Fred Hutch
Cancer Center

SWOG Research in Cancer Prevention, Screening and Surveillance

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June 13, 2025

The mission of the SWOG Prevention, Screening and Surveillance Committee is to conduct impactful cancer prevention clinical trials and epidemiologic studies that change the standard of care and reduce cancer incidence in the United States and around the world.

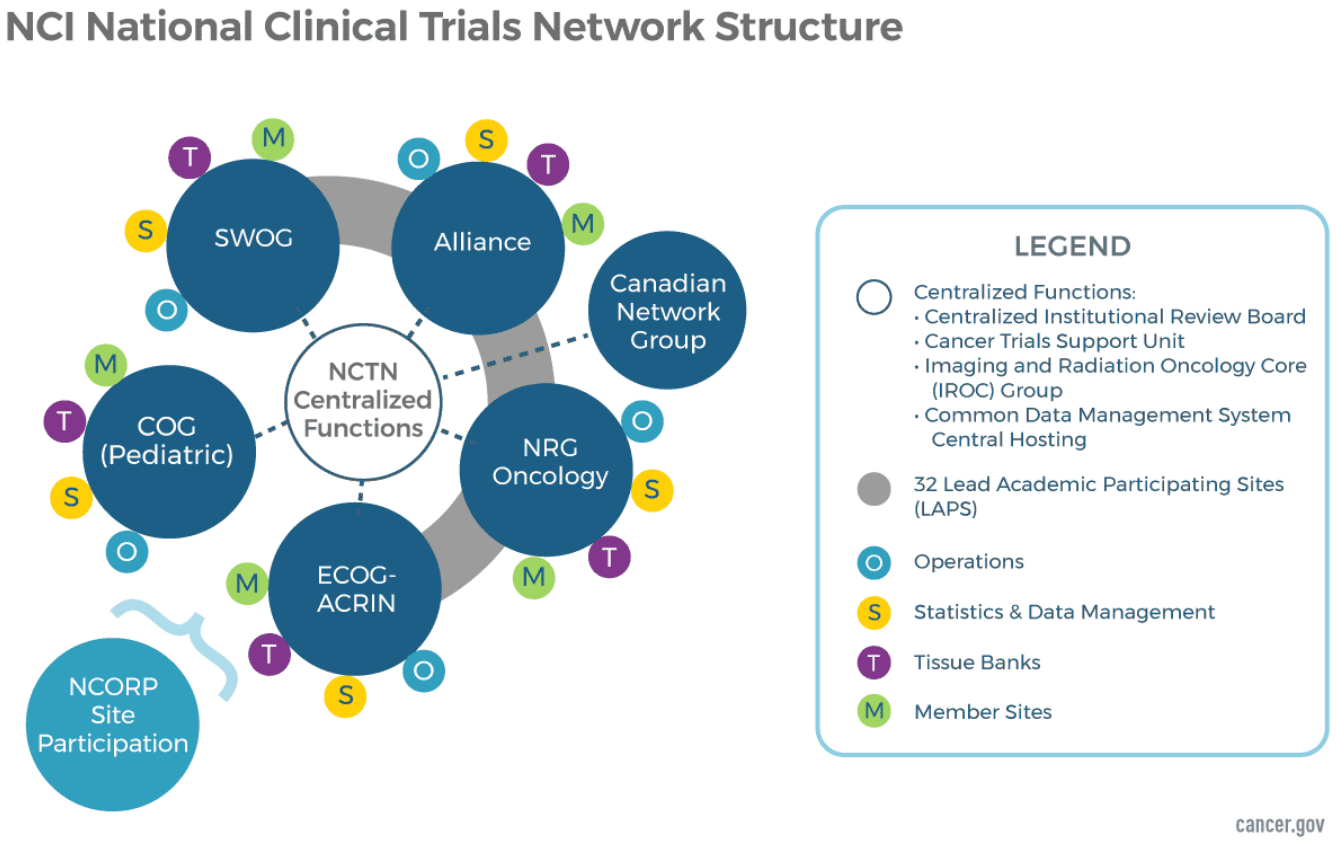
SWOG | CANCER RESEARCH NETWORK

The Committee's mission

is met through designing and implementing studies in these areas:

- Prevention trials in high-risk populations
- Prevention trials in average risk populations
- Screening trials and biomarker studies to identify markers for early detection or recurrence
- Trials to prevent second primary cancers and/or prevent progression of stage 0 or in situ disease
- Behavioral modification studies (i.e. smoking cessation)
- Implementation science to increase uptake of evidence-based, effective prevention practices (i.e., chemoprevention, vaccines).

Why is there a Prevention Committee in a treatment trial group?



Fred Hutch is a LAPS site

THE CANCER CONTROL CONTINUUM

FOCUS

Etiology

- Environmental factors
- Genetic factors
- Gene-environment interactions
- Medication (or pharmaceutical exposure)
- Infectious agents
- Health behaviors

Prevention

- Tobacco control
- Diet
- Physical activity
- Sun protection
- HPV vaccine
- Limited alcohol use
- Chemoprevention

Detection

- Pap/HPV testing
- Mammography
- Fecal occult blood test
- Colonoscopy
- Lung cancer screening

Diagnosis

- Shared and informed decision making

Treatment

- Curative treatment
- Non-curative treatment
- Adherence
- Symptom management

Survivorship

- Coping
- Health promotion for survivors

CROSSCUTTING AREAS

Communications

Surveillance

Health Disparities

Decision Making

Implementation Science

Health Care Delivery

Epidemiology

Measurement

Adapted from David B. Abrams, Brown University School of Medicine

How does the work get done?

Within each of the research groups (SWOG, Alliance etc) there are sets of committees

- **Disease committees**
  - Breast, Lung, GU, lymphoma, leukemia etc
  - Rare cancers

Therapeutic trials

- **Cancer Control Committees** – varies by each Research Base
  - All have Cancer Care Delivery – required by the NCI
  - SWOG has:
    - Prevention, Screening & Surveillance
    - Symptom Management and Survivorship
    - Palliative and End-of-Life Care

These committees have their own studies, but may leverage the treatment trials, depending on the study goals, design

- **Other committees** (research support)
  - Pharmacy, Recruitment & Retention, Radiation etc

Group	Committees
• SWOG	• Prevention Screening & Surveillance • Symptom Management & Survivorship • Palliative Care • Cancer Care Delivery (CCDR)
• NRG	• Cancer Prevention • Cancer Control • Health Disparities • CCDR
• Alliance	• Health Disparities • Older Adults • Health Outcomes • CCDR • Prevention • Symptom Interventions • Dissemination and Implementation
• ECOG-ACRIN	• Prevention, Screening and Surveillance • Cancer Control and Survivorship • CCDR • Health Equity
• URCC	• Cancer Prevention and Control • CCDR
• Wake Forest	• Cancer Prevention and Control • CCDR
• Children's Oncology Group	• Cancer Control and Supportive CCDR • Health Disparities and Diversity Committee

Examples of recent studies in the SWOG Prevention, Screening and Surveillance Committee

14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial

www.thelancet.com Vol 378 August 6, 2011

E Robert Greenberg, Garnet L Anderson, Douglas R Morgan, Javier Torres, William D Chey, Luis Eduardo Bravo, Ricardo L Dominguez, Catterina Ferreccio, Rolando Herrero, Eduardo C Lazcano-Ponce, María Mercedes Meza-Montenegro, Rodolfo Peña, Edgar M Peña, Eduardo Salazar-Martínez, Pelayo Correa, María Elena Martínez, Manuel Valdivieso, Gary E Goodman, John J Crowley, Laurence H Baker

- Promoting cancer prevention and control in low to middle income countries through the SWOG Latin America Initiative
- Gastric cancer is the second leading cause of cancer-related death worldwide, particularly in Latin America and East Asia.
- *Helicobacter pylori* infection accounts for the majority of gastric cancer cases.
- Population-wide eradication programs that are practical and affordable may reduce the health burden of *H.pylori* infection.

S0701: Study Design

- **Study population**: Healthy men and women, age 21-65, positive urea breath test for *H.pylori (N=1469)*
- **Study intervention:**
- 1) Standard triple therapy x14d (lansoprazole/amoxicillin/clarithromycin bid);
- 2) Concomitant therapy x 5d;
- 3) Sequential therapy (lansoprazole/amoxicillin x5d, lansoprazole/ clarithromycin/metronidazole x5d)
- **Primary endpoint:**
- Eradication of *H.pylori* at 6-8wks

S0701: Results

	N	*Helicobacter pylori* eradication	Difference from standard group (adjusted 95% CI for difference)
Intention to treat (N= 1463)			
14-day standard therapy	488	401 (82·2% [78·5 to 85·5])	..
5-day concomitant therapy	489	360 (73·6% [69·5 to 77·5])	8·6% (2·6 to 14·5)
10-day sequential therapy	486	372 (76·5% [72·5 to 80·2])	5·6% (–0·4 to 11·6)
Definitive 6-week UBT (N=1414)			
14-day standard therapy	475	401 (84·4% [80·8 to 87·6])	..
5-day concomitant therapy	471	360 (76·4% [72·3 to 80·2])	8·0% (2·2 to 13·7)
10-day sequential therapy	468	372 (79·4% [75·5 to 83·1])	4·9% (–0·9 to 10·8)
Adherent to therapy (N=1314)			
14-day standard therapy	434	378 (87·1% [83·6 to 90·1])	..
5-day concomitant therapy	442	348 (78·7% [74·6 to 82·5])	8·4% (2·7 to 14·0)
10-day sequential therapy	438	355 (81·1% [77·1 to 84·6])	6·0% (0·3 to 11·8)

Data are number (% [95% CI]) unless otherwise indicated. UBT=urea breath test.

S0701: Conclusions

- The prevalence of *H.pylori* infection was high at ~80% in these Latin American sites.
- Compliance to all three antiobiotic regimens was high at >90%.
- *H.pylori* eradication rates:
- 1) 14d standard therapy (82%) standard therapy remained the best
- 2) 5d concomitant therapy (74%)
- 3) 10d sequential therapy (77%)
- *H.pylori* eradication programs may be cost-effective if they reduced prevented at least 10% of gastric cancer deaths.

SWOG Trial: S0820

"A Double Blind Placebo-Controlled Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers in Patients with Stage 0-III Colon or Rectal Cancer, Phase III"

Jason Zell, DO, MPH

PACES
Preventing Adenomas of the Colon with Eflornithine & Sulindac

SWOG Lead Investigator:

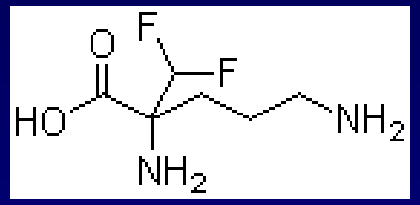
Jason Zell, DO, MPH
Division of Hematology/Oncology
Dept. of Medicine
School of Medicine
Chao Family Comprehensive Cancer Ctr
University of California, Irvine

SWOG co-PI: Powel Brown, MD, PhD
SWOG Lead Statistician: Joe Unger, PhD
SWOG co-I: Robert Krouse, MD

NCTN co-PI's:

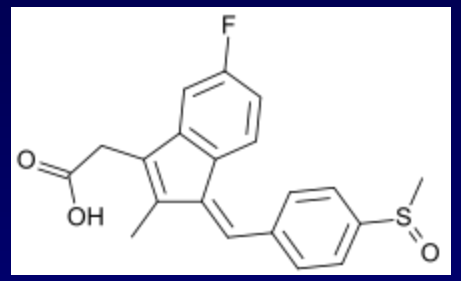
Raymond Bergan, MD (ECOG-ACRIN)
Jennifer Dorth, MD (NRG)
Y. Nancy You, MD (ALLIANCE)

Eflornithine and Sulindac Effects on Polyamine Metabolism



Eflornithine (DFMO)

Sulindac



PPARγ

Ornithine

ODC

Polyamines

SSAT

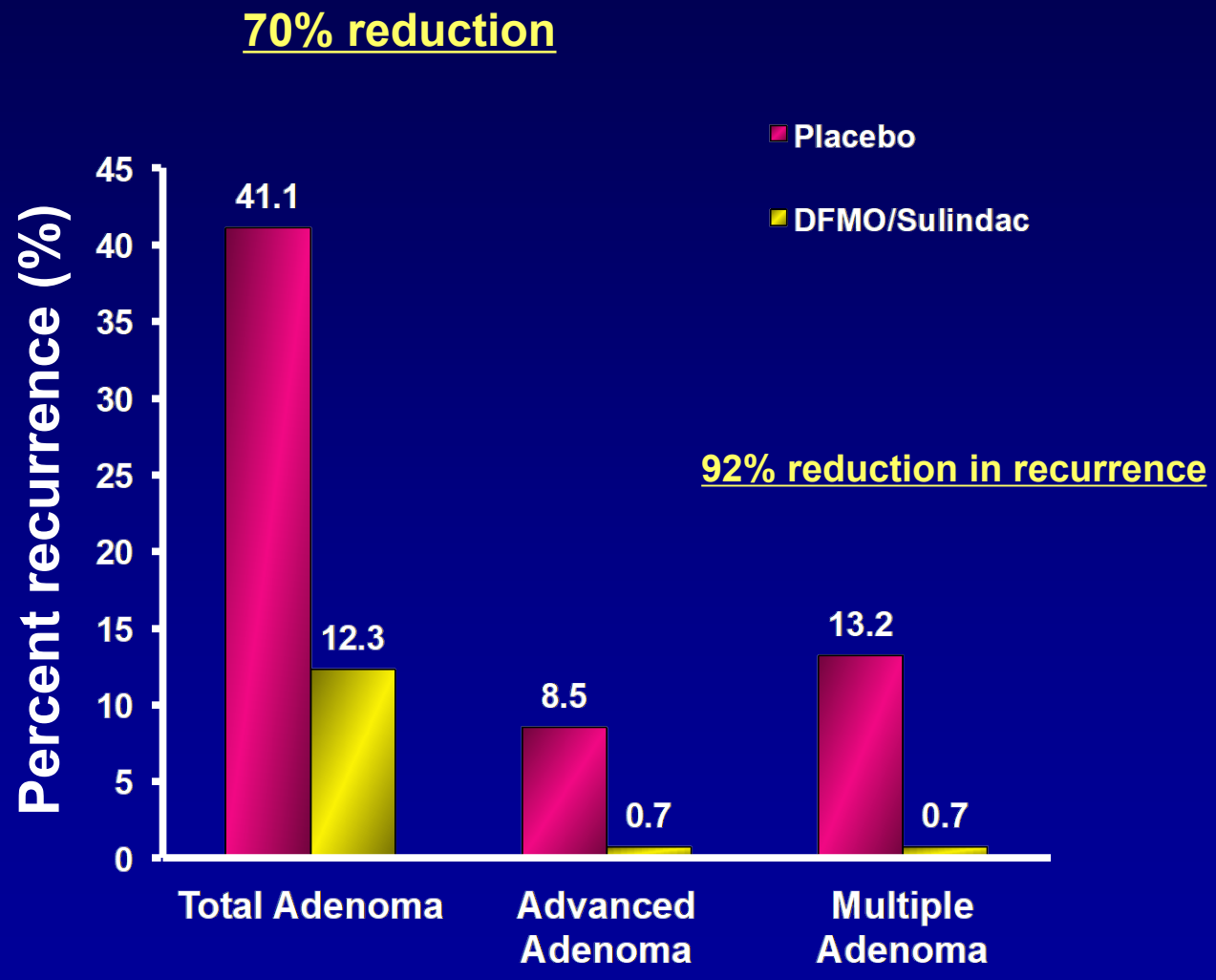
Export

Marked Reduction of Adenomatous Polyps by Eflornithine + Sulindac vs. Placebo[1]

Inclusion:
- ≥ 1 resected adenoma ≥ 3mm
- No hearing loss

Treatment:
- Eflornithine 500mg/d + Sulindac 150mg/d X 3y

Side effects:
- Serious cardiovascular events
  - All: 4.9% v 8.4%, NS
  - High risk: *n*= 3 v 9
  - Low-Mod risk: *n*= 6 v 7
- Hearing
  - Speech range: -0.99 dB difference, NS



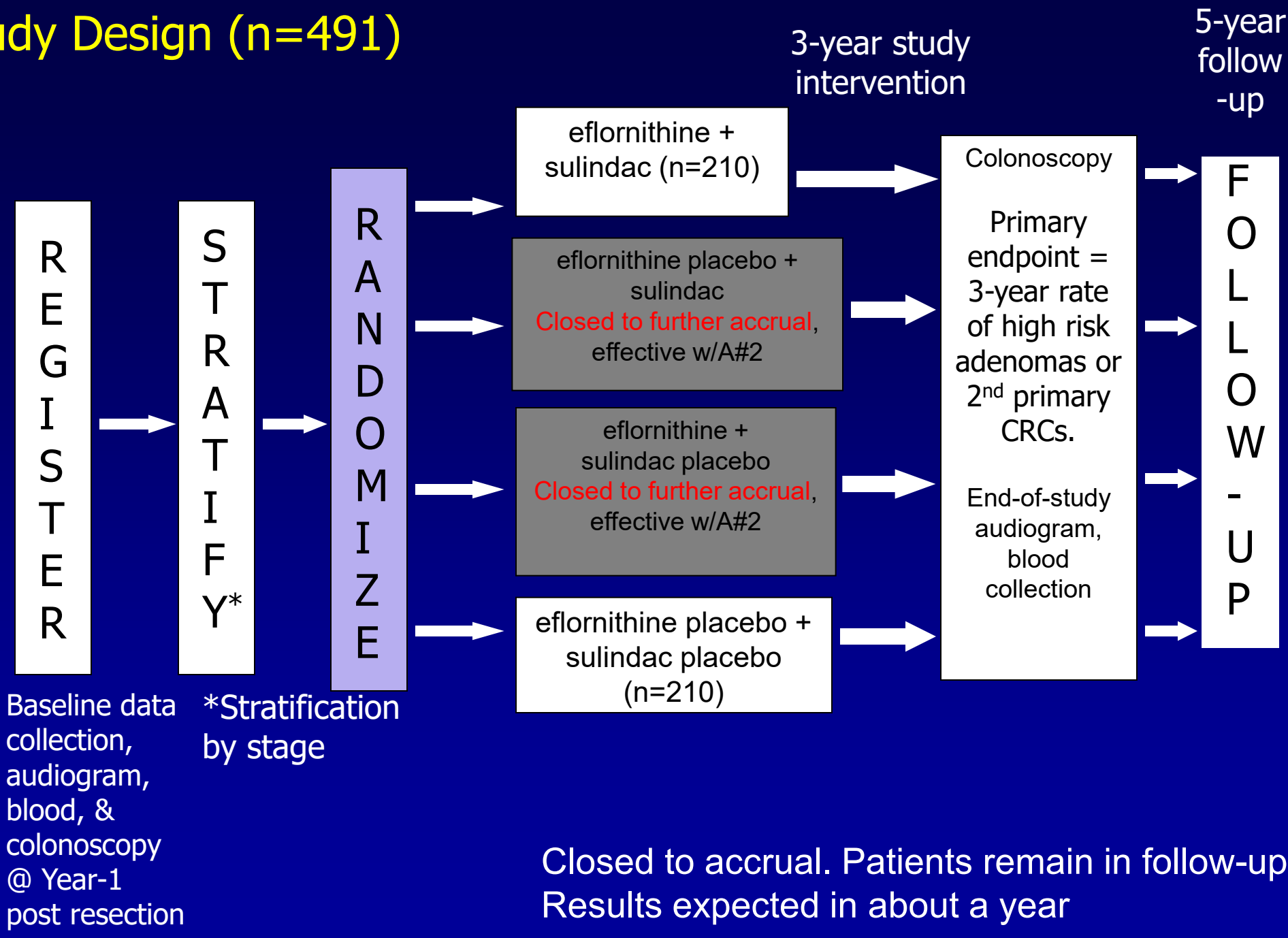
1. Meyskens, *Cancer Prevention Research,* 2008 (1: 9-11).

Primary Objective: to assess whether the polyamine-inhibitory combination: eflornithine 500 mg/d and sulindac 150 mg/d (vs. placebos) are effective in reducing the 3-year rate of high risk adenomas or 2nd primary CRCs in stage 0, I, II, and III colon and rectal cancer patients.

- Primary Endpoint:
  - High risk adenomas (HRA)
    - high-grade dysplasia
    - villous features
    - size ≥ 1 cm
    - Multiple (3 or more) adenomas
  - Second Primary Colorectal Cancers (SPCRC)

Goal is a 50% *(proposed: 60%) reduction in HRAs or SPCRCs at 3 years for combination E+S vs. combination placebos

S0820 Study Design (n=491)



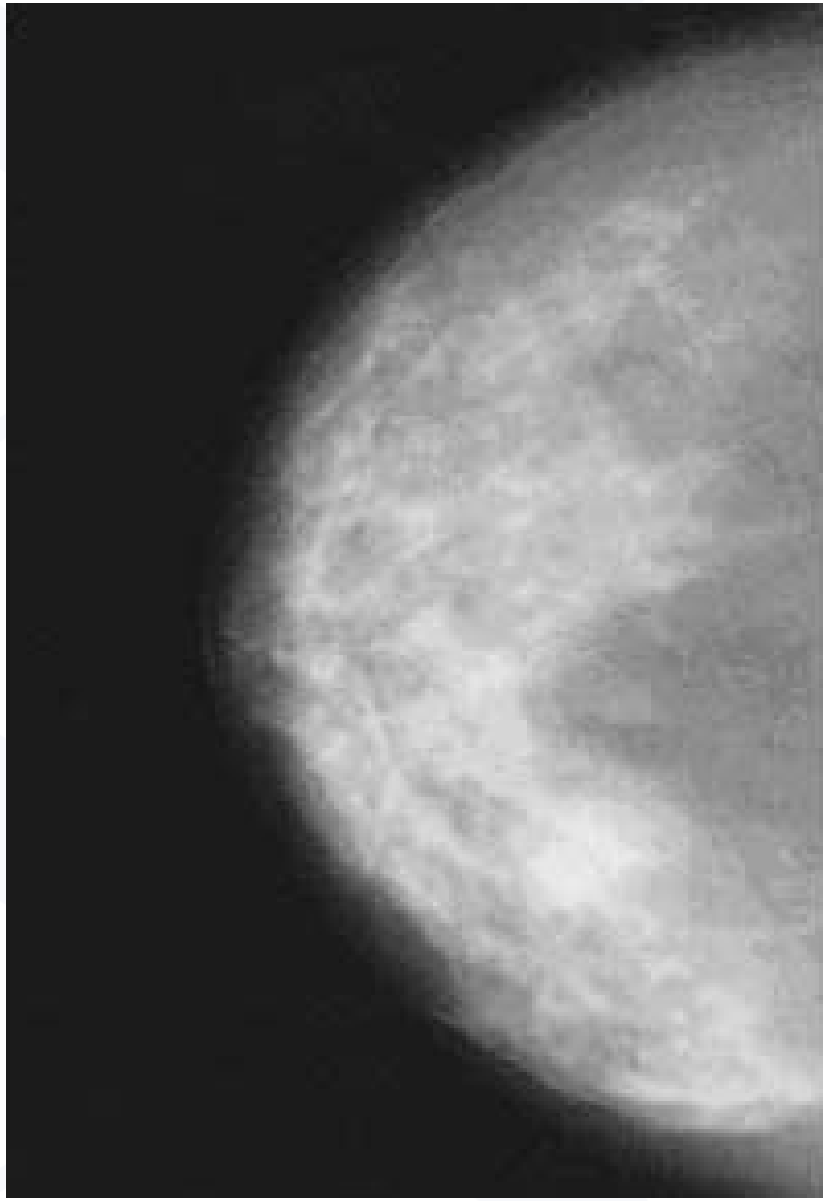
Closed to accrual. Patients remain in follow-up
Results expected in about a year

Early phase chemoprevention trials

- Large-scale chemoprevention trials with cancer incidence as the primary outcome require large sample sizes and long-term follow-up.
- Need for surrogate endpoints for cancer incidence in order to conduct more efficient chemoprevention trials.
- Translational potential with the analysis of tissue and circulating biomarkers of cancer risk to understand underlying mechanisms of carcinogenesis.

Knowledge gaps in breast cancer chemoprevention

- Need for safe and effective chemopreventive agents, particularly for high-risk premenopausal
- No proven chemopreventive agents for estrogen receptor-negative breast cancer
- Development of surrogate endpoint biomarkers which correlate with breast cancer risk and response to therapy. Can mammographic density be such a biomarker?



S0812: Vitamin D supplementation in high-risk premenopausal women

Eligibility:

- 5-yr Gail risk ≥1.67% or lifetime risk ≥20% (Gail, Claus, BRCAPro, IBIS)
- ADH, ALH, LCIS, DCIS
- *BRCA1/2, PTEN, p53* mutation
- stage I-II breast CA, >5yrs in remission
- MD >50%

Premenopausal, Age 18-50
Baseline MD >10%
Serum 25(OH)D ≤32ng/ml
(N = 208)

RANDOMIZE

→ **Cholecalciferol (D3) 20,000 IU weekly x 1yr (very high dose)**

→ **Matching placebo x 1yr**

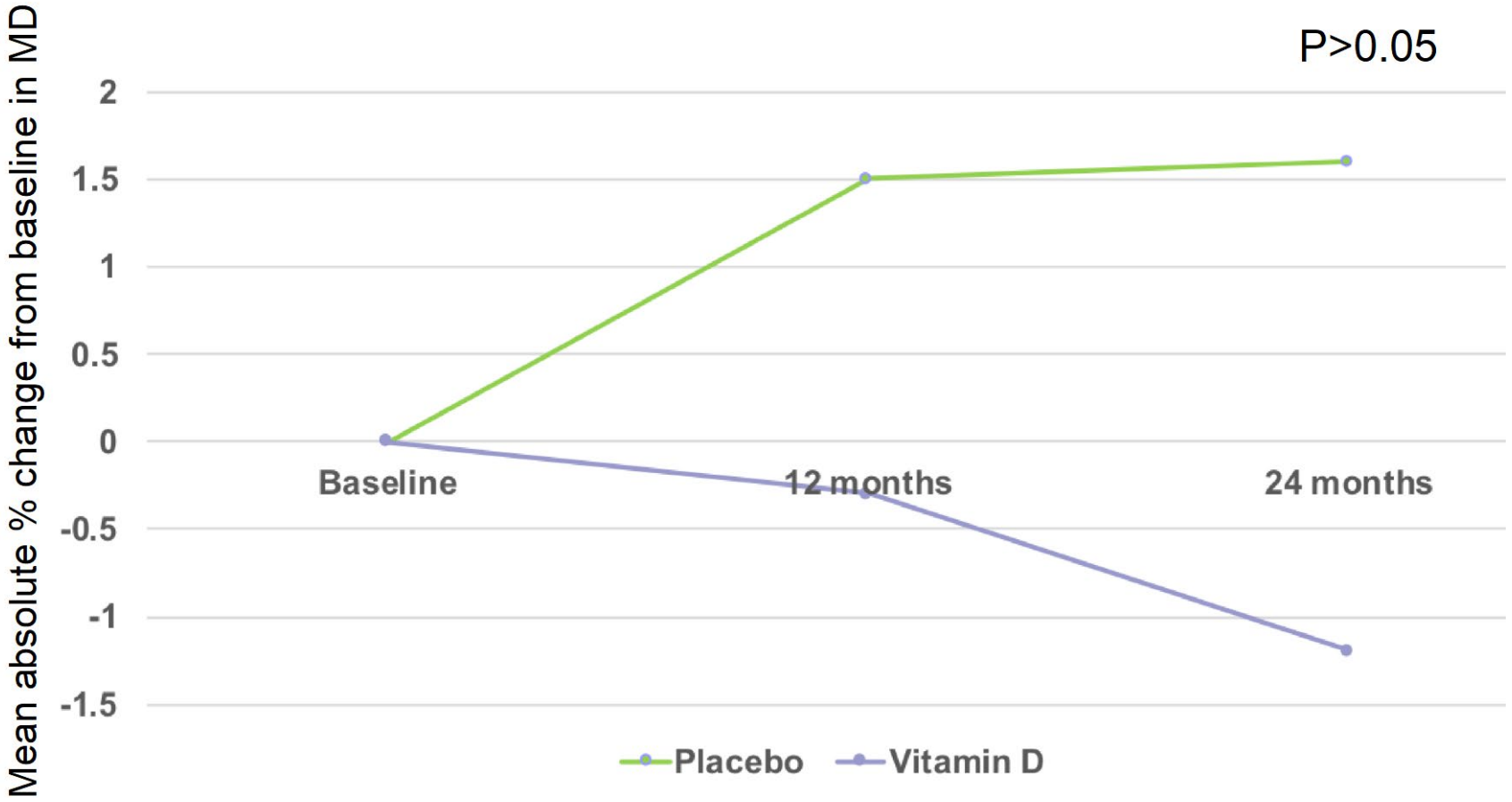
Baseline data:
Mammogram
Core breast biopsy
Blood

Follow-up data
Mammogram
Core breast biopsy
Blood

Primary Endpoint: **Change in mammographic density**
Secondary Endpoints: **Serum and tissue-based biomarkers, toxicity**

Results for S0812

No significant difference for mammographic density



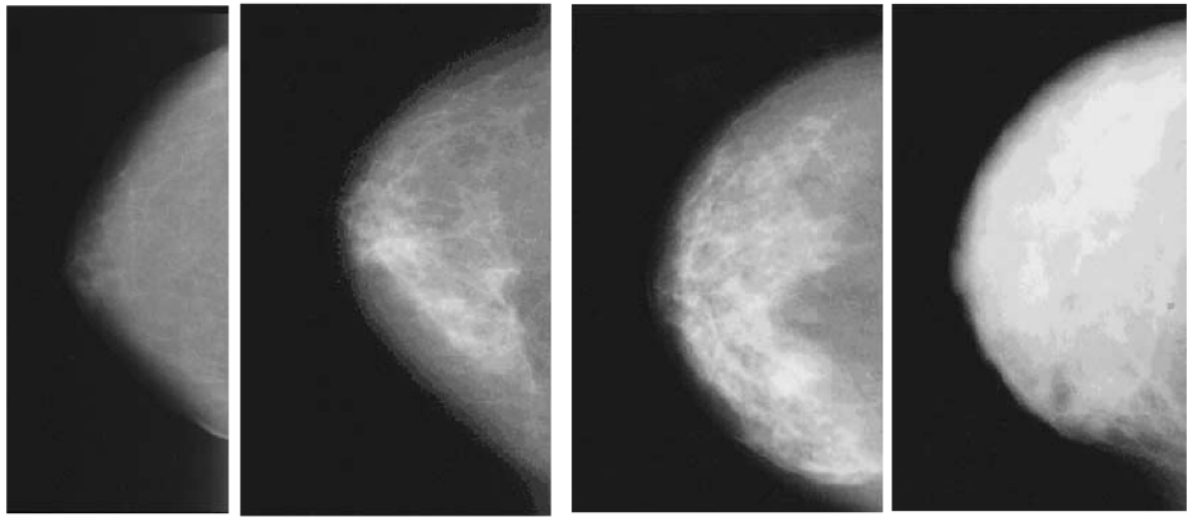
Also no significant difference

For biomarkers: IGF-1, IGFBP3 or their ratio

Interest in MD remains priority

- Breast cancer chemoprevention trials with primary outcomes of breast cancer incidence require large sample sizes and long-term follow-up.
- Mammographic density (MD) is a strong predictor of breast cancer risk and predicts response to tamoxifen in the chemoprevention and adjuvant settings.

(a) BI-RADS classification



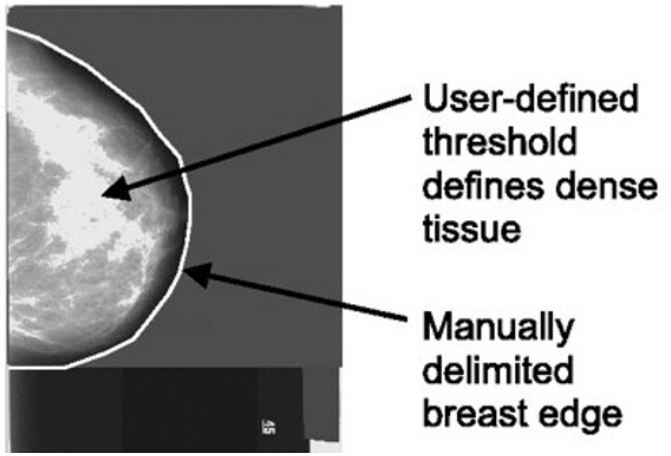
BI-RADS® 1 BI-RADS® 2 BI-RADS® 3 BI-RADS® 4

1 = Almost entirely fat (<25%) 2 = Scattered fibroglandular densities (25-50%)

3 = Heterogeneously dense (51-75%) 4 = Extremely dense (>75%)

(b) Cumulus threshold technique

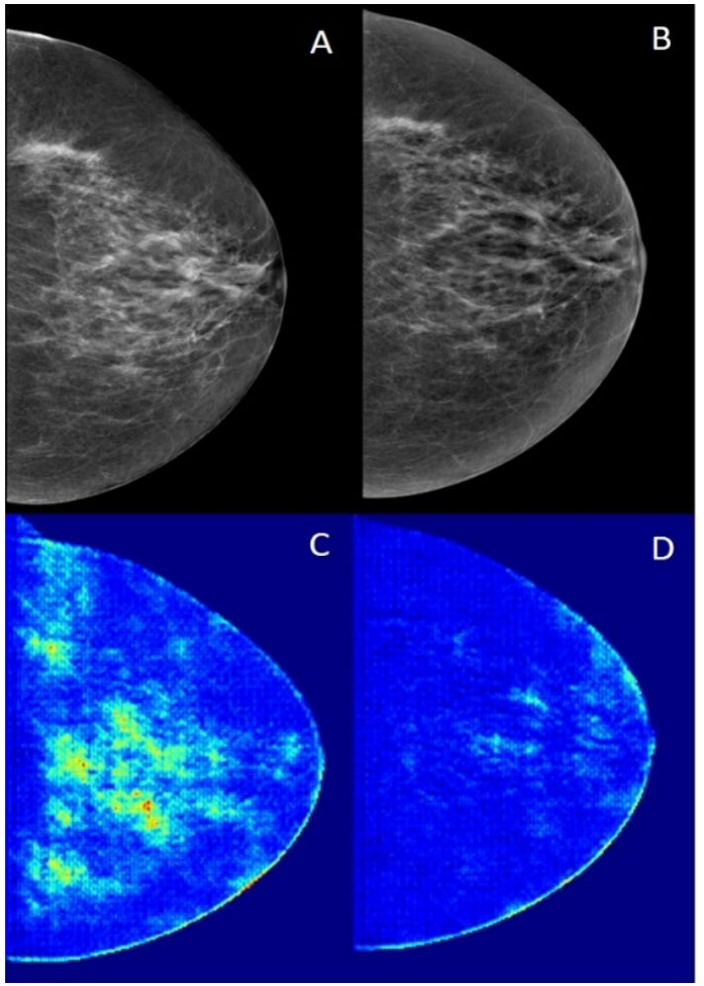
Breast area = 109.6 cm^2 (inside white line)
Dense area = 27.6 cm^2
Percent density = 25.2%



Boyd NEJM 2007
Cuzick JNCI 2011

CNN (convoluted neural network) Breast Cancer Risk Model

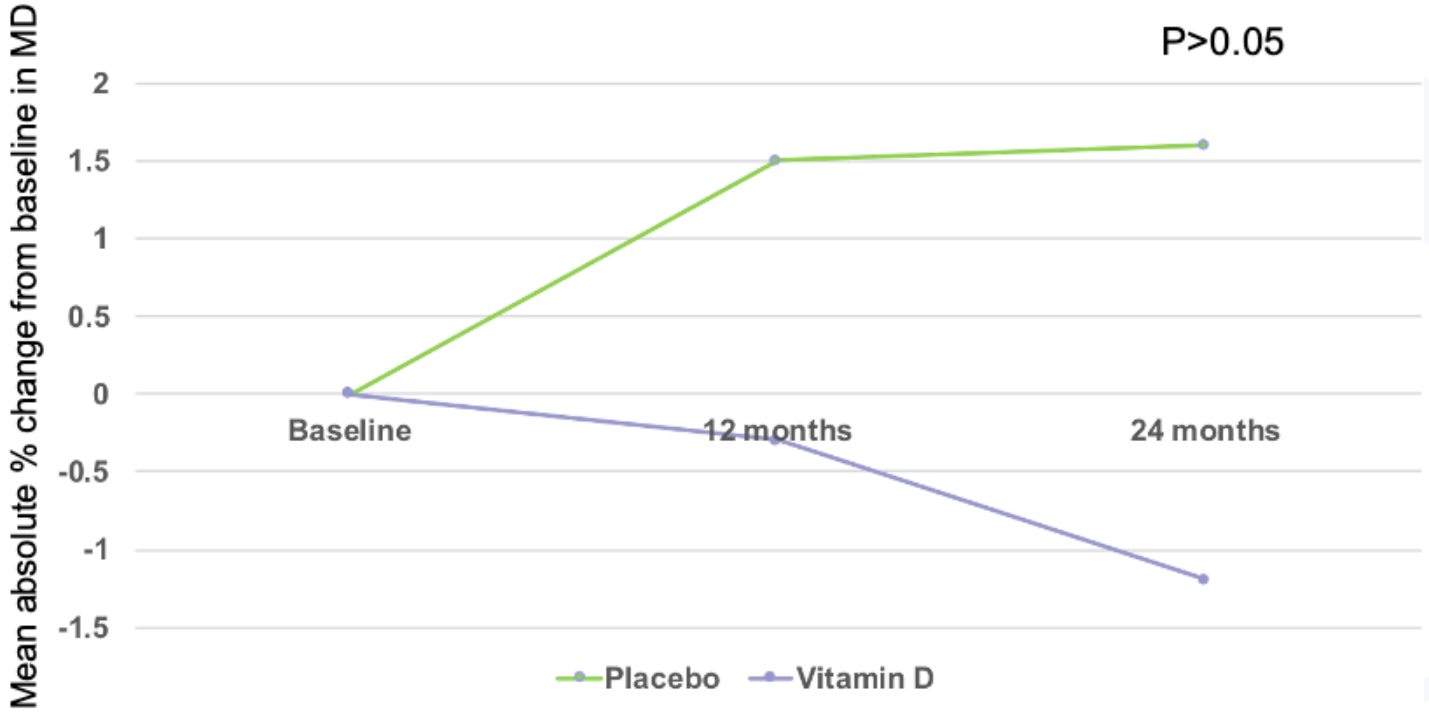
- Novel CNN-derived pixel-wise breast cancer risk model developed in retrospective case-control study of 210 incident breast cancer cases and 527 unaffected controls.
  - CNN risk model showed to greater predictive potential [OR=4.42, 95% CI=3.4-5.7] compared to MD [OR=1.67, 95% CI=1.4-1.9]
  - Overall accuracy of 72% (95% CI=69.8-74.4)
- Compared change in CNN risk score among high-risk women with AH/LCIS/DCIS who took tamoxifen chemoprevention (N=248, 34%) and those who did not (N=480, 66%)
  - Chemoprevention was associated with a greater mean absolute decrease in CNN risk score compared to no chemoprevention (-6.9% vs. -1.9%, p=0.014)



Ha Acad Radiol 2018
Mutasa ARRS 2019

Leveraging existing data

- **Aim 1:** CNN analysis of archived mammograms from S0812



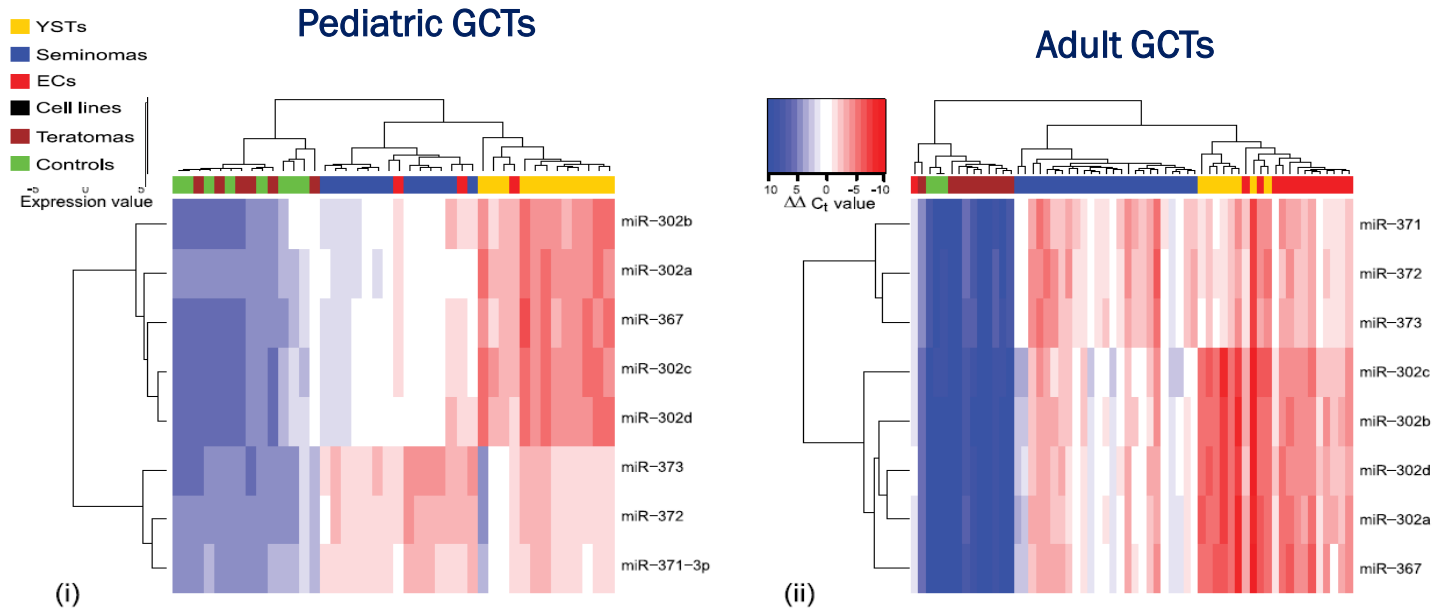
- **Aim 2:** Implement prospective collection and banking of mammograms in other SWOG prevention studies

S1823 Clinical Trial

Dr. Lucia Nappi, MD Ph.D
Assistant Professor, Department of Urologic Sciences
University of British Columbia
Senior Research Scientist, Vancouver Prostate Centre
Medical Oncologist, BC Cancer-Vancouver Centre
Vice-Chair, AYA SWOG Committee
Principal Investigator, S1823 SWOG trial

miRNAs in germ cell tumors (GCTs)

- miRNA 371 is expressed in > 90% of GCT, seminoma AND nonseminoma
- Specific for viable GCT (expressed only in pregnancy other than GCTs!)
- Not expressed by teratoma
- Serum/Plasma levels are correlated with clinical stage
- Rapid decrease and disappearance after successful treatment

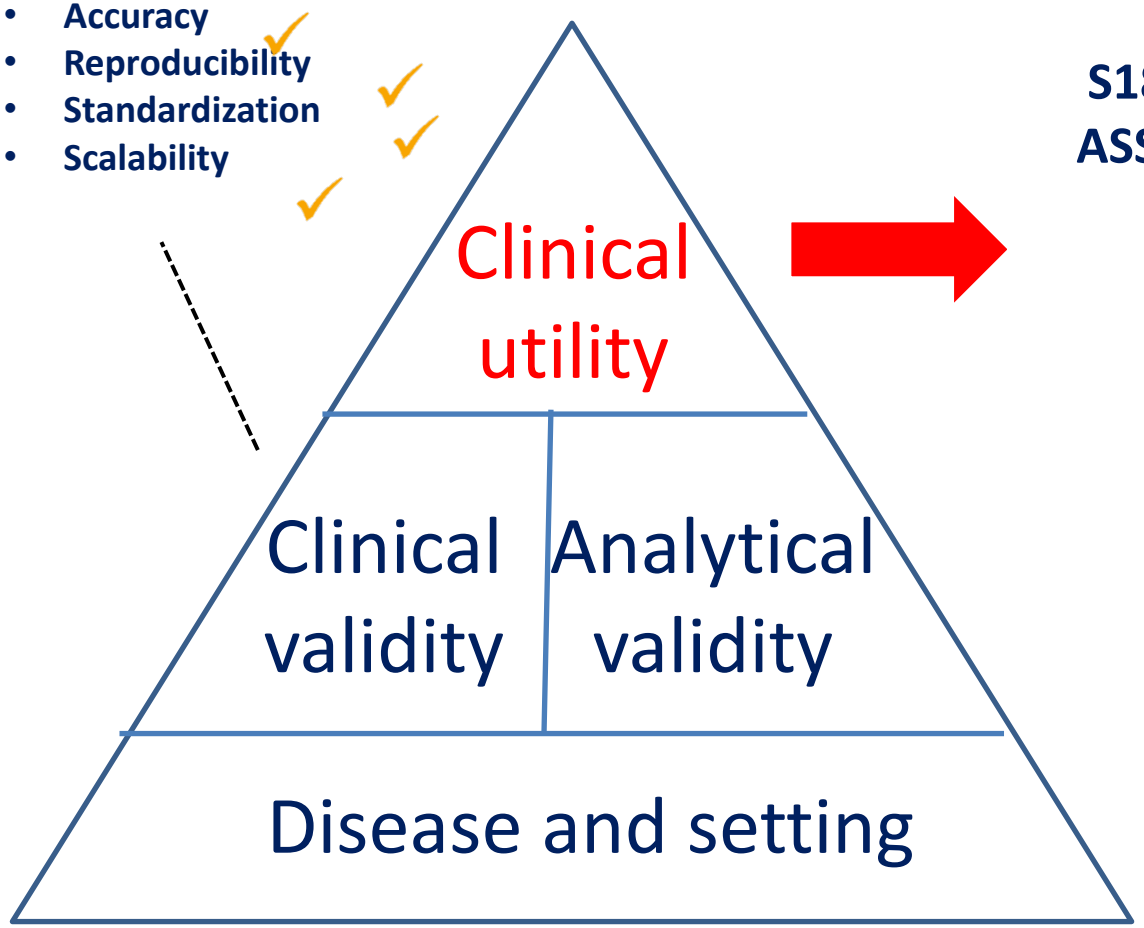


Nappi L et al. JCO 2019
Dieckmann K. et al, JCO 2019
Voorhoeve et al. ,2007
Palmer et al., 2010
Gillis et al., 2010

miR371 clinical utility validation: S1823 trial

Analytical validity (test performance)

- **Accuracy**
- **Reproducibility**
- **Standardization**
- **Scalability**



SWOG

S1823:A PROSPECTIVE OBSERVATIONAL COHORT STUDY TO ASSESS miRNA 371 FOR OUTCOME PREDICTION IN PATIENTS WITH NEWLY DIAGNOSED GERM CELL TUMORS trial

Study chairs: Dr. Nichols – Dr. Nappi

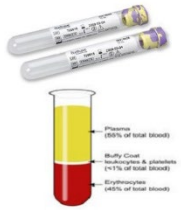
Very simple research question:

Can we use miR371 to predict / anticipate tumor relapse in patients with CSI/IIA GCT?

S1823: Trial concept

Simple question: can miRNA 371 be used to detect tumor relapse in patients with early stage GCTs?

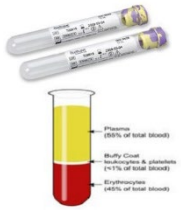
Blood collection: two Streck tubes for micro-RNA plasma extraction



CSI-IIA Post- Orchiectomy

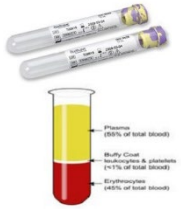
(required for all the participants)

Often declines to undetectable post orch.. *Do those with persistent detectable post-orch miRNA371 always relapse*?



Serial CT scans/markers

Unknown sensitivity in micrometastatic disease with current methodologies. *If post orch miR371 undetectable, does it become always become detectable prior to or concurrent with clinical relapse?*



No Relapse

Relapse

Is miR371 always detectable at the time of tumor relapse?

Canadian Cancer Trials Group
A national program of the Canadian Cancer Society

SWOG

- S1823 was activated in the USA on June 1-2020.
- The first patient was consented on July 27-2020
- Opened in Canada in December 2020
- Accrual completed in May 2024: 964 patients

Low risk	634
Moderate risk	174
High risk	155
Not yet assigned	1

S1823 – Current Status

Lab assays expected to be finished very soon, then data analysis and publication.

Multiple presentations at ASCO and ASCO-GU

MiCHOICE Study Schema

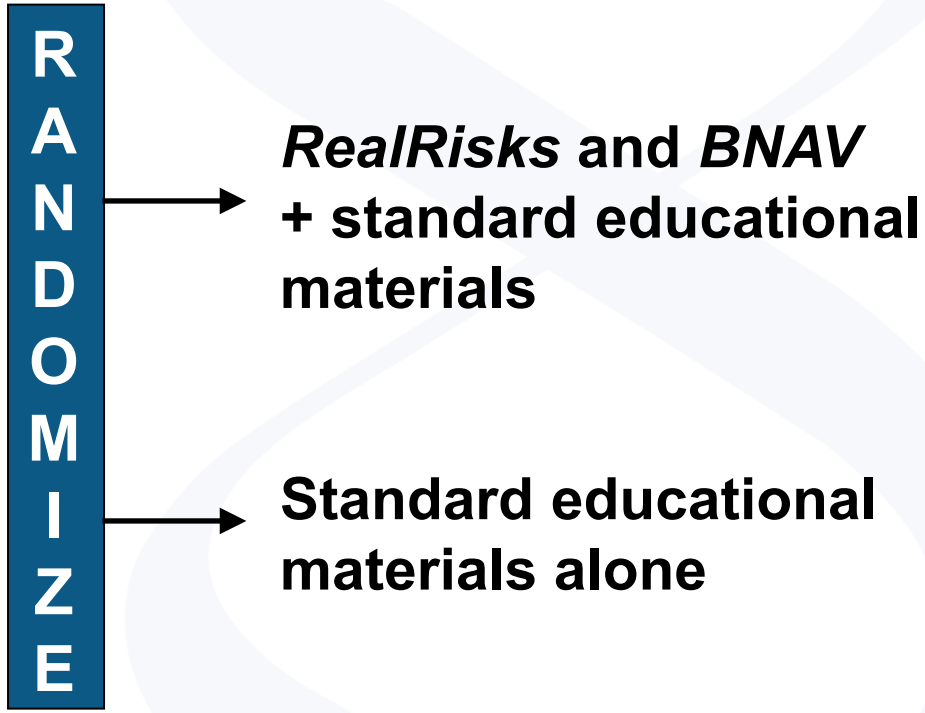
Clinic Eligibility:

- NCORP/NCTN site with common EHR/patient portal
- Exclude very low volume clinics*

Stratification factors:

- Low vs. high volume*
- MU-NCORP vs. non MU-NCORP/NCTN

(N = 26)



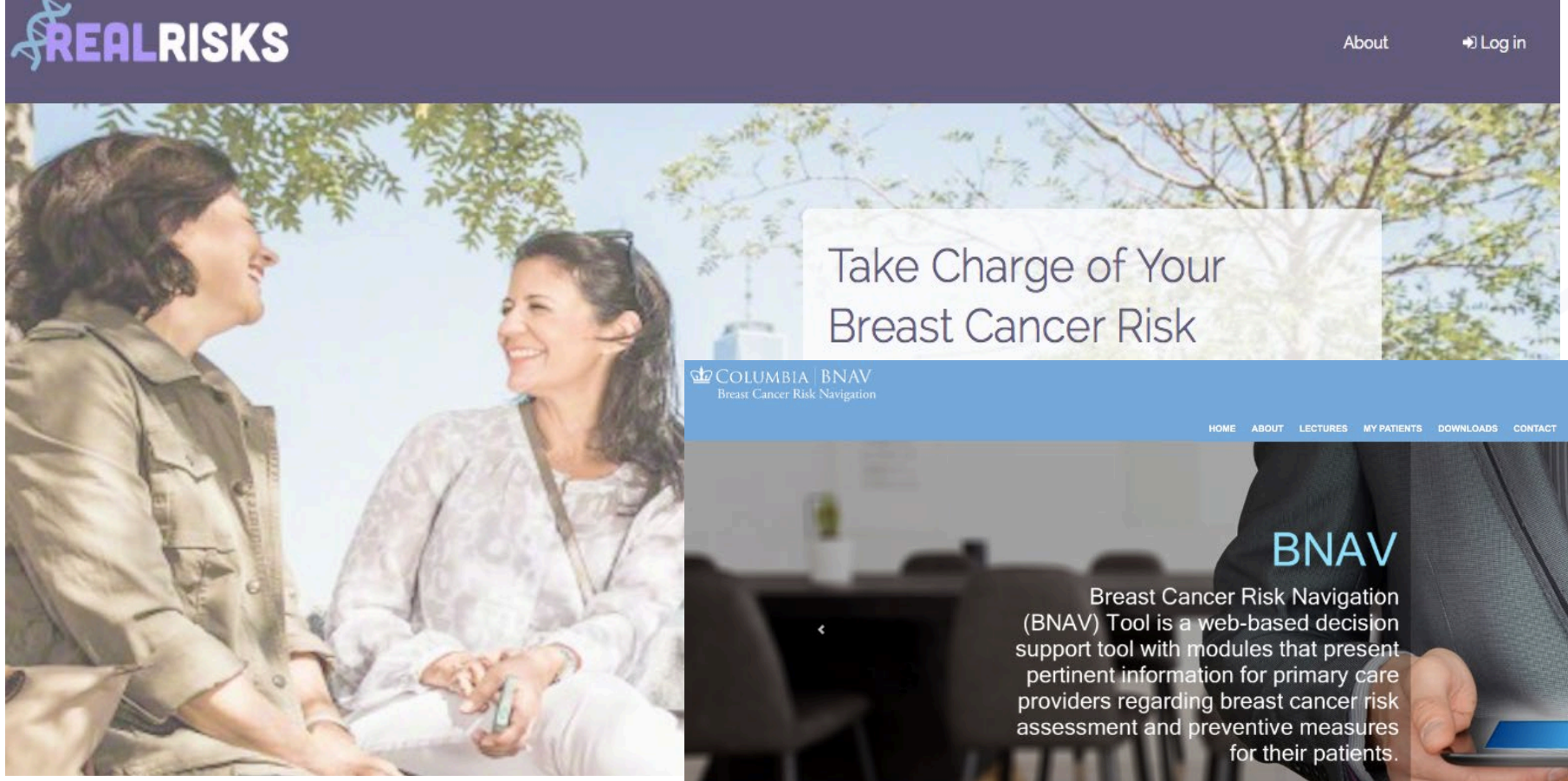
*Number of women with AH or LCIS seen per year by site: very low volume <50; low volume = 50-100; high volume >100.

Primary Endpoint: Chemoprevention informed choice at 6mo

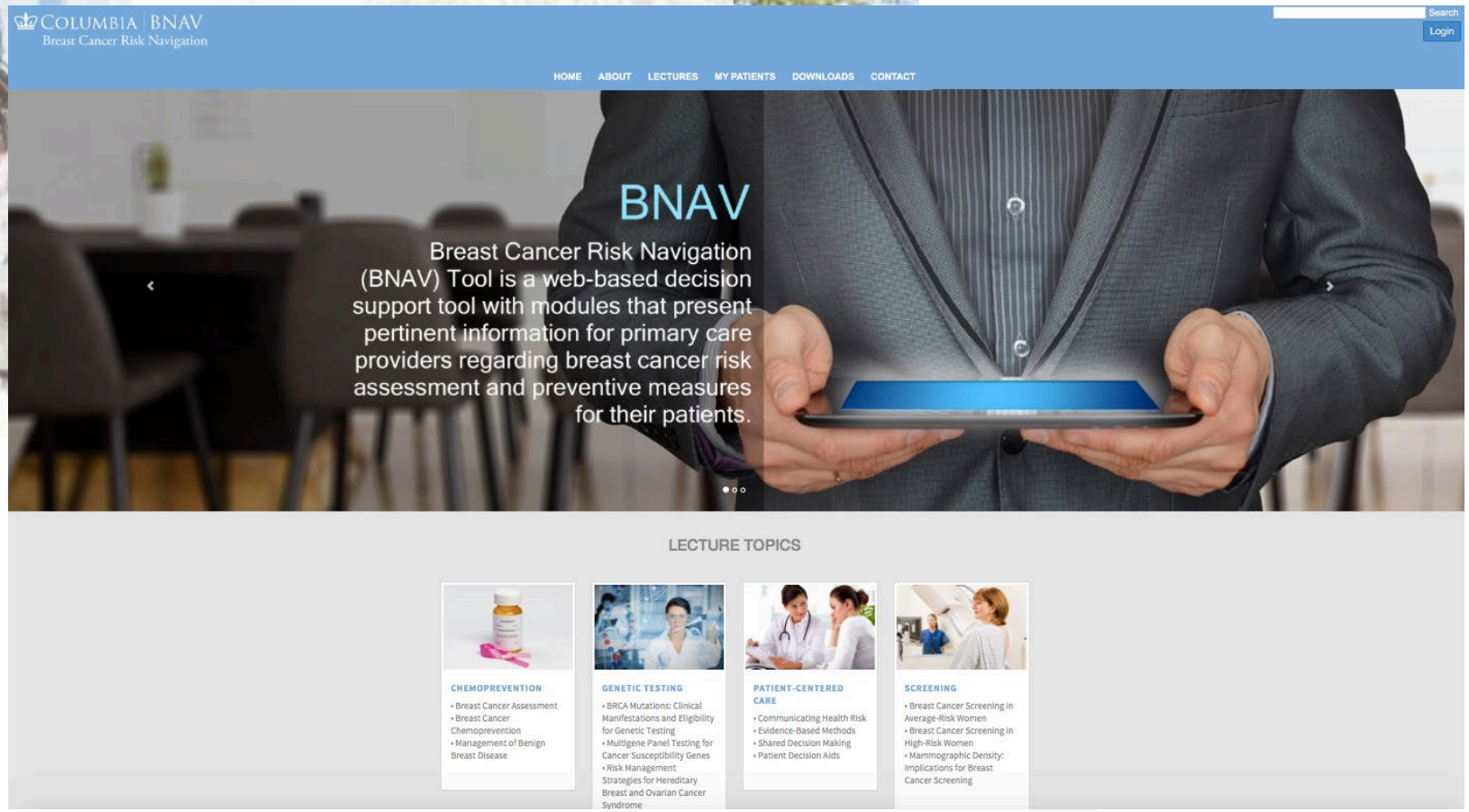
Secondary Endpoints: Breast cancer (BC) knowledge, perceived BC risk/worry, decision conflict/regret, shared decision-making, chemoprevention usage/adherence and reasons for discontinuation, implementation of decision support tools into clinic workflow

Eligibility Criteria – closed to accrual

- **Recruitment Centers** *(N=26)*
  - EHR and patient portal use in outpatient clinics
  - 50+ women with AH or LCIS per year
- **Healthcare Providers** *(N=200)*
  - Specialists and PCPs who see women with AH or LCIS
- **Patients** *(N=415)*
  - Women, age 35-74 years
  - AH or LCIS/lobular neoplasia, no personal history of breast cancer
  - No prior use of SERMs or AIs, no bilateral mastectomies
  - Internet access, able to receive email/text messages
  - English or Spanish-speaking



Realrisksdecisionaid.com



BNAVtool.com

Schedule of Evaluations

	Screening	Baseline	6mo[3]	12mo	Yearly for up to 5yrs
Eligibility	X				
Registration	X				
PROs					
Baseline characteristics[1]		X			
Chemoprevention knowledge		X	X	X	
Perceived breast cancer risk		X	X	X	
Breast cancer worry		X	X	X	
Decision conflict		X	X	X	
Chemoprevention intention/decision		X	X	X	
Informed choice		X	X	X	
Shared decision-making[1,2]			X		
Chemoprevention usage/adherence/ early discontinuation (if applicable)			X	X	X
Clinical outcome					
Breast cancer incidence				X	X

[1]Assessed in both patients and providers; [2]Assessed after clinic visit; [3]Clinic visit

How to get involved

- Anyone who wants to lead a study in the SWOG Prevention, Screening and Surveillance area
  - Present a 10 minute presentation at the monthly committee meeting
  - If there is interest and support, submit a 2 page concept to the SWOG Executive Committee
  - If support and interest, submit a 5-10 page proposal to SWOG Triage Committee
  - **Patient advocates must be involved throughout the process** (they are very helpful)
  - Upon approval and funding is secured, then detailed protocol is written and study is activated.

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Thank you