

Decision Modeling Tools for Genetic Services Coverage

Western States Genetic Services Collaborative

University of Washington – Center for Genomics Healthcare Equality

Medicaid and Genetic Services Regional Conference

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Lou Garrison, PhD

David L. Veenstra, PharmD, PhD

Center for Genomics and Healthcare Equality (CGHE, Wylie Burke, PI)

Pharmaceutical Outcomes Research & Policy Program

Department of Pharmacy



Study Objectives

1. Engage with a range of stakeholders to develop sound policies regarding the application of genetic services in the clinical setting
2. Initiate a partnership with the Western States Genetics Services Collaborative (WSGSC), a federally funded multi-state project that seeks to coordinate and increase access to genetic services among its states and territory.
3. Determine the potential usefulness of decision modeling as a tool in helping decision makers think through the tradeoffs and likely outcomes of policy choices regarding genetic services.



Agenda

- **What are risk-benefit analysis and cost-effectiveness analysis?**
- Current challenges and use of decision modeling for genetic tests
- A framework for risk-benefit analysis in genomics
- Case example: Mitochondrial testing and antibiotic-induced hearing loss
- Questions and issues for discussion



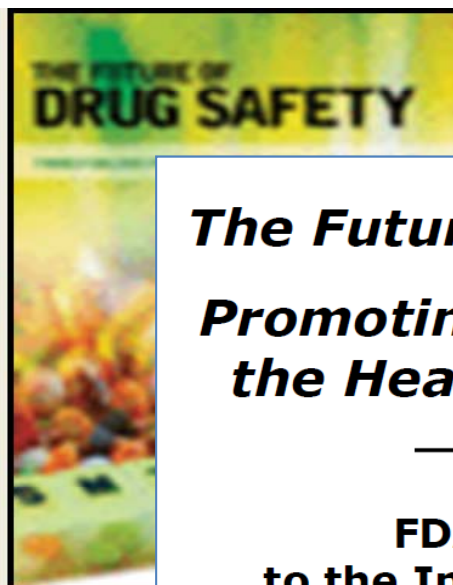
What is the question?

- How and when might decision modeling of **benefits** and **risks**—and **costs** and **cost-effectiveness**— of genetic tests be a useful tool as a part of stakeholder deliberative process concerning genetic services coverage and provision?

Some Terminology— Benefits, Risks, and Clinical Utility

- There is considerable ambiguity about these concepts and terms.
- We mean:
 - **Benefits**—intended positive clinical and health outcomes associated with a specific medical service, procedure, device, or intervention
 - **Risks**—unintended negative clinical and health outcomes associated with a specific medical service, procedure, device, or intervention
 - **Clinical utility**—the balance of benefits and risks

Regulators and Guideline Developers Are Under Increasing Pressures to Be Systematic and Transparent



***The Future of Drug Safety
Promoting and Protecting
the Health of the Public***

**FDA's Response
to the Institute of Medicine's
2006 Report**

The screenshot shows the header of the U.S. Preventive Services Task Force website. It includes the USPSTF logo, navigation links for "USPSTF Home", "Resource Links", and "E-mail Updates", and a breadcrumb trail: "You Are Here: U.S. Preventive Services Task Force > Topic Index > Screening: Breast Cancer". The main heading is "Screening for Breast Cancer", with a release date of November 2009 and an update date of December 2009. A summary paragraph states: "This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on breast cancer screening." A link for "Summary of Recommendations / ..." is visible at the bottom.

**The Recent US Preventive Services
Task Force Guidelines Are Not
Supported by the Scientific Evidence
and Should Be Rescinded**

Daniel B. Kopans, MD^{a,b}

J Am Coll Radiol 2010;7:260-264.



IOM Drug Safety Study (2006) and FDA Response (2007)

- IOM Recommendation 4.5:
 - Center for Drug Evaluation and Research should “develop and continually improve a **systematic approach** to risk-benefit analysis for use throughout the FDA in the pre-approval and post-approval settings.”
- In January 2007, the FDA announced 41 new initiatives on drug safety, including:
 - “[d]eveloping and incorporating new quantitative tools in the assessment of risk and benefit. . .”



Risk-Benefit Decision Modeling

Assessing A Structured, Quantitative Health Outcomes Approach To Drug Risk-Benefit Analysis

Using a health outcomes model to assess drug safety and benefits together could promote consistency and products and diseases.

by Louis P. Garrison Jr., Adrian Towse, and

Health Affairs 26, no. 3 (2007): 684-6

A formal risk-benefit framework for genomic tests: Facilitating the appropriate translation of genomics into clinical practice

David L. Veenstra, PharmD, PhD^{1,4}, Joshua A. Roth, MHA¹, Louis P. Garrison, Jr, PhD¹,
Scott D. Ramsey, MD, PhD^{3,4}, and Wylie Burke, MD, PhD^{2,4}

Genetics in Medicine • Volume 12, Number 11, November 2010



So. What is a Model?



Source: Pettiti, 2011

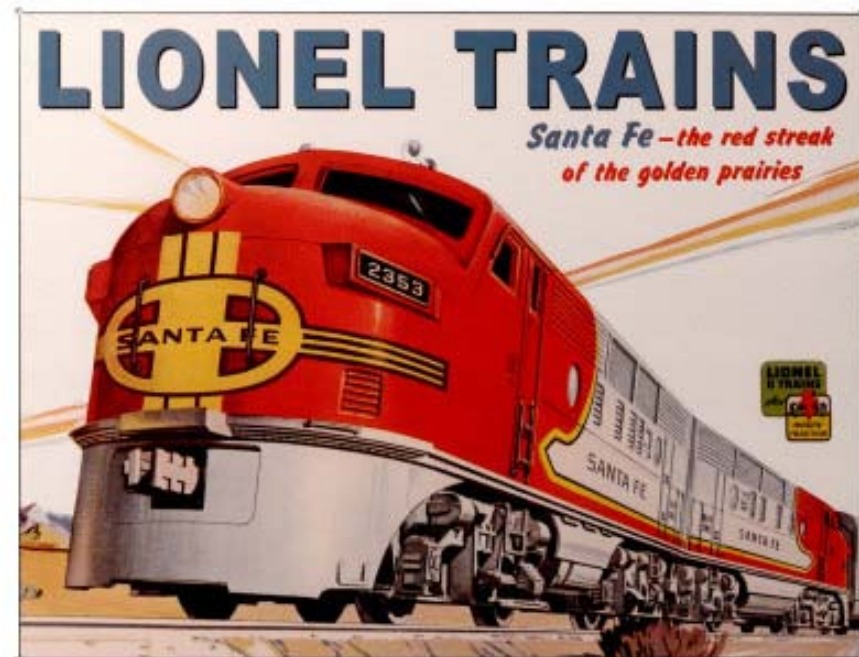


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Models

A Generic View

- A simplification of reality that attempts to capture the 'essence' of the phenomenon with the minimum level of complexity



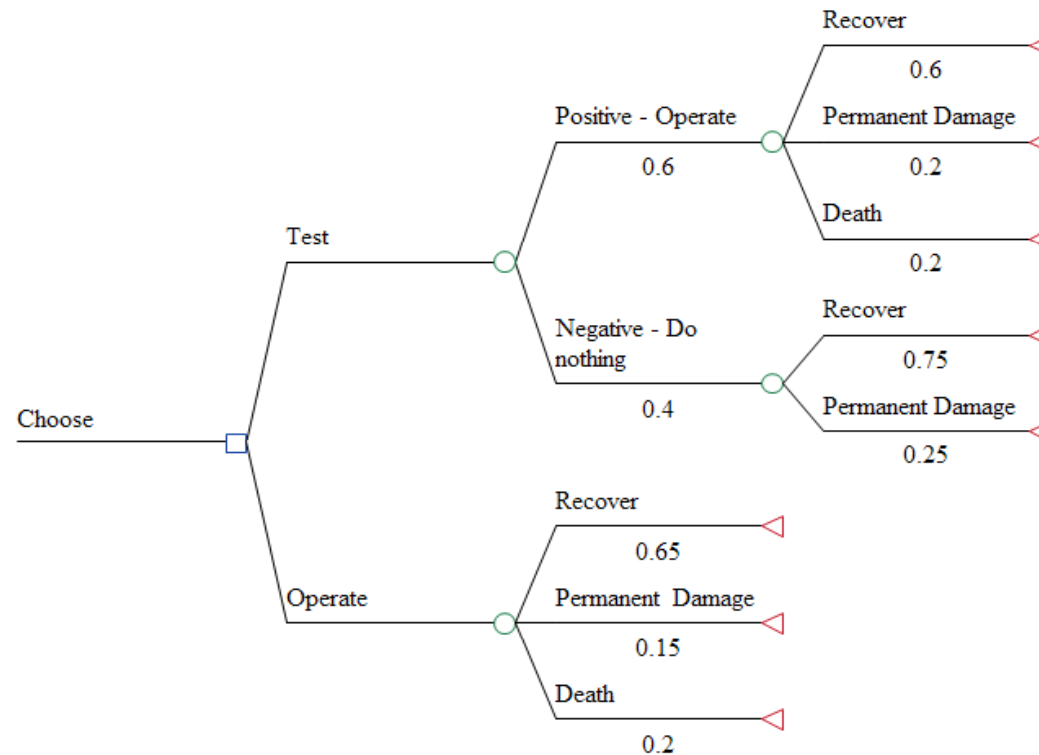
Source: Pettiti, 2011

Decision Models

- Mathematical models to help decision makers sort through and integrate large amounts of information and multiple layers of complexity.
- The models clarify the trade-offs involved in selecting one strategy from a set of alternatives.
- The information from models enables users to make choices with a better understanding of consequences.



Simple Decision Model: Test or Operate

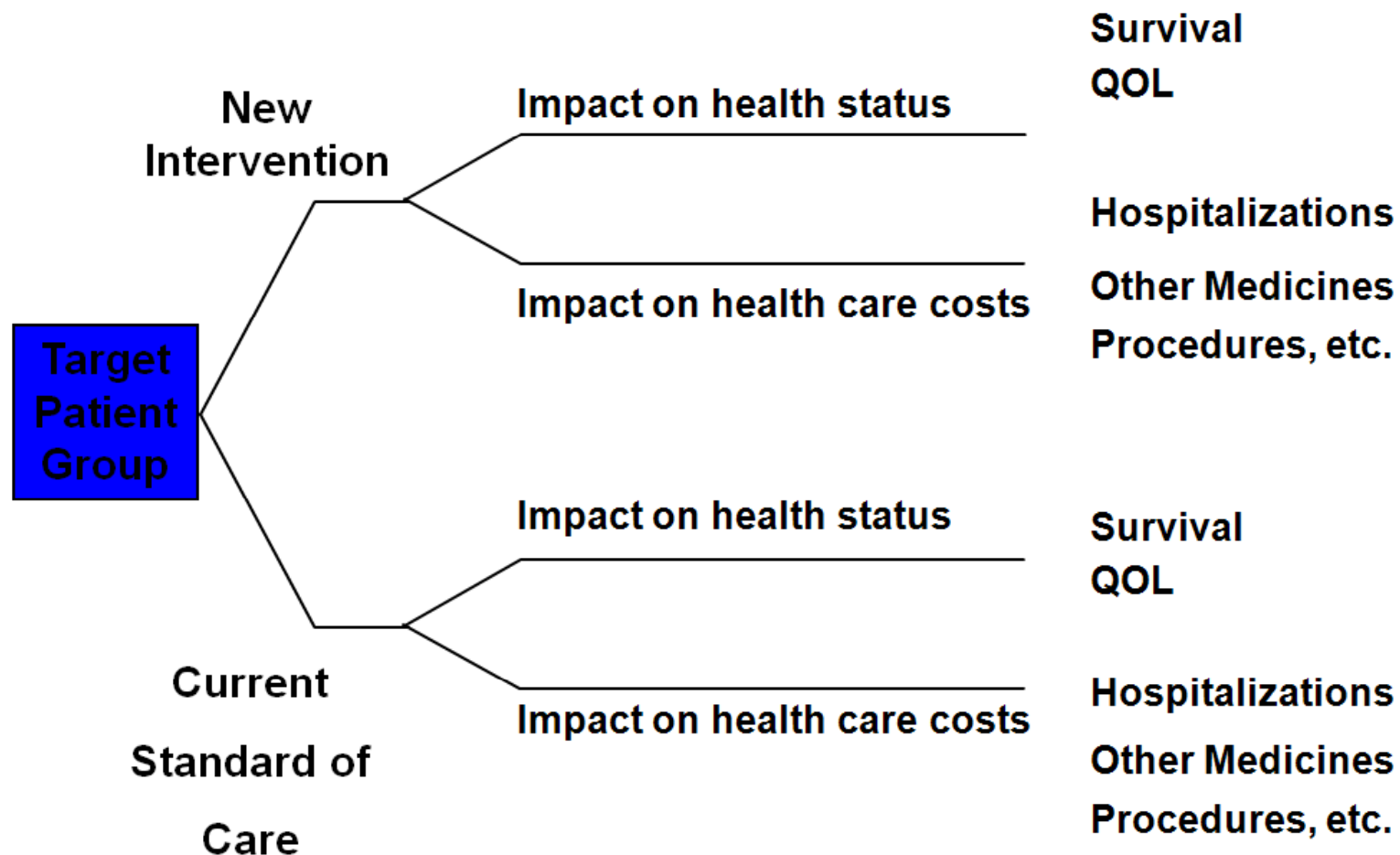


All models are wrong, some are useful.

George Box 1979



Costs can also be incorporated



Warfarin PGx Test?

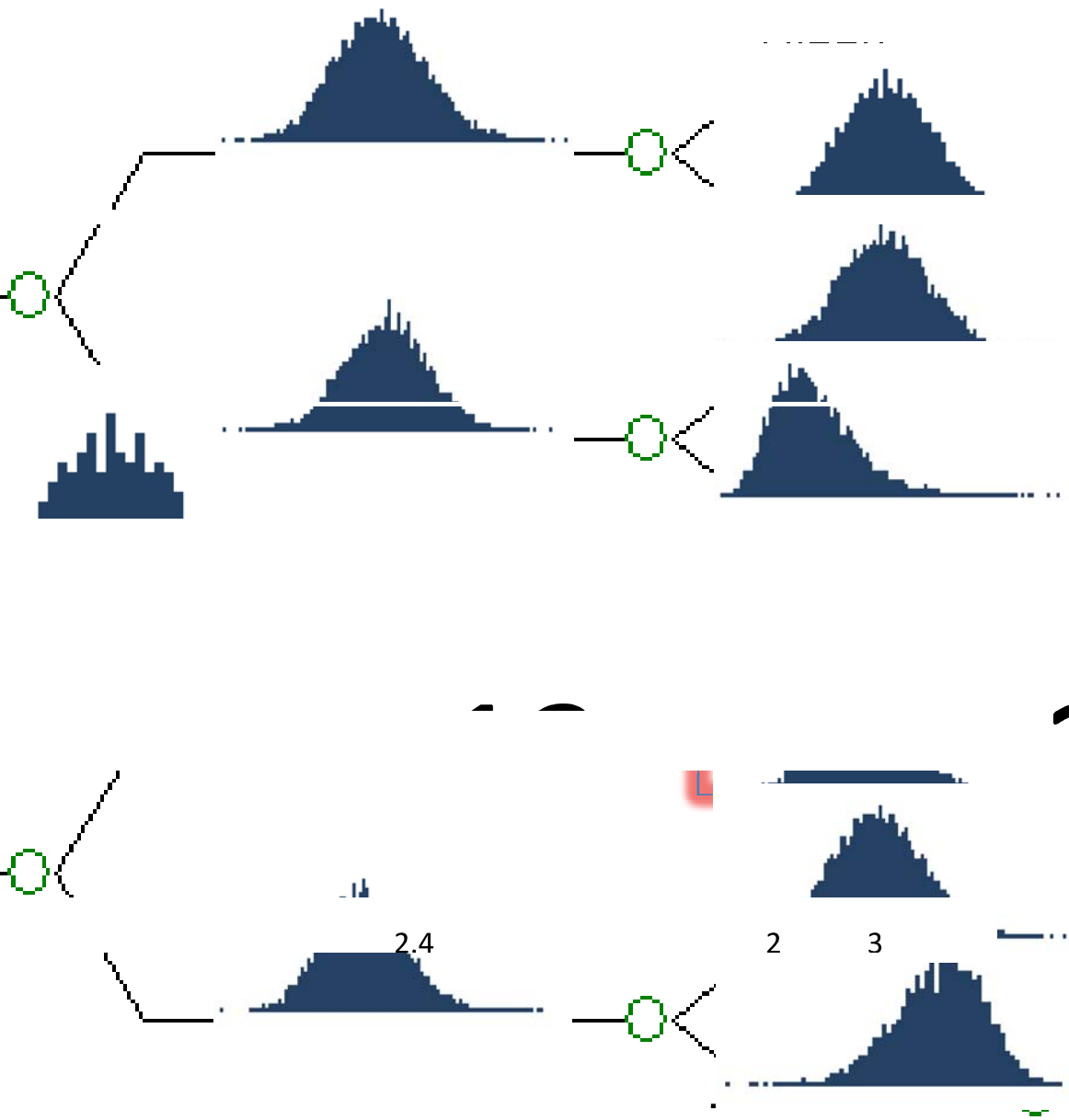


No test

PGx test

j (p g)

TEs (above therapeutic INR range)



NO TEST

Clinical
Outcome

Years
of Life

QALYs

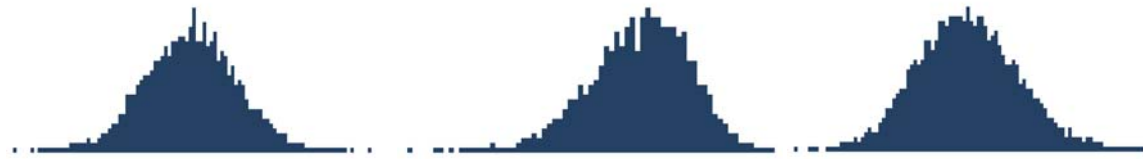


PGx TEST

Clinical
Outcome

Years
of Life

QALYs



Cost-Effectiveness Analysis (CEA) and the Incremental CE Ratio (ICER)

CEA in health care is about comparing two alternatives (1 & 2):

The ICER =

Cost 2 - Cost 1

Outcome 2 - Outcome 1

- Intervention (2) is compared to the next best medical strategy (1).
- Costs are measured in monetary units
- Outcomes can be measured in a variety of ways but must be in the same units for each alternative.
- Measuring outcomes in quality-adjusted life years (QALYs)—called “cost-utility analysis” is the preferred method, where feasible.

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Evidence-Based Medicine (EBM)

- Evidence-based medicine aims to apply the best available evidence gained from the scientific method to medical decision making.
- It seeks to assess the quality of evidence of the risks and benefits of treatments (including lack of treatment)
- The Institute of Medicine (2001) defines evidence-based medicine as the “integration of best researched evidence and clinical expertise with patient values”



Comparative Effectiveness Research

- CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care.
- The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. (IOM)



EGAPP – Evaluation of Genomic Applications in Practice and Prevention

- Independent panel established in April, 2005
- Goal is to develop a systematic process for evidence-based assessment for genetic tests
- Working group currently composed of 16 multidisciplinary experts
- Nonfederal panel supported by the National Office of Public Health Genomics (NOPHG) at the Centers for Disease Control and Prevention (CDC)

EGAPP – Recommendations

- EGAPP's methods are evolving, but analogous to the USPSTF
- One of three possible recommendations:
 - (1) recommend for use of the test;
 - (2) recommend against use of the test;
 - (3) insufficient evidence to recommend for or against use of the test.

EGAPP: Clinical Utility

- EGAPP defines the clinical utility of a genetic test as
 - the evidence of improved measurable clinical outcomes,
 - added value to patient management decision- making
 - information that is of value to the person, or sometimes to the individual' s family or community, in making decisions about effective treatment or preventive strategies



Limitation of EBM

- Traditional evidence-based processes generally rely on direct evidence of clinical utility.
- Recent AHRQ evidence report for gene expression profiling in breast cancer:
 - “... clinical utility...can only be assessed in the context of randomized clinical trials”

Translational Challenge of the Genome-Wide Era

- How do we estimate the clinical risk-benefit tradeoffs of genetic tests in a timely manner?
 - To speed the development and use of beneficial tests
 - To avoid the use of tests that may lead to harm
- Can we identify an evidence framework that meets stakeholders' needs?



Evidence Evaluation Methods Workgroup
April 13, 2011 • Bethesda, MD

- 9:15 AM** Decision Process
Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
Ned Calonge, MD, MPH & Nancy Green, MD
- 10:00 AM** Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
Methods: Evaluating Genomic Tests for Screening
Steven Teutsch, MD, MPH
- Models to Inform Decisions and Policy
Diana Petitti, MD, MPH



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Decision modeling

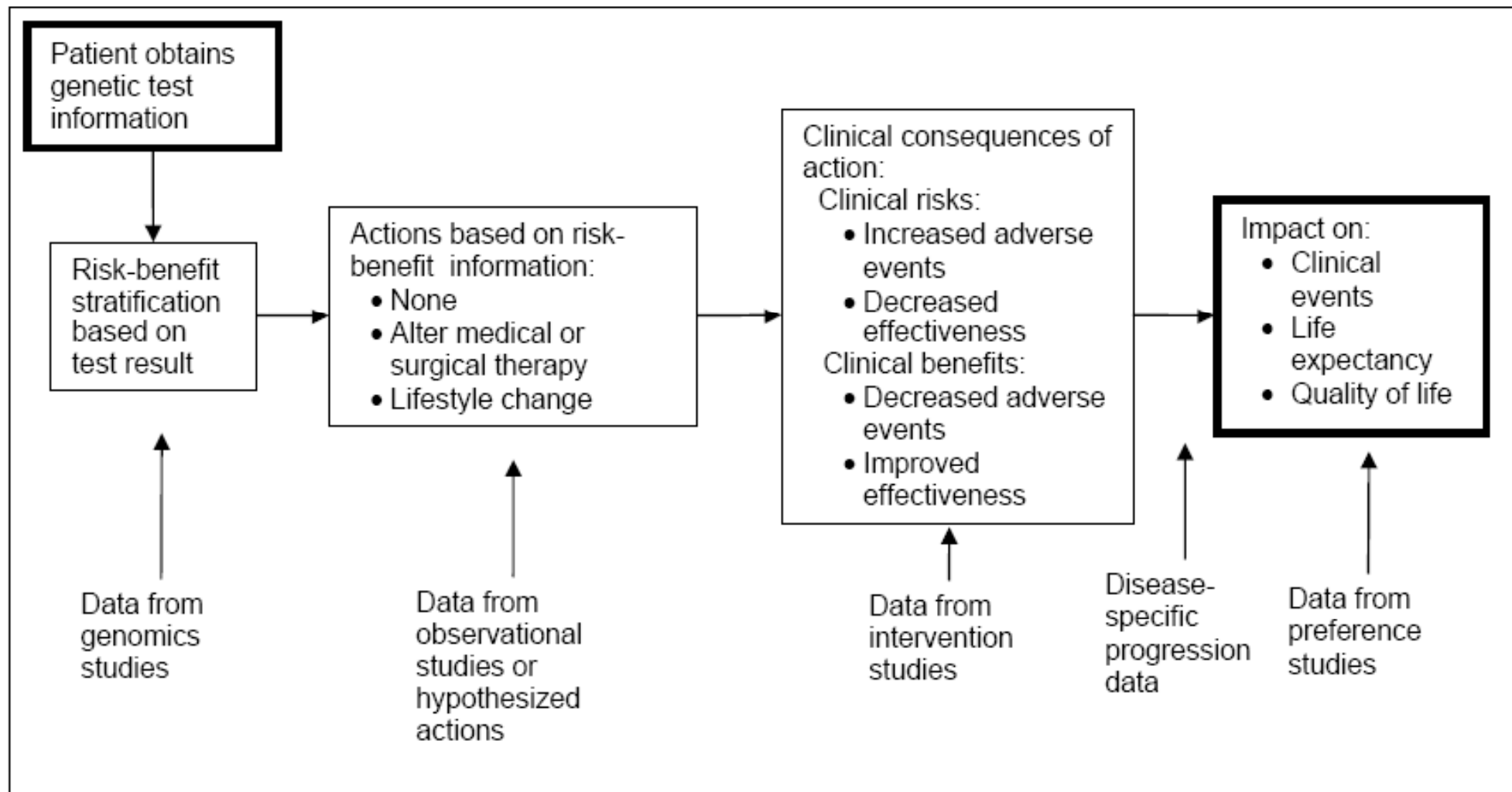
- Quantitative, ‘what-if’ modeling
 - Assess potential clinical impact
 - Estimate NNTest, NNH
 - Threshold analyses, scenario analyses
 - Net benefit measure?
- When?

1. Decision Analysis

- Systematic
 - Consider all available data
 - Evaluate alternative options
- Formal
 - Reproducible
 - Transparent
- Quantitative
 - Probabilities of events
 - Value of events
 - Uncertainty evaluated



Decision Modeling for Genetic Tests



2. Defining Clinical Utility

- Events avoided (Benefit)
 - Absolute risk reduction
 - NNT
- Risks incurred
 - Absolute risk increase
 - NNH
- Net Benefit
 - (Benefits) – (Harms)
 - Difference in (Quantity x Quality) of life

Quality-Adjusted Life-Years (QALY)

- A measure of overall clinical outcomes
- $QALY = \text{life expectancy} \times \text{quality of life (QoL)}$
- QoL estimated on a scale of 0 to 1
- More specifically, health-related QoL
 - physical functioning
 - social functioning
 - emotional functioning
 - mental functioning

3. Risk-Benefit Policy Matrix

	High Uncertainty	Moderate Uncertainty	Low Uncertainty
Favorable Risk-Benefit	Use with evidence-development	Consider use in clinical practice	Appropriate for use in clinical practice
Neutral Risk-Benefit	Do not use, conduct additional research	Use with evidence-development	Consider use in clinical practice
Unfavorable Risk-Benefit	Do not use, conduct additional research	Do not use	Do not use



EGAPP use of models

- Three of the four evidence reports commissioned to date have conducted decision-analytic modeling to consider indirect evidence.
 - Ovarian cancer susceptibility testing
 - Assessed what combinations of inputs would be required to hit a target of 20% reduction in cancer mortality
 - Antidepressant treatment response and CYP-P450 testing
 - Examined under what circumstances genetic testing would lead to a better clinical outcome at 6 weeks
 - HNPCC testing
 - Calculated the number of incident CRC with positive diagnosis for HNPCC, and the number of tests (MMR, MSI, or IHC) needed to detect them

Challenges of Modeling

- USPSTF methods report

“Although formal decision analyses ... have been proposed as an objective method to weigh benefits and harms, ... such analyses can be complex and opaque and ... may rely on various assumptions, each of which may have substantial uncertainty.”



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I. Mitochondrial testing and antibiotic-induced hearing loss

- Mitochondrial mutation (A1555G) predisposes patients to aminoglycoside-induced hearing loss
- Aminoglycosides are a cornerstone of first-line therapy in cystic fibrosis (CF) patients with acute *Pseudomonas aeruginosa* respiratory infections
 - aminoglycoside-induced hearing loss (ranging from mild to severe) may occur in 1-15% of CF patients.



Just do it

- An editorial in BMJ stated:
- “We recommend that the true prevalence of the mutation...be ascertained to determine the cost effectiveness of screening everyone prescribed aminoglycoside antibiotics. In the meantime, patients who are likely to receive multiple courses of aminoglycosides...should be screened.”

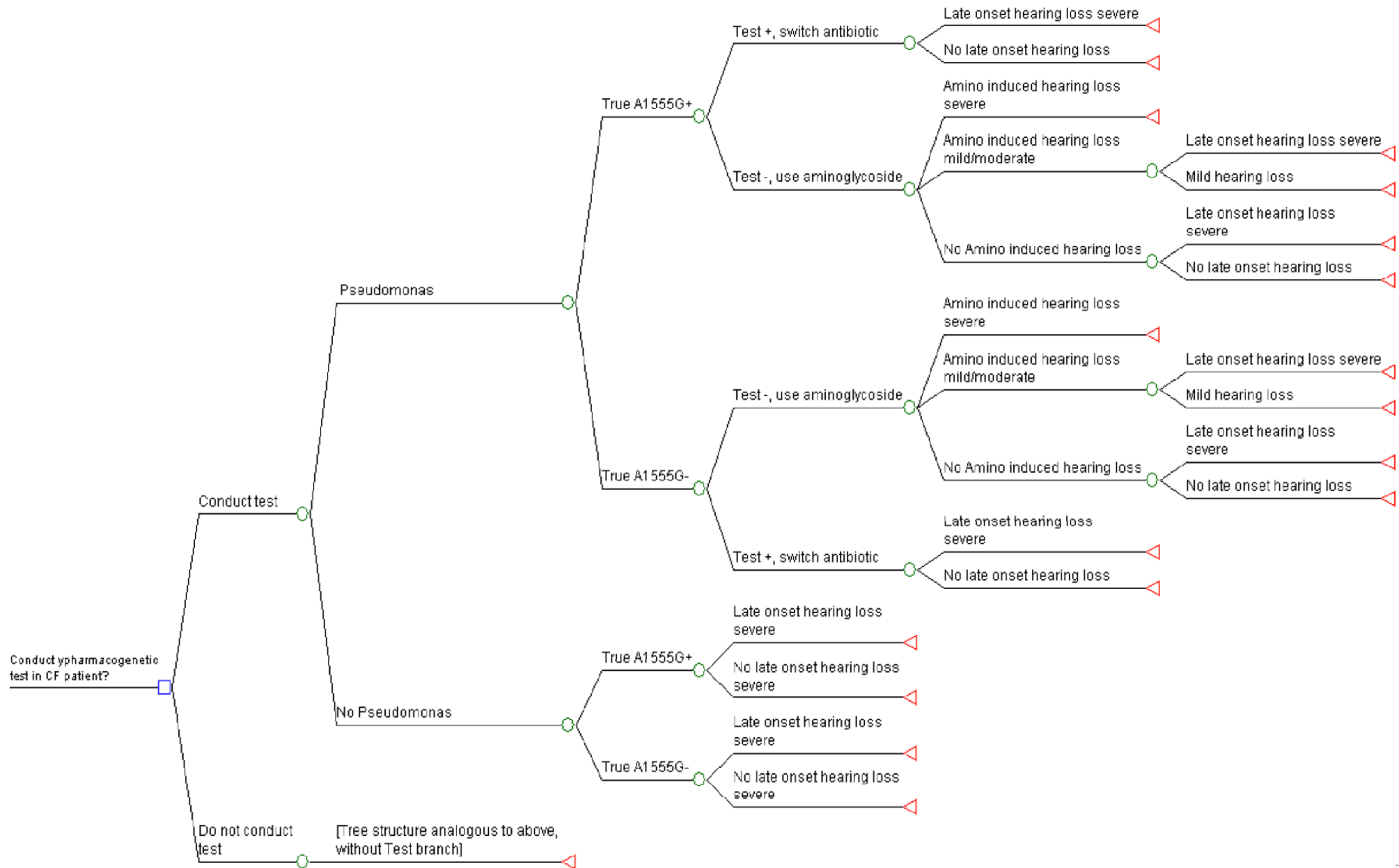


Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes

David L. Veenstra, PharmD, PhD^{1,2}, Julie Harris, MPH¹, Ronald L. Gibson, MD, PhD^{3,4}, Margaret Rosenfeld, MD, MPH^{3,4}, Wylie Burke, MD, PhD^{1,5}, and Carolyn Watts, PhD^{1,6}



Decision model

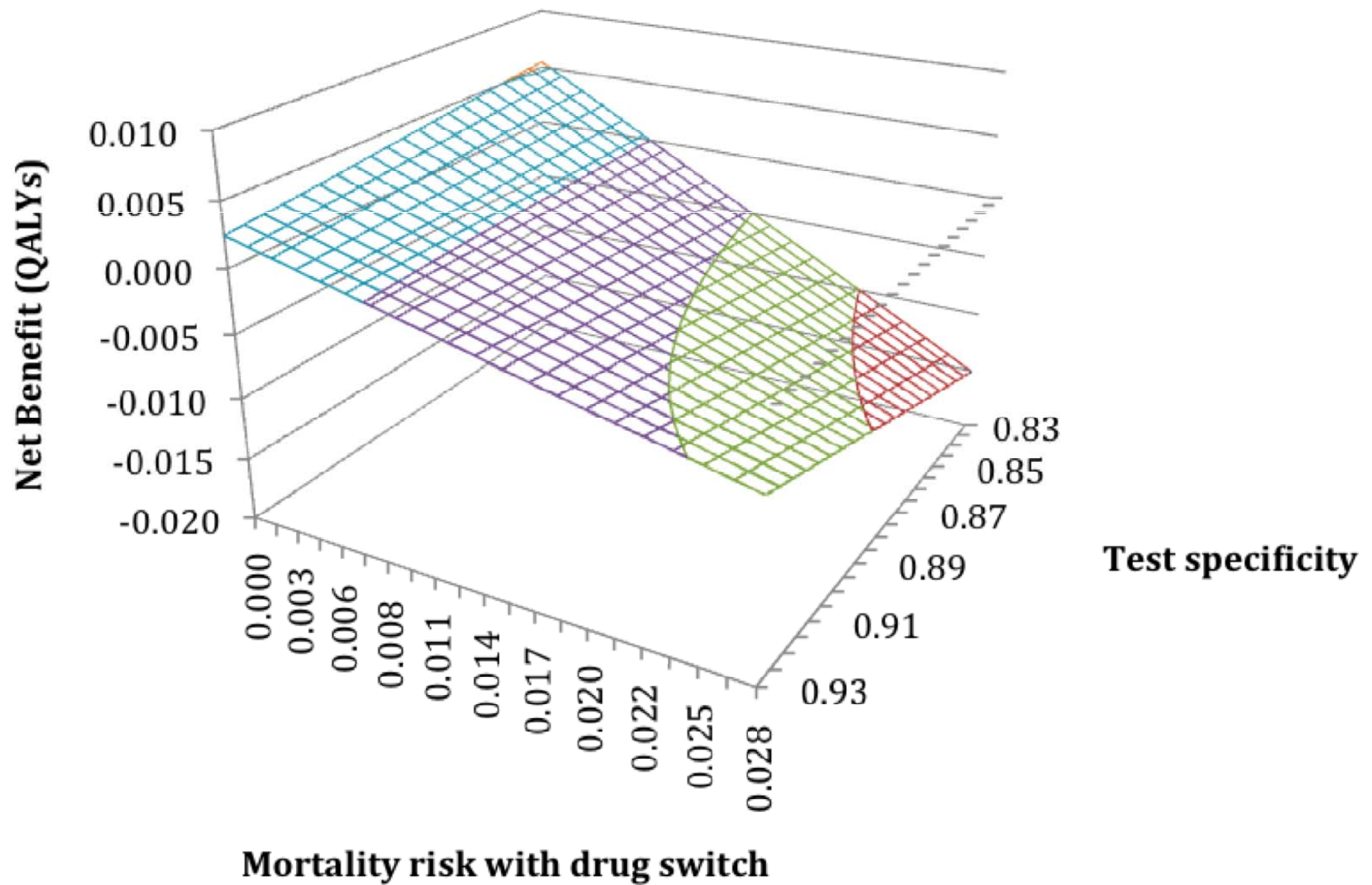


Results

- A1555G testing decreased hearing loss by 0.12%.
- Because of the low prevalence of the mutation, over 800 patients would have to be tested to prevent one case of severe hearing loss
- The magnitude of the benefit in terms of quality of life was relatively small, with an expected increase of 0.0043 quality-adjusted life years (1.6 days) under base-case assumptions.



Uncertainty in Risk-Benefit Tradeoff



Implications

- Further data are needed before this test should be recommended as a standard of care
- Recent data suggest the prevalence of the mutation could be as high as 0.5%. (Bitner-Glindzicz, et al. 2009; Vandebona, et al. 2009)
- However, the specificity of the test likely needs improvement; at a prevalence of 0.5% and with 87% specificity, 96% of children that test positive would be false positives, and inadvertently not receive first-line antibiotic therapy.



Data Limitations

- In our analysis of the A1555G test, many of the most important parameters in the model, including variant prevalence and incidence and aminoglycoside-induced hearing loss severity and timing, had to be based on a paucity of data.
- But sensitivity analyses (changing the assumptions and assessing how the changes affect the results) can offer some indication of the importance of the assumption



Where Does A1555G Testing Belong?

	High Uncertainty	Moderate Uncertainty	Low Uncertainty
Favorable Risk-Benefit	Use with evidence- development	Consider use in clinical practice	Appropriate for use in clinical practice
Neutral Risk-Benefit	Do not use, conduct additional research	Use with evidence- development	Consider use in clinical practice
Unfavorable Risk-Benefit	Do not use, conduct additional research	Do not use	Do not use



Summary

- Assessing clinical utility of genetic tests is challenging
- Lots of data, little information
- Quantitative risk-benefit assessment may be useful



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Questions for Discussion

- What are advantages and disadvantages of using decision-modeling tools such as RBA or CEA for genetic services?
- What do you want to see before using a RBA and/or CEA to inform policy?
 - published study, interactive model
- How should evidence be graded?
- How much uncertainty is too much?
- Patient perspective?
 - How important is the preference for ‘information for information’s sake’?

More Information: Economic Issues

The screenshot shows the website for the Pharmacogenomics Education Program at the University of California San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences. The page features a navigation menu with options like HOME, ABOUT US, CPE/CME, SHARED CURRICULUM, RESOURCES, PUBCASTS, and VIRTUAL COMMUNITY. A sidebar on the left lists various curriculum topics, including Shared Curriculum, Healthcare Practitioners, Pharmacy School Faculty, Asthma, Cardiology I: Warfarin & Statins, Cardiology II: Clopidogrel & Beta Blocker, Concepts and Clinical Applications, Economic Issues, Oncology I: Solid Tumors, Oncology II: Hematologic Malignancies, Psychiatry I: Depression, and Psychiatry II. The main content area is titled 'Economic Issues' and features two profiles: Louis P. Garrison, Jr., Ph.D., Professor of Pharmaceutical Outcomes Research & Policy Program and Adjunct Professor of the Department of Global Health at the University of Washington; and David L. Veenstra, Pharm.D., Ph.D., Associate Professor of the same program at the University of Washington. Each profile includes a headshot and a brief biography.

