Practical Approaches to Improving Diversity in Clinical Trials

Wednesdays
11AM -12noon ET
Disclaimer

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The MRCT Center is supported by voluntary contributions (www.MRCTCenter.org) and grants.
## Practical Approaches to Improving Diversity in Clinical Trials

**Wednesdays**  
**11AM –12noon ET**

### LEANING IN: A WEBINAR SERIES

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Role of Data in Diversity: Genetics and Real World Data

February 10, 2021
11AM -12noon ET

Barbara Bierer, MD
Moderator
Faculty Director,
MRCT Center

Luther Clark, MD, FACC, FACP
Moderator
Deputy Chief Patient Officer,
Merck

Nicole Richie, PhD
Guest Speaker
Global Head,
Health Equity and Population Science,
Genentech Roche

Latha Palaniappan, MD, MS
Guest Speaker
Professor Of Medicine,
Stanford University School of Medicine

LEANING IN: A WEBINAR SERIES
Practical Approaches to Improving Diversity in Clinical Trials

mrcctcenter.org/diversity-in-clinical-trials
Our Vision

Improve the integrity, safety, and rigor of global clinical trials.

Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.
Achieving Diversity, Inclusion, and Equity in Clinical Research

Guidance and Toolkit

Barbara E. Bierer, MD
Sarah A. White, MPH
Laura G. Meloney, MPH, MS
Hayat R. Ahmed, MS
David H. Strauss, MD
Luther T. Clark, MD

mrctcenter.org/diversity-in-clinical-trials

Released 6 August 2020
Leadership

- RADM Richardae Araojo, PharmD, MS, U.S. FDA
- Barbara E. Bierer, MD, MRCT Center
- Luther T. Clark, MD, Merck & Co., Inc.
- Milena Lolic, MD, U.S. FDA
- David H. Strauss, MD, Columbia University
- Sarah White, MPH, MRCT Center

MRCT Center staff:
- Carmen Aldinger, PhD, MPH
- Hayat Ahmed, MS
- Laura Meloney, MS, MPH
- Joshua Smith-Sreen, MPH

And the invaluable contributions of >50 workgroup members, representing:

- Patients, Patient Advocates
- Academia
- Pharmaceutical companies
- CROs
- Non-profit organizations
- Trade associations
- Government agencies
- Research institutes

Each serving in their individual capacity.
Guidance Document

• Multi-stakeholder contributions and consensus
• Practical and actionable recommendations
• Accountability section considers how each stakeholder can change the paradigm
• Toolkit provides adaptable resources not easily found elsewhere

mrctcenter.org/diversity-in-clinical-trials
Starting in April!

Practical Approaches to Improving Diversity in Clinical Trials

Second Wednesday each month
11AM - 12noon ET

LEANING IN: A WEBINAR SERIES

STAY TUNED FOR UPCOMING WEBINAR DETAILS!
Diversity in Clinical Trials Website: mrctcenter.org/diversity-in-clinical-trials

DIVERSITY, INCLUSION, AND EQUITY IN CLINICAL TRIALS

LEARNING IN: A WEBINAR SERIES
Practical Approaches to Improving Diversity in Clinical Trials
REGISTER NOW!

UPCOMING
February 10, 2021: Role of Data in Diversity: Genetics & RWD
More information and registration

Improve Diversity, Inclusion, and Equity in Clinical Trials

The Multi-Regional Clinical Trials Center released Version 1.0 of “Achieving Diversity, Inclusion, and Equity in Clinical Research” in August of 2020.

“Achieving Diversity, Inclusion, and Equity in Clinical Research” is a comprehensive Guidance Document and Toolkit that aims to clarify the importance of, advance the goals of, and provide practical and actionable ways to improve diverse representation of participants in clinical research.

Version 1.1, containing minor editorial updates, was released in January of 2021, and can be downloaded or ordered as a hard copy (priced at cost without royalties) below.

DOWNLOAD THE GUIDANCE DOCUMENT  ORDER THE PRINTED GUIDANCE AND TOOLKIT  DOWNLOAD THE TOOLKIT

New Updates March 2021
Genetics and Clinical Research Diversity: Implications of Recent Advances in Genetics and Genomics

Luther T. Clark, MD
Deputy Chief Patient Officer
Merck
February 10, 2021
## Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Study of heredity; function and composition of single genes</td>
</tr>
<tr>
<td>Genomics</td>
<td>Study of genes, their functions, inter-relationships and related techniques</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>Study of how genes affect a person’s response to particular drugs</td>
</tr>
<tr>
<td>Geographic Ancestry</td>
<td>Geographic locations of family origins</td>
</tr>
<tr>
<td>Genetic Ancestry</td>
<td>Method of quantifying ancestral background statistically by understanding genome history; different genomic segments may have their own ancestral history</td>
</tr>
<tr>
<td>Race</td>
<td>Sociocultural construct; not biologically distinct entities; genetically admixed populations</td>
</tr>
<tr>
<td>Precision Medicine</td>
<td>Identification of which approaches effective for which patients based on genetic, environmental, and lifestyle factors</td>
</tr>
</tbody>
</table>
Potential of Genetics & Genomic Medicine

Genetics, genomics, genomic technology

- Potential to improve health and health care by individual tailoring of prevention/treatment strategies

- Potential for wider adoption due to recent research and technological advances, and the decreasing cost of DNA sequencing

Approximately 20% of newly FDA approved molecular entities (NMEs) indicated differences in exposure and/or response across racial or ethnic groups that resulted in different prescribing recommendations for specific populations


mrctcenter.org/diversity-in-clinical-trials
Race, Ethnicity & Genetic Ancestry

• Self-identified race/ethnicity are crude social constructs; genetically admixed populations

• Geographical ancestry may correlate with race/ethnicity but does not predict an individual’s genotype or response to drugs

• Genomics and precision medicine may advance our understanding of race, ethnicity and their utility in clinical practice and research.

Differences in treatment response based on race, ethnicity, geographic ancestry, and genomics

<table>
<thead>
<tr>
<th>CONDITION/TREATMENT</th>
<th>GEOGRAPHIC/ETHNIC ANCESTRY</th>
<th>SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Anti-platelet therapy)</td>
<td>East Asians, Native Hawaiians</td>
<td>Genetic variation in expression of cytochrome (CYP) enzymes results in less efficacy of anti-platelet therapies in persons with CYP2C19<em>2 or CYP2C19</em>3 allele; frequencies of these genetic variations higher in East Asians, Native Hawaiians, other Pacific Islanders.</td>
</tr>
<tr>
<td>Carbamazepine (Treatment for Seizures)</td>
<td>Asians</td>
<td>HLA allele B*1502 marker for carbamazepine-induced Stevens–Johnson Syndrome and toxic epidermal necrolysis in Han Chinese; high frequency of this allele in many Asian populations; not found in Caucasian patients. FDA recommends genotyping Asians for the allele</td>
</tr>
<tr>
<td>NASH; NAFLD (nonalcoholic fatty liver disease)</td>
<td>Hispanics of Mexican, Dominican and Puerto Rican</td>
<td>Many Hispanics in U.S possess the PNPLA3 gene variation which has been associated with increased risk of NAFLD and NASH. Further studies needed to clarify differences in prevalence found among Hispanic subtypes living in the U.S.</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Northern European</td>
<td>Cystic fibrosis (CF) is a genetic disorder that is most common among people of Northern European ancestry; it is least common in Africans and Asians.</td>
</tr>
</tbody>
</table>
Differences in treatment response based on race, ethnicity, geographic ancestry, and genomics (Black, African Ancestry)

<table>
<thead>
<tr>
<th>CONDITION/TREATMENT</th>
<th>SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>BiDil (ISDN/Hydralazine)</td>
<td>Strong benefits in self-identified Blacks with heart failure; explanation unknown.</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>Individuals of African ancestry at greater risk for HBP; less responsive to ACE-I; greater risk for angioedema</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>Blacks more likely to have the common PCSK9 gene variants associated with loss-of-function (LOF), lower LDL and decreased CVD risk than Whites. Identification of genetic variants and enriched polymorphisms important in discovery and development of PCSK9 inhibitors.</td>
</tr>
<tr>
<td>Sickle Cell trait and Disease</td>
<td>SS results from a mutation in the beta-chain gene resulting in an abnormal hemoglobin beta chain. This mutation is more common in individuals with African ancestry, it is frequently thought of as a disease that only affects those of African decent, though it is found in other ethnicities.</td>
</tr>
</tbody>
</table>

Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a PCSK9<sup>-/-</sup> or PCSK9<sup>+/+</sup> Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 3278 black subjects who did not have a PCSK9<sup>-/-</sup> or PCSK9<sup>+/+</sup> allele (top) is compared with the distribution of levels among the 85 black subjects who had one of these two alleles (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

ARIC Study. Cohen et al 2006 NEJM
Hepatitis C: Interaction between viral genomics and host genomics

- Six major genotypes of the HCV that infect the liver that vary in prevalence (regional and ethnic/racial), disease severity, and response to treatment.
- Hepatitis C is potentially curable; treatment efficacy must be tested and demonstrated for each of the major viral genotypes – thus tested in the populations and regions where these are prevalent.
  - Genotype 1: most common in the U.S.; more common in Blacks than others
  - Genotype 4: most prevalent in the Middle East and Africa;
  - Genotype 5: most prevalent in South Africa; and
  - Genotype 6: most prevalent in Southeast Asia
Genomics and Health Equity

- Genomics has the potential to improve health outcomes broadly but benefits may not be equitably available to all populations
- Racial and ethnic minorities underrepresented in genomic databases
- Lack of diversity in genomic research limits understanding of the relationships of genes and disease in unstudied populations
- Genomic databases need greater inclusion of diverse ancestral populations and ancestral information

Direct-to-Consumer Genetic Testing

- Increasing popularity of DTC Genetic Testing
- Potential to support understanding of relationship between genetics, geography, ethnicity, interactions between biological and SDOH
- Individuals often have multiple geographic ancestries
- Genetic ancestries may be different from what individuals believe and how they self-identify
Key Takeaways

• The prevalence of genetic variants that impact disease can vary across populations.

• Increased diversity and inclusion of research participants in genomic and genetic research is necessary if the promises of genetic and genomic research are to benefit all.

• Greater representation of underrepresented individuals and those from geographically-diverse populations will increase knowledge of genomic variants in population subgroups, geographic ancestry and the genetic and biological mechanisms linking SDOH to health and disease.

• At present, self-identified race continues to have utility
  o correlates with geographic ancestry, a determinant of genomic variation (that can influence responses to drugs)
  o a proxy for other difficult to measure factors, i.e. SDOH (environment, health behaviors, effects of chronic bias, comorbidities, treatment seeking behavior and disease at presentation) that may impact treatment responses
Today’s speaker

Latha Palaniappan, MD, MS,
Professor of Medicine
Stanford University School of Medicine
Role of Data in Diversity
Examples with Real World Data

Latha Palaniappan MD, MS
Professor of Medicine
Stanford University School of Medicine
Role of Data in Diversity

- Real World Data for Diversity Research:
  - National Datasets
    - National Health Interview Survey (NHIS)
    - National Health and Nutrition Examination Survey (NHANES)
  - Electronic Health Records (EHR)
  - Mortality Data

- Clinical Implications
  - Culturally Competent Intervention Studies
  - Pharmacogenetic Differences

- Community Impact (CARE)
60% of the Globe

6% of the U.S.

30% of the Bay Area
< 1% of NIH Funding
Decisions around Asian health are made using mainly non-Asian data.
Global Racial Participation in Clinical Trials
Total Participants = 131,749

- White: 78.6%
- Asian: 4.2%
- Black: 5.4%
- Other: 11.8%

Global Population
Total Population = 7.8 billion

- White: 59.4%
- Asian: 11.5%
- Black: 12.1%
- Other: 17.0%

Source: U.S. Food & Drug Administration. FDA, 2016, p. 15, 2015 - 2016 GLOBAL PARTICIPATION IN CLINICAL TRIALS REPORT.
Source: https://www.census.gov/popclock/world
Asian Americans
Income: % Living in Poverty

Source: Pew Research Center, US census, American Community Survey 2015 (IPUMS)
Role of Data in Diversity
National Datasets: NHIS/NHANES

Psychological Distress and Mental Health Service Utilization Disparities in Disaggregated Asian American Populations, 2006–2018
Kapilana K. Balaraman, BS, Nicholas Ortega, Shozen Dan, Malathi Srinivasan, MD, Latha Palaniappan, MD MS, Jaiveer Singh, Sukyung Chung, PhD, and Shashank V. Joshi MD

Disaggregated Asian American Cigarette and Alternative Tabacco Product Use: Results from the National Health Interview Survey (NHIS), 2006–2018
Maneaha Rao; Lilly Bar; Yunnan Yu; Sid Venkatraman; Malathi Srinivasan, MD; Arnab Mukherjeea, DrPH, MPH; Jiang Li, PhD, MPH; Sukyung Chung, PhD; Latha Palaniappan, MD MS

Effects of Ethnicity on Complementary Therapy Adoption over 10 Years, National Health Interview Survey 2007 and 2017
Yuelin He; Bridgette Han; Darynn Gayle Paragas; Nora Sharp; Latha Palaniappan, MD MS; Sukyung Chung, PhD; Randall S. Stafford, MD, PhD; Malathi Srinivasan, MD

N[Asian Americans] < 1,500
Role of Data in Diversity
Electronic Health Records

N[Asian Americans] = 250,000
Role of Data in Diversity
Mortality Records

Geographic Variations in Cardiovascular Disease Mortality Among Asian American Subgroups, 2003–2011

One Size Does Not Fit All: Marked Heterogeneity in Incidence of and Survival from Gastric Cancer among Asian American Subgroups

Annals of Internal Medicine

Socioeconomic Differences in the Epidemiologic Transition From Heart Disease to Cancer as the Leading Cause of Death in the United States, 2003 to 2015

An Observational Study

The Burden of Cancer in Asian Americans:
A Report of National Mortality Trends by Asian Ethnicity

Research Article

Cancer Epidemiology, Biomarkers & Prevention
Role of Data in Diversity
Examples with Real World Data

Uncovering Consistent Signals on Health

Mortality Records

Electronic Health Records

National Datasets

Electronic Health Records

Dyslipidemia in Special Ethnic Populations

Electronic Health Records

Psychological Distress and Mental Health Service Utilization Disparities in Disaggregated Asian American Populations, 2006-2018

Electronic Health Records

Disaggregated Asian American Cigarette and Alternative Tobacco Product Use: Results from the National Health Interview Survey (NHIS), 2006-2018

Electronic Health Records

Effects of Ethnicity on Complementary Therapy Adoption over 10 Years, National Health Interview Survey 2007 and 2017

Electronic Health Records

“Are All of These Things We Don’t Eat?” A Culture-Centered Approach to Dietary Health-RelatedArts Needs for Asian Indians Living in the United States

Electronic Health Records

Mortality Records

Electronic Health Records

Clinically Identified Postpartum Depression in Asian American Mothers

Electronic Health Records

Disaggregated Asian American Cigarette and Alternative Tobacco Product Use: Results from the National Health Interview Survey (NHIS), 2006-2018

Electronic Health Records

Manaeha Rao; Lilly Bar; Yunnan Yu; Sid Venkatraman; Malathi Srinivasan, MD; Arnab Mukherjea, DrPH, MPH; Jiang Li, PhD, MPH; Sukyung Chung, PhD; Latha Palaniappan, MD MS

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Electronic Health Records

Psychological Distress and Mental Health Service Utilization Disparities in Disaggregated Asian American Populations, 2006-2018

Electronic Health Records

Cross-national comparisons of increasing suicidal mortality rates for Koreans in the Republic of Korea and Korean Americans in the USA, 2003-2012

Electronic Health Records

...
Engaging South Asian women with type 2 diabetes in a culturally relevant exercise intervention: a randomized controlled trial

Alesslu Natesan,1 Vani C Nimbal,2 Susan L Ivey,1 Elsie J Wang,3 Kristine A Madsen,1 Latha P Palaniappan2

Clinical experience with a relatively low carbohydrate, calorie-restricted diet improves insulin sensitivity and associated metabolic abnormalities in overweight, insulin resistant South Asian Indian women

Andrea C Backes BA, Fahim Abbasi MD, Cindy Lamendola RN, Tracey L McLaughlin MD, Gerald Reaven MD, Latha P Palaniappan MD

STRONG-D: Strength training regimen for normal weight diabetes: Rationale and design

Lida Farooqi1, Saniya Bonde1, Danielle Tatiana Goni1, Chi Wai Wong2, Myo Wong2, Khalil Wali1, Saron Araya2, Sayed Azamey2, Gabriella Schreiner2, Monica Bandy2, Sonia Sunita Ragharam2, Anuja Mittal1, Ashish Mukherji1, Tenzin Wangdak1, Ruth Talamoa1, Katherine Vera1, Carla Nazifi-Coelho1, Leah Groppo CDE1, Mary Christensen1, Neil Johansen1, Francois Haddad1, Minal Moharrir1, Latha Palaniappan1
Role of Data in Diversity
Pharmacogenetic Differences

Cardiology
- Rosuvastatin Calcium
- Warfarin
- Clopidogrel (Plavix)

Oncology
- Irinotecan
- Tamoxifen

Infectious Disease and Rheumatology
- Atazanavir
- Voriconazole

Cardiology

Oncology

Infectious Disease and Rheumatology

Cardiology

Oncology

Infectious Disease and Rheumatology
Role of Data in Diversity
Community Impact

CARE seeks to improve the health of Asians by increasing knowledge, empowering education and positively impacting their clinical care.

Promotional Video
https://vimeo.com/504220633

Research
- Heart Risk factors among Asian Immigrants
- Asian Americans and COVID-19 Deaths
- The disaggregation of Asian American Health Data

Education
- Courses on minority health
- CARE Scholars Program
- Chi Li Pao Hong Kong University (HKU) Enrichment Year, 2021-2022
Role of Data in Diversity

Contacts

lathap@stanford.edu
Today’s speaker

Nicole Richie, PhD
Global Head
Health Equity and Population Science
Genentech Roche
Race/Ethnicity vs Ancestry vs Geographic Origin

Ancestry is driven by **genetics**, whereas race and ethnicity are social constructs.

<table>
<thead>
<tr>
<th>Race</th>
<th>Ethnicity</th>
<th>Ancestry</th>
<th>Geographic Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reported</strong> or physician-reported:</td>
<td><strong>Self-reported</strong> or physician-reported:</td>
<td><strong>Calculated</strong> by genetic information compared to continental-level information:</td>
<td><strong>Belonging</strong> to or characteristic of a particular region:</td>
</tr>
<tr>
<td>• American Indian or Alaska Native</td>
<td>• Hispanic or Latino</td>
<td>• AFR (African)</td>
<td>• North Africa</td>
</tr>
<tr>
<td>• Asian</td>
<td></td>
<td>• AMR (Native American, all continent)</td>
<td>• East Africa</td>
</tr>
<tr>
<td>• Black or African American</td>
<td></td>
<td>• EUR (European)</td>
<td>• Central Africa</td>
</tr>
<tr>
<td>• Native Hawaiian or other Pacific Islander</td>
<td></td>
<td>• EAS (East-Asian)</td>
<td>• West Africa</td>
</tr>
<tr>
<td>• White</td>
<td>Other ethnic groups include cultural (e.g. Romani), religious (e.g. Jews), language, or nationality groups (e.g. Puerto Ricans)</td>
<td>• SAS (South Asian)</td>
<td>• Southern Africa</td>
</tr>
<tr>
<td>These categories have been historically used in the United States. Hispanic or Latino is sometimes asked together with Race</td>
<td></td>
<td>Borderline/fringe cases are difficult to assess (e.g. middle-eastern, admixed populations, Pacific-islanders)</td>
<td>etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Geographic distance may be an excellent predictor of genetic differentiation within a region.</td>
</tr>
</tbody>
</table>
The Utility of Data Elements

Ancestry and self reported race/ethnicity

- Ancestry is a way of categorizing genes
- Clinical relevance of ancestry: understanding if variant associated with pathology vs variant associated with ancestry
- Relevance contingent upon understanding biology: requires more diverse genomic data

- Self reported race can provide relevant environmental information on risk and response measurable by epigenetics
Understudied Populations

Biased Genetic Discoveries

Available genomic data and medical research is predominantly based on European ancestry, leaving significant amounts of world wide genotypic and phenotypic variation undiscovered.

Genomic Based Healthcare is becoming the Norm

Without conscious effort, existing inequities will be exacerbated over time, contributing to a widening gap in access to innovation.

Molecular Profiling is Guideline Recommended

Broad molecular profiling to inform genomically-matched therapy is recommended by NCCN Guidelines

“NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.”

References:
NCCN – National Comprehensive Cancer Network


Genentech Proprietary and Confidential. For discussion purposes only.
Disease pattern, clinical presentation, and therapeutic response can vary dramatically by race/ethnicity and ancestral background.

**Clinical Importance**

- **Biomarker Prevalence**
- **Differences in Safety/Efficacy**
- **Scientific Discovery**

#### Lung Cancer
- **KRAS** more common in European ancestry
- **EGFR** more common in east Asian ancestry

#### Breast Cancer
- Genomic study of Latina women led to discovery of novel variant with a protective effect

#### Asthma
- Variable efficacy of beta agonists in African ancestry patients due (in part) to two genetic variants

#### Seizure Disorders
- Carbamazepine Boxed warning for HLA-B*1502 in Asian patients

Genomic data helps us understand how patients react and respond to medicines.
Scientific Importance

Rare variants tend to be population specific and disproportionately important in predicting disease risk and drug response.

Robust, powerful genome sequencing enables greater understanding of disease biology, identification of novel targets.

Single-ancestry genome-wide association studies (GWAS) limits clinical utility

Inferences derived from single-ancestry may be incomplete or inaccurate

- Misdiagnosis of pathogenic hypertrophic cardiomyopathy in African Americans
- Population-enriched GWAS identified novel variants (AD, CRC, RA)

Sources:
1) Genetics for all. [Link](https://www.nature.com/articles/s41588-019-0394-7) (Access March 2020)
2) Genetic disease risks can be misestimated across global populations. [Link](https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1561-7) (Access March 2020)
3) Genetic Misdiagnoses and the Potential for Health Disparities. [Link](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5292722/) (Access March 2020)
4) The more from East-Asian, the better risk prediction of colorectal cancer risk by GWAS-identified SNPs among Japanese. [Link](https://rd.springer.com/content/pdf/10.1007%2Fs00432-017-2505-4.pdf) (Access March 2020)
Prediction of actionable targets can vary based on Ancestry

Frequency of somatic alterations in driver genes in non-small cell lung cancer by SNP-inferred ancestry group

- Recapitulate known EGFR differences
  - East Asian: alteration rate 0.46 (0.44-0.49)
  - European: alteration rate 0.14 (0.12-0.14 95% CI)
  - p<2.2 x 10^-16

- Recapitulate known KRAS differences
  - East Asian: 0.14 (0.13-0.16)
  - European: 0.32 (0.32-0.33)
  - p<2.2 x 10^-16

Genes with significantly different alteration frequency between samples of different inferred ancestry groups

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease ontology</th>
<th>P value</th>
<th>African alteration frequency</th>
<th>European alteration frequency</th>
<th>Odds Ratio 2.5% CI</th>
<th>Odds Ratio 97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>lung adenocarcinoma</td>
<td>1.23 x 10^-19</td>
<td>0.684</td>
<td>0.565</td>
<td>0.601</td>
<td>0.536</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>breast carcinoma (nos)</td>
<td>1.23 x 10^-12</td>
<td>0.234</td>
<td>0.380</td>
<td>1.834</td>
<td>1.540</td>
</tr>
<tr>
<td>KRAS</td>
<td>colon adenocarcinoma (crc)</td>
<td>1.82 x 10^-11</td>
<td>0.596</td>
<td>0.496</td>
<td>0.671</td>
<td>0.596</td>
</tr>
<tr>
<td>TP53</td>
<td>breast invasive ductal carcinoma (idc)</td>
<td>2.33 x 10^-10</td>
<td>0.732</td>
<td>0.607</td>
<td>0.566</td>
<td>0.471</td>
</tr>
<tr>
<td>PTEN</td>
<td>uterus endometrial adenocarcinoma (nos)</td>
<td>9.00 x 10^-12</td>
<td>0.205</td>
<td>0.512</td>
<td>3.024</td>
<td>2.069</td>
</tr>
<tr>
<td>VHL</td>
<td>kidney renal cell carcinoma</td>
<td>1.61 x 10^-9</td>
<td>0.092</td>
<td>0.495</td>
<td>7.433</td>
<td>3.331</td>
</tr>
<tr>
<td>KRAS</td>
<td>lung adenocarcinoma</td>
<td>1.66 x 10^-9</td>
<td>0.319</td>
<td>0.598</td>
<td>1.408</td>
<td>1.295</td>
</tr>
<tr>
<td>BRAF</td>
<td>colon adenocarcinoma (crc)</td>
<td>4.85 x 10^-9</td>
<td>0.052</td>
<td>0.100</td>
<td>1.990</td>
<td>1.549</td>
</tr>
<tr>
<td>RBM10</td>
<td>lung adenocarcinoma</td>
<td>1.29 x 10^-8</td>
<td>0.045</td>
<td>0.085</td>
<td>1.937</td>
<td>1.513</td>
</tr>
<tr>
<td>APC</td>
<td>colon adenocarcinoma (crc)</td>
<td>1.34 x 10^-8</td>
<td>0.026</td>
<td>0.757</td>
<td>0.659</td>
<td>0.564</td>
</tr>
<tr>
<td>TP53</td>
<td>breast carcinoma (nos)</td>
<td>2.18 x 10^-8</td>
<td>0.623</td>
<td>0.516</td>
<td>0.649</td>
<td>0.555</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>breast invasive ductal carcinoma (idc)</td>
<td>8.66 x 10^-8</td>
<td>0.520</td>
<td>0.321</td>
<td>1.888</td>
<td>1.374</td>
</tr>
</tbody>
</table>

Genes with significantly different alteration frequency between samples of African inferred ancestry compared to European inferred ancestry

Source: 1) Conelly et al., 2018, AACR abstract
Data Inclusive of Worldwide Genetic Variation Increases The Ability to Successfully Develop New Drugs for Patients

Value of Broadening Population Specific Data in Early Research and Discovery

50% of clinical trials fail

Genetically supported targets have >2X Success Rate in clinical development

Source: https://www.nature.com/articles/ng.3314
Ability to Develop Personalized Healthcare Requires Understanding Biologic and Social Determinants

Determinants of Health\(^1\)

**Extrinsic**
- 11% Medical Care
- 38% Individual Behavior
- 30% Social Circumstances

**Social**

**Intrinsic**
- 21% Genetics & Biology

Individualized Human Information System

“Always remember that you are absolutely unique. Just like everyone else.”
Margaret Mead

Adapted from Topol Cell 2014
Takeaway

With greater and more refined technology and scientific capabilities there is an unprecedented opportunity to realize the promise of personalized healthcare.

Diversity in genomic and clinical data is fundamental to this notion and must be included throughout the full lifecycle of drug discovery, development, and clinical practice.
Discussion and Questions