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TREATMENTS OF CHLAMYDIA TRACHOMATIS AND NEISSERIA GONORRHOEAE

by

KEN KUN ZHAO

Under the Direction of Dr. Guantao Chen

ABSTRACT

Chlamydia Trachomatis and Neisseria Gonorrhoeae rank as the two most commonly reported sexually transmitted diseases (STDs) in the United States. Under limited budget, publicly funded clinics are not able to screen and treat the two diseases for all patients. They have to make a decision as to which group of population shall go through the procedure for screening and treating the two diseases. Therefore, we propose a cubic integer programming model on maximizing the number of cured diseases. At the same time, a two-step algorithm is established to solve the cubic integer program. We further develop a web-server, which immediately make recommendation on identifying population groups, screening assays and treatment regimens. Running on the empirical data provided by the Centers for Disease Control and Prevention, our program gives more accurate optimal results comparing to MS Excel solver within a very short time.

INDEX WORDS: Sexually Transmitted Disease, Optimization, Cubic Integer Programming, Knapsack Problem, Screening

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by

KEN KUN ZHAO

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by

KEN KUN ZHAO

Major Professor: Dr. Guantao Chen

Committee: Dr. Guantao Chen
Dr. Zhongshan Li
Dr. Jiawei Liu

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

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CHAPTER 1
INTRODUCTION

Chlamydia trachomatis(CT) and Neisseria gonorrhoeae(GC) are the two most commonly reported sexually transmitted diseases (STDs) in the United States. In 2005, there were 976,445 chlamydia infections reported to the Centers for Disease Control and Prevention (CDC) from 50 states and the District of Columbia. This case count corresponds to a rate of 332.5 cases per 100,000 population, an increase of 5.1% compared with the rate of 316.5 in 2004. In 2005, there were 339,593 cases of gonorrhea reported in the United States with the rate of 115.6 cases per 100,000 population, the first increase in gonorrhea since 1999 as reported in [10].

Many cases of CT and GT diseases are screened and treated by publicity funded clinics. In reality, these clinics may not have sufficient budgets to screen all eligible women with the most effective CT/GC tests and to offer these infected ones with more expensive, single-dose treatment that optimizes compliance. To effectively use limited resources, CT and GC control programs usually provide selective screening based on some defined guidelines. CDC recommends annual screening for CT and GC for sexually active adolescents and young women [7]. The U.S. Preventive Services Task Force (USPSTF) recommends screening all sexually active women, including those who are pregnant, for gonorrhea infection if they are at increased risk for infection [8].

For CT and GC control programs, however, identifying which subpopulations to screen for chlamydial and/or gonorrheal infections is just one part of a complicated problem. The availability of several testing assays with various performances and costs presents a challenge for screening strategies: Newer diagnostic tests that are less intrusive and more sensitive

offer increased opportunities for screening, but at a greater cost. So another question is *whether it is better to use a more sensitive and expensive test to screen fewer patients, or to use a relatively cheaper and less sensitive test to screen a greater number of patients.* To further complicate the situation, test manufacturers market combination tests or bundled test at prices that are more lucrative than the price of a single-pathogen test. This situation encourages the testing for GC even when its prevalence in the population is extremely low.

We establish a model to provide an optimal strategy recommendation for screening and treating CT and/or GC with limited budget. Our model maximizes the number of possible **cured cases** for these diseases. We divide the problems into a few cases and reduce the problem to the classical knapsack problem. Moreover, we construct a web-application embedded with our designed algorithm to provide optimal strategy for publicity funded programs. We used JSP, Tomcat and MySql as our web-programming tools. The corresponding web-application has been established for two groups of users: those who can change the all parameters (as super users) and those who only input data on populations and budget (as anonymous users). With our recommended strategy, clinical managers can identify at risk groups from within the patient population and select certain screening assays and treatments for them. Furthermore, we find that our algorithm is more accurate comparing to Excel Solver and easy to implement.

CHAPTER 2

GENERAL SETTING AND MATHEMATICAL MODEL

The object is set to *maximize the number of cured disease cases under a fixed budget.* One patient with both two diseases cured is counted as two cases. We believe this goal is more reasonable than simply maximize the number of cured patients. The general mathematical model for a clinic is described below and the exact model based upon the empirical data from CDC will be given in Section 3 with tedious details. Let b denote the total annual funding available to a clinic for screening and treatment for CT and GC.

1. **Population assumption.** Assume the patient population is divided into m groups. Let x_i be the binary indicator such that $x_i = 1$ if the group i is identified and $x_i = 0$ otherwise.

2. **Screening assumption.** Assume there are s available screening assays. Let y_j be the binary indicator such that $y_j = 1$ if the screening assay j is used and $y_j = 0$ otherwise.

3. **Treatment assumption.** Assume there are t available treatment assays. Let z_k be the binary indicator such that $z_k = 1$ if the assay k is used and $z_k = 0$ otherwise. Since we may choose one assay for CT and one for GC simultaneously, we will present this set of variables slightly differently in the realistic model later.

4. **Target function and constraints.** Let R_{ijk} denote the number of cases of diseases been cured, C_{ijk} denote the cost if group i is identified and screening j and treatment k are used. If a patient has both disease cured, the disease cases will be counted twice. Then the problem can be expressed below:

$$\text{Max} \sum_{i,j,k} R_{ijk} \cdot x_i y_j z_k := \sum_{i=1}^{m} \sum_{j=1}^{s} \sum_{k=1}^{t} R_{ijk} \cdot x_i y_j z_k. \tag{2.1}$$

subject to

$$\sum_{i,j,k} C_{ijk} \cdot x_i y_j z_k \leq b \tag{2.2}$$

where $A := B$ means naming B as A.

5. **Additional constraints.** CDC requires, for each disease, the same screening assay and the same treatment must be applied for all patients treated at the clinic, i.e. no favor is given to particular patient(s) or group(s). Consequently, the following constraints are applied:

$$\sum_{j=1}^{s} y_j = 1 \quad \text{and} \tag{2.3}$$

$$\sum_{k=1}^{t} z_k = 1. \tag{2.4}$$

This model is a binary cubic programming problem. The only known algorithms for solving this model are based on exhausting cases, which runs on exponential time [17]. Although some softwares such as MPL (Mathematical Programming Language), Lingo, Excel Solver were embedded with different algorithms to solve nonlinear integer programming, they only provide approximation solutions when the size of the problem is big. We will create an algorithm that can provide an exact solution rather than approximation solutions.

Because (2.3) and (2.4) that there is only one possible j such that $y_j = 1$ and there is only one possible k such that $z_k = 1$, We can transfer the model into $s \cdot t$ sub-models and each sub-model is a knapsack problem. The knapsack problem in general is a NP-complete problem [16]. We use the well-know branch-and-bound algorithm of Horowitz-Sahni to solve it. We will compare and discuss our algorithm with Excel Solver's algorithm in the algorithm section later.

There are three treatments choices: treating CT alone, treating GC alone, or treating both CT and GC. We find it is more convenient to use double index variable $z_{(k,l)}$ instead of single index variable z_k. Suppose we have t treatment assays in total. Let $z_{(k,l)}$, where $k = 0, 1, ..., q$ and $l = 0, 1, ..., (t - q)$, be the binary indicator such that $z_{(k,l)} = 1$ if the assay k is used for treating CT and assay l is used for treating GC. $z_{(k,l)} = 0$ means either the kth CT treatment or the jth GC treatment is selected. $z_{(0,0)}$ means none of the assays are selected and it is always equal to 0. In another word, we will always treat the patients so $z_{(0,0)} = 1$ never happens. $z_{(0,l)} = 1$ denotes only GC treatment assay l is selected, $z_{(k,0)} = 1$ denotes only CT treatment assay k is selected. So the number of combinations of screening and treatment is not simply $s \cdot t$ although we know it is bounded above by $s \cdot q \cdot (t - q)$.

For each choice of screening assay and treatment, if we assume that the infection rate of each population group is given, the costs and cured patients can be calculated. Under the given screening assay and treatment, the question now is to choose population groups to maximize the number of cured cases with the total costs under a fixed budget, is a typical knapsack problem.

We now give an example for the model to further demonstrate how our model works. Suppose that a clinic has 10,000 patients who can be divided into 12 sub-population groups by ages and races, 2 single CT screening assays, 2 single GC screening assays, 3 combo screening assays; 2 CT single treatment assays, and 2 GC single treatment assays available. According to those assumptions, there are 52 combinations of screening and treatments as described below.

1. Single screening test and single treatment targeting on CT.

   A CT screening test is given to everyone in the sub-population and then a CT treatment is given to those who are tested positively. Given two CT screening assays and two

CT treatments available, there are a total of our combinations using a single screening test and a single treatment for CT.

2. Single screening test and single treatment targeting on GC.

   With the same logic as the previous scenario, we also have four combinations to screen and treat GC.

3. Sequence screening tests that tested for CT first.

   A CT screening test is performed and then an additional GC test is performed to those who tested positively on CT; and a CT treatment is given for those who test positively on CT and a GC treatment is given for those tested positively on GC. This provides 16 combinations (two test assays for CT, two test assays for GC, two treatments for CT and two treatments for GC).

4. Sequence screening tests that tested for GC primarily.

   Same as the previous case, there are 16 combinations of screening and treatment in this case.

5. Combo screening test for both CT and GC.

   In this scenario, a combo test is applied to test both CT and GC at the same time to a sub-population. CT or GC are treated if patients have positive test results for CT or GC. Since there are three combo test assays, two test assays for CT and two test assays for GC, there are $3 \cdot 2 \cdot 2$ combinations.

CHAPTER 3

THE BOUNDS OF BUDGETS

3.1 The Bounds of Budgets.

Insufficient budget occurs in the situation where the budget is not enough for identifying any single group for a screening test and a treatment. The *minimum budget* is the least amount of budget such that there is a way to identify one group to get screened and treated. On the other hand, the *maximum budget* is the least amount budget to identify all population, given the most expensive screen and treatment. We will determine the maximum and minimum budget as following.

The Maximum Budget.

The maximum budget can be obtained if all population are screened for both CT & GC and those with positive tests are treated. Assuming that $x_i = 1$ for all i in calculating cost in Section 3.2., we obtain the maximum budget as below.

$$MaxB := \max_{j,k,l}\{\sum_{i=1}^{m} Pop_i \cdot Cost_{ijkl}\}, \tag{3.1}$$

where i, j, k, and l ($i = 1, ..., m$; $j = 1, ..., s$; $k = 1, ..., t$; and $l = 1, ..., r$) run over each possible screening and each corresponding treatment and we assume that the population is divided into m groups. The number of cases is bounded by $s \cdot t \cdot r$. Furthermore, $\max_{j,k,l}\{Cost_{ijkl}\}$ is the cost for screening and treating one patient in the ith group with the most expensive assay and medication.

The Minimum Budget. The minimum budget is denoted by m when only one group of population is screened and treated. We use the following formula to compute it.

$$MinB := \min_{i,j,k,l}\{Pop_i \cdot Cost_{ijkl}\}, \tag{3.2}$$

where i, j, k, and l run over each possible group and each possible screening test and each corresponding treatment. The number of cases is bounded by $m \cdot s \cdot t \cdot r$.

Reasonable Budget Range.

Any budget between $MaxB$ and $MinB$ is called the *reasonable budget* and the interval $[MinB, MaxB]$ is called the *reasonable budget range*.

CHAPTER 4

SOLVING THE MODEL

The cubic binary programming belongs to nonlinear optimization category. We can use Excel Solver's approximation algorithm to solve the problem. However, we do not know how good those results are. By converting the model to a knapsack problem, we proposed a two-step exact algorithm to solve the problem. With the empirical data from CDC, we compare our solutions generated by our algorithm to the solutions obtained by using Excel Solver.

4.1 Two-step Algorithm

Based on the data in appendix, we used the constrains $\sum_j y_j = 1$ and $\sum_{(k,l)} z_{(k,l)} = 1$ to convert the model in section 2 into 52 knapsack problems. Here, as our first step, we wrote an exhausting algorithm to analyze the number of knapsacks. At each knapsack problem, there are 12 population as the number of items. In addition, we consider the costs $Cost_{ijkl}$ and cured cases Cur_{ijkl} as "weights" and "prices", and the budget becomes the "capacity". Then we use the classical Horowitz-Sahni branch-and-bound algorithm [14] to find the optimal result for each knapsack problem. At the second step, we find the best strategy within these 52 local optimal results. This strategy will be our global optimal result. One may refer our flowchart in Figure 4.1.

4.2 Excel Solver for Knapsack Problems

Microsoft Excel Solver[2] uses the Generalized Reduced Gradient (GRG2) Algorithm for optimizing nonlinear problems. This algorithm was developed by Leon Lasdon, of the Uni-

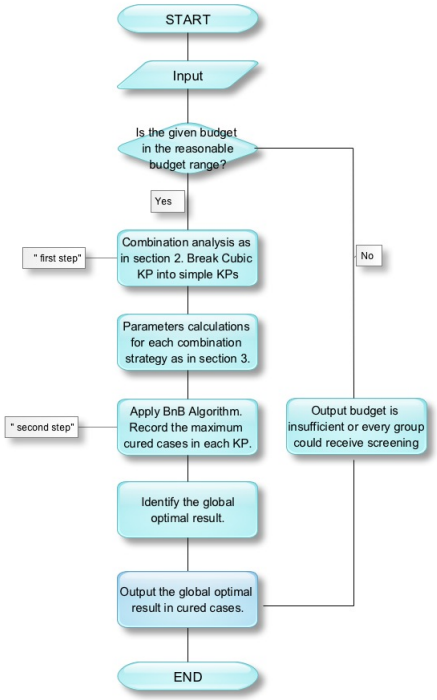


Figure 4.1: The flowchart of the two-step algorithm

versity of Texas at Austin, and Allan Waren, of Cleveland State University. Linear and integer problems use the simplex method with bounds on the variables and the branch and bound method, implemented by John Watson and Dan Fylstra, of Frontline Systems, Inc[2]. Solver can solve our model.

CHAPTER 5
ALGORITHMS DISCUSSION

We implement the model with JAVA and Excel VBA separately. As for the proposed algorithm, the calculation running time mainly depends on the second step calculation after converting the original problem into many knapsack problems. The proposed algorithm is an exact algorithm while using the classic branch-and-bound algorithm as its the second step. We also tried the dynamic programming [14] as for the second step before. However, the calculation space greatly depends on budget with dynamic programming. Greater budget demands a bigger space. Therefore, we abandon the dynamic programming and adopted branch-and-bound for our web-application. We further compared our algorithm to Excel Solver and find that our algorithm is more accurate than Solver's nonlinear algorithm. As for Excel Solver, we use embedded standard Solver in Excel 2003. The following results were run on an Intel Celeron M 1.6GHz processor and a RAM of 512MB.

5.1 Two-step Algorithm v.s. Solver's GRG2 Algorithm

Excel Solver can solve the proposed nonlinear model with GRG2 algorithm. However, Excel Solver is not open source. It has been criticized for its calculation capacity and accuracy. "Solver is NOT a very robust tool and may fail to find solutions! In general, finding roots to nonlinear functions is a very difficult problem. Excel does a poor job compared to more powerful programs such as Matlab."[4]. Solver is using the approximation algorithm which is not as accurate as exact algorithm and it might fail to find a solution or it might time out before reaching a solution[9].

We find that our web-solver with our proposed algorithm has a faster running time and provides more accurate than the Excel Solver. For example, as for budget of $50,000, 110 cured disease in term of cases are achieved under the optimal strategy selected by our algorithm. Our strategy suggests to treat CT and GC together. On contrary, only 101 disease cases were cured with a strategy of single CT treatment by Solver's GRG2 algorithm. Furthermore, under a budget of $70,000, both of two-step algorithm and GRG2 algorithm suggest to treat CT and GC together. However, Solver's result identifies less patient groups than ours. Therefore, Solver's strategy generates 144 cured cases which is less than two-step algorithm's 147 cases. We have examined the optimal strategy selected by the two algorithms under budget of $10,000, $50,000, $70,000, $100,000 and $500,000 in Table 5.1. We notice that our algorithm could generate a better solution than Solver's. If we adopte branch-and-bound as our second step, we could always see that our proposed algorithm has a faster running time on the same machine. As for $500,000, the budget is about to exceed the maximum optimal budget, and the cured cases depend on the assays parameters instead of the budget by a large amount. The two algorithms generate same results.

5.2 Second Step with Excel Solver, Dynamic Program and Branch-and-Bound in Java

The two-step algorithm results given in appendix differ from each other by the second step algorithm. We implement Excel Solver, the dynamic algorithm and branch-and-bound algorithm separately as our second step to calculate the knapsack. We use Excel Solver's linear algorithm and VBA. It produces the optimal results from time to time. However, solving simple knapsack problems and doing loops in VBA demand running time. As one may see that from Table 5.1, Solver's linear programming as our second step is a kind of slow in term

of running seconds.

Both dynamic and branch-and-bound algorithms produce the optimal solutions. However, dynamic programming consumes a huge amount of the computer memory. The dynamic programming algorithm heavily depends on the budget. The nature of $O(nC)$ time and $O(nC)$ space make the calculations difficult when computing large budget over \$200,000 for our data. One may see from the Table 5.1 that the running seconds of the dynamic programming as the second step is increasing dramatically. The computer can not handle the calculation while the budget is \$500,000. Among the three different approaches, Java Branch-and-bound provided the fastest calculation.

Table 5.1: Algorithm results

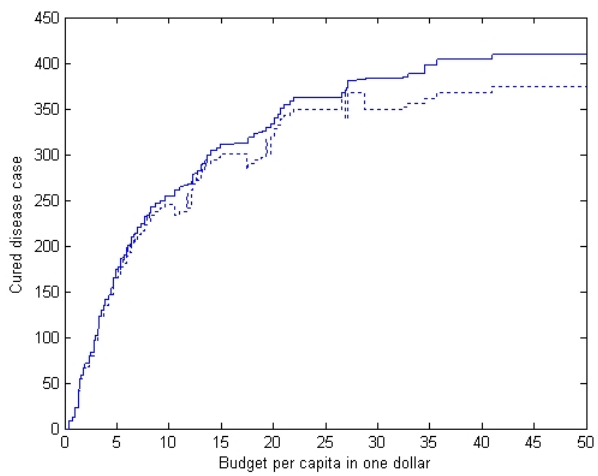
	Two-step Algorithm			Solver's GRG2
	Solver's Linear	Java Dynamic	Java BnB	
$n = 10000$				
Cured cases	12	12	12	12
Costs	7116.67	7116.67	7116.67	7116.67
Running time	17	1	<1	3
Strategy				
Screening	BD ProbeTec CT	same	same	same
Treatment	DXC	same	same	same
$n = 50000$				
Cured cases	110	110	110	101
Costs	47132.36	47132.36	47132.36	41758.62
Running time	14	9	<1	4
Strategy				
Screening	Pace 2 CT	same	same	same
Treatment	DXC+CFX	same	same	DXC
$n = 70000$				
Cured cases	147	147	147	144
Costs	69632.28	69632.28	69632.28	64679.69
Running time	14	11	<1	4
Strategy				
Screening	Pace 2 CT	same	same	same
Treatment	DXC+CFX	same	same	same
$n = 100000$				
Cured cases	198	198	198	197
Costs	97387.32	97387.32	97387.32	96693.52
Running time	14	44	<1	1
Strategy				
Screening	BD ProbeTec CT	same	same	same
Treatment	DXC+CFX	same	same	same
$n = 500000$				
Cured cases	381	out of memory	381	381
Costs	464877.85	n/a	464877.85	464877.85
Running time	14	n/a	<1	1
Strategy				
Screening	BD ProbeTec CT	n/a	same	same
Treatment	DXC+CFX	n/a	same	same

DXC=Doxycycline and CFX=Ceftriaxone

CHAPTER 6

NUMERICAL RESULTS ANALYSIS

Here we give the calculation results based on the given data on table 7.1, 7.2 and 7.3. We also assume that 45% patients infected with GC have CT disease at the same time. We keep all other parameters unchanged and increase budgets per capita by one cent. We record the budget while the cured diseases increases by one case. Thus, the Figure 6.1 shows the relation between the two variables. Solid line in figure represents the total case number of cured diseases regarding CT and GC. The dotted line in figure represents the cured disease number regarding CT. The vertical distance of the two curves is the cured case number regarding GC.



solid line: total cured disease cases.

dotted line: cured CT disease cases.

Figure 6.1: The cure of budget per captica V.S. cured disease case is concave

We could expect to see that the graph is a discrete concave curve. This also implies

that as the budget per capita increases within the reasonable budget region, the total cured disease cases increase for each optimal strategy selected by our model. Why does it look like this? Because both of the money and the number of of cured cases are discrete. We don't have money unit below one penny and case number less than one in reality. Therefore, after increasing budget by one penny, we can see the number of cured cases either increase to another integer or keep unchanged. As for the concave, the increment of cured case number over low unit budget are significantly larger than those over high unit budget. It makes sense in reality: while a clinic increases budget from nothing to $10, the cured case number will be increase to around 200 cases. However, if the clinic increases budget from $70 to $80, the cured case number will be increased by less than 50 cases. This situation demonstrates that the budget does not always play an important role in our model. While the budget is sufficient large, the cured case number does not depend on the budget but the medication effectiveness. That's also the reason while the budget is over $80, the number of cured cases will always keeps to certain level on the graph. Furthermore, the corresponding cost-saving value does not increase as budget per capita increases. This can be shown from the Figure 6.2.

This graph tells us that the positive cost-saving value reaches its highest point while the budget is around $7. In another word, we could save around $50,000 with the earlier testing and treatment strategy under a budget around $7. Beyond the budget, we can see that the cost-saving value decreases to $0 at a budget level around $17. Over the budget level of $17, the cost-saving value is a negative number because the expenditure on testing and treatment exceed the monetary value of averted sequelae of CT and GC infections. While budget is over $80, the cost-saving value will stick to certain level on the graph. This graph is just one of economical factor over the budget to illustrate the relation between the two variable. It does not recommend that we have to stick our budget below $17 because we

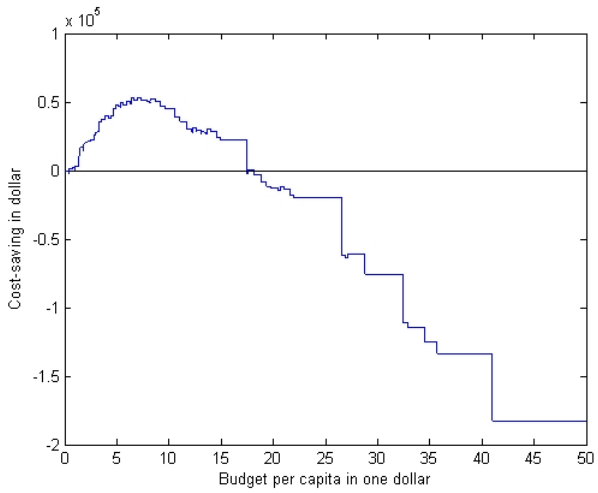


Figure 6.2: The curve of budget per captica V.S. cured disease case shows that the cost-saving value increases at first and then decreases as budget keeps increasing.

can not measure the prevention effect with just one economic factor. On the other hand, as the budget increases to a large amount saying over $20, we do see that cured cases increase while the cost-saving decreases already to negative.

6.1 Economical Efficiency v.s. Human Health

If we want to focus on the cost-saving value and want to spend each penny efficiently, that's another story with absolutely different graphs. In that case, the target function will be changed and the optimal strategy will be selected according to maximize an economical factor. At the same time, a moral question is raised: should our health system target on treating more people at a not perfectly efficient operations, or should our system concern more economic efficiency by leaving some patients who probably have diseases untreated? As more and more researchers criticize the US health system is inefficient, we have to consider the circumstance that there exists a win-lose situation like the problem we exposure

here. Here, we suggest in future study the money measure for individual health should be introduced while researchers use money as a mean to measure the health system efficiency. In another word, health should be mathematically measurable so that we can develop another quantitative model for making an efficient health system decision without hurting any individual health.

6.2 Combo Test v.s. Single Test

Testing procedure plays an important role in selecting to treat one disease or two diseases. If we have combo test assays at the beginning, then we are more likely to treat two diseases together. If we only test one disease at first, then we are going to treat just one disease. However, if we use two single tests that is to test one disease at first and test another later, then we are going to treat two diseases together. Therefore, we find that test assays' type determine if we are going to treat one disease or two diseases.

If we fixed the medications' parameters and other costs, then we can see that the prices of medications have a great effect on the optimal strategies. If the price of single test assays are close to combo tests, then the optimal strategy selected by our model is more favorable to the combo essay test and treat CT and GC together. However, if the prices of combo tests are double to single test assays, then the model does not give more favorite to combo tests based on the data in the tables in section 3. This makes sense in reality. Intuitively speaking, once you can use combo test to treat CT and GC together, you won't use single test with similar price to treat just one disease. Treating two diseases increases the probability of curing more disease cases, while the price gap between combo and single tests are not so huge.

How huge is "huge" and is double or triple "huge" enough? This is another complicated

problem. The selection of testing assays depends not only on the prices of all assays but also the parameters of assays like sensitivity and specificity. The relations between those available assays are competing to each other. That is once we choose one test assay we can never choose others. Here we have to introduce the "comparative advantage" to describe the situation. A essay is chosen at a comparative low price and a comparative high performance under certain budget. However, in the reasonable budget range (defined in section 4), this assay is not always be chosen anytime. Calculation based on table in section 3 are attached at appendix. We found Pace 2C Combo will never be selected in all time for it is expensive and poor performance comparatively.

Table 6.1: Screening test assays

	CT Baseline	GC Baseline	Cost
Test Sensitivity			
Pace 2 CT	0.716	N/A	10.54
BDProbeTec CT	0.928	N/A	10.54
Culture		0.848	8.8
COBAS AMPLICOR CT/GC	0.84	0.924	19.92
Pace 2C Combo	0.716	0.781	4.28
BDProbeTec CT/GC	0.928	0.966	19.92
APTIMA CT/GC	0.942	0.992	25.27
Test Specificity			
Pace 2 CT	0.995	N/A	10.54
BDProbeTec CT	0.981	N/A	10.54
Culture		1.000	8.8
COBAS AMPLICOR CT/GC	0.987	0.995	19.92
Pace 2C Combo	0.995	0.991	4.28
BDProbeTec CT/GC	0.981	0.994	19.92
APTIMA CT/GC	0.995	0.995	25.27

If we keep other parameters unchanged and decrease the price of Pace 2C Combe from \$14.28 to \$4.28 as shown in the table 6.1, Then we see that this assay was selected in the following graph. Furthermore, we expect that Pace 2C Combo will be selected while the budget fall into the lower level of reasonable budget range for it is relatively cheap. On

the upper level of the range, our model won't select the test assay for its poor performance comparatively. Generally speaking, one has the cheapest test assay which is combo and is half price of the second cheapest test assays. Then one may always see that the cheapest assay will be selected in the reasonable budget range.

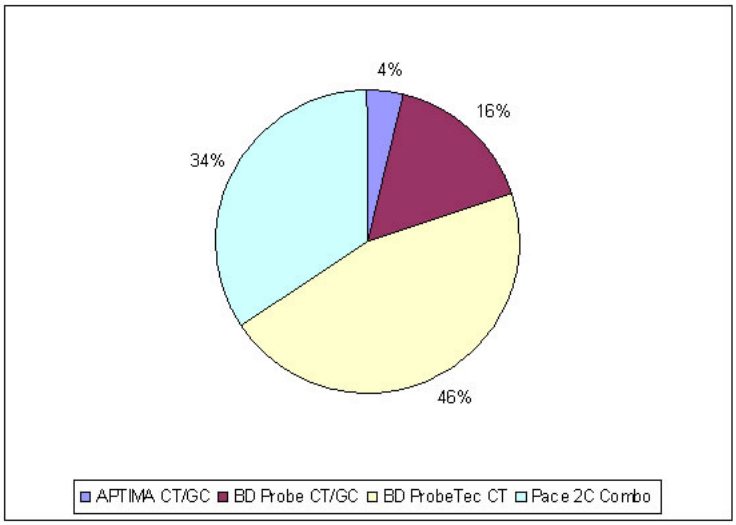
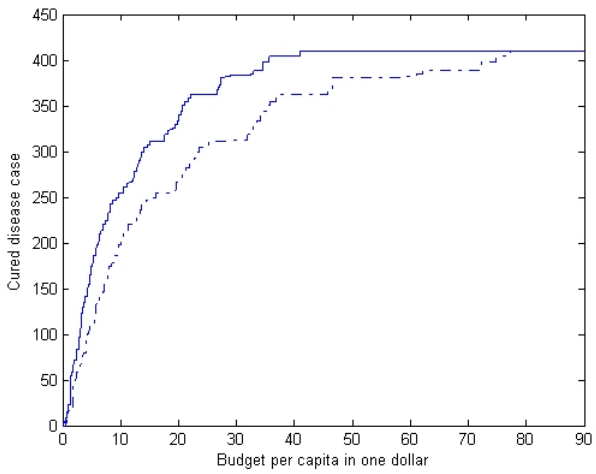


Figure 6.3: The probability of selection on Pace 2C Combo increases to 34% due to price decreased by $10.

6.3 Independence v.s. Dependence

All of above calculations are based on the assumption that 45% of GC patients are CT infected. This is assumption that there exists a dependency between the two diseases. We also calculate the optimal strategy under the assumption that the two diseases are independent to each other. With the independent assumption, GC patients and patients who are not GC infected have the same probability to get CT disease. The probability is P_t. Mathematically speaking, we have $P_{t|g} = P_{t|\overline{g}} = P_t$ under independency. We find that the optimal strategy curve calculated under independent assumption is below the curve under the assumption

of dependence in Figure 6.4. At at budget of $50,000, we could have a cured case number of 110 with the optimal strategy under independent assumption. However, with the same budget, we could have 174 cured cases under dependent assumption. This is because with certain budget we are likely to cure more people under the dependent assumption comparing to independent assumption. Solid line in Figure 6.4 is the total cured disease cases under dependence. Dotted line is the total cured disease cases under independence.

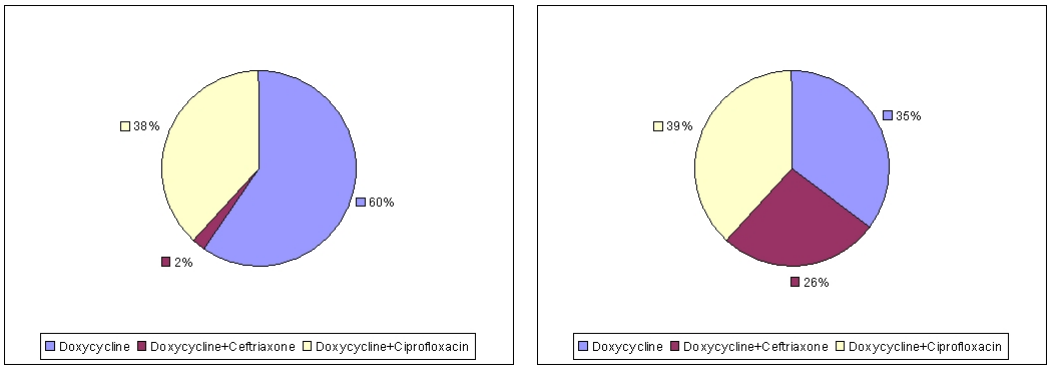


solid line: total cured disease cases under dependence.

dotted line: total cured disease cases under independence.

Figure 6.4: Independent curve is below dependent curve.

In Figure 6.5, we notice that under the independent assumption our model gives a favorite of 60% to treat CT alone and suggests to cured CT and GC together with a partition of 40%. However, under dependent assumption, our model gives more favorates to treat CT and GC togehter with a 57% partition.



(a) Treatment selection under independent assumption

(b) Treatment selection under dependent assumption

Figure 6.5: Our model gives favorite to single treatment under independent assumption.

6.4 Presumptive Treatment v.s. Non-presumptive Treatment

Presumptive treatment is to treat both of CT and GC on those CT test positive patients. Non-presumptive treatment is the procedure to test CT first and and GC secondly with corresponding single test assays, and finally to treat all of identified diseases. Presumptive treatment is not as accurate as non-presumptive treatment and too much of it would lead to antimicrobial resistance. If the two disease are dependent on each other, presumptive treatment will be effective for it can help to identify the second disease at low costs by testing smaller group with a high prevalence rate. With the data provided by CDC, the cured disease case between presumptive and non-presumptive does not have much difference because the procedure always require to test CT as the first step and then treat GC as an additional payoff. However, the costs of non-presumptive treatment will be higher than that of presumptive for it demands additional second test procedure on GC which costs extra money.

CHAPTER 7

CONCLUSION AND FUTURE WORK

With our proposed two-step algorithm, the population groups, test assays and treatment regimens could be easily added or deleted to the models. We could also get the more accurate solution compare to Excel Solver's algorithm for nonlinear model.

In our current model, our object is to maximize the number of cured disease cases and the side effect of the tests and treatments are not concerned. For those mis-tested and mistreated cases, we could add some punishments while calculating the total number of cured cases. In another word, if there are too many mistested or mistreated cases with certain assays, then the bad effects of the assays should be considered while selecting the optimal strategy.

We have restricted our work on one clinic. Government funding agencies, such as CDC, may need to optimize their funds for several clinics. Different clinics may use different screening and treatment assays with more complicated constrains. The optimization problem for the funding agencies is much more involved. We should set a goal in the future to tackle this generalization problem.

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APPENDIX

The Parameters and the Mathematical Model in Details

Basic Parameters: The whole population is divided into 12 groups. The number of patients and the prevalence of CT and GC in each group have been listed in Table 1.

For each group i, let $P_t(i)$ and $P_g(i)$ denote the prevalence rates of the group i with CT and GC, respectively.

Table 7.1: Population distribution based 10,000 women

	White	Black	Hispanics	Others
<20 years	2010	480	360	150
20-24 years	2680	640	480	200
>24 years	2010	480	360	150
CT prevalence				
<20 years	3.8%	15.6%	9.2%	10.7%
20-24 years	2.5%	14.4%	6.3%	7.5%
>24 years	1.2%	11.8%	2.5%	3.3%
GC prevalence				
<20 years	0.1%	1.9%	0.1%	0.2%
20-24 years	0.2%	2.2%	0.1%	0.2%
>24 years	0.2%	1.8%	0.1%	0.2%

Let $P_{g|t}(i)$ be the conditional probability of a CT patient in group i having GC disease and $P_{t|g}(i)$ be the conditional probability of a GC patient in group i having CT. From Bayes' law, we obtain

$$P_{t|g}(i) = \frac{P_t(i) \cdot P_{g|t}(i)}{P_g(i)}. \tag{7.1}$$

Therefore, if $P_{g|t}(i)$ is given, $P_{t|g}(i)$ can be calculated by the above equation.

In order to calculate the cost, we also need the conditional probability of GC infection of a patient without CT infection. $P_{g|\bar{t}}(i)$ can be presented as the following:

$$P_{g|\bar{t}}(i) = \frac{P_g(i) - P_t(i) \cdot P_{g|t}(i)}{1 - P_t(i)} \tag{7.2}$$

Because $P_g(i) = P_t(i) \cdot P_{g|t} + (1 - P_t(i)) \cdot P_{g|\bar{t}}(i)$.

Similarly, we need $P_{t|\bar{g}}(i)$ in the cost estimates. $P_{t|\bar{g}}(i)$ can be presented as the following:

$$P_{t|\bar{g}}(i) = \frac{P_t(i) - P_g(i) \cdot P_{t|g}(i)}{1 - P_g(i)} \tag{7.3}$$

There are seven available screening assays. For each assay j $(1 \leq j \leq 7)$, let $Sn_t(j)$ and $Sp_t(j)$ denote the sensitivity and specificity for CT; let $Sn_g(j)$ and $Sp_g(j)$ denote the sensitivity and specificity for GC; let $Bc(j)$ and $Ac(j)$ be the unit base cost and additional cost. The details are provided in the Table 2.

Table 7.2: Screening test assays

	CT Baseline	GC Baseline
Test Sensitivity		
Pace 2 CT	0.716	N/A
BDProbeTec CT	0.928	N/A
Culture		0.848
COBAS AMPLICOR CT/GC	0.84	0.924
Pace 2C Combo	0.716	0.781
BDProbeTec CT/GC	0.928	0.966
APTIMA CT/GC	0.942	0.992
Test Specificity		
Pace 2 CT	0.995	N/A
BDProbeTec CT	0.981	N/A
Culture		1.000
COBAS AMPLICOR CT/GC	0.987	0.995
Pace 2C Combo	0.995	0.991
BDProbeTec CT/GC	0.981	0.994
APTIMA CT/GC	0.995	0.995

There are two medications for treating CT and two medications for treating GC. Let

$\mathbf{z_{(k,l)}}$ be the binary indicator such that $z_{(k,l)} = 1$ if treatment method (using assay k for CT and/or assay l for GC) is selected and 0 otherwise.

For each CT treatment assay k ($1 \leq k \leq 2$), let $E_t(k)$ denotes the effectiveness of the kth assay. Similarly, let $E_g(l)$ denote the effectiveness of the lth ($1 \leq l \leq 2$) assay for GC treatment. We also denote costs of drugs corresponding to CT and GC, $Dc_t(k)$ and $Dc_g(l)$. The details are provided in Table 3.

A return probability for treatment among patients who had positive test results, P_r was 0.86.

Number of Cured Cases: Let Cur_{ijkl} denote the *ratio* of cured disease cases over population of the ith group using jth screening test and (k, l) method of treatment. So the corresponding number of cases cured is $Pop(i) \cdot Cur_{ijkl}$. There are five different scenarios to calculate the cured disease cases and costs:

(1). Single screening test and single treatment targeting on CT. A CT test is given and then a CT treatment is provided for those who tested positively, so the following holds

$$Cur_{ijkl} = P_t(i) \cdot Sn_t(j) \cdot E_t(k) \cdot P_r. \tag{7.4}$$

(2). Sequence screening tests that tested CT first.

A CT screening test is given to ith population group, then a GC test is given to those who tested positively on CT. A CT medication is given for those who tested positively on CT and a GC medication is given for those in addition tested positively on GC. Extra GC cured cases shall be added to (7.4) in this scenario :

- $P_t(i) \cdot Sn_t(j)$ gives the ratio over the population of group i tested positively by using the jth CT screening test;

- $P_t(i) \cdot Sn_t(j) \cdot P_{g|t}(i) \cdot Sn_g(j) \cdot E_g(l) \cdot P_r$ gives the ratio of the cured number of the GC patients infected by both of CT and GC and tested both positively.

- $(1 - P_t(i)) \cdot (1 - Sp_t(j))$ is the ratio of those not infected by CT but tested positively. So $(1 - P_t(i)) \cdot (1 - Sp_t(j)) \cdot P_{g|\bar{t}}(i) \cdot Sn_g(j)$ gives the percentage of patients who are in a "stroke of good luck" case. In this case, patients only have GC disease and were accidently confided having CT with the jth test firstly and were caught with the second GC test finally, which in turn shows that $(1-P_t(i))\cdot(1-Sp_t(j))\cdot P_{g|\bar{t}}(i)\cdot Sn_g(j)\cdot E_g(l)\cdot P_r$ is the percentage of the cured amount of GC patients in the case of the "stroke of good luck".

$$\begin{aligned} Cur_{ijkl} &= Cur_{ijkl} \ in \ (7.4) + P_t(i) \cdot Sn_t(j) \cdot P_{g|t}(i) \cdot Sn_g(j) \cdot E_g(l) \cdot P_r \\ &\quad +(1 - P_t(i)) \cdot (1 - Sp_t(j)) \cdot P_{g|\bar{t}}(i) \cdot Sn_g(j) \cdot E_g(l) \cdot P_r \end{aligned} \tag{7.5}$$

(3). Single screening and treating for GC only.

A GC test is given and then a GC treatment is given to those who tested positively, so the following holds.

$$Cur_{ijkl} = P_g(i) \cdot Sn_g(j) \cdot E_g(l) \cdot P_r \tag{7.6}$$

(4). Sequence screening tests that tested GC first.

A GC screening test is given to ith population group, then a CT test is given to those who tested positively on GC. A GC medication is given for those who test positively on GC and a CT medication is given for those in addition tested positively on CT . Similar to (7.5), the following holds.

$$\begin{aligned} Cur_{ijkl} &= Cur_{ijkl} \ in \ (7.6) + P_g(i) \cdot Sn_g(j) \cdot P_{t|g}(i) \cdot Sn_t(j) \cdot E_t(k) \cdot P_r \\ &\quad +(1 - P_g(i)) \cdot (1 - Sp_g(j)) \cdot Q_{t|g}(i) \cdot Sn_t(j) \cdot E_t(k) \cdot P_r \end{aligned} \tag{7.7}$$

Note: Since GC prevalence is much smaller than CT prevalence, we expect that the probability of case **(4)** is much smaller than that case **(2)** in reality.

(5). Combo screening test for both CT and GC.

A combo test for both CT and GC is given and then a CT and a GC medicine treatment is given to those tested positively on CT and GC, respectively. The following holds.

$$Cur_{ijkl} \quad = \quad Cur_{ijkl} \; in \; (7.4) + Cur_{ijkl} \; in \; (7.6) \tag{7.8}$$

Unit Costs: Let $Cost_{ijkl}$ denote the *ratio* of the cost over the population of the ith group using jth test and get cured with kth and/or lth treatment assay(s). The corresponding cost is $Pop(i) \cdot Cost_{ijkl}$. There are also five different scenarios for calculating $Cost_{ijkl}$, corresponding to the Cur_{ijkl} one to one. Since screening tests gives false positives, the calculation of $cost_{ijkl}$ is more complicated.

(1). Single screening test and single treatment targeting on CT.

In this scenario, the group i was tested for CT screening test and then CT treatments were given to those tested positively.

- $Bc_t(j) + Vc$ is the unit cost using the jth CT screening test and a unit visit costs at the screening procedure.
- At the treatment procedure, $P_t(i) \cdot Sn_t(j) + (1 - P_t(i)) \cdot (1 - Sp_t(j))$ gives probability of a person having a positive test result, where $P_t(i) \cdot Sn_t(j)$ is the probability of a person having CT infection and tested positively and $(1 - P_t(i)) \cdot (1 - Sp_t(j))$ is the probability of a person not having CT infection but having a (false) positive result. Although we do not consider the later case in estimating the number of cured cases, we include it in costs.

- $Dc_t(k) + Tc$, a charge on drug j and the treatment cost, gives the cost of medicine treatment. So,

$$\begin{aligned} Cost_{ijkl} &= Bc_t(j) + Vc + \{P_t(i) \cdot Sn_t(j) \\ &\quad +(1 - P_t(i)) \cdot (1 - Sp_t(j))\} \cdot (Dc_t(k) + Tc) \cdot P_r \end{aligned} \tag{7.9}$$

(2). Sequence screening tests that tested CT first.

With the strategy from this scenario, extra costs are added to (7.9) while curing GC patients. However, no more visiting costs are charged.

- $\{P_t(i) \cdot Sn_t(j) + (1 - P_t(i)) \cdot (1 - Sp_t(j))\} \cdot Bc_g(j)$ represents the *ratio* over population of GC testing costs for the patients tested positively on CT.

- $\{P_t(i) \cdot Sn_t(j) \cdot P_{g|t}(i) + (1 - P_t(i)) \cdot (1 - Sp_t(j)) \cdot P_{g|\bar{t}}(i)\}$ represents the *ratio* over population of those tested positively on CT and then positively on GC. .

- $\{P_t(i) \cdot Sn_t(j) \cdot P_{g|t}(i) + (1 - P_t(i)) \cdot (1 - Sp_t(j)) \cdot P_{g|\bar{t}}(i)\} \cdot Sn_g(j) \cdot (Dc_g(l) + Tc) \cdot P_r$ is the *ratio* over the population of treatment costs for curing these patient with a positive GC test.

- Summing the above counts, we have

$$\begin{aligned} Cost_{ijkl} &= Cost_{ijkl} \ in \ (7.9) + \{P_t(i) \cdot Sn_t(j) + (1 - P_t(i)) \cdot (1 - Sp_t(j))\} \\ &\quad \cdot Bc_g(j) + \{P_t(i) \cdot Sn_t(j) \cdot P_{g|t}(i) + (1 - P_t(i)) \cdot (1 - Sp_t(j)) \\ &\quad \cdot P_{g|\bar{t}}(i)\} \cdot Sn_g(j) \cdot (Dc_g(l) + Tc) \cdot P_r \end{aligned} \tag{7.10}$$

(3). Single screening and treating for GC only.

A GC screening test is given first and then a GC treatment is given to those tested positively. Similar to (7.9), we have

$$\begin{aligned} Cost_{ijkl} &= Bc_g(j) + Vc + \{P_g(i) \cdot Sn_g(j) \\ &\quad +(1 - P_g(i)) \cdot (1 - Sp_g(j))\} \cdot (Dc_g(l) + Tc) \cdot P_r \end{aligned} \tag{7.11}$$

(4). Sequence screening tests that tested for GC first.

Similar to (7.10), the following holds.

$$\begin{aligned} Cost_{ijkl} &= Cost_{ijkl} \ in \ (7.11) + \{P_g(i) \cdot Sn_g(j) + (1 - P_g(i)) \cdot (1 - Sp_g(j))\} \\ &\quad \cdot Bc_t(j) + \{P_g(i) \cdot Sn_g(j) \cdot P_{t|g}(i) + (1 - P_g(i)) \cdot (1 - Sp_g(j)) \\ &\quad \cdot P_{t|\overline{g}}(i)\} \cdot Sn_t(j) \cdot (Dc_t(k) + Tc) \cdot P_r \end{aligned} \tag{7.12}$$

(5). Combo screening test for both CT and GC.

$Cost_{ijkl}$ *in* (7.4) + $Cost_{ijkl}$ *in* (7.11) will give the basic counting except the visit costs for screening test is counted twice and the treatment cost for those tested positively on both CT and GC is counted twice. Subtracting them, we obtain the following.

$$\begin{aligned} Cost_{ijkl} &= Cost_{ijkl} \ in \ (7.9) + Cost_{ijkl} \ in \ (7.11) \\ &\quad -V_c - P_t(i) \cdot P_{g|t}(i) \cdot Tc \cdot P_r \end{aligned} \tag{7.13}$$

Note: For a combo assay, it has an additional cost which is calculated slightly different from (7.13). Thus, we added the extra costs to the previous formulae and it is

$$\begin{aligned} Cost_{ijkl} &= Cost_{ijkl} \ in \ (7.13) + \{P_t(i) \cdot Sn_t(j) \\ &\quad +P_g(i) \cdot Sn_g(j) - P_t(i) \cdot P_{g|t}(i)\} \cdot Ac(j) \end{aligned} \tag{7.14}$$

Target function and constraints: The target function is to maximize the cured cases with available screening assays and treatment medications for several patient groups.

$$\text{Max} \sum_{i,j,k,l} Cur_{ijkl} \cdot x_i y_j z_{(k,l)} := \sum_{i=1}^{12} \sum_{j=1}^{7} \sum_{k=0}^{2} \sum_{l=0}^{2} Cur_{ijkl} \cdot x_i y_j z_{(k,l)}. \tag{7.15}$$

Subject to

$$\sum_{i,j,k,l} Pop_i \cdot Cost_{ijkl} \cdot x_i y_j z_{(k,l)} \quad \leq \quad b \quad \text{and} \tag{7.16}$$

which means the screening and treatment costs for identified groups should be smaller than the annual funding b available to a clinic.

furthermore,

$$\sum_{j=1}^{7} y_j \quad = \quad 1 \quad \text{and} \tag{7.17}$$

$$\sum_{k,l} z_{(k,l)} \quad = \quad 1. \tag{7.18}$$

which implies that same screening assays and treatments are applied to all patients. At the same time $z_{(0,0)} = 0$.

Table 7.3: All costs[1] and treatment assays

	Baseline[2]	Range L	Range H
Test Cost			
Pace 2 CT	18.5	8.97	28.02
BDProbeTec CT	29.79	10.54	49.04
GC Culture	9.26		9.26
AMPLICOR PCR CT/GC	54.57	11.06	98.07
Pace 2C Combo[3]	35.16	14.28	56.03
BDProbeTec CT/GC	59	19.92	98.07
APTIMA CT/GC	61.67	25.27	98.07
Treatment Efficacy-CT			
Doxycycline	0.92	0.9	0.99
Azithromycin	0.92	0.9	0.99
Treatment Efficacy-GC			
Doxycycline	0.64	0.3	0.9
Azithromycin	0.976	0.957	0.989
Ceftriaxone	0.988	0.979	0.998
Cefpodoxime proxetil	0.959	0.936	1
Treatment Cost[4]			
Doxycycline	8.12	0.57	8.12
Azithromycin	16.65	21.35	27.5
Ceftriaxone	25.74	15.67	31.86
Cefpodoxime proxetil	8.28	8.28	10.52
Test Visit Cost	14		
Treatment Visit Cost	28.43		
Probability of PID	0.20	0.10	0.40
Prob. of return for treatment	0.86	0.76	0.91
Sequelae Cost			
PID	2772	1366	4099

[1]All costs in 2006 US dollars (adjusted with medical CPI where needed).
[2]Baseline of test costs are the averages of Range L and Range H.
[3] For the Pace 2C, a positive test (indicating either CT or GC, but not which organism) is followed by two separate supplemental.
[4] To this should be added a cost of dispensing/administration (treatment visit cost).
For ceftriaxone, the baseline price includes the drug plus the CMS fee for intramuscular injection.