Inter-Disciplinary Evaluation of Genomic Profiles of Clinical Validity and Utility

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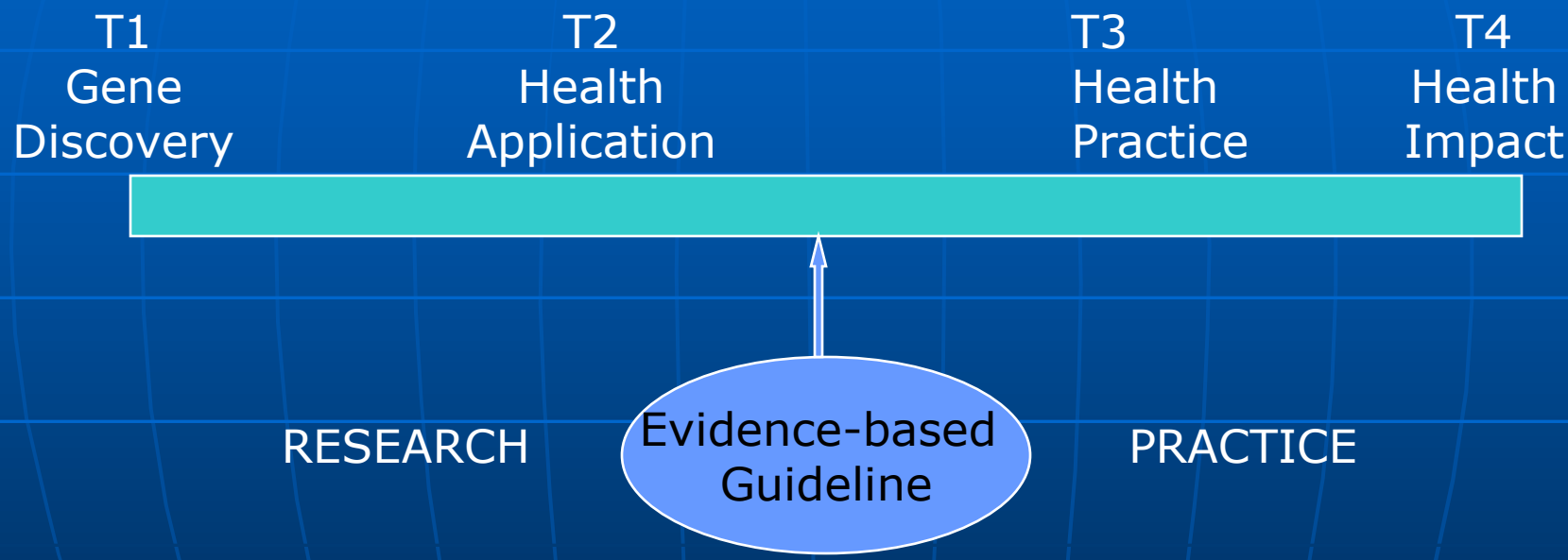
Agenda

- Definition of clinical validity and clinical utility
- Evidence needed to establish clinical validity and utility

The Translational Process

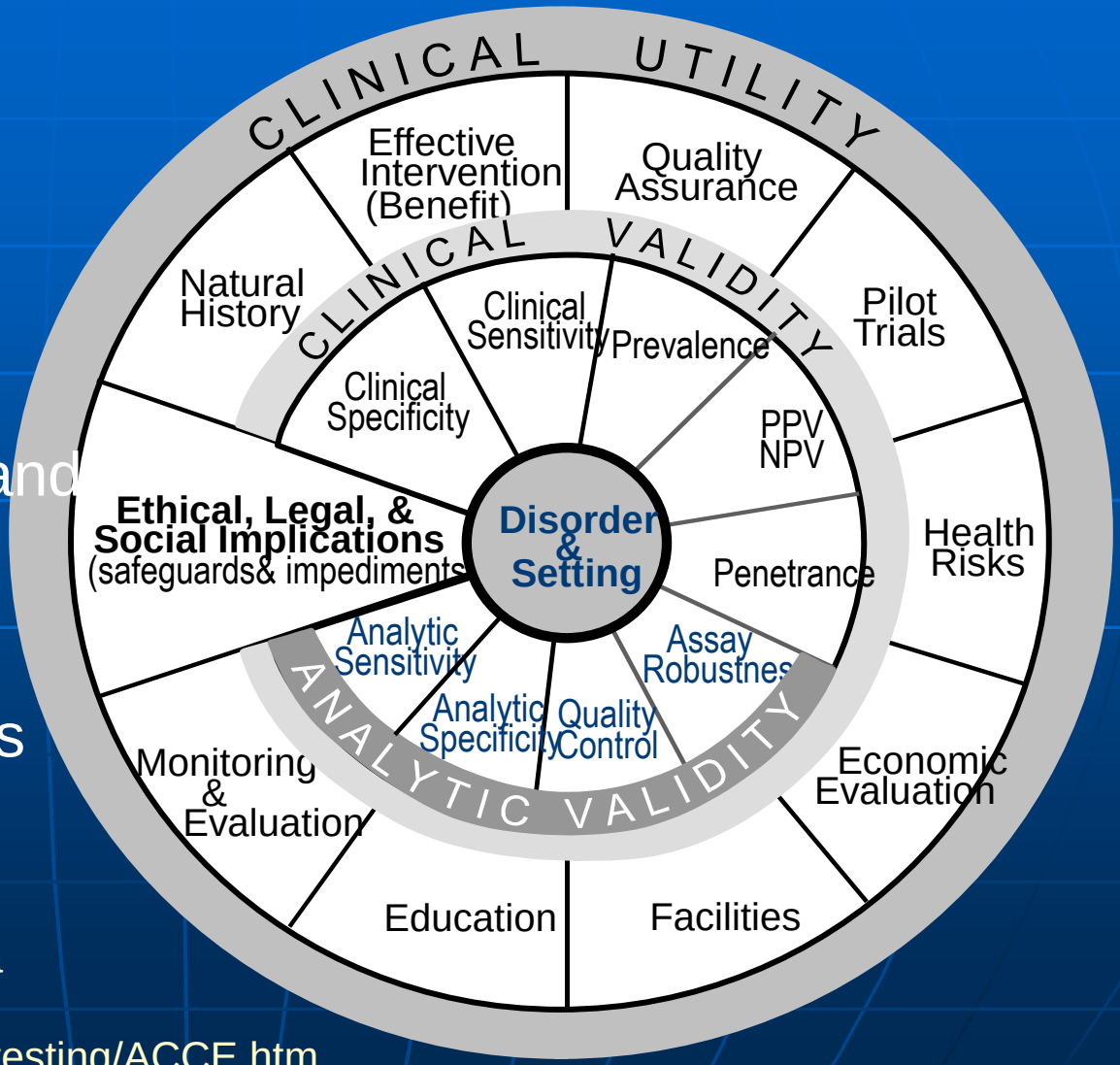


Frameworks

- ACCE
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

A Multidisciplinary Evaluation of Genetic Tests

- ACCE
- Name reflects four components of evaluation
- Define test, disorder, and setting
- Analytic framework – 40+ targeted questions



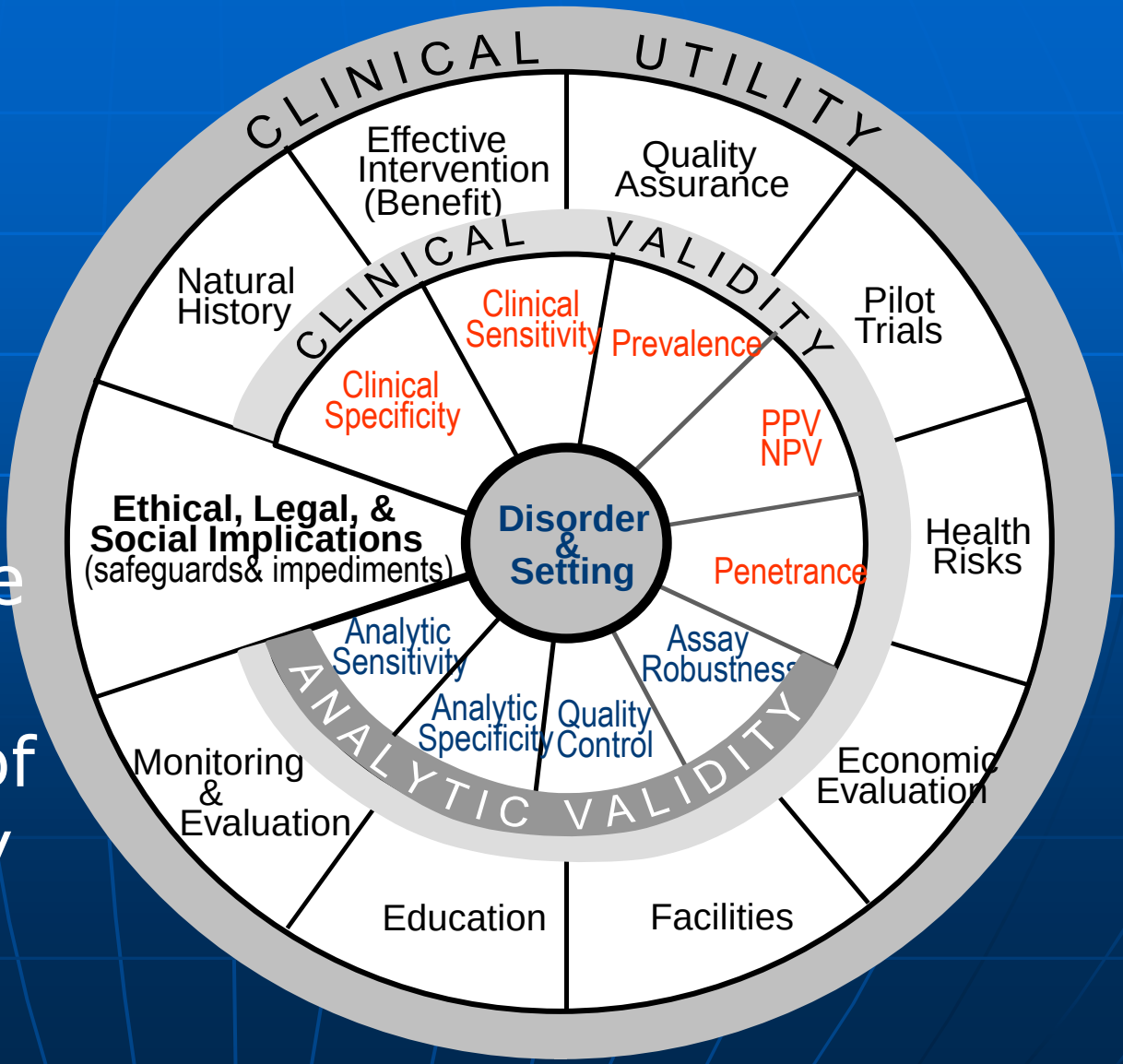
Haddow JE, Palomaki GE: ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests, 2003. http://www.cdc.gov/genomics/gtesting/ACCE.htm.

Clinical Validity

- The degree to which a laboratory test accurately categorizes those with and with and without a health condition: characterized by sensitivity, specificity, positive predictive value and negative predictive value

Clinical Validity

- Defines the ability of a test to detect or predict the phenotype or particular clinical outcome
- Elements build upon analysis of analytic validity



Clinical Sensitivity & Specificity: Genetic Associations Revisited

Test Result	Disease Phenotype: Yes	Disease Phenotype: No
Pos	A	B
Neg	C	D

Sensitivity: Proportion of positive test results in individuals who have the phenotype = A / (A+C)

Specificity: Proportion of negative test results in individuals who do not have the phenotype = D / (B+D)

Discriminative accuracy: ROC analysis combines sensitivity and specificity

Positive & Negative Predictive Values

Test Result	Disease Phenotype: Yes	Disease Phenotype: No
Pos	A	B
Neg	C	D

Positive predictive value = A / (A+B)

Probability that person with positive test will have the phenotype

Negative predictive value = D / (C+D)

Probability that person with negative test will not have the phenotype

Positive & Negative Predictive Values

- Depend on
  - Definition of phenotype
  - Prevalence
  - Characteristics of tested population
  - Penetrance
    - Not every woman with a *BRCA1/2* mutation will develop breast cancer
  - Genetic heterogeneity
    - Absence of an identifiable *BRCA1/2* mutation does not eliminate the risk of breast cancer

Positive Predictive Value (PPV) for a Screening Test with sens=99% and spec=95%

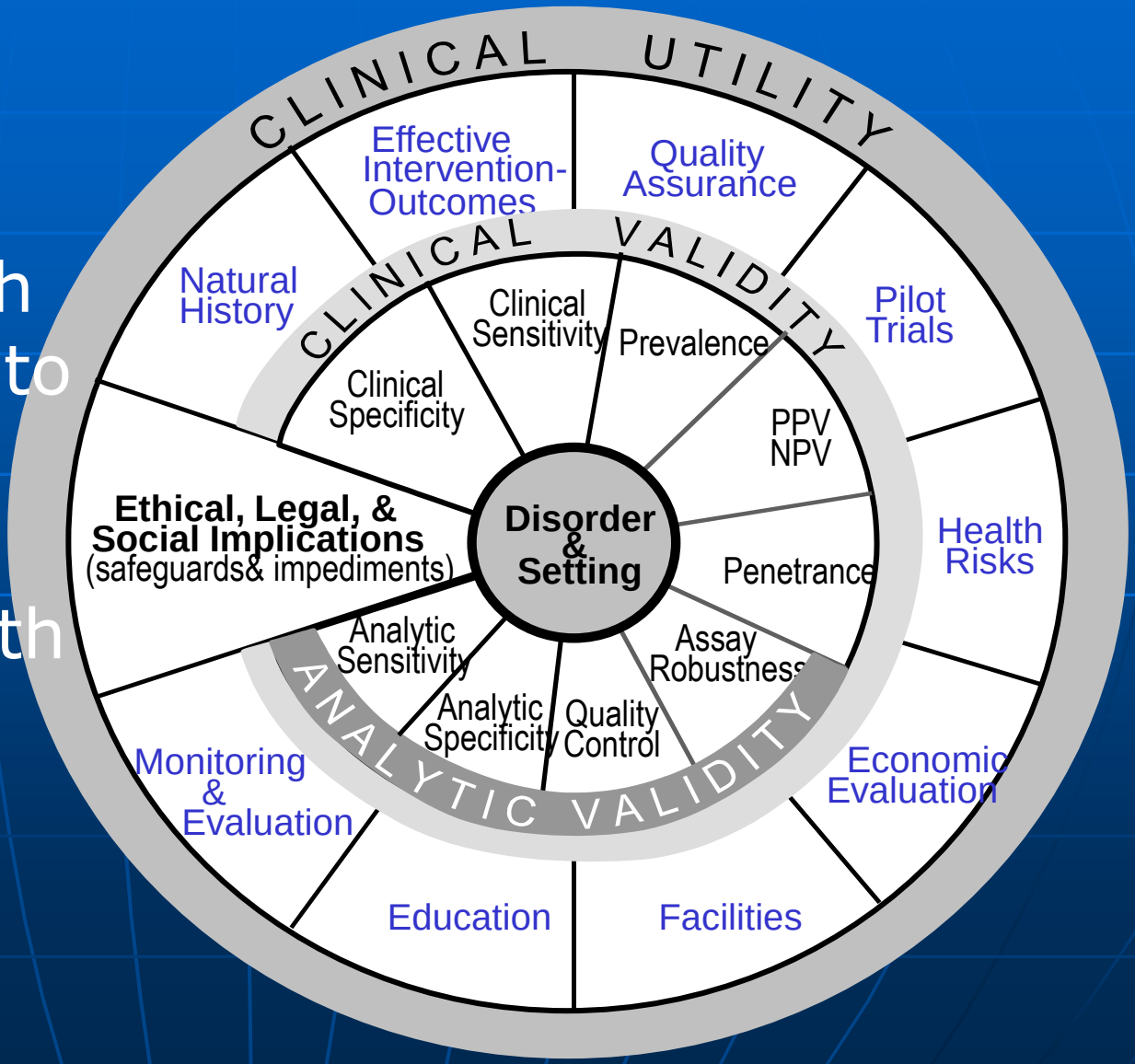
		Disease			
Prev	Test	Present	Absent	Total	PPV
1%	+	99	495	594	17%
	-	1	9,405	9,406	=99/594
	Totals	100	9,900	10,000	
5%	+	495	475	970	51%
	-	5	9,025	9,030	=495/970
	Totals	500	9,500	10,000	

Clinical Utility

- The degree to which a test leads to improvement in the clinical management of patients as measured by net benefit (benefits less harms).

Clinical Utility

- Defining the risks and benefits associated with introduction into practice
- Likelihood of improved health outcome

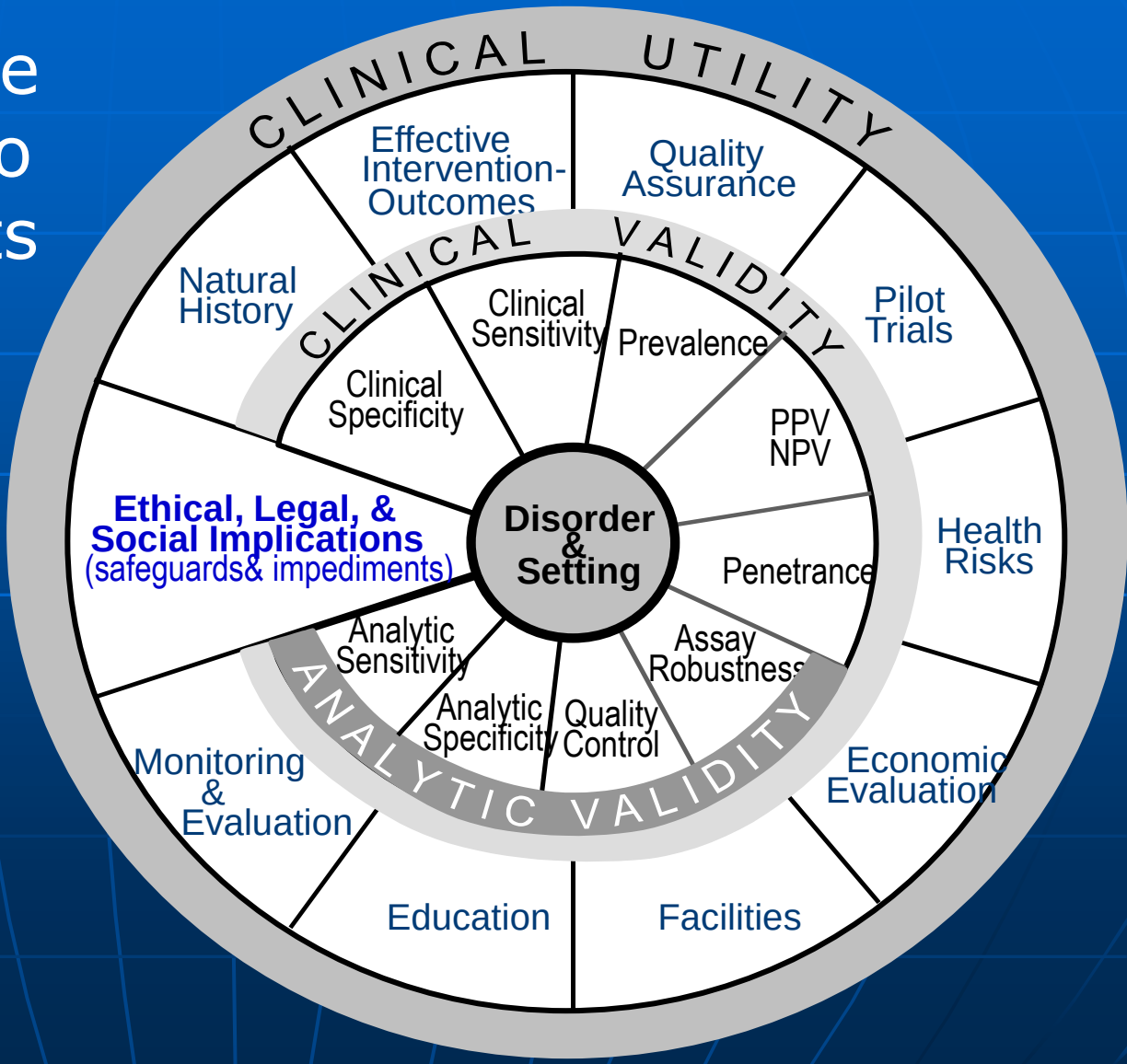


Categories Of Genetic Test Applications And Some Characteristics Of How Clinical Validity And Utility Are Assessed

Application	Clinical Validity	Clinical Utility
Diagnosis	Association with disorder	Improved clinical outcomes Usefulness for decision-making End of diagnostic odyssey
Disease screening	Association with disorder	Improved health outcome Usefulness for decision making
Risk assessment/ Susceptibility	Association with future disorder	Improved health outcomes
Prognosis of diagnosed disease	Association with natural history	Improved health outcomes, or outcomes of value to patients, based on changes in patient management
Predicting treatment response	Association with a state that relates to drug efficacy or ADEs	Improved health outcomes or adherence based on drug selection or dosage

Ethical, Legal and Social Issues

- Penetrating pie slice-applies to all components but can be considered as part of clinical utility
- Contextual issues

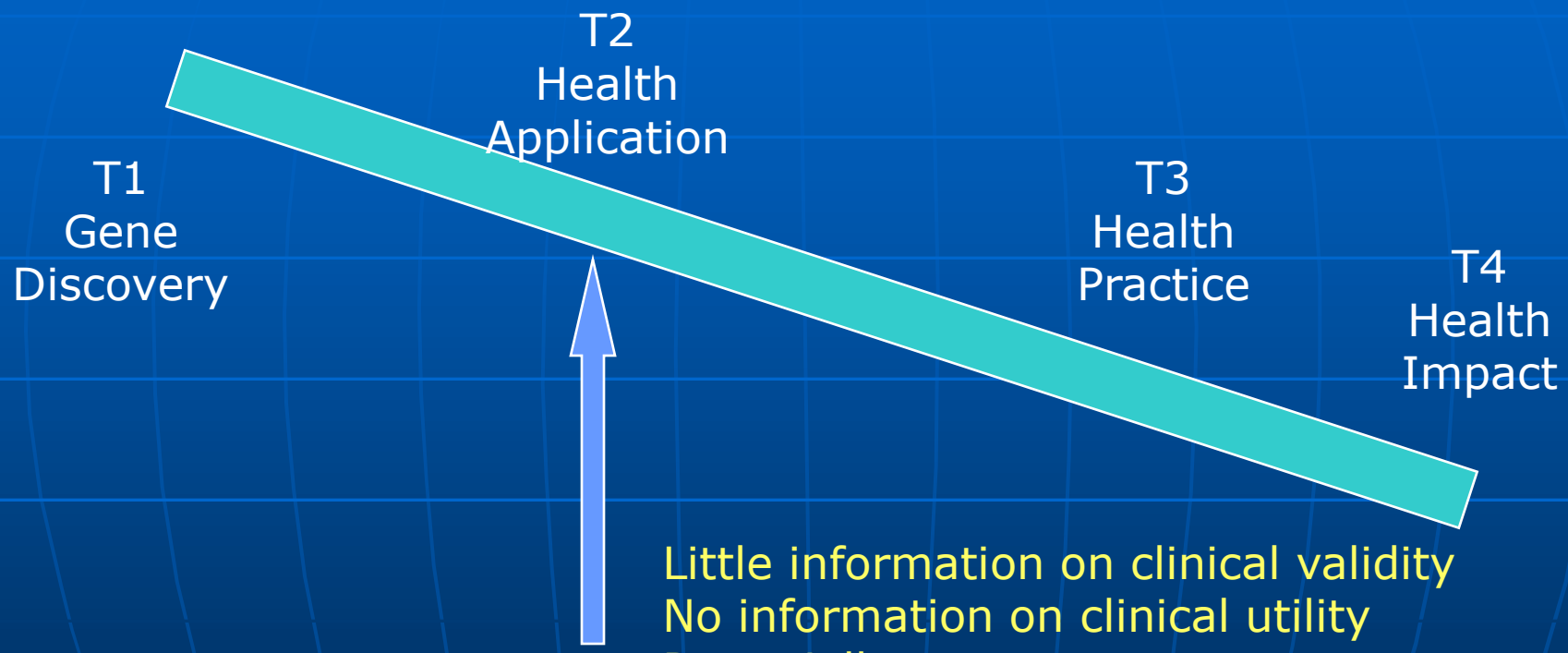


Ethical, Legal & Social implications

- What is the occurrence of negative consequences?
  - Stigmatization or discrimination
  - Health disparities
  - Privacy/confidentiality
  - Personal/family/societal issues
- What safeguards have been described or are in place and effective?
- Legal issues to be considered
  - Consent, ownership and storage of data and samples
  - Patents & licensing or proprietary testing
  - Obligation to disclose

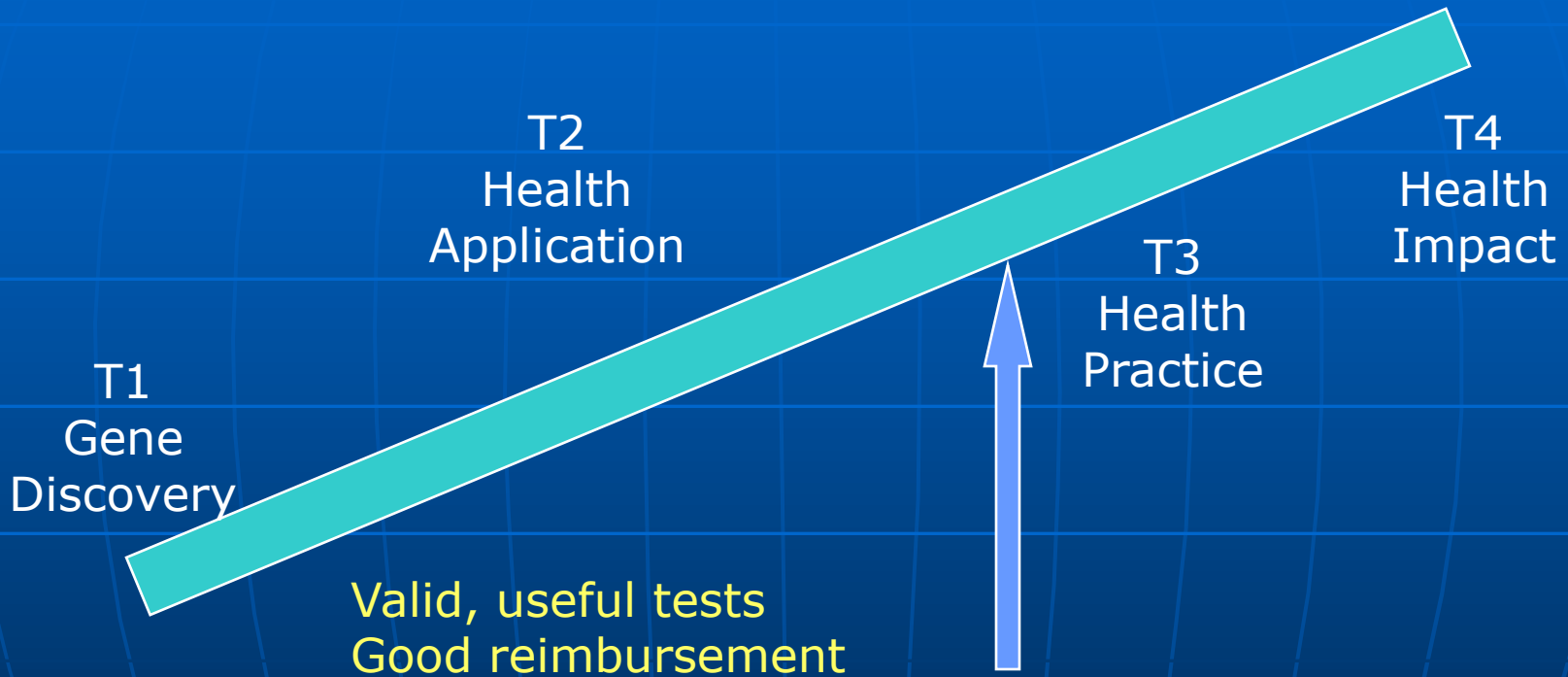
How High Should the Evidence Bar Be?

Lowering the Threshold for Translation into Practice

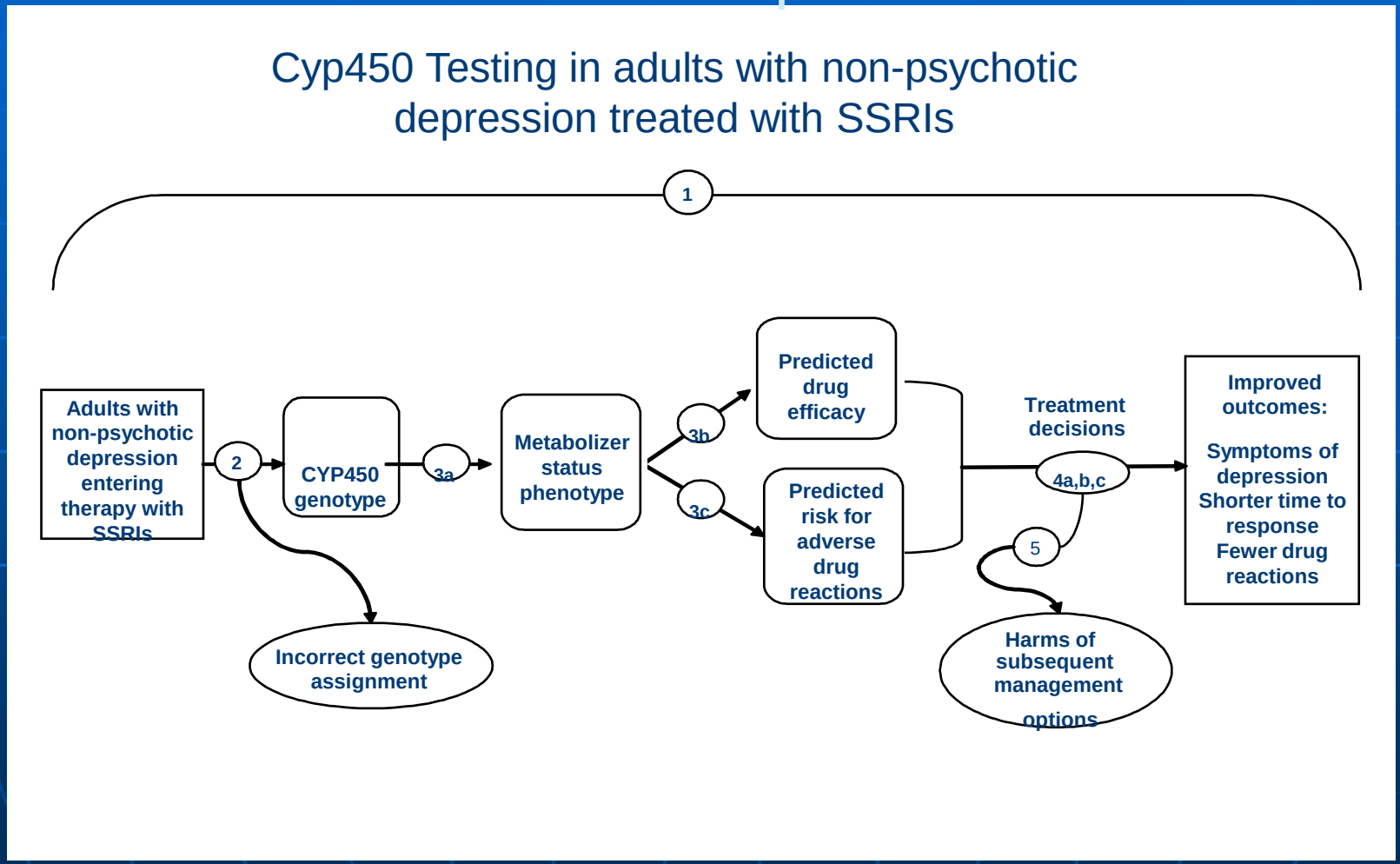


Little information on clinical validity
No information on clinical utility
Potentially no coverage
Potential for increased harms
Potential for increased benefits
Use based on expert opinion
Stimulate innovation

Raising the Evidentiary Threshold for Translation into Practice



Structuring the Review: Constructing an Analytic Framework in the Context of a Specific Problem



Numbers refer to the key questions for which systematic reviews are conducted

Evaluation of Evidence

- Criteria for
  - Evaluation of individual studies (hierarchy of evidence)
  - Evaluation of links in evidence chain
    - Categorize evidence of AV, CV, CU as Convincing, Adequate, Inadequate
  - Evaluation of overall body of evidence

Hierarchies of Data Sources and Study Designs for the Components of Evaluation

Level	Analytic Validity	Clinical Validity	Clinical Utility
1	Collaborative study Summary data from well-designed external proficiency testing	Well designed longitudinal cohort studies Validated clinical decision rule	Meta-analysis of RCTs
2	Other proficiency testing Well designed peer-reviewed studies Expert panel reviewed FDA summaries	Well designed case-control studies	A single RCT
3	Less well designed peer-reviewed studies	Lower quality case-control and cross-sectional studies Unvalidated clinical decision rule	Controlled trial without randomization Cohort or case-control study
4	Other research, clinical laboratory or manufacturer data Studies on performance of the same basic methodology,	Case series Other research, clinical laboratory or manufacturer data Consensus guidelines Expert opinion	Case series Other studies, clinical laboratory or manufacturer data Consensus guidelines Expert opinion

Recommendations Based on Certainty of Evidence, Magnitude of Net Benefit and Contextual Issues

Level of Certainty	Recommendation
High or Moderate	**<u>Recommend for…..</u>** …if the magnitude of net benefit is *Substantial, Moderate*, or *Small*, unless additional considerations warrant caution. Consider the importance of each relevant contextual factor and its magnitude or finding. **<u>Recommend against….</u>** … if the magnitude of net benefit is *Zero* or there are net harms. Consider the importance of each relevant contextual factor and its magnitude or finding.
Low	**<u>Insufficient evidence….</u>** … if the evidence for CU or CV is insufficient in quantity or quality to support conclusions or make a recommendation. Consider the importance of each contextual factor and its magnitude or finding. Determine whether the recommendation should be Insufficient (neutral), Insufficient (encouraging), or Insufficient (discouraging). Provide information on key information gaps to drive a research agenda.

Case Study: Recommendation on Cyp450 Testing in adults with non-psychotic depression treated with SSRIs

- Recommendation: Insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med. 2007 Dec;9(12):819-25

Rationale for Cyp450 Recommendation

- No evidence linking testing for CYP450 to clinical outcomes
- In healthy patients receiving a single SSRI dose, genotypic CYP450 drug metabolizer status is associated with circulating SSRI levels, this association was not supported by studies of patients receiving ongoing SSRI treatment.
- CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment.

Rationale for Cyp450 Recommendation

- No evidence showing CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making.
- Without evidence of clinical utility, it is not known if potential benefits from CYP450 testing will outweigh potential harms. Potential harms may include increased cost without impact on clinical decision making or improvement in patient outcomes, less effective treatment with SSRI drugs, or inappropriate use of genotype information in the management of other drugs metabolized by CYP450 enzymes.

Conclusion

- It is important to understand the clinical validity and utility of tests to inform decision making (clinical, quality improvement, guidelines, coverage)
- Need agreed upon standards for evaluating the value of tests
- Other dimensions of value: ELSI, economics

Thanks!

EGAPP Working Group Roles

- Establish methods and process
- Select topics for review
- Participate in technical expert panels for commissioned evidence reviews
- Develop conclusions or recommendations based on the evidence
- Provide guidance and feedback on other project activities.

Evidence-based Approach

- Adapted methods of the US Preventive Services Task Force
  - Assessing balance of benefits and harms
- Used the ACCE Framework
- Systematic reviews of the Evidence
- Make evidence-based recommendations

Specific Challenges for Genomics

- Many genomic conditions are uncommon with few large, well-done studies
- Tests are available with only descriptive information and pathophysiologic reasoning
- Range of applications
- Actions and outcomes are often unclear
- Technologies change rapidly
- Interpretation is complex
- Results affect others (family members)

Topic Selection

- Adopted broad definition of genetic test as in the SACGHS Oversight report
- Criteria
  - Burden (impact, prev, severity, available intervention, potential benefit/harms)
  - Practice issues (availability, likelihood of inappropriate use, impact on practice or consumers)
  - Other (portfolio to test methods, availability of evidence, other reviews, variety of applications)

EGAPP
Assessing Effectiveness

- Methods to assess diagnostic tests
  - What are outcomes
  - Bridging two cultures– genetic and evidence- based communities
  - Differing framework
    - analytic validity
    - clinical validity
    - clinical utility
    - (clinical value)

Methodologic Challenges

- Titrating evidence to the problem
- How certain do we need to be for
  - Risk assessment (prediction)
  - Diagnosis
  - Treatment
- Modeling
- Economic evaluation
- Adaptive / staged processes

Topics Under Review

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Breast Cancer	Gene expression profile	Women diagnosed with breast cancer	Treatment and recurrence risk
Cardiovascular Disease	Multigene panel	General population	Risk prediction or nutritional/lifestyle management
Colorectal Cancer (CRC)	*UGT1A1*	Individuals diagnosed with CRC	Treatment with irinotecan
Depression	*CYP450*	Individuals diagnosed with depression	Treatment with SSRI drugs
Hereditary Nonpolyposis Colon Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members
Ovarian Cancer	Genomic Tests	1) General pop. of women; 2) women at increased risk for ovarian ca	1) and 2) Detection and management

Completed Topics

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Breast Cancer	Gene expression profile	Women diagnosed with breast cancer	Treatment and recurrence risk
Lynch Syndrome/ Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members
Non-psychotic Depression	*CYP450*	Individuals diagnosed with depression	Treatment with SSRI drugs
Ovarian Cancer	Genomic Tests	1) General population of women and; 2) women at increased risk for ovarian cancer	1) and 2) Detection and management

Topics Under Review

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Diabetes, Type II	*TCF7L2*	General and/or high risk population	Predictive testing/risk assessment
Thrombophilia	*F5, F2*	Individuals with family history or clinical suspicion of thrombophilia	Prevention and management
Cardiovascular Disease	Multigene panel	General population	Risk prediction or nutritional/lifestyle management
Breast Cancer	Gene expression profile	Women diagnosed with breast cancer	Treatment and recurrence risk
Colorectal Cancer (CRC)	*UGT1A1*	Individuals diagnosed with CRC	Treatment with irinotecan

Issues to Consider

- Introduction: Lost in translation
- The continuum of genetic and genomic Information
- What are the elements of "evidence"?
- How do the elements of evidence apply to the continuum of genetic and genomic information and its intended use?
- Case studies
- How should evidence accumulation ideally progress across the translation pipeline?