Risk Assessment in Clinical Practice:
Beyond Identification of Hereditary Cancer Mutation Carriers:

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Sandusky 2022

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 179, JULY 2017

(Replaces Practice Bulletin Number 122, August 2011)

Reaffirmed 2019

Breast Cancer Risk Assessment and Screening in Average-Risk Women

Breast cancer is the most commonly diagnosed cancer in women in the United States and the second leading cause of cancer death in American women (1). Regular screening mammography starting at age 40 years reduces breast cancer mortality in average-risk women (2). Screening, however, also exposes women to harm through false-positive test results and overdiagnosis of biologically indolent lesions. Differences in balancing benefits and harms have led to differences among major guidelines about what age to start, what age to stop, and how frequently to recommend mammography screening in average-risk women (2–4).

Cancer statistics, 2022

Estimated New Cases

Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**

287,850 CASES INVASIVE BREAST CANCER

Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4%
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**

43,250 BREAST CANCER DEATHS

CA A Cancer J Clinicians, Volume: 72, Issue: 1, Pages: 7-33, First published: 12 January 2022, DOI: (10.3322/caac.21708)

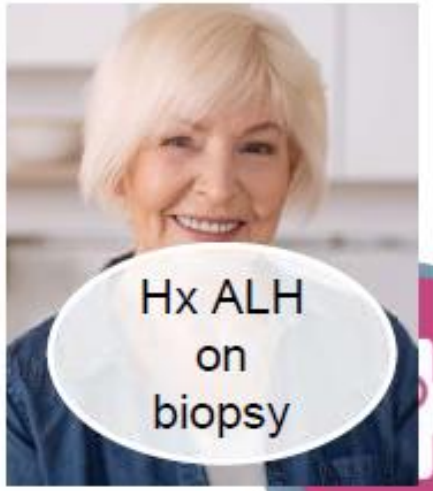
Population risk

The average
woman has a

12.5%

chance of developing breast cancer
at some point in her lifetime

Women All Have Unique Risk: Related to Modifiable and Non-Modifiable Factors



RISK FACTOR	RELATIVE RISK
First degree family Member	1.4-1.5
Early Puberty (1)	1.2
Late menopause (1)	2
Nulliparity (1)	2
Late first pregnancy (1)	1.5
Obesity	1.5
Diet (high fat)	1.2
Alcohol (2)	1.2

RISK FACTOR	RELATIVE RISK
Hormone Therapy (E+P) (3)	1.2 (E only RR 0.8)
Increased Breast Density (4)	Heterogeneously 1.2 Extremely 2.1
Atypical Hyperplasia	4
LCIS or DCIS	5-8
BRCA 1 or BRCA 2	10

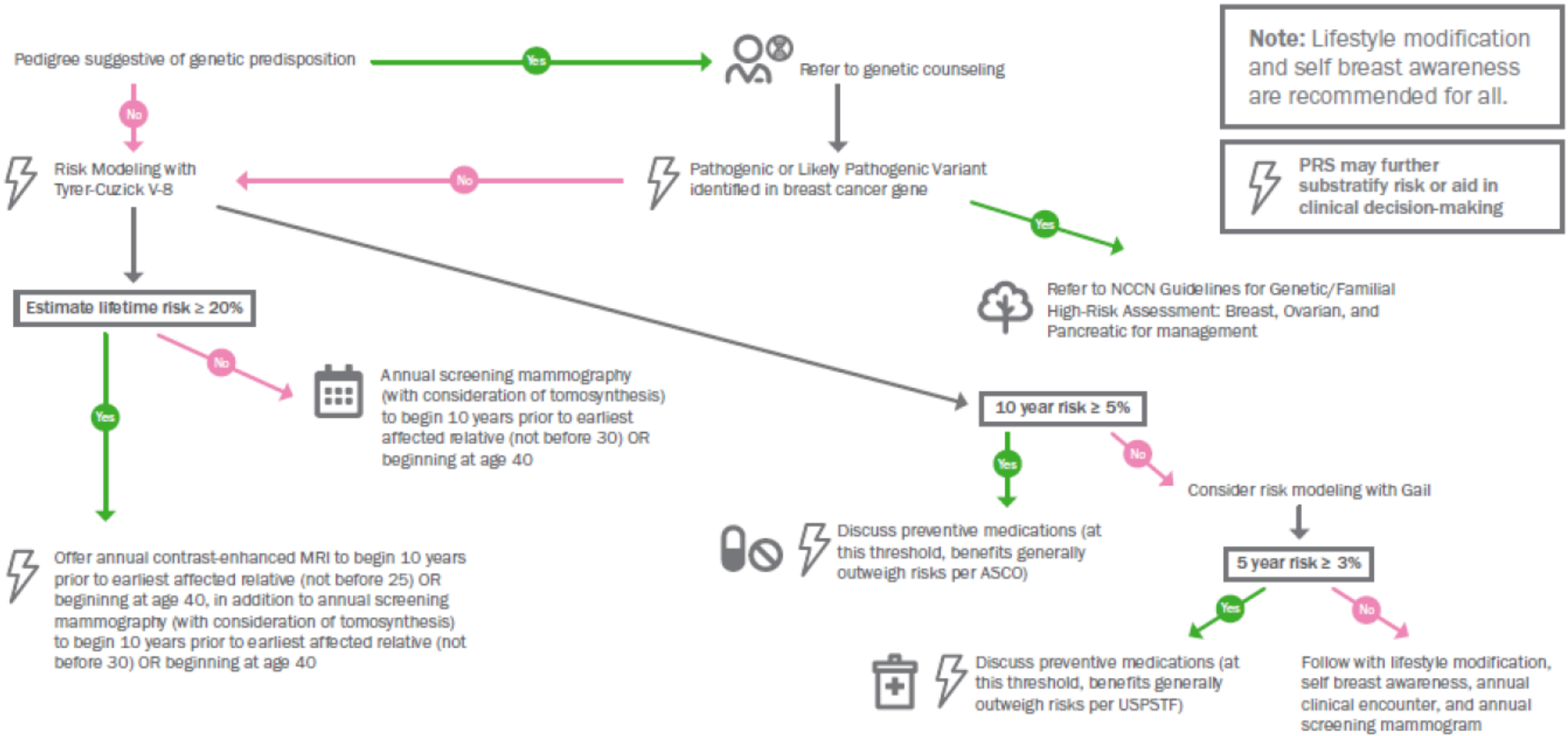
1. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. A Collaborative Group on Hormonal Factors in Breast Cancer ;Lancet Oncol. 2012;13(11):1141.

2. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA. 2011 Nov 2;306(17):1884-90. doi: 10.1001/jama.2011.1590. PMID: 22045766; PMCID: PMC3292347.

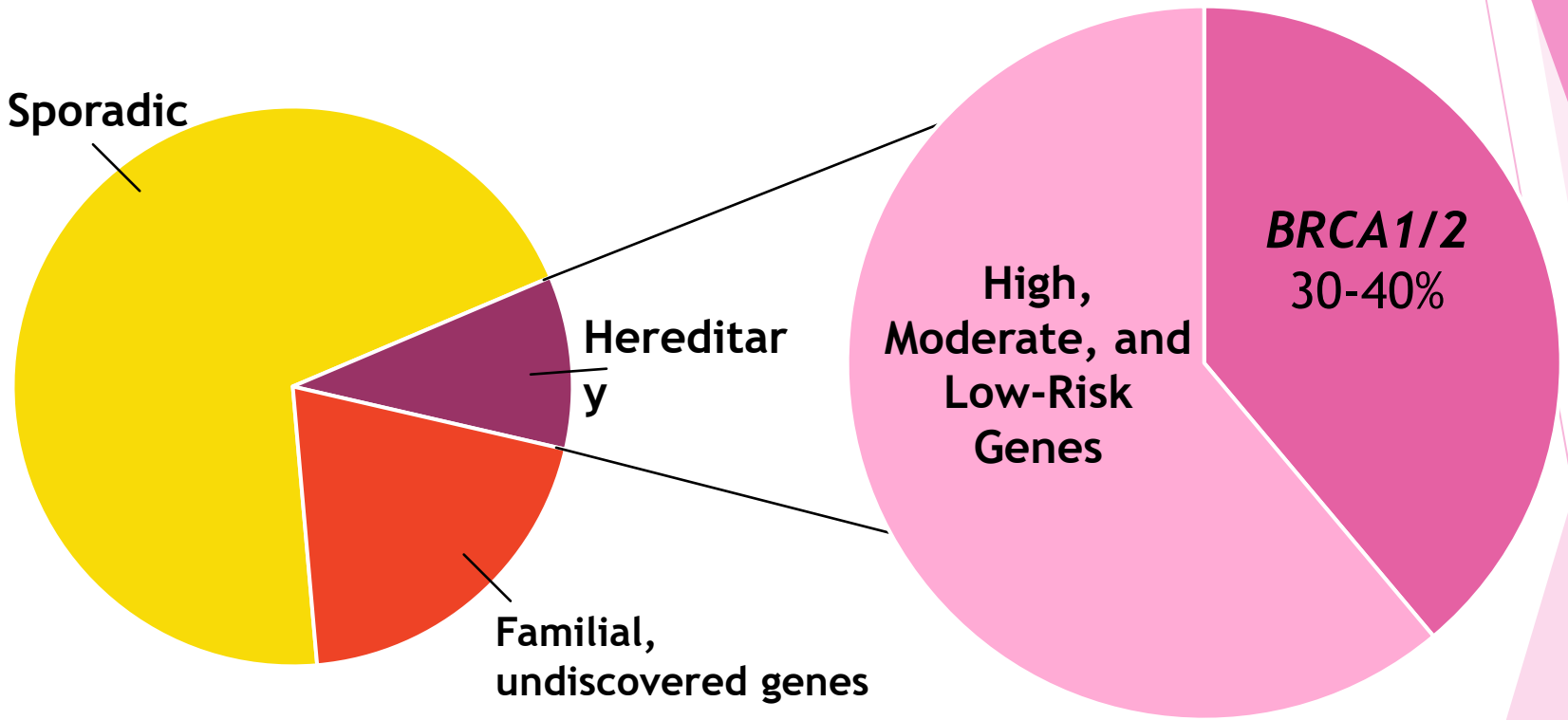
3. Rossouw JE et al Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33.

4. Sickles EA. The use of breast imaging to screen women at high risk for cancer. Radiol Cl. . 2010 Sep;48(5):859-78. doi: 10.1016/j.rcl.2010.06.012. PMID: 20868890.

Risk Assessment based on genetic testing and risk models



Genetics of Breast Cancer



High-Risk genes
- >50% lifetime risk to develop cancer, clear management recommendations
- *BRCA1/2, TP53, PTEN, CDH1, PALB2, CHEK2, ATM*

Moderate-Risk genes
- 25-50% lifetime risk to develop cancer, management recommendations might not be as clear cut
- *STK11, NF1, NBN, BARD1, RAD51C, RAD51D*

"Newer" or Low-Risk genes

Hereditary Cancer Syndromes Involving Breast Cancer	High Risk Breast Cancer Genes	Associated Cancers
Hereditary breast and ovarian cancer syndrome (HBOC)	*BRCA1, BRCA2*	Breast, ovarian, prostate, pancreas
Li-Fraumeni syndrome	*TP53*	Breast, brain, sarcoma, adrenocortical carcinoma, rare cancers, early onset
Cowden syndrome (*PTEN* hamartoma tumor syndrome)	*PTEN*	Breast, uterine, thyroid, colon, benign tumors, skin findings, large head size
Hereditary diffuse gastric cancer	*CDH1*	Breast (lobular), diffuse gastric
***PALB2* hereditary cancer syndrome**	*PALB2*	Breast, pancreatic and possibly ovarian
CHEK2	*CHEK2*	Breast, colon, others
	ATM	Breast, pancreatic, prostate

	General Population Risk	Risk for *BRCA1* Mutation Carrier	Risk for *BRCA2* Mutation Carrier
Female Breast Cancer	12%	Up to 72%	Up to 69%
Second Breast Cancer	2% within 5 years	40% within 20 years; 60% by age 70	26% within 20 years; 62% by age 70
Ovarian Cancer	1-2%	39-58%	13-29%
Male Breast Cancer	0.1%	Up to 1.2%	Up to 7%
Prostate Cancer	6% by age 69	Up to 26%	Up to 61%
Pancreatic Cancer	0.5%	≤5%	2-7%

NCCN Guidelines
v1.2023

Moderate Risk Breast/Ovarian Cancer Genes	Associated Cancers
NF1	Breast, neurofibromas, optic gliomas
STK11	Breast, pancreatic, ovarian, stomach
BARD1, RAD51C, RAD51D, BRIP1	Ovarian, possibly breast
FANCC, NBN, MRE11A, AKT1, AXIN2, PIK3CA, RINT1, SDHB, SDHC, MUTYH **and others**	Low risk or preliminary evidence genes for breast cancer

Breast Cancer Screening/Prevention for *BRCA1/2*

Women: Screening

- Monthly breast self-exams starting at 18y
- Clinical breast exams twice a year starting at 25y
- Annual breast MRI starting at 25y
- Annual mammogram starting at 30y
  - Alternate mammogram and breast MRI every 6 months starting at 30y

Women: Prevention

- Preventative mastectomy (removal of breast tissue)
  - Reduces risk by >90%
- Tamoxifen (estrogen blocking drug)
  - Reduces risk of breast cancer in other breast by up to 53%

Men: Screening

- Monthly breast self-exams starting at 35y
- Annual clinical breast exams starting at 35y

Ovarian Cancer Screening/Prevention for *BRCA1/2*

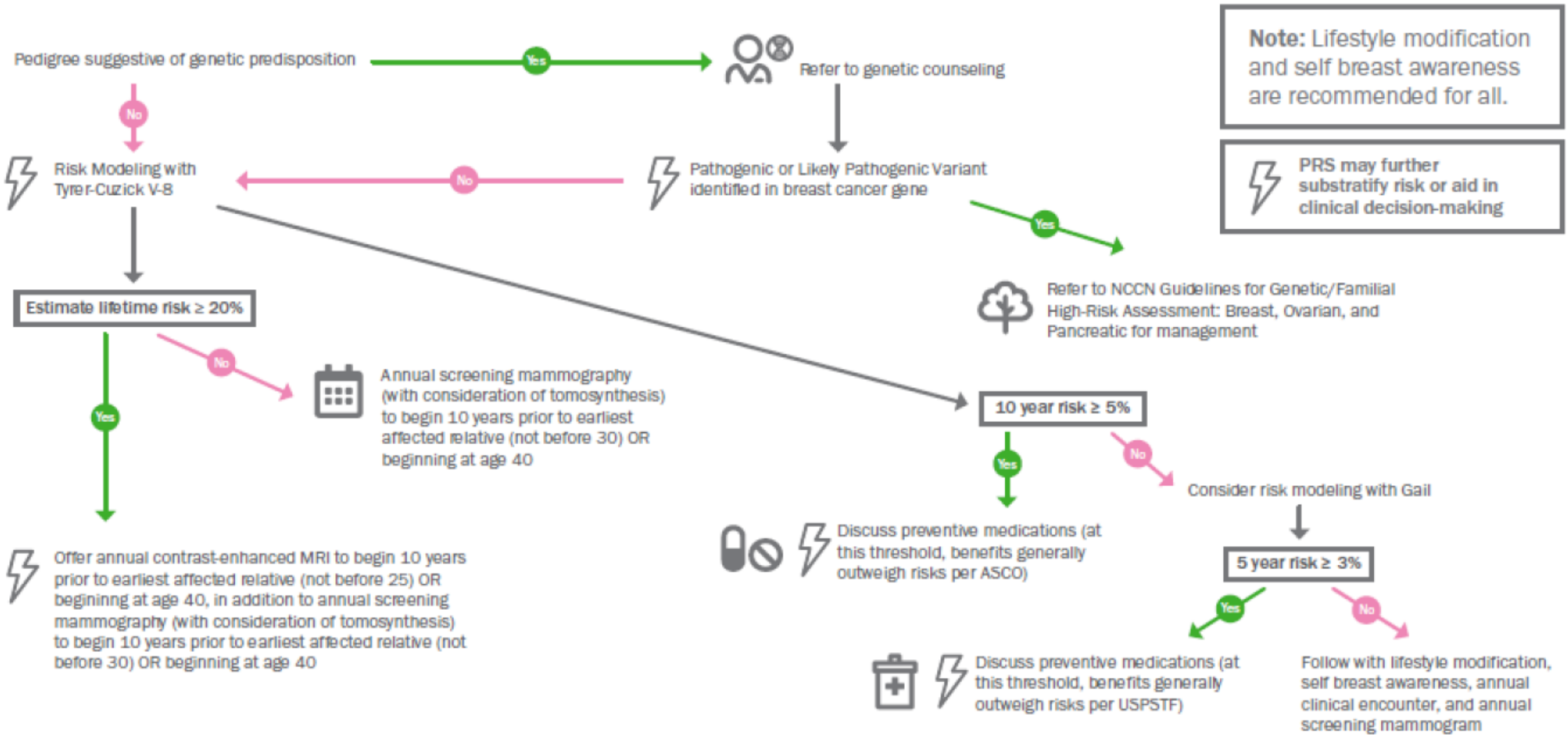
Screening

- No effective screening for ovarian cancer

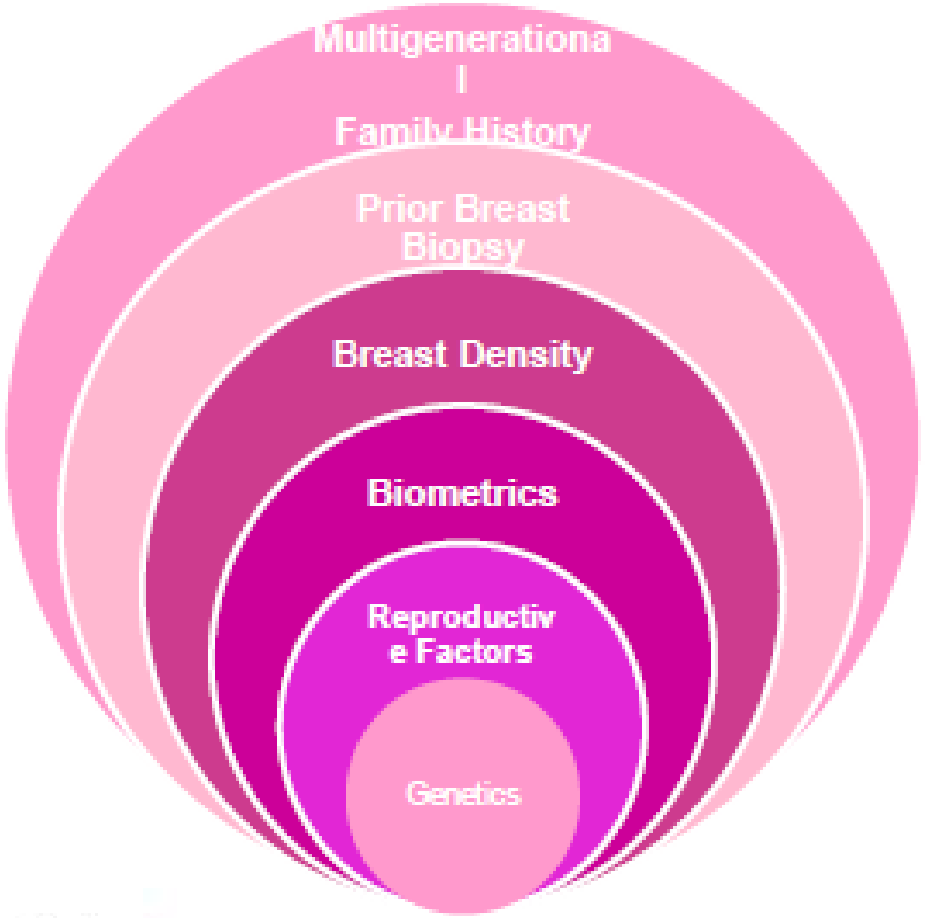
Prevention

- **Preventative salpingo-oophorectomy** (removal of ovaries and fallopian tubes)
  - Reduces risk of ovarian cancer by up to 96% and breast cancer by up to 53%
  - May be done after having children
  - *BRCA1*: 35-40y, *BRCA2*: 40-45y
- **Birth control pills**
  - Reduces ovarian cancer risk by almost 50% when used for a few years
  - Slightly increases breast cancer risk if used for more than 5y

Risk Assessment based on genetic testing and risk models



Validated Risk Assessment Models



Risk Models Supported By Guidelines:

ASCO

NCCN

USPSTF

- Gail/BCRAT
- IBIS/Tyrer-Cuzick V8

Ms.Medicine
Women's Health Matters

Mayo Clin Proc. April 2021;96(4):1033-1040
https://doi.org/10.1016/j.mayocp.2021.01.028

Personal factors

Woman's age: 0

Menarche: ?

Height (m): ?

Weight (kg): ?

Measurements

Metric:

Imperial:

Nulliparous:

Parous:

Age First Child:

Unknown:

Premenopausal:

Perimenopausal:

Postmenopausal:

No information:

Age at menopause:

Hyperplasia (without atypia):

Atypical hyperplasia:

LCIS:

Ovarian cancer:

Calculate Risk

View Family History

HRT use

Never:

5 or more years ago:

Less than 5 years ago:

Current user:

Length of use (years):

Mother:

Ovarian:

Bilateral:

Breast cancer:

Age: ?

Sisters:

Number: 0

Ovarian:

Bilateral:

Breast cancer:

Age:

Ashkenazi inheritance:

Half Sisters

Affected cousins

Affected Nieces

Genetic Testing

Show start up screen

Paternal Gran:

Ovarian:

Breast cancer:

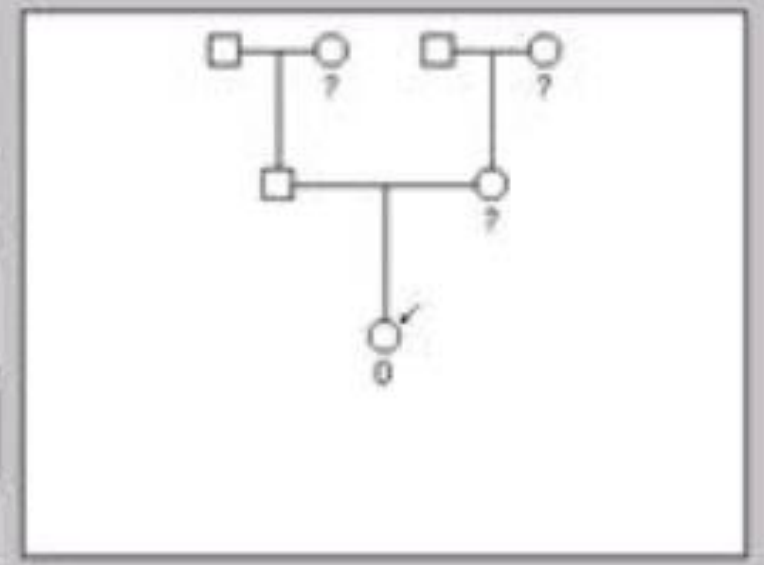
Age: ?

Maternal Gran:

Ovarian:

Breast cancer:

Age: ?



Ovarian:

Ovarian:

Number:

Breast

Ovarian:

Number:

Breast

ACR and NCCN Guidance for Breast MRI

National Comprehensive Cancer Network®

2018

- Lifetime risk of breast cancer 20% to 25% or greater, according to risk assessment tools that are based mainly on family history
- Have a known *BRCA1* or *BRCA2* gene mutation
- Have a first-degree relative (parent, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation, and have not had genetic testing themselves
- Had radiation therapy to the chest when they were between the ages of 10 and 30 years

NCCN Clinical Practice Guideline in Oncology: Breast Cancer Screening and Diagnosis. http://www.nccn.org. Accessed March 15, 2018

American College of Radiology. ACR Appropriateness Criteria: Breast Cancer Screening 2017. Accessed at https://acsearch.acr.org/docs/70910/Narrative/ on 13 August 2018

Monticciolo DL et al. J AM Coll Radiol 2018

Original Investigation

Patterns of Breast Magnetic Resonance Imaging Use in Community Practice

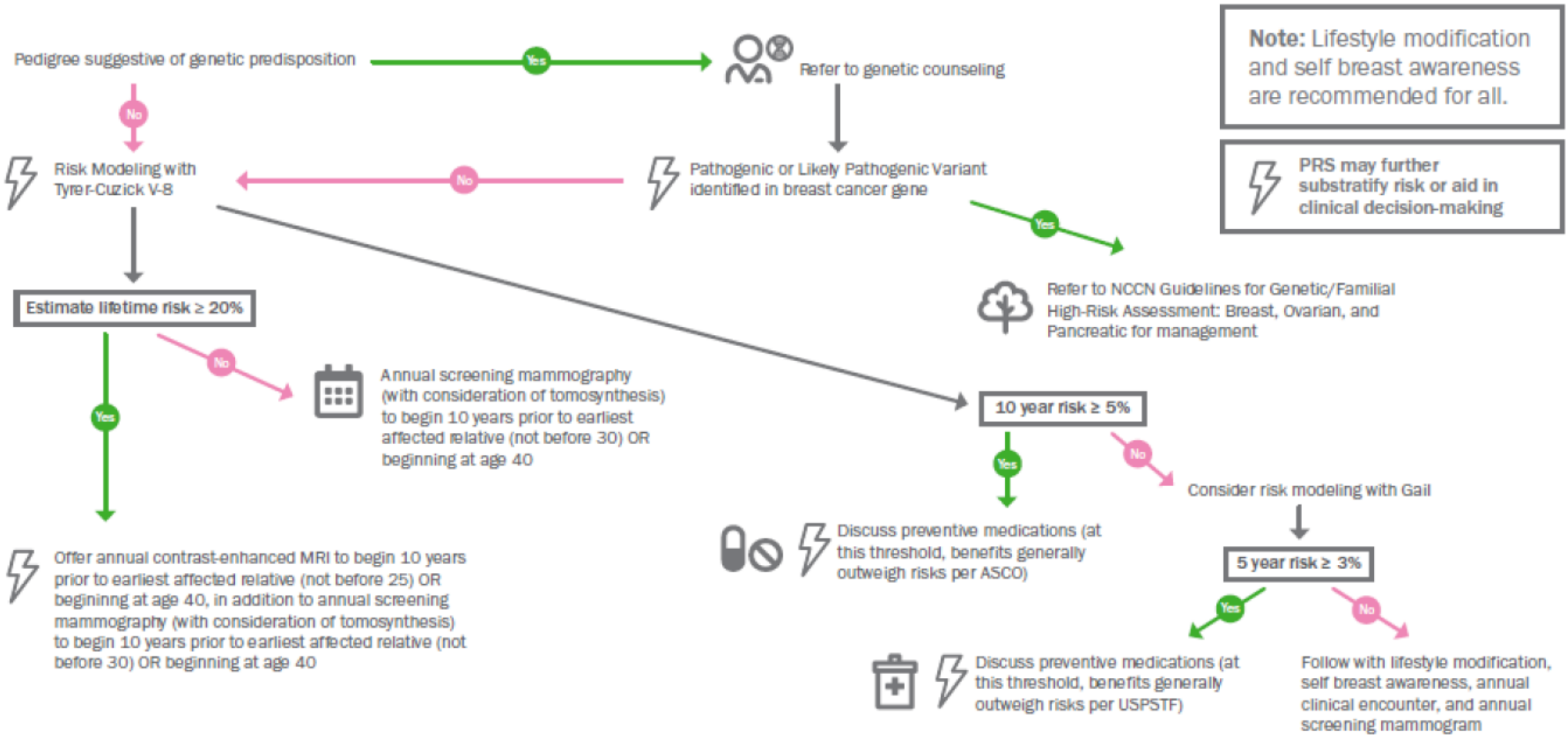
JAMA 2014

Karen J. Wernli, PhD; Wendy B. DeMartini, MD; Laura Ichikawa, MS; Constance D. Lehman, MD, PhD; Tracy Onega, PhD; Karla Kerlikowske, MD, MS; Louise M. Henderson, PhD; Berta M. Geller, EdD; Mike Hofmann, MS; Bonnie C. Yankaskas, PhD; for the Breast Cancer Surveillance Consortium

- 1,131,000 Women
- 25,000 (2.2%) >20% lifetime risk BC
- **Only 383 of eligible women had breast MRI (1.5%)**

We must do more to appropriately screen women
Women who need breast MRI are not getting them
Women who don't need breast MRI are

Risk Assessment based on genetic testing and risk models



IBIS/Tyrer-Cuzick Model (V8)

- http://ems-trials.org/riskevaluator
- Time consuming to complete
- Takes into consideration biometrics, breast density reproductive factors, and multigenerational family history
- Provides 5-year, 10-year and lifetime risk
- Calculated risk often higher than Gail Model risk estimate
- May overestimate risk in patients ADH or LCIS, Hispanic women (1)
- ASCO 2019 Guidelines: consider chemoprevention 10-year risk >5% or 5-year risk >3% (2)

1. Kurian AW et al. J. Clin Oncol. 2020;38:1503
2. ASCO Clinical Practice Guideline
J. Clin Oncol 2019;37(33):3152-3165

Modified Gail Model/Breast Cancer Risk Assessment Tool (BCRAT)

- https://bcrisktool.cancer.gov/index.html

- 5 questions, takes about one minute to complete
- Estimates lifetime risk of breast cancer in women >35
- Not valid in women with a past hx of IBC or DCIS, LCIS
- Does not take into consideration family history beyond first degree relatives
- Does not take into consideration breast density
- Used to determine chemoprevention: 5-year risk >3%

USPSTF 2019;322 (9):857-867

Guidelines for chemoprevention:

Organization	Absolute or estimated risk	Recommendation
USPSTF ASCO	**Gail model - 5 year risk of 3% or greater**	Net benefit appears to be beneficial at this threshold
ASCO	**Tyrer-Cuzick - 10 year risk of 5% or greater**	Most likely to benefit
NCCN	**Absolute risk with atypical hyperplasia (ADH or ALH) is 30% over 25 yrs**	**Encourage preventive medication unless contraindicated**
NCCN	**Lobular carcinoma in situ (LCIS) confers ~2% risk per year**	**Encourage preventive medication unless contraindicated**
NCCN	**Prior therapeutic thoracic irradiation confers ~29% lifetime risk**	Consider preventive medication (data is limited)

NCCN Guidelines: Breast Cancer Risk Reduction Version 1.2021

Randomized Prevention Trials

Study		N	Eligibility	HR
NSABP P-1	Tam v Placebo 5 year	13,388	Pre and Post Meno Gail >1.67	0.51
IBIS 1	Tam vs Placebo	7,152	Pre and Post 50% on HT	0.75
STAR P-2	Tam vs Raloxifene	19,747	Post menopausal	5 years equal Long term Ral 0.62
MAP 3	Exemestane vs Placebo	4,560	Post menopausal	0.35
IBIS 2	Anastrazole vs Placebo	3,964	Post menopausal	0.47
LD Tamoxifen	5 mg Tam for 3 years	500	Pre and Post Meno Including DCIA AH LCIS	0.48

Fisher B et al, JNCI 1998, IBIS Investigators, Lancet 2002, Vogel et al, Ca Res Prev 2010, Goodwin Lancet 2014, DeCensi A et al, JCO 2019

Chemoprevention

CLINICAL GUIDELINE | 2013 | Annals of Internal Medicine

Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation on the use of medications for breast cancer risk reduction.

Methods: The USPSTF reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce the risk for breast cancer—specifically, the selective estrogen receptor modulators tamoxifen and raloxifene. The USPSTF also reviewed a meta-analysis of placebo-controlled trials to understand the relative benefits and harms of tamoxifen and raloxifene.

Population: This recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ.

Recommendation: The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene. (B recommendation)

The USPSTF recommends against the routine use of medications, such as tamoxifen or raloxifene, for risk reduction of primary breast cancer in women who are not at increased risk for breast cancer. (D recommendation)

Ann Intern Med. 2013;159:698-708. www.annals.org

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published online first at www.annals.org on 24 September 2013.

JAMA | US Preventive Services Task Force | EVIDENCE REPORT 2019

Medication Use for the Risk Reduction of Primary Breast Cancer in Women

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Heidi D. Nelson, MD, MPH, MACP, FRCP; Rongwei Fu, PhD; Bernadette Zakher, MBBS, MPH; Miranda Pappas, MA; Marian McDonagh, PharmD

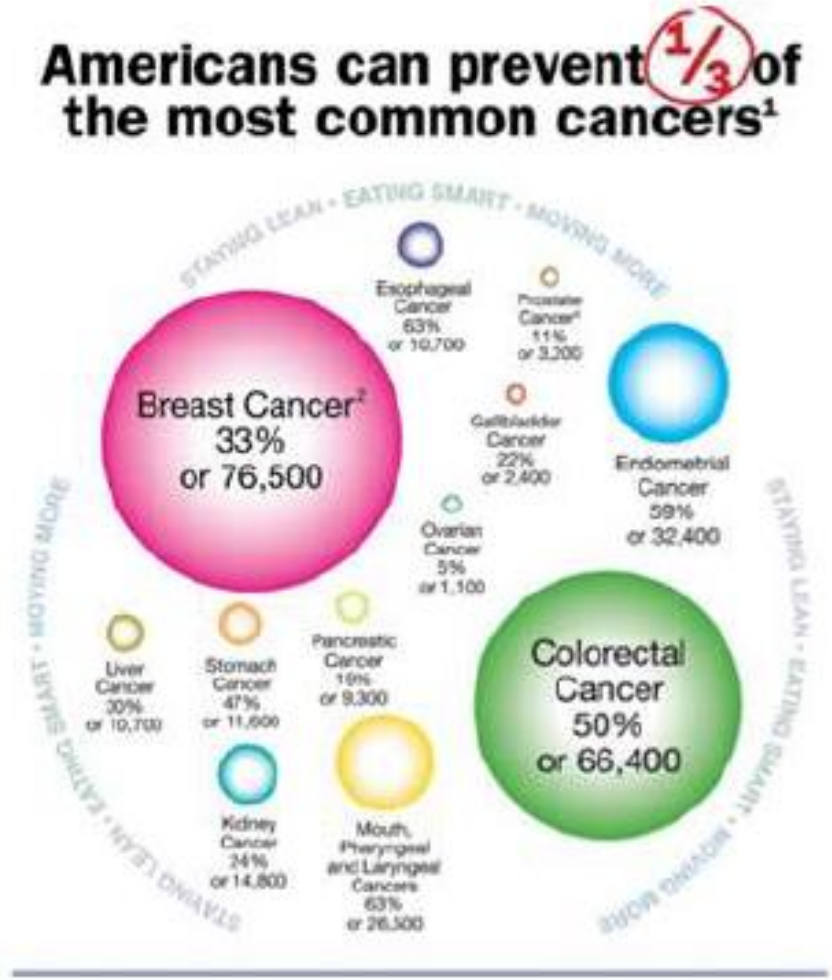
JAMA.2019;322(9):868-886

USPSTF Guidelines JAMA Sept 2013

Ms.Medicine
Women's Health Matters

Lifestyle and Cancer: "The Silver Bullet"

- **Healthy Diet**: Low fat, high in fresh fruits and vegetables, fruits, nuts, whole grains and fish
- **Exercise:** > 150 minutes/week moderate intensity
- **Ideal BMI**: BMI <25; lose weight if obese
- **No smoking**
- **Minimize alcohol intake**



Ms. Women's Health Champ

World Cancer Research Fund International

Circulation

ORIGINAL RESEARCH ARTICLE

Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population

BACKGROUND: Americans have a shorter life expectancy compared with residents of almost all other high-income countries. We aim to estimate the impact of lifestyle factors on premature mortality and life expectancy in the US population.

METHODS: Using data from the Nurses' Health Study (1980–2014; n=78 865) and the Health Professionals Follow-up Study (1986–2014, n=44 354), we defined 5 low-risk lifestyle factors as never smoking, body mass index of 18.5 to 24.9 kg/m², ≥30 min/d of moderate to vigorous physical activity, moderate alcohol intake, and a high diet quality score (upper 40%), and estimated hazard ratios for the association of total lifestyle score (0–5 scale) with mortality. We used data from the NHANES (National Health and Nutrition Examination Surveys; 2013–2014) to estimate the distribution of the lifestyle score and the US Centers for Disease Control and Prevention WONDER database to derive the age-

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Li Y, et al. *Circulation* 2018;137: April 30

Estimated Life Expectancy at age 50 According to Number of Low-Risk Factors

Low-Risk Lifestyle Factors

- Never smoking
- BMI 18.5-24.9 kg/m^2
- ≥ 30 min/d moderate to vigorous physical activity
- Moderate alcohol intake
- High diet quality score

Li Y, et al. *Circulation* 2018;137: April 30

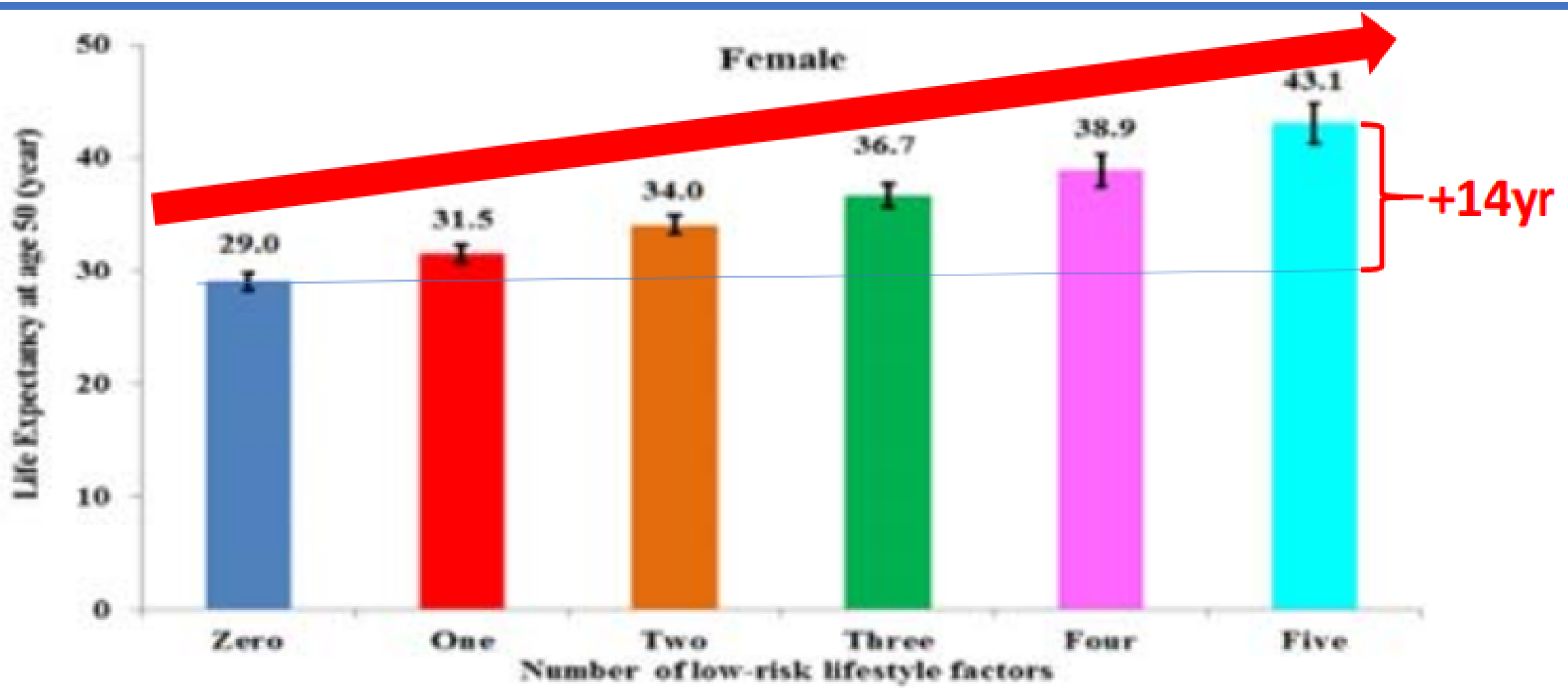
Estimated Life Expectancy at age 50 According to Number of Low-Risk Factors

During 34 y of follow-up, the multivariate adjusted **HR for *mortality*** in adults with 5 compared with zero low-risk lifestyle factors were:

	All-cause	Cancer	CVD
	0.26	0.35	0.18
	(0.22-0.31)	(0.27-0.45)	(0.12-0.26)
Reduced by	74%	65%	82%

Li Y, et al. *Circulation* 2018;137: April 30

Estimated Life Expectancy at age 50 According to Number of Low-Risk Factors



Li Y, et al. *Circulation* 2018;137: April 30

MRS. SAD

- 52 yo patient comes to your clinic to discuss her breast cancer risk following recent benign breast biopsy
- “Doctor, how can I prevent getting breast cancer”
- Chronic Diseases/ Conditions:
  - Class 2 obesity BMI 35, DM2 on oral agents, HTN, hyperlipidemia, non-alcoholic fatty liver, GERD
- Other issues:
  - Menopause, fatigue, hot flashes, insomnia

MRS. SAD

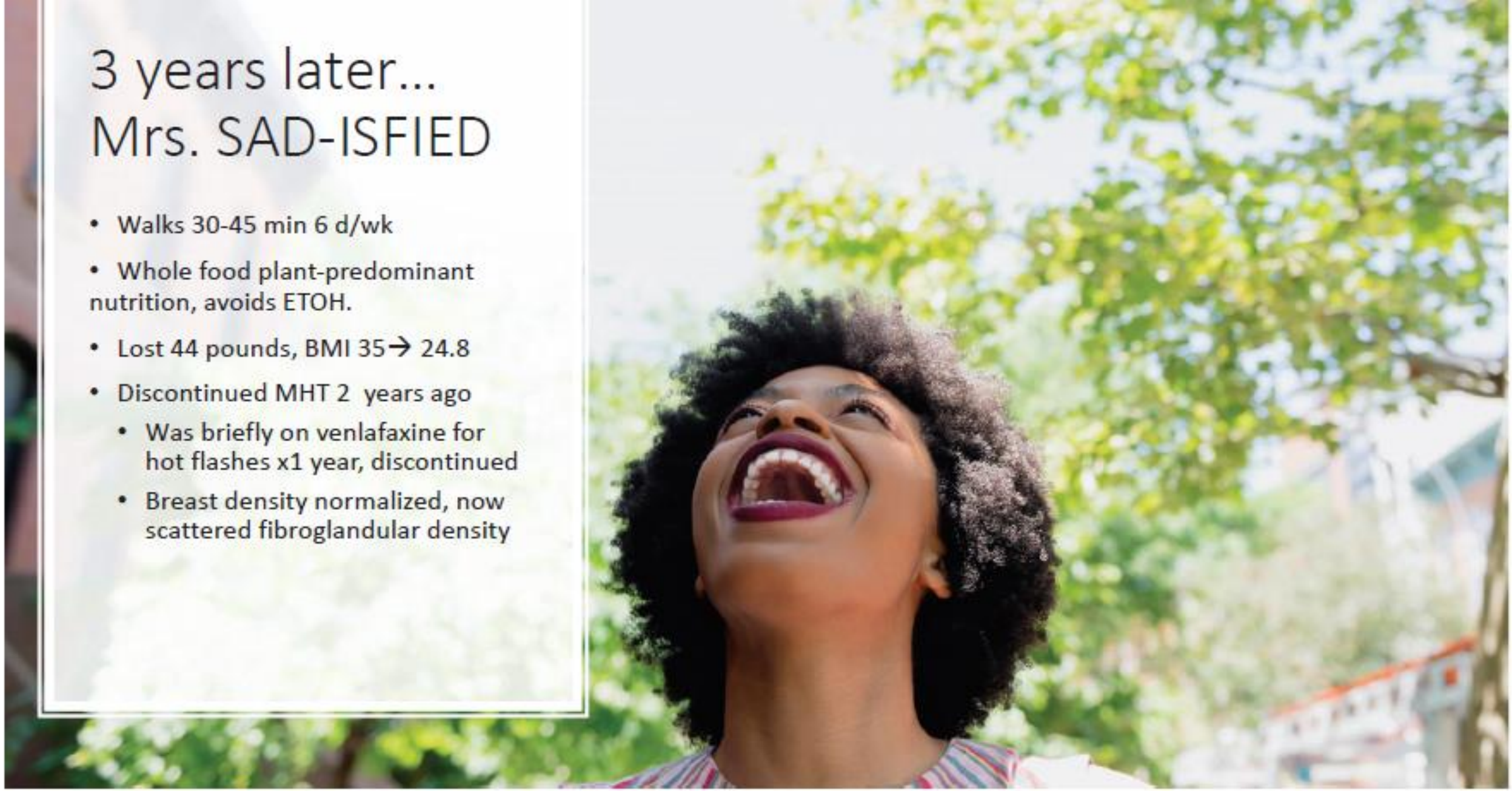
- Medications:
  - Metformin, glyburide, atorvastatin, HCTZ, losartan, oral estradiol and progesterone
- Family hx:
  - Mom DCIS (70)- CAD, DM2
  - 2 maternal aunts- CAD, DM2
  - 1 pa aunt- CAD
  - 3 younger sisters- two with DM2
- Menarche 10; Menopause 51; G0P0
- Breast density: heterogeneously dense
- Breast biopsy: non- sclerosing adenosis, concordant

MRS. SAD

- IBIS/ Tyrer-Cuzick
  - 28% lifetime risk
  - 9.4% risk at 10 years
- Very high risk of breast cancer
- Recommendation(s):
  - Annual mammogram plus high-risk MR
  - Discuss risk reducing medications benefit vs. risk
  - **Lifestyle Medicine approach to Mrs. SAD's breast cancer risk reduction and overall HEALTHcare**

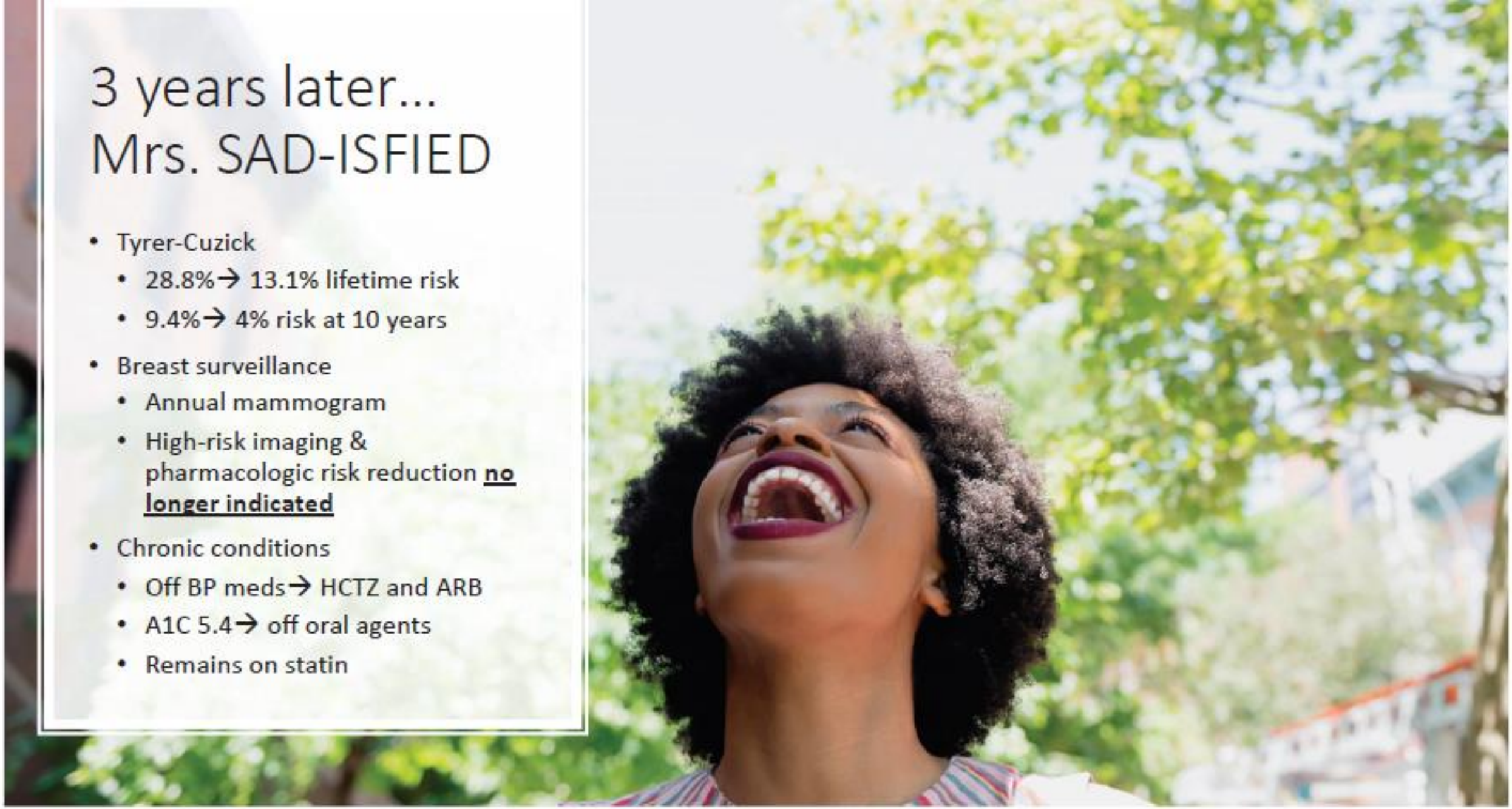
3 years later…
Mrs. SAD-ISFIED

- Walks 30-45 min 6 d/wk
- Whole food plant-predominant nutrition, avoids ETOH.
- Lost 44 pounds, BMI 35→ 24.8
- Discontinued MHT 2 years ago
  - Was briefly on venlafaxine for hot flashes x1 year, discontinued
  - Breast density normalized, now scattered fibroglandular density



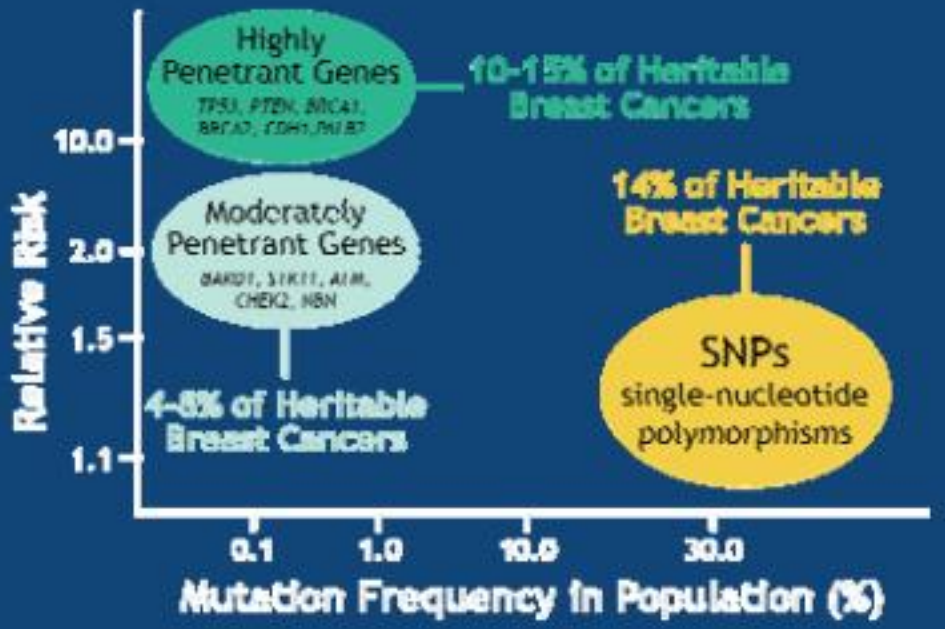
3 years later…
Mrs. SAD-ISFIED

- Tyrer-Cuzick
  - 28.8%→ 13.1% lifetime risk
  - 9.4%→ 4% risk at 10 years
- Breast surveillance
  - Annual mammogram
  - High-risk imaging & pharmacologic risk reduction **no longer indicated**
- Chronic conditions
  - Off BP meds→ HCTZ and ARB
  - A1C 5.4→ off oral agents
  - Remains on statin



Hereditary Breast Cancer Risk

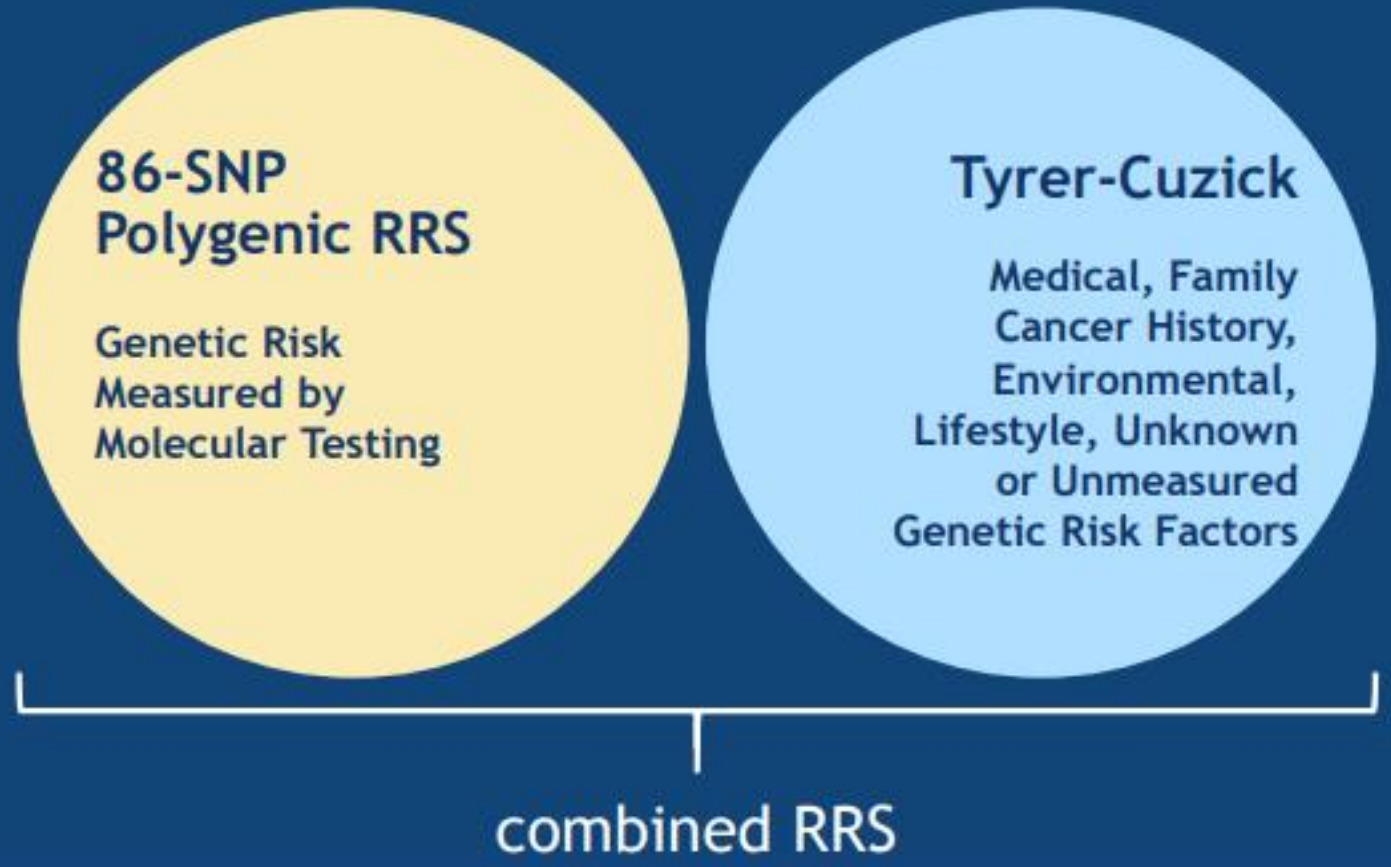
- Fewer than 10% of unaffected women with a family history of breast cancer carry a monogenic mutation in known moderate- or high-penetrance breast cancer-risk genes.
- Some missing breast cancer genetic risk is explained by common variants (SNPs).
- SNPs ***individually*** confer a modest breast cancer risk, but are clinically meaningful when ***combined*** in a polygenic risk score.



Adapted from Foulkes et al. *N Engl J Med*. 2008;13:2143-53

Combined Residual Risk Score (cRRS)

- A **combined residual risk score (cRRS)** was developed to capture:
  - Genetic risk factors: 86-SNP polygenic residual risk score (RRS)
  - Family history risk: Tyrer-Cuzick



Thank you for your attention