Ovarian Cancer Screening

Are we moving the needle?

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4th Annual Cancer Risk and Prevention Symposium

University of Nebraska Medical Center

I have no financial disclosures

Objectives

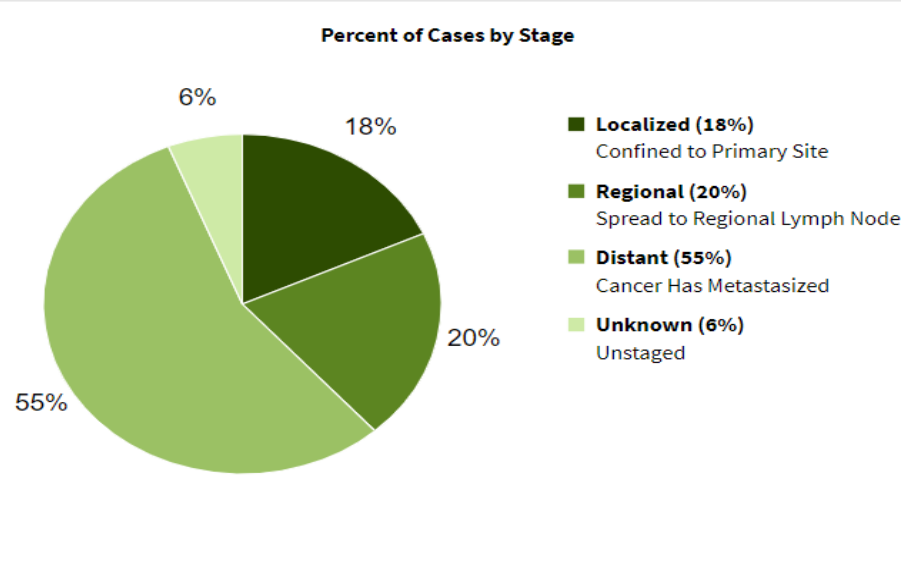
- Review current ovarian cancer statistics
- Discuss hereditary mutations that are associated with ovarian cancer
- Discuss difference between screening, early detection and prevention
- Review landmark studies guiding our recommendations
- Discuss the current state of research in early cancer detection/screening

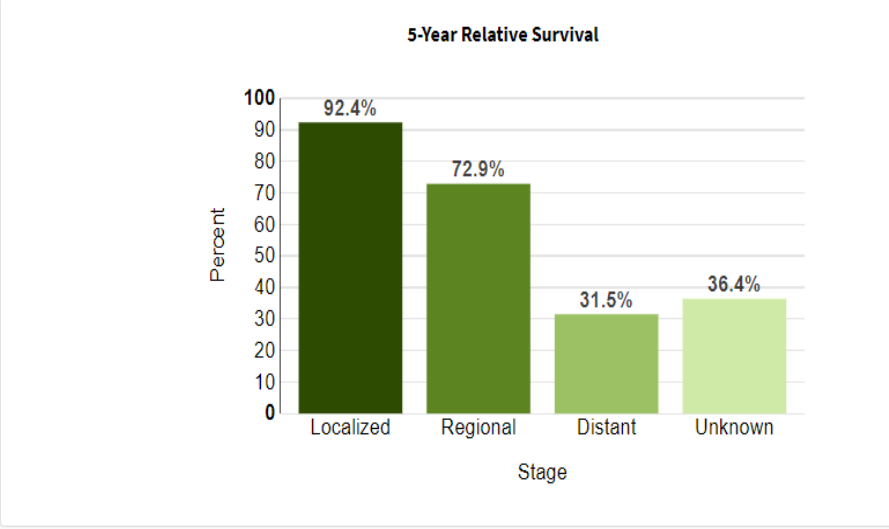
Ovarian Cancer

- The lifetime risk of ovarian cancer is **~1.1%**
- Represents **~1%** of all new cancer cases in the US

  20,890 est. new cases in 2025

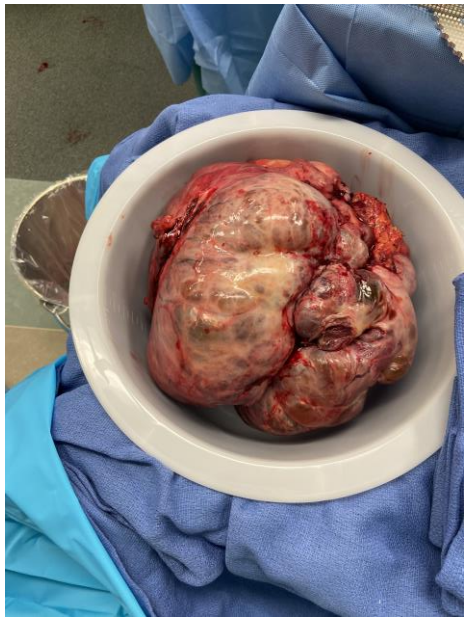
- Most ovarian cancer have spread prior to diagnosis
- When confined to ovary it is associated with better prognosis
- When regional/distant spread has occurred prognosis drops

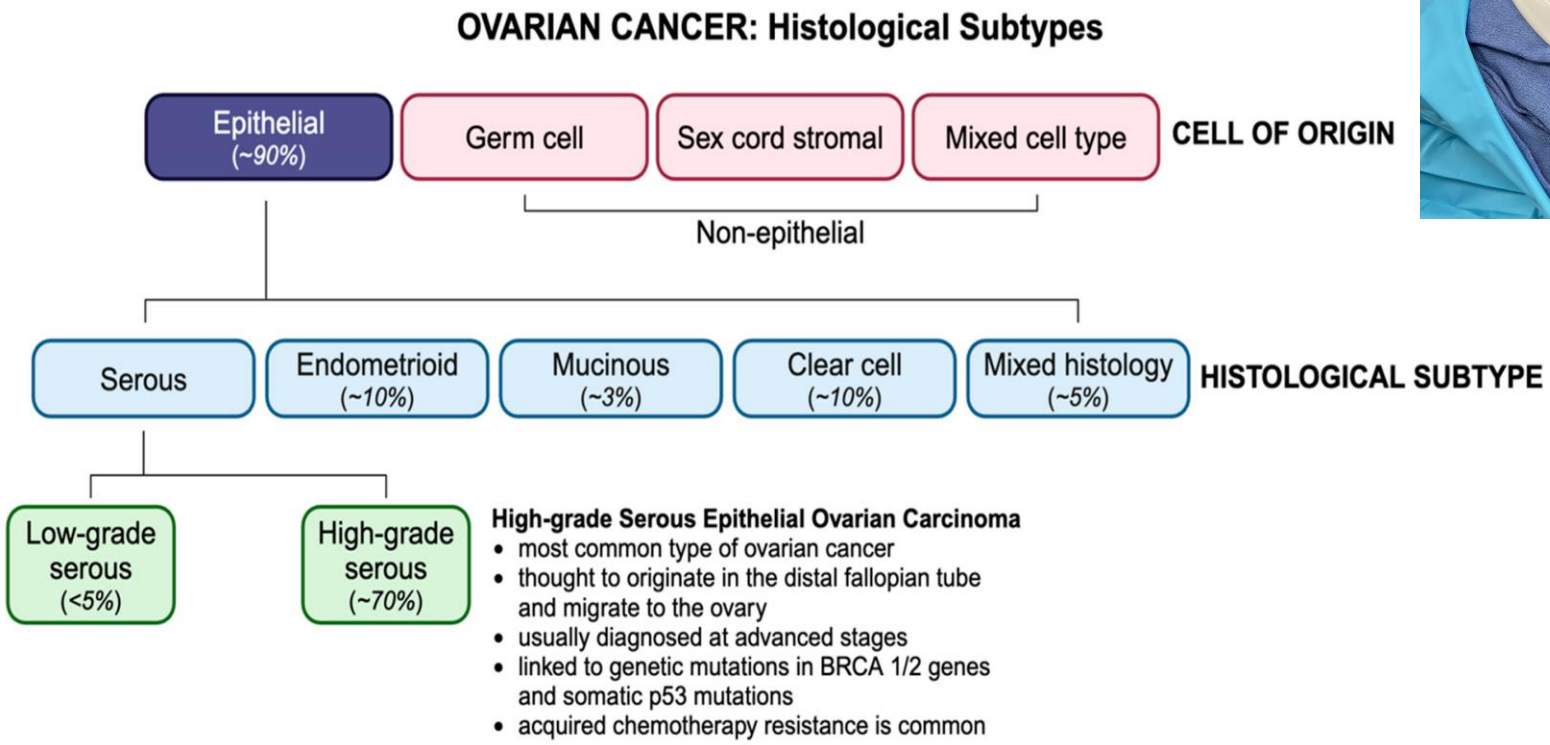




SEER 22 (Excluding IL/MA) 2013–2019, All Races, Females by SEER Combined Summary Stage

Ovarian Cancer





Garlisi, 2024

High Grade Serous Ovarian Cancer (HGSC)

Generally statistics include all histologic subtypes

- Epithelial, Germ Cell, & Stromal
- HGSC is most associated with hereditary mutations involved with HRD (BRCA)
- Non serous more associated with KRAS, BRAF, PTEN, PIK3CA, ARIDIA1A.

HGSC is a driver for poor prognosis

- Associated STIC (serous tubal intraepithelial carcinoma)
- Poor ability to distinguish early ovarian cancer or STIC lesions

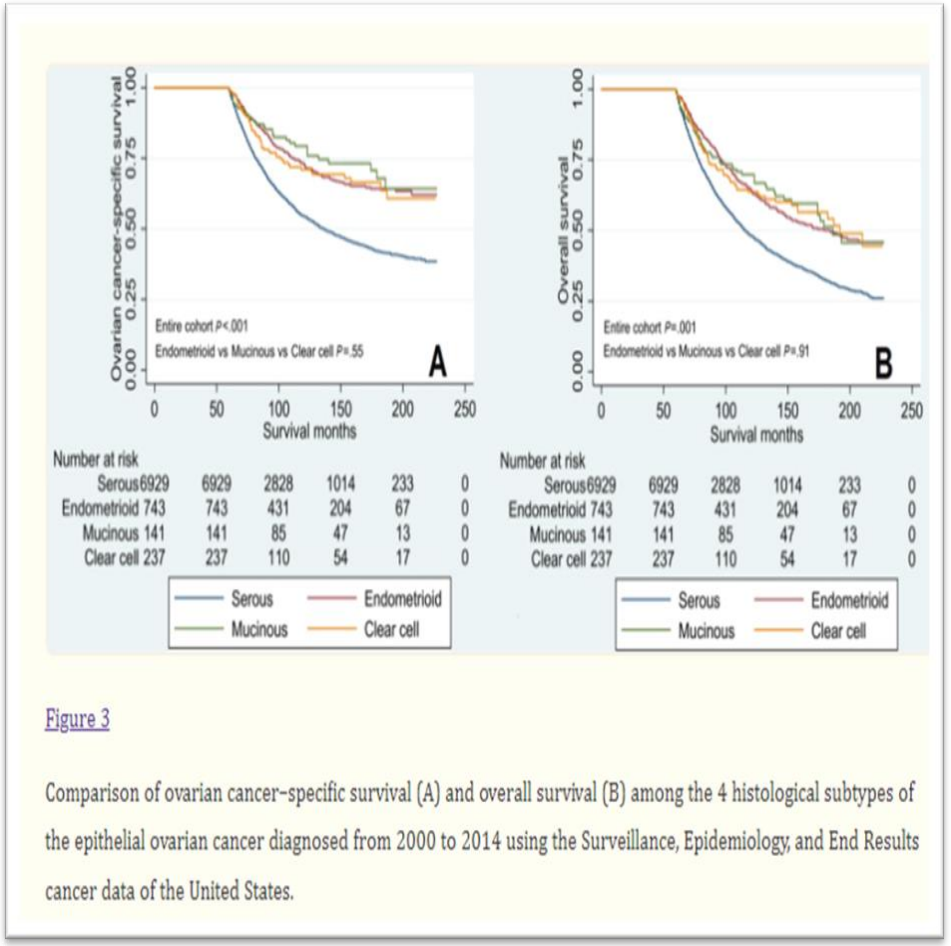
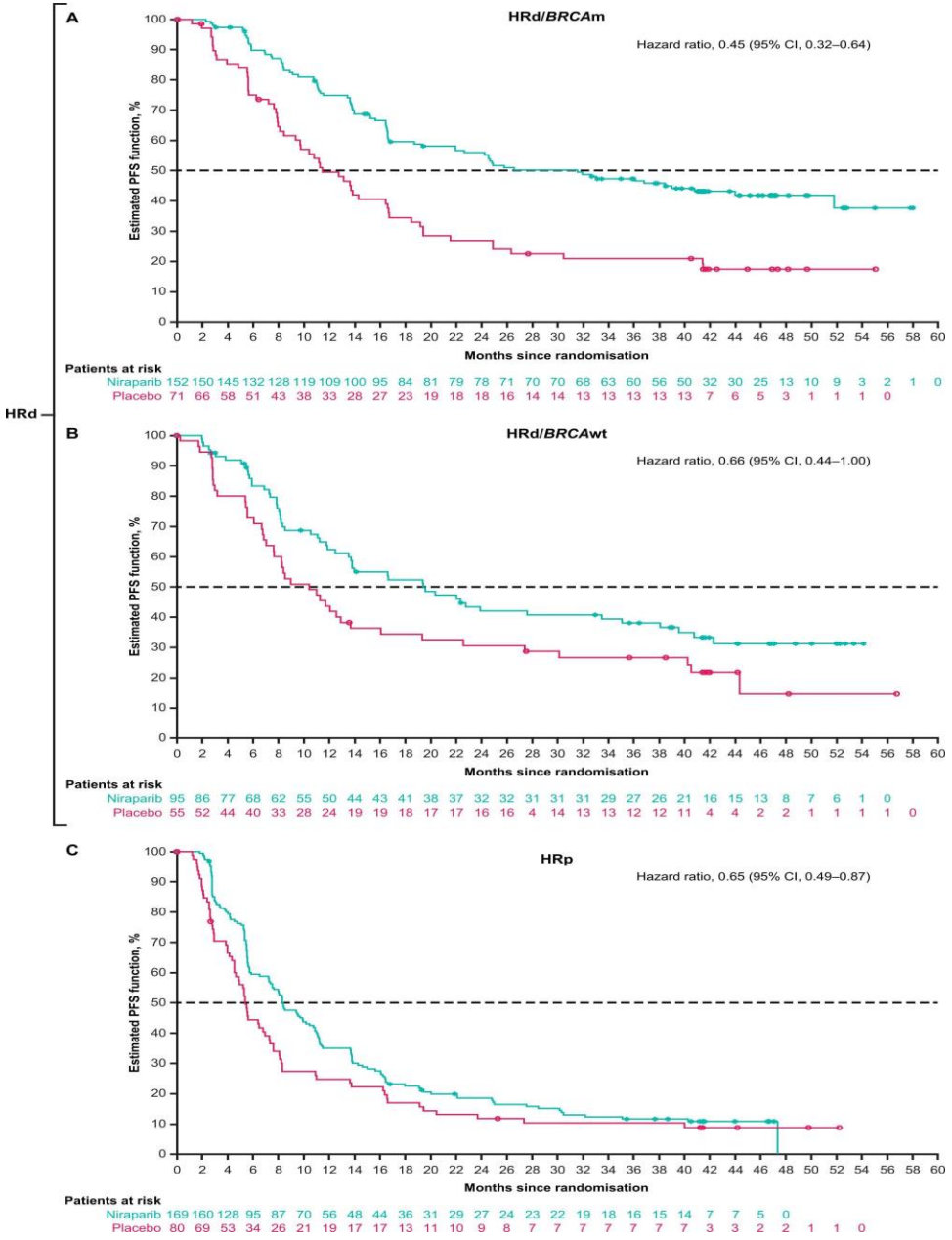
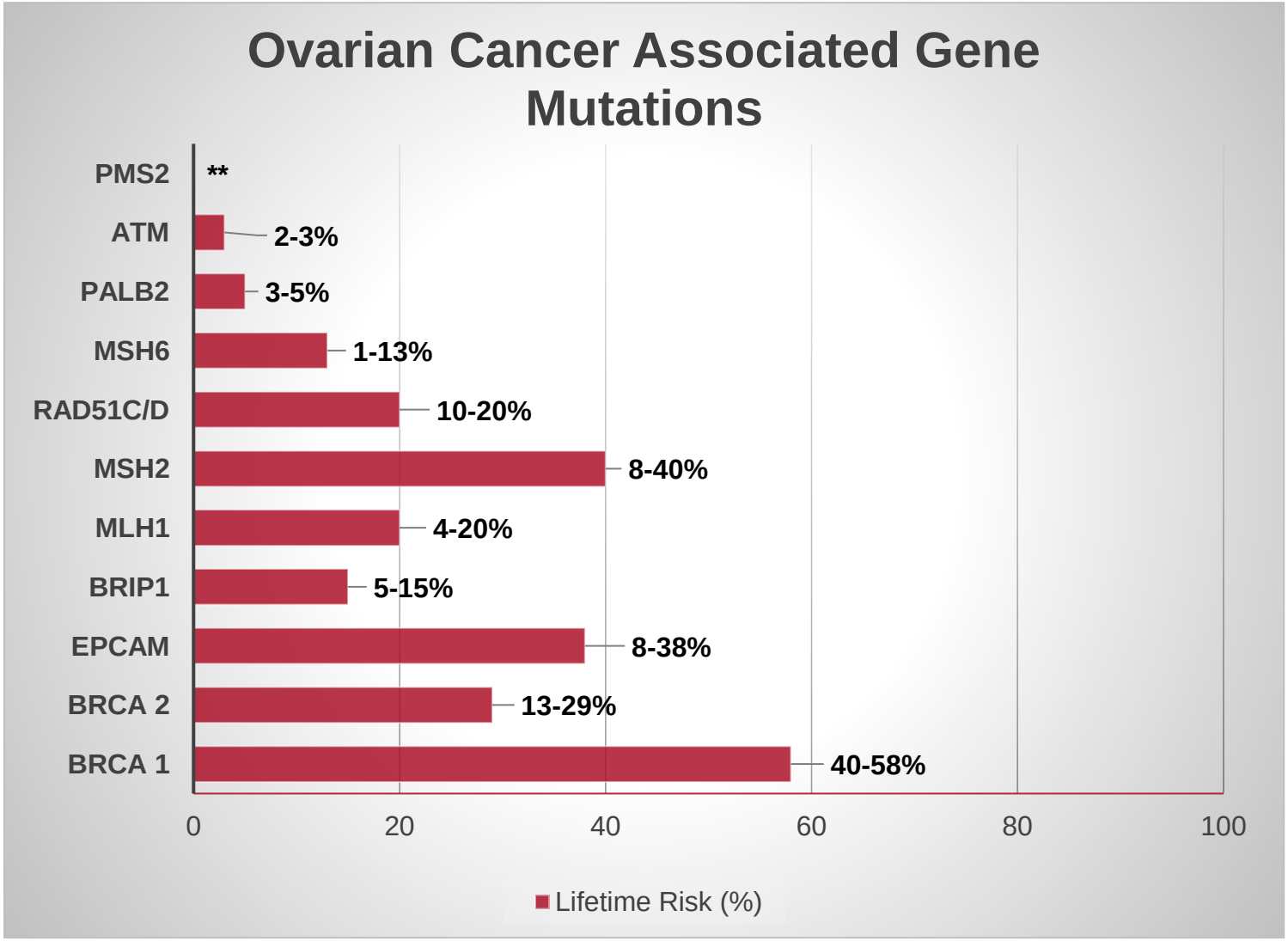


Figure 3

Comparison of ovarian cancer-specific survival (A) and overall survival (B) among the 4 histological subtypes of the epithelial ovarian cancer diagnosed from 2000 to 2014 using the Surveillance, Epidemiology, and End Results cancer data of the United States.



Hereditary ovarian cancer differences



*More data is needed to correlate risk of ovarian cancer with PMS2

Screening, Early Detection, & Prevention

Screening Test

- Goal to detect a high proportion of disease in its preclinical state
- Safe to administer
- Reasonable in cost
- Lead to improved health outcomes
- Widely available with interventions that can follow when a positive result is found.

Early Detection

- Goal is to detect disease in its early stage
- Hope that you improve cancer outcomes by intervening early

Prevention

- Interventions that stop the natural course of the disease from occurring or reduce the risk

Early Detection

Successful early detection strategies for ovarian cancer should diagnose more high grade epithelial ovarian cancers at an early stage and improve outcomes

However, this relies on two basic assumptions

#1. High grade epithelial ovarian cancers currently diagnosed at an advanced stage, if detected earlier, will have the same favorable prognosis as Stage I cancers.

#2. Screening efficacy must control for **lead-time bias.**

Elias, 2018

Review of biostatics

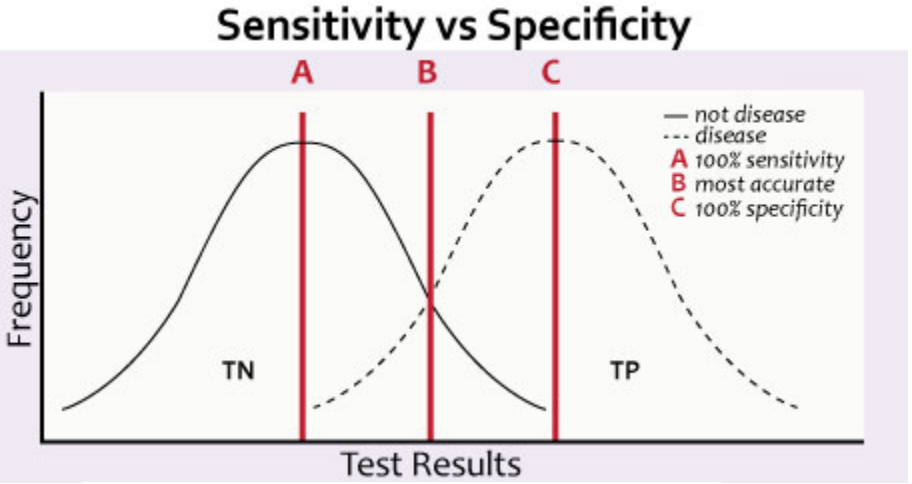
Sensitivity: The proportion of individuals with the disease who test positive. A high sensitivity indicates the test is good at ruling out the disease when negative.

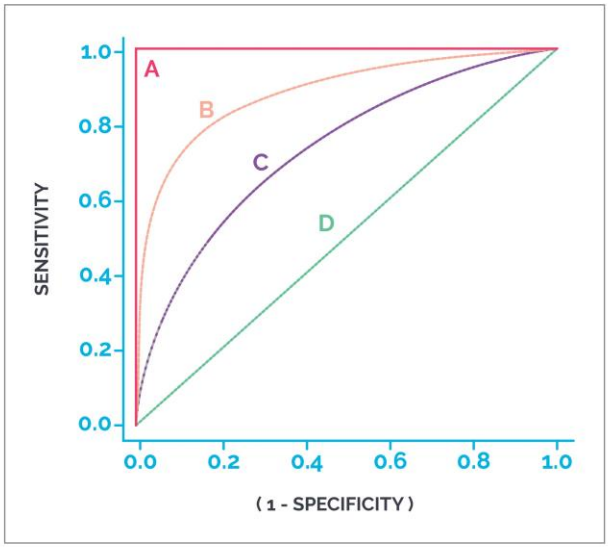
Specificity: The proportion of individuals without the disease who test negative. A high specificity indicates the test is good at ruling in the disease when positive.

Positive Predictive Value (PPV): The probability that a person with a positive test result actually has the disease. PPV is affected by disease prevalence, so a higher prevalence will result in a higher PPV

Negative Predictive Value (NPV): The probability that a person with a negative test result does not have the disease. NPV is also affected by disease prevalence,

Area Under the Curve (AUC): A measure of a test's overall discriminatory ability, AUC values range from 0 to 1, with higher values indicating better performance.





Setting the stage of ovarian cancer screening/early detection

CA125

- Mucin-type glycoprotein often used for ovarian lesions.
- Upper limited 35 U/ml in post menopausal women. Upper limit in premenopausal women can be 200
- Sensitivity of only 23-50% in stage I disease
- Can be elevated in other conditions

HE4

- Glycoprotein overexpressed in epithelial ovarian tumors Increases with age.
- Seems to have higher specificity than CA125 in premenopausal women

RMI: US findings, menopausal status, CA125

ROMA: Menopausal status, CA125 and HE4

ROCA: Algorithm analyzing multiple CA125 values over time in a predictive model.

Test (n)	Sensitivity (%)	Specificity (%)	AUC
CA125 (14)	73-91	53-92	0.78-0.93
HE4 (14)	65-83	78-98	0.82-0.96
CA125 +HE4(5)	89-97	55-81	0.89-0.96
RMI (3)	75-78	90-92	0.84- 0.88
ROMA (8)	74- 97	69-93	0.84- 0.97

Dochez, 2019

Ovarian Cancer Screening CA125 and TVUS

- In women with *BRCA* routine ovarian cancer screening with measurement of serum CA 125 level or TVUS generally is not recommended.
- TVUS or serum CA 125 level may be reasonable for short-term surveillance in women at high risk of ovarian cancer starting at age 30–35 years until the time they choose to pursue risk-reducing bilateral salpingo-oophorectomy
- **RRSO is the only proven intervention to reduce ovarian cancer-specific mortality.**
- Available screening procedures have not been proved to decrease the mortality rate or increase the survival rate associated with ovarian cancer in average or high-risk populations
- False-positive test results are a particular problem in diseases with low prevalence in the target population and in diseases for which further evaluation of an abnormal screen often includes an invasive surgical procedure.

ACOG Practice Bulletin #189

GENERAL OBSTETRICS AND GYNECOLOGY: GYNECOLOGY · Volume 193, Issue 5, P1630-1639, November 2005

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AJOG American Journal of Obstetrics & Gynecology

Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: Findings from the initial screen of a randomized trial

Saundra S. Buys, MD [a] · Edward Partridge, MD [b] · Mark H. Greene, MD [c] · ... · Christine C. Johnson, PhD [j] · John K. Gohagan, PhD [k] · for the PLCO Project Team ... Show more

Large randomized cancer screening trial for prostate, lung, and ovarian cancer with a goal of reduced mortality in healthy subjects age 55-74

Ovarian Cancer Screening Cohort

- Intervention arm was CA125 (cut off 35) annually for 6 years and TVUS for 4 years. Usual care group was not offered screening but receive usual medical care as indicated.
- Participants were followed for 13 yrs initially and extended to 19 years
- Compliance was around 80-85%

Conclusions of PLCO

Of 39,115 women randomized to receive screening, 28,816 received at least 1 test (74%)

Abnormal TVUS was found in 1338 (4.7%) and abnormal CA-125 in 402 (1.4%)

29 neoplasms were identified
9 were low malignant potential and 20 were invasive

The PPV for invasive cancer was 3.7% for an abnormal CA-125, 1.0% for an abnormal TVU, and 23.5% if both tests were abnormal.

A total of 187 (intervention) and 176 (usual care) deaths from ovarian cancer were observed RR of 1.06 (95% CI: 0.87-1.30)

The risk ratio for all-cause mortality was 1.01 (95% CI: 0.97-1.05)

Ovarian cancer specific survival was not significantly different across trial arms (p=0.16)

Table VI Participant-based diagnostic procedures following a positive screen

	No neoplasm		Neoplasms	
Diagnostic procedures	n	%	n	%
CA-125	377	22.5	12	41.4
Ultrasounds	721	43.0	12	41.4
Chest radiograph	68	4.1	7	24.1
Surgery*	541	32.3	29	100.0
CT scan/MRI	150	8.9	12	41.4
Needle aspiration, culdocentesis, or paracentesis	22	1.3	1	3.4
IVP	8	0.5	·	·
Barium enema	7	0.4	·	·
No diagnostic procedure recorded	260	15.5	·	·
Total number of participants	1677	100.0	29	100.0

* Two hundred ninety-eight of the surgeries of the participants without neoplasms were a laparotomy; 27 of the surgeries of the participants with neoplasms were a laparotomy.

ARTICLES · Volume 397, Issue 10290, P2182-2193, June 05, 2021 · Open Access Download Full Issue

THE LANCET

Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Prof Usha Menon, FRCOG [a] · Aleksandra Gentry-Maharaj, PhD [a] · Matthew Burnell, PhD [a] · Naveena Singh, FRCPath [d] · Andy Ryan, PhD [a] · Chloe Karpinskyj, MSc [a] · et al. Show more

Randomized trial of women 50-74 in Europe at average risk of ovarian cancer to Multimodal screening (MMS) with CA125 (ROCA), TVUS alone, or no screening

MMS group: used serum CA125 with risk of ovarian cancer calculation to identify significant rises in CA125. Based on that risk triaged to annual screening, intermediate every 3 month screening, and elevated risk got repeat CA125 and TVUS in 6 weeks.

TVUS group: Initial TVUS used to stratify screening frequency. normal (annual screening), unsatisfactory (repeat in 3 months), or abnormal (scan with a senior ultrasonographer within 6 weeks).

202, 562 patient enrolled in a 1:1:2

- 202 562 were included in the analysis:
- 50 625 (25·0%) in the MMS group
- 50 623 (25·0%) in the USS group
- 101 314 (50·0%) in the no screening group.

In both groups, women with persistent abnormalities referred for further investigation or surgery

Women were followed for 16 years

	Total	Screen positives	Cancers not detected by screening			
			Screen negatives ≤1 year from last test of screening episode	Screen negatives >1 year after last test of screening episode	Never attended screening	Diagnosed >1 year after end of screening*
Multimodal screening (50 625 women, 789 129 women-years)						
Ovarian and tubal cancer	522 (100%)	212 (41%)	41 (8%)	41 (8%)	3 (1%)	225 (43%)
Non-epithelial ovarian cancer	16 (100%)	7 (44%)	2 (13%)	2 (13%)	0	5 (31%)
Borderline epithelial ovarian cancer	54 (100%)	24 (44%)	10 (19%)	5 (9%)	0	15 (28%)
Invasive epithelial ovarian and tubal cancer	452 (100%)	181 (40%)	29 (6%)	34 (8%)	3 (1%)	205 (45%)
Ultrasound screening (50 623 women, 790 231 women-years)						
Ovarian and tubal cancer	517 (100%)	164 (32%)	63 (12%)	50 (10%)	19 (4%)	221 (43%)
Non-epithelial ovarian cancer	13 (100%)	11 (85%)	0	1 (8%)	0	1 (8%)
Borderline epithelial ovarian cancer	59 (100%)	48 (81%)	2 (3%)	1 (2%)	3 (5%)	5 (8%)
Invasive epithelial ovarian and tubal cancer	445 (100%)	105 (24%)	61 (14%)	48 (11%)	16 (4%)	215 (48%)
No screening (101 314 women, 1 577 517 women-years)						
Ovarian and tubal cancer	1016† (100%)	..	..	514 (51%)	..	499 (49%)
Non-epithelial ovarian cancer	17 (100%)	..	..	7 (41%)	..	10 (59%)
Borderline epithelial ovarian cancer	91 (100%)	..	..	50 (55%)	..	41 (45%)
Invasive epithelial ovarian and tubal cancer	905 (100%)	..	..	457 (50%)	..	448 (50%)

Data are n (%). *Screening end Dec 31, 2011. †Includes one case in which histology was not available and two cases of neoplasm of uncertain or unknown behaviour.

Table 1: Ovarian and tubal cancers grouped by primary site and screening status

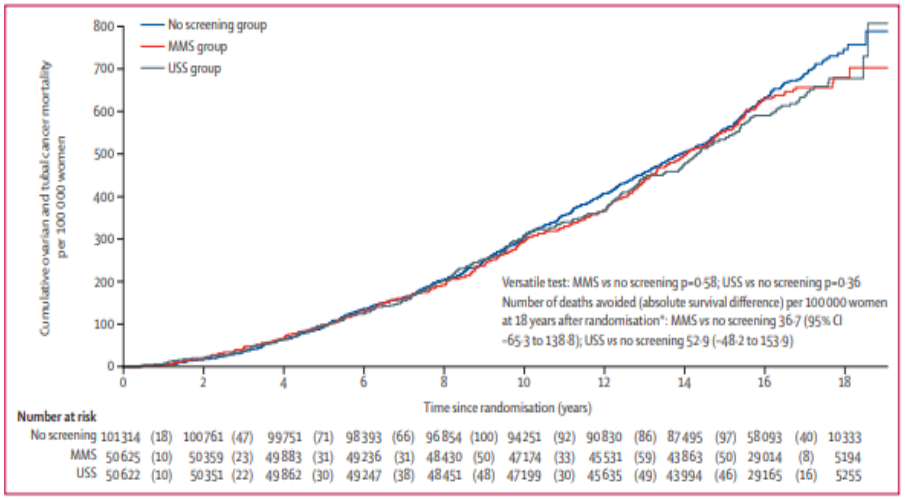


Figure 3: Kaplan-Meier cumulative mortality for ovarian and tubal cancer per 100 000 women

MMS=multimodal screening. USS=ultrasound screening. *Royston-Parmar model based estimates of the effect of screening (appendix p 10).

Results

2055 women were diagnosed ovarian cancer

522 (1·0%) of 50 625 in the MMS
517 (1·0%) of 50 623 in the USS
1016 (1·0%) of 101 314 in the NS

There was a 47·2% increase in stage I and 24·5% decrease in stage IV disease incidence in the MMS group compared to no screening

1206 women died of the disease

296 (0·6%) of 50 625 in the MMS
291 (0·6%) of 50 623 in the USS
619 (0·6%) of 101 314 in the NS

Conclusion: No significant reduction in ovarian and tubal cancer deaths was observed in the MMS (p=0·58) or USS (p=0·36) groups compared with the no screening group.

Evidence of Stage Shift in Women Diagnosed With Ovarian Cancer During Phase II of the United Kingdom Familial Ovarian Cancer Screening Study

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Authors: Adam N. Rosenthal, Lindsay S.M. Fraser, Susan Philpott, Ranjit Manchanda, Matthew Burnell, Philip Badman, Richard Hadwin, ... SHOW ALL ... on behalf of the United Kingdom Familial Ovarian Cancer Screening Study collaborators | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 35, Number 13 • https://doi.org/10.1200/JCO.2016.69.9330

To establish the performance of screening with serum CA125 (ROCA) and transvaginal sonography for women at high risk of ovarian cancer

Women whose estimated lifetime risk of OC/FTC was ≥ 10% were recruited at 42 centers in the United Kingdom and underwent ROCA screening every 4 months.

TVS occurred annually if ROCA results were normal or within 2 months of an abnormal ROCA result.

Risk-reducing salpingo-oophorectomy (RRSO) was encouraged throughout the study.

Performance was calculated after censoring 365 days after prior screen, with modeling of occult cancers detected at RRSO.

UK-FOCSS Trial Results

4,348 women underwent screening

Median follow-up time was 4.8 years

19 invasive OC diagnosed within 1 year of prior screening

13 diagnoses were screen-detected

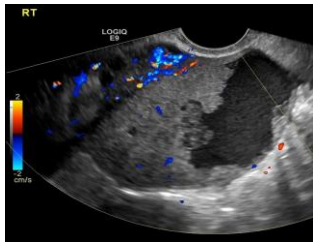
- 5 (38.5%) Stage I-II

6 were occult at RRSO

- 5 (83.8%) Stage I-II

Modeled sensitivity, PPV, and NPV at 1 year

- Sensitivity: 94.7%
- PPV: 10.8%
- NPV: 100 %



7 (36.8%) of the 19 cancers diagnosed < 1 year after prior screen were stage IIIb to IV compared with 17 (94.4%) of 18 cancers diagnosed > 1 year after screening ended

18 (94.8%) of 19 cancers diagnosed < 1 year after prior screen had zero residual disease at surgery compared with 13 (72.2%) of 18 cancers subsequently diagnosed

162 (3.7%) underwent screen positive surgery with 149 underwent false positive surgery (3.4%)

- 30% abnormal ROC alone
- 41% had abnormal scan alone
- 27% had both abnormal

Majority had benign ovarian path, 1.3% had a borderline tumor, and 35% had no pathology identified

Conclusion

ROCA-based screening is an option for women at high risk of OC who defer or decline RRSO, given its high sensitivity and significant stage shift.

However, it remains unknown whether this strategy would improve survival in screened high-risk women

Primary Prevention

ATM Mutation Recommendations Lower Risk

Beginning Age	Recommendation	Additional Information
No set age	Become aware of ovarian and primary peritoneal cancer symptoms. Report to any symptoms that persist for several weeks and are a change from normal to your doctor. Routine ovarian cancer screening using transvaginal ultrasound and a CA-125 blood test has not shown benefit and is not recommended.	Symptoms of ovarian cancer include: • pelvic or abdominal pain • bloating or distended belly • difficulty eating • feeling full sooner than normal • increased urination or pressure to urinate
No set age	More research is needed to show whether people with inherited ATM mutations benefit from risk-reducing surgery to remove their ovaries and fallopian tubes. Currently, experts recommend that you have a discussion with your doctor about the option of risk-reducing surgery based on your family history of cancer.	
Before age 50	Researchers are studying whether the removal of the fallopian tubes only (salpingectomy), while delaying oophorectomy until closer to the age of natural menopause is a safe option for lowering risk in people who are not ready to remove their ovaries. If you are interested in this approach, talk with your doctor about the benefits and risks, and consider enrolling in a research study.	• At this time, it is not known if salpingectomy lowers the risk for ovarian cancer in high-risk people. • Salpingectomy, followed by delayed oophorectomy requires two separate surgeries.
No set age	Oral contraceptives (birth control pills) have been shown to lower the risk for ovarian cancer in people with BRCA1 mutations. Have a discussion with your doctor about the benefits and risks of oral contraceptives for lowering ovarian cancer risk.	Research on the affect of oral contraceptives on breast cancer risk has been mixed.

Source: NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, Prostate, vs. 3 2025.

Moderate Risk

Gynecologic cancer risk management

Beginning Age	Recommendation	Additional Information
45 - 50	Risk-reducing removal of ovaries and fallopian tubes (RRSO). Timing of surgery should take into account plans to have children.	The surgery should be done at a facility that has expertise and follows special precautions for people with inherited mutations. This includes a procedure known as an abdominal wash at the time of surgery. The pathologist should do an extensive exam of the fallopian tubes using a procedure called SEE-FIM to look for any abnormal changes in the tissue. If an abnormality known as a "serous tubal intraepithelial carcinoma" or STIC lesion is noted in your pathology report, you should be referred to a gynecologic oncologist for follow up care. Discuss options for managing the effects of early menopause with your doctor. After RRSO, a very small risk remains for a related cancer known as primary peritoneal cancer (PPC). There is no effective screening for PPC after RRSO. In people with BRCA mutations, risk-reducing surgery has been linked to longer survival compared to people who have not had surgery. Similar research has not been done in people with RAD51C mutations.
45 - 50	Have a discussion with your doctor about the risks, benefits and costs of removing your uterus (hysterectomy) at the time of RRSO.	The following factors may affect your decision about hysterectomy at the time of RRSO: If you have a medical history of fibroids or other issues involving the uterus or cervix you might consider a hysterectomy. If you are considering hormone replacement, the type of hormone recommended depends on whether or not you have your uterus. Estrogen alone increases the risk for uterine cancer. Estrogen combined with progesterone protects against uterine cancer, but is linked to a higher risk for breast cancer than estrogen alone.
Before age 50	Experts believe that most ovarian cancers begin in the fallopian tubes. Researchers are studying whether the removal of the fallopian tubes only (salpingectomy), while delaying oophorectomy until closer to the age of natural menopause is a safe option for lowering risk in people who are not ready to remove their ovaries. Guidelines recommend that people interested in this approach speak with their doctor about the benefits and risks, and consider enrolling in a research study.	At this time, it is not known if salpingectomy is effective for lowering the ovarian cancer risk in high-risk people. For this reason, experts recommend that people who choose salpingectomy have a completion oophorectomy to lower their remaining risk for ovarian cancer when they are ready. Salpingectomy, followed by delayed oophorectomy requires two separate surgeries.

High Risk- BRCA1

Beginning Age	Recommendation	Additional Information
35-40	Risk-reducing removal of ovaries and fallopian tubes (RRSO). Timing of surgery should take into account plans to have children.	• Salpingo-oophorectomy in people with BRCA1 mutations has been linked to longer survival compared to people who have not had surgery. • The surgery should be done at a facility that has expertise and follows special precautions for people with inherited mutations. This includes a procedure known as an abdominal wash at the time of surgery. The pathologist should do an extensive exam of the fallopian tubes using a procedure called SEE-FIM to look for any abnormal changes in the tissue. • If an abnormality known as a "serous tubal intraepithelial carcinoma" or STIC lesion is noted in your pathology report, you should be referred to a gynecologic oncologist for follow up care. • Discuss options for managing the effects of early menopause with your doctor. Research suggests that hormone replacement therapy is safe after oophorectomy in people who are still premenopausal at the time of surgery and have never been diagnosed with breast cancer. • After RRSO, a very small risk remains for a related cancer known as primary peritoneal cancer (PPC). There is no effective screening for PPC after RRSO.

35-40	Have a discussion with your doctor about the risks, benefits and costs of removing your uterus (hysterectomy) at the time of RRSO.	The following factors may affect your decision about hysterectomy at the time of RRSO:
		• BRCA1 mutations slightly increase the risk for a rare but aggressive type of uterine cancer.
		• If you have a medical history of fibroids or other issues involving the uterus or cervix you might consider a hysterectomy.
		• If you are considering hormone replacement, the type of hormone recommended depends on whether or not you have your uterus.
		  ▪ Estrogen alone increases the risk for uterine cancer.
		  ▪ Estrogen combined with progesterone protects against uterine cancer, but is linked to a higher risk for breast cancer than estrogen alone.

Summary

- TVUS and serum CA-125 testing to screen for ovarian cancer has not been shown to be sufficiently sensitive or specific to warrant a routine recommendation.
- Individuals should be educated on the symptoms associated with ovarian cancer
- The decision and timing of BSO as an option should be individualized based on whether childbearing is complete, menopausal status, comorbidities, family history, patient preference, genetic mutation
- Estrogen replacement after premenopausal oophorectomy may be considered
- Considerations for hysterectomy at time of BSO or in a staged procedure can and should be discussed depending on genetic mutation, other medical conditions, and need for HRT/Hormone suppression
- Salpingectomy has been shown to decreased ovarian cancer in general population. SOROC trial is evaluating salpingectomy prior to RRBSO in BRCA1 patients
- Consideration of OCP/IUD to suppress risk of ovarian/uterine cancers
- Early referral to REI/Fertility

Current State of Research

NIH National Institutes of Health
Turning Discovery Into Health

Current State of Research

Protein Biomarkers

- CA125 remains the most sensitive and specific protein biomarker
- Other combinations have been tested such as HE4, transthyretin, CA15.3, CA72.
- No combination as proved to be a better strategy particularly in early stage disease.

Autoantibodies

- TP53 is a common genetic mutation in high grade ovarian cancer
- Using serum samples from UKCTOCS.
    - 20% had elevated TP53 autoantibodies and in the 34 ovarian cancer cases detected with ROCA the titers were elevated 8 months prior to the CA125 and in 9 cases missed by ROCA antibodies were elevated 23m prior to cancer diagnosis
- 6 individual autoantibodies against EPCAM, IL-8, PLAT, MDM2, c-Myc and HOXA7 provide 39–67% sensitivity at 98–100% specificity for detecting ovarian cancer at all stages

Current state of research

Circulating Tumor DNA (ctDNA)

- ctDNA is released from tumor cells
- In a multi-cancer combined ctDNA and protein biomarker panel called CancerSEEK, 46/54 (85%) of the ovarian cancers were identified largely by *TP53* mutations and CA125
- While the overall panel had 98% reported sensitivity for ovarian cancer most were advanced stage high grade serous tumor with only 9 cases of Stage I disease

Circulating miRNA

- miRNAs are short (18–24 nucleotide) non-coding RNAs that regulate gene expression
- Using 8 miRNAs, Yokoi *et al* were able to distinguish early stage ovarian cancers from benign tumors with 86% sensitivity and 83% specificity
- Serum miRNA-seq from 98 incident cases of invasive ovarian cancer, including 53 cases of Stage I or II disease
- Applied to an independent 454-patient sample set with a disease prevalence of 3.3%. At a sensitivity of 75% and specificity of 100%, the model had an AUC of 0.92

Current state of research

Proximate Tumor Fluids

- Use of body fluids near the fallopian tube
- Identification of TP53 mutations in tampons or uterine lavage
- PapSEEK, had 33% sensitivity at 99% specificity for ovarian cancer.
    - This improved to 45% sensitivity and 100% specificity in a smaller cohort of 299 women assessed with an intrauterine brushing

Novel Imaging Techniques

- TVUS is preferred modality for imaging the adnexa.
- Failure to image fallopian tubes is a particular limitation
- MRI is being used in prostate cancer and may have a correlation to ovarian cancer
- Superconducting Quantum Interference Detection (SQUID) can measure delays in magnetic relaxation of antibody-coated iron oxide nanoparticles.
    - Such delays are observed when nanoparticles bind to cancer cells, but not when they are free in the blood or peritoneal cavity.
    - This modality has been applied to detecting breast cancer cells in murine xenografts, minimal residual disease in leukemic bone marrow biopsies, and measuring nanoparticle accumulation in biological samples

Take Homes

True screening with out ability to test prior to cancer forming or catching its STIC form has not be found for ovarian cancer

CA125 particularly done over time via ROCA model with TVUS has some promise in stage shifting & decreasing surgical morbidity

Earlier detection has not been proven to improve overall survival/mortality from ovarian cancer

Prevention of ovarian cancer with surgical removal of ovaries/fallopian tubes is the gold standard but is a very individualize decision

Novel strategies are under development, but we will need continued research support to push the needle forward.

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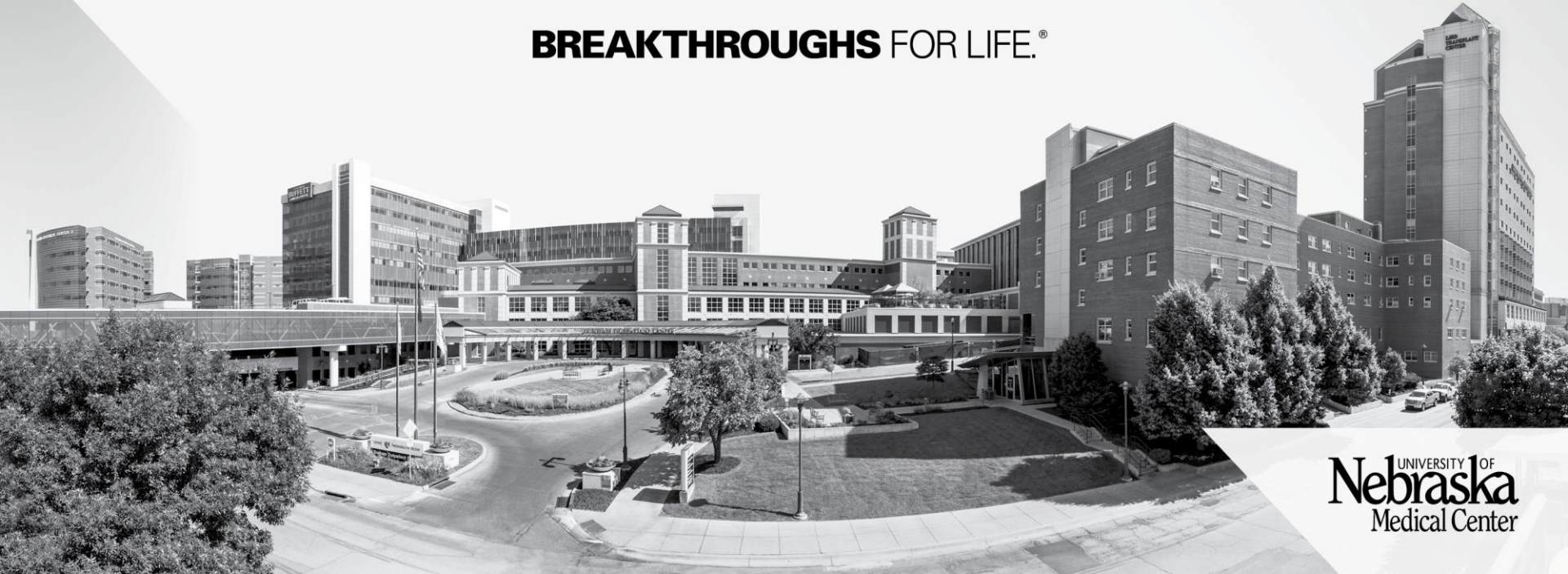

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