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Applying Epidemiology-Based Outcomes Research to Clinical Decision-Making

A Hypothetical Model of Biotechnology Therapy in Gram-Negative Sepsis

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Abstract

Objective: Sepsis occurs in a heterogeneous population. A prospective nationwide surveillance study found that populations stratified by infection type had significant differences in the incidence of sepsis syndrome, rate of complications and mortality. The objective of this study was to explore whether successful identification of population-specific risk factors for disease-associated morbidity and mortality may allow for more accurate assessment of the cost effectiveness of treatment strategies.

Design: A decision analytic model was developed using outcomes data on incidence and resolution of major complications in sepsis syndrome. Healthcare resource utilisation data were based on length of hospital stay, intensive care unit stay versus hospital ward stay, and cost of treating sepsis-related complications.

Setting: This modelling study, conducted from the perspective of the healthcare institution, used actual outcomes data on 2 infection-specific patient populations.

Patients and participants: The 2 populations studied were patients with nosocomial respiratory tract infection or community-acquired urinary tract infection who subsequently developed sepsis syndrome.

Interventions: Treatment options modelled were standard therapy plus biotechnology therapy versus standard therapy alone in the treatment of gram-negative sepsis complications.

Main outcome measures and results: The incremental cost-effectiveness ratios differed between the 2 study populations, due to differences in the incidence and rate of resolution of major sepsis-associated complications. The use of biotechnology therapy is always more cost effective in the respiratory tract infection population.

Conclusions: Cost-effectiveness results for a therapy may change when the epidemiology of the disease state is known and incorporated into the decision analytic model. An infection-specific approach is important in the treatment of sepsis.

Between 1980 and 1992, the rate of death in the US due to septicaemia increased by 83%, from 4.2 to 7.7 per 100 000 patients.[1] During this time, 2 new agents for the treatment of sepsis were developed and underwent clinical trials in the early 1990s. These trials did not show an overall reduction in mortality; rather, they raised many questions regarding the efficacy and cost effectiveness of these agents.[2-5]

Sepsis occurs in a heterogeneous population and no adequate tests exist for its diagnosis. For the majority of patients, the disorder is related to an underlying disease. Sepsis may be the common pathway to mortality for patients with a wide variety of nosocomial and community-acquired infections. Although patients with different underlying disease processes may present with similar clinical signs of sepsis, the probabilities of complications and outcomes are different.[6,7] A prospective nationwide surveillance study conducted by Conboy et al.[8] found that populations stratified by infection type had significant differences in the incidence of sepsis syndrome, rate of complications and mortality. Identification of population-specific risk factors for sepsis-associated complications and mortality may allow targeting treatment to patients with a higher likelihood of response and, thus, improve cost effectiveness.[8-10]

Two cost-effectiveness analyses for the biotechnology therapies nebacumab (HA-1A) and edobacomab (E5), monoclonal antibodies against bacterial endotoxins, were developed in anticipation of their marketing in the early 1990s.[2-4] The studies used decision trees and treatment algorithms to make recommendations for optimising therapy, minimising costs and maximising cost effectiveness under postulated conditions. However, inclusion of additional information such as comorbid complications and disease-specific outcomes would have increased the value of the results of these analyses. In addition, incorporation of advanced decision analysis using epidemiological data would have produced a model more relevant to clinical practice.[5,9,10]

As an exploratory exercise, we incorporated infection-specific patient data from Conboy et al.[8] into a decision analytic model. Specifically, we used outcomes data on incidence and resolution of major complications to assess the cost effectiveness of biotechnology therapy in the treatment of gram-negative sepsis complications in 2 patient populations at different risks for morbidity and mortality. The patients studied had been diagnosed with either nosocomial respiratory tract infection (NRTI) or community-acquired urinary tract infection (CUTI), and subsequently developed sepsis syndrome.[8] These 2 populations were chosen because they are at opposite ends of the spectrum in terms of risk for sepsis-associated morbidity and mortality.

Methods

Data on sepsis were obtained from the work of Conboy et al.,[8] who conducted a prospective surveillance study of US hospitals to determine: (i) the incidence of sepsis and septic shock in various high-risk patient populations; and (ii) the effect of septic shock and organ failure on duration of hospitalisation, intensive care unit (ICU) stay and treatment of sepsis complications.

The sepsis database consisted of 1754 patients enrolled at 80 hospitals; 188 (10.7%) had NRTI and 227 (12.9%) had CUTI. Of the patients with NRTI, 63 (33.5%) developed sepsis syndrome and 31 (49.2%) survived the episode. Of the patients with CUTI, 30 (13.2%) developed sepsis syndrome and 25 (83.3%) survived the episode. Using morbidity data from this report, a decision analytic model was developed for the survivors.[7] This analysis was conducted from the perspective of the healthcare institution.

Decision Tree and Patient Outcomes

A decision tree was used to characterise treatment options and outcomes (fig. 1). The proposed treatments, represented as decision nodes, were standard therapy for sepsis (e.g. antibacterials) and standard therapy plus biotechnology therapy as an adjunct. There were 6 possible outcomes based on the decision tree.[11]

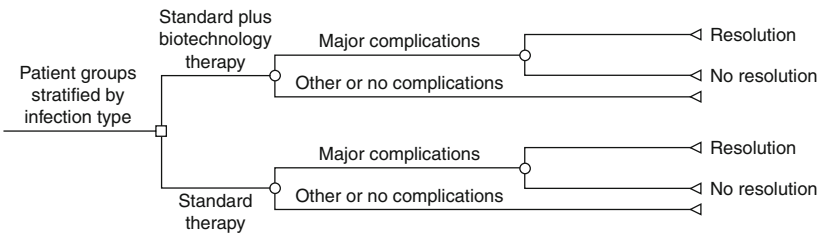

Fig. 1. Decision tree for treatment of gram-negative sepsis in patients with nosocomial respiratory tract infection or community-acquired urinary tract infection. The square indicates a decision node and the circles indicate chance nodes.

Based on previous clinical research, we assumed no difference in mortality rates between biotechnology therapy and standard therapy, and no difference in time to death.[4,5] Rather, the study results suggested improvement in resolution of major complications as the real benefits of biotechnology therapy. Patients with other or no complications did not benefit from the use of biotechnology therapy, and resolution of other complications was not an issue.

Therefore, patient outcomes were defined by the incidence and resolution of sepsis-associated complications. 'Major' complications evaluated paralleled those in the second trial of E5:[4] adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and acute renal failure (ARF). ARDS was defined as arterial partial pressure of oxygen/fractional concentration of inspired oxygen (PaO_2/FIO_2) <175, bilateral pulmonary infiltrates on chest film and/or pulmonary capillary wedge pressure <18mm Hg; resolution was defined as clearing of bilateral lung infiltrates and PaO_2/FIO_2 □175.[8] ARF was defined as serum creatinine increase to □2 mg/dl; resolution was defined as a return to <2 mg/dl, or to baseline in patients with preexisting renal insufficiency.[8] DIC was defined as elevated fibrin degradation products (FDP) titre >1 : 40 or D-dimers >2.0 in conjunction with a decrease of >25% of baseline in platelet count and either an elevated prothrombin time (PT) or partial thromboplastin time (PTT), or clinical evidence of bleeding. Resolution was defined as D-dimers <2.0, FDP titre <1 : 40, return of PT or PTT to normal, and a platelet count increase of 25% over nadir, and return to normal.[8] Other complications included CNS dysfunction and hepatobiliary dysfunction.

Study Time-Frame

Because of the acute nature of the disease, this analysis was applied to a 28-day period starting from the time of diagnosis of sepsis syndrome. Patients discharged before day 28 were considered survivors. In the subsequent calculations of costs of therapy and length of hospitalisation, the date of antibacterial discontinuation was used rather than the actual discharge date to account for patients who remained in the hospital for treatment of underlying disease as opposed to sepsis.

Incidence and Rate of Resolution of Complications

The incidence of major complications in the CUTI and NRTI populations was 12.0 and 22.6%, respectively, and the rate of resolution of major complications was 33.3 and 57.1%, respectively.[8]

In clinical trials, the reported rate of resolution of major complications in patients given biotechnology therapy was between 48 and 62% (table I).[2-4] To mimic this observed range of clinical improvement for our hypothetical model, we postulated a 20% relative increase in resolution rates as the efficacy of biotechnology therapy in both populations. Therefore, we would anticipate improved resolution rates of 40% (= 33.3% □ 1.20) and 68.5% (= 57.1% □ 1.20) in the CUTI and NRTI groups, respectively. A follow-up sensitivity analy-

Table I. Rate of resolution of major complications in patients with gram-negative sepsis

Trial	Rate of resolution (%)	
	placebo	E5 or HA-1A
Ziegler et al.[2]	42	62
Greenman et al.[3]	30	54
Bone et al.[4]	25	48

E5 = edobacomab; **HA-1A** = nebacumab.

sis (see the section 'Sensitivity Analyses') was performed to test the robustness of this assumption.

Charge Determination

Difficulties in obtaining cost data arise from factors such as incompatible accounting systems and the inability to precisely quantify all variable and fixed components of care and services. Because of these difficulties, charges for treatment and hospitalisation of patients with sepsis were used in this analysis. Discounting was not used because of the short study time-frame.

Table II presents the financial data utilised.[12-15] The hospital bed charges used by the Millard Fillmore Health System were adapted from Blue Cross/Blue Shield rates, which were applicable statewide (personal communication from Ms Ruthann Herdle, statistician, Millard Fillmore Health System, 23 January 1996). Other charges were based on itemised treatment procedures listed in the hospital's price listing. Treatment procedures and associated charges for a specific complication were used to compute a total daily treatment charge. Information about the intensity of utilisation of treatment procedures for each complication was not available from the sepsis database. For this reason, sensitivity analyses were performed to account for a wide range of daily charges for treating complications.

The charge for managing major complications was calculated by multiplying the mean duration of each complication by the charge per day associated with the specific complication, stratified by resolution status. The mean duration of stay in the ICU or hospital ward was multiplied by the location-specific charge per day to obtain the corresponding bed charge for all patients. Charges associated with management of a complication and the bed charge were combined to yield an estimate of the total charge for the average patient with major complications.

Studies examining hospital charges have shown varying levels of resource consumption associated with ICU admission and inhospital mortality.[9,16,17] Therefore, patients who died within the 28-day study period were excluded from this analysis. A separate cost analysis is necessary to assess the economic impact of biotechnology therapy in patients who die. This was justified because repeated studies have failed to demonstrate a statistically significant effect of treatment on mortality.

Two baseline charges, $US2000 and $US4000, were used as the price for biotechnology therapy. The $US4000 figure is based on initial estimates of the market price of E5 and HA-1A before the discontinuation of clinical trials for these products.[9,10] The $US2000 figure is based on comparison with the prices of currently marketed biotechnology

Table II. Estimated charges used in this study (personal communication from Ms Ruthann Herdle, statistician, Millard Fillmore Health System, 23 January 1996)

Item	Charge ($US)[a]	Total charge per day ($US)
Day in ICU	1250.00	1250.00
Day in ward	415.00	415.00
ARF[12]		
dialysis[b]	136.50	136.50
ARDS[13]		
ventilator	116.50	
PEEP[c]	18.00	140.00
tubing	5.50	
DIC[14,15]		
cryoprecipitate	22.00	
platelets	65.50	188.50
packed RBCs	101.00	

a Per treatment procedure or day.

b The charge ($US273) was halved to reflect an estimated 50% usage of renal dialysis.

c Although patients may need PEEP multiple times per day, only 1 usage was included in the daily charge.

ARDS = adult respiratory distress syndrome; **ARF** = acute renal failure; **DIC** = disseminated intravascular coagulation; **ICU** = intensive care unit; **PEEP** = positive end-expiratory pressure; **RBCs** = red blood cells.

agents such as recombinant alteplase and colony-stimulating factors.

Cost-Effectiveness Determinations

Effectiveness was defined as improved resolution of major complications. We hypothesised that biotechnology therapy would improve the rate of resolution of major complications, resulting in cost reduction. Multiplication of the dollar value assigned to each outcome by the probability of the specific outcome provided a weighted total charge for each treatment strategy. Incremental cost reflects the cost difference between therapies. The incremental cost-effectiveness ratio (ICER) is the extra cost needed for the additional resolution of major complications using biotechnology therapy plus standard therapy over standard therapy alone. The ICER for each infection-specific population was calculated by the formula:

□total charge/□resolution rates

for biotechnology plus standard therapy versus standard therapy alone.[9,18] The ICER was used for comparison between the 2 infection groups. Ratios were calculated for therapy charges at $US2000 and $US4000.

Sensitivity Analyses

Sensitivity analyses were performed using SMLTREE (J. Hollenberg, Boston, Massacusetts, USA), a DOS-based computer software program.[19] This program was used to systematically evaluate the impact of variations in treatment outcomes and costs on the cost effectiveness of biotechnology therapy. Sensitivity analyses were used also to determine decision thresholds – the values at which the optimal decision changes, or at which the favoured strategy becomes equivalent to the comparator (break-even point).[20]

One-way sensitivity analyses were performed on the following variables to test the robustness of the model: (i) price of biotechnology product; (ii) incidence of major complications; (iii) efficacy of biotechnology therapy in improving resolution of major complications; (iv) daily charges for ICU and hospital ward stay; and (v) daily charges for managing each major complication.

The charge for biotechnology therapy was varied from $US0 to $US4000. The incidence and rate of resolution of major complications were varied from 0.0 to 1.0. Based on published ratios, ICU to ward charges varied from 2 : 1 to 4 : 1.[16,17,21-23] Based on a ward charge of $US415 per day (personal communication from Ms Ruthann Herdle, statistician, Millard Fillmore Health System, 23 January 1996), the upper range of charges for ICU stay was set at $US2500 per day. Daily charges for treating each major complication differed slightly but all were under $US200. The range was set between $US0 and $US1000 per day to account for the possibility that some treatments may have been required multiple times to treat a complication.

Several 3-way sensitivity analyses were performed to determine model behaviour under different combinations of conditions. Incidence of major complications, rate of resolution of major complications and price of biotechnology therapy were varied simultaneously.

Statistical Analysis

The demographics of the infection populations were compared using $\square^2$ or Fisher's exact test for categorical variables (gender, comorbidities, rate of major complications) and analysis of variance (parametric or nonparametric) for continuous variables (age, bodyweight, average length of stay). Statistical significance was defined as $p < 0.05$.

Results

Patient Demographics

Overall, mean age was 75.3 □ 8.5 years, mean bodyweight was 68.3 □ 16.8kg, and 55.4% of patients were men (table III). The small study population may account for the lack of significance noted in demographic parameters between groups.

Of the 3 major complications, ARF was observed only in the CUTI group, and DIC and ARDS were only observed in the NRTI group (table III). Chronic obstructive pulmonary disease was more

Table III. Characteristics of the patient populations used in this study.[8] Values are means □ standard deviation, or absolute numbers and percentages

	CUTI (n = 25)	NRTI (n = 31)	p Value
Demographics			
Age (years)	76.4 □ 8.9	74.5 □ 8.3	NS
Men (%)	44.0	64.5	NS
Bodyweight (kg)	70.2 □ 19.7	66.8 □ 14.2	NS
Comorbidities [n (%)]			
COPD	1 (4.0)	8 (25.8)	0.03
CHF	9 (36.0)	7 (22.6)	NS
Stroke	3 (12.0)	0 (0)	NS
Diabetes	3 (12.0)	5 (16.1)	NS
Hepatic disease	2 (8.0)	2 (6.5)	NS
Malignancy	4 (16.0)	5 (16.1)	NS
Renal disease	6 (24.0)	0	0.005
Dialysis	2 (8.0)	0	NS
Alcoholism	3 (12.0)	6 (19.4)	NS
Complications [n (%)]			
ARDS	0	6 (19.4)	0.03
ARF	3 (12.0)	0	NS
DIC	0	1 (3.2)	NS
Overall	3 (12.0)	7 (22.6)	NS
Duration of hospitalisation with major complications			
ICU (days)	1.7 □ 1.5	21.1 □ 6.0	0.03
Ward (days)	15.0 □ 5.6	2.4 □ 5.6	0.02

ARDS = adult respiratory distress syndrome; **ARF** = acute renal failure; **CHF** = congestive heart failure; **COPD** = chronic obstructive pulmonary disease; **CUTI** = community-acquired urinary tract infection; **DIC** = disseminated intravascular coagulation; **ICU** = intensive care unit; **NRTI** = nosocomial respiratory tract infection; **NS** = not significant.

prevalent in patients with NRTI, and pre-existing renal disease was more prevalent in patients with CUTI. For patients developing major complications, the mean duration of ICU stay was shorter in the CUTI group; furthermore, these patients had a longer mean duration of stay in the hospital ward (table III). The converse was observed in patients with NRTI (i.e. longer ICU stay, shorter ward stay).

There was no significant difference in the mean duration of ICU stay or hospital ward stay for patients experiencing major versus other or no complications, respectively, in the CUTI group. However, the mean number of days spent in the hospital ward was significantly longer for NRTI patients who had other or no complications (6.3 *vs* 2.4 days; p = 0.02).

Cost-Effectiveness Determinations

The ICER differed between the 2 study populations because of differences in the incidence and rate of resolution of major complications. At a charge for biotechnology therapy of $US4000, an extra $US60 303 and $US34 562 per patient is required for the additional resolution of major complications over standard therapy alone in the CUTI and NRTI groups, respectively (table IV). The ratios are proportionately lowered if the biotechnology therapy is priced at $US2000. The use of biotechnology over standard therapy alone is always more cost effective in the NRTI population.

Sensitivity Analyses

Biotechnology Price of $US4000

At a biotechnology therapy price of $US4000, standard therapy was dominant in CUTI patients regardless of the probabilities of major complications or daily charges for ICU or hospital ward stay.

Biotechnology Price of $US2000

Table V shows the decision thresholds obtained from the 1-way sensitivity analyses. Use of biotechnology therapy became cost effective in the CUTI population when the incidence of major complications was □54%. Its use was always more cost effective than standard therapy alone in the NRTI group.

Use of biotechnology therapy became cost effective in the NRTI group when the resolution rate was □65%, representing a 13.8% relative improvement over standard therapy. In the CUTI group, a rate of resolution □41% made biotechnology ther-

Table IV. Cost-effectiveness determinations

Charge of biotechnology therapy ($US)	Incremental cost-effectiveness ratio ($US)	
	CUTI	NRTI
4000	60 303	34 562
2000	30 000	17 049

CUTI = community-acquired urinary tract infection; **NRTI** = nosocomial respiratory tract infection.

Table V. Decision thresholds obtained from 1-way sensitivity analyses. Values represent the critical points at which biotechnology therapy priced at $US2000 becomes cost effective

Infection type	Probability of major complications	Resolution rate	ICU charge per day ($US)	Ward charge per day ($US)	Charge for major complications per day ($US)
NRTI	□0	□0.65	□662	□0	ARDS □0, DIC □0
CUTI	□0.54	□0.41	□1593	□560	ARF □770

ARDS = adult respiratory distress syndrome; **ARF** = acute renal failure; **CUTI** = community-acquired urinary tract infection; **DIC** = disseminated intravascular coagulation; **ICU** = intensive care unit; **NRTI** = nosocomial respiratory tract infection.

apy cost effective, representing a 23.1% relative improvement.

When the ICU charge per day was □$US662, biotechnology therapy was cost effective in the NRTI group. The corresponding break-even point in the CUTI group was □$US1593. Biotechnology therapy was cost effective in the CUTI group when hospital ward charges were □$US560 per day. It was always cost effective in the NRTI group regardless of hospital ward charges. Biotechnology therapy was always cost effective in the NRTI population regardless of the charges for treating ARDS or DIC. It became cost effective in the CUTI group when the charge for treating ARF was □$US770.

Figure 2 depicts the ICER versus the charge for biotechnology therapy in the 2 infection populations. The difference in the ICERs increased as the charge for biotechnology therapy increased from $US0 to $US4000. The NRTI group always had a lower ICER than the CUTI group when compared using the same relative rate of resolution of major complications.

Figure 3 illustrates changes in cost effectiveness that occurred in the CUTI group when incidence of major complications, rate of resolution of major complications and charge for biotechnology therapy were varied in the 3-way sensitivity analyses.

Conclusions

Incorporating epidemiological data into health economic evaluations can improve the external validity of such research, as variations that could not be extrapolated from a retrospective model are taken into account. In this study, actual outcomes data for 2 infection-specific patient populations were utilised to allow for more accurate assessment of the cost effectiveness of treatment strategies. A decision tree was used to characterise treatment options and outcomes. Though useful for modelling purposes, it may be limited by the small population in this study.

Since incidence and resolution of major complications were directly related to infection type, this epidemiological information identifies patients who would benefit most from biotechnology therapy and plays a critical role in determining the cost-effectiveness profile of a treatment.

Because definitive diagnosis of gram-negative sepsis is often difficult at disease onset, treatment decisions are based on clinical observation. The ability to correctly diagnose patients has a profound impact on the cost effectiveness of biotechnology therapy.[9,10] By treating infection-specific

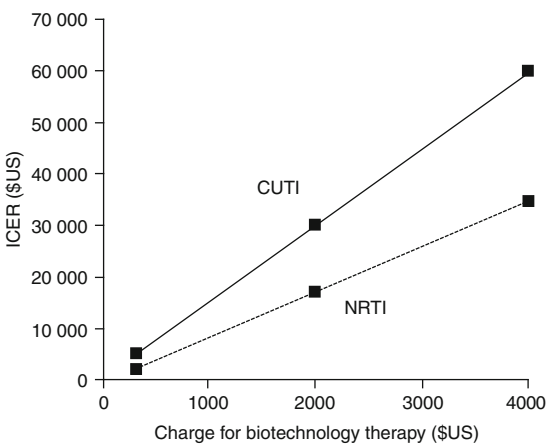

Fig. 2. Relationship of charge for biotechnology therapy to incremental cost-effectiveness ratio (ICER; the extra cost needed for the additional resolution of major complications using biotechnology therapy plus standard therapy over standard therapy alone) in the treatment of gram-negative sepsis in patients with nosocomial respiratory tract infection (NRTI) or community-acquired urinary tract infection (CUTI).

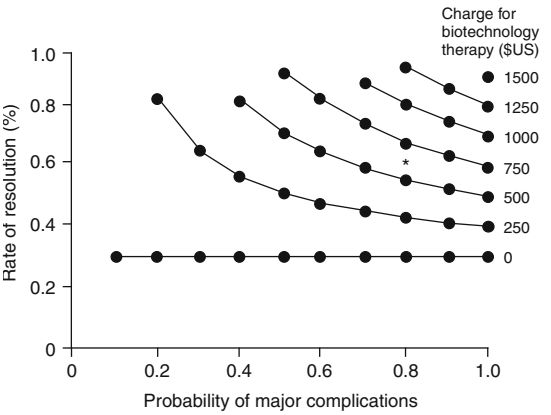

Fig. 3. Three-way sensitivity analyses for the population with community-acquired urinary tract infection, varying the rate of resolution and probability of major complications and the charge for biotechnology therapy. For points that lie above a specific curve, biotechnology therapy is cost effective. For example, if the probability of major complications was 0.80 and the charge for biotechnology therapy was $US500, biotechnology therapy would be cost effective at a complication resolution rate of 0.60 (indicated by asterisk).

patient populations with a high incidence of sepsis-associated complications, diagnostic accuracy is indirectly improved and thus the cost-effective use of relatively expensive therapy is increased. Because of the higher incidence of major complications in the NRTI versus the CUTI population, biotechnology therapy was more cost effective in the former group, given the same efficacy rate. The differences in ICERs among the 2 populations demonstrate the economic importance of considering the population being treated.

The 3-way sensitivity analysis demonstrated an important application of epidemiology-based outcomes research to clinical decision-making. If a desired level of cost effectiveness is established, along with a given efficacy, the incidence of disease-related complications necessary for that level of cost effectiveness could be identified as the threshold for treatment.[10] Although only price and efficacy are included in the conventional formulary decision-making process, consideration of epidemiological data as well can dramatically improve the patient outcomes of such decisions.

The effectiveness of biotechnology therapy in resolving various major complications is important and requires further clinical study. No patients in this study had multiple major complications. For patients with multiple major complications, biotechnology therapy may resolve each equally well, biotechnology therapy may not work as well, or the risk of death may be increased. Since biotechnology therapy does not effectively reduce mortality, it would be of little use in the latter group of patients.

This infection-specific cost-effectiveness evaluation was made possible by the availability of epidemiological data from a clinical database tracking the natural history of sepsis. The results of studies such as this are limited only by the quality of the available data and the small sample size. It is important to establish a system of collecting local and national epidemiological data on disease-specific patient outcomes.

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