Diagnostic and Screening Tests

Ilir Agalliu MD, Sc.D
Associate Professor
Dept. Epidemiology & Population Health
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Diagnostic Information

Obtained from several sources

- Signs and symptoms
- Clinical examinations
  - Imaging (MRI, CT scans etc)
- Biochemical tests (biomarkers)
- Pathology (e.g. tumor)
- Psychological investigations / test

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Diagnostic vs. Screening Tests

- A diagnostic test is any kind of medical test performed to aid in the diagnosis of disease
- The *diagnostic test* is used to confirm a suspected condition once initial testing has revealed its possibility
- Target Population
  - Patients
- A screening test is used in a population to identify an un-recognised disease in individuals without signs or symptoms
- Target Population
  - General Population

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Differences between screening and diagnostic tests

	Screening tests	Diagnostic tests
Purpose	To detect potential disease indicators	To establish presence/absence of disease
Target population	Large numbers of asymptomatic, but potentially at risk individuals	Symptomatic individuals to establish diagnosis, or asymptomatic individuals with a positive screening test
Test method	Simple, acceptable to patients and staff	maybe invasive, expensive but justifiable as necessary to establish diagnosis
Positive result threshold	Generally chosen towards high sensitivity not to miss potential disease	Chosen towards high specificity (true negatives). More weight given to accuracy and precision than to patient acceptability
Positive result	Essentially indicates suspicion of disease (often used in combination with other risk factors) that warrants confirmation	Result provides a definite diagnosis
Cost	Cheap, benefits should justify the costs since large numbers of people will need to be screened to identify a small number of potential cases	Higher costs associated with diagnostic test maybe justified to establish diagnosis.

https://www.healthknowledge.org.uk

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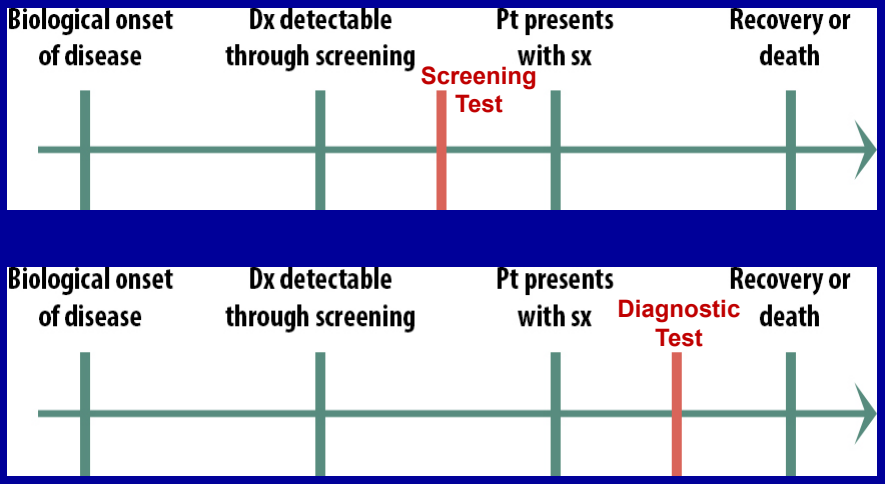
Timing of Screening vs. Diagnostic Tests



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Which diseases do we screen for?

- Pediatrics
  - Hereditary/metabolic screening for PKU- 2 wks
  - Hypothyroidism (2 weeks)
  - Sickle cell disease in African American children at 9 to 12 months of age
  - HIV
- Adults
  - Cancer - CVD
  - Diabetes - HIV

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Goal of Screening

- Early detection of disease and treatment (secondary prevention)
- Screening is aimed to prevent / reduce mortality
- Screening does not prevent disease occurrence (incidence)
  - Indeed, it may increase incidence and exacerbate over-diagnosis

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When is Screening Appropriate?

- Early intervention affects outcome
- Disease is sufficiently prevalent to warrant screening
- An accurate, acceptable and cost-effective test is available

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US Cancer Incidence and Mortality

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	

Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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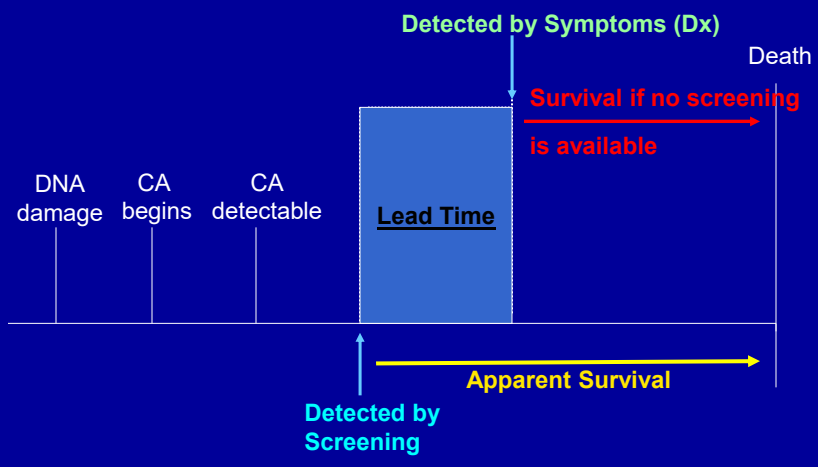
Natural History of Cancer



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Test Performance and Interpretation

How well do screening or diagnostic tests detect the “truth”?

- Sensitivity
- Specificity

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Sensitivity and Specificity

Sensitivity: Proportion of people WITH disease who test positive

Specificity: Proportion of people WITHOUT disease who test negative

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Sensitivity and Specificity

Diagnosis based on a Screening Test	True Status: Based on a Gold Standard Diagnosis (e.g. Biopsy)	
	Cancer Present	Cancer Absent
Test Positive	True Positive (TP)	False Positive (FP)
Test Negative	False Negative (FN)	True Negative (TN)

Sensitivity = TP / (TP + FN)
Specificity = TN / (TN + FP)

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Sensitivity and Specificity of Mammography Screening

Test	Breast Cancer	No Cancer	Total
Positive	850	900	1,750
Negative	150	8,100	8,250
Total	1,000	9,000	10,000

Sensitivity : 850 / 1,000 = 85%

Specificity: 8,100 / 9,000 = 90%

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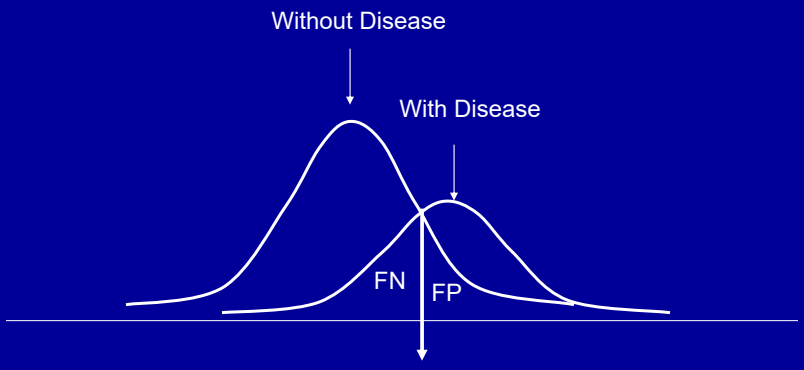
Choice of screening cut-point on sensitivity and specificity (e.g. PSA test)



What would happen if PSA screening cut point moves to 3 ng/ml?

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What is the likelihood of disease given a particular test result?

- Positive Predictive Value (PPV):
  Proportion of individuals testing positive who actually HAVE the disease.

- Negative Predictive Value (NPV):
  Proportion of individuals testing negative who actually DO NOT have the disease.

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PPV and NPV

Diagnosis based on Screening Test	True Status: Based on a Gold Standard Diagnosis (e.g. Biopsy) Cancer Present	Cancer Absent
Test Positive	True Positive (TP)	False Positive (FP)
Test Negative	False Negative (FN)	True Negative (TN)

PPV = TP / (TP + FP)
NPV = TN / (TN + FN)

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PPV & NPV of Mammography Screening

Test	Breast Cancer	No Cancer	Total
Positive	850	900	1,750
Negative	150	8,100	8,250
Total	1,000	9,000	10,000

PPV = 850 / 1750 = 48.6%
NPV = 8,100 / 8,250 = 98.2%

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What is the PPV of mammography if prevalence of breast cancer increases from 10% to 30%?

Prevalence	Sensitivity	Specificity	PPV
10%	85%	90%	48.6%
30%	85%	90%	78.5%

Prevalence increases => PPV increases

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What is the likelihood ratio (LR)?

- LR is percentage of ill people (e.g. cancer) with a given test result (pos) divided by the percentage of well people (e.g. no cancer) with the same test result (pos)
- Positive LR (LR+)
  - LR + = sensitivity / (1- specificity)
- Negative LR (LR-)
  - LR - = (1 – sensitivity) / specificity

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Why LR are appealing?

- Enable clinicians to interpret the full range of diagnostic test results
- Are portable
  - Can be applied to a specific patient
- Reliance of test characteristics (senst/spec) may exaggerate the benefits of test
  - LR can prevent this misinterpretation
- Refine clinical judgment

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Calculations of LR+ / LR-

Diagnosis based on Screening Test	True Status: Based on a Gold Standard Diagnosis (e.g. Biopsy)	
	Cancer Present	Cancer Absent
Test Positive	True Positive (TP)	False Positive (FP)
Test Negative	False Negative (FN)	True Negative (TN)

LR+ = (TP / Cancer) ÷ (FP/ No Cancer)
LR- = (FN / Cancer) ÷ (TN / No Cancer)

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Calculations of LR+ / LR-

Test	Breast Cancer	No Cancer	Total
Positive	850	900	1,750
Negative	150	8,100	8,250
Total	1,000	9,000	10,000

LR+ = 0.85 / (1-0.90) = 8.5

LR- = (1-0.85) / 0.90 = 0.17

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LR for Diagnostic Purposes

	n (%) with appendicitis	n (%) without appendicitis	% with appendicitis/ % without appendicitis	Likelihood ratio
≤7×10⁹ cells per L	1 (2%)	30 (21%)	2/21	0·10
7–9×10⁹ cells per L	9 (15%)	42 (29%)	15/29	0·52
9–11×10⁹ cells per L	4 (7%)	35 (24%)	7/24	0·29
11–13×10⁹ cells per L	22 (37%)	19 (13%)	37/13	2·8
13–15×10⁹ cells per L	6 (10%)	9 (6%)	10/6	1·7
15–17×10⁹ cells per L	8 (14%)	7 (5%)	14/5	2·8
17–19×10⁹ cells per L	4 (7%)	3 (2%)	7/2	3·5
≥19×10⁹ cells per L	5 (8%)	0	8/0	∞
Total	59 (100%)	145 (100%)		

Adapted from reference 19 with permission of the American College of Emergency Physicians.

Table 1: Likelihood ratios for white-blood-cell count in diagnosing appendicitis

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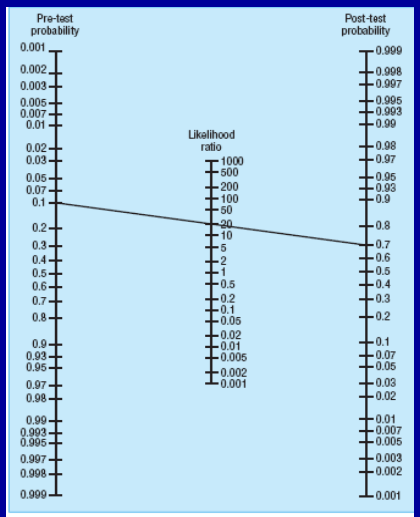
LR can be used to calculate post-test probability of disease

Assume that a patient has a pre-test probability of disease = 0.1
LR+ = 20.43 (for a test)
What is post-test probability?

Pretest probability = 0.1
Pretest odds = p/(1– p) = 0.1/0.9 =0.11

Post-test odds = pretest odds × likelihood ratio
Post-test odds = 0.11×20.43 = 2.27
Post-test probability = odds/(1+ odds)
= 2.27/3.37 = 0.69



Use of Fagan's nomogram for calculating post-test probabilities[7]

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Effectiveness of Screening Tests

- Randomized clinical trial data are needed to confirm whether a screening test improves outcomes
  - Few RCT's of screening exist
- Observational studies of screening are used but their results are limited by biases

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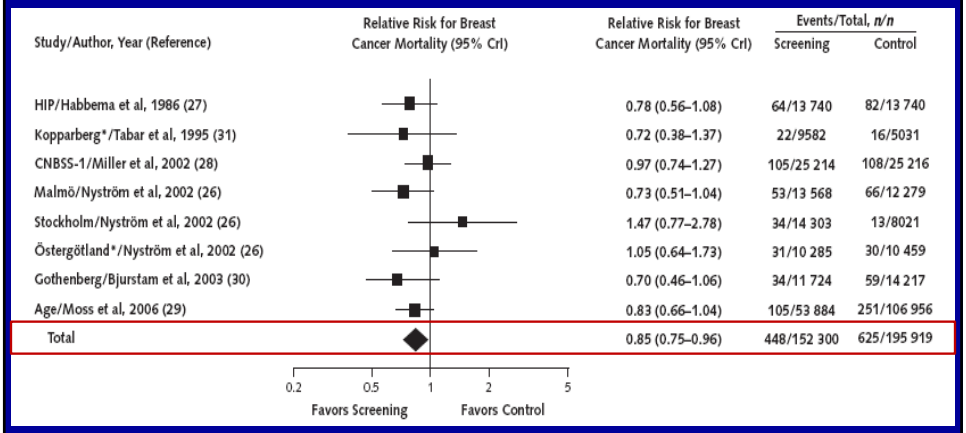
Breast Cancer Mortality and Mammography Screening



What is the Number Needed to Invite to Screening (NNIS) for the overall pooled RR?

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Summary Evaluation of a Screening Program

- Feasibility
  - Acceptability of a screening test
  - Test characteristics
  - Yield: measured by PPV and NPV
  - Cost
- Effectiveness
  - Impact of screening on the course of disease
  - Goal: Reduction of mortality from the disease

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