Ethical and Social Issues Associated with Using Race and Genetics in the Study of Differential Drug Response

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Race

- Generally assumed to identify groups with shared ancestry
- Currently understood to refer to 5 groups: African, European, Asian, Native American, Oceanic

However,

- Definition of racial groups has been variable over time & place
- Personal racial identity is determined by social factors

Indirect relationship between race and pharmacogenomics

- Self-reported race is correlated - although imperfectly - with genetic measures of geographic ancestry
- The prevalence of many gene variants, including variants associated with drug response, varies with geographic ancestry

Prevalence of *CYP2C9* variants associated with reduced dose requirement for warfarin

European — 36% (18-51%)
- Europe (9 studies, mean 39%)
- No. America (6, mean 32%)
- Middle East (2, mean 36%)

African — 8% (3-13%)
- No. America (4, mean 8%)
- Ethiopia (13%)

Asian — 4% (2-11%)
- Asia (8, mean 4%)
- No. America (11%)

Native American — 10% (0-20%)
- Canadian 1st nation (20%)
- Inuit (0%)

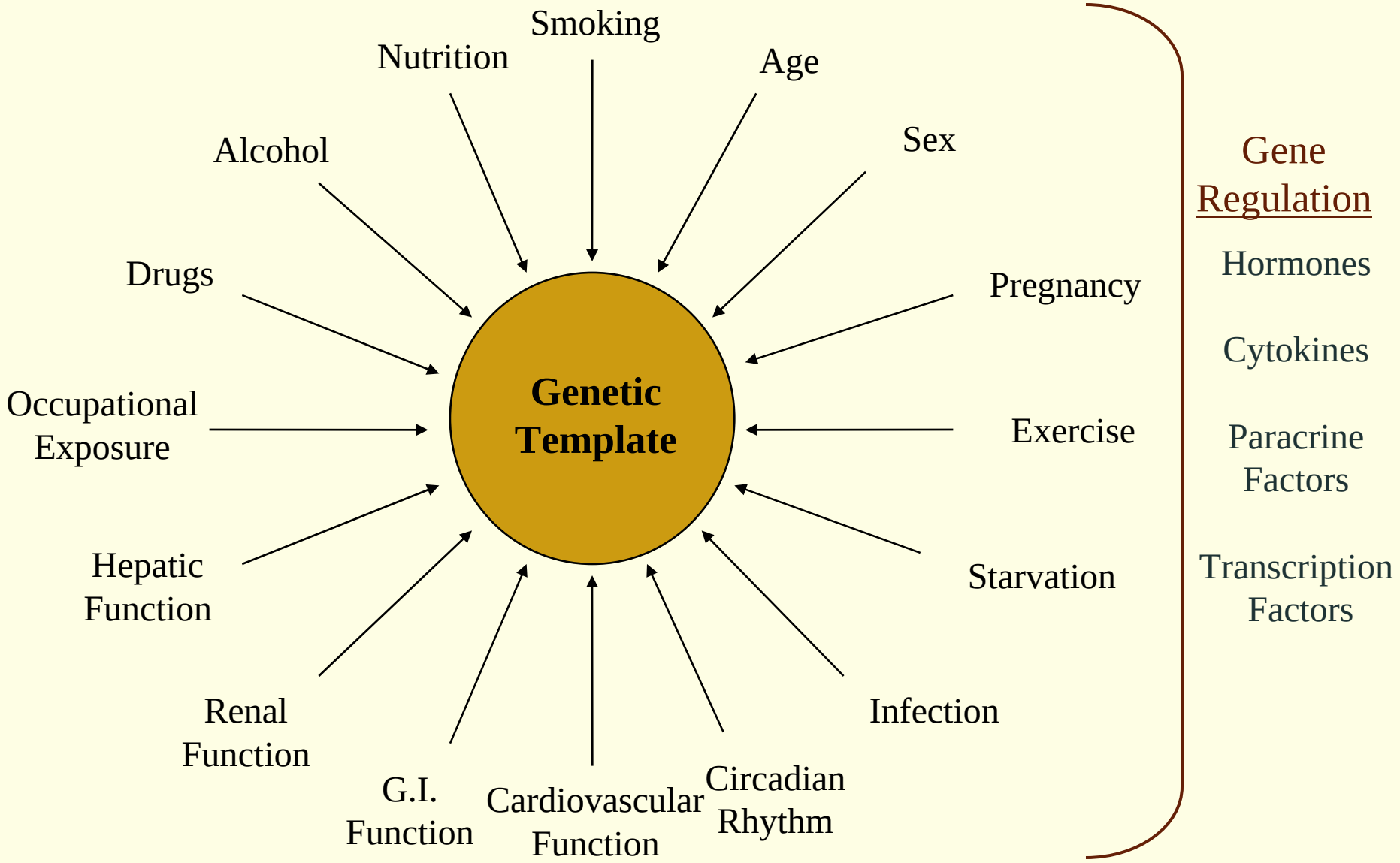
Compiled by D Veenstra

Racial difference in warfarin response - not explained by *CYP2C9* variants

"***Asian patients may require lower initiation and maintenance doses of warfarin***. One ***non-controlled study*** conducted in 151 ***Chinese*** outpatients reported a mean daily warfarin requirement of 3.3 ± 1.4 mg to achieve an INR of 2.0 to 2.5. These patients were stabilized on warfarin for ***various indications***. Patient ***age*** was the most important determinant of warfarin requirement…"

Physicians' Desk Reference 2005, p. 1040

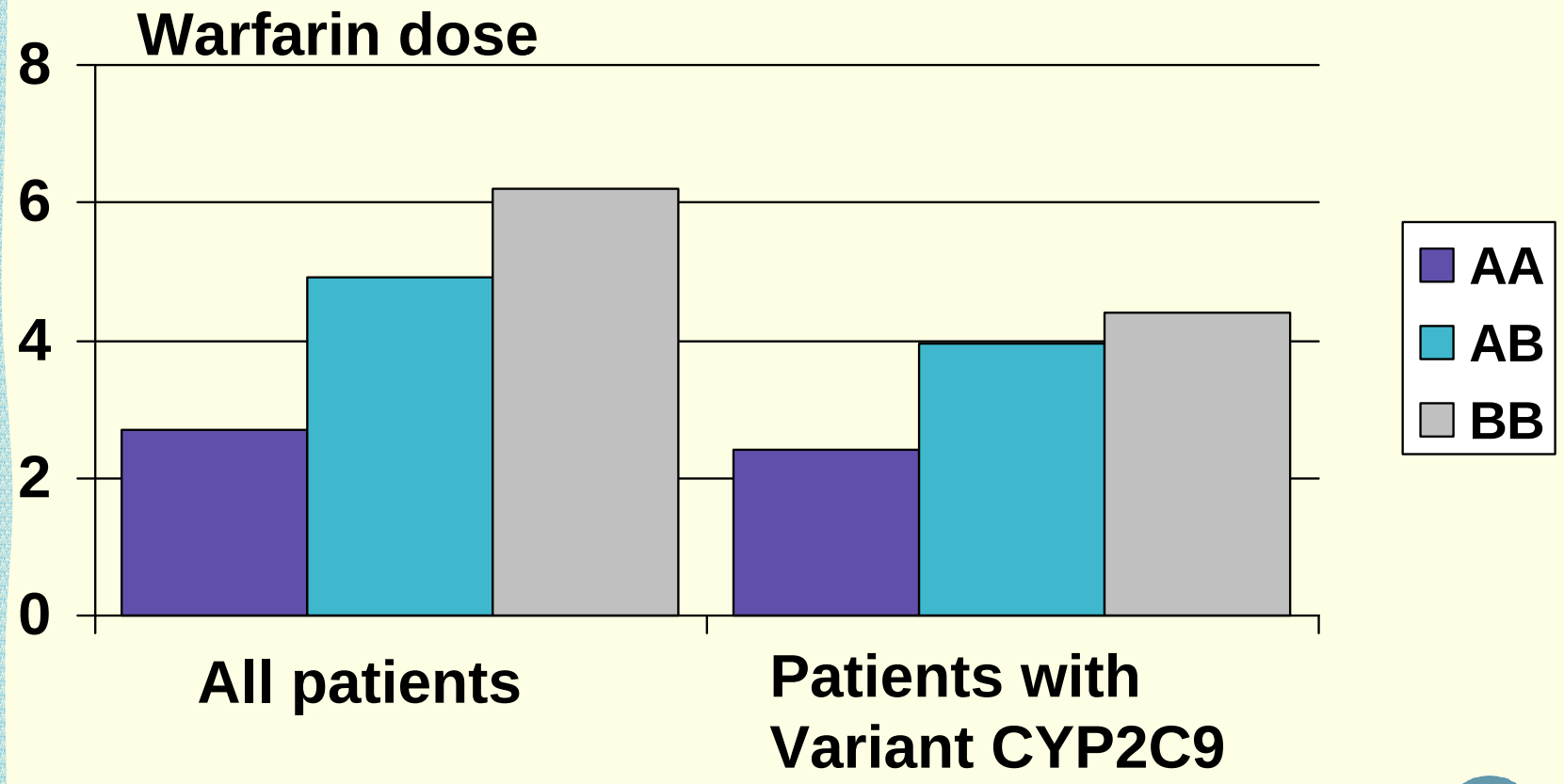
Sources of Interindividual Variability in P450 Expression



Adapted from E. Vesell, 1981

Association between warfarin dose and *VKORC1* variant haplotypes

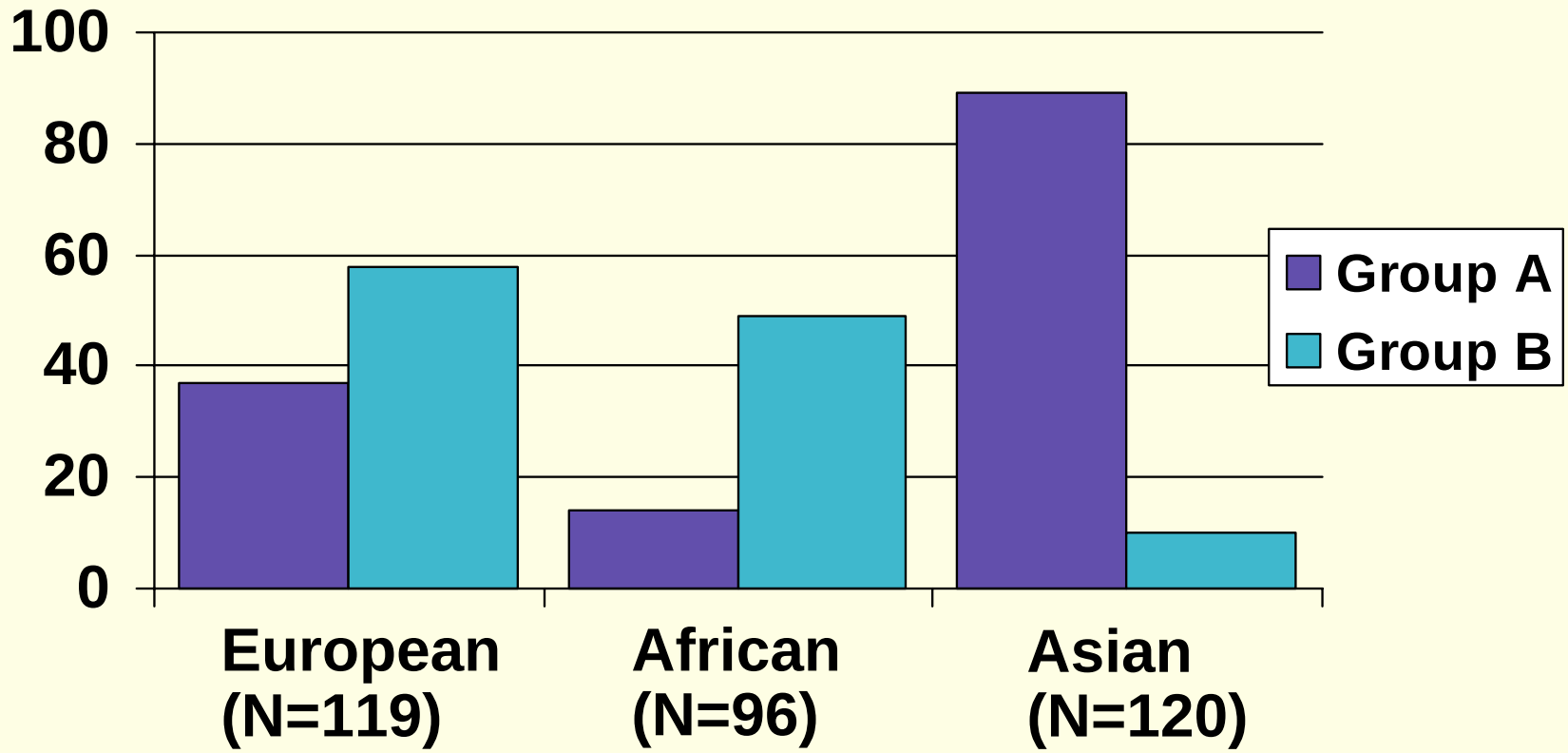
Group A (low dose) & Group B (high dose)



Reider et al NEJM 2005; 352:2285-93

Racial group prevalence of *VKORC1* variant haplotypes

Group A (low dose) & Group B (high dose)



Reider et al NEJM 2005; 352:2285-93

Variance in drug response explained by *CYP2C9* and *VKORC1* variants

CYP2C9
10%

VKORC1
25%

Reider et al NEJM 2005; 352:2285-93

Multifactorial effects on response to warfarin and similar anticoagulants

Gene variants

- CYP2C9
- VKORC1
- APOE
- Other?

Non-genetic factors

- Diet
- Age
- Multiple interacting drugs
- Poor nutritional status, diarrhea
- Other health conditions

Races are genetically heterogeneous

Example:Prevalence of *APOE* ε4 allele

Location	Range
Africa (3)	9 to 41%
Europe (5)	5 to 31%
Asia (3)	7 to 24%
Native American (3)	9 to 28%
Oceania (3)	26 to 37%

Corbo et al, Ann Hum Genet 1999; 63:301

Race and geographic ancestry are related but not congruent

Estimates from genetic testing:

- West African contribution to individual African American ancestry averages 80%, but ranges from 20% to 100%
- Approximately 30% of self-identified European Americans have less than 90% European ancestry
- Admixture highly variable among Hispanic groups

Data cited in Bamshad JAMA 2005;294:937

Is race clinically important in drug treatment?

Race captures many potential group differences

- Diet
- Housing
- Occupation
- Environmental exposure
- Prevalence of gene variants

Uncertain whether race has sufficient predictive value to assist in drug treatment

Implications for pharmacogenomic research

- Identification of all variants relevant to drug response requires studies of adequate numbers in diverse populations
- Multiple genetic and social/ environmental factors are important in drug response
- Gene-gene and gene-environment interactions are likely

Problem of “orphan genotypes”

- Rare genotypes that predict drug response are likely to be
  - less studied
  - neglected in new drug development
- In the US, genotypes that are common in minority populations - but rare in the population as a whole - could become orphan genotypes

Example: Claim of racial bias in federal nutrition policy

Bertron et al. J Natl Med Assoc 1999; 91: 151

- Loss of lactase (enzyme necessary for for digestion of milk lactose) is common in most minority groups:
  - Africans
  - Asians
  - Hispanic Americans
  - Native Americans
- Dietary guidelines recommending milk products as a source of calcium are appropriate for European but not other groups

Mistrust of genetics among minority populations

Examples

- Tribal mistrust related to use of genetic research samples for purposes beyond original study

- Survey of minority pre-medical students:
  Laskey et al Genet Med 2003;5:49
  - 74% strongly agreed that genetic testing may lead to discrimination

Risks from use of race and genetics in study of differential drug response

- Inadequate research in minority populations
  - Need careful attention to
    - Size and sampling of populations
    - Community concerns
    - Research integrity
- Inadequate attention to multiracial groups

Risks from use of race and genetics in study of differential drug response (continued)

- Genetic reductionism
  - Need to recognize genetics as only one of many contributors to drug response
- Potential misrepresentation of race as a genetic entity
  - Need to recognize
    - Many social causes of racial group differences
    - Genetic variation within racial groups

General concerns about pharmacogenomics

- Moving beyond hypotheses of benefit, to proof that drug outcomes are improved by pharmacogenetic testing
- Defining and protecting against risks
- Assuring access for all

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