Wellend Health

Medical curiosity and its role in breast cancer prevention

Dr Stephen Birrell
Dr Tonia Mezzini

AUGUST 2017

Curiosity has been integral to the advancement of medicine. **Curiosity** has saved lives.

‘Curiosity is the hallmark of scholarship and science, but it is also the hallmark of service. Curiosity is not confined to the research laboratory; it is obligatory at the bedside as well. Only by being curious as to the basic mechanisms, with a genuine regard for who is ill, how did they become so, and why this disorder, or that sign or symptom, can one become and remain a competent physician.’

George A Perera, Journal of Medical Education, 1963

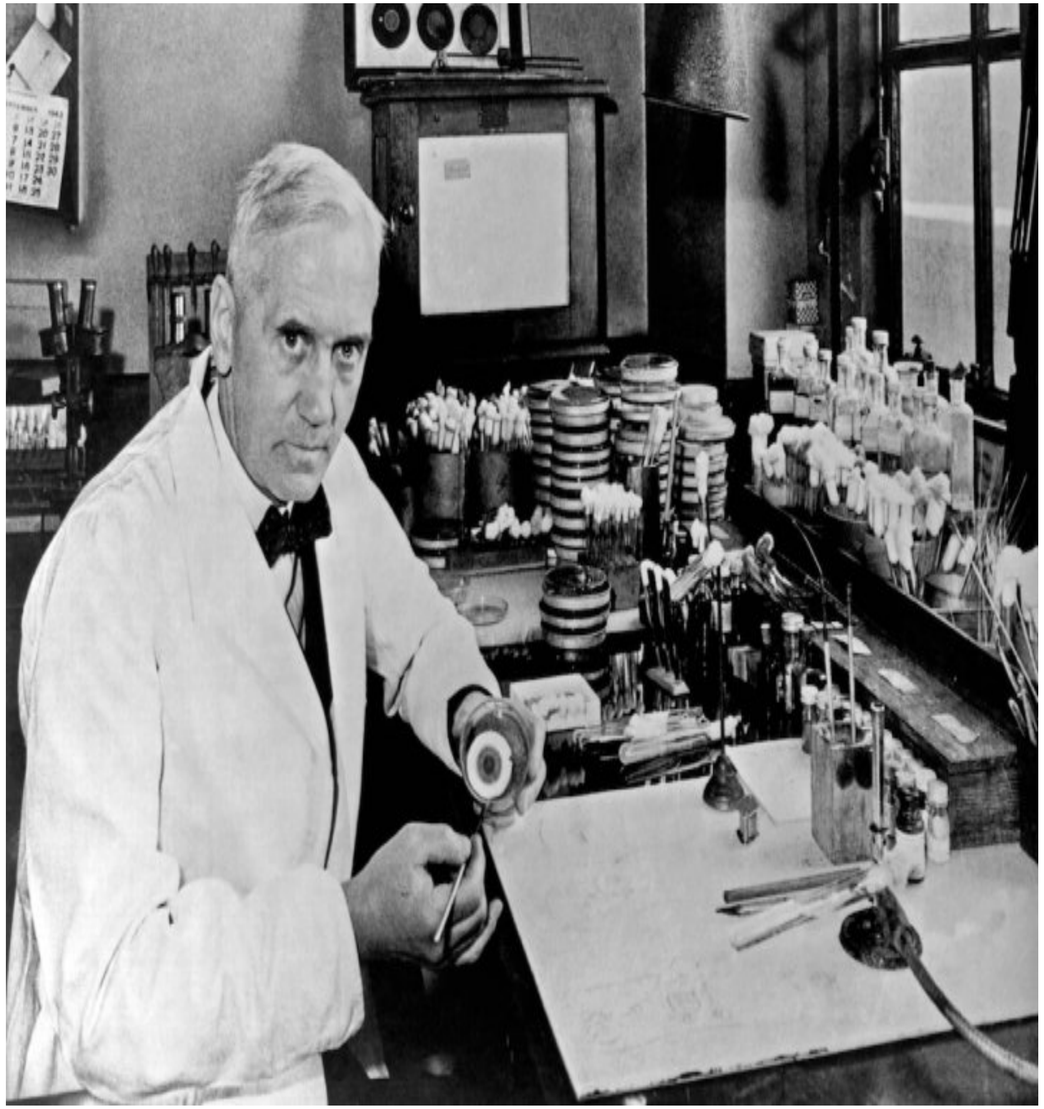
Blood transfusions: the first successful blood transfusion was performed in 1818, and the first blood bank established in 1932 in Leningrad.

Countless lives have been saved since.

Penicillin: discovered by Dr Alexander Fleming in 1928, and developed by Dr Howard Florey.

14 years later, in 1942, it was used to successfully prevent the death of woman with overwhelming systemic infection after a miscarriage.

Countless lives have been saved since.



Triple therapy antiretrovirals: for the treatment of HIV became available in 1996.

Saving the lives of those who took these drugs, and preventing onward transmission of the virus.

Countless lives have been saved since.

None of these life-saving medical interventions would have occurred had it not been for **curiosity**.

Had we not wanted to be better doctors.

In the world of breast cancer medicine, there are have been 4 major developments.

All driven by **curiosity**.

Number 1

Breast cancer has come to be regarded as a systemic disease; not just something you ‘cut out’.

Number 1: Chemotherapy

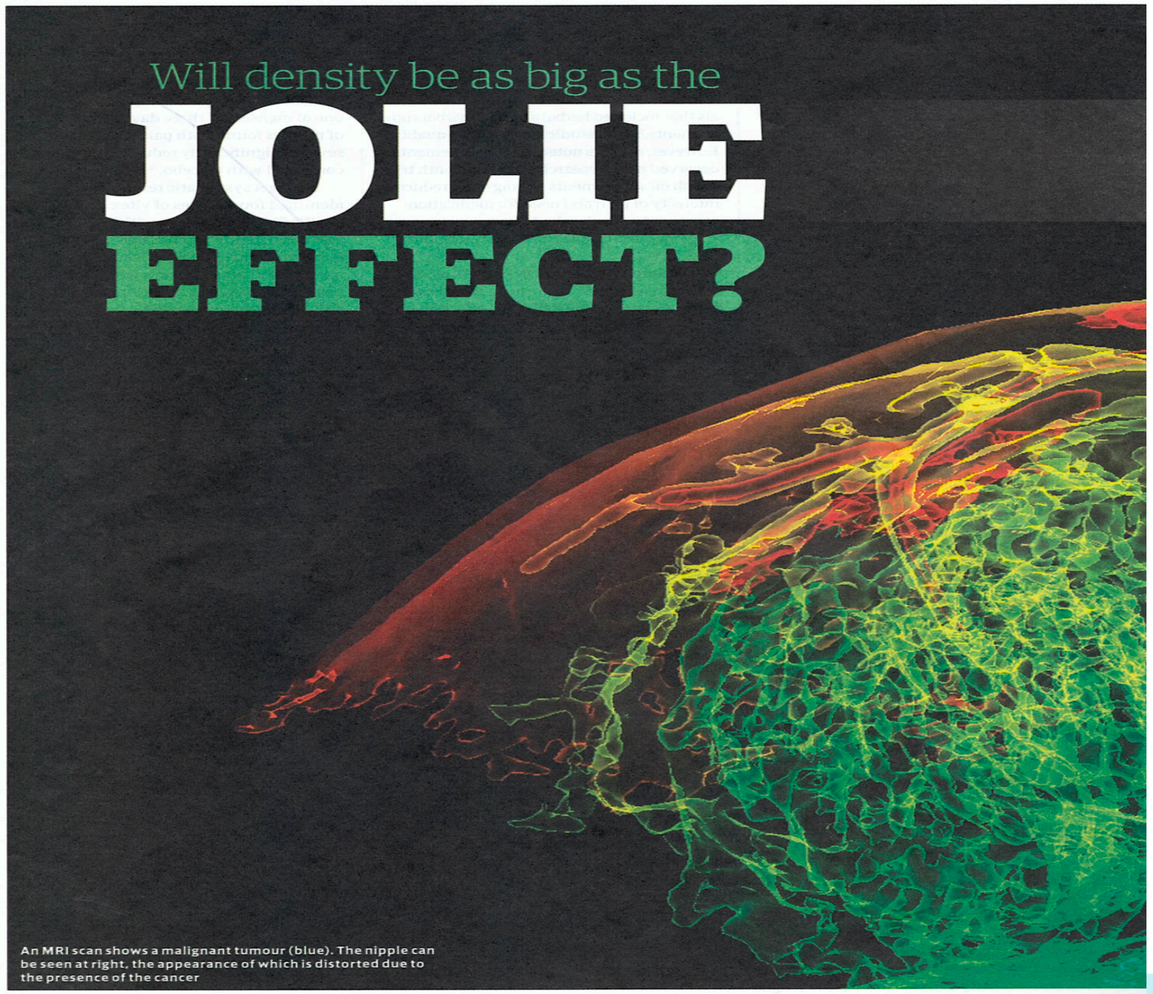
But, in the 1960's those researching chemotherapeutic options were regarded as working from the 'lunatic fringe'.

By the 1970's 'adjuvant chemotherapy' after surgery and radiotherapy to prevent death from metastatic disease offered the hope of cure and America launched its 'war on cancer' with funding for cancer research increasing from $9 million dollars in 1972, to $119 million dollars by 1980.

Number 2: Screening

Will density be as big as the

JOLIE EFFECT?



An MRI scan shows a malignant tumour (blue). The nipple can be seen at right, the appearance of which is distorted due to the presence of the cancer

Number 3: Herceptin

The next big leap came from the observation that breast cancer cells containing abnormally high levels of a protein called HER2 are more likely to spread to other organs in the body.

The lead to the development of **Herceptin**, a drug that has improved survival rates for women with stage 1 to 3 breast cancers by 30%.

Number 4: Prevention – Lifestyle options

- minimal use of additional hormones in the form of the OCP, HRT
- have lots babies - while you are young and breast feed them all,
- don’t smoke,
- don’t drink more than 2 standard drinks per day and have at least two alcohol free drinks per week,
- exercise for at least 30 minutes per day, and
- eat a diet low in fat.

Easy? Well, some more than others…

Back to Number 2: Screening – the future

What other options are there for women?

Improve the screening program by offering breast density information to help identify women who may be at high risk of developing breast cancer.

Cervical screening in 2017/8

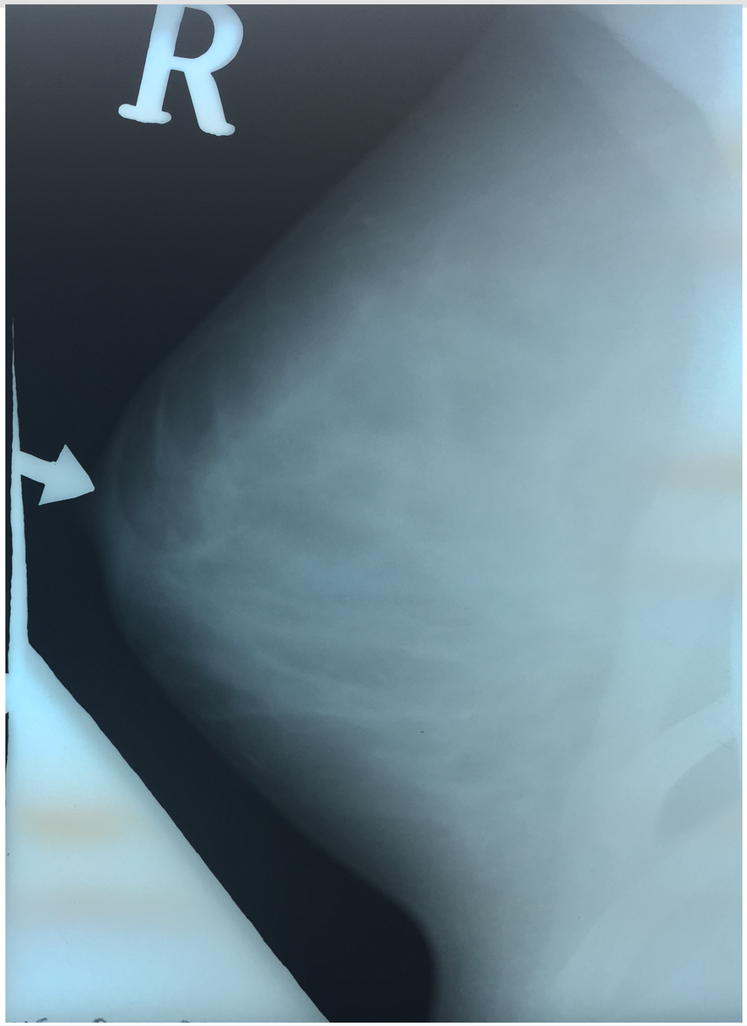
HPV is the new Pap

Density is the new
Black

Evolution of Mammography

Analogue

1975



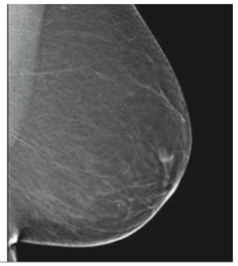
Digital

2015

Bi-Rads

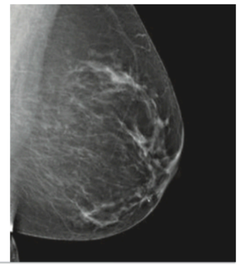
LOWEST DENSITY

Normal Mammograms



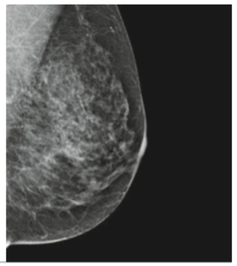
A

The breast is almost all fatty tissue with very little dense tissue.



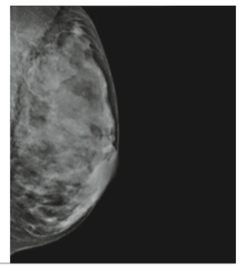
B

The breast contains scattered areas of dense glandular and fibrous tissue.



C

More of the breast is made of dense glandular and fibrous tissue. This can make it hard to see small tumors in or around the dense tissue.



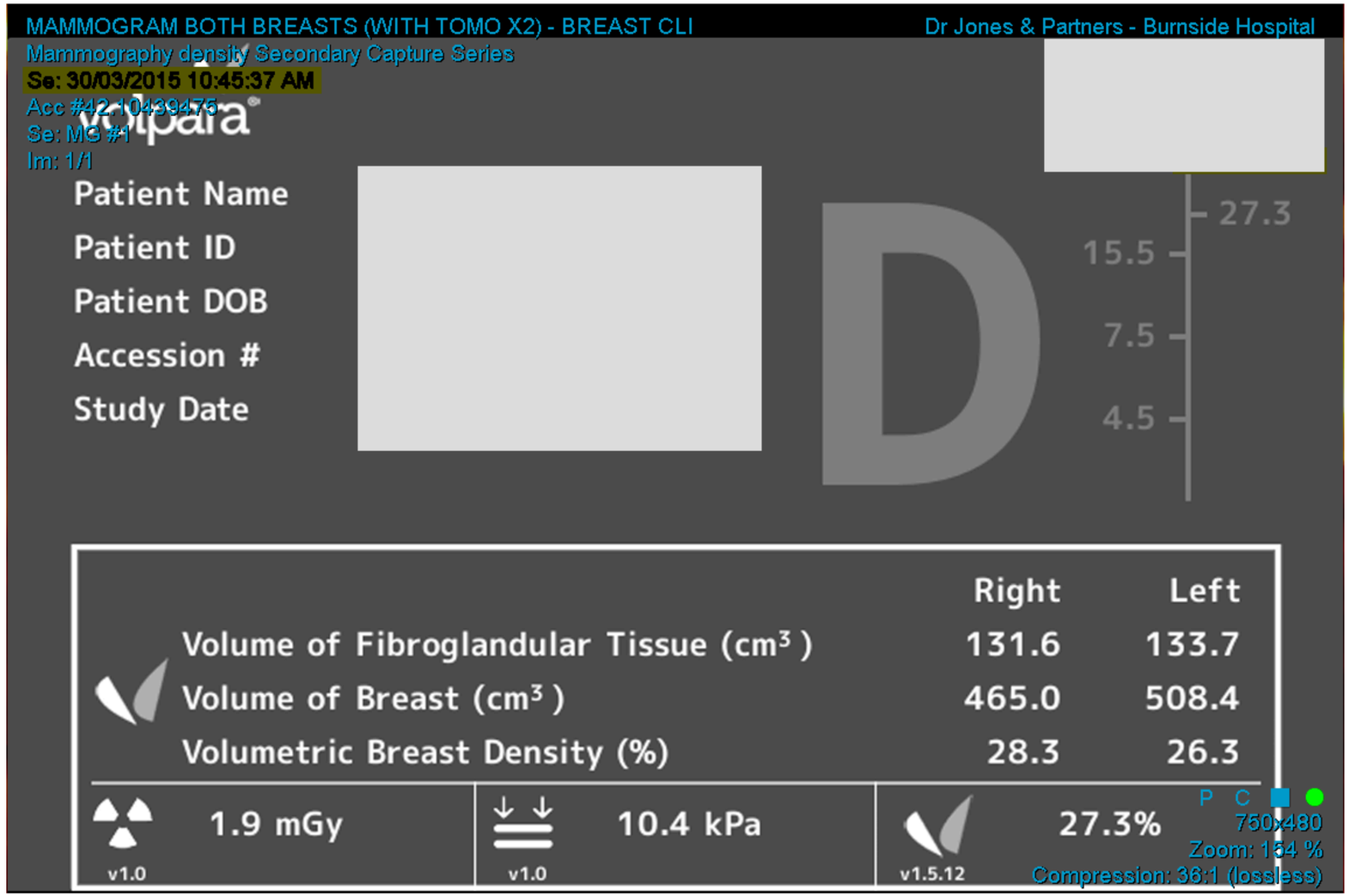
D

The breast is extremely dense, which makes it hard to see tumors in the tissue.

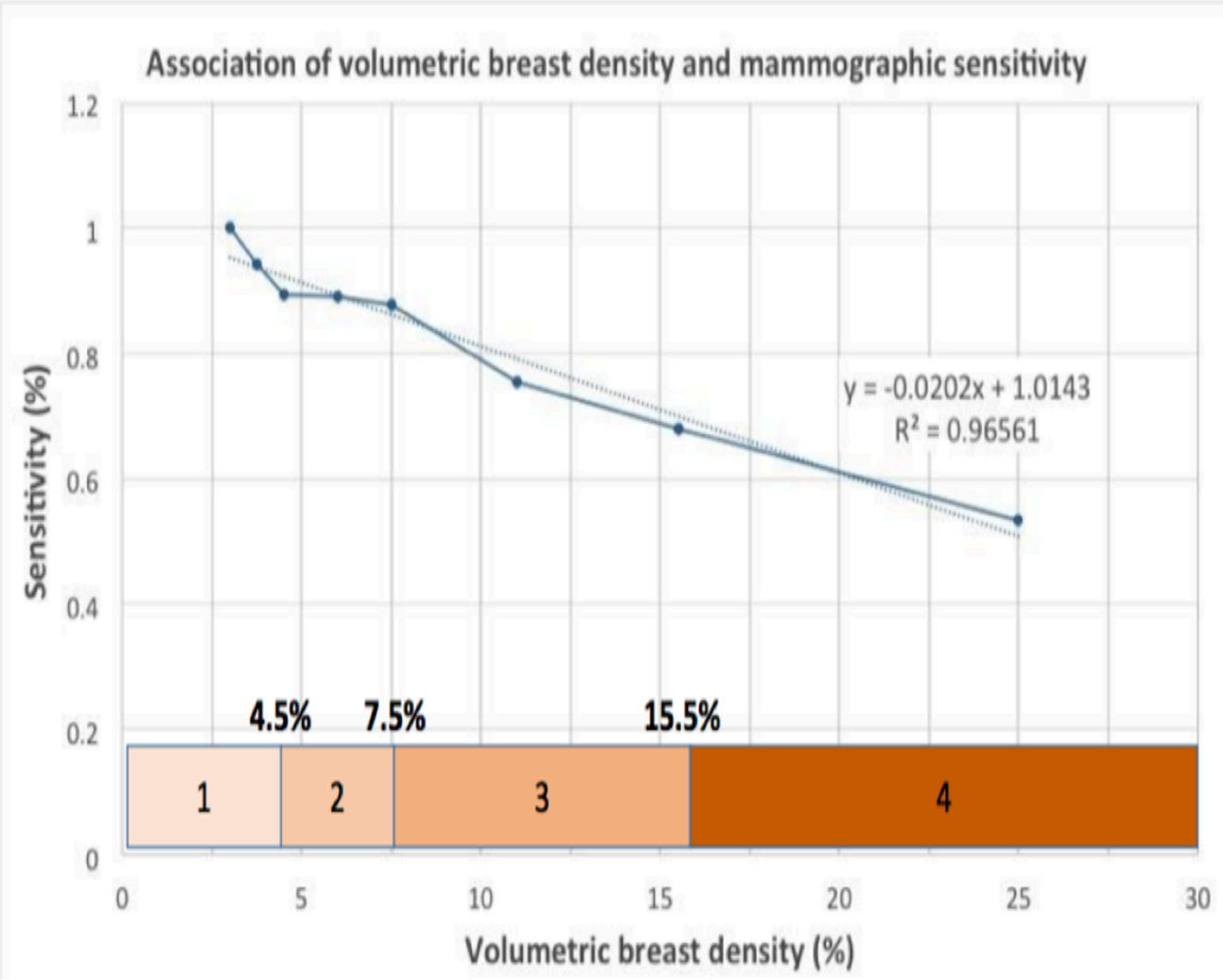
Images and information from American Cancer Society www.cancer.org

HIGHEST DENSITY

Volpara® report



Destounis et al AJR Jan 2017

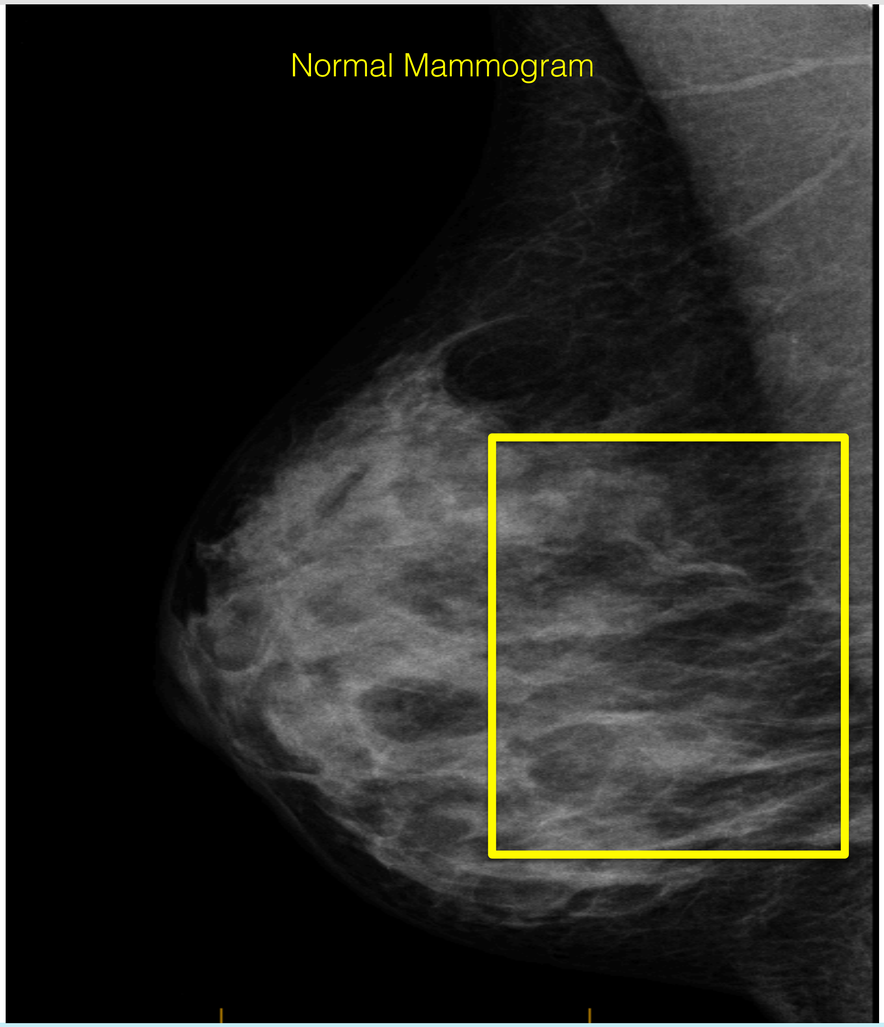


250,000 Norwegian women

In this study, breast density was the only risk factor significantly associated with a diagnosis of interval cancer versus screen-detected cancer.

Quantitative VBD captures the potential masking risk of breast density more precisely than does the widely used visual BI-RADS density classification system.

Decreased Sensitivity of Mammography



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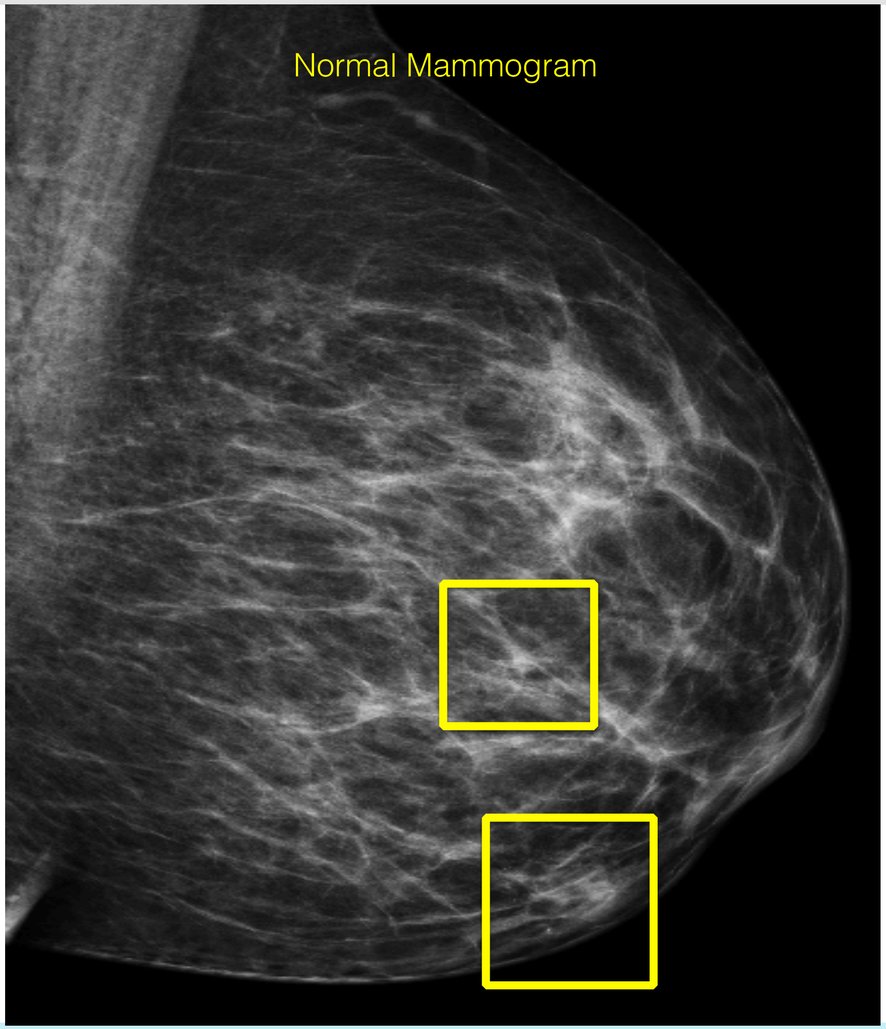

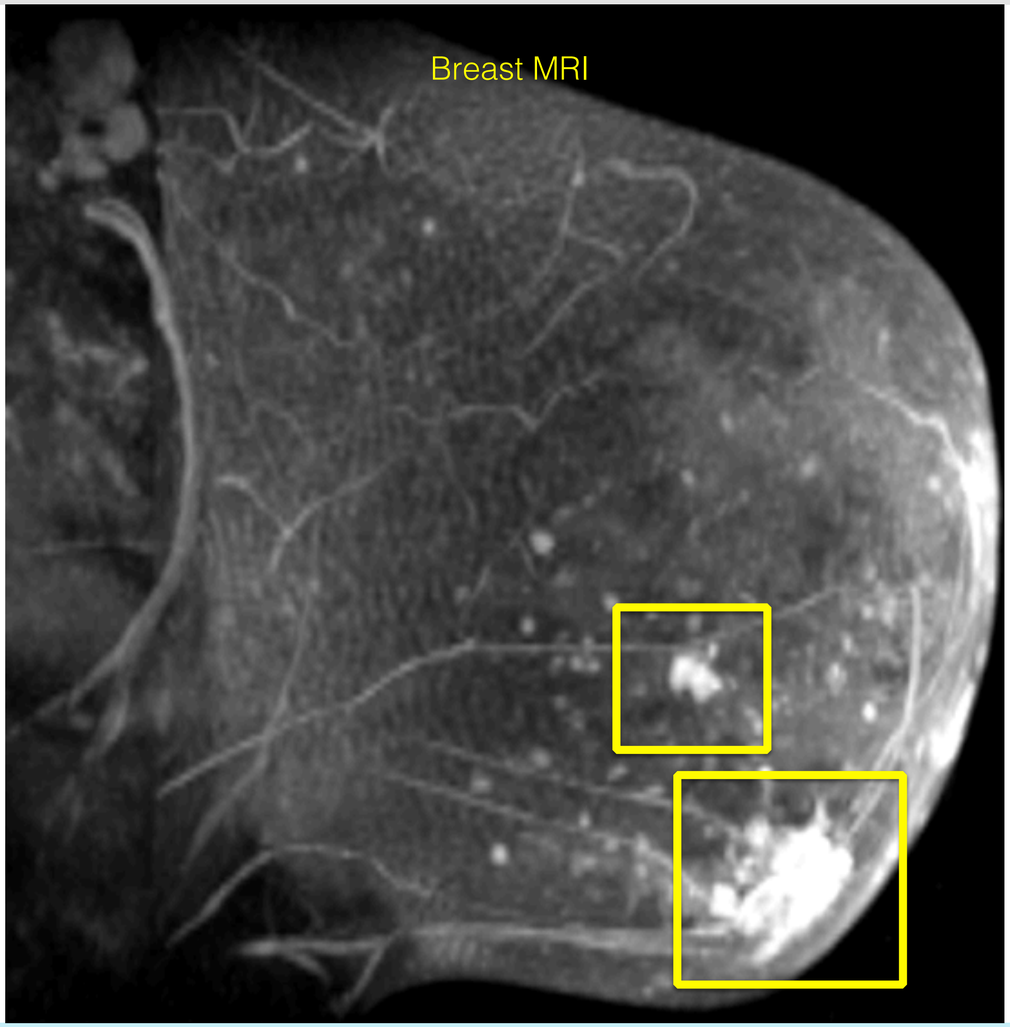

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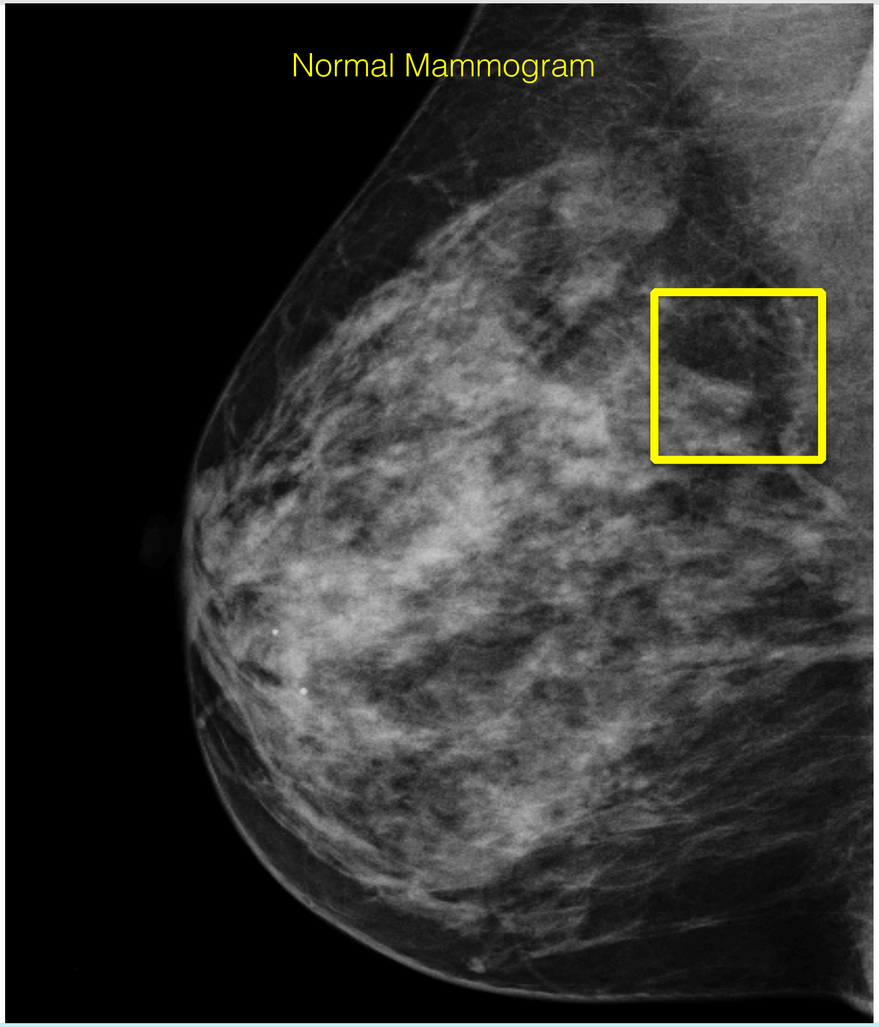

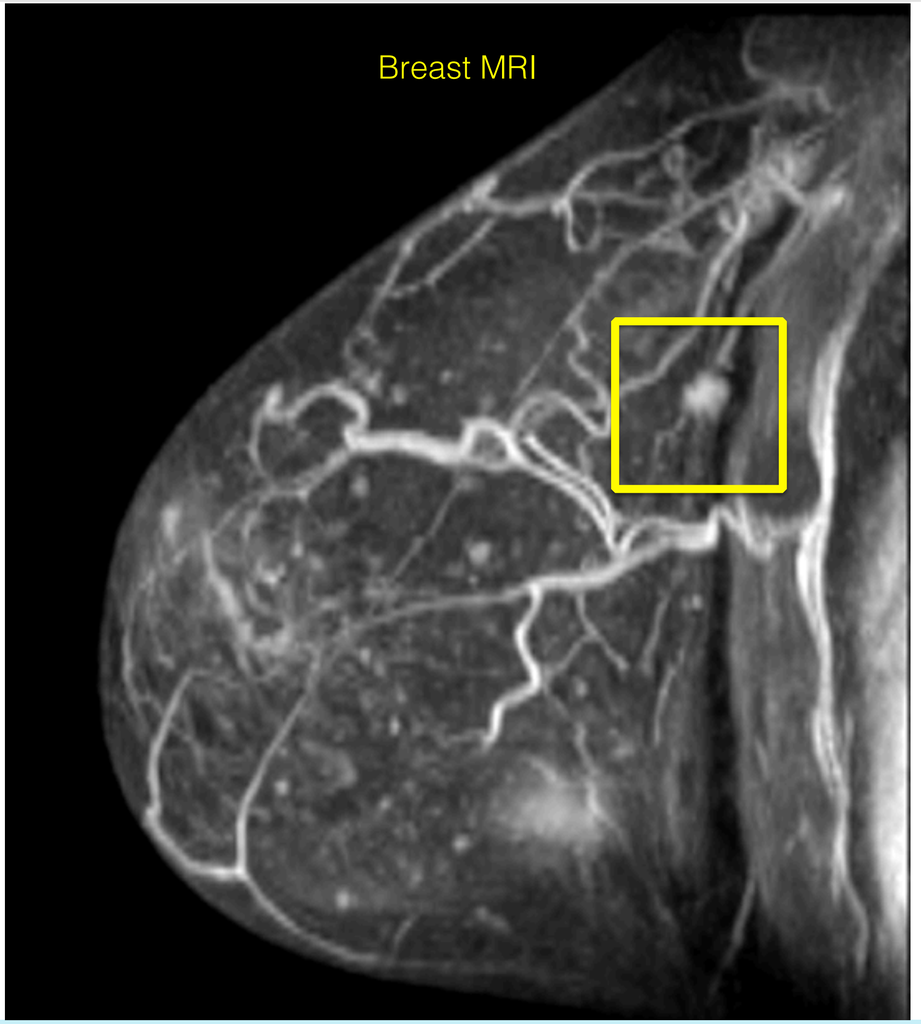

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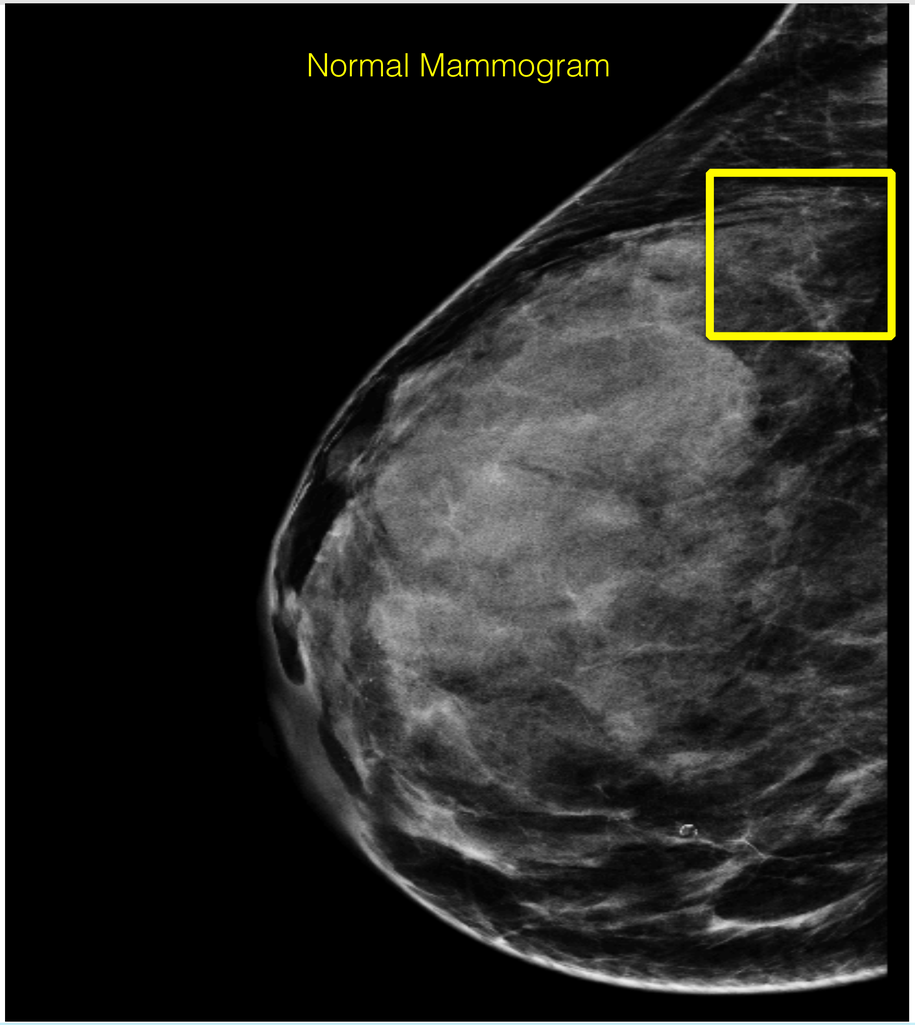
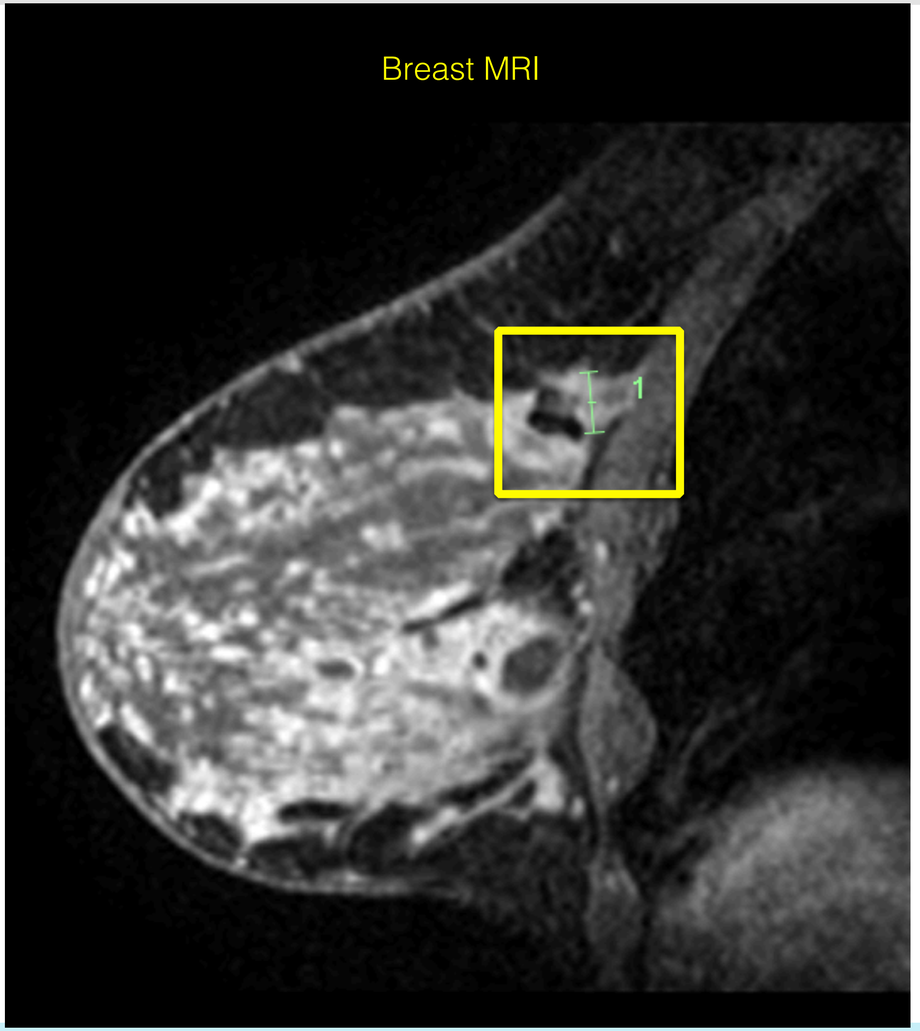




Radiology Providers and Mammographic Breast Density

DR JONES & PARTNERS MEDICAL IMAGING

BreastScreen AUSTRALIA

A joint Australian, State and Territory Government Program

www.informd.org.au

HMBD Increases Breast Cancer Risk

- the greater the density, the greater the risk

- dense tissue is stiff or inelastic, which is known to increase the risk of malignant transformation *(mechanotransduction)*

- cells in HMBD are frequently abnormal

Risk Factors for HMBD

Most (60%) of the risk for developing HMBD is inherited.

Other risk factors include:

1. Family history of breast cancer
2. Early (age 12-17) and/or prolonged use of OCP
3. IVF treatments, particularly if over the age of 35
4. HRT (MHT), particularly combination HRT (progestins)
5. First child after the age of 30
6. Nulliparous

Women's Health Initiative Re-examined
Byrne, et al JNCI March 2017

ARTICLE

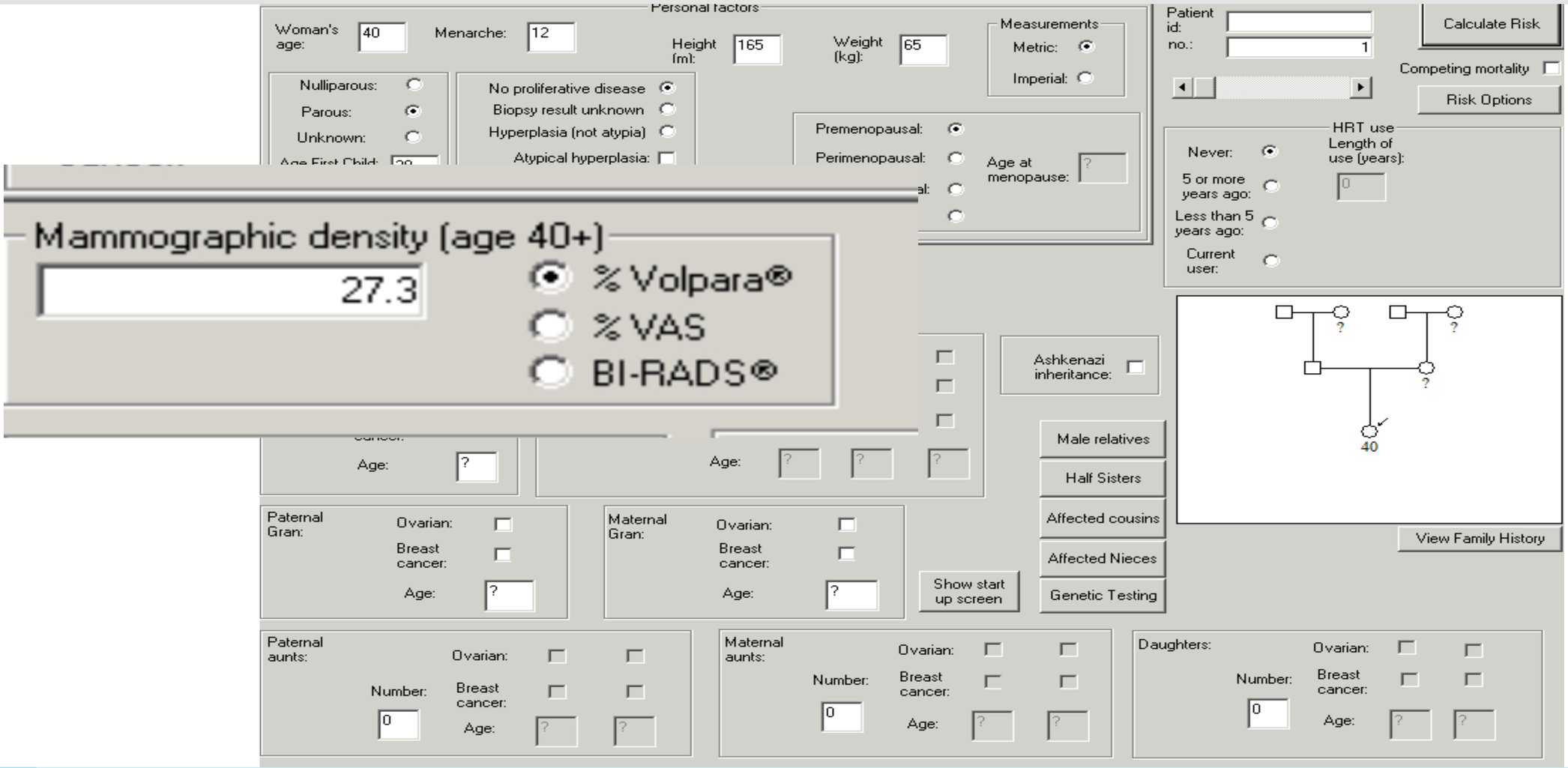
Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk

Celia Byrne, Giske Ursin, Christopher F. Martin, Jennifer D. Peck, Elodia B. Cole, Donglin Zeng, Eunhee Kim, Martin D. Yaffe, Norman F. Boyd, Gerardo Heiss, Anne McTiernan, Rowan T. Chlebowski, Dorothy S. Lane, JoAnn E. Manson, Jean Wactawski-Wende, Etta D. Pisano

- Every 1% increase in MBD = 3.4% increase in BCa risk
- Increase in MBD warrants cessation of HRT
- Significantly reduced detection of BCa
- Top 20th percentile 3.6 fold increase in risk

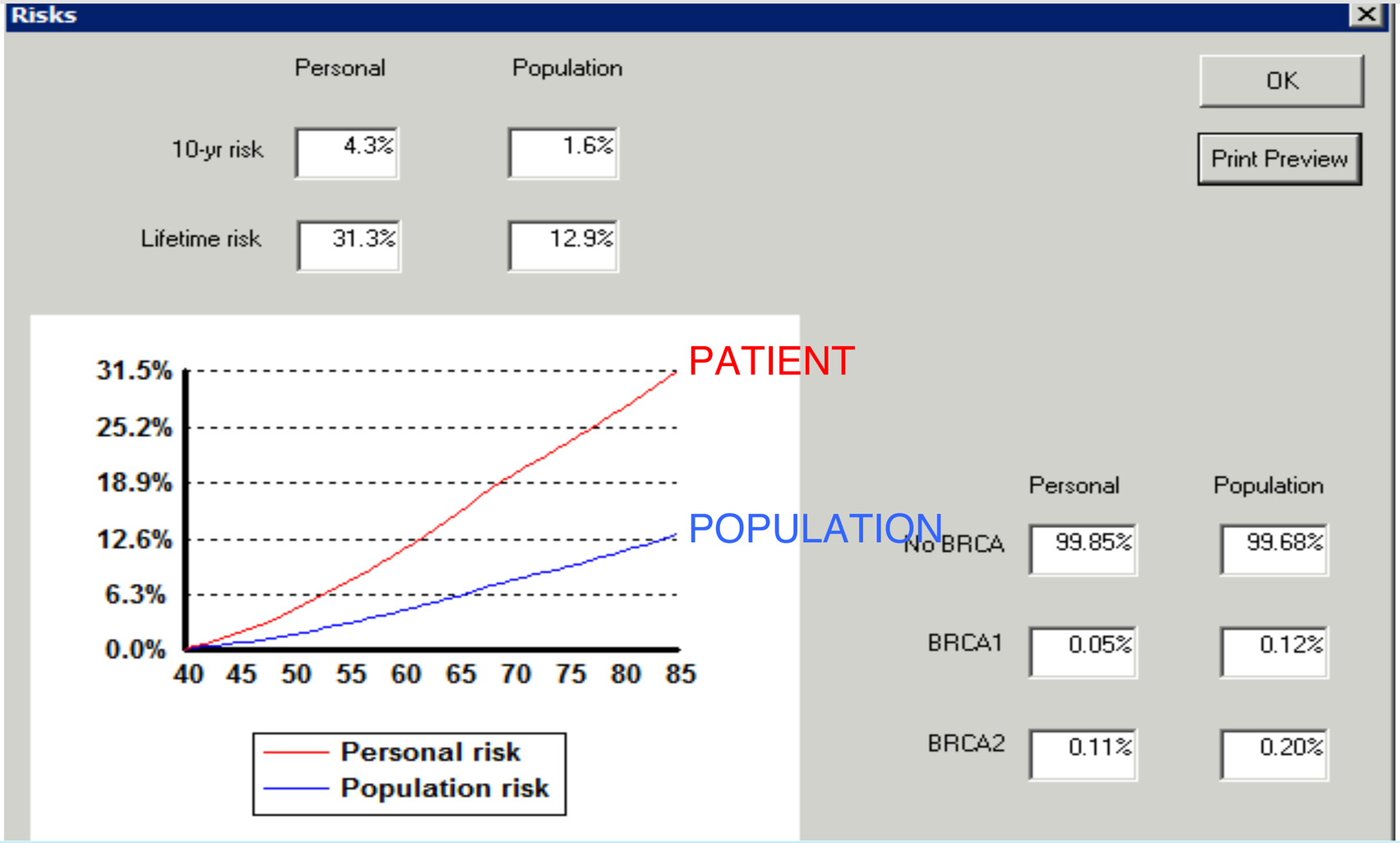
Breast Cancer Risk Calculator

Tyrer-Cuzick Model



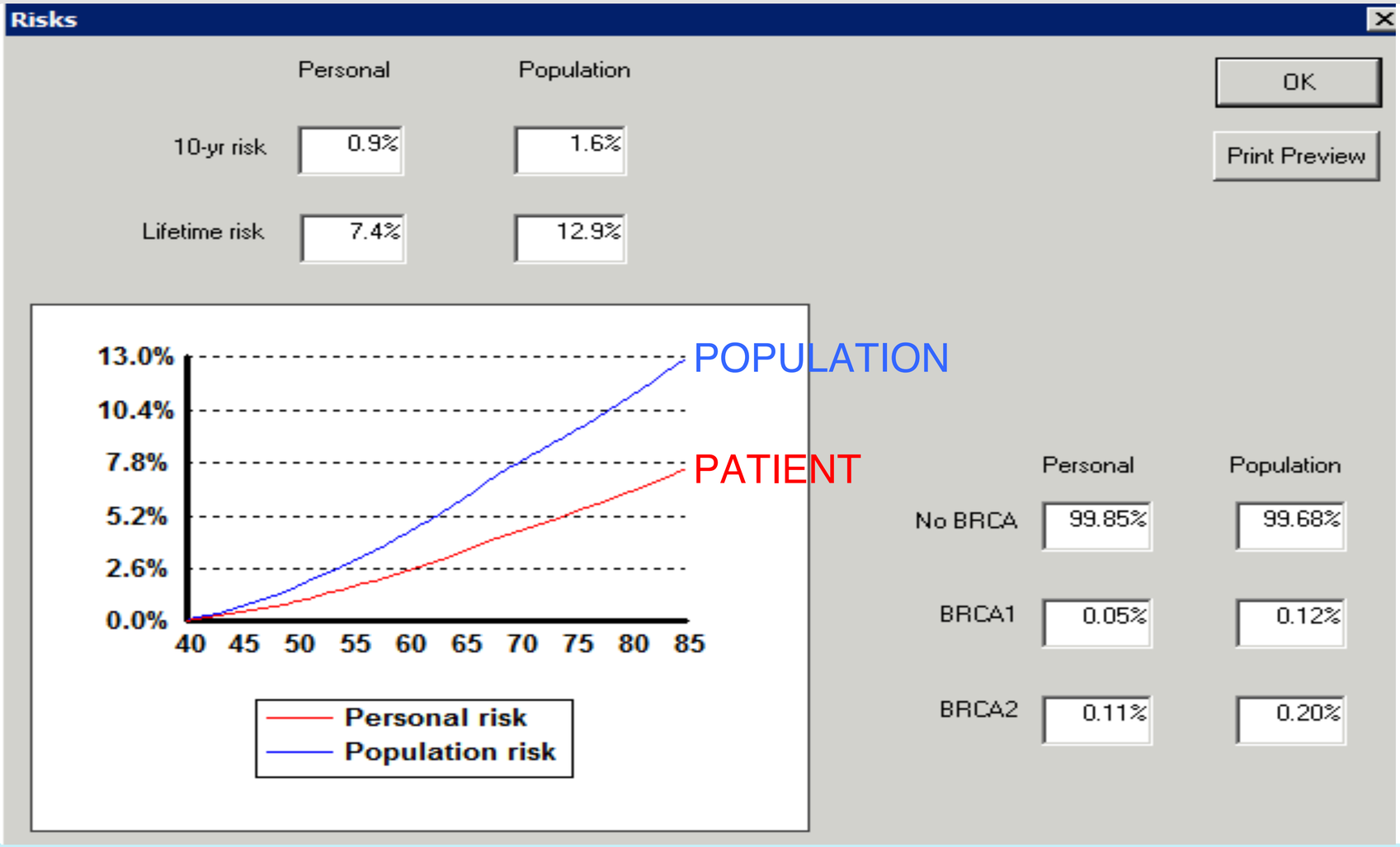
Breast Cancer Risk Calculator

Tyrer-Cuzick Model



Breast Cancer Risk Calculator

Tyrer-Cuzick Model



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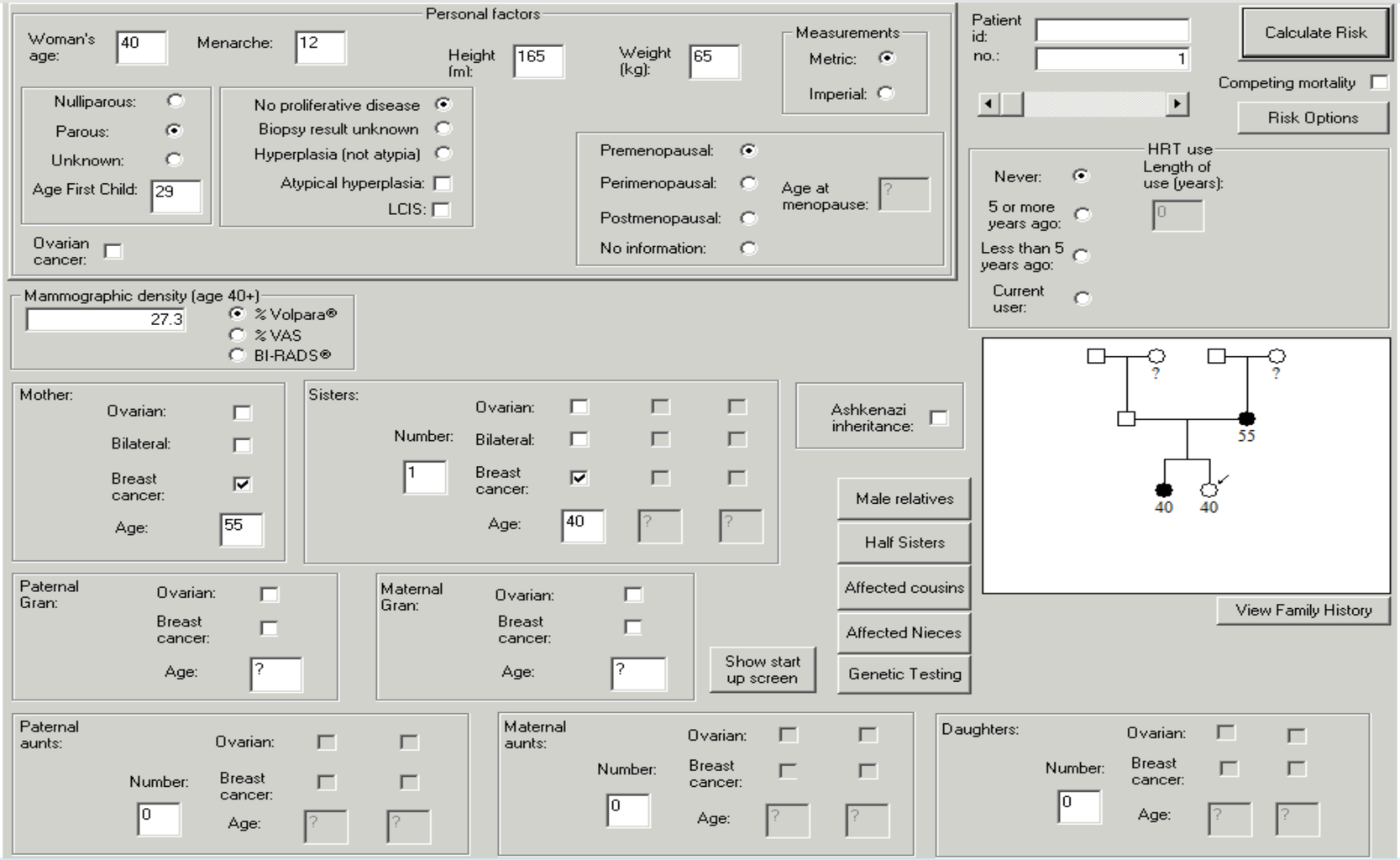

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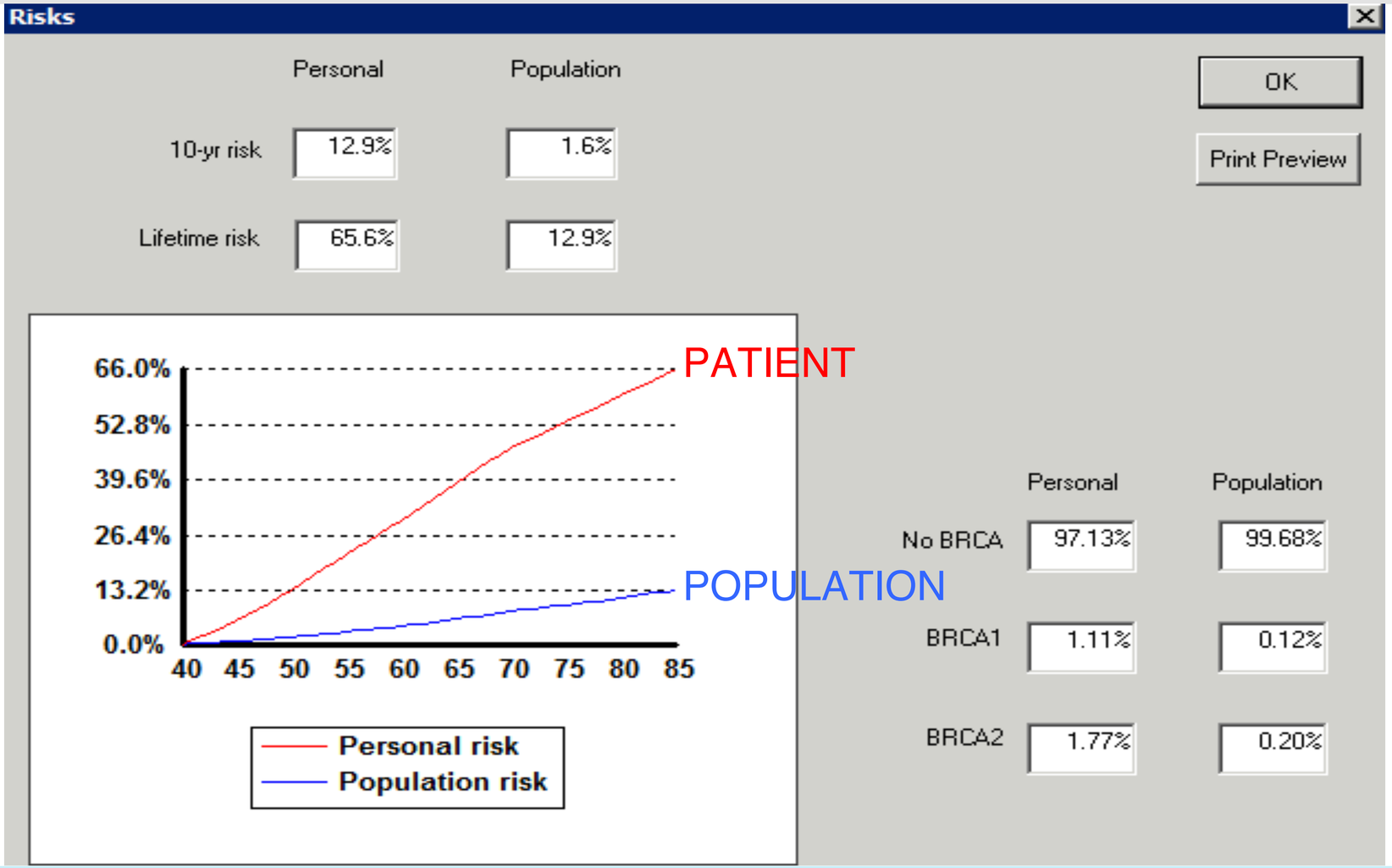

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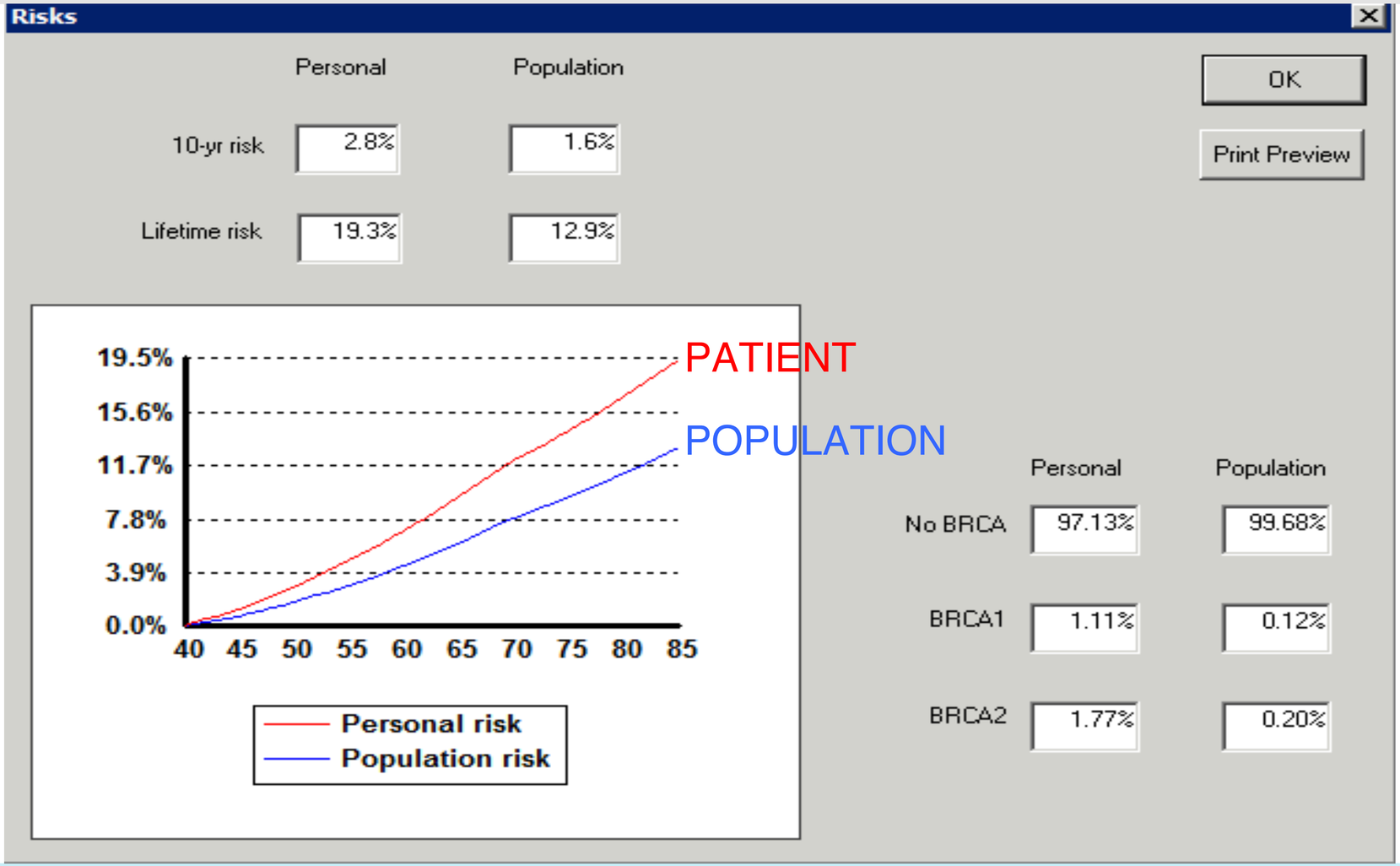


High Mammographic Breast Density (HMBD)

Management Guidelines

Management Guidelines

Imaging Guidelines

1. All women should have a baseline mammogram to establish breast density level at 40 years of age.

2. Assess risk with Tyrer-Cuzick Model
   - FDA approved
   - World-wide acceptance and usage (RACGP Red Book)

3. If the woman's lifetime risk is ≥ 20%, or BIRADS D density, then refer to a specialist for potential prevention therapy and more intensive screening, which may include MRI.

Management Guidelines

Breast Cancer Prevention Strategies

1. Do not increase Mammographic Breast Density

2. MHT (HRT) or OCP for perimenopausal symptom management
   - Before commencing MHT, do a baseline MMG.
   - After one year of MHT, repeat MMG, if breast density increases, reassess usage.

3. OCP
   - Be cautious with young women with family history especially if mother has HMBD.
   - In older women, proceed as for MHT above …consider a Mirena®

Number 4: Prevention Strategies - Medication

Tamoxifen-Induced Reduction in Mammographic Density and Breast Cancer Risk Reduction: A Nested Case–Control Study

Jack Cuzick, Jane Warwick, Elizabeth Pinney, Stephen W. Duffy, Simon Cawthorn, Anthony Howell, John F. Forbes, Ruth M. L. Warren

JNCI August 2011

- In the tamoxifen arm
  46% patients > 10% reduction in breast density at 18 months
- 10% reduction = 63% reduction in BCa risk
  This persisted after 5 years of treatment
- PBS listed Jan 2016
- Tolerability of tamoxifen problematic

Prevention

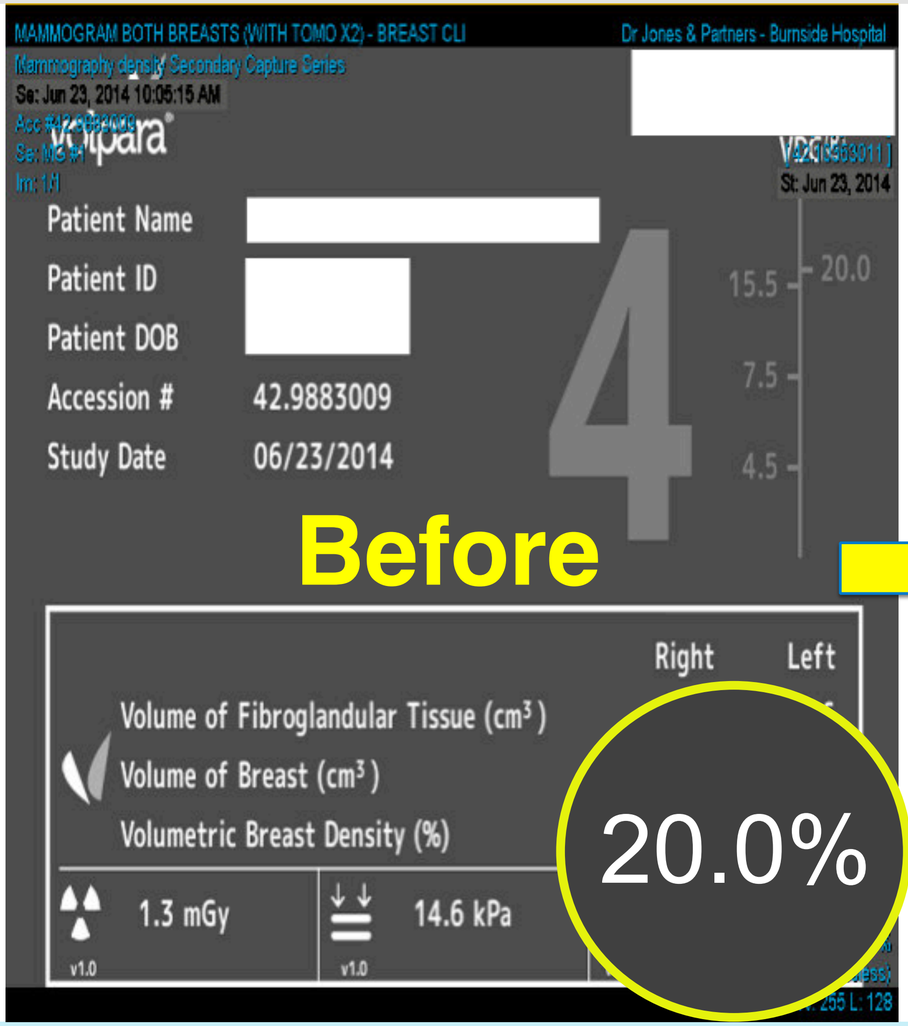
What else is there?

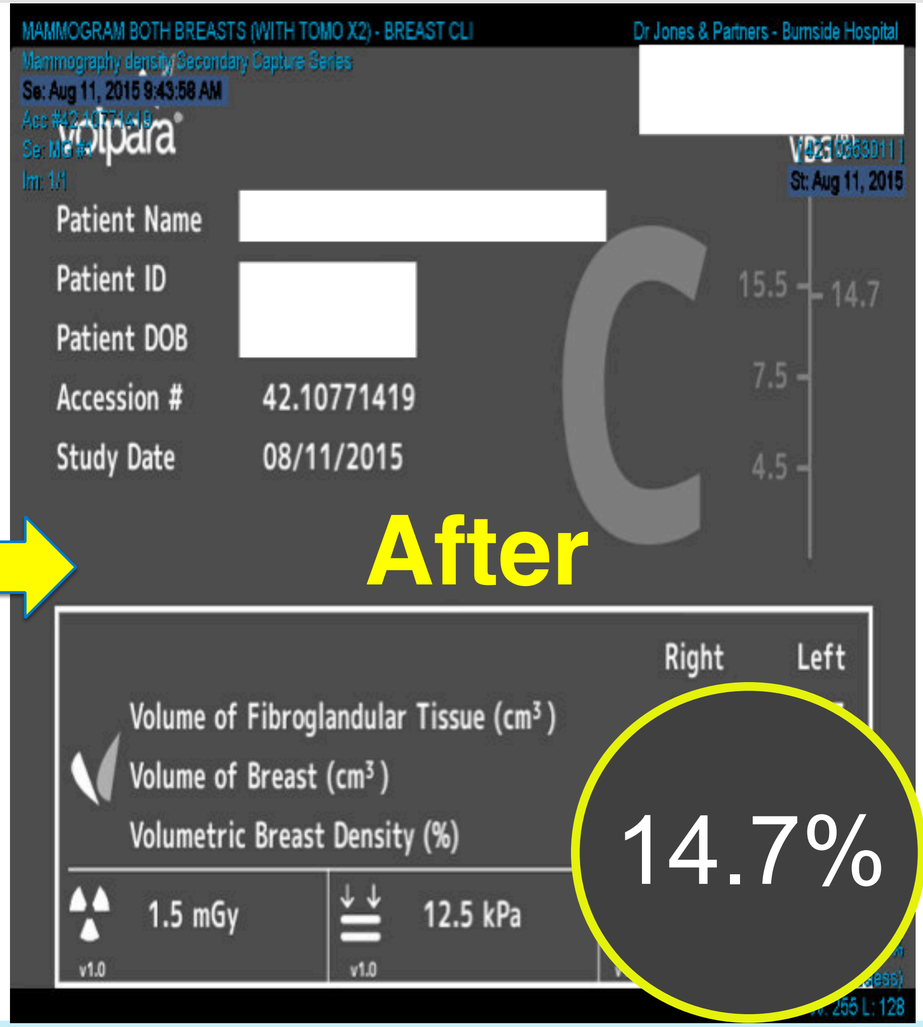
Can we do **more**?

Prevention Strategies

At Wellend Health, we reduce breast density, while at the same time provide perimenopausal symptom relief

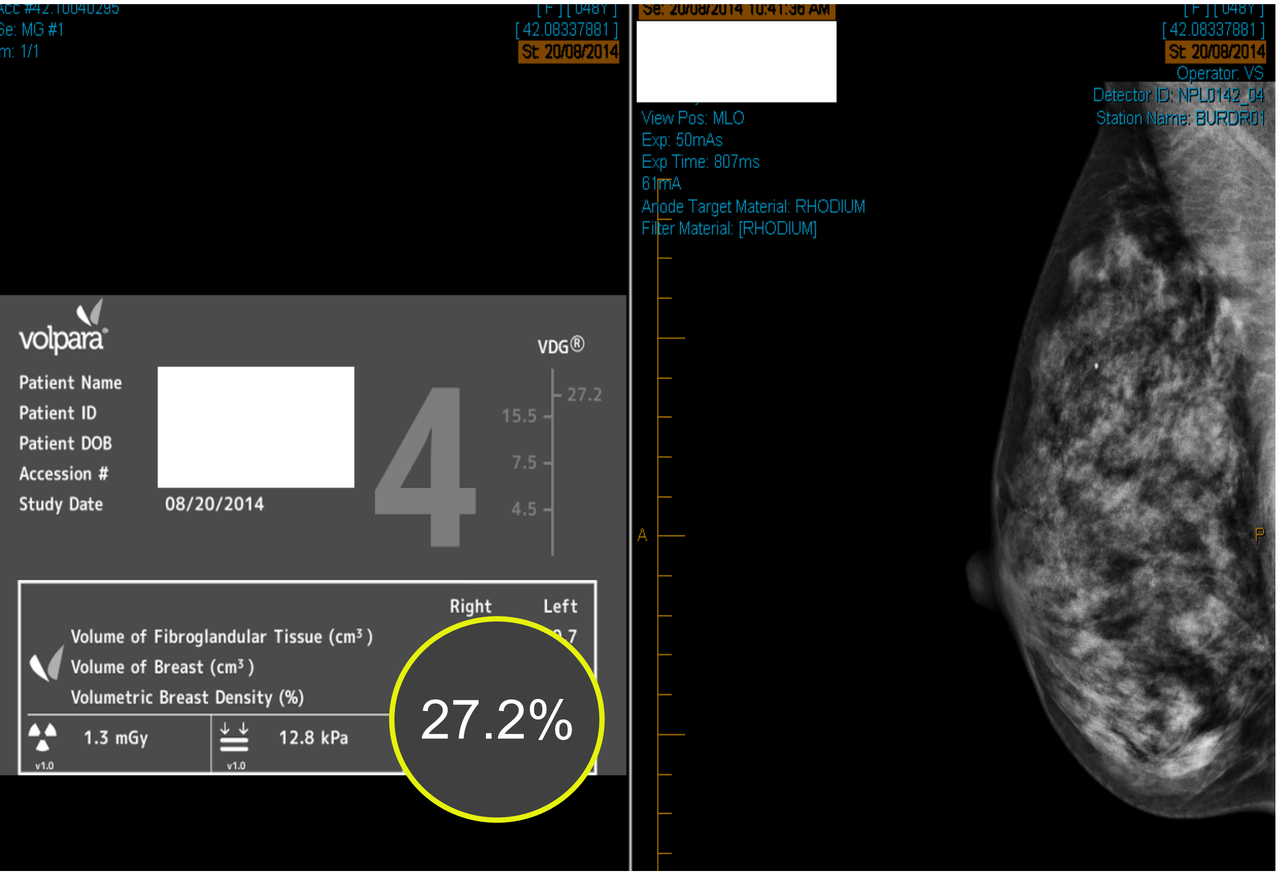
Open labelled trial of androgen/aromatase inhibitor in pre-menopausal women 8th IDM San Francisco June 2017



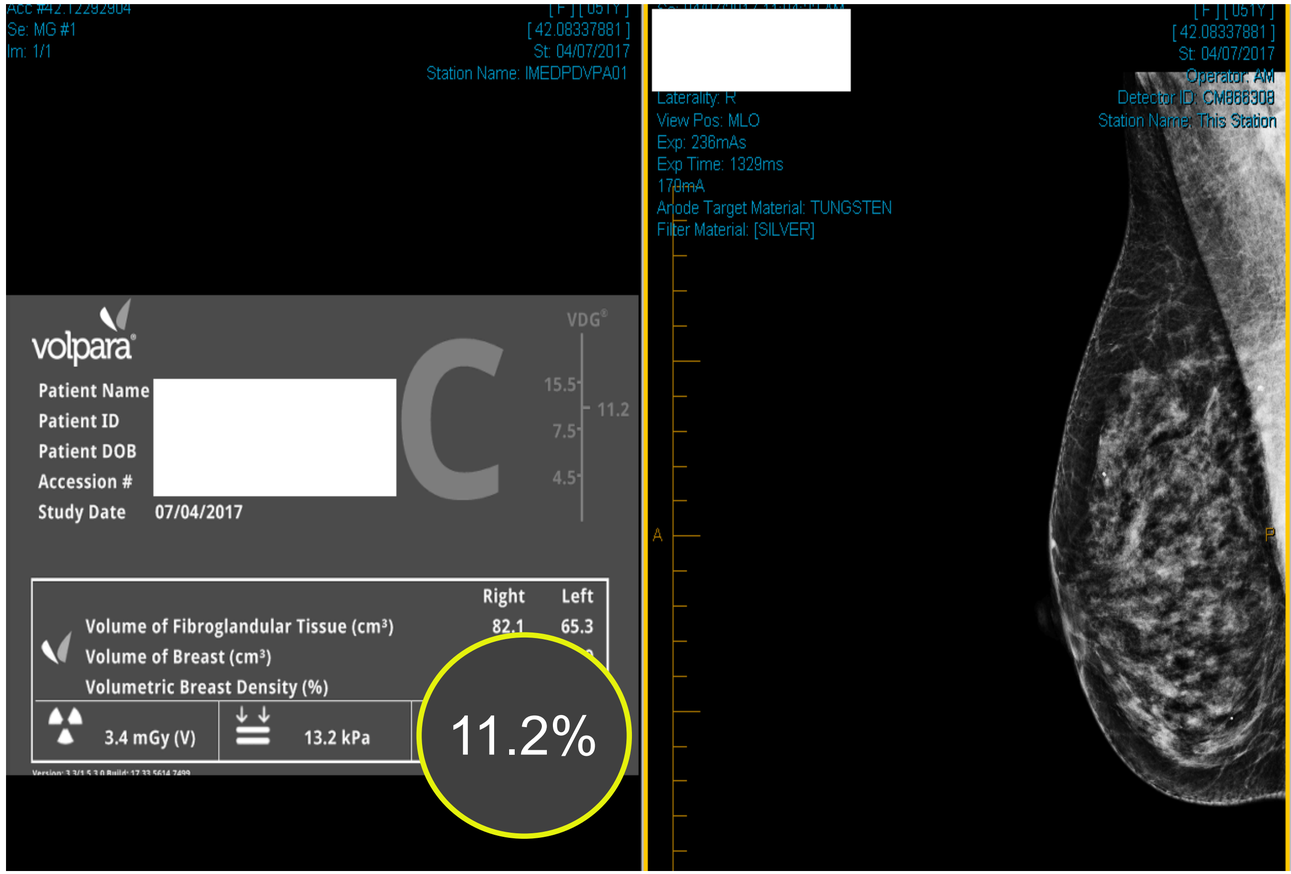


Therapeutic intervention

Before

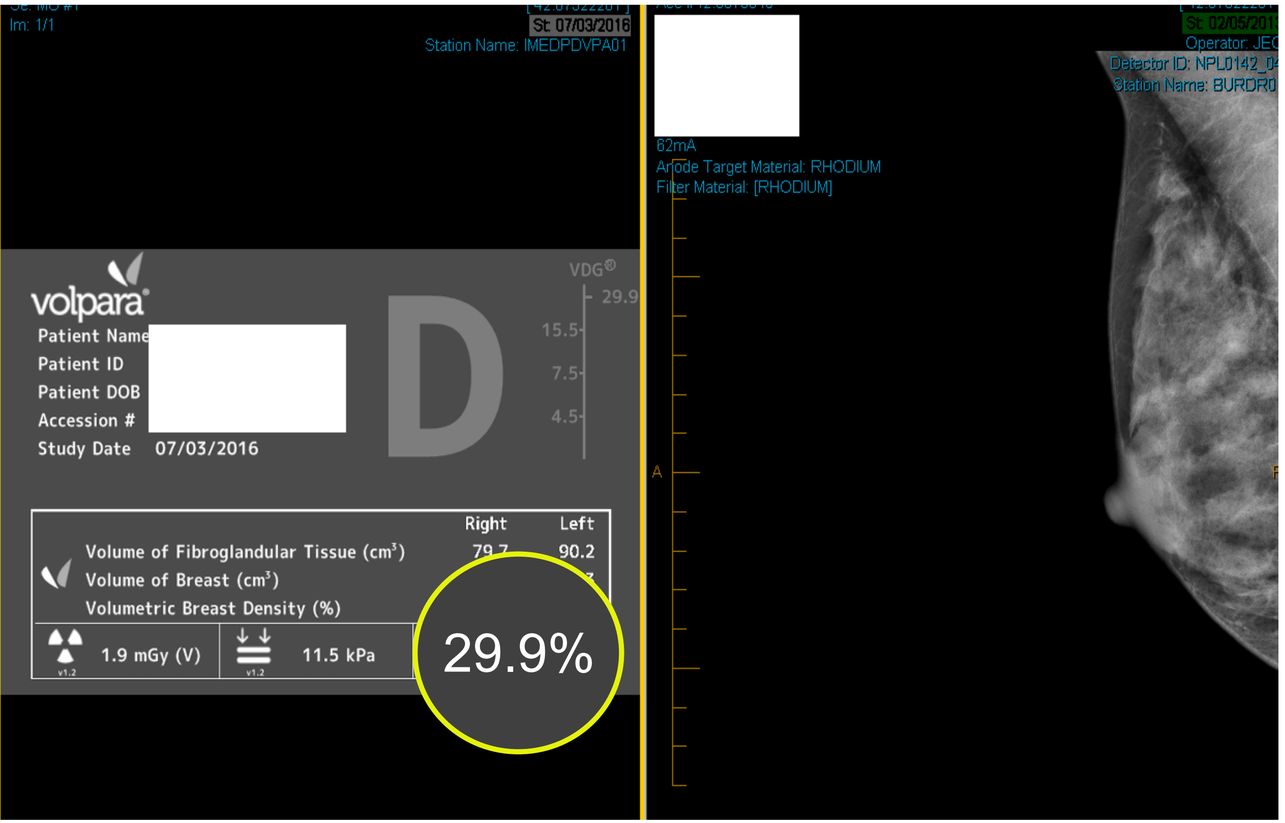


After



Therapeutic intervention

Before



After

Breast Cancer Prevention

Our trial results compared to Tamoxifen

	Tamoxifen	Wellend Health
Efficacy	46% > 10% reduction	82% > 19% reduction
Compliance	< 2% uptake	No subject withdrawals

www.wellendhealth.com/cohort-study

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Wellend Health

GP Info

LOWEST DENSITY

Breast Density summary

12 February 2016 | No Comments

SHARE THIS

A simple explanation of what breast density is

Breasts are made up of lobules, ducts, and fatty and fibrous connective tissue. The more fibrous or glandular tissue (active), the less fat, the more dense the breasts. Women with HBD have very high levels of active tissue. Breast density isn't based on how breasts feel, brea
medical imaging.

Pathway to a new understanding of breast cancer risk

Seminal work began around the 70s/80s, however the diag
tissue was subjective. Mid-00s imaging technology impro
accurate diagnosis of the condition, leading to clearer un
HBD reduces breast cancer risk. Conventional HRT studies
recent years diagnostics have become far more advanced (s
of HBD. There is now international consensus that HBD i
breast cancer.

High breast density is the leading risk factor for breast can

High Breast Density ('HBD') is considered the number one risk factor for the development of breast cancer. Breast cancer affects 12% of the global female population at some point during their lifetime and is the cause of death for nearly 500,000 women per year.

HBD is a global problem

Approximately 45% of women aged 40-65 in Australia (~1.7m women), the U.S.A. (~23.7m women) and U.K (~4.7m women) have HBD. HBD is seriously under-diagnosed in Australia but awareness is growing. In the U.S.A. 28 states have legislated mandatory HBD education for patients and a federal bill has recently been presented to Congress. It is estimated that the prevalence of HBD is as high as 85% in Chinese women (~250m women).

Women with HBD have a higher risk of developing breast cancer

High Breast Density (HBD) is considered the leading independent risk factor for the development of breast cancer. Women with HBD are at 4-6 times increased risk of developing breast cancer.

www.wellendhealth.com

DOWNLOAD REFERRAL FORM

ancer Risk Evaluation Tool (v8)
– Calculates individual risk in comparison to
DOWNLOAD

lpapa® Conversion Chart
ually evaluated in 4 stages (Bi-Rads). This
ires volumetric percentage.
DOWNLOAD

Density Info Brochure for Patients
nsity summary written for non-medicos.
DOWNLOAD

ctors for High Breast Density
anagement guidelines for patients at risk
DOWNLOAD

High Mammographic Breast Density
A brief summary and management guidelines
DOWNLOAD

RISK FACTORS for High Breast Density

Most (60%) of the risk for developing high breast density is inherited but higher breast density can be caused by the following

1. family history of breast cancer[1]
2. early (age 12-17) and/or prolonged use of OCP[2]
3. IVF treatments, particularly if over the age of 35[3]
4. HRT[4]
5. Had first child after the age of 30[5]
6. Had no children[6]
7. Prolonged exposure to air-pollution or other endocrine disrupting environmental toxins.[7]

GUIDELINES

A woman should request a baseline mammogram to establish breast density level at 40 years of age if she has one or more of the risk factors above. The more risk factors, the greater the risk of having high mammographic breast density.

If she has four or more risk factors, having a mammogram at 35 is recommended, unless the woman is currently pregnant, breast feeding or trying to get pregnant.

After breast density is determined by a mammogram, enter patient information into the IBIS Breast Cancer Risk Evaluation Tool. If patient's lifetime risk of developing breast cancer is >20%, then refer to a specialist for potential prevention therapy and more intensive screening, which may include MRI.

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[1] A clinical model for identifying the short-term risk of breast cancer.
Eriksson M, Czene K, Pawitan Y, Leifland K, Darabi H, Hall P.
Breast Cancer Res. 2017 Mar 14;19(1):29. doi: 10.1186/s13058-017-0820-y.

[2] Menstrual and reproductive characteristics and breast density in young women.
Dorgan JF, Klifa C, Deshmukh S, Egleston BL, Shepherd JA, Kwiterovich PO Jr, Van Horn L, Snetselaar LG, Stevens VJ, Robson AM, Lasser NL, Hylton NM.
Cancer Causes Control. 2013 Nov;24(11):1973-83. doi: 10.1007/s10552-013-0273-2. Epub 2013 Aug 10.

[3] Association of infertility and fertility treatment with mammographic density in a large screening-based cohort of women: a cross-sectional study.
Lundberg FE, Johansson AL, Rodriguez-Wallberg K, Brand JS, Czene K, Hall P, Iliadou AN.
Breast Cancer Res. 2016 Apr 13;18(1):36. doi: 10.1186/s13058-016-0693-5.

[4] Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk.
Byrne C, Ursin G, Martin CF, Peck JD, Cole EB, Zeng D, Kim E, Yaffe MD, Boyd NF, Heiss G, McTiernan A, Chlebowski RT, Lane DS, Manson JE, Wactawski-Wende J, Pisano ED.
J Natl Cancer Inst. 2017 Sep 1;109(9). doi: 10.1093/jnci/djx001.

[5] Menstrual and reproductive characteristics and breast density in young women.
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Cancer Causes Control. 2013 Nov;24(11):1973-83. doi: 10.1007/s10552-013-0273-2. Epub 2013 Aug 10.

[7] Association between air pollution and mammographic breast density in the Breast Cancer Surveillance Consortium.
Yaghjyan L, Arao R, Brokamp C, O'Meara ES, Sprague BL, Ghita G, Ryan P.
Breast Cancer Res. 2017 Apr 6;19(1):36. doi: 10.1186/s13058-017-0828-3.

Take Home Messages

- Extreme MBD is a pathological condition
- Order mammography with density score included in the report to enable accurate risk calculation
- Do a risk assessment if >20% lifetime risk - needs specialist opinion
- Preventative strategies are best commenced in specialist setting
- Reducing MBD is a surrogate endpoint for breast cancer prevention
- Offer screening to women using hormonal contraception and HRT from age 45 years
- DO NOT increase MBD if it can be avoided

Take Home Messages

Look at the emerging research on the use of testosterone as an option for to reducing high mammographic breast density, reducing the risk of breast cancer and also improving women's quality of life during and after the menopause.

We owe it to our patients, our mothers, sisters, daughters, ourselves to keep looking.

Keep being **curious.** Because that is science. And that is good medicine.

Lindstrom S, Thompson DJ, Paterson AD, Li J, Gierach GL, Scott C, et al. *Genome-wide association study identifies multiple loci associated with both mammographic density and breast cancer risk*. Nature communications. 2014;5:5303.

Stone J, Thompson DJ, Dos Santos Silva I, Scott C, Tamimi RM, Lindstrom S, et al. *Novel Associations between Common Breast Cancer Susceptibility Variants and Risk-Predicting Mammographic Density Measures*. Cancer Res. 2015;75(12):2457-67.

Huo CW, Chew GL, Britt KL, Ingman WV, Henderson MA, Hopper JL, et al. *Mammographic density-a review on the current understanding of its association with breast cancer*. Breast Cancer Res Treat. 2014;144(3):479-502.

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Stone J, Dite GS, Gunasekara A, English DR, McCredie MR, Giles GG, et al. *The heritability of mammographically dense and nondense breast tissue*. Cancer Epidemiol Biomarkers Prev. 2006;15(4):612-7.

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