Clinical Pharmacology Considerations for Evaluating Race, Ethnicity, Geography, and Ancestry During Drug Development and Regulatory Review

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Topics for Discussion

- Race, Ethnicity, Geography, and Ancestry
- Examples of Differences Across Populations
- Factors Contributing to Differences
- Consequences of Differences
- Role for Clinical Pharmacology
- Summary

Some Definitions: Race & Ethnicity

Self-reported and are considered **social-political constructs** that should not be interpreted as being scientific or anthropological in nature

Ethnicity

- Hispanic or Latino
- Not Hispanic or Latino

Race

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White

Ethnicity: Social group with a shared history, heritage, culture, sense of identity, and territorial identity that occurs despite racial dissimilarity

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Race: Groups based on physical traits regarded as common among people of shared ancestry

American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

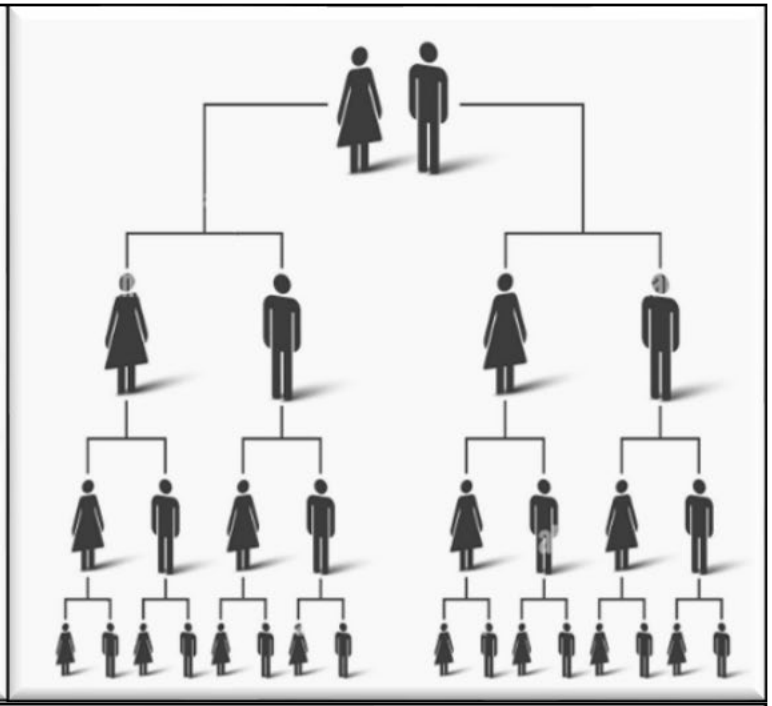
White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Race and ethnicity data collection guidance ; Image source: cancer.gov

Some Definitions: Geography

Geography: A geographical region/country based on the location of clinical study

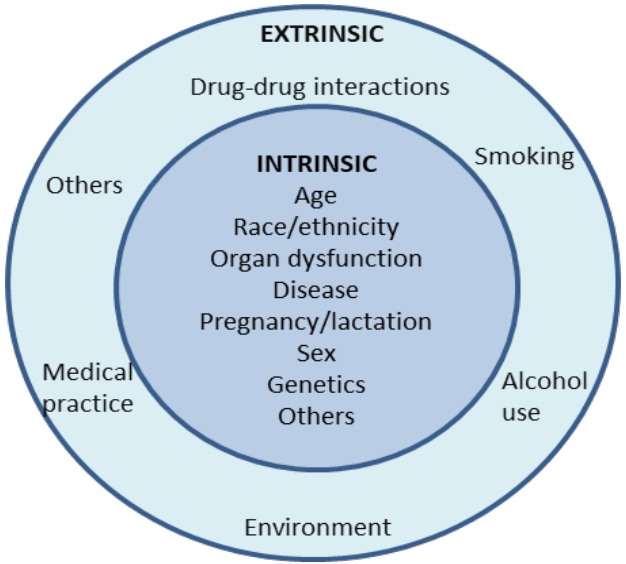
Some Definitions: Ancestry



Ancestry: Biologic or genetic ancestry of an individual and in genetic research studies, ancestry information is replacing the use of racial categories. Note: the term is subject to a variety of interpretations and can be based on geographic, historical, cultural, or religious definitions

Image source: https://www.alamy.com/stock-photo/, https://www.statnews.com/2022/05/02/substituting-genetic-ancestry-for-race-in-research-not-so-fast/; Jorde LB & Bamshad MJ, 2020

Some Definitions: Intrinsic & Extrinsic Factors



Intrinsic & Extrinsic Factors: Factors that can lead to exposure or response difference across subpopulations or impact the interpretation of R/B across subpopulations

Huang S-M & Temple R, 2008

Case Example: Multiple Myeloma

Analysis of racial and ethnic disparities in multiple myeloma US FDA drug approval trials

blood advances 22 MARCH 2022 • VOLUME 6, NUMBER 6

Bindu Kanapuru,[1,*] Laura L. Fernandes,[2,*,†] Lola A. Fashoyin-Aje,[3] Andrea C. Baines,[1] Vishal Bhatnagar,[4] Rachel Ershler,[1] Thomas Gwise,[2] Paul Kluetz,[4] Richard Pazdur,[4] Elizabeth Pulte,[5] Yuan-Li Shen,[6] and Nicole Gormley[1]

Cancer. 2020 January 01; 127(1): 82–92. doi:10.1002/cncr.33208.

African Americans with translocation t(11;14) have superior survival after autologous hematopoietic cell transplantation for multiple myeloma compared in Whites in the United States

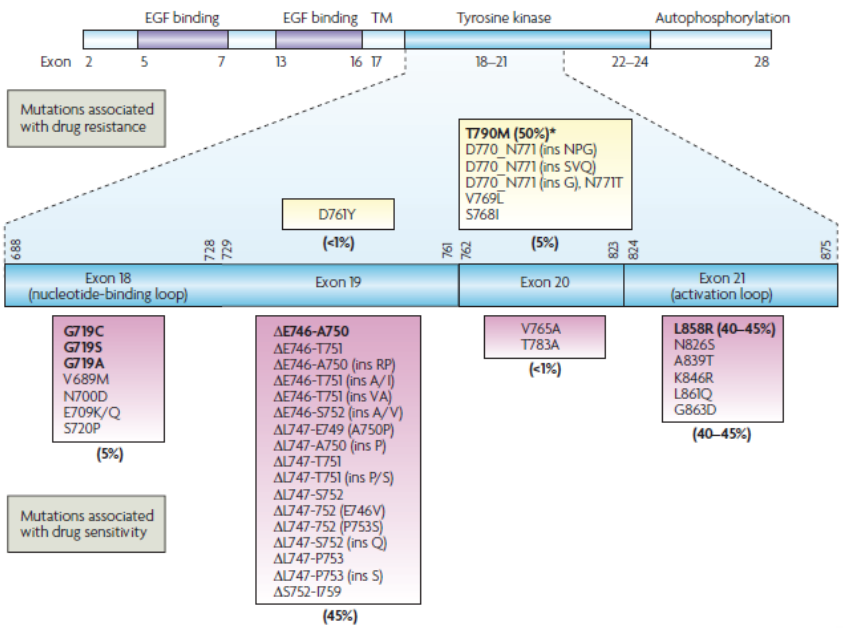
Talha Badar, MD[1], Parameswaran Hari, MD, MS[2], Omar Dávila, MPH[2], Raphael Fraser,

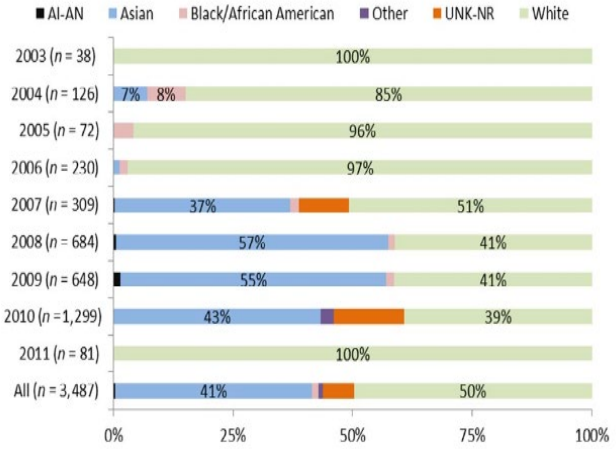
652.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

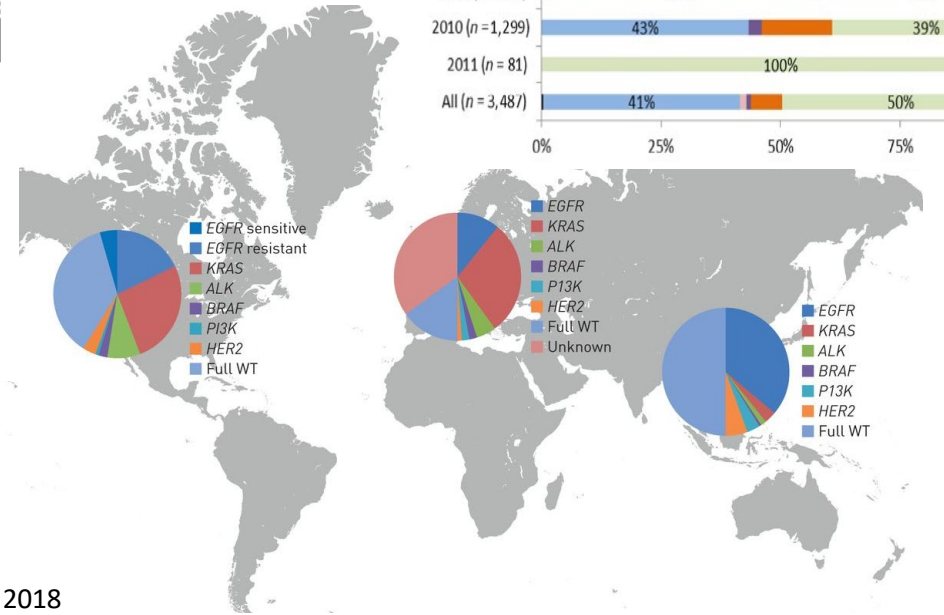
Current Testing Practices for t(11;14) Rearrangements in Patients with Newly Diagnosed Multiple Myeloma in the United States

Linda B. Baughn, Elizabeth S. Mearns, Michael Nixon, Vivek S. Chopra, Allicia Girvan, R. Frank Cornell, Jayeta Saxena, Bethany M. Slifko, Jordan Clark, Shaji K Kumar

Case Example: EGFR TKIs



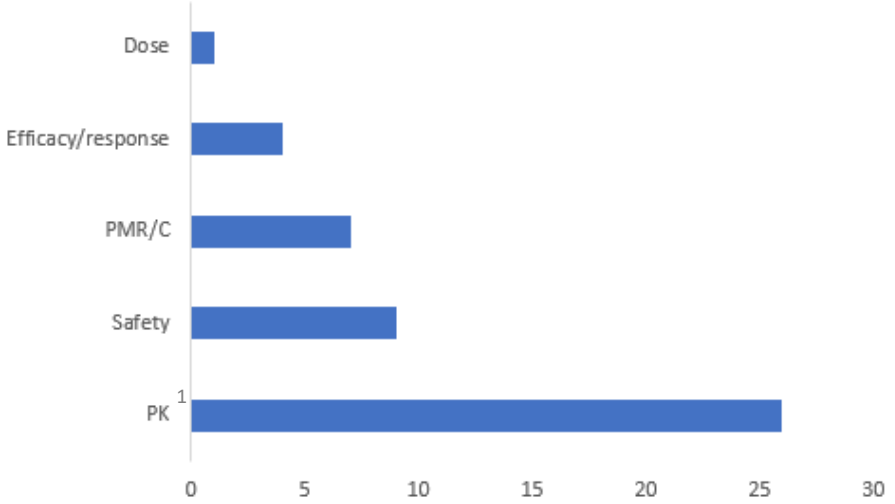




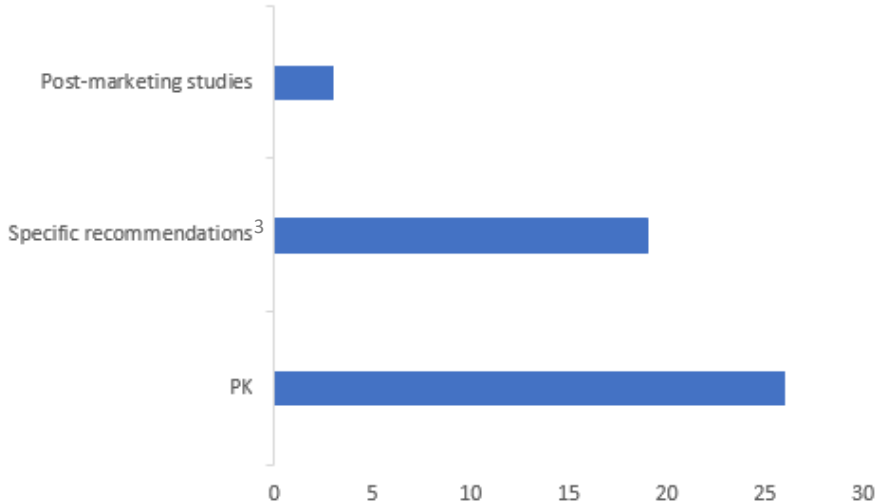
Sharma VS et al., 2007; Calvayrac O et al., 2017; Ramamoorthy A et al., 2018

Differences Reported for FDA-approved New Drugs

Race and ethnicity differences



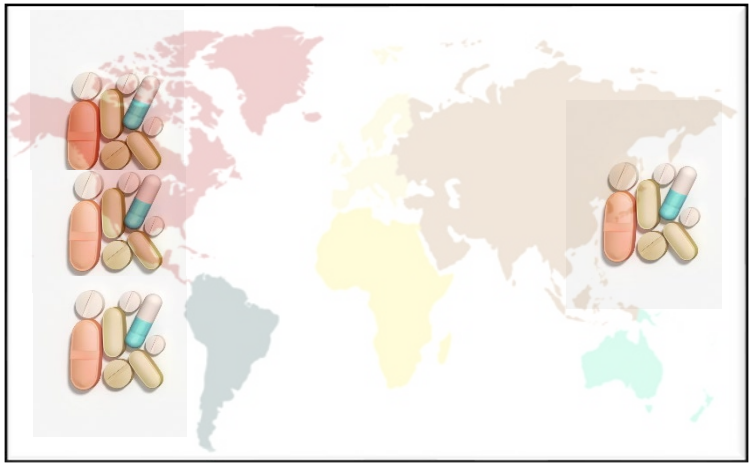
Pharmacogenomic differences[2]

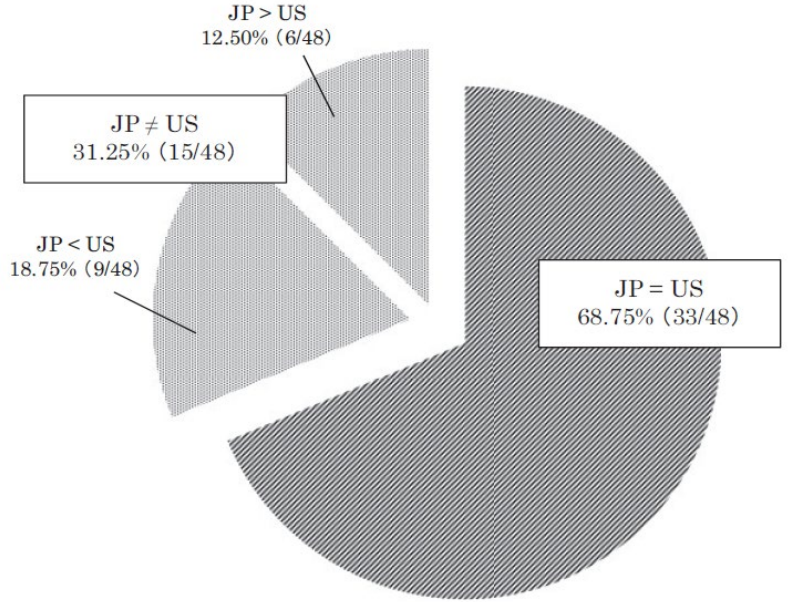


428 new drugs approved between 2008 and 2019; [1] >20% change in AUC, Cmax, etc.; [2] Genotype/phenotype frequency differences across races and ethnicities (e.g., CYP2D6, CYP2C19, NAT2, UGT1A1); [3] specific dosage or usage (monitoring, contraindication) recommendations

Modified from Ramamoorthy A et al., 2015 and Ramamoorthy A et al., 2022

Dose Differences Across Regions

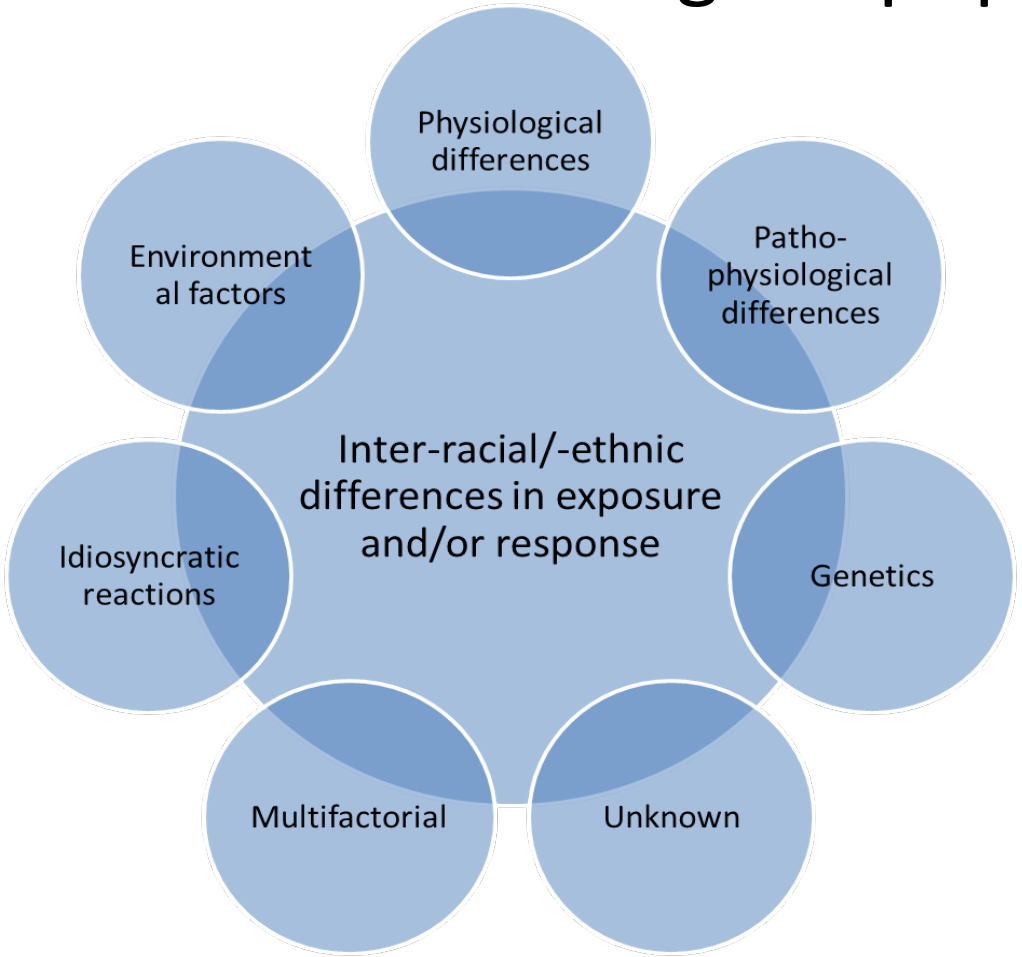




Dose differences potentially driven by PK/PD differences, safety concerns, and other factors (e.g., business decisions)

Takayanagi R et al., 2018; Kenmotsu H & Tanigawara Y, 2015

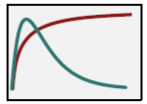
Causes for Differences Among Subpopulations



Ramamoorthy A et al., 2015

What We Look for During Review?

Comprehensive Clinical Pharmacology Review Questions



To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Is the proposed dosing regimen appropriate for the general patient population for which the approval is being sought?

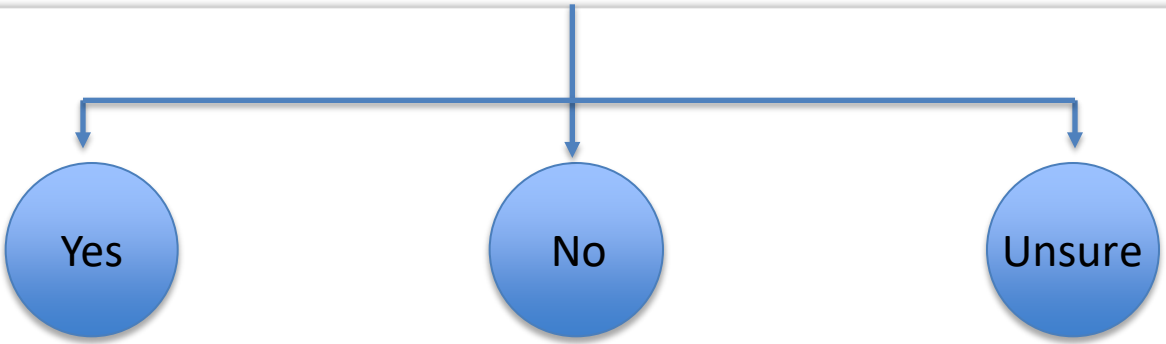
Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Objective

To evaluate **generalizability** of **risk/benefit** data available from the drug development program to a **diverse US population** that is expected to receive the drug upon its approval

Based on our understanding of the
disease, drug, and target
is a clinically relevant difference expected in
drug exposure and/or response
among clinically relevant **subpopulations**?



Enroll diverse population in clinical trials as well as evaluate and report subgroup data as outlined in FDA guidances and regulations

What is in Our Toolbox?

- Understanding intrinsic & extrinsic factors
- In vitro studies
- Pharmacogenomics
- Enriched clinical trials

- Informing I/E criteria
- Clinical PK/PD studies
- Molecular epidemiology
- MIDD

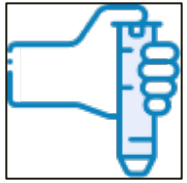
Totality of evidence

Differences Among Subpopulation Can Lead to Differences in Regulatory Recommendations

Geographic differences in drugs or doses approved/withdrawn

Targeted recommendations across subpopulations

Subpopulations Differences Can Lead to Differences in Regulatory Recommendations



No dose adjustment
No specific monitoring recommendations

Different dosing recommendations →

- Rosuvastatin in Asians
- Tacrolimus in Blacks
- Eliglustat based on CYP2D6 metabolizer status

Considerations for therapy selection →

ACE inhibitors (e.g., losartan, cadesartan) in Blacks

Warnings and Precautions →

Carbamazepine for HLAB*1502 in Asians

Indication
Contraindication →

- BiDil for self-identified Blacks
- Rasburicase for G6PD deficiency

Postmarketing Studies to Obtain Additional Information on Safety, Efficacy, or Optimal Use

Conduct a randomized, controlled clinical trial to evaluate the efficacy and safety in **African-American patients** with systemic lupus erythematosus (belimumab, 2011)

Evaluate the safety and PK in patients with wild-type, heterozygous, and homozygous **UGT1A1*28 genotypes** (belinostat, 2014)

Conduct an epidemiologic study to evaluate the incidence of angioedema in **Black patients** (sacubitril and valsartan, 2015)

Include an assessment of PK, PD, safety, and efficacy **in U.S. racial and ethnic minority patients including Black and Asian patients** (daratumumab and hyaluronidase, 2020)

See the PMR/C for the full text

Summary

Diversity is often limited in clinical trials
Disease burden may be high for some disease in some populations

Need for **continued effort to enroll underrepresented populations** during drug development

Understand **exposure and/or response** across clinically relevant subpopulations

Leverage **clinical pharmacology** to understand and evaluate the impact of **intrinsic and extrinsic factors** on drug **exposure and/or response**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