Developing the Reimbursement Story: It's Never Too Early

Commercialization of Molecular Diagnostics

23rd International Molecular Medicine Tri-Conference

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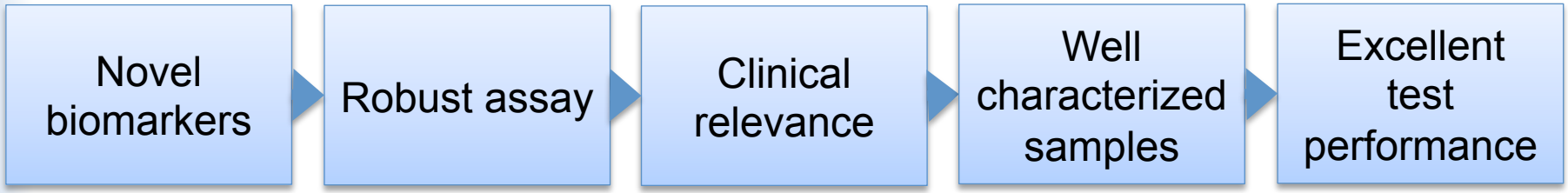
For today's discussion

- ✓Study design for technology assessment and reimbursement dossier
- ✓Framework
  - Centers for Medicare and Medicaid Services (CMS)
  - Centers for Disease Control EGAPP Initiative/ACCE Model
- ✓LDTs/IVDs

- ⃠Companion diagnostics
- ⃠Regulatory trends
- ⃠Coding
- ⃠Pricing

EGAPP: Evaluation of Genomic Applications in Practice and Prevention
ACCE: Analytical validity, Clinical validity, Clinical utility, Ethical/legal/social implications

Achieving success



- Test the market
- Understand current practice/physician behavior
- Achieve literacy in applicable clinical guidelines
- Characterize the reimbursement strategy early

Why build the reimbursement case early?

Design studies

Plan sample accrual

Develop milestones

- Study completion
- Product launch
- Billing

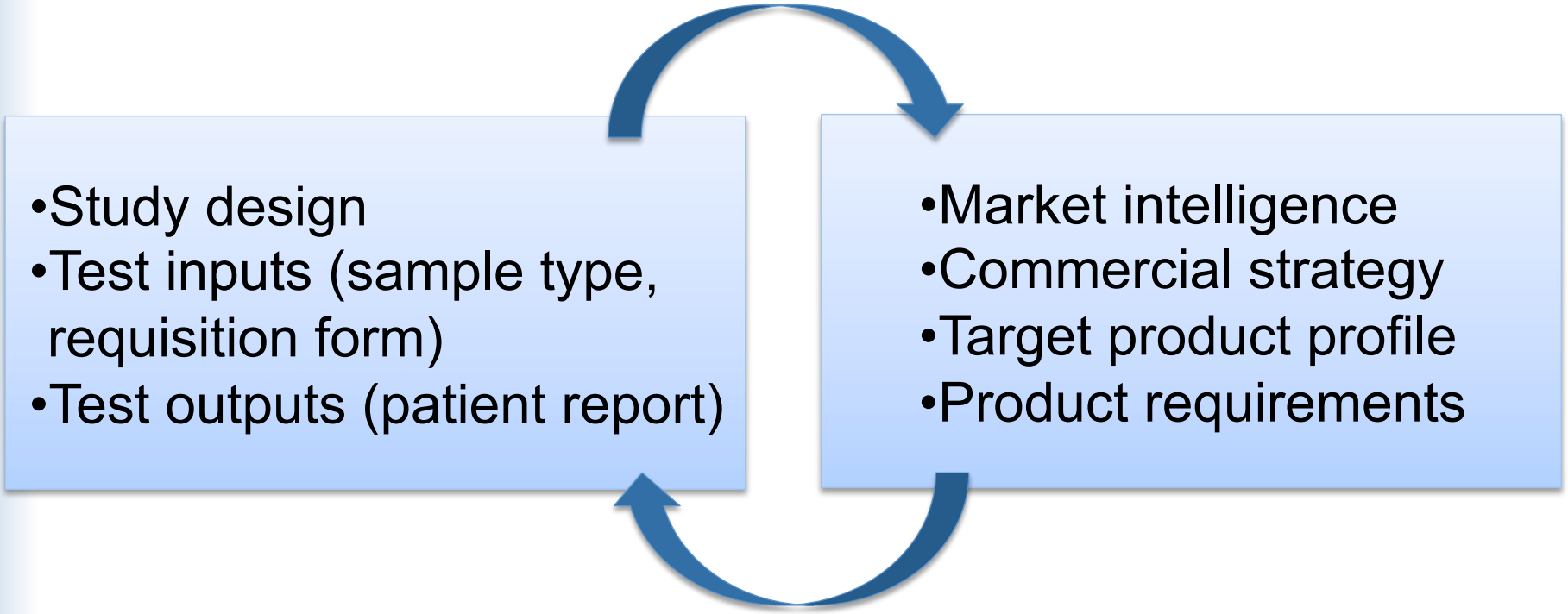
Align with TPP / PRD / marketing strategy

Pricing / revenue / time to cash-positivity

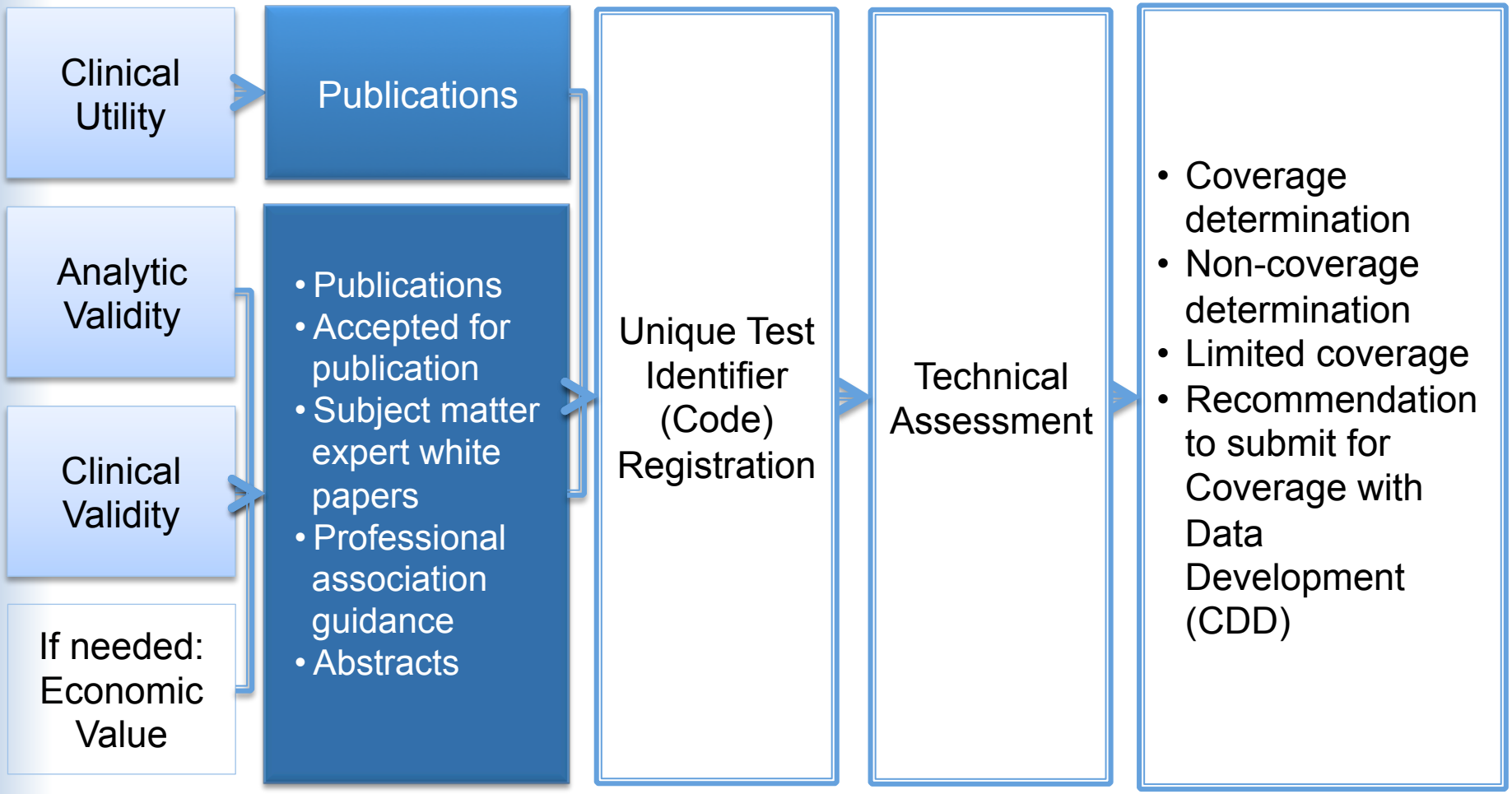
Communicate with investors

TPP: Target Product Profile; PRD: Product Requirements Document

Align study design with commercial strategy



CMS pathway to reimbursement



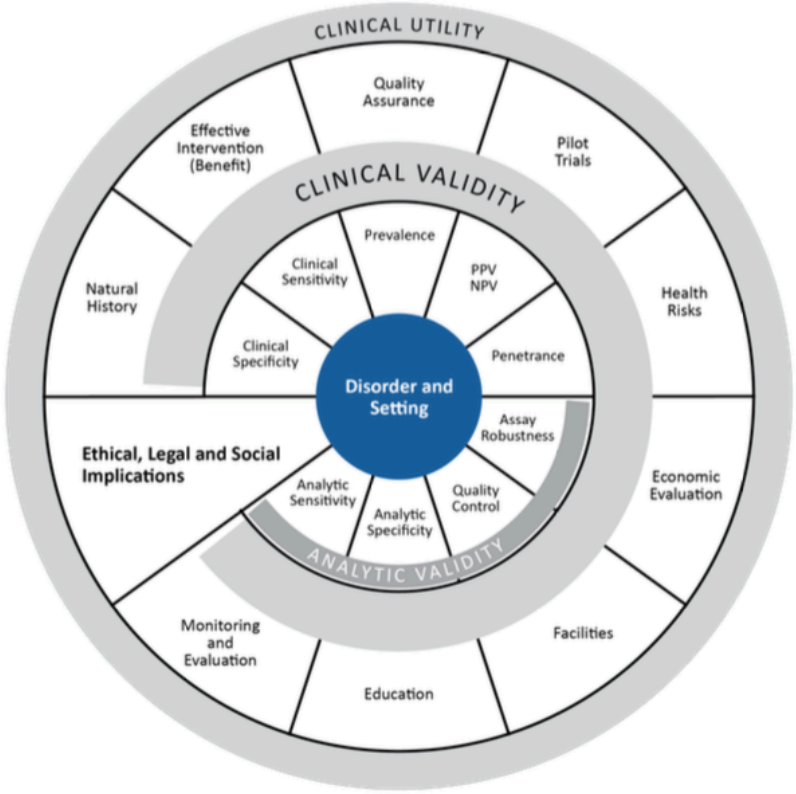
Technical Assessment

Centers for Disease Control Evaluation of Genomic Applications in Practice and Prevention (CDC EGAPP)

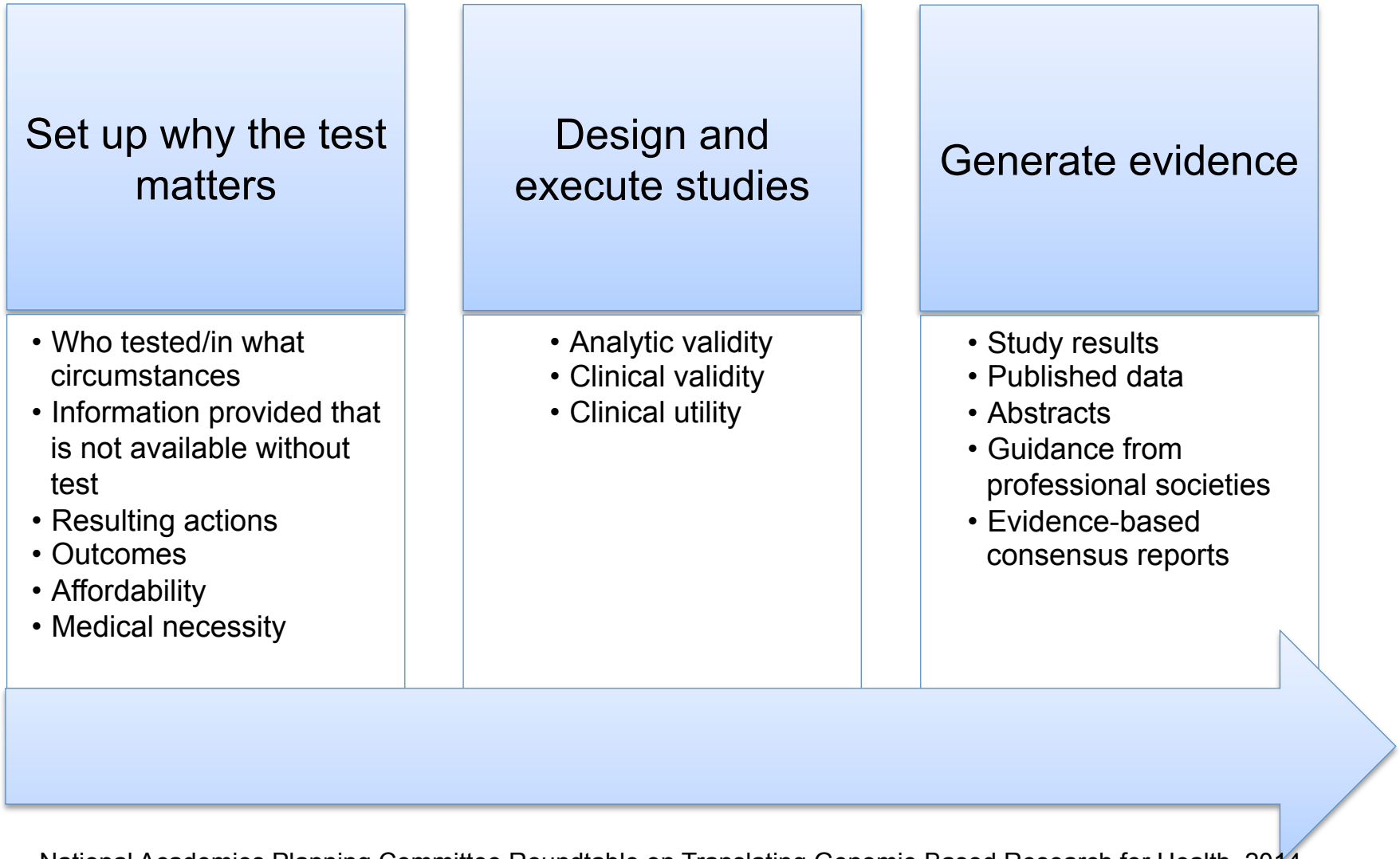
- Independent, non-federal working group that assesses new tests and publishes evidence reports

ACCE Model Process for Evaluating Genetic Tests

- Defined disorder/clinical setting
- Analytic validity
- Clinical validity
- Clinical utility
- ELSI safeguards

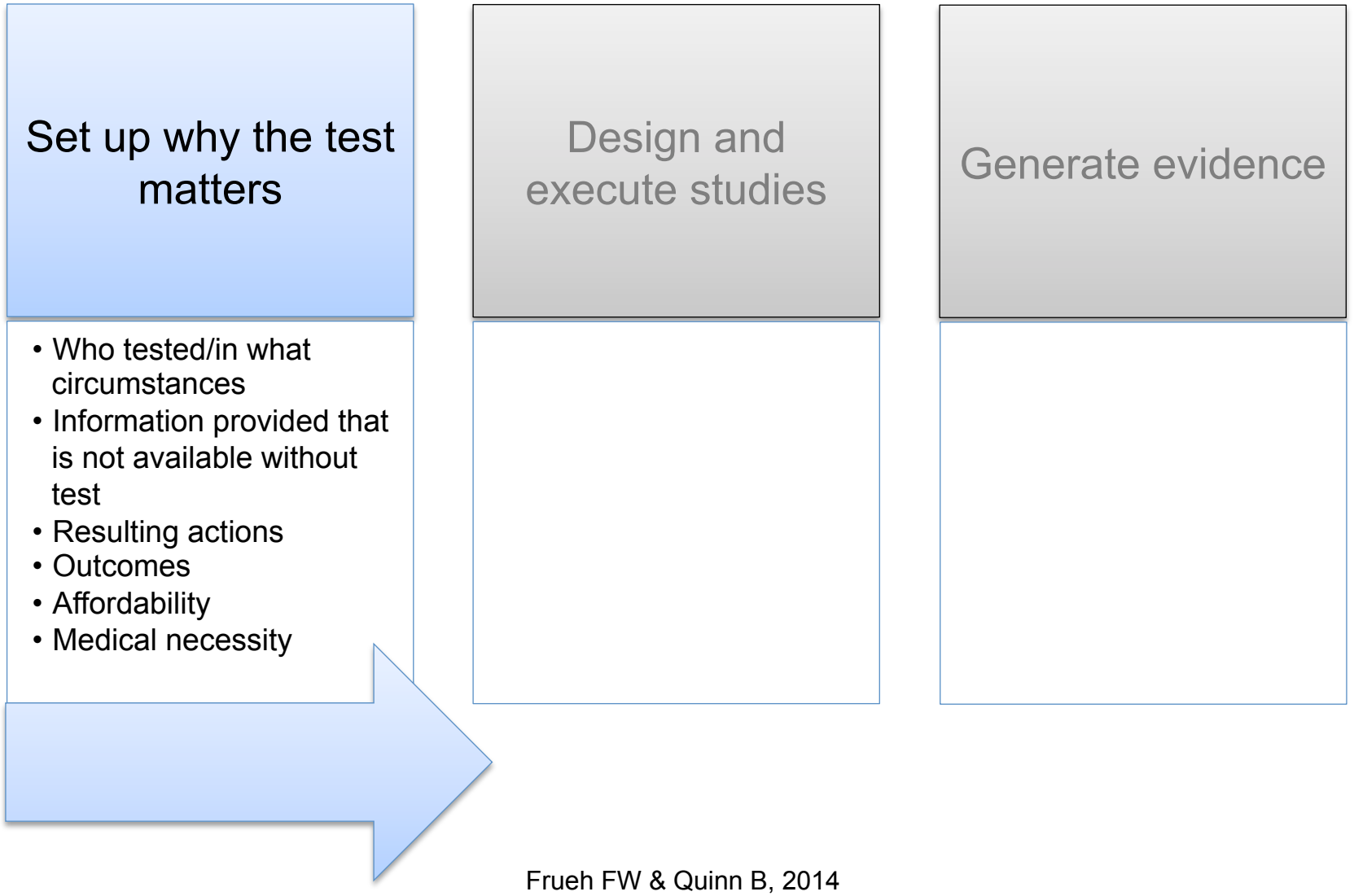


Building the reimbursement story



National Academies Planning Committee Roundtable on Translating Genomic-Based Research for Health, 2014
Frueh FW & Quinn B, 2014

Set up why the test matters



Frueh FW & Quinn B, 2014

CMS: Demonstrate test is medically necessary

Falls within a defined Medicare benefit category

Not excluded from coverage by statute, regulation, National Coverage Determination (NCD), or Local Coverage Determination (LCD)

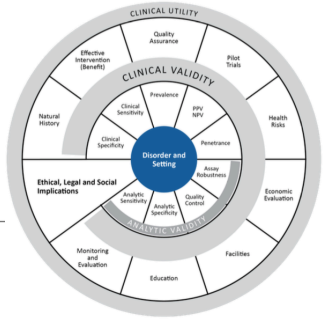
Reasonable and necessary in the diagnosis or treatment of an illness or injury, or to rule out or confirm a suspected diagnosis based on patient has sign(s) and/or symptom(s)

Ordered by a treating physician

Provides data that will be used to manage a specific medical condition

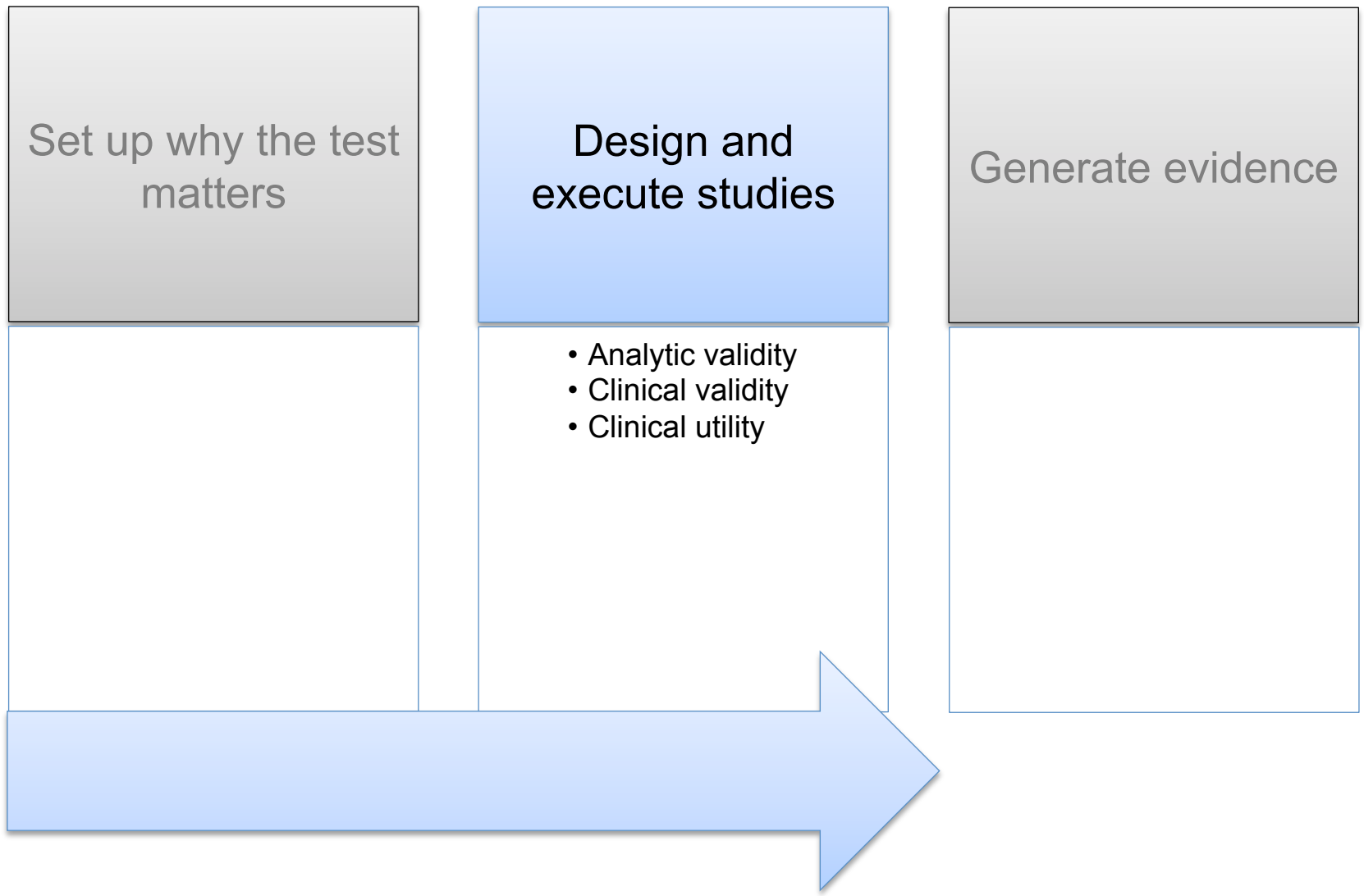
Excludes investigational services

Define the clinical disorder



- Specific condition
- Clinical findings defining the condition
- Clinical setting in which test will be performed
- Tests currently in use for the condition
- How patients are identified/screened to be determined appropriate for use of the test
- Stand-alone vs one of a series of tests
- If one of a series, situations when all vs only some of tests are performed

Design and execute studies

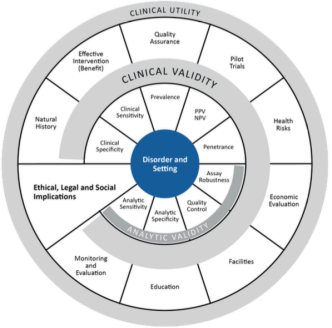


Design and execute studies

Analytic Validity	Clinical Validity	Clinical Utility
How stable and robust is the assay?	How reliably does the test correlate to the clinical condition?	What difference does the test make?
• Accuracy and reliability of measuring analyte	• Accuracy of ability to diagnose, predict or measure clinical condition	• Ability to change patient management/outcomes • Impact on cost of care

- Well characterized samples – clinically and analytically
- Cleanly defined standard use with samples from that population
- Clinical relevance verified by community, literature, guidelines
- Studies that demonstrate test is medically necessary and actionable
- Aligned with TPP, PRD, product launch/marketing strategies

Analytic Validity



Analytic Validity

How stable and robust is the assay?

- Accuracy/reliability of measuring analyt

- Test qualitative vs quantitative
- Frequency of test-positivity when mutation/biomarkers present - sensitivity
- Frequency of test-negativity when mutation/biomarkers not present - specificity
- QC program
- Repeated measurements on specimens
- Within- and between-laboratory precision
- Method for performing confirmatory testing to resolve inaccurate results in a timely manner
- Range of specimens tested
- Frequency of failure to deliver usable result
- Methods for assessing from a clinical perspective the “clinical cost” of delivering a wrong result and degree of allowable error
- Similarity of results across laboratories and technologies, if applicable
- Inputs (test requisition, specimens) and outputs (patient report) aligned with commercial plan

Analytic Validation Studies

Analytic Validity

How stable and robust is the assay?

- Accuracy/reliability of measuring analyt

Validation Element	Measures
Accuracy	Method comparison, e.g., gold standard, target values Specimen types Matrix comparisons
Analytic sensitivity	Limit of detection Limits of quantitation, upper and lower, including analytically measurable and clinically reportable ranges Linearity and reportable range Minimum input quantity and quality Minimum tumor content
Analytic specificity	Primer and probe specificity Interfering substances
Precision	Repeatability – single operator, instrument, lot, day, run Intermediate precision – multiple operators, instruments, lots, days, runs within a lab Reproducibility – multiple labs Lot-to-lot reproducibility – multiple reagent, calibrator, controls lots
Reagent stability	Closed – shelf life Open – in use Freeze-thaw
Reference intervals	Specimens from healthy subjects in intended use population
Sample stability	Shipping Primary and intermediate samples (e.g., extracted RNA or DNA) Freeze-thaw
Software (algorithm)	Verification and validation

Palmetto GBA MolDX Program 2015; clsi.org

Clinical Validity

Clinical Validity

How reliably does the test correlate to the clinical condition?

- Accuracy of ability to diagnose, predict or measure clinical condition

Demonstrate association between test result and clinical condition of interest

Study population = intended use population – that which is intended to benefit from decision guided by the test result

Obtain sufficient prior evidence from the intended use population from early validation studies

Select appropriate gold standard or reference

Define terminology and concepts used

Provide measures of certainty, e.g., 95% confidence intervals

Center for Medical Technology Policy, 2013

Clinical Validity, cont'd

Clinical Validity

How reliably does the test correlate to the clinical condition?

- Accuracy of ability to diagnose, predict or measure clinical condition

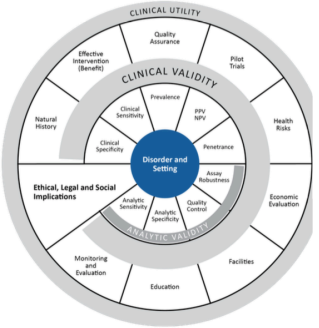
Report strength of association between test and disease state using metrics most useful to clinicians

Apply appropriate weight to false negatives vs false positives based on clinical significance – optimize appropriately for NPV vs PPV

Use appropriate reporting standards

- Binary test: sensitivity, specificity, positive and negative predictive values
- Continuous variable (e.g., risk score): select threshold or cut-off to generate binary score; when clinical outcome is binary, receiver operating characteristic (ROC) curves can be used
- Continuous or time-to-event variable: regression methods to model relationship between discrete or continuous test result and outcome
- Predictive marker: use appropriate control group

Clinical Validity, cont'd



Clinical Validity

How reliably does the test correlate to the clinical condition?

- Accuracy of ability to diagnose, predict or measure clinical condition

Sensitivity – frequency of test positive when disorder present

Specificity – frequency of test negative when disorder not present

Methods to resolve clinical false positive results in timely manner

Prevalence of disorder in the setting

Adequate validation on all populations to which it may be offered

Positive and negative predictive values (PPV, NPV)

Genotype/phenotype relationships

Clinical Utility

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Natural history of disorder

Impact of positive or negative test on patient care

Other diagnostic tests available

Measurable benefit or acceptable action as result of test with access to that benefit/action

Documentation if test will be offered to socially vulnerable population

Quality assurance measures

Results of pilot trials

Health risk identified for follow-up testing and/or intervention

Clinical Utility, cont'd

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Financial costs associated with testing

Economic benefits resulting from testing

Facilities/personnel available

Educational materials validated and available

Informed consent requirements

Methods for long term monitoring

Guidelines for evaluating program performance

Considerations for Clinical Utility

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Inability to demonstrate clinical utility most cited reason for failure to obtain coverage

Additional pitfalls

- Poorly defined population
- Lack of evidence-based decisions
- Coding issues
- Lack of evidence to support medical necessity

If outcomes hard to capture, measure clinical behavior change as proximate to outcomes change

Start clinical utility studies early

Learn from others' successes and failures

May need to involve private payers and providers early

Patient influences: some patients do not get better even when clinical care is done correctly

Provider influences: Providers practice differently, and occasionally poorly

Study design: appropriate and representative

A well-designed clinical utility study demonstrates that the test changes patient management decisions and, ultimately, patient outcomes

Jeter E, Palmetto GBA
Peabody et al. Am J Managed Care 2014

Clinical Utility Study Design/Levels of Evidence

Design	Description	Level of Evidence
Randomized, Prospectively Controlled Trials (RCT)	• Demonstrates therapeutic intervention based on test results leads to statistically and clinical significant improvement in patient outcomes versus standard of care • End points widely considered clinically appropriate	3A
Prospective-Retrospective Trials (PRT)	• Uses archived samples from a previously reported RCT to demonstrate that treatment based on test is associated with improved outcomes in a statistically and clinically significant manner versus standard of care • Samples and study design sufficiently characterized and powered to permit definition of the indications for test use	3B
Prospective Observational Studies (POS)	• Enrolls patients prospectively in registry • Treatment according to defined pathway using test as part of care plan • Demonstrates statistically and clinically significant improvement in healthcare outcomes versus standard of care	2A
Results from at least one study with Level of Evidence 2A or above must be submitted for acceptance for full clinical review		
Retrospective Data Modeling (RDM)	• Uses complex data modeling using large data sets to determine statistically and clinically significant improvement in outcomes when test used to guide treatment versus standard of care	2B
Retrospective Observational Studies (ROS)	• Does not stipulate treatment pathways based on test result	1
Preclinical Studies (PS)	• Preclinical data only, or related studies	0

Randomized Controlled Trials (RCTs)

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Biomarker-stratified design

- Classic clinical trial design
- All comers randomized
- Large sample size

Enrichment design

- All patients tested
- Only test-positive continue to treatment/management
- Smaller sample size

Biomarker-strategy design

- Randomization to arm that uses test to direct therapy or control arm that does not

Prospective-Retrospective Analysis of Previously Conducted RCTs

- RCT design using existing sample cohort
- Faster and less expensive

Time and cost of RCTs often exceeds capacity of small/emerging company

Frieidlin B, McShane LM, Korn EL. J Natl Cancer Inst 2010
Simon RM, Paik S, Hayes DF. J Natl Cancer Inst 2009
Center for Medical Technology Policy, 2013

Non-RCT Study Design

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Single-arm studies

- Test developed to be used with a FDA-approved drug
- Adequate archived samples not available to conduct prospective-retrospective trial
- Feasible to use response as endpoint
- Comparable response data in comparative cohort exists

Prospective observational studies

- Patient registries
- Multiple group, pretest/posttest design
- Acceptable if compelling rationale for not doing RCT is addressed

Decision-analytic modeling

Clinical Performance and Value (CPV) vignettes

- *In silico* simulation of clinical behavior change
- Builds clinical utility case early – completion of validation not required
- Validated against actual practice
- Not affected by patient variation

Cost-effectiveness

- Can be compelling for payers
- May not be sufficient for coverage but should be employed as part of reimbursement strategy

Peabody et al. Am J Managed Care 2014
Center for Medical Technology Policy, 2013

Coverage with Data Development (CDD)

PALMETTO GBA MolDX

Clinical Utility

What difference does the test make?

- Ability to change patient management/outcomes
- Impact on cost of care

Criteria

- Strong evidence analytic and clinical validity
- Potentially significant but unproven potential of clinical utility
- Potential to affect the management of a serious, prevalent disease within Medicare population

Submit study plans to support safety, diagnostic performance and clinical utility (effect on health outcomes)

Can be realistically completed in 3-4 years or less

Adequate resources to complete study

Study protected from conflicts of interest

Study development guided by key stakeholders (e.g., patients, clinicians, professional societies)

Study registered on www.ClinicalTrials.gov prior to enrollment

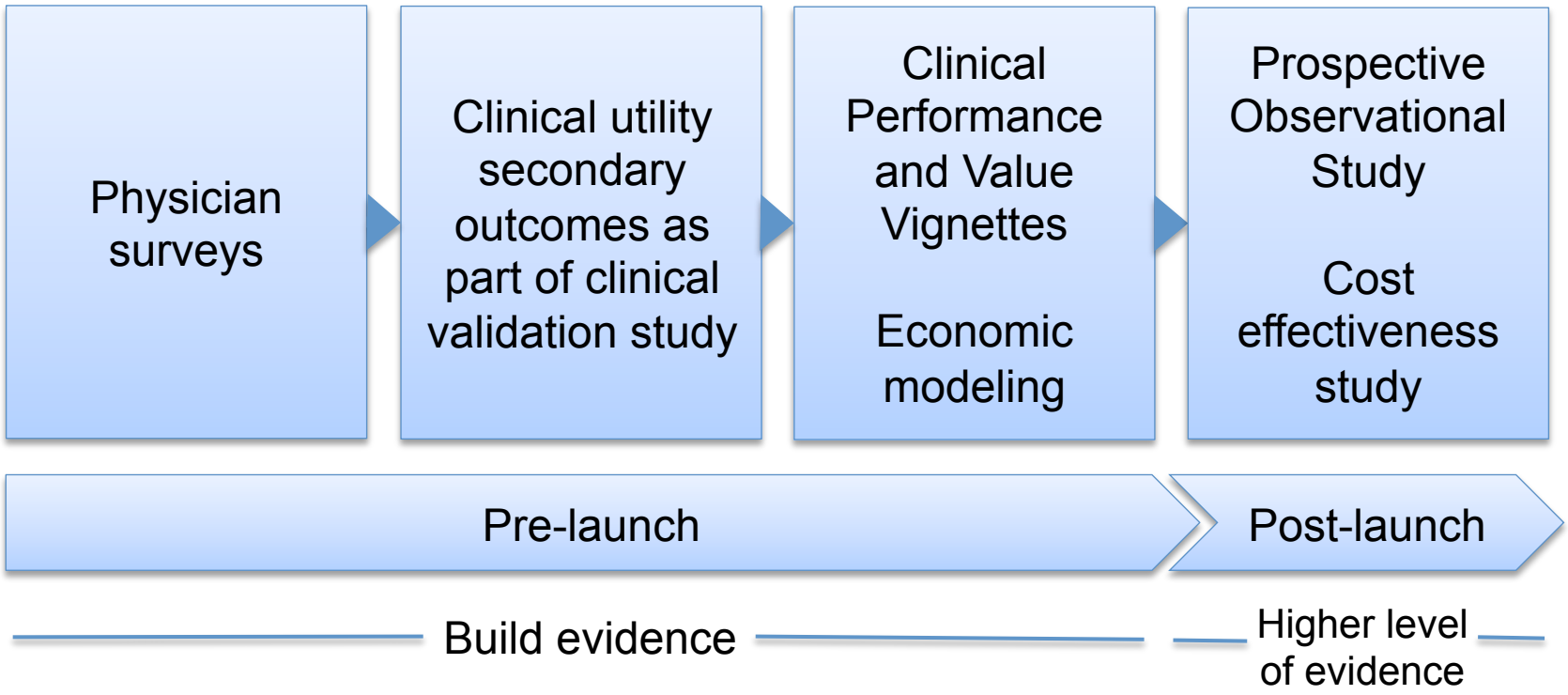
Specified method and timing of public release of results

Successes | Failures

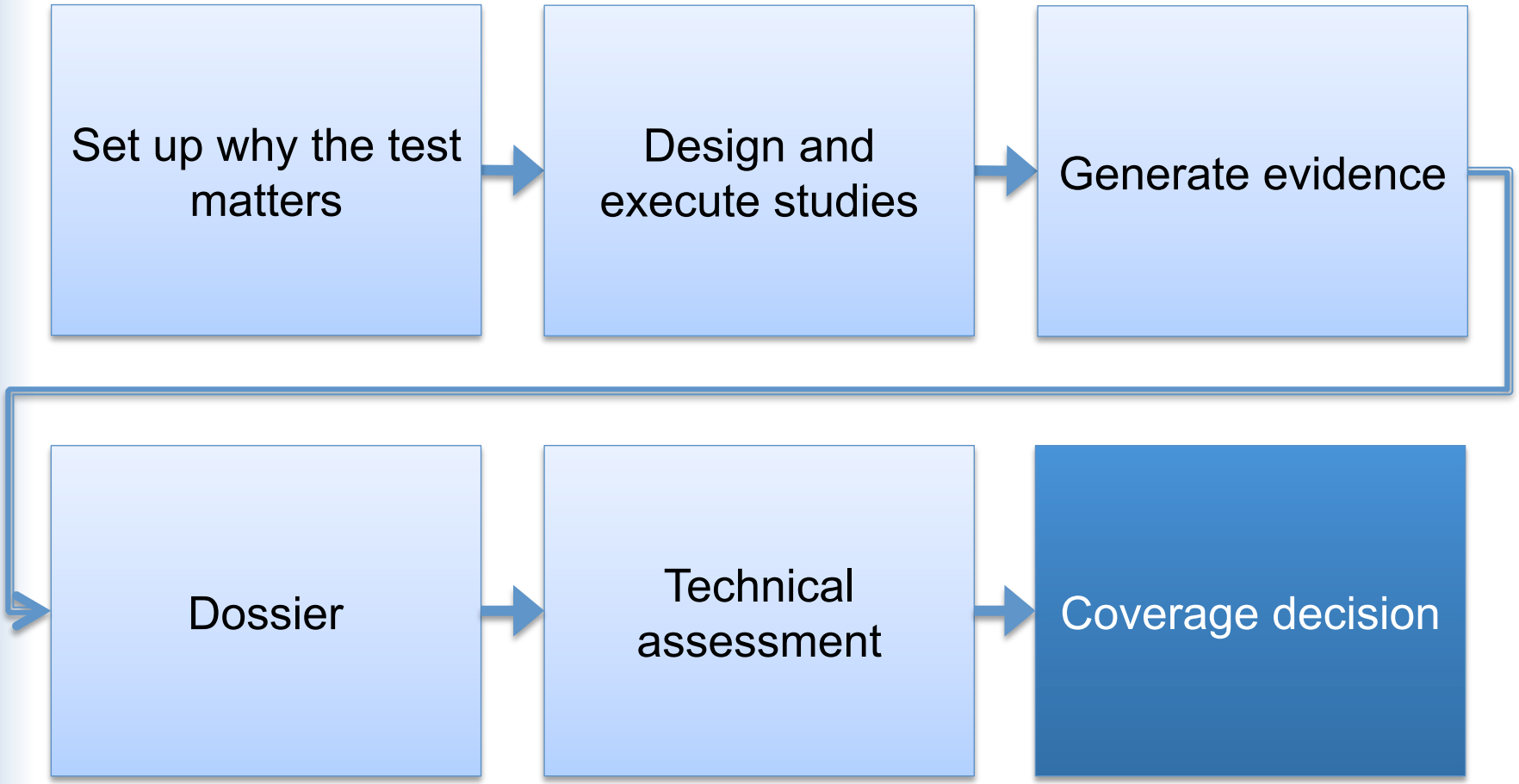
Positive coverage	Negative coverage
Genomic Health Oncotype DX • Strong validation studies • Multiple large, multicenter retrospective and prospective studies looking at multiple outcomes	Tethys PreDX diabetes test • Lack of clinical utility data • Inability to justify test as screening vs test for at-risk population
Crescendo Biosciences Vectra DA (RA) • CPV vignettes in a randomized controlled study, provider assessments and comparative review of cases to compare clinical assessment with test score	Berkeley HeartLab LPA-Aspirin genotype test • Lack of clinical utility data • Failure to demonstrate target population
CardioDx Corus CAD • Large longitudinal study showing significant and clinically relevant utility combined with retrospective chart review showing patient management impact	Agendia subtyping profile tool, breast CA • Insufficient clinical utility data

Peabody et al. Am J Managed Care 2014

Clinical Utility Strategy



Results


Set up why the test matters
Design and execute studies
Generate evidence
Dossier
Technical assessment
Coverage decision

THANK YOU

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