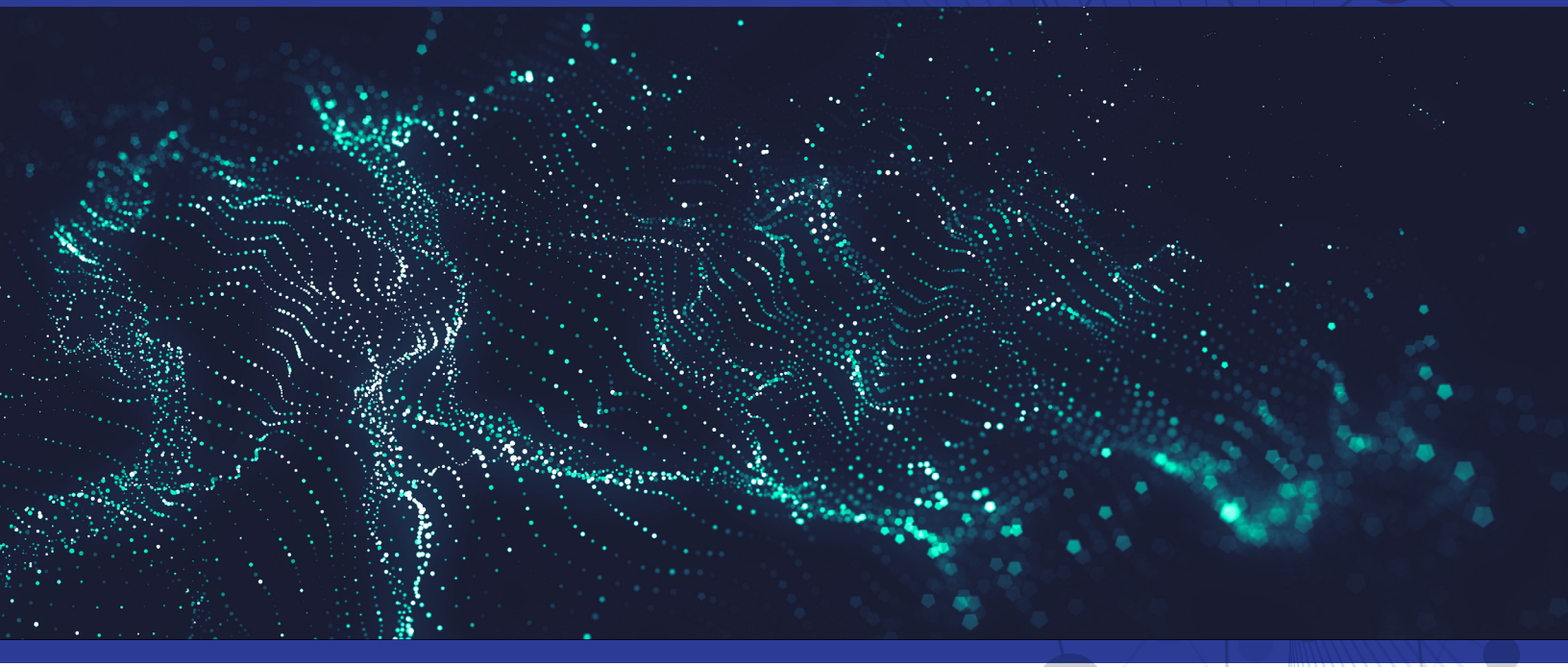
CERTARA

The Importance of Collecting Race/Ethnicity Information in Clinical Trials for Biologics:

A Clinical Pharmacology Perspective



By Jasmine Davda, PhD[1] and Rajesh Krishna, PhD[1-2]

[1]Certara USA, Inc., Princeton, NJ

[2]Corresponding author: rajesh.krishna@certara.com

The Importance of Collecting Race/Ethnicity Information in Clinical Trials for Biologics: A Clinical Pharmacology Perspective

Introduction

Global trials of therapeutic biologics have been historically absent from clinical drug development. This is particularly true for vaccines as they are developed for use in endemic parts of the world, particularly the tropics, with comparisons subsequently made with smaller and/or limited Western trials. This approach is wrought with challenges related to sample imbalance and baseline entry criteria for existing disease. Because biologics do not have the same limiting features of absorption and metabolism as their distant small molecule drug cousins, they are generally not predisposed to significant changes in pharmacokinetics (PK) and/or pharmacodynamics (PD). Thus, when publications refer to racial effects, the paucity of truly global trials limits meaningful consideration of factors that could contribute to a difference, assuming that the noted difference is indeed real.

COVID-19 is a global viral disease, affecting almost anyone, without regard to socio-economic status, disease status, or geographic status. Therefore, clinical trials for COVID-19 monoclonal antibodies (mAbs) and vaccines alike included virtually all known affected regions and this afforded a truly comprehensive means to assess covariates that could explain differences, if any, for the very first time. In this commentary, the authors provide context and reflection about race and ethnicity in the clinical development of biologics based on a sample of published clinical trials and offer an expert opinion on how race/ethnicity effects should continue to be characterized to ensure diversity in clinical trials. To deliver a balanced perspective, we considered both mAbs and vaccines. The authors believe these two modalities are sufficient to ensure a comprehensive outlook on biologics.

Race and ethnicity

New therapeutic development is a global phenomenon. These therapeutics are developed by pharmaceutical and biotechnology enterprises to serve a global need. A single product can be registered in multiple geographies. Because variability in drug/biologic exposure and/or response can be affected by several complex factors, two being race and ethnicity, these can be sometimes rate limiting steps to product registration. In fact, ICH E5 deals specifically with the role of ethnic factors in the acceptability of foreign clinical data and suggests frameworks to facilitate the review and registration of global trials.[1] Often, a bridging study or body of evidence is needed to support a product's registration in a certain market.

Race commonly refers to a subgroup of individuals with shared biological characteristics that distinguish them from other groups, and ethnicity refers to a social group with shared non-biological characteristics such as lineage, heritage, sense of identity, and cultural aspects.[2] In the context of clinical trials, there are specific definitions for race and ethnicity as defined in the recent FDA guideline.[3] However, until the release of this guidance, there has been significant variability in how race and ethnicity were defined and importantly, how such information was collected in clinical investigations.

Figure 1.

An example form for inclusion enrollment [3]

NIH PHS Cumulative Inclusion Enrollment Report Form

View Burden Statement

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title (must be unique):**

* Delayed Onset Study? ☐ Yes ☐ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☐ Planned ☒ Cumulative (Actual)

Using an Existing Dataset or Resource ☐ Yes ☐ No

Enrollment Location ☐ Domestic ☐ Foreign

Clinical Trial ☐ Yes ☐ No **NIH-Defined Phase III Clinical Trial** ☐ Yes ☐ No

Comments:

Racial Categories	**Ethnic Categories**									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			**Total**
	Female	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Report 1 of 1

< Previous Report | Delete Report | Next Report >

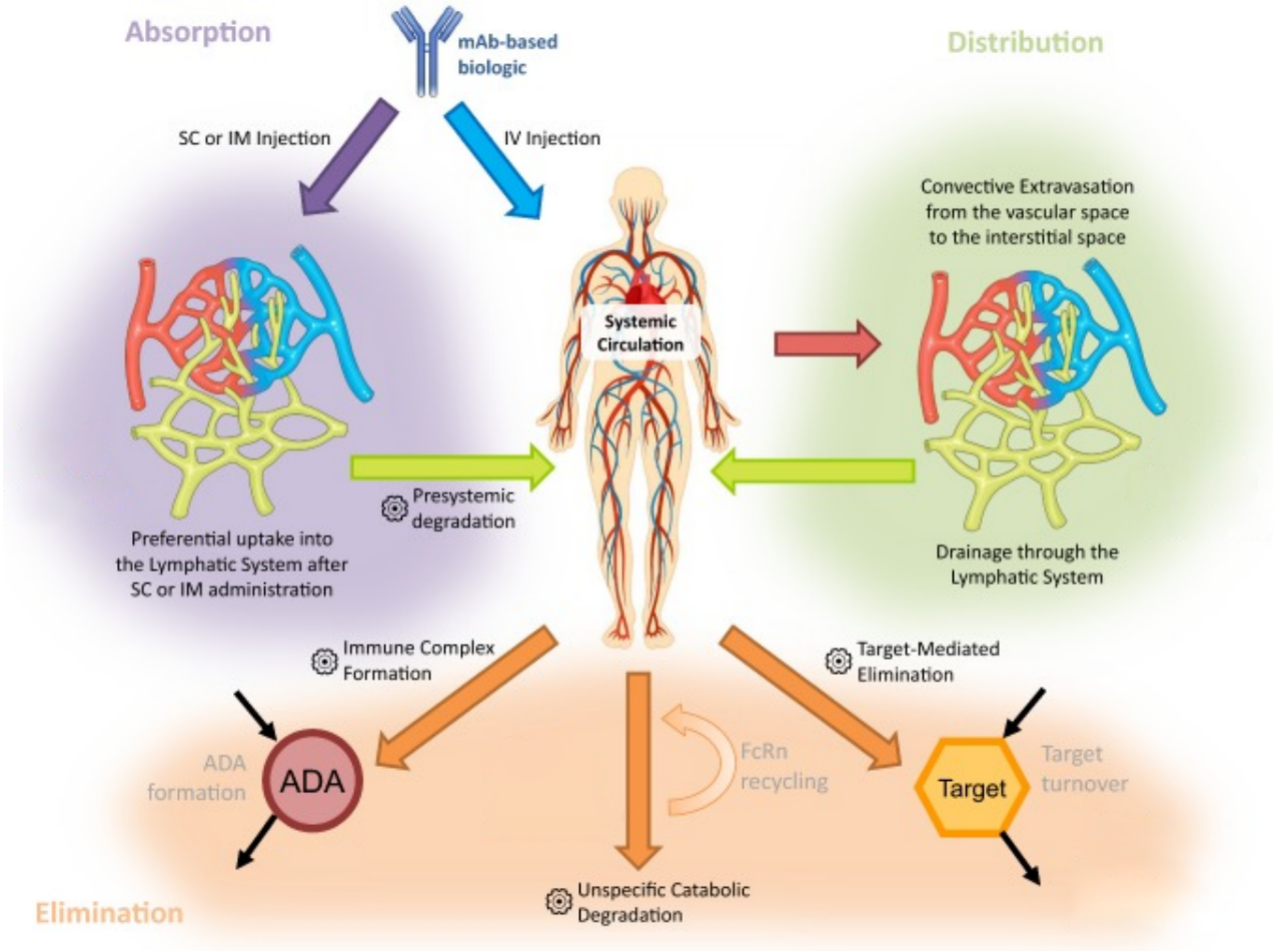
To ensure proper performance, please save frequently.

Monoclonal antibodies

Unlike small molecule drugs, mAbs do not undergo traditional drug-related metabolism or active excretion by polymorphic drug metabolizing enzymes/transporters. Therefore, mAbs have low susceptibility to dietary absorption effects, and little potential for food and drug interactions, making ethnic differences in drug disposition less likely.[4] Indeed, definitive statements regarding the effect of race/ethnicity on drug exposure are not often found on biologics labels. Body weight and body surface area are the most common covariates in population PK models for mAbs[5] and the effect of race/ethnicity on PK is generally insignificant after differences in body weight are considered.[6,7] Nevertheless, to preemptively navigate regulatory barriers and to facilitate entry into new regions, e.g., Japan, pharmaceutical sponsors routinely conduct ethnic sensitivity studies, where safety and PK are evaluated in a small number of healthy Japanese subjects before joining global clinical trials.

Figure 2.

The major pharmacokinetic processes determining the disposition of antibody-based therapeutics and their modulation in young pediatric patients



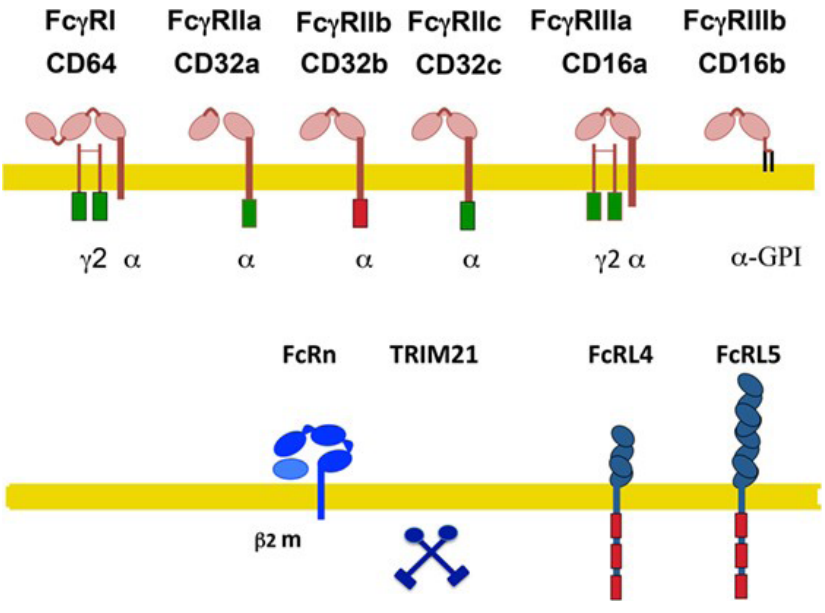
In a systematic evaluation of clinical ethnic sensitivity data across a number of mAbs, both approved and in late-stage clinical development, Matsushima et al.[7] concluded that exposures after a single intravenous (IV) or subcutaneous (SC) administration could be predicted in Japanese healthy subjects from data in non-Japanese healthy subjects, regardless of the incidence of immunogenicity, unless target-mediated disposition was involved. This assessment is supported by the similarity in approved dosing regimens in the United States and Japan for several mAbs across various therapeutic areas.[8]

As a counterpoint, comparable systemic exposures between ethnic groups may not always necessarily translate into comparable efficacy and/or safety profiles. The risk of adverse events such as hypersensitivity reactions, cytokine storms, autoimmunity, and immunosuppression, inherent to immunomodulatory mAbs in particular, has not been rigorously evaluated in relation to racial/ethnic sensitivity.[9]

Differences in clinical response to biologics are often attributed to genetic polymorphisms.[10] Fc receptors play an important role in the PK and PD of mAbs. Changes in expression levels or activity of the neonatal Fc receptor (FcRn) caused by polymorphisms of the encoding gene FCGRT may lead to interindividual differences in the PK of therapeutic mAbs. For example, Billiet et al.[11] reported that the VNTR2/3 genotype in the FcRn gene is associated with 14% lower infliximab area under the concentration-time curve (AUC) and 41% lower adalimumab AUC in patients with inflammatory bowel disease. Similarly, polymorphisms in FcγRs have been found to alter binding to IgG and thereby affect IgG effector functions.[12] For example, FcγRIIa and/or FcγRIIIa polymorphisms have been reported to play a role in the response to rituximab therapy in non-Hodgkin's lymphoma[13,14] and systemic autoimmune diseases.[15] These findings, among others, demonstrate the need for systematic investigation of racial/ethnic differences in genetic polymorphisms and their potential impact on mAb PK and PD in larger cohort trials.

Figure 3.

Human Fcγ receptors (FcγRs)



Vaccines

Vaccination programs across the globe over the years have been implemented against many infectious diseases. Few vaccine studies have carefully assessed whether race and/or ethnicity affected efficacy. Wherever possible, it remains important to consider the genetic variation in populations so that phenotypic variation is delineated.

Mild to moderate variations in immune response by race have been described in the literature for rubella vaccine[16] and influenza vaccine.[17] These findings are briefly discussed below.

In the rubella vaccine study, two independent, large, racially diverse cohorts suggested that subjects of African descent mounted significantly higher rubella-specific neutralizing antibody concentrations compared to individuals of European descent and/or Hispanic ethnicity.[16] The median neutralizing antibody titer for the Somali group was more than twice the median neutralizing antibody titer for the Caucasian group.[16] The authors attributed the higher neutralizing antibody levels in subjects of African descent to higher baseline immunoglobulin (Ig) levels in Blacks as compared with Whites. Because sample sizes are often imbalanced in such studies and because less is known about the subjects' immunization history, the baseline trends in Ig levels are unclear. This is problematic because of pre-existing vaccinations and/or infections that might otherwise perturb the immune system. As the authors noted, rubella-specific Th1/proinflammatory cytokines (IFN and IL-6) did not reveal meaningful associations.[16]

Higher antibody responses to the influenza A vaccine were also observed in African Americans as compared to Caucasians in the study by Kurupati and coworkers.[17] This 5-year study analyzed antibody and B cell responses to the influenza A virus components of the inactivated trivalent or quadrivalent influenza vaccine in age-staggered cohorts of Caucasian and African American subjects. The authors attributed the differences to an observed higher level of circulating B cells in African American subjects compared with Caucasian subjects. They also found that two immune co-regulators, namely programmed death (PD)-1 and the B and T cell attenuator (BTLA) were differentially expressed on B cells of both cohorts. Moreover, there were meaningful differences in the blood transcriptome between the two race groups pre-vaccination. [17]

Other instances of race being proposed as a significant determinant of vaccine efficacy include pertussis, measles, tetanus toxoid, BCG, and rotavirus vaccines.[18-25] Whether the antibody titers were lower in Caucasians[18-22] or there were geographic differences in efficacy[23-25], these other studies postulate race or geographic location was an important determinant.

Clinically meaningful differences in immune responses following vaccines have generally been attributed to variation in genetic host determinants, including polymorphisms in immune function-related genes (e.g., cytokine receptor genes, antiviral effector genes, Toll-like receptors, HLA etc.), and less to demographic factors,

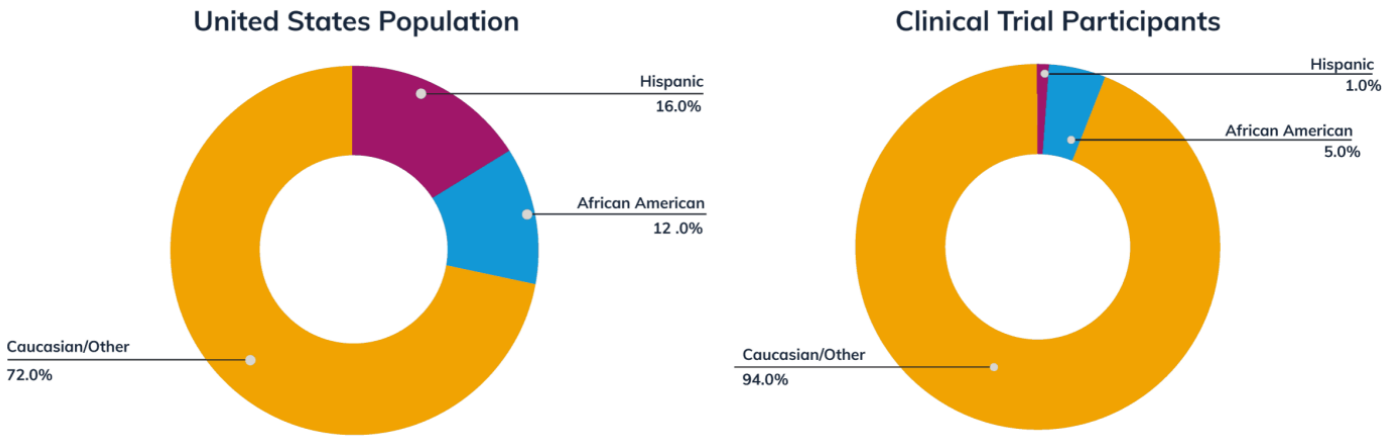
although much remains to be investigated mechanistically. Although studies on the mechanisms of immune response due to racial differences are rare, some studies suggest that there might be differences in immune function-related genes that could contribute to or explain such differences.[26,27]

Reflections and recommendations

The COVID-19 pandemic has further highlighted that patients from minority groups are consistently underrepresented in clinical trials. Early studies examining whether there were meaningful racial differences in vaccine efficacy have been constrained by the lack of race-specific information in the trials and by the imbalance in sample size, leading to wide confidence intervals when assessing vaccine efficacy. Biomarker data suggests that genetic pre-disposition to vaccine response might differ, however, there is no credible information on the specificity of markers that could lead to clinically significant efficacy or safety differences. It is prudent, however, to ensure clinical trials address race factors. It is also important to confirm genetic ancestry where possible and ethically acceptable, to ensure continued assessment of these factors in clinical trial outcomes.

Figure 4.

Underrepresentation of minority racial and ethnic groups in clinical trials. Adapted from the FDA Office of Women's Health [28]



In all trials resulting in an FDA emergency use authorization (EUA) for COVID-19 vaccines, there were no clinically meaningful racial/ethnic effects on the vaccines' safety and efficacy. Furthermore, because regulatory draft guidelines required race assessment, race was prominent as one of the subgroup analyses of the primary endpoint. Based on this emerging body of evidence, there do not appear to be compelling differences by race and/or ethnicity, from a clinical pharmacology point of view.

However, it is important to ensure adequacy of sample size to rule out imbalance and to ensure type 2 error rates are contained. As an example, the demographics of the evaluable efficacy population for the second primary endpoint of COVID-19 occurrence from 7 days after the second dose of the Pfizer-BioNTech Covid-19 vaccine revealed that the population comprised of 7 (active)/146 (placebo) for whites as compared to 0 (active)/7 (placebo) for blacks.[29] While the case can be made for overlapping confidence intervals, the imbalance in sample size is prominent.

Figure 5.

Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity. [30]

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.7x	0.7x	1.1x	1.9x
Hospitalization[2]	3.4x	1.0x	2.8x	2.8x
Death[3]	2.4x	1.0x	2.0x	2.3x

There are many possible ways to mitigate against sample size imbalance as well as address variability in vaccine response. These approaches rely on the first principles of model-informed drug development. For example, quantitative systems pharmacology modeling can be used to inform posology of vaccines. Such models allow the experimentalist to consider longitudinal antibody response from early phase trials to extrapolate dose and longer-term vaccination scenarios virtually. In these in-silico trials, one can consider variability in antibody response as well as any role race/ethnicity can play in affecting that response.

Recently, regulatory agencies have started to streamline the requirement for sponsors to collect race information in clinical trials. The FDA (2016) guidance on race data collection is one such example.[3] Racial and ethnic minorities, particularly Blacks, American Indians, and Hispanics, have been disproportionately affected[31,32] by the pandemic. This fact prompted the Agency to recommend in their guidance regarding developing mAbs targeting SARS-CoV-2, encouraging sponsors to enroll patients from these populations in clinical trials.[33] These efforts by regulators and sponsors will not only lead to harmonizing the way race is defined in clinical trials but also lead to more consistent collection of this information, ultimately allowing for a more definitive answer to the question “Are there clinically important differences in the efficacy and safety of biologics due to race and/or ethnicity?”

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH topic E 5 (R1) ethnic factors in the acceptability of foreign clinical data. https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf. Published 1998. Updated 1998. Accessed October 18, 2021.

2. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L. Racial/ethnic differences in drug disposition and response: Review of recently approved drugs. Clin Pharmacol Ther. 2015;97(3):263-273. doi: 10.1002/cpt.61 [doi].

3. FDA Office of Minority Health. Collection of race and ethnicity data in clinical trials. https://www.fda.gov/media/75453/download. Updated 2016. Accessed October 11, 2021.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Ethnic factors in the acceptability of foreign clinical data e5(r1). Ich Harmonised Tripartite Guideline Web site. https://database.ich.org/sites/default/files/E5_R1__Guideline.pdf. Published 1998. Updated 1998. Accessed September 3, 2021, 2021.

5. Thomas VA, Balthasar JP. Understanding inter-individual variability in monoclonal antibody disposition. Antibodies (Basel). 2019;8(4):10.3390/antib8040056. doi: E56 [pii].

6. Zhao L, Ren TH, Wang DD. Clinical pharmacology considerations in biologics development. Acta Pharmacol Sin. 2012;33(11):1339-1347. doi: 10.1038/aps.2012.51 [doi].

7. Matsushima S, Huang Y, Suzuki H, Nishino J, Lloyd P. Ethnic sensitivity assessment- pharmacokinetic comparability between japanese and non-japanese healthy subjects on selected mAbs. Expert Opin Drug Metab Toxicol. 2015;11(2):179-191. doi: 10.1517/17425255.2015.990438 [doi].

8. Zhou H, Tsukamoto Y, Davis HM. Should clinical pharmacokinetic bridging studies between caucasian and asian populations be required for approval of monoclonal antibodies? J Clin Pharmacol. 2012;52(8):1273-1276. doi: 10.1177/0091270011411192 [doi].

9. Muller PY, Brennan FR. Safety assessment and dose selection for first-in-human clinical trials with immunomodulatory monoclonal antibodies. Clin Pharmacol Ther. 2009;85(3):247-258. doi: 10.1038/clpt.2008.273 [doi].

10. Hlavaty T, Pierik M, Henckaerts L, et al. Polymorphisms in apoptosis genes predict response to infliximab therapy in luminal and fistulizing crohn's disease. Aliment Pharmacol Ther. 2005;22(7):613-626. doi: APT2635 [pii].

11. Billiet T, Dreesen E, Cleynen I, et al. A genetic variation in the neonatal fc-receptor affects anti-TNF drug concentrations in inflammatory bowel disease. Am J Gastroenterol. 2016;111(10):1438-1445. doi: 10.1038/ajg.2016.306 [doi].

12. Dijstelbloem HM, van de Winkel JG, Kallenberg CG. Inflammation in autoimmunity: Receptors for IgG revisited. Trends Immunol. 2001;22(9):510-516. doi: S1471-4906(01)02014-2 [pii].

13. Dall'Ozzo S, Tartas S, Paintaud G, et al. Rituximab-dependent cytotoxicity by natural killer cells: Influence of FCGR3A polymorphism on the concentration-effect relationship. Cancer Res. 2004;64(13):4664-4669. doi: 10.1158/0008-5472.CAN-03-2862 [doi].

14. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol. 2003;21(21):3940-3947. doi: 10.1200/JCO.2003.05.013 [doi].

15. Robledo G, Marquez A, Davila-Fajardo CL, et al. Association of the FCGR3A-158F/V gene polymorphism with the response to rituximab treatment in spanish systemic autoimmune disease patients. DNA Cell Biol. 2012;31(12):1671-1677. doi: 10.1089/dna.2012.1799 [doi].

16. Haralambieva IH, Salk HM, Lambert ND, et al. Associations between race, sex and immune response variations to rubella vaccination in two independent cohorts. Vaccine. 2014;32(17):1946-1953. doi: 10.1016/j.vaccine.2014.01.090 [doi].

17. Kurupati R, Kossenkov A, Haut L, et al. Race-related differences in antibody responses to the inactivated influenza vaccine are linked to distinct pre-vaccination gene expression profiles in blood. Oncotarget. 2016;7(39):62898-62911. doi: 10.18632/oncotarget.11704 [doi].

18. McQuillan GM, Kruszon-Moran D, Hyde TB, Forghani B, Bellini W, Dayan GH. Seroprevalence of measles antibody in the US population, 1999-2004. J Infect Dis. 2007;196(10):1459-1464. doi: JID38505 [pii].

19. Christy C, Pichichero ME, Reed GF, et al. Effect of gender, race, and parental education on immunogenicity and reported reactogenicity of acellular and whole-cell pertussis vaccines. Pediatrics. 1995;96(3 Pt 2):584-587.

20. Poland GA, Jacobson RM, Colbourne SA, et al. Measles antibody seroprevalence rates among immunized inuit, innu and caucasian subjects. Vaccine. 1999;17(11-12):1525-1531. doi: S0264-410X(98)00362-4 [pii].

21. Greenberg DP, Vadheim CM, Partridge S, Chang SJ, Chiu CY, Ward JI. Immunogenicity of haemophilus influenzae type b tetanus toxoid conjugate vaccine in young infants. the kaiser-UCLA vaccine study group. J Infect Dis. 1994;170(1):76-81. doi: 10.1093/infdis/170.1.76 [doi].

22. Guthridge S, McIntyre P, Isaacs D, Hanlon M, Patel M. Differing serologic responses to an haemophilus influenzae type b polysaccharide-neisseria meningitidis outer membrane protein conjugate (PRP-OMPC) vaccine in australian aboriginal and caucasian infants- implications for disease epidemiology. Vaccine. 2000;18(23):2584-2591. doi: S0264-410X(99)00549-6 [pii].

CERTARA

References (cont.)

23. Zodpey SP, Shrikhande SN. The geographic location (latitude) of studies evaluating protective effect of BCG vaccine and it's efficacy/effectiveness against tuberculosis. Indian J Public Health. 2007;51(4):205-210.

24. Ciarlet M, Schodel F. Development of a rotavirus vaccine: Clinical safety, immunogenicity, and efficacy of the pentavalent rotavirus vaccine, RotaTeq. Vaccine. 2009;27 Suppl 6:G72-81. doi: 10.1016/j.vaccine.2009.09.107 [doi].

25. Zaman K, Dang DA, Victor JC, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in asia: A randomised, double-blind, placebo-controlled trial. Lancet. 2010;376(9741):615-623. doi: 10.1016/S0140-6736(10)60755-6 [doi].

26. Van Dyke AL, Cote ML, Wenzlaff AS, Land S, Schwartz AG. Cytokine SNPs: Comparison of allele frequencies by race and implications for future studies. Cytokine. 2009;46(2):236-244. doi: 10.1016/j.cyto.2009.02.003 [doi].

27. Hassan MI, Aschner Y, Manning CH, Xu J, Aschner JL. Racial differences in selected cytokine allelic and genotypic frequencies among healthy, pregnant women in north carolina. Cytokine. 2003;21(1):10-16. doi: S1043466602004891 [pii].

28. FDA Office of Women's Health. Dialogues on diversifying Clinical Trials: Successful strategies for engaging women and minorities in clinical trials. https://www.fda.gov/media/84982/download. Published September 22, 2011. Updated 2011. Accessed October 21, 2021.

29. FDA. Pfizer-BioNTech COVID-19 vaccine: FDA briefing document. https://www.fda.gov/media/144245/download. Published December 10, 2020. Updated 2020. Accessed October 11, 2021.

30. CDC. Risk for COVID-19 infection, hospitalization, and death by Race/Ethnicity. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Published July 16, 2021. Updated 2021. Accessed 9/3, 2021.

31. CDC. Coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html. Published Aug. 28, 2020. Updated 2020. Accessed October 13, 2021.

32. CDC. Provisional COVID-19 deaths by race and hispanic origin, and age. https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-by-Race-and-Hispanic-O/ks3g-spdg. Published October 6, 2021. Updated 2021. Accessed October 13, 2021.

33. FDA. Development of monoclonal antibody products targeting SARSCoV-2, including addressing the impact of emerging variants, during the COVID-19 public health emergency: Guidance for industry. https://www.fda.gov/media/146173/download. Published February 2021. Updated 2021. Accessed October 13, 2021.

About Certara

Certara accelerates medicines using proprietary biosimulation software and technology to transform traditional drug discovery and development. Its clients include more than 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

For more information visit www.certara.com or email sales@certara.com.