Analysis of the Gap in PCR Monitoring Availability for Patients with Chronic Myeloid Leukemia in 60 Low- and Middle-Income Countries

Seth Rowley  
University of Washington

Patricia Garcia-Gonzalez  
The Max Foundation

Jerald P Radich  
Fred Hutchinson Cancer Research Center

Irina Usherenko  
The Max Foundation

Joseph B Babigumira (✉ jobabigumira@gmail.com)  
University of Washington  https://orcid.org/0000-0003-3834-7141

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Abstract

**Purpose:** To estimate the resource gap in the polymerase chain reaction (PCR) monitoring for patients with chronic myeloid leukemia (CML) in low- and middle-income countries (LMICs).

**Methods:** We developed a model of demand and supply of PCR monitoring of CML patients in 60 LMICs. PCR testing was assumed to use Cepheid's GeneXpert® IV system. We included costs of GeneXpert® instruments, uninterrupted power supplies, warranties, calibration kits, test cartridges, and shipping. We calculated the country-specific monetary gap in PCR monitoring, stratified by country priority defined as the availability of tyrosine kinase inhibitors (TKIs) through The Max Foundation initiatives.

**Results:** The five-year gap in PCR monitoring was $29.1 million across all countries, 22% ($6.4 million) in countries with all five TKIs available, 20% ($5.7 million) in countries with four TKIs available, 50% ($14.5 million) in countries with three TKIs available, 8% ($2.2 million) in countries with two TKIs available, and 1% ($0.3 million) in countries with one TKI available. The gap was highest in South Asia (52%; $15.1 million) and lowest in Latin America (6%; $1.9 million). Excluding labor costs, the bulk of the resource needs (86%; $25.2 million) were for procurement of BCR-ABL cartridges.

**Conclusion:** Removing the five-year gap in PCR monitoring capacity for CML in LMICs will require the mobilization of significant resources and will likely lead to better treatment outcomes and reduced treatment costs through optimization of treatment, discontinuation of therapy in appropriate patients, and facilitation of clinical research. Development of streamlined monitoring guidelines for resource-limited countries should be considered.

Background

The advent of tyrosine kinase inhibitors (TKIs) has transformed chronic myeloid leukemia (CML) from a near universally fatal disease into a chronic condition. There are now five TKIs approved for use in newly diagnosed CML in the USA, the pioneering TKI imatinib, and the “second generation” TKIs dasatinib, nilotinib, ponatinib, and bosutinib. All have similarly impressive results and CML patients now experience life expectancy near that of the age matched general population[1].

CML is caused by the genetic juxtaposition of the BCR gene from chromosome 22 with the tyrosine kinase domains of the ABL gene from chromosome 9. This unique gene fusion creates the fusion BCR-ABL1 mRNA, which is the target for polymerase chain reaction (PCR) diagnostic and monitoring assays. The protein product of BCR-ABL translocation drives the pathogenesis of CML and is the target of the TKIs.

Peripheral blood can be used for BCR-ABL monitoring, rather than bone marrow, and guidelines of the European Leukemia Network (ELN) and the National Cancer Care Network (NCCN) include frequent monitoring as a way to track response. In general, both guidelines call for every three-month peripheral
blood PCR testing for BCR-ABL1[2, 3]. Treatment milestones, including changing TKIs for resistance, or discontinuation of TKIs after a durable deep response, are based on the BCR-ABL1 monitoring.

Conventional PCR testing is complicated and labor intensive, demanding trained personnel, many chemicals, and expensive equipment. Quality control is essential to obtain and maintain proper sensitivity and specificity of the assay, and this requires technical and methodological expertise and training. The GeneXpert system from Cepheid is a cartridge-based system that requires minimal hands on sample preparation and is ideal for point of care, real-time assays[4]. The system has a multiple modular design that can run cartridges for multiple diseases including infections and cancer. The assay for BCR-ABL1 was developed in collaboration with U.S. academic centers and is now used in many centers in the U.S. and Europe for CML monitoring in clinical trials and community settings, and is FDA approved in the U.S. The system is widely used in low- and middle-income countries (LMICs) for infectious diseases (e.g., TB, HIV) and utilization is increasing in a handful of oncology applications including BCR-ABL1. The Cepheid platform has many desired features in the LMIC setting, including ease and efficiency of use (less technical training needed, with flexible use between batches or single assays), easy shipping solutions (cartridges rather than many different reagent supplies), high reproducibility, and reliable precision and accuracy.

To bring TKIs to LMICs, The Max Foundation partnered with Novartis to launch the Glivec® International Patient Assistance Program (GIPAP), an innovative access model that made Novartis’ breakthrough oral TKI therapy, Glivec® (imatinib), available to patients who meet program criteria in selected LMICs around the world[5]. The Max Foundation administered the program, working closely with a global network of more than 1,500 trained physicians in 80 LMICs[5].

In the early years of the program, BCR-ABL1 testing was largely performed by shipping blood to outside centers, a procedure that was costly, time-consuming, and inherently unscalable. Recognizing the critically important role that point-of-care systems play in the diagnosis and monitoring of patients in resource poor settings, The Max Foundation next developed a collaboration with Cepheid to increase access to instruments and tests in more than 60 LMICs. Cepheid provided the GeneXpert® System and Xpert® BCR-ABL Monitor Assays through The Max Foundation to public sector end users at a preferential price in order to decrease barriers to access due to cost. The dramatic increases in monitoring meant disease resistance could be detected, so that TKI options to treat resistance could be initiated as needed. The Max Foundation began partnering with four other leading pharmaceutical companies to bridge access to all five TKIs available on the market for the treatment of CML today. As a result of these efforts, patients in thirty of the world’s lowest income economies have access to all available treatment options through The Max Foundation's Max Access Solutions.

Recently, GIPAP evolved into a new partnership model between Novartis and The Max Foundation, CMLPath to Care™. CMLPath to Care™ differs from the GIPAP program in that The Max Foundation assumes from Novartis the responsibility for delivering treatment to patients. The Max Foundation, under
the umbrella of Max Access Solutions (MAS), manages the entire supply chain, while strengthening interactions with local stakeholders and providing hands-on, local patient support[6].

The establishment of collaborations with developers of all TKIs for the treatment of CML enables The Max Foundation to respond to health care providers’ requests for second and third line treatment in many of the lowest income economies in the world. Yet, despite the preferential pricing available for Cepheid products, access to PCR remains one of the most pervasive barriers to achieving optimal clinical outcomes. Without adequate monitoring, physicians are unable to make timely and appropriate clinical decisions that help patients with CML achieve a deep response to available treatments. This analysis was performed to assess the resources needed to close the five-year gap in PCR monitoring capacity for CML patients in countries where The Max Foundation currently operates.

**Methods**

**Analytic overview**

We developed a Microsoft Excel-based demand, supply, and forecast model for the monitoring of CML patients in a selected group of countries covered by access initiatives and using preferential prices available through The Max Foundation for the GeneXpert® system. The gap in PCR capacity for monitoring was estimated as the difference between current demand and current supply over a five-year time horizon from 2017 to 2021. We estimated effective demand as the number of patients that qualify for access to imatinib treatment in each country. This is differentiated from actual demand based on the burden of CML in each country. We estimated supply as the number of patients that are able to access at least 3.5 PCR tests per year, in line with monitoring recommendations. This figure includes off-label use of the Xpert® cartridges for diagnostic purposes, as we are aware that physicians in resource poor settings may utilize the cartridges to confirm presence of BCR-ABL, thereby meeting medical eligibility requirements for treatment access. Countries were categorized for the analysis by availability of one or more of the five TKIs to maximize the potential utility of PCR monitoring results by physicians. Countries were excluded from the analysis if they were known to have appropriate access to PCR and if they did not have preferential pricing for GeneXpert PCR through Cepheid.

**Demand Estimation**

We estimated future demand for PCR monitoring based on historical patient data from The Max Foundation. Of the 60 countries covered by Max Access Solutions and The Max Foundation’s preferential pricing agreement with Cepheid, 56 had 12 years of historical data, four countries had 11 years of historical data, two countries had 10 years of historical data, three countries had 8 years of historical data, one country had 7 years of historical data, and one country had 4 years of historical data. For countries with non-linear historical trends, the earlier, nonlinear years were truncated from the analysis. Estimates of future demand were calculated using a simple linear ordinary-least-squares regression.
Data from The Max Foundation demonstrate that the introduction of GeneXpert® affects the demand for CML treatment, and consequently, the demand for PCR monitoring in a country. We modeled that the rate of growth doubled (2x) after introduction of GeneXpert®, e.g., a country that historically gained 10 additional patients per year before GeneXpert® introduction, was modeled, after introduction, as gaining 20 additional patients per year.

The quantity of required GeneXpert® instruments was based on a number of factors: current demand, anticipated demand, current number of GeneXpert® instruments in place, geographic demand distribution of patients and testing facilities, and expert opinion in the form of NCCN and ELN guidelines.

**Costs**

We estimated the following PCR monitoring-related costs in year 1: (1) GeneXpert® instruments, (2) uninterrupted power supplies (UPS), (3) warranties, (4) calibration kits, (5) test cartridges, and (6) shipping for instruments and test cartridges. During years two to five, the following PCR monitoring-related costs were included: (1) calibration kits, (2) test cartridges, and (3) shipping costs for cartridges. Costs did not include labor to perform the assay. Costs were estimated in 2017 $US.

Our analysis differentiated between fixed costs in the first year (GeneXpert® instruments, UPSs, and instrument warranty) and variable costs (cartridges, shipping, and calibration). Costs for the instruments, warranty, calibration kits, and UPSs, were established by contract (see Table 1). Shipping costs were based on per-country historical shipping data when available and based on a global average when unavailable. Calibration kits are required every 2,000 tests, or once per year, whichever occurs first. Instruments have a factory warranty of two years; additional warranty costs are included in the model for years three through five.

**Credibility Intervals**

We constructed credibility intervals for the mean total five-year gap cost for each country by iteratively drawing single values from a normal distribution for each component cost element (e.g. GeneXpert® cartridges), calculating the resulting mean of many draws, and then summing each component average into an overall cost for each country for each year. The means of the normal distributions from which we drew were set equal to the deterministic cost values. The upper and lower 95% intervals were set to ± 50% of the means. The presented estimates were derived from 1,000 iterations.

**Results**

The total five-year gap in PCR monitoring capacity for each country, categorized by TKI access, is presented in Table 2. Over the five-year period, the estimated gap in PCR monitoring capacity was $29,143,083 across all countries covered by access initiatives. Over the five-year period, due to the combination of country-specific trends and anticipated patient increases due to improved access to PCR testing, the patient population was estimated to grow from 26,915 patients to 30,071 patients at year-end 2021.
The distribution of the total PCR monitoring capacity gap by TKI access level (Table 3) was as follows: 22% ($6,438,176) in countries with all five TKIs, 20% ($5,723,011) in countries with four TKIs, 50% ($14,493,223) in countries with three TKIs, 8% ($2,227,083) in countries with two TKIs, and 1% ($261,590) in countries with one TKI.

In those countries where all five TKIs are currently available through The Max Foundation programs, the five-year gap ranged from $31,681 in Sierra Leone to $1,561,298 in Nepal. In the countries with four TKIs available, the gap ranged from $29,515 in Central Africa Republic to $1,363,279 in Sudan. In the countries with three TKIs available, the gap ranged from $31,144 in Seychelles to $13,238,674 in India. In the countries with two TKIs available, the gap ranged from $35,980 in The Bahamas to $1,422,762 in Vietnam. In the countries with a single TKI available through Max programs, the gap ranged from $36,238 in Ecuador to $68,943 in Gabon.

The distribution of the total PCR monitoring capacity gap by region was as follows (Table 3): 52% ($15,084,618) in South Asia, 25% ($7,284,210) in Africa/Middle East, 10% ($2,954,959) in Europe/Central Asia, 7% ($1,938,714) in Asia Pacific, and 6% ($1,880,582) in Latin America. India alone accounted for 45% ($13,238,674) of the total gap.

The distribution of the total PCR monitoring capacity gap by resource was as follows: 86% ($25,203,261) for cartridges, 7% ($2,014,202) for shipping, 3% ($1,020,000) for GeneXpert® machines, 2% ($522,000) for warranties, 1% ($336,820) for calibration kits, and 0.2% ($46,800) for UPSs (Fig. 1).

Across The Max Foundation's countries in scope, the negotiated purchase agreements with Cepheid result in a nominal cumulative cost reduction of $1,246,667 as compared with GeneXpert IV machine market pricing levels, and additional cost reduction of $30,747,979 for GeneXpert cartridges, as compared with average market prices.

**Discussion**

We estimated the gap in PCR monitoring capacity for CML patients in countries covered by access initiatives available through The Max Foundation. Over a five-year period, the total gap in PCR monitoring capacity amounts to approximately $30 million, including instrument and cartridge subsidies, and $61 million with no subsidies. This estimate corresponds to the cost of monitoring patients with CML every three months over a five-year period, categorized by access to TKIs. Approximately one-fifth of the total gap in PCR monitoring capacity is in countries with access to all five TKIs through the Max Access Solutions current portfolio. One-third of the gap is in countries with access to four out of five TKIs.

There was substantial variability in the country-specific estimates of the gap in PCR monitoring capacity, based largely on the number of patients needing testing. The overall range was from $29,515 in Central African Republic to $13.2 million in India where more than 50% of The Max Foundation's total CML patient population is treated. It would be worthwhile to apply, in addition to a TKI-access-based
prioritization scheme, a prioritization scheme on a country-by-country basis to ensure that countries with GeneXpert® instruments have the resources to procure cartridges in the short- and medium-term.

Given that GeneXpert® cartridges and GeneXpert® instruments are linked resources, it is preferable to take a pragmatic approach and examine access on the basis of potential utility. For example, procuring GeneXpert® instruments to cover all countries would be inefficient, likely resulting in idle instruments due to the lack of resources to procure sufficient amounts of the BCR-ABL assay. In order to remove the PCR monitoring barrier and improve clinical care for patients with CML, it will be essential to adopt a comprehensive plan to engage partners who are vested in strengthening health systems supporting cancer care in LMIC. Drug manufacturers, non-governmental organizations, governments, interest groups, and/or philanthropists may find value in aiding specific countries to improve capacity for PCR. Since the oncology portfolio for the GeneXpert® system includes testing for breast cancer, bladder cancer, and HPV, this multi-sector approach requires collaboration and coordination among agencies and organizations within LMICs to maximize partner investments and avoid the inefficiency of duplicated efforts. Moreover, investment in PCR monitoring in these countries might lead to strengthening health systems so that physicians and specialized treatment centers are able to respond to the needs of a more diverse patient population.

Nearly 90% of the overall gap in PCR monitoring capacity for CML is in the procurement of cartridges. Even at a preferential (below market) cost of $50, single-test cartridges are still costly, particularly in resource-poor settings. Although CML is a relatively rare disease worldwide, a buy-down approach consisting of an up-front, pre-purchase of Xpert® cartridges at higher volumes and reduced prices might further reduce costs. A similar approach was employed by the Bill and Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID), and Unitaid[7, 8].

A limitation of our analysis is that we used estimates of the burden of disease by country based on the number of CML patients enrolled in GIPAP and Max Access Solutions from 2002–2017. This is an underestimate of the true gap based on burden of disease estimates obtained from epidemiological data. It is possible that there might be significant numbers of patients that did not enter these programs because of access limitations due to geography, culture, cost, and other social determinants of health. Future analyses might consider this epidemiological burden, combined with estimates of the gap in diagnostic and treatment (with TKIs) capacity. Ongoing research in this area can also examine to what degree the gap in CML treatment capacity is a subset of a general prevailing gap in health system capacity in infrastructure and personnel that may not be amenable to targeted solutions such as increased access to GeneXpert® machines and supplies.

Removing the gap in PCR monitoring capacity for CML can help improve health outcomes. While quantifying the health outcomes benefit was beyond the scope of this analysis, we expect that removing the gap in PCR diagnostic capacity would increase the demand for CML care. Future studies might consider quantifying the health outcomes benefits in terms of quality-adjusted life-years gained or
disability-adjusted life-years averted using state-transition (Markov) models as in multiple economic evaluations of TKIs[9–13]. NCCN and ELN monitoring guidelines are based on monitoring intervals used in TKI clinical trials, and thus it is not clear what optimal testing intervals actually are. For example, optimal design might include how long a patient has been on a TKI, and the kinetics of their BCR-ABL1 decline, rather than a simplistic q3 month rule. Thus, revisiting guidelines with limited resources in mind may allow for a CML monitoring scheduled tailored to the LMIC setting, optimizing the benefits of frequent monitoring without sacrificing patient outcomes.

Conclusions

By treating thousands of patients since 2001 in eligible countries, The Max Foundation’s access programs have added thousands of life-years thereby improving the quality of life for thousands of people now living with CML. Removing the five-year gap in PCR monitoring capacity for CML in these countries will require the mobilization of significant resources and will likely lead to better treatment outcomes and reduced treatment costs through optimization of treatment, discontinuation of therapy in appropriate patients, and facilitation of clinical research. Clinical outcomes will be further improved by the development of streamlined monitoring guidelines for resource-limited countries.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study, including modeling framework, available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors’ contributions

SR, PG-G, and JBB conceived of the study. SR and JBB designed the study, developed the model, and performed the analysis. SR and JBB developed the first version of the manuscript. SR, PG-G, JR, IU, and JBB further developed the manuscript and contributed important intellectual content to the final version. All authors approved the final version of the manuscript for submission.

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Tables

| Table 1 — Cost parameters | Normal Distribution Values |
|---------------------------|-----------------------------|
| Variable                  | Base Value  | Mean | Lower | Upper |
| Glivec pills (per year)   | 365         | 365  | 182.5 | 547.5 |
| Patient visits per year   | 3.5         | 3.5  | 1.75  | 5.25  |
| GeneXpert®                | $17,000     | $17,000 | $17,000 | $17,000 |
| Uninterrupted Power Supply| $780        | $780 | $390  | $1,170|
| GeneXpert® cartridges     | $50         | $50  | $25   | $75   |
| GeneXpert® warranty (yrs. 3–5) | $2,900 | $2,900 | $1,450 | $4,350 |
| GeneXpert® calibration kit| $450        | $450 | $225  | $675  |
| Annual Patient Growth Rate| 2x          | 2x   | 1x    | 3x    |
### Table 2 — Total 5-year gap

| Country       | Region                    | TKIs | Total 5-year Gap | 95% CI        |
|---------------|---------------------------|------|------------------|---------------|
| Benin         | Africa/Middle East        | 5    | $88,758          | $86,510 to $89,150 |
| Bhutan        | Asia Pacific              | 5    | $49,031          | $48,250 to $49,160 |
| Burkina Faso  | Africa/Middle East        | 5    | $92,401          | $90,060 to $92,870 |
| Cambodia      | Asia Pacific              | 5    | $108,594         | $104,680 to $109,390 |
| East Timor    | Asia Pacific              | 5    | $36,976          | $36,590 to $37,050 |
| Ghana         | Africa/Middle East        | 5    | $200,603         | $192,860 to $201,580 |
| Haiti         | Latin America (LATAM)     | 5    | $50,842          | $50,040 to $51,040 |
| Honduras      | Latin America (LATAM)     | 5    | $284,589         | $273,850 to $286,210 |
| Kyrgyzstan    | Europe/Central Asia       | 5    | $272,886         | $263,750 to $274,330 |
| Madagascar    | Africa/Middle East        | 5    | $98,186          | $95,700 to $98,750 |
| Malawi        | Africa/Middle East        | 5    | $70,677          | $69,080 to $71,040 |
| Moldova       | Europe/Central Asia       | 5    | $162,785         | $157,760 to $163,700 |
| Mongolia      | Europe/Central Asia       | 5    | $123,690         | $119,890 to $124,130 |
| Nepal         | South Asia                | 5    | $1,561,298       | $1,506,040 to $1,571,720 |
| Nicaragua     | Latin America (LATAM)     | 5    | $161,998         | $157,000 to $162,790 |
| Niger         | Africa/Middle East        | 5    | $58,210          | $57,040 to $58,370 |
| Nigeria       | Africa/Middle East        | 5    | $1,173,867       | $1,131,180 to $1,183,210 |
| Papua New Guinea | Asia Pacific             | 5    | $90,538          | $88,360 to $91,170 |
| Republic of Congo | Africa/Middle East     | 5    | $93,545          | $91,130 to $93,990 |
| Rwanda        | Africa/Middle East        | 5    | $102,710         | $98,830 to $103,250 |
| Sierra Leone  | Africa/Middle East        | 5    | $31,681          | $31,490 to $31,830 |
| Tajikistan    | Europe/Central Asia       | 5    | $73,353          | $71,290 to $73,330 |
| Togo          | Africa/Middle East        | 5    | $65,240          | $63,630 to $65,460 |
| Country                   | Region                        | Years | Total 5-year gap | Confidence Interval |  |
|---------------------------|-------------------------------|-------|------------------|---------------------|---|
| Uzbekistan                | Europe/Central Asia           | 5     | $1,385,716       | $1,336,100 to $1,395,670 |
| Cameroon                  | Africa/Middle East            | 4     | $164,268         | $159,150 to $165,090 |
| Central Africa Republic   | Africa/Middle East            | 4     | $29,515          | $29,210 to $29,530  |
| Cote d'Ivoire             | Africa/Middle East            | 4     | $207,340         | $200,920 to $208,790 |
| Democratic Republic Congo | Africa/Middle East            | 4     | $40,534          | $40,100 to $40,700  |
| Ethiopia                  | Africa/Middle East            | 4     | $964,173         | $926,070 to $969,910 |
| Georgia                   | Europe/Central Asia           | 4     | $375,196         | $362,310 to $377,190 |
| Kenya                     | Africa/Middle East            | 4     | $1,102,988       | $1,063,540 to $1,110,340 |
| Mali                      | Africa/Middle East            | 4     | $129,666         | $125,850 to $130,250 |
| Philippines               | Asia Pacific                  | 4     | $177,153         | $172,700 to $178,080 |
| Senegal                   | Africa/Middle East            | 4     | $247,913         | $238,460 to $249,220 |
| Sri Lanka                 | South Asia                    | 4     | $284,646         | $273,970 to $286,080 |
| Sudan                     | Africa/Middle East            | 4     | $1,363,279       | $1,313,480 to $1,371,390 |
| Tanzania                  | Africa/Middle East            | 4     | $197,892         | $191,470 to $199,000 |
| Uganda                    | Africa/Middle East            | 4     | $339,760         | $328,270 to $341,910 |
| Zambia                    | Africa/Middle East            | 4     | $98,688          | $95,950 to $99,020  |
| Bolivia                   | Latin America (LATAM)         | 3     | $302,636         | $293,390 to $304,270 |
| El Salvador               | Latin America (LATAM)         | 3     | $210,811         | $203,830 to $211,630 |
| Guatemala                 | Latin America (LATAM)         | 3     | $339,146         | $327,800 to $341,310 |
| India                     | South Asia                    | 3     | $13,238,674      | $12,849,210 to $13,457,480 |
| Paraguay                  | Latin America (LATAM)         | 3     | $146,770         | $142,670 to $147,700 |
| Seychelles                | Africa/Middle East            | 3     | $31,144          | $30,960 to $31,290  |
| Suriname                  | Latin America (LATAM)         | 3     | $51,723          | $50,890 to $51,920  |
| Country       | Region                      | Notes | 5-year gap ($US) | Range of 5-year gap ($US) |
|---------------|-----------------------------|-------|-----------------|--------------------------|
| Zimbabwe      | Africa/Middle East          | 3     | $172,320        | $166,040 to $173,410     |
| Azerbaijan    | Europe/Central Asia         | 2     | $476,120        | $461,130 to $481,150     |
| Bahamas       | Latin America (LATAM)       | 2     | $35,980         | $35,690 to $36,110       |
| Belarus       | Europe/Central Asia         | 2     | $47,129         | $46,400 to $47,220       |
| Fiji          | Asia Pacific                | 2     | $53,660         | $52,710 to $53,820       |
| Jamaica       | Latin America (LATAM)       | 2     | $112,265        | $109,310 to $112,920     |
| Kazakhstan    | Europe/Central Asia         | 2     | $38,083         | $39,390 to $40,380       |
| Saint Lucia   | Latin America (LATAM)       | 2     | $41,084         | $40,650 to $41,270       |
| Vietnam       | Asia Pacific                | 2     | $1,422,762      | $1,372,220 to $1,435,050 |
| Dominican Republic | Latin America (LATAM) | 1   | $53,976         | $51,800 to $54,040      |
| Ecuador       | Latin America (LATAM)       | 1     | $36,238         | $36,010 to $36,460       |
| Gabon         | Africa/Middle East          | 1     | $68,943         | $67,410 to $69,210       |
| Namibia       | Africa/Middle East          | 1     | $49,909         | $49,130 to $50,110       |
| Peru          | Latin America (LATAM)       | 1     | $52,524         | $51,740 to $52,860       |
Table 3 — Aggregate Costs by Region and TKI Count

| Region               | 5-Year Cost (%) | TKI Access | First Year Fix. | First Year Var. | 5-Year Cost  |
|----------------------|-----------------|------------|-----------------|-----------------|--------------|
| South Asia           | $15,084,618 (52%) | 5          | $540,850        | $909,370        | $6,438,176   |
| Africa/Middle East   | $7,284,210 (25%)  | 4          | $323,610        | $865,947        | $5,723,011   |
| Europe/Central Asia  | $2,954,959 (10%) | 3          | $579,310        | $3,031,829      | $14,493,223  |
| Asia Pacific         | $1,938,714 (7%)  | 2          | $188,510        | $308,242        | $2,227,083   |
| Latin America (LATAM)| $1,880,582 (6%)  | 1          | $161,580        | $32,770         | $261,590     |
| Total                | $29,143,083      | Total      | $1,740,000      | $5,148,158      | $29,143,083  |

Figures
Figure 1

Costs by resource