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Creating a "Learning Health System" in Breast Imaging

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Departments:
Radiology
Population Health
Biostatistics and Medical Informatics
Industrial and Systems Engineering

Learning Health System?

- General Overview
  - Motivation
- Methodological Considerations
  - Algorithms & metrics to measure performance
- Projects
  - Improving mammographic predictions
  - Improving image-guided core biopsy

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Motivation

- Information overload
  - Medical articles in pubmed-online
  - EHR information
  - Genetic risk factors
- Human decision making involves heuristics that may not scale up alone

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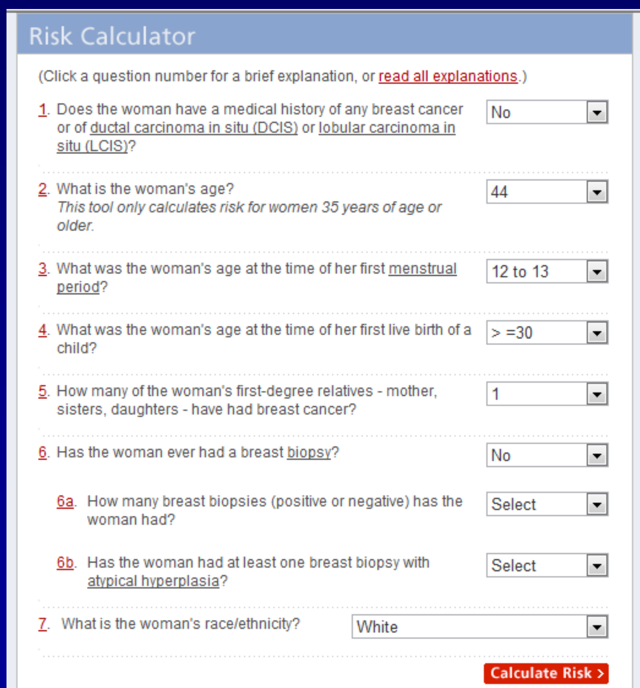
The Gail Model


Risk Calculator

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)? — No
2. What is the woman's age? *This tool only calculates risk for women 35 years of age or older.* — 44
3. What was the woman's age at the time of her first menstrual period? — 12 to 13
4. What was the woman's age at the time of her first live birth of a child? — > =30
5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer? — 1
6. Has the woman ever had a breast biopsy? — No
   - 6a. How many breast biopsies (positive or negative) has the woman had? — Select
   - 6b. Has the woman had at least one breast biopsy with atypical hyperplasia? — Select
7. What is the woman's race/ethnicity? — White

Calculate Risk >

- Uses data (BCDDP)
- Predicts Breast CA
  - Five year/lifetime risk

Low signal predictors

http://www.cancer.gov/bcrisktool/Default.aspx

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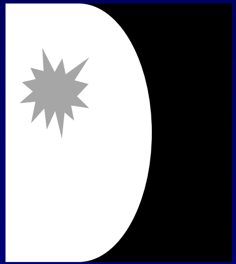
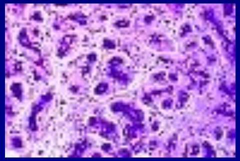
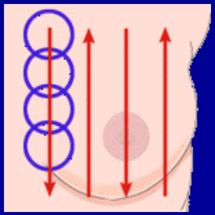
Predictive Information

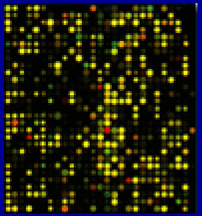


AGE

Breast Cancer







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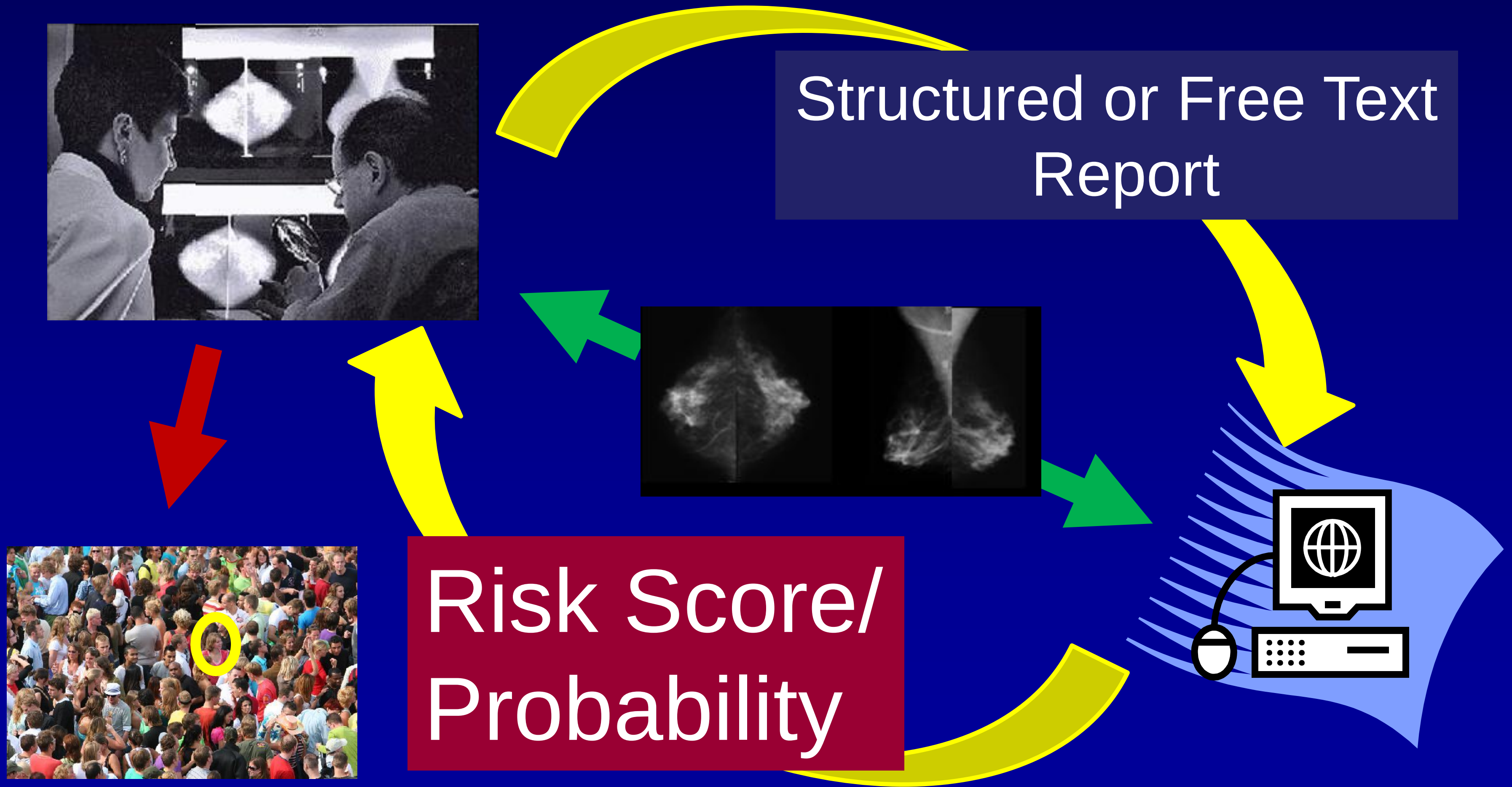
Human Computer Interaction
COMMUNICATION



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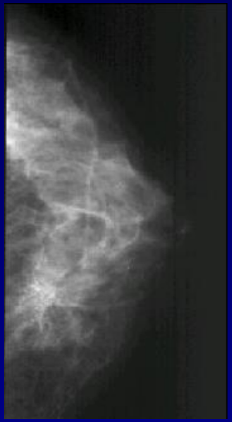
The Mammography Risk Prediction Project

Elizabeth Burnside, MD, MPH, MS
C. David Page, PhD
Jude Shavlik, PhD
Charles Kahn, MD (MCW)

Background-Opportunity



- 200,000 breast cancer diagnosed in US
- 20 million mammograms per year
  - False positives
    - Millions of diagnostic mammograms/US
    - Hundreds of thousands biopsies
  - False negative
    - 10-30% of breast cancers not detected on mammography
- Variability of practice impacts many women
- **Evidence-based decision support has the potential to drive substantial improvement**

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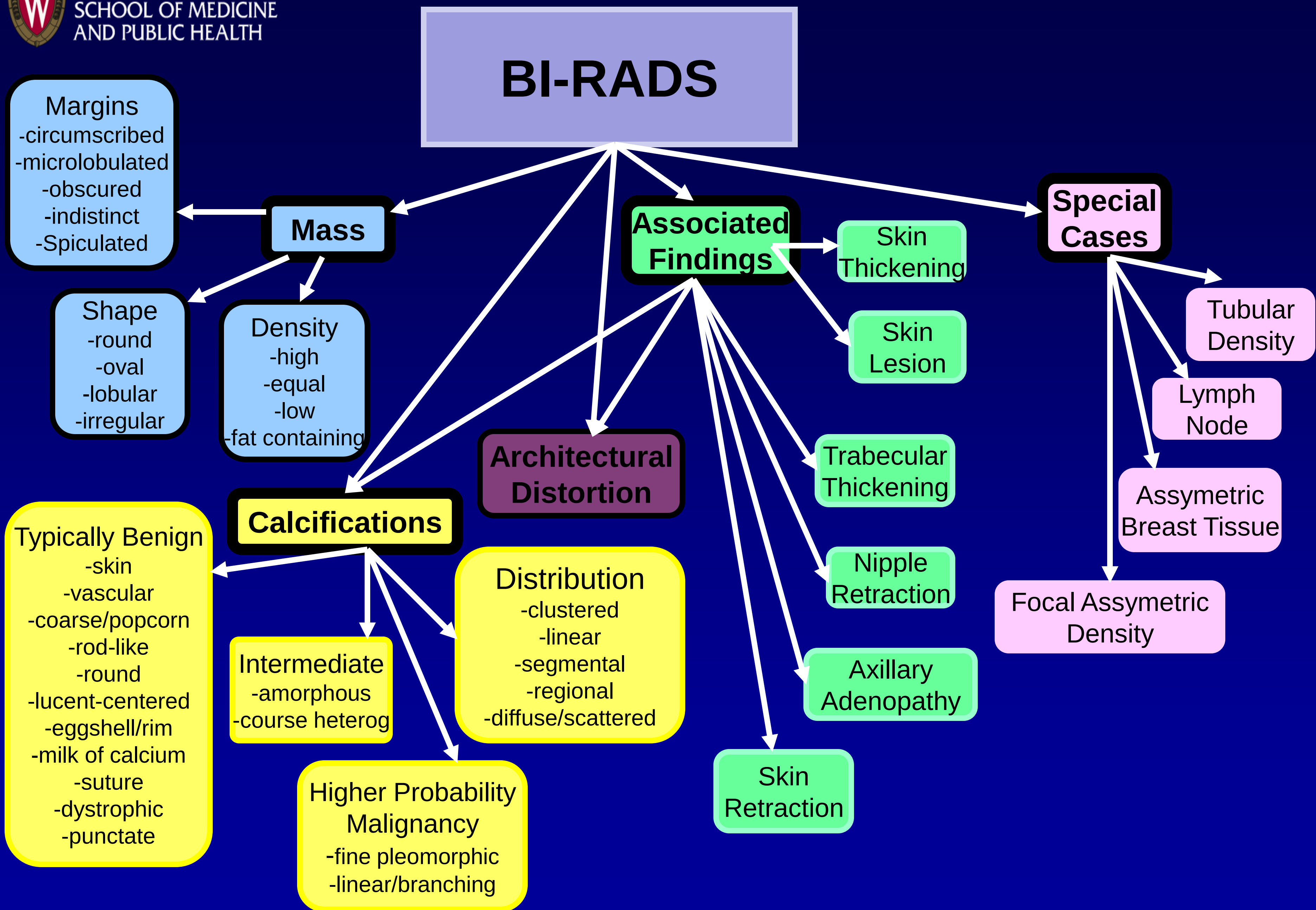
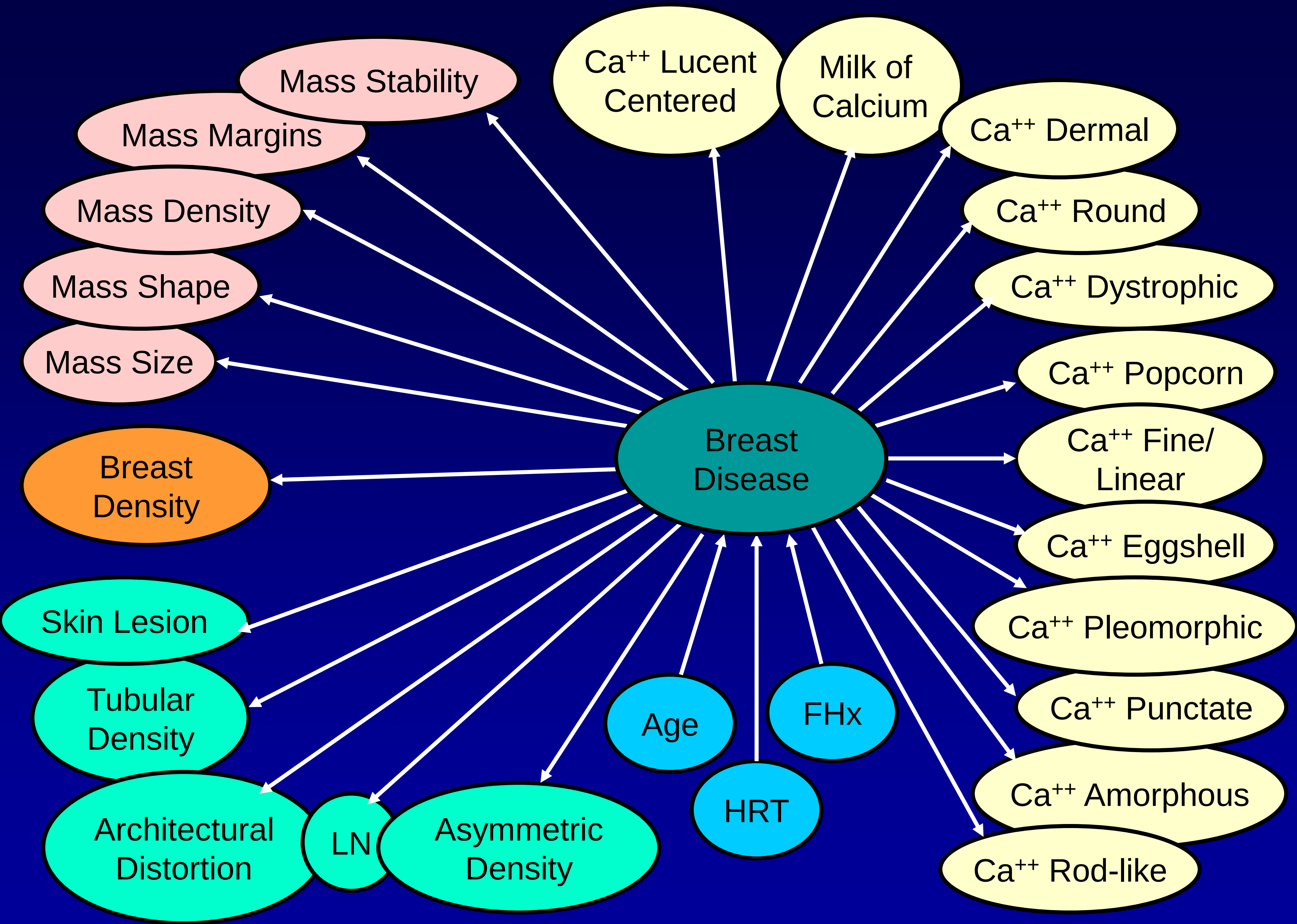
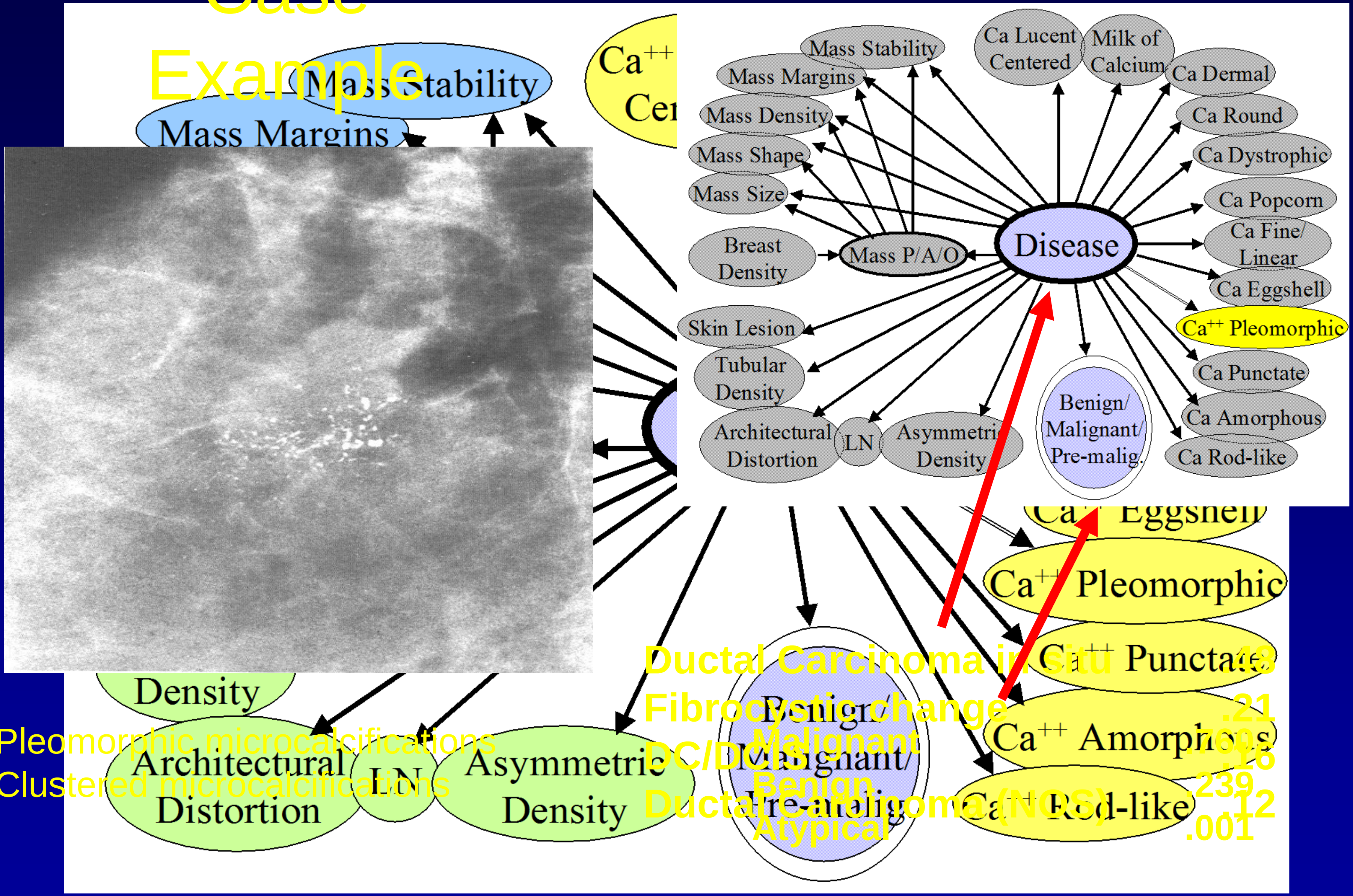


Breast Cancer Probability Based on BI-RADS Category

BI-RADS 0:	Needs Additional Imaging
BI-RADS 1:	Negative
BI-RADS 2:	Benign
BI-RADS 3:	Probably Benign
BI-RADS 4:	Suspicious for malignancy
BI-RADS 5:	Highly suggestive of malignancy


Breast Disease
Mass Stability
Mass Margins
Mass Density
Mass Shape
Mass Size
Breast Density
Skin Lesion
Tubular Density
Architectural Distortion
LN
Asymmetric Density
Age
HRT
FHx
Ca++ Lucent Centered
Milk of Calcium
Ca++ Dermal
Ca++ Round
Ca++ Dystrophic
Ca++ Popcorn
Ca++ Fine/ Linear
Ca++ Eggshell
Ca++ Pleomorphic
Ca++ Punctate
Ca++ Amorphous
Ca++ Rod-like

Case Example



Pleomorphic microcalcifications
Clustered microcalcifications

Ductal Carcinoma in Situ	.48
Fibrocystic change	.21
DC/DCIS	.16
Ductal Carcinoma (NOS)	.12

Malignant	.760
Benign	.239
Atypical	.001

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Training on Data

- Motivation
  - Accurate probabilities are critical
  - Some are not available in literature
  - Modeling the relevant patient population is possible with training

Expert & Rule Based → ***Machine Learning***

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Idea: Data Driven Decisions

Patient Table
Age
Personal Hx Breast CA
Family Hx Breast CA
…..

Abnormality Table
Mass shape
Mass margins
Mass density
Mass size
Mass stability
MicroCa^{++} shape
MicroCa^{++} distribution
BI-RADS category
…..

Registry Table
Patient ID
Margin status
Grade
Prior radiation
…..

Biopsy Table
Needle size
Number of samples
Post-proc appearance
Accurate clip position
…..

Pathology Table
Pathology Result
Concordance
Recommendation
…..

Data

- Our dataset contains
  - 350 malignancies
  - 65,630 benign abnormalities
- Linked to cancer registry data
  - Outcomes (benign/malignant)

Training the BN

- Standard Machine learning
  - Use known cases to train
  - Use the tuning set for optimal training
  - Performance based on hold out test set

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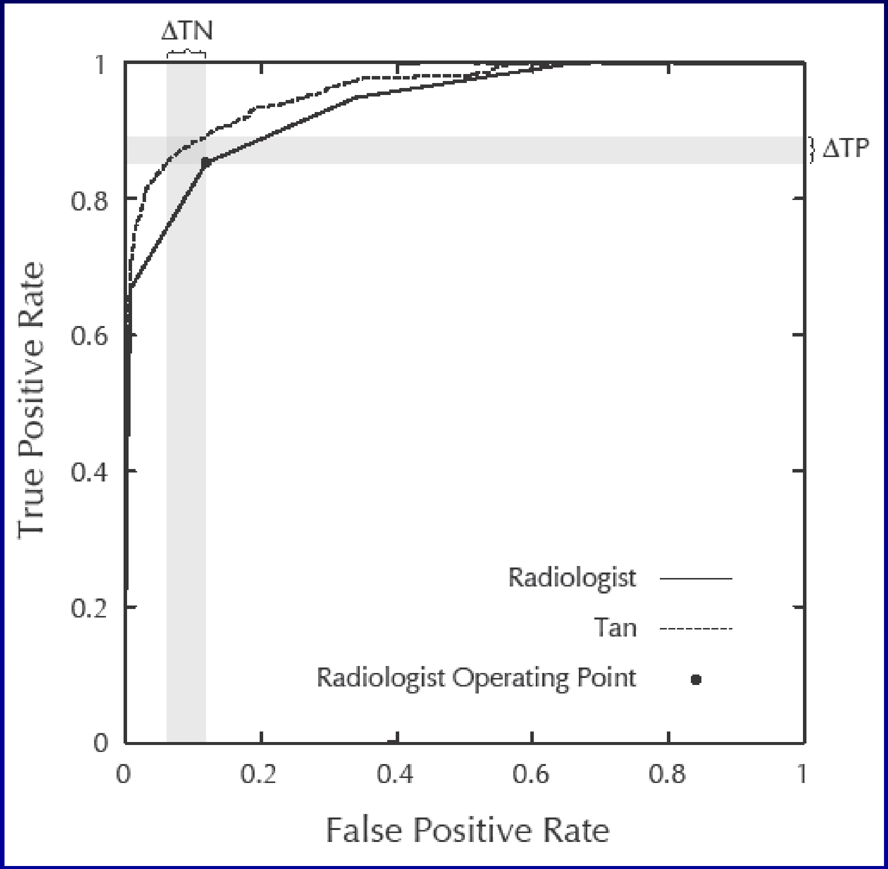
Performance



- AUC 0.960 *vs*. 0.939
  - $P < 0.002$
- Sensitivity
  - 90.0% *vs*. 85.3%
  - $P < 0.001$
- Specificity
  - 93.9% *vs*. 88.1%
  - $P < 0.001$

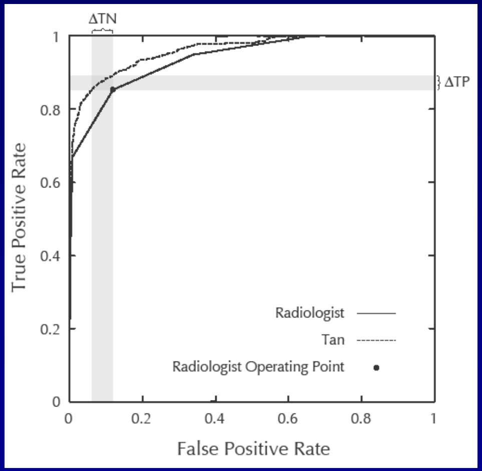
What does that mean?

- At a specificity of 90%

  38 conversions FN → TP

- At a sensitivity of 85%

  4226 conversions FP → TN



Ultimately Decision Support Aids the Physician

- Output of the system is
  - Advisory
  - Utilized in the clinical context
  - System performance alone is not the point
  - Performance/Physician performance is the key to improvement of care

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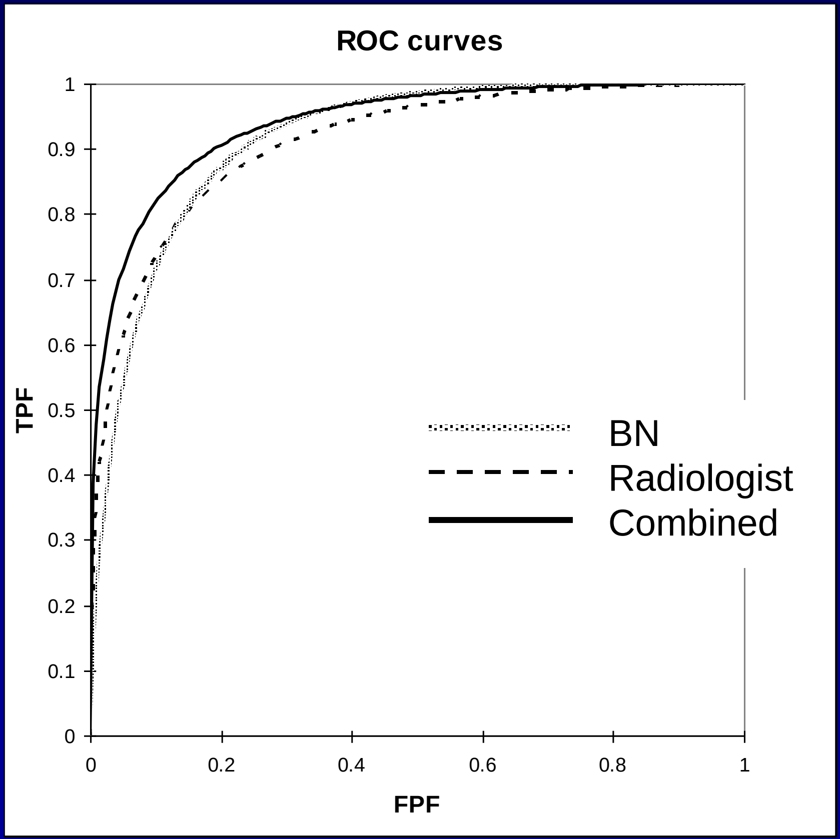
Collaborative Experiment



Radiologist

.916

Bayes Net

.919

Combined

.948

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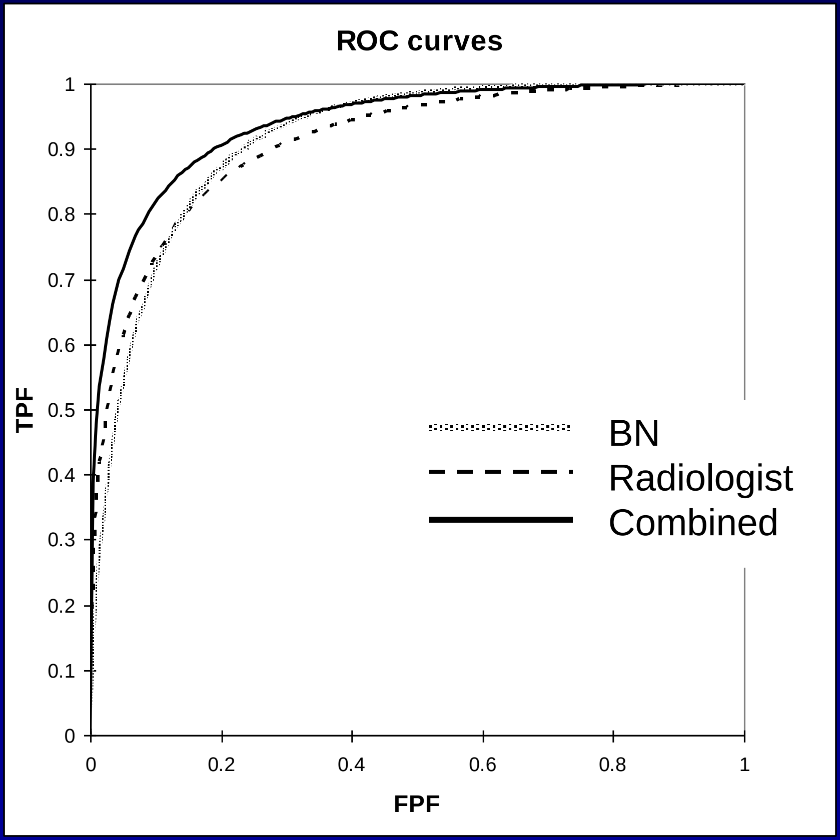
Results



Radiologist

.916

Bayes Net

.919

p=.03

Combined

.948

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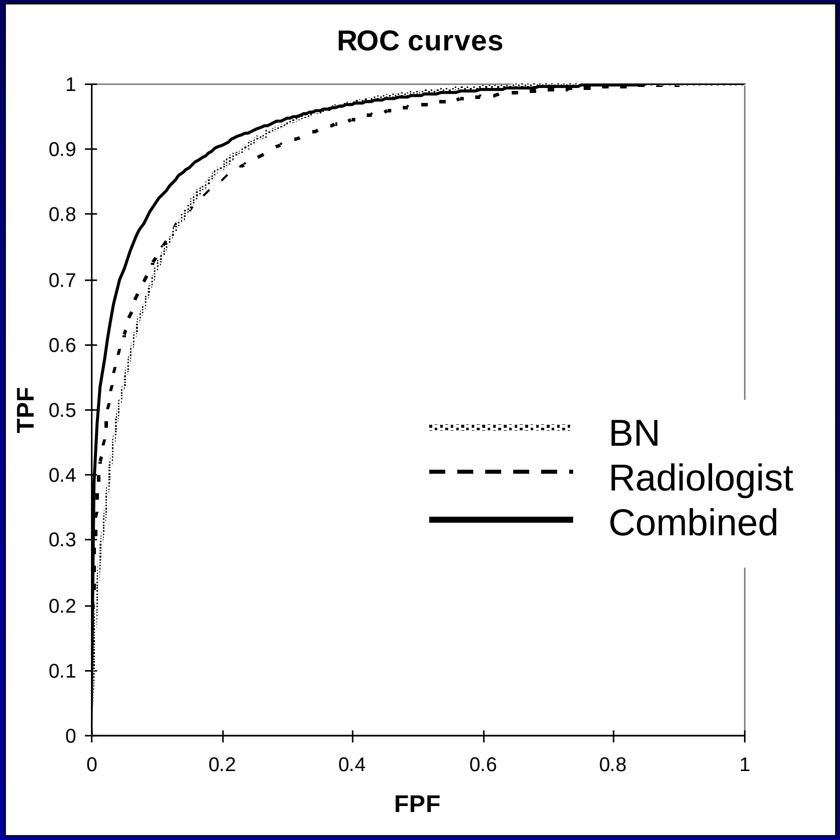
Results



Radiologist
.916

Bayes Net
.919

p=.065

Combined
.948

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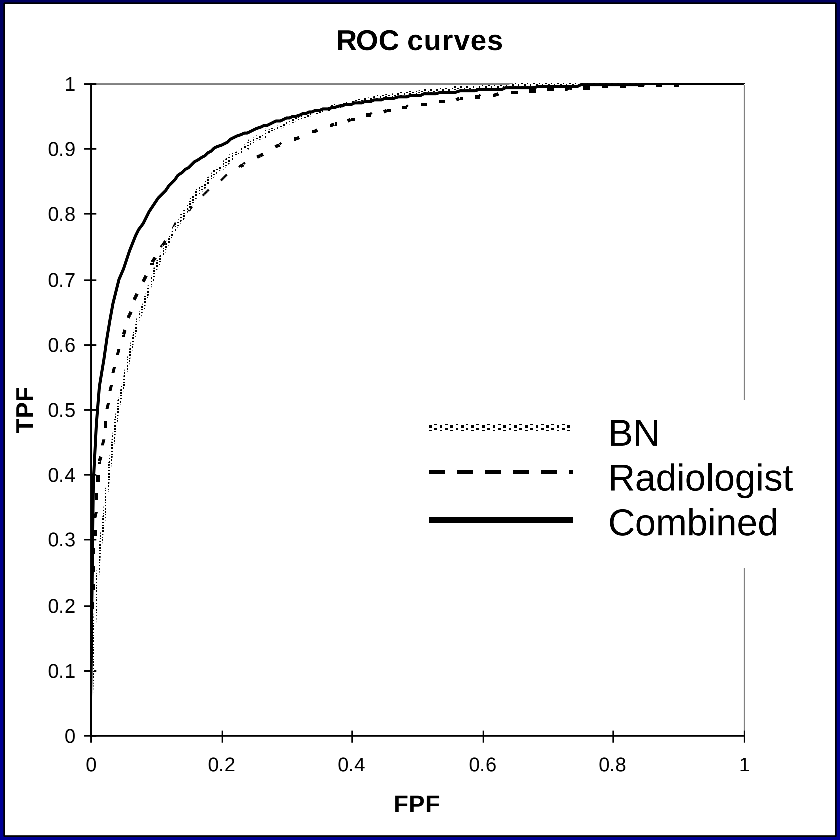
Results



Radiologist

.916

p=.99

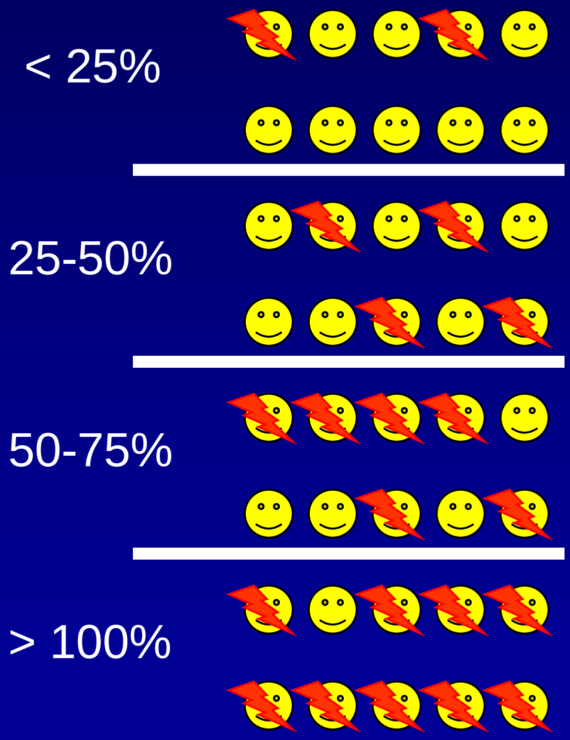
Bayes Net

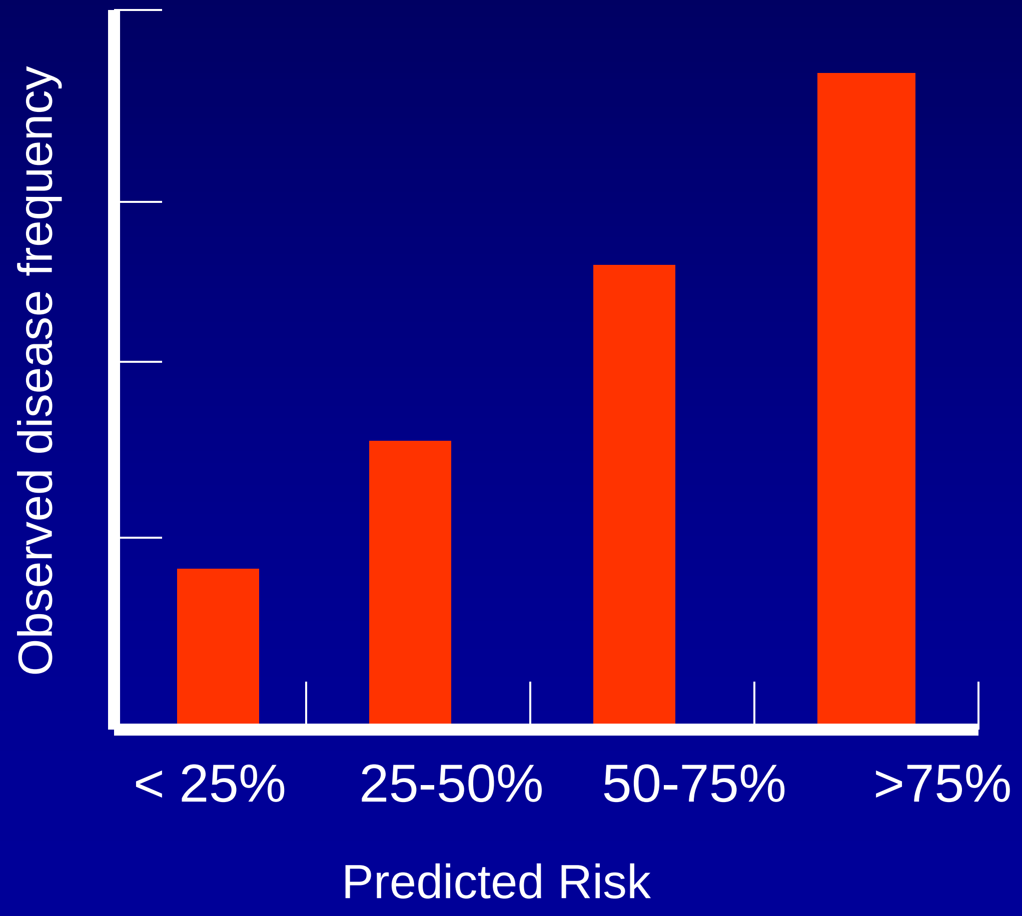
.919

Combined

.948

Calibration Curves





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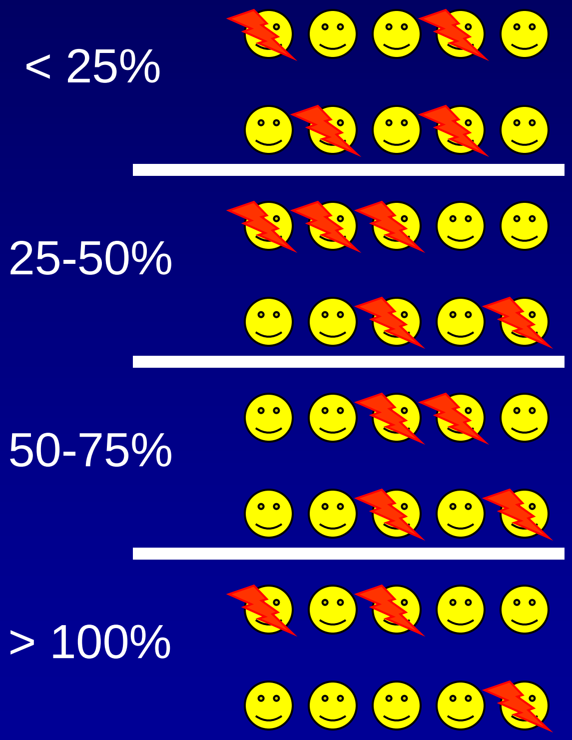

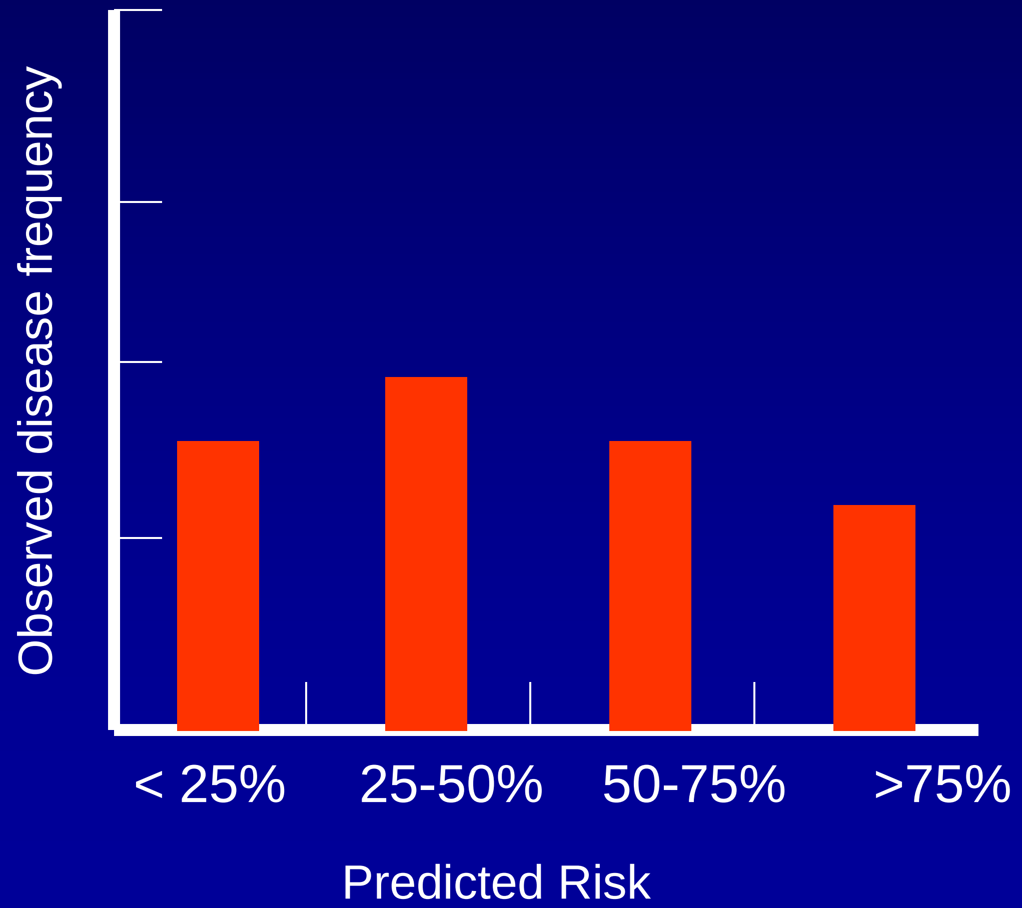

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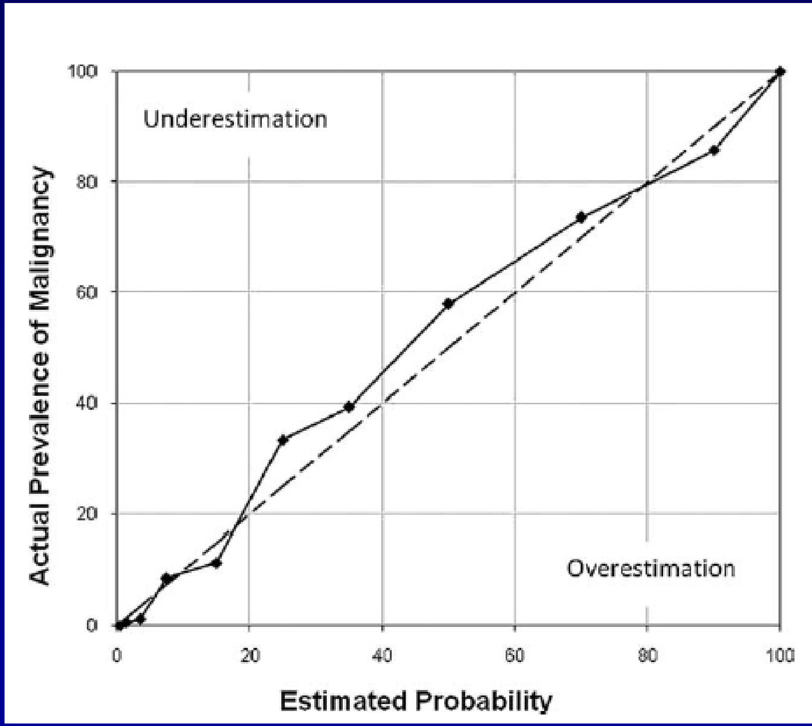
Calibration



- Hosemer-Lemishow goodness of fit

Ayer, T., et al., *Breast cancer risk estimation with artificial neural networks revisited: discrimination and calibration.* Cancer, 2010. **116**(14): p. 3310-21.

Creating a Learning Health System

- Capturing directly from the EHR
- Using it to inform future practice
- Can it be done?

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UW Dataset

Date range: from Oct 1, 2005 to Mar 30, 2012

Number of patients: 30,024

Number of mammograms: 89,610

- Number of screening mammograms: 69,484
- Number of diagnostic mammograms: 20,126

Number of MRIs: ~ 3000

Number of US: ~10,000

What is the Key?

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The Breast Biopsy Project

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Heather Neuman, MD, MS
Ines Dutra, PhD
C. David Page, PhD
Jude Shavlik, PhD

ILP

Abnormality A in
Mammogram M for
Biopsy B in
Patient P

Is malignant if:

Malignant (A) IF

A has mass present
A has stability increasing
P has family history of breast cancer
B has atypia

How does it work?

- Learn if-then rules that will become features in a predictive model
  - Inductive logic programming (ILP) to learn the rules
  - Integrated search strategy for constructing and selecting rules for classifcation algorithm

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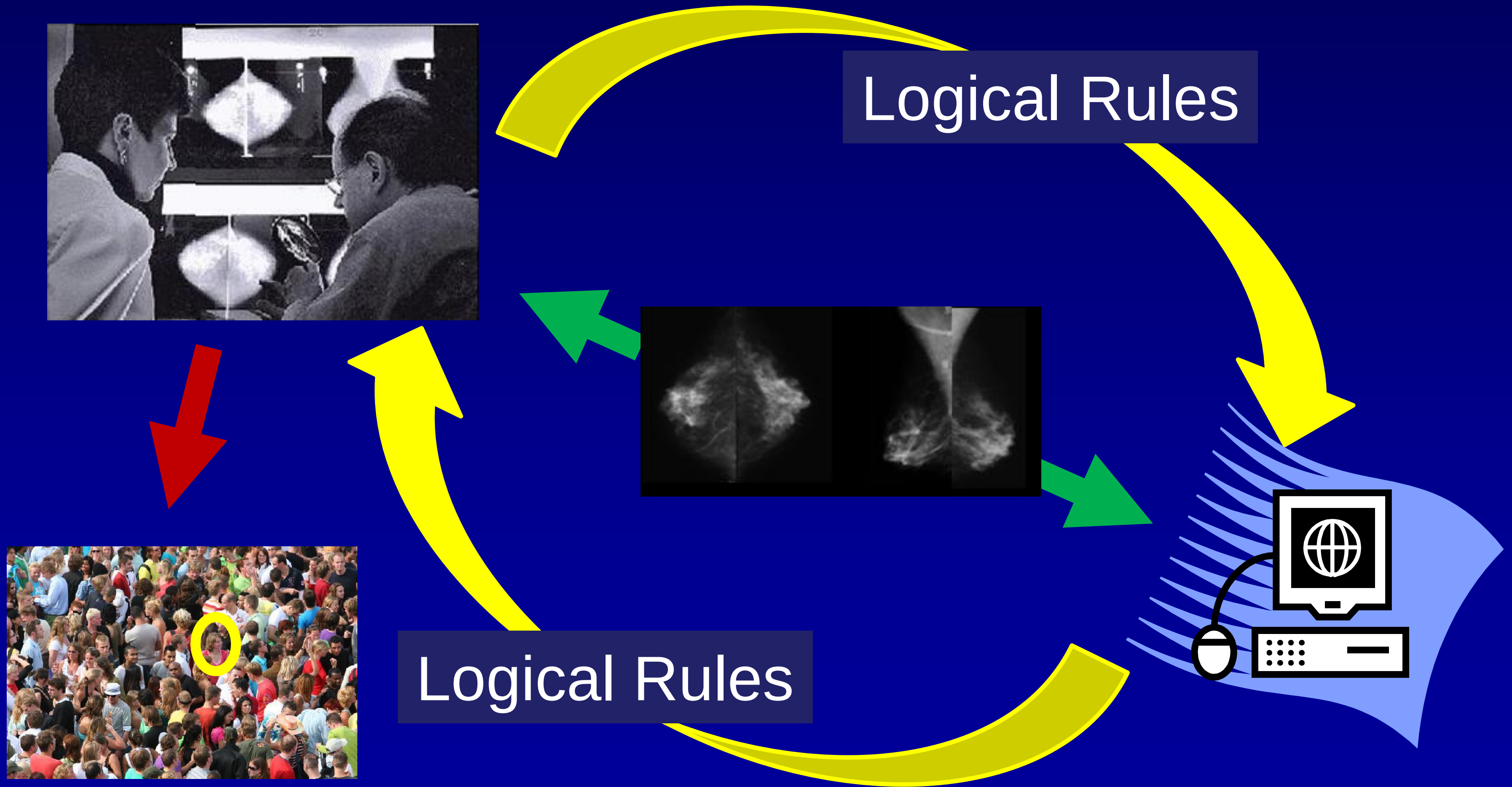
Human Computer Interaction COMMUNICATION



Breast Biopsy

- Biopsy: single most costly component of a breast cancer screening program

- Annual breast biopsy utilization in 2010

62.6/10,000 women

➢ 700,000 women

~35,000-105,000 non-definitive

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Non-Definitive Breast Biopsy

Screening Mammography

# women	1000
# cancers	5

False Positives

Diagnostic Work-up/Biopsy

# women	115
# cancers	4

# women	10
# cancers	1

Non-definitive?

What should I tell my patient?

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Breast Biopsy at UW

- 6 year experience at UW
  - 2808 consecutive image-guided core biopsies
    - 30% Malignant; 70% Benign
    - 238 were deemed non-definitive ← **Excision**
- Hypothesis: ILP rules from the data and from physicians could improve the accuracy of upgrade prediction

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All biopsies (2006-2011)

2808 core biopsies

GUIDANCE

892 Stereo

1743 US

173 MRI

96 (non-definitive)

124 (non-definitive)

18 (non-definitive)

23 D

65 ARS

4 I

4 N

61 D

24 ARS

34 I

5 N

5 D

12 ARS

1 I

0 N

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Biopsies in Practice (2006-11)

2808 core biopsies

1,909 breast core biopsies with diagnostic mammograms

601 M

1,308 B/HR

130 (non-definitive)

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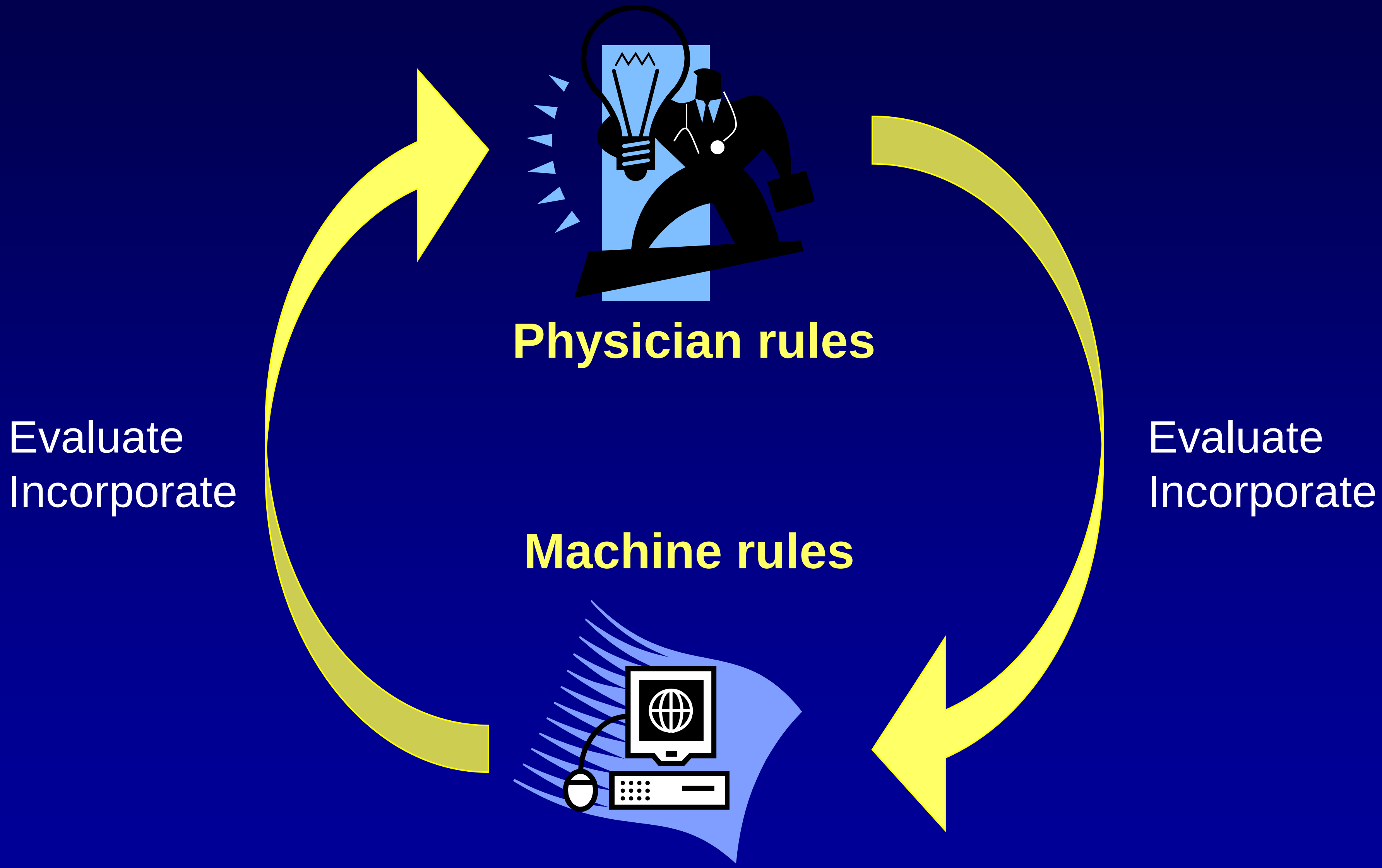

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Biopsy data

- Example rule:

Upgrade (A) IF
    concordance (A, d),
    biopsyProcedure (A, US_core) and
    pathDx (A, benign_breast_tissue)

- Incorporate physician and machine rules into a Bayesian Network

Discordant Biopsies (2006-11)

Discordant Biopsy
60

Malignant (upgrade)
10

Benign (non-upgrade)
50

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Results

	Data	Rules	Data + Rules
Malignant Excisions Missed (%)	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Benign Excisions Avoided (%)	**5 (10.0%)**	**5 (10.0%)**	**12 (24.0%)**

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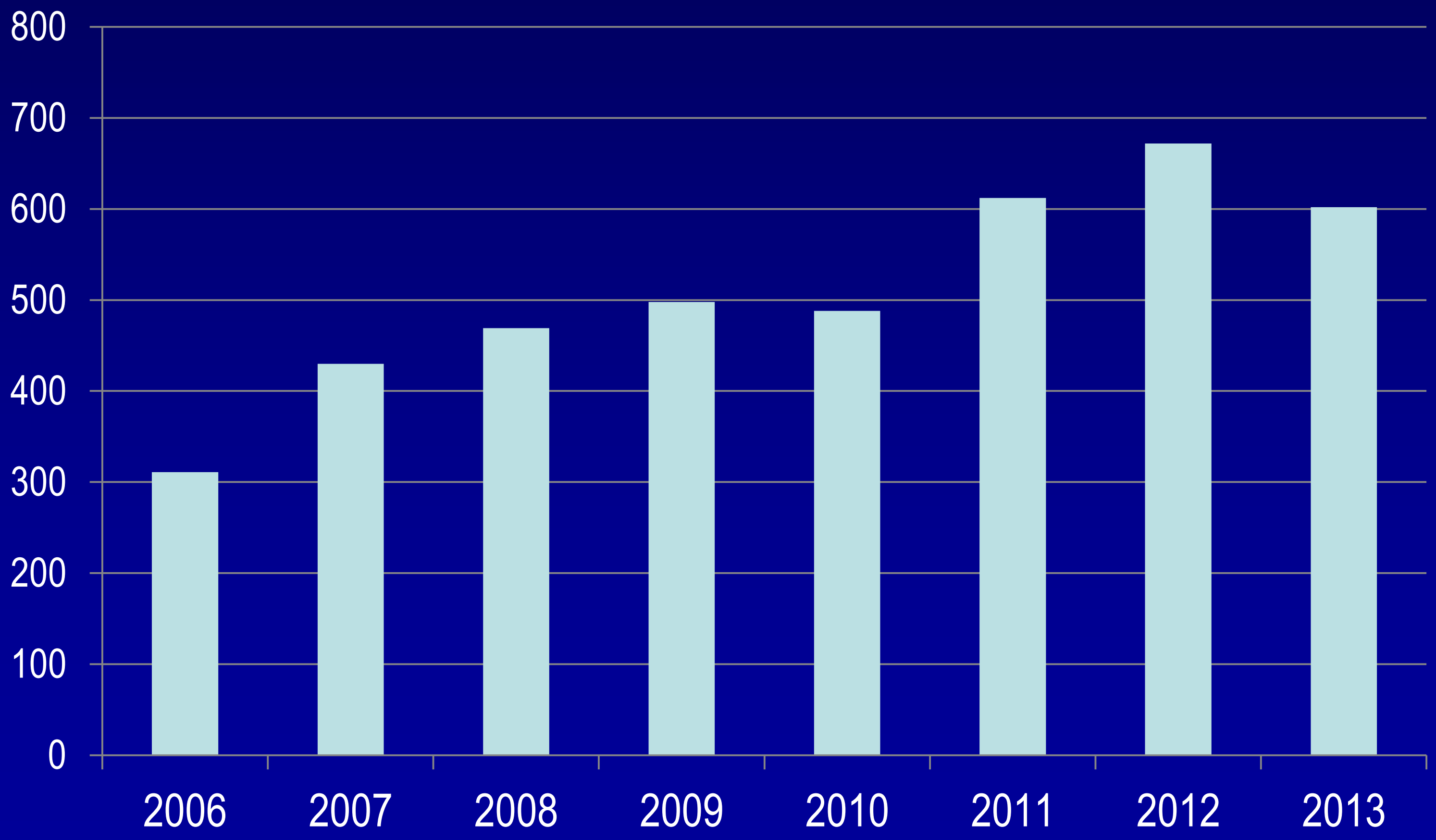
Total core biopsies



Total Non-Definitive

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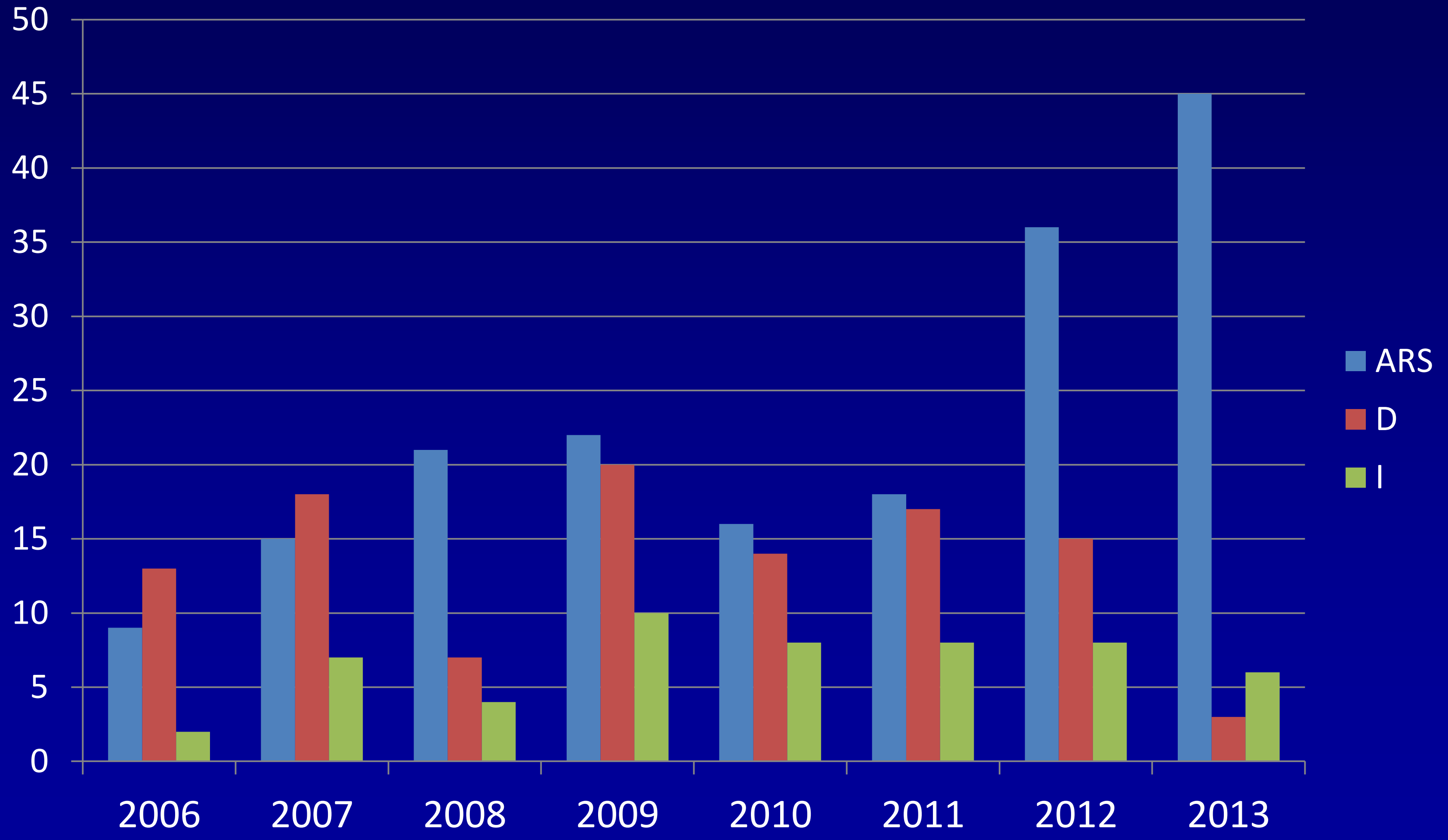
Subtype Trends



Why?

- Discordant decreased
  - Relied more heavily on BI-RADS descriptors
  - Improved our practice
- ARS increased
  - Digital mammography

ARS in Modern Mammography

- 142 consecutive cases (2004-2010)
  - ARS
    - Film
      - 52 (36.6%)
      - **RATE = 0.37/1000**
    - Digital
      - 90 (63.4%)
      - **RATE = 1.24/1000**

AJR Am J Roentgenol 2013;201(5):1148-54

Creating a Learning Health System

- Non-definitive biopsy
  - Discordant (maybe)
  - ARS (not yet)

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Creating a Learning Health System

- Non-definitive biopsy
  - Discordant (maybe)
  - ARS (not yet)

History

- Tools first conceived in:
  - Leeds Abdominal Pain System went operational in 1971

System = 91.8%
Physician = 79.6 %

Creating a Learning Health System

- Discordant can be tackled
  - In our practice we look to be successful
  - Remains to be generalized
- ARS emerges as more important
  - Next goal to improve practice through decision support

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Learning Microsystem!

New goal…

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Questions?

FIG. 1. Bayes' theorem in practice.

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The Marshfield Project:

Epidemiology/Breast Imaging/Genetics

eBIG

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Cathy McCarty, PhD, MPH., RD
Adedayo Onitilo, MD, MSCR
Peggy Peissig, MBA

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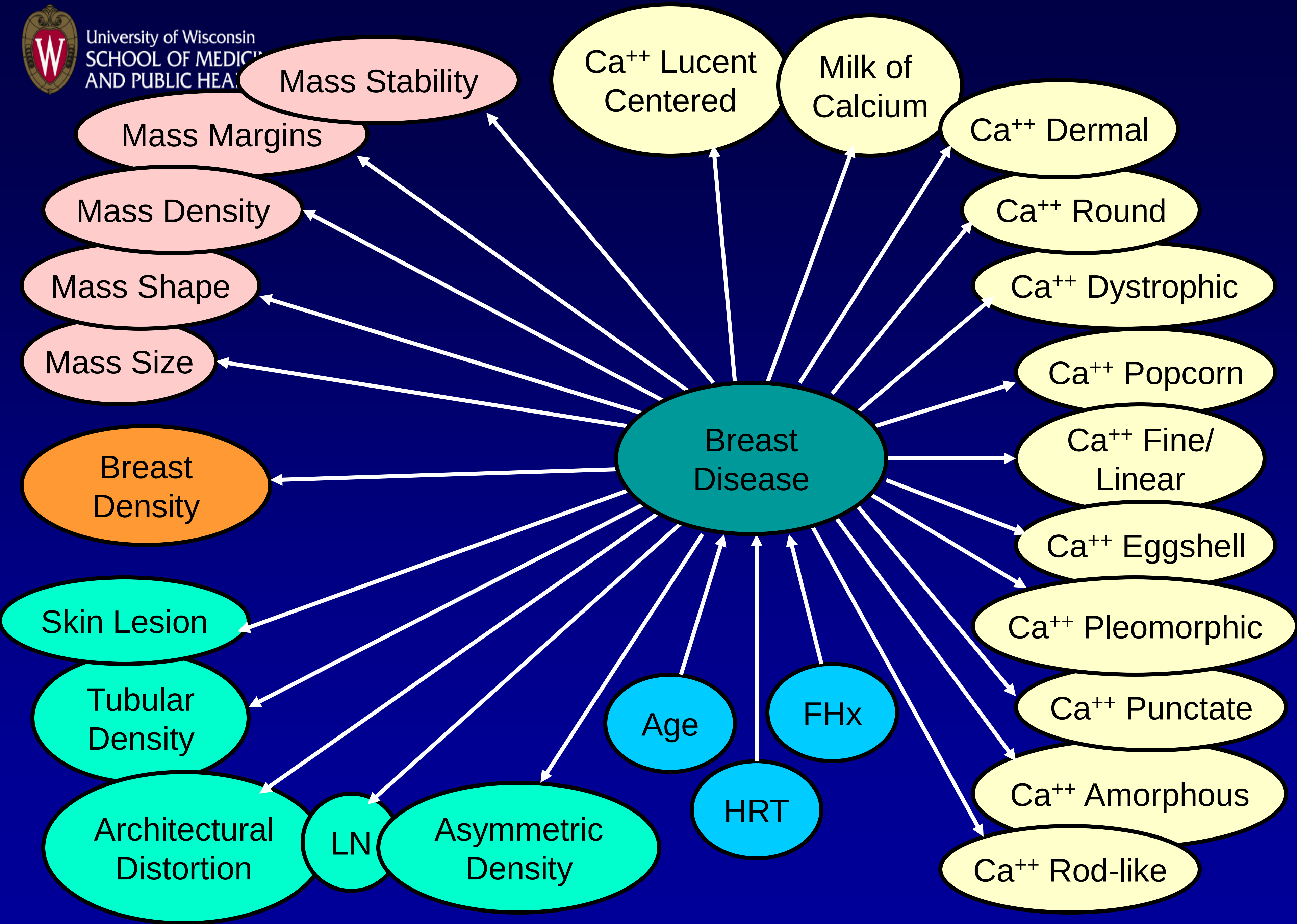

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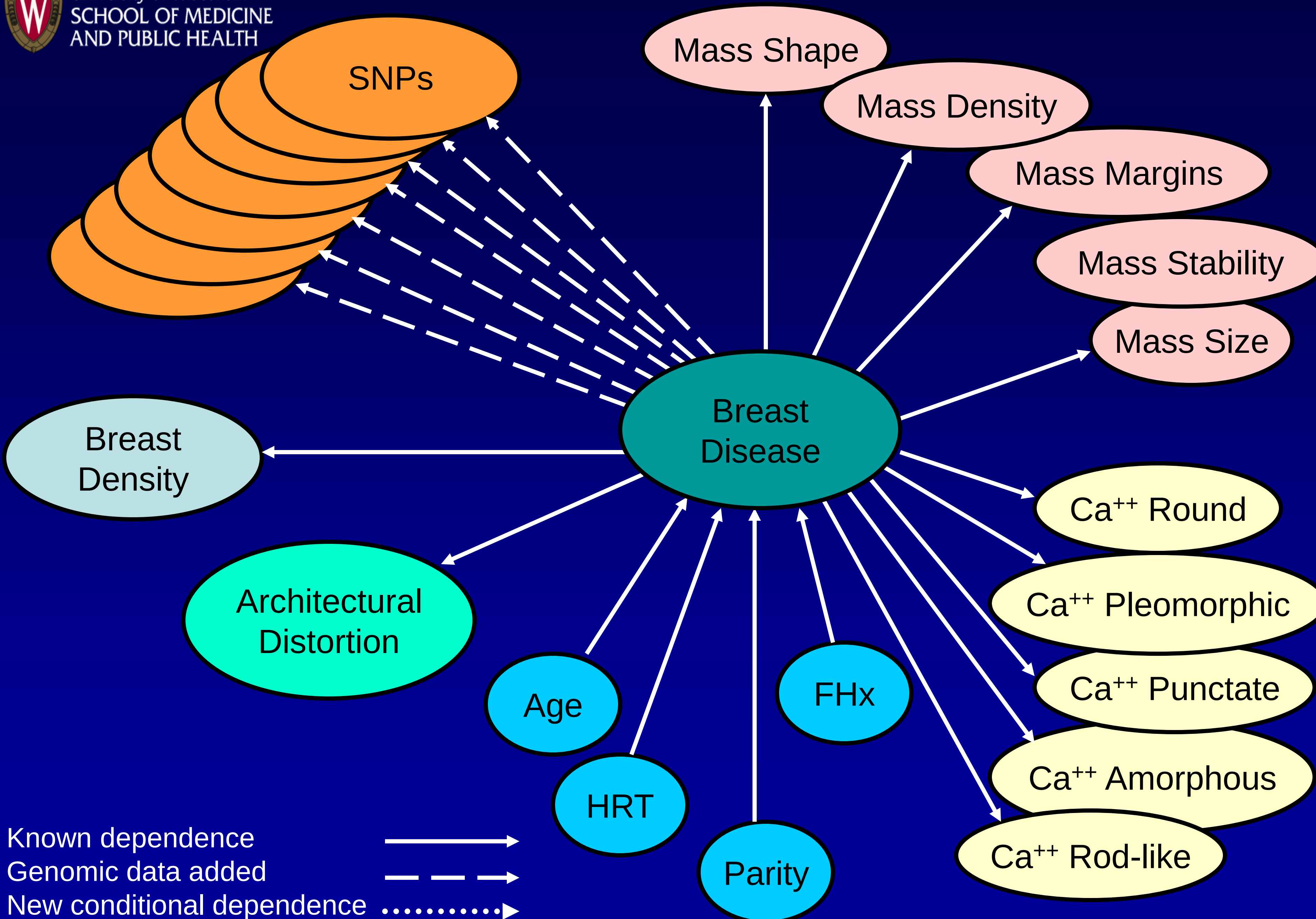

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Specific Aim 1

- Establish a multi-relational dataset to improve the risk prediction accuracy of our Bayesian model
  - patient specific genomics data
  - mammography findings
  - clinical/demographic risk factors

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Data Elements

Epidemiologic data	Clinical Variables	Targeted SNPs
Gender	Mammography descriptors (current)	rs11249433
Age	Mammography BI-RADS categories (current)	rs4666451
Race/Ethnicity	Mammography descriptors (prior)	rs13387042
Family History	Mammography BI-RADS categories (prior)	rs4973768
Number of full-term pregnancies	Personal History of Breast Cancer/InSitu	rs10941679
Breast Feeding History	Pathologic diagnosis	rs981782
Menses <12 yrs	Stage	rs30099
Menopause >55 yrs	Grade	Rs889312
Exogenous hormone ever	Receptor status- (ER/PR-her2)	rs2180341
Smoking history ever > 1 year	Known Genetic Risk- BRCA1 / BRCA2	rs2046210
Alcohol use > 1 drink/day ever	Prior Chest Irradiation / DES exposure	rs13281615
Physical activity >3 hrs/week	Oral Contraceptive	rs2981582
	Prior Biopsy	rs3817198
	Body Mass index (BMI)	rs2107425
		rs999737
		rs3803662
		rs8051542
		rs6504950
		rs6476643
		rs2182317
		rs12443621
		rs1045485
		rs1982073

Study Design

- Retrospective case control design
- **Cases**
  - women mammo <12 months/biopsy/breast cancer **422**
- **Controls**
  - women mammo <12 months/biopsy/no breast cancer **422**
- ***Create an age match to the cases—5 year interval bins***
- ***Calculate % or mammograms that are abnormal***
- Collect
  - Demographic risk factors
  - Mammography features
  - SNPs from serum samples

Study Design-Training

- Model training
  - Build baseline prediction model
  - Develop rules for inclusion in model
  - 10-fold cross validation
- Post-test probabilities used for performance
  - Area under the ROC curve
  - Calibration

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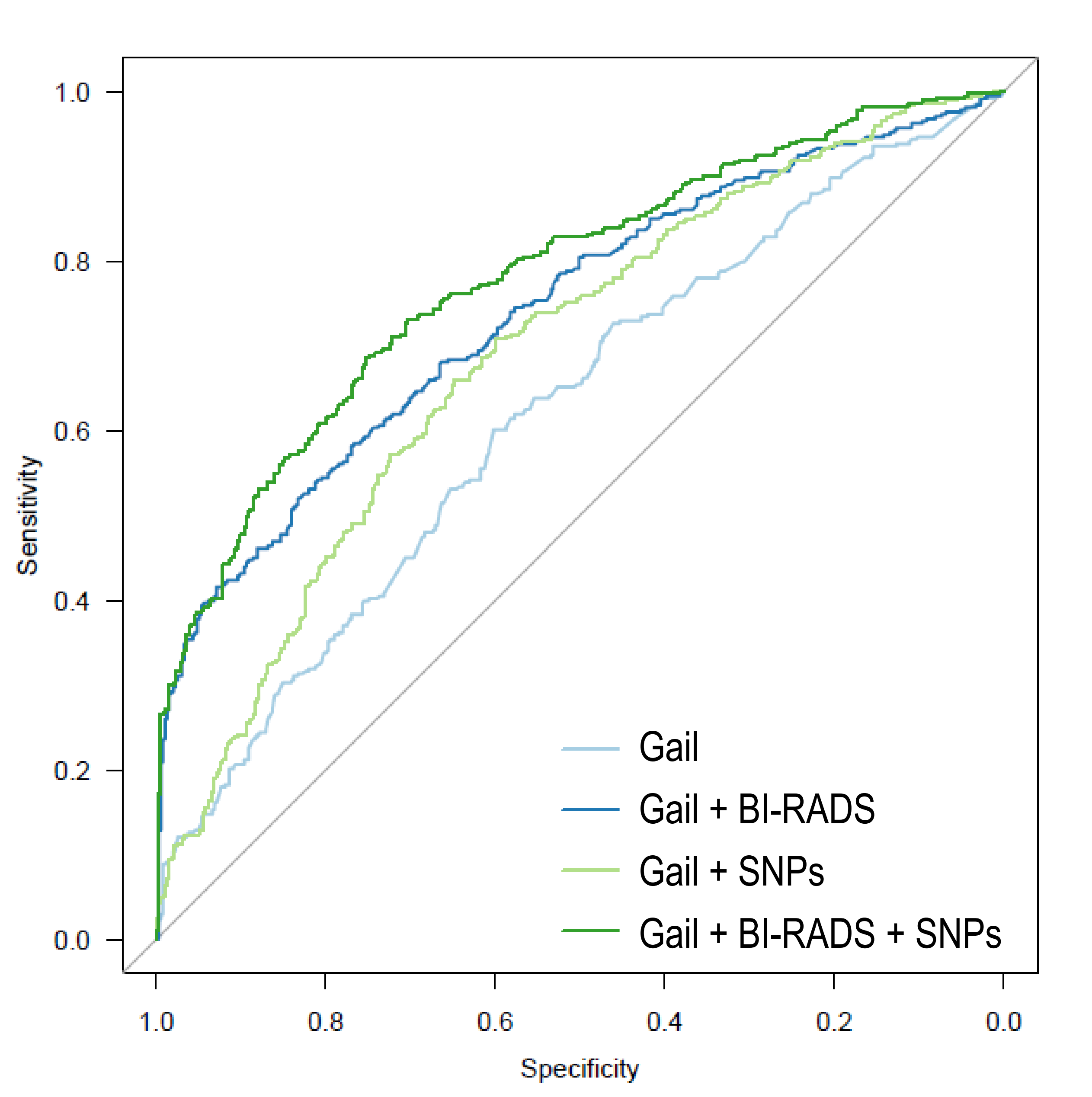
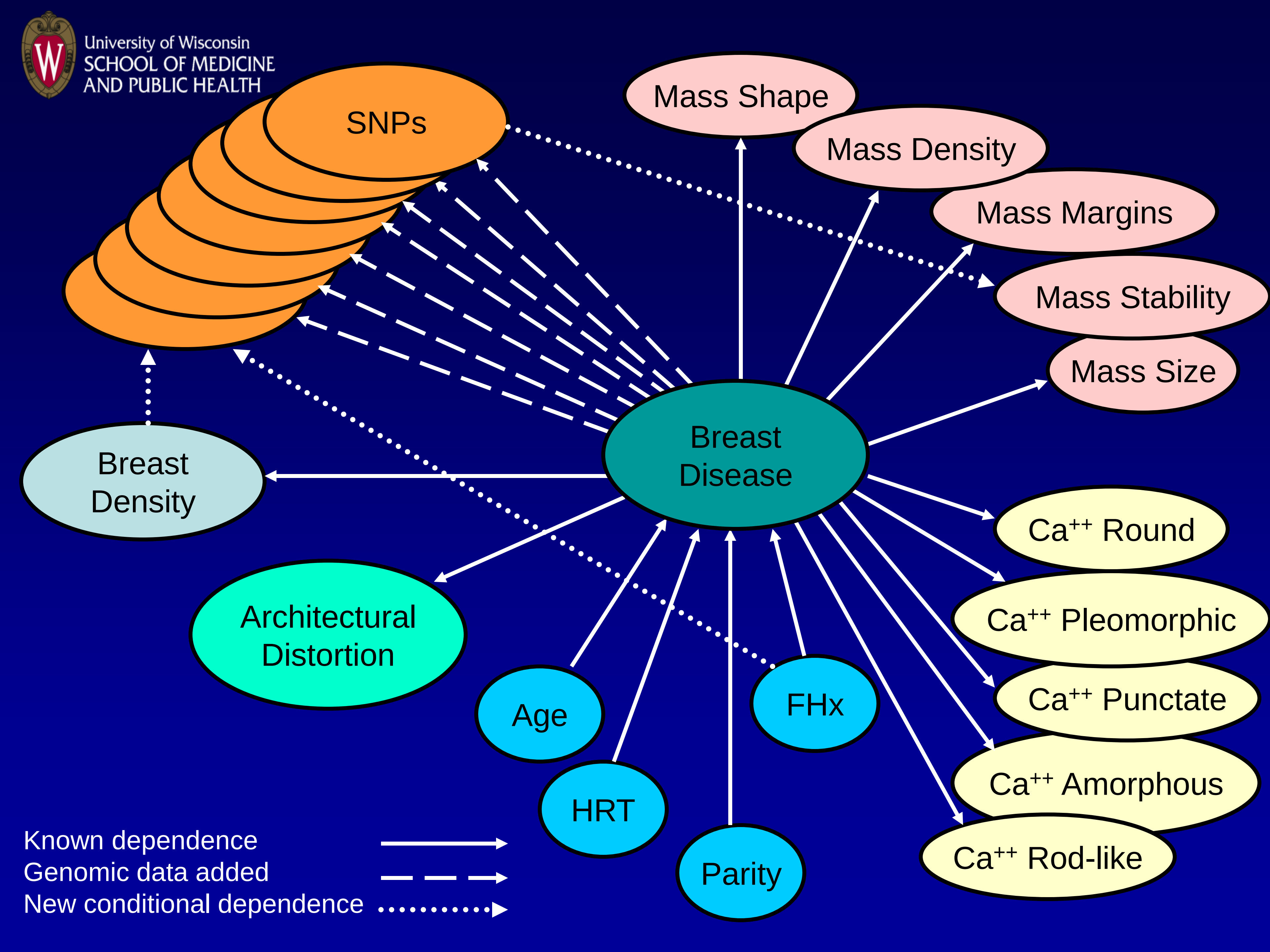


Specific Aim 2: Data Mining

Analyze conditional dependence relationships

To discover novel hypotheses

- Study design
  - Identify conditional dependence relationships from structure of trained BN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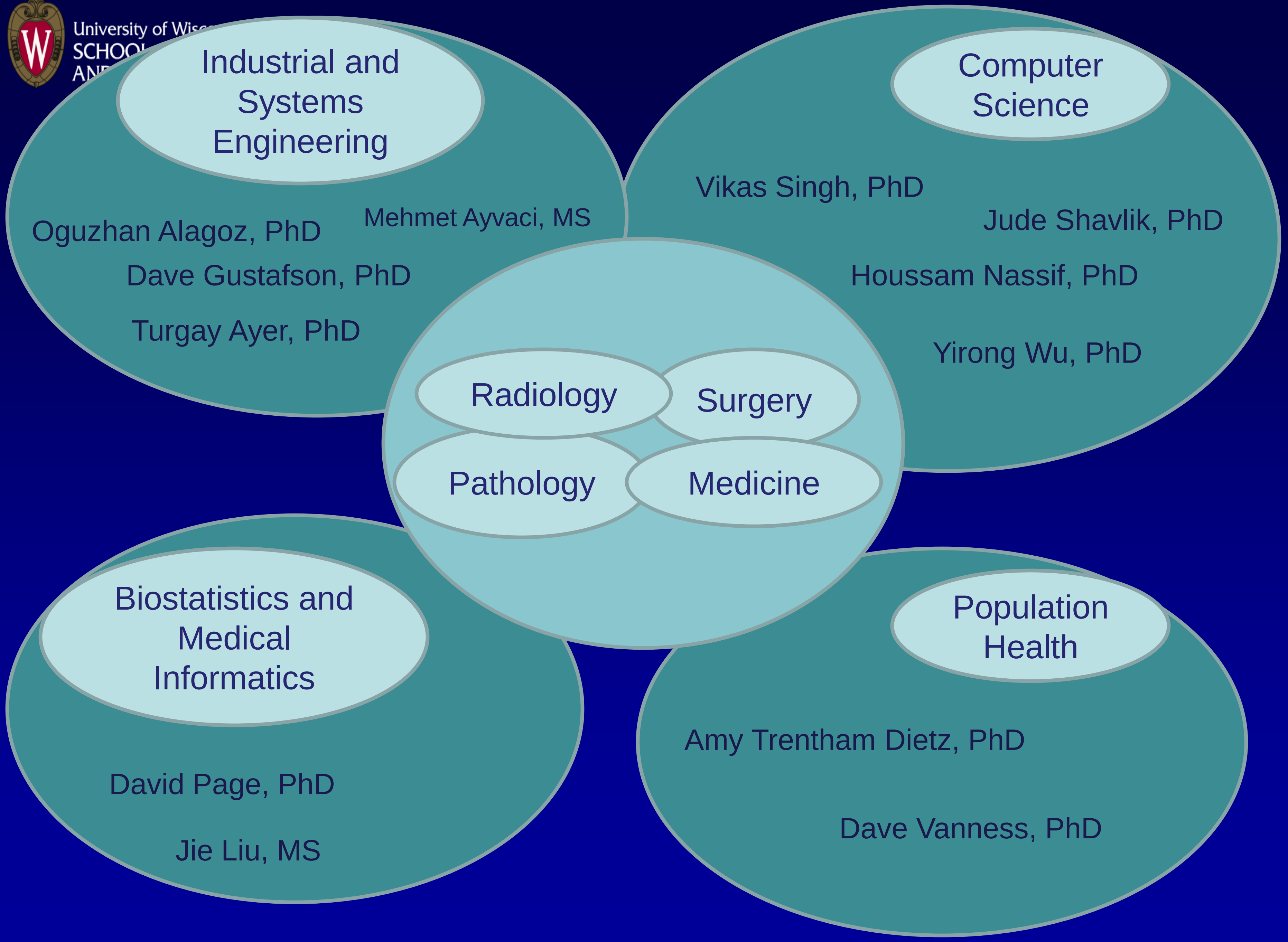
SNPs
Mass Shape
Mass Density
Mass Margins
Mass Stability
Mass Size
Breast Density
Breast Disease
Architectural Distortion
Age
HRT
Parity
FHx
Ca++ Round
Ca++ Pleomorphic
Ca++ Punctate
Ca++ Amorphous
Ca++ Rod-like
Known dependence
Genomic data added
New conditional dependence


Industrial and Systems Engineering
Oguzhan Alagoz, PhD
Mehmet Ayvaci, MS
Dave Gustafson, PhD
Turgay Ayer, PhD
Computer Science
Vikas Singh, PhD
Jude Shavlik, PhD
Houssam Nassif, PhD
Yirong Wu, PhD
Radiology
Surgery
Pathology
Medicine
Biostatistics and Medical Informatics
David Page, PhD
Jie Liu, MS
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