AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

EDITORIAL

# A List To Cement the Rightful Place of Diagnostics in Health Care

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**KEYWORDS** World Health Organization, diagnostics, essential diagnostics list, laboratories, rapid tests

When health systems do not sufficiently plan for or fund diagnostic services, health workers have to rely on empirical and/or syndromic diagnoses, leading to both missed cases and unnecessary treatments (1–5). Diagnostics, implemented via tiered, high-quality laboratory networks, have the potential to bring precision and clarity to patient care, improve antimicrobial stewardship, and enhance disease surveillance (6–8; https://www.ghsagenda.org/packages/d1-national-laboratory-system).

While diagnostic services are usually taken for granted in high-income countries, many barriers prevent such services in resource-limited settings (9, 10). Addressing both demand and supply issues requires a concerted effort of all stakeholders: global health agencies, governments, donors, academics, health care providers, and advocacy groups (11).

The state of access to medicines in low- and middle-income countries in the past looked a lot like the state of access to diagnostics today. The World Health Organization's Essential Medicines List (EML), first released 40 years ago, helped transform the provision and rational use of essential medicines, and over 100 countries now have national EMLs (12; http://www.who.int/topics/essential_medicines/en/). After calls to replicate this model for diagnostics (13, 14), the WHO released the first version of the Essential Diagnostics List (EDL) on 15 May 2018 (15).

The WHO EDL defines essential diagnostics as those "that satisfy the priority health care needs of the population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and accuracy, and comparative cost-effectiveness" (15), similar to the definition of essential medicines.

In its first version, the EDL contains 113 tests. Fifty-eight of these are considered general laboratory tests, and 55 are considered disease-specific tests with public health importance, covering HIV infection, tuberculosis (TB), malaria, hepatitis B and C, syphilis, and human papillomavirus (HPV) infection (see Table 1 for EDL tests relevant to infectious disease).

Tests for the first version of the EDL were chosen from existing WHO resources: guidance, guidelines, technical manuals, priority medical device lists, and the Prequalification of *In Vitro* Diagnostics program.

The EDL identifies tests that should be present at different health system tiers: primary care facilities as well as facilities with clinical laboratories. In primary care, general tests include urine dipstick testing, complete blood count, lactate testing, glucose testing, and microscopy (which can be used to diagnose a range of conditions, such as sickle cell anemia, malaria, TB, and stool parasite infection).

Disease-specific testing in primary care includes rapid diagnostic tests to detect HIV infection, malaria, syphilis, and viral hepatitis. For example, hepatitis C virus (HCV) serological testing will become increasingly important as prices for direct-acting anti-

**Accepted manuscript posted online** 25 July 2018

**Citation** Schroeder LF, Pai M. 2018. A list to cement the rightful place of diagnostics in health care. J Clin Microbiol 56:e01137-18. https://doi.org/10.1128/JCM.01137-18.

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**TABLE 1** Tests relevant to infectious disease included in the first WHO Essential Diagnostics List[a]

| Category | Tests used in: | |
|---|---|---|
| | **Primary health care facilities** | **Health care facilities with clinical laboratories (additional tests)** |
| General | General microscopy | Culture/blood culture |
| | Urine dipstick/microscopy | Drug susceptibility testing |
| | Complete blood count | Comprehensive metabolic panel |
| | Whole-blood lactate | Blood gas testing |
| | Glucose | C-reactive protein |
| | | Urinalysis (automated analyzer) |
| Disease specific (for infectious diseases) | HBsAg, HBeAg | HBV DNA (quantitative) |
| | Anti-HCV | IgM anti-HBc, anti-HBs |
| | Anti-HIV, anti-HIV/p24 antigen | HCV cAg |
| | Malaria Ag (HRP2, pLDH) | HCV RNA (qualitative/quantitative) |
| | Malaria light microscopy | HIV DNA/RNA (qualitative/quantitative) |
| | TB microscopy | T lymphocyte CD4 count |
| | TB-LAMP | Cryptococcal antigen |
| | Tuberculin skin test | G6PD activity |
| | Syphilis (antitreponemal) | HPV DNA |
| | Combined antitreponemal/anti-HIV | TB: culture, DNA (cartridge based), LPA, DST, LAM, IGRA |
| | | Blood product testing (HBV, HCV, HIV, syphilis, Chagas disease, HTLV) |

[a]Anti-HBc, hepatitis B core antibodies; anti-HBs, hepatitis B surface antibodies; CD4, cluster of differentiation 4; CMP, comprehensive metabolic panel; DST, drug susceptibility testing; G6PD, glucose-6-phosphate dehydrogenase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCV cAg, HCV core antigen; HIV, human immunodeficiency virus; HPV, human papillomavirus; HRP2, histidine-rich protein 2; HTLV, human T-cell lymphotropic virus; IGRA, interferon gamma release assays; LAM, urine lipoarabinomannan; LAMP, loop-mediated isothermal amplification; LPA, line probe assay; pLDH, *Plasmodium* lactate dehydrogenase; TB, tuberculosis.

virals decline, making universal HCV treatment a realistic possibility. Included also at this level is TB microscopy and loop-mediated isothermal amplification (TB-LAMP).

At facilities with formal laboratories, general tests include the comprehensive metabolic panel, blood gas testing, C-reactive protein testing, urinalysis, and blood culture with drug susceptibility testing. Traditional bacteriology with culturing capacity is fundamental to any microbiological approach to diagnosis. It provides a gold standard as well as directing antimicrobial stewardship. It hardly needs reminding that with predictions of a cumulative US$100 trillion lost due to antimicrobial resistance by 2050, culture and resistance testing must become a cornerstone of hospital laboratories (8).

For disease-specific testing in formal laboratories, the EDL recommends additional antigen and serological assays for targeted infectious diseases, lymphocyte CD4 counts, glucose-6-phosphate dehydrogenase enzyme testing, and blood product testing. Also recommended are WHO-endorsed TB diagnostics: cartridge-based molecular assays, culture and drug susceptibility testing, urine lipoarabinomannan assays, line probe assays, and interferon gamma release assays. At this level, the EDL includes nucleic acid testing for TB, HBV, HCV, HIV, and HPV. With the ability to test for multiple conditions and steadily declining prices, nucleic acid testing is becoming more important in low- and middle-income countries.

Like the EML, the EDL will evolve. The first EML included 208 medicines and now contains over 450. Similarly, the WHO plans to update the EDL and will call for applications for tests to be included in the second edition. These applications can be submitted by any WHO department or country office or other stakeholders (e.g., academia or nongovernmental organizations). While the WHO prequalification program (http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/) approves diagnostic products for accuracy, only a subset of the EDL tests are covered by the prequalification program. Thus, in future, it would be helpful if the EDL contained acceptable performance requirements such as sensitivity, specificity, and total allowable error.

One way to understand the EDL is as those diagnostics essential to the safe and effective use of EML medicines (14, 16). Currently, the WHO EDL contains tests that address some but not all of these medicines. High-quality, evidence-based guidelines as well as prioritization according to disease burden (e.g., disability-adjusted life years) should be considered by the WHO as they review applications and evaluate the addition of tests.

To have any impact, the WHO EDL must be adopted and owned by countries. While any country can develop a national EDL, the biggest impact will likely be in low- and middle-income countries with poor access to diagnostics. The list of reasons a country should adopt an EDL is long (17), but they all lead to a common end goal: to improve patient access to reliable, high-quality diagnostic testing. With effort, it should be possible to improve the quality of diagnostics services, as many low-income countries currently have no effective quality requirements for laboratories to operate (18, 19). An EDL could focus governmental regulatory agencies on a limited set of tests, thus simplifying the task of regulation.

Additionally, an EDL will emphasize the importance of diagnostics to providers who have learned to practice with either a lack of diagnostics or access only to low-quality diagnostics. Much of the care cascade must be reengineered to leverage diagnostics, and an EDL will encourage embracement of country-level guidelines. Finally, an EDL may reduce testing costs (e.g., through price controls and import tariff waivers) as well as provide guidance to international funders on diagnostic priorities.

Importantly, without provision of resources and focusing of internal national efforts, a country-level EDL will not benefit patients. The roadmap to strengthen diagnostic capacity will include establishing a strong national laboratory strategic plan, providing funds for that plan, and including laboratory experts on planning committees (20). It may also require restructuring administrative bodies to ensure a well-defined diagnostic working group responsible for laboratory regulation, procurement, and updating the national EDL.

Four decades after the WHO EML, we know that medicines alone are insufficient. Without diagnostics and laboratories, medicines are used inappropriately, antimicrobial resistance emerges, and outbreaks are discovered late. The WHO EDL is pivotal for cementing the rightful place of diagnostics in providing universal health coverage.

## ACKNOWLEDGMENTS

L.S. was commissioned by the WHO to support the EDL development by creating a database of diagnostic indications for the safe and effective use of WHO EML medicines. He has no industry or financial conflicts. M.P. served on the WHO SAGE IVD group that drafted the Essential Diagnostics List. He is a member of the Scientific Advisory Committee of Foundation for Innovative New Diagnostics (FIND). He has no industry or financial conflicts.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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