Current Imaging Issues, Including CT Colonography ("Virtual Colonoscopy")

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Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults

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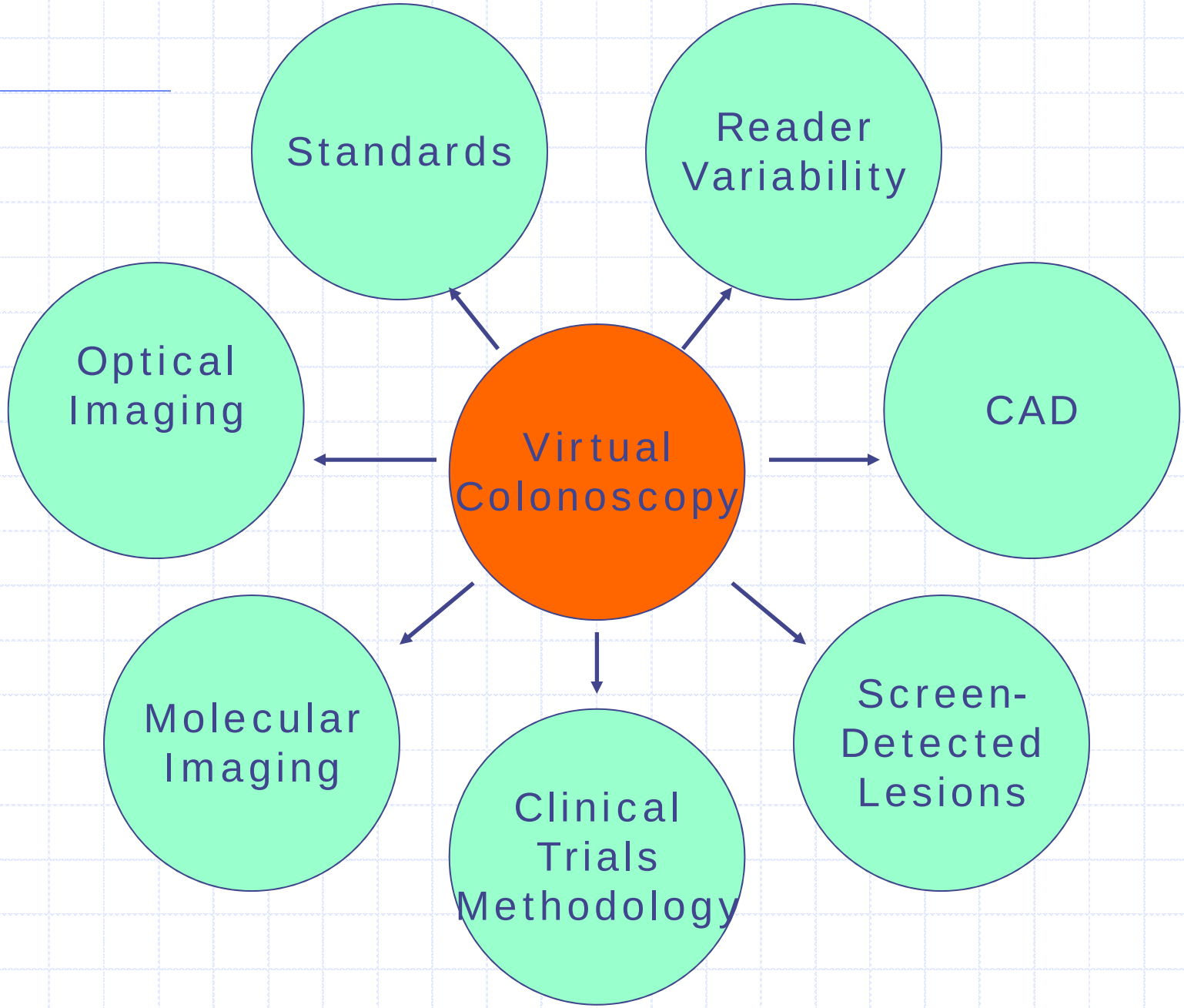
Imaging Issues Raised by CT Colonography or Screening

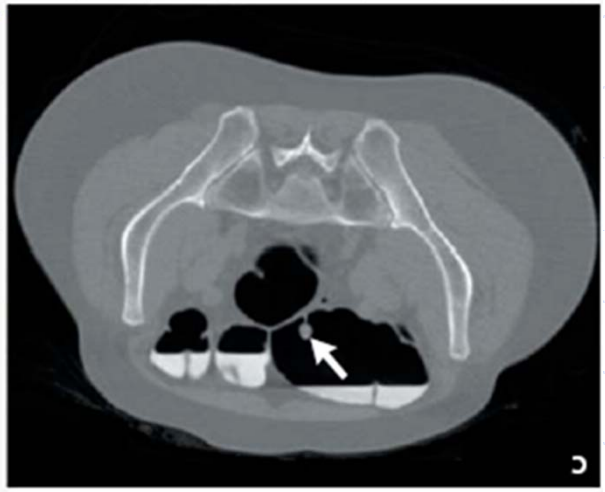


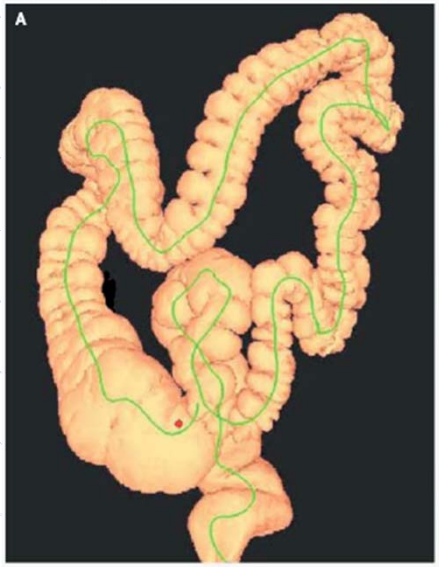
Questions to NCAB:

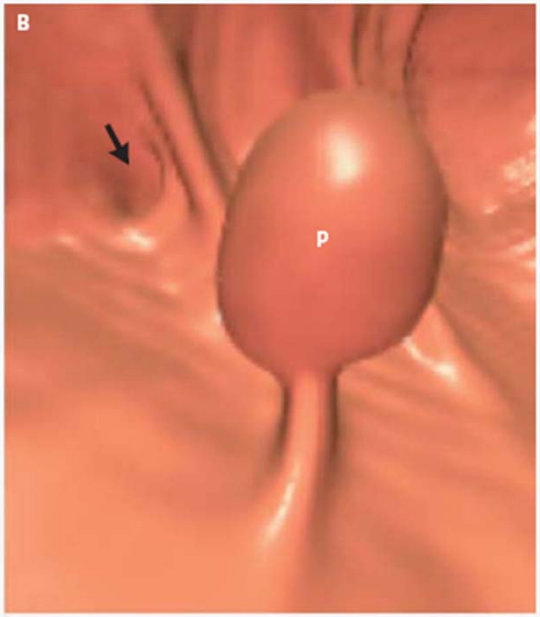
- Relative priority for an NCI-funded multi-center trial of CT Colonography ("Virtual Colonoscopy")?
- Relative priority for increased NCI activity in any of the related issues?

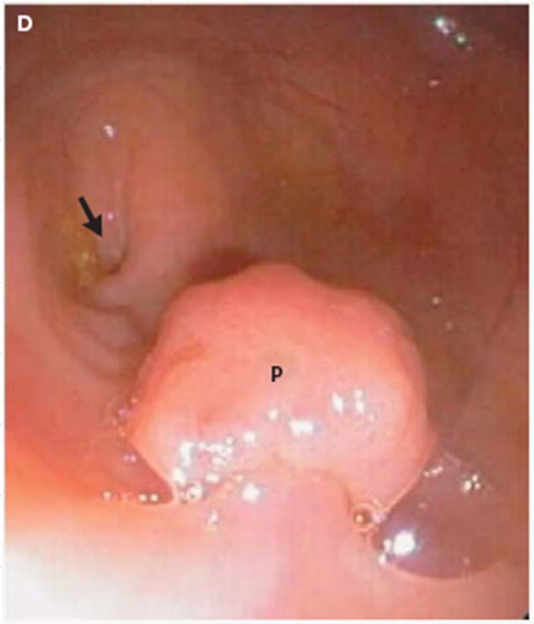
What is Virtual Colonoscopy and Why is it potentially important?

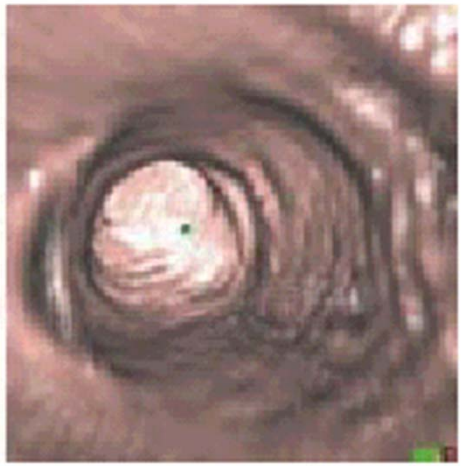
CT or “Virtual Colonoscopy”

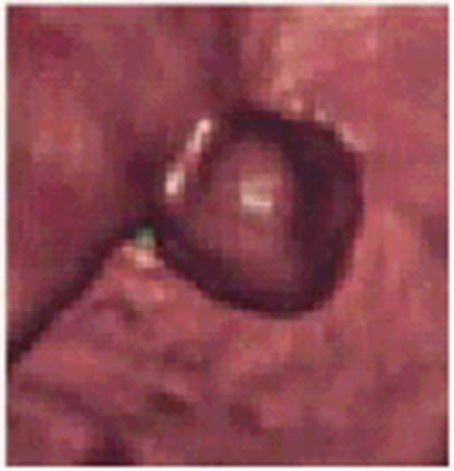












MR Colonoscopy

Why is CTC (VC) potentially important?

- 60,000 deaths each year
- Second leading cause of cancer-related deaths in US
- Screening of adults at average risk recommended
- Current recommended tests:
  - FOBT
  - Flexibility sigmoidoscopy
  - Double contrast barium enema
  - Colonoscopy
- Compliance is very low. Less than half of the average-risk population of the US has been screened.

Endoscopic (optical) colonoscopy

- OC may not be practical for population screening
  - Backlog: 80 M adults eligible; 8,000 gastroenterologists
  - Clinic and procedure time ~ 2 hrs
  - IV sedation or anesthesia
  - False neg rate ~ 6 %
  - Cost (~$2000)
  - Risk (for low yield - 85% n/s findings)

CT Colonography

- Could serve as alternative, or pre-screen for ‘as necessary’ optical colonoscopy
  - More available
  - Less time (< 15 min procedure; 15 min interpretation)
  - No sedation
  - More acceptable? (same colon prep)
  - Less costly (~$1000)

Background

- Several clinical trials in past 5 years compared CTC with OC for colon screening
- Results variable, but CTC inferior to OC
- CTC technology has been progressing
  - Multi-detector scanners
  - 3-D vs. 2-D views
  - Improved image processing, including “electronic cleansing”

Three recent screening trials (CTC detecting >1cm polyps):

- Mayo (2-D) 703 subjects;
  - Sens 63%/Spec 95%
- MUSC (2D, 3-D for 'trouble shooting') 615 subjects;
  - Sens 55%/Spec 96%
- Other (2-D)
  - ~ 600 subjects; CTC inferior to OC

DOD screening trial:

- 3 military sites
- 1233 subjects
  - For >1cm adenomatous polyps
    - CTC: Sensitivity 93%/Specificity 96%
    - OC: Sensitivity 87%
- Conclusion: CTC equivalent to OC

Pickhardt, et al NEJM 349(2003) 2191-2200

Why did they get better results?

- Multi-detector vs. single detector CT scanners
- Vigorous bowel prep
  - Laxatives
  - Clear liquid diet
  - Oral barium (500 ml)
  - Oral iodine solution (120 ml)
- 3-D “fly-through” evaluation was primary evaluation for all studies

Perspective for the Oncologist: Commentary by Bernard Levin MD, 01/26/2004

- … we clearly need additional data before advocating its widespread use.

ACRIN

- American College of Radiology Imaging Network
- Completed retrospective study or reader variability
- Prospective protocol development in progress (Dan Johnson, Mayo, PI)
- Monitoring evolution of technology

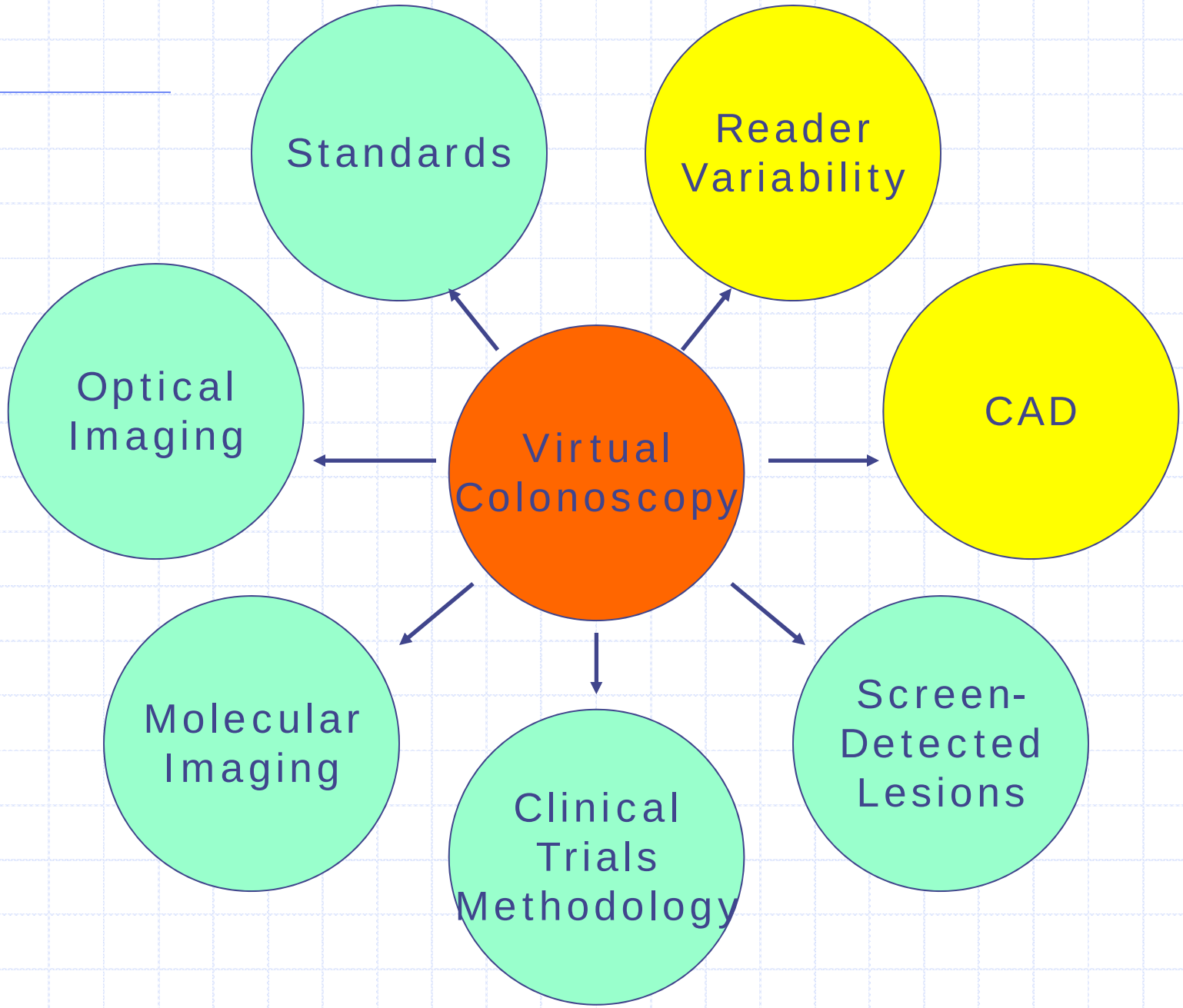
Dec 9 Meeting of Stakeholders

- 8 Extramural (radiology, gastroenterology, biostatistics, epidemiology)
- 7 NCI (DCP; DCCPS; DCTD)
- 7 CMS (Coverage; Reimbursement)
- 2 FDA (CAD; radiation exposure)

Recommendations (Dec. 9)

- Multi-site trial (Rad/GI)
- MDCT; 3-D software; prep issue
- Size: 2000-4000 subjects
- Power for inter-site variability
- Compare to other screening tests (e.g., FOBT), if possible (modeling)
- Cost-effectiveness analysis
- Biorepository

Imaging Issues Raised by CT Colonography or Screening



Getting the Best Mammogram - Microsoft Internet Explorer

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Address http://www.nabco.org/index.php/39/index.php/213 Go Links

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Getting the Best Mammogram

All women are at risk for breast cancer, and most know that the best way to treat breast cancer successfully is to find it early. A mammogram can find breast cancer before it can be felt, yet many women wonder when to begin getting mammograms, how often, and how to know for certain that they are getting the best quality mammograms available.

In 1992, Congress passed the act which gives the Food and Drug Administration (FDA) regulatory authority over all mammography facilities, which as of October 1994 must be certified by the FDA as well as accredited by the American College of Radiology (ACR) or a qualifying state.

Here are NABCO's recommended steps for getting the best possible mammogram:

- **Look for the FDA certificate, which should be prominently displayed at the facility.** Facilities not meeting FDA requirements may not lawfully perform mammography.

- **Know what to expect.** Order and read *Things to Know About Quality Mammograms*, the consumer version of the government's Agency for Health Care Policy and Research (AHCPR) quality guidelines. Share a copy with other women you know, and ask your doctors to obtain a supply for their patients. Order this free booklet in English or Spanish by calling (800) 358-9295. A quick reference guide and a detailed booklet for clinicians are also available.

- **Get regular mammograms.** Once is not enough. NABCO recommends that annual screening begin at age 40. In addition, schedule an annual clinical breast exam to be performed by a physician or nurse. Also, be familiar with how your breasts feel and examine them

NABCO
NATIONAL ALLIANCE OF BREAST CANCER ORGANIZATIONS

Founded in 1986, NABCO is the leading non-profit information and education resource on breast cancer in the U.S.

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Support Groups - search nationwide

NABCO E-Mail Reminder

NABCO Publications view and order online

NABCO News - our quarterly newsletter

Post Office - e-mail

Done Internet

start Inbox - Micr... Address Book RE: slides fo... You receive... 2 Microsof... Getting the ... Google Ans... 5:14 PM

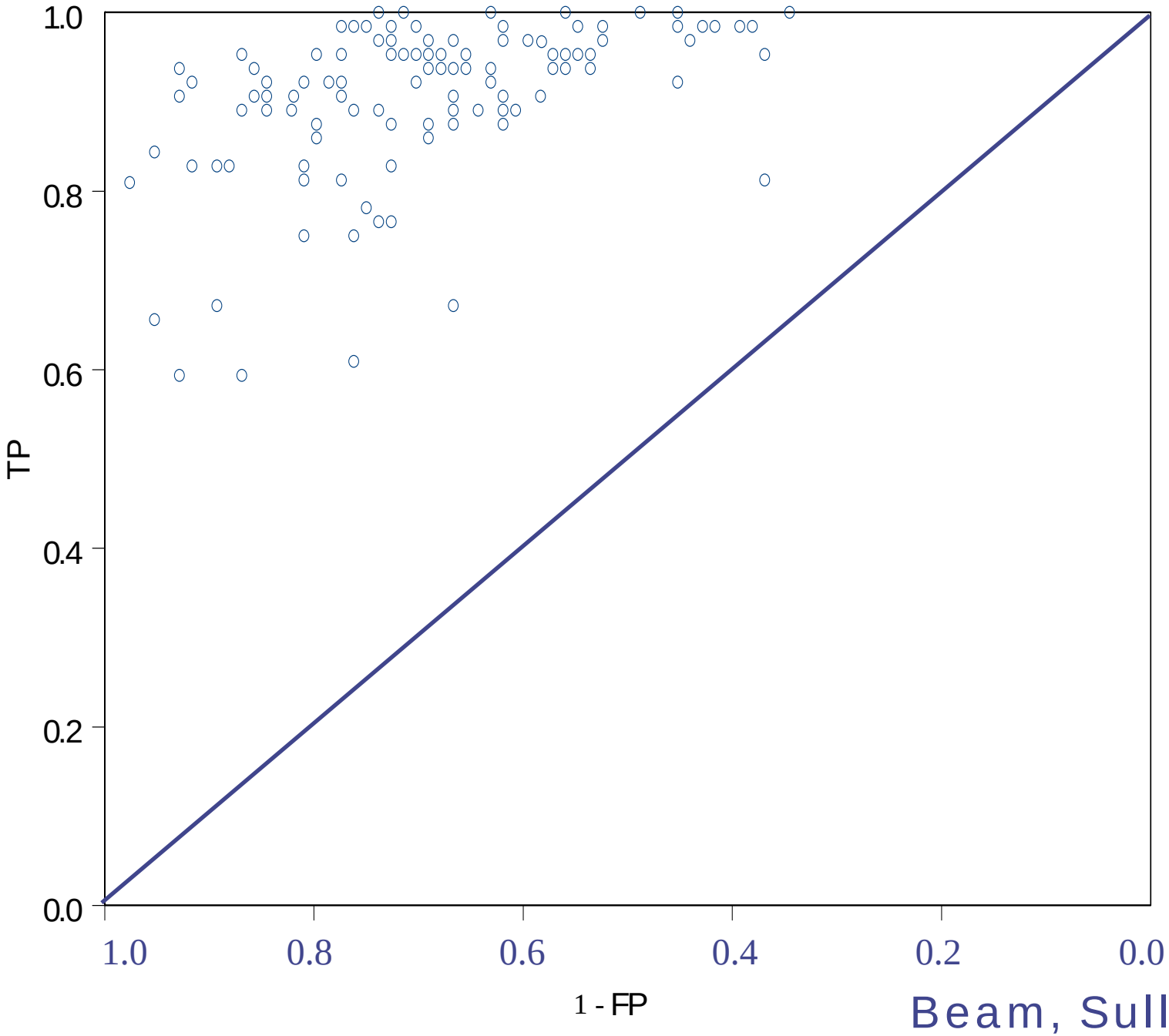
Accurate diagnosis depends on:

- Quality of the image acquisition
- Quality of the image interpretation
  - Perception
  - Cognition

Technology Development

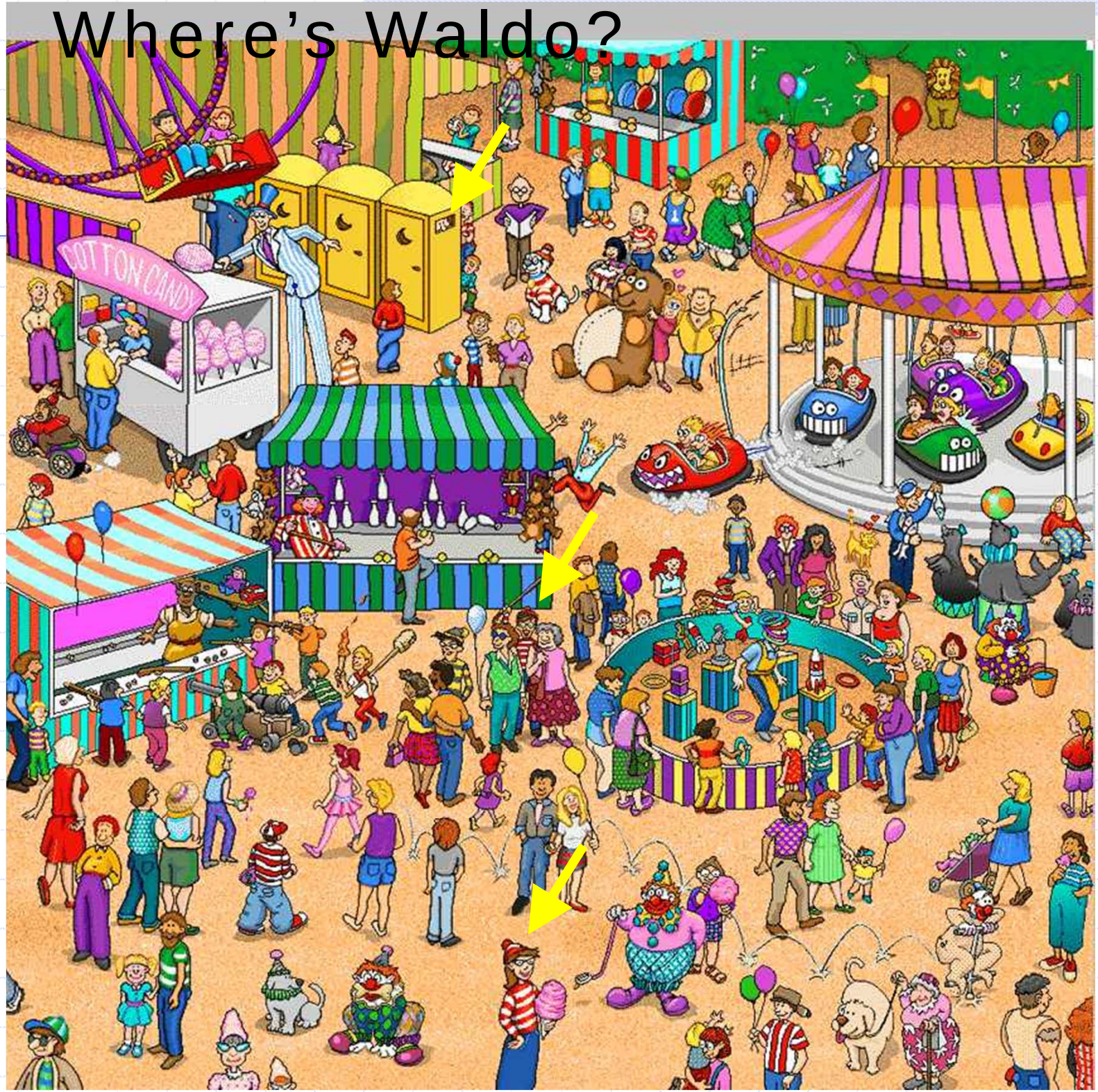
- Stage 1 Discovery
- Stage 2 Development
- Stage 3 Maturation
- Stage 4 Dissemination

Operating points of 108 radiologists



Beam, Sullivan 1996

Where's Waldo?



“Artificial Intelligence”

- As of today, it does not truly exist.
- “No computer has ever learned what any 2-year-old human knows”
  - Dan Gruhl, IBM, 2-15-04

Computer-Aided Diagnosis (CAD)

- Assist with “data deluge”
- Reduce false negatives and false positives (detection and diagnosis)
- Reduce inter- and intra-observer variation
- Quantification and change analysis (lesion growth)
- Integrate multiple sources of data

Evaluation of CAD Systems

- How does one CAD algorithm perform versus another.
- How is radiologists' performance, in practice, affected with and without a CAD system (the ultimate test).

CAD Concerns

- CAD performance varies because:
  - Developmental databases vary
  - Methods of scoring vary
  - “Truth” determination varies
- How do consumers evaluate?
- Need large national databases to expedite CAD development
- Need “protected” databases for testing

Lung Image Database Consortium (LIDC)

- **Goal: Develop a web-accessible image database for the comparison of CAD methods, and encourage standards for software assessment. (5 academic sites).**
- **Some images will be collected from ACRIN/NLST**
- **LIDC Steering Committee includes FDA scientists.**
- **A consensus process for database and software analysis methods has been completed. LIDC is ready for data accrual.**

RSNA 2003: Space Number: 0116CE – e: LIDC: Consensus process for data base creation for evaluation of CAD methods.

THE LIDC AND ITS MISSION

The LIDC is a Consortium of 5 Institutions funded by the National Cancer Institute under the Cancer Imaging Program (CIP). These institutions are:

* The University of Chicago School of Medicine
* University of Iowa Roy J. and Lucille A. Carver School of Medicine
* The David Geffen School of Medicine at UCLA
* Weill Medical College of Cornell University
* The University of Michigan Medical School

Members of other institutions also participate in key roles such as statistical design.

MISSION

The mission of the LIDC is the sharing of lung images, especially low-dose helical CT scans of adults screened for lung cancer, and related technical and clinical data for the development and testing of computer-aided detection and diagnosis technology.

PRINCIPAL GOALS

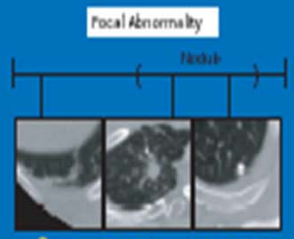
To establish standard formats and processes for managing thoracic CT scans and related technical and clinical data for use in the development and testing of computer-aided diagnostic algorithms.

To develop an image database as a web-accessible international research resource for the development, training, and evaluation of computer-aided diagnostic (CAD) methods for lung cancer detection and diagnosis using helical CT.

CHALLENGES IN CONSTRUCTING THE DATABASE

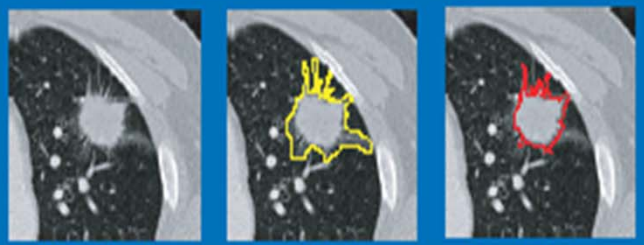
1. Defining a Nodule- The Nodule Visual Library

Difficult to arrive at a written definition. We are developing a Nodule Visual Library. This will attempt to describe the full spectrum of "Focal Abnormalities" , of which Nodules are a subset.



2. Establishing Spatial "Truth" for Nodule Boundary

Difficult to arrive at consensus on boundary (see below). We will assess reader variability of contours and construct a probabilistic description of boundaries.



VISIT THIS EXHIBIT FOR CME CATEGORY 1 CREDIT
MONDAY THRU THURSDAY
12:15 pm to 1:15 pm

At that time, LIDC members will be here to describe

* **The efforts of the consortium,**
* **This exhibit and any other questions you might have**
* **Demonstrate some of the boundary drawing/contouring tools**

DATABASE IMPLEMENTATION STEPS

TASKS COMPLETED (see current reports on website):

(1) Specification of Inclusion Criteria:
  (a) CT scanning technical parameters
  (b) Patient inclusion criteria
(2) Process Model for Data collection
  Determination of Spatial "truth" Using Blinded and and Unblinded reads
(3) Development of Boundary Drawing/Contouring Tools

TASKS ONGOING (expected completion date):

(1) Definition of Nodule - Nodule Visual Library (Feb 04)
(2) Evaluation of Boundary Variability (Feb 04):
  (a) Inter-Reader Variability
  (b) Boundary Drawing Tool Variability

IMPLEMENTATION TIMELINE

Task	Date Expected
Specify Complete Data Model	Jan 04
Specify LIDC internal workflow Data passing, Performing reviews	Jan 04
Initial implementation, testing of workflow	Jan/Feb 04
Database Implementation- Start	Jan 04
Database Implementation- Completion	Mar/Apr 04
Implementing Public Interface to Database	Apr/May 04
PUBLIC ACCESS TO CASES - EXPECTED	**MAY 04**

LIDC WEBSITE

Overview - www3.cancer.gov/bip/steer_lidc.htm
Committee Reports - www3.cancer.gov/bip/lidc_comm.htm
Contains publicly available documents describing inclusion criteria, process model details, etc.

NCI/FNIH Image Database Resource Initiative

- **Purpose:** Partnership with industry, academia and government to develop multiple large image archives
  - For the development and validation of application-specific software, such as CAD methods and therapy response metrics.

- Coordinating with NEMA
- Meetings with industry, 12/03, 1/04
- Positive response to concept
- Specific proposal requested

Proposed Timeline (3 months)

- Enlist industry representatives and establish the steering committee
- Engage NCI cooperative groups to enable data distribution responsive to this initiative
- Initiate the first demonstration project.
- Expand NCI informatics and image archive infrastructure to meet the needs of this initiative.

Proposed Timeline (1-3 years)

- **Complete a demonstration project:**
  - **Single modality database with > 1,000 subjects**
  - **Images linked to demographics, clinical data, and interpretations / reports**
- **Satisfy requirements of ACRIN, Cooperative Groups, Cancer Centers, SPORE's etc.**
  - **Data access, security, confidentiality, investigator rights to enable project expansion.**
- **Distribute the database to industrial partners and assist in regulatory processes for new CAD product(s).**

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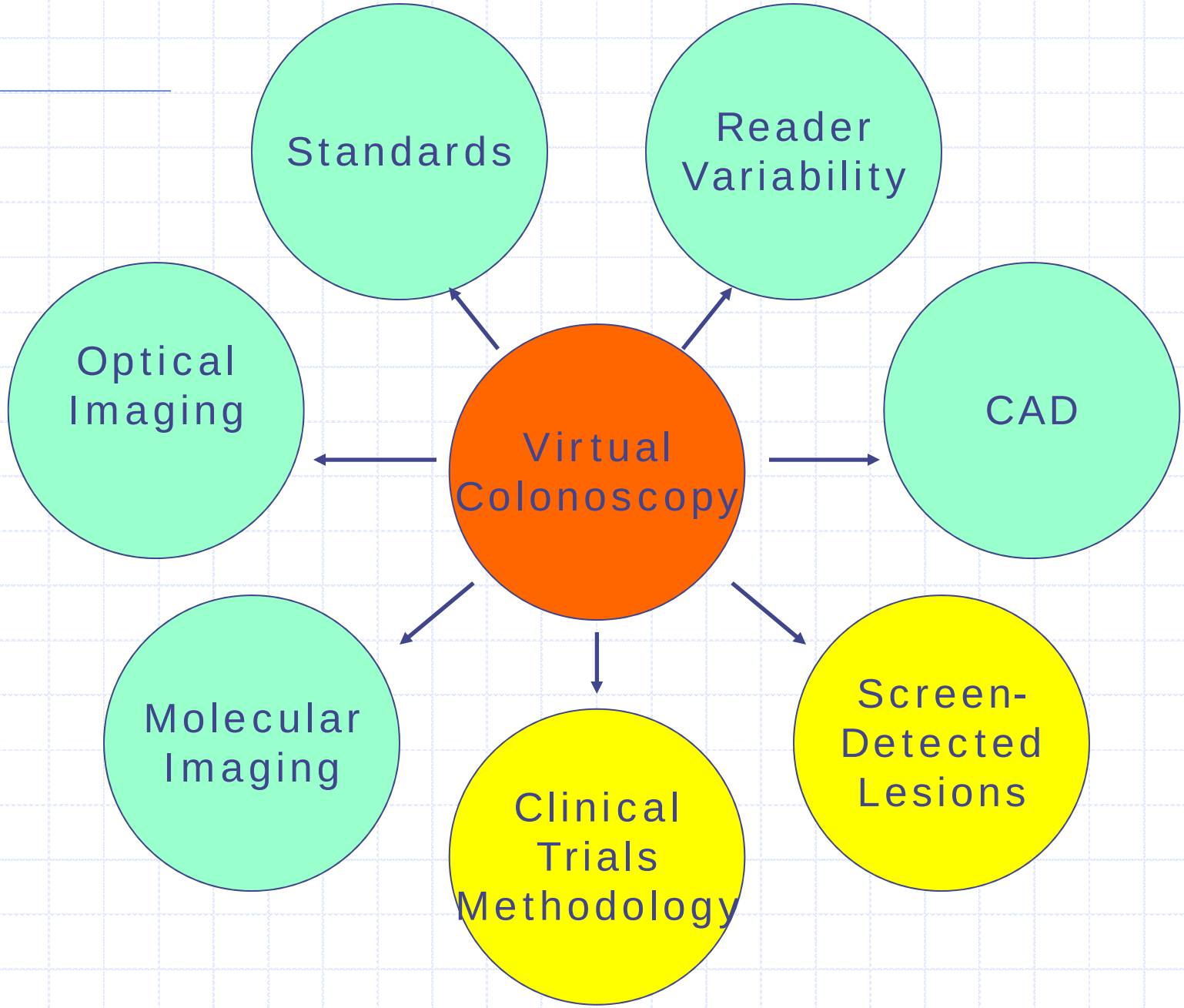
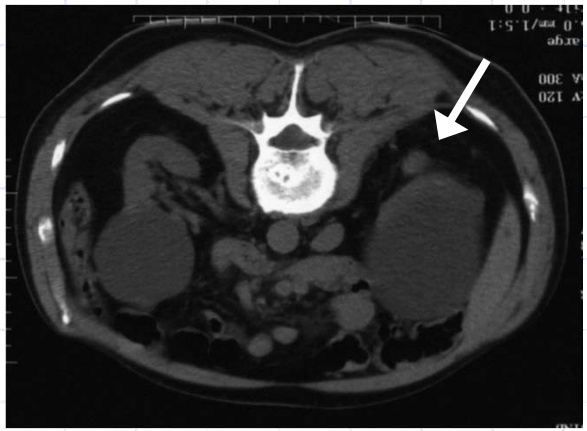


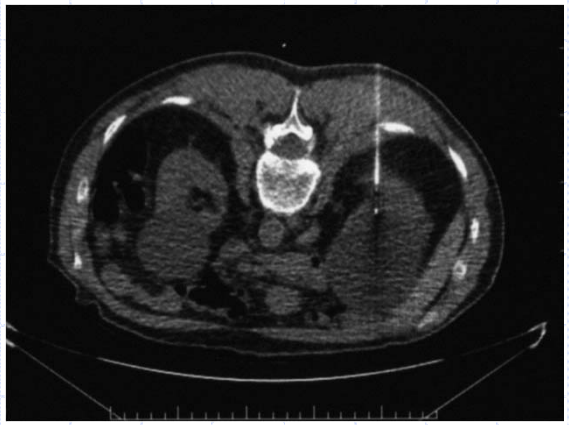
Image-Guided Interventions

- Screening tests also detect false positives in organ or tissue of interest, and “incidental” lesions (which may or may not be significant).
- Need improved methods to deal with screened-detected lesions.

Example: Incidental Renal Cell Carcinoma (RCC)

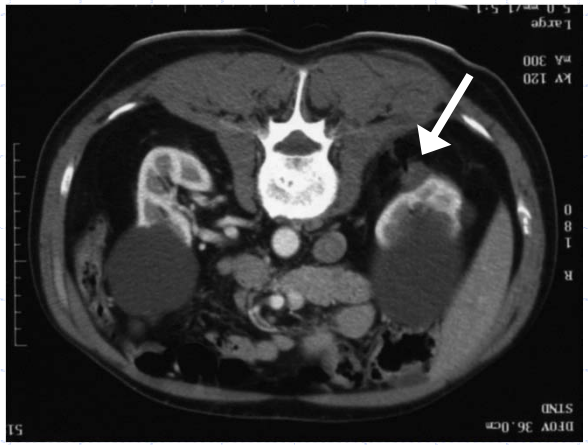


Incidental RCC



Biopsy

RFA



Post-Contrast shows complete thermocoagulation

Screening concern: False Positives

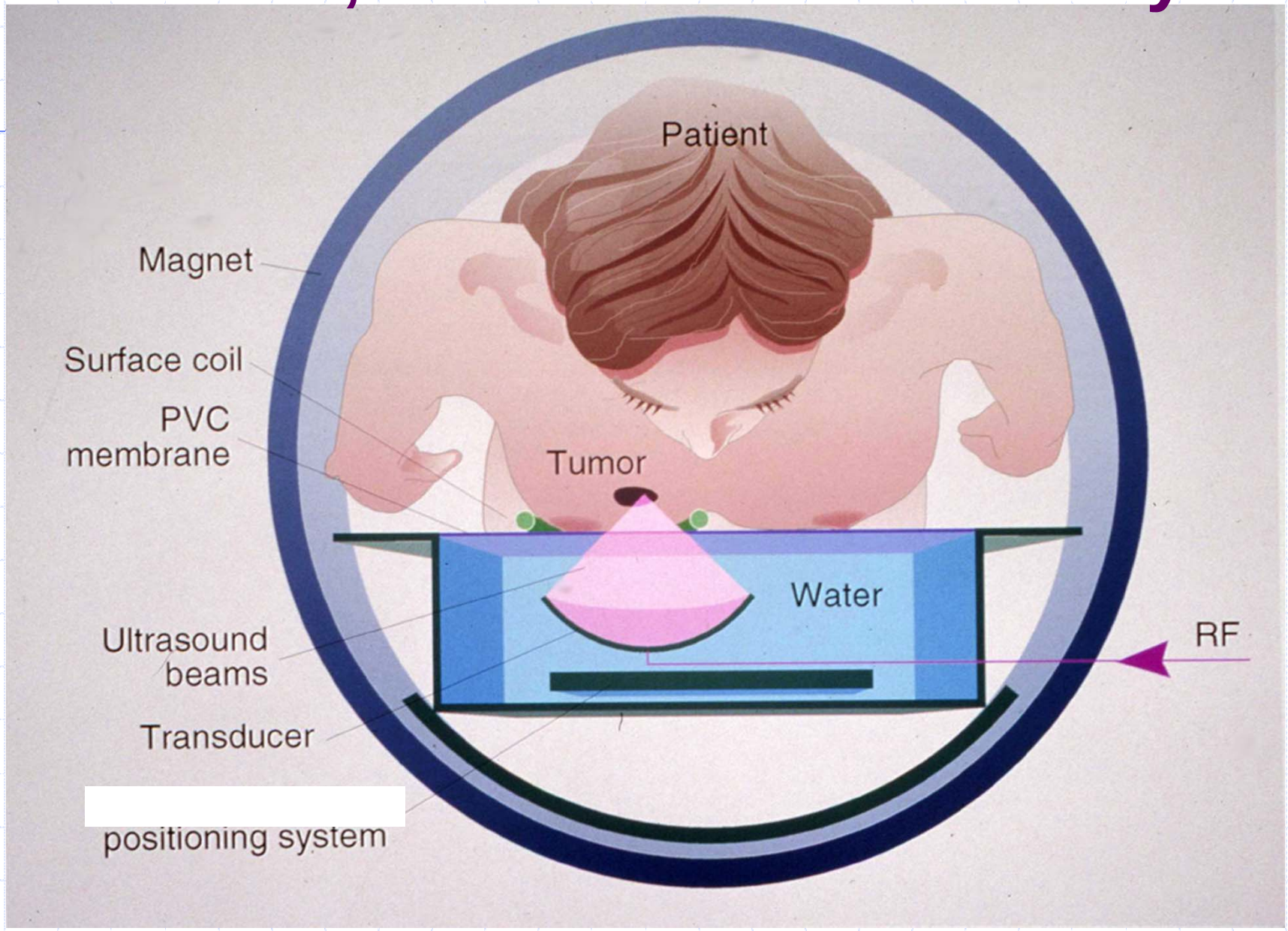
- Over-diagnosis and Over-treatment
- Cost and Morbidity

- Importance of false positives is inversely proportional to what can be done about them.
- We need relatively cheap, safe and targeted means to treat screen-detected lesions.

Targeted ablation

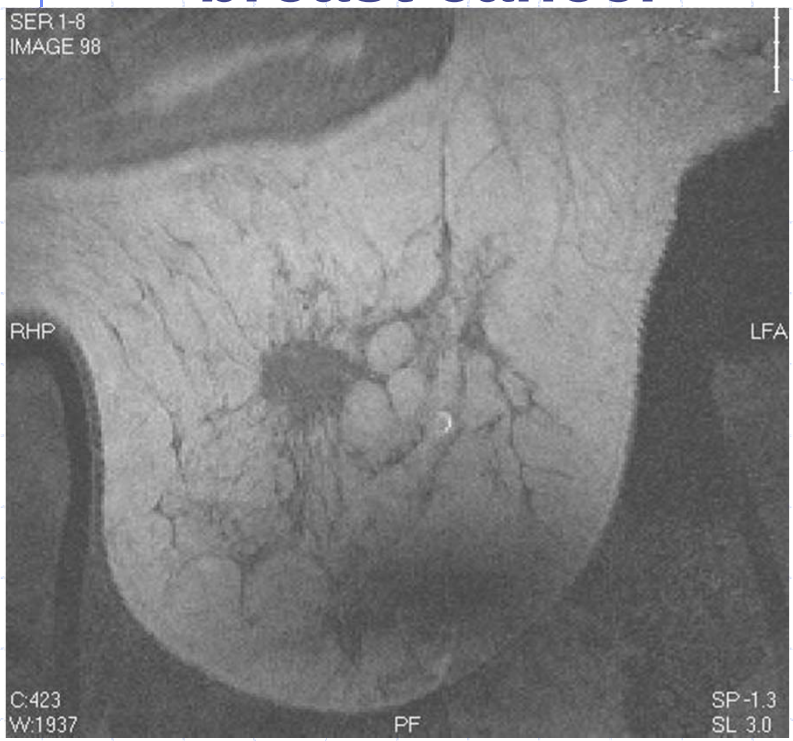
- Minimally-invasive, or non-invasive image-guided ablative techniques are one such approach.
- Targeted energy delivery, e.g.:
  - RFA
  - HIFU
- Toxic agents, e.g.:
  - Ethanol, acetic acid
  - Doxorubicin, etc.

MRI-Guided, Focused Ultrasound System



MRI-guided, focused ultrasound therapy

Ductal invasive breast cancer



Treatment plan

80 ultrasound foci

IGI Methodology Workshop Feb 2-3, 2004

- Focus on protocols for interventional trials related to:
  - Brain
  - Lung
  - Prostate
  - Liver

IGI Methodology Workshop Feb 2-3, 2004

- 37 Extramural investigators
- 5 Extramural biostatisticians
- 29 NCI staff (4 intramural)
- 10 FDA staff
- 9 Industry representatives

- Major theoretical and practical issues identified and discussed.
- Future plans identified.

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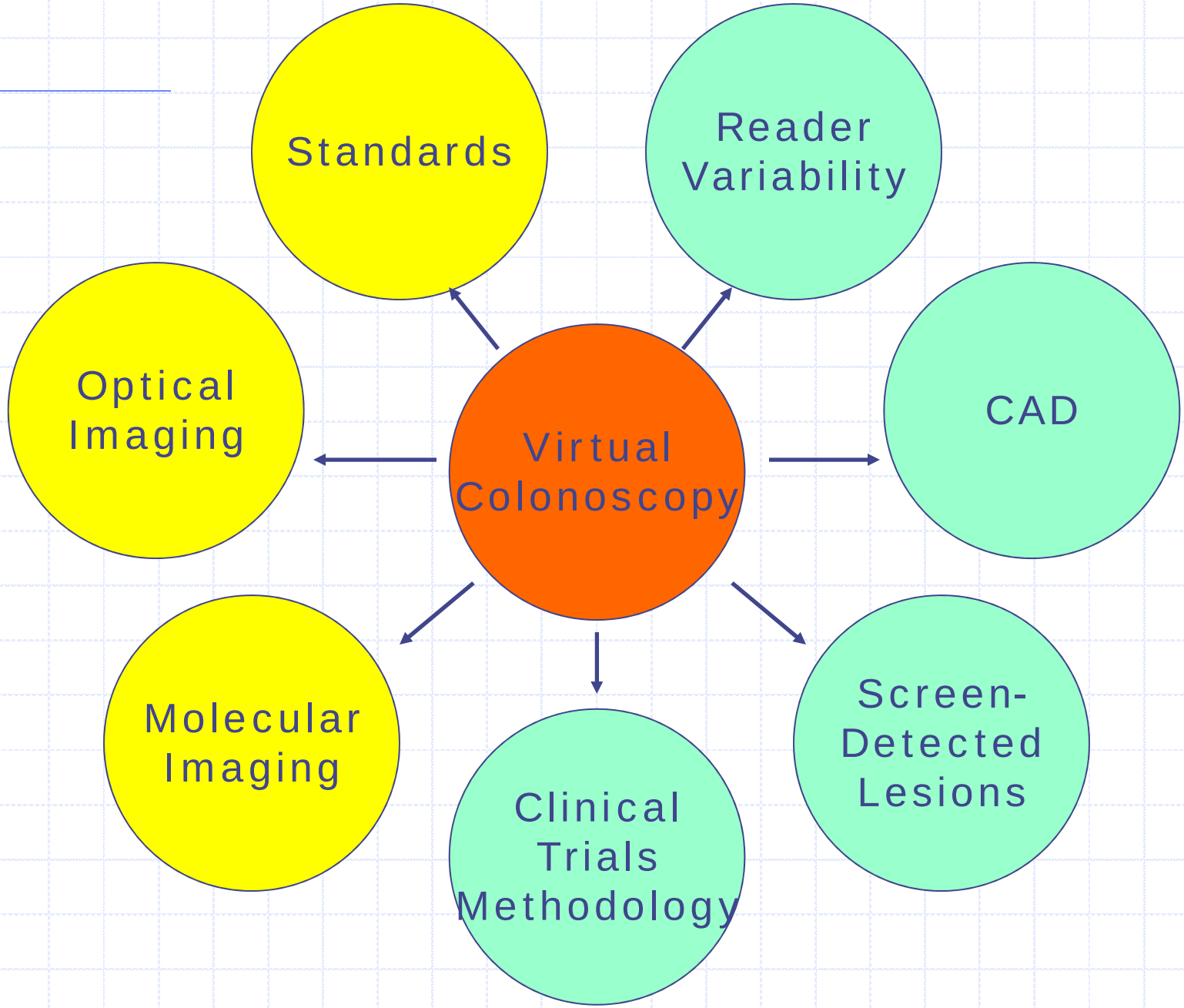
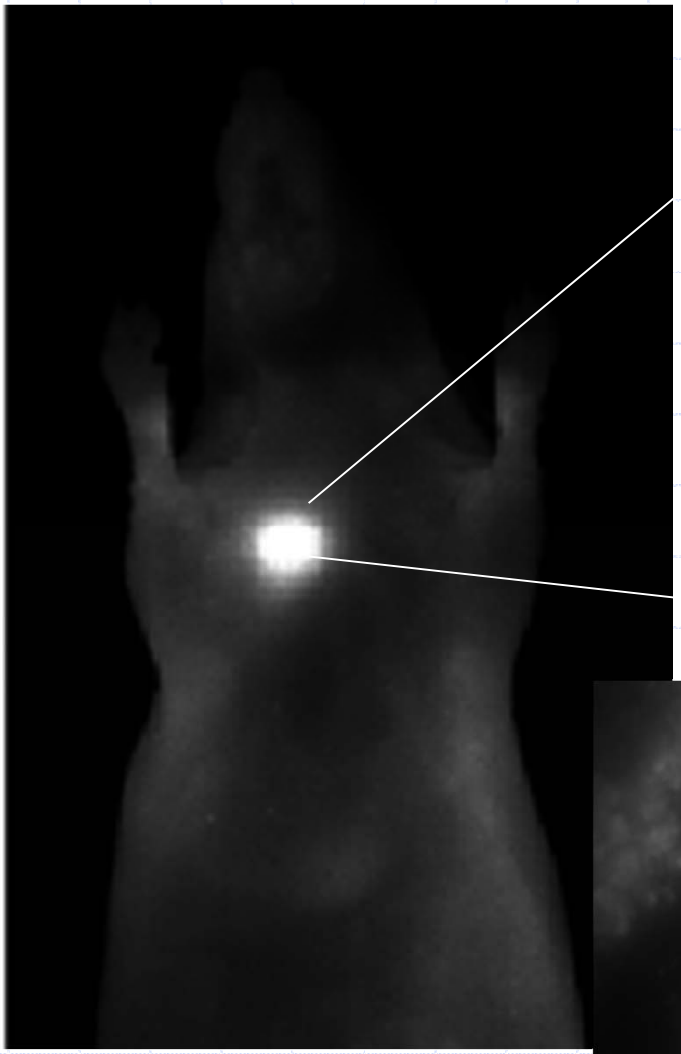


Prevalence of polyps (Pickhardt)

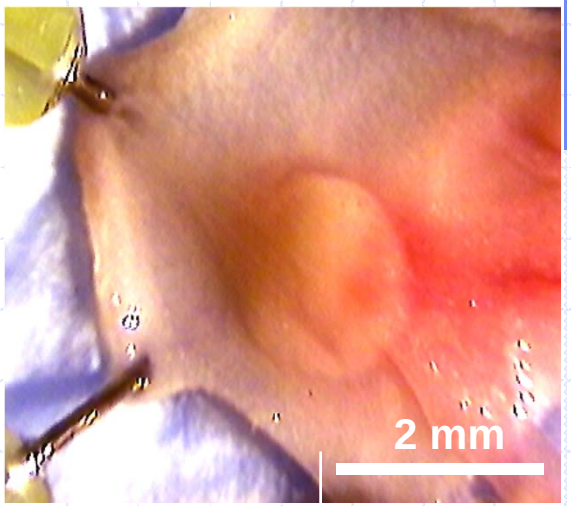
	All	>10mm	6-9mm	<5mm
Adeno-matous	42%	4%	12%	26%
Non-adeno-matous	58%	2%	8%	47%

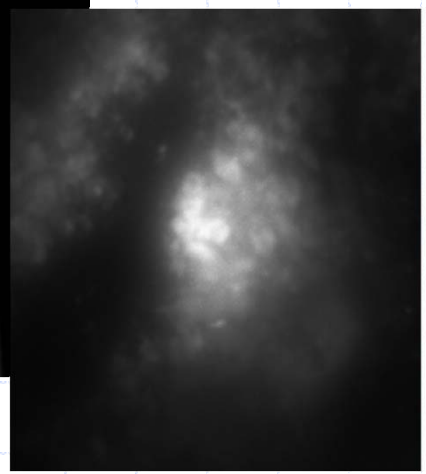
Tumor detection by targeting Cathepsin B

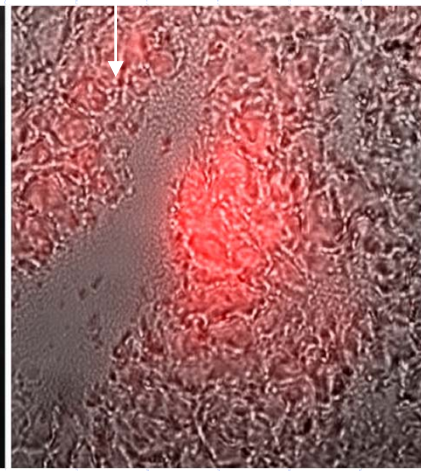
Light image



NIRF image



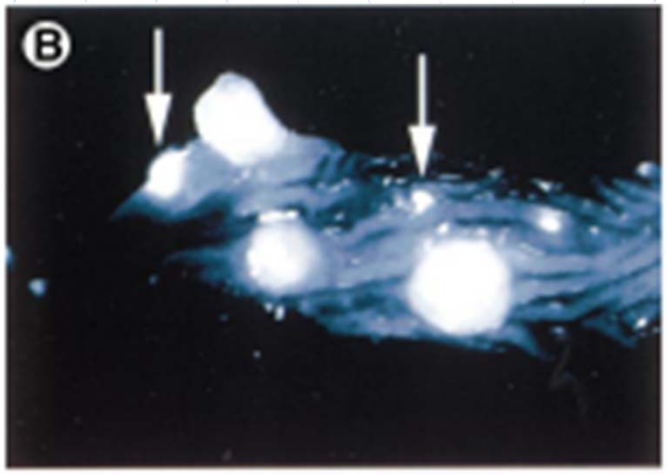




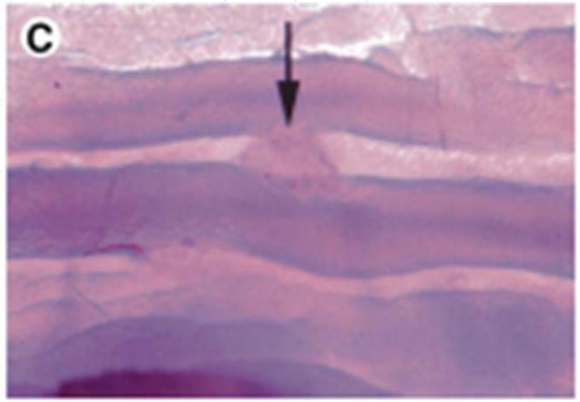
Nature Biotech; 1999;17:375-378

Colonic adenomas in a 7-month-old APCMin/1 mouse; Imaged with VM102, Now being commercially developed by VisEn Medical

White light

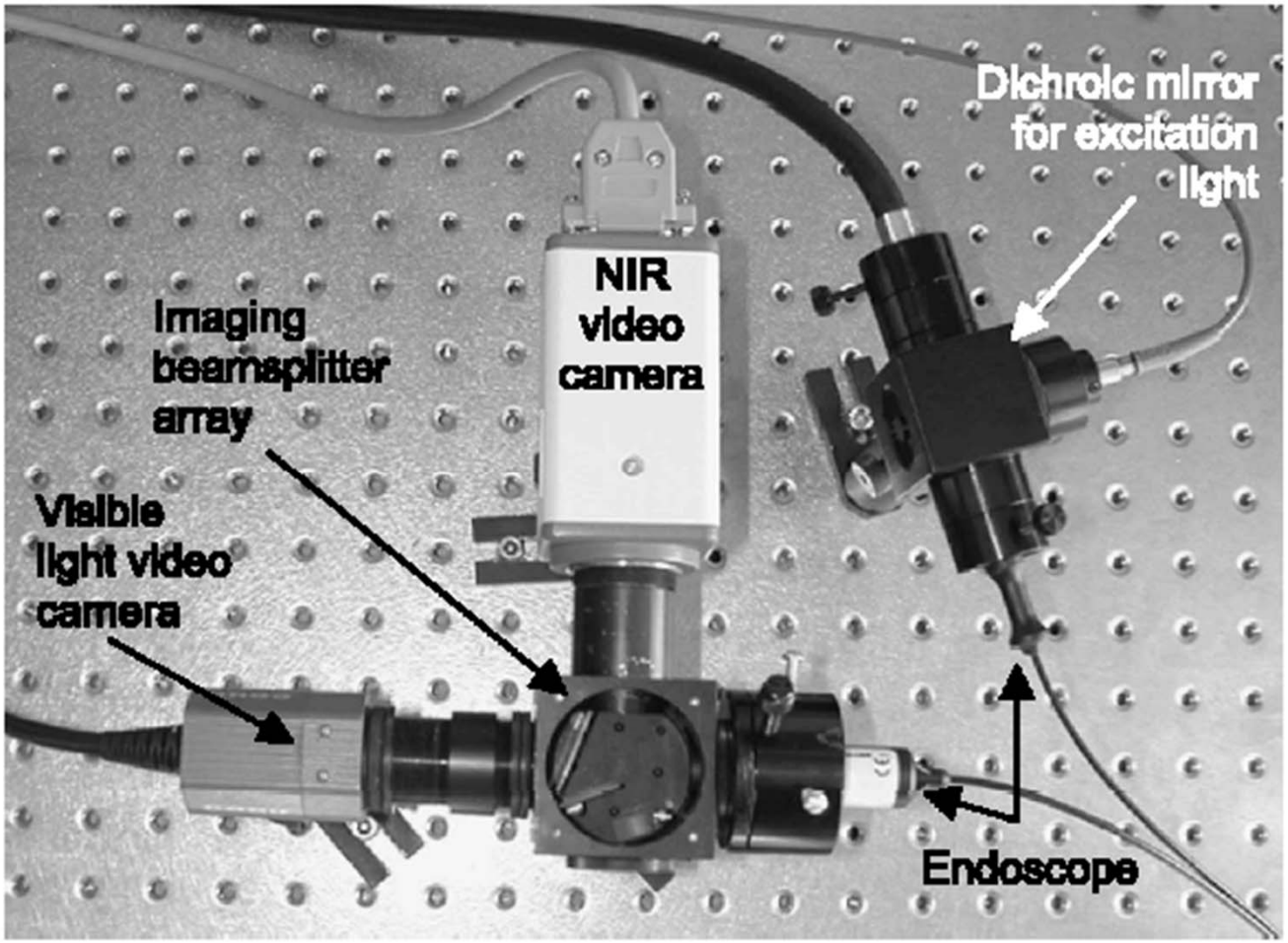


NIR



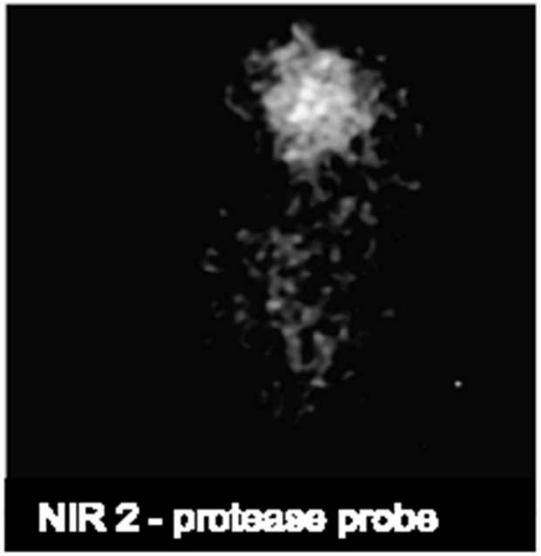
Adenoma on histology

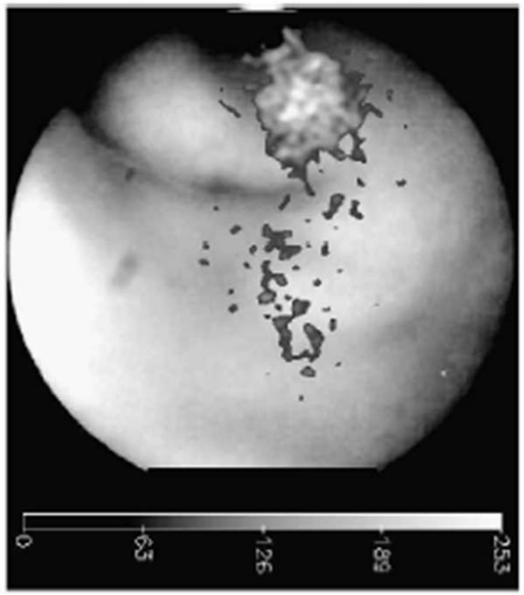
Mouse Near-Infrared (NIR) Colonoscope

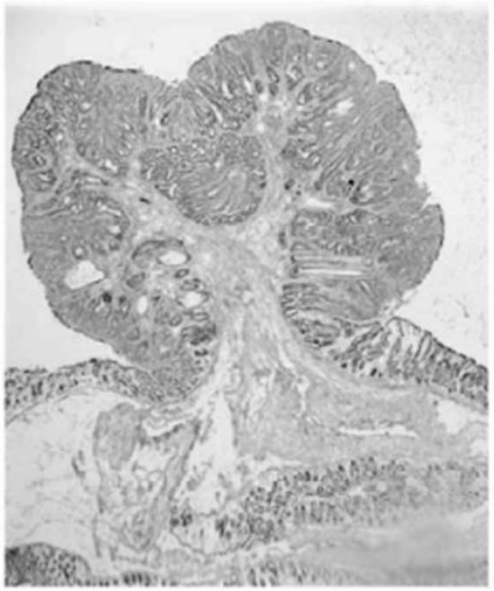


MGH

Images from mouse colonoscopy, Protease probe







HTS

- High throughput screening technologies are becoming commonplace in:
  - Genomics
  - Proteomics
  - Drug development
  - Biologic probes

An imaging agent is a “drug” …

… but it’s not a drug.

Screening process for imaging agents

"Chemical" libraries

Synthetic libraries

Organic scaffolds

Phage display

→

Library of imaging agents.

Conjugation strategies

Linkers/spacers

Multivalency modifications

↓

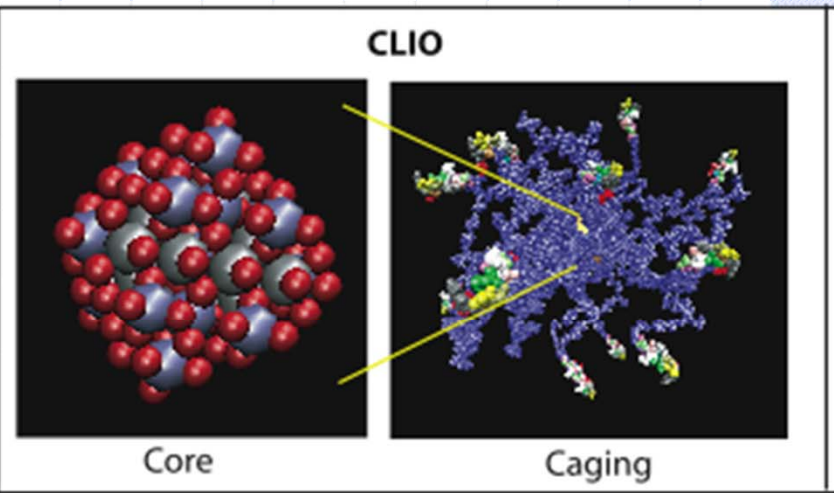
Biological assays using different targets: proteins, cells, physiological processes.

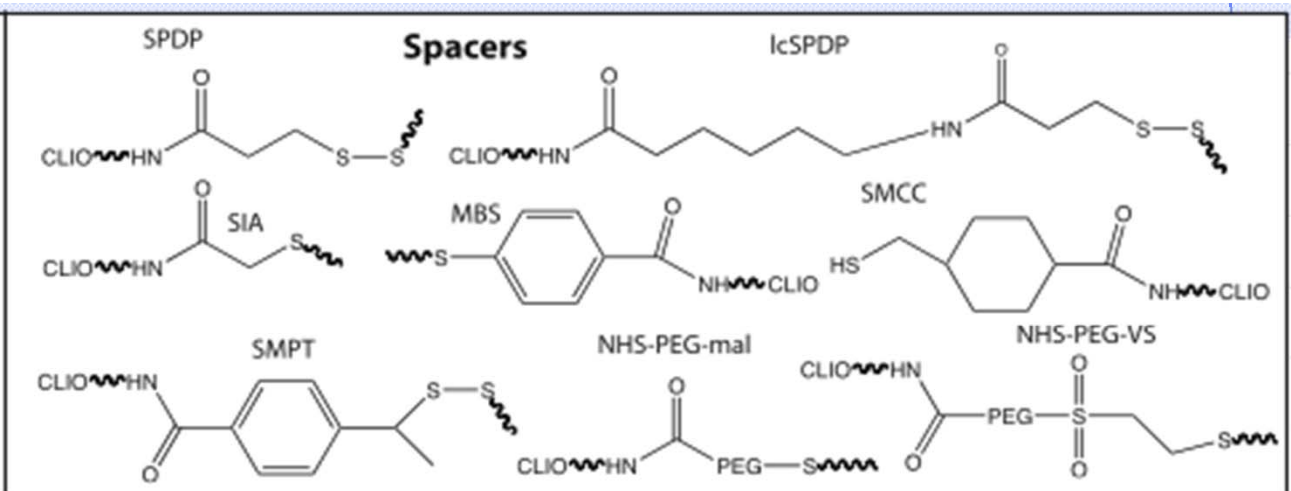
Fluorescence screens;

Magnetic screens

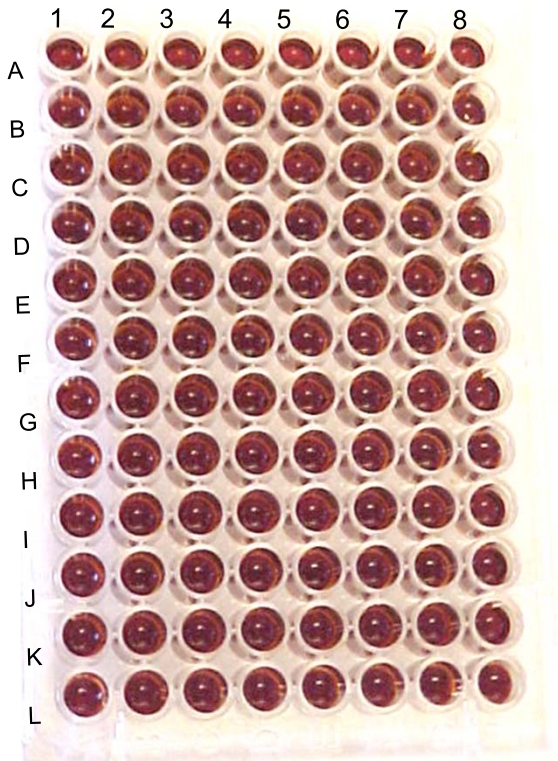
↓

Usable Probes





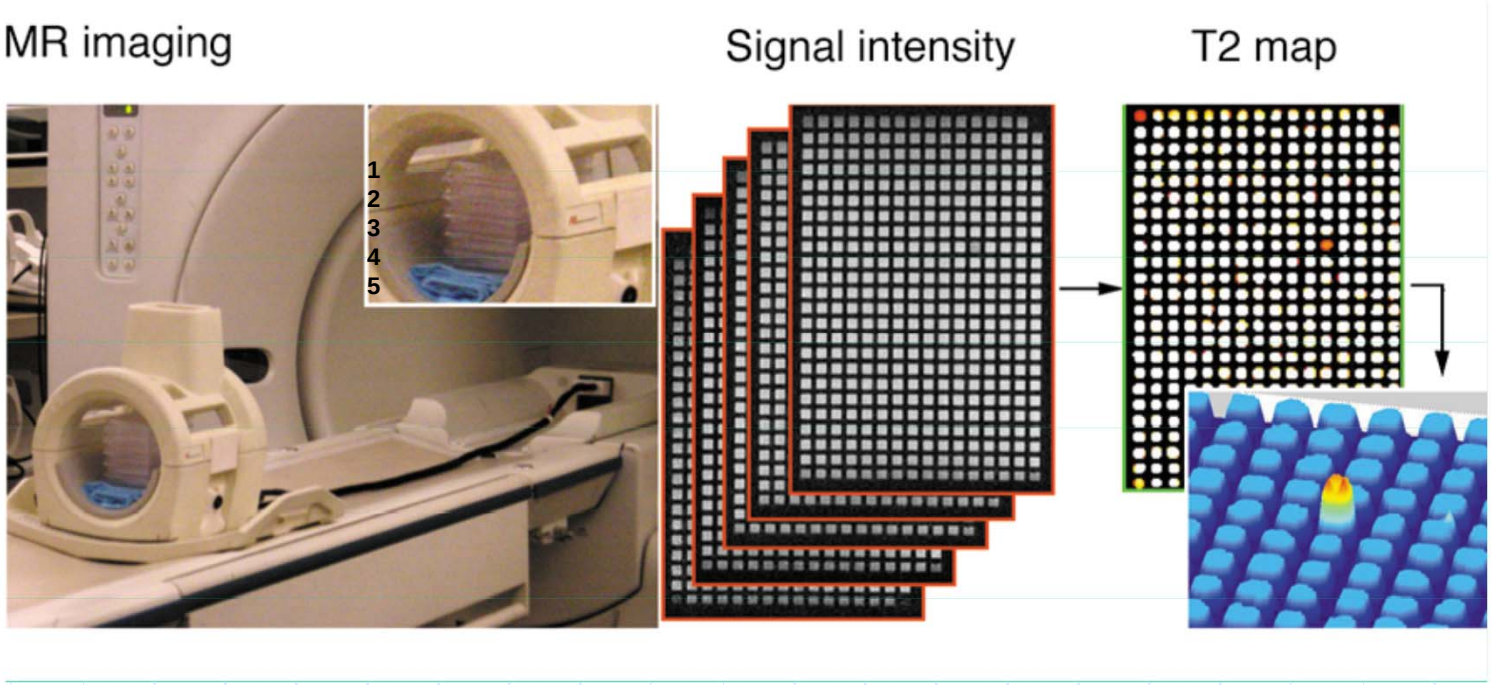
Positionally encoded arrays

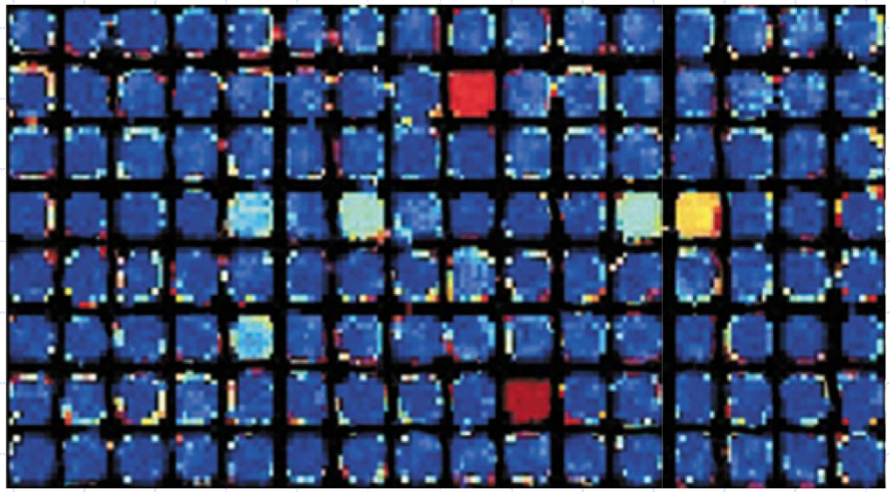


Specific peptides

DITWDQLWDLMKGGC
CGGDITWDQLWDLMK
DITWDQLWDLMKdsdsC
CdsdsDITWDQLWDLMK
IELLQARGGC
CGGIELLQAR
IELLQARdsdsC
CdsdsIELLQAR
Cyc{RGDcK}
Cyc{RGDfK(SATA)}
Cyc{RGDC-Mamb}
Cyc{RGDK(SATA)-Mamb}
SATA-GG-cyc{CNGRC}
Cyc{CNGRC}GGK(SATA)
SATA-dsds Cyc{CNGRC}
Cyc{CNGRC}dsdsK (SATA)
pEQRLGNQWAVGHLM
GrrrrrGrrrrGyK(FITC)G
GrrrrrGRRRRGyK(FITC)
GrrrrrGrrrrGyK(DOTA)G
GrrrrrGRRRRGyK(FOTA)
GRRRRRGRRRRGyK(FITC)
CK(FITC)YGGQWAVGHLM
CGGGPQRYGNQWAVGHLM
CGVYGWGMGLHGPQRNQA
rrrrGrrrrGrrrrGC
kkkkGkkkkGkkkkGC
GRKKRRQRRRGYK(FITC)
CrrrGQRLGNQWAVGLHLM
GCGK(FITC)GPQRYGNQWAVGHLM
GRKKRRQRRRGYK(FITC)C
GRRRRGRRRRGYK(FITC)C
(FITC)GrrrrGrrrrGYC
(FITC)GRRRRGRRRRGYC
GK(FITC)rrrrGrrrrGYC
GK(FITC)RRRRGRRRRGYC
CGQWAVGHLM
CeQWAVGHLM
CrrrQWAVGHLM
CeeeQWAVGHLM
CkkkQWAVGHLM
CsssQWAVGHLM
CGQRLGNQWAVGLHLM
CeQRLGNQWAVGLHLM
CrrrGQRLGNQWAVGLHLM
CeeeGQRLGNQWAVGLHLM
CkkkGQRLGNQWAVGLHLM
CsssGQRLGNQWAVGLHLM
rGC
kGC
rrrrGrrrrGC
kkkkGkkkkGC
SGPYVIWL
SGESLAYYTA
SGRSLSRLTA
SGRSLSRILA
KHpGPCGVRGPHpR
KHpGPLGVRGHpR
KHpGPLGVRGK(biotin)R
GDSDSGK(FITC)C

Screening by MR imaging: Telomerase assay of cell extracts





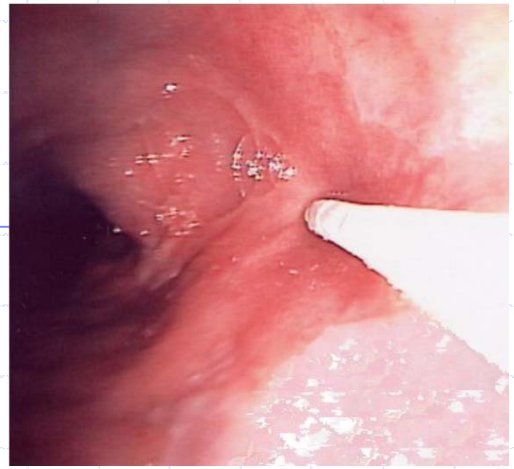
CLIO-tat limited library (9L)
Bioconj Chem 2002;13:116-121

Molecular Imaging Gap Areas

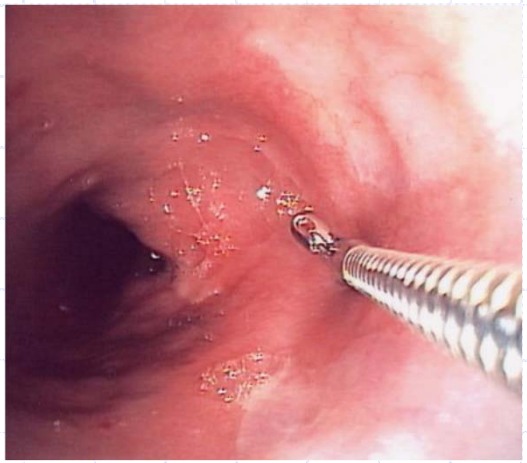
- **Need: Technologies for High-throughput Screening of Potential Imaging Agents**
  - **Combinatorial libraries and libraries of chemical diversity biased toward imaging agent chemistry**
  - **Assays constructed to identify *signaling* properties as opposed to *perturbing* properties.**

GI endoscopy with elastic scattering spectroscopy

(Barrett's esophagus study)

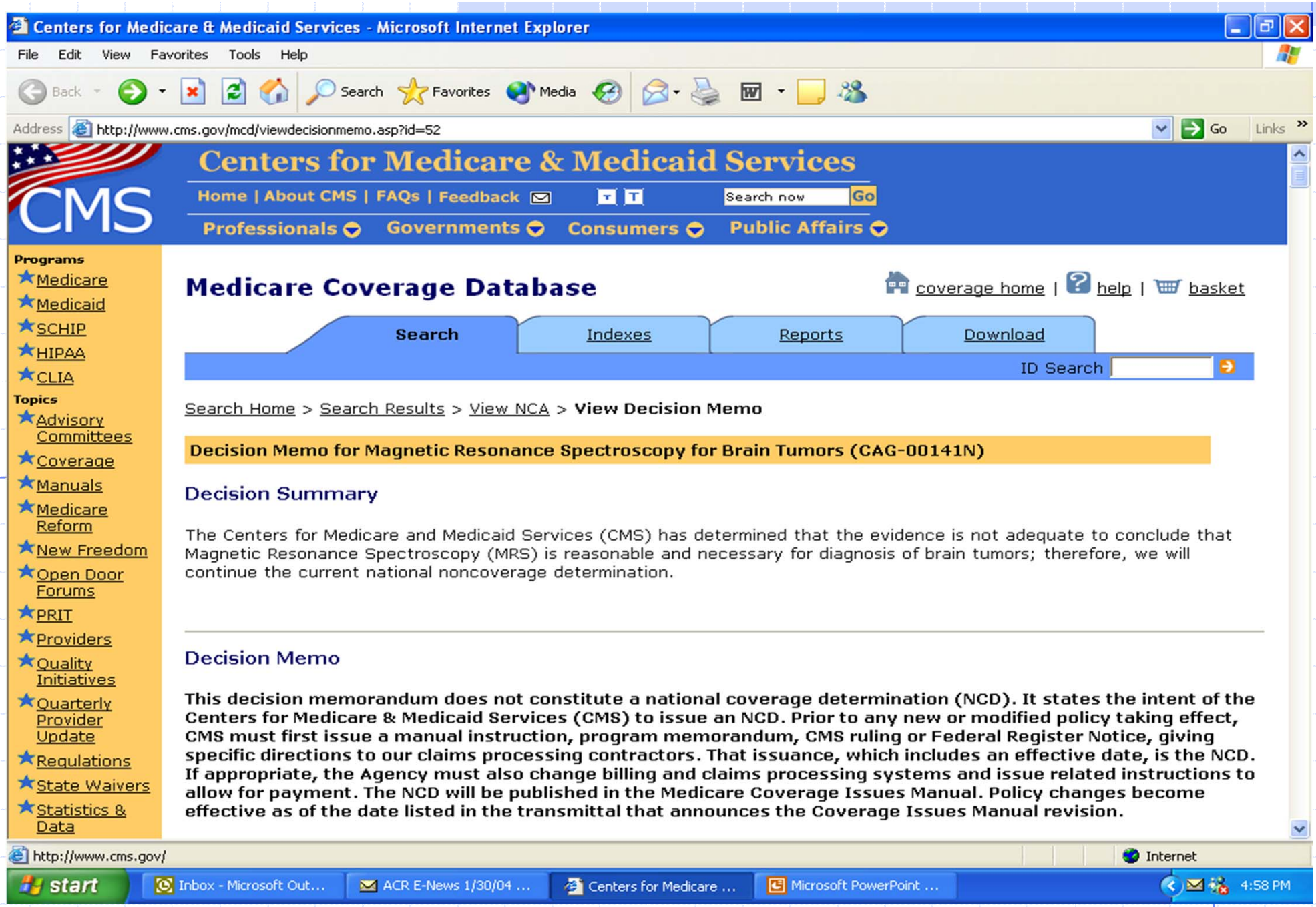


Optical "biopsy"



Surgical biopsy

BOSTON UNIVERSITY



“However, standardized techniques for acquiring and interpreting MRS spectra are lacking …,” Jan. 29, 2004

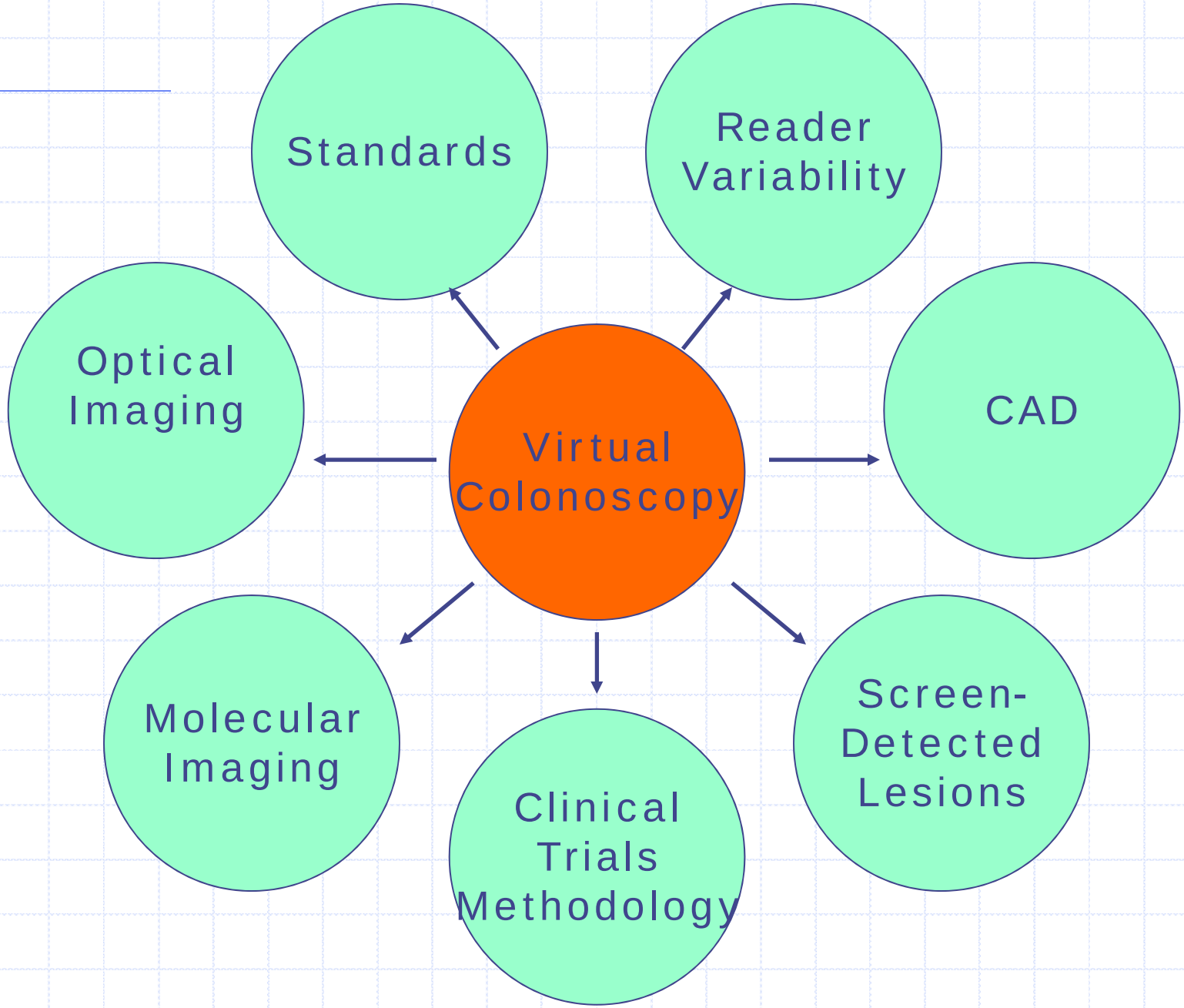
Network for Translational Research in Optical Imaging (NTROI)

Key Challenges for NTROI

- Complex, multi-institutional collaboration
- Standardize technology and analysis platforms
- Develop reference standards (NIST?):

  -e.g., optical index of angiogenesis, optical index of metabolism, etc.
- Demonstrate value added to conventional imaging
- Define Optics clinical role

Imaging Issues Raised by CT Colonography or Screening



CIP Vision Statement:

Cancer Imaging – Visualize the problem and direct the solution.