Cervical Cancer: How can we overcome our history?

BJ Rimel, MD

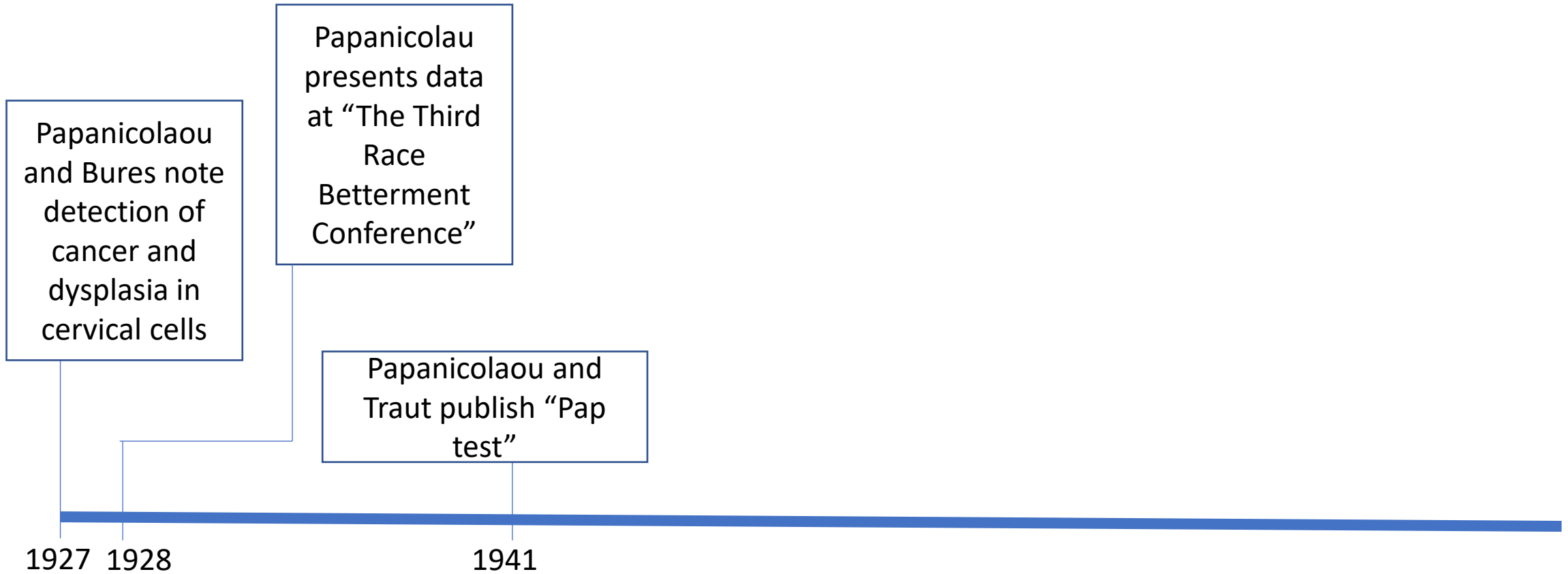**Associate Professor, Gynecologic Oncology**

Cedars Sinai Medical Center

October 20, 2021

Los Angeles, CA

Disclosures:

- Advisory Board participation: GSK/Tesaro, Merck, AstraZeneca
- Consultant: Deep6AI

National Institutes of Health
Office of Research on Women's Health

Cervical cancer- a brief history of screening

1927 — Papanicolaou and Bures note detection of cancer and dysplasia in cervical cells

1928 — Papanicolau presents data at "The Third Race Betterment Conference"

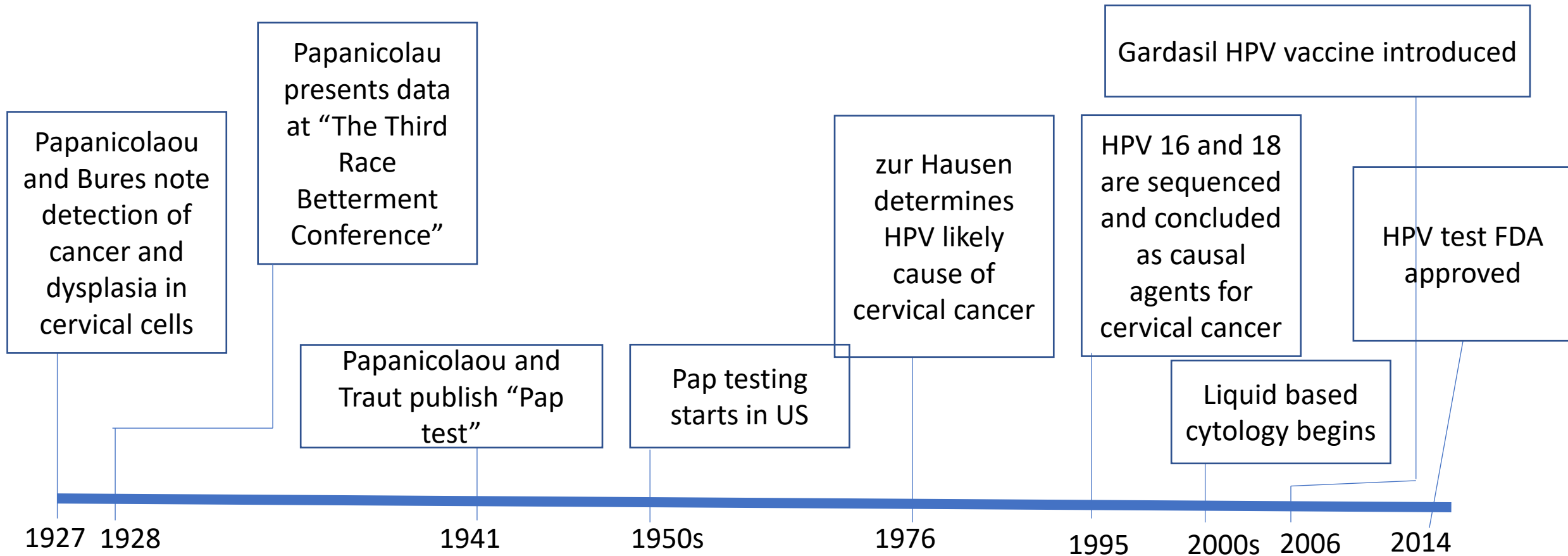**1941** — Papanicolaou and Traut publish "Pap test"

The Shero behind the pap smear

Mrs. Andromahi Papanicolaou

- Worked with her husband in pathology laboratory at Cornell
- Underwent daily Pap smears for 20 years

Cervical cancer- a brief history of screening

Papanicolaou and Bures note detection of cancer and dysplasia in cervical cells

Papanicolau presents data at "The Third Race Betterment Conference"

Papanicolaou and Traut publish "Pap test"

Pap testing starts in US

zur Hausen determines HPV likely cause of cervical cancer

HPV 16 and 18 are sequenced and concluded as causal agents for cervical cancer

Gardasil HPV vaccine introduced

HPV test FDA approved

Liquid based cytology begins

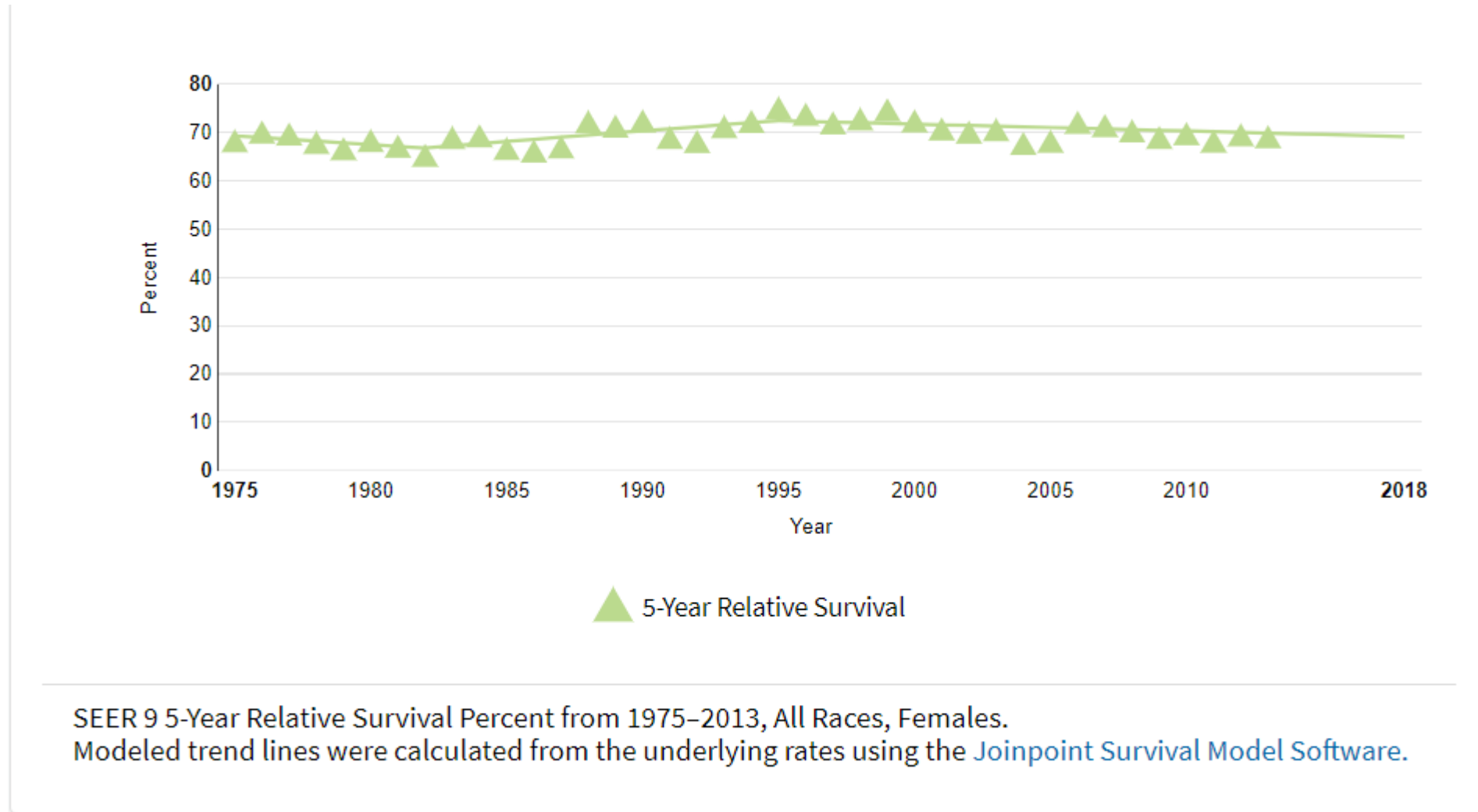1927   1928   1941   1950s   1976   1995   2000s 2006   2014
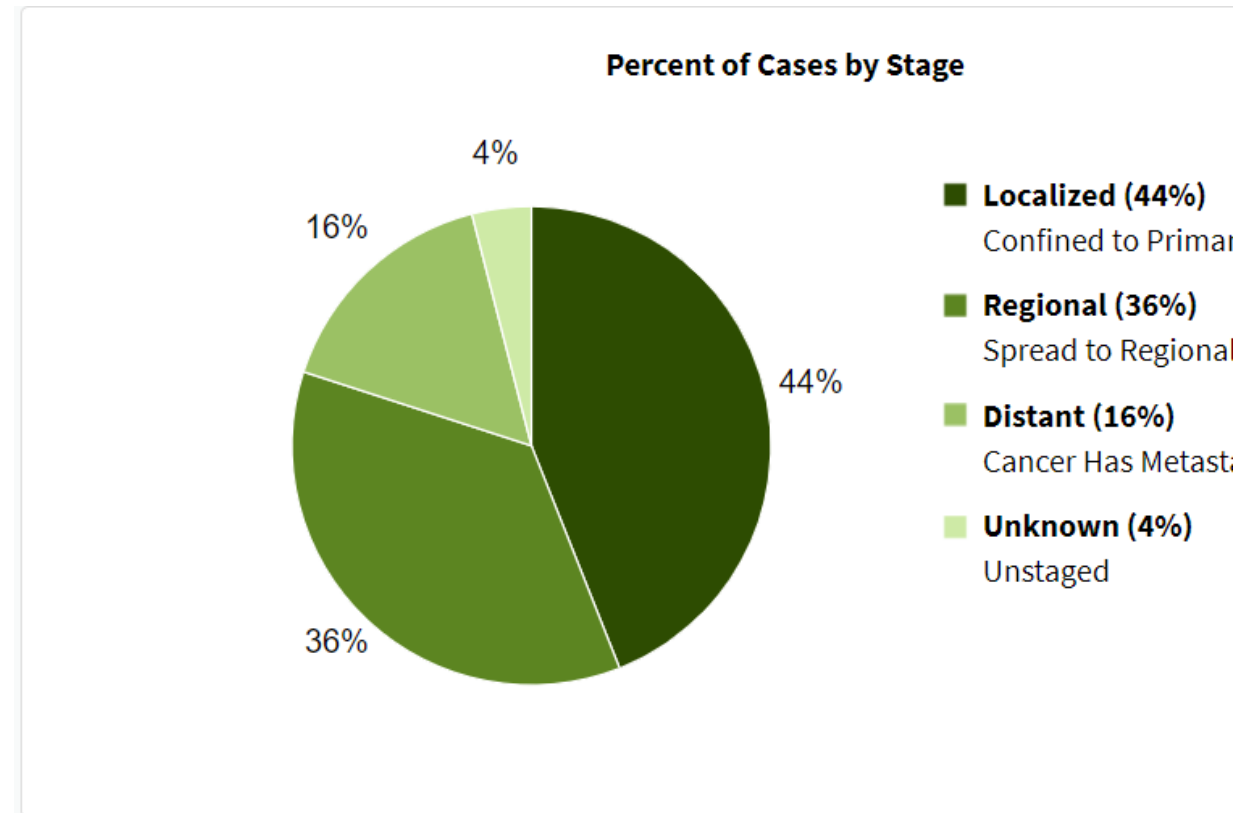
5

Cervical cancer incidence was reduced by screening

14.81 per 100,000 in 1975

6.67 per 100,000 in 2018

Cervical cancer mortality did not decrease

SEER 9 5-Year Relative Survival Percent from 1975–2013, All Races, Females.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Survival Model Software.

Stage of disease dictates cure

5-Year Relative Survival

Localized: 91.9%
Regional: 58.2%
Distant: 17.6%
Unknown: 52.4%

Percent of Cases by Stage

- Localized (44%) — Confined to Primar...
- Regional (36%) — Spread to Regional...
- Distant (16%) — Cancer Has Metast...
- Unknown (4%) — Unstaged

44%
36%
16%
4%

SEER 18 2011–2017, All Races, Females by SEER Summary Stage 2000
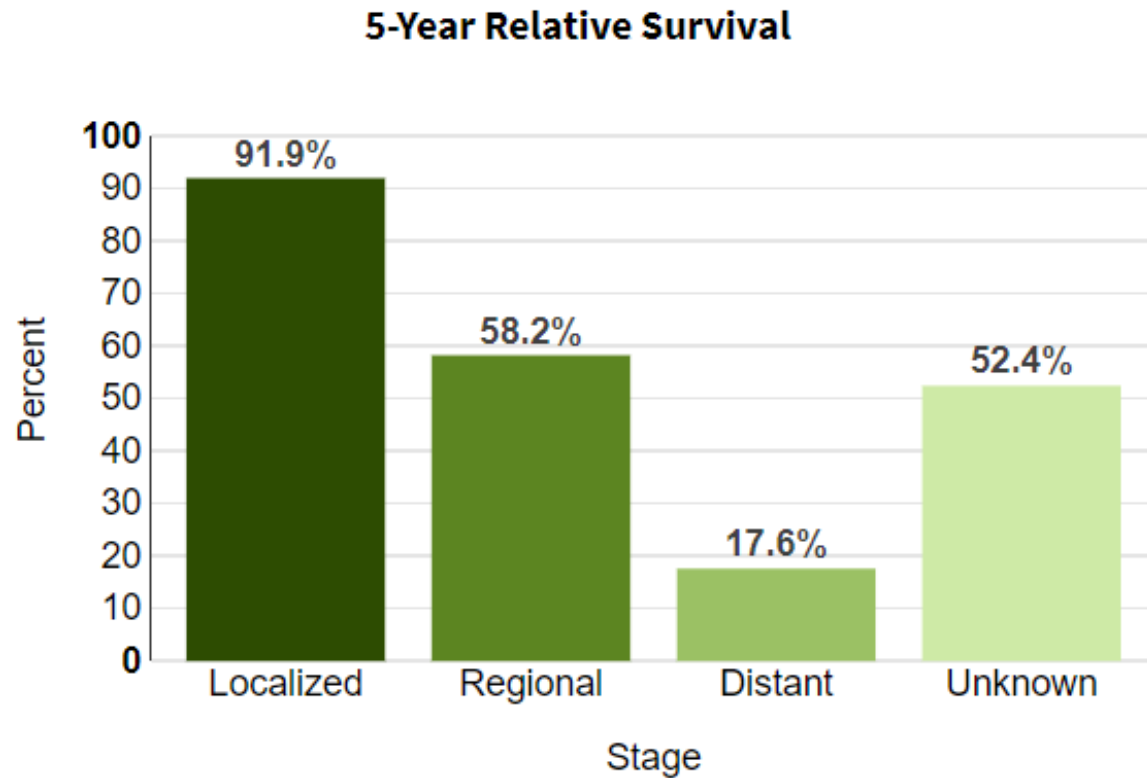
Rate of New Cases per 100,000 Persons by Race/Ethnicity: Cervical Cancer

	MALE		FEMALE
Sex-specific cancer type		All Races	7.5
		White	7.3
		Black	8.6
		Asian / Pacific Islander	6.4
		American Indian / Alaska Native	7.6
		Hispanic	9.3
		Non-Hispanic	7.1
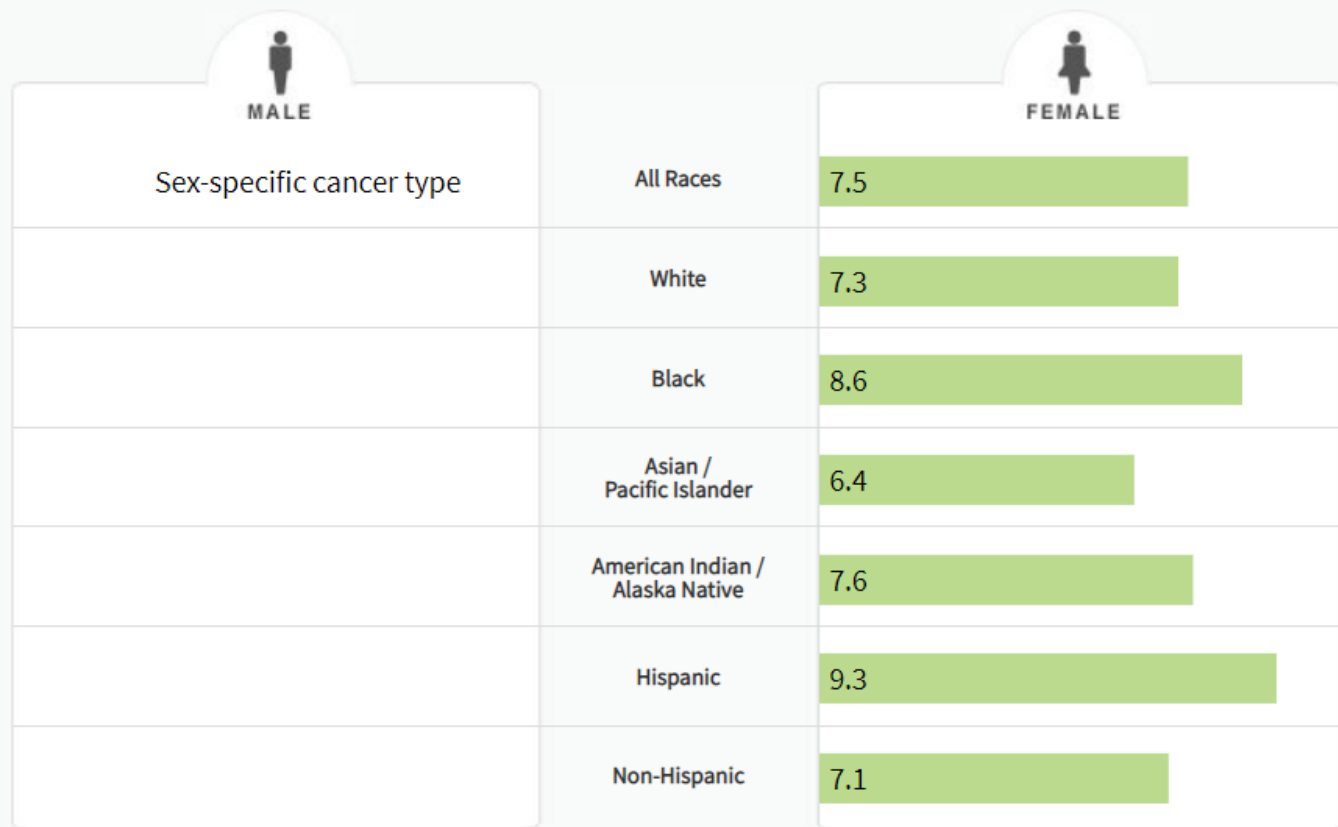
SEER 21 2014–2018, Age-Adjusted

Death Rate per 100,000 Persons by Race/Ethnicity: Cervical Cancer

Sex-specific cancer type		MALE	FEMALE
	All Races		2.2
	White		2.1
	Black		3.3
	Asian / Pacific Islander		1.7
	American Indian / Alaska Native		2.4
	Hispanic		2.6
	Non-Hispanic		2.2
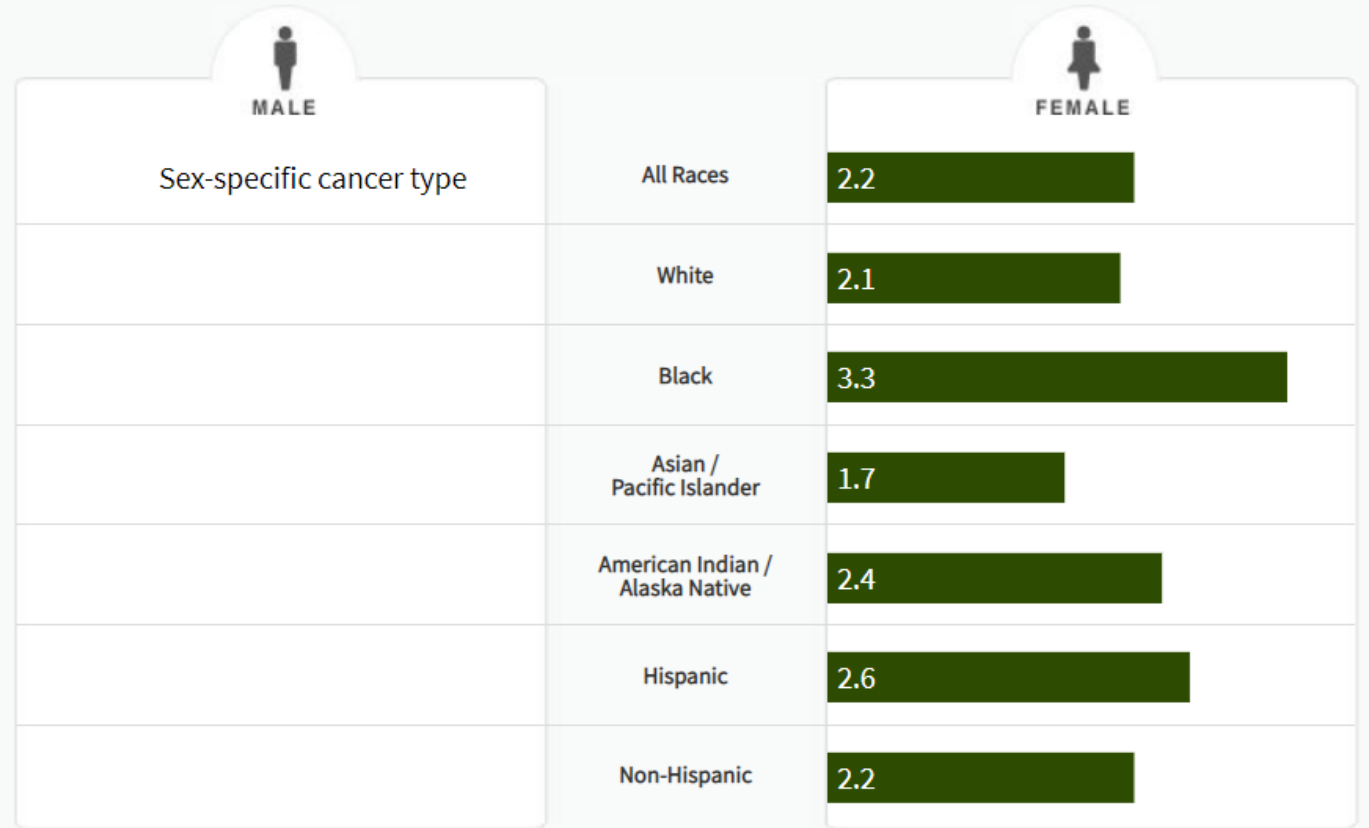
U.S. 2014–2018, Age-Adjusted

Treatment for advanced stage disease remains palliative

Sentinel phase III GOG clinical trials in recurrent cervical cancer (30–35, 39,40)

Protocol	Chemotherapy	N	RR	CR	PR	PFS (mos)	OS (mos)
GOG 43	CP 50mg/m2 D1	150	20.7%	10%	10.7%	3.7	7.1
	CP 100mg/m2 D1	166	31.4%*	12.7%	18.7%	4.6	7.0
	CP 20mg/m2 D1–5	128	25%	8.6%	16.4%	3.9	6.1
GOG 110	CP	140	17.8%	6.4%	11.4%	3.2	8.0
	CP + I	151	31.1%*	12.6%	18.5%	4.6*	8.3
	CP + M	147	21.1%	9.5%	11.6%	3.3	7.3
GOG 149	CP+I	146	32.0%	NR	NR	4.6	8.5
	CP+I+B	141	31.2%	NR	NR	5.1	8.4
GOG 169	CP	134	19%	6%	13%	2.8	8.8
	CP+P	130	35%*	15%	21%	4.8*	9.7
GOG 179	CP	146	13%	2.9%	10.1%	2.9	6.5
	CP+T	147	26.7%*	10.4%	16.3%	4.6*	9.4*
GOG 204	CP+P	103	29.1%	2.9%	26.2%	5.8	12.9
	CP+T	111	23.4%	1.8%	21.6%	4.6	10.3
	CP+G	112	22.3%	0.9%	21.4%	4.7	10.3
	CP+V	108	25.9%	7.4%	18.5%	4.0	10.0
GOG 240	CP+P+Bev	115	50%	16%	35%	8.2*	17.5*
	CP+P	114	46%	10%	36%	6.0°	15.0
	T+P+Bev	112	48%	12%	37%		16.2
	T+P	111	25%	5%	20%		12.0

Novel agents in cervical cancer suggest improvement is possible

- Cemiplimab improved OS compared to investigators choice chemotherapy in recurrent cervical cancer (EMPOWER-Cervical1/GOG-3016/ENGOT-cx9)
  - 12 months vs. 8.5 months (HR 0.69 (95% CI 0.56-0.84)
- Tisotumab vedotin – recurrent cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6)
  - ORR 24%, median duration of response 8.4 months
- Pembrolizumab +platinum/paclitaxel +/-bevacizumab in advanced stage chemo naïve cervical cancer (KEYNOTE-826 trial)
  - Met its primary PFS and OS endpoints (Merck press release)

How can we address both equity and therapy?

- Can we design trials for patients that will improve cervical cancer mortality for ALL those in the United States?

- We must ask ourselves the hard questions.

Characteristic	Category	Total	Chemotherapy Alone N (%)	Chemotherapy plus Bevacizumab N (%)	P value
Ethnicity	Hispanic	54	33 (15)	21 (9)	0.2316
	Non-Hispanic	374	183 (81)	191 (84)	
	Unknown/Unsp.	24	13 (6)	11 (5)	
Race	Asian	19	11 (5)	8 (4)	0.7409
	Black	60	30 (13)	30 (13)	
	Amer. Indian	5	2 (1)	3 (1)	
	Pacific Islander	1	1 (0)	0 (0)	
	White	351	179 (80)	172 (76)	
	Unknown/Unsp.	16	6 (3)	10 (4)	

Tewari et al NEJM Feb 20 2014

What are the opportunities to do better?

Traditional clinical trial design

Reality

Rare Disease

- Treat it like a rare disease

Address structural racism

- Create clinical trials that address the inequities of participation

Cervical cancer affects low SES patients

- Create opportunities for patients who need tangible stuff to participate

Location matters

- Urban solutions are not the same as rural solutions

Feasibility

Structural

- Where are humans with cervical cancer?
- Where do they get their care?
- Do these centers open cervical cancer trials?
- If not, why? Cost? Lack of enrollment (insurance coverage/language/trust)?

Trial specific

- Are the inclusion criteria representative of a population that exists in sufficient quantity to study?
- Is there testing required for screening that has a significant time or requires multiple visits?
- Is there a role for a smaller or broader study?

Rare disease

- 13,800 newly diagnosed cervical cancer cases estimated in 2020.

- 4290 deaths due to cervical cancer

- Context: Myeloma cases in women estimated 14,740 in 2020

- Included on National Organization for Rare disorders.

- Cervical cancer is not.

Rare disease Magnets

- Registries
  - Large national well-annotated datasets

- Support groups-local and national and VIRTUAL

- Strategies utilizing electronic medical record data to screen populations in real time.

- Data sharing

Address structural racism

- "Diversity is silent on the subject of equity. In an anti-oppression context, therefore the issue is not diversity but rather equity. Often when people talk about diversity, they are thinking of only the non-dominant groups." – Baltimore Racial Justice Action

EQUALITY

EQUITY

https://dialectic.solutions/blog-posts/equity-vs-equality-whats-the-difference/
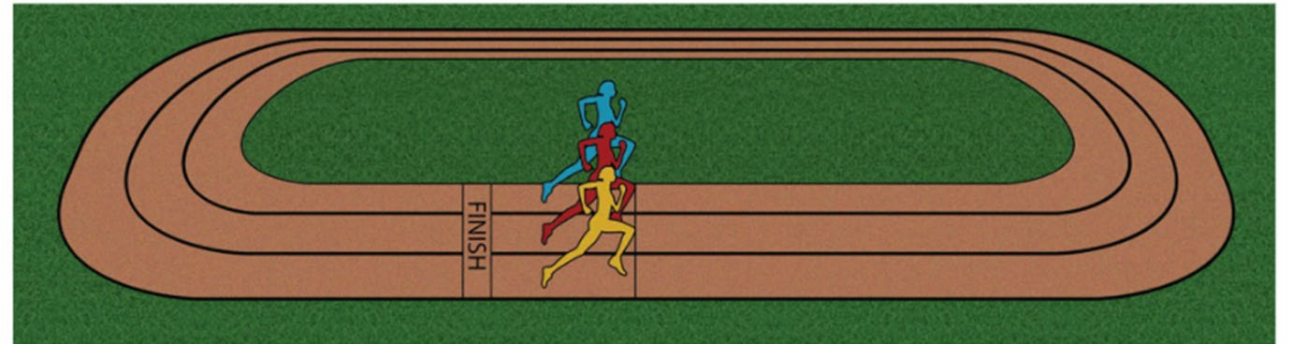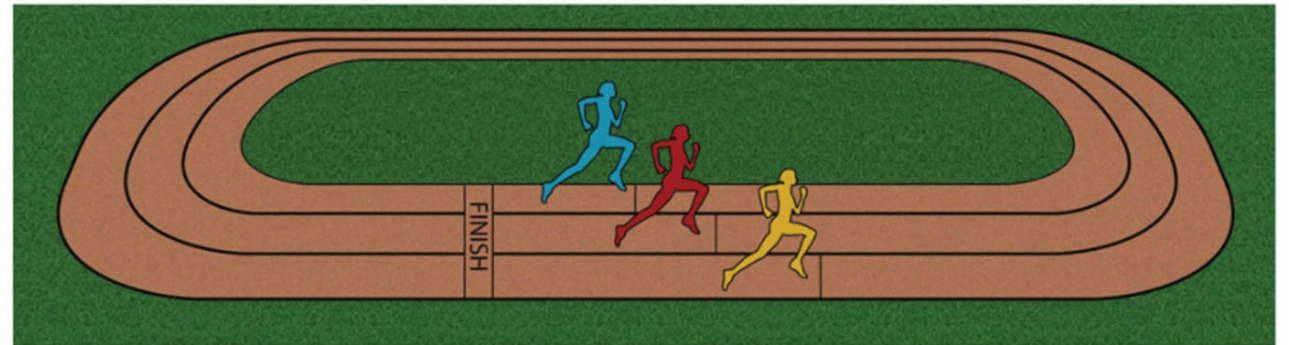
UC Berkeley Center for Equity, Inclusion and Diversity, "Glossary of Terms" (page 34 in 2009 Strategic Plan). Baltimore Racial Justice Action, "Our Definitions" (2018).

Rate of New Cancers in the United States
Cervix, All Ages, All Races and Ethnicities, Female

Rate per 100,000 people

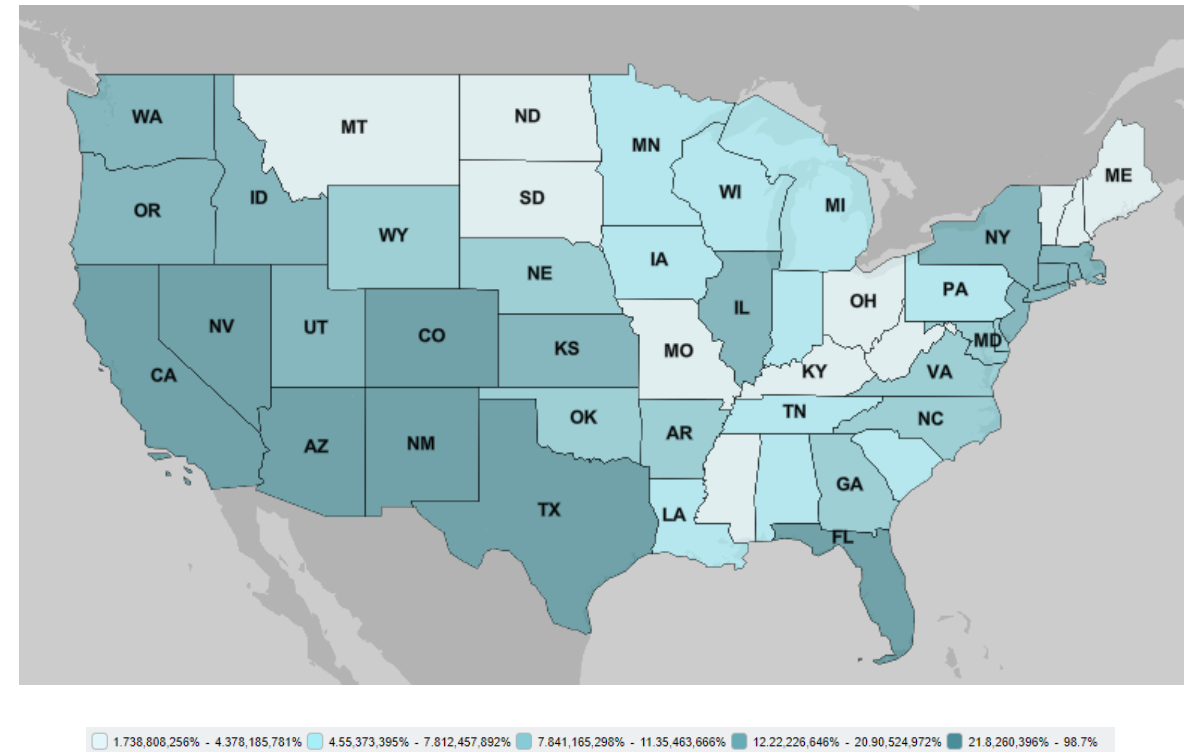| No data/data suppressed | 4.3 - 6.0 | 6.1 - 7.4 | 7.5 - 8.5 | 8.7 - 10.8 |

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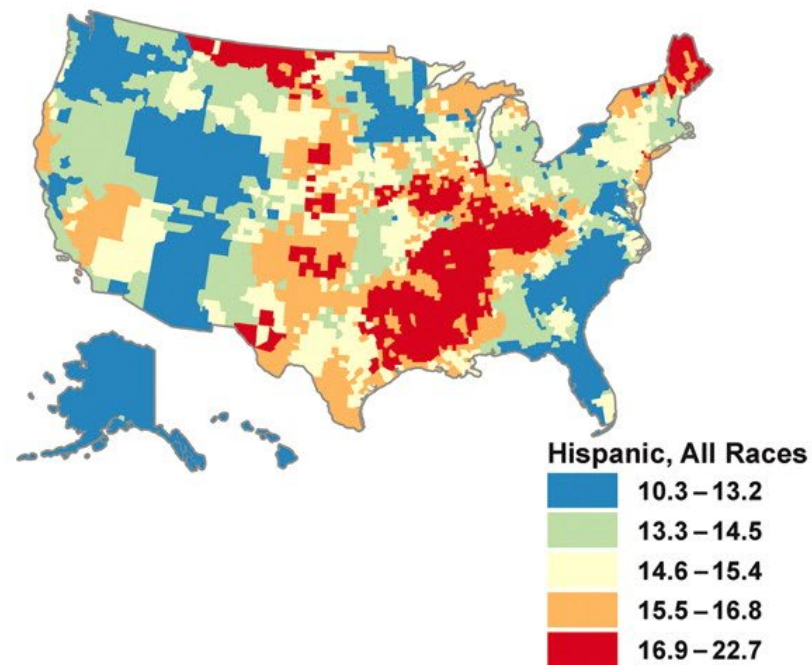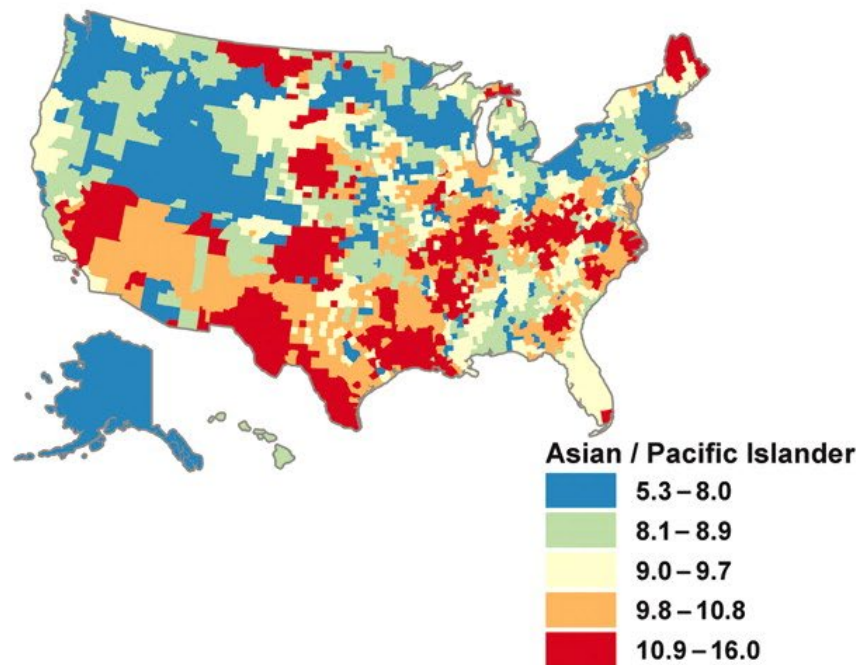| No data/data suppressed | 4.3 - 6.0 | 6.1 - 7.4 | 7.5 - 8.5 | 8.7 - 10.8 |
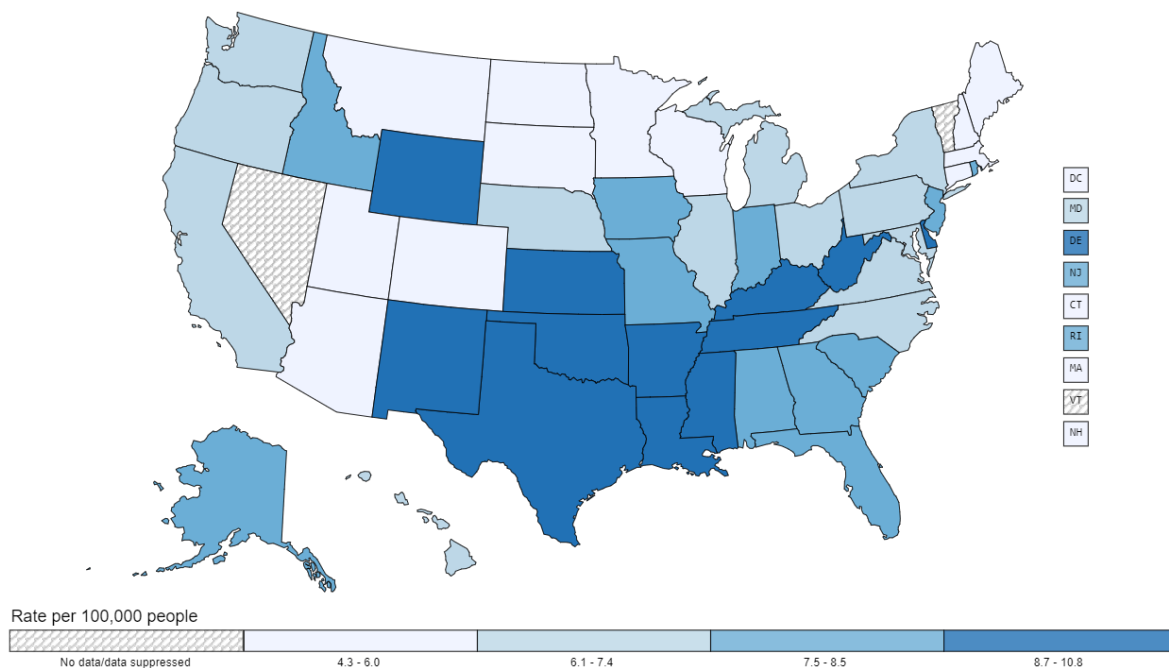
U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021

US Census 2016: Black or African American alone, Percent
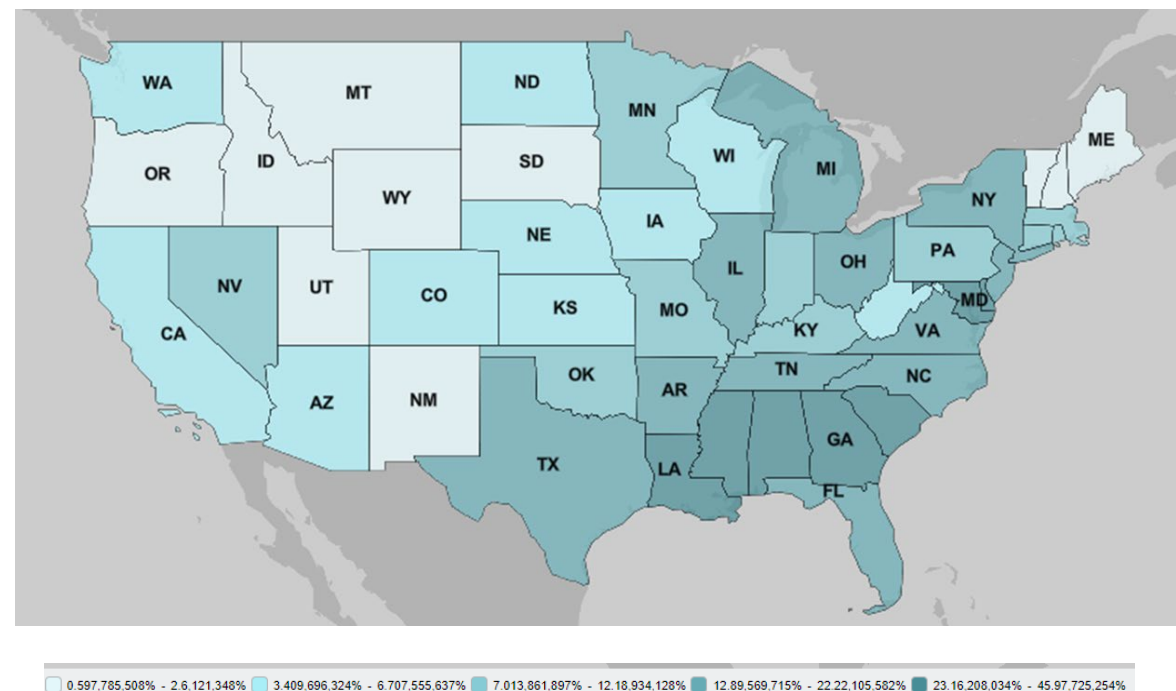
| 0.597,785,508% - 2.6,121,348% | 3.409,696,324% - 6.707,555,637% | 7.013,861,897% - 12.18,934,128% | 12.89,569,715% - 22.22,105,582% | 23.16,208,034% - 45.97,725,254% |

https://www.census.gov/quickfacts/fact/map/US/RHI225219

Rate of New Cancers in the United States
Cervix, All Ages, All Races and Ethnicities, Female

Rate per 100,000 people

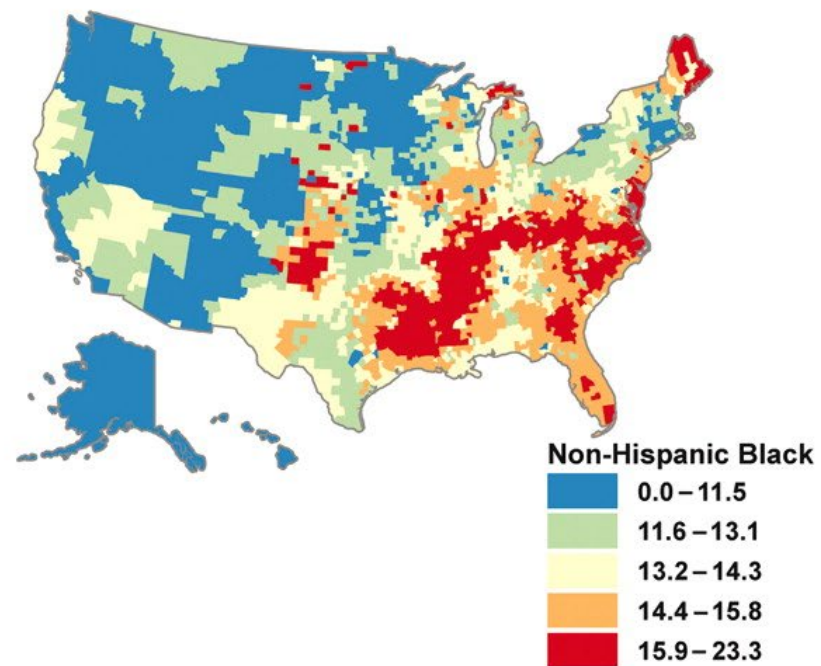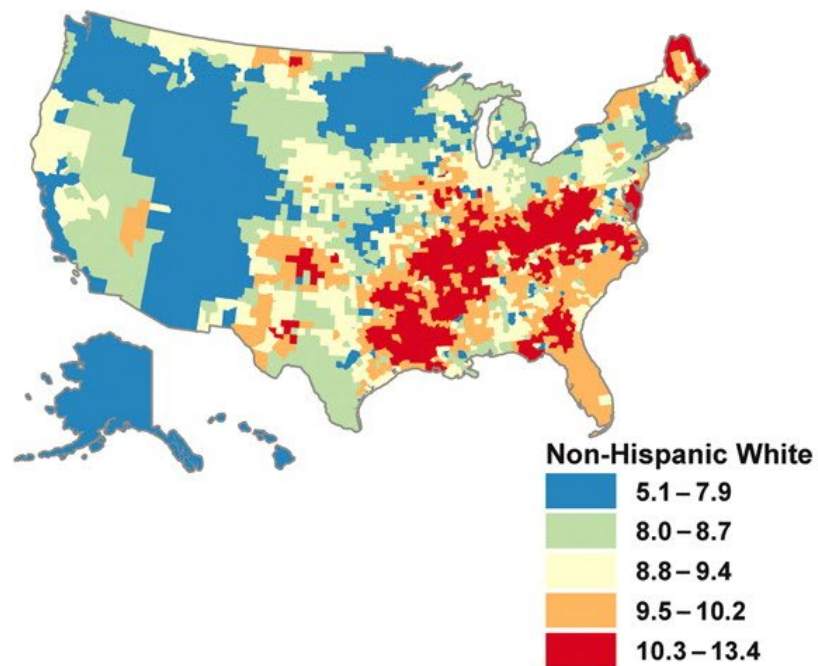| No data/data suppressed | 4.3 - 6.0 | 6.1 - 7.4 | 7.5 - 8.5 | 8.7 - 10.8 |
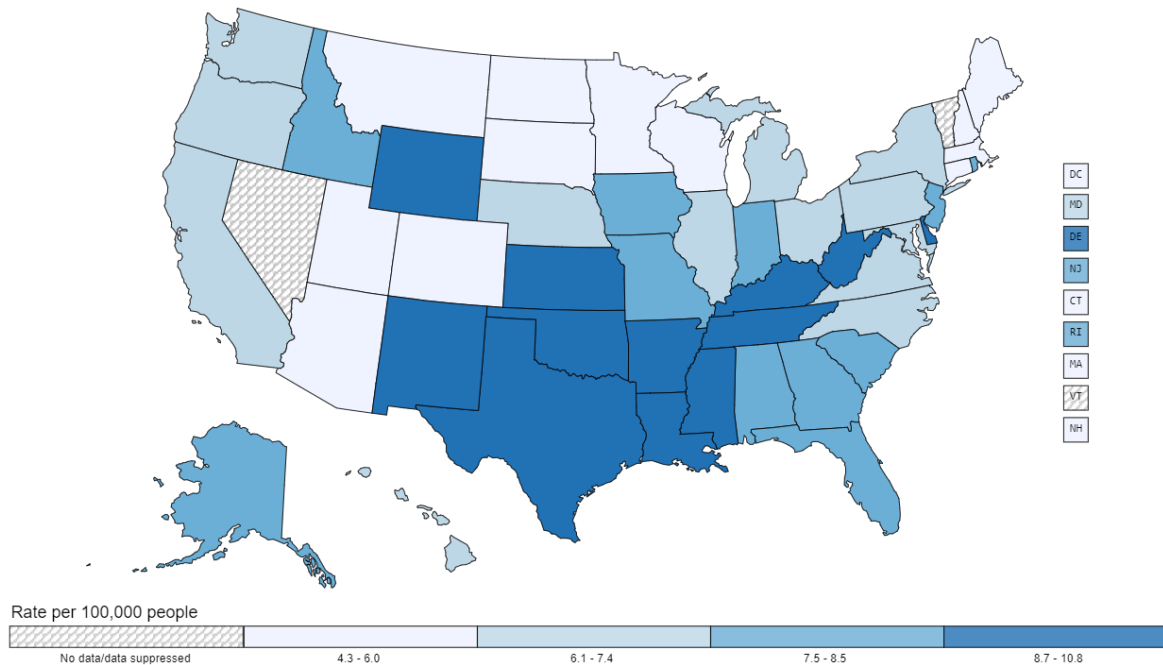
U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021

US Census 2016: Hispanic or Latino, percent

| 1.738,808,256% - 4.378,185,781% | 4.55,373,395% - 7.812,457,892% | 7.841,165,298% - 11.35,463,666% | 12.22,226,646% - 20.90,524,972% | 21.8,260,396% - 98.7% |

https://www.census.gov/quickfacts/fact/map/US/RHI7252 19

Geographic distributions of estimated U.S. cervical cancer incidence rates among racial and ethnic groups by county, 1995 to 2004

Non-Hispanic White
- 5.1 – 7.9
- 8.0 – 8.7
- 8.8 – 9.4
- 9.5 – 10.2
- 10.3 – 13.4

Non-Hispanic Black
- 0.0 – 11.5
- 11.6 – 13.1
- 13.2 – 14.3
- 14.4 – 15.8
- 15.9 – 23.3

Asian / Pacific Islander
- 5.3 – 8.0
- 8.1 – 8.9
- 9.0 – 9.7
- 9.8 – 10.8
- 10.9 – 16.0

Hispanic, All Races
- 10.3 – 13.2
- 13.3 – 14.5
- 14.6 – 15.4
- 15.5 – 16.8
- 16.9 – 22.7

U.S. Geographic Distribution of Prevaccine Era Cervical Cancer Screening, Incidence, Stage, and Mortality Marie-Josèphe Horner, Sean F. Altekruse, Zhaohui Zou, Louise Wideroff, Hormuzd A. Katki and David G. Stinchcomb Cancer Epidemiol Biomarkers Prev April 1 2011 (20) (4)

Poverty in the United States

Percentage of people in poverty by state: 2015

Percent

- 18.0 or more
- 16.0 to 17.9
- 13.0 to 15.9
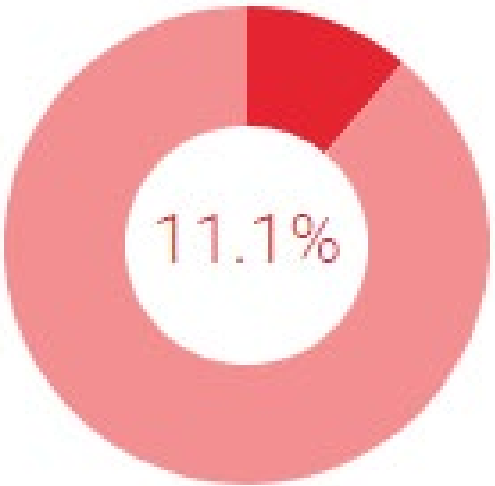- 11.0 to 12.9
- Less than 11.0

U.S. percentage is 14.7
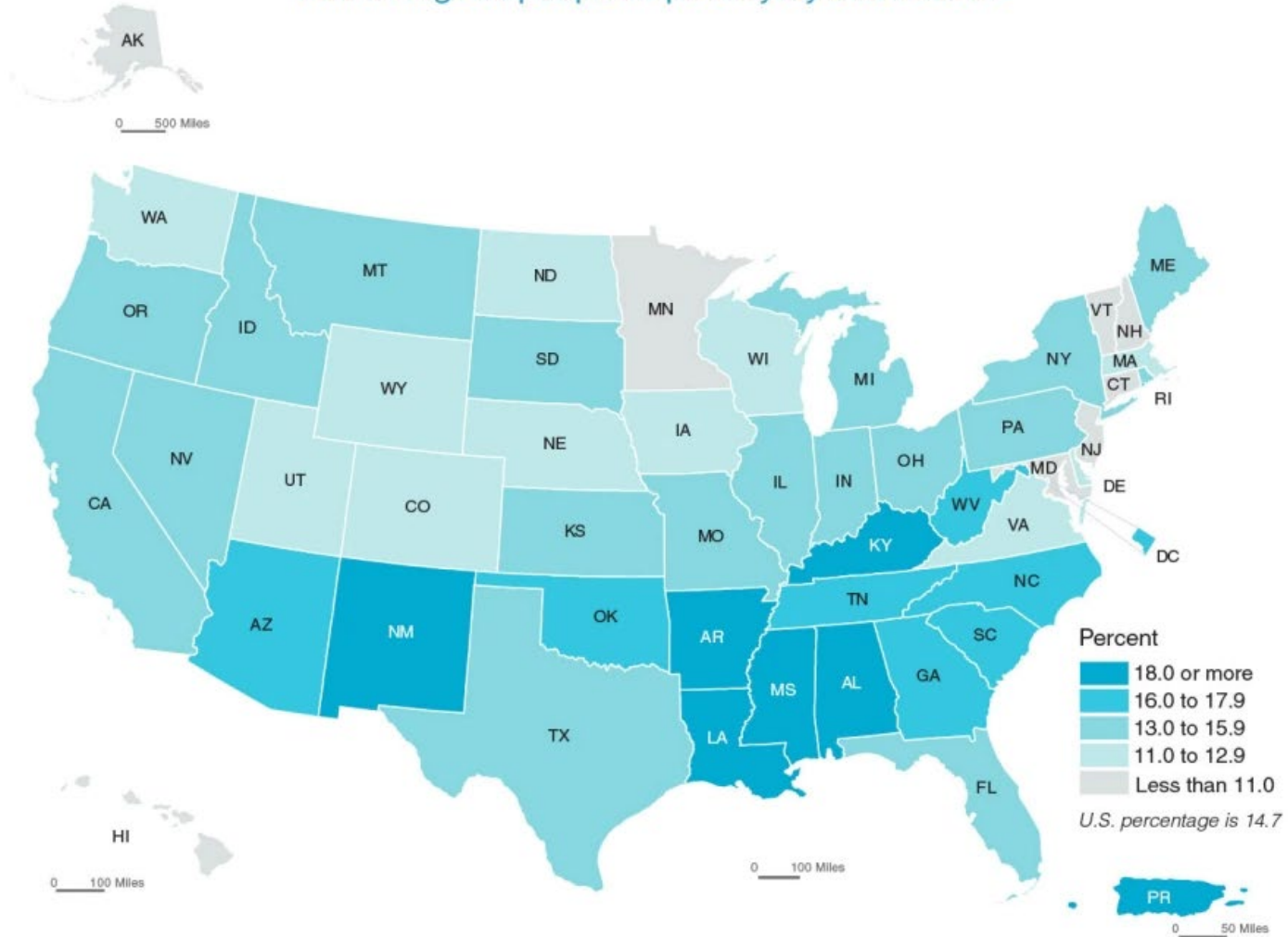
Note: U.S. percentage does not include data for Puerto Rico.

Rate of New Cancers in the United States
Cervix, All Ages, All Races and Ethnicities, Female

Rate per 100,000 people

No data/data suppressed | 4.3 - 6.0 | 6.1 - 7.4 | 7.5 - 8.5 | 8.7 - 10.8
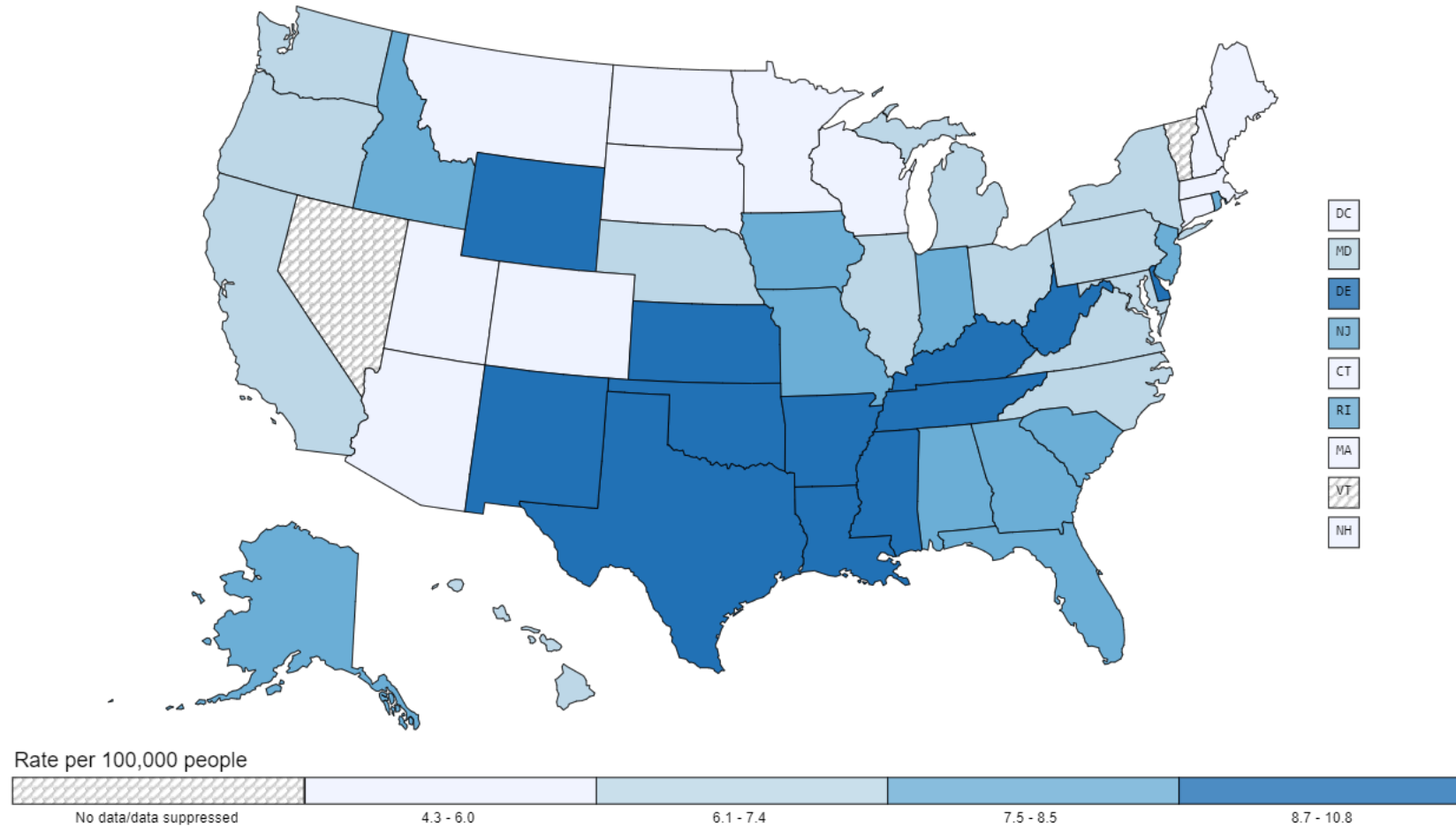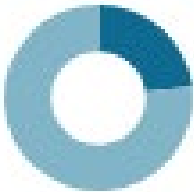
Percent in Poverty by Race
Povertyusa.org/data/2019

11.1%
White

Hispanic
19.6%

Black
23.0%
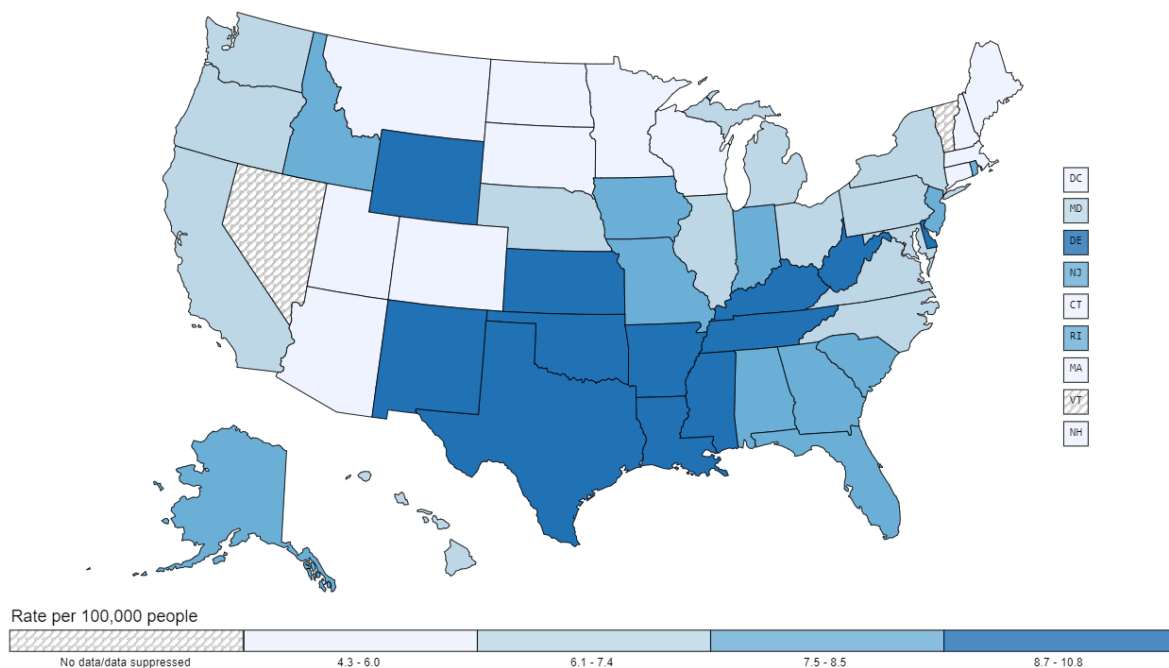
Asian
10.9%

Native American
24.9%

Low English fluency is a barrier to clinical trial enrollment

- In-person translation is essential for consent
  - Hospital based translator services are strongly preferred
  - Clinical trial budgets must reflect this requirement

- Patient reported outcomes need to be in the patient's preferred language
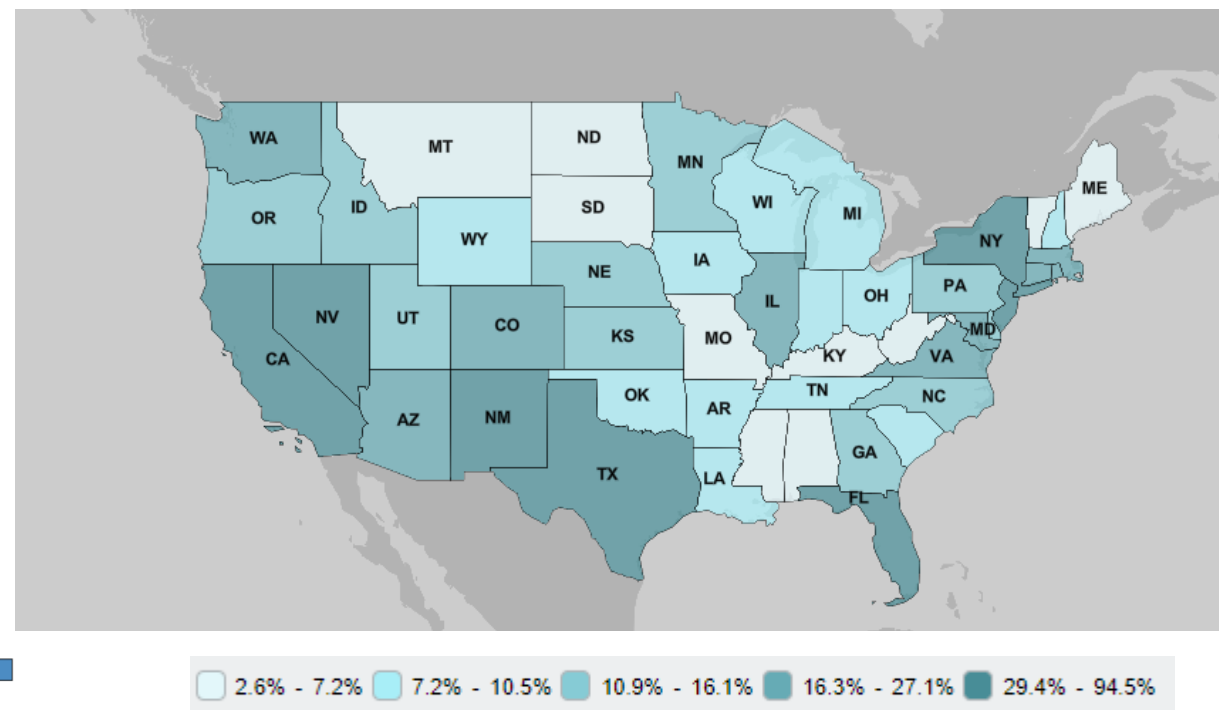 - *This includes online content!!*

Squires A, Sadarangani T, Jones S. Strategies for overcoming language barriers in research. *J Adv Nurs*. 2020;76(2):706-714. doi:10.1111/jan.14007

Staples, J.N., Lester, J., Li, A. *et al.* Language as a barrier to cancer clinical trial accrual: assessing consenting team knowledge and practices for cancer clinical trial consent among low English fluency patients. *Appl Cancer Res* **38,** 14 (2018)

Rate of New Cancers in the United States
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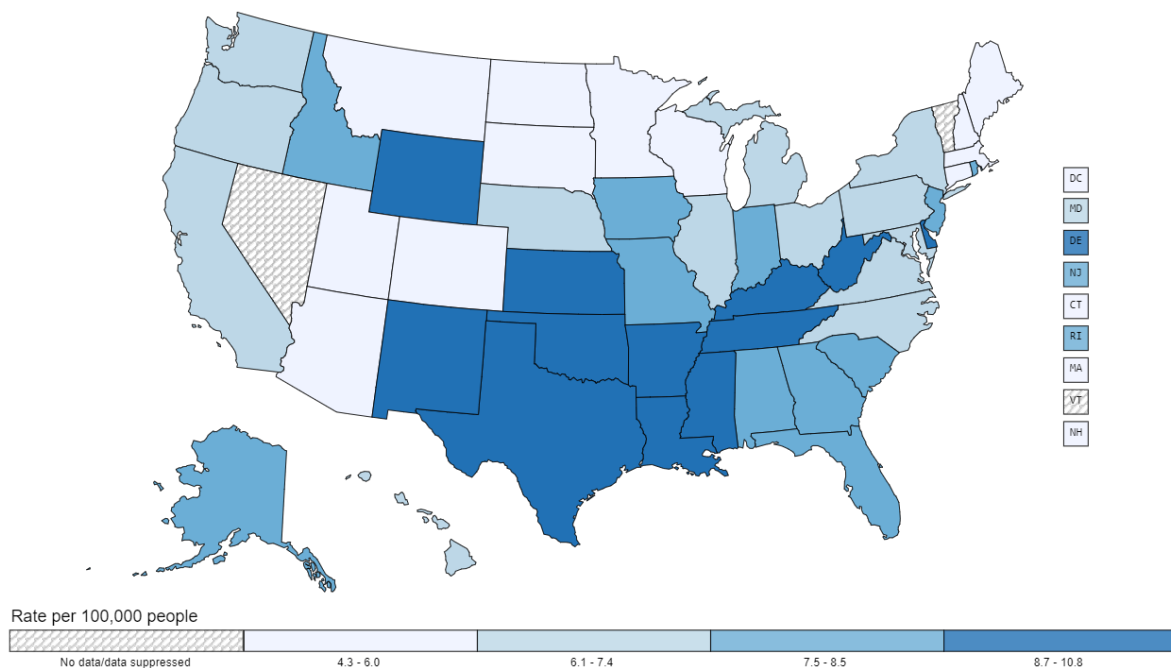
Language other than English spoken at home, percent of persons age 5 years +, 2015-2019

| 2.6% - 7.2% | 7.2% - 10.5% | 10.9% - 16.1% | 16.3% - 27.1% | 29.4% - 94.5% |

https://www.census.gov/quickfacts/fact/map/US/POP815219

Location Matters

Incidence is higher in some places.

Rural and Urban areas differ.

Rate of New Cancers in the United States
Cervix, All Ages, All Races and Ethnicities, Female

Rate per 100,000 people

| No data/data suppressed | | 4.3 - 6.0 | 6.1 - 7.4 | 7.5 - 8.5 | 8.7 - 10.8 |

Households with a broadband Internet subscription, percent 2015-2019

| 60.4% - 78.6% | 80.1% - 81.5% | 81.8% - 83.2% | 83.4% - 85.8% | 85.9% - 88.3% |

U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999-2018): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, released in June 2021

https://www.census.gov/quickfacts/fact/map/US/INT100219

#burnerphones4research

Final thoughts

- Reimagine cervical cancer as a disease of patients who are historically underrepresented due to race, language, poverty and location.

- Recognize that cervical cancer is rare disease.

- Consider clinical trial designs that improve equity
  1. Allow smaller enrollment numbers per site
  2. Promote non-English fluent patients to participate
  3. Compensate patients for their travel or provide them with tech to allow for off-site monitoring

Thank you

NIH

United States of America

Dr. Sarah Temkin

Dr. Janine Clayton

Dr. Vivian Pinn

https://en.wikipedia.org/wiki/Vivian_Pinn

The Office of Research on Women's Health