Gynaecologic Management of Hereditary Breast and Ovarian Cancer

Presented by: Michelle Jacobson MD FRCSC MHSc MSCP

Director, Familial Ovarian Cancer Clinic, Women's College Hospital

Assistant Professor, University of Toronto

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NCCN Guidelines Version 2.2024
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11,* and *TP53*. See GENE-A)[a,f,g,h,i]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - Treatment indications
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[l]
    - Pathology/histology
      - Triple-negative breast cancer
      - Multiple primary breast cancers (synchronous or metachronous)[m]
      - Lobular breast cancer with personal or family history of diffuse gastric cancer NCCN Guidelines for Gastric Cancer
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - Family history[n]
      - ≥1 close blood relative[o] with ANY:
        - breast cancer at age ≤50
        - male breast cancer
        - ovarian cancer
        - pancreatic cancer
        - prostate cancer with metastatic,[p] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Family history of cancer only
  - Individuals affected with breast cancer (not meeting testing criteria listed above) or individual unaffected with breast cancer with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[q]
  - Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[r]

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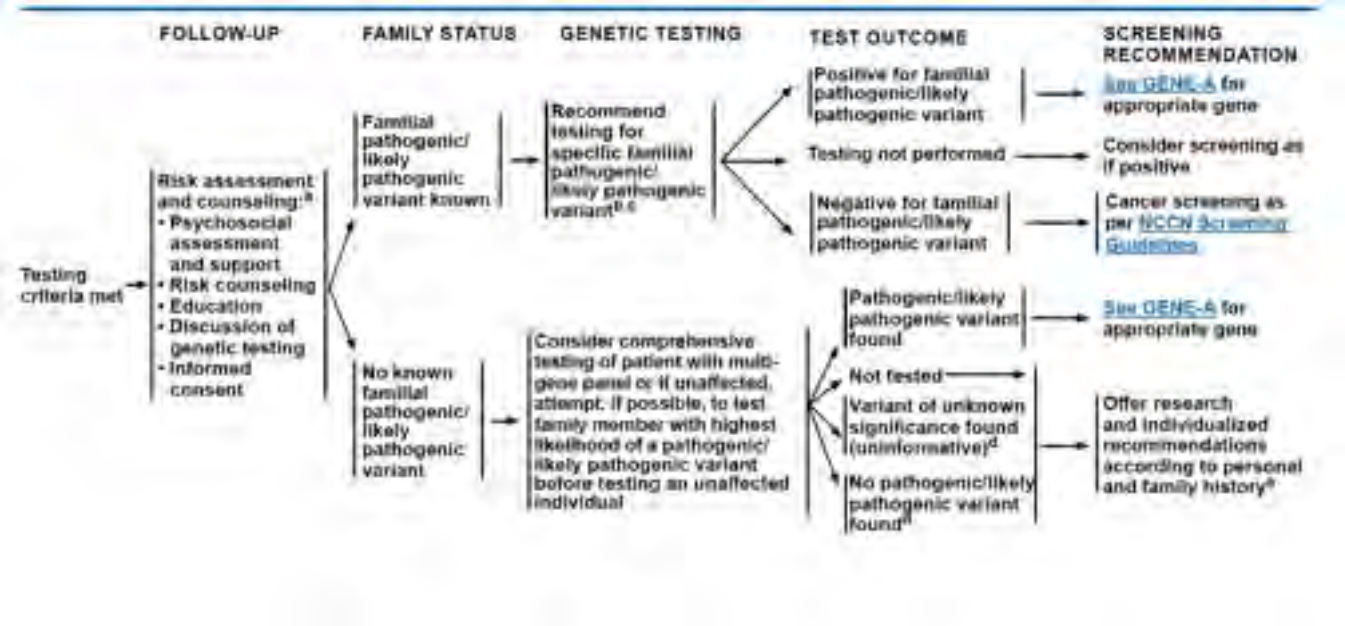
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR OVARIAN CANCER SUSCEPTIBILITY GENES[a,t]
(Specifically *ATM*, BRCA1, BRCA2, BRIP1, Lynch syndrome genes [*MLH1, MSH2, MSH6, EPCAM*], PALB2 RAD51C, and RAD51D; see GENE-A)[u]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of epithelial ovarian cancer[v] (including fallopian tube cancer or peritoneal cancer) at any age
- Family history of cancer only
  - An individual unaffected with ovarian cancer (with a first- or second-degree blood relative with epithelial ovarian cancer[v] (including fallopian tube cancer or peritoneal cancer) at any age[q]
  - An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[r]

Crash course in genetic counselling



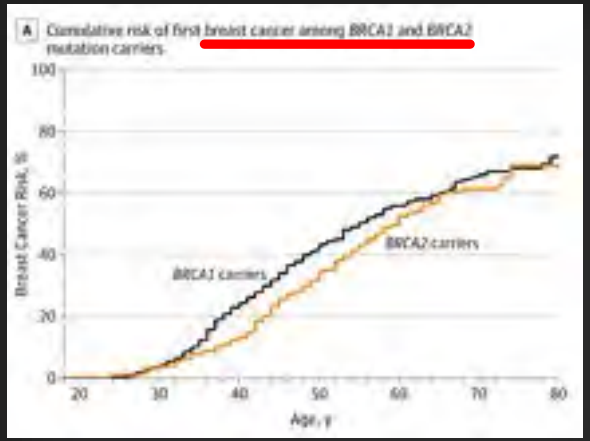
How to interpret genetic test results

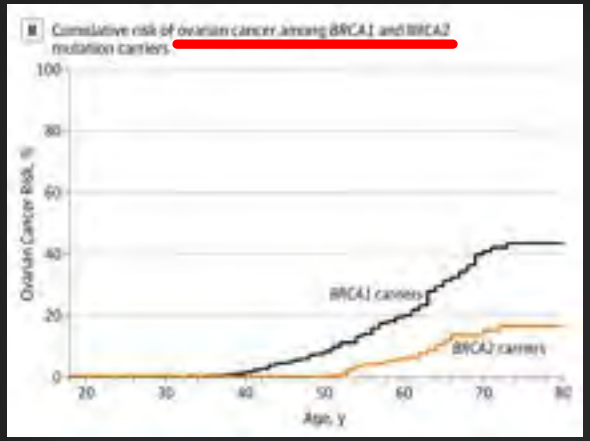
Table 2. Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene

Result	*Description*
True-positive	The person is a carrier of an alteration in a known cancer-predisposing gene.
True-negative	The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member.
Indeterminate (uninformative)	The person is not a carrier of a known cancer-predisposing gene, and the carrier status of other family members is either also negative or unknown.
Inconclusive (variants of unknown significance)	The person is a carrier of an alteration in a gene that currently has no known significance.

Gene	Ovarian Cancer Risk	Breast Cancer Risk
ATM	Potential increase in ovarian cancer risk, insufficient evidence for recommendation of RRSO	Yes
BRIP1	RRSO at 45-50yo (or earlier based on family hx of early onset ovarian ca)	Unknown/insufficient evidence
PALB2	RRSO at 45-50yo (or earlier based on family hx of early onset ovarian ca)	Yes
RAD51c/RAD 51d	RRSO at 45-50yo (or earlier based on family hx of early onset ovarian ca)	Unknown/insufficient evidence
STK11	Increased risk of non-epithelial ovarian cancer (Peutz-Jeghers Syndrome) – recommended pap smear and pelvic exam annually beginning at 18-20yo	Yes
MSH2 **MSH6** **MLH1** **PMS2** **EPCAM**	Lynch Syndrome Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy following completion of child-bearing depending on genetic mutation	Unknown/insufficient evidence depending on genetic mutation

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers





BREAST CANCER		
BRCA1 mutation	72 %	(65 to 79 %)
BRCA2 mutation	69 %	(61 to 77 %)

OVARIAN CANCER		
BRCA1 mutation	44 %	(36 to 53 %)
BRCA2 mutation	17 %	(11 to 25 %)

The lifetime risk of breast cancer is higher with *BRCA1* than *BRCA2* mutations.

***BRCA1* carriers have earlier-onset disease, particularly before age 50**

Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA 2017; 317:2402.

UK Familial Ovarian Cancer Screening Study

The results suggest a potential stage shift when a ROCA based ovarian cancer screening protocol is followed in high-risk women

Undetermined if screening affects survival

- 4348 Women whose estimated lifetime risk of HGSC was ≥ 10%
- CA-125 every 4 months interpreted with ROCA and TVUS (annually or within 2 months if abnormal ROCA score)
- Thirteen patients were diagnosed with ovarian cancer as a result of the screening protocol,
  - 5/13 patients stage 1-2
  - Sensitivity 94.7%
  - positive predictive value 10.8%
  - negative predictive value 100%

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The decision to undergo RRSO is complex and should be made ideally in consultation with a specialist

- **Topics that should be addressed include the impact on:**
  - **Reproduction**
  - **Breast and ovarian cancer risk**
  - **Risks associated with premature menopause (eg, osteoporosis, cardiovascular disease, metabolic syndrome, cognitive changes, vasomotor symptoms, mood, libido, sexual functioning, body image)**
  - **Cancer anxiety**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Genetic/Familial High-risk Assessment: Breast and Ovarian. Version 2.2019.

Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a *BRCA1* or *BRCA2* Mutation

- **Observational study of 5783 women with a *BRCA1/2* mutation**
- **Median Follow up 5.6 years showed that RRBSO:**
  - **Reduces risk for ovarian, fallopian, or peritoneal cancer by 80% (HR, 0.20; 95% CI, 0.13– 0.30)**
  - **Decreases all-cause mortality by 77% (HR, 0.23; 95% CI, 0.13–0.39).**

Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, Rosen B, et al. J Clin Oncol. 2014 May 20;32(15):1547-53.

Reproduction considerations

- Options include prenatal diagnosis and assisted reproduction using preimplantation genetic testing (PGT)
- Several factors must be weighed in the decision to utilize PGD
  - Personal history of breast cancer/ovarian reserve
  - Geographical access
  - Affordability
  - In cases where both partners carry a BRCA2 mutation, there may be a high risk for the offspring to develop Fanconi anemia

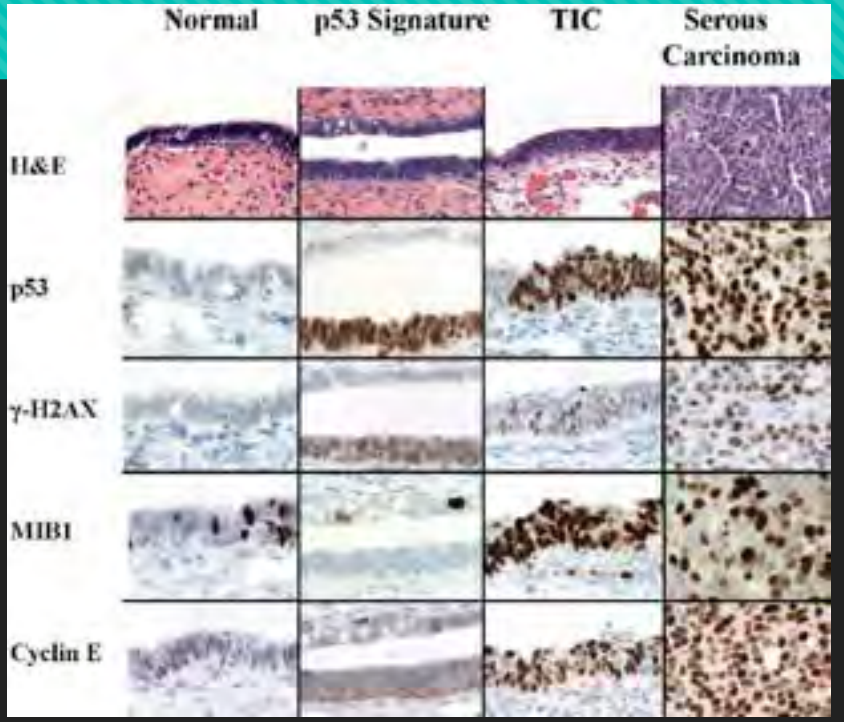
Fallopian tube as the precursor lesion

- At least 50 percent of serous cancers diagnosed in *BRCA* mutation carriers are of distal fallopian tube origin
- The lifetime risk of developing fallopian tube carcinoma in *BRCA* mutation carriers is estimated to be 0.6 %, while the general population risk is 0.2 %
- This risk may be an underestimate, given that many high-grade serous ovarian cancers appear to originate in the fallopian tubes.

Reade CJ, McVey RM, Tone AA, et al. The fallopian tube as the origin of high grade serous ovarian cancer: review of a paradigm shift. J Obstet Gynaecol Can 2014; 36:133.

Risk Reducing Salpingectomy

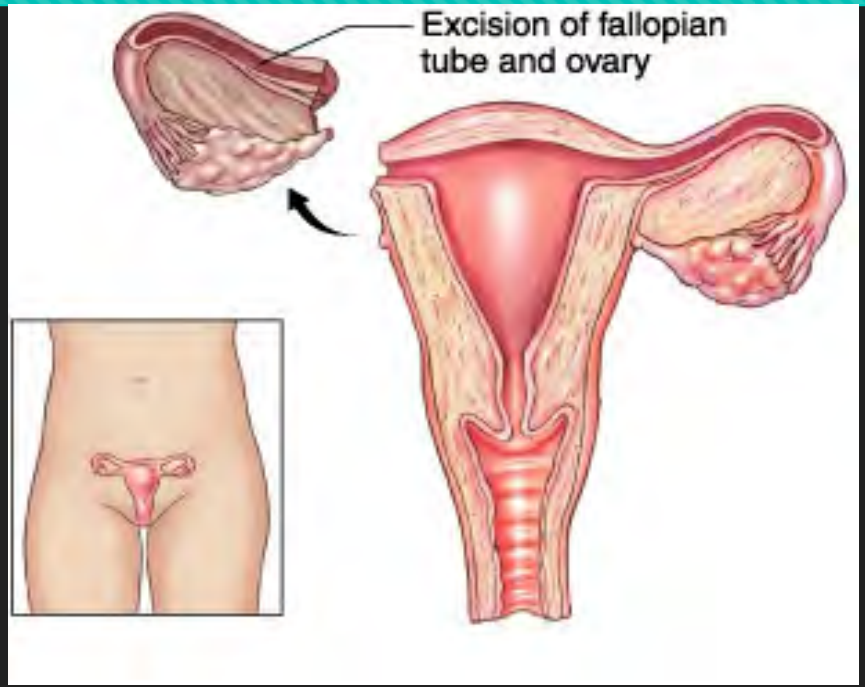
- Benefit:
  - Prevention of iatrogenic premature menopause
- Risks:
  - Unknown protection
  - Residual fimbrial tissue
  - Follow-up strategy



Based on statistical models, no mortality increase with RRS upon completion of childbearing and RRO at age 40-45 (BRCA1) or 45-50 (BRCA2)

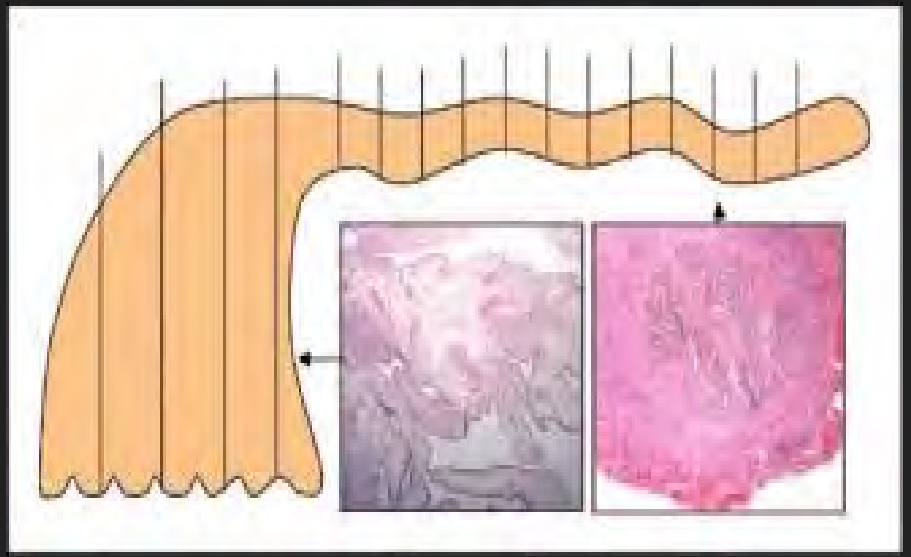
Surgical Considerations

- Careful inspection
- Pelvic washings for cytology
- IP 2cm distal to ovary
- Transect adnexa at uterus
- Endoscopic bag
- SEE-FIM protocol



Sectioning and Extensively Examining the FIMbria (SEE-FIM) protocol

Detection from 2.5% to 17%



Crum et al, 2007. Current opinion in obstetrics & gynecology. 19. 3-9.

BRCA and Papillary Serous Uterine Cancer

- Some studies have suggested an increased risk specifically of serous uterine cancer in BRCA1 mutation carriers
  - Multicenter prospective cohort study of 1083 BRCA1 carriers who underwent RRSO without hysterectomy showed an increased risk for serous and/or serous-like endometrial cancer but overall no increased risk of endometrial carcinoma
  - **Overall risk for uterine cancer was not increased when controlling for tamoxifen use**
- Matanes 2020 – Meta-analysis of 13871 BRCA1/2 carriers suggest a slightly increased but not significant risk of endometrial/PSUC ca in carriers
- The increased risk for endometrial cancer observed in some carriers of BRCA1/2 may be due to the use of tamoxifen therapy

Hysterectomy and Menopausal Aftercare

- From a hormone-replacement perspective negates the need for a progestogen
- Prospective data showing no benefit in menopause management
- There are other ways to mitigate this potential breast cancer risk:
    - Specific drug selected (TSEC)
    - Dosing regimen - cyclic progesterone use, CEE
    - Long cycle HRT

Risk of Peritoneal Cancer following RRSO

- Risk factors:
  - older at time of RRSO (P = .025)
  - Higher rate of serous tubal intraepithelial carcinoma (STIC) in their RRSO specimen (P < .001)
  - BRCA1

Table 3. Risks and recommendations for gynaecologic management of BRCA1 and BRCA2 deleterious variants

Risk and recommendation	BRCA1	BRCA2
Ovarian cancer	36%–53%	11%–25%
Breast cancer	65%–80%	45%–85%
Recommended age for risk-reducing oophorectomy	35–40 y	40–45 y
Risk of ovarian cancer after breast cancer diagnosis	12.7%	6.8%
20-year risk of primary peritoneal cancer after oophorectomy	3.9%	1.9%

Sequellae of RRSO

- Abrupt and early surgical menopause
  - Vasomotor symptoms
  - Changes in sexual function
  - Mood changes
- In younger women, increased risk of cardiovascular disease, metabolic syndrome, osteoporosis, cognitive impairment
- Improved breast cancer mortality
- Reduced risk of premenopausal breast cancer (in BRCA2?)

Menopausal hormone therapy in BRCA1/2 variant carriers

- Women remain fearful of hormone therapy despite its benefits
- Risks difficult to assess, especially in special populations (eg, premature/surgical menopause, BRCA mutation carriers)
- Markov Model - BRCA carriers having mastectomy and oophorectomy prophylaxis at age 30, plus HRT to age 50 = 0.79 years gained (Armstrong 2004)

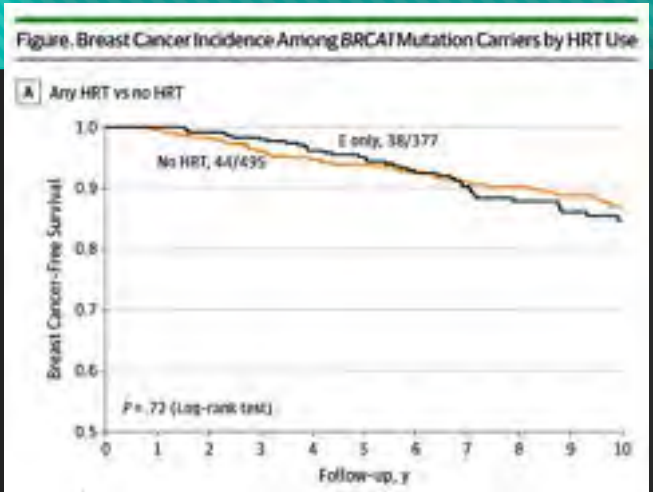
HRT, BRCA and Breast Cancer Risk:

- Case-control study by Eisen, showed no increased risk of breast cancer among 472 BRCA patients who used HRT (OR for breast cancer associated with ever use of HT = 0.58, 95% CI = 0.35 to 0.96; P = .03)

- PROSE study - HRT after RRSO in 462 carriers did not alter the reduction in breast cancer risk associated with RRSO (HR = 0.37; 95% CI, 0.14 to 0.96)

JAMA Oncology | Original Investigation

Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among *BRCA1* Mutation Carriers



In the sub-group of carriers taking estrogen alone, there was no increase in risk of subsequent breast cancer compared with controls.

- **Overall HRT was not associated with an increased risk of breast cancer at a median follow-up of 7.6 years (HR 0.97, 95% CI 0.62-1.52, *P* = .89)**

Kotsopoulos J, Gronwald J, Karlan BY, Jacobson MR, et al. Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. JAMA Oncol 2018; 4:1059.

WHAM Study

- Vasomotor symptoms increase by 3 months after RRSO but do not worsen over the next 12 months. Hormone Therapy reduces but does not resolve vasomotor symptoms and may improve QoL, but not to pre-oophorectomy levels.
- Most non-HT users are highly symptomatic for VMS with little chance of improvement by 12 months. In contrast, two-thirds of HT users have fewer symptoms and a much higher chance of improvement.
- Sleep disturbance significantly increases after premenopausal RRSO ($p < 0.001$). Risk factors include severe vasomotor symptoms, obesity and smoking. Hormone therapy reduces but does not resolve sleep disturbance after RRSO.
- RRBSO leads to a rapid increase (2-3X) in clinically significant depressive and anxiety symptoms despite Hormone Therapy use.
- Cardiometabolic risk markers are largely unchanged 12 months after RRBSO. Hormone Therapy after RRBSO may prevent against an increase in waist circumference.