Disparities in breast cancer: a biology, health services and solutions story

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Objectives

- Review the epidemiology of racial disparities in breast cancer and most affected subtypes
- Discuss how tumor biology impacts racial differences in breast cancer
- Review evidence for disparities in treatment access and costs of treatment as a factor in racial outcome differences
- Highlight potential solutions

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Breast Cancer Subtypes… in One Slide

- Defined by two sets of receptors on cell surface: hormone (HR) and HER2
- **HR+/HER2-:** overall best prognosis, treatment includes endocrine therapy
- **HER2+:** aggressive, but very responsive to treatment including biologic targeted therapy trastuzumab
- **"Triple Negative":** aggressive, no targeted therapies available

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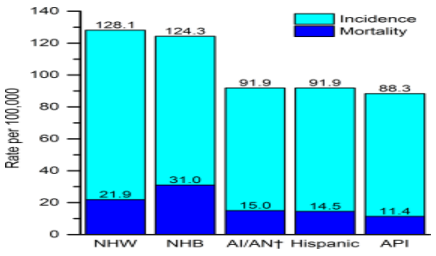
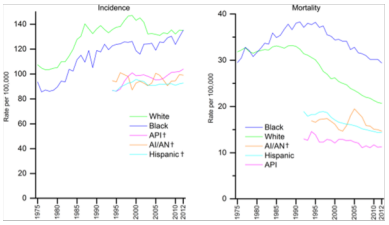
The Breast Cancer Survival Gap



CA: A Cancer Journal for Clinicians (used with permission)
Volume 66, Issue 1, pages 31-42, 29 OCT 2015 DOI: 10.3322/caac.21320

Mind the gap: incidence closing, mortality opening



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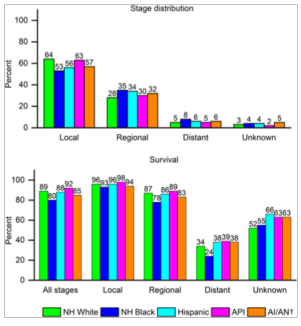
http://onlinelibrary.wiley.com/doi/10.3322/caac.21320/full#caac21320-fig-0001

The Perfect Storm:

Advanced Stage

meets

Aggressive Biology and Under-treatment



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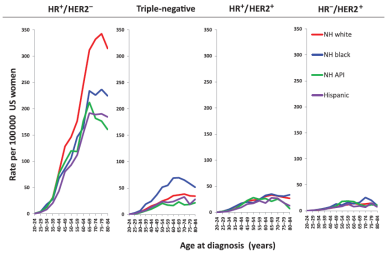
Volume 66, Issue 1, pages 31-42, 29 OCT 2015 DOI: 10.3322/caac.21320
http://onlinelibrary.wiley.com/doi/10.3322/caac.21320/full#caac21320-fig-0001

SEER 2010: Breast Cancer Incidence by Race + Subtype



From Howlader N et al, *US Incidence of Breast Cancer Subtypes Defined by Joint Hormone Receptor and HER2 Status.* JNCI 2014; 106(5).

Where is the disparity?

- The high risk "triple negative" subtype is over-represented among young black women
  BUT
- HR+/HER2- subtype is responsible for most breast cancer cases and deaths among black patients

Subtype	% of Cases NH White	% of Cases AA/Black	5 year DFS or BCSS
Triple Negative	10.7%	22.5%	62%-75%
HR+/HER2-	75.5%	60.2%	~77-86% (AA) ~84-91%(NHW)

Black Women with HR+ Cancer Have Double the Risk of Whites

Source*	Adjustment Factors	HR (95% CI)
Carolina Breast Cancer Study 1993-2006 5 marker (HR/HER2/HER1/CK 5/6)	Age, diagnosis year, stage	1.9 (1.3-2.9) for BCSS
City of Hope 1994-98 [2] 4 marker (HR+/HER2-/P53-)	Age, stage	1.9 (0.9-3.9) for BCSS
ECOG 1199 trial participants (stage II-II chemo-treated) HR+/HER2-	Age, BMI, tumor size, nodes, surgery type, hormonal tx	1.6 (1.2-2.1) for DFS

**In all studies, outcomes for women with triple negative disease were similar between black and white patients*

[1] O'Brien KM, Cole S et al, Clin **Cancer** Res. 2010 Dec 15;16(24):6100-10.
[2] Ma H, Lu Y et al, BMC Cancer 2013 13:225
[3]Sparano J, Wang M et al, JNCI 2012 Mar 7;104(5):406-14.

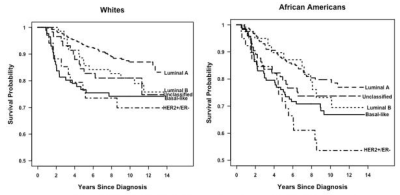
Historical Disparities in HR+ and HR-/HER2+ Phenotypes

CBCS I-II (1993-2006)

Pre-targeted therapy for adjuvant use

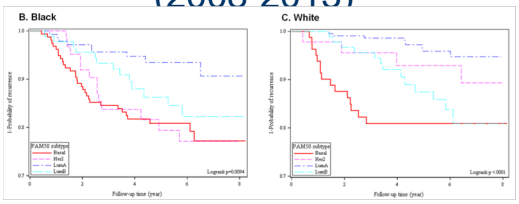
HER2+ patients with ~15% difference in long term breast cancer mortality

HR 2.2, borderline significance



Hazard Ratios for the Effect of Race on Breast Cancer Specific Mortality		
	HR for race (AA vs. white) adjusted for age at diagnosis and date of diagnosis (95% CI)	HR for race (AA vs. white) adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)
Luminal A	1.9 (1.3, 2.8)	1.9 (1.3, 2.9)
Luminal B	1.4 (0.6, 3.1)	1.3 (0.6, 3.0)
Basal-like	1.2 (0.7, 2.1)	1.3 (0.8, 2.3)
HER2+/ER-	1.7 (0.8, 3.8)	2.2 (1.0, 5.1)
Unclassified	1.4 (0.7, 2.9)	1.2 (0.6, 2.6)

CBCS III RFS by subtype (2008-2013)



- RFS at median 5.5 years: difference of 12% for HER2+ disease, 4% HR+
- Likely static or widening survival gaps

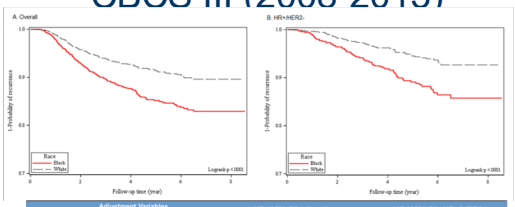
Why does the survival gap grow as targeted therapy improves?

Fundamental cause theory of health disparities (Phelan and Link, 1995):
advantaged group status "embodies an array of resources, such as money, knowledge, prestige, power, and beneficial social connections that protect health no matter what mechanisms are relevant at any given time."

Fundamental Cause Theory and Targeted Therapy

- Few intervenable targets→ poor overall outcomes but small disparities (e.g. polio prior to vaccination, breast cancer prior to 1950s)
- Development of effective/targeted therapies→ disparities widen due to differential resources and access

HR+/HER2- patients, CBCS III (2008-2013)[1]



	Adjustment Variables	HR (95% CI), all patients	HR (95% CI), HR+/HER2-
Model 1	age only	1.69 (1.24, 2.13)	2.01 (1.40, 2.88)
Model 2	age, stage, grade, clinical phenotype, chemotherapy	1.31 (1.01, 1.71)	1.62 (1.11, 2.36)
Model 3	Model 2 + ROR-PT score	1.41 (0.91, 2.19)	1.506 (0.81, 2.81)
Model 4	Model 2 + molecular subtype (luminal A versus other)	1.24 (0.83, 1.85)	1.443 (0.77, 2.69)

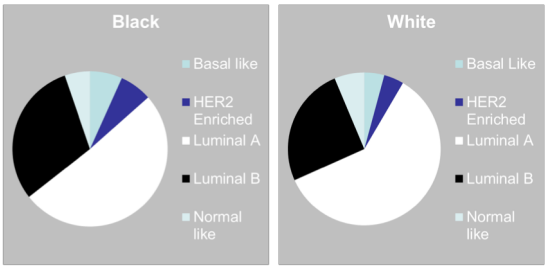
[1] presented at SABCS 2017, Reeder-Hayes et al, P2-13-05, Sun et al P6-08-01

Why disparities in HR+ disease?

- **A biologic hypothesis**: biologically aggressive HR+ disease might be more common in black patients, in ways we don't identify well in the clinic
- **A health services hypothesis:** outcome disparities increase as targeted therapy becomes more effective due to fundamental barriers to healthcare access that disproportionately affect minorities

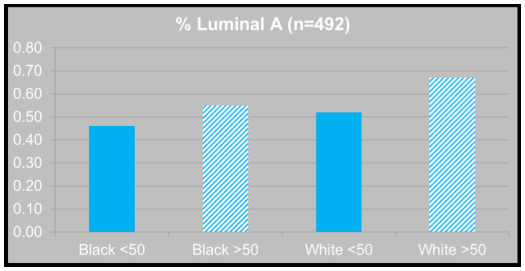
The Biologic Hypothesis

CBCS III Molecular Profile of HR+/HER2- tumors by race

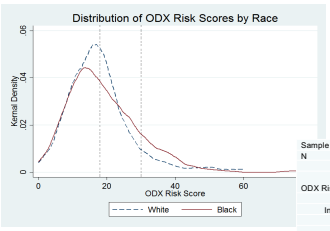


Data from Troester et al, JNCI 2018 Feb 1

Luminal A proportion among HR+/HER2- tumors by race and age



Racial Differences in 21 gene recurrence scores



Sample	Overall	Non-AA	AA	
N	541	355	186	p
	Mean (Standard Deviation) or %			
ODX Risk Group				0.23
Low	54.2	54.8	49.8	
Intermediate	37.5	37.4	37.9	
High	8.3	7.7	12.3	
ODX Risk Score				
Overall	18.0 (9.9)	17.7 (8.6)	19.4 (16.8)	0.10
Low	11.2 (4.3)	11.2 (3.9)	11.3 (6.6)	0.85
Intermediate	22.5 (3.7)	22.3 (3.2)	23.5 (5.9)	0.04
High	41.2 (8.7)	41.6 (7.2)	39.6 (13.1)	0.42

Roberts MC, Weinberger M, Dusetzina SB, Dinan MA, Reeder-Hayes KE, Troester MA, Carey LA, Wheeler SB. Racial variation in adjuvant chemotherapy initiation among breast cancer patients receiving oncotype DX testing. Breast Cancer Res Treat. 2015 Aug;153(1):191-200.

Gene Expression Profiles Suggest Higher Risk Biology

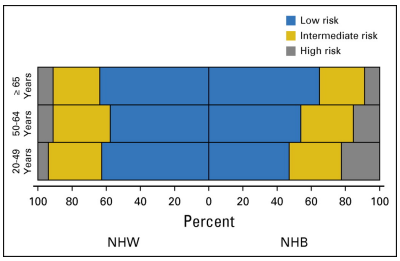


Fig 3. Age patterns by race and 21-gene recurrence score. Proportions of women within 21-gene recurrence score categories are shown by age category and race. Blue: low risk, < 18; gold: intermediate risk, 18 to 30; gray: high risk, ≥ 31. NHB, non-Hispanic black; NHW, non-Hispanic white.

Published in: Andreana N. Holowatyj; Michele L. Cote; Julie J. Ruterbusch; Kristina Ghanem; Ann G. Schwartz; Fawn D. Vigneau; David H. Gorski; Kristen S. Purrington; JCO **2018**, 36, 652-658.
DOI: 10.1200/JCO.2017.74.5448

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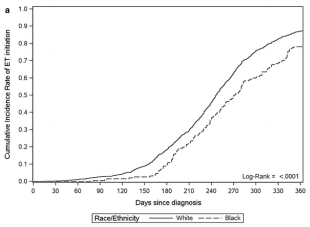
The Health Services Hypothesis

Endocrine therapy initiation after chemo among high-risk HR+ patients by race (adjusted for clinical factors).



Reeder-Hayes, K.E., Meyer, A.M., B. Dusetzina, S… Wheeler, S. Breast Cancer Res Treat (2014) 145: 743.
Used with permission.

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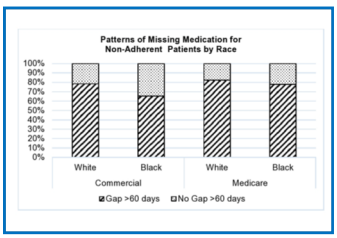
Insurance Data After Initiation (n=1,362)



- Black women under 65 were 29% more likely to be non-adherent
- Race was not a predictor of adherence for women >65
- Young black women more often have "spotty" adherence rather than quitting altogether

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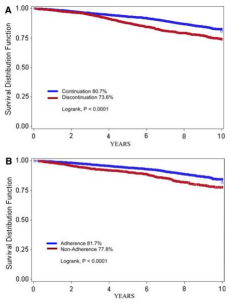
Does Adherence Affect Survival?

- Hershman et al analysis of 8,769 women in Kaiser Permanente N California
- early discontinuers: 7% decrement in 10 year overall survival (HR 1.26, 95% CI 1.09–1.46)
- non-adherent but remained on therapy: 4% decrement in 10 year overall survival (HR 1.49, 95% CI 1.23–1.81)



Hershman et al, Breast Cancer Res Treat. 2011 Apr; 126(2): 529–537.

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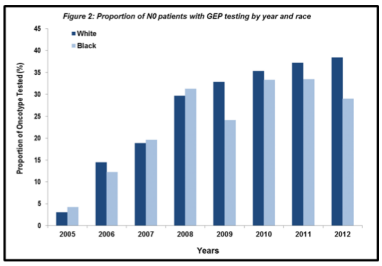
Disparities in Genomic Testing

Proportion of eligible patients receiving gene expression profile testing by race



Reeder-Hayes KE, Wheeler SB et al, *Cancer*, 2018 Jan 16

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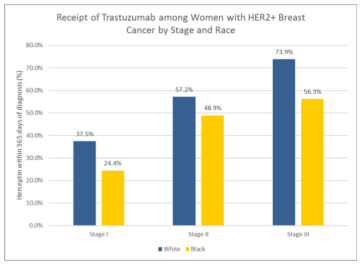
Disparities in HER2 Targeting

Proportion of HER2+ Medicare patients receiving trastuzumab by race



Reeder-Hayes K, Peacock Hinton S, Meng K, Carey LA, Dusetzina SB. J Clin Oncol. 2016 Jun 10. Used with permission.

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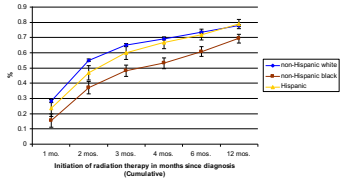
Disparities in RT after BCS

Proportion of early stage Medicare patients receiving RT after BCS by race



Wheeler et al, BCR&T, 2012

Breast Cancer Res Treat (2012) 133:333–345
DOI 10.1007/s10549-012-1955-2

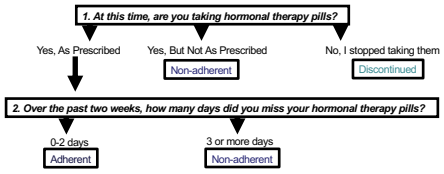
EPIDEMIOLOGY

Structural/organizational characteristics of health services partly explain racial variation in timeliness of radiation therapy among elderly breast cancer patients

Stephanie B. Wheeler · William R. Carpenter · Jeffrey Peppercorn · Anna P. Schenck · Morris Weinberger · Andrea K. Biddle

Disparities in Endocrine Therapy (ET)

Proportion of HR+ patients (all ages) taking endocrine therapy at 2 years post-dx



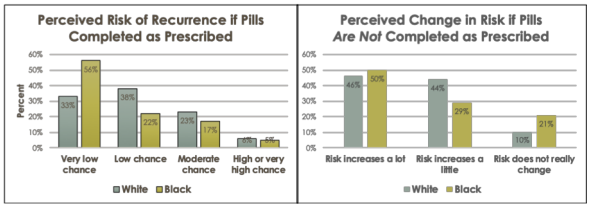
	White	Black	
Adherence			**<.0001*** **
Adherent	83% (618)	75% (428)	
Non-Adherent	5% (40)	13% (76)	
Discontinued	11% (83)	11% (63)	

Reasons for ET non-adherence by race

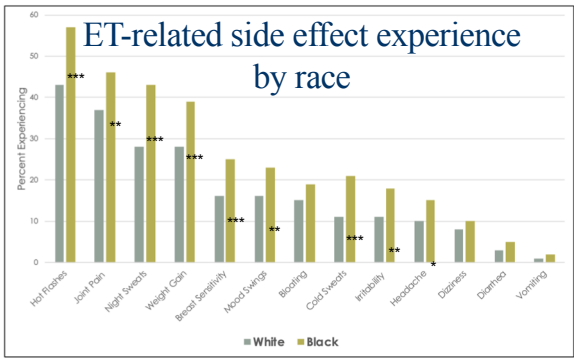
	Percent (n)		P value
	White 57% (741)	**Black** 43% (567)	**N= 1308**
Overall Adherence			**0.0004*** **
Non-Adherent / Discontinued	17% (123)	25% (139)	
Forgets meds when traveling			**.0048****
Yes	18% (135)	25% (142)	
Difficulty sticking to treatment plan			**<.0001*** **
Hard/Very Hard	13% (98)	26% (145)	
Trouble remembering to take meds			**<.0001*** **
Often/Sometimes	12% (91)	26% (148)	
Missed pills due to cost			**<.0001*** **
Often/Sometimes	6% (47)	16% (89)	
Missed due to not refilling promptly			**.0001*** **
Often/Sometimes	6% (43)	12% (69)	
Skipped due to concerns about long- term medication use			**<.0001*** **
Often/Sometimes	14% (101)	28% (160)	
Opinion of ET overall^			**.0002*** **
Good outweighs bad	77% (568)	67% (382)	
Neutral	12% (87)	20% (112)	
Bad outweighs good	8% (58)	7% (40)	

* p<.05
** p<.01
*** p<.0001
^ 3% and 6% of responses missing for whites, blacks, respectively
Wheeler et al., 2015, ASCO

ET-related recurrence risk assessment by race



ET-related side effect experience by race



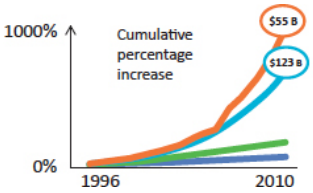
* p<.05
** p<.01
*** p<.0001

Multivariable analysis of ET non-adherence by race

Factor	OR	CI		P Value
Race	**1.44**	**1.05**	**1.99**	**0.03**
ET Type (Tamoxifen vs. Aromatase Inhibitors)	1.11	0.77	1.61	0.34
Stage (2 vs 1)	0.87	0.59	1.28	0.31
Stage (3 vs 1)	0.54	0.29	1.02	0.07
Received Herceptin	1.61	1.00	2.60	0.06
Received Chemotherapy	0.89	0.59	1.33	0.34
Received Radiation	1.32	0.84	2.09	0.20
Mastectomy (vs. Breast Conserving Surgery)	1.21	0.80	1.84	0.27
Age at Diagnosis	**0.98**	**0.96**	**0.996**	**0.02**
Endocrine Symptom Subscale	0.99	0.98	1.003	0.14
ET Decision Making (ref: Shared Decision Making)				
No Discussion	2.15	1.19	3.90	**0.02**
Primarily Patient Decision	2.12	1.43	3.15	**<0.001**
Primarily Provider Decision	1.35	0.91	1.98	0.13
Perception of Recurrence Risk if ET Completed (ref: Low/Very Low)				
High/Very High	1.23	0.57	2.65	0.35
Moderate	**2.10**	**1.44**	**3.07**	**<0.001**
Perception of Risk if ET Discontinued (ref: Increases a lot)				
Risk increases a little	**2.46**	**1.67**	**3.62**	**<0.001**
Risk does not change	**8.51**	**5.47**	**13.22**	**<0.001**

OR= OddsRatio, CI= 95% Confidence Interval, ET= Endocrine Therapy
Results were generated through 50 replications of multiple imputation for missing data.

Cancer care is expensive



	Annual Increase
Cancer Drugs	20%
Cancer Medical	12-18%
Health Care	9%
US GDP	3%

Figure: Increase in cancer care and drug costs relative to overall health care costs. SOURCES: Kolodziej presentation, June 9, 2014; 2010 CY claims; commercial and Medicare; all funding; http://www.cancer.gov/newscenter/newsfromnci/2011/CostCancer2020 (accessed August 20, 2014).

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The rising cost of cancer care in the U.S. poses real problems to individual patients

- Health behaviors
  - Skipping, foregoing, delaying care
  - Non-adherence to doctor-recommended treatments
- Health-related outcomes
  - Higher stress, anxiety, depression
  - Worse quality of life
- Financial toxicity
  - Debt, inability to acquire loans
  - Medical bankruptcy

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Black women with breast cancer are more financially vulnerable than Whites at diagnosis

	White	Black	p-value (X^2)
N	1256	1205	
Annual Household Income			
<$15,000	76 (6.4%)	283 (24.8%)	<0.001
$15,000-29,999	154 (12.9%)	293 (25.6%)	
$30,000-49,999	206 (17.3%)	236 (20.6%)	
>$50,000	758 (63.5%)	331 (29.0%)	
Insurance status			
Private Insurance	1101 (87.7%)	734 (61.0%)	<0.001
Medicare	52 (4.1%)	91 (7.6%)	
Medicaid	66 (5.3%)	287 (23.8%)	
Uninsured	37 (2.9%)	92 (7.6%)	

[33] Wheeler et al. 2017, under review

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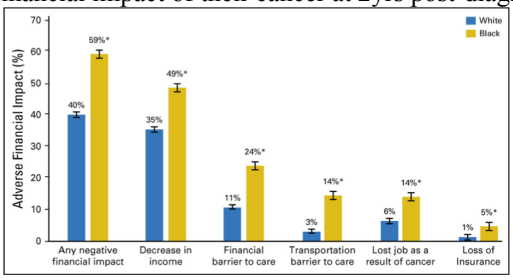
Black women with breast cancer report worse financial impact of their cancer at 2yrs post-diagnosis



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Wheeler, Reeder-Hayes et al, J Clin Oncol. 2018 Jun 10;36(17):1695-1701. doi: 10.1200/JCO.2017.77.6310. Epub 2018 Apr 18

34

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Black women with breast cancer report worse financial impact of their cancer at 2yrs post-diagnosis

Table: Unadjusted and Adjusted Marginal Effect of Black Race on Adverse Financial Impact

	Model 1 Unadjusted	Model 2 Adjusted-Clinical	Model 3 Adjusted-Clinical & SES
Any Financial Impact	18.92***	14.21***	5.49*
	(1.98)	(2.13)	(2.18)
Income Loss[a]	13.25***	9.76***	5.09*
	(1.99)	(2.14)	(2.26)
Financial Barrier	13.23***	10.34***	2.92
	(1.50)	(1.60)	(1.62)
Transportation Barrier	11.65***	9.91***	3.97***
	(1.12)	(1.14)	(1.15)
Job Loss[b]	7.13***	5.89***	3.62**
	(1.20)	(1.27)	(1.34)
Insurance loss[c]	3.18***	2.71**	1.30
	(0.82)	(0.84)	(0.78)

Results interpreted as average change in probability of outcome relative to the referent category. Standard errors in parenthesis. Model 2 adjusts for: stage, receipt of mastectomy, chemotherapy, radiation, hormone therapy, and Herceptin, and comorbidities. Model 3 adjusts for all these characteristics and for insurance, household income, education, and marital status.

[a]Analysis excludes women who had never worked prior to diagnosis or declined to respond n=2408

[b]Analysis excludes women who had never worked prior to diagnosis n=2446

[c]Analysis is only for women privately insured at the time of the baseline survey n=1834

35

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How might we intervene?

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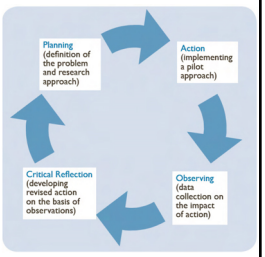
Designing multilevel interventions to improve cancer equity, access, outcomes

- Offering **motivational interviewing** to improve guideline-recommended therapy use (moving away from 'one-size-fits-all' strategies)
- **Monitoring costs** and engaging **financial counselors** routinely in cancer care
- Engaging **settings** in treatment (e.g., oncology clinics, workplaces, etc.)
- Using **behavioral economics** to subtly change the choice architecture in which decisions are made
- Exploring **preferences** around intervention design in diverse underserved populations
- Developing **social support networks**
- Leveraging **mobile technology**



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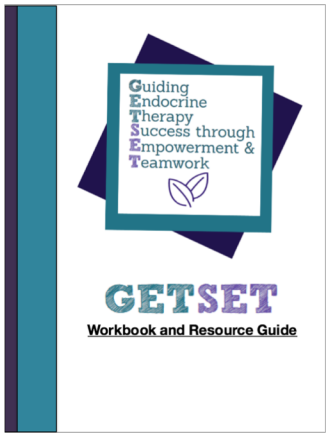

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GETSET overview

- Design informed by data collected in study phases 1 & 2
- Elements
  - Introductory Video
  - 5 MI sessions with trained MI counselor
  - Workbook/resource guide
- Evidence-based strategies to support ET use
- Linkage to support groups and other resources

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How to prevent and mitigate financial burden

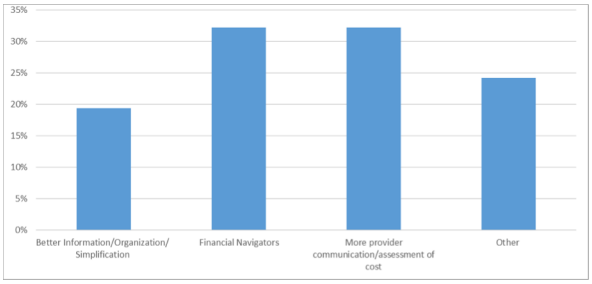
Prevention- More systematic, early identification of patients at risk for high financial burden
- Financial distress screening

Treatment- Use of navigation to help patients identify resources, understand eligibility, and complete applications.
- New financial advocate position

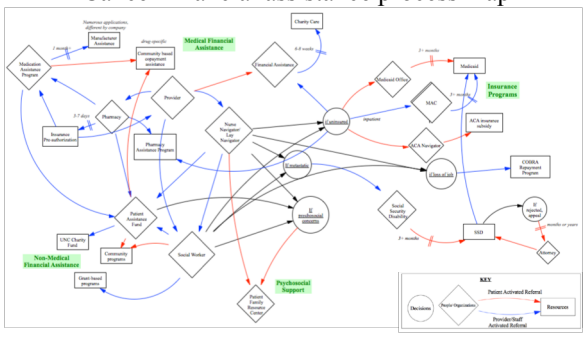
Simplification- Better coordination of current efforts & reduction in duplicative processes.
- A 'universal' or 'common' application for multiple resources

40

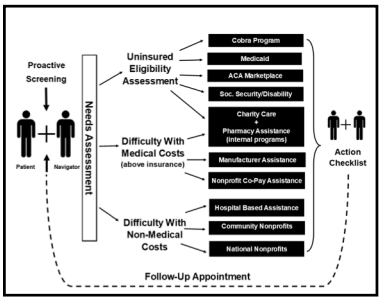
[cancer navigators] If you could make one improvement to the system, what would it be?



Cancer financial assistance process map



What We're Testing Now



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"If you always do what you've always done, you always get what you've always gotten."

-motivational speaker Jessie Potter

"The definition of insanity is doing the same thing over and over again and expecting a different result."

-anonymous (misattributed to Einstein)

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