AAHRPP
Association for the Accreditation of Human Research Protection Programs, Inc.®

2023 “HRPP Innovations” Webinar Series

The Importance of Diversity in Genetic Studies

July 26, 2023

1:00 pm – 2:30 pm ET

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Format for 2023

Attendee Hub

- Livestreamed Content
- Live Q&A
- Chat/Discussions

Webinar Sessions

- Three Webinars: April, July, November
- One Attendee Hub

Community

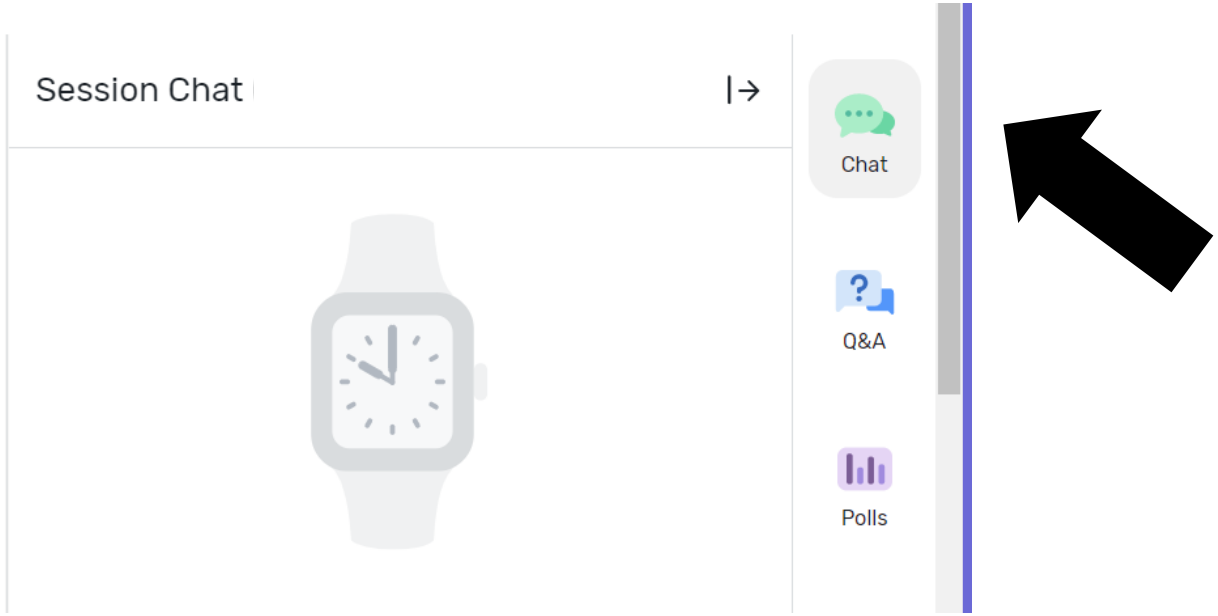
- Continue Discussions after Webinars Conclude
- Check Upcoming AAHRPP Events
- Resources from Speakers

On-Demand Content

- Webinar Recordings on Hub
- Available for the Whole Year

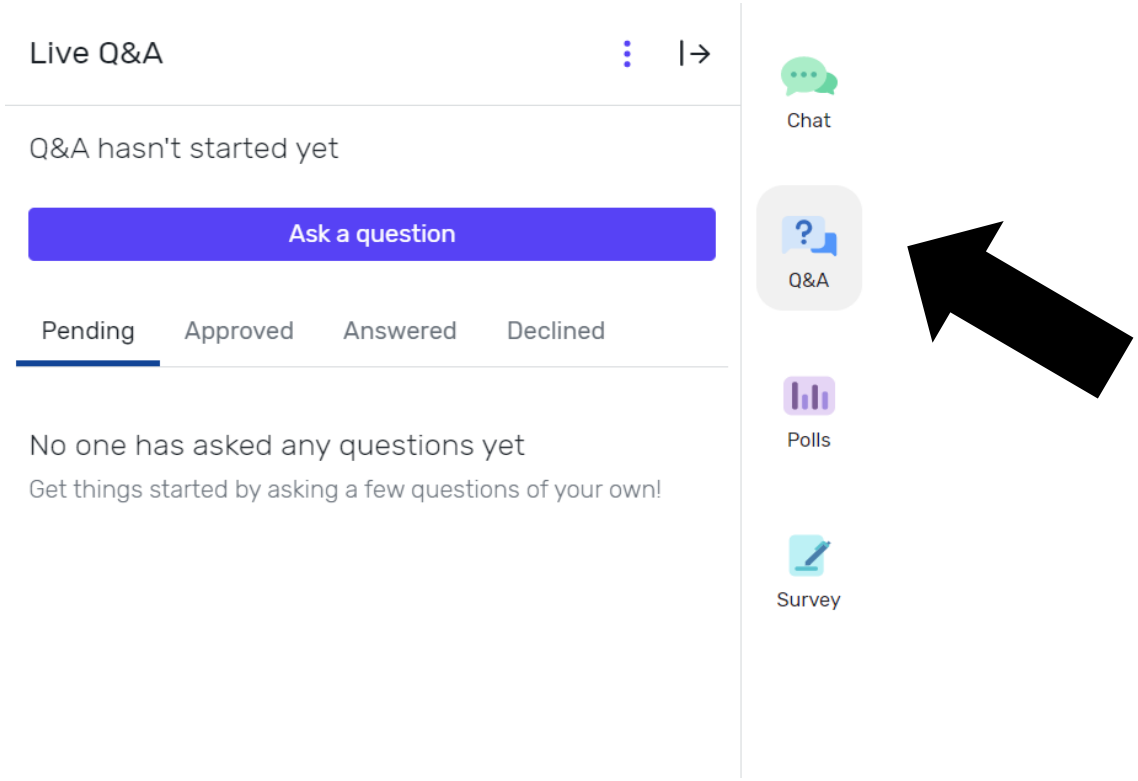
Chat Feature

To chat with your colleagues before and after the session, or if you have technical questions, use the “Chat” icon



Questions

To ask questions about the topic for the presenters, please use the “Q&A” icon:



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Join Us for These Upcoming AAHRPP Webinars:

August 8, 2023: 3:00 pm – 4:00 pm ET:

Ask AAHRPP Webinar: **Evaluation of Practice (the Site Visit) –** 4th of the six-part series
Speakers: Robert Hood, AAHRPP; AAHRPP Operations Team Members
Moderator: Nichelle Cobb, AAHRPP

October 10, 2023, 3:00 pm – 4:00 pm ET:

Ask AAHRPP Webinar: **Council on Accreditation Review –** 5th of the six-part series
Speakers: Robert Hood, AAHRPP; AAHRPP Council Members
Moderator: Nichelle Cobb, AAHRPP

November 14, 2023, 1:00 pm – 2:30 pm ET:

HRPP Innovations Webinar: **Innovative Practices by AAHRPP-Accredited Organizations**
Speakers: Representatives from three AAHRPP-accredited organizations will present their "Areas of Distinction"

December 12, 2023, 3:00 pm – 4:00 pm ET:

Ask AAHRPP Webinar: **Response to Council Review –** Last of the six-part series
Speakers: Robert Hood, AAHRPP; AAHRPP Consultants/Operations Team Members
Moderator: Nichelle Cobb, AAHRPP

Join Us in San Diego, CA:

2024 AAHRPP ANNUAL CONFERENCE:

Science and Standards in San Diego

MARK YOUR CALENDARS FOR ONE OF THE RESEARCH COMMUNITY'S MUST-ATTEND ANNUAL EVENTS. MORE DETAILS TO FOLLOW.

DATE:
May 21 - May 23, 2024

LOCATION:
Sheraton San Diego Hotel & Marina
1380 Harbor Island Dr, San Diego, CA 92101

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Ivy Tillman, EdD, CCRC, CIP
Director of Research Operations
Mayo Clinic

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Omar Rahman, MD

Director of Clinical Genetics, Department of Pediatrics

Weill Cornell Medicine

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of Human Research Protection Programs, Inc.®

Bruce Gordon, MD

Assistant Vice Chancellor for Regulatory Affairs

University of Nebraska Medical Center

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2023 AAHRPP Webinar Series

The Importance of Diversity in Genetic Studies

Dr. Ivy Tillman
Mayo Clinic

Objectives

This webinar will explore:

- Why genomic research in diverse populations is important to addressing health disparities and advancing clinical knowledge
- How an increase in diversity of genomes has changed the understanding of some health conditions and approaches to treatment
- The current state of genomic research and barriers to the inclusion of diverse populations
- The issues researchers, IRBs and HRPPs should consider when designing, reviewing, and conducting research involving biospecimen collection for genomic analysis to ensure equitable subject selection and sound study design that promotes generalizability to diverse populations

Genetics Primer

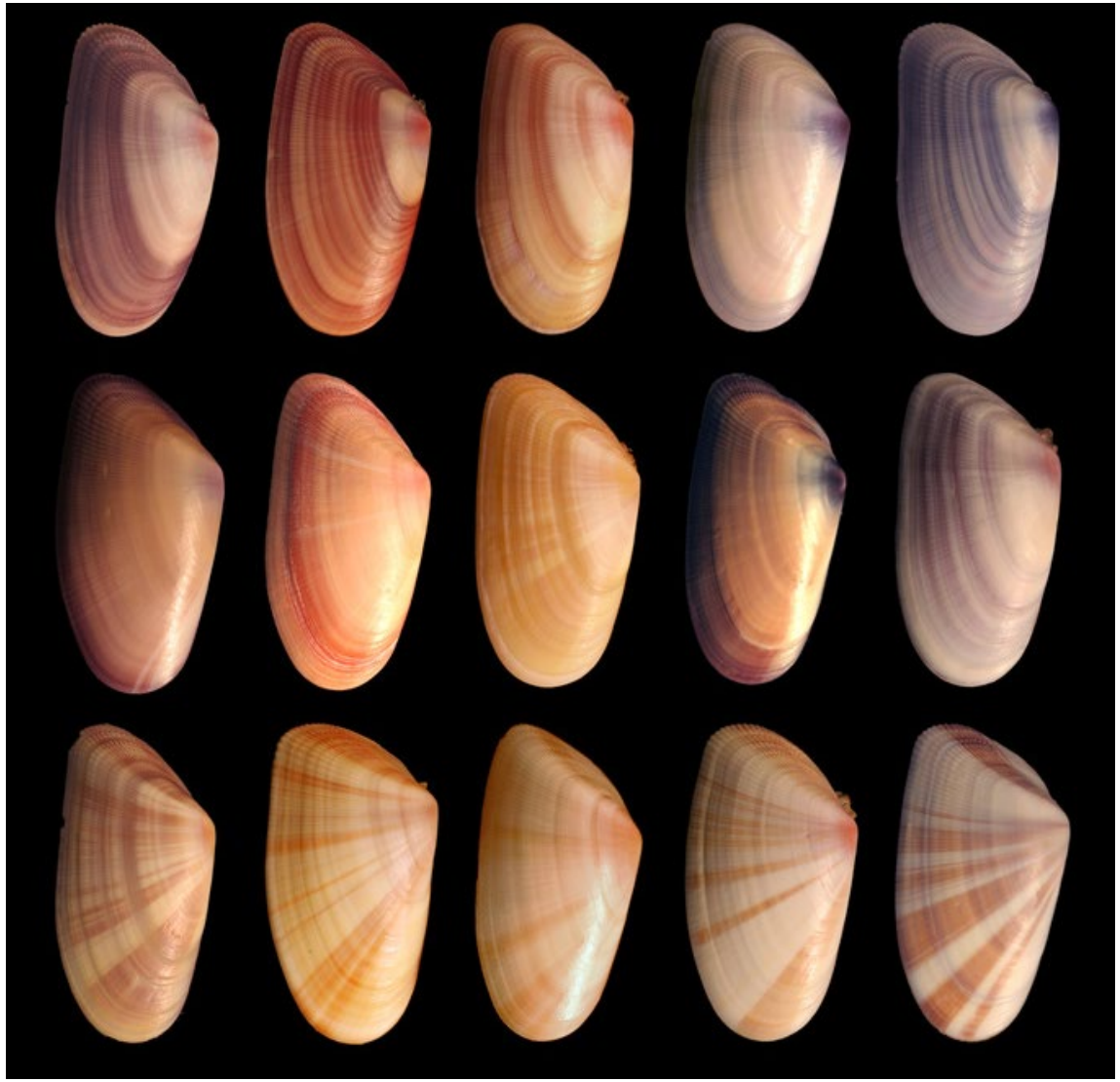
- **Gene:** segment of DNA that contains instructions for building the molecules that make the body work. Parents pass their genes to their offspring.

- **Genetic variation & Disease**: Some diseases cluster in families, similar to other inherited traits. Genetic variation can influence how people respond to certain medicines as well.

https://engineering.tufts.edu/deij/about/definitions
https://www.biologyonline.com/dictionary/genetic-diversity
https://www.nigms.nih.gov/education/Documents/Studying_genes

Genetics Primer

- **Diversity:** individual and group/social differences
- **Genetic Diversity:** range of different inherited traits within a species



https://engineering.tufts.edu/deij/about/definitions
https://www.biologyonline.com/dictionary/genetic-diversity
https://www.nigms.nih.gov/education/Documents/Studying_genes

Genetic Diversity & Health Disparities

- Lack of diversity in genetic research challenges the generalizability of findings from large scale genomic databases.

- Genetic diversity:
  - Has a direct impact on the diagnosis and treatment of diseases
  - Assists in addressing health disparities
  - Not solely defined by the social construct of race. Consider genetic diversity to include ethnicity and ancestry

Fatumo, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). A roadmap to increase diversity in genomic studies. *Nature medicine*, *28*(2), 243-250.
Tan, S. H., Petrovics, G., & Srivastava, S. (2018). Prostate cancer genomics: recent advances and the prevailing underrepresentation from racial and ethnic minorities. *International journal of molecular sciences*, *19*(4), 1255.

The Case for Genetic Diversity

Current State

Genetic imbalance

Future State

Genetic equity

Fatumo, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). A roadmap to increase diversity in genomic studies. *Nature medicine*, *28*(2), 243-250.
Tan, S. H., Petrovics, G., & Srivastava, S. (2018). Prostate cancer genomics: recent advances and the prevailing underrepresentation from racial and ethnic minorities. *International journal of molecular sciences*, *19*(4), 1255.

Addressing Barriers to Genetic Equity

- Scientific challenges
- Logistical challenges
- Individual vs. collective needs
- Expanding our focus: systems that perpetuate genetic imbalance

Fatumo, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). A roadmap to increase diversity in genomic studies. *Nature medicine*, *28*(2), 243-250.
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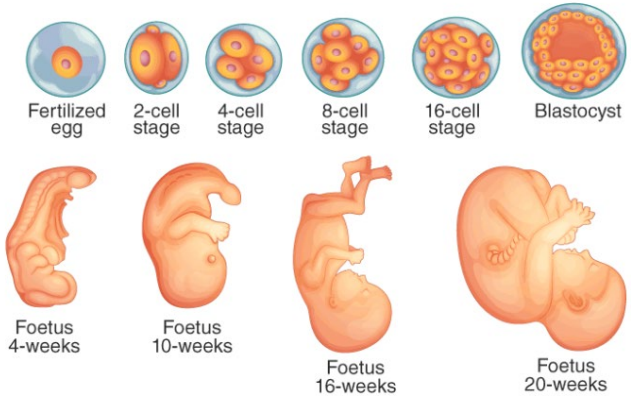
2023 AAHRPP Webinar Series

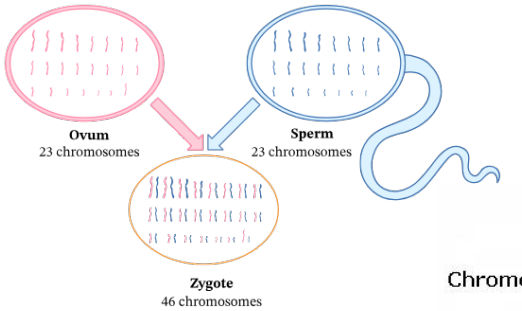
Genetics, Research, & Diversity

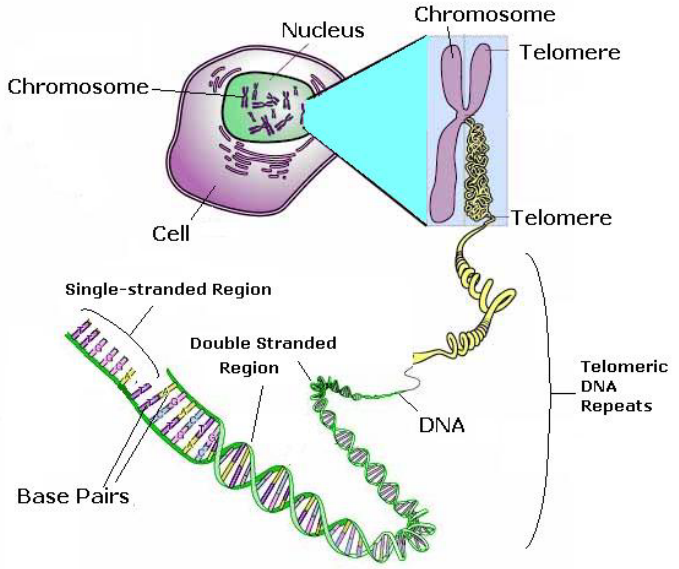
Omar Rahman, MD
Weill Cornell Medicine

Introduction to Genetics

- DNA carries genetic material from parent to offspring and contains the instructions to create a human being
- Chromosomes are each made up of a single coiled DNA molecule
  - Alphabet of DNA is four letters long (ATCG)
  - 6 billion base pairs of DNA in one nucleus

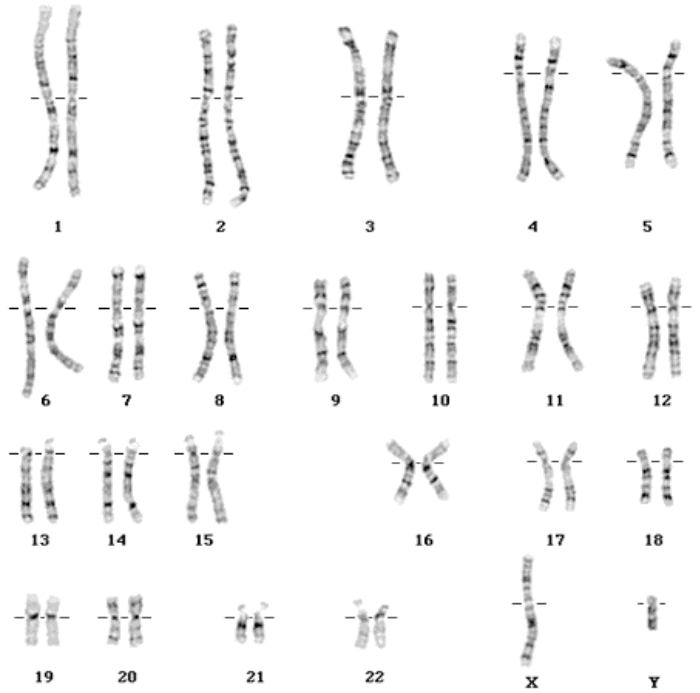






Genes and chromosomes

- Genes are carried on 46 chromosomes
- Chromosomes come in 23 pairs: 1-22, and sex chromosomes
- Human Genome Project identified 22,000 genes in humans
- Approximately 500-1000 genes per chromosome



Genetic Testing

- Chromosome analysis

DNA analysis

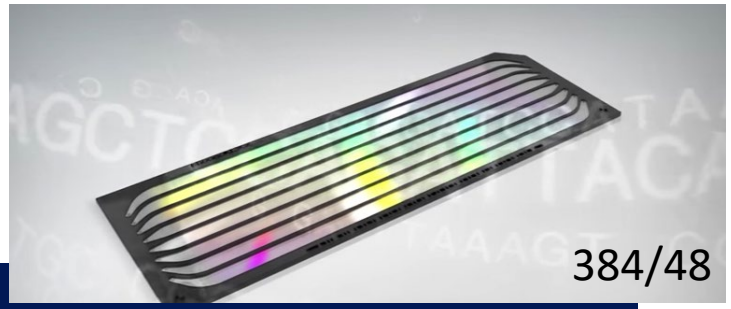
- Exome sequencing
  - Coding regions of 22,000 genes
  - Makes up 1% of the entire genome
  - Only 7000 genes have been associated with human disease
- Genome sequencing
  - Includes non-coding regions
  - Much of this part is not understood

DNA databases (e.g. gnomAD)

- 125,000 exomes
- 15,000 genomes

All of Us RESEARCH PROGRAM

biobank uk
Enabling scientific discoveries that improve human health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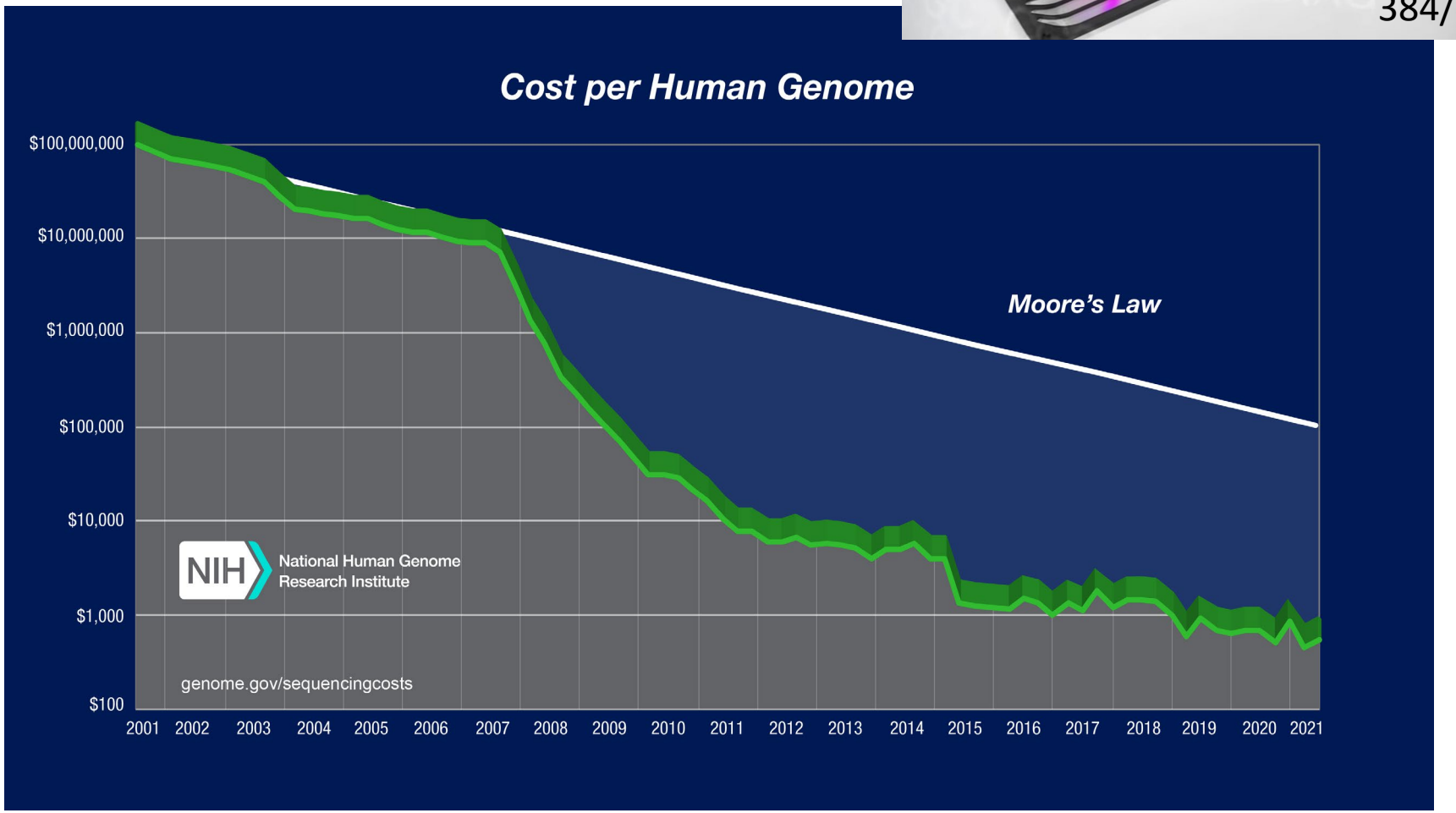
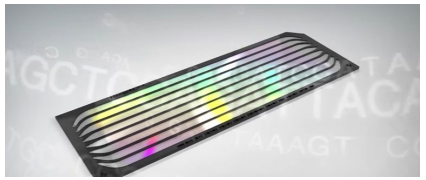
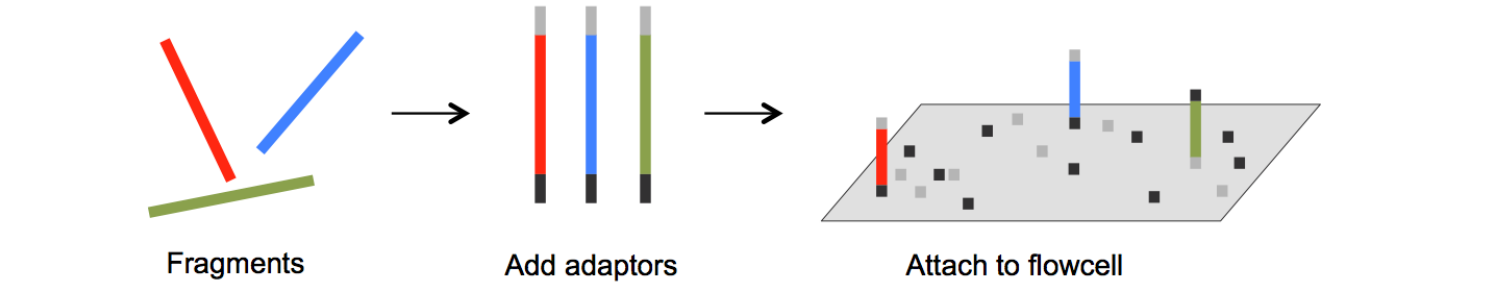
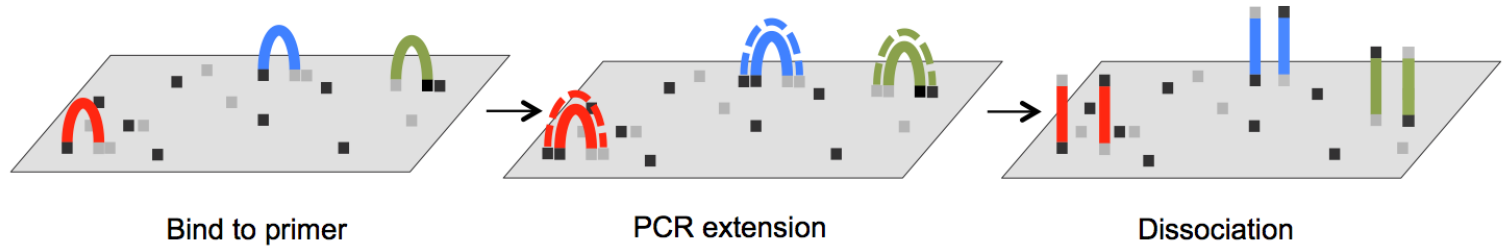
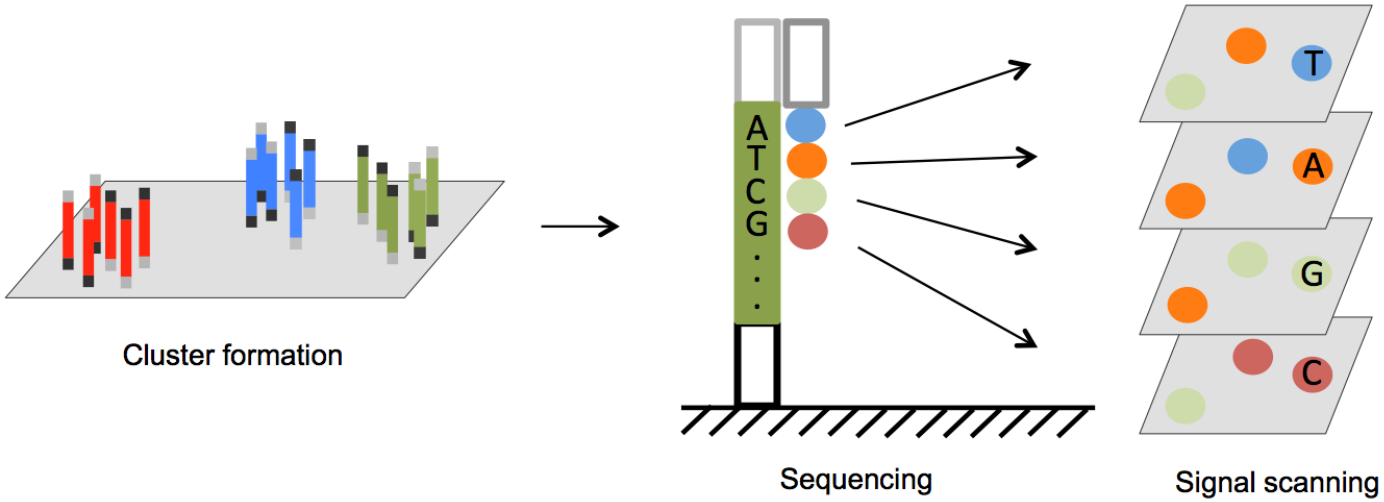

Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
Moore's Law
NIH
National Human Genome
Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021



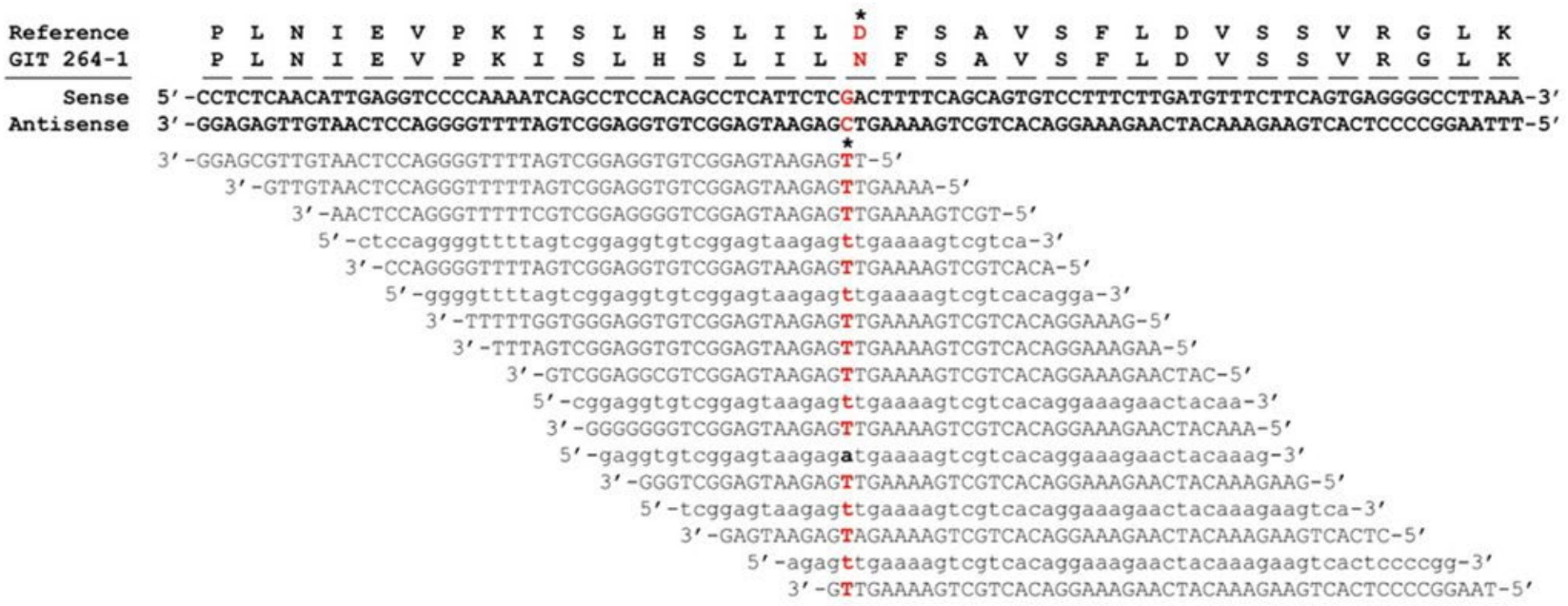






- Next-generation sequencing
- Massively parallel sequencing

Coverage


Reference P L N I E V P K I S L H S L I L D F S A V S F L D V S S V R G L K
GIT 264-1 P L N I E V P K I S L H S L I L N F S A V S F L D V S S V R G L K
Sense 5′-CCTCTCAACATTGAGGTCCCCAAAATCAGCCTCCACAGCCTCATTCTCGACTTTTCAGCAGTGTCCTTTCTTGATGTTTCTTCAGTGAGGGGCCTTAAA-3′
Antisense 3′-GGAGAGTTGTAACTCCAGGGGTTTTAGTCGGAGGTGTCGGAGTAAGAGCTGAAAAGTCGTCACAGGAAAGAACTACAAAGAAGTCACTCCCCGGAATTT-5′
3′-GGAGCGTTGTAACTCCAGGGGTTTTAGTCGGAGGTGTCGGAGTAAGAGTT-5′
3′-GTTGTAACTCCAGGGTTTTTAGTCGGAGGTGTCGGAGTAAGAGTTGAAAA-5′
3′-AACTCCAGGGTTTTTCGTCGGAGGGGTCGGAGTAAGAGTTGAAAAGTCGT-5′
5′-ctccaggggttttagtcggaggtgtcggagtaagagttgaaaagtcgtca-3′
3′-CCAGGGGTTTTAGTCGGAGGTGTCGGAGTAAGAGTTGAAAAGTCGTCACA-5′
5′-ggggttttagtcggaggtgtcggagtaagagttgaaaagtcgtcacagga-3′
3′-TTTTTGGTGGGAGGTGTCGGAGTAAGAGTTGAAAAGTCGTCACAGGAAAG-5′
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5′-gaggtgtcggagtaagagatgaaaagtcgtcacaggaaagaactacaaag-3′
3′-GGGTCGGAGTAAGAGTTGAAAAGTCGTCACAGGAAAGAACTACAAAGAAG-5′
5′-tcggagtaagagttgaaaagtcgtcacaggaaagaactacaaagaagtca-3′
3′-GAGTAAGAGTAGAAAAGTCGTCACAGGAAAGAACTACAAAGAAGTCACTC-5′
5′-agagttgaaaagtcgtcacaggaaagaactacaaagaagtcactccccgg-3′
3′-GTTGAAAAGTCGTCACAGGAAAGAACTACAAAGAAGTCACTCCCCGGAAT-5′

Types of DNA variants

Clinical testing

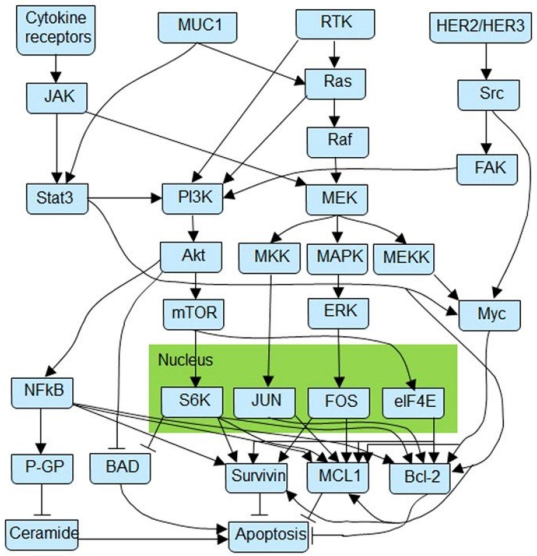
- QA/QC required (CLIA certification)
- High coverage
- Reporting of all variants based on phenotype
- TAT weeks to months
- Reclassification of variants automatic
- Reanalysis of data every 1-2 years
- Secondary variants (opt-in)

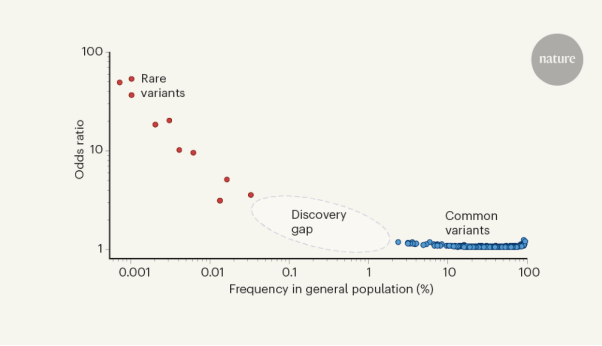
Research testing

- CLIA certification may apply in some circumstances
- Lower coverage due to cost
- Reports out pathogenic and LP variants only
- TAT months to years
- Reclassification and reanalysis are not scheduled
- Secondary variants (opt-out)

Benefits of Genetic Research

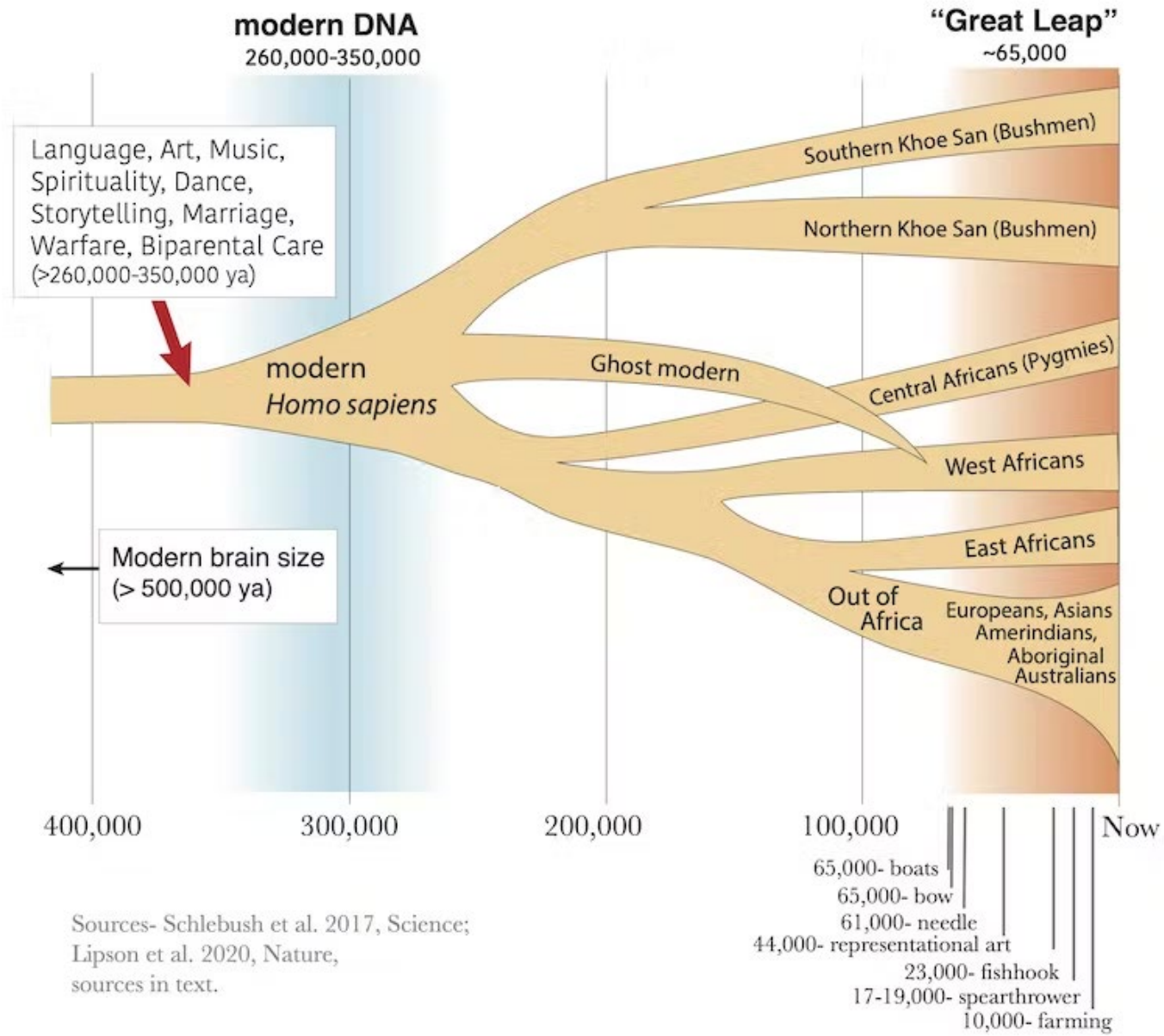
- Rare diseases
- Learn about the biology of major networks
- Common disorders
- Therapeutic targets





Diversity in Genetic Research

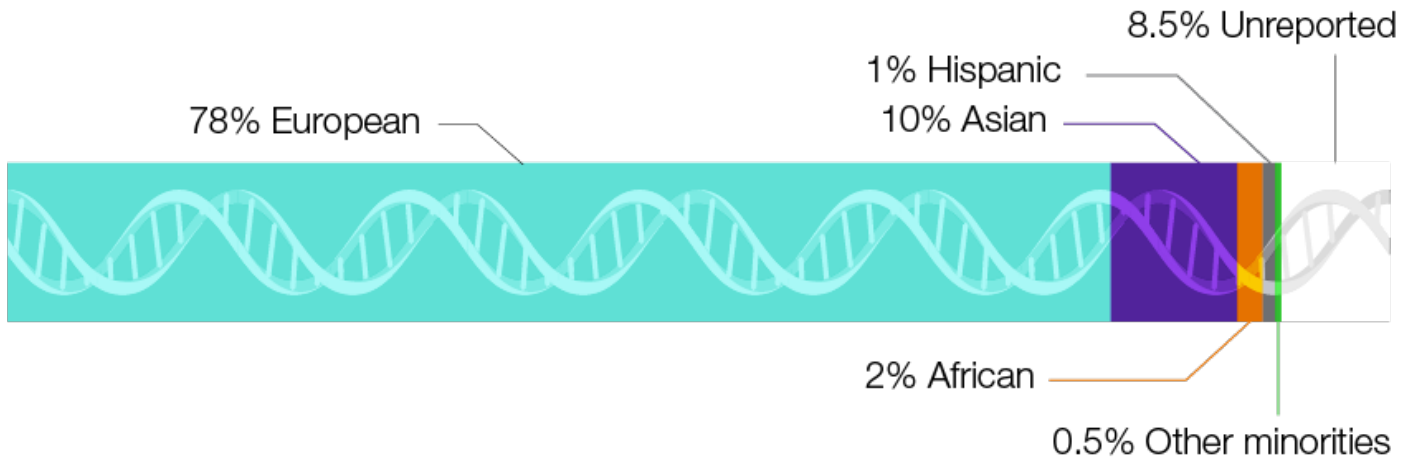
- Why is it important?



Sources- Schlebush et al. 2017, Science;
Lipson et al. 2020, Nature,
sources in text.

Diversity in Genetic Research

- Why is it important?
- How diverse is our current research participant population?
  - As of 2019…



Diversity in Genetic Research

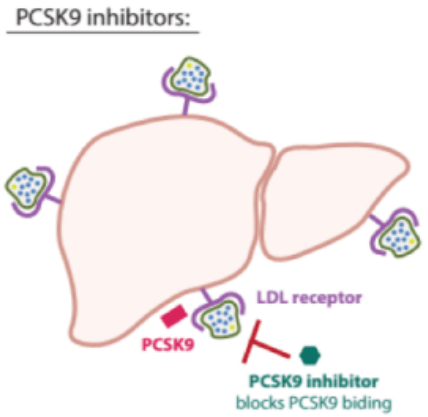
- Why is it important?
- How diverse is our current research participant population?
- What can we learn by including diverse populations?

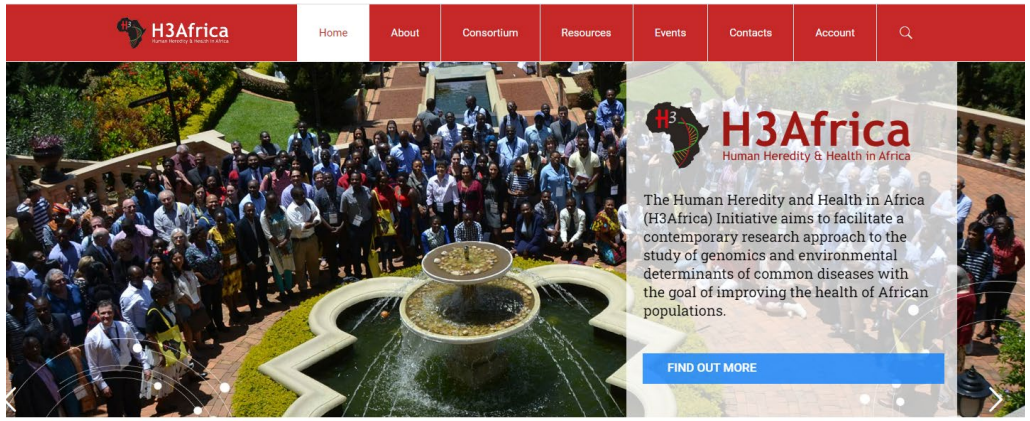
Examples of Research Findings in Diverse Populations

- Analysis of 910 individuals of African descent found 300 million variants (10%) absent from the reference genome
- Discovery of PCSK9 variants in Africans is a new target for treatment of dyslipidemia
- Study of 1000 Xhosa individuals had equivalent power to detect associations as a study of 5000 Swedish individuals
- Congenital hearing loss in Europeans is commonly due to a gene deletion from a common ancestor, but in Africans is due to novel variants allowing for discovery of new mechanisms

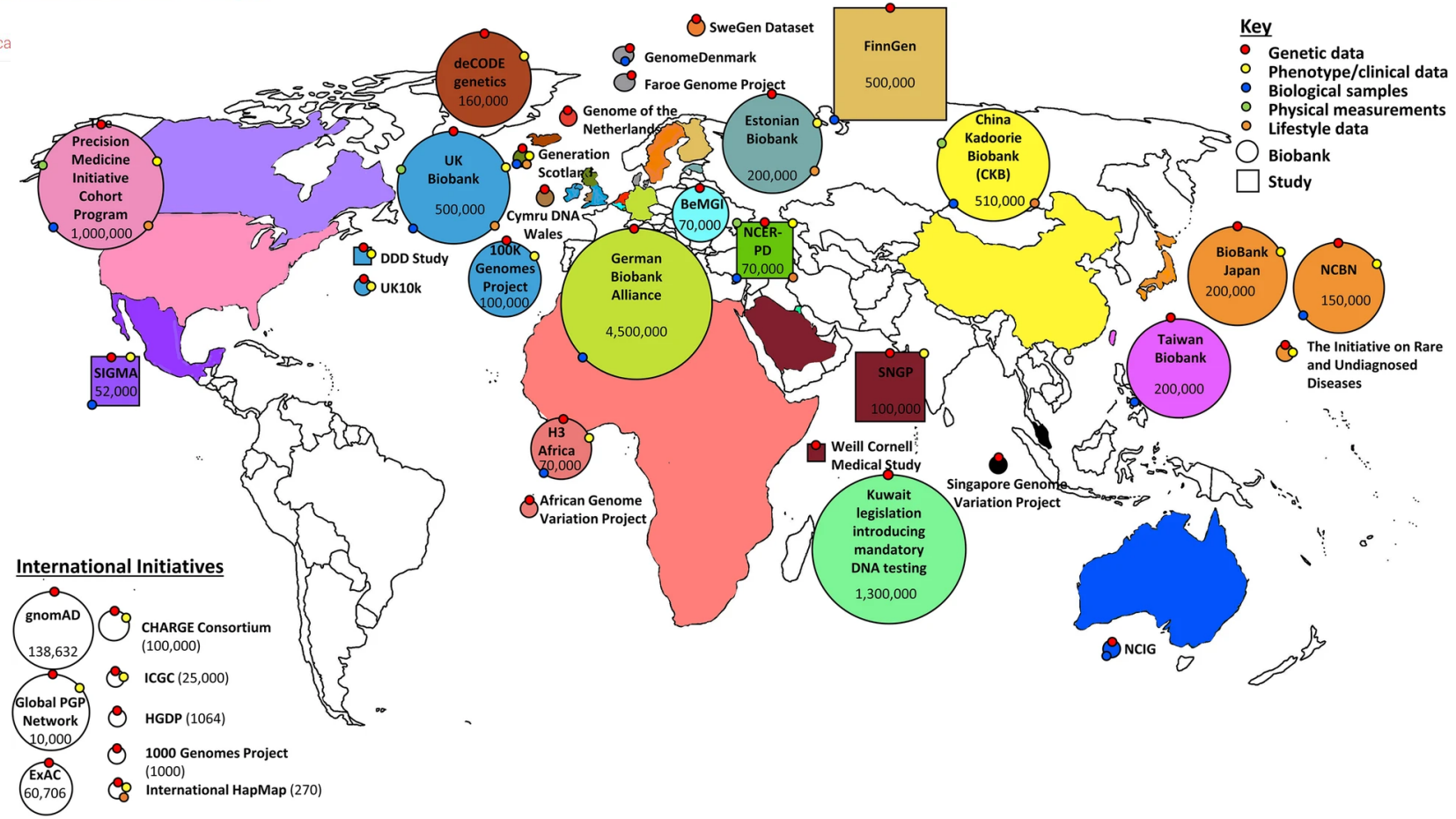
Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in *PCSK9*

Jonathan Cohen[1–3], Alexander Pertsemlidis[2,3], Ingrid K Kotowski[4], Randall Graham[1], Christine Kim Garcia[1–3] & Helen H Hobbs[1–4]





Twentieth H3Africa Consortium Meeting, Cape Town, South Africa



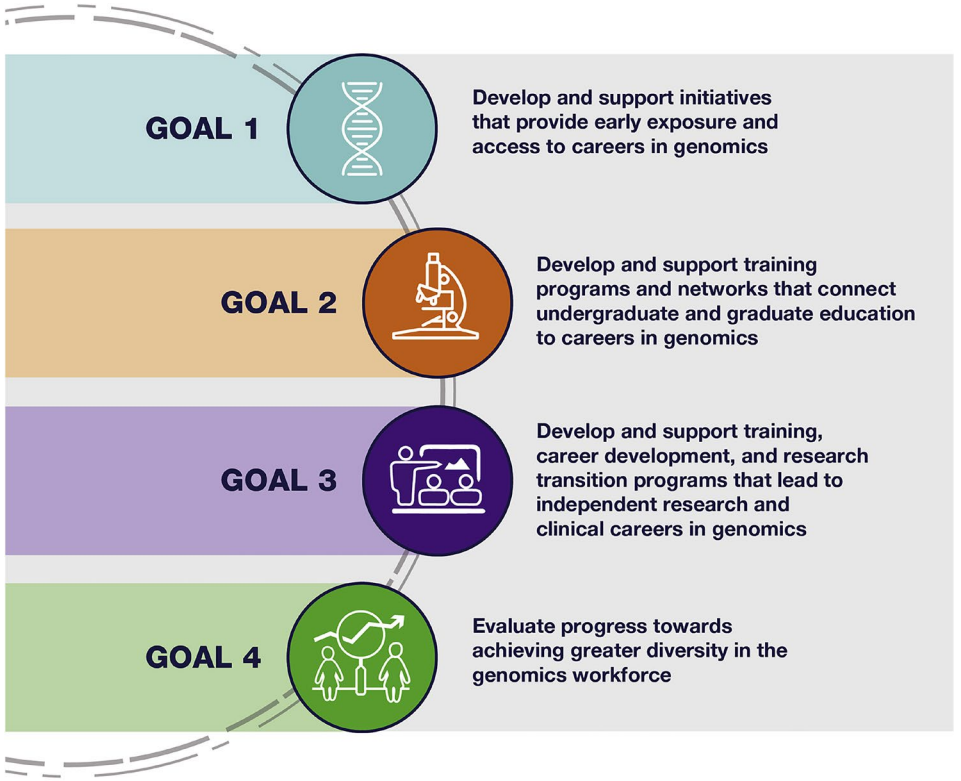
COMMENTARY

The genomics workforce must become more diverse: a strategic imperative

Vence L. Bonham[1,*] and Eric D. Green[1,*]

Summary

The National Human Genome Research Institute (NHGRI) recently published a new strategic vision for the future of human genomics, the product of an extensive, multi-year engagement with numerous research, medical, educational, and public communities. The theme of this 2020 vision—The Forefront of Genomics—reflects NHGRI's critical role in providing responsible stewardship of the field of human genomics, especially as genomic methods and approaches become increasingly disseminated throughout biomedicine. Embracing that role, the new NHGRI strategic vision features a set of guiding principles and values that provide an ethical and moral framework for the field. One principle emphasizes the need to champion a diverse genomics workforce because "the promise of genomics cannot be fully achieved without attracting, developing, and retaining a diverse workforce, which includes individuals from groups that are currently underrepresented in the genomics enterprise." To build on the remarkable metamorphosis of the field over the last three decades, enhancing the diversity of the genomics workforce must be embraced as an urgent priority. Toward that end, NHGRI recently developed an "action agenda" for training, employing, and retaining a genomics workforce that reflects the diversity of the US population.



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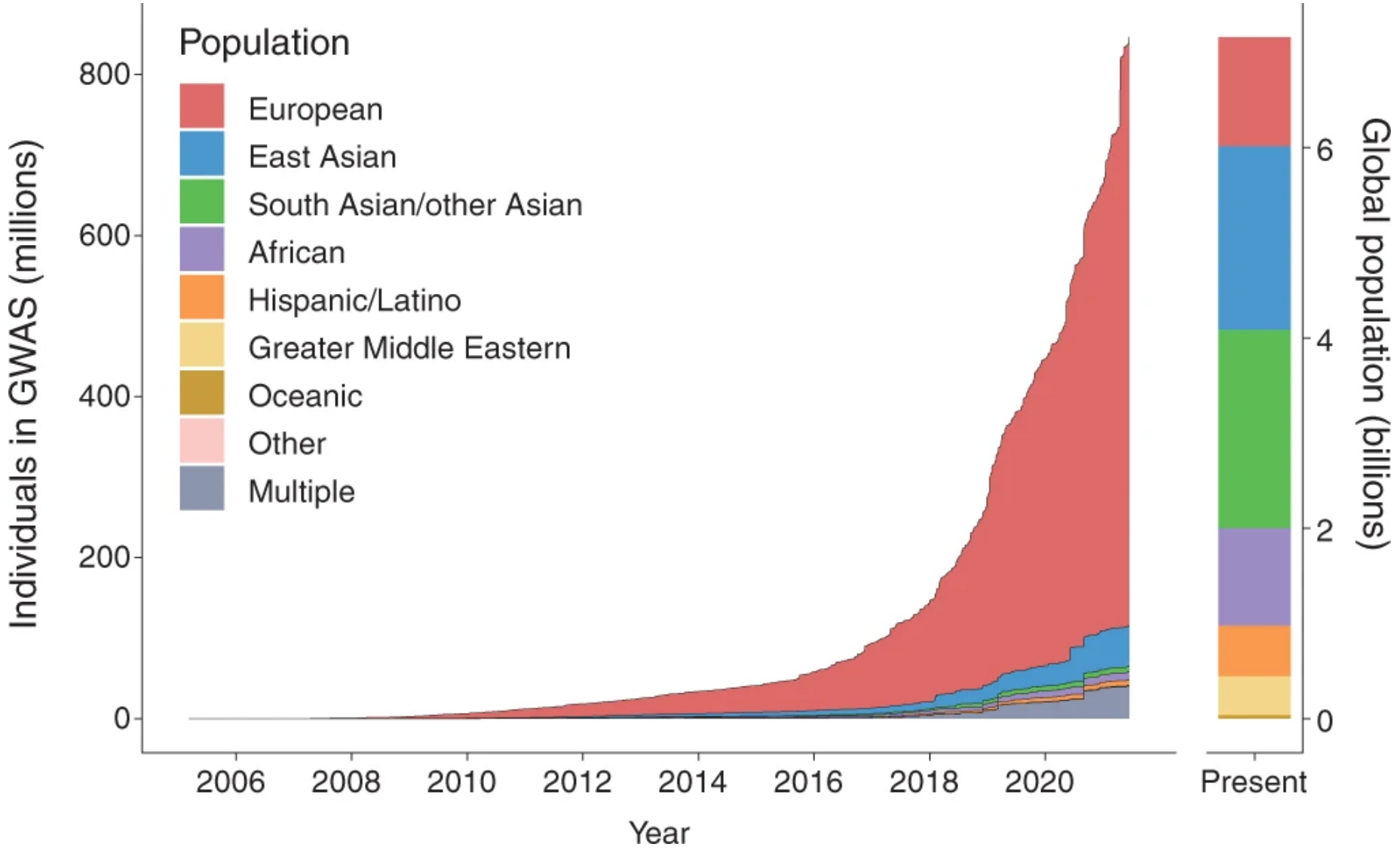
Working towards diversity in genomic studies: the role of the HRPP and the IRB

Bruce Gordon, MD

University of Nebraska Medical Center



Fatumo et al; Nature Med 28:243, 2022

What is the problem?

- Genetics and genomics research is fundamentally dependent on leveraging genetic diversity to identify genetic variants that contribute to disease risk, diagnosis and prognosis
- Under-representation of ethnic and racial groups (especially from LMIC and marginalized populations) limits utility of genomic data
  - leads to an incomplete understanding of human genetic diversity
  - limits the generalizability of findings from genomic research
  - impedes translating findings into clinical care
    - disproportionate adverse impact on the groups who are already marginalized

Why don't people from under-represented communities participate in genomic research?

- Mistrust of medical research
- Lack of knowledge about genetic research
  - "genetic illiteracy"
- Concern about use of genomic data
  - individual privacy
  - loss of insurability or benefits
  - group harms

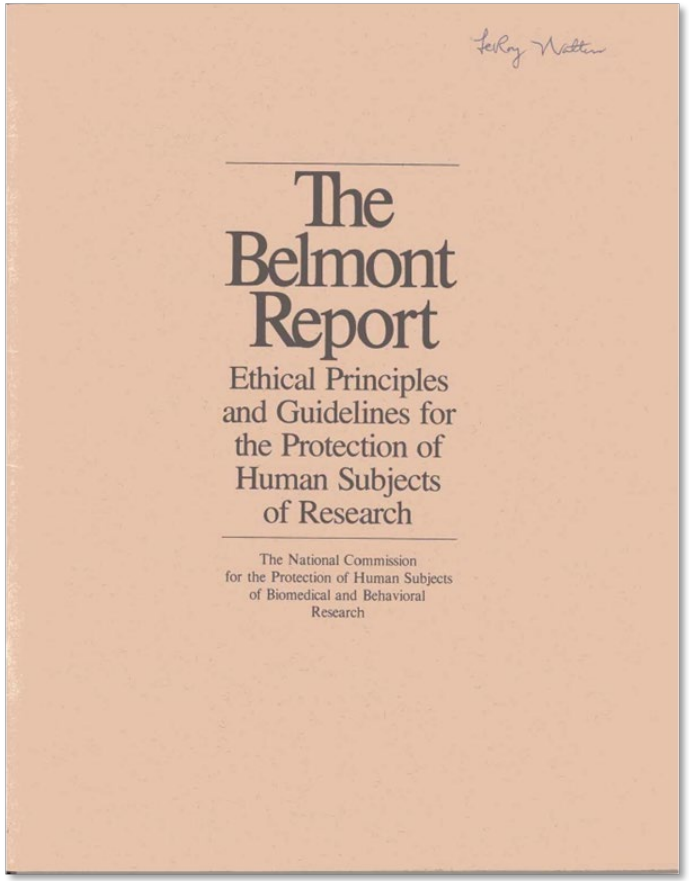
Why don't people from under-represented communities participate in genomic research?

- Scarcity of genomic research trials in LMICs and under-served areas
  - research funding inequities
  - need "big data" infrastructure (institutional capacity and skilled workforce)
  - lack of expertise in ELSI of genomics research
  - lack of diversity among researchers
  - lack of access to existing genomic trials

How can Institutions approach the problem?

- Researchers and institutions can foster participation of under-represented populations in genomic research by
  - establishing meaningful partnerships with local research scientists
  - being sensitive to local customs and cultural concerns
  - obtaining both community and individual consent
  - returning results to communities that participated
  - training and capacity building so that genomic research can be conducted locally

What is the IRB's role in this? Is this even an IRB issue?



- three basic ethical principles that should govern human subject research:
  - respect for persons
  - beneficence
  - justice

Justice

- "Justice requires that we treat persons fairly and we give each person what he is owed … An injustice occurs when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly."

  Belmont Report, 1979

- The principle requires that both benefits and burdens be distributed fairly

Justice

- "Selection of subjects is equitable."
- "The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence ..." [45 CFR 46.111(a)(3)]
  - equitable subject selection requires the balancing of inclusion and protection...

Beneficence

- "Beneficence is understood … as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do no harm, and (2) maximize possible benefits and minimize possible harms"

Belmont Report, 1979

Beneficence

- "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" [45 CFR 46.111(a)(3)]

- reducing the general applicability of genomic research reduces societal benefit of the research
  - even if the R/B is still favorable, lack of diversity fails the Belmont injunctive to maximize potential benefits

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
    - do the demographics of the proposed sample reflect those of the population affected by the condition or for whom the intervention is intended?
      - when they do not, is the deviation adequately justified?
      - is planned under- or over-representation by age, race, ethnicity, gender, or social determinants of health in the sample scientifically justified?
      - is there a statistical plan for examining heterogeneity in outcome or across subgroups?

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
  - inclusion & exclusion
    - will inclusion and exclusion criteria inadvertently or unnecessarily result in under- or over-representation of certain (marginalized or underserved) subgroups?
    - have alternative approaches to minimizing risk that do not rely on exclusion been considered?

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
  - inclusion & exclusion
  - recruitment
    - have recruitment procedures considered specific approaches to engage underserved populations?

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
  - inclusion & exclusion
  - recruitment
  - study conduct
    - are study procedures flexibly organized to accommodate the needs of under-represented groups?
    - do all participant-facing materials conform to health literacy principles?
    - are participant materials translated?

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
  - inclusion & exclusion
  - recruitment
  - study conduct
  - payment
    - is payment sufficient to cover costs of participation?

How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- initial review
  - study aims and subject selection
  - inclusion & exclusion
  - recruitment
  - study conduct
  - payment
  - return of results
    - are study results intended to be returned in a manner that meets the needs of populations studied?

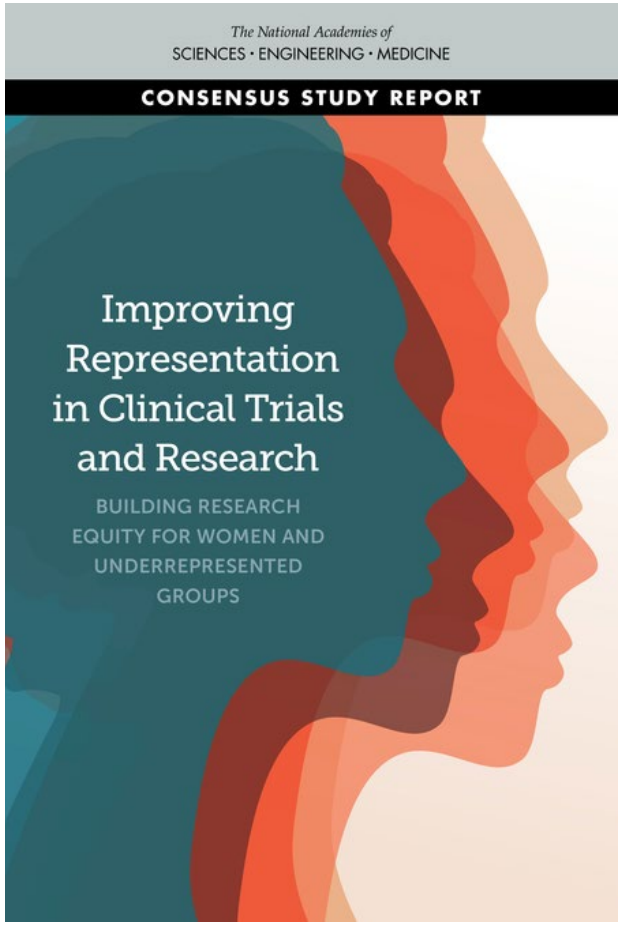
How might an IRB help encourage diversity in genomic research (or in clinical research in general)?

- Continuing review
  - has the study fulfilled its recruitment and accrual goals?
  - is demographic distribution on track to approximate the study goals?
    - if not, are adequate corrective actions described, sufficient, and likely to be successful?

MRCT 2021 "Achieving Diversity Inclusion and Equity in Clinical Research"

- Ensure the IRB is composed of a diverse group of individuals, optimally representing local underserved and minority communities
- Provide training to IRB members and administrators on implicit bias and cultural competence
- Develop an index of recruitment and retention strategies unique to the institution and its specific study populations
- Provide a prototype recruitment and retention strategy document for investigators to emulate

National Academy of Science 2022



- "OHRP and FDA should direct local IRBs to assess and report the representativeness of clinical trials as one measure of sound research design that it requires for the protection of human subjects."
- "Protocols in which the planned enrollment diverges substantially from disease prevalence should require justification."


grimmy.com
GENOME PROJECT
WHEN I ASKED WHAT LITTLE GIRLS ARE MADE OF, I WAS HOPING HE WOULD SAY "SUGAR AND SPICE."

Specific IRB considerations for genomic research

- Genomic data privacy and confidentiality
  - individual privacy
  - loss of insurability or benefits

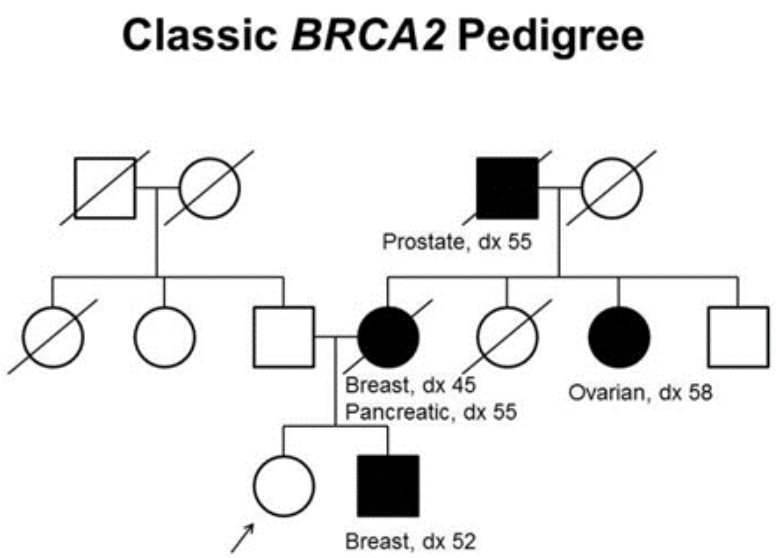
Specific IRB considerations for genomic research

- Genomic data privacy and confidentiality
  - individual privacy
  - loss of insurability or benefits
    - Burlington Northern Santa Fe Railroad (2001) secretly tested employees applying for disability for a rare genetic condition (hereditary neuropathy with liability to pressure palsies - HNPP)
    - Genetic Information Nondiscrimination Act of 2008
    - ADA, ACA, HIPAA, state laws

Specific IRB considerations for genomic research

- Cost of testing and insurance coverage
  - including cost of f/u for incidental findings (especially VUS)

Specific IRB considerations for genomic research



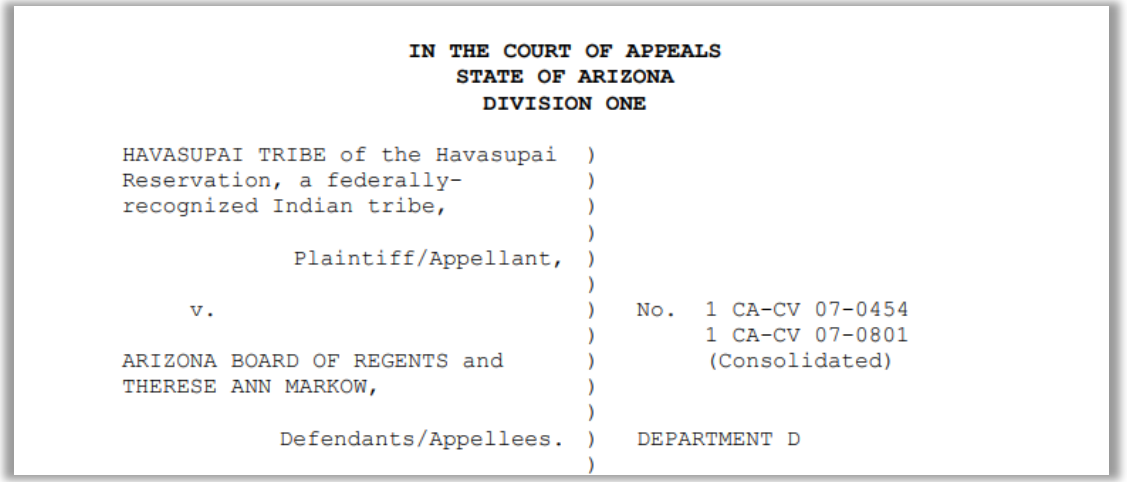
- secondary subjects
  - potential psychological harm to at-risk relatives
  - potential violation of at-risk relatives' autonomy, privacy, and right not to know

Specific IRB considerations for genomic research

- Sharing of genomic and phenotypic data
  - NIH Genomic Data Sharing (GDS) Policy requires investigators to obtain explicit consent for individual participants' genomic and phenotypic data to be shared broadly through data repositories
  - NIH Policy also requires unrestricted access to genomic summary results (GSR) from most genomic studies
  - Consent issues
    - broad consent vs specific (± tiered) consent
    - tracking individual choices, and allowing for changes

Specific IRB considerations for genomic research

- Group harms
  - Group harms are damages or injury, tangibly experienced or perceived, that impact the welfare interests of a group and its people



IN THE COURT OF APPEALS
STATE OF ARIZONA
DIVISION ONE

HAVASUPAI TRIBE of the Havasupai Reservation, a federally-recognized Indian tribe,

Plaintiff/Appellant,

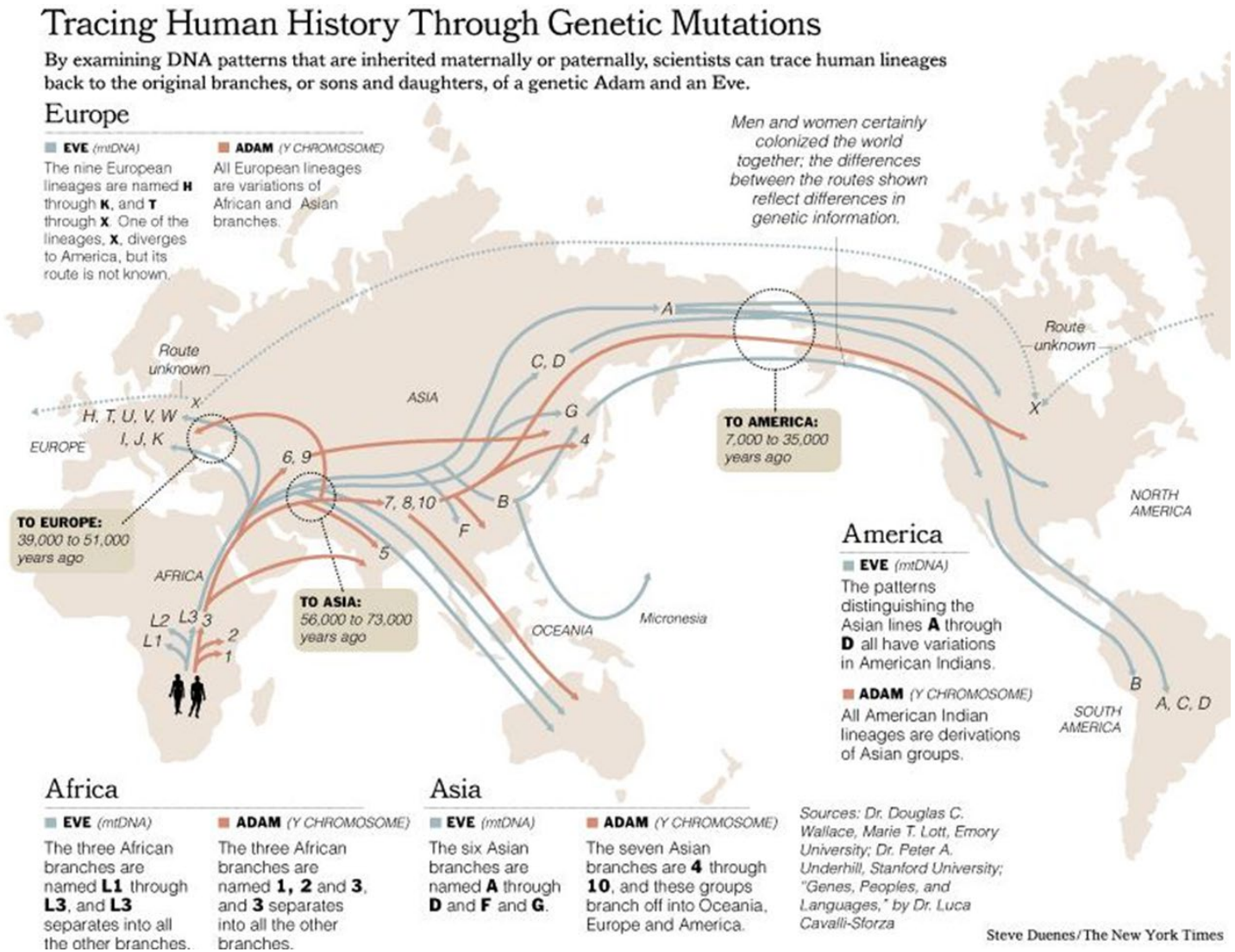
v.

ARIZONA BOARD OF REGENTS and THERESE ANN MARKOW,

Defendants/Appellees.

No. 1 CA-CV 07-0454
1 CA-CV 07-0801
(Consolidated)

DEPARTMENT D



- can shed light on the ancestral origins, migration patterns, and demographic history of populations
- may challenge cultural and cosmological beliefs and can sometimes have economic or legal impact on a group's claims or attributions.

Specific IRB considerations for genomic research

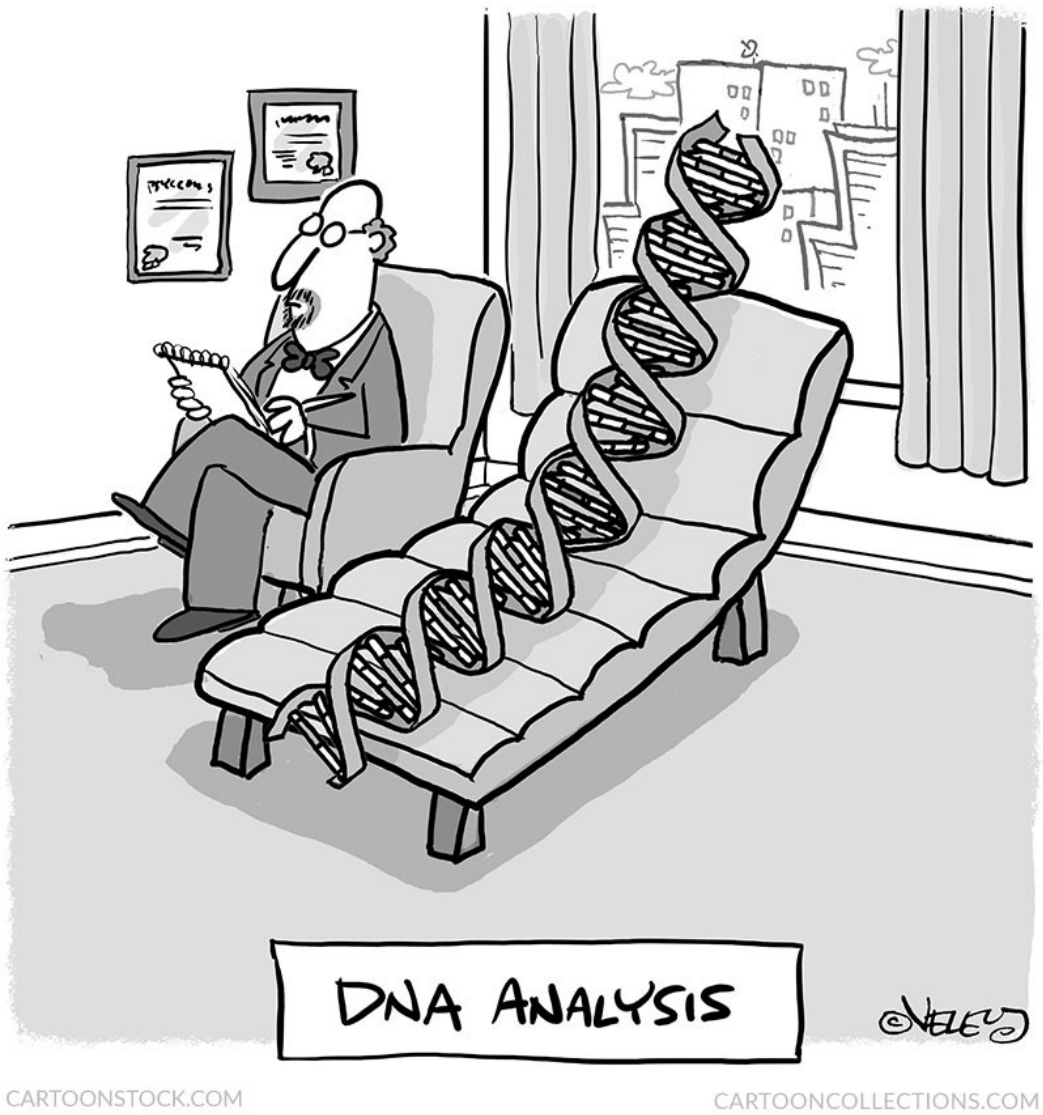
- Biosample storage
  - future use of samples
  - return or destruction of samples
- Incidental and secondary findings
  - especially VUS which might be expected to be more common in populations that are under-represented in genomic databases

Specific IRB considerations for genomic research

- Considerations for families
  - subjects as "gatekeepers" of information
    - healthy persons informed of a genetic predisposition may struggle with whether this incurs an obligation to report these vulnerabilities to family members
  - unexpected information about family relationships
  - "recruitment" of family members
    - unwelcome intrusions, undue pressure

Specific IRB considerations for genomic research

- Genetic literacy
  - Only 1.2% of 5400 participants in a multinational study of genetic knowledge answered all 18 questions correctly; average score was 65.5% (J Comm Genet 10:73, 2019)
    - Genetic knowledge was related to peoples' attitudes towards genetic testing
  - Within the United States, over 30% of a 2,093-person sample indicated that they were unfamiliar with genetic concepts (Am J Hum Genet 107:743, 2020)
  - Have sufficient efforts been made to ensure genetic literacy during consent?


DNA ANALYSIS
CARTOONSTOCK.COM
CARTOONCOLLECTIONS.COM

Summary

- under-representation of ethnic and racial groups, especially from LMIC and marginalized populations, limits accuracy and utility of genomic research
- reasons are varied, and may, in part, be structural
- institutions and researchers may be able to improve participation by focusing on core ethical values (respect, equity, beneficence, reciprocity, …)
- IRBs have a responsibility to assist in removing barriers


J. Harris
"BUT IF YOU WANT THE REAL LOWDOWN, WE'LL NEED SOME OF YOUR DNA."

Questions?