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Investigating Racial Disparities in Endometrial Cancer in Risk of Disease and Treatment
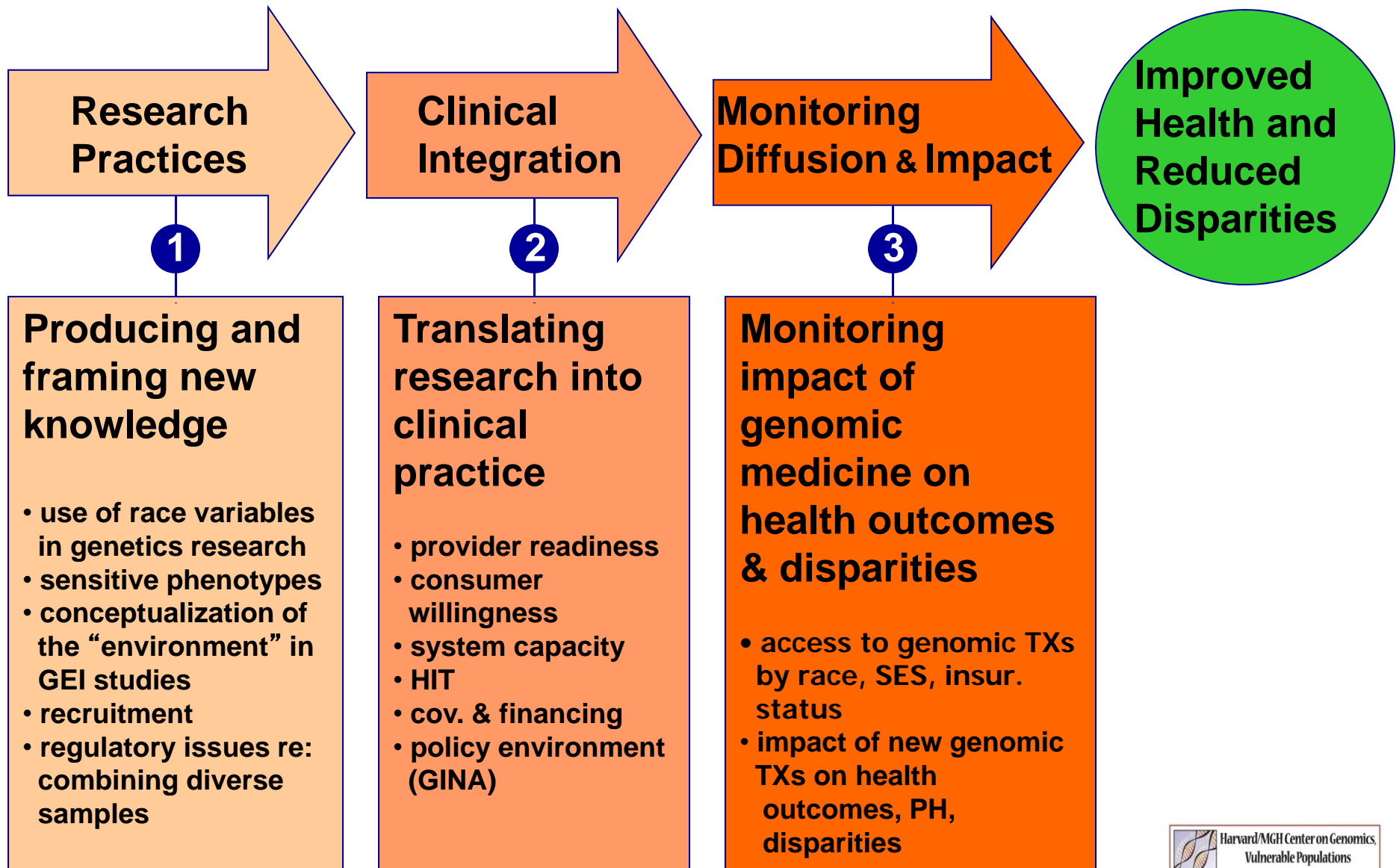
Advances in Endometrial Cancer Epidemiology and Biology Symposium

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Intersections of Genomics & Health Disparities Throughout the Research Trajectory

Research Practices → **Clinical Integration** → **Monitoring Diffusion & Impact** → **Improved Health and Reduced Disparities**

① Producing and framing new knowledge

- use of race variables in genetics research
- sensitive phenotypes
- conceptualization of the "environment" in GEI studies
- recruitment
- regulatory issues re: combining diverse samples

② Translating research into clinical practice

- provider readiness
- consumer willingness
- system capacity
- HIT
- cov. & financing
- policy environment (GINA)

③ Monitoring impact of genomic medicine on health outcomes & disparities

- access to genomic TXs by race, SES, insur. status
- impact of new genomic TXs on health outcomes, PH, disparities

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Overview

I) Cutting Edge Methods for Exploring Risk of Endometrial Cancer

    a. Inclusion of minority women in discovery data sets – need to understand etiology of histology

    b. Addressing genetic, social, environmental, and behavioral factors concomitantly

    c. Identifying novel pathways and mechanisms

II) Ensuring equitable access to novel treatments in clinical practice

    a. Equitable access to novel, effective treatments

    b. Making health plans accountable

Overview

I) Cutting Edge Methods for Exploring Risk of Endometrial Cancer

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Composition of Study Populations: Why is Inclusion Important?

- <u>Justice argument</u>: Access to trials = access to TX

- <u>1978 Belmont Report</u>: Justice requires that the **burdens and benefits** of research be fairly distributed

- Capturing clinically significant genetic variation across **all** human beings
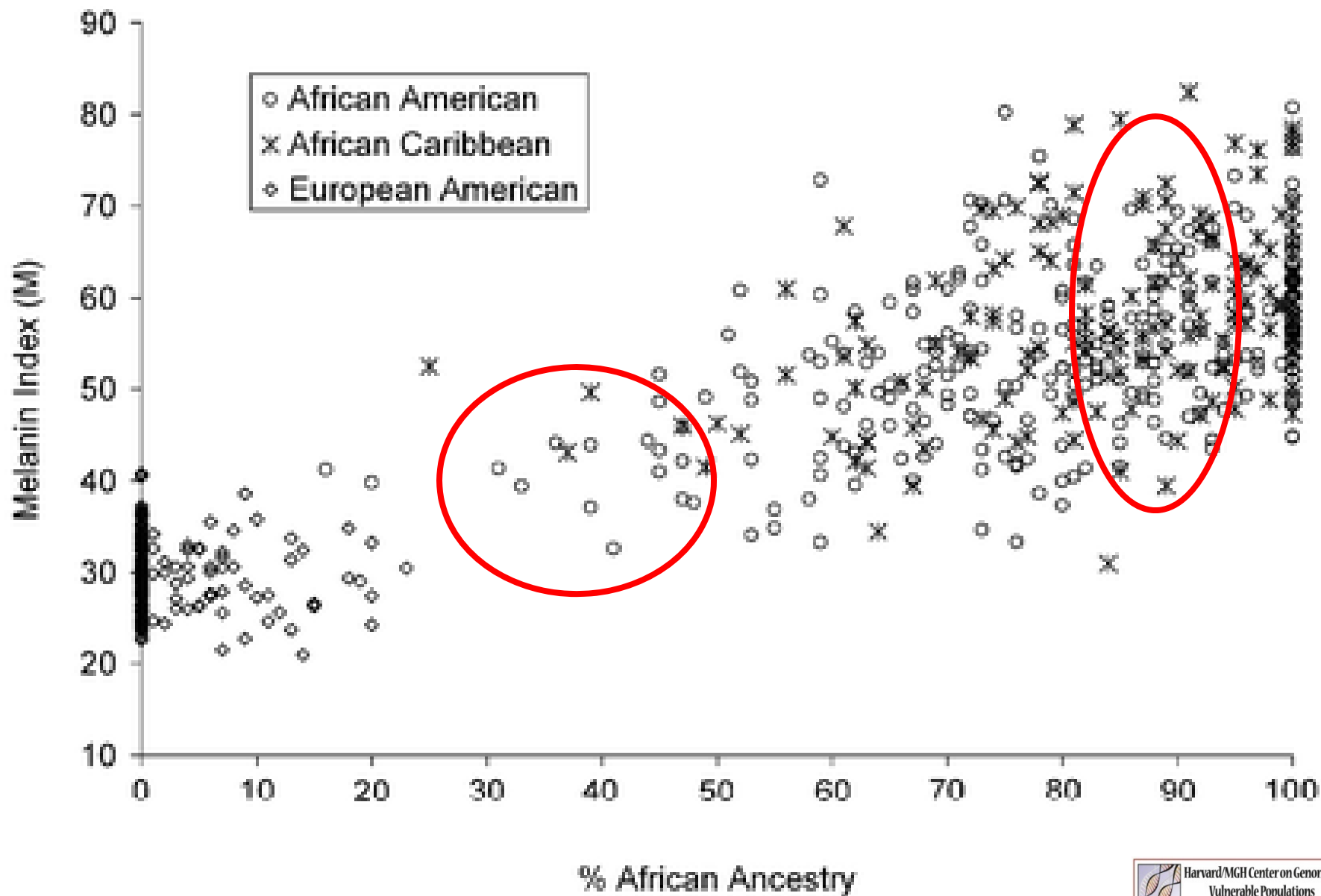
Minority Inclusion in Genome Discovery Data Sets

Most discovery data sets used in genomics research thus far include only white participants.

- "75% of genomics studies to date have included only persons of European ancestry"[1]

- A 2010 study of genome-wide association (GWA) study participants found that **92% of US GWAS participants were white**, followed by African-Americans (3%)[2]

- "Systematically lower effect sizes in African ancestry populations have been found for variants validated in European ancestry populations because of **incomplete characterization of African-ancestry haplotypes**[3]

(1) Rosenberg et al. Genome-wide association studies in diverse populations. *Nature Reviews: Genetics*. 2010; 11(5):356-66. **(2)** Haga S. B. Impact of limited pop. diversity of genome-wide association studies. *Genetics in Medicine*. 2010; 12(2):81-4. **(3)** Deo et al. (2009) Genetic Differences between the Determinants of Lipid Profile Phenotypes in African &European Americans: The Jackson Heart Study. *PLoS Genetics*. 5(1): e1000342.

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A Note about the Use of Race Variables in Genomics Research

Poor Validity: Self-Identified Race v. AIMs

Shriver et al. Skin pigmentation, biogeographical ancestry and admixture mapping. *Human Genetics*. 2003:112(4):387-399

"Race" in the Context of Genomics Research

- Self-identified race:
  - is a social construct that remains important to monitor access/disparities
  - captures cultural identity/practices
  - is a proxy for a host of social and environmental exposures

- Race is not the same as geographical ancestry

- Human genetic variation is a continuous variable!

Cavalli-Sforza. *The History and Geography of Human Genes* (1994)

Increasing Precision:

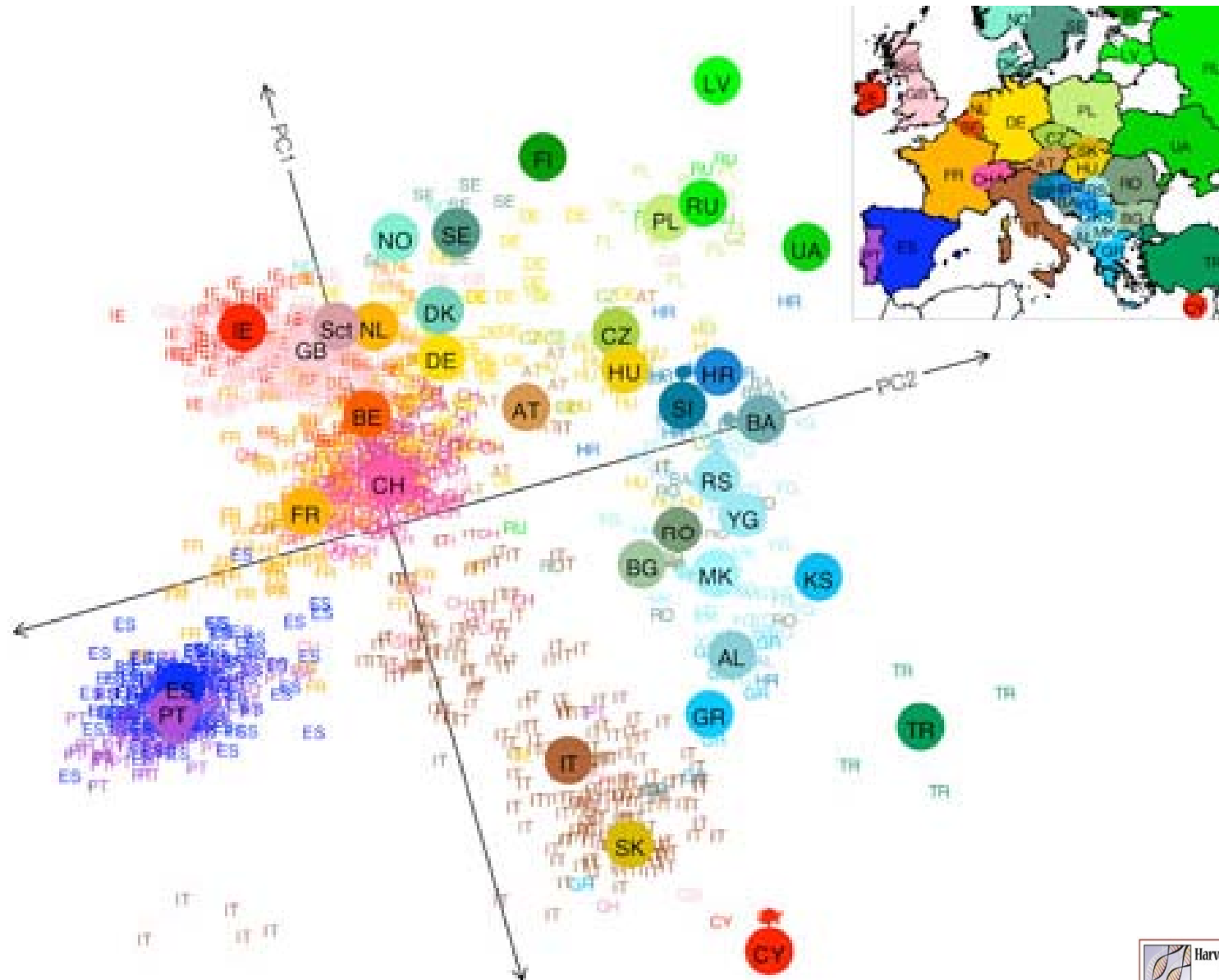## New Capacity for Fine-Scale Mapping → Drilling Down on "African Ancestry"

Bryc and colleagues (2009) analyzed population structure among:

- 146 individuals representing 11 different populations in West and South Africa
- 57 Yoruba genotyped as part of the HapMap project
- 365 African Americans from throughout the U.S.
- 400 individuals from Europe

Bryc et al. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proceedings of the National Academy of Sciences of the United States of America*. 2010. 107(2):786-91.

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Results

- Although the mean West African ancestry for African Americans was 77% (using sample of 146 individuals from West Africa as benchmark), **estimates of African Americans' individual variation ranged from <u>less than 1% to more than 99%</u> West African ancestry**

Bryc et al. Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proceedings of the National Academy of Sciences of the United States of America*. 2010. 107(2):786-91.

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"European" Ancestry is also Limited: Genetic Diversity within a European Population

Novembre et al. Genes mirror geography within Europe. *Nature*. 2008; 456(7218): 98-101.

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Constructs appropriate for <u>monitoring</u> health disparities are not appropriate for genetic studies aimed at understanding the <u>etiology</u> of disease.

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Determinants of Population Health
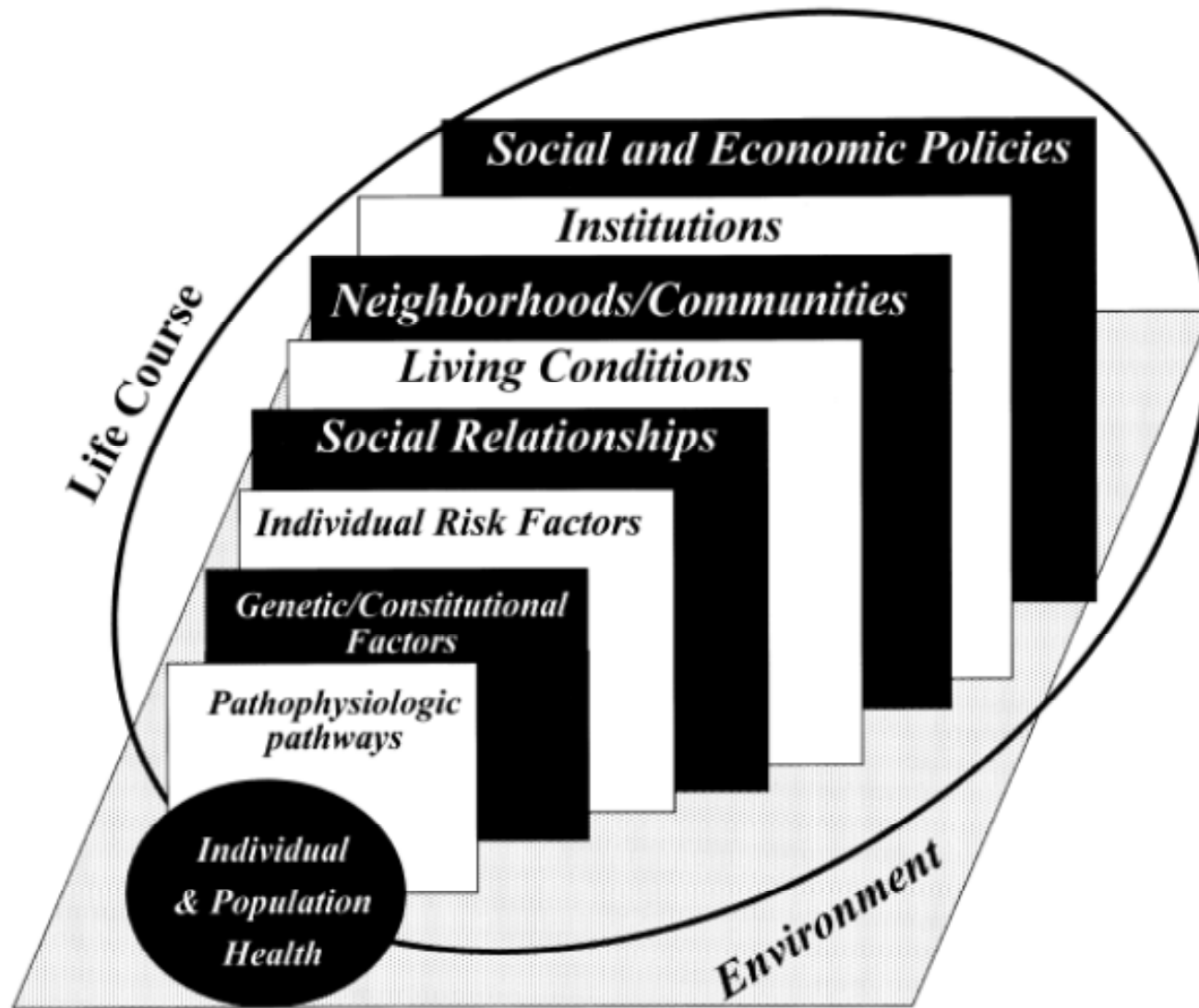
Social and Economic Policies

Institutions

Neighborhoods/Communities

Living Conditions

Social Relationships

Individual Risk Factors

Genetic/Constitutional Factors

Pathophysiologic pathways

Individual & Population Health

Life Course

Environment

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The Harvard Gene, Environment, and Disparities Research Initiative

- Transdisciplinary: 16 faculty from diverse fields working together over 2 years

- Disparities-focused = self-selected group

- Grappling with complexity – how to create research designs that do better at capturing the complexity we seek to understand?

- Keeping our eyes on the prize: improving human health & reducing disparities
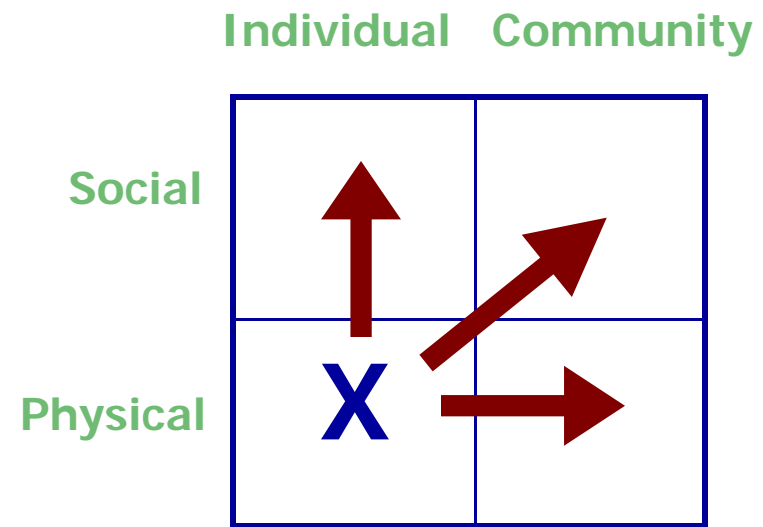
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Conceptualization of the "Environment" in GEI Studies: Breast Cancer

Systematic review of all studies examining GEIs for <u>breast cancer</u> susceptibility (n=407) through 2011:

SOCIAL & PHYSICAL ENVIROMENTAL BREAST CANCER RISK FACTORS	# OF GEIs TESTING FOR THIS MEASURE
Reproductive Factors	217
Smoke Exposure	83
Diet	50
Alcohol	32
Pollution and Radiation	18
Physical Activity	6
Other non-modifiable risk factors	69
Stress, Socioeconomic Status, Poverty, Social Class, Urbanicity, Acculturation, and Immigrant Status	NONE!

Shields et al. 2011 (Unpublished Data)

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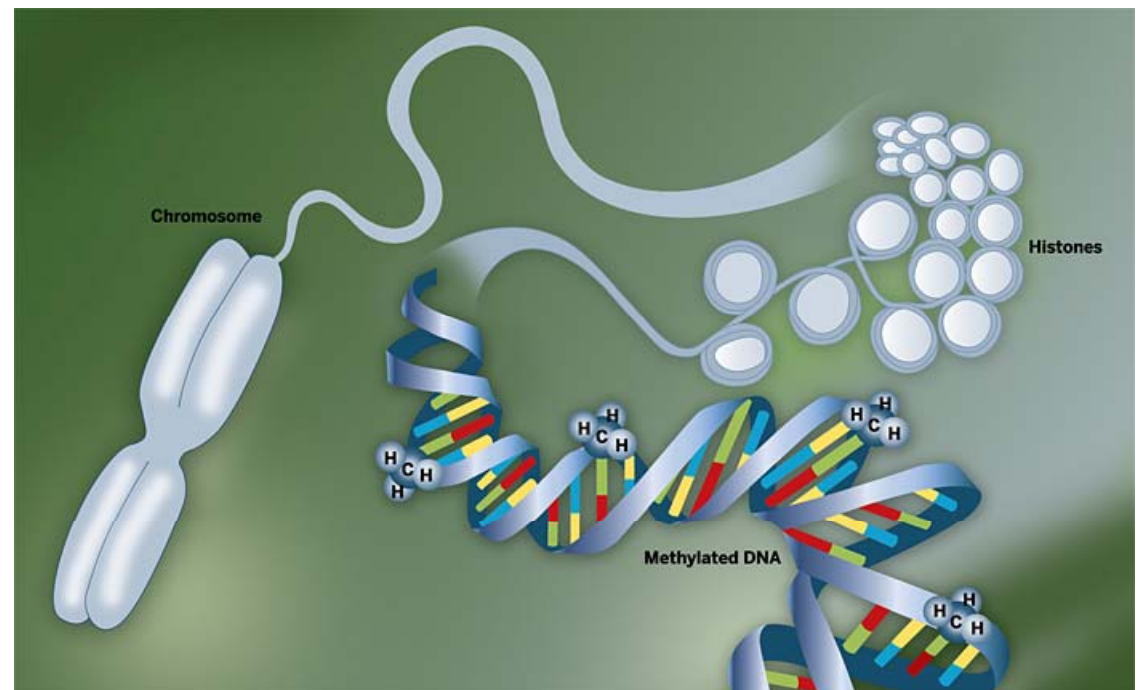
Need to Re-Conceptualize the "Environment"

- Expand our repertoire of "exposures" included in our analyses

- Pay particular attention to exposures disproportionately visited upon minority communities

Individual Community

Social

Physical

X

- Capture exposures at individual & community levels

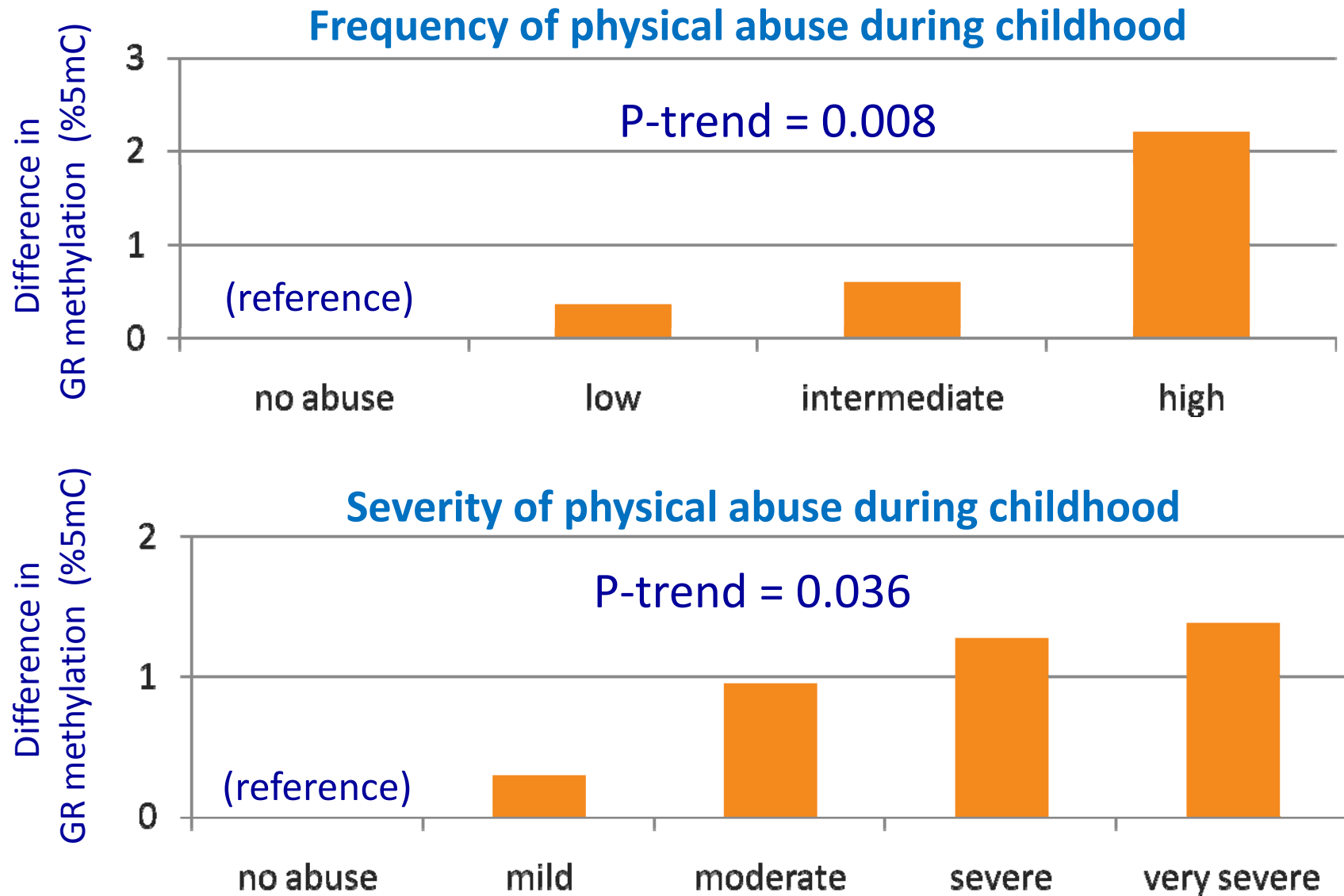Harvard/MGH Center on Genomics, Vulnerable Populations & Health Disparities

Exploring Biological Hypotheses: DNA Methylation

- A gene silencing mechanism – turns genes "off"

- Epigenome regulates gene expression & dynamically responds to environment

- HPA dysregulation mediated by epigenetic reprogramming[1]

Bollati V, Baccarelli A. Environmental epigenetics. Heredity 2010;105:105-12.

Blood GCR Methylation & History of Child Abuse

Frequency of physical abuse during childhood

P-trend = 0.008

Difference in GR methylation (%5mC)

(reference)

no abuse | low | intermediate | high

Severity of physical abuse during childhood

P-trend = 0.036

Difference in GR methylation (%5mC)

(reference)

no abuse | mild | moderate | severe | very severe

A. Baccarelli, A. Shields, J. Palmer,
L. Rosenberg, Y. Cozier (unpublished)

Analyses adjusted for age at baseline and parental education

Endometrial Cancer & Stress

- **Telepak 2013, Br J Health Psych**: Greater use of active coping prior to surgery for suspected endometrial cancer is associated with lower probability of all-cause mortality 4-5 years post-surgery.

- **Pereira 2010 Brain Behav Immun**: Greater HSP70 antibody levels (implicated in tumorigenesis) associated with greater impact of recent negative life events, anxious symptomatology, depressive symptomatology, and total mood disturbance.

Endometrial Cancer & Stress
(cont'd)

- <u>Nielsen 2007 Psychosomatic Med</u>: For each increase in self-reported stress level on a 7-point stress scale, there was a lower risk of primary endometrial cancer, particularly in women who received hormone therapy and in normal-weight women.

- <u>Shively, 2004 Menopause</u>: In monkeys, social subordination stress was associated with initial cellular changes that may increase endometrial cancer risk.
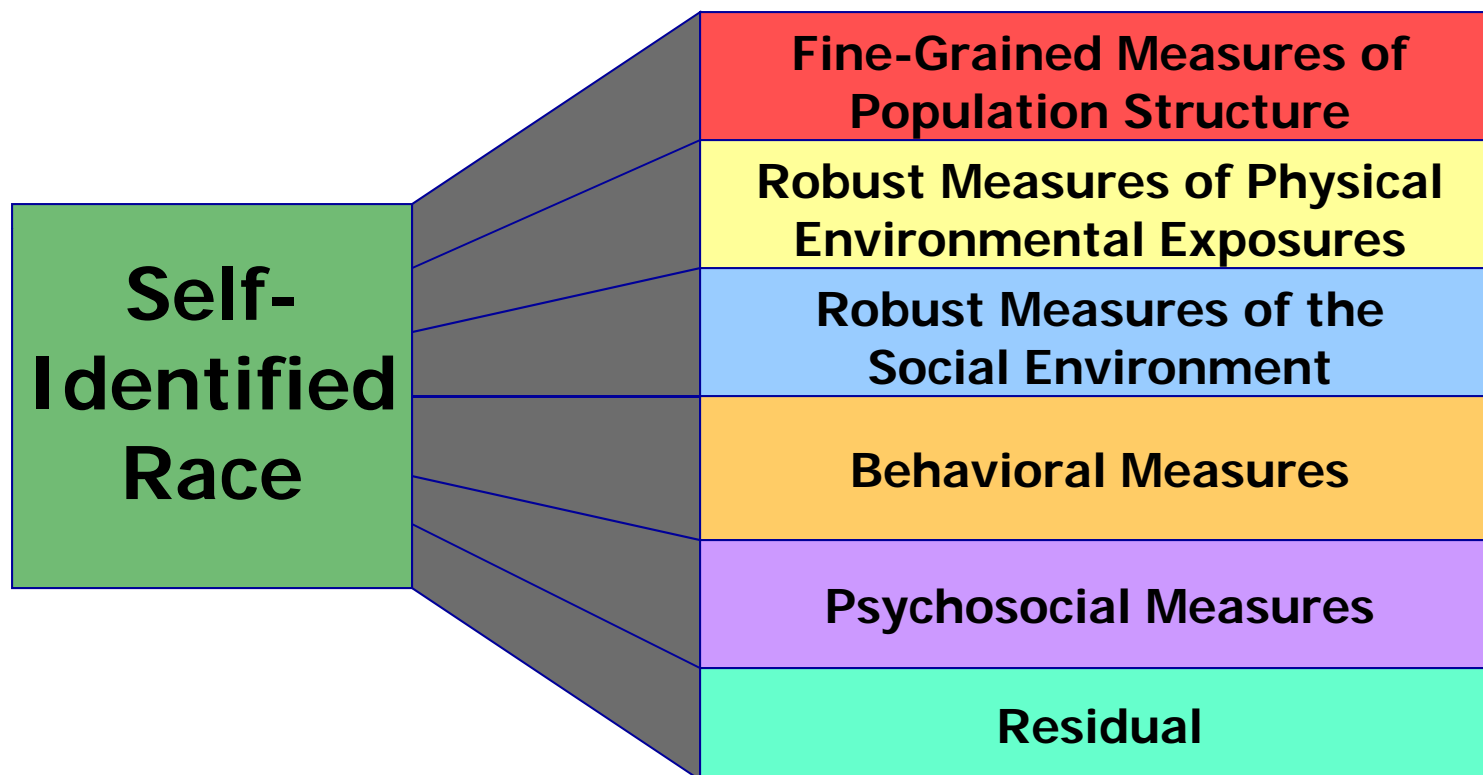
Barriers to Conducting Disparities-Focused Gene-Environment Research

- Limitations of available measures across cohorts or at all!

- Quality of available measures – don't measure lived experience of poor/min pts

- Availability of biospecimens needed to conduct epigenetic analyses

- Need for even more collaborative networks

- Need to develop a real culture of transdisciplinary research – still countercultural!

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Overview

II) Ensuring equitable access to novel treatments in clinical practice

    a. Equitable access to novel, effective treatments

Developing Novel PGx Therapies

Non-Small Cell Lung Cancer (NSCLC)

- 85% of all lung cancer cases

- ~70% of NSCLC patients are incurable at the time of diagnosis

- Improved knowledge of NSCLC's molecular pathogenesis → identification of druggable mutations (e.g., within epidermal growth factor receptor [EGFR], an unregulated growth promoting gene in cancer cells)

- EGFR-inhibiting drugs (e.g., gefitinib, erlotinib) found to be helpful in treating tumors with EGFR gene mutations

- Other promising therapeutic targets have been identified (e.g., EML4-ALK, KRAS and MET), with drugs directed against these proteins being tested in clinical trials.

- The discovery datasets used were mostly white

Example of Non-Small Cell Lung Cancer (NSCLC)
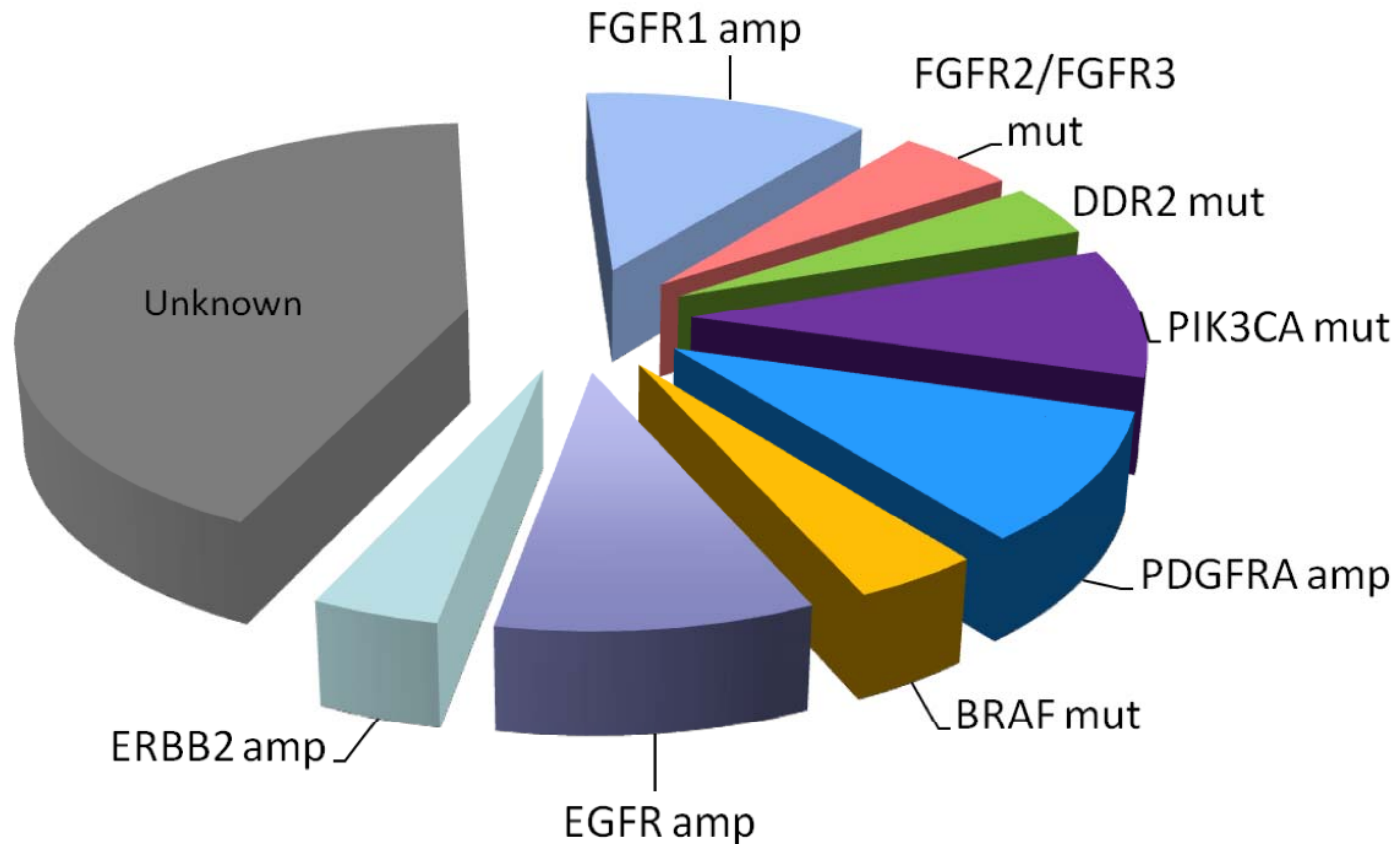
Molecular subsets of lung adenocarcinoma. Pie chart showing the percentage distribution of clinically relevant driver mutations identified to date in individuals with lung adenocarcinoma. The newly identified KIF5B-RET fusion subset, which accounts for approximately 1% of this distribution, is boxed. NRAS, neuroblastoma RAS viral (v-ras) oncogene homolog; MAP2K1, mitogen-activated protein kinase kinase 1; AKT1, v-akt murine thymoma viral oncogene homolog 1; PIK3CA, phosphoinositide-3-kinase, catalytic, α polypeptide; BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER2, human epidermal growth factor receptor 2; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog. (Pao W. E. and Hutchinson K. E. *Nature*. 2012)

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Replication Research in Diverse Populations

- Matthew Meyerson's Project: "Racial" Differences in Lung Adenocarcinoma Mutations

- Our Supplement: Improving Treatment for Black Lung Cancer Patients: Perspectives of the Providers Who Serve Them

Overview

II) Ensuring equitable access to novel treatments in clinical practice

 a. Equitable access to novel, effective treatments

 b. Making health plans accountable

Racial/SES Differences in *BRCA1/2* Testing in a Nationally-Insured Population

- **Large National Insurer** (15M covered lives)
- 2004-2007 Data (medical claims, prescriptions, demographics)
- Inclusion Criteria
  - Age 20-64
  - 3+ months continuous enrollment prior to initial cancer treatment
  - No Medicare
  - No personal history of cancer prior to first treatment date
- **Breast Cancer Denominator (n=14,320)**
  - All women with breast cancer diagnosis
  - Some form of treatment (chemo/radiation/surgery)
  - 6 month clean period/6 month treatment period
- Identified patients who had genetic test related to breast cancer (all covered by insurance)

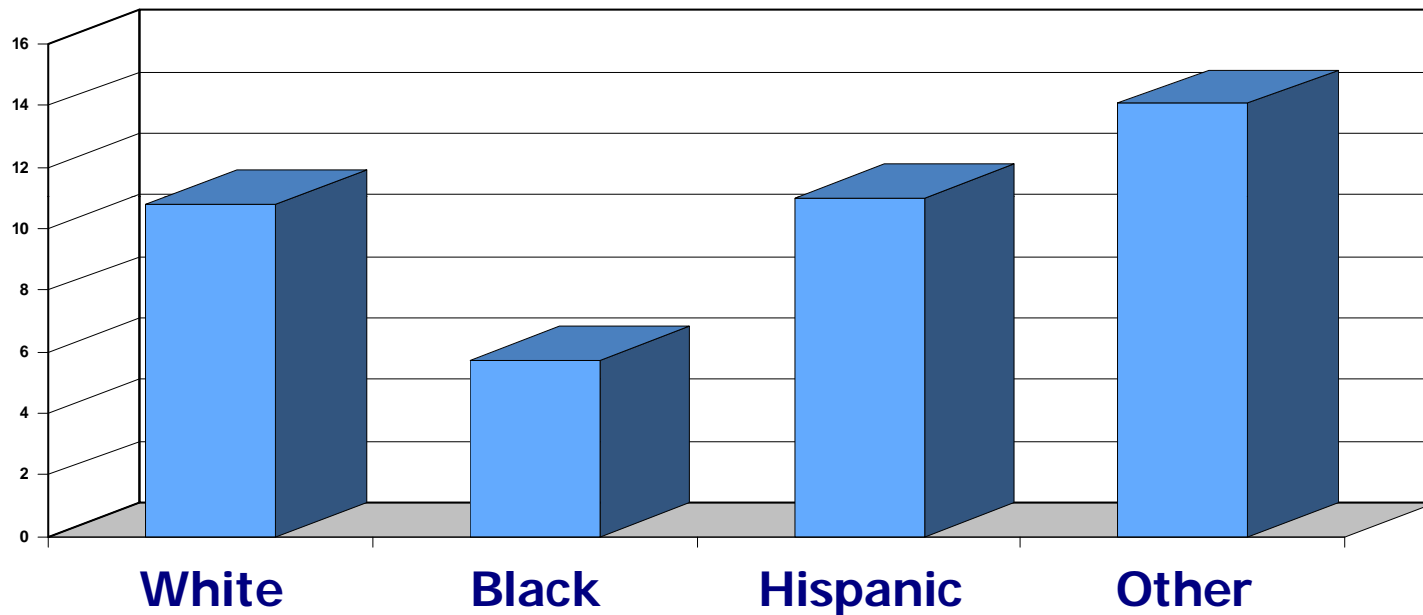Levy et al. Underutilization of *BRCA1/2* testing to guide breast cancer treatment: black and hispanic women particularly at risk. *Genetics in Medicine*. 2011;13(4):349-55.

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Results

	Female Breast Cancer (BC)
Incident Cases	**14,235**
Proportion of Cancer Patients ≤40 Receiving *BRCA1/2* Testing	**30**%

Levy et al. Underutilization of *BRCA1/2* testing to guide breast cancer treatment: black and hispanic women particularly at risk. *Genetics in Medicine*. 2011;13(4):349-55.

Utilization of *BRCA1/2* Testing among Incident BC Cases (age 40 or less)

Received Test (%)

Race/Ethnicity

White   Black   Hispanic   Other

Levy et al. Underutilization of *BRCA1/2* testing to guide breast cancer treatment: black and hispanic women particularly at risk. *Genetics in Medicine*. 2011;13(4):349-55.

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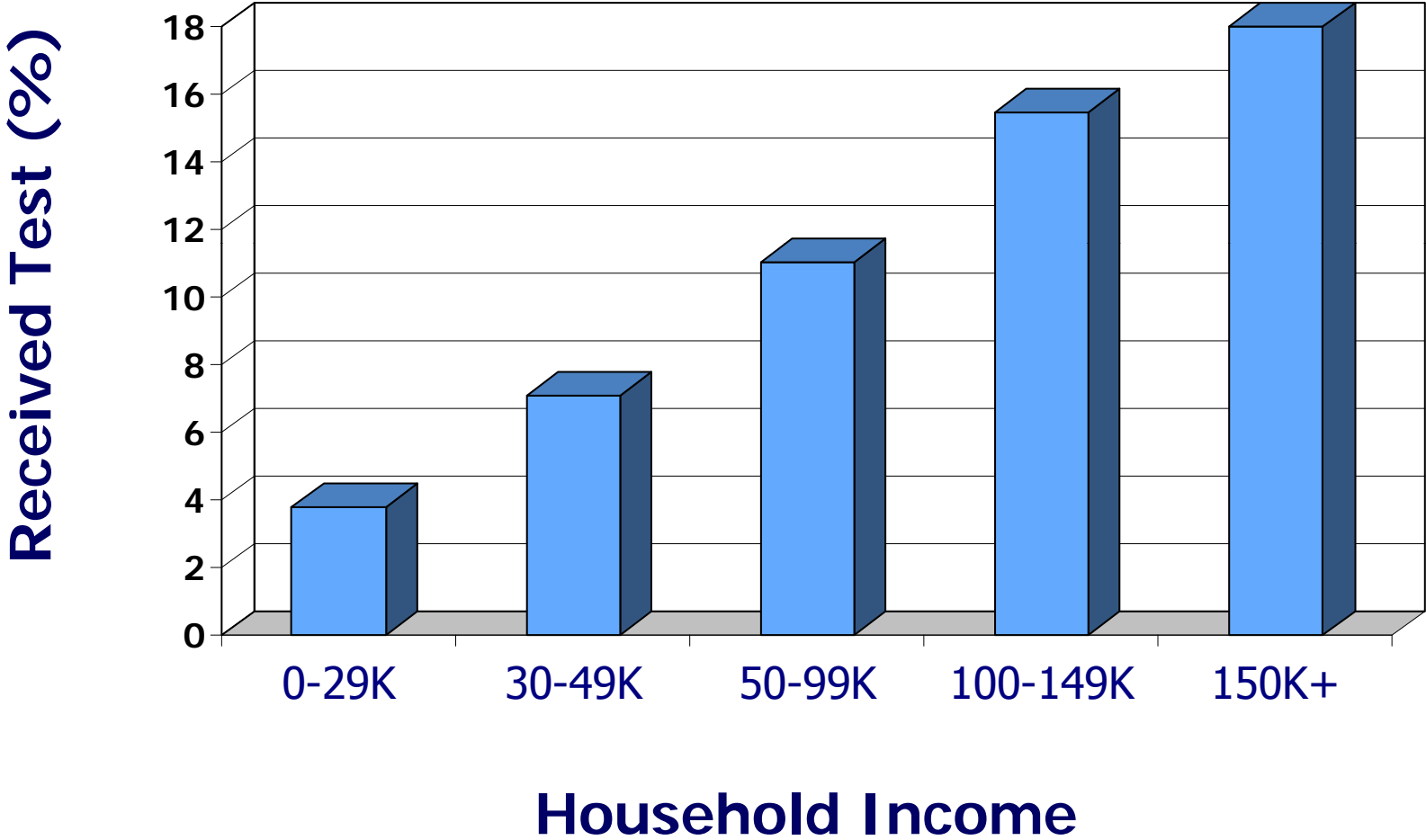# Utilization of *BRCA1/2* Testing (age 40 or less)

(within same plan; all covered)

Levy et al. Underutilization of *BRCA1/2* testing to guide breast cancer treatment: black and hispanic women particularly at risk. *Genetics in Medicine*. 2011;13(4):349-55.
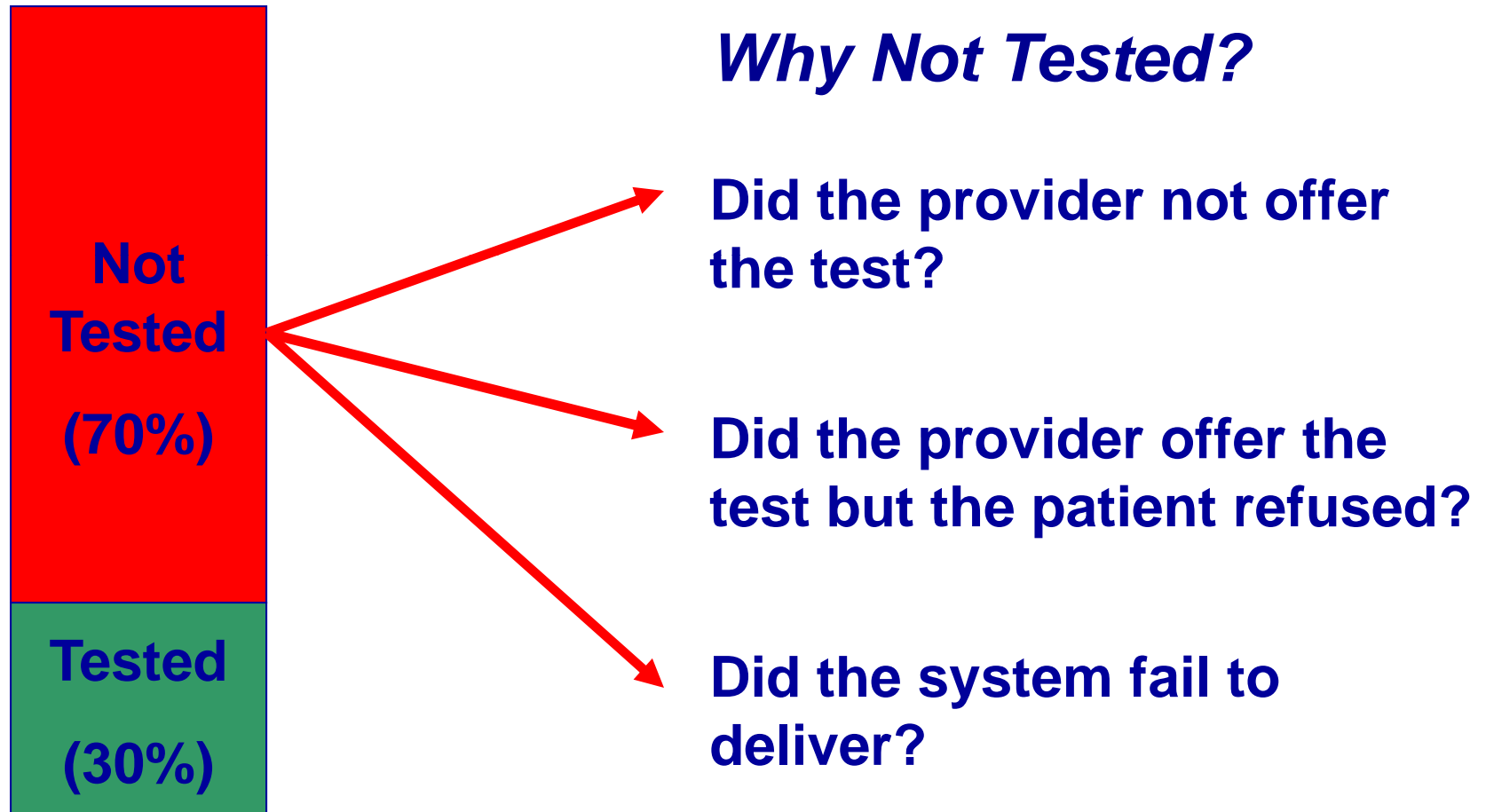
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Understanding *BRCA1/2* Testing Underutilization Among High-Risk Women

Why Not Tested?

Did the provider not offer the test?

Did the provider offer the test but the patient refused?

Did the system fail to deliver?

Not Tested (70%)

Tested (30%)

Levy et al. Guidelines for Genetic Risk Assessment of Hereditary Breast and Ovarian Cancer: Early Disagreements and low Utilization. *Journal of General Internal Medicine*. 2009; 24(7):822-8.

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Minority-Serving Physicians' Experience Ordering a Genetic Test

(N=2000; Response Rate: 62.3%)

	Breast Cancer N=938	Colon Cancer N=938	Any Genetic Test N=944
High Minority	.42**	0.39**	0.67
High Medicaid	1.15	1.59	0.96

* p<0.05, ** p<0.01

Note: Controlling for physician age, self reported race, region, practice setting (independent practice versus those practicing in a health maintenance organization, hospital-based practice, community health center or other setting), training in genetics.

Shields et al. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. *Genetics in Medicine*. 2008; 10(6): 404-414.

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Minority-Serving Physicians' Experience Referring Patients for a Genetic Test

	Ever Referred to Genetics Center or Counselor	Ever Referred to Specialist	Ever Referred to a Clinical Trial	Any Site of Care
	N=943	N=941	N=934	N=945
High Minority	0.73	0.63	0.46*	0.60*
High Medicaid	0.58*	0.64	1.04	0.49**

* p<0.05, ** p<0.01

Note: Also included in model but not shown: physician age, self reported race, region, practice setting (independent practice versus those practicing in a health maintenance organization, hospital-based practice, community health center or other setting), experience with genetic education.

Shields et al. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. *Genetics in Medicine.* 2008; 10(6): 404-414.

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2006 National Survey of CHCs
(N=672; response rate: 80%)

Provision* of Genetic Testing

	N	%
Provides Genetic Counseling	28	4.3%
Provides Any Testing	73	11.7%
Breast Cancer	32	5.3%
Colorectal Cancer	34	5.5%

* Provided and covered by CHC or elsewhere

N= 917 (727 responded; excluded: 55 homeless or migrant only; final N=672)

Shields et al. 2011 (Unpublished data)

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