effect minor repairs with remote assistance. These sorts of adaptations have been made for sophisticated equipment ranging from automobiles to computers, and they should be applied to laboratory equipment. Heat-stable formulations of reagents also need to be developed where possible to make shipping less dependent on cold chains, and the more that can be manufactured and procured locally, the better. All of these issues can be avoided in all but reference laboratories if equipment-free point-of-care tests are developed.

Many of the laudable recent laboratory capacity building and diagnostic development projects have unfortunately been focused on a single disease. There are now a few excellent laboratories dotted across Africa that focus on diagnosis of tuberculosis alone, or on diagnostic tests needed to detect and manage HIV patients. In remote clinics that have any kind of diagnostics at all, rapid diagnostic tests for malaria introduced after 2006 often comprise the entire diagnostic portfolio. These laboratories, and tests, came to Africa following diagnostic advocacy from researchers and health policymakers focused on those high-burden conditions. However, when they do not build capacity for diagnosing most common infections, they lead to expensive duplication of resources and deprive institutions of more broadly applicable diagnostics. As in the case of rapid diagnostics for malaria, where patients who test negative may still receive antimalarials, disease-specific initiatives that do not address confounders may undermine

their own programs. The recent Maputo Declaration on Strengthening of Laboratory Systems calls for integration of laboratories but it does not go far enough in that it still advocates principally for laboratories for HIV, malaria, and TB diagnosis.[55] There are equally pressing diagnostic needs for sexually transmitted diseases other than AIDS, for blood-borne bacteria, and for respiratory and enteric pathogens—to name a few—and these needs are critically neglected. Laboratories can specialize for control programs, research, or surveillance, but they need to be able to offer a broad range of basic diagnostic services.

As with specialist laboratories, it would be valuable to reexamine the way centers of medical research excellence operate in Africa.[56] Some research institutes on the continent do offer diagnostic support for care, but commonly on an informal and ad hoc basis. Although their work demonstrates the urgent need for reliable diagnostics, researchers are often powerless to do anything about the problem in the areas they study. These laboratories are few and far between and must continue to focus on the underaddressed research needs of Africa. However, if health ministries affiliate regional or national diagnostic laboratories with these institutions, they could take advantage of some resources and training that these centers of excellence could offer. Providing auxiliary diagnostic services, or at least diagnostic oversight, from an expanded number of research institutes is one way to stimulate diagnostic development.

It makes sense to support and develop existing diagnostic facilities and technical personnel. Where required, we must improve the quality as well as the breadth of services they offer, and encourage prescribers to use them. Quality assurance is an essential and often neglected aspect of laboratory diagnosis. Without adequate built-in quality assurance, diagnostic tests can be more misleading than if they were not performed at all.[57] Many laboratories supply susceptibility test results but lack control organisms to ensure that their discs are working properly. An unpublished report on "Resistance to Antimicrobial Drugs in Ghana" demonstrated that a 53 percent to 75 percent discrepancy was seen in the susceptibility data reported from seven regional hospitals when the same isolates were tested in a reference laboratory. Some laboratories had improvised rather than followed protocol on small but crucial steps in the key methods used to determine susceptibility. Similar reports have come from Nigeria and Kenya, emphasizing the need for quality control and regional monitoring and supervisory programs.[58] The first step in this direction would be for national ministries of health to establish formal bodies to accredit existing laboratories and ratify testing standards. Such institutions exist in countries on other continents.

Key challenges in the development of diagnostic infrastructure in Africa require development of other sectors. A well-run diagnostic laboratory must be able to procure materials regularly via a secure supply chain. The supply chain

and regulatory framework for diagnostics in many African countries is even weaker than the well-documented weak situation for pharmaceuticals. Currently several tests are sold without evidence of effectiveness. Recent initiatives by WHO to precertify rapid diagnostic tests for some conditions such as malaria and syphilis could serve as a model for implementing quality assurance in a cost-effective manner. Predeployment assessments are not enough, however; diagnostics, which are often heat sensitive and moisture labile, must be quality assured at purchase and at point of use. Additionally, laboratory technicians' testing must be continually assessed and supported by external monitors in home-country reference labs. Laboratory safety must also be built in parallel with capacity to assure the well-being of workers, patients, and the wider community.

As evidenced by the cases of malaria and HIV, diagnostic tests can be developed and quality assured in a remarkably short time once a commitment is made. Malaria rapid diagnostic tests were developed and field tested in the early 1990s. Pilot studies revealed problems with quality assurance, which were addressed by a quality evaluation program spearheaded and managed by the WHO with input from the Foundation for Innovative New Diagnostics (FIND) and the U.S. Centers for Disease Control. By 2009, rapid diagnostic tests had been deployed at sentinel sites in many countries and nationally in Madagascar. Uganda, Zambia, and Ethiopia were at the time discussing or designing national programs that would target artemisinin-based combination therapies to malaria patients based on parasite-based diagnosis made with rapid diagnostic tests.[59] Spurred by very recent global interest in the disease, malaria rapid diagnostic tests made it from the laboratory bench to public health impact in Africa in less than two decades. Although more went into product optimization and quality assurance, the estimated cost of the innovation that brought us point-of-care malaria diagnostics was a mere US$100,000.[60] Thus, if other neglected diseases are properly prioritized, with political will and donor interest diagnostic development can be rapid, affordable, and successful.

For malaria diagnostics, scaling up is the remaining challenge. The surreptitious battle against diagnostic development is fought as fiercely within Africa as on the outside. Christopher R. Polage and his co-investigators found that even though diagnostic development has become a priority of the Komo Anokye Teaching Hospital in Kumasi, Ghana, physicians were underutilizing diagnostic resources to the detriment and cost of their patients. Physicians claimed that laboratory tests were underresourced, improperly performed, and prohibitively expensive. Contradicting this misperception, Polage and his co-workers found that the most critical tests were available and implemented to high standard. Patients' medical expenses were unreasonably high because expensive antimicrobials were routinely being used without testing to determine whether they were

necessary. Fifty-one of the eighty physicians polled said that they frequently or always diagnosed malaria without laboratory support. However, only 24 percent of malaria smears were positive in the lab. Almost all the physicians expressed the opinion that tests were too costly, but medicine costs far outstripped laboratory testing expenses. The investigators concluded that "perhaps the most significant barrier to laboratory use was physicians' reliance on clinical judgment" and "this attitude is not surprising in resource limited regions where clinical algorithms are often promoted as the diagnostic standard."[61] Promoting diagnosis based on signs and symptoms alone, typically in a non-evidence-based manner, is a principal reason why diagnostic insufficiency is ingrained.

Physicians' insistence on the reliability of their clinical judgment, even in the absence of supporting evidence to this effect, is the product of a century of struggling to provide care without support and the absence of systems to measure the success of treatment programs. As malaria control interventions take root and reduce the incidence of this common febrile disease, the number of misdiagnosed fevers is set to rise. Prolonged illnesses and even the deaths of a "small" proportion of the misdiagnosed are unacceptable. Prescribers provided with reliable laboratory services need to be educated and encouraged to use them.

Shifting attitudes may be the most challenging aspect of diagnostic development and they extend to patients, who tend to regard testing as applicable to research but not to treatment. Blood draws in particular are considered a research activity, and benefits to study participants, including financial compensation, medicines, and other items, are often seen as payment for blood.[62] If the collection of blood and other body fluids is to become integral to health care practice, the use of blood for research might be viewed more positively, for what it actually is—a diagnostic medium.

Patients may be more receptive than we think. In the case of life-threatening diseases, laboratory diagnosis is generally appreciated. During focus group discussions conducted in Malawi, participants associated involvement in research projects and access to quality care, including better diagnosis, with blood and urine tests.[63] Clearly, patients can recognize optimal and suboptimal care even when they rarely encounter best practices. Physicians, other health workers, and those who dictate Africa's health policy have the responsibility of offering more to those receiving care, and more to those who pay for it.

Any sustained effort at diagnostic development for Africa must be spearheaded by Africa's clinicians, scientists, and governments, who are directly responsible for their patients.[64] Pilot projects and new technical initiatives to build diagnostic capacity that were initiated in the mid-2000s must be viewed as key germinating seeds. These programs must be nurtured, grown and then harnessed toward improving the practice of medicine on the continent. Their success will

depend first on an appreciation in political circles of the importance of science and technology to medical practice. Second, this appreciation must be translated into practical outcomes. Laudable programs such as the Wellcome Trust–supported African Institutions Initiative, which is directed at the first problem, and the African Network for Drugs and Diagnostic Innovation, focused on the second, have the potential to move African research in these directions as do country-specific initiatives launched by governments sensitive to this need.[65]

Tropical parasitic diseases and bacterial infections are among the easiest to diagnose, as they have been for almost a hundred years. Throughout this time, they have remained the most common causes of death in equatorial Africa. Each syndrome is produced by a specific pathogen, and in most cases it can be eliminated by a specific and often inexpensive treatment. These facts have been known to biomedical science since its importation to Africa. Biomedicine is the dominant form of health care delivered in Africa and commonly the only form sanctioned by the state and the global community. However, poor health remains one of the most important impediments to productivity and quality of life. This situation prevails in spite of the efforts of millions of qualified health workers who are largely focused on disbursing medicines in a manner that is difficult to delineate from the parallel practices of unsanctioned providers. This approach is akin to the "activity without insight" disparaged by German philosopher and writer Johann Wolfgang von Goethe. Only judicious testing will provide the diagnostic insight every infected patient deserves.