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Authors

Islam, Md

Shrestha, Ram

Hoch, Jeffrey

et al.

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Estimating the cost-effectiveness of HIV self-testing in the United States using net benefit regression

Md Hafizul Islam, Ph.D.[1], **Ram K. Shrestha, Ph.D.**[1], **Jeffrey S. Hoch, Ph.D.**[2], **Paul G. Farnham, Ph.D.**[1]

[1]Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention;

[2]Division of Health Policy and Management, Department of Public Health Sciences, University of California, Davis.

Abstract

Background: Cost-effectiveness analysis of HIV self-testing using patient-level data from a randomized clinical trial can inform HIV prevention funding decisions. Cost-effectiveness analysis using net benefit regression addresses the sampling uncertainty in the trial data and the variability of policymakers' willingness to pay (WTP).

Methods: We used published data from a 12-month longitudinal randomized clinical trial that enrolled 2665 men who sex with men (MSM) randomly assigned to the self-testing arm (participants receiving self-test kits) and control arm (participants receiving standard-of-care), and the self-testing arm identified 48 additional new HIV cases. We used net benefit regression to investigate the cost-effectiveness of an HIV self-testing intervention, which compared the incremental cost per new HIV diagnosis with policymakers' WTP thresholds. We addressed the uncertainties in estimating the incremental cost and the policymakers' WTP per new diagnosis through the incremental net benefit (INB) regression and cost-effectiveness acceptability curve (CEAC) analyses.

Results: From the healthcare provider's perspective, the INB analysis showed a positive net-benefit of HIV self-testing compared to standard-of-care when policymakers' WTP per new HIV diagnosis was $9,365 (95% CI: $5,700 – $25,500) or higher. The CEAC showed that the probability of HIV self-testing being cost-effective compared to standard-of-care was 58% and >99% at a WTP of $10 000 and $50 000 per new HIV diagnosis, respectively.

Conclusion: The INB and CEAC analyses suggest that HIV self-testing has the potential to be cost-effective for relatively low values of policymakers' WTP.

Corresponding Author: Md Hafizul Islam, Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd. MS E-45, Atlanta, GA. 30329; qla0@cdc.gov; Fax: (404) 639-8642.

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Keywords

HIV self-testing; net benefit regression; willingness-to-pay threshold; cost-effectiveness acceptability curve

Introduction

An estimated 1.2 million people in the United States are currently living with HIV, with 13% of them being unaware of their infection.[1] HIV diagnosis is one of the four pillars under the Ending the HIV Epidemic in the U.S. (EHE) initiative whose goal is to reduce annual HIV infections in the United States by 75% by 2025 and by 90% by 2030.[2] Due to the disruption caused by the COVID-19 pandemic in health care delivery, HIV testing decreased substantially in 2020 compared to 2019, and new HIV diagnosis reported to CDC decreased by 17% in 2020 compared to 2019.[3,4] To recover from the aftermath of the COVID-19 pandemic and enhance support for the EHE initiative, CDC emphasizes collaborative efforts from federal organizations, state and local health departments, community-based organizations, and health care systems to increase access to HIV testing services, including strategies such as self-testing and routine opt-out testing in clinical settings.[4]

Several randomized clinical trials (RCT) in the United States focused on strategies for screening people for potential new HIV diagnosis.[5–7] RCTs of HIV screening strategies have also been reported in studies outside of the United States, including Africa[8–11], Australia[12], UK[13], and China[14–16]. Cost-effectiveness analyses of HIV screening strategies have employed conventional modeling methods, such as decision trees, Markov models, dynamic models, and individual- and population-based models[17–22] while mostly using cohort data as model inputs with a few studies using RCT data to calibrate the model.[22,23] However, net benefit regression[24] can also be employed to conduct cost-effectiveness analyses of HIV screening strategies using person-level data obtained from a RCT.

HIV self-testing provides an opportunity for HIV testing to persons potentially unable to seek clinic- or community-based testing.[25] Studies in the United States have shown that access to HIV self-tests is effective in increasing testing frequency, increasing awareness of HIV infection, and preventing transmission among MSM.[6,7,26,27] In this paper, we use net benefit regression to estimate the cost-effectiveness of HIV self-testing from patient-level data obtained from a CDC sponsored randomized clinical trial, eSTAMP (Evaluation of Rapid HIV Self-Testing among MSM Project).[6,28] Cost-effectiveness analysis using net benefit regression provides additional information compared to a previously published cost-effectiveness analysis of HIV self-testing using data from the eSTAMP study, addressing the sampling uncertainty in the data and the variability in the WTP threshold. Sampling uncertainty in cost and effect estimation can arise from various sources, e.g., inherent randomness, insufficient sample size or human error. On the other hand, a consensus on policymakers' WTP threshold is hard to reach, as the threshold tends to vary widely across countries and with reference to the data sources, e.g., Gross Domestic Product (GDP), opportunity cost, historical or empirical estimates.[29–31] Our goal is to demonstrate how net benefit regression can address the uncertainty in the RCT data and variability in WTP in

estimating the cost-effectiveness of HIV self-testing. Moreover, to our knowledge, this is the first study to apply the net benefit regression technique to estimate the cost-effectiveness of an HIV testing strategy.

Methods

Costs and effects data from the eSTAMP study

The eSTAMP project, which was implemented from October 2014 to September 2016, studied the effect of providing HIV self-tests on the frequency of testing, diagnosis of HIV infection, sexual risk behaviors, and the use of self-tests by the trial participants and their social network associates.[6] We used published data from the eSTAMP trial, and the aggregate outcome and cost data from the HIV self-testing intervention as presented in Shrestha et al.[28] In eSTAMP, 2665 participants were randomly assigned to either the self-testing arm (n = 1325) receiving HIV self-test kits by mail or to the standard-of-care control arm (n = 1340) receiving access to the eSTAMP website with a link to AIDSVu.org, where all eSTAMP participants could find information on the standard-of-care HIV testing services in the local community. In the self-testing arm, 938 participants completed HIV self-tests. In the control arm, 619 participants completed an HIV test. In addition, the self-testing participants also distributed 2864 self-tests to 2152 social network associates (e.g., friends or sexual partners). The number of new HIV diagnoses was 25, 34, and 11 among the self-testing participants, social network associates, and control arm participants, respectively.

The total program implementation cost of the HIV self-testing program was $449,510 (in 2016 U.S. dollars).[28] The authors assumed all costs associated with the self-testing program were in addition to the costs of standard-of care HIV testing services received by the control group participants. The authors estimated costs per person for self-testing participants and social network associates by dividing the total costs by the total number of participants completing self-tests and the number of social network associates receiving self-tests. The estimated cost per-person tested was $145. There were 48 additional new HIV diagnoses from the HIV self-testing intervention compared with the standard-of-care, and the estimated incremental cost per new diagnosis was $9,365 (Table 1). All costs are reported from the healthcare provider's perspective and are in 2016 US dollars.

Net-Benefit Regression

The cost-effectiveness of a given HIV testing intervention can be assessed (typically) by measuring the additional cost and additional health changes due to the intervention relative to an alternative, and dividing the incremental cost (ΔC) by the incremental effects (ΔE).[32] The extra cost of an extra unit of effect is referred to as the incremental cost-effectiveness ratio (ICER), which mathematically can be expressed as, $ICER = \Delta C/\Delta E$, where ΔC = Expected cost of the new intervention – Expected cost of standard-of-care, and ΔE = Expected effect with new intervention – Expected effect with standard-of-care.[33] The ICER estimate is compared to the policymakers' willingness-to-pay (WTP)[34] to determine the cost-effectiveness of the new intervention, and a new more effective intervention is cost-effective if the ICER < WTP or in other words, $\Delta C/\Delta E < WTP$. With an intervention that

is more effective, $\Delta E > 0$ so the cost-effectiveness requirement is $\Delta C < \Delta E \times WTP$ which can be rewritten as $\Delta E \times WTP - \Delta C > 0$. The calculation on the left of the inequality sign is the incremental net benefit (INB). When the INB > 0, a new treatment or intervention is cost-effective. The INB can be calculated as the difference in the average net benefits for the new intervention vs. a standard-of-care.

Using the data reported in Shrestha at al.,[28] we calculated the net benefit (nb_i) for each participant (i) completing an HIV self-test if in the self-testing arm and completing any HIV test if in the control arm as,

$$nb_i = WTP \times effect_i - cost_i, \tag{1}$$

where $effect_i$ and $cost_i$ are the corresponding intervention effect and cost for participant i.

In the self-testing arm, 48 participants, including the participants completing HIV self-tests and their network associates, had an outcome equal to 1 (new HIV diagnosis) and 3042 participants had an outcome equal to 0, all at an additional cost of $145 per participant. In the control arm, 608 participants had an outcome equal to 0, all at no additional cost per participant. The net benefit for each participant was calculated in the manner described above. For example, with a $WTP = \$10{,}000$, the net benefit for a participant in the self-testing arm with a new HIV diagnosis is $nb = 10000 \times 1 - 145 = \$9855$.

We estimated coefficients using ordinary regression least squares (OLS) in a net benefit regression specified as,

$$nb_i = \beta_0 + \beta_1 ST + \varepsilon, \tag{2}$$

where ST is an indicator variable with $ST = 1$ for participants in the self-testing arm and $ST = 0$ for persons in the control arm. The estimate of the regression coefficient on the indicator variable ST $\left(\widehat{\beta}_1\right)$ is the INB estimate. The p-value for $\widehat{\beta}_1$ can be used to create the cost-effectiveness acceptability curve (CEAC) that illustrates the probability of cost-effectiveness of HIV self-testing. Because the p-value from our OLS regression involves a parametric distributional assumption, we also applied an alternate approach of non-parametric bootstrapping to avoid any distributional assumptions. We conducted the regression analysis and the non-parametric bootstrapping using R 4.3.0.

Incremental net benefit and cost-effectiveness acceptability curve

Two major challenges when analyzing cost-effectiveness data involve sampling uncertainty in clinical trial data and an assumption about the policymakers' WTP. We employed two methods to address these uncertainties. The first method involved estimating pointwise 95% confidence intervals of the INB and plotting the INB estimate against a reasonable range of pre-specified potential WTP values. This plot demonstrates the variability in the

net benefit estimates in relation to WTP assumptions and identifies when the intervention will be considered cost-effective compared to the standard-of-care testing. We also constructed the cost-effectiveness acceptability curve (CEAC).[34–37] The CEAC addresses the joint variability of the cost and effectiveness estimates and depicts the probability of the intervention being cost-effective at various WTP values, i.e., the probability that a policymaker's WTP for the outcome is greater than the ICER.

Results

We estimated that the incremental net benefit of HIV self-testing ranged from -$145 to $631 per new HIV diagnosis as the policymakers' WTP varied from $0 to $50,000 (Table 2). The corresponding probabilities of cost-effectiveness ranged from 0% to 99.4%. A negative incremental net benefit, e.g., - $145 at WTP of $0 per new HIV diagnosis, implies that the HIV self-testing intervention is $145 more expensive than the extra effect (additional new diagnosis) valued as $0 added by it. Hence, the intervention is not cost-effective at a WTP of $0 per new HIV diagnosis. The INB estimates are plotted (solid line) on the vertical axis against the corresponding values of WTP on the horizontal axis (Figure 1). The pointwise 95% confidence intervals of the INB estimates are also plotted on this figure and are connected by two dashed lines. Our INB analysis estimated the ICER of HIV self-testing at $9,365, the value of policymakers' WTP, where the INB estimate (solid line) crosses the horizontal line in Figure 1 and this estimate is the same as reported in Shrestha et al.[28] HIV self-testing is cost-effective for WTP at or greater than $9,365. The two dashed lines in Figure 1 represent the pointwise 95% confidence interval of the ICER estimates at approximately $5,700 – $25,500, indicating the upper and lower limits of the 95% confidence interval.

Figure 2 shows the CEAC of HIV self-testing for WTP per new HIV diagnosis ranging from $0 to $50,000. For a WTP value of $5,700, there was a very small probability that the self-testing intervention was cost-effective, whereas for the WTP value of $25,500, there was above 97% probability that the intervention was cost-effective. The results were very sensitive to the WTP up to $20,000 per new HIV diagnosis. For example, we see that if the policymakers are willing to pay $10,000 to diagnose one new HIV infection through HIV self-testing, then the probability of HIV self-testing being cost-effective is 57.8%, whereas this jumps to 95% when the policymakers are willing to pay double the amount (i.e., $20,000) to diagnose one new HIV infection through self-testing. For WTP > $20,000 per new HIV diagnosis, the CEAC curve was flat showcasing low sensitivity to WTP. In other words, for policymakers with an unknown WTP, but one assumed to be > $20,000, the intervention has a highly likelihood of being cost-effective. The non-parametric analysis with bootstrapping, which generated 1000 bootstrapped samples of the original sample (n=3698), showed that the estimates of the probabilities of cost-effectiveness of HIV self-testing followed a similar trajectory (Table 2).

Discussion

We used net benefit regression to estimate the incremental net benefit for various WTP values for an additional diagnosis through HIV self-testing. HIV self-testing was cost

effective when policymakers were willing to pay at least $9,365 to diagnose one additional HIV infection. In CEAC analysis, we illustrated the magnitude of the uncertainty in identifying an HIV self-testing strategy being cost-effective.[38] The probability of HIV self-testing being cost-effective is 57.8% when the policymakers are willing to pay $10,000 per additional HIV diagnosis through HIV self-testing and 95% when the policymakers are willing to pay $20,000 per additional HIV diagnosis through HIV self-testing.

The literature shows that the estimates of cost-effectiveness of HIV testing intervention varies substantially. Farnham et al. discuss the case of how much to pay for a new HIV diagnosis and present a range of $3,059 - $76,839 (in 2016 U.S. dollars) cost per new diagnosis.[39] The ICER estimate of HIV self-testing as obtained in our study is $9,365 with a 95% CI of approximately ($5,700 – $25,500), which falls within the range presented in Farnham et al. The CEAC figure shows the different probability values when the self-testing intervention becomes cost-effective.[40] Our results compare favorably with Farnham et al. estimates that the costs per new diagnosis can be as high as $76,839 for an HIV testing intervention to be cost effective, based on conventional measure of WTP threshold per QALY saved.[39] Considering this value, our results suggest that HIV self-testing intervention has very high likelihood (>99%) of being cost effective. Both the INB and CEAC analyses suggest that HIV self-testing has the potential to be cost-effective for relatively low values of policymakers' WTP.

While our analysis is based on published cost-effectiveness data from a randomized clinical trial, the results offer valuable information on sampling uncertainty in the cost-effectiveness analysis and variability in decision maker's willingness-to-pay (WTP) for an additional unit of health gain. We estimated the 95% CI of the ICER ($9,365) of HIV self-testing to be $5,700–$25,500, which gives policymakers additional information about the potential range of the ICER. We also provided a 95% CI for the INB and the probability that HIV self-testing is cost-effective at different value of the policymakers' willingness-to-pay, which can guide the policymakers in making an informed decision.

Based on studies[6,7,26,27] that demonstrated the value of self-testing for increasing the frequency of HIV testing, identifying new diagnoses, and reaching people who reported that they had never previously tested for HIV, the CDC has launched Together TakeMeHome (TTMH), a project with the goal of distributing up to 1 million free HIV self-tests over five years[41], which is a continuation of CDC's effort to increase HIV testing in the United States.

Limitations

Cost-effectiveness analysis using clinical trial data has some limitations. In this article, we used the data from the study that reported only additional costs of the treatment group with no estimate of the cost for the control group. Hence, our analysis didn't include the participants with a new HIV diagnosis from the control group. We have used data obtained from a randomized clinical trial conducted in 2015–2016. Considering the impact of COVID-19 on HIV testing, data from a more recent study may be more appropriate for reporting the current cost-effectiveness of HIV self-testing. Moreover, we used data obtained from a single randomized clinical trial, which may have over- or under-estimated the actual implementation costs and effects. This can limit the generalizability of our results.

Conclusions

We conducted a net benefit regression analysis of HIV self-testing, using person-level data reported in the literature. We estimated the incremental net benefit and developed a cost-effectiveness acceptability curve showing the probability of cost-effectiveness of HIV self-testing at various level of policymakers' willingness-to-pay. The probability of HIV self-testing being cost-effective is greater than 0.95 for WTP of $20,000 and can be higher than 0.99 for larger WTP values. The INB and CEAC analyses help address sampling uncertainty in the trial data and the unknown WTP of the decision-makers. The results can guide policymakers in planning for the implementation of HIV testing interventions.

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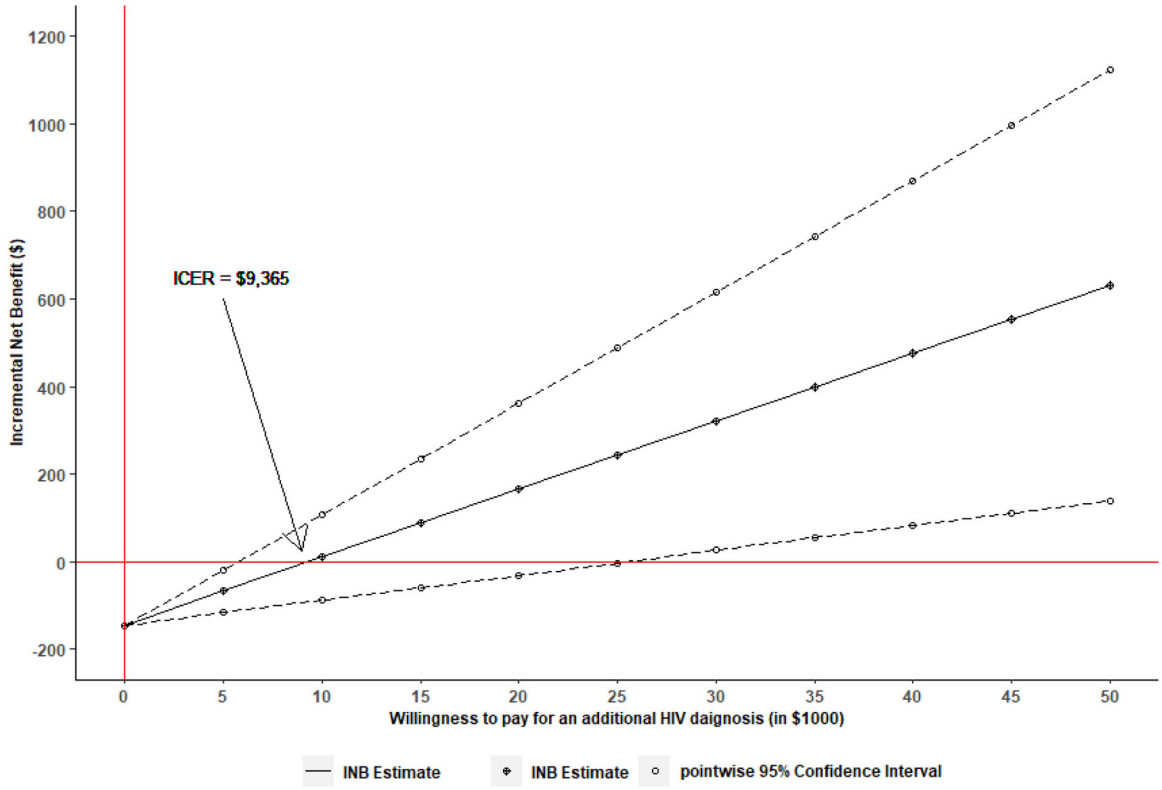

Figure 1:

Incremental net benefit (INB) estimates of HIV self-testing for policymakers' willingness-to-pay (WTP) varying from $0 to $50,000. The incremental cost-effectiveness ratio (ICER) can be obtained from the WTP value for which the INB estimate equals to Zero.

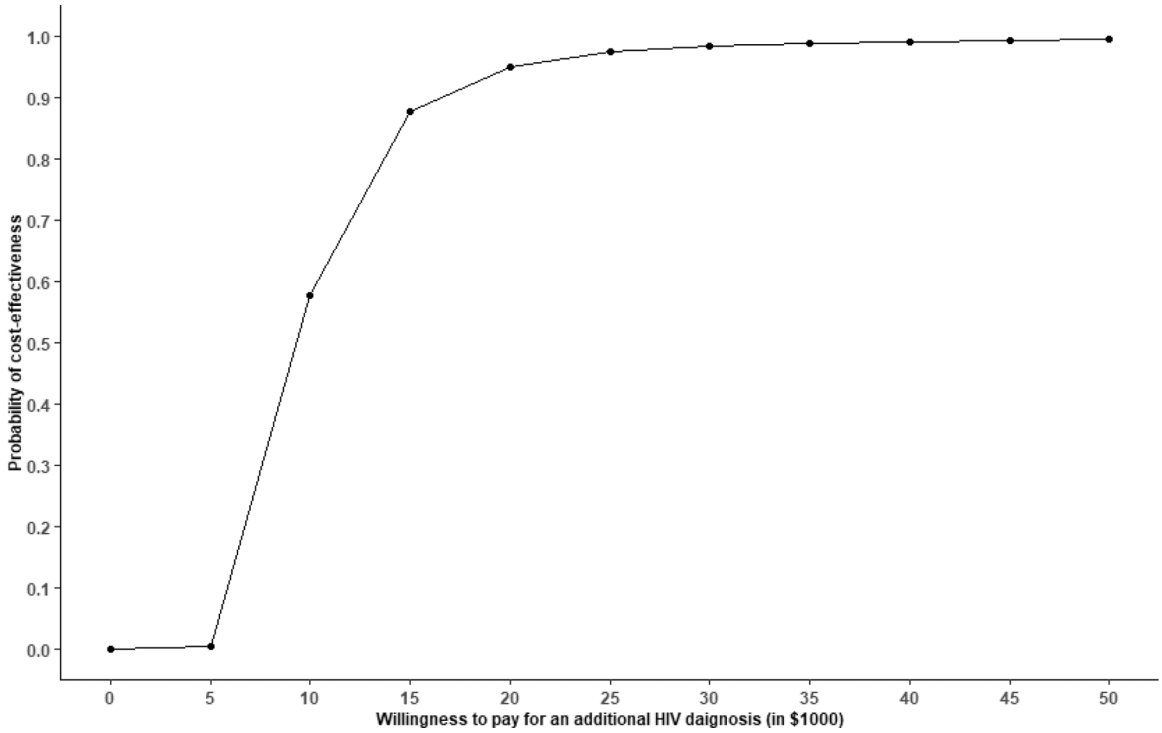

Figure 2:
Cost-effectiveness acceptability curve (CEAC) of HIV self-testing.

Table 1:

Health outcomes and costs of HIV self-testing program from the randomized controlled trial *

	HIV self-testing	Control
Participants		
Participants enrolled in the trial	1325	1340
Participants completing any HIV tests	971	619
Participants completing HIV self-test	938	-
Participants with new HIV diagnosis	25	11
Social network associates		
Social network associates using self-tests	2152	-
Social network associates with new HIV diagnosis	34	-
No. of additional new HIV diagnoses under self-testing arm	48	-
Program costs		
Total cost	$449,510	-
Cost per person tested	$145	-
Incremental cost-effectiveness		
Cost per new HIV diagnosis	$9,365	-

* Health outcomes and costs are used as inputs to our analysis, and data were obtained from the Evaluation of Rapid HIV Self-Testing among MSM Project (eSTAMP) trial.[28]

Table 2:

Net benefit regression results at different levels of policymakers' willingness-to-pay (WTP) and probability of the self-testing intervention being cost-effective

WTP ($)	Self-testing Indicator Coefficient				one-sided p-value	probability of cost-effectiveness	
	Estimate ($\widehat{\beta}_1$)	95% CI (lower limit)	95% CI (upper limit)	p-value		Regression	Bootstrapping
0	−145.472	−145.472	−145.472	0.00000	0.00000	0.0%	0.000%
5,000	−67.803	−100.917	−34.688	0.00690	0.00345	0.3%	0.000%
10,000	9.867	−56.361	76.096	0.84408	0.42204	57.8%	68.200%
15,000	87.537	−11.805	186.880	0.24478	0.12239	87.8%	99.700%
20,000	165.207	32.751	297.664	0.09972	0.04986	95.0%	100.00%
25,000	242.877	77.306	408.448	0.05287	0.02644	97.4%	100.00%
30,000	320.547	121.862	519.232	0.03324	0.01662	98.3%	100.00%
35,000	398.217	166.418	630.016	0.02339	0.01169	98.8%	100.00%
40,000	475.887	210.974	740.800	0.01776	0.00888	99.1%	100.00%
45,000	553.557	255.529	851.584	0.01425	0.00712	99.3%	100.00%
50,000	631.227	300.085	962.368	0.01189	0.00595	99.4%	100.00%

CI = Confidence Interval