The Role of Clinical Pharmacology in Dosage selection and Design of Multi-Regional Clinical Trials

Reflections from Experiences with Asia-Inclusive Drug Development

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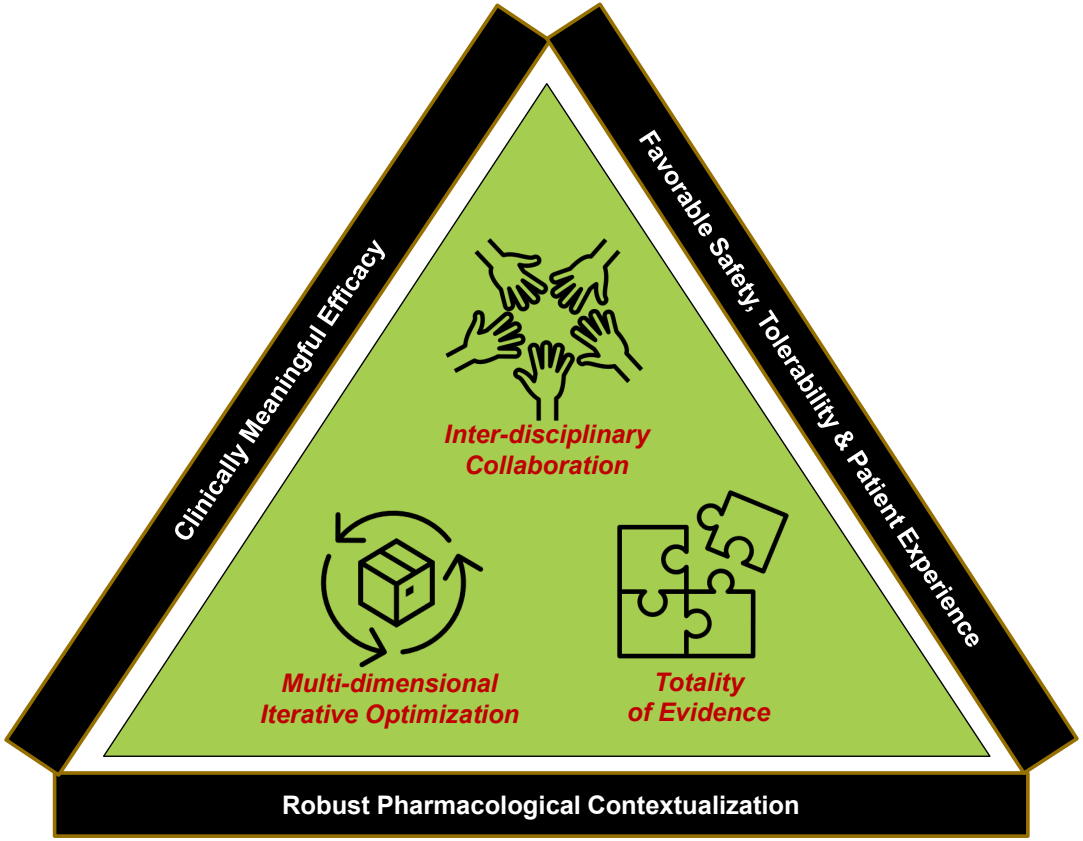
FDA-ISoP Workshop
Optimizing Dosages for Oncology Drug Products: Using Modeling and Simulation to Evaluate Effects of Intrinsic and Extrinsic Factors

October 16, 2023

Vision and Purpose Statement

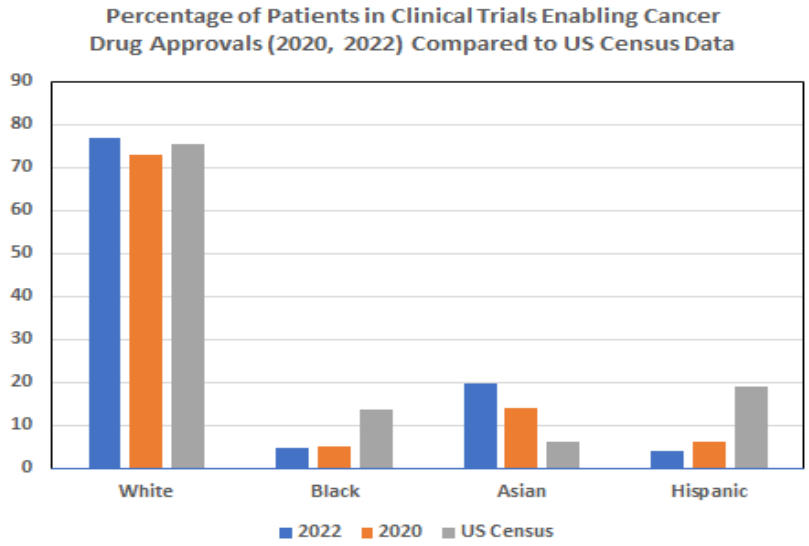
"To enable **efficient drug development** and **rational dose selection** through the integration of pharmacokinetics, pharmacodynamics, safety, efficacy and **population variability** with a purpose of **maximizing benefit versus risk** of cancer medicines **for all patients**"

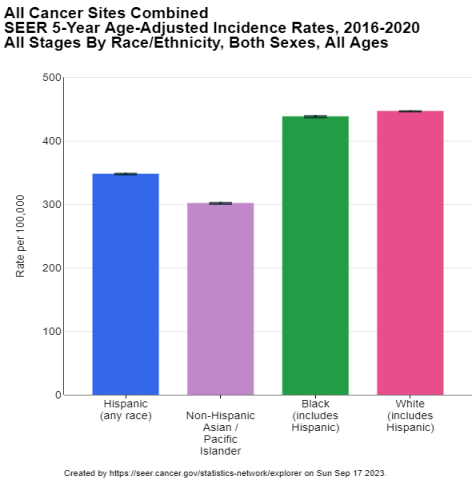


Adapted from Venkatakrishnan K and van der Graaf PH. Clinical Pharmacology and Therapeutics. 112(5):927-932, 2022

Every Patient's Data Matters –

An Opportunity for Clinical Pharmacology & Pharmacometrics to Enhance Clinical Trial Diversity and Maximize Value of Emerging Data for All Patients





July 15, 2021

Promoting Inclusion of Members of Racial and Ethnic Minority Groups in Cancer Drug Development

Lola Fashoyin-Aje, MD, MPH[1]; Julia A. Beaver, MD[1]; Richard Pazdur, MD[1]

» Author Affiliations

JAMA Oncol. 2021;7(10):1445-1446. doi:10.1001/jamaoncol.2021.2137

GUIDANCE DOCUMENT

Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability

Draft Guidance for Industry

APRIL 2022

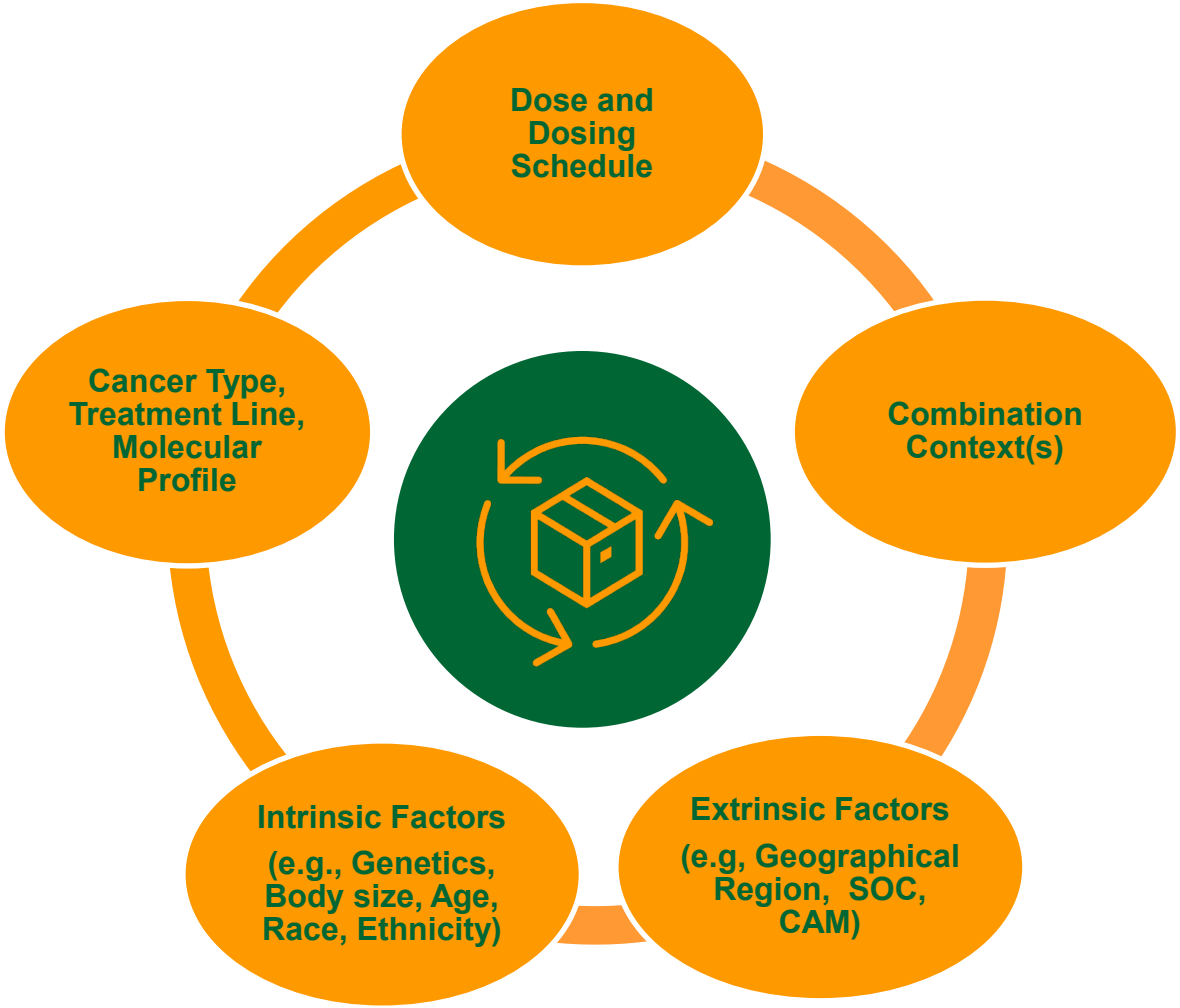
E17 General Principles for Planning and Design of Multiregional Clinical Trials

Guidance for Industry

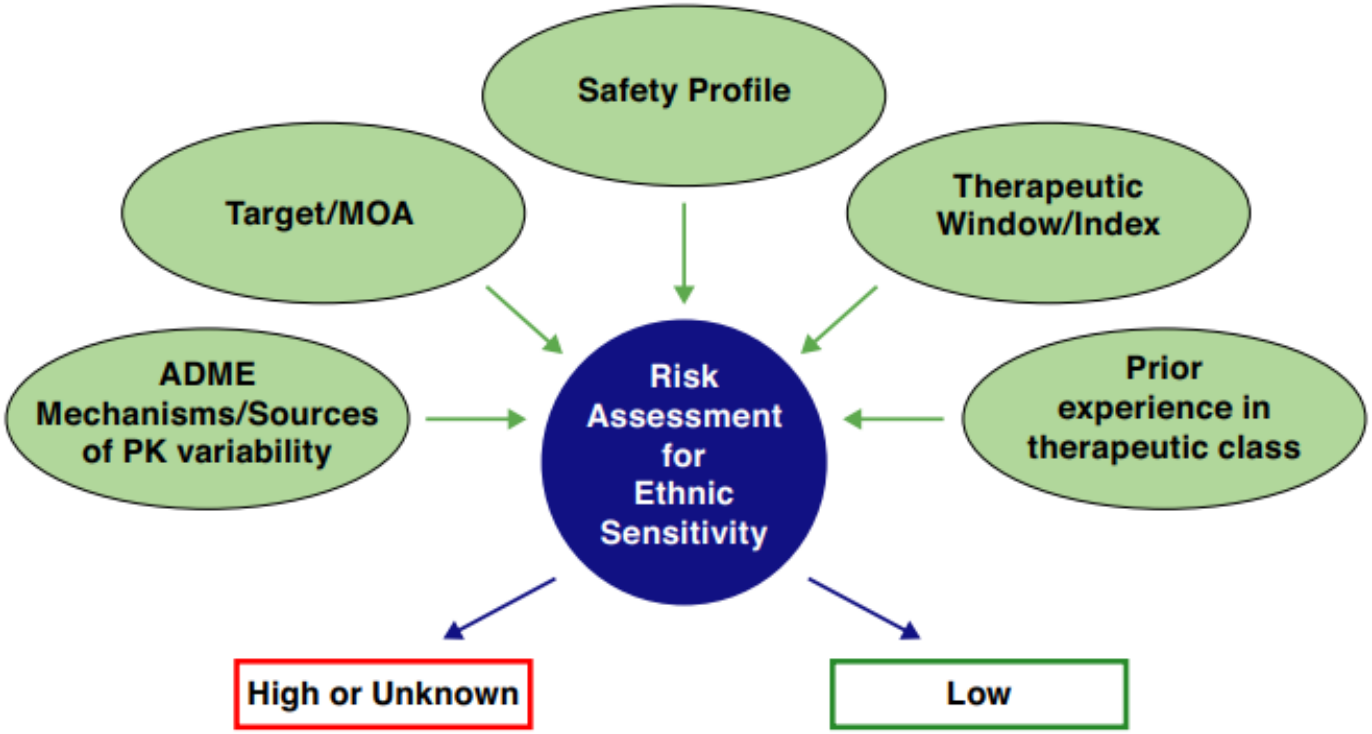
Data from https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots; https://seer.cancer.gov/statistics-network/explorer/

Acknowledgments: Melaina Boyce and Dina Oksen

Dosage Optimization in Oncology is a Multi-Dimensional and Iterative Problem Demanding Inter-Connected Evidence Generation



Ethnic Sensitivity Assessment Beginning Early in the R&D Lifecycle



Adapted from Venkatakrishnan K, Gupta N, et al., Clinical Pharmacology and Therapeutics, 113(2):298-309, 2023

ICH E5 Principles offer a Question-Based Traffic Light Approach to Ethnic Sensitivity Assessment –

The following properties of a compound make it less likely to be sensitive to ethnic factors:

- Linear pharmacokinetics (pK)
- A flat pharmacodynamic (PD) (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the medicine is well-tolerated)
- A wide therapeutic dose range* (again, possibly an indicator of good tolerability)
- Minimal metabolism or metabolism distributed among multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug, drug-diet and drug-disease interactions
- Nonsystemic mode of action
- Little potential for inappropriate use

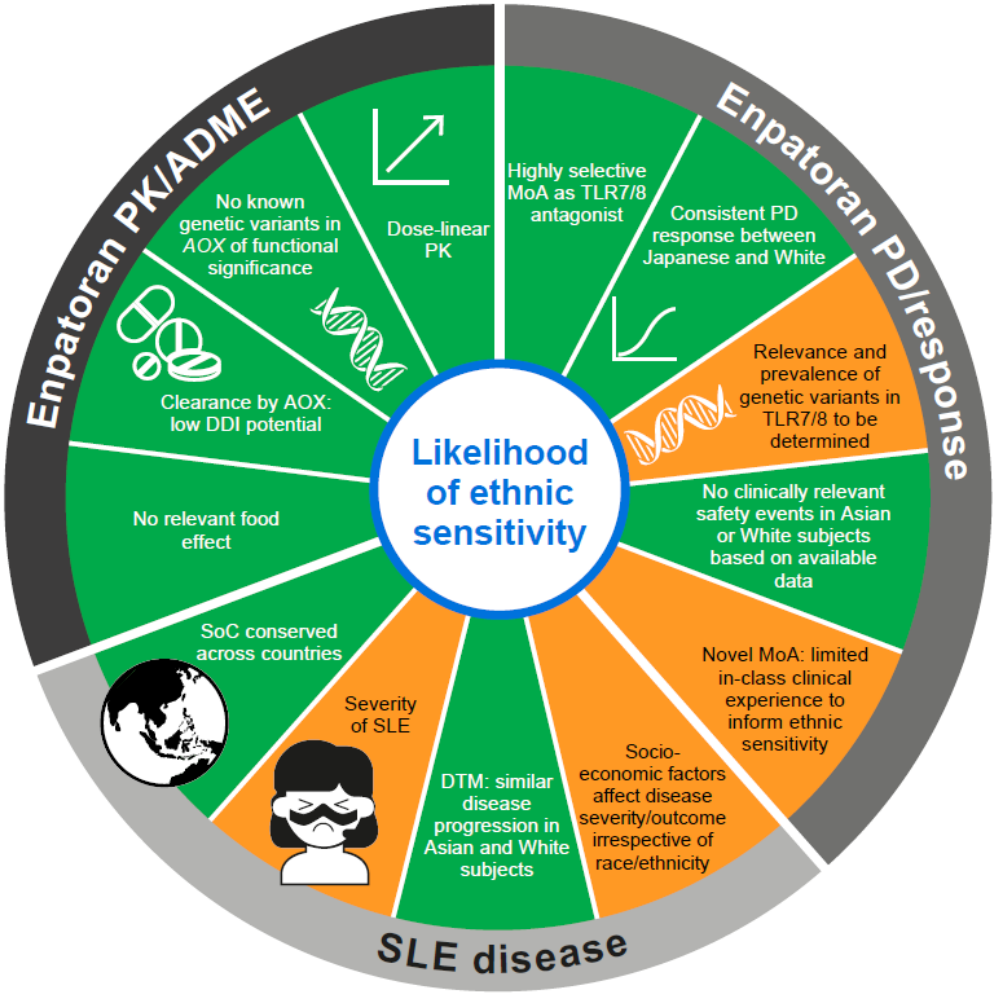
The following properties of a compound make it more likely to be sensitive to ethnic factors:

- Nonlinear pharmacokinetics
- A steep pharmacodynamic curve for both efficacy and safety (a small change in dose results in a large change in effect) in the range of the recommended dosage and dose regimen
- A narrow therapeutic dose range
- Highly metabolised, especially through a single pathway, thereby increasing the potential for drug-drug interaction
- Metabolism by enzymes known to show genetic polymorphism
- Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
- High inter-subject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple co-medications
- High likelihood for inappropriate use , e.g., analgesics and tranquilizers.

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-5-r1-ethnic-factors-acceptability-foreign-clinical-data-step-5_en.pdf

ICH E5 Principles in Ethnic Sensitivity Assessment –

Illustration of Application to Asia-Inclusive Development of the TLR7/8 Inhibitor Enpatoran in Systemic Lupus Erythematosus



Ethnic sensitivity

● Likely ● Unclear* ● Unlikely

*due to lack/limited of knowledge to date

Acknowledgments: Lena Klopp-Schulze

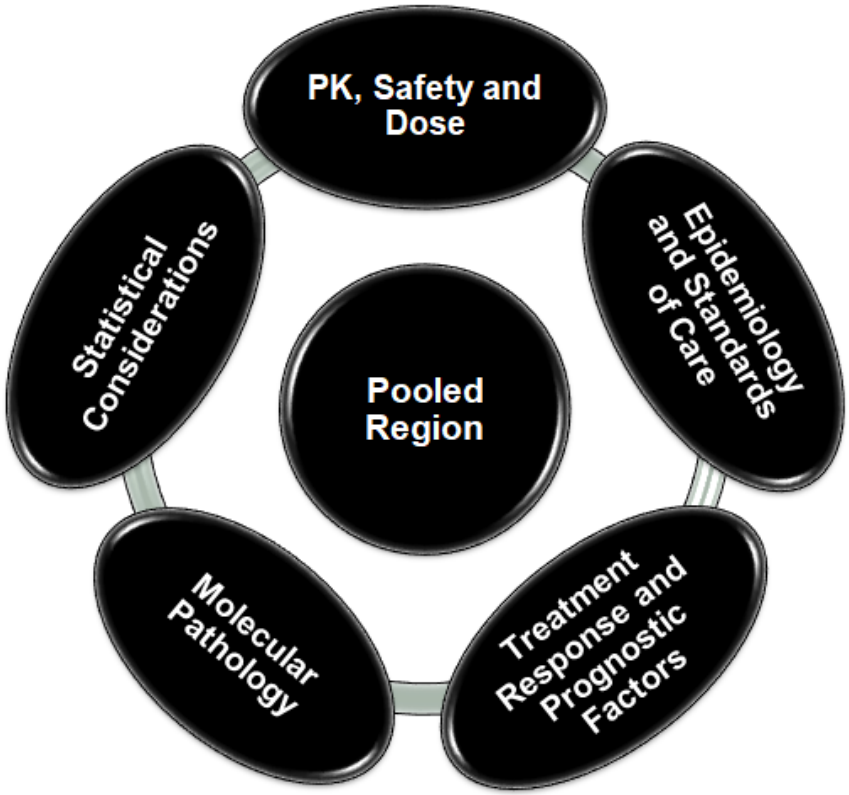
ICH E17 –
Guiding Principles

1. Well-designed MRCTs can increase drug development efficiency and support regulatory decision-making across regions
2. Relevant intrinsic and extrinsic factor effects should be understood early
3. Sample size allocation by region to verify consistency in treatment effect while allowing feasibility in recruitment and timely trial conduct
4. Pre-specified pooling of regions based upon similarities
5. Single primary analysis supported by structured exploration of consistency
6. High trial quality
7. Sponsor-HA communication encouraged during MRCT design

ICH E17 Guideline: https://www.fda.gov/media/99974/download

ICH E17 –
Pooled Region Concept

*"Pooling some geographical regions, countries or regulatory regions at the planning stage, if subjects in those regions are thought to be **similar enough** with respect to **intrinsic and/or extrinsic factors** relevant to the **disease** and/or **drug** under study."*



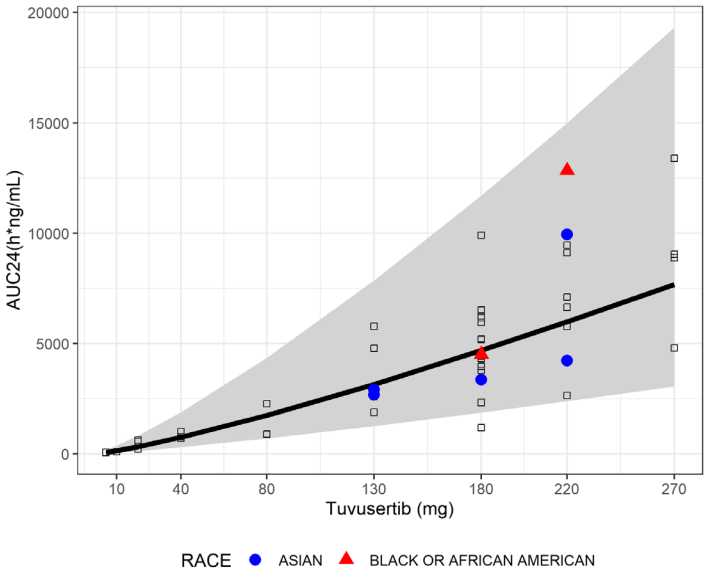
ICH E17 Guideline: https://www.fda.gov/media/99974/download
Adapted from Venkatakrishnan K, Gupta N, et al., Clinical Pharmacology and Therapeutics, 113(2):298-309, 2023

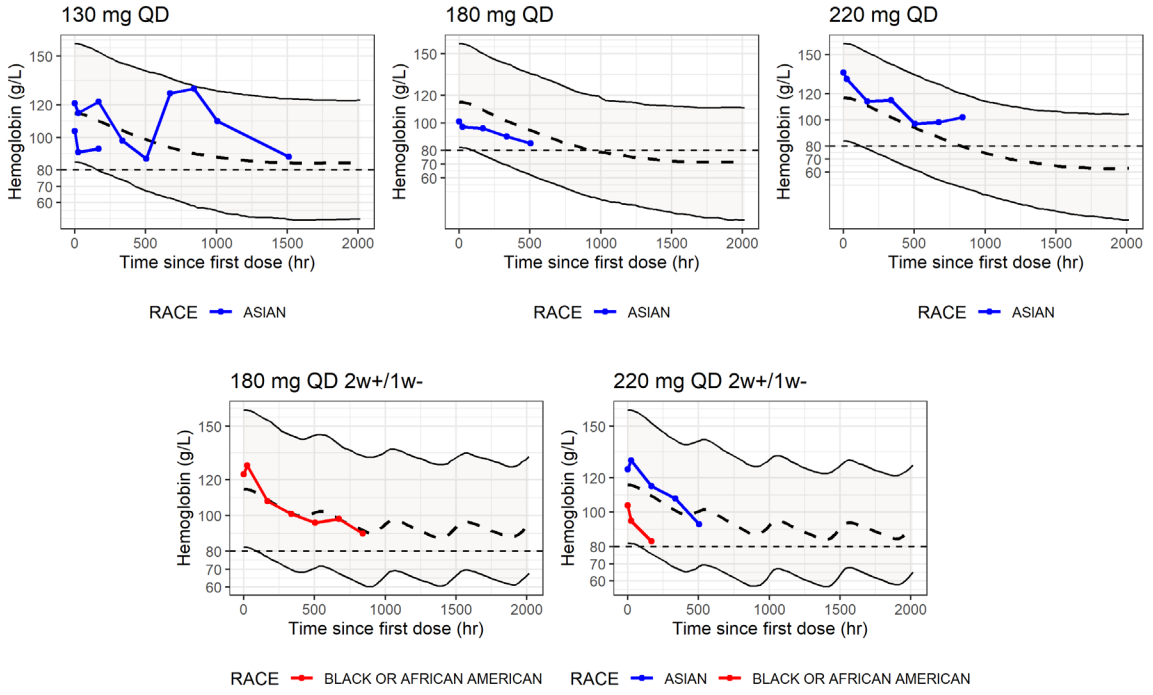
Drug-Related Intrinsic and Extrinsic Factors

Pharmacokinetic/ Pharmacodynamic Considerations
for Ethnic Sensitivity Assessment and Dosage Justification

Population PK/PD Modeling for Ethnic Sensitivity Assessment

Application to the Investigational Anticancer Agent Tuvusertib



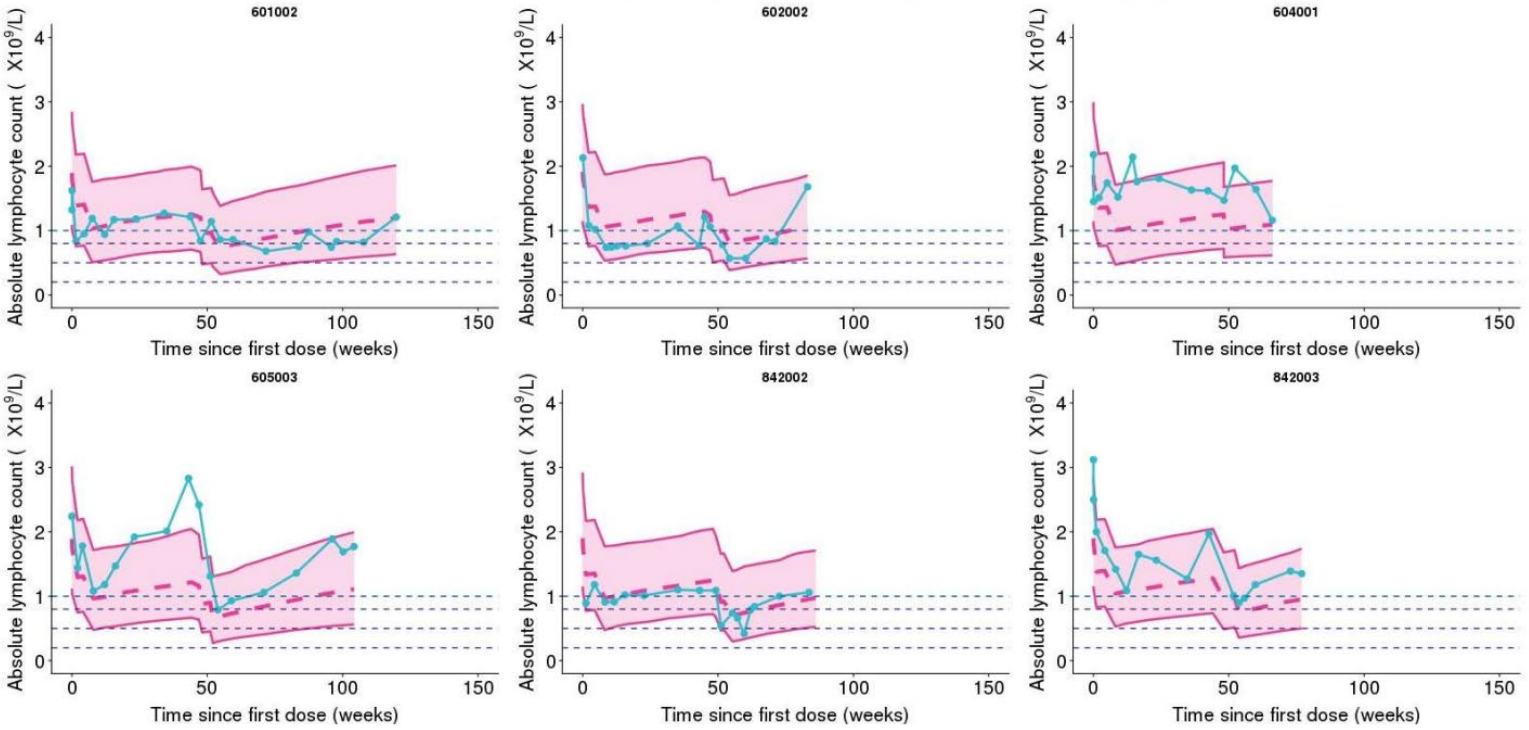


- Model-based analyses enabled continuous assessment of emerging data in FIH study for consistency in exposures and hemoglobin dynamics in relation to intrinsic/extrinsic factors.

Jatinder Mukker et al., Poster presentation at ASCPT 2023

Population PK/PD Modeling for Ethnic Sensitivity Assessment

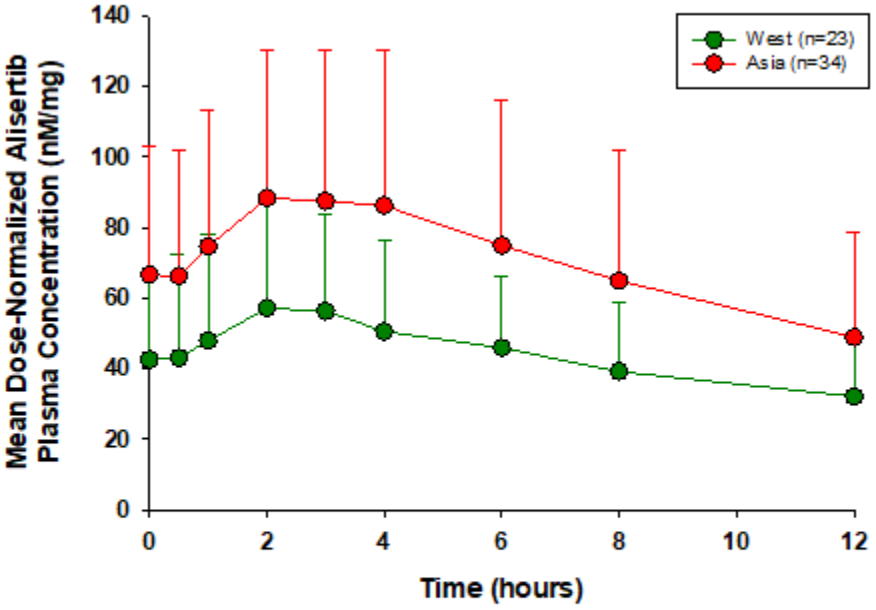
Application to Development of Cladribine Tablets for Multiple Sclerosis

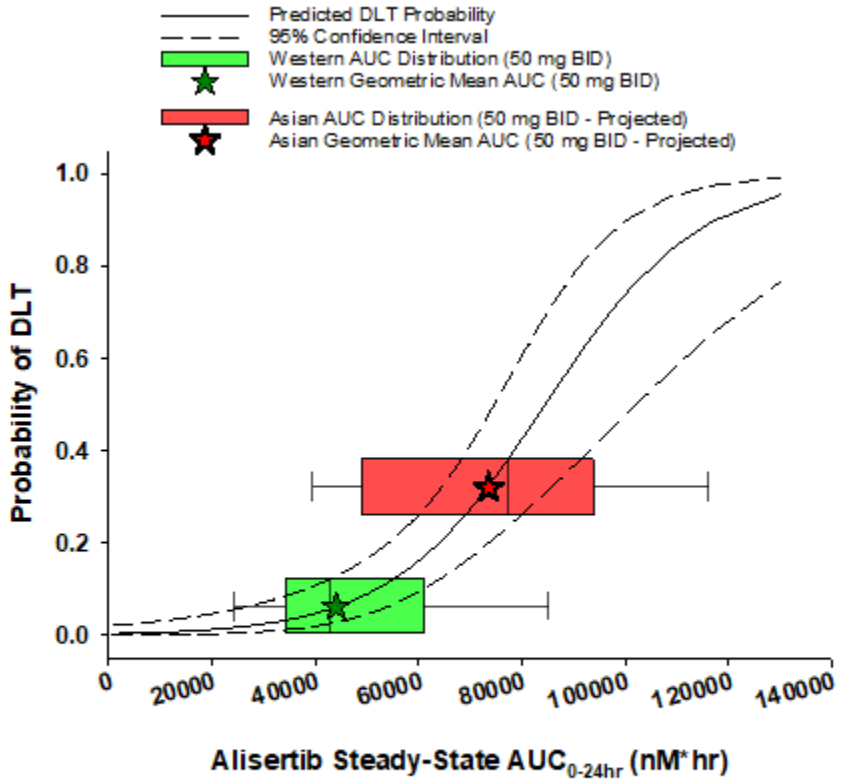


- Absolute Lymphocyte Count (ALC) dynamics in Asian patients are consistent with expectations from a population pharmacodynamic model of data from global clinical trials
- These pharmacometric analyses enabled conclusion of lack of ethnic sensitivity and dosage justification for Asian populations

Munafo A, Terranova N et al., Clinical and Translational Science. 15(2):297-308, 2022

Illustrative Example of Clinically Relevant Differences in PK Translating to Differences in Recommended Dosage for Clinical Investigation in East Asia





Western MTD/ RP2D: 50 mg BID x 7 days in 21-day cycles
East Asia MTD: 30 mg BID x 7 days in 21-day cycles

Venkatakrishnan K et al., Investigational New Drugs 33(4):942-53, 2015
Venkatakrishnan K et al., Clinical and Translational Science. 9: 9-22; 2016
Zhou X et al., British Journal of Clinical Pharmacology. 84(1):35-51, 2018

When Clinically Relevant Ethnic Sensitivity is Observed, ICH E17 supports Differential Dosing in MRCTs when Justified by Exposure-Response Principles

"The acceptability of dose-selection strategies should be discussed with the relevant regulatory authorities in advance. If substantial differences are anticipated (e.g., the drug response is sensitive to intrinsic and/or extrinsic factors), further investigations may be needed. These could include a PK-PD or dose-response study conducted in a particular ethnic population or studies conducted for a broader population that would allow further evaluation of the impact of intrinsic and extrinsic factors on dose-response.

The dose regimens in confirmatory MRCTs (based on data from studies mentioned above) should, in principle, be the same in all participating ethnic populations. However, if earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and provided it is scientifically justified in the study protocol. Prospective careful planning of assessment strategies for which different doses are used should be tailored to each case and described in the analysis plans."

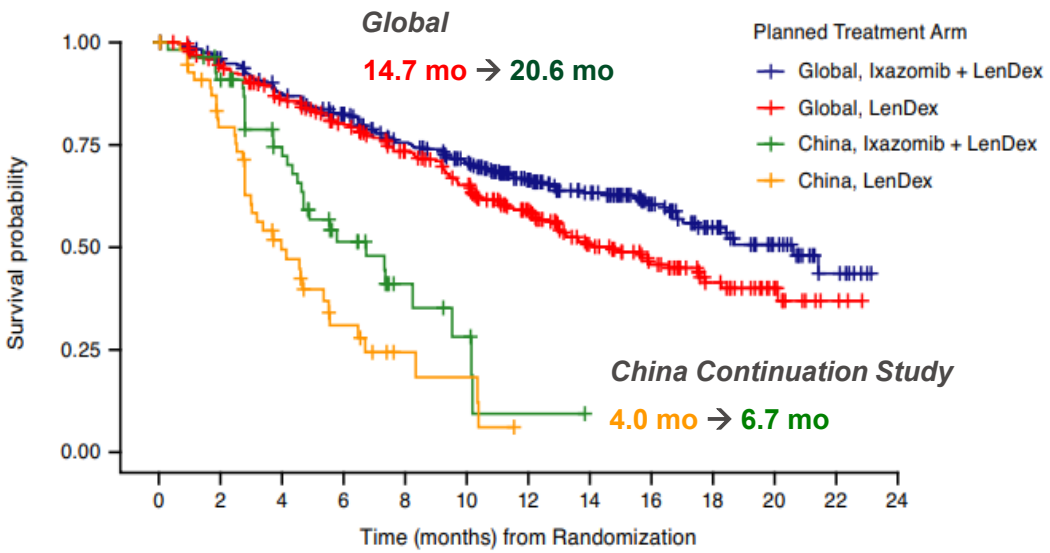
ICH E17 Guideline: https://www.fda.gov/media/99974/download

Disease-Related Intrinsic and Extrinsic Factors

Understanding Disease Similarity Between Populations as a Component of MRCT Design

Inter-Population Differences in Disease Progression/ Prognosis – *An Example in Relapsed/ Refractory Multiple Myeloma*

Progression-free survival in Chinese and global populations in the phase III TOURMALINE-MM1 trial of Ixazomib + Lenalidomide/Dexamethasone



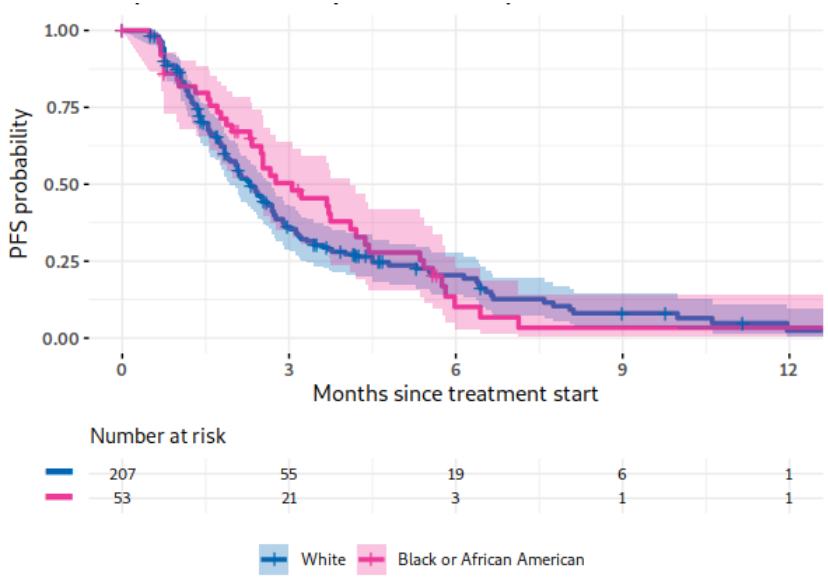
- Although the treatment effect of ixazomib, when added to Len/Dex, was statistically and clinically significant in both populations, absolute PFS in the Chinese population was substantially shorter than in the global population
  - More advanced/ refractory disease and differences in prior treatment
- Intriguing lessons illustrating importance of disease-related intrinsic/ extrinsic factors in MRCT design

Venkatakrishnan K, Gupta N, et al., Clinical Pharmacology and Therapeutics, 113(2):298-309, 2023
Moreau P et al., New England Journal of Medicine., 374(17):1621-34, 2016
Hou J et al., Journal of Hematology and Oncology. 10(1):137, 2017

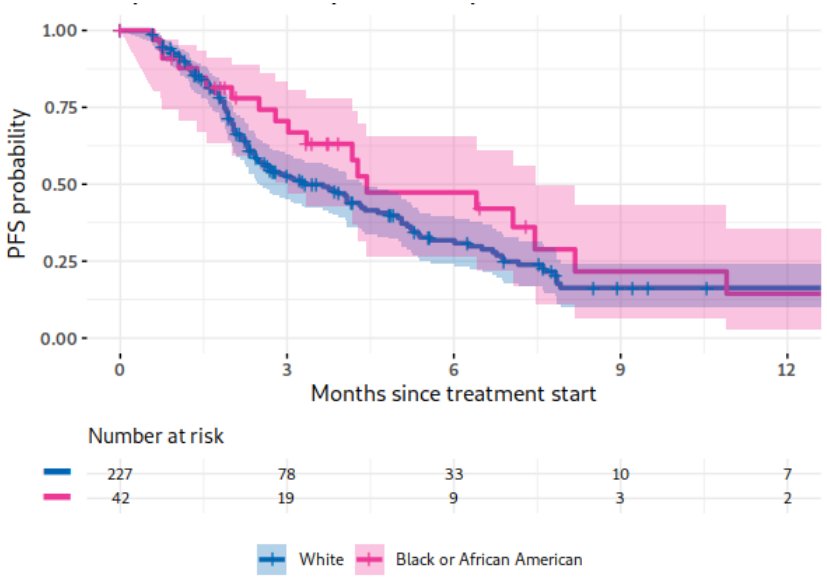
Illustration of Leveraging RWD to Assess Effects of Race/ Ethnicity

PFS for Docetaxel-based 2L treatment of NSCLC in Tempus database

Without Prior ICI treatment*



With Prior ICI treatment*

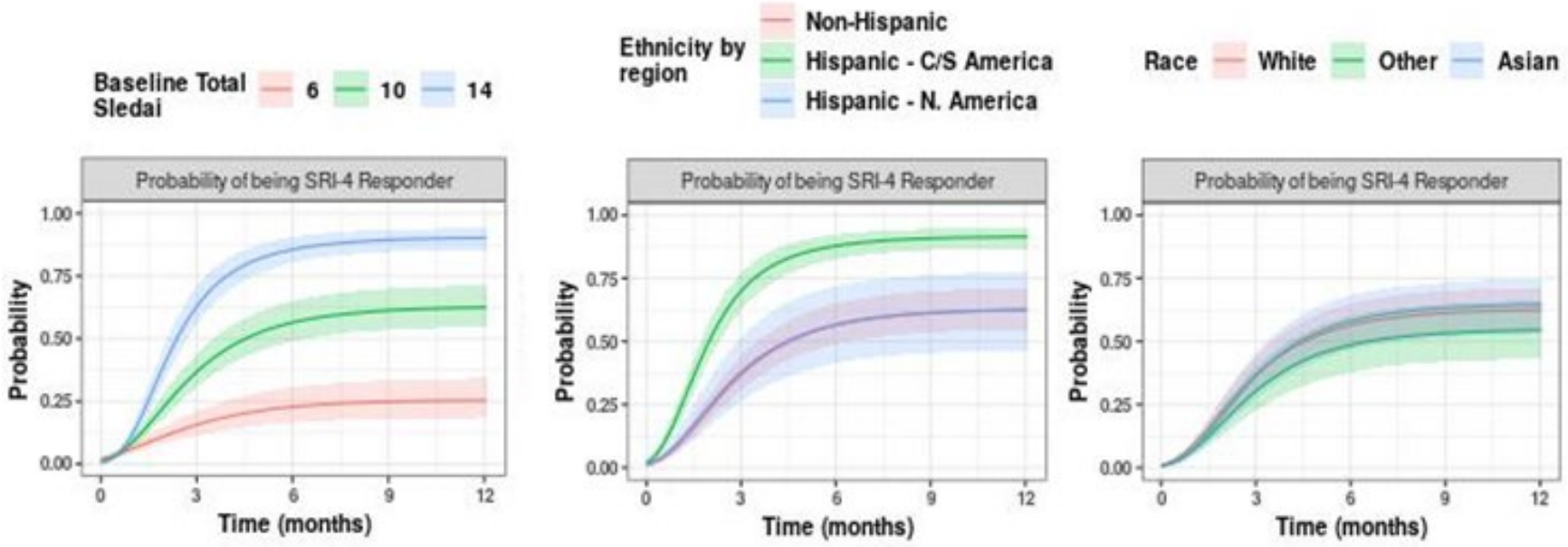


** Exploratory analyses*

- Exploring RWD can help assess variability in outcomes in different patient populations ahead of initiating Proof-of-Concept studies.

Acknowledgments: Aslihan Gerhold-Ay, Jan Feifel, Jatinder Mukker, Dina Oksen

Illustration of Disease Modeling of Population Heterogeneity – *Disease Trajectory Modeling of Pooled Patient-Level Placebo Arm (Placebo + Standard of Care) Data in Systemic Lupus Erythematosus (SLE)*

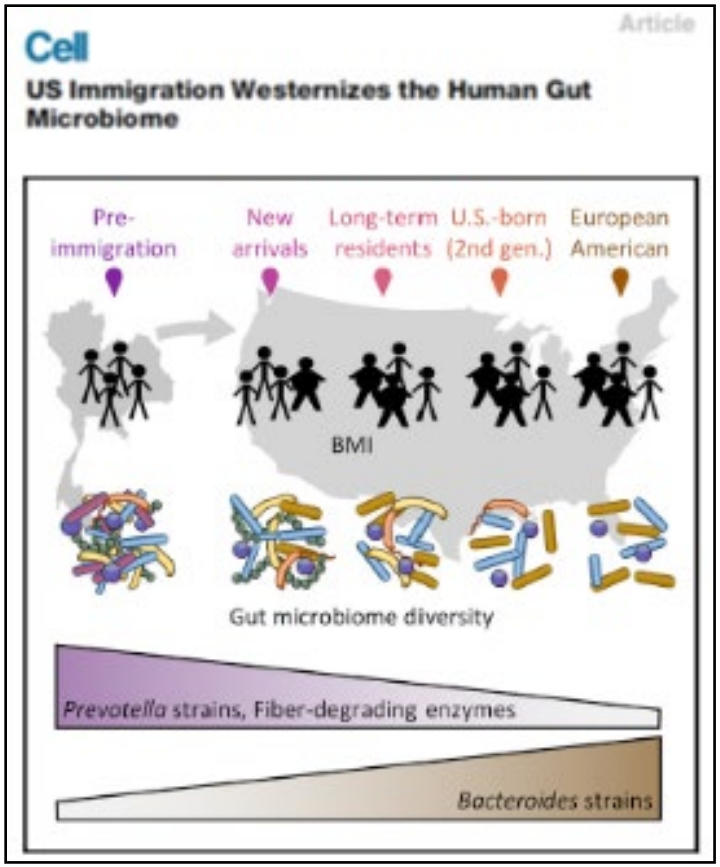


- Baseline disease severity (e.g., SLEDAI) influences probability of response (e.g., SRI-4)
- Greater response probability in Hispanic patients in Central/South America
- Consistency in disease trajectory in Asian vs. non-Asian populations supports Asia-inclusive SLE MRCTs

Goteti K et al., Clinical Pharmacology and Therapeutics: Pharmacometrics and Systems Pharmacology 12(2):180-195, 2023

Global Population Variability in Intrinsic and Extrinsic Factors May be More Dynamic than Typically Considered...

Emerging Role of the Gut Microbiome



The ISME Journal (2020) 14:1639–1650
https://doi.org/10.1038/s41396-020-0630-6

ISME

ARTICLE

US nativity and dietary acculturation impact the gut microbiome in a diverse US population

Guo *et al.*
Allergy Asthma Clin Immunol (2020) 16:67
https://doi.org/10.1186/s13223-020-00465-7

Allergy, Asthma & Clinical Immunology

RESEARCH Open Access

Linking the westernised oropharyngeal microbiome to the immune response in Chinese immigrants

Kaplan *et al. Genome Biology* (2019) 20:219
https://doi.org/10.1186/s13059-019-1831-z

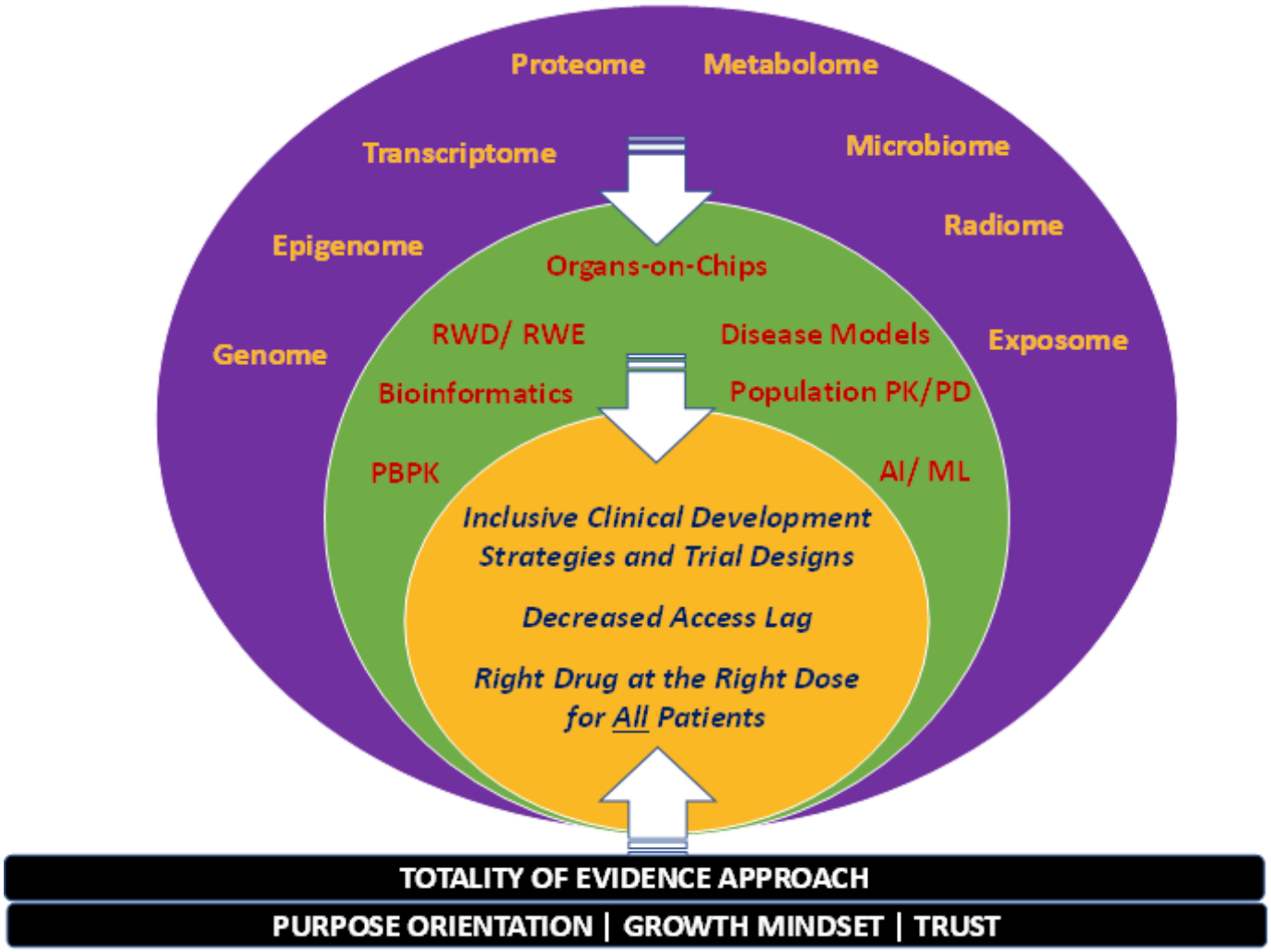
Genome Biology

RESEARCH Open Access

Gut microbiome composition in the Hispanic Community Health Study/Study of Latinos is shaped by geographic relocation, environmental factors, and obesity

Vangay P et al., Cell. 175(4):962-972, 2018.e10; Kaplan RC et al., Genome Biology. 20: 219, 2019
Peters BA et al., ISME J. 14: 1639-1650, 2020; Guo J et al., Allergy, Asthma & Clinical Immunology. 16: 67, 2020

Evaluating Population Diversity in Drug and Disease-Related Intrinsic and Extrinsic Factors Demands a Multi-Disciplinary Approach



Venkatakrishnan K and Benincosa LJ. Clinical Pharmacology & Therapeutics. 112(2):204-207, 2022

Thank you!