Association of Medical Diagnostics Manufacturers
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Meeting the Clinical Utility Needs of Payers and Regulators for Molecular Diagnostics

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Supporting a New Era of Precision Medicine

Agenda

- Clinical Utility Definition
- Our Hypothesis
- FDA and Third-Party Payers — Utility Evidence Requirements
- Evidence Development — Commonalities to Clinical Utility
- Study Design Efficiencies

How do Key Stakeholders Define "Clinical Utility"?

FDA: Positive impact of assay results on patient by improving the outcome of drug therapy. Improved outcomes include benefits, harm reduction, & patient-reported improved outcomes.

Clinical utility: the ability of the assay to improve clinical decision-making and patient outcomes. Depends on clinical situation; availability of effective therapies; magnitude or lack of clinical benefit in one marker-designated group versus another

Palmetto MolDx Program: Demonstrates improved patient outcomes or changed physician treatment behavior

ACCE Model: likelihood of improving patient outcomes; e.g., impact on patient care; availability of an effective remedy or acceptable action; financial costs and economic benefits

Understanding how different stakeholders' definitions overlap enables dual-purpose clinical trial designs.

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Our Hypothesis

Clinical utility evidence development often is the most expensive aspect of Dx test creation and commercialization

Two main access gatekeepers – the FDA and third-party payers – are significant consumers of clinical utility evidence

Their clinical utility evidence needs may differ, but with foresight and planning often can be addressed simultaneously

Finding and taking advantage of synergies in development of clinical utility evidence can be the key to cost-effective studies for the test's development and commercialization

"There have been cases where the payer has heard what we were planning to do for a study, and they say…that maybe with a small tweak, that clinical study would meet their needs. In those circumstances, it's not requiring much effort on the part of the sponsor, but they save themselves from having to do a whole new clinical study for getting the payer support."

CDRH Director Jeff Shuren*

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*Source: The Gray Sheet, August 26, 2013

Evidence Needs are Sensitive to Value Perspective: "Safe and Effective" Blends into "Useful"

Regulator Evidence for Dx

- **Safe**: "For IVD products, the safety of the device relates to the impact of the device's performance, and in particular on the impact of false negative and false positive results, on patient health"
- **Effective**: Does what the label says it does; e.g., quantifies an analyte, or indicates the suitability of a therapeutic
- Unless claimed, clinical outcomes are outside the purview
- Cost evaluation is outside the purview

Payer/Financial Risk-Holder Evidence for Dx

- Objectively improved clinical outcomes
- Changed physician treatment behavior (to an accepted/better alternative)
- Changed referral patterns (reduced, or more appropriate)
- Same or better clinical results, at reduced cost

FDA: "Is this test fit for purpose?"
Payers: "Is the purpose useful enough that we should spend our money on it?"

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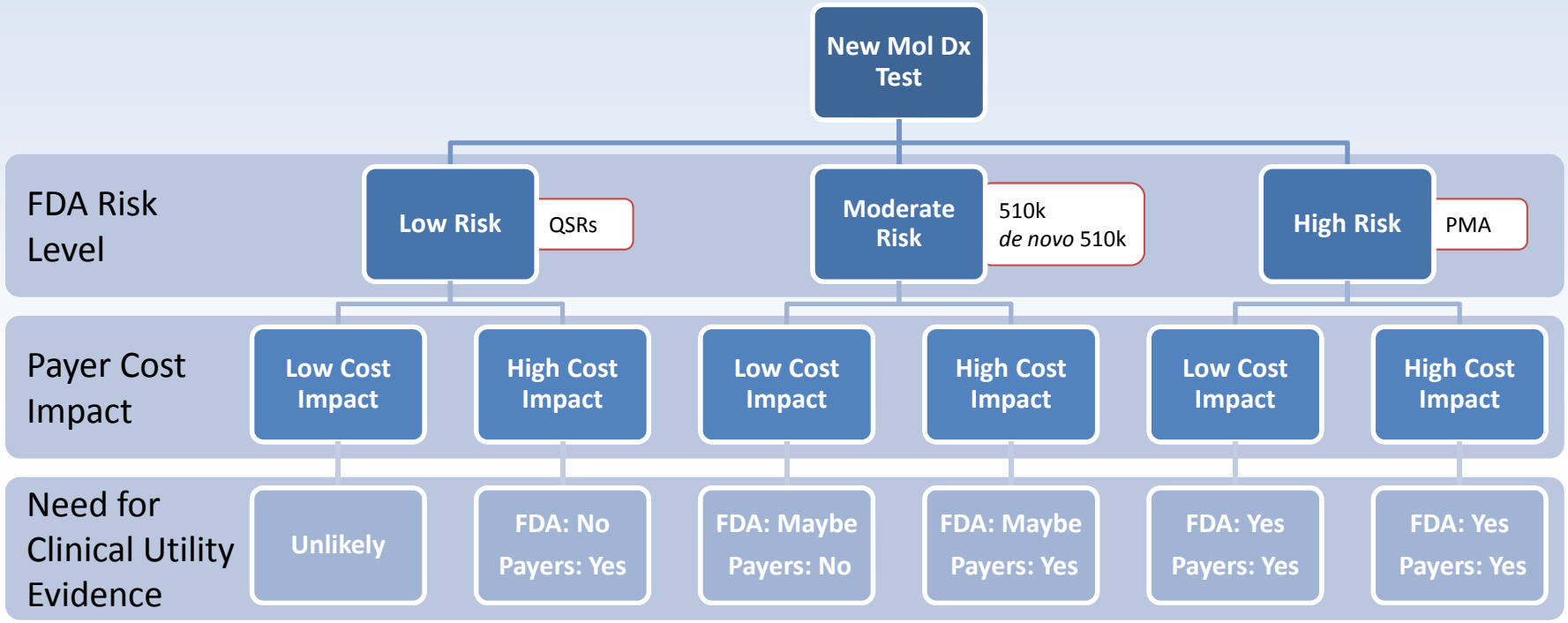
The FDA's Evidence Requirements Vary by the Relevant Risk and Resulting Regulatory Path

510(k)	• Demonstration of equivalence to previously cleared product • Clinical validation (laboratory clinical sample studies); analytical validation • Clinical patient studies for clinical validity evidence possibly required for new indication or population
de novo 510(k)	• Same as 510(k), *except* • Because no predicate exists, a clinical patient study to develop evidence of clinical validity is likely to be required
PMA	• Requires evidence of safety and effectiveness for the population and use specified in the labeling • *"a device is effective when it can be determined, based upon valid scientific evidence…[that it] will provide **clinically significant results**. The valid scientific evidence used to determine the effectiveness of a device shall consist principally of **well-controlled investigations**."**

*Source: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050419.htm#determination

How do FDA Risk and Cost Impact Interact to Define Clinical Utility Evidence Needs?



These three categories offer possibilities for clinical study synergies

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Dual-purpose Study Design Considerations

What is the intended use?

- **Screening**
- **Diagnosis (alone or as an aid)**
- **Prognosis**
- **Treatment selection**

What is the intended population?

- **Asymptomatic individuals**
- **Signs and symptoms**
- **Mid-treatment**
- **Specific sub-groups among the above**

What are the endpoints?

- **Correlation to diagnostic gold standard**
- **Determination of disease risk**
- **Likelihood of recurrence**
- **Treatment segmentation of the population**

Answering these questions from both FDA and payer perspectives will help the clinical trial meet the needs of each

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Beyond FDA Requirements: Alignment of Study Outcomes with Payer Perceptions of Clinical Utility

Type

- Mortality? Morbidity? How much?
- Peace of mind?

Timing

- When would the clinical benefit be realized from the diagnostic information?
- Could it be so long before the benefit is seen that it's unclear what really caused it?

Likelihood

- How directly does the test relate to the projected benefit?
- Can something beneficial be done for the patients that the test identifies?
- Could other factors be stronger drivers of that clinical decision?

Cost

- How much does the test itself cost?
- Are downstream/dependent costs increased or decreased? Overall costs?
- (for some payers) Is it cost effective?

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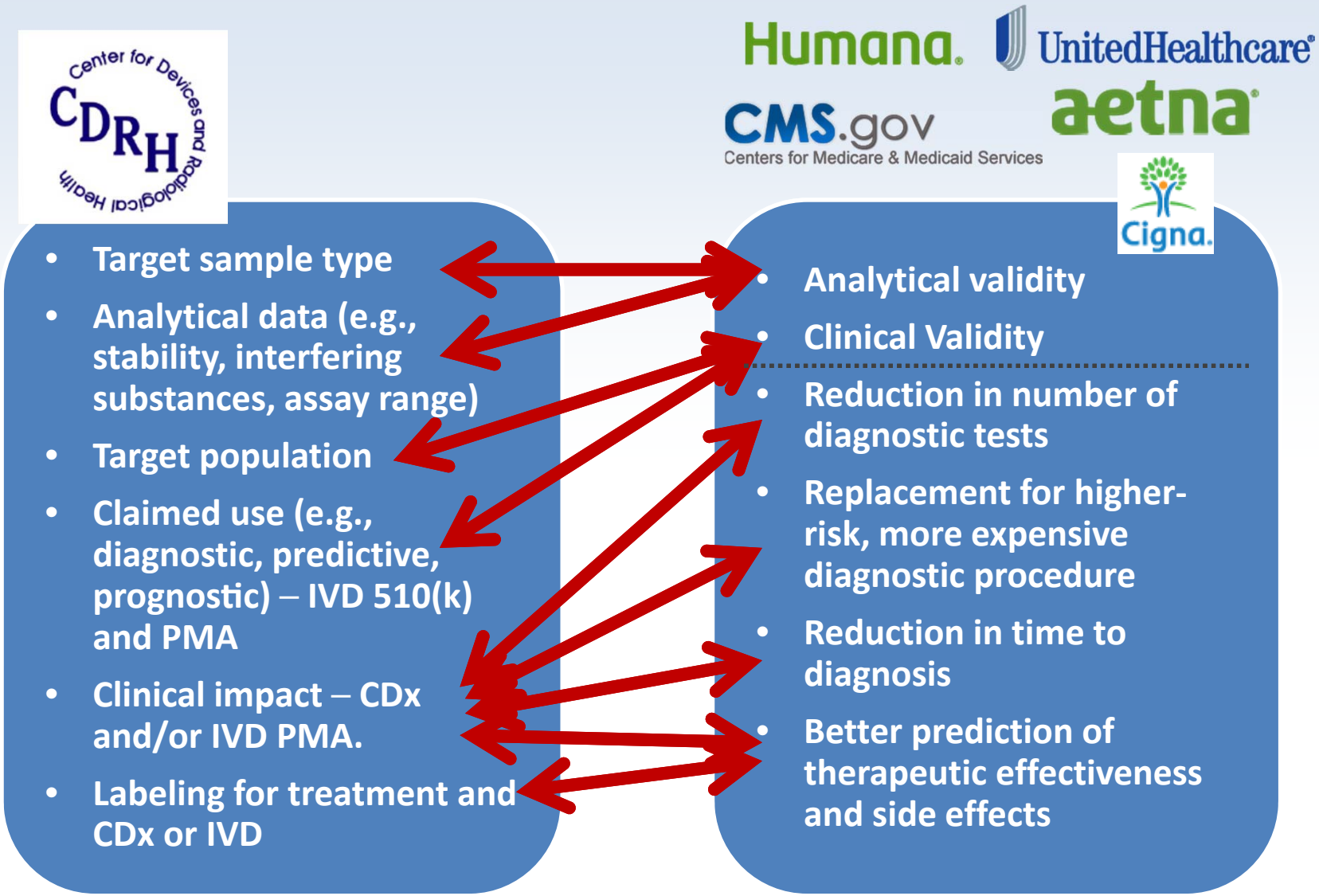
FDA and Third-Party Payers — Relationships Between FDA Study Design and Third Party Payer Measures of Utility



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What Kind of Clinical Study Might Meet the Evidence Needs for this Hypothetical Molecular Dx?

Risk-prediction test based on specific pathway genomic markers or gene expression

	FDA	PAYERS
POTENTIAL UTILITY ENDPOINTS	1. Correlation with gold-standard risk-prediction measures 2. Follow-up for incidence of adverse events (study endpoint) 3. Health outcomes 4. Correlation with targeted drug response (Used as CDx)	1. Patient behavior (risk reduction) 2. Incidence of adverse events 3. Health outcomes 4. Likely benefit from targeted drug
POTENTIAL STUDY TYPES	1. Retrospective study of relationship between CDx marker and risk of pathway-specific adverse events 2. Medium-term prospective interventional study	1. Long term, high-enrollment prospective observational study 2. Medium-term prospective interventional study

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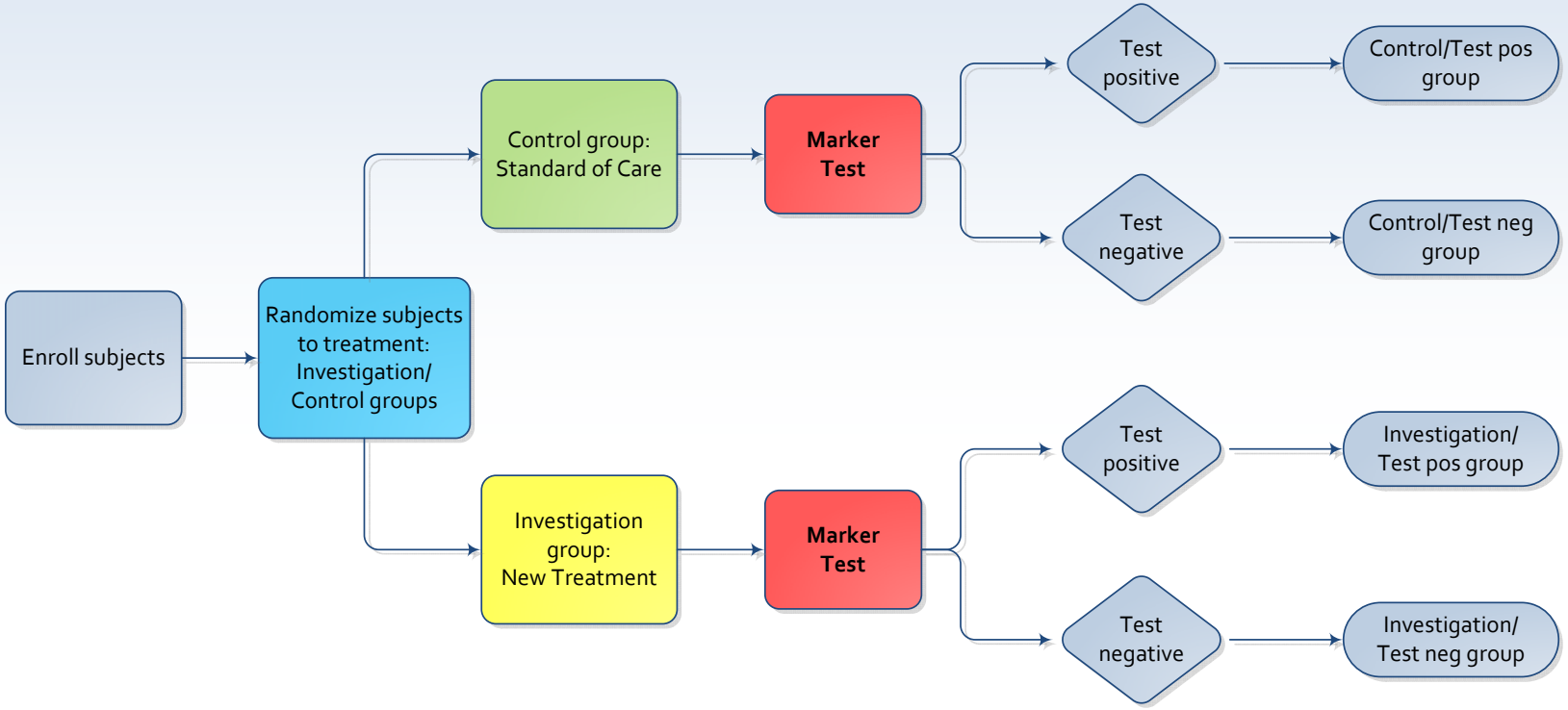
Clinical Utility Study Example #1

☑ Test/Diagnostic Effectiveness Data (FDA)
☒ No Treatment or Clinical Impact Data (Payers)



- ☑ Study can be retrospective (unrelated to randomization into treatment groups)
- ☑ Clinical Utility – shows correlative relationship of test to treatment; e.g., predictive or prognostic
- ☒ No effect on treatment
- ☒ Not conclusive regarding clinical impact of test
- ☑ Early proof-of-concept study

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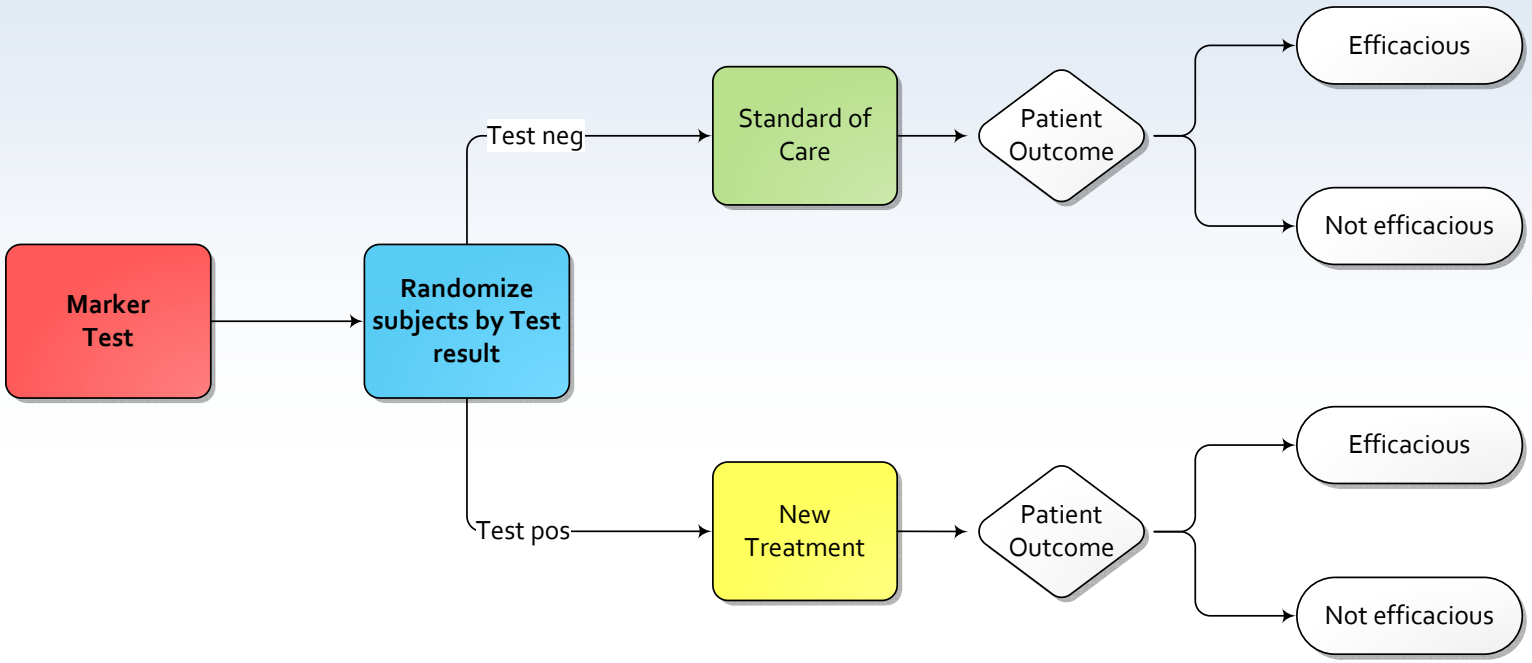
Clinical Utility Study Example #2

☑ Test/Directed-Treatment Effectiveness Data (FDA)

☒ No Test-Specific Clinical Impact Data (Payers)



- ☑ Study is prospective
- ☑ Evaluation of response rate with New Treatment/Test-positive subjects vs. response rate of SOC/Test-negative subjects
- ☑ Efficient study if biomarker is well-characterized in the literature, and research has been done regarding relationship between biomarker and disease/condition (i.e., don't need to prove the relationship as part of the study)
- ☒ No evaluation of New Treatment on Test-negative subjects

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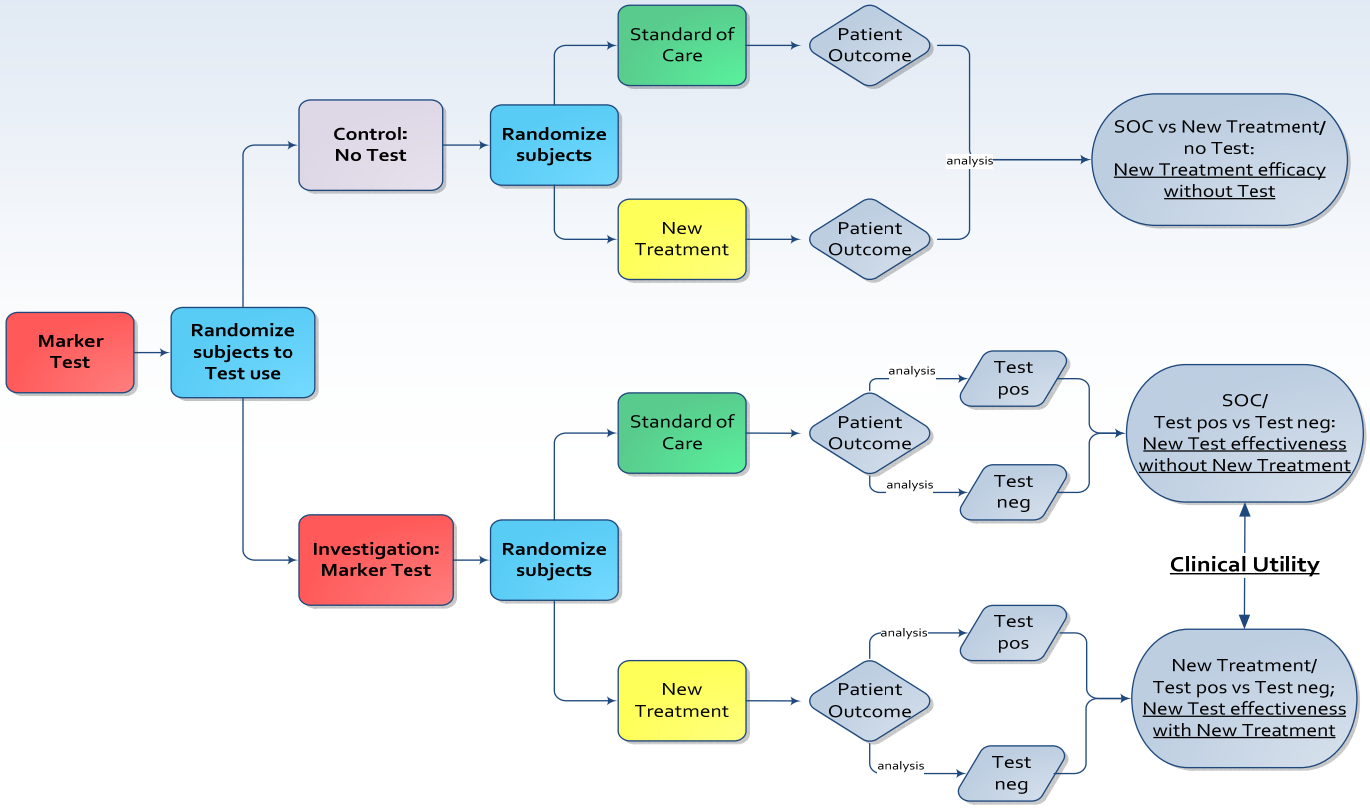
Clinical Utility Study Example #3

☑ Test/CDx Directed-Treatment Effectiveness Data (FDA)
☑ Treatment/CDx Clinical Impact Data (Payers)



- ☑ Provides multiple combination analyses for evaluation of SOC vs. New Treatment, with and without the biomarker test
- ☑ Maintains blinding of subjects and biomarker test results during treatment and follow-up
- ☑ Provides clinical utility evidence for both FDA and payers
- ☑ Control arm may be eliminated if biomarker is well-characterized regarding the relationship between the marker and disease/condition

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Questions?

For additional questions please contact:

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