Principles of Radiology Study Design

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Outline

- What is “study design”?
- Building blocks of radiology studies
- Strategies to improve study efficiency

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What is “study design”?

- Where are you going?
  - Research goals, study objectives
- How will you get there?
  - Available resources (Examples: patients, funding, expertise, time)
- What will you do?
  - Examples: Prospective vs. retrospective; paired vs. unpaired; randomization; study population; imaging test readings and endpoint collection

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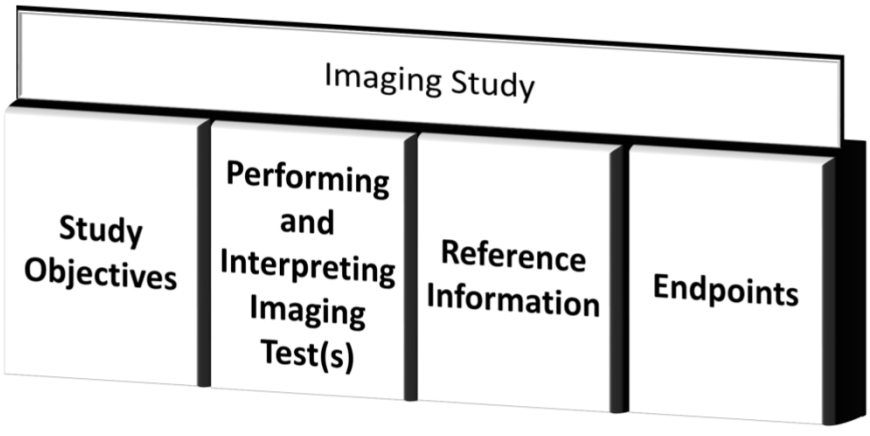
Building Blocks of Imaging Studies



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Developmental stages

Phase I: Discovery
- Technical performance

Phase II : Introductory
- Diagnostic accuracy
- Impact on diagnostic thinking

Phase III: Mature
- Diagnostic accuracy
- Impact on diagnostic thinking
- Impact on therapeutic planning
- Effect on health outcomes

Phase IV: Disseminated
- Effect on health outcomes
- Costs & benefits to society

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Study Objectives

- Where are you going?
- Active statement about the specific steps to answer the research question.

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Study Objectives

- Where are you going?
- Active statement about the specific steps to answer the research question.

- Should not re-state the research hypothesis
- Should not state investigators' hope for a statistically significant finding

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Example

Suppose you want to compare the accuracy of contrast-enhanced mammography (CEM) and abbreviated breast MRI (AB-MRI)…

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Choice of Study Objective:

#1: To show that AB-MRI is better than CEM.

What aspect of performance is being evaluated?

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Choice of Study Objective:

#2: To show the diagnostic accuracy of AB-MRI is better than CEM.

Be specific about the endpoint.

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Choice of Study Objective:

#3: To show that breast-level sensitivity and specificity of AB-MRI are better than CEM.

What is the population(s) of interest?

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Choice of Study Objective:

#4: To show that board-certified mammographers interpreting AB-MRIs of high-risk women have better breast-level sensitivity and specificity than when interpreting CEM.

State the objective in a detached way.

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Choice of Study Objective:

#5 To estimate and compare the breast-level sensitivity and specificity of AB-MRI and CEM in high-risk women when read by board-certified mammographers

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Performing and Interpreting Imaging Tests

- Timing of the imaging tests
  - When in patients' history?
  - Sequential vs. cross-over? Wash-out period?
- Collecting data from the imaging tests

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Design of Studies Involving Readers

- Environment for reader interpretations
  - "In the field" vs. "test per se" (Begg and McNeil, 1988)
- Single reader vs. multi-reader
- Selection of readers
  - Target-reader population?
    - Early phase studies, narrow target-reader population
    - Late phase studies, broad target-reader population
  - Single institution, multi-institution, core-lab

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Design Options for Accuracy Studies of Tests Requiring Reader Interpretation

Options	Convenience	Inter-reader variability	Generalizeable estimate of accuracy
Single reader	****		
Consensus reading	**		
Core-Lab reading	*	***	**
Multi-Reader study	*	****	****

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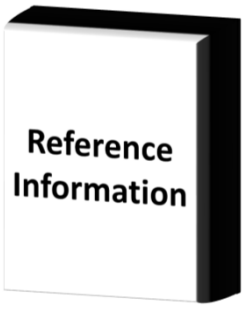

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Reference Information

- Source of information, completely different from the test or tests under evaluation, which tells us the true condition status of the patient

Zhou et al 2011

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Reference Standard

- Sometimes called “gold standard”
- Rarely is it “gold”

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Examples of Reference Standards

- Pathology
- Surgery
- Reference standard expert panel
- Another imaging test
- Follow-up

You can use multiple, but equally good, reference standards in the same study –

Composite reference standard

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What if there is no reference standard?

- Some types of studies do not require reference standards
- Examples:
  - Correlation study: New test results correlate with standard test
  - Agreement study: New test results agree with standard test
- For an accuracy study, it's very important to have a reference standard

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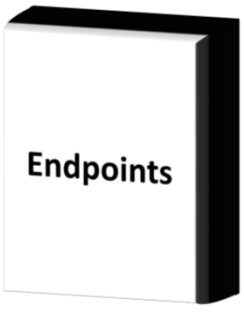

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Endpoints

- Measurements required by study objectives
- The success of a study, of any phase, depends critically on the choice of a primary endpoint.
- Endpoint must:
  - Correspond to the study objectives
  - Be sensitive to the effect you are measuring
  - Be reliably measured
  - Be clinically relevant

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Choice of Endpoints

- Should be appropriate for development phase

	Technical parameter	**Accuracy**	**Effect on patient care decisions**	**Patient outcome**	**Effect on society**
Discovery	yes	yes			
Introduction		yes	yes		
Mature		yes	yes	yes	
Disseminated		yes		yes	yes

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Details Make a Difference!

- Consider a study of the accuracy of CT for detecting colon polyps.
- Suppose you want to compare accuracy with vs. without knowledge of artificial intelligence-assisted polyp detection (AI)

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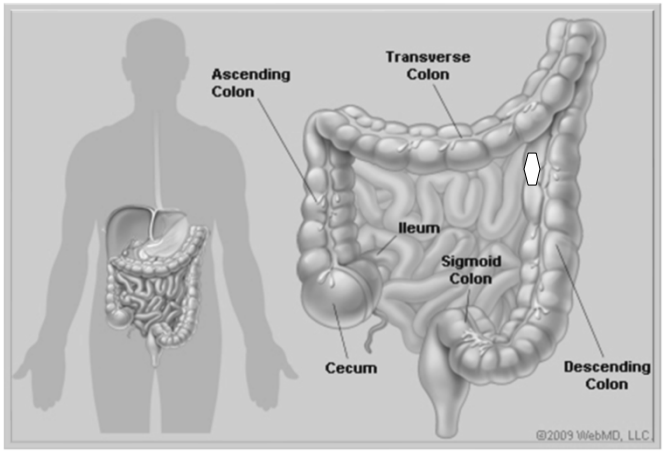
Without AI, reader finds a polyp in descending colon



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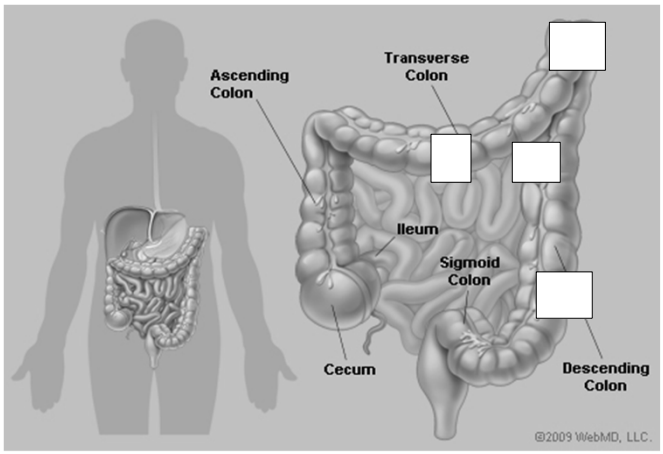
AI marks 4 suspicious areas



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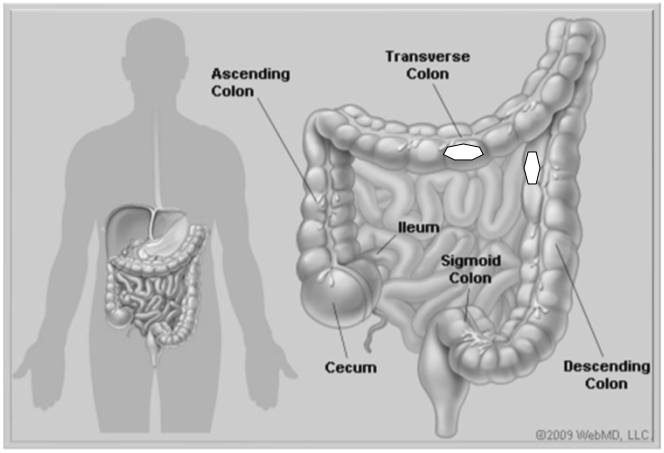
AI, reader finds a second polyp.
Did AI increase the reader's accuracy?



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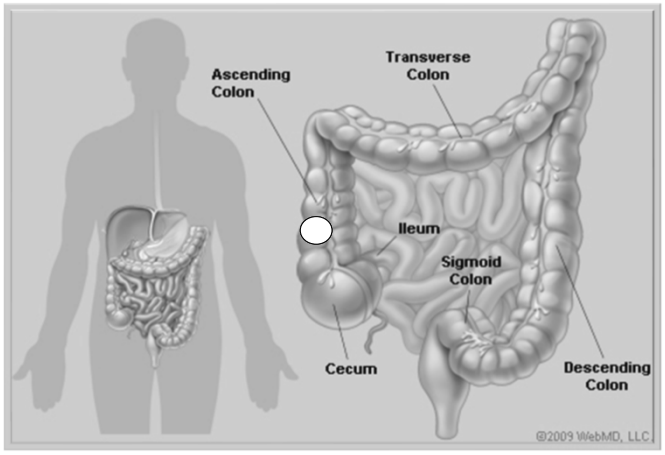
Second example:
Without AI, reader finds a FP in the ascending colon but misses the actual polyps



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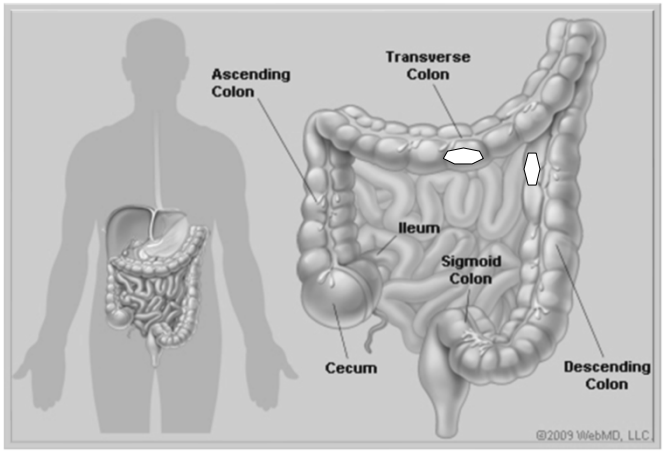
With AI, reader finds the polyps.
Did AI increase the reader's accuracy?



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How Do You Define a True Positive?

- If a patient has disease, is it sufficient to find *anything* (even a FP)?
- Does the reader need to correctly locate the lesion?
- Does the reader need to find all lesions?

You need to state these details in study protocol.

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Order of Building Blocks is Not Fixed

- Prospective
- Retrospective

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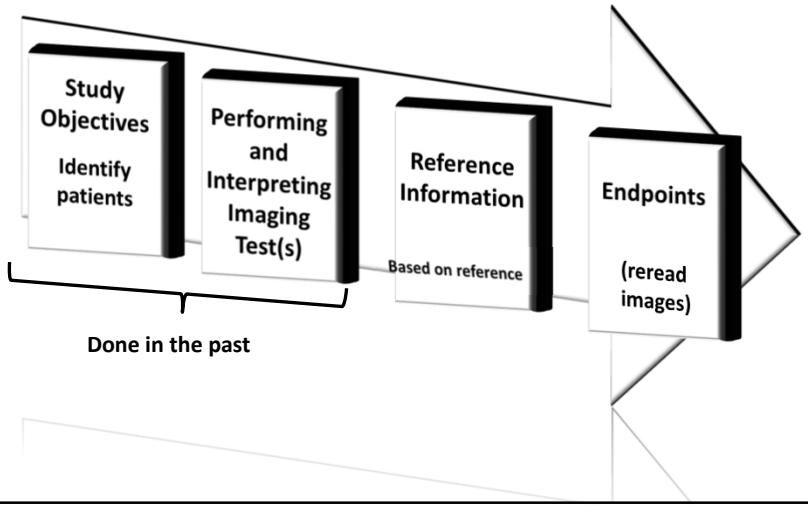
Retrospective Study Flow



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Two Examples of Diagnostic Accuracy Studies

1) Prospective design
2) Retrospective design

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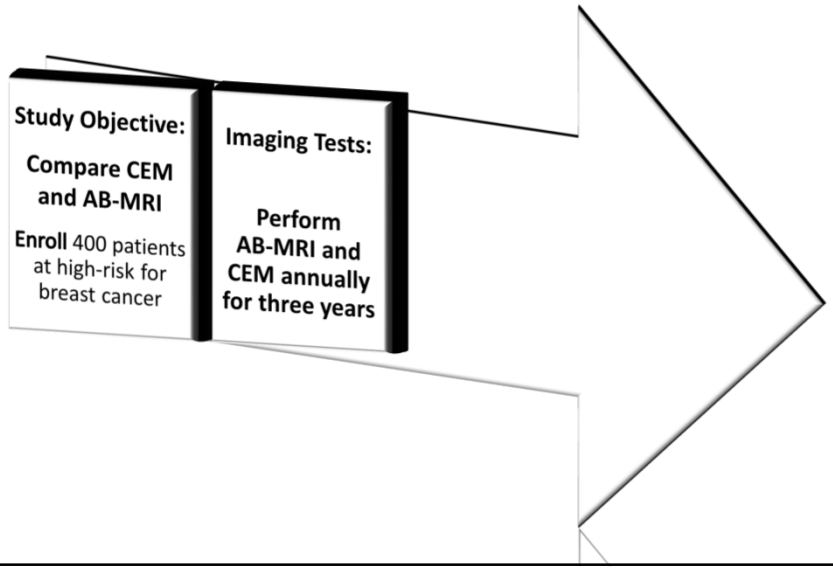
Prospective study example



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Breast Imaging Example

- Paired design: All patients have both AB-MRI and CEM
- Paired (vs. unpaired) designs
  - Control for case-difficulty, eliminate confounding
  - Statistically more efficient → smaller sample size
  - Pairing *ensures* that two groups are same
    - (Randomization makes two groups *similar.*)

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Breast Imaging Example

- Blinded design:

  Technicians perform MRI without knowledge of mammogram (and vice versa), AND images read by radiologists who haven't seen competing images.

- Images read by scheduled radiologist at time of scan, but design calls for a multi-reader interpretation at a later date.

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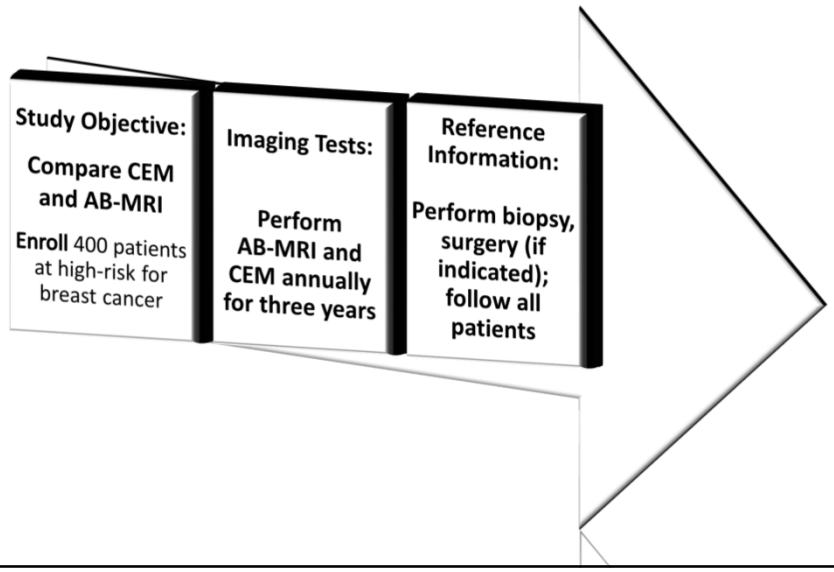
Prospective study example



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Breast Imaging Example
Reference Standard

- Breast cancer defined by combination of biopsy results within 365 days of the imaging tests and clinical follow-up at 1 year
  - Includes interview with participant and medical record review.

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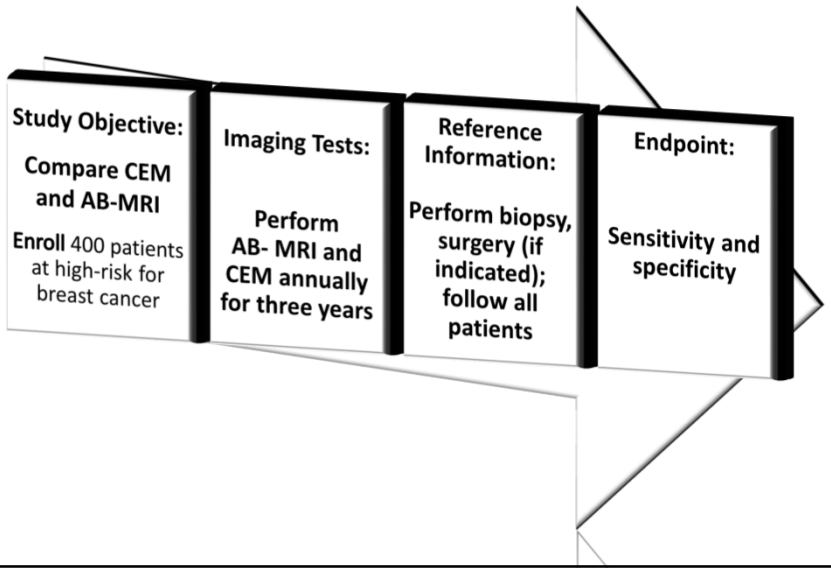
Prospective study example



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Breast Imaging Example
Reference Standards - Endpoints

- Of 400 high-risk patients, only 5 developed cancer over the three-year study.

  Unable to reliably estimate sensitivity!

- This is one reason why retrospective designs are used often for accuracy studies

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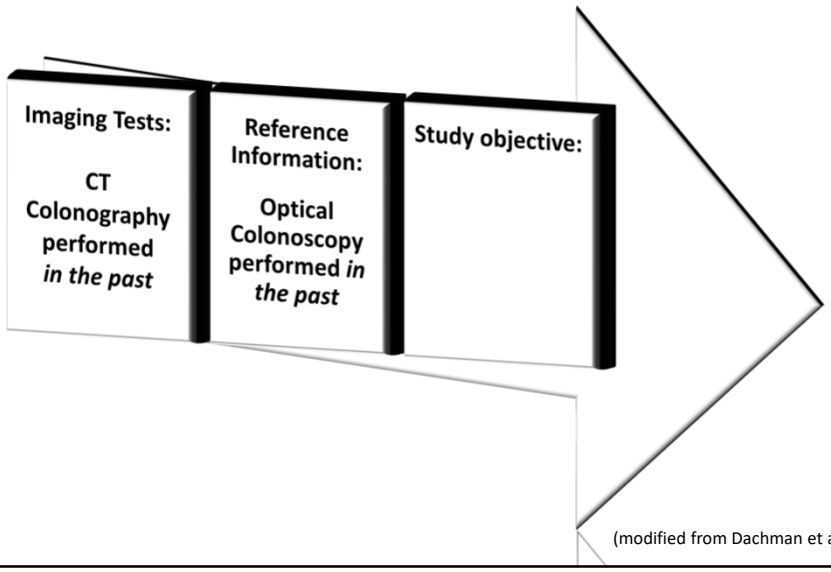
Retrospective study example



(modified from Dachman et al 2010)

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Colon CAD CT Study Example
Study Objectives

- Primary objective:
  Estimate and compare the segment-level area under the ROC curves for board-certified radiologists evaluating CT Colonography images for polyps with and without AI

- Secondary objective:
  Estimate and compare the patient-level area under the ROC curves for board-certified radiologists evaluating CT Colonography images for polyps with and without AI

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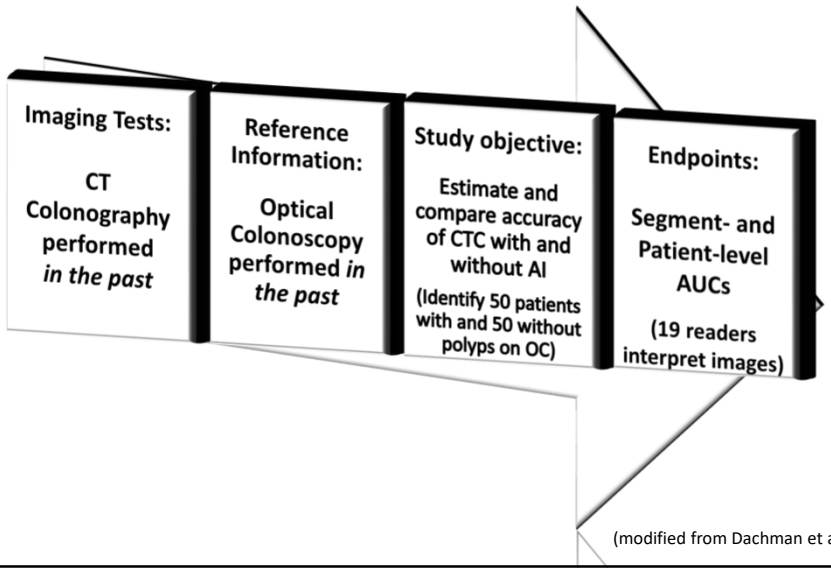
Retrospective study example



(modified from Dachman et al 2010)

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Colon CT Study Example
Re-Reading Images for Endpoints

Cross-Over Design

19 readers interpreted images in 4 reading sessions:

- Session 1: 50 cases without AI
- Session 2: 50 cases with AI

- **One month wash-out**

- Session 3: first 50 cases with AI
- Session 4: second 50 cases without AI

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Colon CT Study Example
Endpoint Definitions

Primary Analysis: (segment-level)

True Positive: reader must correctly locate at least one polyp in segment

Secondary Analysis: (patient-level)

True Positive: reader must correctly locate at least one polyp in patient

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Results of Colon CT Study

Primary Analysis:

Without AI:	AUC=0.74	(95% CI: 0.73-0.75)	
With AI:	AUC=0.76	(95% CI: 0.75-0.77)	p=0.015

Secondary Analysis:

Without AI:	AUC=0.71	(95% CI: 0.69-0.72)	
With AI:	AUC=0.73	(95% CI: 0.72-0.75)	p=0.071

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Augmenting Retrospective Studies

- Augment sample with diseased patients
  Increase prevalence of diseased cases.
- *Increasing prevalence doesn't cause bias in estimates of sensitivity, specificity, and ROC curves!*

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Enriching Studies

- **Enrich sample with challenging cases.**
  - Ensures we have a good idea of how the modality works in hard cases.
  - In study comparing two modalities, many cases will be obvious, thus easily diagnosed by both modalities. It doesn't help the study power to have these cases in study.
- Enriching the sample with difficult cases improves study power, *but estimates of accuracy will be lower* (so need to understand/discuss this in paper).

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Disadvantages of Retrospective Readings:

Reader interpretations may suffer from lab-effect:

- Reading conditions may be substantially different from typical clinical reading
- Behavior of readers may be affected by knowledge that decisions won't impact patient, and that they are being watched

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What about Randomization?

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Appropriate when there is *Equipoise*

- Genuine uncertainty as to whether one intervention or one imaging test will be more beneficial than another

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Strategies for Randomization

- Basics: Simple, Block, Stratified
- Stratified Randomization
  - –Generate separate strata for each combination of covariates
  - –Potential advantages:
    - Ensures balance for known covariates
    - May increase efficiency
  - –Rarely harmful, but careful of over-stratification!
  - –Best when stratification factors have a large effect on patient outcome / primary endpoint
  - –Adjust for stratification factors in the analysis

Kernan *et al. J Clin Epidemiol* 1999

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Example: Patient Outcome Study

- Randomized Clinical Trial (RCT) of lower back pain patients randomized to either rapid MRI or x-ray
- 380 patients recruited from 4 diverse sites
  - – University outpatient clinic
  - – Private, nonprofit teaching hospital
  - – Private, for-profit multispecialty clinic with onsite radiology
  - – Private, for-profit, free-standing imaging center

Jarvik *et al JAMA* 2003

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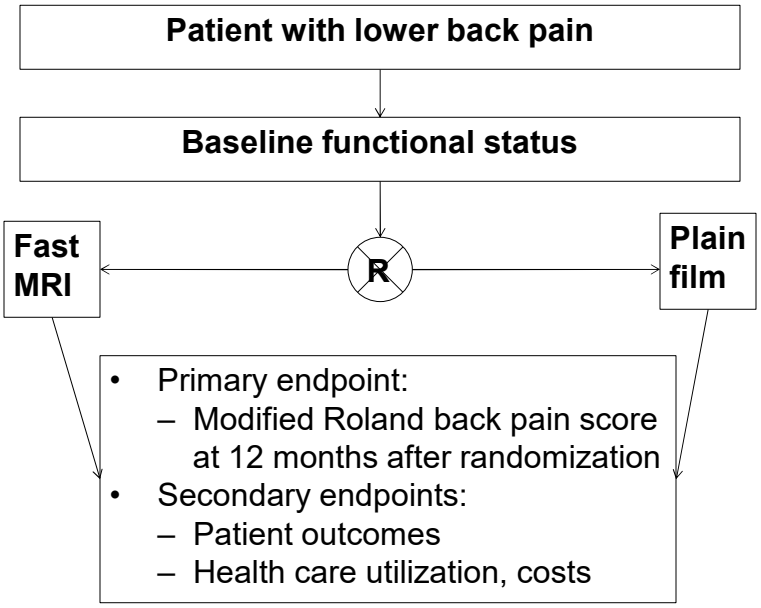
A Randomized Study Comparing Test Outcomes



Jarvik *et al JAMA* 2003

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Stratified Randomization in the Trial

Recruitment site	Radiograph (n=190)	Rapid MRI (n=190)	Total (n=380)
1	73	75	148
2	30	30	60
3	46	46	92
4	41	39	80

- Block randomization within strata with varying block sizes

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Why did the investigators recruit patients from 4 diverse sites?

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Why did the investigators recruit patients from 4 diverse sites?

- External validity – results are generalizable to other institutions
- Internal validity – results are free of bias (i.e. there is no systematic error that skewed the results)

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Trial Results

- No statistically significant difference in the primary endpoint:
  - Mean Roland score: 8.75 (x-ray) vs. 9.34 (MRI)
  - 95% CI for difference: -1.69 to 0.87
- Is this a type II error?

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Interpreting Negative Results

When your results are not statistically significant (p-value>0.05), there are two possibilities:

1. There really is no difference between MRI and x-ray and your study correctly reflects that.
2. There really is a difference between MRI and x-ray and your study missed it.

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Interpreting Negative Results

When your results are not statistically significant (p-value>0.05), there are two possibilities:

1. There really is no difference between MRI and x-ray and your study correctly reflects that.
2. There really is a difference between MRI and x-ray and your study missed it.

   This can happen because there is a bias, your sample is too small, or just by chance.

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Clinical vs. Statistical Significance

- Need to define *clinically relevant difference*
  - Is the difference big enough to matter to patients or their physicians?
- Statistical significance is related to whether or not a statistical tests meets a criterion
  - Not the same thing as clinical significance
- Could have a statistically significant difference that is not clinically relevant
- Important part of the design is the sample size calculation
  - Match the sample size to the minimal clinically relevant difference

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Clinical vs. Statistical Significance Example

- Jarvik et al: 2-unit difference in Roland score
  - Need 372 patients to detect this difference with 80% power (so 20% risk of type II error)
  - Study used N=380
- The observed difference and corresponding confidence interval were < 2
  - Mean difference -0.59, 95% CI (-1.69, 0.87)
- Authors concluded that there is no difference between MRI and x-ray.

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Interim Analyses

- Analyze data mid-way through data collection
- Used often in clinical trials to identify:
  - if there are safety issues
  - if the results are unimpressive ("futility")
  - if the results are impressive ("benefit")
- Interim analyses are planned during the design phase of the study

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Stopping Rules

- Formal statistical rules
  - Control trials' operating characteristics
- In design phase, set up stopping rules that control "multiplicity problem" (Type I error).

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"Multiplicity Problem"

- Statisticians calculate a test statistic to test hypotheses.
- At the start of a study, the test statistic = 0
- If there is benefit, test statistic randomly fluctuates and gradually moves away from zero.
- If there is no benefit, test statistic randomly fluctuates near zero.

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"Multiplicity Problem"

- If there is no benefit, test statistic randomly fluctuates near zero.
- If you calculate test statistic often, you will find instances when it is far from zero just by chance.

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Stopping Rules

- Formal statistical rules
  - Control trials' operating characteristics
- In design phase, set up stopping rules that control "multiplicity problem" (type I error).
- There are lots of methods to do this.
- Should be written into the protocol:
  - Which method you will use
  - How many interim looks and when they will take place

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Conclusion

- Studies of diagnostic tests are important, nationally recognized.
- Many possible study designs for imaging studies
- Details of the study design determine its worth

- ❑ This week take time to carefully consider details of your study's design
- ❑ Listen to other students deliberate their designs

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