Genetic Variants Improve Breast Cancer Risk Prediction on Mammograms

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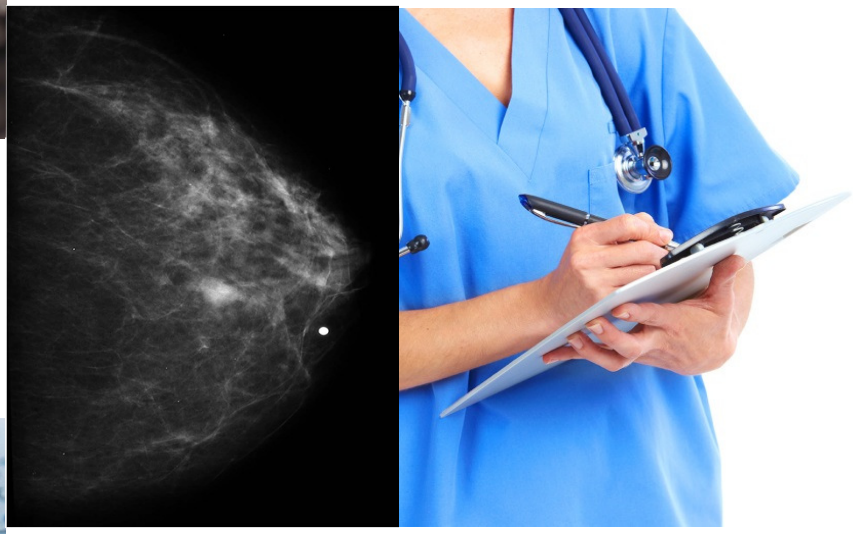
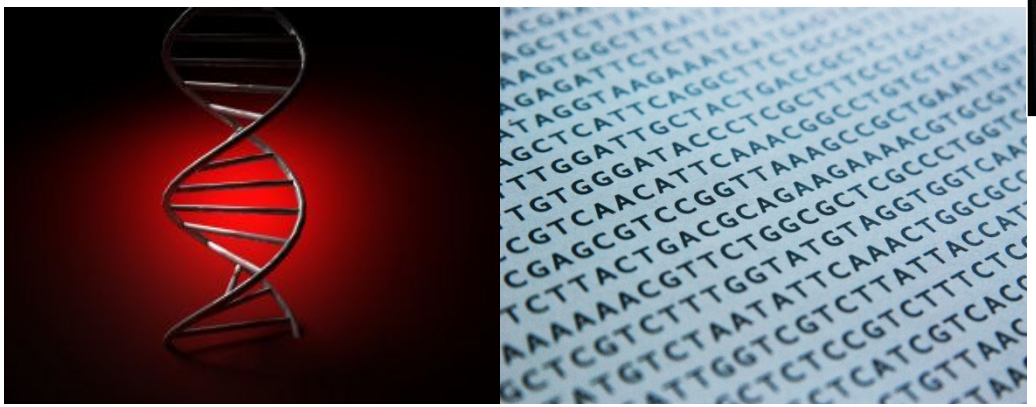
Personalized Medicine

EHR and informatics tools



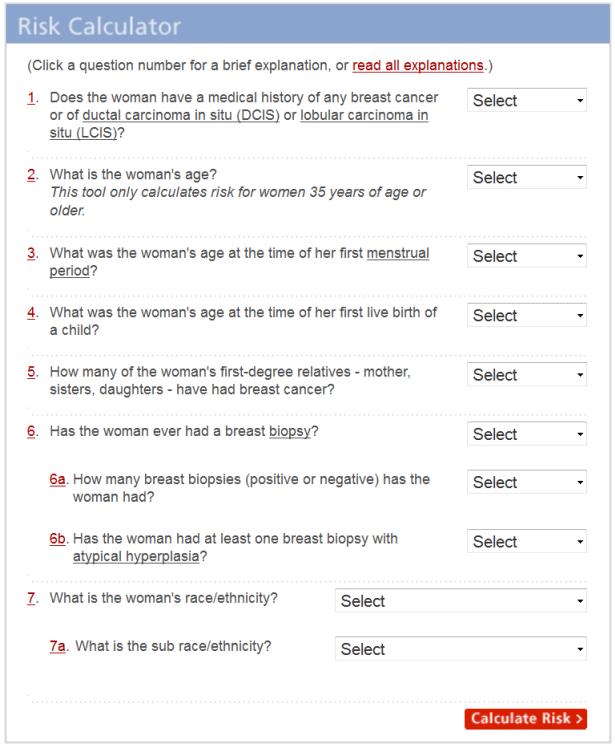
Individualized risk



Discoveries in genetics

Related Work

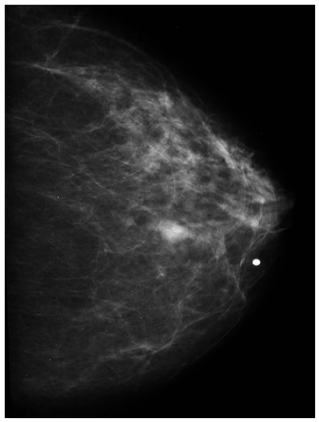
- Gail Model (http://www.cancer.gov/bcrisktool/)

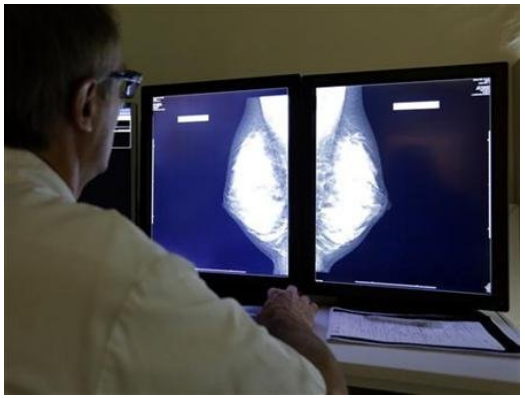


- 7 SNPs + Gail model: AUC-ROC 0.607 → 0.632
  - **Gail, M.H**., *Value of adding single-nucleotide polymorphism genotypes to a breast cancer risk model.* J Natl Cancer Inst, 2009. **101**(13): p. 959-63.
- 10 SNPs + Gail model: AUC-ROC 0.580 → 0.618
  - **Wacholder, S., et al**., *Performance of common genetic variants in breast-cancer risk models.* N Engl J Med, 2010. **362**(11): p. 986-93.

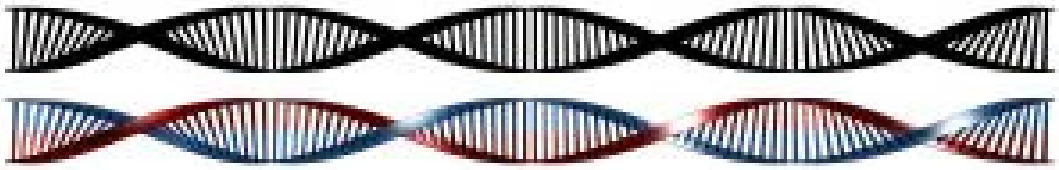
Assess 10-year or lifetime risk of breast cancer

Combine SNPs with Mammograms





Breast cancer diagnosis



Assess breast cancer risk at mammogram

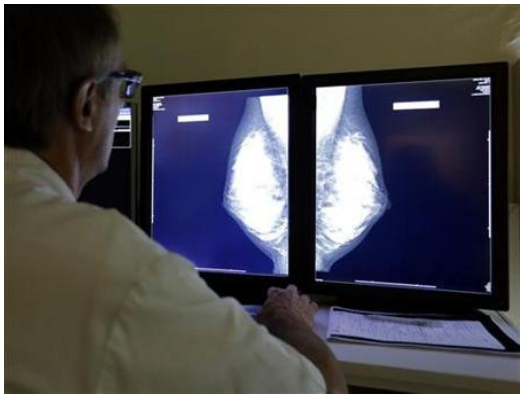
Subjects

- From PMRP at Marshfield Clinic
- Cases: a confirmed diagnosis of breast cancer obtained from the institutional cancer registry
- Controls: absence from the cancer registry and no breast cancer diagnosis in EHR
- Age matching
- Include both invasive breast cancer and DCIS
- Sample size: 404 cases / 399 controls

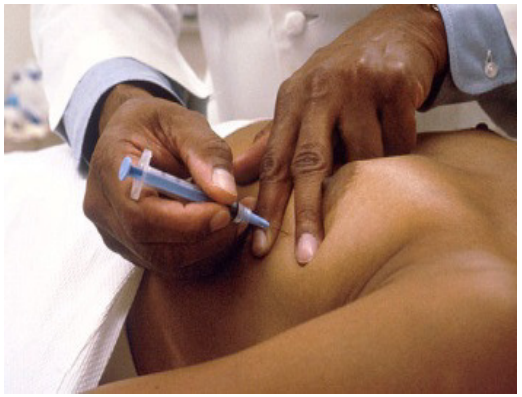
Inclusion Criterion

plasma

mammogram



biopsy



Within 12 months

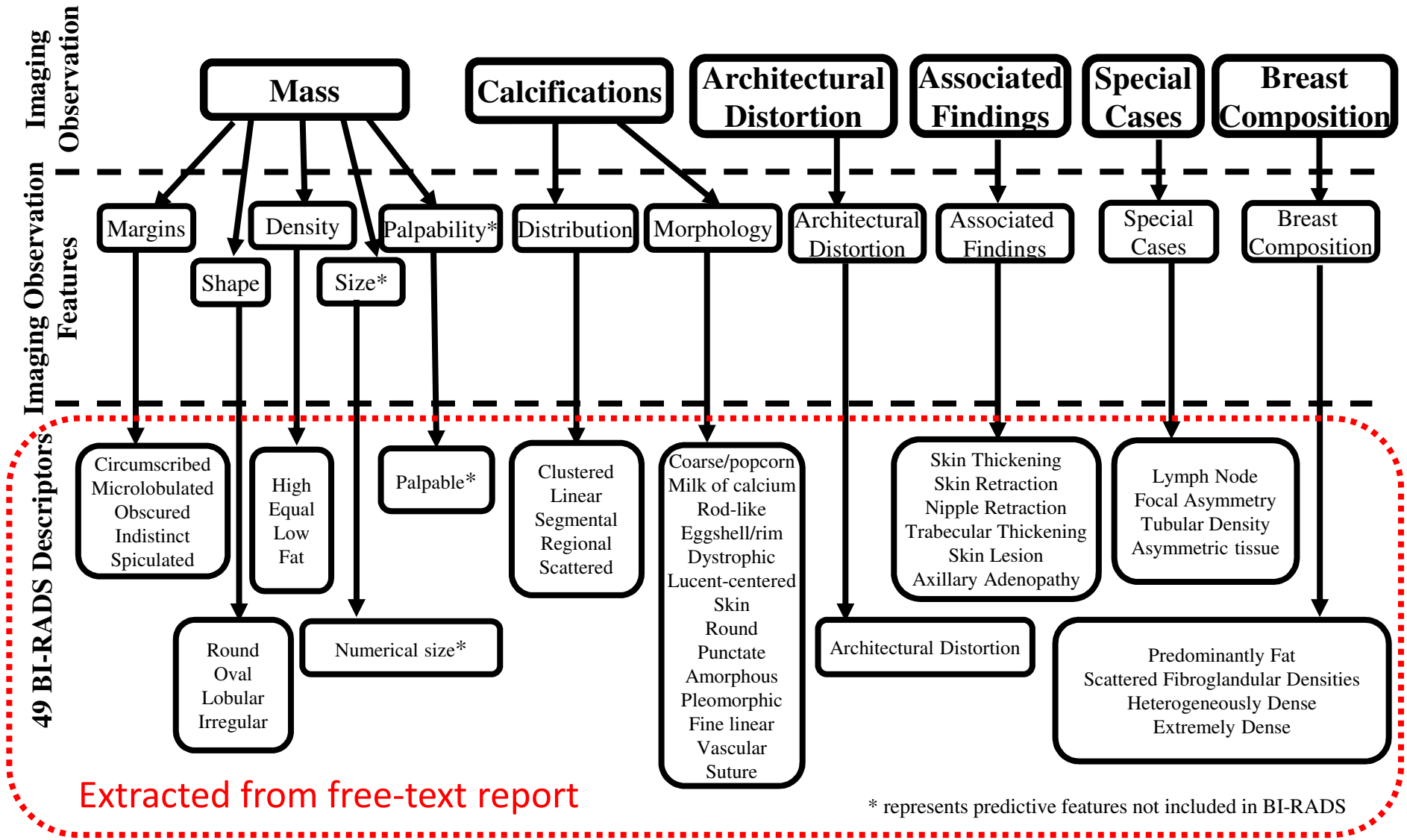
Controls are false positives!

Can genetics help eliminate false positives?

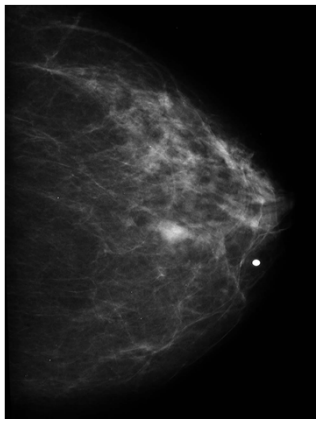
Genetic Variants

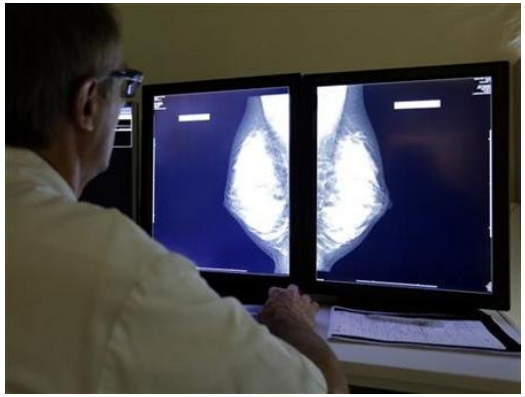
SNPs	Chr	Minor Allele	Source	In Gail (2009)	In Wacholder et al (2010)
rs11249433	1	C	Thomas et al. 2009		×
rs4666451	2	A	Easton et al. 2007		
rs13387042	2	G	Stacey et al. 2007,Thomas et al. 2009	×	×
rs1045485	2	C	Cox et al. 2007	×	×
rs17468277	2	T	Odefrey et al. 2010		
rs4973768	3	T	Ahmed et al. 2009		
rs10941679	5	G	Stacey et al. 2008, Thomas et al. 2009		×
rs981782	5	G	Easton et al. 2007		
rs30099	5	T	Easton et al. 2007		
rs889312	5	C	Easton et al. 2007	×	×
rs2180341	6	G	Gold et al. 2008		
rs2046210	6	T	Zheng et al. 2009		
rs13281615	8	G	Easton et al. 2007	×	×
rs2981582	10	T	Easton et al. 2007, Hunter et al. 2007	×	×
rs3817198	11	C	Easton et al. 2007, Thomas et al. 2009	×	×
rs2107425	11	T	Easton et al. 2007		
rs6220	12	G	Kelemen et al. 2008, Biong et al. 2010		
rs999737	14	T	Thomas et al. 2009		×
rs3803662	16	T	Easton et al. 2007, Stacey et al. 2007	×	×
rs8051542	16	T	Easton et al. 2007		
rs12443621	16	G	Easton et al. 2007		
rs6504950	17	A	Ahmed et al. 2009		

Mammogram Features



BI-RADS Category

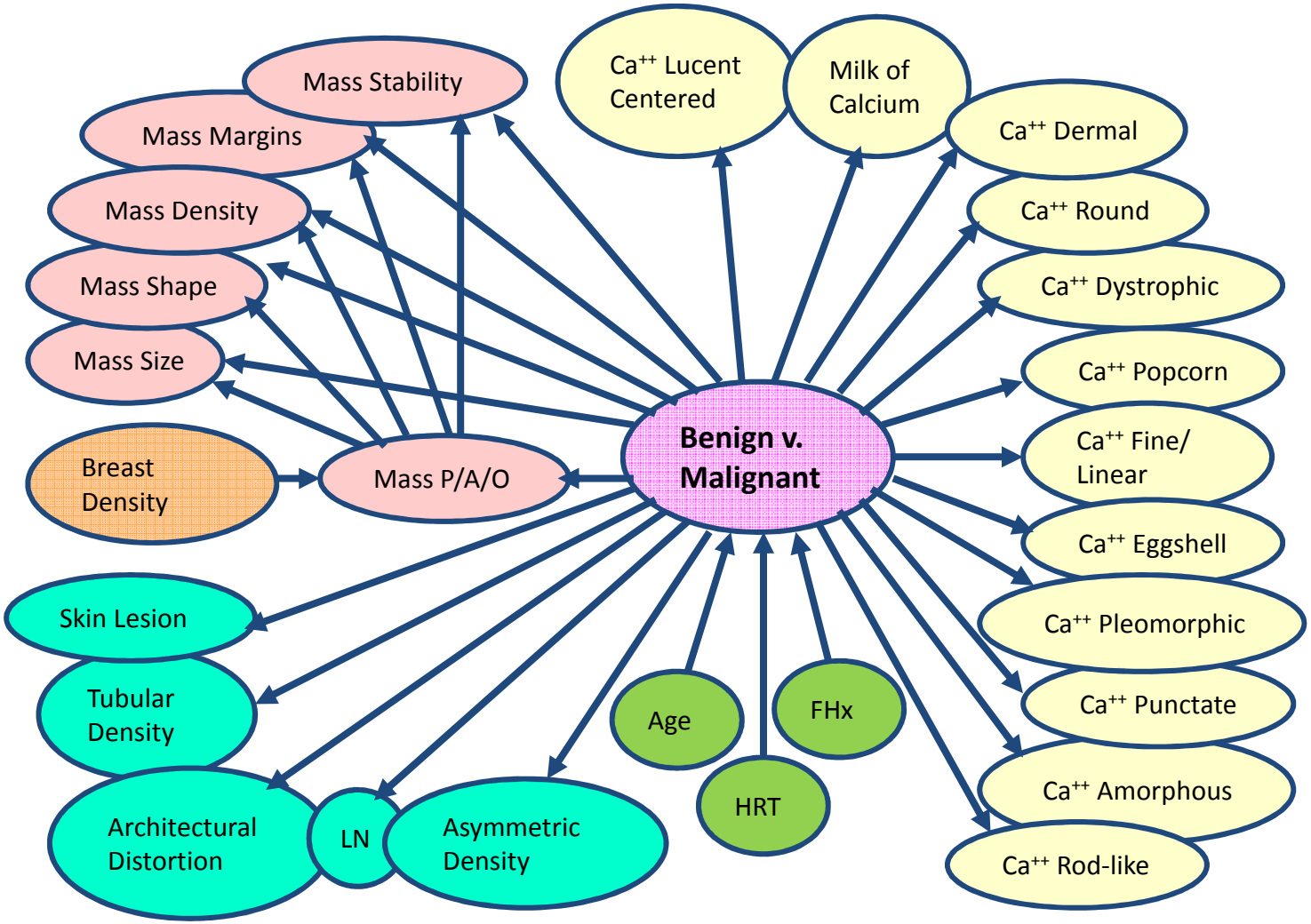




1	negative
2	benign findings
3	probably benign
0	incomplete
4	suspicious abnormality
5	highly suspicious of malignancy

Baseline clinical assessment

Bayesian Network

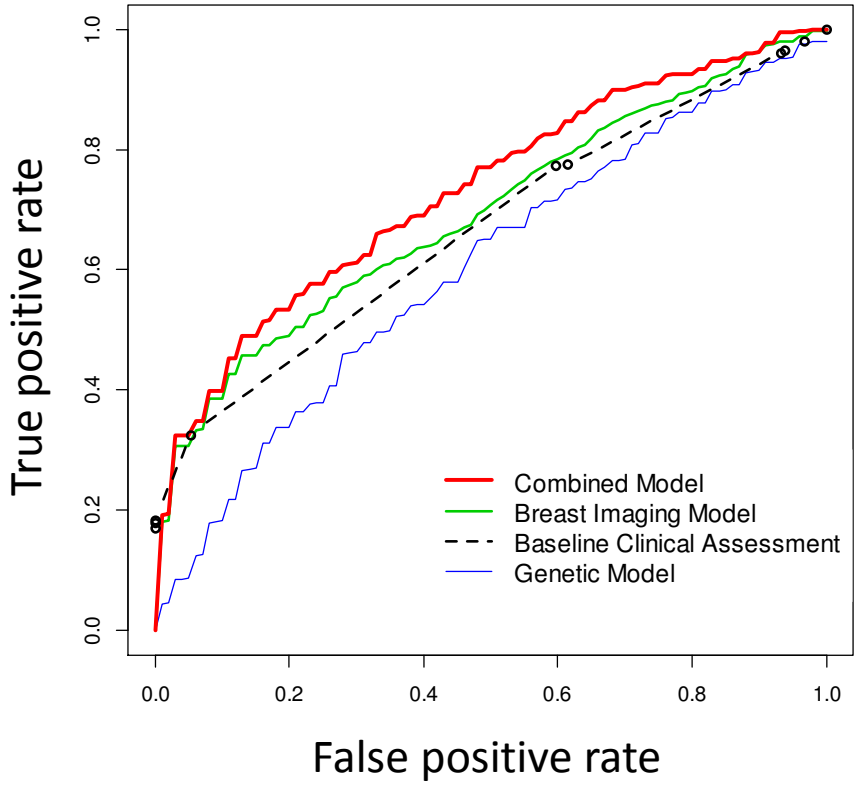


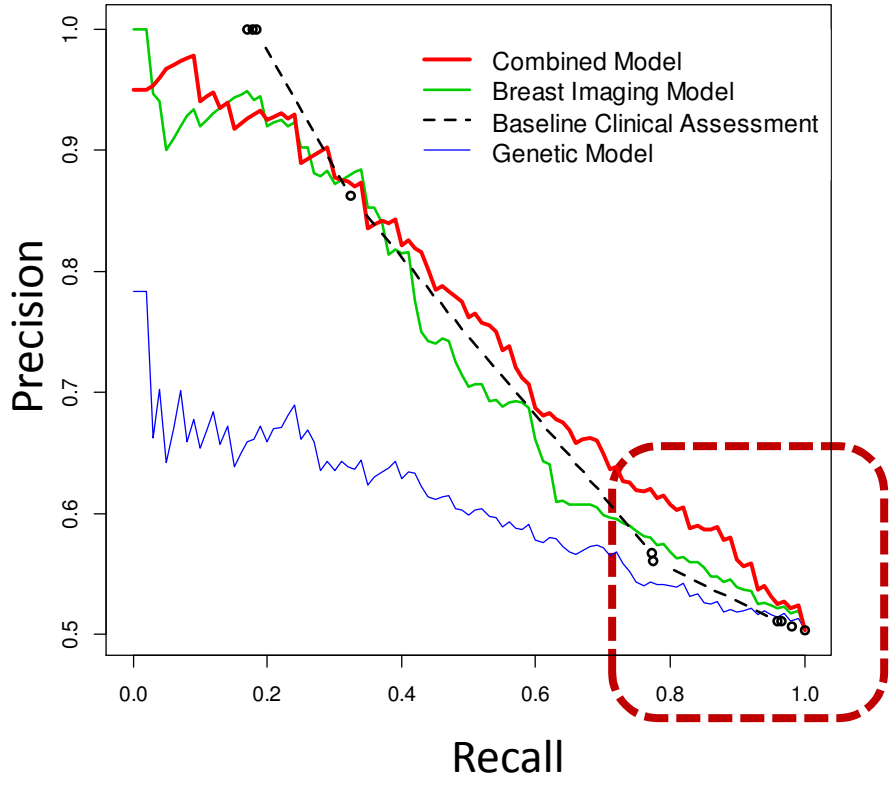
Elizabeth S. Burnside. Bayesian networks : Computer-assisted diagnosis support in radiology. *Academic Radiology*, Volume 12, Issue 4, April 2005, Pages 422–430.

Models

- **TAN (tree augmented naive Bayes)**
  - **Genetic model**: use the 22 SNPs only
  - **Breast imaging model**: use the 49 imaging features
  - **Combined model**: use both SNPs and imaging features
- **Baseline clinical assessment**: use the BI-RADS scores from radiologists
- **ROC, PR (precision-recall) analysis**
- **10-fold cross validation**

ROC and PR Curves





AUC-ROC: 0.693 (breast imaging model)
→ 0.731 (combined model) (P=0.02)

Significant improvement in high recall region (recall > 0.8)

Interaction

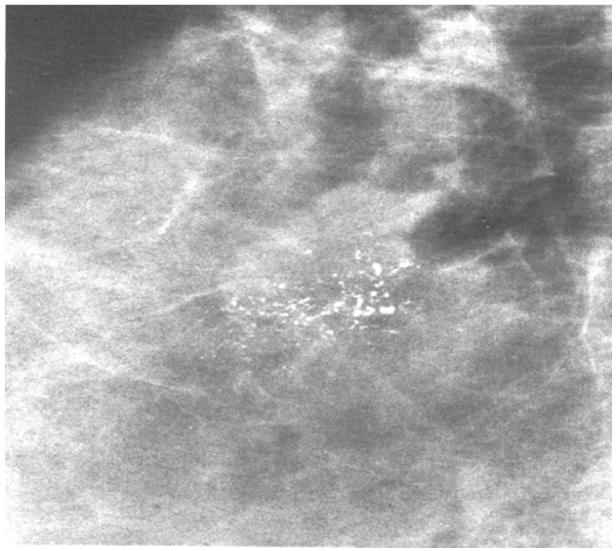
SNP-Name	Associated Gene	BI-RADS Feature with Highest CMI	CMI 95% C.I.
rs1045485	CASP8	calcification shape: pleomorphic	0.0141 (0.006,0.030)
rs17468277	CASP8	calcification shape: pleomorphic	0.0141 (0.005,0.032)
rs2180341	RNF146	calcification shape: dystrophic	0.0115 (0.006,0.021)
rs2981582	FGFR2	calcification distribution: diffuse	0.0112 (0.006,0.021)
rs4666451		mass shape: oval	0.0100 (0.004,0.017)
rs11249433		special case: focal asymmetry	0.0095 (0.003,0.024)
rs12443621	TNRC9/TOX3	calcification shape: dystrophic	0.0091 (0.004,0.020)
rs13281615		calcification shape: dystrophic	0.0087 (0.002,0.023)
rs3803662	TNRC9/TOX3	calcification distribution: linear	0.0086 (0.002,0.024)
rs2107425	H19	mass shape: round	0.0080 (0.003,0.017)
rs889312	MAP3K1	breast composition: extreme	0.0078 (0.001,0.019)
rs981782	HCN1/MRPS30	breast composition: fat	0.0076 (0.004,0.015)
rs8051542	TNRC9/TOX3	calcification distribution: linear	0.0076 (0.002,0.021)
rs3817198	LSP1	calcification shape: punctate	0.0075 (0.002,0.022)
rs13387042		breast composition: extreme	0.0069 (0.003,0.011)
rs999737	RAD51L1	calcification distribution: linear	0.0069 (0.001,0.021)
rs30099		calcification shape: amorphous	0.0063 (0.000,0.018)
rs4973768	SLC4A7	calcification shape: amorphous	0.0058 (0.003,0.010)
rs6504950	STXBP4	mass shape: lobular	0.0058 (0.001,0.019)
rs2046210	C6orf97	associated finding: architectural distortion	0.0053 (0.001,0.018)
rs6220	IGF-1	calcification shape: amorphous	0.0050 (0.001,0.014)
rs10941679	HCN1/MRPS30	mass shape: oval	0.0048 (0.000,0.014)

CASP8 and Pleomorphic Calcification Shape

GWAS OR = 0.88

Our OR = 0.86

CASP8 has decreased risk of ductal tumors
(MacPherson et al. 2004, Frank et al. 2005)



pleomorphic calcification shape

	# minor allele
60 cases	3
70 controls	13

Conclusion

- The first exploration of combining genetic variants and mammography features
- Statistically significant improvement
- Limitations
  - Small sample size
  - Extraction of mammography features
- Ongoing work
  - More SNPs from COGS (Michailidou et al. 2013)

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