UNIVERSITY of WASHINGTON

Economic Considerations in SJS/TENS Eradication

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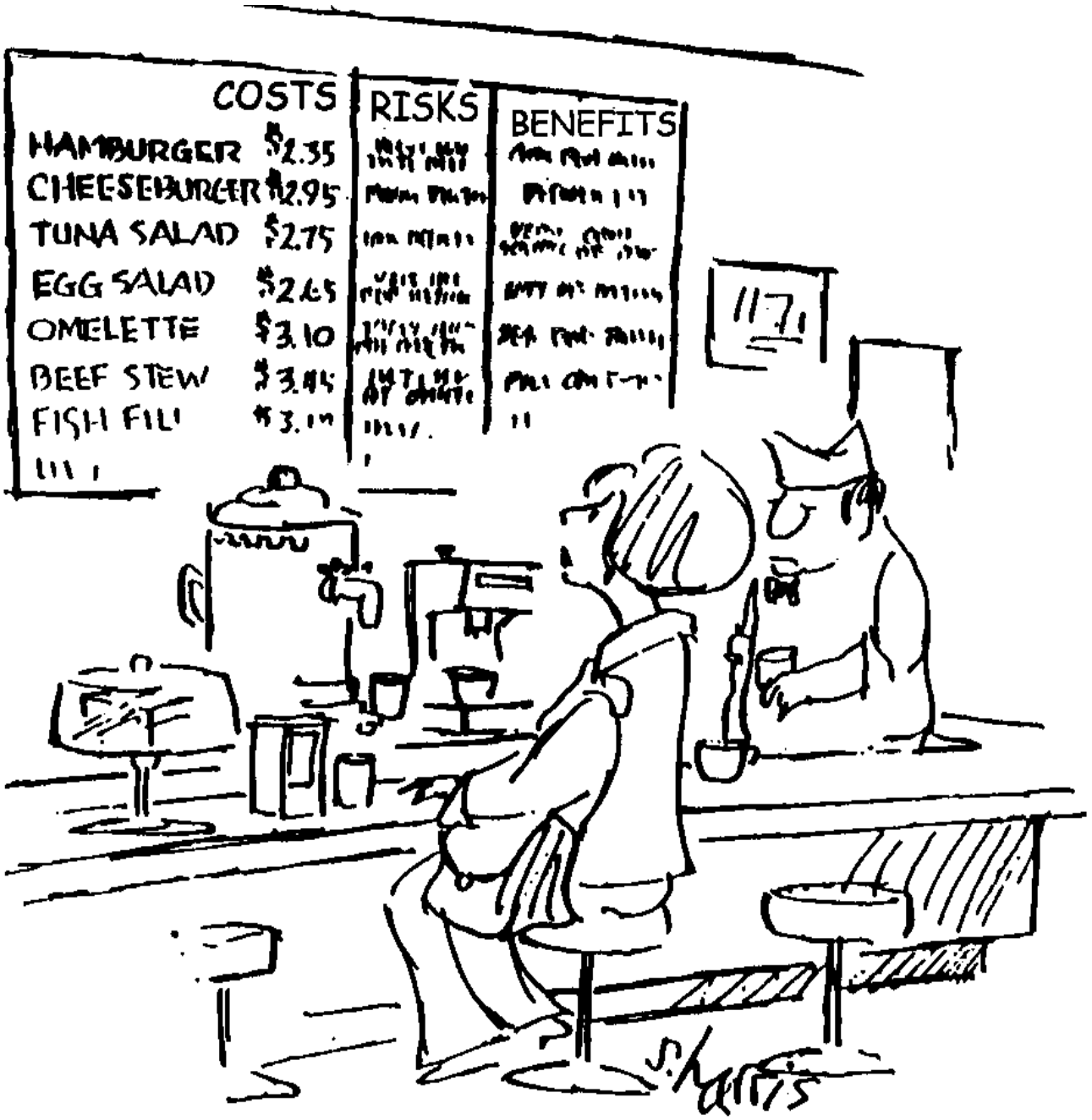
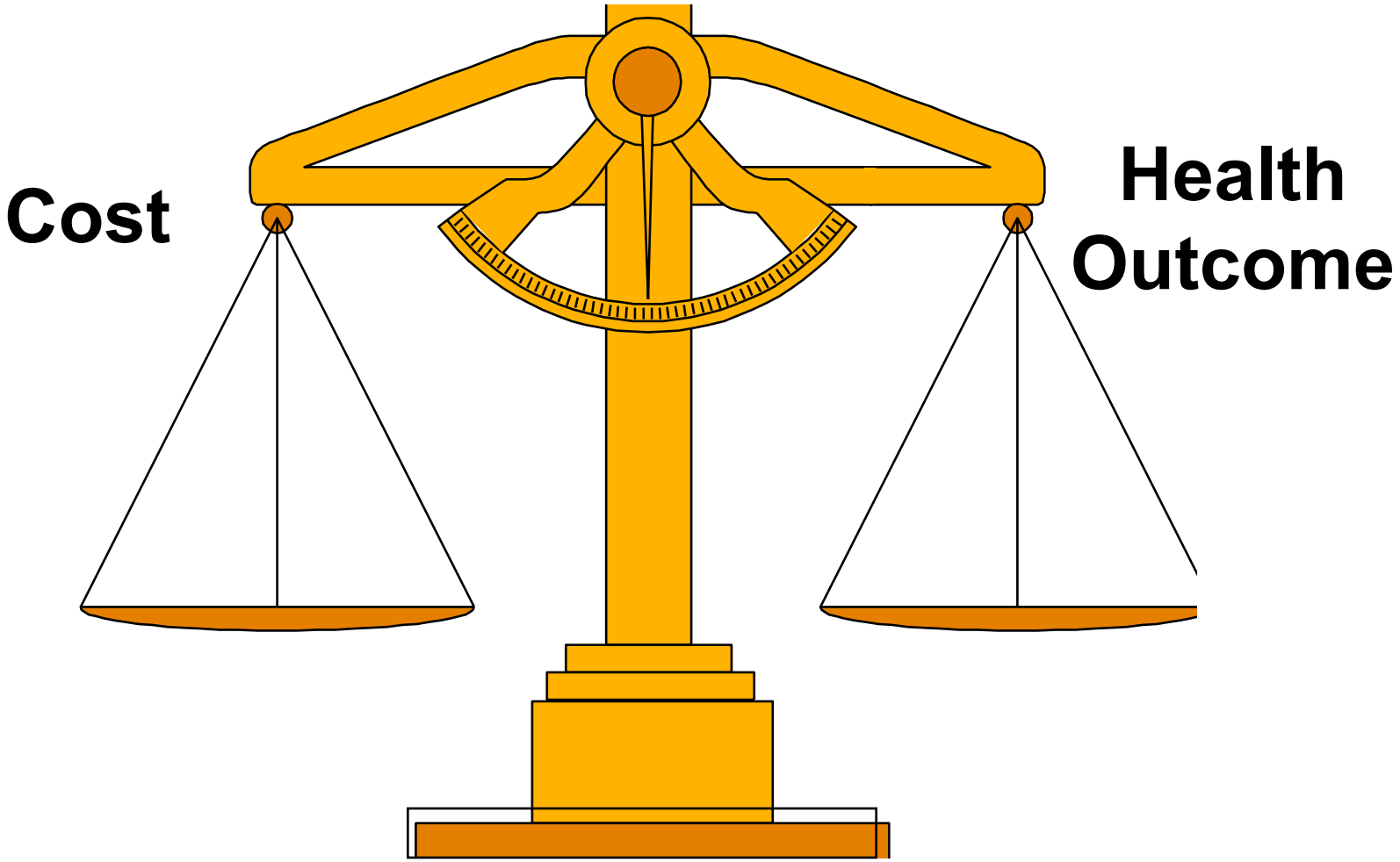
I. What does 'cost effective' mean?


COSTS
HAMBURGER $1.35
CHEESEBURGER $2.95
TUNA SALAD $2.75
EGG SALAD $2.65
OMELETTE $3.10
BEEF STEW
FISH FILI
RISKS
BENEFITS

Cost-effectiveness

- Does NOT mean
  - Cost saving
  - Cost minimization
- Is about value

VALUE



Health Outcomes

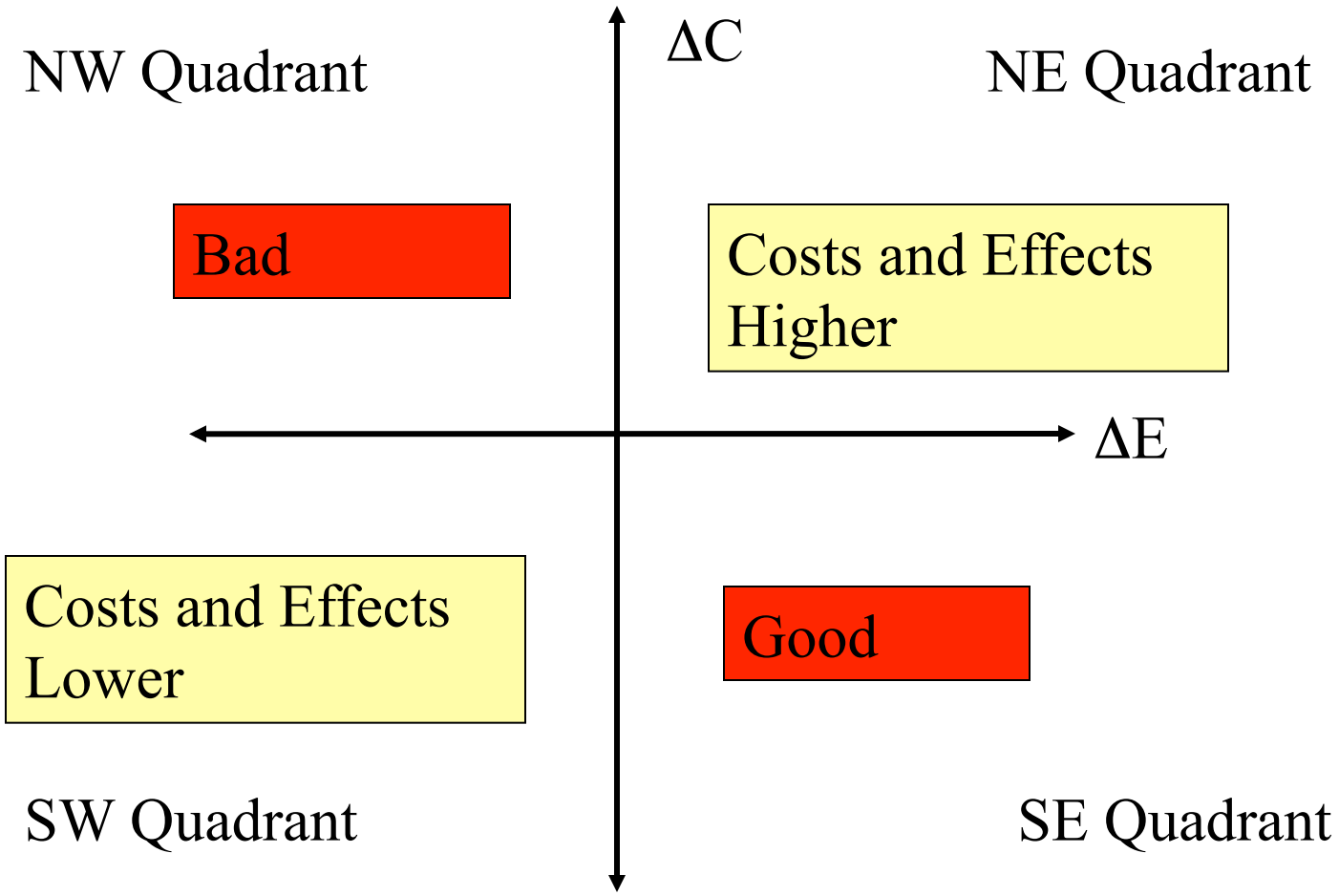
- Can be measured in clinical events
- Can be measured in life years (life expectancy)
- But what about quality of life?
- **QALY: quality-adjusted life-year**
  - Consider it a year of life with perfect health
  - QALY = LE x quality of life

Incremental cost-effectiveness ratio (ICER)

- Ratio of difference in cost to difference in effectiveness

$$ICER = \Delta C / \Delta E = (C_T - C_C) \Big/ (E_T - E_C)$$

Interpretation of CEA results



What's our 'ICER' threshold?

- Informally, about $100K/QALY in the U.S

Neumann et al, NEJM 2014

II. What do payers want?

Payer comment regarding companion diagnostic tests

"There is so much smoke out there around the variety of types of tests that can be useful. I would want to have specific information that would give you real measurable data about how the diagnosis affects the individual."

– *Payer*

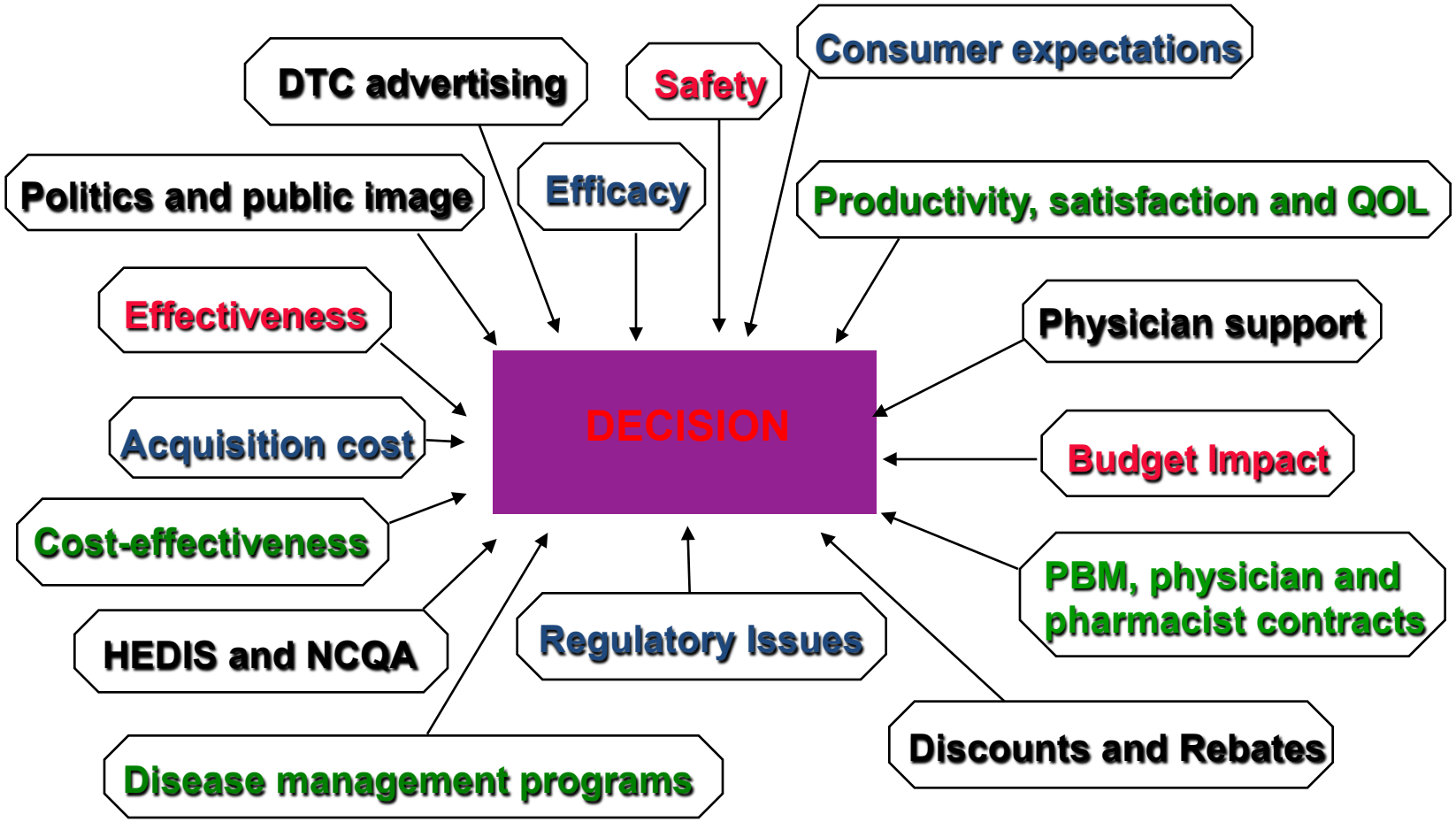
Payer comments regarding NGS

- *"If you focus on the economic impact of only clinically actionable results based on an ACMG list, won't you miss the impact of results of uncertain clinical significance and the impact of mutations in genes not on the ACMG list but included in the broader panels available for testing?"*
- *"This is one of our main concerns with broad panels …"*

What information does CEA provide to decision makers?

- Quantitative Risk-Benefit trade-off
- Value for money
- Uncertainty

But just one of the factors in reimbursement decisions!



III. A framework for evaluating the cost-effectiveness of PGx

1. How severe and frequent are the outcomes of interest?

- Is the outcome frequent?
  - No
  - 1 per 1,000 for patients on drug (Thailand, Allopurinol)
  - 1 per ~400 for CBZ (Singapore)
- Is the outcome severe?
  - Yes, very severe
  - mortality SJS 5-20%, TEN 30-70%

Flowers and Veenstra, Pharmacoeconomics 2004
Higashi and Veenstra, Am J Manag Care. 2003
Veenstra et al, AAPS PharmSci. 2000;2(3):E29

2. What is the alternative?

- Other drugs (e.g., valproate) have similar efficacy, potentially more expensive

3. What is the Strength of the Genotype-Phenotype Association? Prevalence of variant?

Example:

- 50% of patients with mutation get an ADR
- avoiding drug in **all** patients with mutation
- half of the patients (the "false positives") would unnecessarily be deprived of medication.

- RR for SJS
  - Thailand 5801 RR ~ 350
    - 1 per 100 in 5801 carriers vs. 1 per 100,000 in non-carriers (Thailand)
- Prevalence
  - Thailand 5801 15%, 1502 4%
  - Singapore 1502 ~15%
- PPV
  - 90+% false positives

4. Direct and induced costs?

- Direct cost
  - Target drugs not expensive – alternatives?
  - moderate to large AE for SJS/TENS
  - ~$200 USD for test
- Induced costs
  - additional clinic visits, genetic counseling
  - not likely significant
- Additional use of information
  - used throughout the lifetime of the patient for other dxs or drugs
  - not likely
- Time costs
  - For pharmacogenomics, turn-around time may be critical
  - Pre-emptive?

Other considerations

- Are alternative drugs less effective?
- Would family members be tested, or never take SJS/TENS-risk drugs?

IV. Economic Evaluation of HLA Testing to Prevent SJS

citation

Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore

Di Dong, BSc
Cynthia Sung, PhD
Eric Andrew Finkelstein, PhD

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ABSTRACT

Objective: Asians who carry the HLA-B*1502 allele have an elevated risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) when treated with the antiepileptic drugs (AEDs) carbamazepine (CBZ) and phenytoin (PHT). With a focus on Singapore, this analysis identifies circumstances in which genotyping and targeted treatment with alternative AEDs that do not induce SJS/TEN is likely to be more cost-effective than 1) treatment with CBZ or PHT without genotyping or 2) providing a more expensive drug that does not induce SJS/TEN to all patients without genotyping.

Figure 1 **Decision tree model of 3 treatment strategies for adult patients with newly diagnosed epilepsy in Singapore for whom carbamazepine (CBZ)/phenytoin (PHT) is considered appropriate treatment**

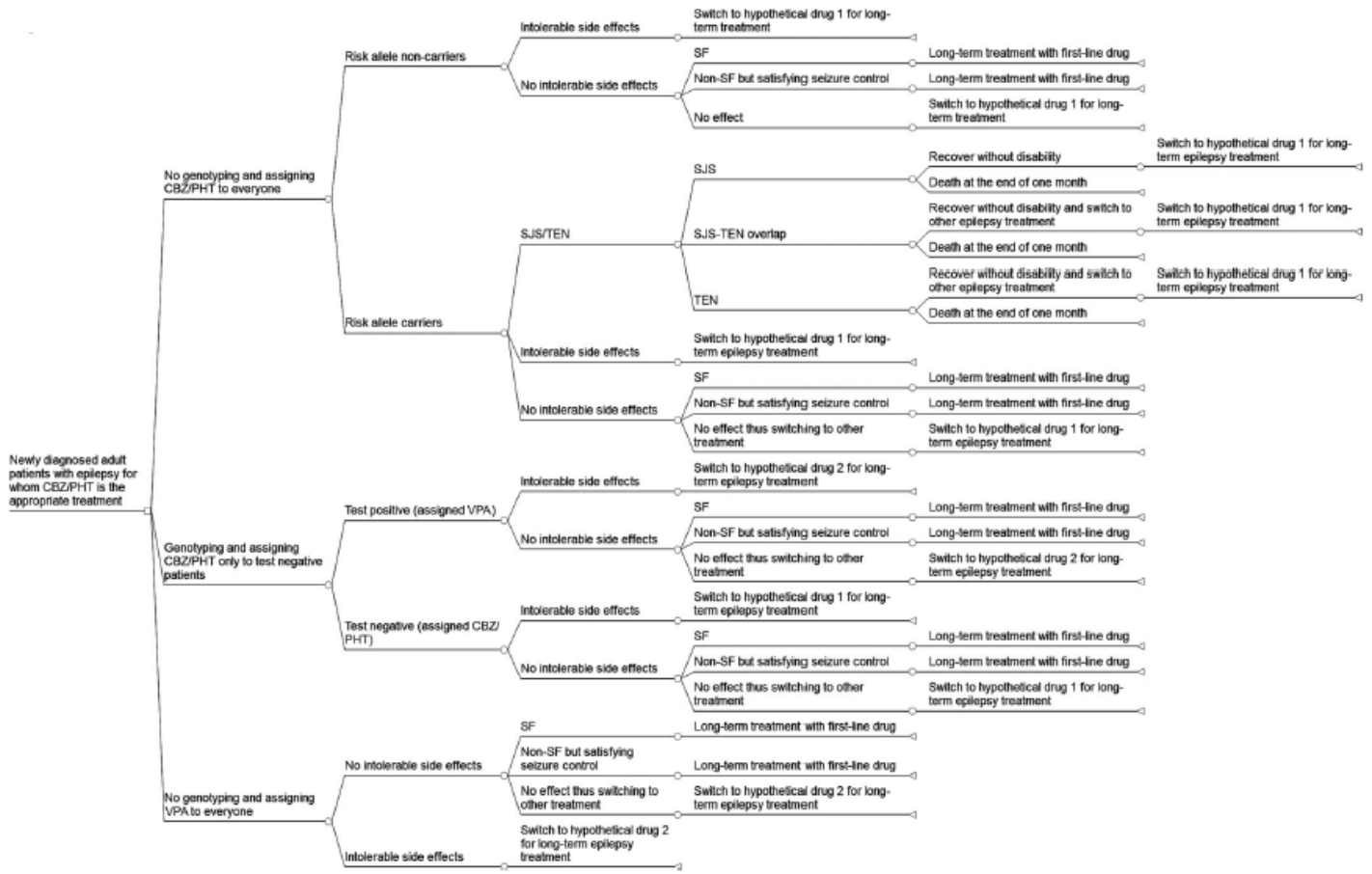
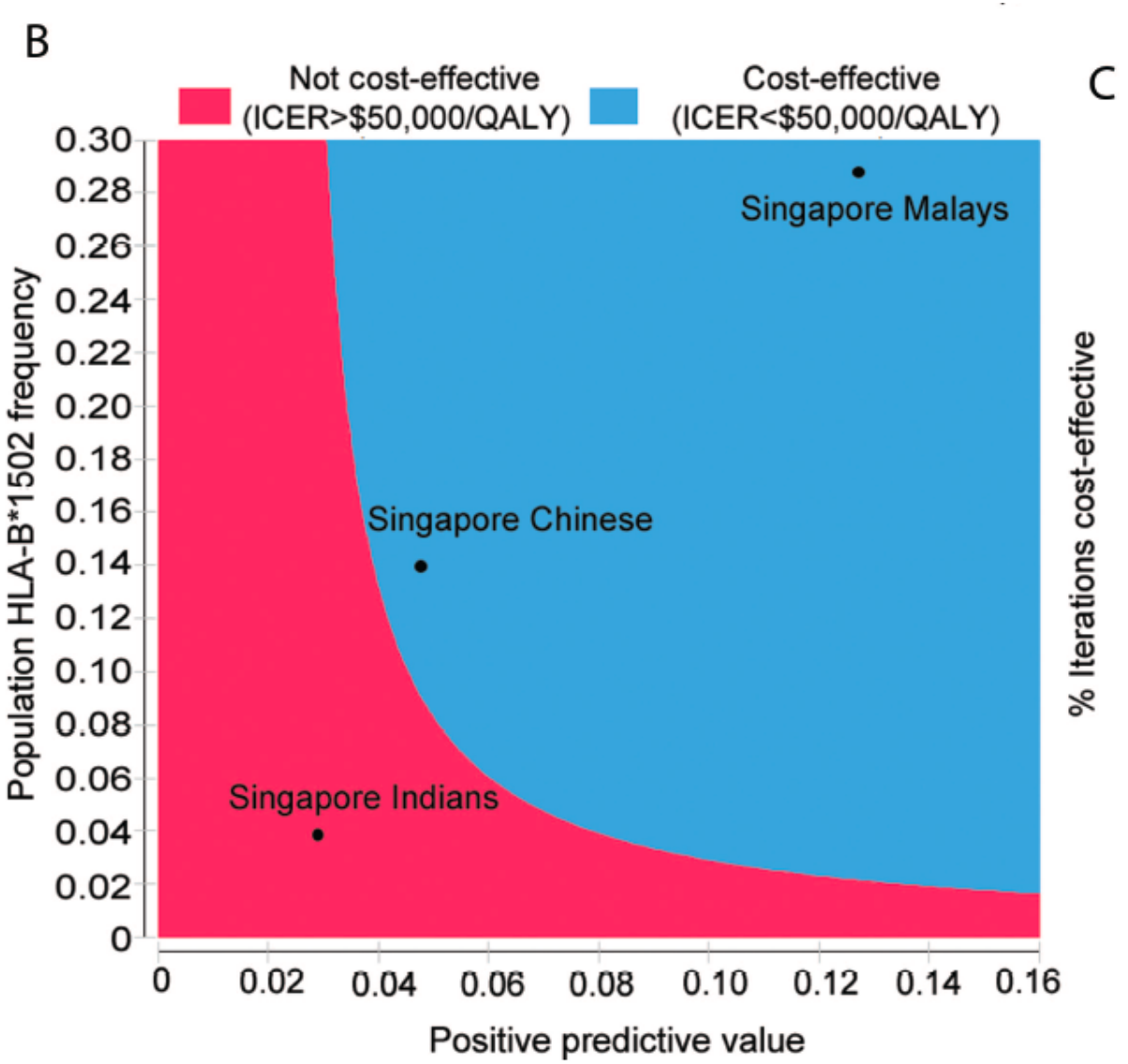


Table 1 Model Inputs

Variable name	Base case value	Range for sensitivity analysis	Source
Cost, 2010 US dollars[a]			
Average annual cost of CBZ/PHT (daily median dosage = 420 mg/300 mg)	170	85–340	Selling prices were from IMS Health and median daily dosage prescribed by local clinicians
Average annual cost of VPA (daily median dosage = 1,050 mg)	470	235–940	
Average annual cost of hypothetical therapy for patients who fail CBZ/PHT treatment	1,100	550–2,200	
Average annual cost of hypothetical therapy for patients who fail VPA treatment	1,860	930–3,720	
Cost of HLA-B*1502 genotyping	270	80–380	
Cost of per case SJS treatment	3,480	1,740–5,220	Singapore public hospital discharge data
Cost of per case SJS-TEN overlap treatment	10,250	5,125–15,380	
Cost of per case TEN treatment	17,030	8,510–25,540	
SJS/TEN fatality and incidence, %			
Fatality of SJS	5	2.5–7.5	Roujeau and Stern[1]
Fatality of SJS-TEN overlap	15	7.5–22.5	
Fatality of TEN	30	15–45	
HLA-B*1502 genotyping, %			
Population frequency of HLA-B*1502	14.87	11–18.74	Williams et al.[21] and unpublished data from Singapore Genome Variation Project and Singapore Immunology Network

Influence of *1502 frequency and PPV on Value



Other studies supporting value of HLA testing to prevent SJS/TENS

- Rattanavipapong et al, Epilepsia 2013
  - Thailand *1502 testing for CBZ
  - Cost effective for neuropathic pain
  - Not for epilepsy (alternative drug cost high)
- Saokaew et al, PLOS One 2014
  - Thailand *5801 testing for Allopurinol
  - Cost effective

What about the US?

citation

US Economic Data

- None
- Budget impact?
  - 30M Asian Americans x 5% ever exposed x $200 = $300M [?]
- Cost effectiveness (value)?
  - Population prevalence and risk
  - Cost of SJS/TENS likely higher than elsewhere
  - Cost of alternative drugs higher also?

Payer policies in the US

Medical Policy

Subject: Genotype Testing for Genetic Polymorphisms to Determine Drug-Metabolizer Status
Policy #: GENE.00010 **Current Effective Date:** 10/14/2014
Status: Revised **Last Review Date:** 08/14/2014

Description/Scope

Genotype testing for polymorphisms can identify variants of specific genes associated with abnormal and normal drug metabolism. This document addresses the use of such testing, based on the theory that individuals with certain gene variants may potentially be able to receive higher or lower doses of some drugs, or should avoid some drugs altogether, to improve the likelihood of achieving clinical goals as well as lessening the risk of adverse drug effects.

Note: For additional information regarding pharmacogenomics, please see:

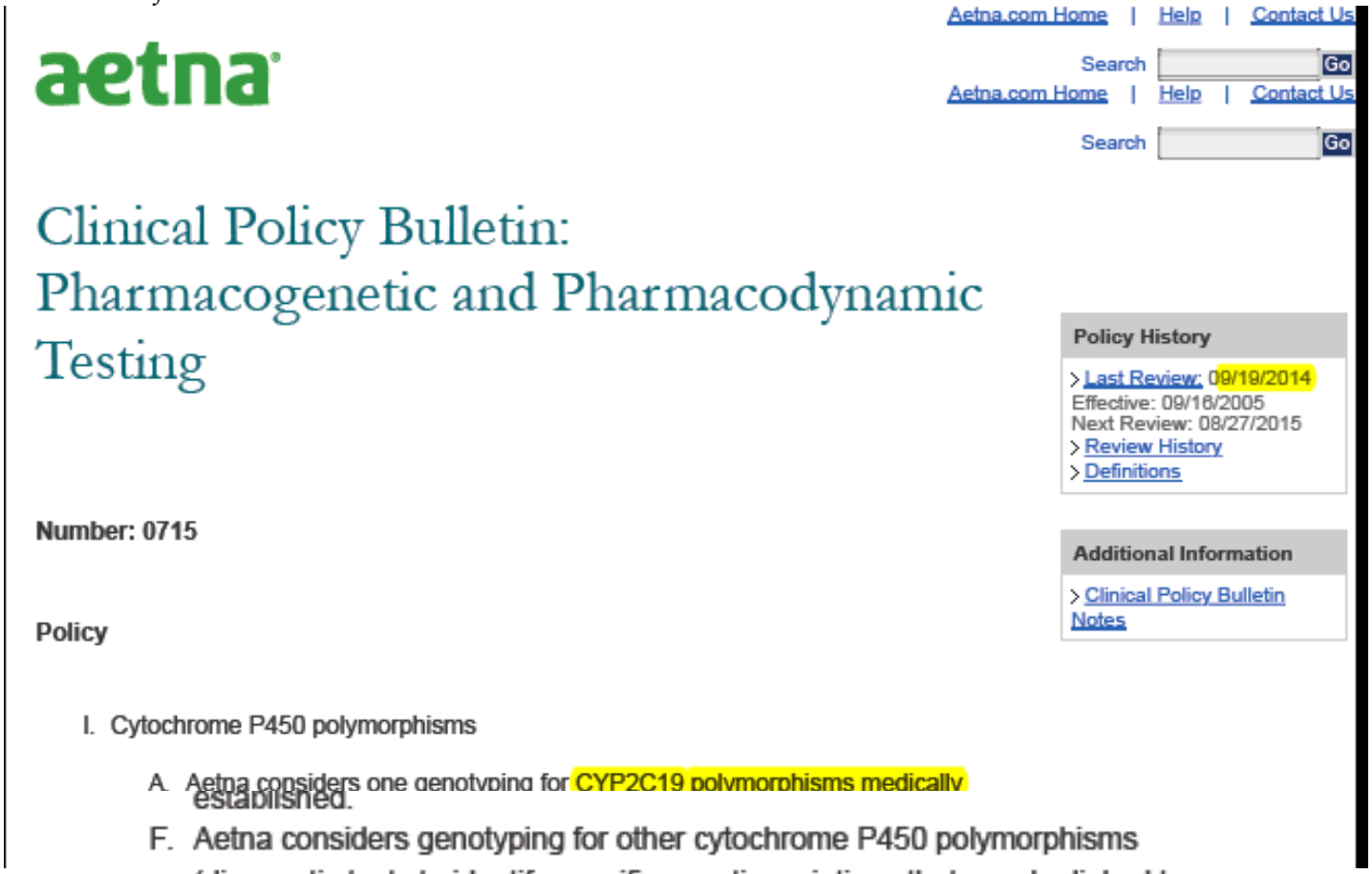
- GENE.00013 Diagnostic Genetic Testing of a Potentially Affected Individual (Adult or Child)
- GENE.00019 BRAF Mutation Analysis
- GENE.00021 Chromosomal Microarray Analysis (CMA) for Developmental Delay, Autism Spectrum Disorder, Intellectual Disability (Intellectual Developmental Disorder) and Congenital Anomalies

Position Statement

Medically Necessary:

Genotype testing for genetic polymorphisms of Human Leukocyte Antigen B*1502 (HLA-B*1502) to determine the drug-metabolizer status of individuals for whom the use of carbamazepine is being proposed is considered **medically necessary** when the criteria below have been met:

1. The individual is of Asian descent; and
2. There are no other alternatives to the use of carbamazepine.



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Clinical Policy Bulletin: Pharmacogenetic and Pharmacodynamic Testing

Policy History

> Last Review: 09/19/2014
Effective: 09/16/2005
Next Review: 08/27/2015
> Review History
> Definitions

Additional Information

> Clinical Policy Bulletin Notes

Number: 0715

Policy

I. Cytochrome P450 polymorphisms

A. Aetna considers one genotyping for CYP2C19 polymorphisms medically established.

F. Aetna considers genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgeics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) experimental and investigational because the clinical value of this type of genetic testing has not been established.

II. Aetna considers genotyping for HLA-B*1502 medically necessary for persons of

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Clinical Policy Bulletin: Pharmacogenetic and Pharmacodynamic Testing

F. Aetna considers genotyping for other cytochrome P450 polymorphisms (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system including opioid analgeics, warfarin, tamoxifen, proton pump inhibitors, antipsychotic medications, and selective serotonin reuptake inhibitors) experimental and investigational because the clinical value of this type of genetic testing has not been established.

II. Aetna considers genotyping for HLA-B*1502 medically necessary for persons of Asian ancestry before commencing treatment with carbamazepine (Tegretol).

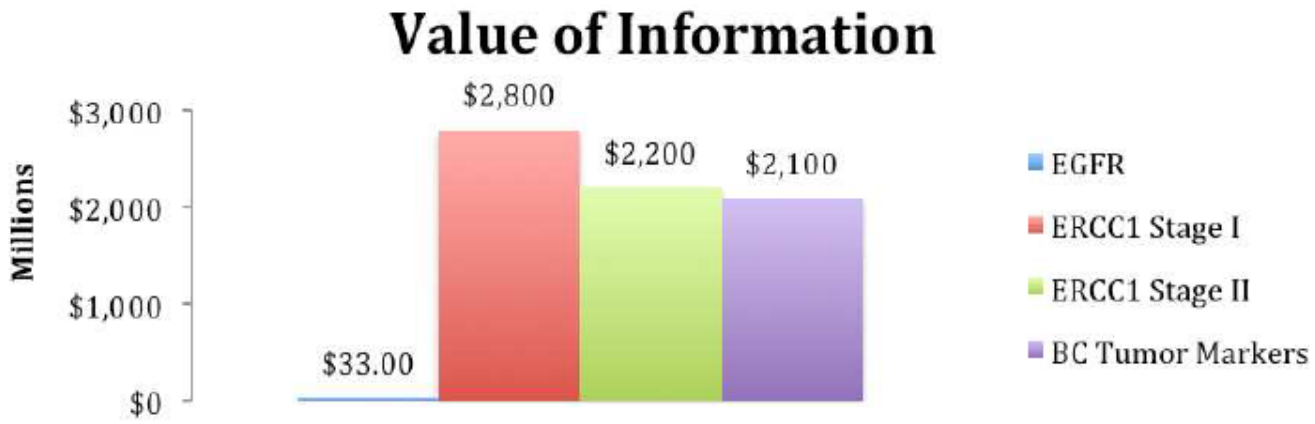
Research and Implementation

1. Better assessment of epidemiology
   - incidence, relative risk
2. Understand how patients and clinicians respond to use of testing
   - treatment avoidance
   - drug switching
   - observational pilot study N ~1K order of magnitude
3. Keep testing simple
   - avoid adding less compelling alleles
4. Develop/incentivize efficient test platform?
   - economic prize

Value of Research: Value of Information (VOI) Analyses

- New tool in health economics increasingly being used to prioritize research investments
- Future research decreases our uncertainty about optimal treatment decisions
- Value of future research function of
  - current probability of making optimal decision
  - impact of making non-optimal decision
  - improvement in decision making with new data

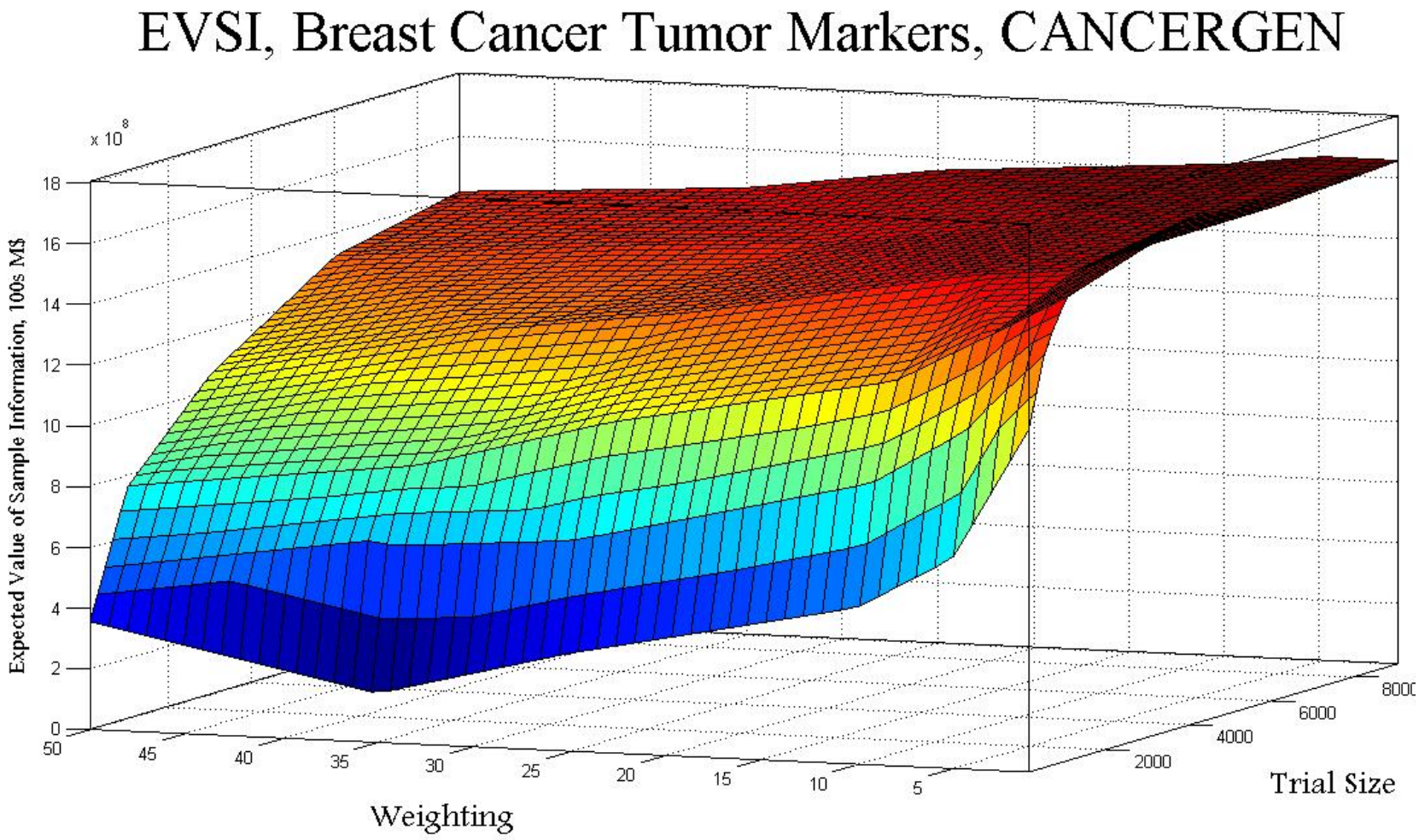
Investment in Cancer Genomics



Cancer Genomic Application	Affected Population[a]	Probability of Making the Wrong Decision about Testing, %	Consequences of Making the Wrong Decision about Testing	Value of Information[b] (Millions)
EGFR mutation testing in maintenance treatment in advance NSCLC	170,253	12	$1600	$33
ERCC1 testing in early stage NSCLC: stage I	234,051	26	$47,300	$2800
ERCC1 testing in early stage NSCLC: stage II	234,051	42	$22,500	$2200
BC tumor marker testing	416,746	43	$11,700	$2100

BC, breast cancer; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; NSCLC, non–small cell lung cancer.
[a]Over 10 years.
[b]Calculated at $150,000 per quality-adjusted life year willingness to pay, discounted at 3%.

Trial Design



Summary

- Evidence from Asian countries indicates that HLA testing to prevent SJS/TENS is a good economic value
- In the US, evidence of economic value in specific patient populations is needed
  - Epidemiology
  - Behavior
  - Costs
  - Research prioritization
- Budget impact must be considered