EXECUTIVE SUMMARY

The COVID-19 pandemic has uncovered what has long been appreciated in the field of diagnostics: the need to improve production and supply capacity of diagnostic tests through local research, development and manufacturing in low- and middle-income countries (LMICs). Expansion and diversification of local production is particularly needed in LMICs where there is currently limited local manufacturing capacity. We cannot rely only on manufacturers primarily in high-income countries (HICs) if global needs are to be met.

As an international medical humanitarian organisation, Médecins Sans Frontières (MSF) relies on diagnostic tests daily as an entry point for appropriate clinical care in our medical projects in more than 70 countries. MSF teams have seen first-hand how insufficient access to diagnostics hinders effective medical care and can lead to worse outcomes for people's health.

In light of growing recognition of LMIC needs and accompanying efforts to increase access to diagnostics in these countries through improved local production, this brief offers an analysis of local production of diagnostics in LMICs with limited capacity and makes recommendations for improvement. It is based on a desk review, mappings of select local manufacturers of diagnostics in LMICs (primarily in Africa and South America) and global health initiatives, and interviews with 67 manufacturers, donors, and global health actors.

Figure 1 highlights examples of local manufacturers in Africa and South America, categorised by business model and level of local production, ranging from local assembly of imported semi-finished end products to full local production starting from raw materials, including local research and development (R&D). LMICs in any region may have limited diagnostic manufacturing capacity nationally; however, LMICs in Africa and South America were prioritised for this initial mapping given the limited local diagnostic production capacity region wide. An online supplement provides a more detailed, non-exhaustive list of manufacturers involved in technology transfer and local production of diagnostics in LMICs. A second online supplement provides an analysis of global health organisations and initiatives to accelerate technology transfer and local production of COVID-19 diagnostics in LMICs.

Poor access to quality-assured diagnostics is a challenge in many LMICs, in part because of the limited number of local manufacturers, leaving these countries largely reliant on imported diagnostic tests from the US, Europe and Asia. These LMICs struggle to import the tests they need to detect diseases that primarily affect LMICs, especially when only low volumes of tests are needed, for example for neglected tropical diseases (NTDs). Manufacturers in HICs and high-volume manufacturers, primarily based in China, India and South Korea, have limited interest in developing these tests or may discontinue production because of the limited market.

LMICs also struggle to import the tests they need when they are in high demand globally, leaving LMICs competing for supply with HICs that can outbid them, such as for COVID-19 diagnostics.
Since 2011, the World Health Organization (WHO) has worked to improve local manufacturing by supporting member states to implement the Global Strategy and Plan of Action on Public Health Innovation and Intellectual Property. This work includes two published reports and an unpublished framework and strategic plan to improve local diagnostic production in LMICs. In May 2019, WHO, UNIDO, UNCTAD, UNAIDS, UNICEF, and the Global Fund to Fight AIDS, Tuberculosis and Malaria committed to work with governments and other stakeholders to strengthen local production of health technologies. A resolution on local production was adopted at the World Health Assembly in May 2021, and the first WHO local production forum took place in June 2021.

A manufacturer is considered a ‘local manufacturer’ in this report if they are based in an LMIC and supply the local market with a final diagnostic test or raw materials of a diagnostic test under their own label.

Regardless of the type of test, production of diagnostics is a long process beginning with R&D, production of raw materials, production of diagnostic tests, and finally distribution locally, regionally or for international export. Where local manufacturing is happening, in most cases these manufacturers are focused on local assembly of imported semi-finished products. Few local manufacturers outside of Asia produce any raw materials or work on any original R&D for new tests to meet LMIC’s local health needs.

Expansion of local production is currently stymied by a lack of funding, lack of demand for locally produced tests, lack of infrastructure and know-how, misalignment of the standard for-profit model with public health needs, and insufficient national and regional regulatory oversight. Fortunately, there are a number of steps LMIC governments, regional bodies, donors, manufacturers and other global health actors can take to increase the number of local manufacturers and to advance local manufacturer’s capacity to produce quality-assured diagnostic tests that meet local health needs (Box: Key recommendations to improve LMIC local diagnostics manufacturing). Access to diagnostics in LMICs can and should be improved sustainably for current and future health challenges with increased local production.

References continued

A nurse is taking blood from the fingertip of a person in Bili, Democratic Republic of Congo, to test it for sleeping sickness antibodies. Because sleeping sickness is endemic only in sub-Saharan Africa and diagnostic tests are needed in low volumes, local production could help ensure sustainable supply to meet local health needs.

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a Since 2011, the World Health Organization (WHO) has worked to improve local manufacturing by supporting member states to implement the Global Strategy and Plan of Action on Public Health Innovation and Intellectual Property. This work includes two published reports and an unpublished framework and strategic plan to improve local diagnostic production in LMICs. In May 2019, WHO, UNIDO, UNCTAD, UNAIDS, UNICEF, and the Global Fund to Fight AIDS, Tuberculosis and Malaria committed to work with governments and other stakeholders to strengthen local production of health technologies. A resolution on local production was adopted at the World Health Assembly in May 2021, and the first WHO local production forum took place in June 2021.
b A manufacturer is considered a ‘local manufacturer’ in this report if they are based in an LMIC and supply the local market with a final diagnostic test or raw materials of a diagnostic test under their own label.
c See Online Supplement 1, available here.
d See Online Supplement 2, available here.
KEY RECOMMENDATIONS TO IMPROVE LOCAL PRODUCTION OF DIAGNOSTICS IN LMICs

1. Create an enabling funding and procurement environment to promote local production
   a. Governments, donors and development banks should invest more funding to support local research and development, manufacturing of diagnostics and raw materials, capacity building and technology transfer.
   b. Governments, regional bodies and global health programmes should develop ‘buy local’ policies domestically and regionally to support local manufacturers of quality-assured diagnostic tests in-country and within the region. Local procurement could be further supported by the creation of regional pooled procurement mechanisms.

2. Promote open IP, technology transfer and access-oriented research and development for local manufacturers
   a. Diagnostics innovators should openly license technologies and openly share know-how globally to expand and diversify global production and supply capacities. Countries that are excluded from or restricted by any licensing agreements should explore the use of all possible legal public health safeguards and tools to promote technology transfer when needed.
   b. Governments should support both end product and raw material technology transfer, as well as local research and development. Successful technology transfer must aim to go much further upstream in the test production pathway to produce the raw materials that go into locally manufactured diagnostics. Countries should seek to build local capacity for progressively more advanced technology transfer to ultimately develop strong enough local capacity for local research and development.
   c. Governments and other funders should mandate open science principles and access conditions in public funding agreements for diagnostics research and development. To maximise the impact of public funding, enforceable conditions should be put in place from the beginning of the research and development process so that open sharing of technologies and know-how, including transfer to local manufacturers in LMICs, can be guaranteed. Farther down the pipeline, originators should also include access conditions in technology transfer agreements they sign.

3. Ensure that local production is sustainable and meets local health needs
   a. Local manufacturers should make tests that fill local testing gaps. Local manufacturers should prioritise tests meeting public health needs for the local epidemiology first, especially if they are not currently available or require low production volumes. Tests needed in LMICs in high volumes but usually imported or supplied through donor programmes could also be considered for local manufacture to reduce a country’s dependence on imports.
   b. Governments should invest in non-profit and public manufacturers. As governments develop strategies to support local manufacturers, they should promote publicly owned or other non-profit models of manufacturing to better align local production with health needs.

4. Strengthen regulatory mechanisms and public trust in locally manufactured products
   a. Governments and donors should strengthen national regulatory authorities and ensure regional harmonisation. Governments and donors should strengthen capacity building for external certification bodies, regional bodies such as the Africa Centres for Disease Control and Prevention, and national regulatory authorities. These authorities should be able to competently assess the quality of diagnostics to be used locally and do so in a timely manner to avoid delaying access to new and better products.
   b. Experienced manufacturers and global and regional regulatory bodies should support local manufacturers for regulatory submissions. Large manufacturers and global and regional regulatory bodies should support local manufacturers needing guidance to successfully implement a quality management system, become certified by the International Organization for Standardization (ISO) and successfully submit a dossier to national regulatory authorities and global stringent regulatory authorities and/or WHO prequalification.
FIGURE 1: EXAMPLES OF LOCAL MANUFACTURERS IN AFRICA AND SOUTH AMERICA

For details and additional local manufacturer examples, see Online Supplement 1, available here.

- ⭐ Non-profit or public manufacturer
- ✭ The finished product is a test component, not a complete diagnostic test

**Level of local production**

1. Local assembly of semi-finished products
2. Local production of finished products
3. Local production of finished products and some raw materials
4. Local production of finished products and some raw materials and/or local innovation
5. Level of local production unknown

Médecins Sans Frontières Access Campaign | Local diagnostics to meet local health needs
RECOMMENDATIONS TO IMPROVE LOCAL PRODUCTION OF DIAGNOSTICS IN LMICS

CREATE AN ENABLING FUNDING AND PROCUREMENT ENVIRONMENT TO SUPPORT LOCAL PRODUCTION

Governments, donors and development banks should invest more funding for local production

Local production requires significant upfront investments. Local manufacturers need funding support for research and development (R&D), infrastructure to equip laboratories, capacity building, supplies procurement (such as for raw materials), manufacturing set-up and scale-up, and setting up the supply chain to health programmes. In addition to appropriate funding, manufacturers need informed support on design decisions and formalised volume guarantees.

The current diagnostics funding landscape is not well suited to the needs of local manufacturers. Many available grants for diagnostics are too small and too short term, primarily provided by donors and national health or science and technology budgets. These small grants from public and philanthropic funders typically cannot support the capacity building required to set up quality and sustainable local commercial manufacturing sites.

For example, FIND and Unitaid provided US$40 million to support scaling production and lowering prices of COVID-19 antigen rapid diagnostic tests (RDTs) as well as technology transfer and local production in LMICs for COVID-19 antigen RDTs. The funding could support two manufacturers for technology transfer and local production. FIND and Unitaid prioritised manufacturers that already had initial capacity who could deliver a long-term and sustainable impact on local production of diagnostics in the region.

Although some private investors also contribute funding to diagnostics, they seek out profit-generating products that do not usually meet LMIC public health needs and the required characteristics outlined in target product profiles. Private investors are typically not interested in the lower volumes local manufacturers produce, especially for products with low profit margins like RDTs.

Funding opportunities to support later stage clinical trials necessary for product validation, quality management and regulatory approval processes, manufacturing, market entry and distribution of successful products are also much less common than initial investments in R&D.

While government funding from health budgets may be too small, bigger pools of government funding in industrial development budgets could also be offered. This funding could support development of a local production industry and initiatives to decrease start-up costs and sustain the local industry.

For example, it could support industrial parks set up with shared infrastructure, common administration, and price-lowering demand aggregation for pooled procurement of manufacturing supplies. However, this would require governments to open up and expand these funding opportunities.

There are already some examples of development banks funding local manufacturers’ industrial development at a regional level.

For example, the African Development Bank’s Export-Import Bank (Afreximbank) is offering financing instruments aimed at boosting local production of medical supplies, including diagnostics, in response to the COVID-19 pandemic in Africa. To boost local production of essential medical supplies, the bank is supporting small- and medium-sized manufacturers regionally with financing to improve facilities, build capacity and manufacture high-quality products.

Although some important funding sources are available for local diagnostics manufacturers, as a result of the overall funding misalignments, the system typically advances the success of larger companies globally that continue to gain public and donor support, entrenching the positions of a few dominant manufacturers. The enormous public funding support provided to Cepheid, a large, US-based diagnostics corporation, despite Cepheid’s continued test access and affordability issues, is one of the best examples of this entrenchment.

To fill the gaps in the limited patchwork of funding opportunities for local manufacturers, governments, donors and development banks should offer more funding to support the full pipeline of diagnostics production. This should include R&D, infrastructure, capacity building, technology transfer locally and regionally, manufacturing scale up, and market entry. Government funding should come from larger industrial budgets in addition to health and science and technology budgets, offered over longer terms to see prototype products from the R&D or technology transfer stages through commercialisation and the full local production process.

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e Capacity building in this context includes development of sustained skills for manufacturing high-quality diagnostics and preparing regulatory authority dossiers.

f An antigen test detects the presence of a pathogen by detecting the pathogen’s proteins or peptides.

g Rapid diagnostic tests provide same-day results, typically in approximately 15-20 minutes, and can typically be used at the point of care to deliver a result during the same visit/consultation.
Governments, regional bodies and global health programmes should enact ‘buy local’ policies
domestically and regionally

In addition to investments needed to support local manufacturers
starting up and bringing a diagnostic product to market,
successful local production also relies on sustainable demand
for locally produced, quality-assured diagnostics. (See “Strengthen
regulatory mechanisms and public trust in locally manufactured
products” for a more detailed discussion on quality assurance.)

Currently many governments do not plan for the use and
integration of diagnostics programmatically and across diseases.
Ordering volumes are often relatively low per country and hard
to predict. As a result, local manufacturers are left with uncertainty
about how big the potential market is for locally made diagnostics,
particularly if they are competing with imported products.

Some manufacturers have seen some success in countries
with policies favouring procurement of locally made products
by the local health system, providing greater certainty for local
industries. Molbio Diagnostics is an example of a successful Indian
diagnostics manufacturer benefiting from this procurement
support from a local government. Molbio manufactures the
Truelab polymerase chain reaction (PCR) system for point-of-care
molecular testing with cartridge-based tests (Truenat), which is
recommended by WHO for diagnosing pulmonary tuberculosis
and is similar to Cepheid’s GeneXpert. Molbio is now also
distributing their tests to 31 countries via distributors.

Policies favouring procurement of local, quality-assured diagnostics
can also improve LMICs’ autonomy to support their own public
health needs. A local manufacturing industry can be an appealing
investment to governments as it offers the prospect of well-paid,
high-tech jobs that can help grow the biopharmaceutical industry.
Importantly, it represents an investment in public health to ensure
people in the country have access to the diagnostics tools they
need. Governments can utilise local production to secure
sustainable public procurement and supply of diagnostics
for national health systems with greater domestic self-reliance.

In addition to national purchasers, pooled procurement mechanisms
(PPMs) can help create demand for quality-assured diagnostics.

PPMs aggregate demand by grouping multiple countries’ orders
together. They help to coordinate the supply of approved tests
needed globally or regionally and can also help secure favourable
pricing deals. For example, the Stop TB Partnership’s Global
Drug Facility (GDF) procures tuberculosis (TB) diagnostics. It is a
key example of effective use of pooled procurement and ‘volume
staircases’ to secure lower prices with increasingly higher volumes.

Unfortunately, most PPMs only focus on one or a few diseases, which
cannot ensure access to all needed tests. There is currently no PPM
for all diagnostics, although there may be opportunities to broaden
the scope of some existing PPMs. The recently established African
Medical Suppliers Platform marketplace for African governments is
also limited to just one disease, COVID-19, but the platform may be
able to be extended beyond emergency response and include more
locally produced products and more diseases in the future.

To address the challenges of small and
uncertain demand for locally produced
diagnostics, domestic, regional and
donor-funded health purchasers should
develop policies that favour procurement
of locally produced diagnostics that meet
performance and quality standards in-
country and within the region. Governments
can also offer volume guarantees through
orders and longer tenders. Demand creation
and volume certainty could be further
amplified with the creation of regional
PPMs that aggregate demand for locally
manufactured, quality-assured diagnostics
across diseases.
PROMOTE OPEN IP, TECHNOLOGY TRANSFER AND ACCESS-ORIENTED RESEARCH AND DEVELOPMENT FOR LOCAL MANUFACTURERS

Diagnoses innovators should openly license technologies

Local production of diagnostic tests can face potential intellectual property (IP) barriers, including copyrights, patents, trademarks, industry design, and undisclosed information such as know-how and trade secrets. Access to know-how is of particular concern for diagnostic production, leading many local manufacturers to pursue technology transfer arrangements with originator manufacturers. This know-how is especially important for complicated closed diagnostics systems like Cepheid’s automated, cartridge-based GeneXpert tests.

Outside of patents on Cas enzymes used in CRISPR-based diagnostic tests, there are few current examples of clear blocking patents for tests for infectious diseases (Box: Putting public health before CRISPR patents in the COVID-19 pandemic). The foundational patents on lateral flow RDTs and PCR did act as blocking patents but have since expired. However, some patents may exist on innovations based on those original technologies.

Although few blocking patents have been identified for infectious disease diagnostics, IP on diagnostic tests can include patents and patent thickets on reagents, instruments, methods and software. Diagnostic companies typically file many patents. Despite the cost of filing for and upholding patents in various jurisdictions, developers prioritise this to discourage competition, attract investors, and support an ‘exit strategy’ of being purchased by a larger company.

Legal public health safeguards exist to help overcome some IP barriers under the World Trade Organization’s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement). For example, countries can decide not to allow patents for diagnostic methods and can issue compulsory licenses for patents. However, countries often experience political pressure not to use compulsory licensing. The United States, other HIC governments and large pharmaceutical companies themselves have all exerted pressure over countries who issue compulsory licenses to remove patent barriers to protect public health. Thus, even if there is expertise in LMICs to reverse engineer diagnostics, as already done for medicines in some countries, manufacturers will likely not expend the energy and expenses to do so. This would risk setting up production facilities without legal certainty – a challenge especially for a product such as an RDT that can only be profitable when there is a market.

To enable local manufacturers to produce needed diagnostics, expand production capacities and diversify supply through technology transfer, innovators should openly share technologies and know-how. Public-health-mandated voluntary licensing organisations like the Medicines Patent Pool (an implementing partner of the COVID-19 Technology Access Pool [C-TAP]) should proactively reach out to IP holders of key COVID-19 and other health technologies to pursue transparent pooled licensing that is globally non-exclusive and ‘open source.’

i Cas proteins are enzymes associated with the CRISPR bacterial adaptive immune response that can be used in diagnostic techniques to detect specific genetic targets (similar to PCR but using a different technique).

k A patent thicket is an overlapping set of patent rights. The individual patents can apply differently in different jurisdictions, can expire at different times, and cannot be covered by a single patent license, which complicates the freedom to operate assessment of whether local manufacturers can legally make a local version of a diagnostic product, potentially inhibiting or delaying local production.

l A compulsory license is a permit granted by the government to allow alternative production or importation of a generic version of a patented medical product without the prior consent of the patent holder.

m A diagnostic method refers to the way a diagnostic can be used to achieve an effective testing. It can be excluded from patentability per Article 27.3 (a) of the TRIPS Agreement (for more info, see here).

n Open source license terms require all parties to share any changes or improvements to the original technologies under the same terms and conditions as the original license, to ensure continued open sharing.
Putting public health before CRISPR patents in the COVID-19 pandemic

CRISPR-based DNA or RNA detection is adapted from a naturally occurring genome editing system in bacteria and can be simpler and faster than the standard DNA or RNA detection system, PCR. In addition to increased speed and simplicity, CRISPR-based tests could potentially be made available at lower prices due to lower production costs for components and devices as compared to PCR-based tests.\(^1\) CRISPR-based innovations could thus offer diagnostics that deliver quicker test results closer to the point of care and be made more widely available under LMIC health budgets to ensure more people are connected to appropriate care sooner.

Although CRISPR holds potential to broadly improve access and affordability of testing, use of this new technology to develop diagnostics has been restricted by blocking patents. All of the CRISPR-related patents declare NIH funding and the majority are held by the University of California and Harvard University. These patents are exclusively licensed to the universities’ spin-out diagnostics companies, Mammoth Biosciences (California) and Sherlock Biosciences (Harvard). Despite the public origins of these innovations, the licensing agreements do not include appropriate access conditions and the patents block use of CRISPR-based technologies for local manufacturers.

During the COVID-19 pandemic, amid an ongoing and bitter patent dispute, the two rival teams decided to temporarily put their work creating CRISPR-based diagnostic tests for COVID-19 in the public domain for open, patent-free and non-exclusive use to encourage the development of simple, cheap tests for COVID-19.\(^1\) The simple testing platforms that have been developed could easily be repurposed for diagnosing other infections, if shared openly for use beyond just COVID-19. Given the significant public funding invested, these technologies should be permanently openly available for all public health needs, not only for use for COVID-19 tests and not only for a limited time.

Governments should support both end product and raw material technology transfer, as well as research and development

Local production capacity varies and can generally be classified into four levels. Different countries are at various stages of industrial development and may have differing capacities for certain tests or raw materials, depending on their complexity.

**Levels of local production:**

1. **Local assembly of semi-finished products.**
   The local manufacturer receives a partial technology transfer as needed for basic assembly locally of imported semi-finished diagnostic tests. The skills required for this are a feasible first step at the beginning of the local production spectrum. The process is similar to the less-desirable scenario of ‘contract manufacturing.’ However, contract manufacturing gives no ownership or decision-making capacity to the recipient manufacturer. In contrast, this level of local assembly of semi-finished products may offer the local manufacturer more legal rights to further develop the transferred technology and to supply the diagnostic tests independently.

2. **Local production of finished products.**
   The next level to advance local production capacity is local production of a finished product starting from imported raw materials. This level requires more local capacity to produce test components, but still does not include production of raw materials.

3. **Local production of finished products and some raw materials.**
   A third level in the progressive development of local production capacity is technology transfer of all information and IP needed to produce the entire diagnostic test locally, including local production of at least some raw materials.

4. **Local production of finished products and some raw materials and/or local innovation.**
   The fourth and most advanced level of production capacity is original R&D of a new test and local production of finished products and potentially some raw materials (such as proteins or plastic cassettes).

Local manufacturers in LMICs have typically started at one of the earlier levels of local production (i.e., level 1 or 2). Raw materials production is generally only a much longer-term and more challenging aim. In fact, many manufacturers, regardless of where they are based, do not produce all of their own raw materials. Most manufacturers rely on the purchase of the same raw materials (e.g. nitrocellulose sheets needed for lateral flow RDTs)\(^2\) from the same few high-volume, high-quality suppliers from China, India and South Korea.

The costs of these imported raw materials have implications not only for countries’ self-sufficiency, but also for the cost of the finished tests produced by local manufacturers. Small raw materials procurers like local manufacturers may pay more because they will not benefit from bulk purchase discounts.

Innovative manufacturers in countries at all income levels face challenges taking tests from a prototype to manufacturing and scale up. WHO and other relevant UN agencies working to promote local production should provide innovators with a clear roadmap to ensure promising prototypes can make it through regulatory approval, to market and ultimately into the hands of local healthcare providers.

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\(^1\) A nitrocellulose sheet is a specialised paper-based material used in lateral flow RDTs made by treating cellulose with nitric acid. It is a sticky membrane used for immobilising antibodies or antigens to coat its surface, which form the basis of the lateral flow RDT.
For countries just starting to promote a local manufacturing industry, prioritising support for technology transfer makes the most sense. Depending on licensing fees, this is typically less costly because the technology is already developed. It can also serve as a good litmus test to check whether local manufacturing is feasible and meets quality requirements. If the test need is urgent, then usually the only choice is technology transfer to an already-established, quality-assured, reputable manufacturer who has the capacity to manufacture an additional test without disrupting the manufacture of current tests.

In parallel, initiatives could be established to build additional capacity longer term for greater autonomy. While it may make sense to continue importing complex raw materials, local capacity could be developed for producing some raw materials like plastics and proteins (e.g., antigens and antibodies for RDTs and enzymes for PCR). Although this may not be feasible in every country or with every type of test, regional self-sufficiency should at least be possible for a number of diagnostics.

Governments and other funders should mandate open science principles and access conditions in public funding agreements for diagnostics research and development

Traditionally, R&D of diagnostics benefits from significant amounts of public and philanthropic funding invested up front, but the process still results in privately-owned finished products that are not assured to be accessible, affordable or fit for purpose in LMICs. From university research onwards, the system directs innovation to a for-profit model that relies on monopolies and secrecy to advance promising technologies through the pipeline, disincentivising open sharing of diagnostic innovations.19

As with CRIPSR-based COVID-19 diagnostic innovations currently being made openly available (Box: Putting public health before CRISPR patents), at least temporarily, the COVID-19 pandemic has in some cases changed the usual dynamics of research exchanges on diagnostics for the better. Still, despite all the public money that has been invested in the development of health tools to respond to the COVID-19 pandemic,20 there remains little to no obligation of disclosure or open sharing of technologies attached to the public funding agreements, making it challenging for governments and the public to demand these afterwards. For example, although the US government has paid Cepheid $4.7 million to develop a COVID-19 test cartridge,21 on top of the enormous public funding Cepheid received to develop the technology in the past decade,4 Cepheid has not shared this technology with any manufacturers in LMICs. Worse still, Cepheid has been unwilling to offer more than 15% of their supply to LMICs that have invested for over a decade in Cepheid’s GeneXpert diagnostic machines for other diseases.22

Conditions for public funding of research and development

An enforceable and mandatory framework by governments and funders23 could ensure that publicly and philanthropically funded diagnostics R&D will be made conditional on:

1. Publication of all data (including evaluation trial protocols and results), production processes, sales prices, sales volumes, manufacturing costs, and supply capacities;
2. Non-exclusive, open source, global licensing and full transfer of technologies and know-how to LMICs without restrictive terms;
3. Transparent negotiations and publication of final contracts and licensing agreements;
4. Innovators forgoing patents and other IP exclusivities;
5. Supply of products to public health services within the country and to other countries; and
6. Pricing based on manufacturing costs without excessive profit margins.

To build capacity for robust local diagnostics industries, successful technology transfer must go farther upstream in the test production pathway to produce the raw materials that go into locally manufactured tests. Governments should seek to build local capacity for progressively more advanced technology transfer and ultimately develop strong enough local capacity for R&D that does not rely on technology transfer. Technology transfer with local assembly can be a first step or interim solution with longer-term raw material production and R&D capacity building developed in parallel.

To maximise the impact of public R&D funding, explicit and enforceable conditions should be put in place from the beginning of the R&D process so that open sharing of innovations, as well as collaboration and transfer of know-how and technologies to LMIC counterparts, can be guaranteed (Box: Conditions for public funding of research and development). Governments should request that technologies and know-how are made available in the public domain. Originators should adopt these principles and clauses for technology transfer agreements they sign, and funders should build these access principles and conditions into their grant contracts as mandatory clauses.
ENSURE THAT LOCAL PRODUCTION IS SUSTAINABLE AND MEETS LOCAL HEALTH NEEDS

Local manufacturers should make tests that fill local testing gaps

LMICs struggle to access the diagnostic tests they need both in circumstances when there is too little demand and when there is too much demand relative to supply. For diseases that primarily affect LMICs and at relatively low prevalence rates, the low annual volumes required for these diagnostics are not of interest to major manufacturers. For example, Bio-Rad, the US-based manufacturer of a test to diagnose visceral leishmaniasis, announced in April 2021 that the company will be discontinuing production of the test.24 The company does not consider it worth the time and investment needed to meet new European diagnostics regulations and maintain the CE marking.25,26 LMICs’ higher-volume needs are mostly addressed by high-volume suppliers based in the Asia, Europe and the US, leaving LMIC countries largely dependent on imports for these essential health products. During the COVID-19 pandemic, while global demand for diagnostic tests is high, LMICs are often left out or only supplied after HIC orders, as observed for Cepheid’s automated cartridge-based GeneXpert tests for COVID-19.

Tests that address local needs and require low production volumes, such as diagnostic tests for leishmaniasis and other neglected diseases, would represent the highest added value for local production given the current testing gaps for these products.

Governments should invest in non-profit and public manufacturers

Most local manufacturers are for-profit commercial businesses, although some are publicly owned or other non-profit entities. Because the traditional for-profit model relies on the promise of profits through high-priced products, these manufacturers rarely prioritise public health needs over profit. In contrast, a non-profit or public model could help to direct priorities towards public health needs and sustainability. These models could ensure prices are based on manufacturing costs. However, without the draw of high prices after market entry, non-profit and public entities will likely need larger-scale industrial budget funding upfront to produce needed diagnostics.

One example of a successful public diagnostics manufacturer is Brazil’s Bio-Manguinhos (Fundação Oswaldo Cruz). Bio-Manguinhos is a local manufacturer that is part of the Brazilian Ministry of Health and produces about six million diagnostic kits annually for diagnosis of HIV, Chagas disease, dengue, leishmaniasis, leptospirosis and other diseases.27 Bio-Manguinhos conducts R&D and produces tests as requested by the Brazilian government at agreed upon non-profit prices. They can only export beyond Brazil when they have surplus and only to other non-profit entities.

The newly launched Senegal-based diagnostic manufacturer, diaTROPIX, is an example of a non-profit manufacturing model and is affiliated with the Institut Pasteur of Dakar (IPD). Although it is still early in their operations, they may have the potential to better align diagnostic production with public health needs in Senegal and regionally.

 diaTROPIX currently produces COVID-19 RDTs and intends to introduce additional RDTs and possibly molecular tests in the future, mostly for outbreak diseases. diaTROPIX was founded in 2018 and the Mérieux Foundation provided its technical expertise for the construction of the site and contributed to its equipment. A major opportunity for success is that it is part of the existing ecosystem in IPD. This allows diaTROPIX to access well characterised clinical samples, clinical trial know-how, and logistics support. DiaTROPIX collaborates with the UK-based social enterprise Global Access Diagnostics and Mologic for technology transfer.

To help align local production of diagnostics with LMIC health needs, governments should consider establishing publicly owned manufacturers and support other non-profit models of manufacturing. These approaches may help ensure that local production meets health needs and that resulting diagnostic test prices are based on manufacturing costs without excessive profit mark-ups.
STRENGTHEN REGULATORY MECHANISMS AND PUBLIC TRUST IN LOCALLY MANUFACTURED PRODUCTS

Governments and donors should strengthen national regulatory authorities and ensure regional harmonisation

To increase public trust in locally manufactured diagnostics, there is a need for more stringent regulatory bodies nationally and regionally in LMICs. In Africa, for example, currently only 7% of countries have moderately developed regulatory capacity and over 90% have minimal to no capacity. These countries often have more experience in the management of small-molecule medicines than diagnostics, and even then the process can take years.

Given the essential improvements needed for some national and regional quality oversight mechanisms, some diagnostic products can make use of stringent oversight mechanisms available at a global level. The WHO prequalification (PQ) programme for vitro diagnostics (IVDs) ensures that diagnostics for a select group of diseases meet global standards of quality and publishes all reports online. This is particularly useful for UN- and donor-funded purchases of tests for PQ-eligible diseases.

The PQ programme is an important step for countries without strong regulatory authorities who rely on the WHO assessment to gauge which products they should use programmatically, along with following the WHO guidelines for implementation and recommendations on use cases.

WHO PQ also offers a collaborative registration procedure (CRP) for countries with limited regulatory resources to limit “unclear pre-market registration processes, repetitive performance evaluations and lengthy product selection procedures,” in order to fast-track product registration and uptake. Moreover, donors who fund or procure products for LMICs, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the US President’s Emergency Plan for AIDS Relief (PEPFAR), use WHO PQ as a requirement for product purchase (where applicable) or require authorisation for use by one of the regulatory authorities of the founding members of the Global Harmonization Task Force (GHTF).

WHO also uses an Emergency Use Listing (EUL) for diagnostics during emergencies, such as for COVID-19 diagnostic tests. It aims to expedite the availability of diagnostics needed in public health emergency situations by assisting procurement agencies and member states with their decisions regarding the suitability for use of a specific diagnostic, based on a minimum set of available quality, safety and performance data. In May 2021, WHO developed an accompanying ‘facilitated procedure’ for NRAs to make use of the WHO EUL assessment outcomes in a timely way for national authorisation of WHO EUL approved COVID-19 diagnostics, similar to the CRP but with shorter timelines.

Another challenge for local manufacturers is that regulatory harmonisation is often lacking in LMIC regions, making the process of registering a test in multiple countries difficult for manufacturers. Small companies are particularly affected by a lack of regulatory harmonisation as their limited regulatory experience adds to the burdens of navigating different systems and sets of requirements for each regulatory authority.

Regional harmonisation in Africa promises to improve through the establishment of the African Medicines Agency (AMA), which will include diagnostics and medical devices. Although the treaty to create the AMA was adopted in 2019, of 55 African countries, only 9 of the necessary 15 countries have ratified it as of June 2021, causing a delay in implementation. Once implemented, enforcement will need to be ensured, including to monitor the black market, to build trust in the agency and the products it authorises.

Additionally, an Africa Medical Devices Forum (AMDF) already exists within the African Union, which aims to establish a harmonised framework for regulation of medical devices in Africa, including diagnostics, based on the WHO’s Medical Devices Regulatory Framework Model. This sits within the African Medicines Regulatory Harmonisation (AMRH) initiative, which intends to serve as the foundation of the AMA. The AMA aims to expand its scope of work gradually, commencing with generic medicine registration and moving towards oversight of vaccine clinical trials, pharmacovigilance, and the registration of new chemical entities, medical devices and diagnostics.

To build trust in locally manufactured diagnostics, governments should strengthen NRA capacity so that they can competently assess the quality of diagnostics to be used locally in a timely way and prevent supply of sub-standard or falsified products. Governments should also cooperate regionally to establish regional regulatory agencies, like the proposed AMA, or at a minimum ensure harmonisation of NRAs. Doing so can facilitate test approval based on regional relevance and minimise the number of required local validation studies. Governments should also ensure regulatory harmonisation of NRAs with SRAs to standardise dossier templates and avoid any unnecessary performance study duplication. As with the WHO PQ programme, all diagnostic assessment reports and other manufacturer documentation should be publicly available online to ensure transparency.
Experienced manufacturers and global and regional regulatory bodies should support local manufacturers for regulatory submissions

The risk of insufficient or unknown quality is an often-cited concern with respect to diagnostic tests produced in LMICs. Due to concerns of reputational and business risks of low-quality versions, originators sometimes say they do not wish to consider technology transfer to local manufacturers if they cannot control the quality of the procedures and end products.

In addition to national regulatory approval, there are a number of mechanisms and processes available globally to assess the quality of locally manufactured diagnostic tests (Box: Key elements of strong quality assurance).

However, small local manufacturers often lack experience navigating the regulatory approval processes at national, regional and WHO levels. To address this, some experienced manufacturers are offering regulatory support in their technology transfer agreements. For example, Mologic and Global Access Diagnostics’ technology transfer agreement with diaTROPiX to produce COVID-19 tests, includes support for regulatory submissions to ensure public trust in the tests and encourage their use.

To build the regulatory capacity of local manufacturers, established manufacturers and global and regional regulatory bodies should support local manufacturers needing guidance to meet key elements of strong quality assurance (Box: Key elements of strong quality assurance). Contracts with established manufacturers for technology transfer to sites in LMICs should contain the condition to support quality assurance as the transferring manufacturers have the internal capacity and know-how to do so. This should include capacity building for pre- and post-market processes and recognised mechanisms of strong quality assurance must be employed and enforced to ensure quality and build trust in locally produced products.

Key elements of strong quality assurance

Local manufacturers should ensure that their diagnostics meet these key elements indicating a high-quality product:

• ISO13485 certification, the quality management system standard for medical devices for regulatory purposes, assessed by an inspection agency endorsed by the International Medical Device Regulators Forum (IMDRF).

• Mandatory assessment of the diagnostic test quality and performance independently of the manufacturer and across all relevant geographies and populations where the test will be performed, but without redundant studies, in submissions for regulatory approval.

• Collaborative registration, prequalification or Emergency Use Listing with the World Health Organization (WHO) programmes, or authorisation for use by one of the regulatory authorities of the founding members of the Global Harmonization Task Force (GHTF), when stringently assessed (with a high-risk classification).

• Proactive post-market surveillance (PMS) lot verification testing and reactive PMS complaint reporting, proficiency testing and end-user quality control programmes.

1 In Africa, the Africa Centres for Disease Control and Prevention is currently setting up a biobanking network to support test validation in the region.
CONCLUSION

To meet the day-to-day health needs of people in LMICs, as well as exceptional needs during a global health pandemic, there are many advantages to a robust industry of local production for diagnostics. LMICs can greatly improve local production of diagnostics by providing funding and product demand, promoting open and accessible models of sharing IP and building production capacity, aligning local production efforts with local health needs, and ensuring appropriate quality oversight.

Doing so will require commitment from LMIC governments, regional bodies, donors, manufacturers and other global health actors to help expand, diversify and improve supply sustainability of diagnostics that meet LMICs’ health needs. This improved access to needed diagnostics can ensure that healthcare providers in these countries have the tools they need to guarantee that people can receive timely and appropriate care.

LIMITATIONS

Data summarised in the brief and online supplements were acquired through desk review and interviewing respondents.

While every effort was made to map the most important examples and include the most relevant information on technology transfer and local production in Africa and South America in Online Supplement 1, the mapping contains a non-exhaustive list of organisations, initiatives and companies working in this space. Those not included may have provided information that would have changed the summary and influenced recommendations. A few prioritised respondents were unable to be contacted or interviewed within the project timeframe.

Due to language constraints, more manufacturers based in Africa were interviewed than manufacturers based in South America. Countries in Asia and the Middle East were not prioritised in this mapping and could be the subject of future diagnostic manufacturing capacity mappings.

For the case studies listed in online supplements, interview respondents were not asked to fact check the content of Online Supplement 2 and thus inadvertent inaccuracies may exist.

REFERENCES


References continued


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