Genomic Medicine Implementation in Diverse Healthcare Settings and Populations

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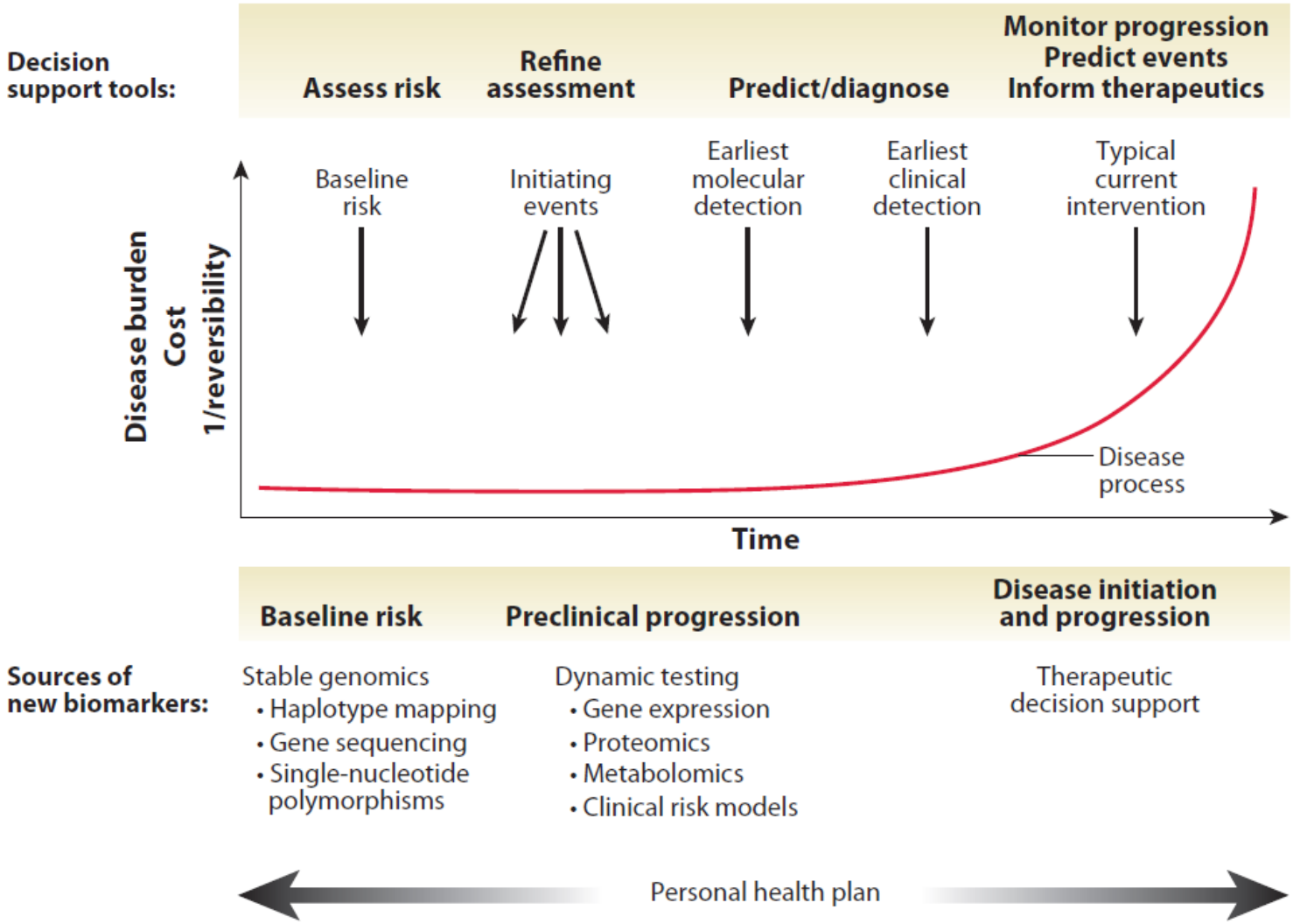

Figure 1

The role of genome-based information across the continuum of health to disease. Currently, in the time course of a chronic disease (*red line*), treatment usually occurs at the point in the disease process indicated by "typical current intervention"—a point where it is most costly to treat and where prospects for reversibility are low. Novel genome-based biomarkers can help clinicians identify baseline risks as well as early initiating events in disease. Figure adapted from Reference 66.

State of the Science and Gaps

- Era of Precision Medicine - take an active role in clinical decision making
- Precision Medicine may actually increase Health Disparities.
- Most information currently based on populations of European ancestry.


GIVE IT TO ME STRAIGHT, DOC... I CAN TAKE IT... WHAT'S WRONG WITH ME?
YOU'RE NOT A WHITE MALE.

State of the Science and Gaps

- **Variants of unknown significance – Precision Oncology**
  - Develop shared databases across institutions
- **Misclassification of pathogenic variants**
  - Inadequate patient samples and lack of diversity
- **Leverage genetic ancestry in diverse populations**

Table 1. Insights from studies conducted in diverse race/ethnic groups.

Trait	Findings
Breast cancer	Differences in Native American ancestry at the estrogen receptor locus led to discovery of a genetic variant that was protective against breast cancer in Latinas [11].
Heart failure	A post-hoc analysis of clinical trials of fixed-dose combination of hydralazine and isosorbide dinitrate suggested that black, but not white patients had a significant reduction in mortality compared to placebo [12].
Increased preterm birth rate	Exposures to endocrine disrupting chemicals such as bisphenol-A (BPA) are more common among minorities who live in low socioeconomic strata. BPA causes epigenetic alterations of the germ line resulting in increased preterm birth rate; these alterations can pass down to future generations [13].
Stevens-Johnson syndrome	The risk of carbamazepime-induced Stevens-Johnson syndrome due to HLA-B*1502 is highest in populations of Southeast Asian and East Asian ancestry [14].
Kidney disease	Genetic variants of *APOL1* have been associated with kidney disease in individuals of African ancestry whose ancestors lived in regions of Africa endemic with trypanosomiasis; these renal risk variants are largely absent in individuals of European or Asian ancestry [15].
Response to efavirenz	Blood levels and treatment response to this antiretroviral drug are influenced by individual ancestral make up, which can be accounted for by polymorphisms of cytochrome 2B6 and genetically defined ancestry [16,17].

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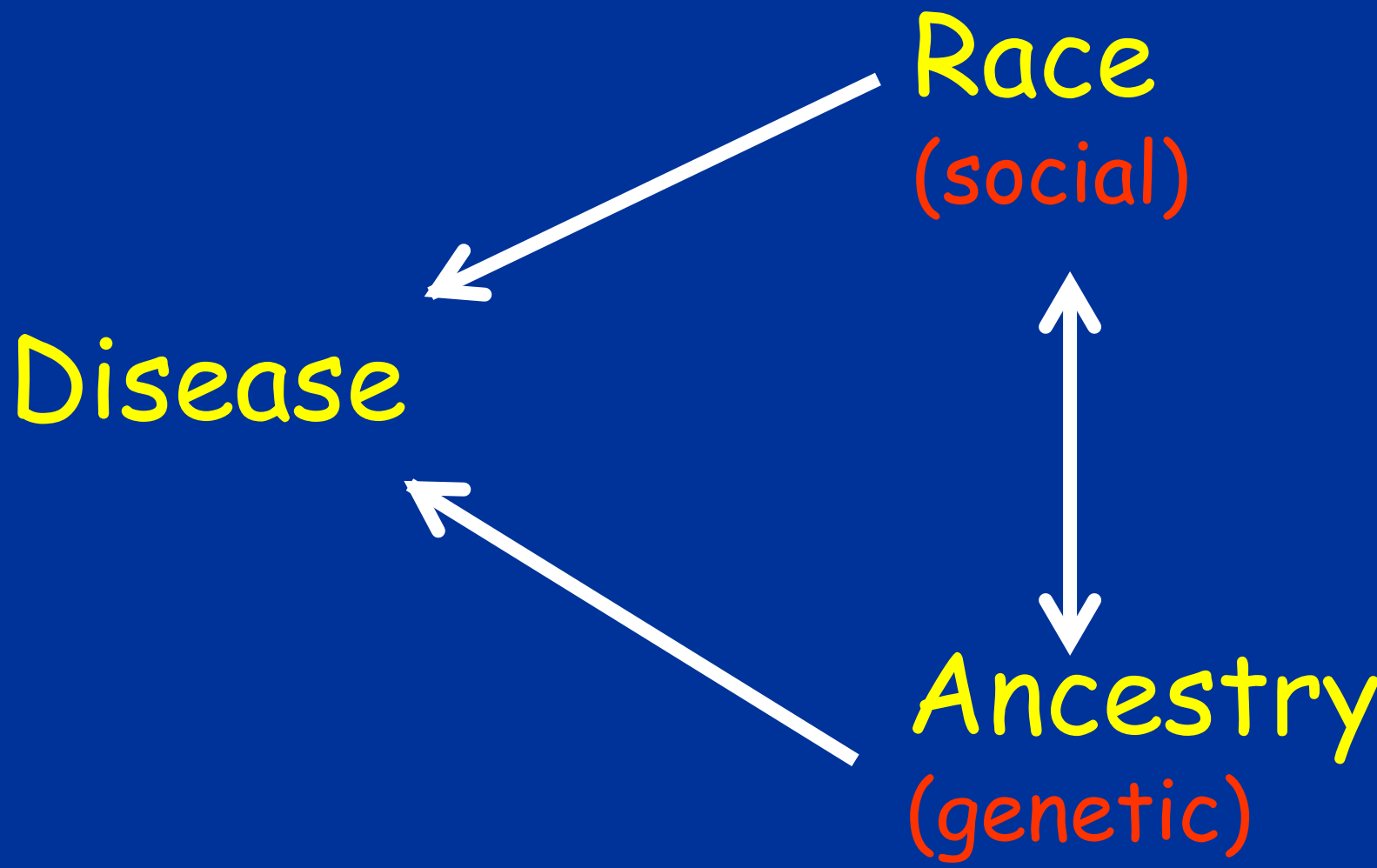
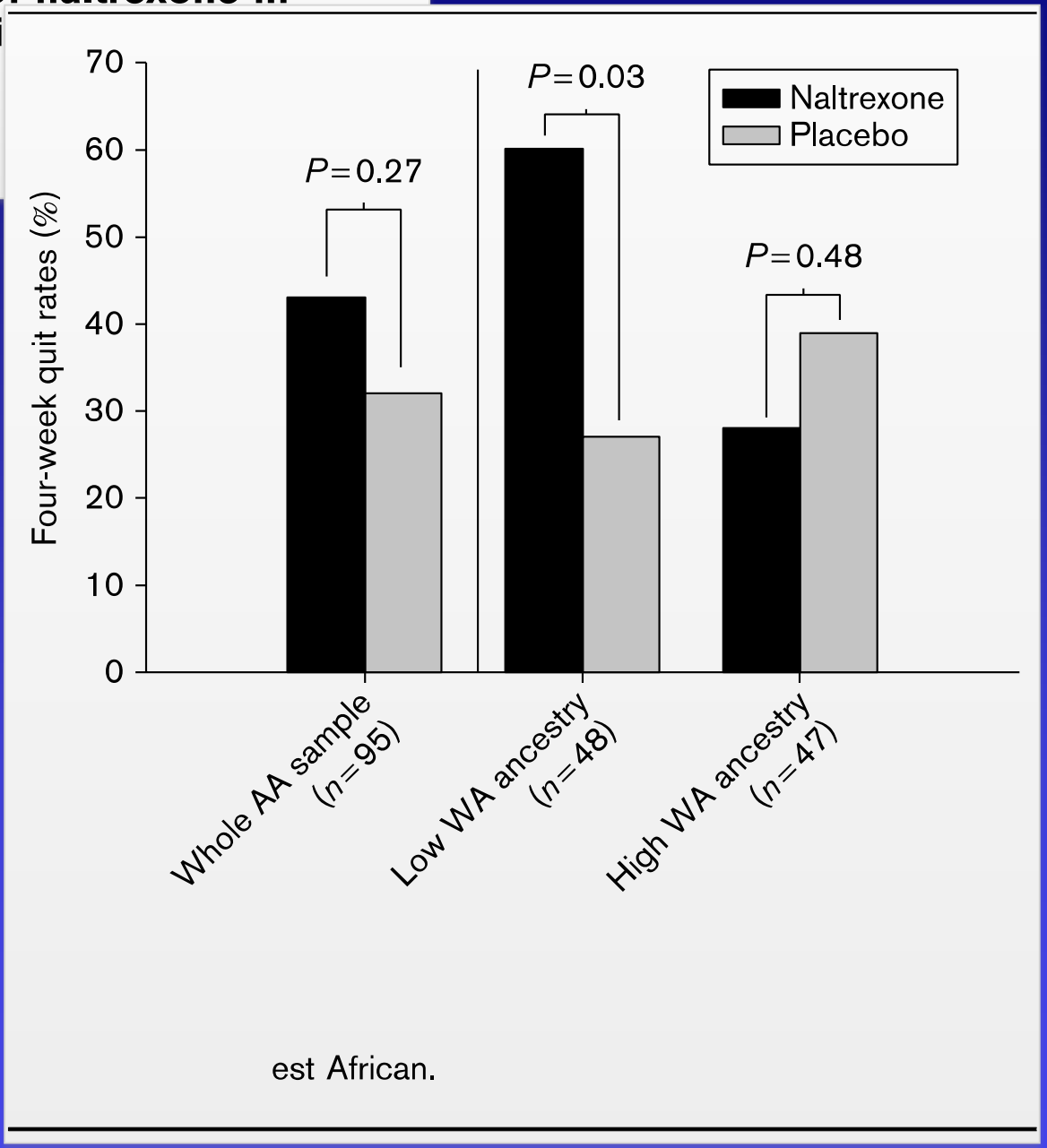
Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, et al. (2015) Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. PLoS Med 12(12): e1001918. doi:10.1371/journal.pmed.1001918
http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001918


Race
(social)
Disease
Ancestry
(genetic)

Genetic ancestry as an effect modifier of naltrexone in smoking cessation among African Ameri
randomized controlled trial

Adam Bress[a], Rick Kittles[b], Coady Wing[c], Stanley
Andrea King[e]



est African.

Pharmacogenetics and Genomics 2015

ARTICLES

nature genetics

The contribution of rare variation to prostate cancer heritability

Nicholas Mancuso[1,14], Nadin Rohland[2,3,14], Kristin A Rand[4,5], Arti Tandon[2,3], Alexander Allen[2,3], Dominique Quinque[2,3], Swapan Mallick[2,3], Heng Li[2,3], Alex Stram[4], Xin Sheng[4], Zsofia Kote-Jarai[6], Douglas F Easton[7], Rosalind A Eeles[6,8], the PRACTICAL consortium[9], Loic Le Marchand[10], Alex Lubwama[11], Daniel Stram[4,5], Stephen Watya[11], David V Conti[4,5], Brian Henderson[4,5,13], Christopher A Haiman[4,5,15], Bogdan Pasaniuc[1,12,15] & David Reich[2,3,15]

nature genetics

The contribution of rare variation to prostate cancer heritability

Table 1 Sizes for each ancestry group and the coverage and standard deviation in coverage achieved

	Number of samples		Average coverage per sample (s.d.)	Average coverage per locus (s.d.)	Variants		
Ancestry	Cases	Controls			Rare 0.1% ≤ MAF < 1%	Common MAF ≥ 1%	Total
African	2,054	1,952	8.3 (5.1)	8.4 (5.2)	58,699	63,972	122,671
European	900	853	8.8 (6.0)	8.8 (6.0)	33,606	53,164	86,770
Japanese	914	856	11.8 (5.2)	11.9 (5.2)	29,121	40,742	69,863
Latino	864	844	8.0 (5.7)	8.1 (5.7)	46,374	45,932	92,306
Overall	4,732	4,505	9.3 (5.4)	9.4 (5.4)	–	–	–

nature genetics

The contribution of rare variation to prostate cancer heritability

Table 2 Estimates of h_g^2 and standard errors using sequencing data

Ancestry	Sample size	h_g^2 index SNPs (s.e.)	$h_{g,\text{rare}}^2$ (s.e.)	*P* value	$h_{g,\text{common}}^2$ (s.e.)	*P* value
African	4,006	0.06 (0.01)	0.12 (0.05)	2.29×10^{-3}	0.17 (0.03)	7.08×10^{-13}
European	1,753	0.10 (0.01)	0.00 (0.06)	5.00×10^{-1}	0.27 (0.06)	5.83×10^{-11}
Japanese	1,770	0.08 (0.01)	0.05 (0.07)	2.68×10^{-1}	0.13 (0.04)	3.09×10^{-5}
Latino	1,708	0.06 (0.01)	0.00 (0.06)	5.00×10^{-1}	0.14 (0.05)	2.38×10^{-5}

The results for index SNPs correspond to h_g^2 contributed solely from the targeted index variants. Estimates for h_g^2 attributable to rare and common components were obtained from joint REML analysis on the underlying liability scale. Rare variants are defined as those with $0.1\% \leq \text{MAF} < 1\%$, whereas common variants are defined as those with $\text{MAF} \geq 1\%$.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.

n engl j med 375; August 18, 2016

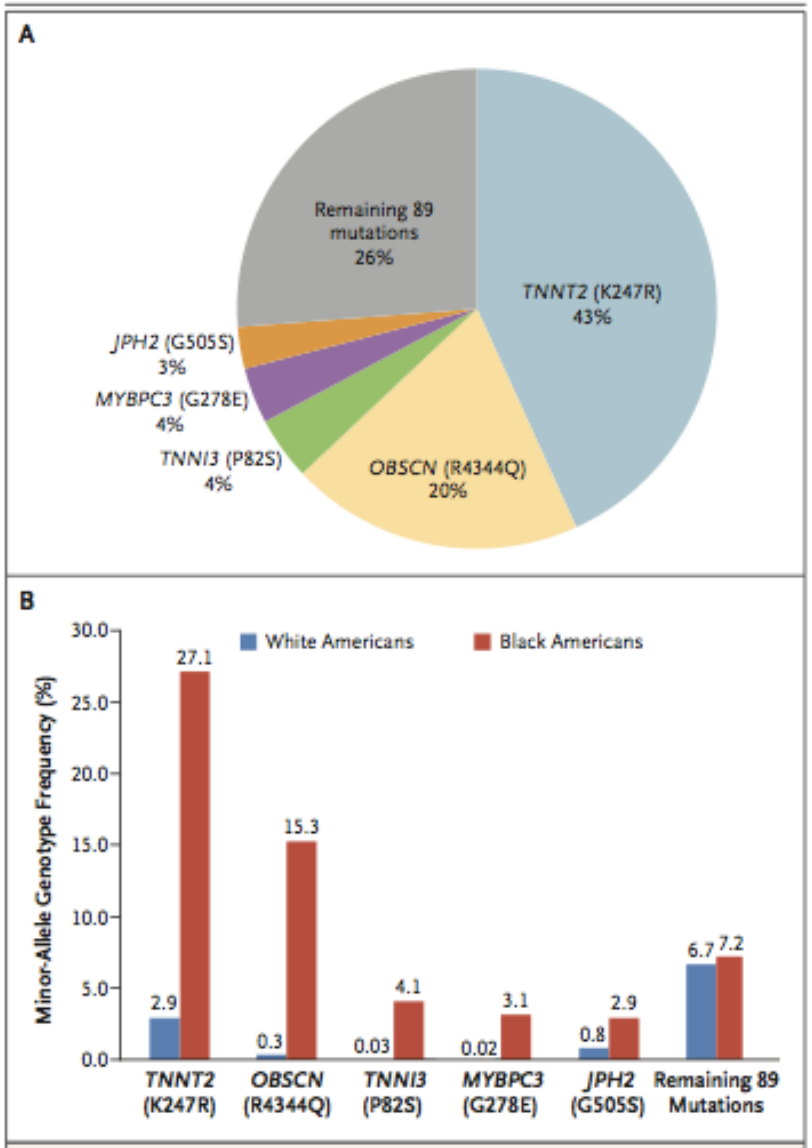


Figure 1. Genetic Variants Associated with Hypertrophic Cardiomyopathy.
Panel A shows variants associated with hypertrophic cardiomyopathy that are overrepresented in the general population. The five highest-frequency variants account for 74% of the misclassified variation in the general population. Panel B shows the minor-allele genotype frequencies for high-frequency variants associated with hypertrophic cardiomyopathy; all variants are significantly more common among black Americans than among white Americans ($P<0.001$ by the chi-square test for all five variants).

n engl j med 375; August 18, 2016

Summary

- Attention must be paid to increasing diversity in Genomic Medicine implementation.
  - Identify barriers and develop aggressive strategies.

- Equitable benefits from personalized medicine depends on overcoming barriers in education, accessibility, regulation, reimbursement (market economics), and most importantly on diversity in genetic studies.