

Study Design for Clinical Validation of Diagnostic Tests

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Intended Use

What type of test?



Right claims

How should the test be evaluated?



Right study design

Who is the test for?



Right patient

What is being measured?



Right analyte

What is being tested?



Right sample

Where will testing occur?



Right conditions for use

What will test report?



Right data type

Right Claims

Diagnosis: Target condition present or absent at time of testing

Screening: General population or asymptomatic with specific risk factors

Risk: Predisposition to future condition

Prognosis: Separating diagnosed patients into different outcome groups

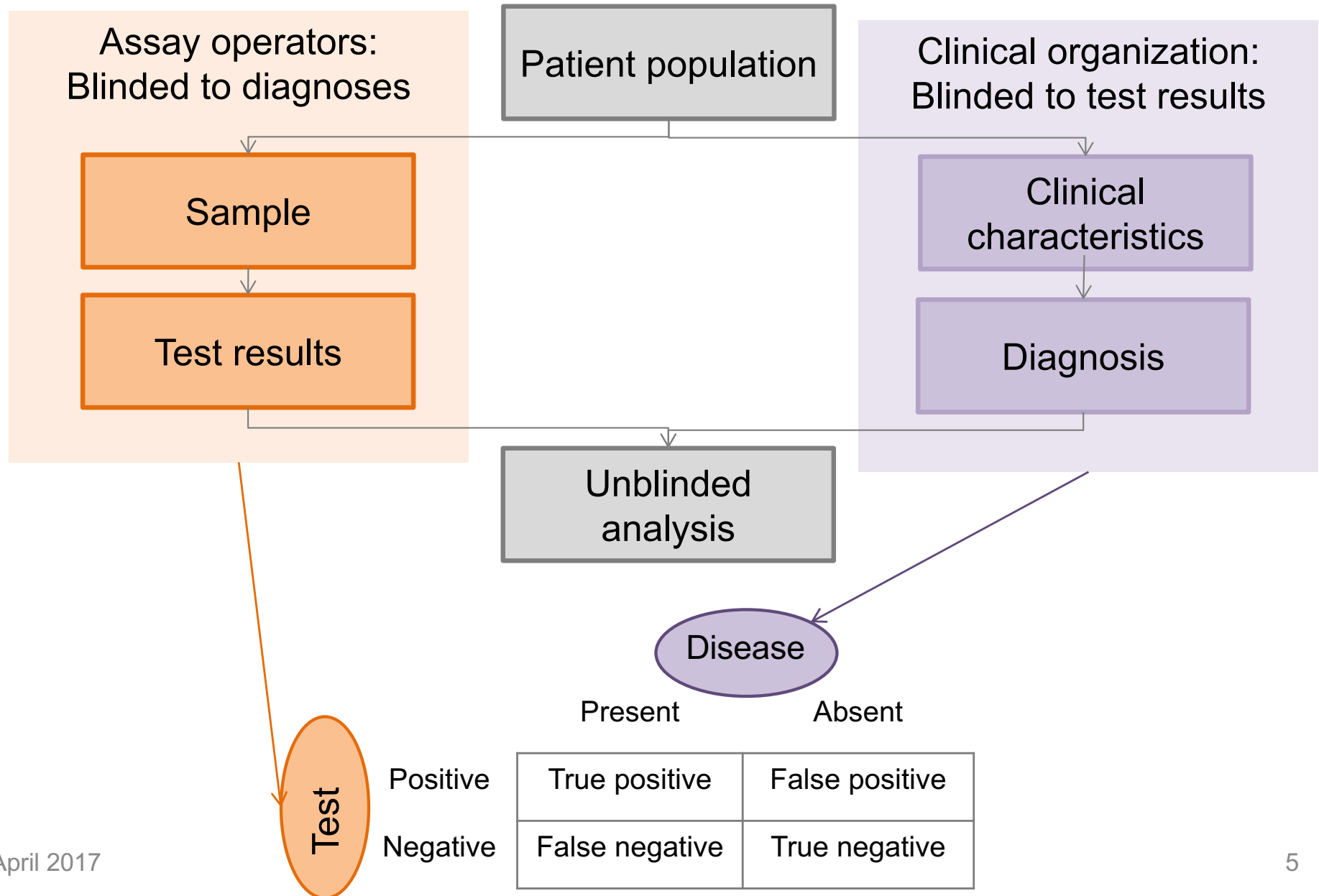
Monitoring: Evaluating change in condition

Companion: Co-development associated with particular therapy

Right Study Design

- Different claims → different study designs
 - Low prevalence of disease: large cross-sectional study
 - Monitoring of disease: longitudinal study with pre-specified definition of relevant change in disease/health status
- Evidence to support multiple claims may require multiple studies
- Clinically recognized and supported by literature/current practice
 - Disease prevalence – study population vs. adjusted
 - Reference/gold standard

Right Study Design



Right Data Type

- Performance characteristics
 - Sensitivity
 - Specificity
 - Negative predictive value
 - Positive predictive value
- Test results
 - Continuous score, e.g., risk score
 - Time-to-event variable
 - Discrete result
 - Predictive marker
- Clinically significant/actionable

Right Data Type

		Disease	
		Present	Absent
Test	Positive	TP	FP
	Negative	FN	TN

Sensitivity	% with disease who test positive	$TP/(TP+FN)$
Specificity	% without disease who test negative	$TN/(FP+TN)$
Positive predictive value (PPV)	% positive test results that are true positives	$TP/(TP+FP)$
Negative predictive value (NPV)	% negative test results that are true negatives	$TN/(TN+FN)$
Prevalence	% of population that are disease positive	$TP+FN/TP+FP+FN+TN$

Study Design: Potential Pitfalls/Biases

- Study population \neq target population
- Disease prevalence \neq expected prevalence
- Confounded/inconsistent reference/gold standard diagnoses
- Sample handling inconsistencies
- Inconsistent test results
- Test performance not clinically relevant
- Clinical validation not performed on analytically validated assay
- Validation test set not independent
- Blinding between laboratory operators (test results) and clinical personnel (patient diagnoses) not maintained

Right Patient

- Gender
- Age
- Condition
- Clinical findings defining condition
- Tests currently in use for condition
- How patients determined to be appropriate for test use
- Stand-alone vs. one of a series of tests
 - If one of a series, situations when all vs. only some of the tests are performed
- If study population enriched for diseased patients, rationale for enrichment and expected vs. study prevalence are well characterized

Right Analyte

- Define what is being tested
- Measure
 - Accuracy
 - Analytic sensitivity and specificity
 - Precision
 - Reagent stability
 - Reference intervals
 - Sample stability
 - Software verification and validation

Right Sample

- Pre-analytic
 - Sample type
 - Collection
 - Method
 - Timing
 - Tube/ampule
 - Media
 - Processing, storage and shipping
 - Conditions
 - Materials
 - Methods
 - Well characterized chain of custody
- Run in accordance with analytically validated requirements

Right Sample

- Prospective vs. retrospective
- For retrospective cohorts:
 - Represent target population
 - Sufficient sample volume
 - Sufficiently characterized
 - Demographics
 - Clinical characteristics
 - Reference/gold standard
 - Storage has no impact on analyte being measured
 - Provides no unbiased estimates of performance
 - Disease characterization (verification bias)
 - Disease prevalence (spectrum bias)

Right Conditions for Use

- Location
 - Hospital, clinic or private practice
 - General care vs. specialty setting
 - Point of care

THANK YOU

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