

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

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# Race

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- 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

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- 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%)
<ul style="list-style-type: none"><li>• Europe (9 studies, mean 39%)</li><li>• No. America (6, mean 32%)</li><li>• Middle East (2, mean 36%)</li></ul>	
African	8% (3-13%)
<ul style="list-style-type: none"><li>• No. America (4, mean 8%)</li><li>• Ethiopia (13%)</li></ul>	
Asian	4% (2-11%)
<ul style="list-style-type: none"><li>• Asia (8, mean 4%)</li><li>• No. America (11%)</li></ul>	
Native American	10% (0-20%)
<ul style="list-style-type: none"><li>• Canadian 1st nation (20%)</li><li>• Inuit (0%)</li></ul>	



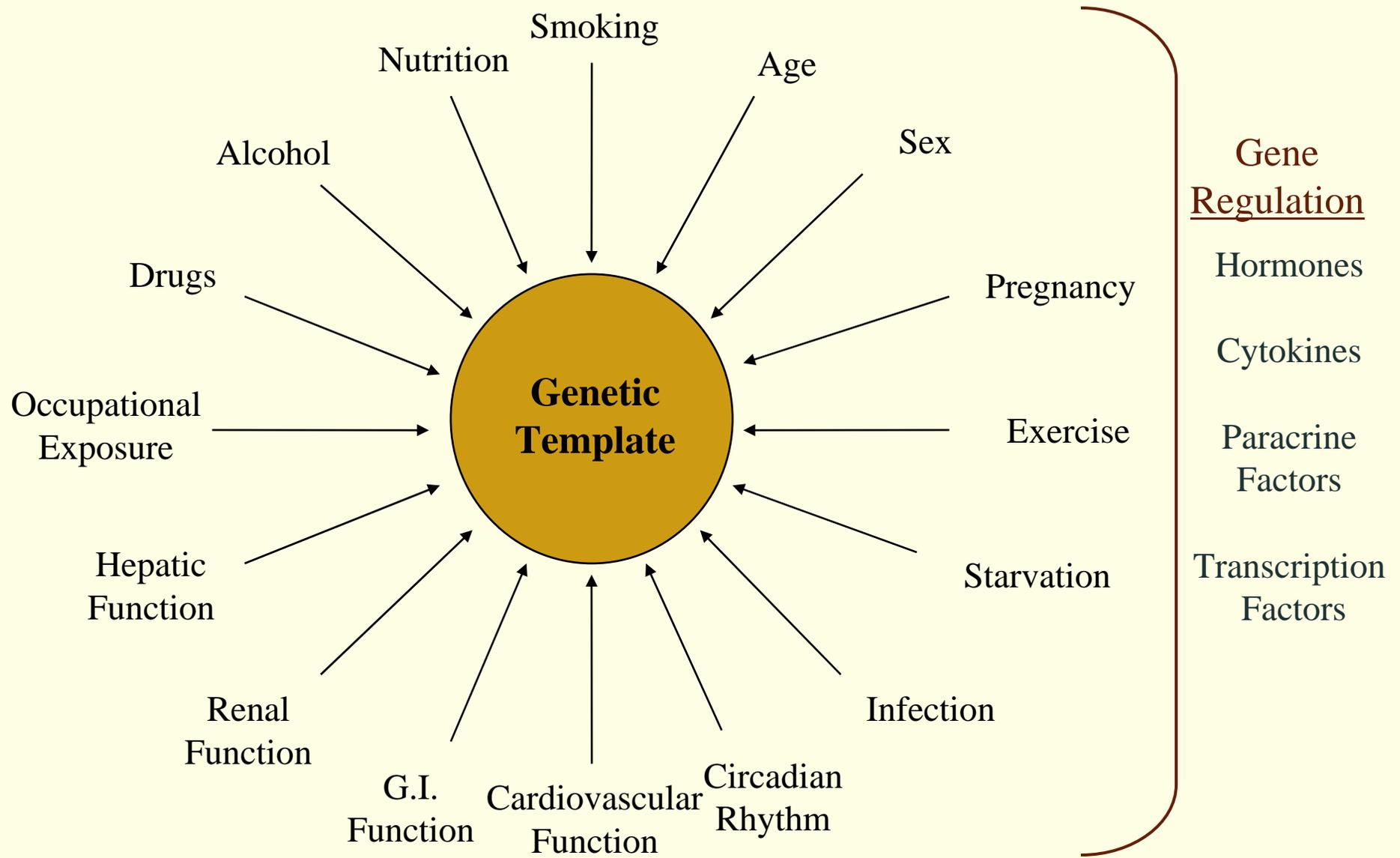
# Racial difference in warfarin response - not explained by *CYP2C9* variants

**“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  $3.3 \pm 1.4$  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



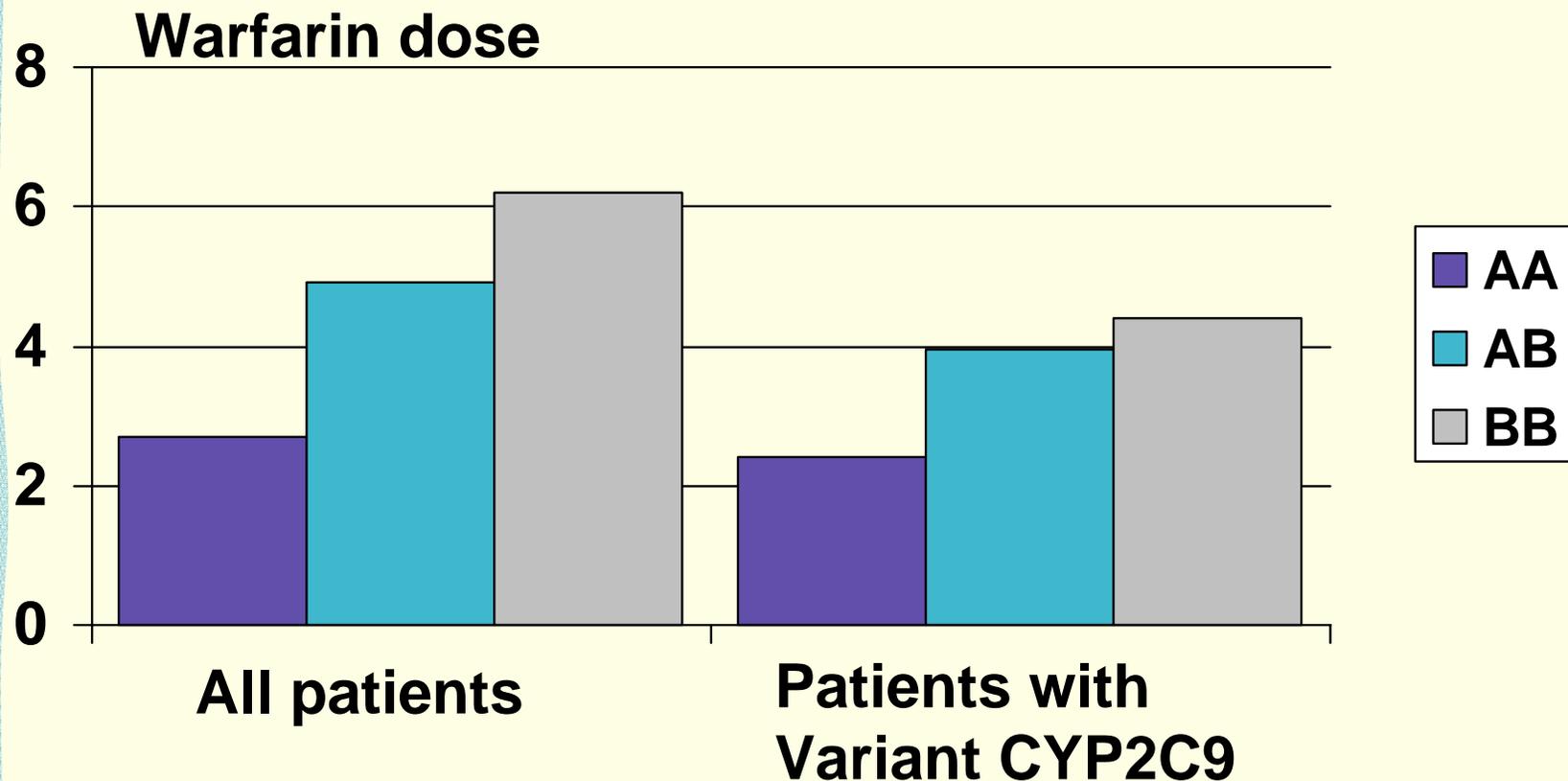
# Sources of Interindividual Variability in P450 Expression



*Adapted from E. Vesell, 1981*

# Association between warfarin dose and *VKORC1* variant haplotypes

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

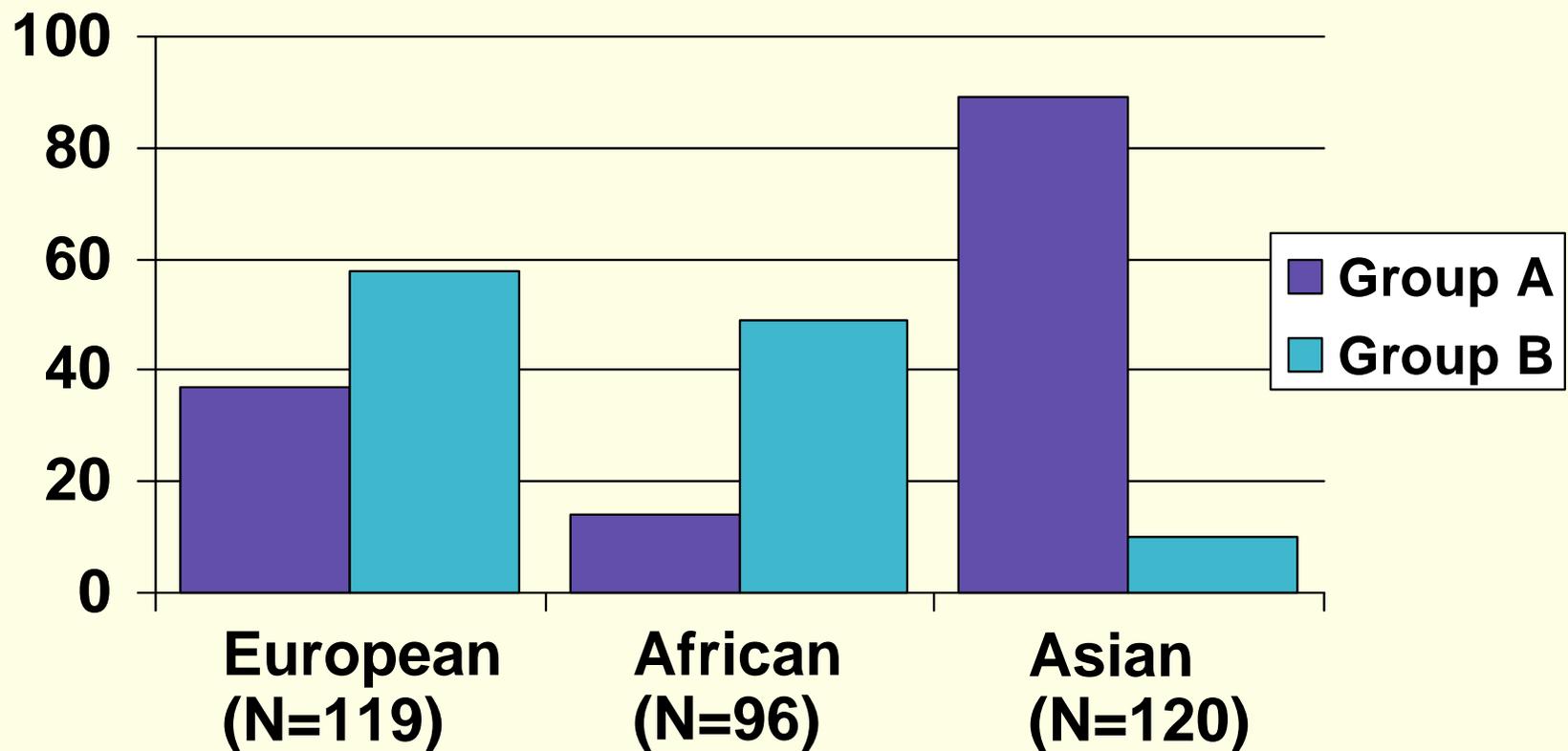


Reider et al NEJM 2005; 352:2285-93



# 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

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*CYP2C9*

10%

*VKORC1*

25%

Reider et al NEJM 2005; 352:2285-93



# Multifactorial effects on response to warfarin and similar anticoagulants

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## 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*  $\epsilon$ 4 allele

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<u>Location</u>	<u>Range</u>
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?

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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

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- 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”

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- 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

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## 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

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- 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)

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- 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

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- 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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