Diversity in Clinical Pharmacology Coming of Age

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In the Editorial of the October 2021 issue of *Clinical Pharmacology & Therapeutics* (*CPT*), it was proposed that "if diversity is defined as the inclusion of a range of many people that are different from each other, then it is obviously a core principle guiding best practices in clinical pharmacology and the foundation for personalized medicine and precision dosing."[1]

Diversity spans at least four main dimensions in clinical pharmacology: gender/biological sex, ethnicity/race, specific populations, and age.[1] The latter is the topic of a series of articles in the current issue of *CPT*, which covers therapeutic treatment and evaluation in patient groups across the full age range, from preterm infants to geriatrics (**Figure 1**).[2–6]

On one end of the patient age spectrum, Engbers *et al.*[2] examine the exposure-response relationship of ibuprofen on closure of the patent ductus arteriosus in preterm infants. Their model-based analysis provides new insights into the role of ibuprofen exposure, covariates, and timing of treatment on clinical outcomes. Based on this, the authors propose that higher, yet unstudied, doses may increase treatment success. Another very young specific population is the topic of the study by Damoiseaux and co-workers,[3] who address the question of what the presence of chemotherapy drugs in breast milk is to inform and aid clinicians in making an informed decision about possible risks of exposure to the infant for women who want to breastfeed their infants during cancer treatment. They studied the distribution of five chemotherapeutics (doxorubicin, cyclophosphamide, paclitaxel, carboplatin, and cisplatin) into breast milk and provide specific clinical guidance for each of them. The third paper focusing on pediatric patients comes from the *Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee*, who demonstrate how physiologically-based pharmacokinetic (PBPK) modeling of real-world data (RWD) can be used to guide dosing of the commonly prescribed low-molecular-weight heparin, enoxaparin, in obese children.[4] In a more general sense, this case study demonstrates that combining PBPK with RWD can offer a novel approach to guide precision dosing in clinical practice that can be applied to other drugs and specific populations.

Wang and Chan applied a similar model-informed approach at the other end of the age spectrum and report how PBPK provided prospective guidance for dose adjustments of baricitinib and tofacitinib in geriatric patients with coronavirus disease 2019 (COVID-19).[5] Because pharmacokinetic (PK) differences between younger adults and the elderly have been relatively well-characterized for many drugs, there seems to be little in the way for such an approach to become a standard paradigm in clinical practice. However, as pointed out by Liu *et al.*[6] in their White Paper "Roadmap to 2030 for Drug Evaluation in Older Adults" in this issue, typically much less is known about altered pharmacodynamics (PDs) with aging and dose adjustments based on exposure-matching alone may not always provide the optimal clinical outcome. The White Paper[6] was developed following a public workshop hosted by the US Food and Drug Administration (FDA), which brought together national and international stakeholders from academia, government agencies, the pharmaceutical

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Figure 1 *Clinical Pharmacology & Therapeutics* August 2022 cover image: Diversity in Clinical Pharmacology Coming of Age.

industry, and patients to discuss the inclusion of older adults in clinical trials. It not only provides a comprehensive gap analysis but, importantly, also a set of potential, actionable solutions, and a proposed action plan. The latter is a key factor used by the *CPT* editorial leadership team to prioritize submissions of White Papers and Perspectives in this and other areas.

Of course, age is only one of the factors to consider in the broader context of diversity and inclusion in clinical trials and Venkatakrishnan and Benincosa discuss another dimension (ethnicity) in their Perspective, advocating for a "Totality of Evidence" approach.[7] How such a concept can be implemented in drug development and regulatory filing is demonstrated by Retout and co-workers,[8] who describe a "model-based ethnic sensitivity strategy" which successfully supported new drug applications for baloxavir marboxil in different ethnic patient groups with Influenza A or B in South Korea and China.

CPT is deeply committed to be a catalyst for change for further embracement of Diversity, Equity, and Inclusion as core guiding principles in our field and to provide a platform for publication of the best science and innovations pertaining to the core role of clinical pharmacology in elucidating and harnessing diversity in disease biology and pharmacologic response to enable safe and effective use of therapeutics in all patients. To that end, the journal plans to devote the March 2023 themed issue to this topic, and we encourage all our readers to consider submitting manuscripts for this landmark themed issue.[9]

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CONFLICT OF INTEREST
P.H.vdG. is a co-author of Liu et al.[6] referred to in this Editorial and declared no other competing interests for this work.

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