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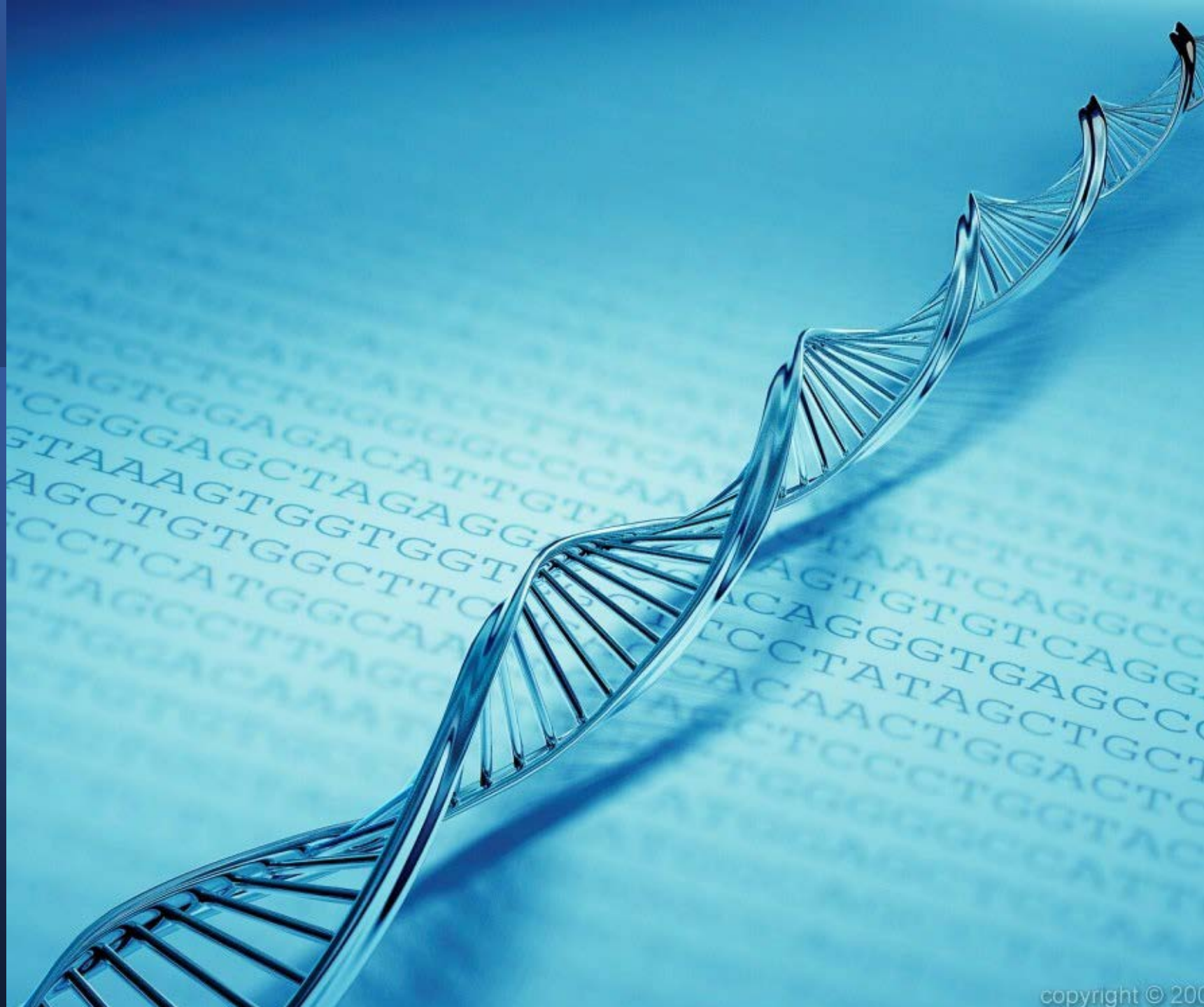
September 16, 2021

Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer



Disclosures

No conflicts of interest

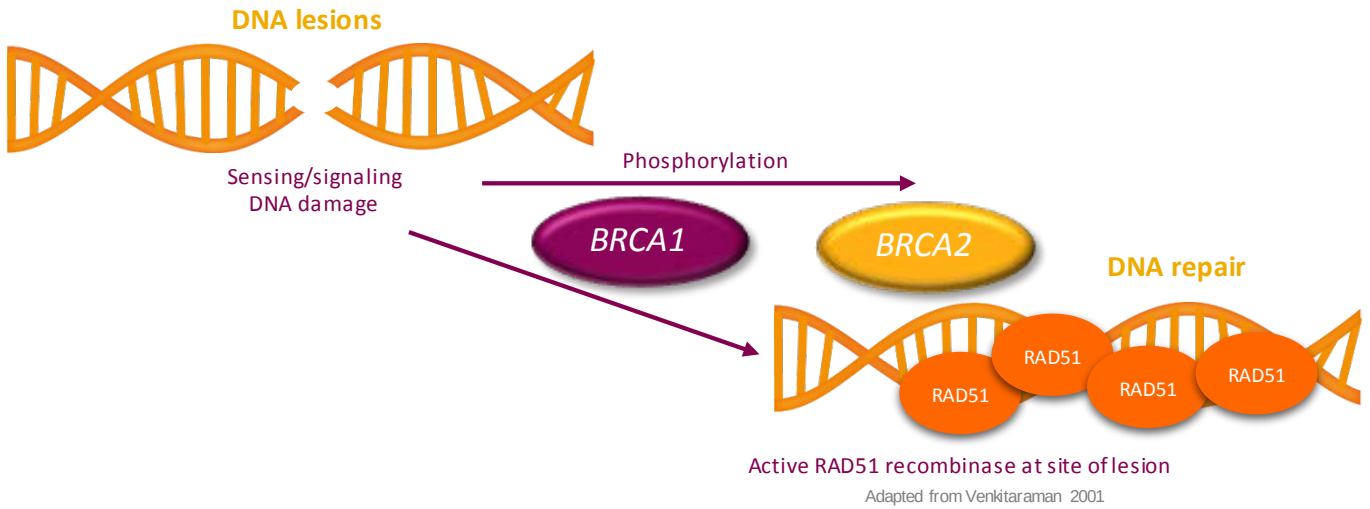
Objectives

Identify	Identify the features of family history and ethic background that influence hereditary risk
Describe	Describe the referral recommendations for genetic assessment of hereditary breast and ovarian cancer syndrome including the associated other cancer risks.
Summarize	Summarize the cancer risks associated with BRCA1 and 2 mutations from women and men as well as that of less common mutations associated with breast cancer risk
Recommend	Ovarian and breast cancer risk management options
Cite	Cite the management of other cancer risks associated with BRCA mutations

What is the BRCA gene?

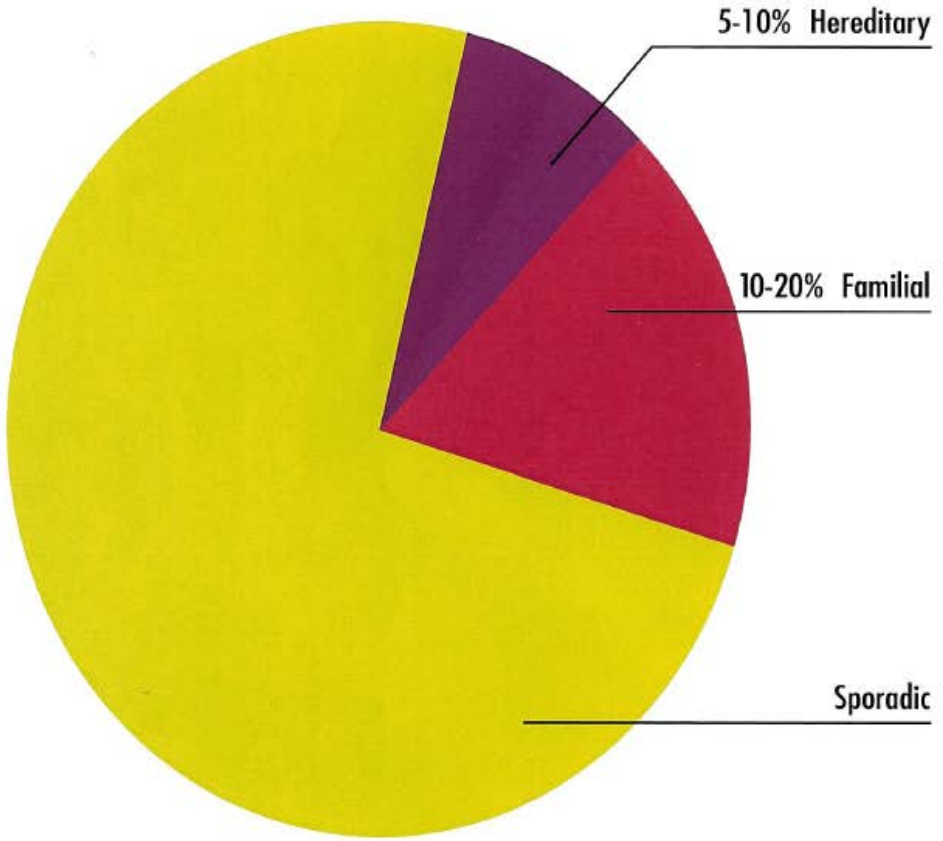
BRCA1 and *BRCA2* are tumour suppressor genes

They encode proteins involved in the repair of DNA double-strand (dsDNA) breaks via the homologous recombination (HR) pathway



Functional *BRCA* proteins regulate cell growth and prevent abnormal cell division that might otherwise lead to tumour development

Role of Inherited Causes in Cancer

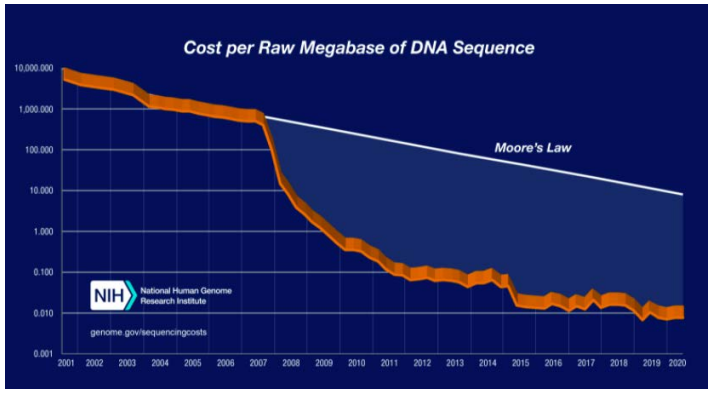


Hereditary
- Gene mutation is inherited in family
- Significantly increased cancer risk

Familial
- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

Sporadic
- Cancer occurs by chance or related to environmental factors
- General population cancer risk

Cancer Genetics is Evolving



- Family History is always a key component of oncologic care
- Technology testing changing
- Approaches to testing are changing
- Value of genetic information for patients is expanding i.e. parp inhibitor
- Different pathways to patient access
- Prevention in family members is highly effective
- Many new genes to consider

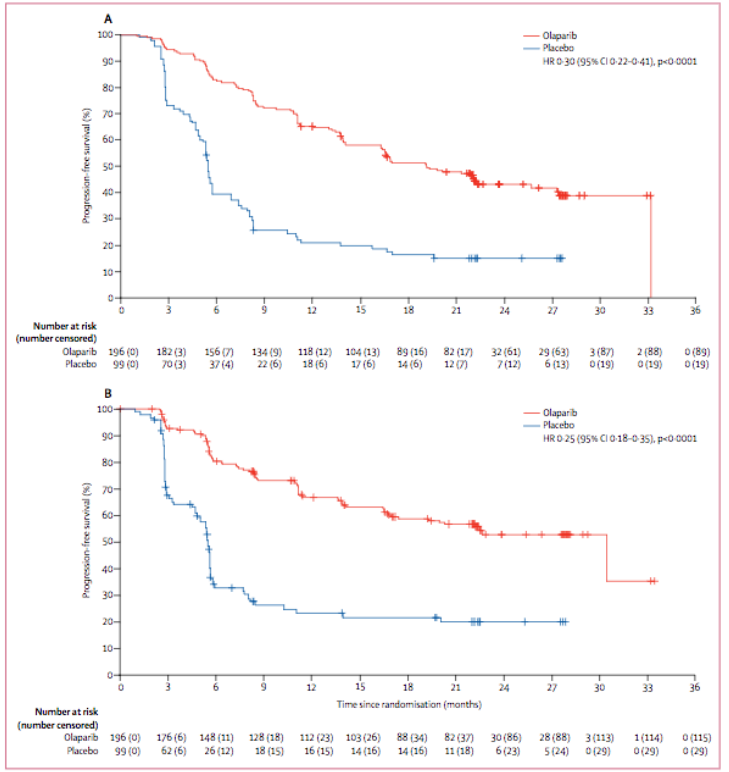
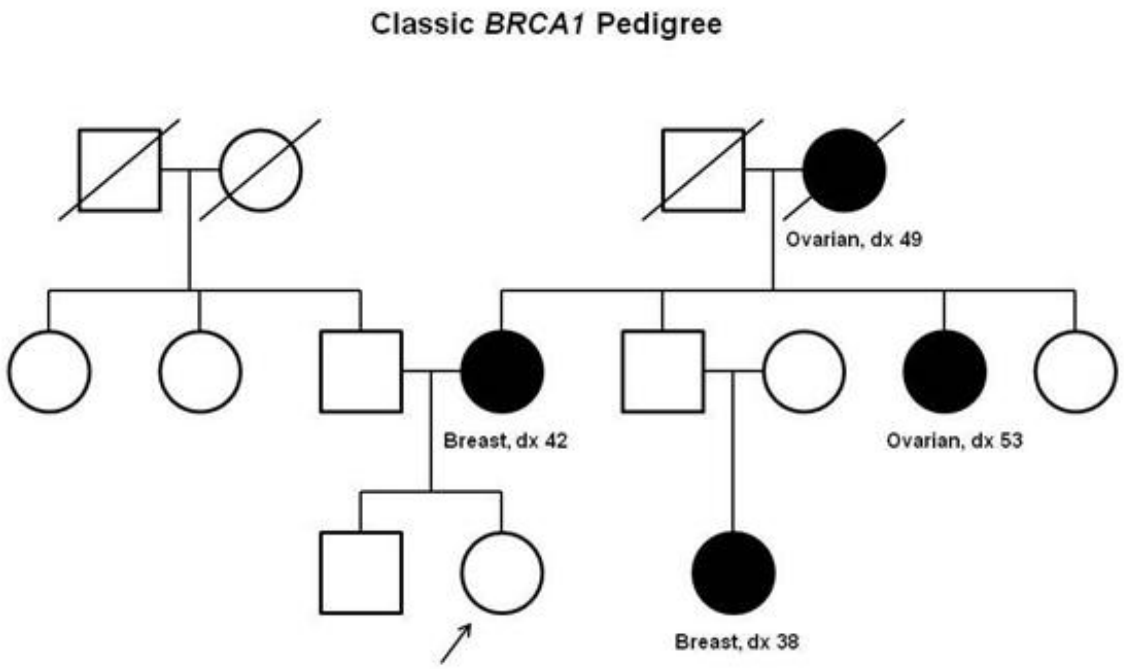


Figure 2: Kaplan-Meier estimates of progression-free survival by (A) investigator assessment and (B) blinded independent central review
HR=hazard ratio.

Family History Factors to Consider

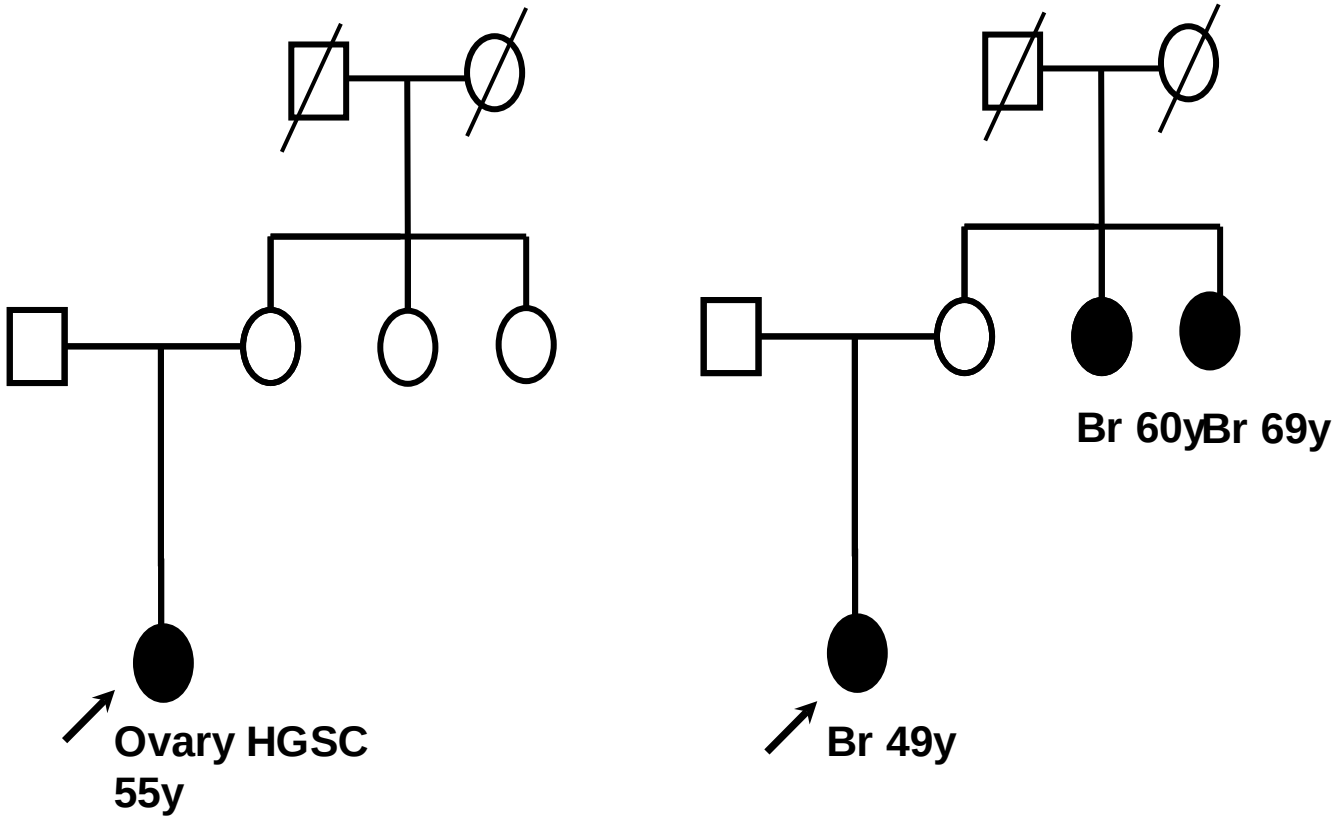


- Limited paternal history
- Few women in the family
- Adopted
- Ashkenazi Jewish Ancestry 1/40

Actual population rates are high than previously thought 1.64% in large studies*

*Couch NEJM CARRIERS Study 2021

The proportion of cancers that are hereditary varies by **type** and **age** at diagnosis



Which family is at higher risk for HBOC?

A: One Ovarian Cancer at 55y
B: Three Breast Cancers

Br = breast cancer

HGSC = high-grade serous carcinoma

GENE	Breast	Ovarian	CRC	Endometrial	Melanoma	Pancreatic	Stomach	Prostate	Other
BRCA1	o	o				o		o	
BRCA2	o	o			o	o		o	
MLH1		o	o	o		o	o		o
MSH2		o	o	o		o	o		o
MSH6		o	o	o		o	o		o
PMS2		o	o	o		o	o		o
EPCAM		o	o	o		o	o		o
APC			o			o	o		o
MUTYH			o						o
TP53	o	o	o	o	o	o	o	o	o
PTEN	o		o	o	o				o
STK11	o	o	o	o		o	o		o
CDH1	o		o				o		
BMPR1A			o			o	o		o
SMAD4			o			o	o		o
PALB2	o					o			
CHEK2	o		o						
ATM	o					o			
BRIP1		o							
RAD51C		o							
RAD51D		o							
NBN	o							o	

Multi-gene Panels are the norm.

Specific combinations may differ.

BRCA and Lynch always included

What do I look for?

Red flags for HBOC

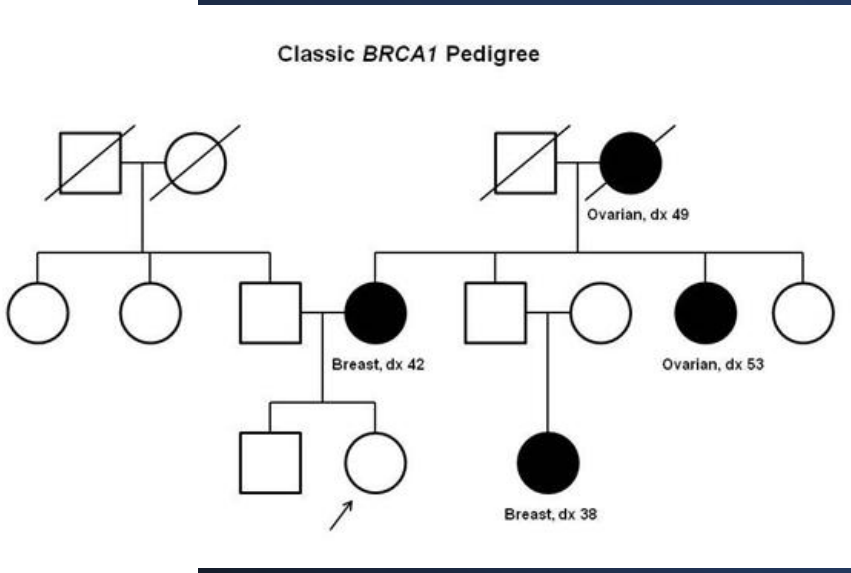
- **Earlier age at diagnosis of breast cancer (e.g. <50y)**
- **“Triple negative” type breast cancer (ER/PR/HER2-)**
- **High-grade serous ovarian/fallopian tube cancer**
- **>1 HBOC-related cancer in the same person**
- **Multiple individuals affected on same side of the family (paternal or maternal)**
- **Male breast cancer**
- **Pancreatic, melanoma**
- **Prostate cancers, eso aggressive, metastatic**

Poll

This unaffected patient has private pay genetic testing from Color Genomics. Her report is a negative 30 gene panel

Which of the following is true(more than one):

A. Her mother should cancel her HCP appointment as this is a BRCA negative family
B. The aunt with ovarian cancer should have genetic counselling and testing
C. The negative test in this patient does not explain the family
D. This result is an uninformative negative
E. The mom should still have testing



The rates of pathogenic mutations are higher than we thought

- Family history criteria alone will miss ~50% of carriers
- The future likely will include increasingly broad testing rules
  - public demand increases
  - costs diminish
  - prevention is proven cost effective for health systems

Table 2. Associations between Pathogenic Variants in Established Breast Cancer–Predisposition Genes and Risk of Breast Cancer.*

Breast Cancer–Predisposition Gene[1,2,7]	Case Patients (N=32,247)	Controls (N=32,544)	Odds Ratio (95% CI)†	P Value
	no. with pathogenic variant (%)			
ATM	253 (0.78)	134 (0.41)	1.82 (1.46–2.27)	<0.001
BARD1	49 (0.15)	35 (0.11)	1.37 (0.87–2.16)	0.18
BRCA1	275 (0.85)	37 (0.11)	7.62 (5.33–11.27)	<0.001
BRCA2	417 (1.29)	78 (0.24)	5.23 (4.09–6.77)	<0.001
CDH1	17 (0.05)	6 (0.02)	2.50 (1.01–7.07)	0.06
CHEK2	349 (1.08)	138 (0.42)	2.47 (2.02–3.05)	<0.001
NF1‡	19 (0.06)	11 (0.03)	1.93 (0.91–4.31)	0.09
PALB2	148 (0.46)	38 (0.12)	3.83 (2.68–5.63)	<0.001
PTEN	8 (0.02)	3 (0.01)	NA	NA
RAD51C	41 (0.13)	35 (0.11)	1.20 (0.75–1.93)	0.44
RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	0.12
TP53‡	19 (0.06)	2 (0.01)	NA	NA
Total	1621 (5.03)	531 (1.63)	—	—

BC CANCER

1. Personal History Criteria - path/test report required if not in

Age-specific:

- ☐ breast cancer diagnosed ≤ age 35
- ☐ 2 primary breast cancer diagnoses, at least 1 ≤ age 50
- ☐ triple negative (ER- PR- HER2-) breast cancer ≤ age 60
- ☐ breast cancer OR colorectal cancer ≤ age 50 AND no family history known due to adoption
- ☐ colorectal cancer diagnosed ≤ age 40
- ☐ 2 or more colorectal adenomas ≤ age 40
- ☐ colorectal or endometrial cancer ≤ age 50 AND ≥ 5 adenomas
- ☐ 2 Lynch syndrome related diagnoses, at least 1 ≤ age 50
- ☐ diffuse gastric cancer age ≤ 40 *additional HDGC criteria on website
- ☐ renal cancer ≤ age 45
- ☐ biliary tract cancer ≤ age 50 *additional criteria on website

- ☐ pathogenic gene variant identified via tissue test (e.g. Oncopan

At least 1 of the following diagnoses at any age:

- ☐ Lynch syndrome related cancer with dMMR (IHC def)
- ☐ male breast cancer
- ☐ non-mucinous epithelial ovarian, fallopian tube or peritoneal cancer (includes STIC)
- ☐ pancreatic ductal adenocarcinoma
- ☐ medullary thyroid cancer
- ☐ paraganglioma or pheochromocytoma
- ☐ 2 or more hamartomatous polyps
- ☐ 10 or more colorectal adenomas (cumulative)
- ☐ serrated polyps meeting WHO 2019 criteria
- ☐ Ashkenazi Jewish heritage & personal or family history of breast, ovary, pancreatic cancer

2. Family History Criteria - on 1 side of the family & may include

- ☐ a close relative with personal history as above
- ☐ 2 close female relatives with breast cancer, both ≤ age 50
- ☐ 2 close relatives with Lynch syndrome cancer, both ≤ age 50
- ☐ 3 breast cancers in close female relatives, at least 1 ≤ age 50
- ☐ 3 or more Lynch syndrome cancers, at least 1 ≤ age 50
- ☐ 3 melanomas in close relatives at any age

Carrier testing: Pathogenic variant in Family Member

NEW!!!
Female first degree relative of ovarian cancer eligible for testing in BC

Interpreting genetic test results

Positive

- Deleterious mutation identified
- Mutation affects gene function
- Gene is associated with phenotype
- Can test other relatives
- Presence of mutation impacts medical management

Maybe (VUS)

- Typically a missense variant
- Unclear if variant affects gene function
- May be present in population databases
- Not clear if variant associated with disease
- Testing relatives may be unhelpful

Negative

- No mutation identified
- Cause of cancer in patient/ family remains unexplained
- Multifactorial etiology vs. other causative gene(s)
- Limited value to testing other relatives
- Management based on family hx

Private Testing

- Patients are increasingly interested
- “Buyer Beware”
- Reputable companies will include genetic counselling with the test.
- Do not allow a patient to act on Variant Uncertain Significance
- We are here to help

In 2021 Genetic Testing → Prevention

You only find
what you look for.

You only diagnose
what you know.

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HCP High Risk Clinic

Breast Cancer Risk and Risk Management

Lifetime Breast Cancer Risk in Women

- **High Risk Genes** (BRCA1/2)
  - BRCA1 72%
  - BRCA2 69%
- General Population 12%
- Contralateral Cancer Risk
  - BRCA1 40%
  - BRCA2 26%

Kuchenbaecker et al JAMA 2017 317(23): 2402-2416

Breast Cancer Risk non BRCA

High Risk Genes

- TP53 79%
- PTEN 67-85%
- STK11 40-60%

Moderate Risk Genes

PALB2,CHEK2,ATM, CDH1,NF

- 15-60% life time risk

NCCN guidelines 2021
https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

BRCA1 Breast Cancer Risk

BRCA1-Breast cancer risks*		
Current age (yrs)	Approximate remaining lifetime risk to 80 yrs	Approximate 5 yr risk
20-25	70%	5%
26-30	70%	5%
31-35	65%	5%
36-40	65%	10%
41-45	60%	10%
46-50	55%	15%
51-55	50%	15%
56-60	40%	10%
61-65	30%	10%
66-70	25%	10%

Royal Marsden Cancer Genetic Clinical Protocol

BRCA2 Breast Cancer Risk

BRCA2-Breast cancer risks*

Current age (yrs)	Approximate remaining lifetime risk to 80 yrs	Approximate 5 yr risk
20-25	70%	~1%
26-30	70%	2%
31-35	65%	5%
36-40	65%	5%
41-45	60%	10%
46-50	55%	10%
51-55	50%	10%
56-60	50%	10%
61-65	45%	15%
66-70	35%	15%

Royal Marsden Cancer Genetic Clinical Protocol

Risk Management: Hereditary High Risk Clinic

- Referral via the genetic counsellor for women with confirmed mutations or 50% risk and as yet untested
- Telephone or in-person (Vancouver) consultation
- Wait time currently 3-5 months (depending on mutation)

Risk Management: Hereditary High Risk Clinic

- Complete history and breast exam
- Review of risks for given mutation
- Discussion of risk management options
- Written information as needed
- Referrals for surgery
- Imaging (mammo and MRI)
- Annual follow-up

Polling Question

True or False?

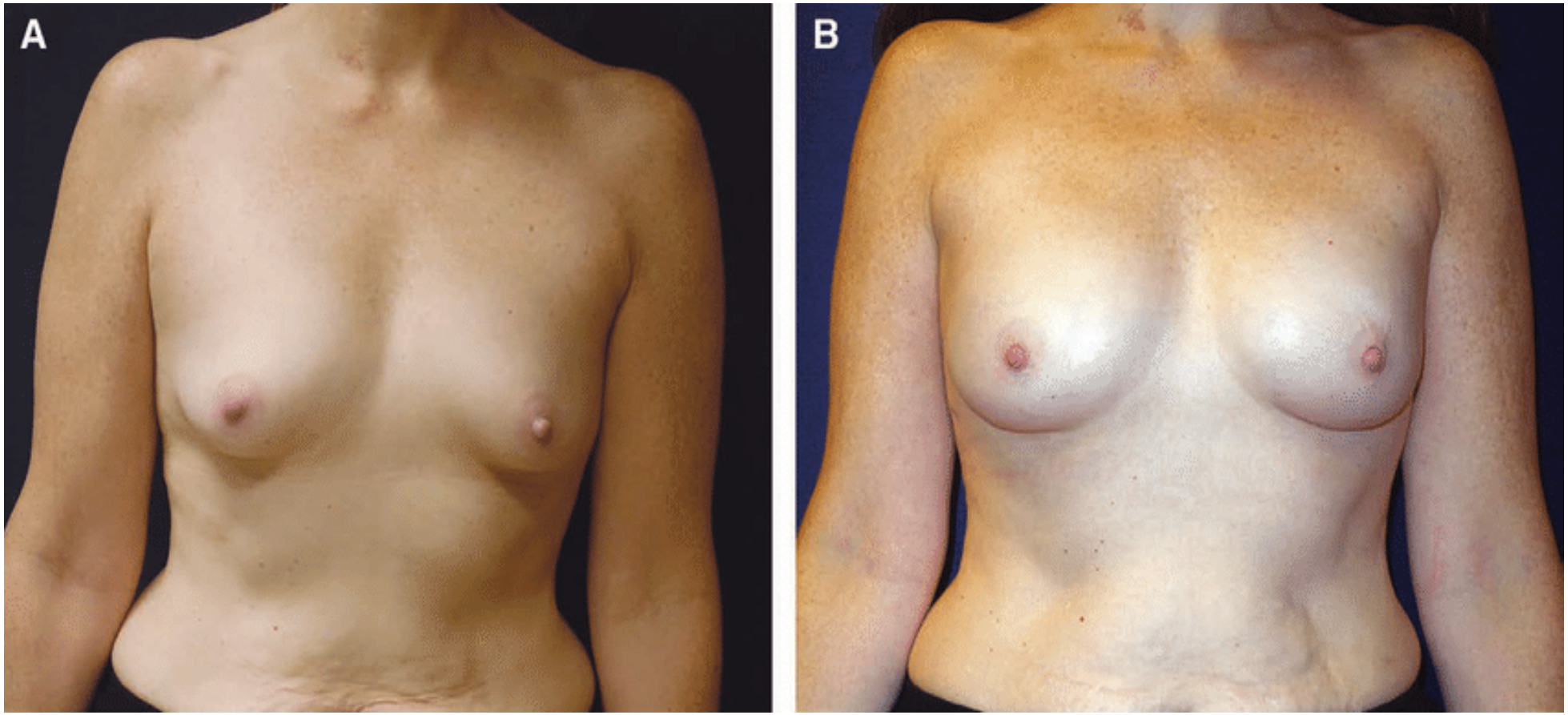
Women who carry a BRCA1 or BRCA2 mutation should have prophylactic mastectomies.

1. True
2. False

Management of Known Carriers: Surgical Prevention

- Prophylactic mastectomy +/- reconstruction
- Can be nipple sparing
- >90% reduction in breast cancer risk
  - Rebbeck, et al, J. Clin Oncol 2004 (26): 1055-62
- No screening imaging after surgery
- Annual clinical exam with GP
- Investigate any new masses
- Small survival benefit (2-5%) function of age
  - Kurian et al, J Clin Oncol 2010 (28):222-31

Nipple-Sparing Mastectomy with Implant Reconstruction



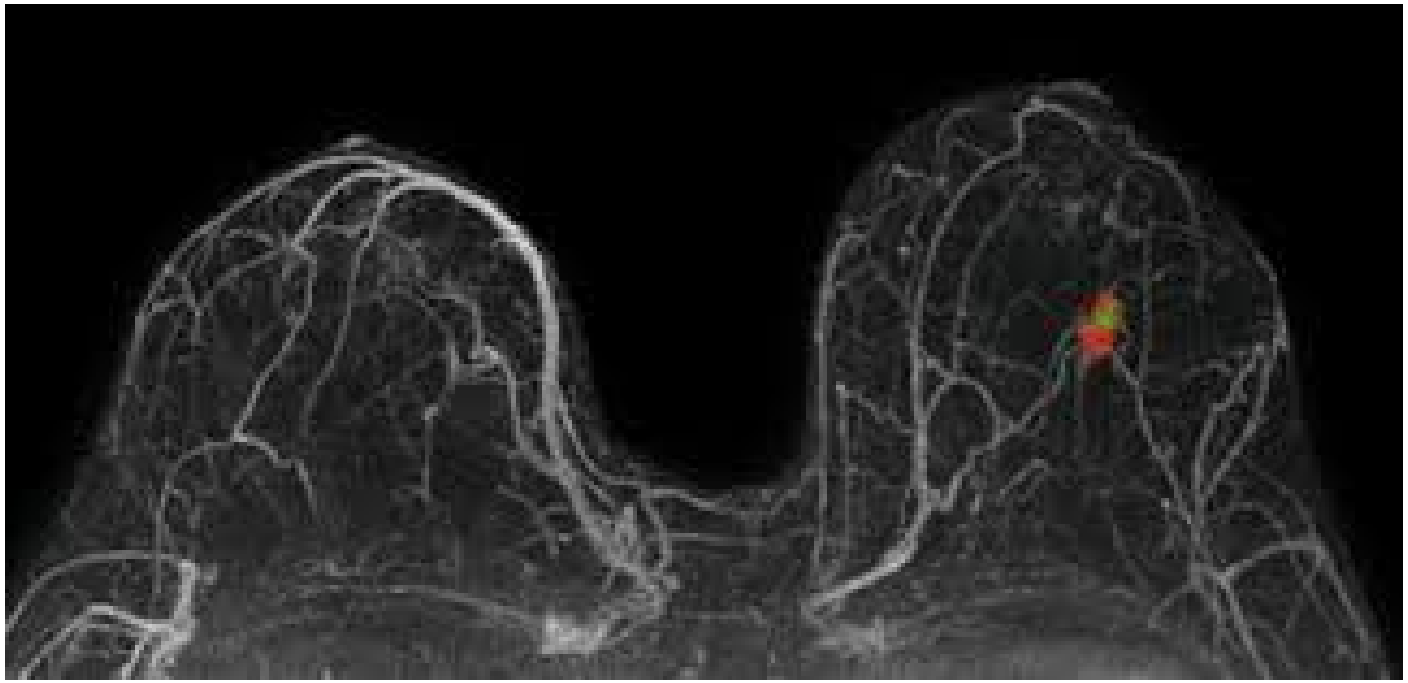
Colwell et al. Plastic and Recon Surg. 2017

Management of Known Carriers: Increased Surveillance

- Annual mammography age 30 to 75(+)
- Annual breast MRI from age 25 to 70
- Annual clinical breast exam
- Breast awareness
- Note preventative task force recommendations to not do CBE or self exam do not apply to this population

MRI vs Mammography for Screening

- Contrast enhanced (gadolinium) (preferably with CAD) is more sensitive
  - 80-90% vs 36.8-37.5%
    (ASCO 2015)
    (Ontario Review 2007/2018)
- Specificity 93% vs 97.5 % (MRI vs Mammo)
- Concurrent imaging for diagnostic workup
- No evidence for alternating protocol
- No added value with the addition of US



Breast Cancer on MRI with GAD

Polling Question

- Chemopreventative medication reduces breast cancer risk by what percentage?
    - 1. less than 20%
    - 2. 20-45%
    - 3. 46-65%
    - 4. 66-80%
    - 5. more than 80%

Management of Carriers: Medical Prevention

- Chemoprevention
- No trial specific for mutation carriers
- Only for patients at risk of ER+ tumours
- Options
  - Tamoxifen
  - Raloxifene
  - Aromatase inhibitors

Tamoxifen for Risk Reduction

- 49% reduction in invasive and non-invasive breast (prevented 4 of 10 cancers)
- Premenopausal or post menopausal
- Endometrial Cancer- 2.5 X RR (higher if >50yo)- 4 in 1000 women
  - Not in premenopausal women
- Thromboembolism
  - 1.6 X for DVT
  - 1.59 for stroke, 3.01 for PE
  - Increased risk in smokers
- Cataracts

Tamoxifen – Side Effects

- Generally well tolerated
- 1% discontinue rate in trials
- Hot flashes
- Vaginal dryness
- Basically “menopausal” symptoms

- Can’t take if on OCP or HRT
- Some medications interfere (antidepressants CYP2D6 inhibitors)

Raloxifene for Risk Reduction

- Almost as effective as tamoxifen for invasive cancer (prevented 3 of 10 cancers vs 4 of 10 for tam)
- Postmenopausal only
- No increase in endometrial cancer
- Lower risk of thromboembolism
- Not if on HRT

Aromatase Inhibitors for Risk Reduction

- More effective than tamoxifen or raloxifene
- Prevented 5-6 of 10 cancers
- Only for post-menopausal women
- No increase in endometrial ca or DVT
- Increased risk osteoporosis
  - Need baseline bone density
  - Ca and vit D supplementation

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Ovarian Cancer Risk and Risk Management

THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA

British Columbia's GCI Gynecologic Cancer Initiative

Motivated by the goal **Decreasing death and suffering from gynecologic cancers by 50%**

Funded by **UBC Cluster grant**

THE UNIVERSITY OF BRITISH COLUMBIA

Led by Dr. Gavin Stuart

BC CANCER

Vancouver Coastal Health

BC WOMEN'S HOSPITAL+ HEALTH CENTRE

An agency of the Provincial Health Services Authority

VGH UBC hospital foundation

BC CANCER FOUNDATION

FACULTY OF MEDICINE

BC WOMEN'S HOSPITAL+ HEALTH CENTRE FOUNDATION

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

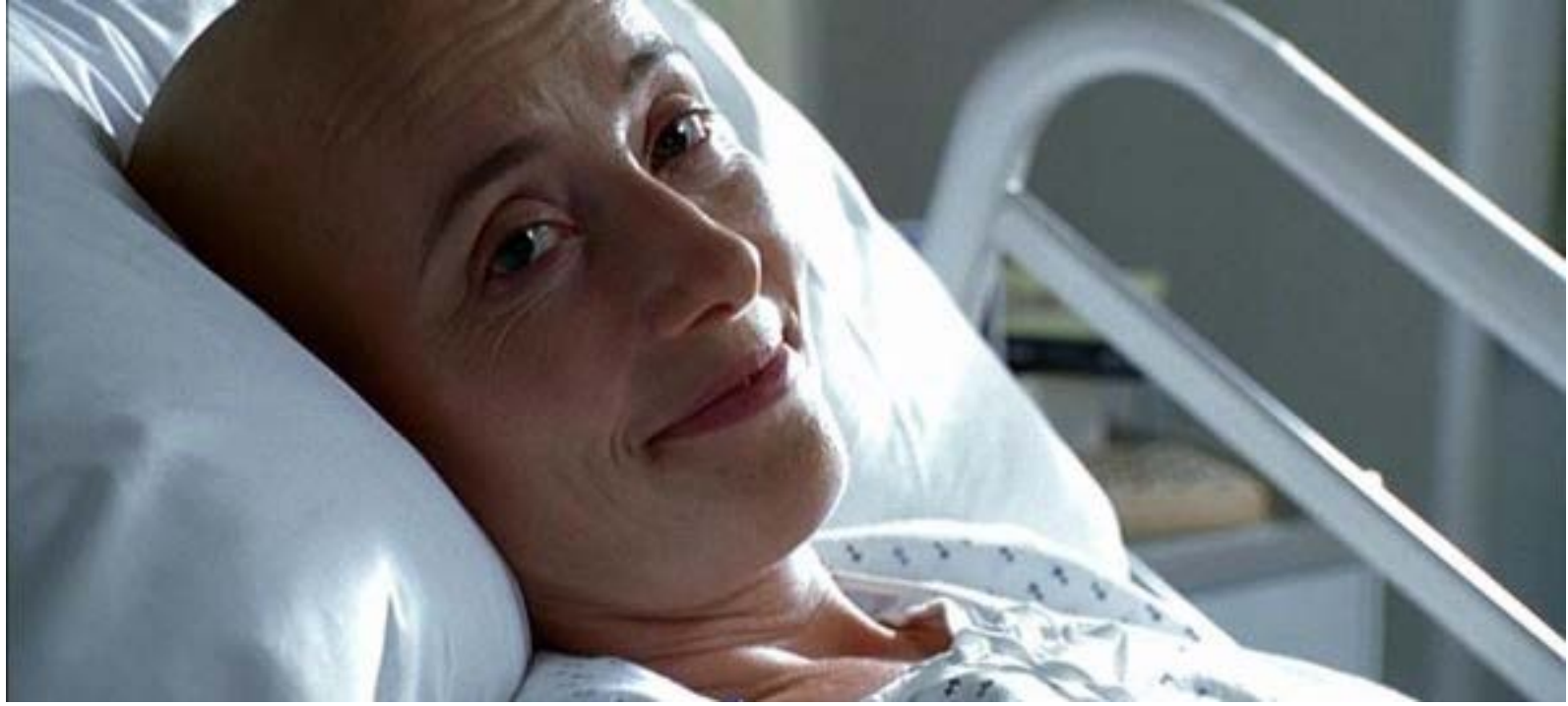
Version 1.2022 — August 11, 2021

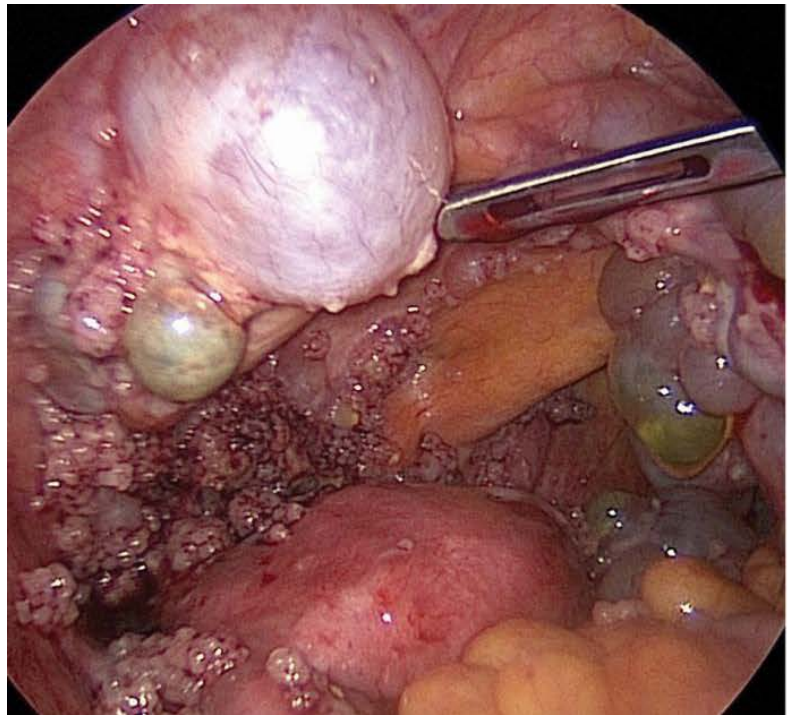
Over 2800 Canadian women are diagnosed with ovarian cancer every year

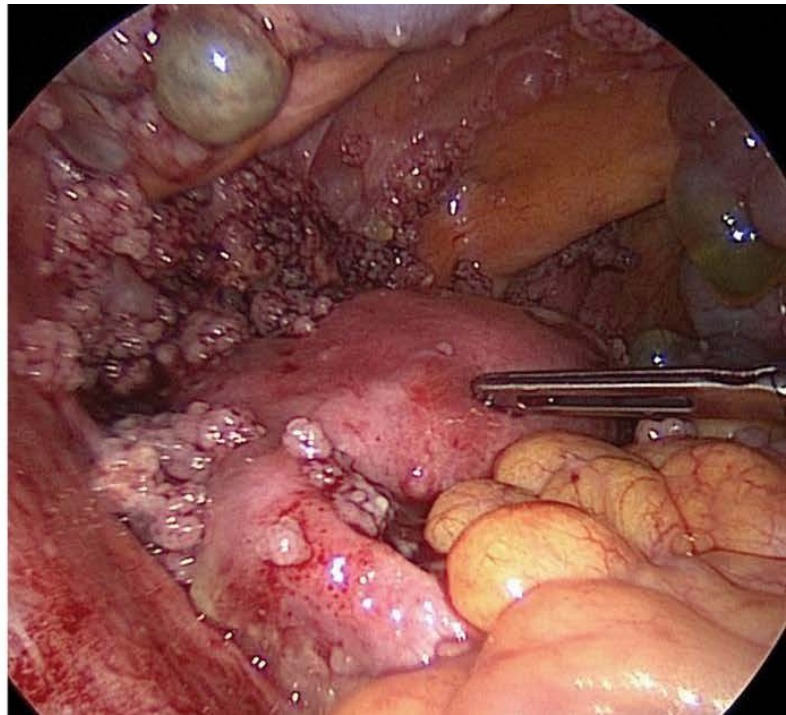
1800 succumb to disease annually

Second most common gynecologic malignancy.

Most lethal gynecologic malignancy, and the 5th ranking cause of cancer death for women







Ovarian Cancer	BRCA 1		BRCA 2	
Antoniou	40%	30-60%	18%	5-20%
Chen	59%		16%	
Rebbeck	12%		5%	
Mavaddat	35%		11%	

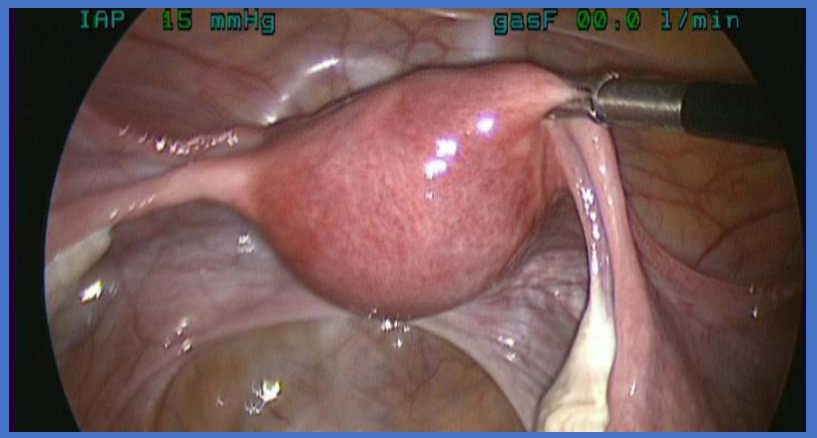
What is the real risk of ovarian cancer in BRCA carriers?

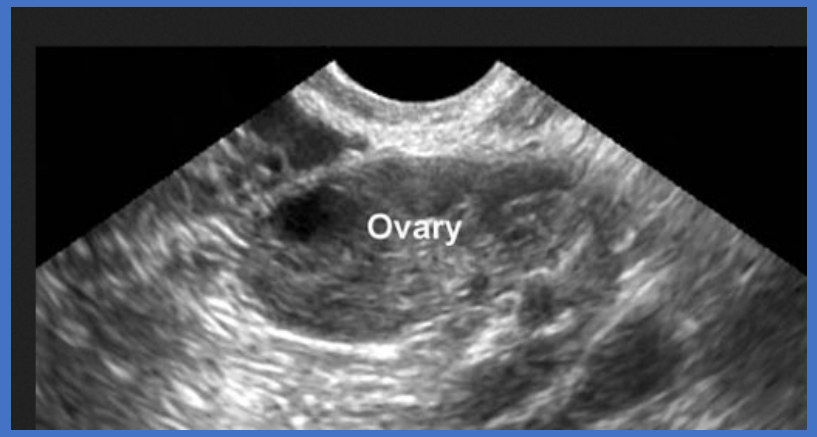
Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-1130.

Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329-1333

Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. Jama 2015;313:1347-1361.

Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105:812-822.





How to manage that risk?

Articles

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Ian J Jacobs*, Usha Menon*, Andy Ryan, Aleksandra Gentry-Maharaj, Matthew Burnell, Jatinderpal K Kalsi, Nazar N Amso, Sophia Apostolidou, Elizabeth Benjamin, Derek Cruickshank, Danielle N Crump, Susan K Davies, Anne Dawnay, Stephen Dobbs, Gwendolen Fletcher, Jeremy Ford, Keith Godfrey, Richard Gunu, Mariam Habib, Rachel Hallett, Jonathan Herod, Howard Jenkins, Chloe Karpinskyj, Simon Leeson, Sara J Lewis, William R Liston, Alberto Lopes, Tim Mould, John Murdoch, David Oram, Dustin J Rabideau, Karina Reynolds, Ian Scott, Mourad W Seif, Aarti Sharma, Naveena Singh, Julie Taylor, Fiona Warburton, Martin Widschwendter, Karin Williamson, Robert Woolas, Lesley Fallowfield, Alistair J McGuire, Stuart Campbell, Mahesh Parmar†, Steven J Skates†

Summary

Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Methods In this randomised controlled trial, we recruited postmenopausal women aged 50–74 years from 13 centres in National Health Service Trusts in England, Wales, and Northern Ireland. Exclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, and active non-ovarian malignancy. The trial management system confirmed eligibility and randomly allocated participants in blocks of 32 using computer-

Lancet 2016; 387: 945-56

Published Online
December 17, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01224-6

This online publication has been corrected. The corrected version first appeared at thelancet.com

ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of Screening on Ovarian Cancer Mortality

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial

Saundra S. Buys, MD
Edward Partridge, MD
Amanda Black, PhD, MPH
Christine C. Johnson, PhD, MPH
Lois Lamerato, PhD
Claudine Isaacs, MD
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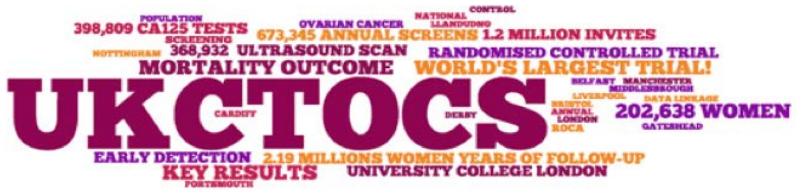
Robert T. Greenlee, PhD, MPH

Context Screening for ovarian cancer with cancer antigen 125 (CA-125) and transvaginal ultrasound has an unknown effect on mortality.

Objective To evaluate the effect of screening for ovarian cancer on mortality in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Design, Setting, and Participants Randomized controlled trial of 78 216 women aged 55 to 74 years assigned to undergo either annual screening (n=39 105) or usual care (n=39 111) at 10 screening centers across the United States between November 1993 and July 2001.



Intervention	Patients	Deaths	False positive surgery/ case detected
USS Yearly Ca125	50 624	148	2
USS	50 623	154	10
No screening	101 299	347	NA

Screening in high-risk women

- UK Familial Ovarian Cancer Screening Study (UK FOCSS)
  - 8000 women
  - U/S and ca125 4 monthly
  - High risk by family history or mutation
  - Completed recruitment 2013
- National Ovarian Cancer Screening Prevention (GOG0199)
  - ROCA (risk of ovarian cancer)
  - Completed recruitment 2011
  - Quality of life analysis
  - Prophylactic surgery data
- Stay Tuned!
- CHARM Study
  - cDNA screening via blood test is open in BC

Chemoprevention

Meta-analysis of OCP in BRCA carriers

- 2855 breast cancer cases
- 1503 ovarian cancer cases
- RR 0.50 (0.33-0.75)
- 36% reduction in ovarian cancer with each additional 10 years of use
- Breast cancer 1.13 (0.88-1.45)

Eur Jour Cancer 2010;46:2275-2284

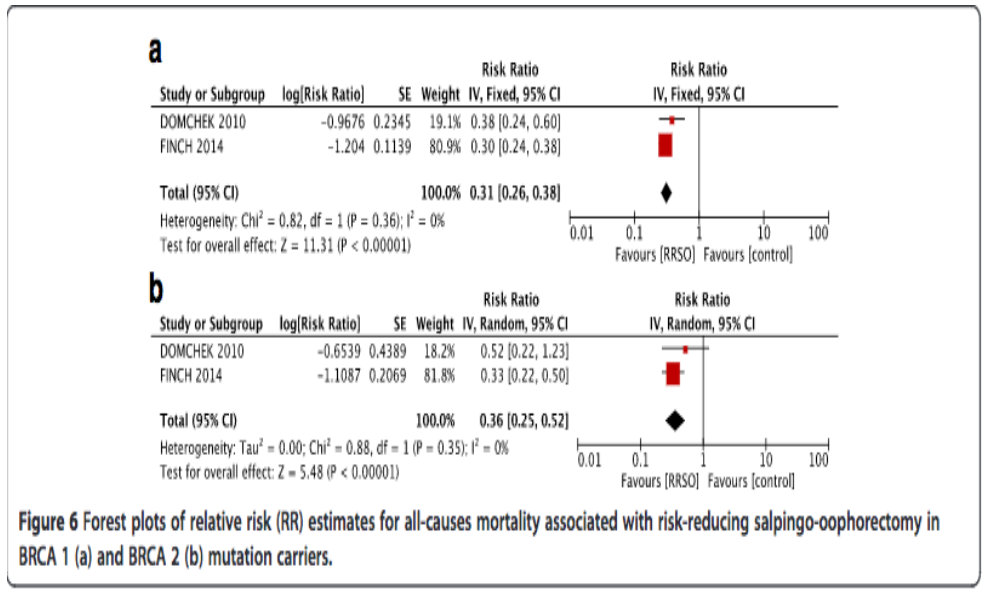
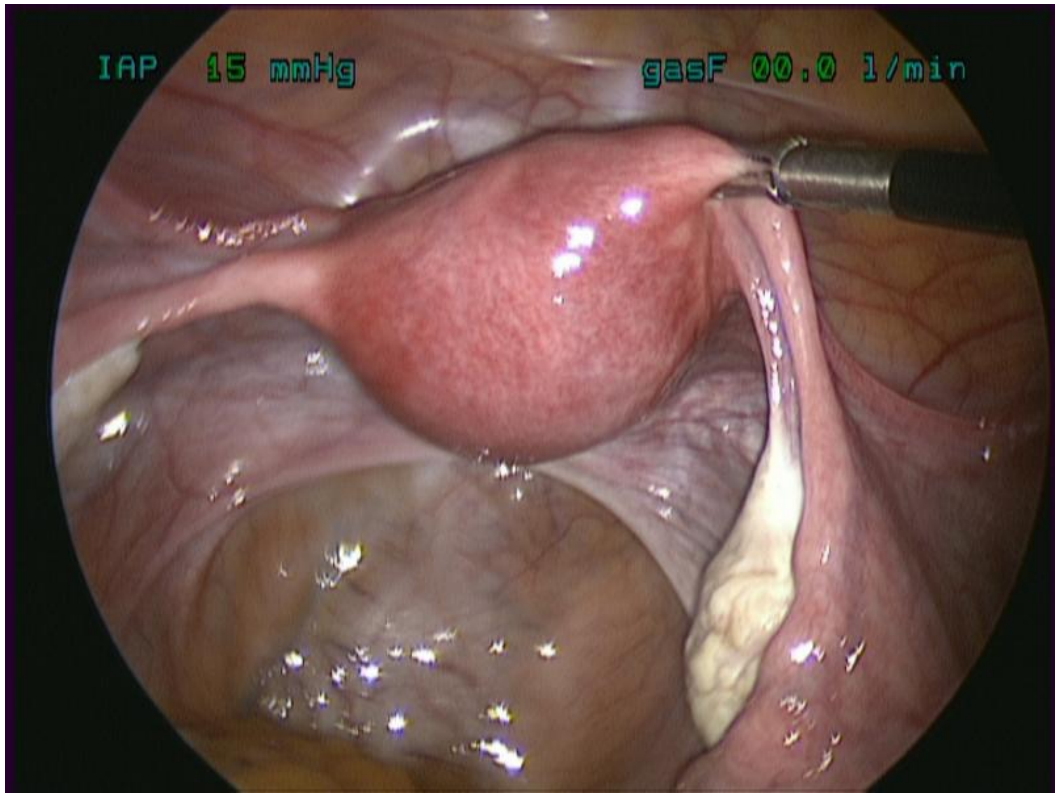


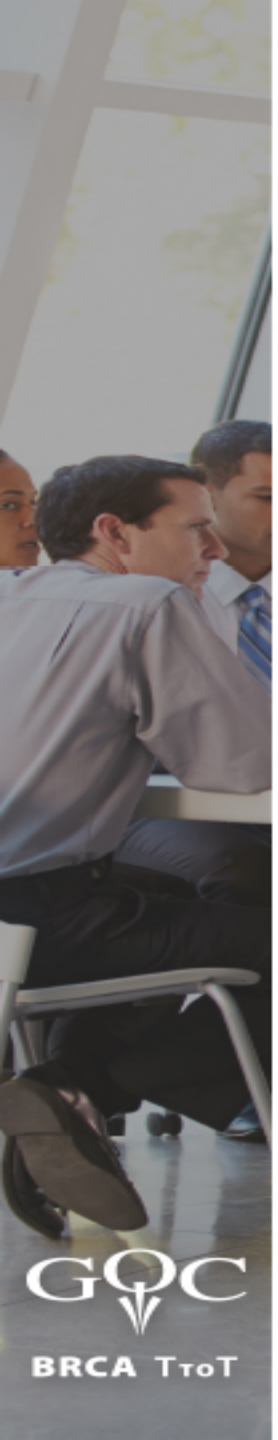
Figure 6 Forest plots of relative risk (RR) estimates for all-causes mortality associated with risk-reducing salpingo-oophorectomy in BRCA 1 (a) and BRCA 2 (b) mutation carriers.



JCO 2014 20;32(15):1547-53.

RRSO is associated with a 70% reduction in all cause mortality

- BRCA 1 HR 0.30 (0.24-0.38 p<0.001)
- BRCA 2 HR 0.33 (0.22-0.50 p<0.001)



Cochrane Library

Cochrane Database of Systematic Reviews

Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations (Review)

Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO

- 10 cohort studies
- 8087 participants (2936 surgery and 5151 control participants
- BRCA1 and BRCA2
- RRSO versus no RRSO
- Follow-up period ranged from 0.5 to 27.4 years.

- Overall survival was longer with RRSO (HR 0.32, 95% CI 0.19 to 0.54; P < 0.001
- HGSC cancer mortality (HR 0.06, 95% CI 0.02 to 0.17; I2 = 69%; P < 0.0001
- Breast cancer mortality (HR 0.58, 95% CI 0.39 to 0.88; I2 = 65%; P = 0.009;
- None of the studies reported bone fracture incidence.
- Ovarian cancer risk perception quality of life (MD 15.40, 95% CI 8.76 to 22.04; P < 0.00001

Ovarian Prevention Canadian Data

BRCA 1 carriers

27/1196 on screening died of ovarian/fallopian tube cancer

2/658 deaths after risk reducing salpingo-oophorectomy

The hazard ratio for oophorectomy versus ultrasound
0.23 (95% CI: 0.05 to 0.97; p = 0.05)

Gynecol Oncol. 2019 Sep 6, 2019

Society of Gynecologic Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

GOC THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA

NCCN National Comprehensive Cancer Network®

Royal College of Obstetricians & Gynaecologists

RRSO Recommended in BRCA Carriers

35-40y *BRCA 1*

40-45y *BRCA 2*

Pathologic Review of Fallopian Tubes

SEE FIM Protocol

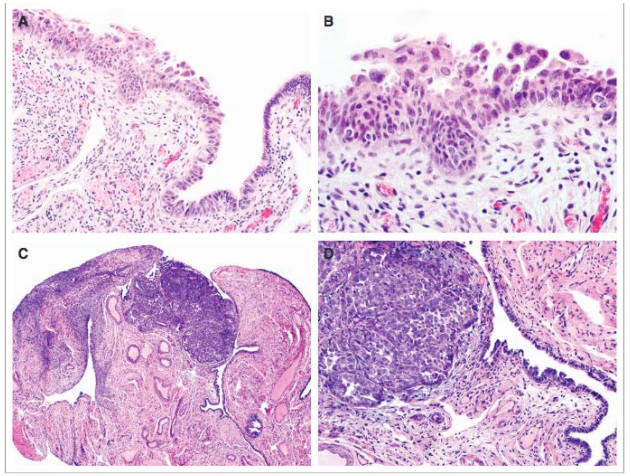


Fig 2. Neoplastic lesions arising in fallopian tube. (A) Low-power (×10 magnification) photomicrograph showing transition from benign fallopian tube epithelium composed of uniform columnar cells (far right) to serous tubal intraepithelial cancer. (B) High-power (×20 magnification) view of (A), demonstrating malignant-appearing cells with pleomorphic nuclei. (C) Nodule of invasive high-grade serous cancer with suggested origin from fallopian tube epithelium (×10 magnification). (D) High-power (×20 magnification) view of (C), showing solid sheets of tumor cells with suggestion of irregular gland formation; right side of image shows benign fallopian tube epithelium.

COLLEGE of AMERICAN PATHOLOGISTS

tocol for the Examination of Specimens From Patients
cinoma of the Fallopian Tube

ocol applies to all carcinomas presumed to be arising from the muc
allopian tube.

l on AJCC/UICC TNM, 7th edition, and FIGO 2006 Annual Report
ol web posting date: August 2015

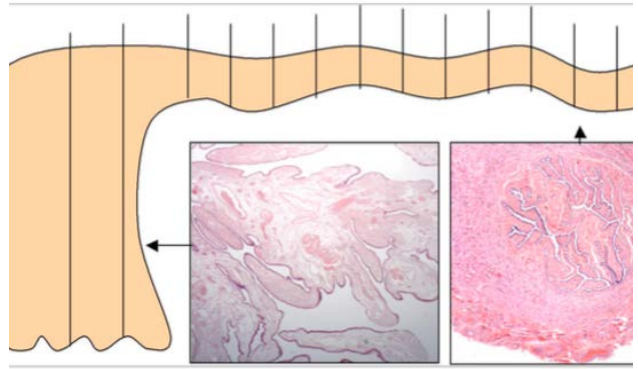
dures
teral Salpingectomy
ngo-Oophorectomy
erectomy With Salpingo-Oophorectomy

rs
A. Clarke, MBBCh, FRCPC*
Department of Pathology, University of Toronto, Toronto General Hospital, Toronto, Ontario,
opher P. Crum, MD, FCAP
Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts

Specimen: 16:SU26042 SOUT Rec

DIAGNOSIS:

UTERUS, CERVIX, BILATERAL FALLOPIAN TUBE
SALPINGO-OOPHORECTOMY:
- LEIOMYOMA
- ADENOMYOSIS
- SECRETORY PHASE ENDOMETRIUM
- SEGMENT OF RIGHT FALLOPIAN TUBE,
- SEGMENT OF LEFT FALLOPIAN TUBE, U
- PARATUBAL CYST, LEFT FALLOPIAN TU
- OVARIES, UNREMARKABLE, BILATERAL
- NEGATIVE FOR MALIGNANCY



ol for Sectioning and Extensively Examining the FIMbriated End (SEE-F
ails amputation and longitudinal sectioning of the infundibulum and fimbrial se
e of the tubal plicae. The isthmus and ampulla are cut transversely at 2- to 3-

Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic ser
2007;19:5. Copyright © 2007 Lippincott Williams & Wilkins. Reproduced with

Should hysterectomy be done at the time of RRSO?

Disadvantages	Benefits
OR time	Simplifies post surgery HRT
Recovery time	? Risk of serous endometrial cancer *
Complication Rate	Eliminates endometrial cancer risk if on tamoxifen

* Prophylactic specimens 1083 BRCA 1 carriers
Incidental uterine cancer in 8 patients

JAMA Oncol. 2016 Nov 1;2(11):1434-1440.

- Cardiovascular Disease
  - Metabolic syndrome 2x
- Bone Health
  - 30-40% more osteopenia
- Cognition
  - Word finding, memory
  - Dementia HR 1.9
  - Parkinson's HR 1.8
- Quality of Life
  - Vasomotor symptoms
  - Significant Sleep Disruptic
- Sexual Health
  - Libido
  - Desire
  - Lubrication

SOGC CLINICAL PRACTICE GUIDELINE

It is SOGC policy to review the content 5 years after publication, at which time the document may be re-affirmed or revised to reflect emergent new evidence and changes in practice.

No. 366, November 2018

No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer

This Committee Opinion has been prepared by the by the Familial Ovarian Cancer Prevention Programme, reviewed by the Society of Obstetricians and Gynaecologists of Canada (SOGC)'s Gynaecology Committee and the Society of Gynecologic Oncology of Canada (GOC) Guidelines Committee, and approved by the Board of the SOGC.

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Marcus Bernardini, MD, Toronto, ON

Mara L. Sobel, MD, Toronto, ON

Raymond H. Kim, MD, PhD, Toronto, ON

Disclosure Statement: Disclosure statements have been received from all authors.

Key Words: BRCA, hereditary breast ovarian cancer (HBOC), familial ovarian cancer, genetic cancer syndrome, BRCA1, BRCA2

KEY MESSAGES

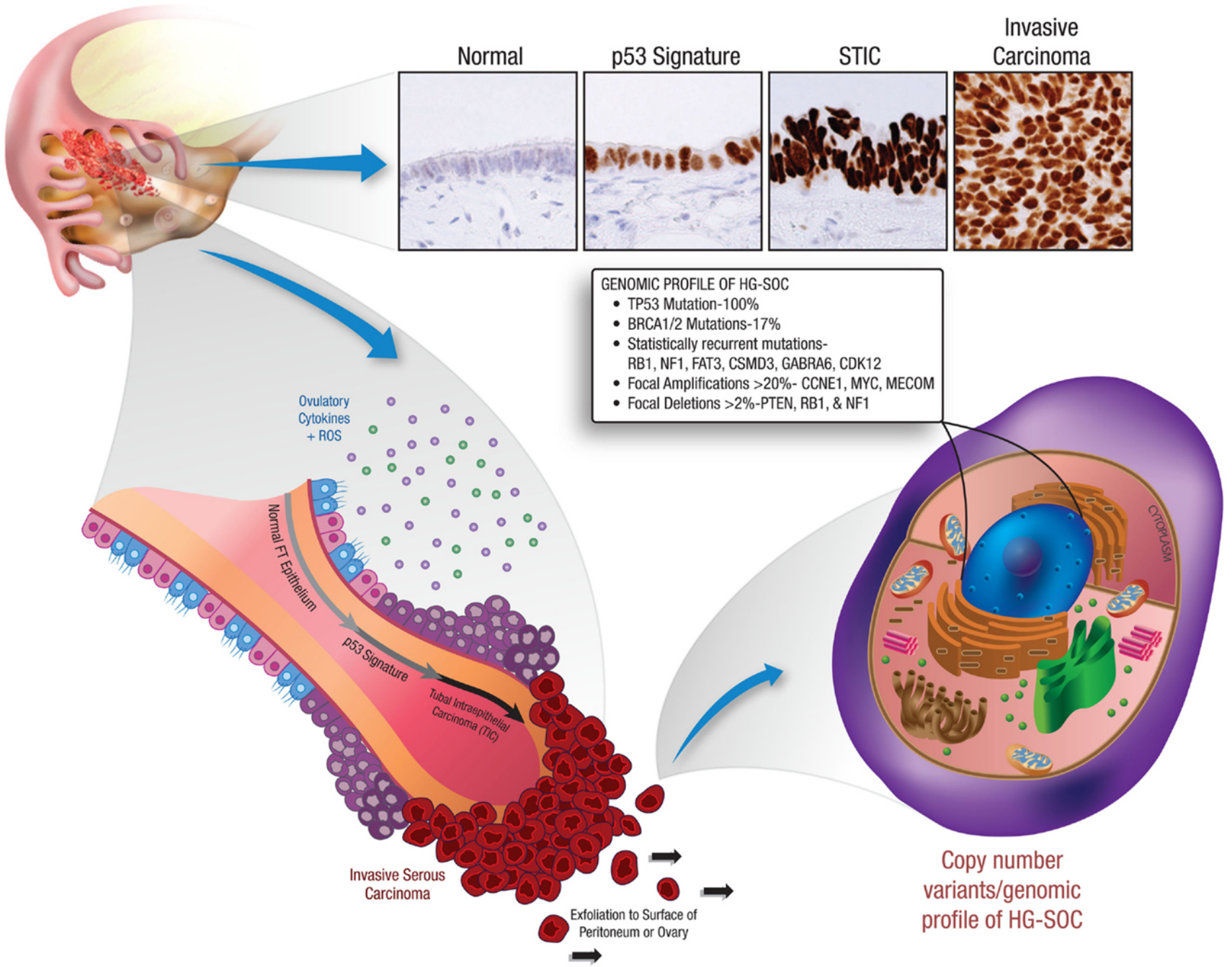
1. BRCA variant status is not a contraindication to hormone therapy.

IS HORMONE THERAPY SAFE? HRT, BRCA and Breast Cancer Risk:

- Rebbeck 2005 (PROSE study)
  - 462 *BRCA1/2* carriers
  - HRT after RRSO did not alter the reduction in breast cancer risk associated with RRSO (HR = 0.37; 95% CI, 0.14 to 0.96)
- Kotsopoulos 2016
  - 432 matched pairs of women with *BRCA1* mutation
  - Mean duration of HRT 4+ years
  - OR for breast cancer for HRT to never users = 0.80 (95 % CI 0.55-1.16; P = 0.24)
- Eisen 2008
  - 472 *BRCA1+*
  - OR for breast cancer with ever use of HT = 0.58 (95% CI = 0.35 to 0.96; P = .03)

IS HORMONE THERAPY SAFE?

- Kotsopoulos 2018
  - 872 *BRCA1* mutation carriers
  - mean follow-up 7.6 years (range, 0.4-22.1)
  - HRT use after BSO not associated with an increased risk of breast cancer (HR 0.97 (95% CI, 0.62-1.52; *P* = .89))
  - Higher breast cancer incidence in E+P users (consistent with literature)



Salpingectomy first ?

- Biologically plausible
- Quality of life gains
- Extent of risk reduction is unknown
- RRS and RRO Trials
  - Tubectomy (Netherlands)
  - France
  - UK
  - US GOG 019-9

Not a recommendation at present

Personalized care is essential

Ongoing clinical relationships are essential

Alternatives to oophorectomy need research

Practical Approach to RRSO

Timing

- BRCA 1 or 2
- Work around
  - breast cancer recovery
  - mastectomy/reconstruction
- Personal considerations

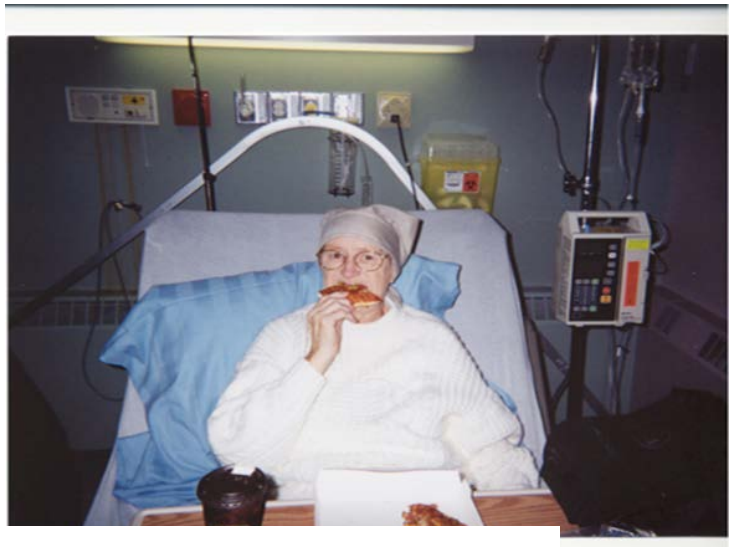
Pathologic processing of specimens

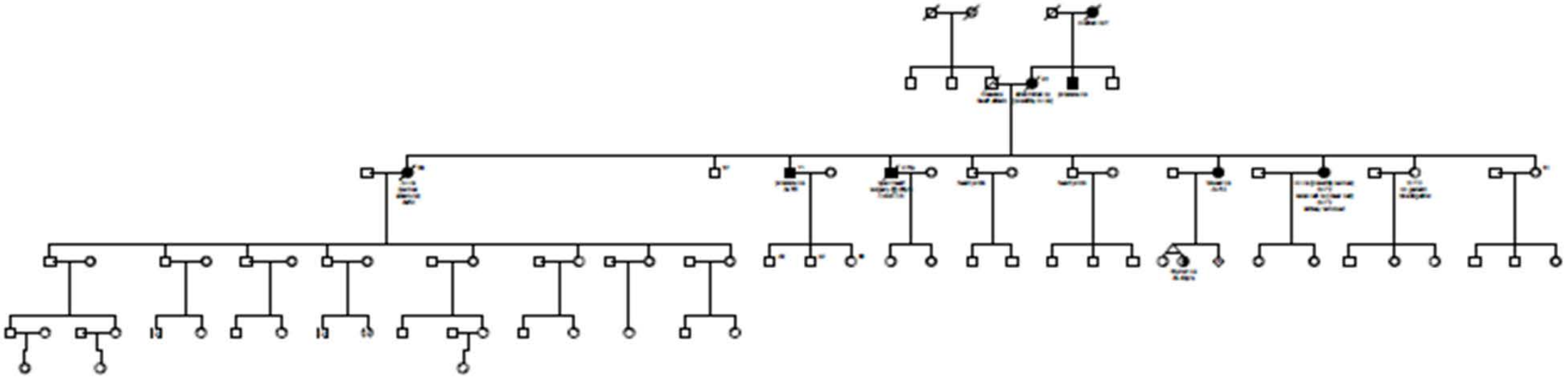
Unexpected findings at OR

- occult pre-invasive findings
- overt cancer

Role of hysterectomy

BRCA2 c. 6065 C >G





Rona Cheifetz MD FRCSC
HCP High Risk Clinic

BRCA Cancer Risks Other than Female Breast and Ovary

Polling Question

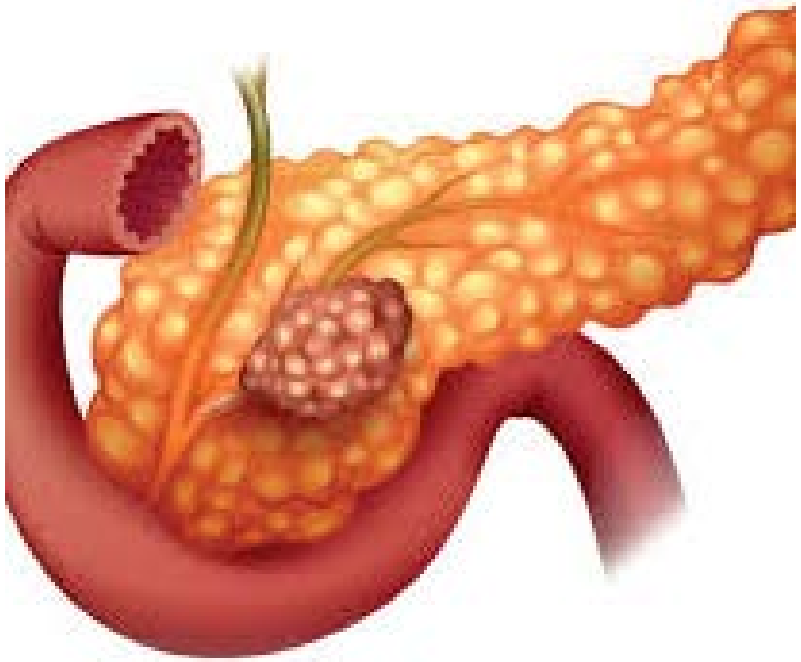
Which of the following statements are false?

1. Pancreatic cancer occurs more frequently is BRCA2 carriers
2. Prostate cancer in BRCA2 carriers is more aggressive than in the general population
3. Colorectal Cancer is more common is BRCA mutation carriers
4. Melanoma is more common in BRCA2 mutation carriers

Pancreatic Cancer

- BRCA2
  - lifetime risk 5-10% (3-8 times)
- BRCA1
  - life time risk 2-3% (2-4 times)
- General Population
  - 1%

- Genetic testing:
  - anyone with pancreatic cancer should be considered
  - Anyone with a FH of pancreatic cancer or other syndrome associated cancers



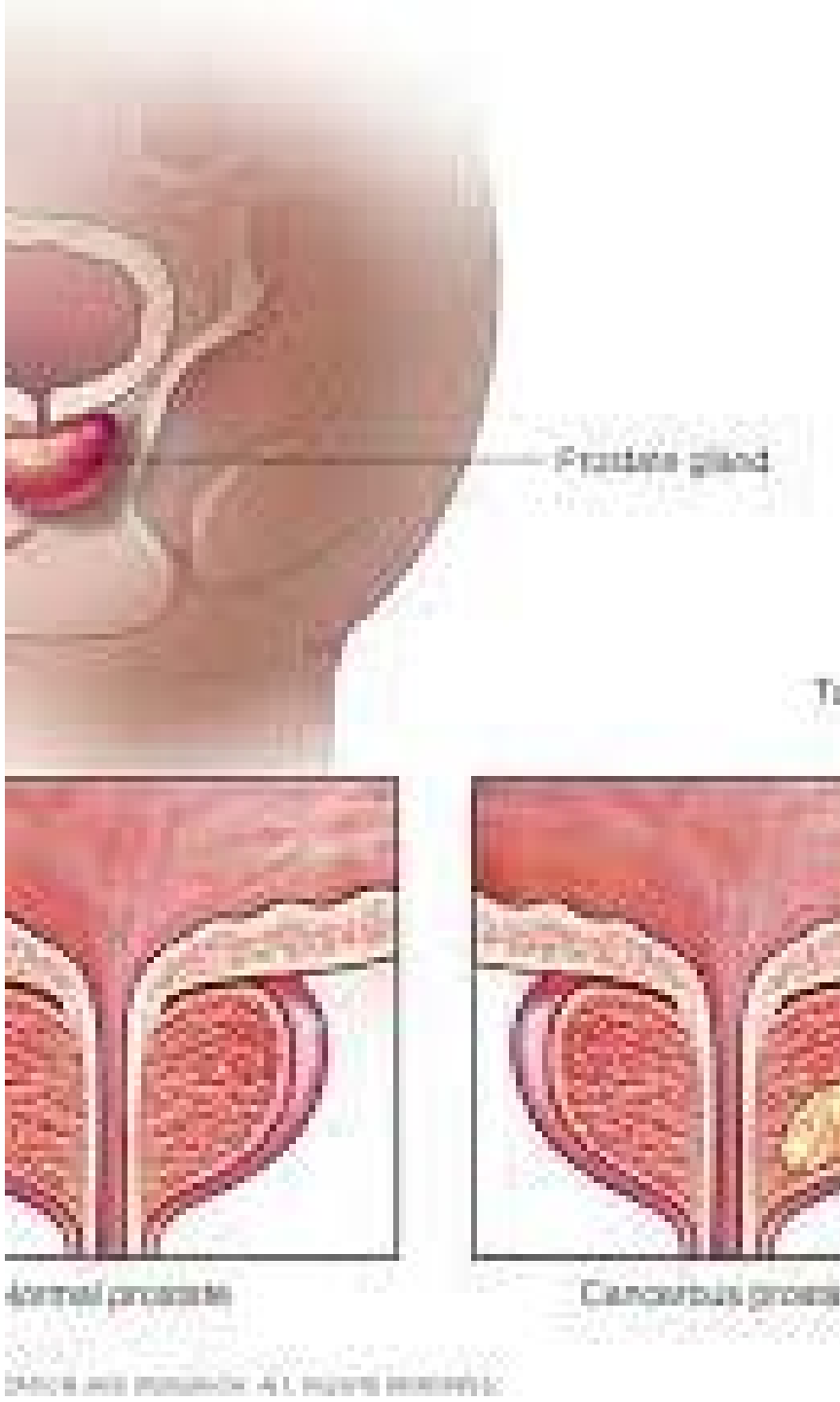
Pancreatic Cancer Risk Management

- Screening- no evidence of improved survival overall
- Research
  - alternating MRI and endoscopic US for carriers with first degree relative with pancreatic cancer.
  - Age 50 or 10 years younger than affected family member
- Investigation on upper abdominal symptoms or new diabetes
- Avoid smoking (known risk factor)

Goggins et al. Gut 2020; 69(1):7–17.

Prostate Cancer

- BRCA 2 – 3-8.5 X increased risk (15-25%)
  - Typically younger age of onset
  - Higher grade
  - Poorer prognosis
- BRCA1 – 3.8 times increased risk (8.6%)
- General population risk 5.9%



Prostate Cancer Risk Management

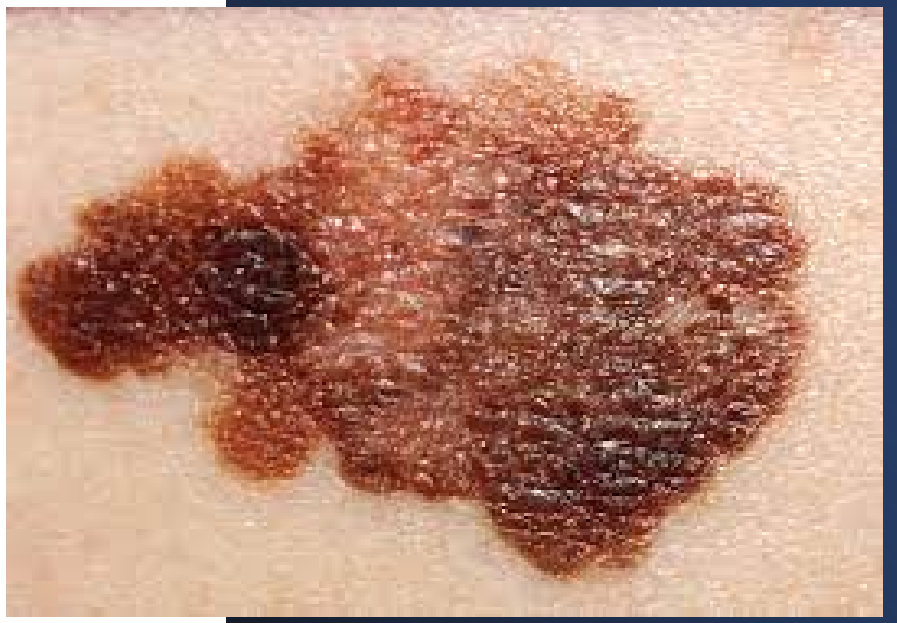
- Genetic testing recommended (in development in BC)
  - Metastatic prostate cancer
  - High grade (Gleason 7+)/ Intraductal or cribiform histology
    - Family history – breast, ovarian, pancreatic, prostate
    - Ashkenazi Jewish heritage
    - African descent

- BRCA2 – PSA and DRE from age 40
- BRCA1 – Consider screening

NCCN Prostate Cancer Early Detection. Version 2.2020. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2020.

Melanoma

- BRCA2 only
- Possible 3-5% (2.7X increase) including uveal
- Not confirmed in all studies
- Patient awareness and consideration of annual skin examinations



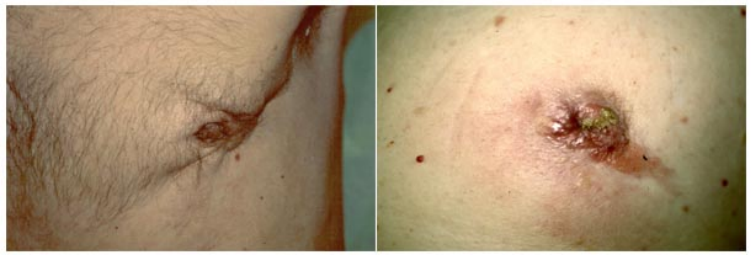
Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, McLellan B. Skin cancer risk in BRCA1/2 mutation carriers. *Br J Dermatol*. 2015;172(6):1498-1506. doi:10.1111/bjd.13626
The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91:1310–16

Male Breast Cancer

- BRCA 1 1-5%
- BRCA 2 5-10%
- General population 0.1%

Clinical breast examinations beginning at the age of 35 years

Consideration of baseline mammography at the age of 40 years



Male Breast Cancer

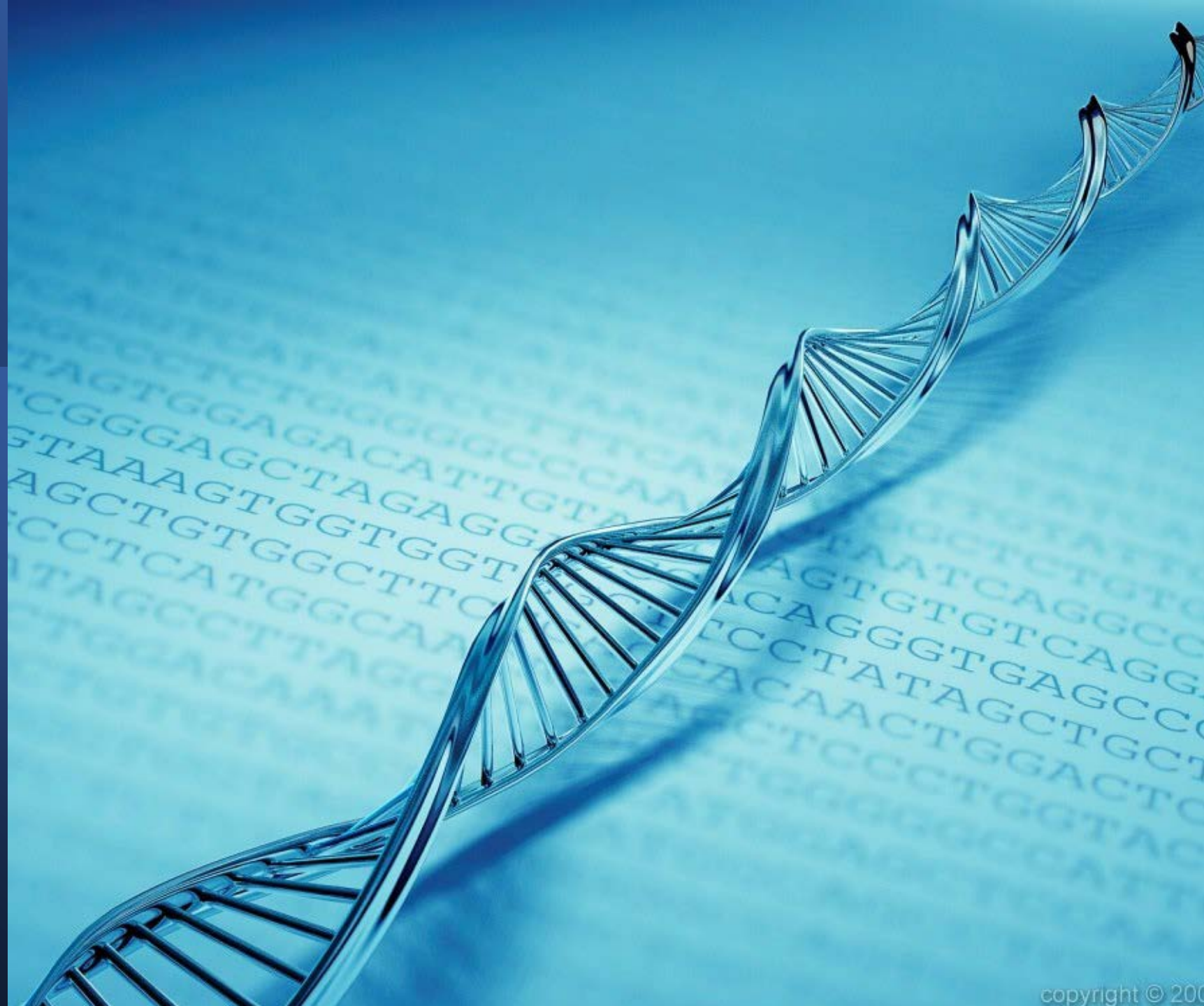
Other Cancers

- Many possibly increased cancer risks reported in the literature
- Data is very variable
- Statistical significance inconsistent
- Bone, pharynx, buccal cavity, larynx esophageal, gallbladder and bile duct, stomach, uterine, colorectal, cervix, etc
- No enhanced screening
- Index of suspicion

THANK YOU!

Lesa Dawson
Rona Cheifetz

Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer



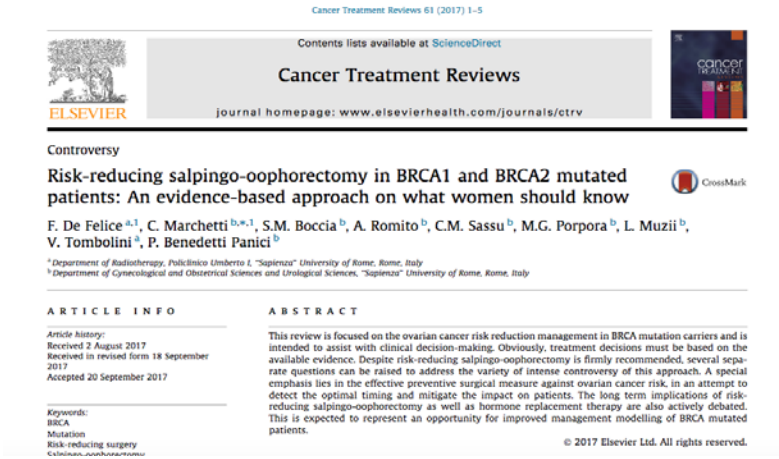
Extra slides for discussion

NCCN.org

GECKO geneticseducation.ca

SOGC guidelines

No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer



Cancer Treatment Reviews 61 (2017) 1–5

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Controversy

Risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutated patients: An evidence-based approach on what women should know

F. De Felice [a,1], C. Marchetti [b,*,1], S.M. Boccia [b], A. Romito [b], C.M. Sassu [b], M.G. Porpora [b], L. Muzii [b], V. Tombolini [a], P. Benedetti Panici [b]

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ABSTRACT

This review is focused on the ovarian cancer risk reduction management in BRCA mutation carriers and is intended to assist with clinical decision-making. Obviously, treatment decisions must be based on the available evidence. Despite risk-reducing salpingo-oophorectomy is firmly recommended, several separate questions can be raised to address the variety of intense controversy of this approach. A special emphasis lies in the effective preventive surgical measure against ovarian cancer risk, in an attempt to detect the optimal timing and mitigate the impact on patients. The long term implications of risk-reducing salpingo-oophorectomy as well as hormone replacement therapy are also actively debated. This is expected to represent an opportunity for improved management modelling of BRCA mutated patients.

No. 366, November 2018

No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer

This Committee Opinion has been prepared by the by the Familial Ovarian Cancer Prevention Programme, reviewed by the Society of Obstetricians and Gynaecologists of Canada (SOGC)'s Gynaecology Committee and the Society of Gynecologic Oncology of Canada (GOC) Guidelines Committee, and approved by the Board of the SOGC.

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Disclosure Statement: Disclosure statements have been received from all authors.
Key Words: BRCA, hereditary breast ovarian cancer (HBOC), familial ovarian cancer, genetic cancer syndrome, BRCA1, BRCA2

KEY MESSAGES

1. BRCA variant status is not a contraindication to hormone therapy.
2. There is no validated screening for ovarian cancer in high-risk

GEC•KO
Genetics Education Canada - Knowledge Organization
on the run

HEREDITARY BREAST AND OVARIAN CANCER

Bottom line: Breast cancer is relatively common in the general population (12% lifetime risk) and the majority of cases occur sporadically. About 5-10% of breast cancer is due to an inherited gene change. Mutations in the genes *BRCA1* or *BRCA2* are the most common cause of hereditary breast and ovarian cancer (HBOC) and *BRCA1* and *BRCA2*

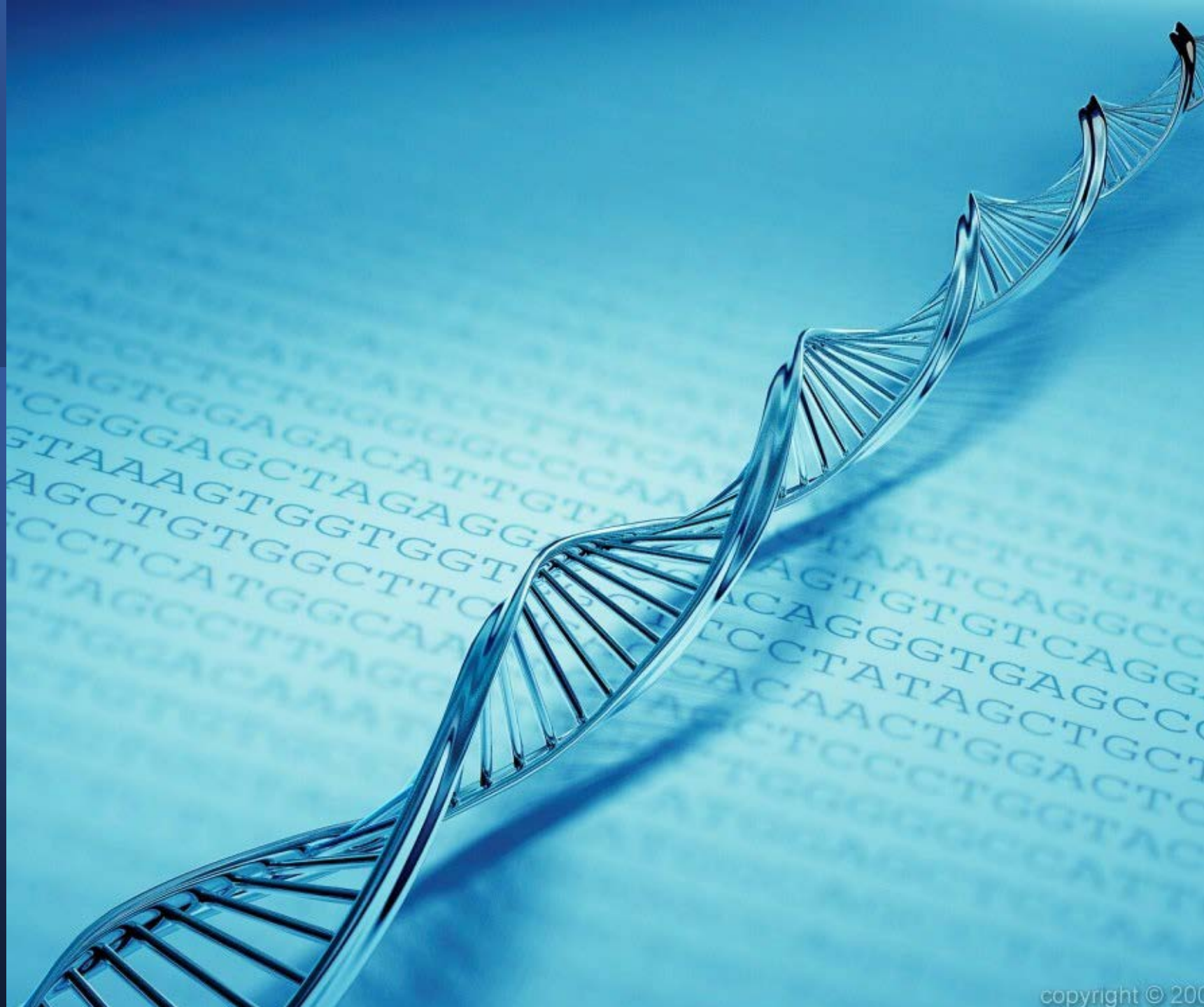
Emerging counselling issues

- Distributive justice- how do we determine fair, equitable access to genetic testing?
- Management of couples when one partner carries a heterozygous mutation in a gene associated with AR disease
  - *ATM*- Ataxia Telangiectasia
  - *BRCA2, BRIP1, PALB2*- Fanconi Anemia
- Insurance discrimination and genetic privacy
  - Bill S-201 (Genetic Non-Discrimination Act)
- Variants of uncertain significance (VUS)
  - More genes analyzed = more VUSs!
  - Follow-up / ressources / over-surveillance and worry for patient when we know about 90% of VUS will be reclassified as polymorphisms
- Prenatal diagnosis and pre-implantation genetic diagnosis (PGD) for cancer survivors or young previvors

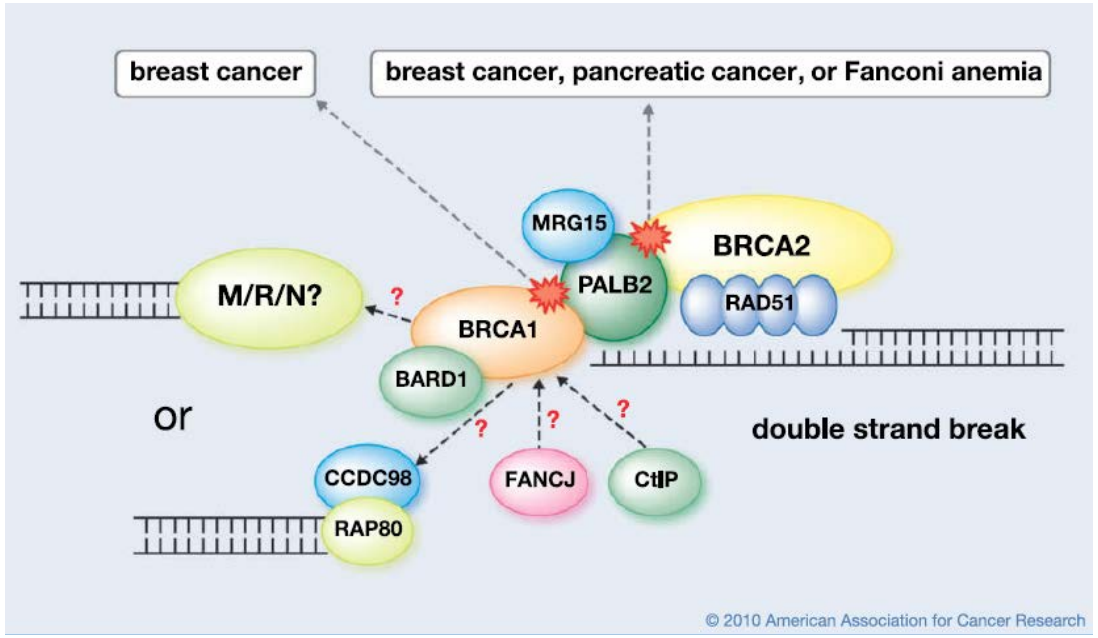
THANK YOU!

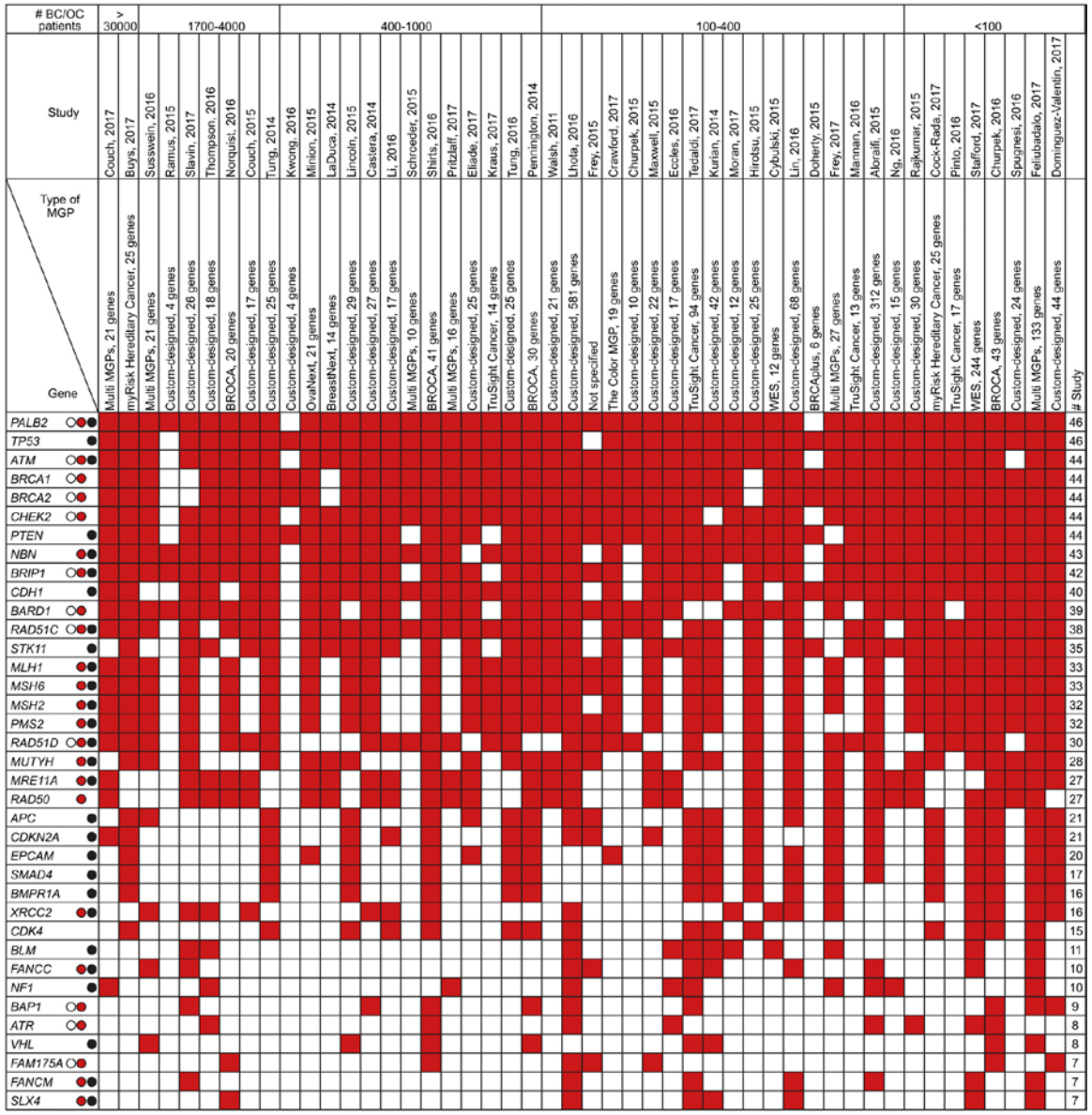
Lesa Dawson
Rona Cheifetz

Beyond Angelina Jolie: Diagnosis and Management of Hereditary Breast and Ovarian Cancer

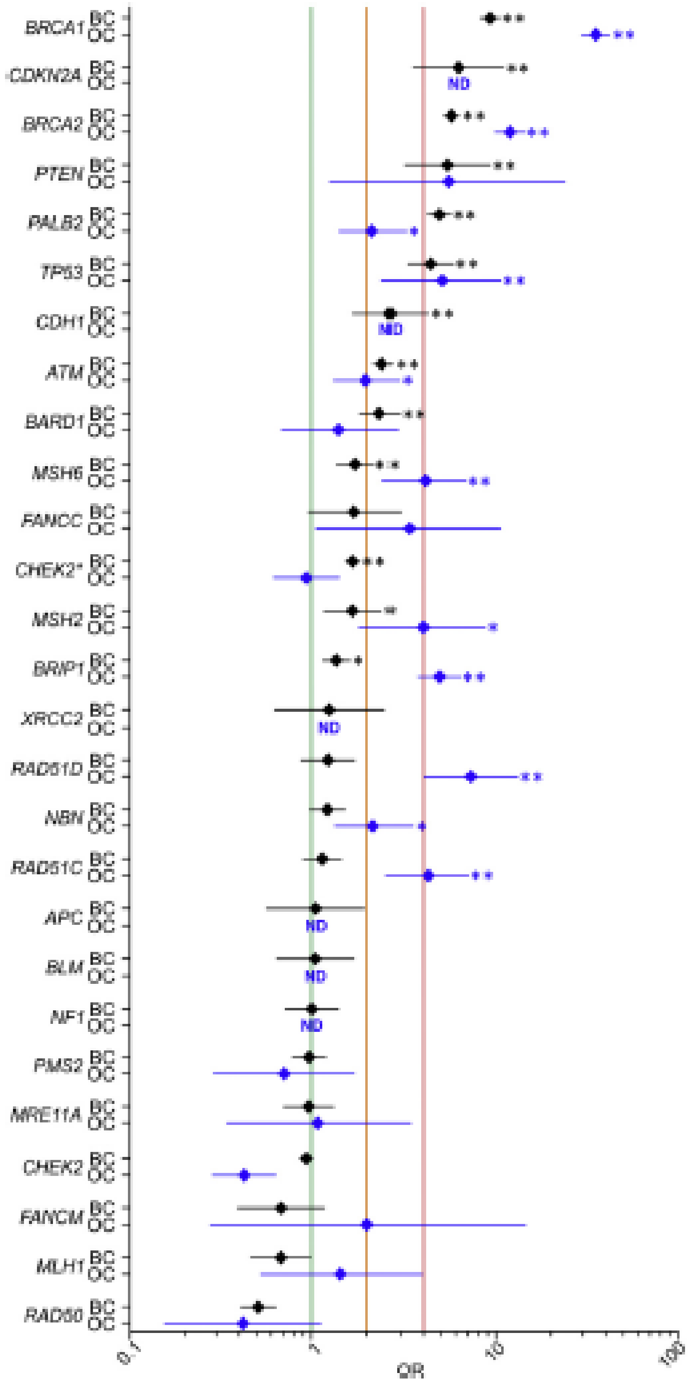


Hereditary Ovarian Cancer is more than BRCA 1 & 2





M. Suszynska et al. / Gynecologic Oncology 153 (2019) 452–462


BRCA1 BC OC
CDKN2A BC OC
BRCA2 BC OC
PTEN BC OC
PALB2 BC OC
TP53 BC OC
CDH1 BC OC
ATM BC OC
BARD1 BC OC
MSH6 BC OC
FANCC BC OC
CHEK2* BC OC
MSH2 BC OC
BRIP1 BC OC
XRCC2 BC OC
RAD51D BC OC
NBN BC OC
RAD51C BC OC
APC BC OC
BLM BC OC
NF1 BC OC
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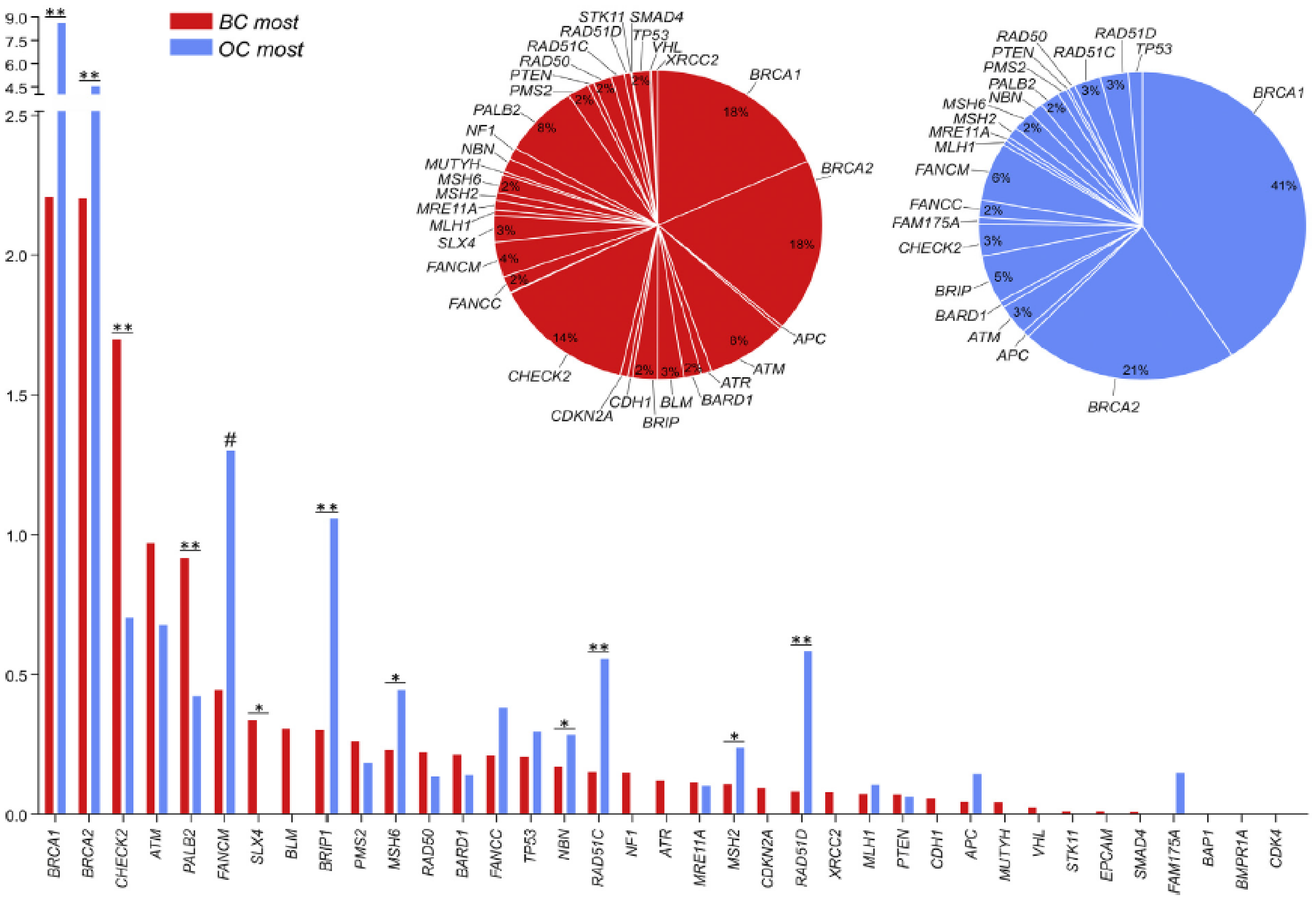
BC most
OC most
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0.0
BRCA1
BRCA2
CHECK2
ATM
PALB2
FANCM
SLX4
BLM
BRIP1
PMS2
MSH6
RAD50
BARD1
FANCC
TP53
NBN
RAD51C
NF1
ATR
MRE11A
MSH2
CDKN2A
RAD51D
XRCC2
MLH1
PTEN
CDH1
APC
MUTYH
VHL
STK11
EPCAM
SMAD4
FAM175A
BAP1
BMPR1A
CDK4
18%
18%
8%
14%
8%
41%
21%
6%
5%

RAD51C, RAD51D , BRIP1

Important Contributors to. Ovarian Cancer Risk

BRIP1 Ovarian Cancer Risks	
2.62 (1.72-3.98)	Kurian 2017
11.22 (3.22-34.1)	Ramus 2015 case-control
3.41 (2.12-5.54)	Ramus 2015 segregation
6.4 (3.8-10.6)	Norquist 2015
4.99 (3.79-6.45)	Lilyquist 2017
19.17 (11.13-33)	Webber-Lasalle 2018
4.98 (3.73-6.38)	Suszynska 2019 meta-analysis

	RAD51C	**RAD51D**
Ovarian Cancer	RR 3-10 *(counsel 4)*	RR 4-12 *(counsel 8)*
All breast cancer	increased	modestly elevated
TN Breast Cancer (*stay tuned)*	RR 1- 6	RR 4 - 30
Recommendations NCCN Risk Reducing Salpingo-oophorectomy 45-50y		

https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

WOMEN'S HEALTH RESEARCH INSTITUTE AT BC WOMEN'S

Gynecologic Cancer Initiative

diamond FOUNDATION

BC WOMEN'S HOSPITAL+ HEALTH CENTRE

FACULTY OF MEDICINE

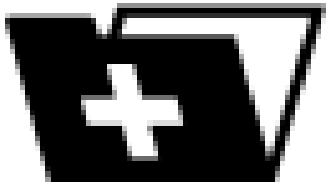
Gynecologic Oncology Survivorship Clinic

Personalized Gynecologic Cancer Prevention & Survivorship

Division of Gynecologic Oncology
Diamond Health Care Centre
2775 Laurel Street
Vancouver, BC V5Z 1M9

The Division of Gynecologic Oncology is launching a new clinic to serve patients in BC with high hereditary risk for gynecologic cancer. The mission of this clinic is to improve the quality of peri-operative care, education and hormone therapy support for patients embarking on preventative gynecologic surgery.

What does this clinic offer?



Menopause management

Patients who have had risk-reducing oophorectomy require ongoing expert advice about management of menopause. Our specialty service offers evidence-based guidance about hormone use and post-operative care.

Preventative Surgical Decision Support

Many families have inconclusive or negative genetic testing but may still be at high risk for ovarian or endometrial cancer. We can assess patients with a worrisome family history of ovarian cancer and assist with decisions about surgery or prevention.

Access to Research

Patients at high hereditary risk benefit from access to research about prevention and risk reduction. Our team will ensure that patients and families in BC have access to research studies and clinical trials.

Who to refer?

- Patients having risk reducing gynecologic surgery due to a known mutation in BRCA1&2, BRIP1, RAD51C, RAD51D, PALB2 or Lynch Syndrome.
- Patients with uninformative genetic testing (no mutation OR variant of uncertain significance) and concerns about family cancer history.
- Patients requiring complex post-surgical menopause care.
- Patients requesting individualized assessment and advice regarding hereditary risk and prophylactic surgery options.

WOMEN'S HEALTH RESEARCH INSTITUTE AT BC WOMEN'S

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BC WOMEN'S HOSPITAL+ HEALTH CENTRE

FACULTY OF MEDICINE

Referrals Lisa.Andres@vch.ca 605 875 4260