UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

UNC CANCER CARE

Obesity-driven Endometrial Cancer: Gaps and Barriers to Improving Outcomes

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CAROLINA ENDOMETRIAL CANCER STUDY

UNC TREND
PROGRAM ON TRANSLATIONAL RESEARCH IN ENDOMETRIAL CANCER DISPARITIES

Endometrial Cancer (EC) and Obesity

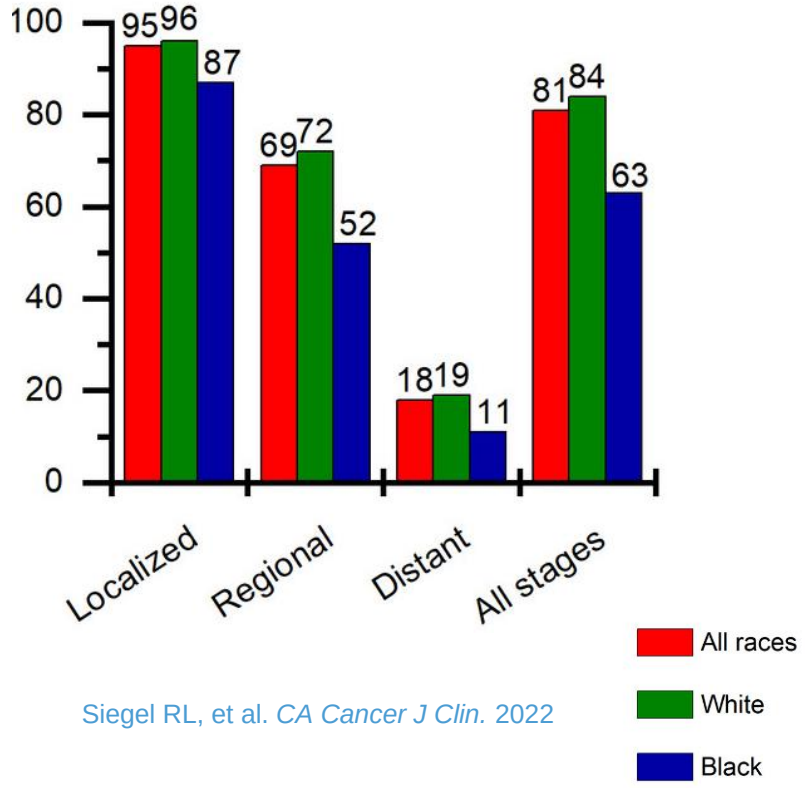
- 4th most common cancer among women in the U.S.[1]
- **Increasing in frequency and mortality** due to the obesity epidemic, rise in more aggressive EC subtypes.[2]
- In 2024, 67,880 new cases of endometrial cancer will be diagnosed in the US. [1]
- **Obesity, diabetes and insulin resistance** are well-known risk factors associated with a higher risk of developing and dying from endometrial cancer.[3]

[1] Seigel et al. Cancer Statistics. 2024
[2] Annual Report to the Nation on the Status of Cancer, 2019
[3] Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. Int J Gynecol Cancer. 2007;17(2):441-6.

Endometrial Cancer and Racial Disparities

- Incidence rates are **increasing 3-fold** for Black compared to White and mortality rates are **twice as high** for Black Women.[4]
- The overall 5-year survival is 81%; yet 5-year survival among Black women is **62%** vs. **83%** for White women.
- Black women have **the lowest survival rates**, regardless of stage or histologic subtype, and mortality rates are increasing disproportionately by race.

5-Year Relative Survival by Race and Stage at Diagnosis



Siegel RL, et al. *CA Cancer J Clin.* 2022

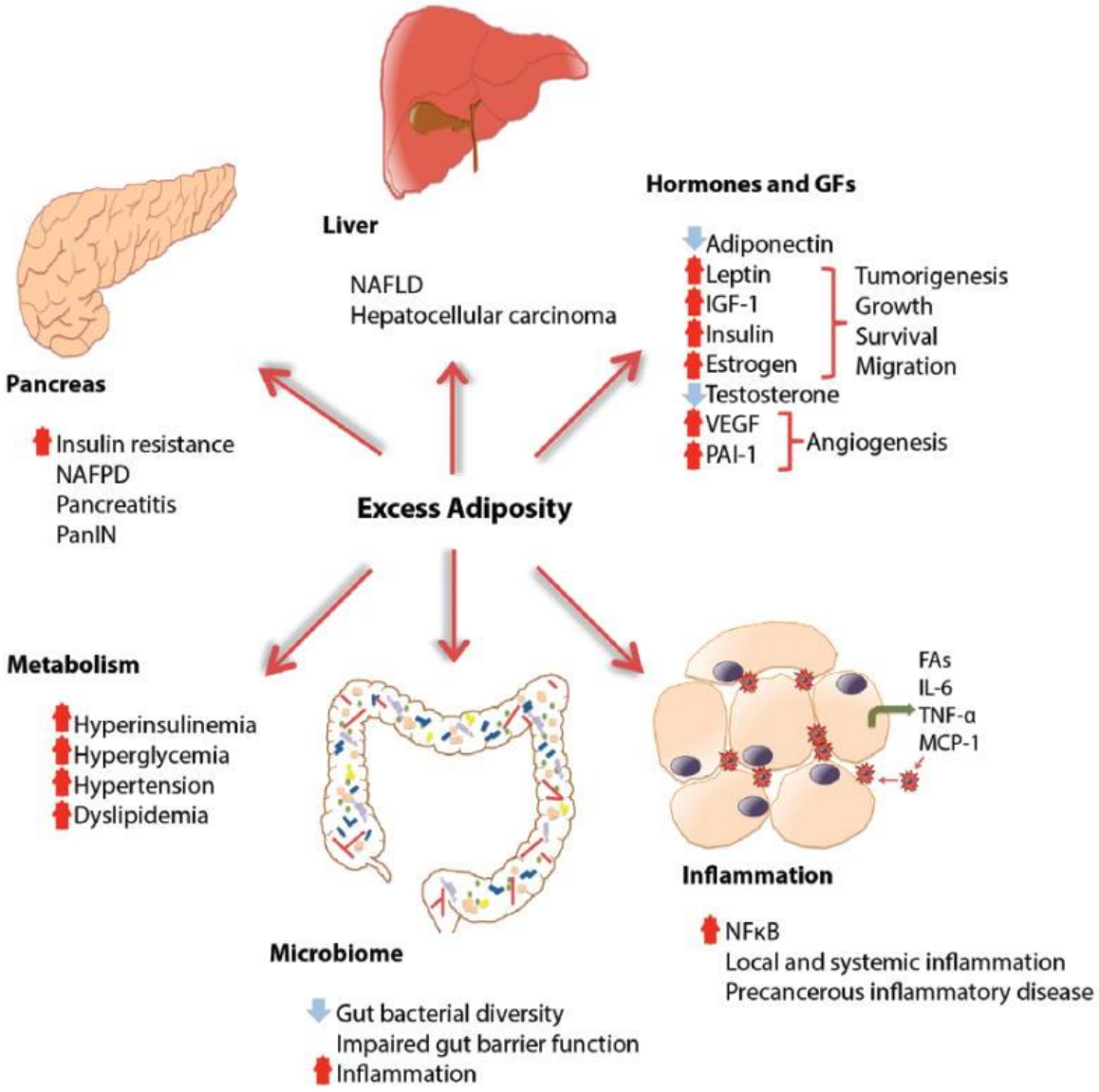
[4]Cote ML, Ruterbusch JJ, Olson SH, Lu K, Ali-Fehmi R. The Growing Burden of Endometrial Cancer: A Major Racial Disparity Affecting Black Women. *Cancer Epidemiol Biomarkers Prev*. 2015;24(9):1407-1415


Wall Street Journal
February 2024
Uterine Cancer Was Easy to Treat. Now It's Killing More Women Than Ever.
Case rates are increasing, especially for Black and Hispanic women

Why are outcomes worsening for endometrial cancer?

- Limited public awareness
- Obesity epidemic
- Rise in more aggressive subtypes of endometrial cancer
- Worsening disparities for Black women
- Lack of funding for endometrial cancer
- Lack of new FDA approved drugs in endometrial cancer treatment
  - Progestin approved in 1971
  - Lenvatinib + pembrolizumab in 2019
  - Carboplatin + paclitaxel + pembrolizumab/dostarlumab moves to front line treatment in 2023
  - **48 year dry spell!**

Underlying mechanisms of the obesity-cancer link



- **Hyperglycemia and hyperinsulinemia resulting from overnutrition**
- **Chronic inflammation**
- **Immunosuppression**
- **Increased cytokine production**
- **Elevated endogenous hormone concentrations (i.e. estrogen)**
- **Microbiome changes in the gut/uterus**

How can we break the obesity-endometrial cancer link?

Diet
Exercise
Drugs
Bariatric Surgery

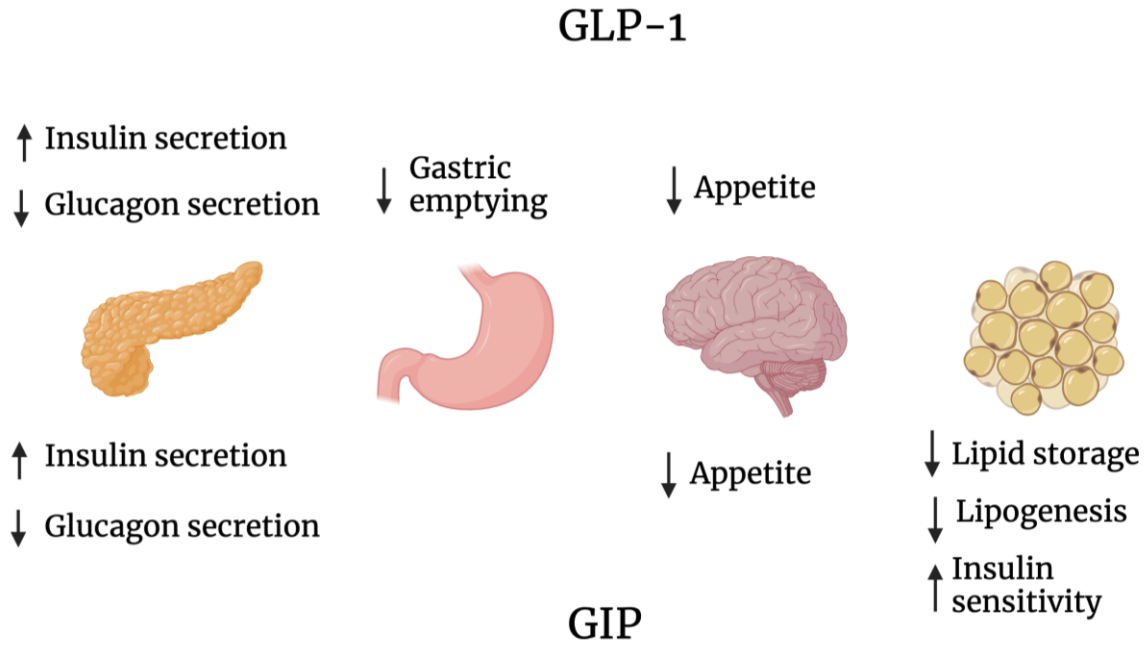
Metabolism
Inflammation
Immune Cells
Microbiome

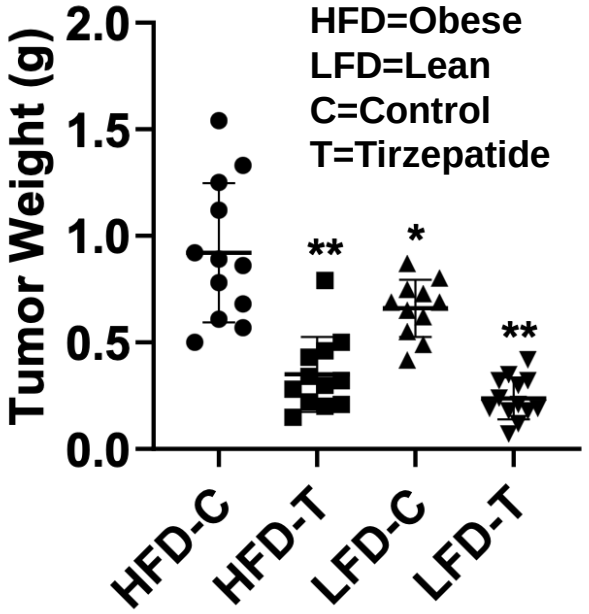
- **Created mouse models of obesity-driven endometrial cancer.**
  - **Genetically engineered mouse models**
  - **Paucity of endometrial cancer mouse models derived from the tumors of Black women**
  - **Mouse models created from the tumors of Black and White women**
- **Study interventions to break the obesity-endometrial cancer link.**
- **Mouse models (bench) → Clinical Trials (bedside)**

Interventions to break the obesity-cancer link….

Lauren Bates-Fraser, MA
Exercise & Sports Med

- **Diet changes** – intermittent fasting
- **Exercise** – high intensity interval training (HIIT), decrease sedentary behavior
- **Bariatric Surgery** – sleeve gastrectomy
- **Weight Loss Drugs** – tirzepatide, retatrutide





Stephen Hursting, PhD
Nutrition

Abbie Smith-Ryan, PhD
Exercise & Sports Med

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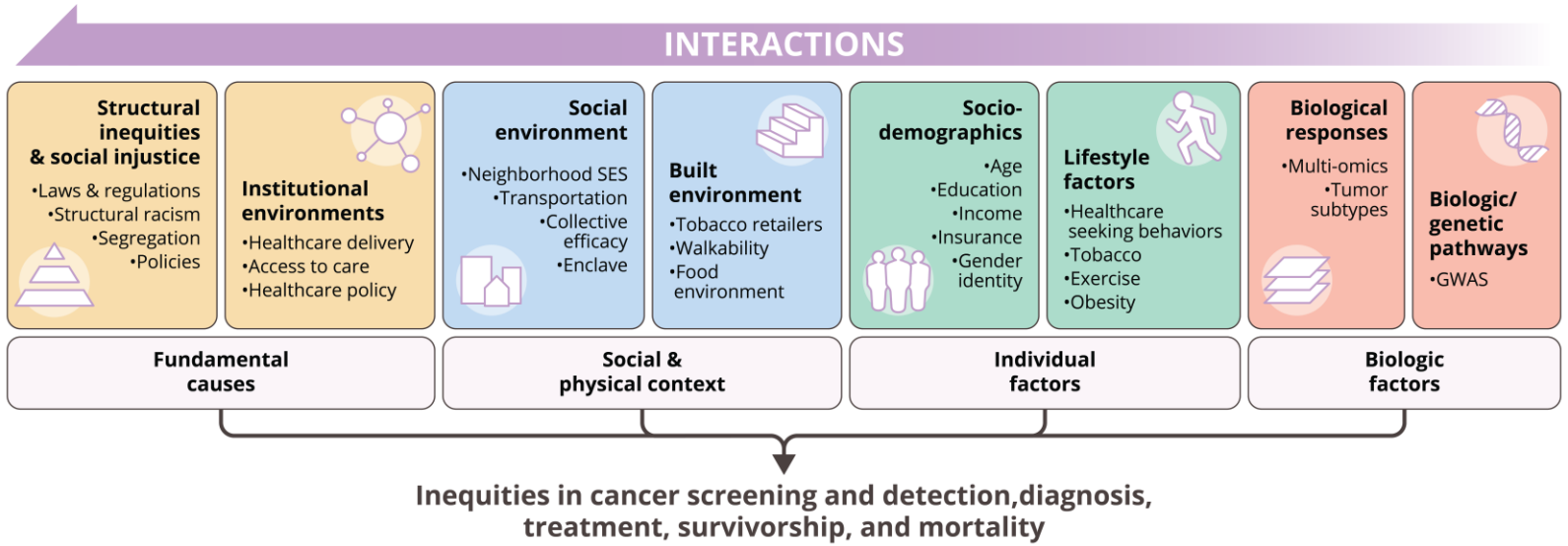
Why are there racial disparities for endometrial cancer?



The “Cell to Society” model created by the UNC Lineberger Cancer Center, adapted from Warnecke *et al. Am J Public Health* 2008

- Access to equitable care
- Social determinants of health
- Host environment and response to treatment
- Higher risk of more lethal histologic and molecular subtypes
- Higher rates of obesity and/or diabetes
- Other unknown social and biological factors?

Endometrial Cancer –Type 1 and 2

- **Type I (80%)**
  - Endometrioid histology
  - Most diagnosed Stage I
  - High 5-year survival
  - Unopposed estrogen stimulation
  - Associated with obesity, diabetes and hypertension
- **Type II (20%)**
  - Non-Endometrioid – serous, clear cell, carcinosarcomas
  - Aggressive
  - Often present in advanced stage
  - Poorer 5-year survival
  - **More common in Black patients**

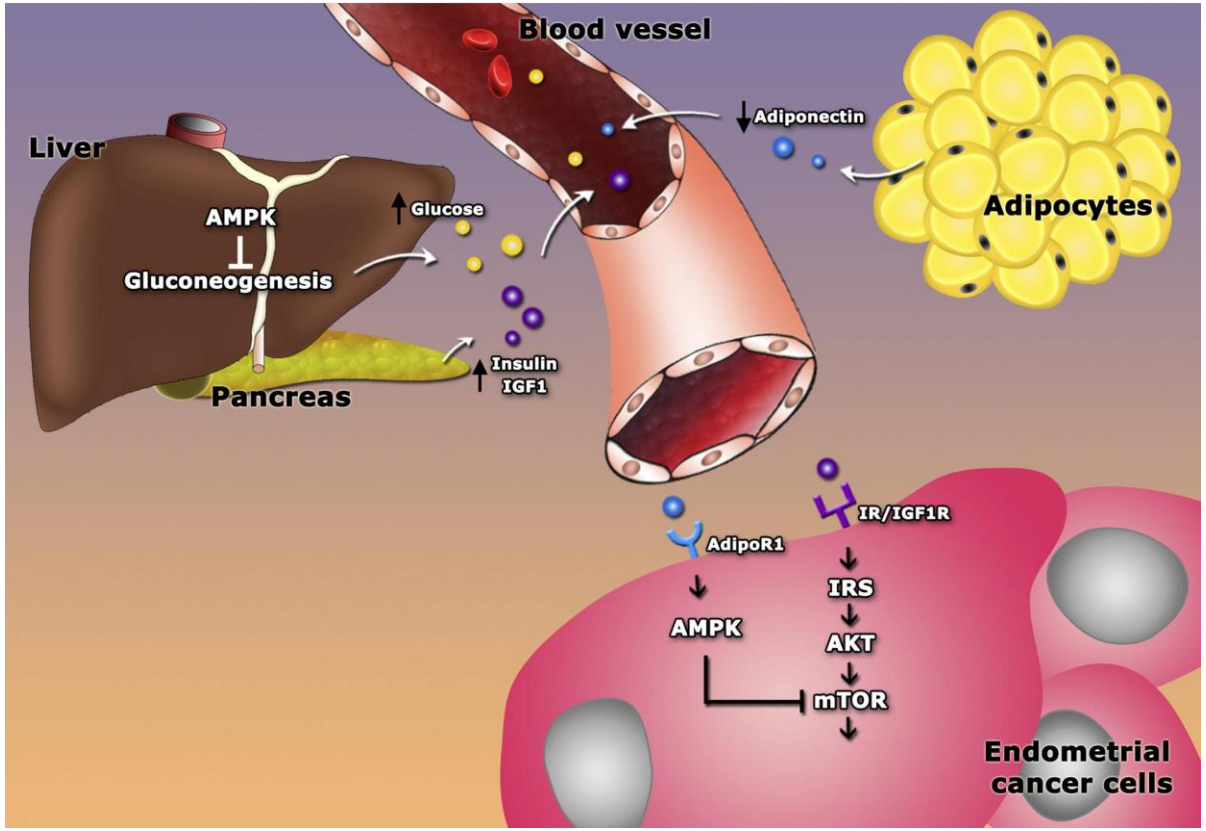
- **Obesity and diabetes are associated with both endometrioid and non-endometroid endometrial cancers.**

Mutch, GOG Symposium, 2007

Genetic Alterations by Subtype

- **Type 1 - Endometriod**
  - Microsatellite instability
  - PTEN deletions/mutations
  - PIK3CA mutations/amplification
  - PIK3R1/PI3KR2 mutations
  - Activation of K-ras
  - ARID1A mutations
  - β-catenin mutations
- **Type II - Non-Endometrioid**
  - p53 mutations
  - Overexpression of HER-2/neu
  - p16 inactivation
  - PIK3CA mutations/amplification
  - E-cadherin alterations

Obesity and Endometrial Cancer



J Clin Oncol 34:4225-4230. © 2016 by American Society of Clinical Oncology

- Increased signaling via the insulin/IGF-1 pathway culminates in activation of the mTOR pathway.
- Alterations in the mTOR pathway is common in endometrial cancer.
  - PTEN mutations
  - PI3KCA/PI3KR1/R2 mutations and amplification

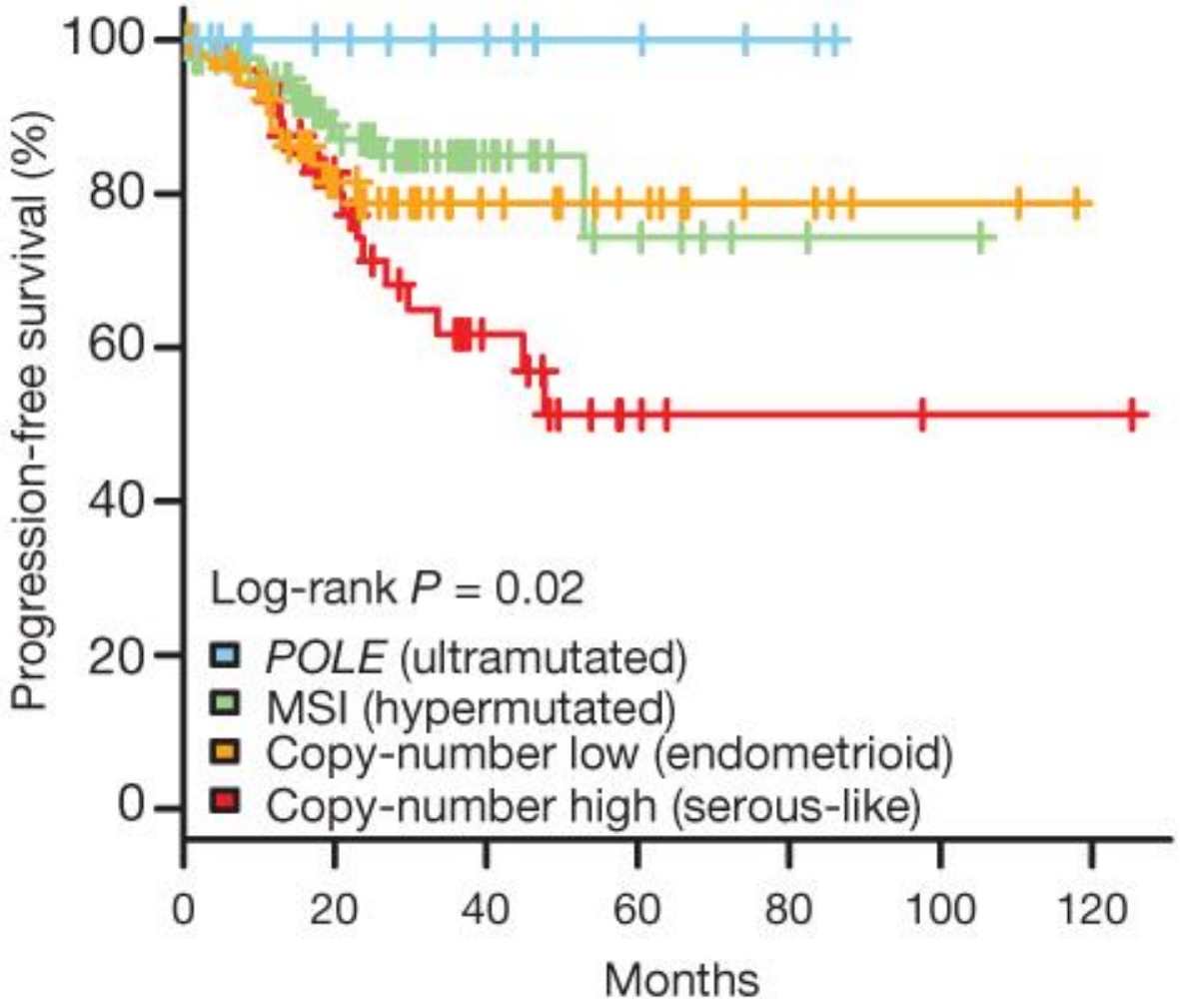
The Cancer Genome Atlas (TCGA) Project

	POLE (Ultramutated)	MSI (Hypermutated)	COPY-NUMBER LOW	COPY-NUMBER HIGH (Serous-like)
Copy Number Alterations	Low	Low	Low	High
MSI/MLH 1 Methylation	Mixed MSI high, low, stable	MSI High	MSI stable	MSI stable
Mutation Rate	Very High (232 x 104 Mutations/Mb)	High (18 x 104 Mutations/Mb)	Low (2.09 x 104 Mutations/Mb)	Low (2.3 x 104 Mutations/Mb)
Genomic Profile	POLE (100%) PTEN (94%) P1K3CA (71%) P1K3R1 (65%) FBXW7 (82%) AR1D1A (76%) KRAS (53%) AR1D5b (47%) PD1/PD-L1 Overexpression	PTEN (88%) RPL22 (32%) KRAS (35%) P1K3CA (54%) P1K3R1 (40%) AR1D1A (37%) PD1/PD-L1 Overexpression	PTEN (77%) CTNNB1 (52%) P1K3CA (53%) P1K3R1 (33%) AR1D1A (42%) FGFR2 (10.9%)	TP53 (92%) PPP2R1A (22%) FBXW7 (22%) P1K3CA (47%) PTEN (11%) FGFR Amplifications & mutations (7%) HER2 amplified 25%
Histology	Endometrioid	Endometrioid	Endometrioid	Serous, Endometrioid, and Mixed
Grade	Grades 1-3	Grades 1-3	Grades 1-2	Grade 3

- Classification into Type 1 and 2 was too simplistic.
- The POLE, MSI and CNL clusters were composed mostly of endometrioid ECs.
- Serous and 25% of endometrioid ECs were found in the CNH.
- **Clinically actionable targets for treatment differ by subtype.**

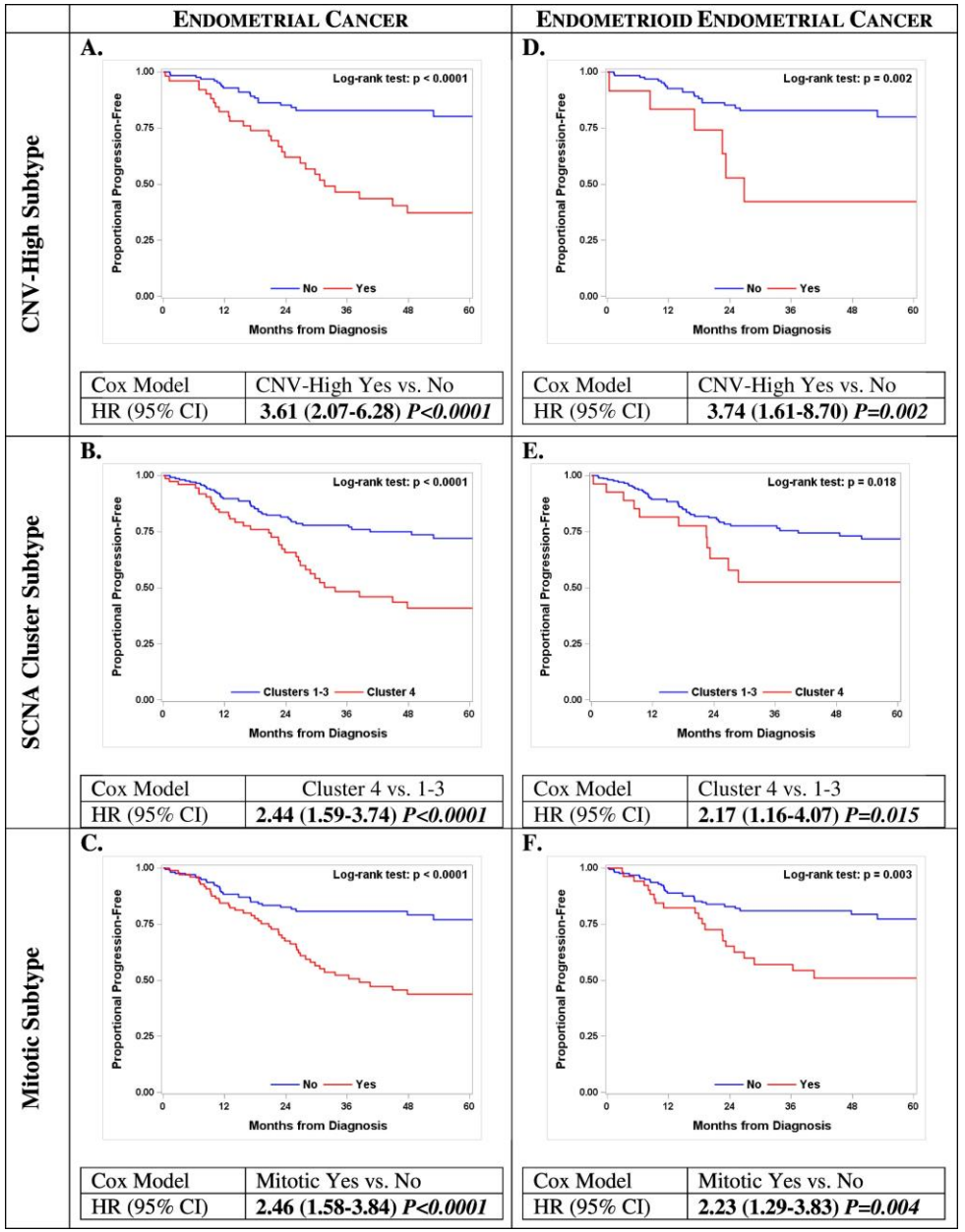
Kandoth et. al. Nature. 2013;497(7447):67-73.

The Cancer Genome Atlas (TCGA) Project



- POLE had the best PFS.
- CNH had the worst PFS than other subtype.

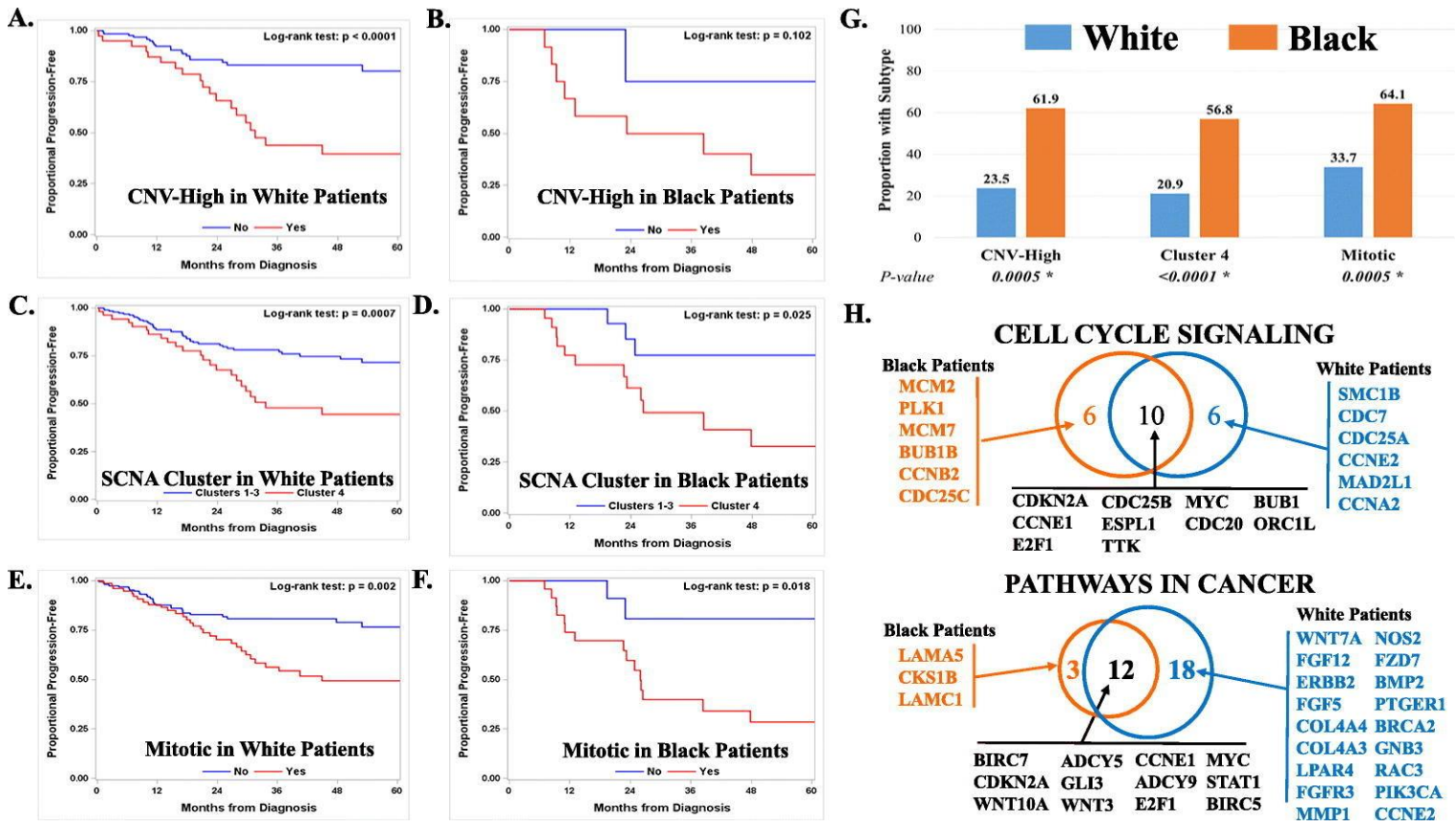
Kandoth et. al. Nature. 2013;497(7447):67-73.



- TCGA identified several aggressive molecular subtypes in EC
- CNH vs POLE, MSI, CNL
- Somatic copy number alteration (SCNA) clusters - Subtype 4 vs 1, 2 and 3
- RNAseq - Mitotic Subtype vs Immunoreactive, Hormonal
- 14% Black (46 cases)

Kandoth et. al. Nature. 2013;497(7447):67-73.
Dubil et. al., Gynecol Oncol. 2018;149(1):106-16.

Racial Disparities in Molecular Subtypes of EC – TCGA



- CNH, SCNA cluster subtype 4 and mitotic subtype all more common in Black vs White women.
- CNH subtype – 62% of Blacks versus 24% of Whites.
- Worse PFS for Black vs White women for each of these subtypes.
- Race associated enrichment in cell signaling pathways (PLK1,BIRC7).

Kandoth et. al. Nature. 2013;497(7447):67-73.
Dubil et. al., Gynecol Oncol. 2018;149(1):106-16.

UNCseq – Endometrial Cancer Cohort

- Black vs White patients had a higher BMI (41 vs 34), more grade 3 (52% vs 36%) and non-endometrioid (48% vs 22%) ECs, more often presented at an advanced stage (33% vs 25%) and had a greater risk of recurrence (30% vs 18%).
- *TP53* mutations as a surrogate for CNH; CNL defined as MSI stable, POLE wildtype and *TP53* wildtype, or more simply *TP53* wildtype.
- Higher mutation rate of PIK3CA in serous ECs of White versus Black women.

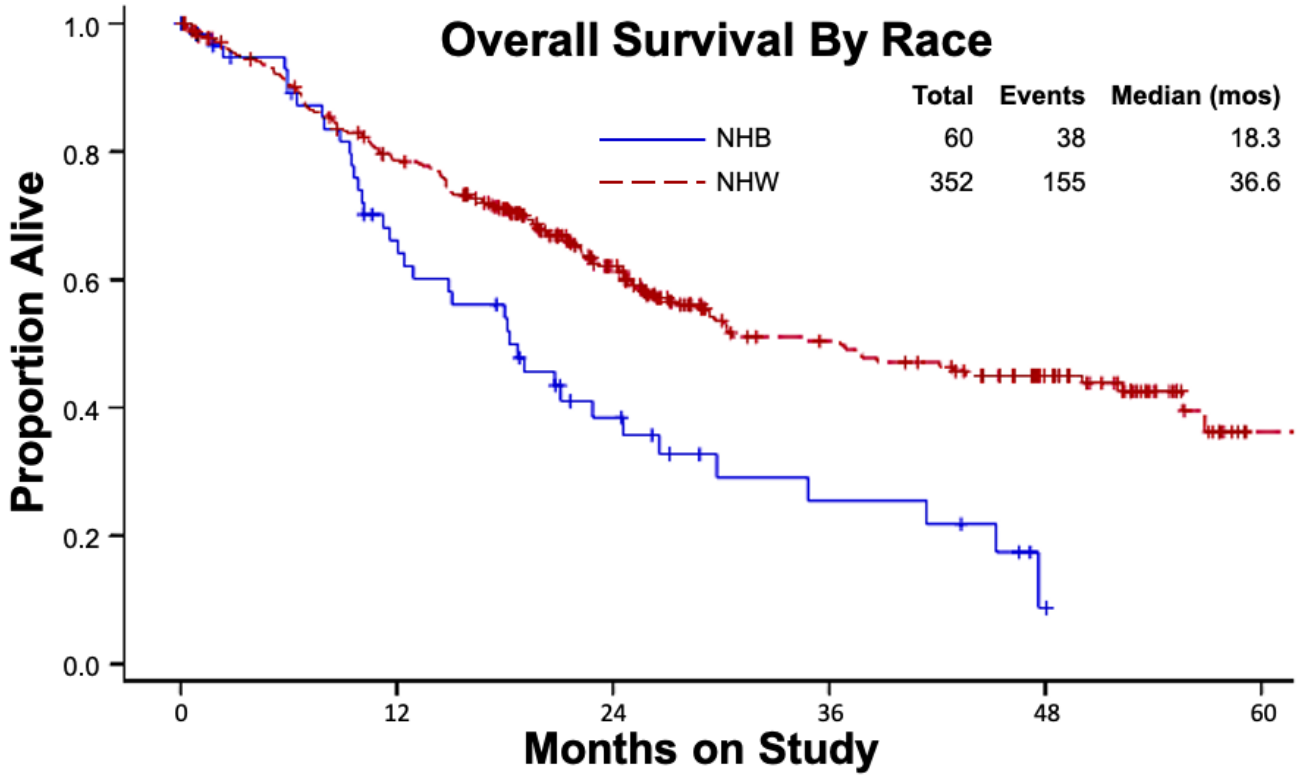
Jason Merker, MD, PhD
Pathology

David Corcoran, PhD
Genetics

Modified TCGA classification	Black % (# of cases)	White % (# of cases)
POLE (ultramutated)	5.9% (3)	6.9% (19)
MSI (hypermutated)	21.6% (11)	25.5% (70)
TP53 mutated (CNH)	47.1% (24)	19.3% (53)
TP53 wildtype (CNL)	25.5% (13)	48.2% (132)
Total cases	51	274

Meredith Newton, MD
Gyn Onc

GOG286B: Randomized Phase 2/3 Trial of Metformin vs Placebo + Paclitaxel/Carboplatin in Advanced and Recurrent EC



- Black race was associated with worse PFS than White race (HR = 1.5 95%; CI 1.098– 2.024) and worse OS than White race (HR = 2.03 95%; CI 1.429 – 2.890).
- Response rate also differed – 64% overall for White women, 43% for Black women.
- Obesity rates differed – 64% of Black women were obese vs 48% of White women.

Annual Meeting of the Society of Gynecologic Oncology, April 2020

GOG286B: Randomized Phase 2/3 Trial of Metformin vs Placebo + Paclitaxel/Carboplatin in Advanced and Recurrent EC

- Differences were noted in the **distribution of TCGA subtypes** between Black and White women.
- Black vs White women had **worse survival** for the MSI, *TP53* wildtype and *TP53* mutant TCGA subtypes.

Jason Merker, MD, PhD
Pathology

Molecular Subtype	Black	White
MSI	12% (OS 36 months)	22% (OS 39 months)
TP53 Wildtype (CNL)	24% (OS 29 months)	42% (OS 56 months)
TP53 Mutant (CNH)	61% (OS 18 months)	35% (OS 25 months)

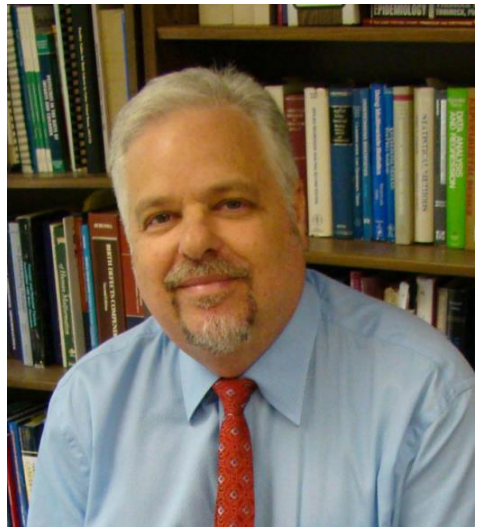
David Corcoran, PhD
Genetics

Challenges in Cancer Disparities Research in Endometrial Cancer

- Lack of prospective population-based epidemiologic studies detailing histologic and molecular subtype with race, obesity and related co-morbidities, social determinants of health, access and receipt of NCCN recommended treatment and follow-up care.
- Small representative numbers of EC samples from Black women in large scale molecular profiling studies such as TCGA (46 Black cases, 291 White cases; Nature. 2013;497(7447):67-73).
- Limited understanding of the impact of obesity and its related co-morbidities as modulators of EC progression and treatment efficacy in Black women.

https://unclineberger.org/cecs/

CAROLINA ENDOMETRIAL CANCER STUDY



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Hazel Nichols, PhD
Epidemiology

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Russell Broaddus, MD, PhD
Pathology

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Gastroenterology

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Carolina Endometrial Cancer Study

CAROLINA ENDOMETRIAL CANCER STUDY

- NC state-wide population-based prospective study of **>1,800 endometrial cancer patients** (>500 Black women) - opened in February 2021, all 100 NC counties.
- Participant surveys, medical records data, tumor samples, and ongoing follow-up.
- Integrate **epidemiologic factors** (obesity and its co-morbidities), **social determinants of health** (social deprivation, structural racism) and **tumor biology** (genomics, microbiome) as contributors to worse outcomes in Black EC patients.
- Comprehensive picture of this disparity – delineate the best social, behavioral and biologic interventions to address.

Carolina Endometrial Cancer Study (CECS)

- **Baseline and follow-up telephone interviews (12, 24 months)**
  - Information on medical history, weight change, racism, sociodemographic factors, physical activity, access to care, financial impact, quality of life.
- **Medical Records and Outcome Assessment**
  - Abstraction of medical records related to diagnosis, treatment and outcomes.
- **Biospecimen collection**
  - Acquisition of FFPE tumor blocks
- **Molecular/Microbiota Subtyping**
  - NGS (1400 gene panel), RNA sequencing
  - IHC, DNA methylation, 16S bacterial profiling

CAROLINA ENDOMETRIAL CANCER STUDY

Overall Summary

- Outcomes worsening for endometrial cancer!
- How do we best break the obesity-endometrial cancer link?
- TCGA molecular subtypes – precision medicine
- Endometrial cancer harbors one of the worse cancer disparities for Black women than any other cancer.
- Why do Black women develop these aggressive molecular subtypes of endometrial cancer? Upstream social determinants? Is obesity a potential driver of these more aggressive molecular subtypes?
- Critical to addressing this disparity is to define the molecular alterations in the ECs of Black women in the context of other social and biologic factors that may drive more aggressive behavior of EC or lead to worse outcomes – Carolina Endometrial Cancer Study (CECS)

COLLABORATORS & LAB:

- **Chunxiao Zhou, MD, PhD**
- Wendy Brewster, MD, PhD
- Tope Keku, PhD
- Jeffrey Roach, PhD
- Jason Merker, MD, PhD
- David Corcoran, PhD
- Xianming Tan, PhD
- Russel Broaddus, MD, PhD
- Andrew Olshan, PhD
- Amber Nicole McCoy, BS
- Stephen Hursting, PhD
- Hazel Nichols, PhD
- Andrew Gladden, PhD
- Bernard Weissman, PhD

GRANT SUPPORT:

- NIH/NCI - 1R21CA220269, 1R21CA267584
- NIH/NCI R37CA226969
- V Foundation
- Foundation for Women's Cancers
- Department of Defense (DOD)
- American Cancer Society (ACS)
- LCCC/UCRF Tier 2 Grants

Thank you!

The Becky Black Memorial Fund to Fight Endometrial Cancer

UNC SCHOOL OF MEDICINE

DINA'S DYNASTY

fighting cancer below the belt

2020 INAUGURAL Golfing for the Gals

SHE ROCKS
RESEARCH OVARIAN CANCER KNOWLEDGE SUPPORT

	Baseline	12 mo	24 mo
Disease			
Disease Charecteristics	MR, Lab	MR	MR
Individual Survivor			
Pre-diagnosis symptoms	Q		
SES, insurance, employment, and finances	Q		Q
Medical mistrust/perceived racism/access to care	Q		Q
Comorbidities, medications, and preventive health care NCCN Survivorship concerns-immunizations, COVID-19	Q	Q	Q
Genetic/genomic testing (germline/tumor)	Q, MR		
Treatment, Follow-up Care			
Cancer Treatment (modality, dose, dates)	MR	MR	MR
Surveillance, recurrences, new cancers, SGO symptoms		Q, MR	Q, MR
Cardiac history, symptoms: NCCN Survivorship concerns - cardac toxicity	Q	Q	
Anxiety, Depression: NCCN Survivorship concerns, PROMIS	Q	Q	Q
Hormone-Related symptoms, Pain, Fatigue: NCCN Survivorship concerns		Q	
Behavioral / Lifestyle Factors			
Weight change, Physical activity, Fruits & vegetables: NCCN Survivorship concerns - Healthy Lifestyle; Godin	Q	Q	Q
Sleep: NCCN Survivorship concerns	Q	Q	Q
Quality of Life Outcomes			
Sexual function: NCCN Survivorship concerns; IMPACT		Q	
Lymphadema: NCCN Survivorship concerns; Gynecologic cancer lymphadema questionnaire (GCLQ)		Q	
GI Symptoms: IMPACT (initial measurement of patient-reported pelvic floor complaints tool)		Q	
QoL: FACT-G and FACT-EN at baseline; PROMIS at follow-up	Q		Q