Addressing the Challenges of Genomic Screening in Populations Underrepresented in Genomic Databases

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Assistant Professor

Baylor College of Medicine

Figure 1.

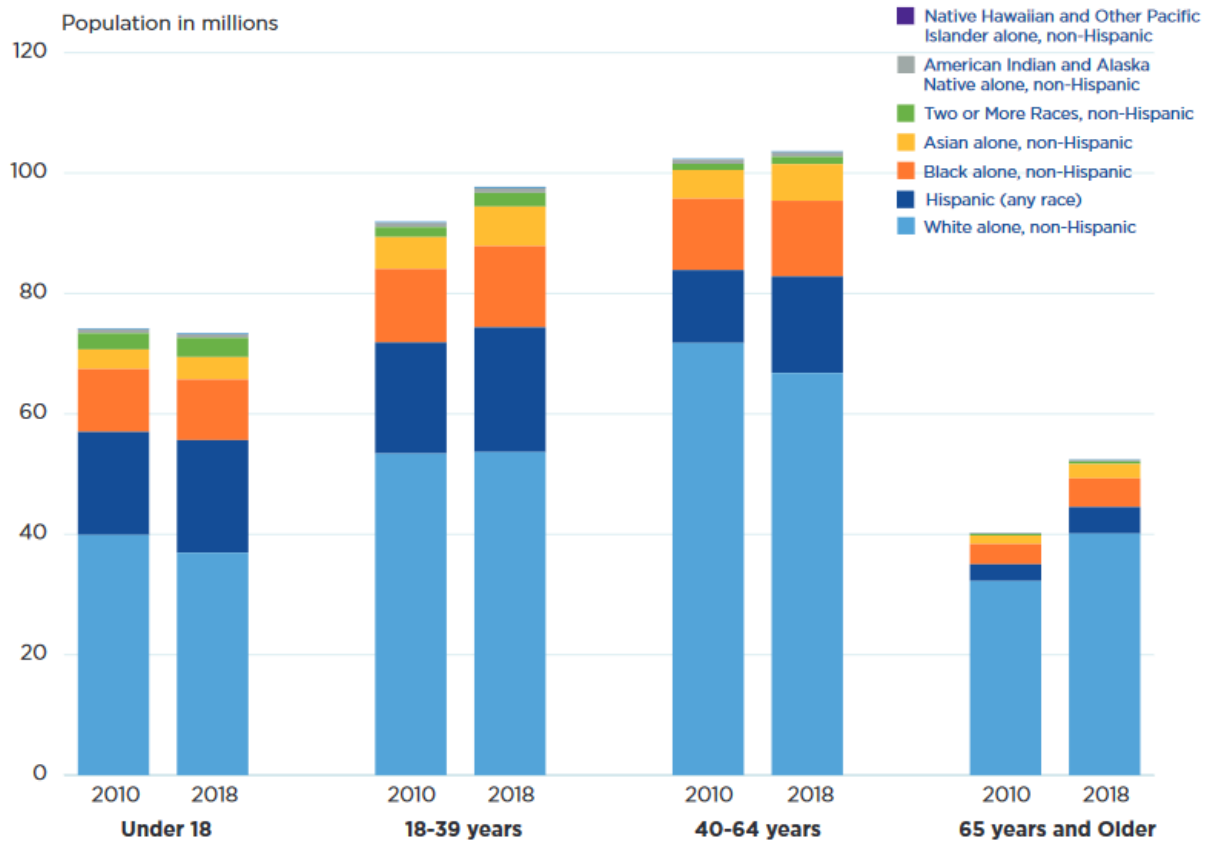
Race and Prevale State:

- White alone non-H … in 2010).
- Hispanic or Latinc
- Black or African Ar … ed 12.1%
- Remaining racial a

Source: U.S. Census Bureau, 2020 Census

A More Diverse Nation

Distribution of Race and Hispanic Origin by Age Groups



United States Census Bureau

U.S. Department of Commerce
Economics and Statistics Administration
U.S. CENSUS BUREAU
census.gov

Source: Vintage 2018 Population Estimates
www.census.gov/programs-surveys/popest.html

racial or ethnic group — Diffusion score

11.4%
6.0%
17.9%
11.5%
8.0%
10.8%
8.5%
9.5%
9.4%
8.0%
5.9%
7.5%
16.0%
4.6%
14.2%
6.9%
14.3%
8.6%
9.3%
7.3%
17.8%
8.3%
7.9%
9.6%
6.2%
7.6%
6.5%
9.2%
5.9%
3.9%
12.6%
13.0%
3.2%
7.6%
4.2%
0.2%

Reference: U.S. Census Bureau.gov

Population and Cultural Processes Impact Genetic Diversity

Relationship between Deleterious Variation, Genomic Autozygosity, and Disease Risk: Insights from The 1000 Genomes Project

Trevor J. Pemberton[1,*] and Zachary A. Szpiech[2]

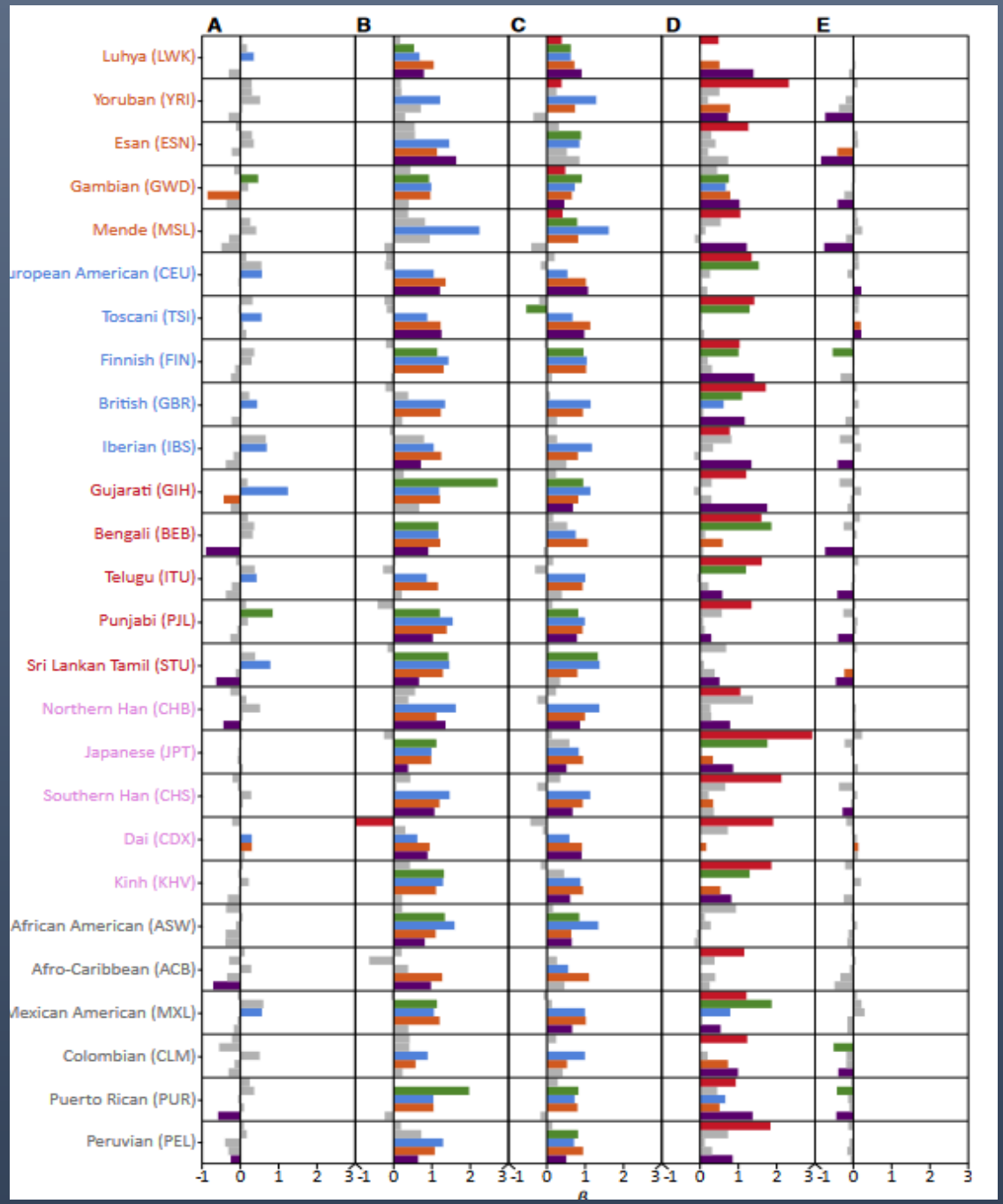
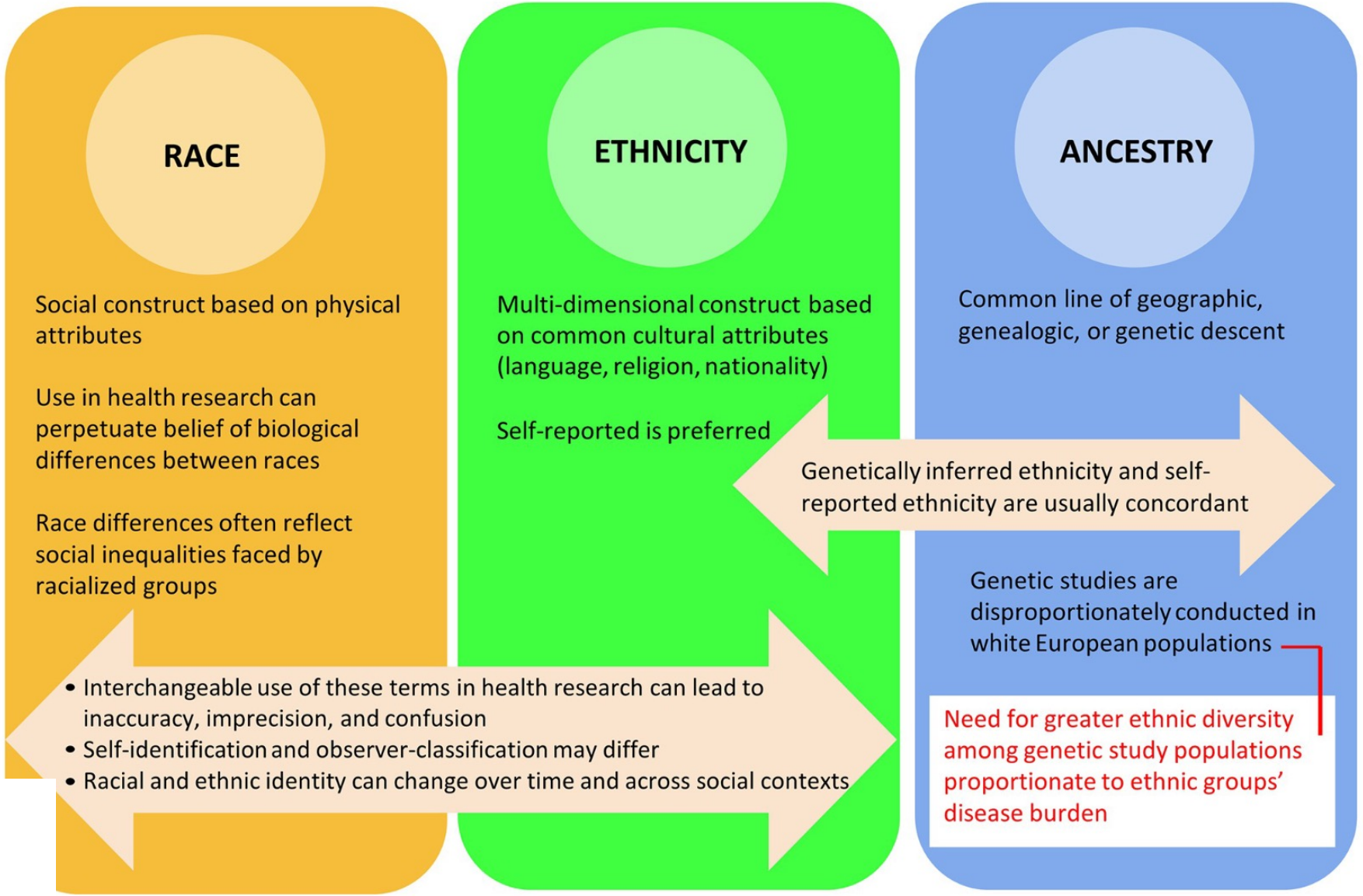


Figure 9. Differences in the Rate of Gain of Damaging Homozygotes in Disease and Non-Disease Gene Sets in Each Population
Bar plots showing for each population and ROA class the magnitude of β_3 from regressions comparing the rates of gain of damaging nonreference homozygotes in disease-associated and non-disease-associated gene sets with increasing genomic ROA coverage.
(A) OMIM dominant genes.
(B) OMIM recessive genes.
(C) ClinVar genes.
(D) FDA-approved drug target genes.
(E) Genes located nearest to reported GWAS signals.

Our Identity is mult-dimensional



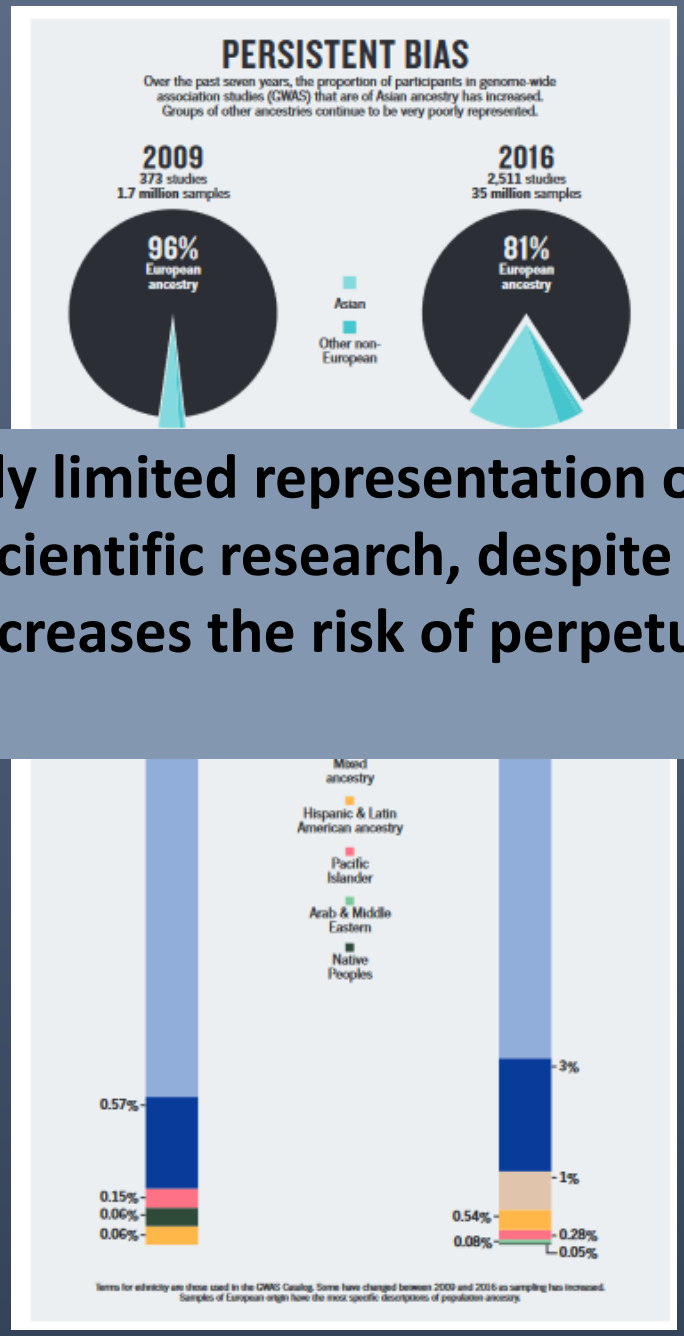
Race, ethnicity, and ancestry considerations in health research.

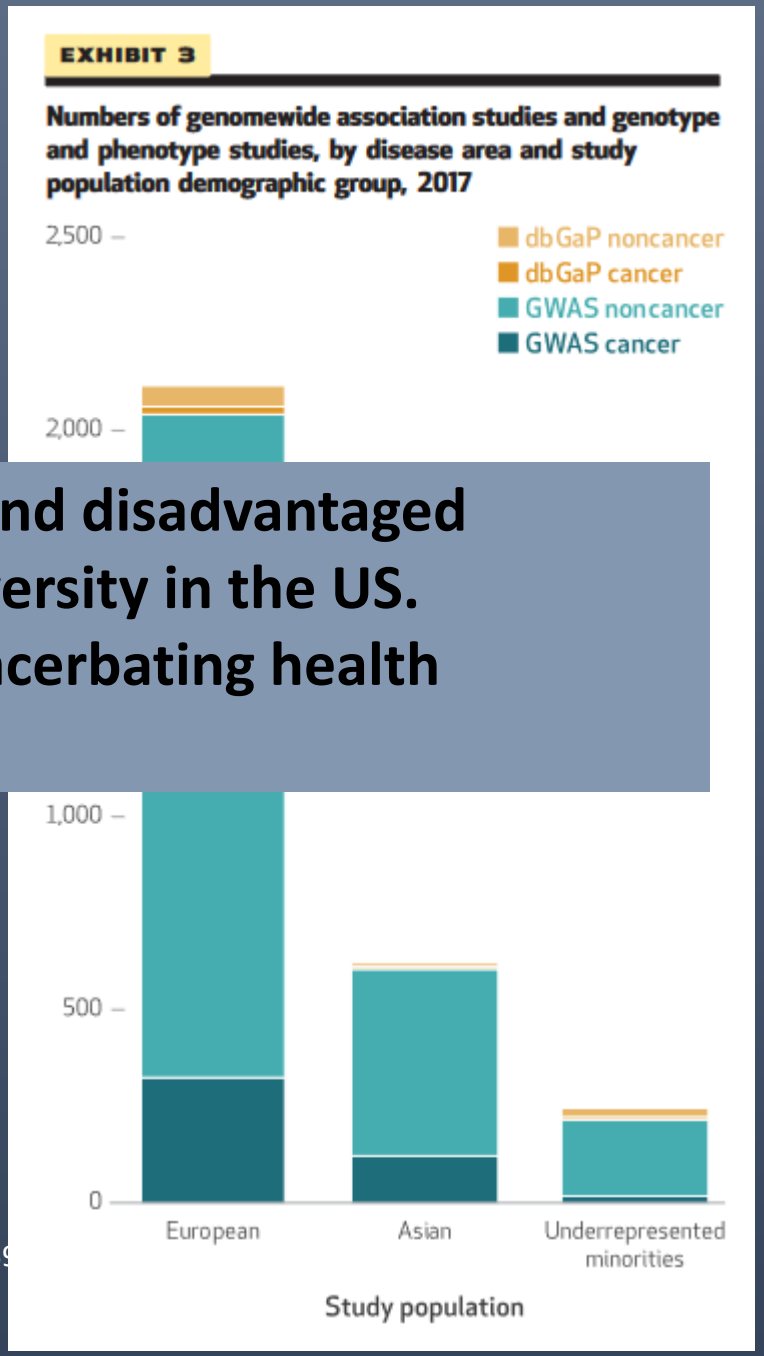
Use of race, ethnicity, and ancestry data in health research

Clara Lu[1], Rabeeyah Ahmed[2], Amel Lamri[1], Sonia S. Anand[1,3]*

1 Department of Medicine, McMaster University, Hamilton, Ontario, Canada, **2** Arts and Science Program, McMaster University, Hamilton, Ontario, Canada, **3** Department of Health Research Methods, Evidence & Impact, McMaster University, Hamilton, Ontario, Canada

The promise of precision medicine?



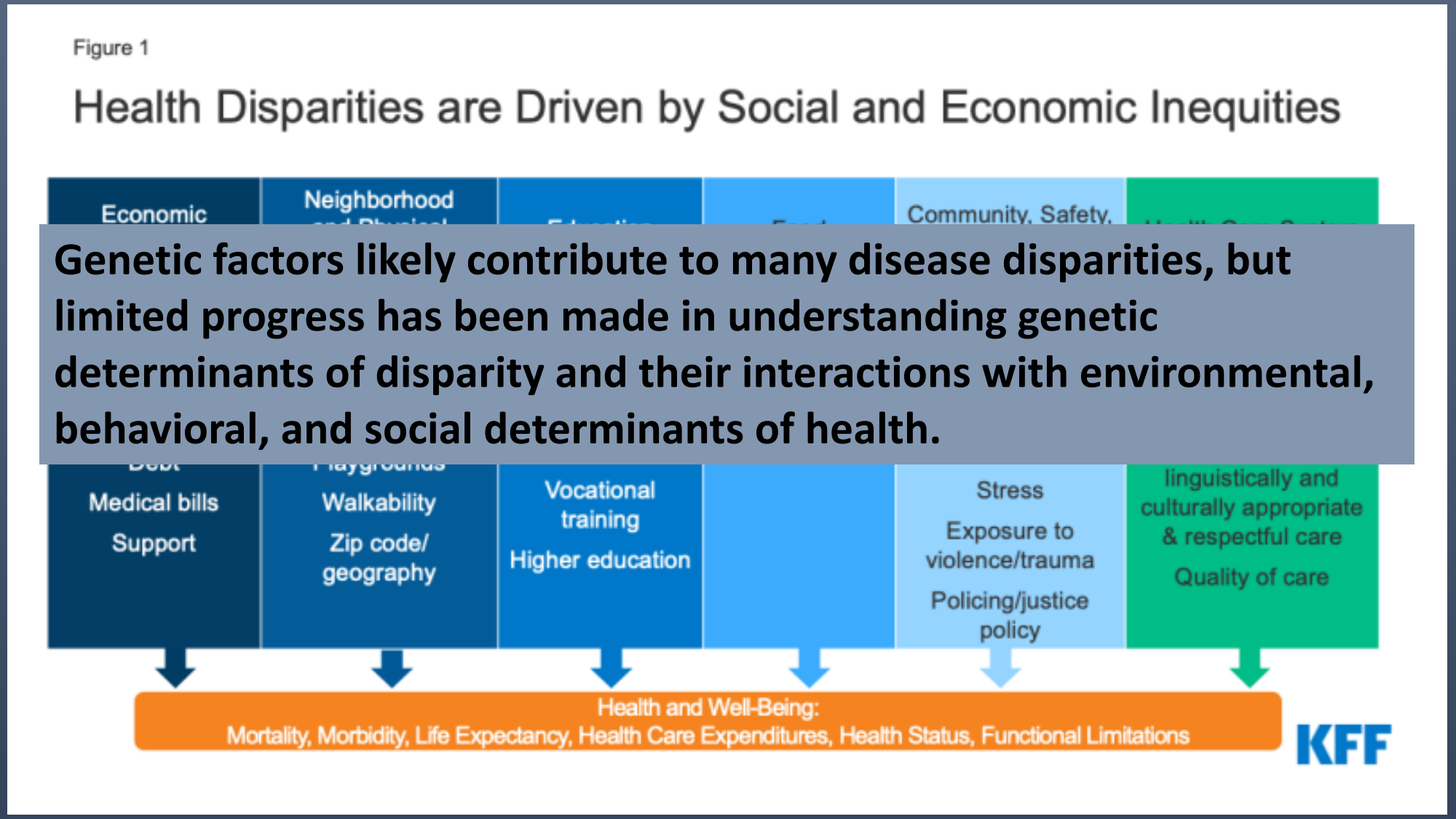


- **There is currently limited representation of minorities and disadvantaged populations in scientific research, despite increasing diversity in the US.**
- **This situation increases the risk of perpetuating and exacerbating health disparities.**

Popejoy AB, Fullerton SM. Genomics is failing on diversity. Nature. 2016. doi: 10.1038/538161a.

10.1377/hlthaff.2017.15
HEALTH AFFAIRS 37,
NO. 5 (2018): 780–785

What are the drivers of disparity?



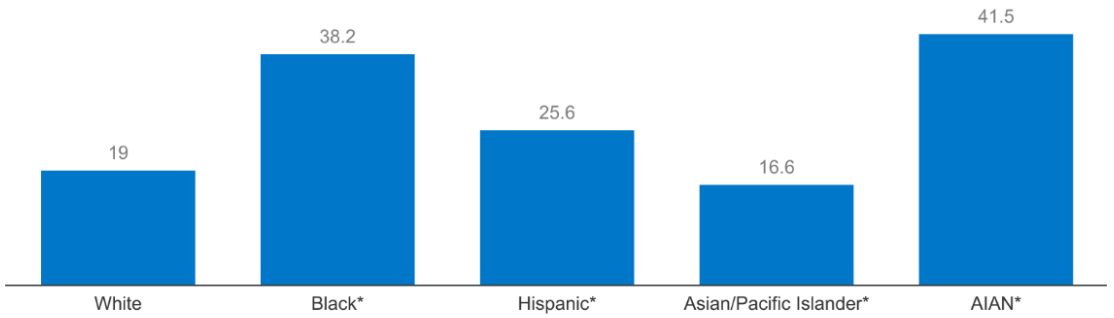
Genetic factors likely contribute to many disease disparities, but limited progress has been made in understanding genetic determinants of disparity and their interactions with environmental, behavioral, and social determinants of health.

Health Outcomes by Race and Ethnicity

Figure 23

Age-Adjusted Death Rates per 100,000 for Selected Diseases by Race/Ethnicity, 2019

Diabetes Heart Disease



NOTE: * Indicates statistically significant difference from White people at the p<0.05 level. Persons of Hispanic origin may be of any race but are categorized as Hispanic for this analysis; other groups are non-Hispanic. AIAN refers to American Indian or Alaska Native. Persons of Hispanic origin may be of any race but are categorized as Hispanic for this analysis; other groups are non-Hispanic. Includes individuals of all ages. Data for Native Hawaiian and Other Pacific Islander people were not reported separately from data for Asians. Data for some groups should be interpreted with caution; see https://wonder.cdc.gov/wonder/help/ucd.html#Racial

SOURCE: Centers for Disease Control and Prevention, National Center for Health Statistics, WONDER Online Database, Underlying Cause of Death, 2019. Accessed at https://wonder.cdc.gov/ucd-icd10.html

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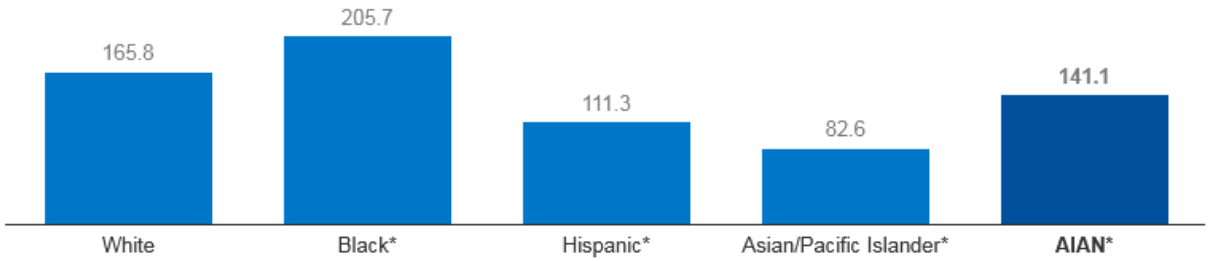
Figure 23

Age-Adjusted Death Rates per 100,000 for Selected Diseases by Race/Ethnicity, 2019

Diabetes **Heart Disease**



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SOURCE: Centers for Disease Control and Prevention, National Center for Health Statistics, WONDER Online Database, Underlying Cause of Death, 2019. Accessed at https://wonder.cdc.gov/ucd-icd10.html • PNG

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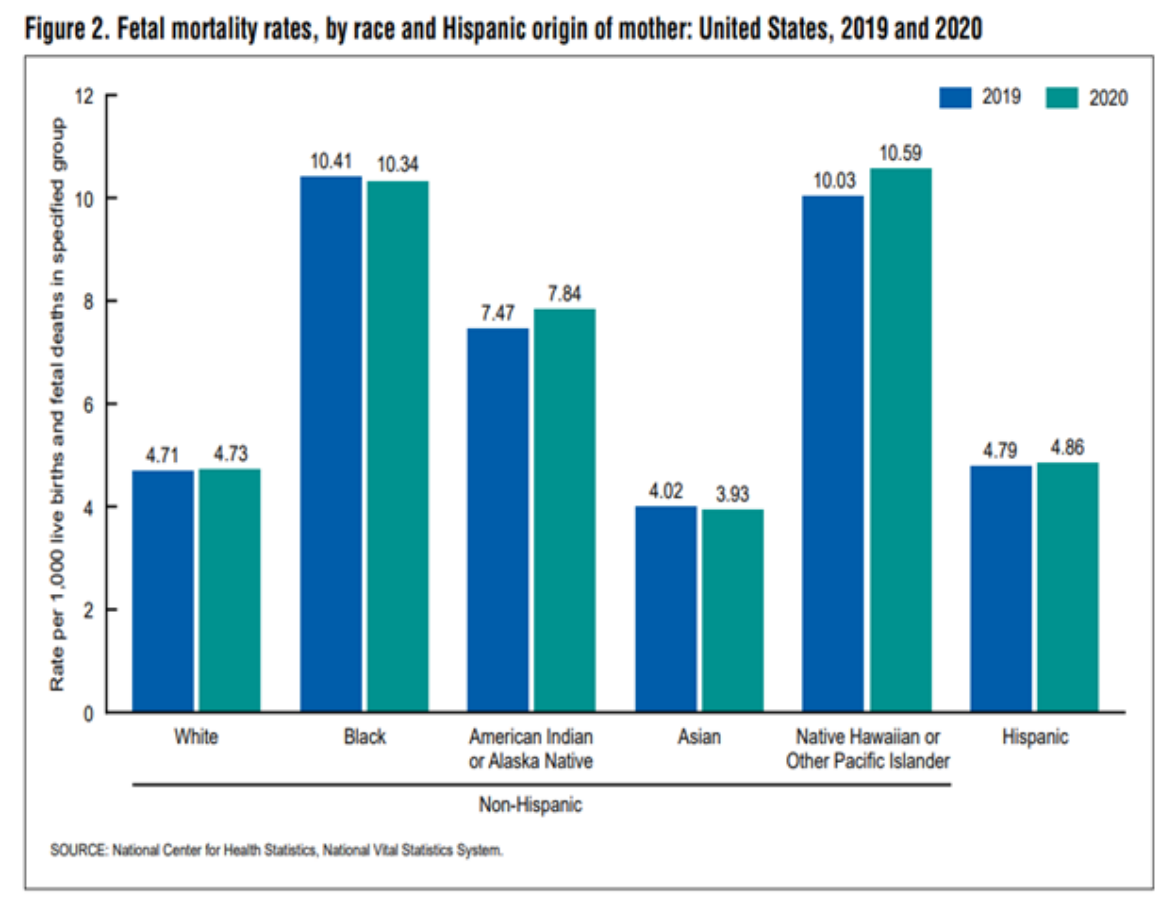
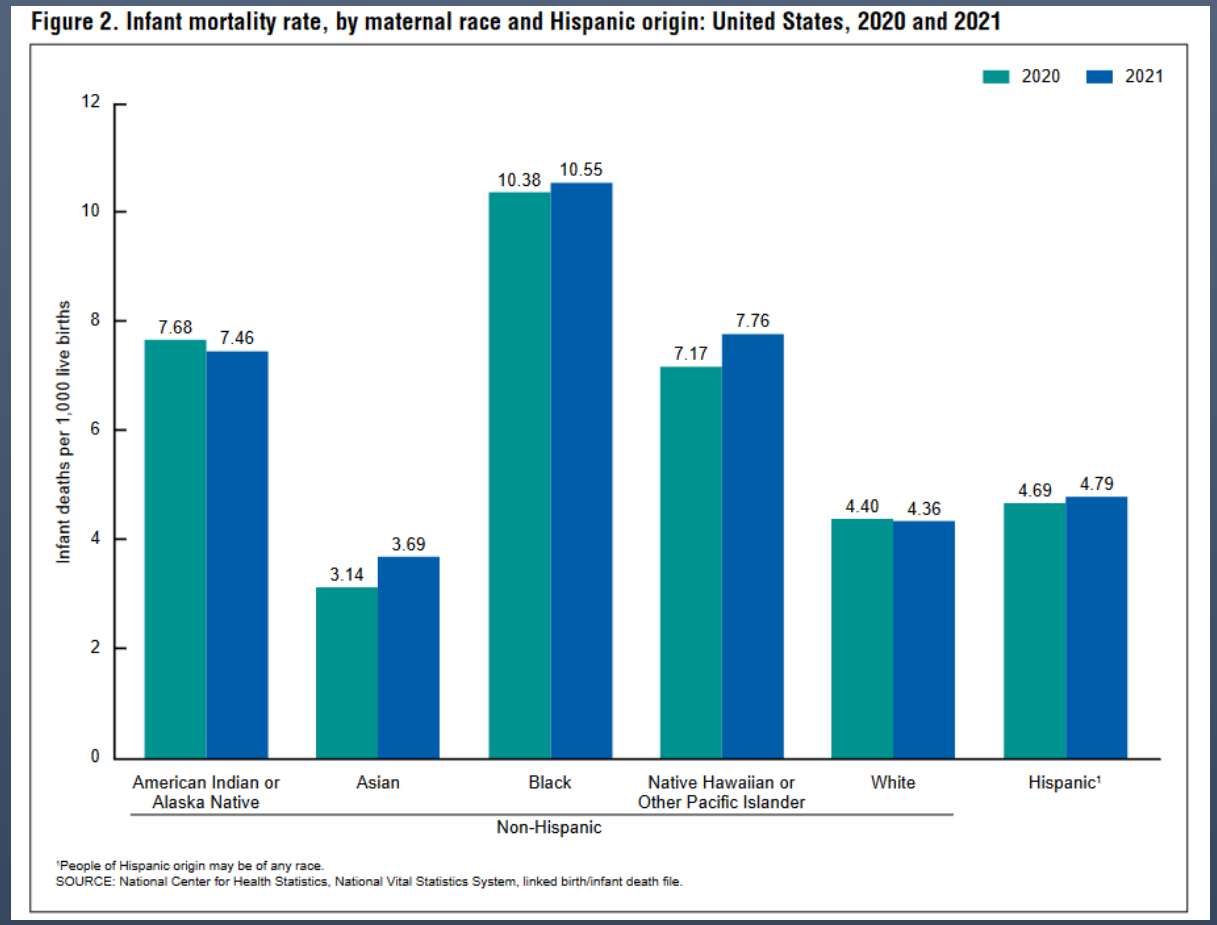
Maternal and Child Health Disparities by Race/Ethnicity



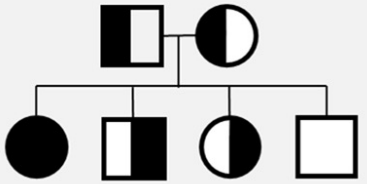


Case Example: Reproductive Carrier Screening

- Genetic conditions are a leading cause of morbidity and mortality in infants and children.
- Carrier screening is a method of identifying asymptomatic individuals at risk for having a child with an autosomal recessive or X-linked genetic condition
- Ideal time to begin to address familial genetic risk is prior to pregnancy
- The clinical utility of carrier screening is represented by its ability to provide individuals an opportunity to discuss their risks and consider reproductive options that are available pre-pregnancy, during pregnancy, or after birth.

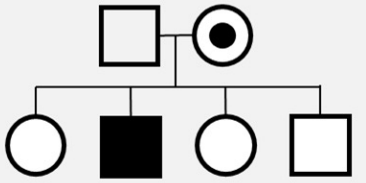
Autosomal recessive disease

→ find the carrier parents



X-linked disease

→ find the carrier mothers



Traditional Carrier Screening

Condition	ACOG	ACMG	NSGC	Screening Approach	Method
Hemoglobinopathies	African/African American, Mediterranean, Middle Eastern and South/Southeast Asian ancestry	No Guideline	No guideline	Ancestry Based	• CBC with differential, • Hemoglobin electrophoresis • Molecular testing
Ashkenazi Jewish Ancestry	Offer screening for Tay-Sachs disease, Cystic Fibrosis, Canavan disease, familial dysautonomia	Offer screening for Tay-Sachs disease, Cystic Fibrosis, Canavan disease, familial dysautonomia, Niemann-Pick type A, Bloom syndrome, Fanconi anemia group C, Mucolipidosis IV and Gaucher disease	No current guideline	Ancestry Based	• Molecular testing. Biochemical screening for Tay-Sachs is most sensitive
Cajun and French Canadian Ancestry	Tay-Sachs	No current guideline	No current guideline	Ancestry Based	• Biochemical Testing
Cystic Fibrosis	All women of reproductive age.	Population screening with 23-mutation panel.	All women of reproductive age.	Panethnic	• Molecular testing
Spinal Muscular Atrophy	All women of reproductive age.	Offer Regardless of ancestry or family history	No current guideline	Panethnic	• Molecular Testing
Fragile X syndrome	Individuals with a family history of intellectual disability suggestive of FXS, unexplained intellectual disability, developmental delay, autism or primary ovarian insufficiency	Individuals with a family history of intellectual disability suggestive of FXS	Individuals with a family history of intellectual disability suggestive of FXS	Targeted	• Molecular Testing (Population screening not recommended)

Traditional Carrier Screening Limitations

- >7,000 Mendelian diseases:
  - 10% of infant mortality
  - 20% of pediatric hospital admissions
- Population admixtures
  - 14.6% of all marriages were between different race/ethnicities
  - 40% of Americans cannot correctly identify the ethnicity of all four grandparents
- In California Newborn Screening Program:
  - 1/3 of newborns with sickle cell disease were not African American
  - 1/3 with HbH disease were not Asian

Affects residual risk counseling

Wang W et al., Pew Research Center (2012); Condit, et al. 2003. Genetics in Medicine: (5): 385–92.
Langlois, Benn and Wilkins-Haug. Prenatal Diagn 2015 (and references therein).

Targeted vs. Expanded Carrier Screening

Two Concepts

More diseases

- ~100 to >500
- ACMG/ACOG diseases included
- Most not in ACMG or ACOG panels

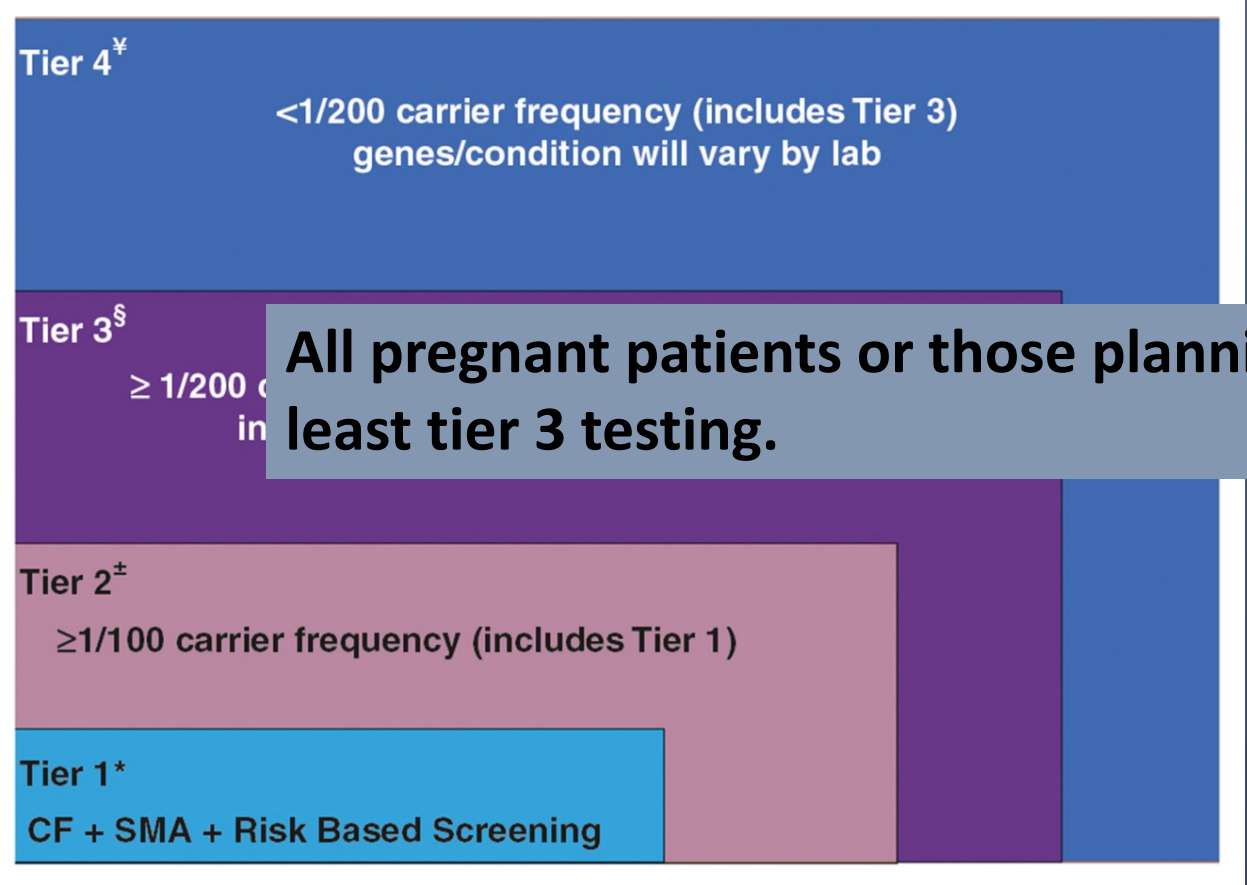
Pan-ethnic

- No selection based on ethnicity
- Entire population screened for the same conditions

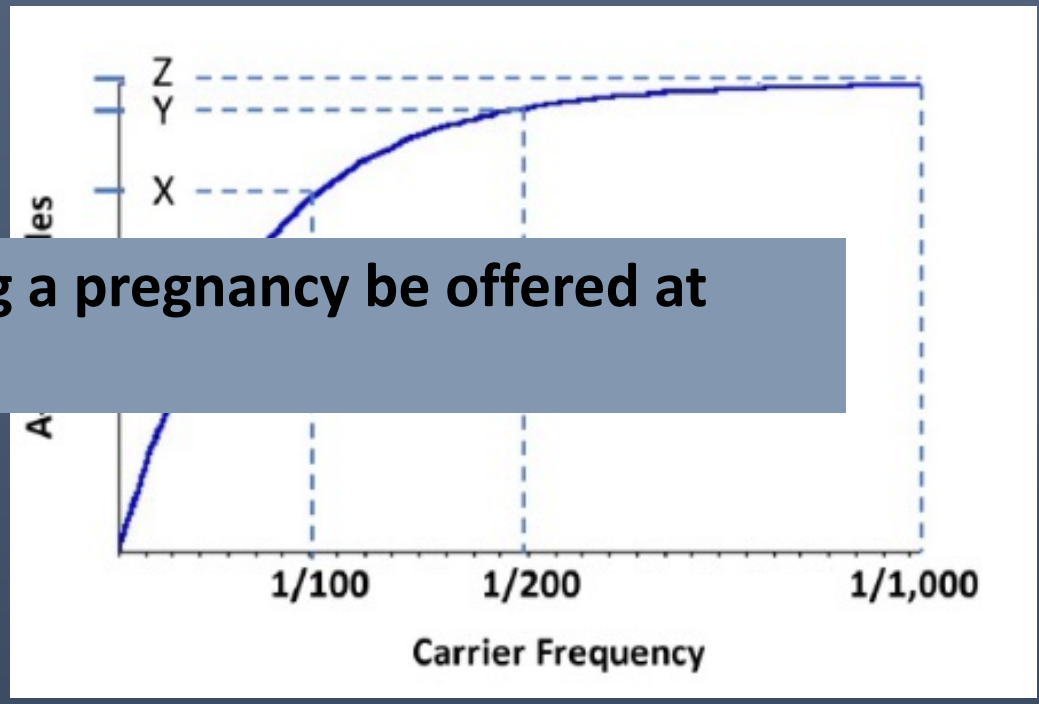
Multiplexed assays → Cost favorable compared to individual tests,
but what about total cost, including follow-up and counseling?

With 158 diseases → >50% carriers for 1 or more conditions
With > 300 diseases → >85% carriers for 1 or more conditions

ACMG 2021 Recommendations



All pregnant patients or those planning a pregnancy be offered at least tier 3 testing.



The relationship between Carrier Frequency and identification of an At-Risk couple.

Challenges with Expanded Carrier Screening

1. Inclusion of very rare conditions: carrier frequency unclear and residual risk can be inaccurate. Accurate ancestry affects residual risk calculation.
2. Which diseases? → Inclusion of conditions with variable severity and presentation. (Not all ECS are the same).
3. Occasional diagnosis of affected parents (deafness, adult Pompe disease).
4. Reproductive autonomy (pre-conception, pre-IVF, gamete donors)
5. What do patients and providers want?
6. Equal access and cost – prioritization of healthcare resources.
7. "Routinization"; concern for stigmatization of individuals with disabilities.

Modified from Langlois, Benn and Wilkins-Haug. Prenatal Diagn 2015.

Lack of Representation in research studies

Expanded carrier screening in the United States: A systematic evidence review exploring client and provider experiences

Aarti Ramdaney[1] | Lauren Lichten[2] | Lauren Propst[3] | Caitlin Mann[4] | Gabriel A. Lazarin[5] | Malorie Jones[1] | Amy Taylor[6] | Jennifer Malinowski[7]

TABLE 3 Number of at-risk couples identified through expanded carrier screening

Study	Participant characteristics	Test characteristics	CF and/or SMA ARCs	ECS ARCs
Akler et al. (2020)	Study Population: Self-reported Jewish (Ashkenazi, Sephardi, and Mizrahi) individuals Cohort: 6805 (4621 F/2184 M) Linked couples: 831	ECS (96 condition panel) Methodology: sequencing	6 ARCs	50 ARCs
Beauchamp et al. (2019)	Study Population: Modeled population Cohort: 66036 (F/M NR) Linked Couples: Varies by gene	ECS (176-condition panel) Methodology: sequencing	Not reported*	
Bristow et al. (2019)	Study Population: Infertility patients Cohort: 7700 (Panel A: 4232, 2880 F/1352 M; Panel B: 3468, 2204 F/1264 M) Linked couples: 2392 (Panel A: 1206, Panel B: 1186)	ECS (Panel A: 102, Panel B: 307) Methodology: genotyping (both panels)	5 ARCs	49 ARCs
Franasiak et al. (2016)	Study Population: Infertility patients Cohort: 6643 (F/M NR) Linked couples: 3738	ECS (97–102, multiple panels used) Methodology: genotyping/ sequencing	3 ARCs	4 ARCs
Giles Choates et al. (2020)	Study Population: Known carriers and clients that elected carrier screening Cohort: 6087 (F/M NR) Linked couples: 274	ECS (unspecified, multiple panels used) Methodology: genotyping/ sequencing	9 ARCs	31 ARCs
Haque et al. (2016)	Study Population: Modeled population Cohort: 346,790 (273,618 F/73172 M) Linked couples: Varies by gene	ECS (110) Methodology: genotyping/ sequencing	56 ARCs	703 ARCs
Punj et al. (2018)	Study Population: Average risk/general population Cohort: 202 (131 F/71 M) Linked couples: 71	ECS (728) Methodology: sequencing	0 ARCs	12 ARCs
Shapiro et al. (2021)	Study Population: Infertility patients Cohort: 202 (131 F/71 M) Linked couples: 71	ECS (102–175) Methodology: sequencing	2 ARCS identified; conditions not specified	
Simone et al. (2021)	Study Population: Average risk/general population Cohort: 907 (513 F/394 M) Linked couples: 394	ECS (unspecified) Methodology: genotyping, sequencing	4 ARCs	32 ARCs
Westemeyer et al. (2020)	Study Population: Average risk/general population; modeled population Cohort: 381,014 (339,739 F/41275 M) Linked couples: Varies by gene	ECS (4–274) Methodology: sequencing	Not reported	

Abbreviations: ARCs, at-risk couples; ECS, expanded carrier screening; F, females; M, males.

55.6% European Ancestry

51.8% European Ancestry

78% European Ancestry

55.9% European Ancestry

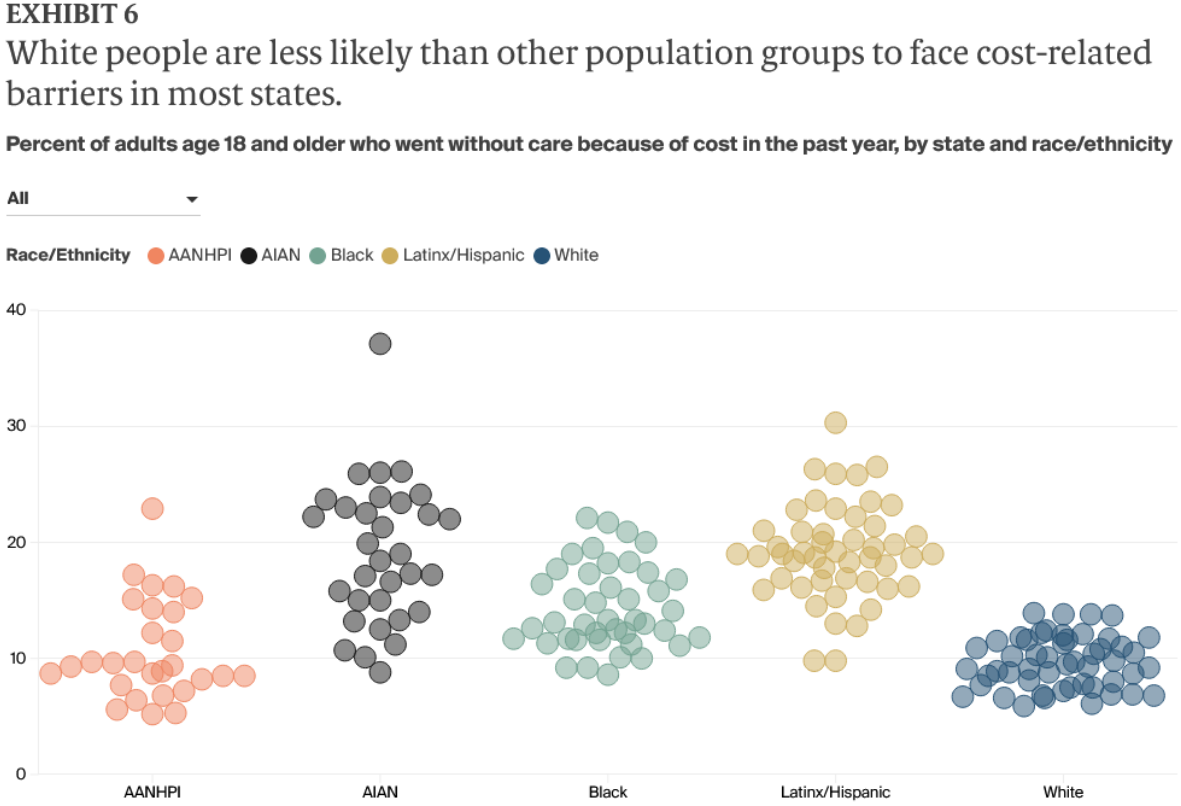
39.4% European Ancestry

Barriers to Healthcare

EXHIBIT 6

White people are less likely than other population groups to face cost-related barriers in most states.

Percent of adults age 18 and older who went without care because of cost in the past year, by state and race/ethnicity



Note: Dots represent states. Missing dots for a particular group indicate there are insufficient data for that state. AANHPI = Asian American, Native Hawaiian, and Pacific Islander; AIAN = American Indian/Alaska Native.

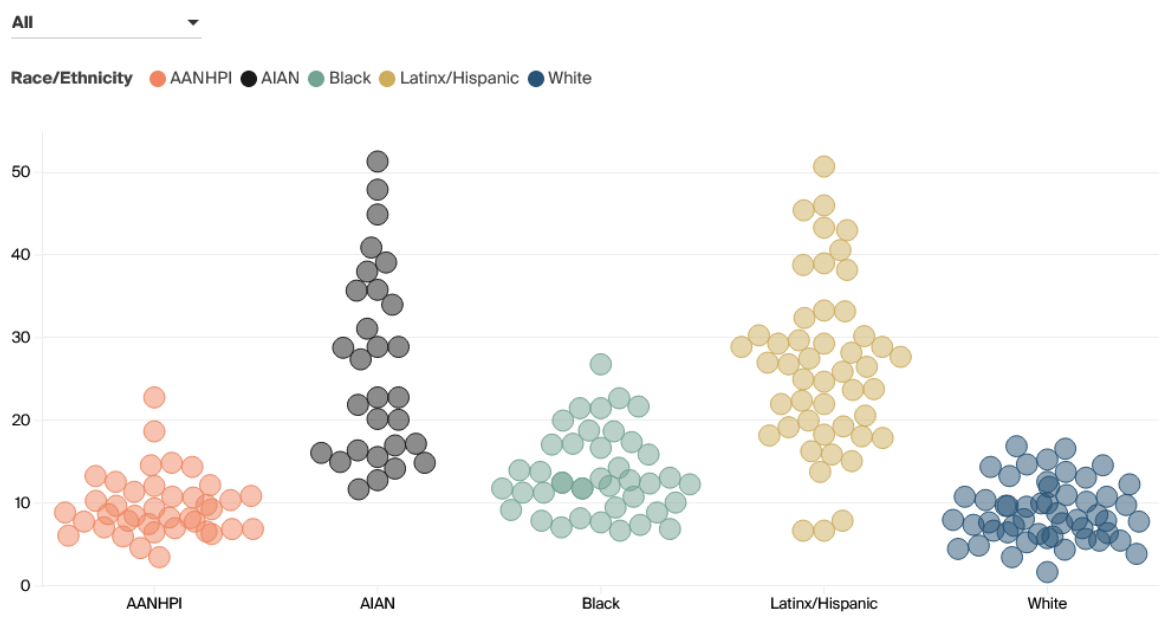
Data: Behavioral Risk Factor Surveillance System (BRFSS), 2019–20.

Source: David C. Radley et al., *Achieving Racial and Ethnic Equity in U.S. Health Care: A Scorecard of State Performance* (Commonwealth Fund, Nov. 2021).

EXHIBIT 5

Although the ACA's coverage expansion improved inequities, state uninsured rates are generally higher and more variable for Black, Latinx/Hispanic, and AIAN adults compared to AANHPI and white adults.

Percent of adults ages 19–64 who are uninsured, by state and race/ethnicity

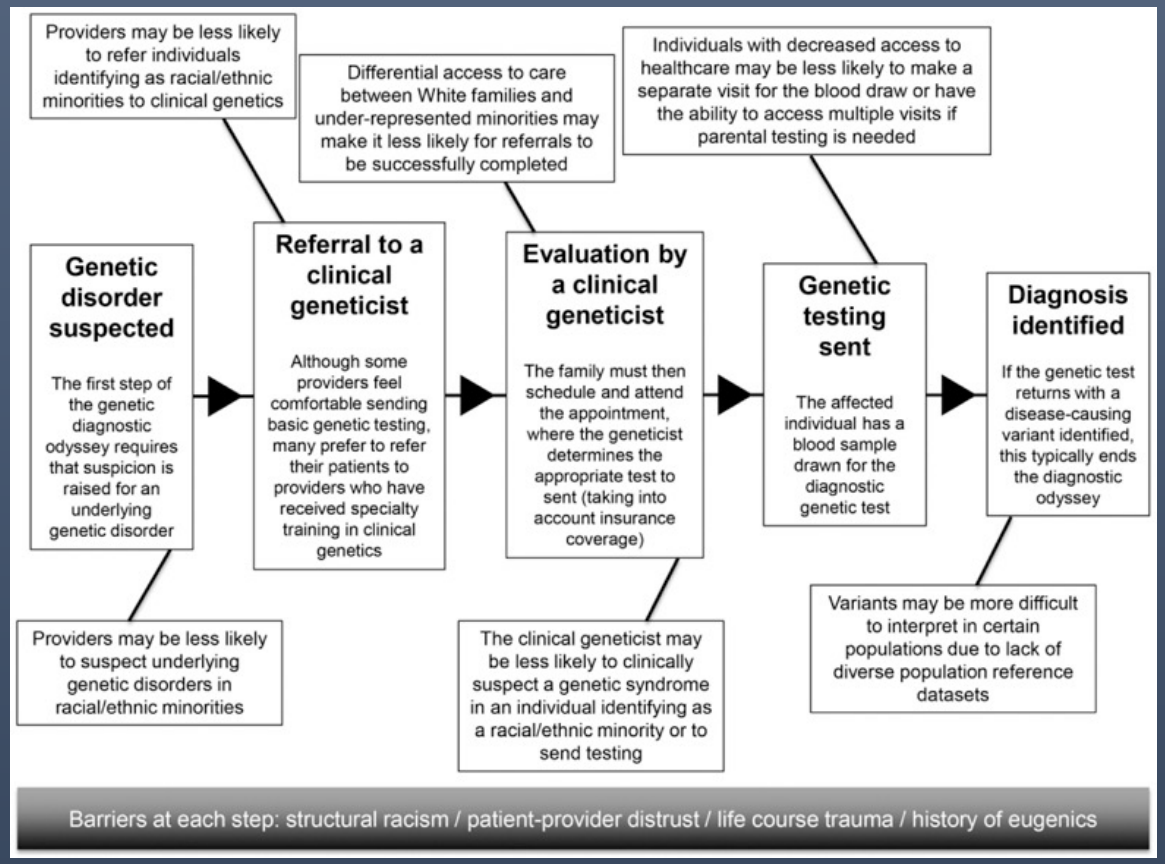


Note: Dots represent states. Missing dots for a particular group indicate there are insufficient data for that state. AANHPI = Asian American, Native Hawaiian, and Pacific Islander; AIAN = American Indian/Alaska Native. ACA = Affordable Care Act.

Data: American Community Survey Public Use Micro Sample (ACS-PUMS) 2019 1-year file.

Source: David C. Radley et al., *Achieving Racial and Ethnic Equity in U.S. Health Care: A Scorecard of State Performance* (Commonwealth Fund, Nov. 2021).

Provider Bias and Discrimination



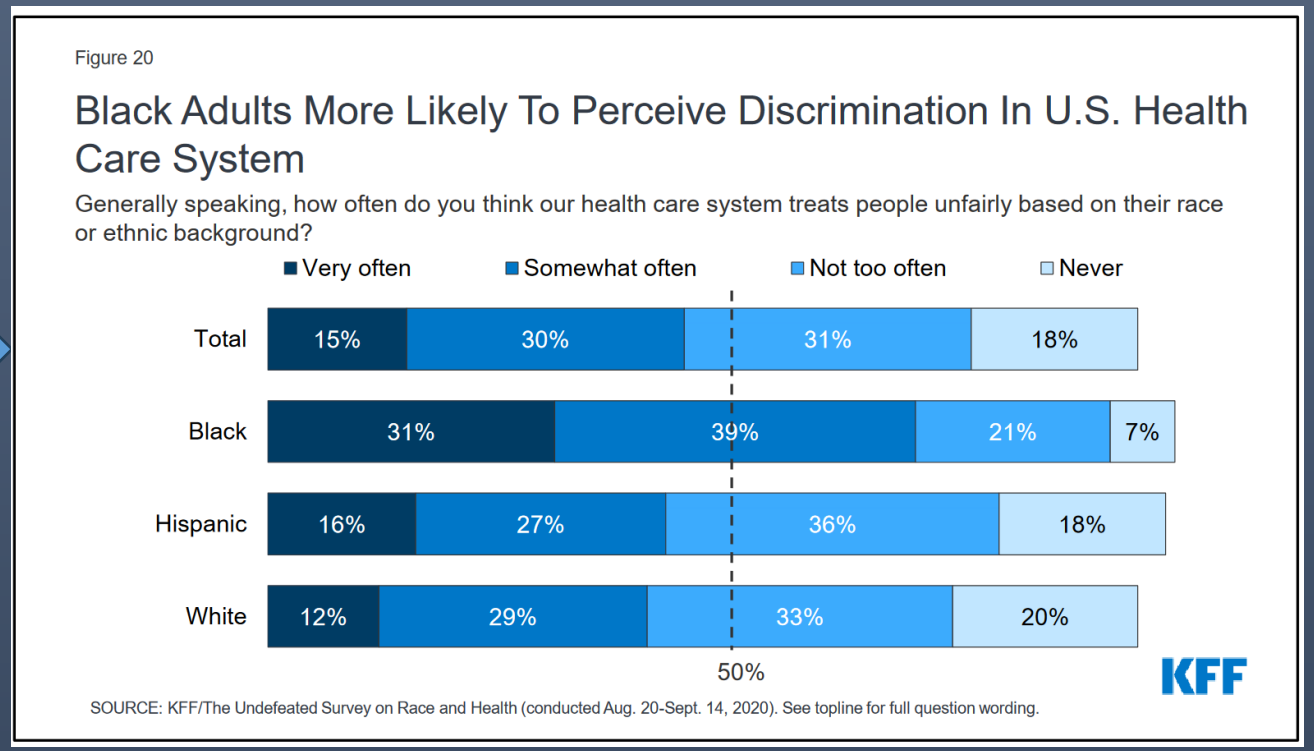


Table 2. Wilson and Jungner criteria in the context of DNA-based screening and population health.

	Wilson and Jungner criteria	Criteria in DNA-based screening and population health context
1	The condition sought should be an important health problem.	Screening should focus on the identification of genomic risk(s) for important health problems.
2	There should be an accepted treatment for patients with recognized disease.	Options for evidence-based clinical actions should be communicated to patients in whom the genomic risk is identified.
3	Fa[illegible]d be available	Clinical implementation strategies should be in place and available to anyone identified as having genomic risk.
4	There should be a recognizable latent or early symptomatic stage.	Screening should have the capability of identifying at-risk individuals during both presymptomatic and early symptomatic disease stages.
5	There should be a suitable test or examination.	The DNA-based strategy should constitute an improvement over existing strategies for risk identification and risk reduction.
[illegible]	[illegible]lati[illegible]	Proven screening applications should be available to all but individual participation should be optional.
[illegible]	[illegible]development from[illegible]ly understood.	Anticipated penetrance and expressivity (i.e., natural history) should be understood based on data from comparable populations.
8	There should be an agreed policy on whom to treat as patients.	Consensus should exist on clinical classification and management for those patients who screen positive for genomic risk but in whom the evidence of the associated health problems is absent (i.e., nonpenetrant risk).
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	Appropriate health economic analyses should be in place to understand programmatic costs and benefits.
10	Case-finding should be a continuing process and not a "once and for all" project.	There should exist plans for both: - Periodic *reanalysis of DNA variants* using updated information. - Periodic *clinical re-evaluation* of individuals with nonpenetrant risk.

Lack of healthcare access

Provider bias and lack of education

Lack of representation in genomic databases

But this isn’t theoretical

Inheritest® Panels

Inheritest 500 PLUS Panel — 578 genes
Expanded coverage of more than 500 clinically relevant genetic disorders, empowering your patients with even more relevant genetic information.
See list of disorders

Inheritest 300 PLUS Panel — 350 genes
Covers more than 300 clinically relevant genetic disorders, including all the genes in the 14-Gene and 100 PLUS Panels as well as additional genes in the American College of Medical Genetics and Genomics (ACMG) Tier 3 category, focusing on high-frequency disorders.
See list of disorders

Inheritest 100 PLUS Panel — 143 genes
Includes analysis of more than 100 clinically relevant genetic disorders.
See list of disorders

Inheritest High Frequency Panel — 110 genes
110 of the genes included in the ACMG Tier 3 category (≥ 1/200 carrier frequency).
See list of disorders

Inheritest 14-gene Panel — 14 genes
Includes disorders associated with ethnicity listed in the ACOG recommendations.
See list of disorders

Inheritest Core Panel — 3 genes
Screens for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome, some of the more common genetic disorders.
See list of disorders

Inheritest CF/SMA Panel — 2 genes
Screens for cystic fibrosis and spinal muscular atrophy, two of the more common genetic disorders.
See list of disorders

Invitae Comprehensive Carrier Screen
Up to 569 genes
Test code: 60100 • 10-21 days turnaround time
The Invitae Comprehensive Carrier Screen is appropriate for those of all ethnicities who want an expanded assessment of their risk of having an affected child.
See test details | Add to order

Invitae Broad Carrier Screen
Up to 115 genes
Test code: 60101 • 10-21 days turnaround time
The Invitae Broad Carrier Screen includes select genes associated with disorders that may have a severe presentation and are prevalent across ethnicities.
See test details | Add to order

Invitae Core Carrier Screen
Up to 3 genes
Test code: 60102 • 10-21 days turnaround time
The Invitae Core Carrier Screen includes select genes associated with common, severe, disorders seen across ethnicities, including cystic fibrosis, spinal muscular atrophy (SMN1), and fragile X syndrome (FMR1).

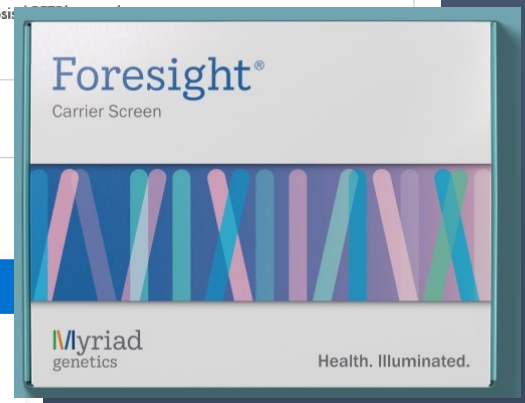
Flexible panel choices for personalized care

Foresight offers three panel choices that allow you to test for up to 176 genes associated with serious and prevalent inherited conditions.

Fundamental Panel
Screens for cystic fibrosis and spinal muscular atrophy (recommended by ACMG and ACOG).[3,4]
Fundamental Panel Disease List

Fundamental Plus Panel
Screens for a guideline-based set of 14 genes.
Fundamental Panel Disease List

Universal Panel
Screens for 176 genes associated with serious and prevalent inherited conditions.
Universal Panel Disease List



Addressing the complex nature of health

Equitable delivery of expanded genetic technologies: Considerations for prenatal and reproductive care

April D. Adams[1,2] | Naana Jumah[3,4] | Nanette Okun[5] | Vence L. Bonham[6]

Figure 1. Proposed Framework for the Equitable Delivery of Reproductive Genetics Services[1,2]

		Level of Influence			
		Individual Factors	**Interpersonal Relationships**	**Community Networks**	**Societal Systems**
Domain of Influence	**Biological** **Barrier: Lack of knowledge of genetic variation**	• Individual Genetic Variation/Ancestry • Genetic Mechanisms	• Partner and Familial Genetic Variation	• Intra-population genetic variation	• Inter-population genetic variation
	Behavioral **Barrier: Lack of trust and privacy concerns**	• Health Seeking Behaviors • Coping Strategies	• Family Functioning/Support	• Community Functioning/Support	• Policies and Laws • Privacy Protections
	Physical/Built Environment **Barrier: Access to decision support**	• Personal Environment	• Household Environment • School/Work Environment • Education	• Community Environment/Resources	• Societal Structure
	Social/Cultural Environment **Barrier: Access to culturally sensitive care**	• Sociodemographic Characteristics • Language Barriers • Cultural Identity • Response to Discrimination • Historical and ongoing trauma	• Social Networks • Social Integration/Engagement • Family/Peer Norms • Interpersonal Discrimination	• Community Norms/Traditions • Community Engagement • Local Structural Discrimination	• Social Norms • Societal Structural Discrimination
	Health Care System **Barrier: Access to affordable patient-centered care**	• Insurance Coverage • Health Literacy • Treatment Preferences	• Patient-Clinician Relationship • Shared decision making • Clinical cultural competence • Clinician implicit bias • Cultural construct of health/Stigma	• Availability of Genetics Services/Providers • Appropriate referrals and consultation • Access to linguistically and culturally appropriate care	• Quality of Care • Health Care Policies • Work force • Diversity • Communication between stakeholders
Level of Health Outcome Impact		Individual Reproductive Impact (*decisions regarding current or impending pregnancy*)	Family Reproductive Impact (*decision regarding future pregnancies*)	Community Reproductive Impact (*decisions regarding community testing practices*)	Population Reproductive Impact (*decisions regarding societal testing practices*)

1. *Adapted from: National Institute on Minority Health and Health Disparities (2017). NIMHD Research Framework. Retrieved from https://nimhd.nih.gov/researchFramework. Accessed on (February 3, 2023).*

Principles for Equity

- Incorporate person-centered models in health care delivery and implementation of research protocols to empower marginalized individuals and communities.
- Acknowledge historical and ongoing harms, including those perpetuated by healthcare systems and research institutions.
- Address barriers to care including structural racism and economic inequality.
- Respect bodily autonomy.
- Avoid creating environments that shame or (re)traumatize individuals through community partnerships.
- Create systems that meet people's needs both inside and outside of the formal healthcare system.
- Patient and participant materials that support a range of health literacy/numeracy, language, and cultural linguistics needs

Addressing the Research Gaps

- Increase diversity and inclusion in the workforce
- Identify and limit barriers to participation
- Incorporate principles of equity into all levels of implementation
- Expand beyond race and incorporate social determinants of health with ancestry into the research questions

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Thank You