Early Detection of Ovarian Cancer

What Target Sensitivity and Specificity for an Early Detection Test Might Confer Clinical Utility?

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Usual Approach

1. Set goals: “high” sensitivity and “high” specificity
   - 95% specificity
   - 90% sensitivity

   } Looks good!
2. Estimate sensitivity and specificity in case-control study
3. Calculate PPV & NPV
4. Statistical “due diligence” – publish Test X is highly sensitive and specific test for disease Y

But should Specificity be: 90% 95% 98% 99% 99.9%

Stakeholder Approach

1. Define existing clinical pathway for early detection
2. Position Test within Clinical Pathway
3. Benefits and Harms without Test
4. Benefits and Harms with Test
5. Minimum Net Benefits equals Net Harms – ALL Stakeholders
6. Work backwards: Sensitivity = X% Specificity = Y% so that:

Nbenefit > NHarm

Stakeholder

1. Patients
2. Primary Care
3. Surgeon
4. Investigators
5. Regulatory Agencies – FDA, CMS
6. Payors – Government, private insurers

Benefits exceed harms

Better scale for judgment

Early Detection vs. Therapy

Hippocrates: First, do no harm!

Screening: Evidence required - More complex than standard intervention

Difference in the relationship of doctor to patient

- Standard care: symptomatic patient seeks doctor
- Screening: doctor seeks asymptomatic patient

First – do no harm

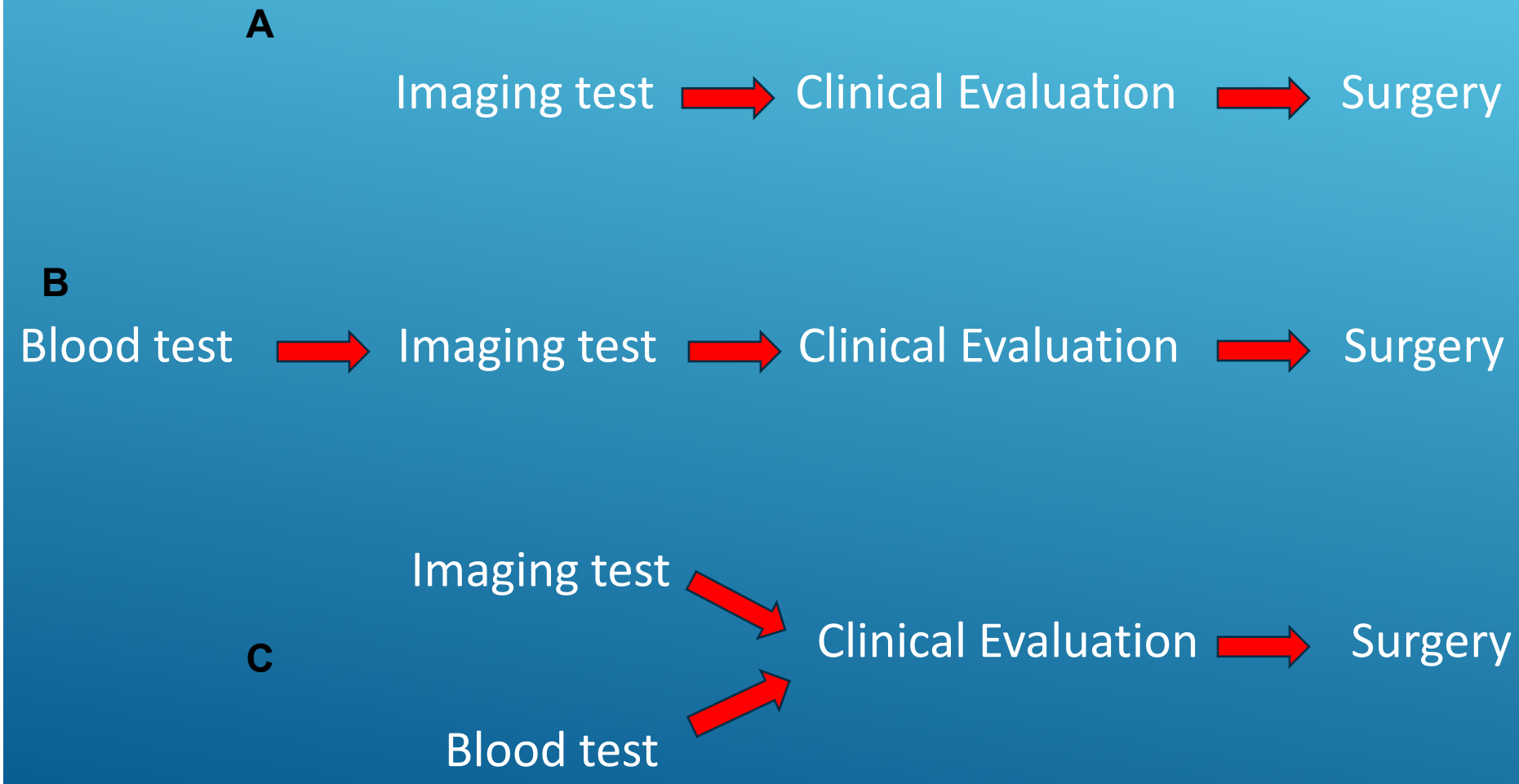
Hippocrates: First, do no harm!

Hippocrates translates as:

- Net benefits should outweigh net harms
- Set minimum Nbenefit to Nharm ratio (PPV) – “do no harm”
- Maximize sensitivity ensuring minimum PPV – “maximize benefits”

Clinical Pathway for Early Detection of Ovarian Cancer

No existing pathway for early detection of ovarian cancer



B Setting Goals – postmenopausal population

- Sensitivity 80%
- Ovarian Cancer has low incidence
- Required specificity?
    - 90%
    - 95%
    - 98%
    - 99%
    - 99.8%

All seem like suitable high specificity

But: False positive rate: 10%, 5%, 2%, 1%, 0.2% - 50-fold range!
Impact hard to judge on this scale

Specificity NOT inclusive scale for all stakeholders

B Setting Goals

Final Diagnostic Procedure for Ovarian Cancer – Laparotomy

Bast & Jacobs set minimum goal for ovarian cancer early detection program as “at most 10 surgeries to detect 1 ovarian cancer”

Human Reproduction vol.4 no.1 pp.1-12, 1989

UKCTOCS

- Patient consent: At most 10 surgeries to find 1 ovarian cancer.

Minimum ratio: Net benefit 1 detected ovarian cancer per 10 surgeries

B Setting Goals

Blood test → Imaging test → Clinical Evaluation → Surgery

Annual Incidence in postmenopausal women: 1 in 2,500

No benefits and no harms without test

Minimum Net Benefit to Net Harm: 1 to 10
Aim to Achieve: 1 to 5

- 500-fold increase from 1 in 2,500 to 1 in 5

B Setting Goals

Blood test → Imaging test → Clinical Evaluation → Surgery

- 500-fold increase from 1 in 2,500 to 1 in 5

TVS: false positive blood test reduced 10-fold
Blood test: false positive blood test: 1 in 50

] 500-fold

- 5 years of screening trials to determine this factor of 10 for TVS
- Blood test: **2%** false positive rate

- 98% Specificity (not 95, nor 99, nor 99.8%)

Benefits to Harms Scale

Inclusive Scale for ALL Stakeholders

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Benefit to Harms Scale

1. HCC – how many MRIs to detect one liver cancer?
2. Gastric – how many EGDs with biopsy to detect one gastric cancer?
3. Pancreatic – CT -> endoscopic ultrasound and biopsy - # per pancreatic cancer detected
4. Breast – existing screening modality – but 12-33 biopsies per breast cancer detected by mammography. Same goal for blood test?
5. Lung Cancer – LDCT -> Bx via thoracotomy - # thoracotomies/cancer
6. Ovarian – # surgeries per OVCA detected

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