# COST-EFFECTIVENESS ANALYSIS OF A WHOLE GENOME SEQUENCING TEST COMPARED TO THE STANDARD CARE AMONG PATIENTS WITH HOSPITAL-ACQUIRED BACTEREMIA

by

**Zhijie Ding**

BS, Biological Sciences, Fudan University, China, 2003

PhD, Bioengineering, University of Pittsburgh, 2009

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Zhijie Ding

It was defended on

June 19th, 2017

and approved by

**Thesis Advisor:**
Hawre Jalal, MD, MS, PhD
Assistant Professor
Department of Health Policy and Management
Graduate School of Public Health
University of Pittsburgh

**Committee Member:**
Mark Roberts, MD, MPP
Professor
Department of Health Policy and Management
Graduate School of Public Health
University of Pittsburgh

**Committee Member:**
Partha Roy, PhD
Associate Professor
Department of Bioengineering
Swanson School of Engineering
University of Pittsburgh

Hawre Jalal, MD, MS, PhD

# COST-EFFECTIVENESS ANALYSIS OF A WHOLE GENOME SEQUENCING TEST COMPARED TO THE STANDARD CARE AMONG PATIENTS WITH HOSPITAL-ACQUIRED BACTEREMIA

Zhijie Ding, MS

University of Pittsburgh, 2017

## ABSTRACT

**Background**: *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria have becoming increasingly prevalent in the US in the past decade. *Klebsiella pneumoniae* presents significant clinical challenges, as they are frequently misclassified and highly resistant to all commonly available antimicrobials, leading to delay in treatment and rapid spread in the hospital. With its high sensitivity and significantly reduced price, whole genome sequencing (WGS) has been considered a viable approach to help facilitate the identification of KPC-positive *K. pneumonia* from patient isolates from gastrointestinal endoscopy. However, evidence for its cost-effectiveness is lacking, which is of high public health significance.

**Objective:** to compare the cost-effectiveness of WGS and the standard of care (SOC, high-level disinfection), in the detection and prevention of KPC-positive *K. pneumonia.*

**Methods:** A hypothetical cohort of 1000 patients was simulated for ten years using a four-state Markov model. KPC-positive *K. pneumoniae*-caused infection-related healthcare costs and quality-adjusted life year (QALY) were estimated for both the WGS strategy and the SOC strategy.

**Results:** The base case analysis showed that with the infection rate assumed to be 1% and the cost of WGS at $100 per test, the ten-year mean cost for a patient in the WGS strategy

was $3,281.80 with 8.0819 QALYs gained, while the total cost for the SOC strategy was $4,583.50 with 8.0507 QALYs gained. Under these conditions, the SOC strategy was dominated by the WGS strategy. One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) revealed that WGS remained economically dominant compared to SOC with the willingness-to-pay level at $50,000.

**Conclusion:** In summary, the WGS strategy is more cost effective in identifying PC-positive *K. pneumonia* than SOC strategy.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF EQUATIONS

# 1.0 INTRODUCTION

Since the innovation of the next generation sequencing (NGS) technologies and the subsequent drop in sequencing costs, there has been enthusiasm for the use of whole genome sequencing in various clinical settings. NGS is advantageous over traditional Sanger sequencing because NGS is massively parallel, sequencing millions of short DNA fragments in a high throughput manner. As a result, NGS is significantly faster and cheaper than classical methods. Thus, it is anticipated that whole genome sequencing can be readily performed, leading to improvement in diagnostic sensitivities and decision-making in precision medicine. Therefore whole genome sequencing will not only enhance patient care, but also reduce the skyrocketing healthcare costs through prevention and more effective treatment in the long-term. However, concerns remain that there is not sufficient evidence demonstrating the effectiveness of genetic testing and the high cost and lack of reimbursement could be the largest barrier to incorporating genetic testing into routine clinical practice [2].

## 1.1 EPIDEMIOLOGY OF KPC-POSITIVE *K. PNEUMONIAE*

Recent epidemiological studies suggest that there has been an increasing trend in carbapenem-resistant Enterobacteriaceae in the US in the past decade [3 4]. Carbapenem-resistance is conferred by organisms harboring carbapenemase, among which Klebsiella pneumoniae carbapenemase is

the most common one in the US [3]. The initial outbreak of Carbapenem-resistant *K pneumoniae* occurred in hospitals in New York city and quick spread to states in the Mid-Atlantic region [5]. Nationwide SENTRY surveillance data from 2007 to 2009 revealed that Mid-Atlantic states continued to show a significantly higher frequency of KPC-positive organisms than other regions in the US: 28.6% in Mid-Atlantic vs 5.5% nationwide [6]. In addition, KPC-positive *K. pneumoniae* isolates used in the SENTRY study were found from bloodstream infections (BSI, respiratory tract infections (RTI), urinary tract infections (UTI), and skin and skin structure infections and other sites of infection (SSSI/O), where BSI was the primary source of infection[6].

## 1.2 RESISTANCE OF KPC-POSITIVE *K. PNEUMONIAE*

KPC-positive *K. pneumoniae* isolates are essentially resistant to all the commonly available antimicrobials. The only remaining options are colistin and tigecycline [6]. However, these agents are associated with serious disadvantages, such as nephrotoxicity due to dosing challenges, development of resistance, safety concerns[6]. Therefore it is critically important that KPC-positive *K. pneumoniae* isolates be identified in a timely and accurate manner to effectively control the spread. Antimicrobial susceptibility tests are routinely performed in clinical microbiological laboratories to identify KPC-positive *K. pneumoniae*. During testing minimal inhibitory concentrations (MICs) for each antimicrobial are determined for the isolate. If any MICs fall into the susceptible range, further testing such as PCR will be employed. Although susceptibility testing has been implemented on a regular basis, clinical laboratories still face significant challenges to accurately detect KPC-positive *K. pneumoniae*. Detection accuracy in part depends on the choice of carbapenem and the associated screening methods. Different

carbapenem agents have different MICs and unique sensitivity and specificity profiles. Moreover, different expression levels of carbapenemase and the presence of other extended-spectrum β-lactamases also add another layer of complexity to accurate detection. Even with the updated Clinical Laboratory Standards Institute (CLSI) interpretative criteria, it is difficult to differentiate between KPC-positive K. pneumoniae and other extended-spectrum β-lactamases producing organisms, the latter of which may be treated with carbapenem [7].

Recently researchers at the University of Pittsburgh reported the detection of KPC-positive *K. pneumonia* from patients undergoing endoscopic retrograde cholangiopancreatography from a single hospital [1]. In addition to routine detection approaches, such as antimicrobial susceptibility test and PCR analysis, the authors also employed novel methods, including comparative whole genome sequence analysis and plasmid analysis. Whole genome sequence analysis was carried out for both patient and endoscope isolates, which allowed the authors to subsequently compare single nucleotide polymorphisms (SNPs) between patient and endoscope samples and identify two clusters among the samples. Further analysis based on whole plasmid sequencing provided high-resolution genetic signatures enabling the tracking of KPC gene transmission and reconstruction of the outbreak.

## 1.3 HOSPITAL ACQUIRED INFECTION

Improvement in patient safety and reduction of hospital acquired infections has been a priority of the department of health and human services [8]. A multistate point-prevalence survey of health care–associated infections conducted by cdc showed that 4.0% of inpatients in acute care hospitals in the US had at least 1 health care–associated infection it is estimated that there were

about 721,800 infections in 2011 [9]. *Klebsiella pneumoniae* and k. Oxytoca was the third most common pathogen causing these infections.

Bacteremia is a form of infection where there are bacteria present in the bloodstream. Majority of KPC-positive *K. pneumoniae* infections are bacteremia. Bacteremia is a serious infection that can lead to life-threatening events. Patients with bacteremia not only have higher short-term mortality but also have higher long-term mortality rates [10], reduced quality of life after hospital discharge [11,12], and significantly higher health care costs [13]. A more accurate and faster turnaround whole genome sequencing (WGS) strategy-detecting infection in order to prevent a potential outbreak (by reducing the number of new cases infected) was compared with the standard of care using cost-effectiveness framework in this study.

# 2.0 METHODS

## 2.1 DECISION TREE

A decision tree with two Markov subtrees was developed with the Treeage Pro software (Treeage Software Inc., Williamstown, MA) (Figure 1). We compared two strategies with the decision trees. The two strategies were using whole genome sequencing (WGS) to detect hospital acquired infection vs the standard of care (SOC) in the case of potential infection of KPC-positive *K. pneumoniae* from patients undergoing endoscopic retrograde cholangiopancreatography (Figure 1). Markov models (described below) were used in both branches (WGS vs SOC) to estimate costs and quality-adjusted life years (QALYs). These outcomes come from the initial infected patient and those who get subsequent infection from this patient. Future costs and benefits were discounted at an annual rate of 3%.

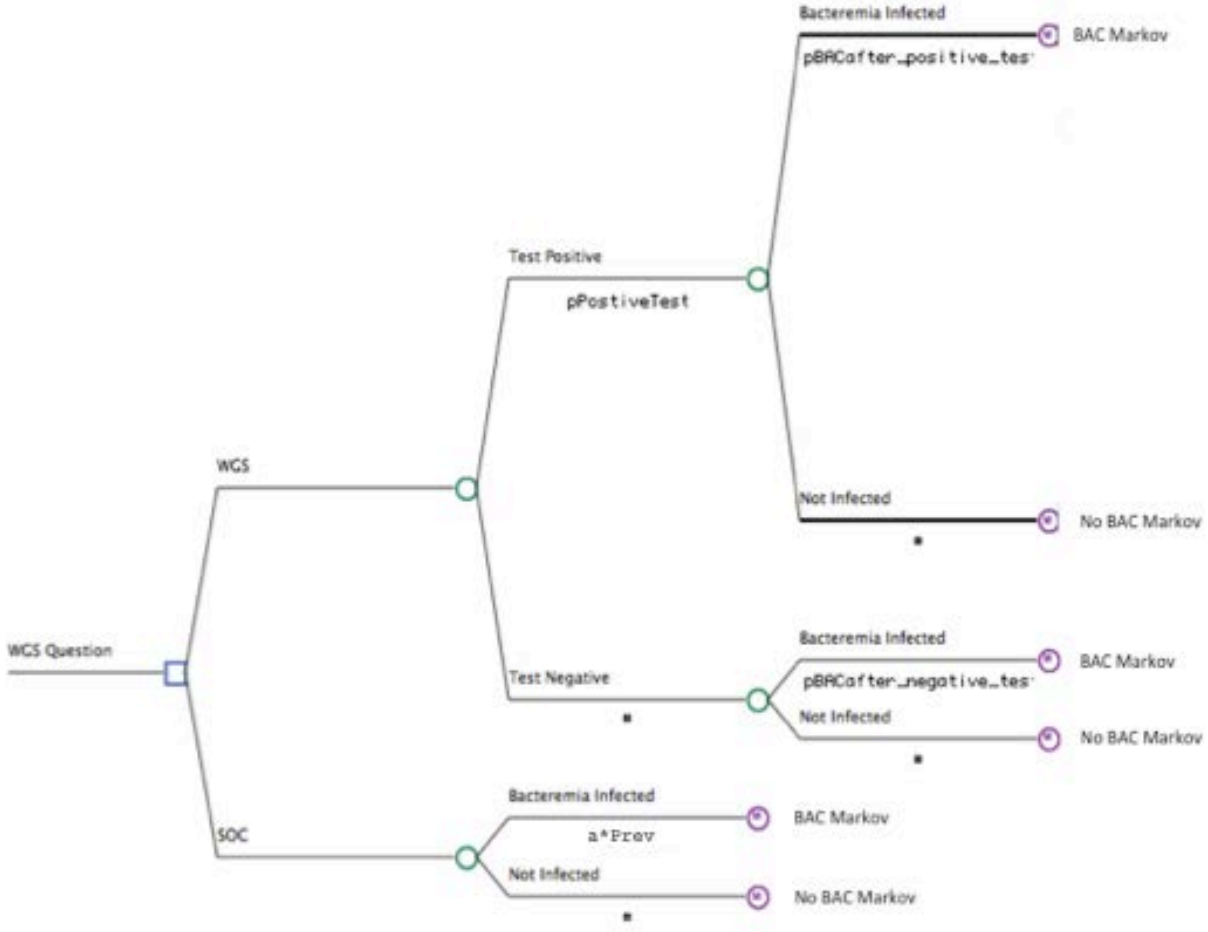



**Figure 1. The cost-effectiveness decision model.**

## 2.2 MARKOV SUBTREES

Markov subtrees were developed using the Treeage Pro software (Treeage Software Inc., Williamstown, MA) to simulate disease progression and estimate costs and quality-adjusted life years (QALYs) of patients with suspected infection of *Klebsiella pneumoniae* from using endoscopes in the University of Pittsburgh Medical Center (UPMC) Presbyterian Hospital and patients without infection. Since the mortality rate in the first three months of patients infected

with bacteremia is very different from that after three months we used cycle length of three-month in the Markov subtrees to capture the different mortality rates.

There are four health states in the Markov subtree for patients who get infected with bacteremia (represented by "BAC Markov" in Figure 1): 1) healthy state; 2) bacteremia state; 3) post-bacteremia state; 4) death state (Figure 2). We defined the post-bacteremia state because sepsis survivors (a similar disease) usually experience residual physical, cognitive and psychosocial problems lasting from 5 to 15 years after intensive care unit (ICU) discharge. During this post-bacteremia state the rate of a major illness recurring and/or mortality is also increased [14]. While the Markov model for patients who are not infected with bacteremia (represented by "NO BAC Markov" in Figure 1) only has two states: live and death. Both Markov subtrees were ½ cycle corrected.

Since the cycle length is 3 months, four cycles are needed to represent a whole year of the four states. We modeled a 10-year span, and 40 cycles were needed. Age-specific probabilities were applied as the transition probabilities in the first year (first 4 cycles) were different from the next year, and so on.

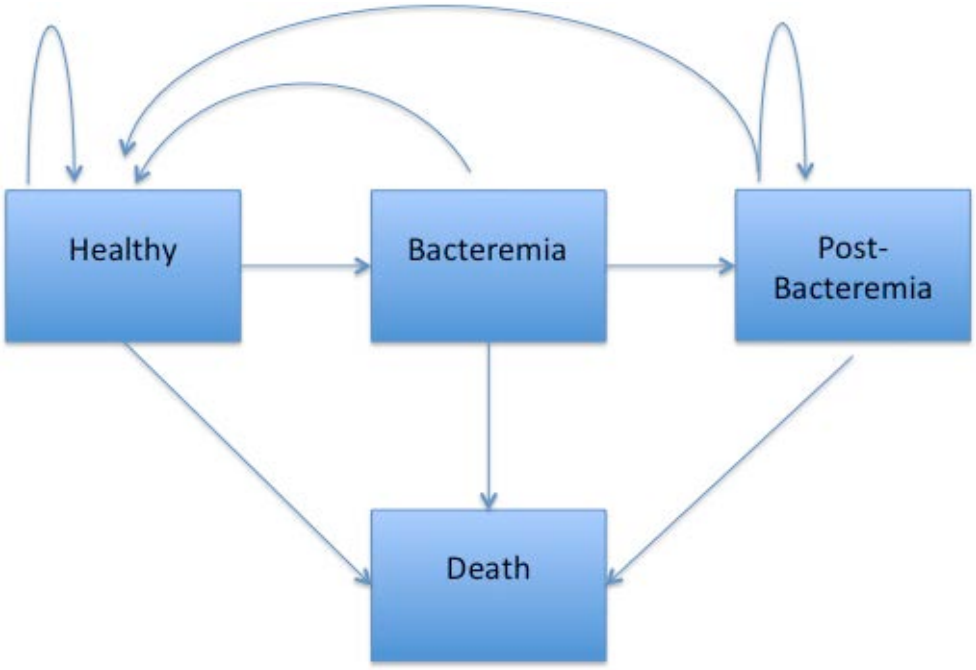



**Figure 2. Markov subtree structure.**

Markov subtree ("BAC Markov") structure for patients who are infected with bacteremia. Patients occupied one state at a time and transitioned every three months according to transition probabilities.

## 2.3 LIFE EXPECTANCIES AND MORTALITY RATES

The age-specific probability of dying was used to calculate the transition probability from healthy state to death. The baseline probability of dying of patients was taken from 2011 US life table. The transition probability from healthy state to death was estimated by directly using the values in the life table from age 60.

The mortality rate associated with patients with infection of *Klebsiella pneumoniae* from our data was calculated according to the DEALE method [15]. There are several steps involved in this method. First, annual population mortality rate ($\overline{\mu}_{pop}$) was calculated as reciprocal of life expectancy of the simulated population using US life table. Second, $\overline{\mu}_{pop}$ was converted to 3-month mortality rate ($\bar{\mu}_{3mpop}$). Third, the annual compound mortality rate (for patients with infection of *Klebsiella pneumoniae* was calculated from our hospital data using this relationship

**Equation 1**

$$\overline{\mu}_{C} = -\frac{1}{t}\ln(S)$$

**Equation 2**

$$\bar{\mu}_{3mD} = \bar{\mu}_{3mC} - \bar{\mu}_{3mpop}$$

In the equation 1, the average annual compound mortality rate ($\bar{\mu}_{C}$) can be expressed as a function of time of survival (t) and probability of survival. Fourth, $\bar{\mu}_{C}$ was converted to 3-month compound mortality rate ($\bar{\mu}_{3mC}$). In the equation 2, the 3-month bacteremia-specific mortality rate ($\bar{\mu}_{3mD}$) is the difference between 3-month compound mortality rate ($\bar{\mu}_{3mC}$) and 3-month population mortality rate ($\bar{\mu}_{3mpop}$). The last step was conversion of the 3-month bacteremia-specific mortality rate into probability.

## 2.4 PREVALENCE ESTIMATES

Since the hospital is located in the Mid-Atlantic geographic region, with the highest prevalence of KPC-positive *K. pneumoniae* in the nation at 28% and the percentage of its resistance to high-level disinfection is higher than 6%, the transition probability from healthy state to bacteremia state was assumed at 1% (assume both the prevalence and percentage of resistance are higher in the hospital setting).[6] In the one-way sensitivity analysis and probabilistic sensitivity analysis, a range from 0.1% to 5% was used for the prevalence of KPC-positive *K. pneumoniae* (Table 2).

## 2.5 SENSITIVITY AND SPECIFICITY

The point estimates of sensitivity and specificity of the WGS test were obtained from Kosar et al.[19] These values represent the "intrinsic" detection capability of the WGS test, namely accuracy, which is critical to prevention of a outbreak by limiting the number of new cases infected. In the WGS strategy branch, both sensitivity and specificity along with prevalence were used to determine probability of a positive test (pPositiveTest in Figure 1), probability of bacteremia infection after a positive test (pBACafter_positive_test in Figure 1), and probability of bacteremia infection after a negative test (pBACafter_negative_test in Figure 1). The three equations are listed here:

**Equation 3**

$$pPositiveTest=Prevalence*Sensitivity+(1-Prevalence)*(1-Specificity)$$

**Equation 4**

$$pBACafter\_positive\_test=\frac{Prevalence*Sensitivity}{(Prevalence*Sensitivity+(1-Prevalence)*(1-Specificity))}$$

**Equation 5**

$$\text{pBACafter\_negative\_test}=\frac{\text{Prevalence}*(1-\text{Sensitivity})}{(\text{Prevalence}*(1-\text{Sensitivity})+(1-\text{Prevalence})*\text{Specificity})}$$

In addition, WGS test has a much faster turnaround time, which is also critical to determining the number of new cases infected leading to prevention of an outbreak. In order to model this time-related variable that contributes to number of new cases infected, a prevalence-adjusting factor – "a" was created. Since there is a general agreement that WGS tests are faster, meaning they have the ability to reduce the number of new cases, the prevalence-adjusting factor – "a" was assumed at 2 for the SOC branch in the base case. In the SOC branch, the probability of getting infection was defined as "a"*prevalence. In the base case(a=2), the probability getting infection in the SOC branch is higher than that in the WGS branch. But in both sensitivity analyses, this prevalence-adjusting factor (a) was varied in the range from 0.1 to 4.

## 2.6 TRANSITION PROBABILITIES

There are several transition probabilities in our Markov model including 1) The three-month transition probabilities from healthy state to bacteremia, post-bacteremia or death state; 2) the three-month transition probabilities from bacteremia state to healthy, post-bacteremia or death state; 3) the three-month transition probabilities from post-bacteremia state to healthy, bacteremia or death state.

Table 1 lists all the transition probabilities for a cohort of patients at age 60 in the base case, and most of these values were obtained from literatures [10,16]. Since the age-specific transition probability of death was used, the transition probabilities from healthy state to death

state are different for different ages. In addition, the transition probability from healthy state to bacteremia state is based on the reported prevalence of KPC-positive *K. pneumoniae* and the percentage of its resistance to high-level disinfection.[6]

**Table 1. Transition probabilities for the model.**

| | Base Case Estimate | References or Sources |
|---|---|---|
| Clinical Parameters | | |
| Transition probability from healthy state to bacteremia state | 0.01 | Kaiser et al. |
| Transition probability from healthy state to death state | 0.006589 | Life table USA 2011 |
| Transition probability from bacteremia state to healthy state | 0.23 | Eddleston et al. |
| Transition probability from bacteremia state to post-bacteremia state | 0.44 | 1-PBH-PBD |
| Transition probability from bacteremia state to death state | 0.3298 | DEALE method |
| Transition probability of post-bacteremia state to remain in the same state | 0.8 | Estimate |
| Transition probability from post-bacteremia state to death state | 0.0569 | Winters et al. |

Transition probabilities for a cohort of patients at age 60 entering the Markov model.

## 2.7 COST ESTIMATES

Table 2 lists all the estimates, the range of these estimates, and the references for cost in the base case. The estimated average total direct medical cost for treating bacteremia is $19350 per

patient, and most patients on average only require one such treatment.[17] The annual direct medical cost for post-bacteremia patients is estimated at $5391 per patient. [18]

## 2.8 HRQL AND QALY ESTIMATES

Table 2 lists all the estimates of health-related quality of life (HRQL), the range of these estimates, and the references for the four states. Healthy patients are considered to have perfect health (HRQL = 1), while HRQL of patients who are dead equals 0. The mean estimate of HRQL for bacteremia patients is assumed at 0.3. After discharged from the hospital, survived patients are moved to the "Post-bacteremia" state. Patients with bacteremia will have reduced quality of life after discharge [11,12]. The estimate of HRQL for post-bacteremia patients is 0.68, which was measured with the EuroQol-5D (EQ-5D) instrument in sepsis patients after discharging from hospitals.

**Table 2. Costs, HRQL estimates for the model.**

| | Base Case Estimate | Range | References or Sources | Notes |
|---|---|---|---|---|
| Quality of Life Parameters | | | | |
| HRQL in the bacteremia state | 0.3 | 0.2-0.4 | Estimate | Ranges ±50% of base case estimates. |
| HRQL in the post-bacteremia state | 0.68 | 0.5-0.9 | Orwelius et al. | Ranges from IQR. |
| Cost Parameters | | | | |
| Direct medical cost in the bacteremia state | $19,350 | $5,800-$32,900 | Eber et al. | Average cost for base case estimate. |
| Annual medical cost in the post-bacteremia state | $5,391 | $2,696-$8086 | Iwashyna et al. | Ranges ±50% of base case estimates. |
| WGS cost | $100 | $25-$300 | ACGT, Inc. | Ranges estimated from market price. |
| Clinical Parameters | | | | |
| Prevalence | 0.01 | 0.001-0.05 | Kaiser et al. | |
| Prevalence-adjusting factor ("a") | 2 | 0.1-4 | Estimate | Ranges estimated |
| Sensitivity of WGS test | 0.97 | 0.96-0.98 | Kosar et al. | Ranges estimated |
| Specificity of WGS test | 0.99 | 0.985-0.995 | Kosar et al. | Ranges estimated |

Costs, HRQL estimates for patients in healthy, bacteremia, post-bacteremia, and death states.

# 3.0 RESULTS

## 3.1 MODEL VALIDATION

The red curve in Figure 3 shows the predicted survival curve for the patients with bacteremia from our model over 3 years after the first incidence, while the blue curve Figure 3 shows the observed survival curve from the hospital data over 3 years after the first incidence. The predicted results were consistent with the survival curve we observed from the hospital data.

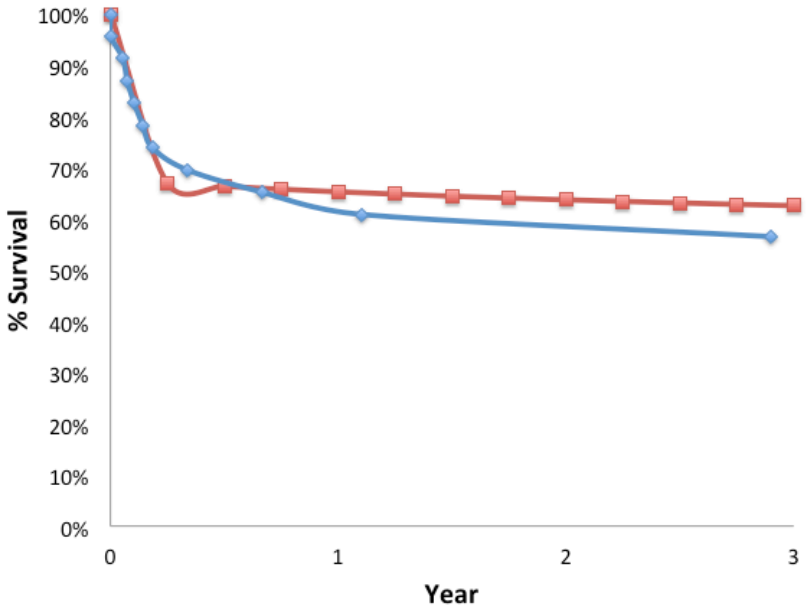



**Figure 3. Predicted and observed survival curves.**

Predicted survival curve for patients infected with bacteremia with our model over 3 years after first incidence (red curve) and observed survival curve from hospital data over 3 years after first incidence (blue curve).

## 3.2 BASE-CASE ANALYSIS

A hypothetical cohort of 1000 of 60-year-old patients was simulated for ten years using the four-state Markov model described earlier. *Klebsiella pneumoniae carbapenemase* (KPC)-positive *K. pneumoniae*-caused infection-related healthcare cost over ten years and quality-adjusted life year (QALY) were estimated for both the WGS strategy and the standard of care (SOC, high-level disinfection) strategy. These outcomes come from the initial infected patient and those who get subsequent infection from this patient. The transition probability from healthy state to bacteremia state per year was assumed at 1% in a hospital in the Mid-Atlantic geographic region, where the prevalence of the disease was 28% [6], and the cost for WGS was assumed at $100 per test based on market price.

In this model, the strategy using WGS test were more cost effective than the SOC at UPMC Presbyterian Hospital by reducing the number of new cases infected (Table 3). In fact, the SOC was dominated by the WGS test strategy given the sensitivity of the test was 0.97 and the specificity was 0.99[19], and the prevalence-adjusting factor (a=2).

**Table 3. Results of base case analysis.**

| Strategy | Cost | QALY (years) | ICER* (per QALY gained) |
|---|---|---|---|
| SOC | $4,583.50 | 8.0507 | $4,173.36 |
| WGS | $3,281.80 | 8.0819 | - |

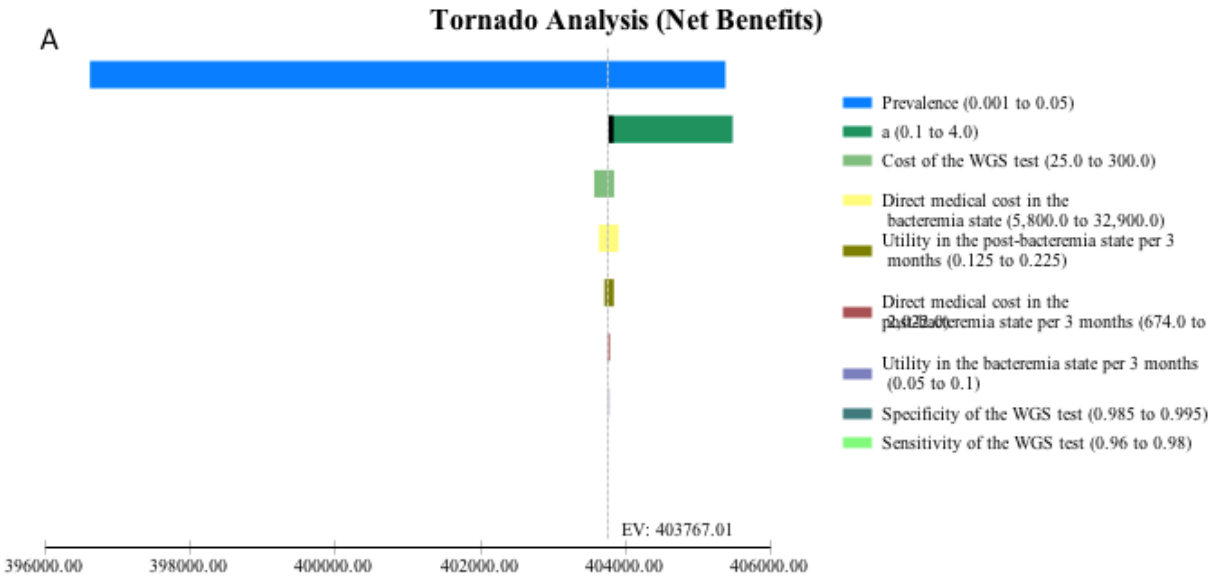
When the hospital adopted the WGS test strategy, given the sensitivity of the test was 0.97 and the specificity was 0.99, the 10-year costs for a cohort of 1000, the QALYs, and the incremental cost-effectiveness ratios (ICERs) were estimated with our model. Since the hospital is located in the Mid-Atlantic geographic region, with the highest prevalence of KPC-positive *K. pneumoniae* in the nation at 28% and the percentage of its resistance to high-level disinfection is higher than 6%, the transition probability from healthy state to bacteremia state was assumed at 0.01 (assume both the prevalence and percentage of resistance are higher in the hospital setting).[6] Under these conditions, the total 10-year mean cost for one patients was $3,281.80; while the mean QALYs the patient gained was 8.0819.

In the SOC strategy, since 6.1% of the KPC-positive *K. pneumoniae* is resistant to high-level disinfection there is an expectation of consistent rate of bacteremia infection for the patient after undergoing endoscopic retrograde cholangiopancreatography (ERCP) [6]. Due to slow turnaround time and resistance to disinfection, the probably of healthy patients getting bacteremia was assumed with the prevalence-adjusting factor (a) equaled 2. The mean 10-year cost for one patient (including treatment cost for bacteremia and inpatient cost during the post-bacteremia period) was $4,583.50; while the mean QALY gained was 8.0507 during that span.

The SOC strategy (high-level disinfection) was a dominated strategy. Compared with the best strategy – the WGS with the sensitivity of the test was 0.97 and the specificity was 0.99. From cost-effectiveness analysis (CEA) perspective, the ICER was $4,173.76 per QALY. (Table 3)

### 3.3 SENSITIVITY ANALYSIS

One-way sensitivity analysis of important model parameters (see Table 2), and the results are shown in Figure 4. In the WGS strategy, varying all the critical parameters resulted in similar cost effectiveness as in the base case. Net monetary benefits were plotted in the Figure 4. The WGS strategy remain the dominant strategy when variables like prevalence of KPC-positive *K. pneumoniae*, prevalence-adjusting factor (a), sensitivity and specificity of the WGS test, annual cost in the post-bacteremia state, WGS cost, inpatient cost in the bacteremia state, HRQL in the post-bacteremia state, and HRQL in the bacteremia state varied (Figure 4A and 4B). Figure 4B shows the same results as in Figure 4A in the absence of variables of prevalence and prevalence-adjusting factor (a).



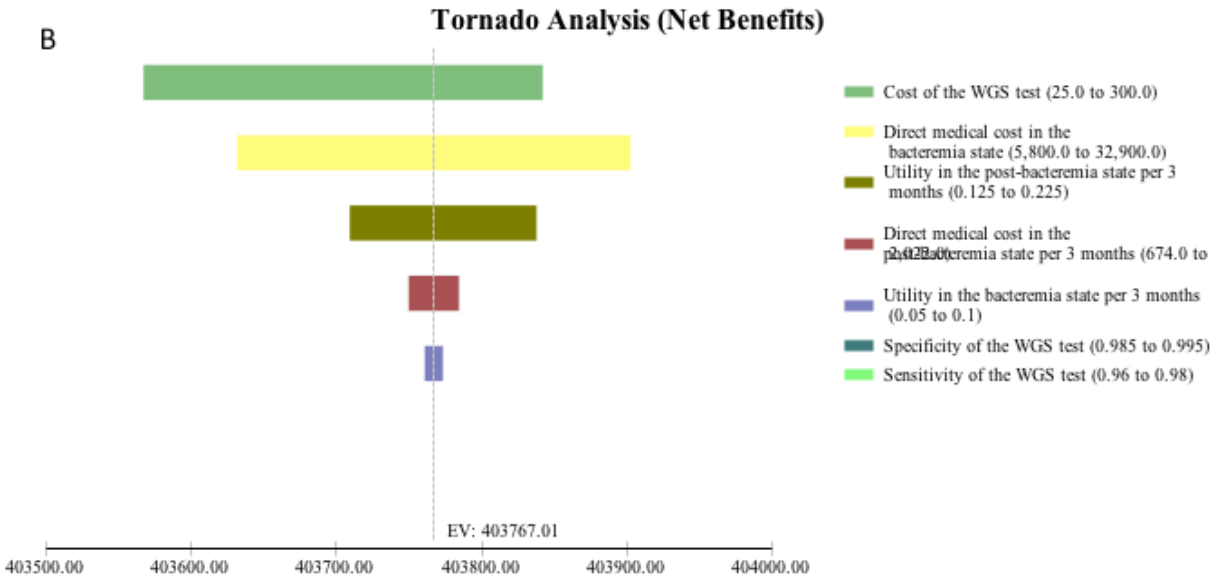



**Figure 4. One-way sensitivity analyses of critical model parameters for the WGS.**

A) A tornado diagram of net monetary benefits of all variables that varied within the range indicated. B) A tornado diagram of net monetary benefits of all variables but prevalence or prevalence-adjusting factor (a).

## 3.4 PROBABILISTIC SENSITIVITY ANALYSIS

In the probabilistic sensitivity analysis (PSA), we took 1000 random values for several parameters simultaneously. The median ICER was -$4985.91/QALY. Figure 5 (the Incremental Cost-Effectiveness (CE) scatter plot) shows 89.6% of all 1,000 PSA simulations fell in the 4$^{th}$ quadrant when comparing the WGS strategy to the SOC one, meaning the SOC strategy is more expensive and less effective. With a willingness-to-pay (WTP) level at $50,000, none of the simulations had an ICER higher than the $50,000/QALY threshold (Figure 5). This calculation

suggests that there is 0% chance that the SOC strategy is cost effective compared with the WGS strategy at that threshold.

The Cost-Effectiveness acceptability curve (Figure 6) shows that at no level of WTP the SOC strategy is cost effective than the WGS strategy.

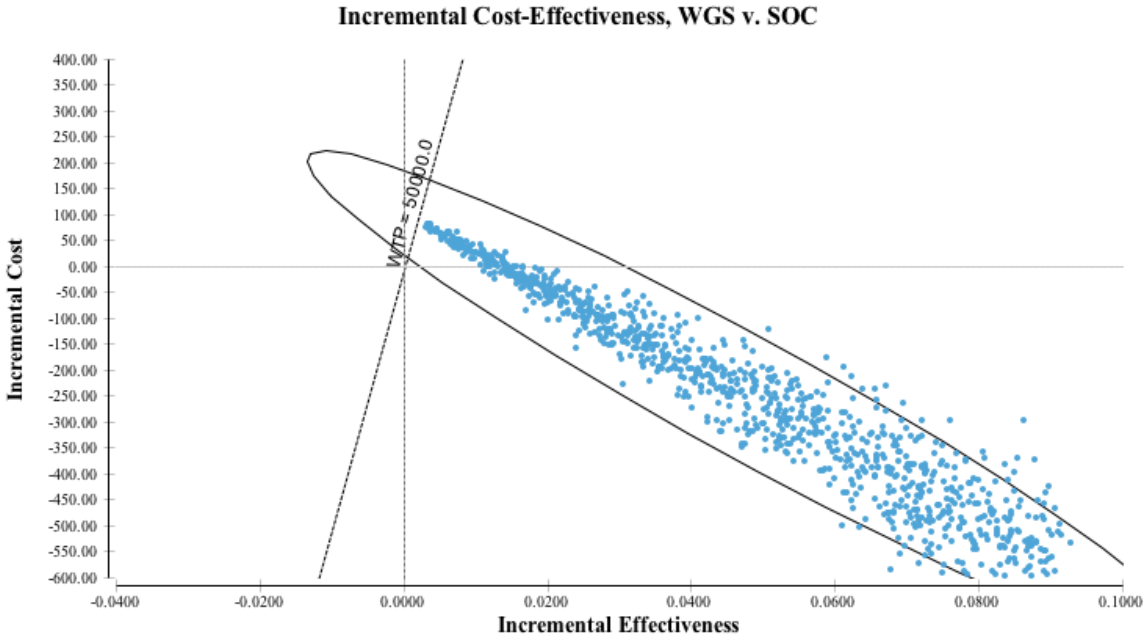



**Figure 5. Incremental cost-effectiveness plot.**

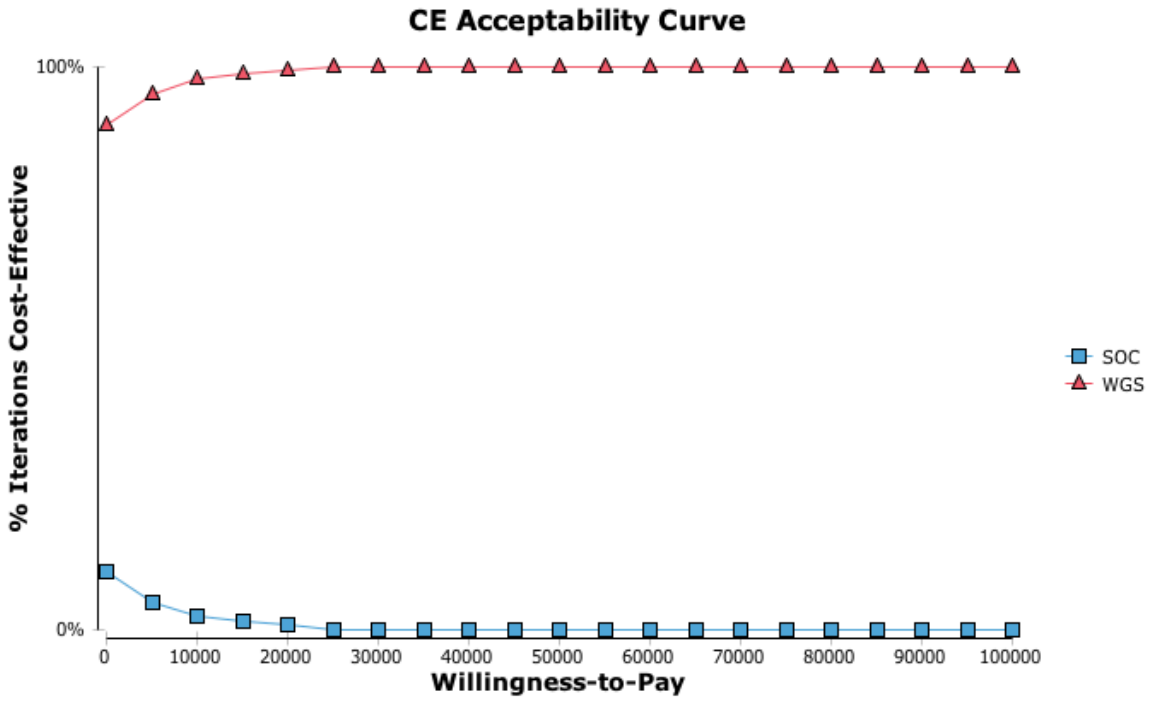



**Figure 6. Cost-effectiveness acceptability curves.**

Cost-Effectiveness Acceptability Curve of the WGS strategy vs the SOC strategy.

# 4.0 DISCUSSION

The results from the current study suggest the WGS strategy is more cost effective than the SOC strategy in preventing number of new cases of PC-positive *K. pneumoniae* in an outbreak of antimicrobial-resistant KPC-positive *K. pneumoniae* from patients undergoing endoscopic retrograde cholangiopancreatography in a Mid-Atlantic hospital. In our model, the SOC strategy is dominated by the WGS test strategy. When the sensitivity of the WGS was 0.97, the specificity was 0.99, and prevalence-adjusting factor (a=2) the mean total 10-year cost for one patient was $3,281.80; while the patient on average gained 8.0819 QALYs; while the SOC strategy over the same time frame had the mean 10-year cost of $4,583.50 for one patient; while gaining on average 8.0507 QALYs. The reduction in total healthcare cost over 10 years accompanied with higher total QALYs is likely due to the both high accuracy (high sensitivity and specificity) and faster turnaround time (high prevalence-adjusting factor for SOC strategy) of the WGS strategy. In one study, researchers found that the turnaround time of 72 hrs, which is significantly shorter than a standard diagnosis testing. [20]

Since the next generation sequencing technology becomes more and more affordable in recent years, some researchers have considered adopting it in the clinical setting to help detect infections. [20,21] In the study conducted by Cirillo et al., the authors assumed the cost for the WGS test is €150, very close to the assumption in this study ($100). The authors concluded that WGS is a rapid, cost-reasonable technique that can replace the current routine laboratory test for an

accurate diagnosis of drug-resistant tuberculosis, although there was no cost-effectiveness analysis done in the literature to this day. [20] In another study, Roe et al. also highly praised the WGS tests allowing precise identification or exclusion of transmission of hospital-acquired infections. [21] It is reasonable to speculate that one day in the near future, routine WGS tests will become the new SOC in the hospital setting to identify hospital-acquired infections given its combination of high accuracy, fast turnaround time, and affordable cost as a cost-effective alternative to the current SOC.

Recent outbreak of antimicrobial-resistant KPC-positive *K. pneumoniae* from patients undergoing endoscopic retrograde cholangiopancreatography in the University of Pittsburgh Medical Center (UPMC) Presbyterian Hospital did lead to potentially preventable life lost, increase in healthcare cost, and reduce in health-related quality of life [1]. Indeed, preventing outbreak of KPC-positive *K. pneumoniae* is very important in the Pittsburgh area for the following reasons. First, in a previous study, Nationwide SENTRY surveillance data from 2007 to 2009 revealed that Mid-Atlantic states continued to show a significantly higher frequency of KPC-positive organisms than other regions in the US: 28.6% in Mid-Atlantic vs 5.5% nationwide.[6] Geographically, Pittsburgh is within the Mid-Atlantic region, and therefore, prevention of dramatic higher prevalence of KPC-positive organisms is critical for public health. Second, KPC-positive *K. pneumoniae* isolates are resistant to all the commonly available antimicrobials, so routine high-level infection is not able to remove it.[1] Third, the consequence of infection of KPC-positive *K. pneumoniae* is very serious since it can increase mortality rate and lower quality of life.

It becomes clear after this study, the WGS test is particular cost-effective for a hospital located in Pittsburgh, a region of Mid-Atlantic. Mid-Atlantic has a five-fold increase in

frequency of KPC-positive organisms, and this is likely to dramatically increase the chance of infections in the healthcare systems. As the sensitivity analyses showed, when the prevalence of KPC-positive *K. pneumoniae* was the most sensitive factor in our model (Figure 4). However, even when this is the case, implementing the WGS strategy will represent a cost-effective option since the ICER is far less than what is considered good value for money ($50,000-$100,000/QALY). Overall, the sensitivity analysis suggested the robustness of the current model.

The current study has a few limitations. First, the current study was limited by few data of clinical information regarding mortality rate, comorbidities of patients infected with KPC-positive *K. pneumoniae*. Estimates were mostly collected from cases of sepsis patients, which might not be accurate. Second, the utilities for patients in bacteremia state and post-bacteremia state were estimated separately. It would be more accurate to have these estimates from the same source. Third, the study lacked data for subgroup analyses.

In conclusion, from the healthcare provider's perspective, the whole genome sequencing strategy is despite its high initial costs, WGS can save lives, reduce morbidity, and be cost-saving on the long-run compared to the SOC.

## BIBLIOGRAPHY


1. Marsh JW, Krauland MG, Nelson JS, et al. Genomic Epidemiology of an Endoscope-Associated Outbreak of Klebsiella pneumoniae Carbapenemase (KPC)-Producing K. pneumoniae. PloS one 2015;10:e0144310.

2. Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics. Working Paper 7. 2012. (Accessed Jan, 8, 2017, at http://www.unitedhealthgroup.com/~/media/uhg/pdf/2012/unh-working-paper-7.ashx.)

3. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53:60-7.

4. Pitout JD, Nordmann P, Poirel L. Carbapenemase-Producing Klebsiella pneumoniae, a Key Pathogen Set for Global Nosocomial Dominance. Antimicrob Agents Chemother 2015;59:5873-84.

5. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med 2005;165:1430-5.

6. Kaiser RM, Castanheira M, Jones RN, Tenover F, Lynfield R. Trends in Klebsiella pneumoniae carbapenemase-positive K. pneumoniae in US hospitals: report from the 2007-2009 SENTRY Antimicrobial Surveillance Program. Diagnostic microbiology and infectious disease 2013;76:356-60.

7. Endimiani A, Perez F, Bajaksouzian S, et al. Evaluation of updated interpretative criteria for categorizing Klebsiella pneumoniae with reduced carbapenem susceptibility. J Clin Microbiol 2010;48:4417-25.

8. National action plan to prevent healthcare-associated infections: roadmap to elimination. Washington, DC. (Accessed Jan, 8, 2017, at https://http://www.performance.gov/content/improve-patient-safety.)

9. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198-208.

10. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Critical care medicine 2010;38:1276-83.

11. Battle CE, Davies G, Evans PA. Long term health-related quality of life in survivors of sepsis in South West Wales: an epidemiological study. PloS one 2014;9:e116304.

12. Granja C, Dias C, Costa-Pereira A, Sarmento A. Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. Critical care 2004;8:R91-8.

13. Talmor D, Greenberg D, Howell MD, Lisbon A, Novack V, Shapiro N. The costs and cost-effectiveness of an integrated sepsis treatment protocol. Critical care medicine 2008;36:1168-74.

14. Paratz JD, Kenardy J, Mitchell G, et al. IMPOSE (IMProving Outcomes after Sepsis)-the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes-a double-blinded randomised controlled trial: protocol. BMJ open 2014;4:e004966.

15. Beck JR, Pauker SG, Gottlieb JE, Klein K, Kassirer JP. A convenient approximation of life expectancy (the "DEALE"). II. Use in medical decision-making. The American journal of medicine 1982;73:889-97.

16. Eddleston JM, White P, Guthrie E. Survival, morbidity, and quality of life after discharge from intensive care. Critical care medicine 2000;28:2293-9.

17. Eber MR, Laxminarayan R, Perencevich EN, Malani A. Clinical and economic outcomes attributable to health care-associated sepsis and pneumonia. Archives of internal medicine 2010;170:347-53.

18. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. Journal of the American Geriatrics Society 2012;60:1070-7.

19. Koser CU, Ellington MJ, Peacock SJ. Whole-genome sequencing to control antimicrobial resistance. Trends in genetics : TIG 2014;30:401-7.

20. Cirillo DM, Cabibbe AM, De Filippo MR, et al. Use of WGS in Mycobacterium tuberculosis routine diagnosis. International journal of mycobacteriology 2016;5 Suppl 1:S252-S3.

21. Roe CC, Horn KS, Driebe EM, et al. Whole genome SNP typing to investigate methicillin-resistant Staphylococcus aureus carriage in a health-care provider as the source of multiple surgical site infections. Hereditas 2016;153:11.