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Examining the distribution of the TB diagnostic tool, GeneXpert: A Case Study

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2020

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Examining the distribution of the TB diagnostic tool, GeneXpert: A Case Study

By Emma Gile

In this case study, I describe some of the determinants of GeneXpert distribution including price and cost, intellectual property protections, and other determinants including supply delays, COVID-19, and health system weaknesses. While some broad conclusions can be made about GeneXpert distribution including that GeneXpert are not widely available in all high-burden countries and in recent years, there has been an increase in the presence of GeneXpert in public sectors globally, the specifics of global distribution of GeneXpert is unknown. A key takeaway from this case study is the elusiveness of the data related to GeneXpert procurement and distribution. The global distribution of GeneXpert is unavailable but there is data on the use of rapid molecular tests more broadly. However, data on rapid molecular tests still allow for discussions of equity. The distribution of GeneXpert has many inequitable aspects, which calls into question the obligations of justice to address this inequity. Despite concessional pricing agreements, price is still prohibitive for GeneXpert distribution in high TB burden countries. Price, however, is not easily fixable. One aspect of pricing that is highly complicated are intellectual property protections. For diagnostic tools in particular, little is understood about the specific impacts of IP on diagnostic access. Lastly, determinants beyond price include supply delays, COVID-19, and the need for health systems strengthening. Many countries have GeneXpert machines installed within a health system but cannot continue to afford the cartridges needed for diagnosis, especially through domestic funding alone. Additionally, many health systems still require strengthening to continue to use GeneXpert. Given the murkiness of GeneXpert distribution, we need to think about manufacturing differently. Rethinking manufacturing includes efforts to finance and strengthen health systems adequately beyond just the installment of a GeneXpert machine and rethinking how we think about diagnostic tools as potentially more of a global good than a private commodity. GeneXpert distribution and access is a component of the greater global health challenge of access to public health products.

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Chapter I. Introduction

Purpose: Describe the determinants of the global distribution of GeneXpert for TB diagnosis

Introduction

Tuberculosis (TB) is one of the most common infectious diseases globally. While effective TB treatment has existed for several decades, millions still die each year, most of whom are in low-and-middle-income countries (LMICs). In fact, only eight countries made up over 2/3 of all new cases in 2021 (WHO, 2022a). While many factors contribute to the ongoing TB epidemic, one major challenge to the TB response is that 1/3 to 2/3 of all TB cases globally are never diagnosed or go unreported (WHO, 2022a). TB infects people around the globe, but the distribution of the cases and the subsequent access to high-quality diagnostic tools, such as GeneXpert, are not equal.

Despite having a higher TB burden, LMICs have a lower diagnosed rate, or the percentage of all cases officially diagnosed, than high-income countries (HICs). In LMICs with high TB burdens, there is a 65% diagnosed rate, and in high-income countries, which are generally low-burden countries, the diagnosed rate is 80% (Kim, Keshavjee, and Atun. 2019). Ensuring early and quality diagnosis with a WHO-recommended rapid molecular test is a key strategy of WHO's End TB Strategy and is crucial to ensuring appropriate treatment (WHO, 2022b). TB has a near 50% mortality rate without treatment, and the threat of drug resistance persists, with around 3.9% of new cases having some form of drug resistance (WHO, 2022a). Also, if a diagnosis is delayed because of inadequate diagnostic capacity or the TB strain is drug-resistant, there will be delays in receiving effective treatment, which can be very costly and even fatal. Leaving people with drug-resistant TB strains untreated or delaying their treatment impacts

their prognosis and has broader public health implications. The presence of drug-resistant TB threatens the current effective TB treatment regimens. It is much more challenging and expensive to treat drug-resistant TB, which increases costs for the health system and the individual who is infected.

Additionally, uncontrolled TB has broader implications for the prognosis of the HIV epidemic and country economies. Uncontrolled TB can increase the TB/HIV coinfection burden. TB is currently the most common killer of people with HIV, and of the newly diagnosed TB cases in 2021, 76% also had HIV (WHO, 2022a). Lastly, beyond the immediate public health implications, TB leads to high economic costs for individuals, families, communities, and health systems, especially in high-burden settings. Diagnosis access is just one aspect of TB control and treatment, but it is a vital to ending TB. A contributor to diagnostic disparities between countries and the millions of people who are never officially diagnosed is that many still do not have adequate access to diagnostic tools, including the current most sophisticated diagnostic tool, GeneXpert (Pai & Furin, 2017).

Brief Overview of TB Disease

Before outlining the current diagnostic landscape for TB, I will provide a brief overview of TB disease and its different forms, which will provide context to TB diagnostic practices. TB is a respiratory infectious disease caused by *Mycobacterium tuberculosis.* It most often impacts the lungs, which leads to pulmonary active TB disease, but it can also impact other organs, otherwise known as extrapulmonary TB. However, just because a person is infected with *M.tuberculosis* does not mean they will become sick. People infected with *M.tuberculosis* and who are not sick have latent TB infection (LTBI). Nearly a ¼ of the world is estimated to be

infected with latent *M.tuberculosis*, but most will never develop active TB (Houben & Dobb, 2016).

In 2021, 10.6 million people fell ill with active TB, and 1.6 million died (WHO, 2022a). Figure 1 provides an overview and a sense of the distribution of the estimated global incidence rates for TB in 2021. The continued transmission of TB is significant because it is both preventable and treatable and because of the increasing threat of drug-resistant TB, especially in the highest-burdened countries. Treatment for drug-resistant TB strains is more complicated, takes more time, and is less effective than treatment for drug-susceptible TB. There are various forms of drug-resistant TB, some of which involve only resistance to one type of drug and others that are resistant to all TB medicine. The threat of drug resistance is significant to both a person who has TB, as it is considerably more difficult to treat, and also to the effectiveness of existing treatment regimens.

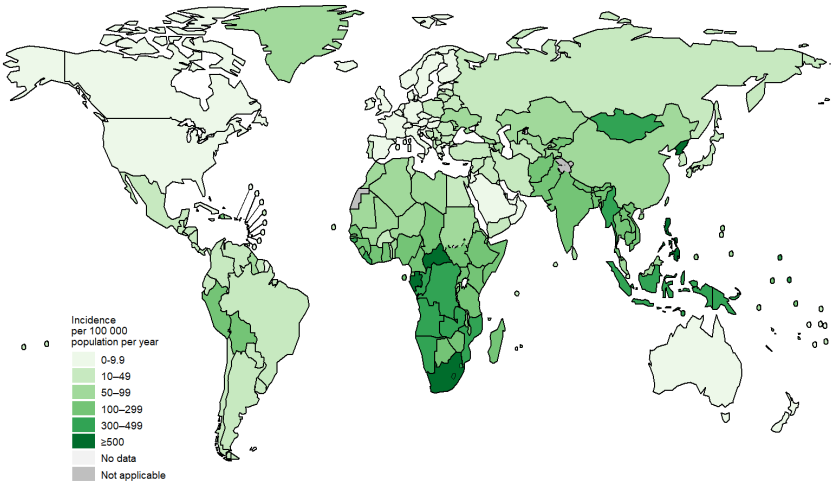


Figure 1. Estimated TB incidence rates in 2021 (WHO, 2022a)

TB Diagnostic Practices and Policies

WHO recommends that TB diagnosis be determined by bacteriological methods, which include a rapid molecular test, lateral flow urine lipoarabinomannan assay, microscopy, or a culture (WHO, 2022a). Other methods that could potentially be used for a TB diagnosis are methods recommended for TB screening, including a symptom screen, where a medical practitioner diagnoses TB based on a person's signs and symptoms. WHO recommends this method as a screening tool for who should be tested for TB rather than for diagnosis (WHO, 2015). A chest X-ray is another TB screening tool WHO recommends as a TB diagnostic method if no bacteriological tool is available. Other tools that health workers should not use to diagnose TB are the Mantoux tuberculin skin test (TST) and immune response by interferon-gamma release assay (IGRA). These diagnostic tools are recommended for detecting latent TB infection and cannot provide a diagnosis for active TB.

The WHO recommends GeneXpert, a rapid molecular test, as the first or initial test for all suspected TB cases. GeneXpert also referred to as Xpert, is the top WHO recommended diagnostic tool for TB because it is fast and can detect rifampicin-resistant TB (RR-TB) bacteria (WHO, 2021). Xpert is a polymerase chain reaction (PCR) test that is fully automated and provides results in less than 2 hours. One of the most critical components of GeneXpert is that it can detect TB and RR-TB simultaneously. Before GeneXpert, a TB diagnosis was slow, and detecting drug resistance was much more difficult. GeneXpert can also diagnose other diseases, such as HIV, COVID-19, and Hepatitis B and C. It is also able to detect TB in people who have HIV. While GeneXpert is currently the most sophisticated tool on the market for TB (see **Appendix A** for an overview of current TB diagnostic tools), it does have some limitations. It is expensive, requires significant upkeep and regular maintenance, the use of cartridges, and

requires a constant power supply meaning it cannot be battery operated. Cepheid, an American company and a company in the Danaher corporation, manufactures GeneXpert.

Another WHO-approved bacteriological diagnostic method is smear microscopy, which is still the most common diagnostic method in LMICs, even though WHO recommends using a rapid molecular test for an initial TB diagnosis (WHO, 2022a). Additionally, WHO recommends a lateral flow urine lipoarabino-mannan assay (LF-LAM) antigen to test people with HIV—who are very sick and have a low CD4 count—for TB. Lastly, WHO still considers a culture to be the reference standard for TB diagnosis. Following diagnosis, smear microscopy or a culture is needed to monitor treatment progress. Culture testing can also detect more forms of drug-resistance TB (WHO, 2022a.).

Current Distribution of Diagnostic Tools

TB infects people around the globe, but the distribution of the cases and the subsequent access to diagnostic tools, such as GeneXpert, are not equal. Additionally, while most people were diagnosed with TB with bacteriological confirmation methods, there is substantial variation between countries regarding the percentage of people diagnosed with bacteriological methods compared with other methods (see Appendix A; WHO, 2022). The WHO reported disparities between high-income countries (HICs) and LMICs on the type of diagnostic tool used for diagnosis, with the highest rates of bacteriological confirmation in high-income countries and the lowest rates in low-income countries (WHO, 2022a). Figure 2 shows the difference in the percentage of people diagnosed with TB using a bacteriological method between countries.

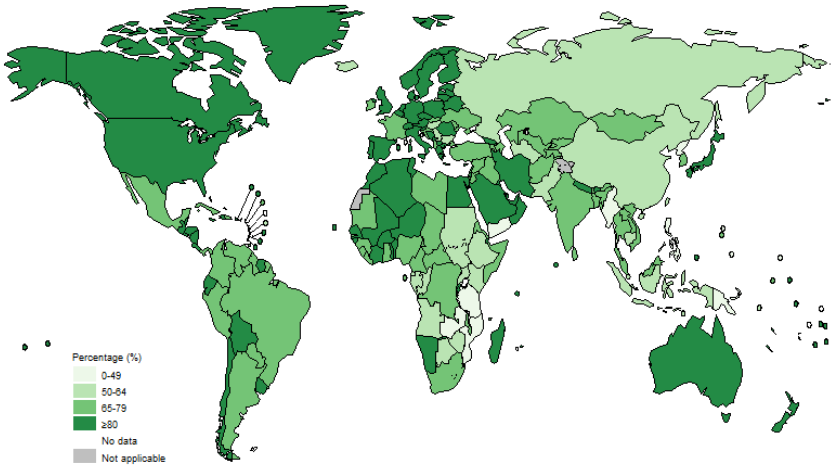


Figure 2. Percentage of people newly diagnosed with pulmonary TB who were bacteriologically confirmed at a country level, 2021 (WHO, 2022a)

Further, WHO recommends all people suspected to have TB should be tested initially with the rapid molecular test, GeneXpert. Despite WHO recommendations, only 38% of all newly diagnosed cases in 2021 were initially diagnosed using a rapid molecular test (WHO, 2022a). Only 25/49 countries of the highest burden countries reported using a rapid molecular test for the initial TB diagnostic test (WHO, 2022). Access to a rapid molecular test also varied by country. A median of 25% of TB diagnostic sites globally had rapid diagnostic tests. Also, only 7 of the 30 high TB burden countries reported more than 50% of their TB diagnostic sites having a rapid molecular test available (WHO, 2022). Moreover, in HICs, about 80% of TB cases were confirmed with a rapid molecular test, while 53% of cases in "high burden" TB countries were confirmed with a rapid molecular test (WHO, 2020). So globally, GeneXpert is not the first diagnostic test used to diagnose most TB cases, especially in countries with high TB burdens. Also, there are disparities between the percentage of cases diagnosed using a rapid molecular test between HICs and LMICs.

Background and Significance

In this thesis, I will focus on the determinants of distribution of GeneXpert because of its ability to provide a prompt diagnosis for both drug-susceptible and rifampicin-resistant strains of TB and is the WHO-recommended diagnostic tool for all potential active TB cases. GeneXpert distribution is an example of how technology to combat a disease that most heavily burdens poorer individuals and communities is not always widely accessible to those communities. In this thesis, I define global distribution in terms of where a GeneXpert machine is available and presumed to be in use as well as where the number of fully functional GeneXpert machines are in proportion to the burden of TB disease.

The general trends for GeneXpert distribution are that GeneXpert machines are in use more often in high-income countries, and there has been an increase in the presence of GeneXpert in public sectors globally. However, there is limited data on all rapid test usage as the initial diagnostic test and GeneXpert—more specifically. Figure 3 shows recently published data by the WHO on the percentage of people newly diagnosed with a rapid test at the country level. Figure 3 also shows a wide variation between countries, but the figure has limits because of the lack of data, particularly in HICs, which are known to have considerable availability of rapid tests. The WHO report did not include information on why these countries did not provide data. Nonetheless, figure 3 shows the wide variation between high-burden TB countries regarding access, availability, and reach of rapid testing.

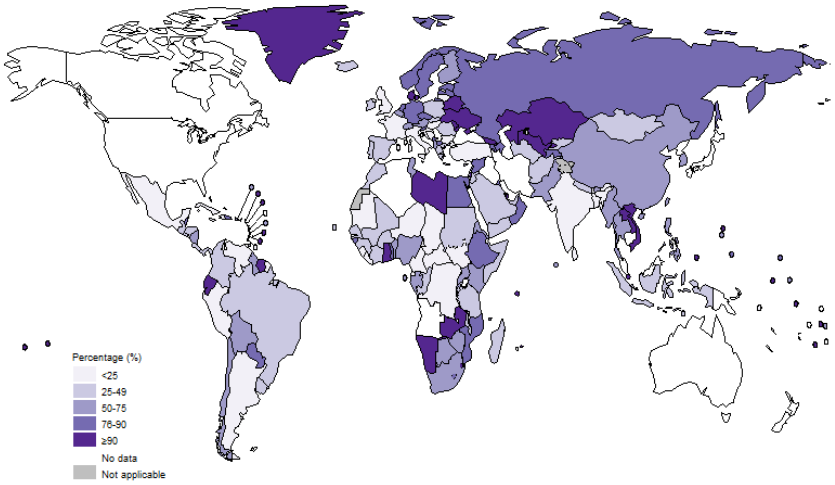


Figure 3. Percentage of people newly diagnosed with TB who were initially tested with a WHO-recommended rapid test at country level, 2021 (WHO, 2022).

Country-level studies and reviews provide some insight into GeneXpert distribution and implementation, particularly in high-burden settings. Cazabon et al. (2018) conducted a market penetration trend analysis, and they found that in 21 high-burden countries, there was a positive overall trend in Xpert market penetration in the public sector but still found that GeneXpert was underutilized for TB diagnosis and not adequately exploited for its multi-disease technology. Additionally, Williams et al. (2022) conducted a study to evaluate trends in tuberculosis diagnosis and outcomes pre-and post-introduction of GeneXpert in Democratic Republic of Congo (DRC), Nigeria, and South Africa. They found that overall there were improvements in treatment outcomes in all three countries but not much progress in new case notifications following the introduction of GeneXpert. These conclusions indicate in these three countries, GeneXpert diagnosis may be associated with improved treatment outcomes when used; however, given that there was not much improvement in new case notifications implies that availability alone does not equate to use of GeneXpert for diagnosis They attributed the little improvement in case notifications to varied implementation and scale-up of Xpert in the three countries as well as

implementation barriers related to weaknesses in the health system that were left unaddressed. Both studies found that there has been an increase in GeneXpert availability within the last decade but varied results in whether this leads to adequate and regular use.

Cazabon et al. (2018) concluded that continued close monitoring of the impact of "TB diagnostic procurement, utilization, and market penetration" is crucial to addressing barriers to access. While it is known how many GeneXpert have been procured either by purchase or donation globally and that GeneXpert is not evenly distributed according to TB burden, there is a gap in knowledge about specific determinants of global distribution. Without fully understanding the determinants of distribution, there is the risk that solutions to address access gaps will be inadequate or misdirected to the wrong parts of the problem.

Additionally, understanding the various determinants of the distribution of GeneXpert involves exploring notoriously ambiguous and opaque processes such as pricing, intellectual property, financial reports, and business practices. Describing some of the determinants of distribution for GeneXpert may disentangle some of these murky processes so that useful solutions to achieve a global distribution that better reflects the public health goals of TB control can become more clear. Ignorance of determinants may lead to gaps in ensuring that the most burdened communities have access to this tool.

GeneXpert access and distribution sit within the context of a broader global health challenge which is public health tool access. High-income countries having more access to a tool that primarily addresses a condition that burdens LMICs is not unique to GeneXpert. So this analysis could clarify the distribution of GeneXpert and medical products more broadly.

Chapter II. Methods

The design of this thesis is a descriptive case study. I started my exploration for this thesis after seeing Médecins Sans Frontières' (MSF) call for lowering the price of GeneXpert. Given that the diagnostic gap among people with TB is a major issue for the response to end TB, I decided to explore how access to GeneXpert, the most sophisticated TB diagnostic tool, plays a role in this diagnostic gap. Table 1 provides an overview of the method I used in this thesis, including what information I was looking for, what sources I ended up using, and the justification for using the sources I chose. I initially wanted to know how many people with TB were diagnosed with TB using a GeneXpert tool. For this information, I explored the WHO Global TB Reports and academic articles to look for specific statistics. I also wished to know about the existing GeneXpert distribution. I looked for this information through WHO Global TB reports, scholarly articles, TB NGO websites, Cepheid's website, and TB databases.

To get some initial ideas of determinants of distribution, I read through several scholarly reviews of the current state of the TB epidemic, tools, and challenges. One recurring limitation about GeneXpert access was its cost. So I wanted to learn more about GeneXpert's pricing. Information on pricing, particularly market pricing as opposed to concessional pricing, was elusive, so I had to look through many different sources and still did not end up with a clear answer. In this process, I learned about some of the efforts to lower the price for some countries namely through the Cepheid "Buy Down Agreement." I found information about the agreement from press releases and the websites of Cepheid and FIND— a global NGO that works to improve diagnostic innovation and access and who was a part of the Buy Down Agreement negotiation. I also wanted to learn about the effectiveness of this agreement in actually

improving access to GeneXpert, which I got through a USAID program evaluation and academic studies.

Additionally, I inquired about Cepheid's business model and practices. For this information, I looked through Cepheid's website and Cepheid and Danaher's most recent financial reports.

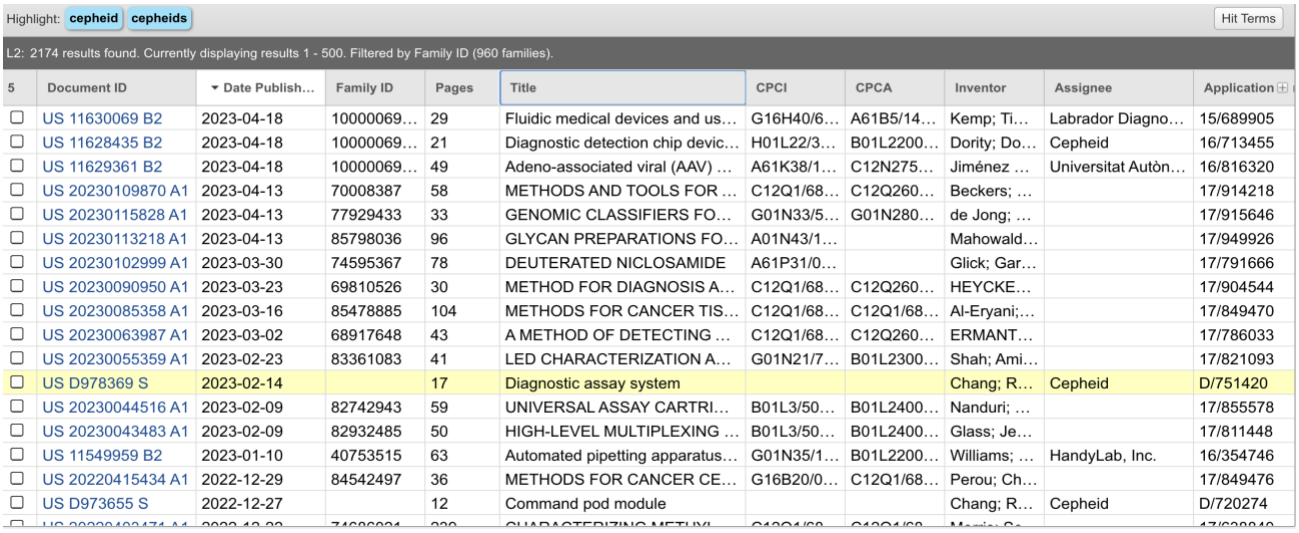
I knew beforehand that intellectual property is a barrier to public health tool access, so I explored if this was the case for GeneXpert. I read through the World Trade Organization's (WTO) TRIPS Agreement, which outlines global trade IP protections, and tried to find what IP Cepheid had for GeneXpert. For this information, I looked through patent databases (figure 4) and a Patent Landscape Analysis conducted by MSF.

Lastly, I was trying to find information on any other determinants of distribution. For this I used personal communications with TB experts, who provided some insight from their work. I also read through academic articles and reviews that explored the rollout of GeneXpert in high-burden settings and found various barriers to implementation. Additionally, I also found some news articles which provided information on distribution determinants of GeneXpert that have been created or exacerbated by the COVID-19 pandemic.

Information I looked for	**Sources Used**	**Justification for Source**
Proportion people who were diagnosed with GeneXpert	• WHO Global TB Report	This report provided data on the proportion of people who were diagnosed using a rapid molecular test.
Global Distribution of GeneXpert	• Cepheid Global Access Program website • Danaher financial report • Academic literature	I had to use information from all of these sources to get an idea of GeneXpert distribution since there was not one source that explicitly provided this information
Price of GeneXpert for TB (market and concessional price)	• Cepheid website • FIND website • MSF Access Project • Stop TB Partnership TB Reach Budget Tool	Stop TB partnership budget tool and FIND clearly outlined concessional pricing. Market price was a challenge to find and so several sources were required to get an idea it

Impact of Concessional Price Agreement	• Academic literature • USAID and UNITAID Program Evaluations	Both academic studies and program evaluations provided information on the impact of the concessional agreement on GeneXpert rollout, particularly in high-burden countries.
Intellectual Property information for GeneXpert and diagnostic products	• Cepheid and Danaher financial reports • TRIPS Agreement • Public Patent Database • MSF Xpert Patent Landscape Analysis	Financial reports provided insight on how Cepheid and Danaher handle IP and the MSF Analysis provided information patents for GeneXpert. The Public Patent Database has on record all of Cepheid's public IP. The TRIPS Agreement primary text provided broader information on international IP regulations for public health products.
Other distribution determinants	• Personal communications • Journal articles • News articles	Personal communication provided on the ground insight into some other determinants. Journal articles on the rollout of GeneXpert in high-burden countries found barriers to the implementation. News article provided more recent information related to the impact of COVID-19 on GeneXpert distribution determinants.

Table 1. An overview of the information I was looking for, where I found the information, and the justification for the sources I used.



Highlight: cepheid cepheids — Hit Terms

L2: 2174 results found. Currently displaying results 1 - 500. Filtered by Family ID (960 families).

5	Document ID	Date Publish…	Family ID	Pages	Title	CPCI	CPCA	Inventor	Assignee	Application
☐	US 11630069 B2	2023-04-18	10000069…	29	Fluidic medical devices and us…	G16H40/6…	A61B5/14…	Kemp; Ti…	Labrador Diagno…	15/689905
☐	US 11628435 B2	2023-04-18	10000069…	21	Diagnostic detection chip devic…	H01L22/3…	B01L2200…	Dority; Do…	Cepheid	16/713455
☐	US 11629361 B2	2023-04-18	10000069…	49	Adeno-associated viral (AAV) …	A61K38/1…	C12N275…	Jiménez …	Universitat Autòn…	16/816320
☐	US 20230109870 A1	2023-04-13	70008387	58	METHODS AND TOOLS FOR …	C12Q1/68…	C12Q260…	Beckers; …		17/914218
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☐	US 20230090950 A1	2023-03-23	69810526	30	METHOD FOR DIAGNOSIS A…	C12Q1/68…	C12Q260…	HEYCKE…		17/904544
☐	US 20230085358 A1	2023-03-16	85478885	104	METHODS FOR CANCER TIS…	C12Q1/68…	C12Q1/68…	Al-Eryani;…		17/849470
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☐	US D978369 S	2023-02-14		17	Diagnostic assay system			Chang; R…	Cepheid	D/751420
☐	US 20230044516 A1	2023-02-09	82742943	59	UNIVERSAL ASSAY CARTRI…	B01L3/50…	B01L2400…	Nanduri; …		17/855578
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☐	US 11549959 B2	2023-01-10	40753515	63	Automated pipetting apparatus…	G01N35/1…	B01L2200…	Williams; …	HandyLab, Inc.	16/354746
☐	US 20220415434 A1	2022-12-29	84542497	36	METHODS FOR CANCER CE…	G16B20/0…	C12Q1/68…	Perou; Ch…		17/849476
☐	US D973655 S	2022-12-27		12	Command pod module			Chang; R…	Cepheid	D/720274

Figure 4. A screen shot of the Public Patent Database when I searched Cepheid in the advanced search. I used this database to get a sense of the patents assigned to Cepheid. The highlighted row is an example of some of the information provided in this database for a patent assigned to Cepheid.[1]

[1] The Public Patent Search database is provided by the United States Patent and Trade Office. For a more thorough list of the patents I looked through, go directly to the website and search 'Cepheid.' https://ppubs.uspto.gov/pubwebapp/

Chapter III. Findings

The investigations described above produced findings in the following categories: price, intellectual property, and determinants beyond price including market factors, COVID-19, and weak health systems.

The Global Distribution of GeneXpert

One of the first steps I took to begin describing the determinants of the global distribution of GeneXpert was to explore the existing global distribution. However, the intricacies are unclear and GeneXpert distribution data remains elusive. The WHO reported that only 38% of active TB cases were diagnosed using a WHO recommended rapid molecular test, which includes Xpert MTB/RIF tests (WHO, 2022a). While this proportion indicates that the vast majority of TB cases are not diagnosed with a rapid molecular test, it does not specifically provide information on the percentage of TB cases that were diagnosed with Xpert, since rapid molecular tests also include Loop-mediated isothermal amplification (LAMP) and a Line Probe Assay (LPA) (refer to Appendix A). Other potential clues to GeneXpert distribution are through Cepheid's reporting on their Global Access Program, which includes their concessional pricing agreement for GeneXpert machines and cartridges that test for TB. Danaher the corporation that owns Cepheid, reports that there are over 40,000 GeneXpert machines worldwide and 14,000 of those were distributed to eligible countries through the company's Global Access program (Danaher, 2021; Cepheid, n.d.). For all of Danaher's diagnostic tools, it's largest markets are in North America (Danaher, 2021).

Information on the distribution of GeneXpert remains elusive. For example, the global proportion of people diagnosed with TB using a rapid molecular test is not specific to the use of GeneXpert. I have had to supplement information about GeneXpert availability and use with

program evaluations and country-level studies to get a better understanding of GeneXpert distribution because there is not, to my knowledge, publicly available global data. Moreover, a potential reason large-scale distribution information on GeneXpert is not easily accessible is because Cepheid might consider distribution strategy and outcomes a trade secret (World Intellectual Property Organization (WIPO), n.d.). If so, this would constitute private IP which they are under no obligation to share.

Price: GeneXpert is still not widely affordable

Price is a determinant of distribution because it impacts which countries can afford the concessional or market price, which influences the availability of GeneXpert machines in a country. A factor that has influenced the distribution of GeneXpert is the "Cepheid Buy Down Agreement," which is an agreement that lowers the price of GeneXpert for certain countries. The agreement started in 2010 and continues today. The goal of the agreement was to make GeneXpert more affordable given that its price has contributed to the disparities in GeneXpert availability between HICs and LMICs (FIND, 2022a; USAID, 2019). There are conditions to the agreement. Only countries with certain income levels and TB burden are eligible. Another condition is that the concessional pricing is only available to public sector health facilities (USAID, 2019). The buy down agreement has been successful in increasing the availability of GeneXpert in eligible countries. For example, 130 low income countries are currently eligible for the concessional pricing and, over 14,000 GeneXpert machines have been procured and installed exclusively in public sector health facilities within these countries (Cepheid, n.d.). However, even though there has been an increase in the presence of GeneXpert in nearly all eligible countries nearly a decade after the start of the agreement, the concessional price is not low enough to ensure that GeneXpert, and the diagnostic cartridges, are widely available in high-

burden settings to reach global TB targets (USAID, 2019; Piatek et al. 2019). In 2021, 24 high burden countries were still short 73,066 GeneXpert modules and required a 3-fold increase in cartridges to meet full testing needs (A. Piatek. personal communication, October 20, 2022).

While the GeneXpert machine is expensive with a price of tens of thousands of US dollars, even with concessional pricing, having enough diagnostic cartridges is a major contributor to a lack of utilization of GeneXpert, even in health systems with the machine. The high cost of diagnostic cartridges keeps health systems in high-burden countries from adequately incorporating GeneXpert into routine practice and utilizing its multi-disease diagnostic features (Dalberg, 2017; Lewis & Martell, 2021). Table 2 outlines the concessional price per cartridge. Currently, the concessional price is $9.98 per cartridge. (FIND, 2022a; Stop TB Partnership, n.d). Médecins Sans Frontiers (MSF) (2019) argues that the concessional price for a GeneXpert cartridge should be $5 per cartridge, based on a ‘cost-of goods sold’ (COGS) analysis, to ensure that it is affordable to all. Table 3 is an estimate of the cost of the GeneXpert machine (referred to in table 3 as a module), cartridge, maintenance costs, and shipping for purchasers eligible for the concessional price. Table 3 also shows the costs in addition to the machine itself which include the upkeep of GeneXpert. GeneXpert requires annual recalibration or a system check as well as more regular maintenance to ensure high quality results (FIND, 2022a). Maintenance costs are not included in the concessional pricing agreement and the maintenance requirements are a reoccurring cost for health systems. All maintenance services are provided only by Cepheid (FIND, 2022a).

Type of GeneXpert Machine	Concessional Price per cartridge
Xpert MTB/RIF Ultra*	$9.98 USD
Xpert MTB/RIF*	$9.98 USD
Xpert MTB/ XDR	$19.80 USD

*WHO recommended first initial TB diagnostic test

Table 2. Concessional pricing for GeneXpert TB cartridges (FIND, 2022a). This price does not include shipping.[2]

Item	Unit cost (USD)	Shipping cost
GeneXpert 2 Module With Laptop (GXIV-2-L)	12,280	600
GeneXpert 2 Module With Desktop (GXIV-2-D)	11,780	600
GeneXpert 4 Module With Laptop (GXIV-4-L)	17,500	600
GeneXpert 4 Module With Desktop (GXIV-4-D)	17,000	600
GeneXpert 16 Module With Laptop (GXIV-16-L)	71,500	700
GeneXpert 16 Module With Desktop (GXIV-16-D)	71,100	700
GeneXpert Omni[3]	4,950	700
Annual Calibration kit (XPERTCHECK-CE-5)	450	
Individual Test Cartridge	9.98	1.28
GeneXpert 4 module Service Pack and warranty extension for 1 additional year (WX04RG12 - This is a request for further warranty extension for one more year)	2,900	
GeneXpert 4 module, 3-year warranty extension (WX04UP36 - paid upfront together with the system purchase)	7,900	
16 module Service Pack and warranty extension for 1 additional year (WX16RG12)	7,800	
GeneXpert 16 module, 3-year warranty extension (WX16UP36 - paid upfront together with the system purchase)	18,600	

Table 3. Provides an estimate of concessional pricing for eligible countries eligible. The table is taken from TB REACH Xpert Budget Estimation Tool from the Stop TB Partnership (Stop TB Partnership, n.d)

The market price for the GeneXpert machine and cartridge was difficult to find. For example, I looked at Cepheid and FIND's websites, WHO policy documents, financial reports, and advocacy reports; none had a market price. I derived nearly all of the information I found on market price from academic studies and program evaluations. For example, Ponnudurai et al.

[2] Xpert MTB/RIF Ultra and MTB/RIF can both detect *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin (RIF) simultaneously. Xpert MTB/RIF Ultra is just a newer version of the Xpert MTB/RIF test. Xpert MTB/XDR can detect *M.tuberculosis* and resistance to six drugs simultaneously or extensively drug-resistant (XDR) TB.

[3] Note that GeneXpert Omni is no longer being commercialized but since it is still included in the TB Reach Budget Estimation tool I have decided to keep it in this table.

(2018) found that patients who received care for TB in private sector facilities with a GeneXpert machine available in 12 high-burden countries paid an average of $84.53 per GeneXpert test. Determining the market price was valuable because it is the required price for high-income countries but also the private sector in high-burden countries. In many high-burden countries, the private sector provides significant portions of the healthcare to people with TB (Pai&Furin, 2017).

Additionally, market price varies widely. For example, Ponnudurai et al. (2018) found that among the 8 countries with GeneXpert in the private sector facilities, the cost per diagnostic test for the patient varied from $46.70 to $175.00. While the cost paid by patients is not necessarily what the private purchasers pay for the GeneXpert machine and or cartridge, it gives an idea of the difference in price for unsubsidized Xpert tests in the private sector. The price paid by patients in the private sector also varied widely between the 8 countries. Ponnudurai et al. (2018) attributed the variation to shipping and import costs, distributor margins, incentives to doctors, mark-ups by private laboratories and hospitals, and high commercial costs set by the manufacturer. Additionally, reports from advocacy groups provide varying numbers for the market price of GeneXpert. Public Citizen (n.d.) cited the market price as $180,000 for the entire machine and $60 per cartridge. Whereas, a UNITAID Program evaluation cited the price of GeneXpert at its launch was $35,000 per module and an additional $17 per test (Dalberg, 2017).

GeneXpert pricing is not low enough for widespread procurement even with the Buy Down Agreement in place which impacts the distribution of GeneXpert based on which countries can afford GeneXpert, at market price or concessional pricing, or who has donor purchased GeneXpert tools.

Intellectual Property

The TRIPS Agreement, an international agreement that outlines minimum standards of protection for intellectual property, has long been criticized by public health advocates, scholars, and other stakeholders for, at best, not prioritizing access and at worst, inhibiting access to medical products such as medicine, vaccines, and diagnostic technology, such as GeneXpert (Coriat, Orsi, & d'Almeida, 2006). The first finding pertaining to intellectual property is that Cepheid reported relying on a combination of patents, trade secrets, copyrights, and non-disclosure agreement, and licenses in a financial report to "maintain and develop [their] competitive position" (Cepheid, 2015). Intellectual property protections for a tool like GeneXpert are complex and numerous. For example, GeneXpert has 32 *known* patent families, 7 of which are assigned to Cepheid meaning that Cepheid now has ownership of the patented IP (MSF, 2017). Patent families are a "collection of patent applications covering the same or similar technical content" (EPO, n.d.). Additionally, I found 80 patent applications that were assigned to Cepheid in the patent public search database. It is not possible to identify which of these patents are applicable to GeneXpert. While patents are a part of the IP protections for GeneXpert, manufacturing know-how and trade secrets are generally more important for diagnostics (Gotham et al., 2021). This is important for transparency because know-how and trade secrets are considered "private IP" and so unlike patents, which are "public IP," there are no requirements to file with a government patent office (FIND, 2022b).

Additionally, another finding related to IP is that Danaher and Cepheid both noted in their financial statements the importance of protecting their IP and that pressures to submit to, or support, TRIPS flexibilities are not in the best interest of either company. For example, Cepheid reported in a 2015 financial report if they "fail to maintain and protect [their] intellectual

property rights, [their] competitors could use [their] technology to develop competing products and [their] business will suffer" (Cepheid, 2015). Danaher notes a similar sentiment and bemoans the risk of inadequately protecting intellectual property which includes "becoming subject to compulsory licensing." Compulsory licensing is considered a risk that could "adversely impact [their] business and financial statements" (Danaher, 2021).

Further, there are flexibilities in the TRIPS agreement for intellectual property rights for products of public health importance, such as diagnostics, but the flexibilities vary in clarity. For example, articles 30 and 31 provide flexibilities to patents through compulsory licensing particularly for public health tools (WTO, 1994). Compulsory licensing only applies to patents and is outlined quite clearly. Whereas flexibilities for private IP such as trade secrets and know-how are more complicated. For example, IP flexibilities for know-how work through technological transfer and the TRIPS articles provide little information on how to decrease access barriers to technological know-how. The TRIPS flexibilities for know-how are outlined in Article 66, section 66.2 which states that "developed country Members shall provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to least-developed country Members in order to enable them to create a sound and viable technological base" (WTO, 1994). This means that "developed" countries should incentivize voluntary transfer of know-how to "least developed" countries. The Doha Declaration on the TRIPS Agreement and Public Health was adopted after the TRIPS agreement in 2001. It was meant to provide more clarity for IP flexibilities for public health tools. Still, for technological transfer it did not provide more information than was in the original agreement and just reaffirmed the original article (WTO, 2001).

GeneXpert IP protections are a determinant of GeneXpert distribution because of the impact on the price, limitations on local manufacturing, and the complexity of providing flexibilities for "private IP" like trade secrets.

Determinants Beyond Price: Supply delays, COVID-19, weak health systems

Some determinants beyond price that I found were supply delays or constraints for cartridges of GeneXpert, the impact of external factors such as COVID-19, and limited investment in health systems beyond the investment in technology of GeneXpert. Distribution of GeneXpert implies the availability of the tool in a specific facility/area but I don't think this is the best proxy indicator for use of the tool due to the challenges some health systems have with continuing to afford the cartridges once the machine is installed within the health system. This has led to limited supply of the cartridges in some LMICs.

In recent years, external factors such as COVID-19 impacted the market, leading to supply constraints for LMICs with a high TB and COVID-19 burden. In addition to TB diagnosis, GeneXpert can also diagnose COVID-19. However, during the pandemic, countries with a high TB burden who procured the GeneXpert machine with concessional pricing before COVID-19, could not utilize the Xpert machines' capability to diagnose COVID-19 because they did not have a supply of cartridges for COVID-19 diagnosis (Lewis & Martell, 2021). Initially, Cepheid did not have enough supply of COVID-19 cartridges to meet the high demand. Wealthier countries, which could afford the market price, were then prioritized for the limited cartridge supply over countries eligible for the concessional price (Lewis & Martell, 2021).

Additionally, during the pandemic, supply delays occurred for TB diagnostic cartridges in high-burden countries. For example, in the past year, supplies were delayed to these countries for nearly six months (MSF, 2022; Stop TB Partnership, 2022). Some of the delays were due to

unavoidable complications because of COVID; however, MSF highlighted that this is an example of the problems with relying on just one manufacturer for such an important test for multiple diseases (MSF, 2022). This is significant because underutilization of GeneXpert as a multi-disease diagnostic tool due to challenges such as limited cartridge supply and health system infrastructure weaknesses was also a problem pre-pandemic. An overall finding for this section is that health system infrastructure weaknesses and consistent supply of cartridges continue to be issues to GeneXpert utilization even when GeneXpert machines are technically available in a health system.

Chapter IV: Discussion

The Distribution of GeneXpert: An issue of equity

When exploring the global distribution of a public health good, such as a diagnostic tool like GeneXpert, a key consideration is whether or not the distribution is equitable. Determining whether the distribution of GeneXpert is inequitable can be useful in determining what questions need to be addressed, through policy, to resolve the inequity. Equity is an ideal often proclaimed in the public and global health field. But to actually determine whether something is equitable requires ethical justification (Asada, 2005). In this discussion, I define inequity as an inequality that is unjust or without moral justification.

I have found that there is data on the distribution and access of rapid molecular tests more broadly but there is no publicly available data on the global distribution of GeneXpert specifically. Although the precise distribution of GeneXpert is impossible to determine, our understanding of the global distribution of rapid molecular tests (including GeneXpert) is sufficient to make some observations about equity. The distribution of GeneXpert has several

components that are arguably inequitable including the cause of the current distribution, the impact of the distribution, and that the current distribution is preventable.

First, there is an unfair disparity in the availability of GeneXpert and GeneXpert cartridges between low-and-middle income countries, which have the most burden of TB, and high-income countries, which notably have lower TB burdens, overall. This disparity is inequitable because some factors contributing to the inequitable distribution are due to unfair systems. It is clear that GeneXpert and rapid diagnostic tool access is *unequal* globally. One factor that can make an inequality unjust, and thereby inequitable, is the cause of the inequality (Hunter and Dawson, 2011). In the case of GeneXpert distribution, intellectual property protections are a key determinant. Pogge (2005) argues that the TRIPS agreement is markedly unjust because of the avoidable morbidity and mortality that it causes. The TRIPS Agreement has flexibilities for public health tools such as diagnostics; however this has not been shown to improve access (Tripathi, 2021). Therefore, the distribution of GeneXpert is partly caused by an unfair system that contributes to the inequality of GeneXpert availability between countries. Intellectual property protections, such as those described above, make it very difficult for LMICs to access medical tools.

Additionally, another aspect of the distribution of GeneXpert that is not equitable is that limited access to GeneXpert because of its distribution can cause needless suffering in a variety of ways such as delayed or inaccurate diagnosis, which could have dire consequences, for the individual and the perpetuation of TB transmission. Additionally, those in most need and in the most heavily burden settings are the least likely to have a GeneXpert, including Xpert cartridges, available. TB already disproportionately impacts the most impoverished and marginalized and so the current distribution of GeneXpert means there is differential access to a tool for TB diagnosis

depending on someone's power, resources, access to a certain quality of care, and location. The factors that contribute to differential access are widely believed to reflect unfair or unjust conditions, which is another reason why this difference in access is not ethical.

Finally, another inequitable aspect of the distribution of GeneXpert is that many of the determinants limiting GeneXpert distribution are preventable and that those who establish trade rules and those who might have the authority to re-shape some of the determinants described above have obligations to prevent the current distribution. Protecting IP over widespread access or increasing the price of GeneXpert cartridges are technically preventable. IP is protected over widespread access because of the economic incentives for firms to do so. Moreover, some argue that the cost of the cartridges could be lowered based on a COGS analysis (MSF, 2019;Gotham et al., 2021). Both total IP protection and price are not necessarily unchangeable but supported by the economic system. Singer's theory of preference utilitarianism is an ethical theory to situate this issue. The core idea in Singer's theory is that if we can prevent something bad without sacrificing something of equal moral importance, than we are *morally obliged* to act (Stapleton et al., 2014). There is consistent evidence that the current system of distribution of GeneXpert, even with concessional pricing agreements, is not ensuring that all who need access to GeneXpert for a TB diagnosis actually have access. The consequences of not having access to this type of test can result in a domino effect, including where a lack of or a delayed diagnosis can limit the likelihood that a person receives appropriate treatment which would constitute "something bad." There are meaningful ethical obligations on those who might have the authority to re-shape some of the determinants, even though it is difficult to determine who exactly should own these obligations.

Power, Pricing, and Intellectual Property

GeneXpert pricing and distribution is centered in the middle of geopolitical and economic power dynamics. So what does this mean for determining a price for a diagnosis tool for a disease that largely impacts the world's most impoverished? GeneXpert is arguably priced too high—even with concessional pricing—to ensure that countries can afford it and continue to afford the cartridges once the machine is installed. Pricing is acting as an obstacle to realizing the full public health value of the GeneXpert technology. However, pricing is just one aspect of ensuring equitable access to GeneXpert. Pricing is complex and is decided based on various components including cost of goods, to maximize profit, and IP rights (MSF, 2019). Intellectual property protections provide a framing in which the influence of power on pricing of medical products, such as GeneXpert, is more clear.

IP protections limits who and where a product can be manufactured and distributed. IP protection also gives the company more discretion in setting the price since there are no other manufacturers competing for the price, which can make it easier for manufacturers to keep the price more expensive and lead to the price being too high for some countries. Cepheid is also the only provider of the different components of a GeneXpert machine and maintenance services for Xpert. Advocacy organizations such as MSF Access Project have argued that Cepheid monopolizes GeneXpert (MSF,2020). Monopolies are a "market structure where a single seller or producer is the sole supplier of a good or service in a market" (Hayes, 2022). According to this definition, it would seem that Cepheid's control of GeneXpert fits this description. Monopolies limit competition. Competition would lower the price and presumably increase distribution or not act as an obstacle to distribution. So, it is unfair that Cepheid is prioritizing its interests in preserving monopoly status over the public health needs of millions of people.

IP rights also factor into pricing. A tension exists between IP and equitable access to public health goods. IP is assumed to promote more innovation for new public health tools by guaranteeing a return on investment on research and development. However, IP also serves as a barrier to access to public health products. Based on my observations, there seems to be more scholarship and knowledge on the impact of IP on access to pharmaceuticals than on diagnostics. Heijden (2017) also argues that there is a need for more exploration of how IP impacts access to diagnostics and that there is limited understanding compared to other medical products. Utilizing what is known on IP and access to medicine could provide some insight into some of the challenges to IP and diagnostics. The TRIPS agreement was signed in 1994 and was a major shift in how IP was regulated and lead to a stricter patent regime globally that shifted the power to HIC countries (Coriat, Orsi, & d'Almeida, 2006). Tenni et al. (2022) found that the stronger pharmaceutical monopolies created by TRIPS and IP rules were associated with "increased drug prices, delayed availability, and increased costs to consumers and governments" and that the use of TRIPS flexibilities to improve access to medicine has been limited.

Lastly, power shapes IP regimes, resulting in these regimes tending to protect companies to keep prices high. A FIND Policy Brief (2022b) highlights that most know-how for diagnostics are "currently based in a small subset of G20 countries" and "is a major driver of global diagnostics inequity." For TB in particular, this is a problem throughout TB programming. There is an overall lack of solidarity in "addressing the complex sociopolitical contexts of technological development and implementation" in TB programs, overall (Komparic et al., 2018). HIC and corporate resistance to TRIPS reform in the face of public health crises is a continuation of such behavior. For example, low and middle income countries have pushed for TRIPS reform and World Trade Organization changes, especially during the COVID-19

pandemic. However, high income countries and companies are largely against any reform (Tripathi, 2021; Meijer, 2021). The intellectual property regime— the policies and institutions that govern IP and trade— and the processes that created them are largely biased in the interest of wealthy governments and corporations. Coriat, Orsi, & d'Almeida (2006) argued that the TRIPS agreement shifted IP to prioritize the private interests and the home countries of firms over the public interest of access. The current context of international trade and intellectual property protection mechanisms reflect historically unequal power dynamics. Neoliberal norms maintain these dynamics particularly through the insistence on the protection of intellectual property even at the expense of access to public health tools (Benatar, Upshur, & Gill, 2021)

GeneXpert distribution and access reflects a larger issue in the field of global health where IP for public health products, such as diagnostic tools, are assigned to companies and other actors in wealthier countries, such as the US, and those products are most needed in LMICs. IP protections facilitate a situation where Cepheid is the only manufacturer of this specific type of technology and the only provider of system maintenance, which is regularly required. While intellectual property protection may play a role in incentivizing innovation for medical products, there must be a balance to protecting IP and ensuring access to medical products, like GeneXpert.

Do we need to think about manufacturing diagnostics differently?

Given the highly complex nature and interconnectedness of global politics, intellectual property regimes, corporate power and pricing complexity, there is no easy way to solve GeneXpert access. Solutions to ensure equity of distribution of diagnostic tools such as GeneXpert are not just about one aspect of distribution but must challenge the systemic economic and political norms that uphold them. This is a daunting goal but we could start by

rethinking equitable distribution of diagnostic tools. For example, Boeheme Hannay, and Pai (2021) argue for diagnostics to become a global good. They argue that we must diversify manufacturing rather than relying on the current "trickle down" model where "a small number of high income countries develop a product and it trickles down years later to low-middle income countries," who are often in the most need. Diagnostic companies are not incentivized to support IP reform and lower the price of their products. Both Cepheid and Danaher's financial reports explicitly say so (Cepheid, 2015; Danaher, 2021). So I do not think we can rely solely on private firms to adequately consider equitable access of their product nor can we rely on the market alone to ensure access, given that GeneXpert is a diagnostic tool for TB, a disease that largely burdens the most impoverished.

Moreover, distribution is not the only problem for GeneXpert access. Distribution, or possession of GeneXpert, does not mean that the machine will be utilized to its full potential. Reasons for underutilization are due to some countries inability to afford a consistent supply of cartridges and also, the need for health systems strengthening. The development and rollout of GeneXpert was largely due to the $252 million in public investments; yet, many do not have access to this product because of the cost (Gotham et al., 2021). While public investments were crucial in financing the development of GeneXpert, the public sector still struggles to secure fair pricing and maintenance agreements that would improve equitable access to the tool (Gotham et al., 2021). Additionally, while more fair public sector pricing is needed, many have argued for concessional pricing in the private sector of high TB burden countries, given the extent to which people with TB seek care in private facilities (Albert et al., 2016; Ponnudurai et al., 2018). It is reasonable to presume that ensuring that GeneXpert benefits the public interest, subsidized pricing is available where the public seeks care, including private healthcare facilities.

Lastly, more funding is needed for the implementation of technology like GeneXpert into under-resourced health systems that strengthen the health system where the tool will be used. Monedero-Recuero (2018) argues that without health systems strengthening, GeneXpert implementation and the ideal positive impact will not be achieved. Similarly, Williams et al. (2022) argue that implementation barriers associated with underutilization such as modular failures, poor power supply, inefficient sample transport, weak data management, and inadequate human resources must be addressed. Not equitably distributing GeneXpert and strengthening health systems so that it is utilized to its full potential—particularly in areas with a high-burden of drug-resistant TB— may have the long-term effect of limiting the public health value of the tool.

Chapter V. Limitations

A limitation to this case study was that data on pricing, intellectual property, and distribution was elusive and not accessible to me. For example, to determine market price, I had to look through multiple sources for one piece of information and compile information from multiple sources. Market pricing also varies based on country and health facility which also made it difficult to determine the commercial price. Also, Cepheid does not provide commercial pricing on their website. Additionally, intellectual property protections such as trade secrets and other private IP are not publicly available. So it is difficult to grasp what trade secrets look like for GeneXpert other than knowing that Cepheid has trade secrets for this product. Moreover, the distribution of GeneXpert is largely based on proxy data of the proportion of people diagnosed with rapid molecular tests globally. Specifics on the percentage diagnosed with GeneXpert were left to country level studies. While this observation on the elusiveness of the data was a part of

my findings, this could easily have biased my interpretations since I had a limited view of distribution and what is happening on the ground.

Further, given the difficulty in finding information, another limitation is that I did not include expert interviews other than brief personal communication in my data collection. More in-depth interviews particularly with experts with intimate knowledge of GeneXpert could have provided more insight into some of these opaque processes such as business practices and IP. Lastly, the determinants described in this case study are not exhaustive. Global medical product distribution and access is highly complex, so many other determinants could be described and analyzed in future papers.

While this case study does have its limitations, the findings in this paper provide some insight into the highly complicated nature of diagnostic tool distribution and more broadly public health tool access. The elusiveness of the data, which is both a finding and a limitation, is indicative of some of the challenges in both researching public health product procurement and distribution globally and improving efforts to ensure equitable access.

Chapter VI. Conclusion

In this case study, I have described some of the determinants of GeneXpert distribution including price and cost determinants, intellectual property protections, and other determinants including supply delays, COVID-19, and health system weaknesses.

While some broad conclusions can be made about GeneXpert distribution including that GeneXpert are not widely available in all high-burden countries and in recent years, there has been an increase in the presence of GeneXpert in public sectors globally, the specifics of global distribution of GeneXpert is unknown. A key takeaway from this case study is the elusiveness of the data related to GeneXpert procurement and distribution. The global distribution of

GeneXpert is unavailable but there is data on the use of rapid molecular tests more broadly. However, data on rapid molecular tests still allow for discussions of equity. The distribution of GeneXpert has many inequitable aspects because of the cause, impact, and that the current distribution is preventable, which calls into question the obligations of justice of some organizational entities or individuals to address this inequity.

Despite concessional pricing agreements, price is still prohibitive for GeneXpert distribution in high TB burden countries. Price, however, is not easily fixable. One aspect of pricing that is highly complicated are intellectual property protections. For diagnostic tools in particular, little is understood about the specific impacts of IP on diagnostic access. IP protections are upheld even at the determinant of access to public health tools like GeneXpert because of current norms, incentives, and power.

Lastly, determinants beyond price include supply delays, COVID-19, and the need for health systems strengthening. Many countries have GeneXpert machines installed within a health system but cannot continue to afford the cartridges needed for diagnosis, especially through domestic funding alone. Additionally, many health systems still require strengthening to continue to use GeneXpert. While GeneXpert distribution does play a role in availability and access, it not the only factor.

Given the murkiness of GeneXpert distribution, we need to think about manufacturing differently. Rethinking manufacturing includes efforts to finance and strengthen health systems adequately beyond just the installment of a GeneXpert machine and rethinking how we think about diagnostic tools as potentially more of a global good than a private commodity. GeneXpert distribution and access is a component of the greater global health challenge of access to public health products. Access to medical products such as diagnostics is highly

complex and many of the drivers of distribution are due to opaque processes such as business practices and IP protections. Moving forward, rethinking diagnostics as a global good may mean ensuring more transparency for these processes so all may have access to a diagnosis.

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Appendix A

Current Diagnostic Tools for TB

Type of Test	Examples of Test	WHO Indications	Advantages	Limitations
Latent TB (LTBI) Diagnosis (note: there is no "gold standard" for diagnosing LTBI)				
Blood Test	• Mantoux tuberculin skin test (TST) • Immune response by interferon-gamma release assay (IGRA)	Use to diagnose latent TB infection. Do not use to diagnose active TB In LMICs, TST recommended over IGRA	**TST** • **Widely used** • Not expensive • No lab required **IGRA** • Single patient visit • Faster than TST (24-48hr) • Can detect LTBI among people with BCG vaccine	• Additional tests are required to confirm TB disease • Trained staff required **TST** • Requires two visits to health facility • Refrigerator needed • Poor sensitivity in certain groups **IGRA** • Expensive, not cost effective (compared to TST) • Lab required
Screening Methods (Screening is not a diagnosis but is used to check for signs of TB in people who may be at risk and determine who should be tested)				
Symptom Screen (also called empiric therapy)	N/A	Screening method. Not recommended as diagnostic method if other diagnostic tools available	• Low cost • Low technology • Rapid • Non-invasive	• Misdiagnosis possible • Persons must adhere to certain signs and symptoms to ensure diagnosis • Only can be used for pulmonary TB
Chest Xray	N/A	Used to triage and screen for pulmonary TB. Useful when TB cannot be confirmed bacteriologically	• Inexpensive • Fast • Widely available in urban areas • Highly sensitive	• Only for pulmonary TB • Requires trained workers and special equipment • Follow up tests required • Limits to diagnosing TB in people with HIV • Cannot detect drug resistance • Adequate power needed • Limited availability in LMICs, especially in rural areas
Bacteriological Confirmation (can not detect drug susceptibility)				
Microscopy	N/A	Used to diagnose and monitor treatment of active TB	• Simple • Inexpensive • Suitable for different levels of labs • Low risk of lab acquired TB infection • Widely available	• Relatively insensitive, especially for extrapulmonary TB, children, and people living with HIV • Difficult to ensure quality assurance • Cannot distinguish TB Mycobacterium from other non-TB mycobacterium or drug-resistant and drug susceptible strains • Relies on sputum (difficult for people to provide)
Bacteriological Confirmation (can detect drug susceptibility)				

Rapid Molecular Test	**GeneXpert** (Cepheid, USA) • Xpert MTB/RIF • Xpert MTB/ RIF Ultra **Other rapid molecular tests:** Line Probe Assay (LPA) Loop-mediated isothermal amplification (LAMP)	WHO TB standard 6: all patients with signs of pulmonary TB (including children and people with HIV) should have Xpert MTB/RIF Ultra assay as their *initial* diagnostic test.	• Fast (<2hrs) • Simple • Can diagnose multiple diseases • Highly sensitive and can detect resistant TB strains • Detects TB among people with HIV • Little training needed • Low biosafety requirements • Detects both pulmonary and extrapulmonary TB	• Expensive • Requires constant electrical supply • Shelf life of cartridge is 18 mo. • Requires annual recalibration • Requires lab infrastructure (incl. laptop/computer) • Does not eliminate need for conventional microscopy and culture to monitor progress of treatment and detect resistance to drugs other than rifampicin
Urine Test	Lateral flow urine Lipoarabino-mannan assay (LF-LAM) antigen	Recommended by WHO to assist in diagnosis of TB among people with HIV who are seriously ill or have a low CD4 count (Xpert is still initial test) (WHO TB Standard 8)	• Easy sample to obtain and simple test • Fast (25 min) • No lab • Inexpensive (2 USD per test)	• Only for detecting TB in patients with HIV, who are very sick, • Cannot detect drug susceptibility • Cannot differentiate mycobacterium TB from other mycobacterium • Negative test has to be followed up with another test

Culture	**Solid and Liquid**	Detect resistance to first and second-line drug resistance
		
		Used to monitor treatment (recommended by WHO, take culture samples monthly)
		
		The reference standard for TB diagnosis
			• Most definitive drug-resistant and drug-susceptible TB diagnosis
			• Liquid
			  • More sensitivity than solid culture
			  • Faster than solid
			• Diagnoses more cases than microscopy (30-50% increase)
				• Liquid culture (max 10 days)
				• Solid culture 28-42 days
				• Require certain lab infrastructure and electricity, biosafety precautions, technical complexity
				• Liquid drug sensitivity testing fails to detect some clinically relevant resistant strains
				• Often too late to inform treatment decisions
				• Potential to get lost in transport
				• Need reagents to run test

Sources: TAG, 2017; WHO, 2015; WHO, 2018