

TIME FOR \$5: GENEXPERT DIAGNOSTIC TESTS

MSF and others call on Cepheid for \$5 all-inclusive price for Xpert tests for TB and HIV, and price reductions across all assays

KEY MESSAGES:

1. The Xpert MTB/RIF (standard and Ultra) test run on Cepheid's GeneXpert platform is the best test for rapidly diagnosing tuberculosis (TB) and rifampicin-resistant TB in one step.
2. The 2012 donor-negotiated price of US\$9.98 per cartridge helped with uptake in many countries but is still too high for use as the initial TB test for everyone who needs it.
3. Given high sales volumes and public investments for GeneXpert product development and commercialisation, further price reductions are feasible and long overdue.
4. Xpert cartridges for other diseases (HIV, hepatitis, sexually transmitted diseases, cervical cancer) use the same technology and, by extension, with pooled upstream manufacturing costs, need price reductions.
5. Cepheid's existing service and maintenance package is too costly and ineffective for most countries. Changes in service provision are needed, with costs either included within an all-inclusive cartridge price (US\$5) or through a reasonable standardised global surcharge per cartridge (US\$1) per any assay.
6. It's time for a single, lower, all-inclusive price of US\$5 for all Xpert MTB/RIF (Ultra) cartridges in all settings for all people who need testing.
7. It's time for Cepheid to include lower pricing options for all assays used for high-burden diseases to maximise the feasibility of introducing other tests on the same platform.



Testing a sample from a person with suspected TB in a GeneXpert machine, Bangassou Hospital, Central African Republic.

EXECUTIVE SUMMARY

The GeneXpert diagnostic testing technology has revolutionised rapid, accurate diagnosis of tuberculosis (TB) since entering the market in 2010. The World Health Organization (WHO) recommends the Xpert MTB/RIF assays (standard and Ultra) as the initial test for all people with signs and symptoms of TB. Yet, due to the high cost of the GeneXpert instrument and its assays, most high TB-burden countries are not able to scale up testing for all people who need diagnosis.^{1,2} Instead, TB care providers continue to rely on cheaper, less accurate sputum smear microscopy.

To scale up testing and close the gap in diagnosis for people with TB, Médecins Sans Frontières (MSF) calls on Cepheid to reduce the price of Xpert MTB/RIF (Ultra) cartridges to US\$5, inclusive of service and maintenance.³

In addition to TB, several other Xpert assays have been developed to tackle other challenging diseases, which have been added to Cepheid's concessional pricing program for high burden developing countries (HBDC). These diseases

include HIV, hepatitis B/C, human papillomavirus (HPV), and various sexually transmitted diseases (chlamydia, gonorrhoea, trichomonas). Data from a recent analysis commissioned by MSF reveals that the costs to make the various assays should not be significantly different and that pooled volume-based discounts are likely across the entire menu of tests, given that most commodities (plastics and reagents) are common to all assays and target-specific reagents (e.g. primers and probes) are inexpensive. In addition, production costs are estimated to have significantly decreased over the years thanks to improvements in manufacturing efficiencies, expiration of royalties and increased volumes of sales.

But these cost savings are not reflected in Cepheid's prices. Given the economies of scale with respect to current and projected volumes as countries continue to increase testing for high-burden diseases such as TB, HIV and hepatitis – and taking advantage of integration of testing on one common instrument, the GeneXpert – a price reduction across all assays to US\$5, including service and maintenance, is a reasonable request.

Over the past two decades, Cepheid and the research and development (R&D) behind Xpert assays have had significant support from public and philanthropic funding, including an estimated US\$120 million from the US Department of Defense (DOD), US\$45 million from the US National Institutes of Health (NIH), and over US\$20 million via the Foundation for Innovative New Diagnostics (FIND), which was largely funded in past years by the Bill & Melinda Gates Foundation (BMGF).⁴ In addition, recent US government and philanthropic contributions allowed the advancement of testing cartridges for Ebola (BMGF, Paul G. Allen Family Foundation),^{5,6} the 10-plex extensively drug-resistant (XDR)-TB assay (NIH, FIND),^{7,8} and for syndromic panels for both tropical and viral haemorrhagic febrile illnesses, as well as mRNA-based differential host biomarkers (US DOD).⁹

This document provides evidence to support a reduction of pricing across all Cepheid's HBDC concessionally priced assays to reach the people in need of testing for TB and other high-burden infectious diseases. By reducing prices, countries will be able to improve infectious-disease control efforts by increasing and decentralising testing through expanded use of GeneXpert technology.

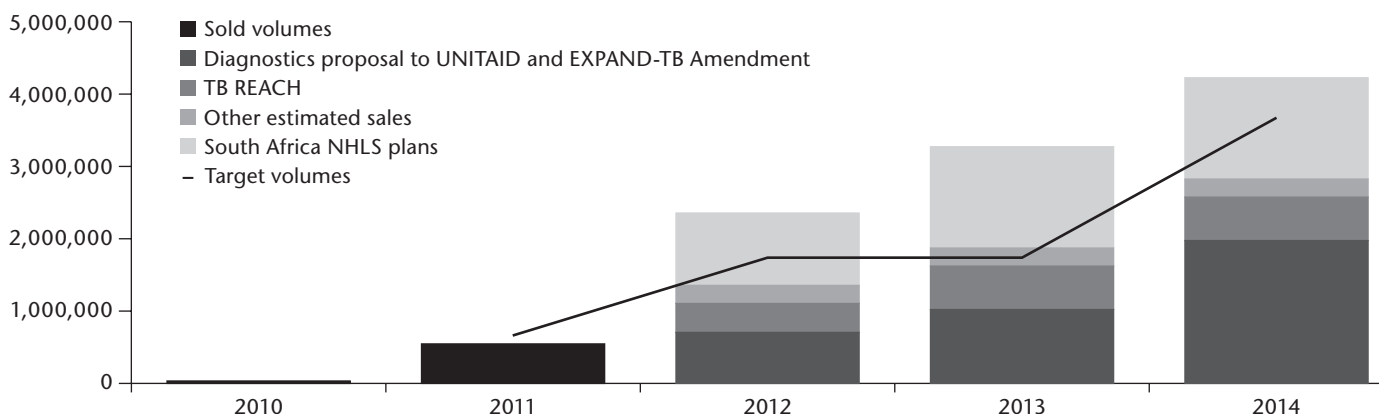
A LOOK BACK: THE 2012 BUY-DOWN AGREEMENT FOR US\$9.98/TEST

In 2011, realising that the cartridge price was driving overall high costs for routine testing, global health actors including the leading donor agencies explored different strategies to reduce the cartridge price. They modelled global volumes expected from 2012 to 2014 (Figure 1),^{10,11,12,13,14} in line with the WHO recommendations at the time (for people living with HIV or those in need of evaluation for MDR-TB), and for expected future recommendations (all people needing testing for pulmonary and extrapulmonary TB).¹⁵ These analyses estimated that, by 2014, 3.7 million assays could be sold, and a volume-based price reduction could occur each year to reach a price point of about US\$10 per cartridge (Table 1). Rather than wait for the volumes to bring about a reduction in price, these actors were interested in reaching this US\$10 price immediately to catalyse rollout of this test and increase people's access to rapid diagnosis for drug-sensitive and resistant TB.^{16,17}

In 2012, Unitaid, USAID, BMGF and the US President's Emergency Plan for AIDS Relief (PEPFAR) negotiated a "buy-down" with Cepheid, based on achieving volumes of >4.7 million assays a year. Cepheid was given an upfront payment of US\$11.1 million to establish a ceiling ex-works^a price of US\$9.98 per Xpert MTB/RIF assay for a 10-year period.¹¹⁻¹⁴ Furthermore, according to the agreement with Cepheid, any improved assay would be priced at that same amount, or lowered in price, if any component was removed, or if any royalties had expired during the time period (original or improved assays).

In addition, the buy-down agreement stipulated that all Cepheid instruments were locked in at ex-works pricing based on prepayment (the GXIV with desktop computer at US\$17,000 and with a laptop at US\$17,500). The primary market was focused on public-sector purchasers in 145 eligible low- and middle-income countries (LMICs), namely government ministries, agencies, institutes, hospitals and prisons; NGOs and UN agencies (MSF, IOM, ICRC, Oxfam); and global funding mechanisms (Global Fund, Unitaid, PEPFAR, USAID, CDC, GDF).¹¹⁻¹⁴

FIGURE 1:
PROJECT-BASED PROCUREMENT PROJECTIONS OF XPERT MTB/RIF CARTRIDGES, 2012-2014



^a "Ex works" means that the seller fulfils their obligation to deliver when they have made the goods available at the premises (i.e. works, factory, warehouse, etc) to the buyer. The buyer bears all costs and risks involved in taking the goods from the seller's premises to the desired destination.

Table 1: Volume-based pricing reduction scheme used in 2012 buy-down agreement for Xpert MTB/RIF assays

Global volume of cartridges, estimated annual	FIND-negotiated price, US\$
>600,000	16.86
>1,700,000	14.00
>3,700,000	10.72
>4,700,000	9.98

FIND, Foundation for Innovative New Diagnostics

TODAY: VOLUMES AND COST OF GOODS

Volumes sold to date

To date, the cost of the Xpert MTB/RIF assay remains the same as negotiated in 2012, despite higher sales volumes and future forecasts for TB testing. Global sales in the **public sector alone** surpassed the original predictions of 3.7 million cartridges, as modelled in 2012, reaching actual annual sales of nearly 12 million cartridges in 2018 (Figure 2). Over 45 million cartridges and more than 45,000 modules were sold in 2010-2018, again in just the public sector, as reported by Cepheid under their HBDC concession-pricing program (Figure 3).¹⁸

Over the years, cartridges have become available through HBDC concessional pricing for other priority diseases, including HIV, hepatitis B and C, HPV, and the common sexually transmitted infections (STIs) of *Chlamydia trachomatis*, *Neisseria gonorrhoea* and *Trichomonas vaginalis*.¹⁹ While a useful way to expand testing beyond TB, the HBDC concessional-pricing list of assays available for LMICs is a fraction of the complete menu of assays offered by Cepheid. Additional assays for other pathogens or resistance that could be useful to include in the concessional-pricing program are Xpert Flu/RSV (respiratory syncytial virus), Carb-R (carbapenem resistance, for testing resistance to the TB drugs imipenem and meropenem), or GBS (group B streptococcus). Current donor and domestic funding mechanisms could then utilise the broader HBDC menu of tests as the networks continue to scale up, thus increasing manufacturing and production volumes across all assays (Figure 4).^{20,21}

Today, all viral assays have been locked in at a price of US\$14.90, which is far higher than the current price (US\$9.98) for the MTB assays. However, previous pricing projections related to volume-based expansion proposed lower price marks (Figure 4). If one considers total volumes across all assays in the HBDC programme, then all assays should be considered for the lower price mark (at or near US\$5), since the assays are produced on the same production lines and show little difference in components and assembly.

FIGURE 2: XPERT MTB/RIF ASSAY CARTRIDGES SOLD, 2010-2018

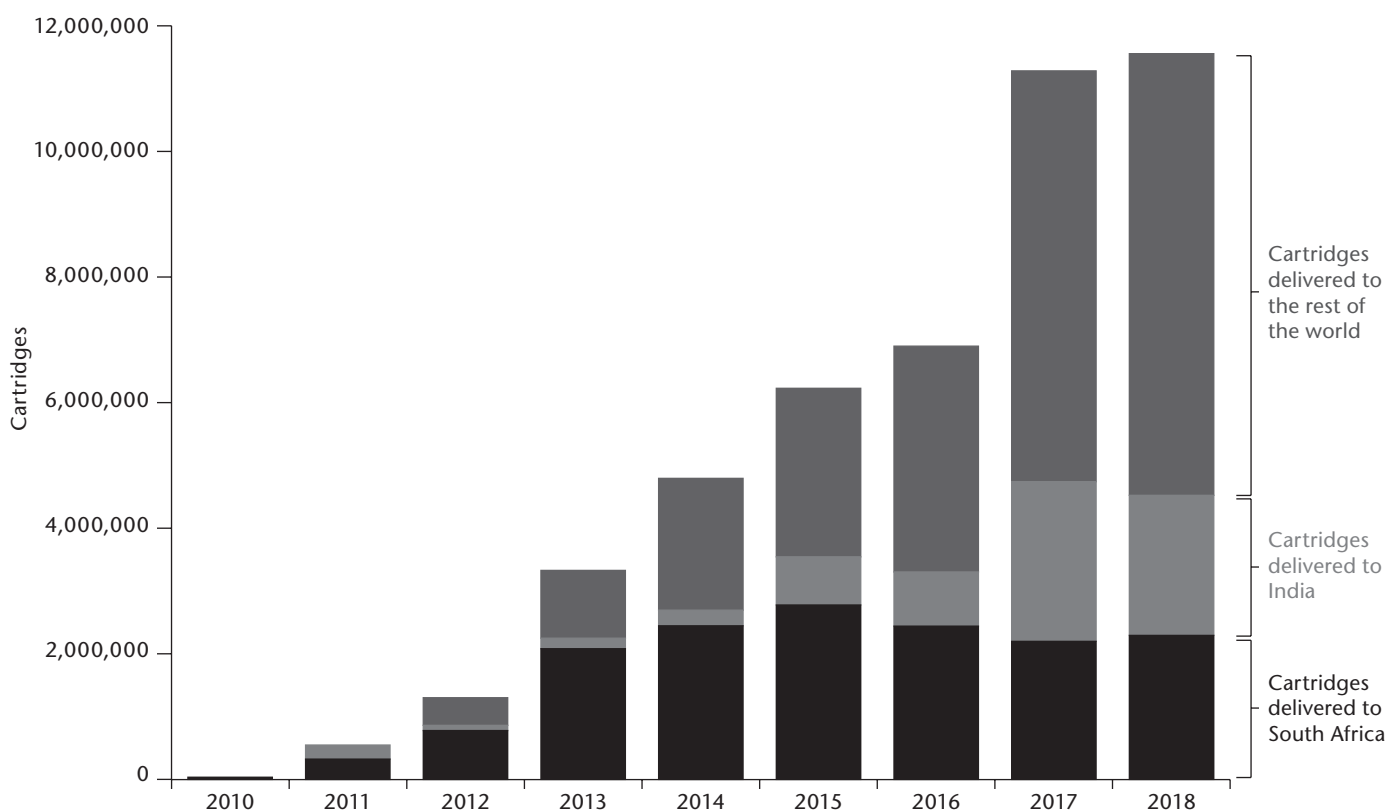


FIGURE 3:
CONCESSION PRICING SALES FOR GENEXPERT MODULES AND XPERT MTB/RIF CARTRIDGES, 2010-2018

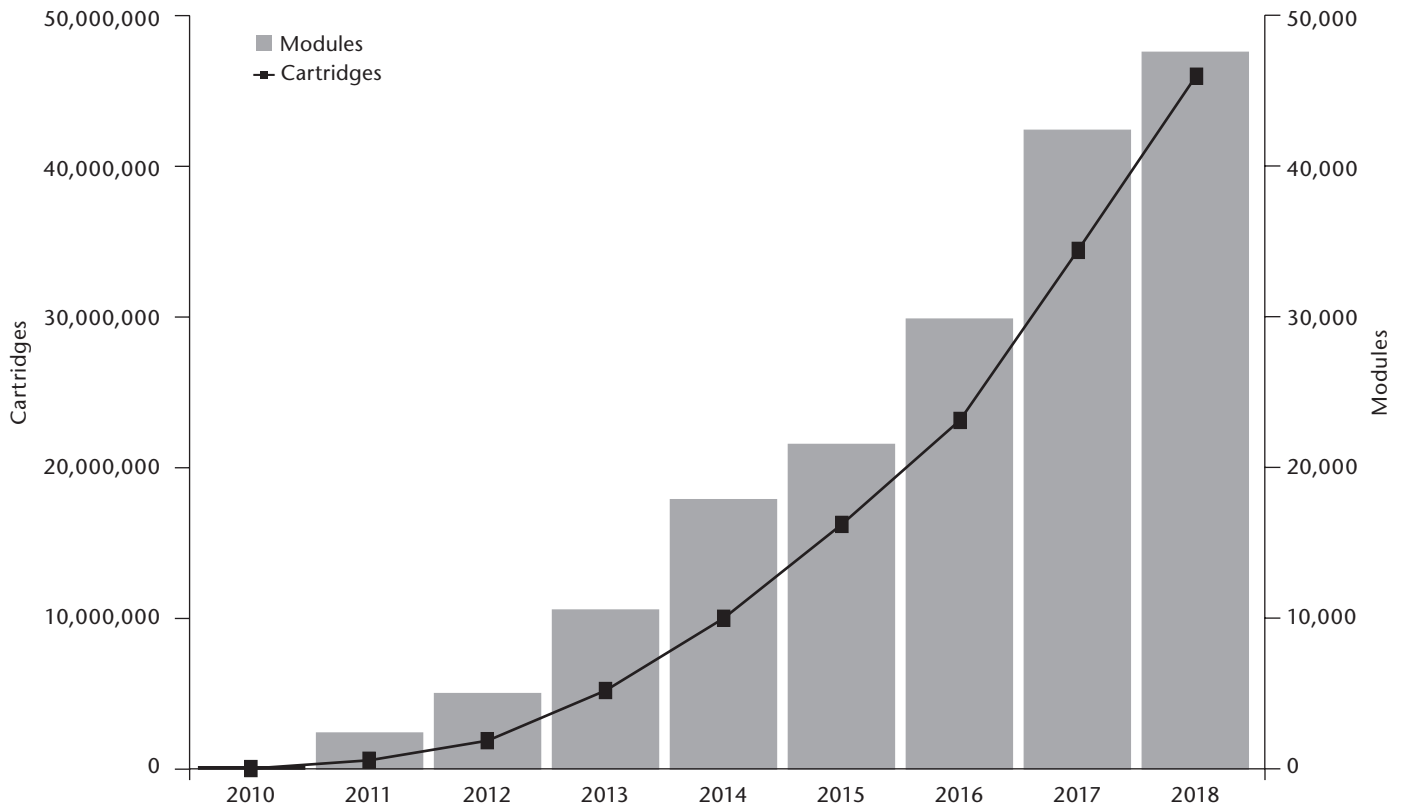
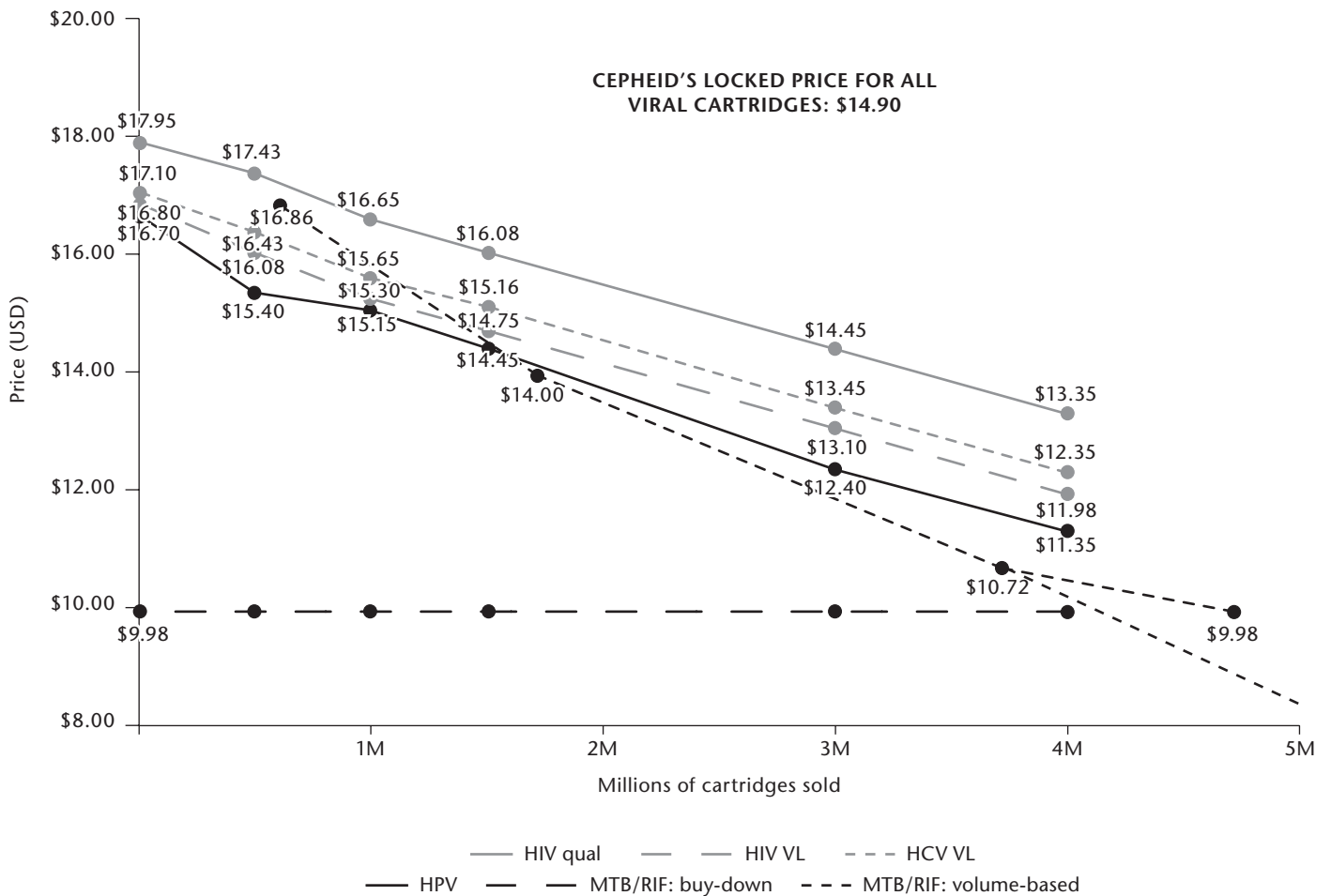


FIGURE 4:
VOLUME-BASED PRICE-REDUCTION MODEL FOR XPERT VIRAL ASSAYS



Estimated cost of goods

Questions are raised as to the difference in cost of goods sold (COGS) and manufacturing for all Cepheid products. COGS is the direct cost attributable to the production of the goods sold by a company, including the cost of materials, labour, manufacturing overhead, intellectual property (IP) and various indirect expenses.²² In a 2011 public communication, Cepheid identified the ex-works price breakdown under the initial agreement with FIND in 2006 (US\$16.86) as “Cepheid’s manufacturing cost + applicable royalties + 20% mark-up + a distributor mark-up of 5%, if applicable.”²³ The question arises today as to how the variables outlined above have changed in the past decade and the impact these changes may have on the actual cost of assays of public health importance.

In recent years, MSF has contracted an external group (Cambridge Consultants, Cambridge, UK) to estimate COGS for various assays from different manufacturers,²⁴ including the Xpert MTB/RIF (\$18.00, 2012),²⁵ HIV viral load (\$10.91, 2015)²⁶ and MTB/RIF Ultra (\$8.82, 2018) assays,²⁷ all using 1 million assays manufactured per year on an automated production line (Table 2). The 2018 assessment included investigations with regards to the differences in both COGS and manufacturing of viral and bacterial cartridges using the MTB/RIF Ultra and HCV assays as examples. The analysis was done to identify differences in cartridge elements, configuration, assembly and manufacturing that might support the price of US\$14.90 per viral assay.

Although the study found a few qualitative differences between cartridge structure and reagents (Table 3), these factors did not justify a significant higher cost for manufacturing. However, standing royalties on specific components remained uncertain. A formal transparent COGS evaluation should be provided by Cepheid to justify cost differences.

Table 3: Qualitative differences between Xpert bacterial MTB/RIF Ultra and viral HCV assays

Cartridge Component	Technical Specification	
	MTB/RIF Ultra assay	HCV viral load assay
Lid	Orientation of heat-sealed film above interface with reagent chamber lumens	
Reagent chamber	3 retaining beads, 2 filter inserts	2 retaining beads, no filter, added piece in collection chamber
Cuvette	Different geometry, same fabrication	
Plunger valve	3 parts: ultrasonic coupler, circular filter, plunger rod	3 parts: plunger rod, no ultrasonic coupler, rectangular filter
Base	No difference	

When modelling the expansion of annual volumes to 10 million assays, a conservative estimate, the price for the Ultra assay significantly decreases to US\$4.64. Indeed, increase in sales volumes is one of the considerations for reducing the price that was outlined by Cepheid in their 2011 communication and is a well-accepted mechanism to lower manufacturing costs for diagnostic tests.²³ However, to date, no price reduction of the Xpert MTB/RIF assay has been implemented despite a continuous increase in volumes over the past decade. Current volumes hover at 12 million per year in the public sector in LMICs and are expected to increase to fulfil the WHO recommendations as the recommended first test for TB for all. If we consider that this volume does not include purchases for any other assays being sold under the Cepheid HBDC concessional pricing programme (as those volumes are not publicly disclosed), and that a 20-30% reduction in price may be overdue, related to the probable expiry of at least two royalties, the price could be further reduced to an estimated US\$3 per assay (US\$4.64 - US\$1.69 [royalty expiry estimate] = US\$2.95) (Figure 5).

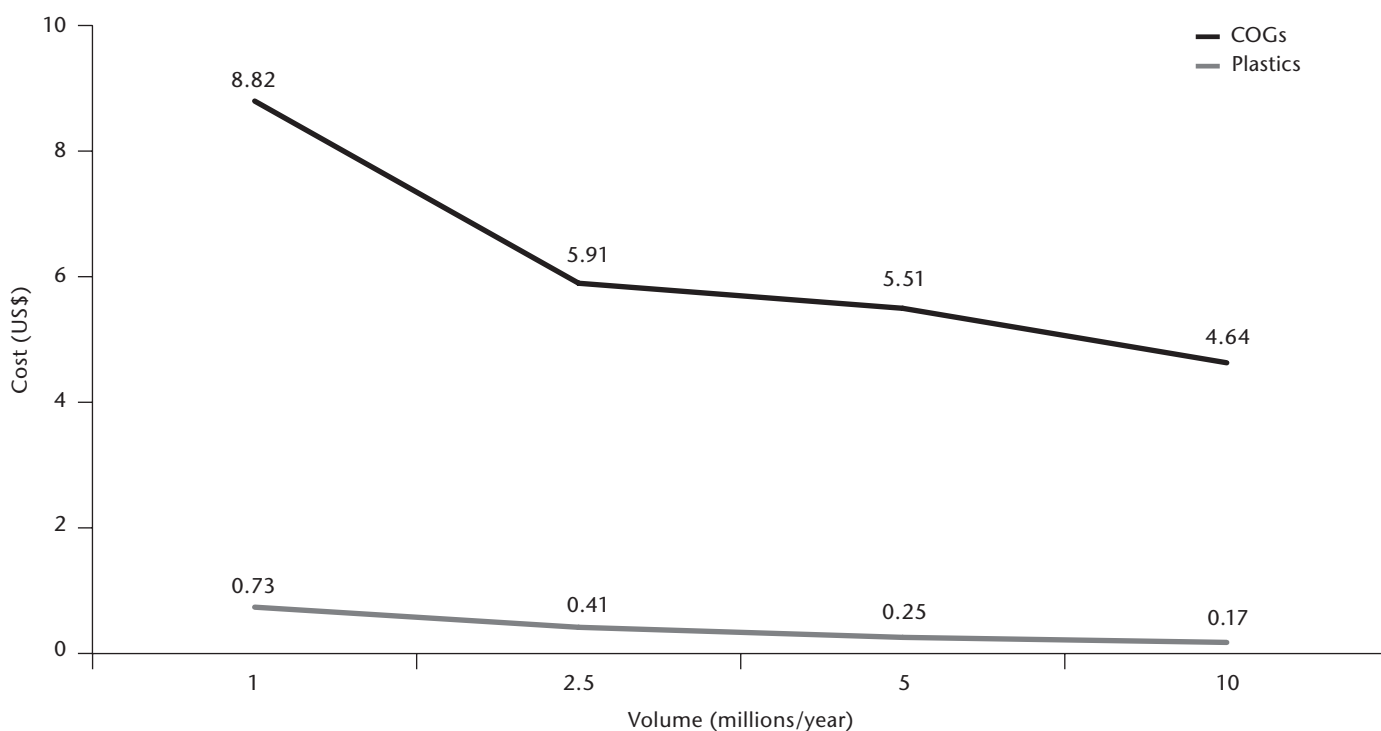
Table 2: Estimates of cost of goods per 1 million Xpert cartridges sold annually

Assay Component	Cost of Goods Sold (COGS)* by Assay			
	MTB/RIF 2012 ²⁵	HIV Viral Load 2015 ²⁶	MTB/RIF 2018 ²⁷	MTB/RIF Ultra 2018 ²⁷
Total (components and overhead†)	\$18.00	\$10.91	\$8.63	\$8.82
Breakdown costs				
IP estimates	\$2.00	\$1.91	\$1.69	\$1.69
Reagents/chemistry	\$4.30	\$1.78	\$1.23	\$1.42
Parts and moulding assembly (base/cuvette holder, cuvette, plunger valve, reagent reservoir, lid)	\$7.80	\$5.47	\$3.50	\$3.50
Final assembly	\$3.90	\$1.75	\$2.21	\$2.21

* Per 1 million tests sold

† QC, facilities, clean room, support staff, management, supplier, etc IP, intellectual property

FIGURE 5:
MODELLING PRICE REDUCTION WITH INCREASED VOLUMES SOLD OF XPERT ULTRA CARTRIDGES



For detailed methodology and findings of the COGS analysis conducted by Cambridge Consultants, please see the online annexes at msfaccess.org/time-for-5

CONCLUSION: LOOKING AHEAD

Based on the 2018 independent COGS analysis, the cost of Xpert MTB/RIF and Ultra cartridges should be closer to US\$4.64 per cartridge (or lower), at volumes of 10 million per year. A decrease in the company’s royalty commitments due to expired patents would result in an even lower cost. Service and maintenance should be included within the cartridge price to allow for all countries to have well-functioning fleets of GeneXpert instruments to meet public health needs.

With WHO recommending the use of Xpert MTB/RIF (standard and Ultra) as the initial upfront test for all people in need of evaluation for TB, predicted volumes to cover testing would reach nearly 30 million tests per year or even higher. But the current price of US\$9.98 per cartridge is limiting this needed increase in scale-up to fill the diagnostic gap. Cepheid has been benefitting from the buy-down price for many years but has not provided further volume-based price reductions to test many more people in need all over the world.

We urge manufacturers to price their products as affordably and fairly as possible, in line with their costs of goods, and to decrease prices at frequent intervals to reflect cost savings from improved manufacturing

efficiencies, expired royalties and increased global sales volumes over time. We also urge countries and regions to use proven cost-lowering mechanisms, such as pooled procurement, competition and price transparency; to waiver taxes and duties on products critical to global health; and to regulate price mark-ups by in-country distributors to better reflect a reasonable margin.

In an open letter to Cepheid in October 2019,³ MSF together with over 120 public health and civil society groups and individuals called on the company to lower the price of Xpert cartridges to US\$5, inclusive of service and maintenance. Cepheid’s response fell far short of the request,²⁸ with no plans to reduce the price nor to incorporate service and maintenance into the price of the cartridge. The company stated they “share” the desire for more affordable TB tests, and they hope for “breakthroughs” to enable affordable pricing in the future.

If these statements are true, then Cepheid should work to transparently demonstrate how they can break through the barriers to lowering the price for these lifesaving assays. It’s time for people with urgent health needs to benefit from all the global investment driving the success of this technology and the company.

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