

ADVANCING INCLUSIVE RESEARCH: ESTABLISHING COLLABORATIVE STRATEGIES TO IMPROVE DIVERSITY IN CLINICAL TRIALS

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Well-characterized disparities in clinical research have disproportionately affected patients of color, particularly in underserved communities. To tackle these barriers, Genentech formed the External Council for Advancing Inclusive Research, a 14-person committee dedicated to developing strategies to increase clinical research participation. To help improve the recruitment and retention of patients of color, this article chronicles our efforts to tangibly address the clinical research barriers at the system, study, and patient levels over the last four years. These efforts are one of the initial steps to fully realize the promise of personalized health care and provide increased patient benefit at less cost to society. Instead of simply acknowledging the problem, here we illuminate the collaborative and multi-level strategies that have been effective in delivering meaningful progress for patients. *Ethn Dis.* 2022;32(1):61-68; doi:10.18865/ed.32.1.61

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INTRODUCTION

Health care disparities between the sexes and among racial or ethnic groups have been well-documented for decades and continue to exist despite clinical advancements in prevention, detection, and treatment of disease. Currently, less than 10% of US patients participate in clinical trials and, of those, only 5% to 15% are non-White.^{1,2} Some differences in the incidence, severity, and prognosis of different diseases between sexes and racial or ethnic groups result from genetic variants. Genomic profiling of diseases among patients of color will provide useful information about biological differences within a disease. As the global population continues to diversify and health care evolves to-

ward personalized medicine, it is essential that the biological differences among populations—and how these differences affect disease pathology, experience, and outcomes—are comprehensively investigated using novel approaches (eg, genetic ancestry trials).

Representation of real-world patient populations in medical research is essential to address disparities in clinical research, advance science, support access, and improve outcomes in all patients. To advance these goals, Genentech, a member of the Roche Group, developed Advancing Inclusive Research, an enterprise-wide initiative focused on tackling disparities in clinical research by leveraging insights to optimize health care. In 2018, the initiative was established to highlight the need for greater real-

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world representation in clinical research. It expanded with the launch of the External Council (EC) for Advancing Inclusive Research. This council comprises a multidisciplinary group of physicians, thought leaders, academic researchers, contract research organization executives, and patient advocates with expertise across different therapeutic areas, including: oncology, ophthalmology, and neuroscience; clinical care; research; and genomics. The 14 members of the EC ac-

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tively work to raise awareness of racial health disparities and address barriers that currently prohibit patients of color from participating in clinical trials.

This article reviews the holistic approach that has been applied to proactively address key barriers to enrolling diverse patients into clinical trials, expand understanding of dis-

eases, improve access to high-quality health care, and develop investigation-al medicines that benefit all patients.

OVERCOMING CLINICAL RESEARCH DISPARITIES AND INEQUITIES IN COMMUNITIES OF COLOR

Through extensive collaboration with the EC, Genentech developed a portfolio of actionable, effective, inclusive research solutions for clinical research operations. These tactics are categorized into interventions addressing system-, study-, and patient-level barriers (Figure 1).

System-Level Barriers

Numerous barriers exist across the health care ecosystem that prevent or limit diverse participation in clinical trials, including challenges related to policy, provider education, and clinician diversity.

Policy Solutions

Several environmental barriers could be mitigated through policy actions. The most pressing issues include inadequate access for low-income patients to participate in clinical research, insufficient patient education and outreach, a lack of resources and hospital infrastructure to support clinical trials, the limited availability of trials in rural communities, and the impact of the digital divide on households of low socioeconomic status and people of color.

To make meaningful progress in these areas, comprehensive partnerships must be forged across the health care ecosystem along with policy mak-

ers to develop new patient-centric solutions. The EC has identified several productive areas for exploration such as roundtables with policy makers, clinical trial sponsors, health care providers, and patient advocacy organizations to discuss the barriers and how to overcome them.

Provider Education

System-level barriers also extend throughout medical research and the health care industry. Across medical schools and health care provider education programs, focus on health care disparity training has been limited or irregular.³ This contributes to a medical field that is not uniformly prepared to recognize or address disparities in patients of color. Recommendations include identifying and supporting education and medical school programs that are actively developing programs to address these education gaps, as well as identifying education opportunities for currently practicing health care providers.

Another barrier is providers' lack of awareness of available clinical trials. Studies show that primary care providers often possess little knowledge of relevant clinical trials and, despite treatment guideline recommendations, fail to discuss this option with patients.^{4,5} Therefore, improving awareness of health care disparities and clinical trial availability and promoting understanding of the importance of representative populations in clinical trials are vital and yet overlooked mechanisms for increasing participation in clinical research.⁶ Recommended initiatives include convening community stakeholders to discuss local barriers to raising awareness

RECOMMENDATIONS FOR THE FUTURE OF CLINICAL TRIALS

Based on the collaborative efforts between Genentech and the External Council, we have several key system-, study-, and patient-level recommendations for future clinical trials to improve the diversity of their patient enrollment



Figure 1. Recommendations for the future of clinical trials
CROs, clinical research organizations

and developing action plans to enhance communication flow on health equity issues across the local area.

Clinician Diversity

The limited diversity of clinicians and research personnel is also a factor that prevents recruitment of patients of color. This has led to a sense of mistrust and fear within underrepresented patient populations, who may already have concerns about the ethical motivations of clinical research.^{7,8} At the individual level, unconscious bias and preconceived perceptions may lead physicians to underestimate the likelihood of patients of color participating, preventing them from informing their patients about available trials.⁸ This research suggests that physicians may limit offers for enrollment to patients they perceive as good study candidates to enable studies to be conducted in a timely and efficient manner, and that this decision may be influenced by racial stereotypes.

Collectively, these factors contribute to the systemic racial disparities seen in clinical trials and the provision of suboptimal care to patients of color. Consequently, systemic racism in medicine must be addressed through evidence-based interventions to reduce discriminatory behavior and implicit attitudes among health care professionals. As physicians of color continue to provide a disproportionate share of care to underserved populations, improvement in the racial and ethnic diversity of the physician workforce can help to build trust with communities of color.^{9,10}

To recruit more students of color into medical and clinical research professions, the EC

recommended supporting students of color early in their educational process (eg, primary school) through early career development.

Study-Level Barriers

As a clinical trial sponsor, Genentech has prioritized resources and head count to develop strategies addressing study-level barriers.

Overly restrictive study design, stringent eligibility criteria, and continually using clinical trial sites based on their speed of enrollment often has resulted in the exclusion of underserved patient populations—much to the detriment of inclusive research—adding to the widening disparities seen between patients who enroll in trials and those who are treated in real-world practice.^{7,8,11}

To design more inclusive trials, Genentech and the EC have developed a framework defining several types of inclusive research studies, including: 1) Population-based: Clinical trials throughout the molecule development life cycle that aim to include patients of color commensurate with their size in the general population; 2) Epidemiology-based: Epidemiology driver studies with populations aligned to disease prevalence (eg, trials that over-index recruitment of patients of color through the selection of underserved community sites but do not exclude the general population from participating); and 3) Hypothesis-based: Dedicated clinical driver studies with a population-specific hypothesis (eg, trials that enroll a specific population to investigate the differences in clinical outcomes for certain racial/ethnic groups).

Another key area of focus for trial

sponsors has been reevaluating inclusion and exclusion criteria. Eligibility criteria often include the presence of specific molecular aberrations or normal laboratory test values, for which the normative range was established using data from White patients, which has resulted in disproportionately excluding specific patient groups, including patients of color.^{12,13} Therefore, the EC suggested critical scientific evaluation of inclusion/exclusion criteria and adjusting them to accommodate ancestry-based differences. As a result, study teams across clinical development programs at Genentech are provided with protocol templates that have race-adjusted laboratory reference intervals that will allow for inclusion of more understudied patient populations. To eliminate biased assessment of ineligibility, protocol templates have also removed specific criteria that are based on investigators' discretion and/or judgment.

Study recruitment and conduct are another critical facet that can be improved to be more inclusive. To increase access, trials need to be targeted at institutions where patients of color regularly seek health care. Additionally, cultural sensitivity training should be conducted with contract research organizations and site research staff, as well as allowing patients to include family members when reviewing informed consent forms and considering trial participation. Finally, telemedicine and digital technologies should be incorporated into trial conduct to improve patient convenience.

Patient-Level Barriers

Mistrust of academic and research institutions and investigators is fre-

quently cited as a critical attitudinal barrier to the participation of patients of color.^{14,15} In addition to feelings of mistrust, other barriers that prevent patient participation include a lack of awareness of opportunities to participate in clinical trials, inconvenience, availability of transportation, distance to the study site, and patient and family concerns about associated risks.^{1,14} To establish trust with communities of color, sponsors of clinical trials must seek to engage communities early in the process and provide sustained engagement with community stakeholders and patient advocacy groups. This type of engagement can take many forms, including convening community and health care stakeholders to identify local barriers and develop plans to facilitate outreach and awareness programs in underrepresented communities, and educating patients on the benefits of clinical research participation.

Financial issues also represent a significant barrier to clinical trial participation, as patients may experience the additional costs of more frequent hospital visits, travel to and from the study site, potential lodging and meals, and extra child care while absorbing the loss of income due to missed work.^{7,8} Sponsors should work toward a variety of solutions to cover these additional costs, as well as clearly communicate to patients the available assistance to minimize adverse financial impact during clinical trial participation. At the conclusion of the trial, sponsors should ensure they return to participating communities and share results and information on how participants' efforts contributed to scientific advancement.

REDESIGNING CLINICAL TRIALS TO BE MORE INCLUSIVE

As a result of Genentech's collaborations with the EC, new approaches and strategies have been implemented into the structure and design of several clinical programs across the enterprise, including the innovative CHIMES (CHaracterization of ocrelizumab In Minorities with Multiple Sclerosis) and EMPACTA (Evaluating Minority Patients with Actemra) studies.

CHIMES

CHIMES is a prospective, phase 4 trial (NCT04377555) designed with a population-specific hypothesis to evaluate the knowledge gaps and needs of patients of color with multiple sclerosis (MS), and is enrolling Black, Latino, and Hispanic American patients with relapsing MS. A heterogeneous disease, MS is thought to result from complex interactions among genetic predisposition, sex, and environmental factors. African Americans and Latino/Hispanic Americans have a higher incidence of MS compared with counterparts in their ancestral countries of origin.^{16,17} Although African Americans are at a higher risk of developing MS compared with Black Africans, they have a lower relative risk compared with Northern Europeans and White Americans¹⁸ but are more likely to experience more aggressive disease, more frequent relapses, and greater disability than White patients.¹⁶⁻¹⁸

Significant underrepresentation of Black and Latino patients in clinical trials for MS has made it challenging to accurately assess treatment re-

sponses in these populations.¹⁷ Special attention has been paid to the design and implementation of CHIMES to ensure equitable access and recruitment of a representative patient population through targeting trial access, eligibility, and site engagement. Eligibility criteria, including age and kidney function parameters, have been broadened and MS centers that serve large communities of color have been selected as study sites. The study's findings will advance the current understanding of MS disease biology and indicators of disease severity and elucidate whether observed differences in clinical phenotypes can be attributed to disparities in social determinants of health or underlying genetic factors.

EMPACTA

As COVID-19 disproportionately affected people of color, dedicated efforts were employed to rapidly establish an epidemiology-based clinical trial protocol that would reach the most at-risk communities. The phase 3 EMPACTA trial (NCT04372186) assessed the treatment benefit and safety of tocilizumab in patients with COVID-19-associated pneumonia. Executing on the principles of Advancing Inclusive Research, EMPACTA was specifically designed using targeted and intentional actions to address inequitable health care access and the barriers to recruitment of patients of color.¹⁹ With strategic input from the EC, the study prioritized the recruitment of patients at nontraditional sites known to provide critical care to underserved populations but not commonly selected for clinical trials, including public hospitals in New York City, New Mexico,

and Louisiana. Other atypical trial sites such as community-based and rural institutions were engaged to facilitate recruitment of patients from underserved communities. However, when the trial expanded globally, the lack of universal definitions (eg, minority, underrepresented, and underserved have different definitions across countries) presented a challenge for identifying study sites that provide care to underserved patients.

From the early stages, investigators and staff were informed of the study's goal to recruit an enriched population of patients of color and were encouraged to promote awareness of the study among colleagues and the local community, helping to enhance patient referral to established trial sites. Support was provided to sites that were unfamiliar with clinical research, with training in trial compliance standards as well as frequent and consistent communication.

Barriers to study entry were reduced through broadening inclusion criteria and streamlining study assessments. Other dedicated efforts to support enrollment focused on facilitating patient communication and building trust through the provision of study companion documents that were translated into multiple languages. Ultimately, of the 389 enrolled patients, approximately 85% were from racial and ethnic groups.

Despite an unprecedented pandemic, prioritization of inclusive research did not cause any delays in the design and execution of the EMPACTA trial; patient enrollment was initiated 16 days after protocol finalization and full enrollment was achieved within approximately 10

weeks. This highlights how the overall study accrual timeline vs study startup time is a much more informative and clinically relevant metric that should be evaluated across clinical trial programs.

EMPACTA met its primary endpoint, finding that tocilizumab reduced the likelihood of progression in hospitalized patients with COVID-19-associated pneumonia compared with patients who received placebo plus standard of care.¹⁹ Following study completion, a layperson summary of the trial results with translations in all patient languages was provided to study sites for distribution to participants and made publicly available online.

EMPACTA not only demonstrated the benefit of tocilizumab in this patient population but also illustrated the viability of inclusive trials, highlighting that prioritizing enrollment of underrepresented patients of color can accelerate scientific knowledge and improve patient access to beneficial therapies without additional time constraints or financial burden. Knowledge and learnings acquired from EMPACTA will be applied across existing and future studies to enhance the diversity of clinical trial populations²⁰ and further calls for increased research at community health centers.

Clinical Trial Site Network

Another innovative program that has been developed to address the multitude of barriers is the Advancing Inclusive Research Site Alliance network. To identify clinical research sites with a vested interest in prioritizing Advancing Inclusive Research, the EC recommended evaluating diverse enrollment capabilities in site selection

as well as feasibility questions to identify sites capable of and committed to enrolling appropriate racial and ethnic representation of different diseases.

The network will begin its focus on specific indications in oncology (multiple myeloma, breast cancer, and non-small cell lung cancer) across all phases of studies. Genentech will collaborate with the investigators and operational staff at selected cancer center sites to test and identify

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the most effective strategies to raise awareness of clinical research disparities, highlight ongoing clinical trials at these centers, and promote the benefits of clinical research to recruit patients of color in clinical cancer trials.

CONCLUSIONS

Overcoming racial disparities in clinical research and across the health care ecosystem requires multilevel approaches, policy solutions, and collaborative partnerships to advance health equity in communities of color. Given

the changing demographics of the US population and the growing proportion of diverse ethnic and racial communities, clinical research can no longer be conducted without representative numbers of participants of color.

Eliminating the barriers to trial participation would expedite trial completion and improve the generalizability of study results. Study sponsors should seek to cover out-of-pocket costs and broaden eligibility criteria that may otherwise limit or prevent underrepresented communities from participating in clinical research. By combining these with other practices, such as identifying catchment areas where minorities seek health care and activating clinical trial sites in those regions, sponsors can begin to mitigate the long-standing barriers that prevent participation. Because trials frequently provide patients with the opportunity to receive new and novel treatments, increased trial accrual is critical for all patients, and the inclusion of more diverse and representative patient populations would provide a stronger foundation to deliver on the promise of personalized health care and improved patient experience.

The ongoing collaboration between Genentech and the EC has instilled confidence across the organization to successfully implement inclusive research principles, and more importantly, resulted in an established road map that enabled the development of the CHIMES and EMPACTA studies. The EMPACTA trial is a testament to the progress that can be made in advancing inclusive research, highlighting that diversity in clinical trials can advance scientific knowledge and improve pa-

tient access to beneficial treatments.

Our goal through this work is to empower others in the scientific community to successfully implement their own efforts to promote equitable racial and ethnic representation. Only by working together to proactively challenge the systemic inequities and racial disparities in clinical research can we achieve lasting change and create a more diverse, equitable, and inclusive health care system for all patients.

CONFLICT OF INTEREST

Susan Begelman - Employee of Genentech, a member of Roche Group, and owner of Roche stock. Member, The Genentech Foundation Board, a U.S.-based, private charitable foundation whose donations are made possible by contributions from Genentech

Otis Brawley - Receives consulting fees from: Genentech, EGRX, Grail; Meeting support from Lyell Immunopharma, PDS Biopharma, Jackson Labs; and owns stock or stock options in Lyell Immunopharma, PDS Biopharma, Grail.

John Carpten - Receives consulting fees from Genentech

Keith Carter - Receives consulting fees from Genentech

Asha Collins - Former employee of Genentech, a member of Roche Group, and owner of Roche stock.

Joseph Coney - Receives research support from: Aerpio, Alcon Laboratories, Alimera, Allergan, Genentech/Roche, Novartis; consulting fees and honoraria from Alimera Sciences, Allergan, Genentech, Novartis, Regeneron; and has participated on advisory boards for Alimera Sciences, Allergan, Genentech, Notal Vision, Novartis, Regeneron

Andrea Ferris - none

Jamie Freedman - Employee of Genentech, a member of Roche Group, and owner of Roche stock.

Owen Garrick - Receives consulting fees, Genentech External Council for Advancing Inclusive Research

Melissa Gonzales - Former employee of Genentech, a member of Roche Group, and owner of Roche stock.

Evan Grove - Bravo Group, my employer, received fees from Genentech

Quita Highsmith - Employee of Genentech, a member of Roche Group, and owner of Roche stock.

Edward S. Kim - Receives consulting fees from: BI, AZ, Genentech/Roche, G1, Takeda

Ruben Mesa - Receives consultant fees from Genentech/Novartis/Sierra Onc/LaJolla/Pharma/Constellation; receives research support from Celgene/Incyte/Abbvie/Samus/Genentech/Promedior/CTI/ Constellation

Edith Mitchell - Receives consulting fees from Genentech, Taiho, BMS

Stephanie Monroe - none

Edith Perez - Receives consulting fees from: Genentech

Nicole Richie - Employee of Genentech, a member of Roche Group, owner of Roche stock.

Fabian Sandoval - Receives consulting fees from Genentech

Mitzi Williams - Receives research support from EMD Serono, Genentech, Novartis; participated in advisory committees and been a consultant for AbbVie, Biogen Idec, Bristol Myers Squibb, EMD Serono, Genentech, Novartis, Sanofi Genzyme

Gerren Wilson - Employee of Genentech, a member of Roche Group, owner of Roche stock.

Robert Winn - Receives grants from National Institutes of Health, National Cancer Institute; consulting fees and Honoraria from Genentech, Taiho Oncology, Bio Ascend; meeting support from Bristol Myers Squibb

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Freedman, Gonzales, Wilson; Administrative: Garrick, Mesa, Ferris, Kim, Mitchell, Brawley, Carpten, Carter, Coney, Winn, Monroe, Sandoval, Perez, Williams, Grove, Highsmith, Richie, Begelman, Collins, Freedman, Gonzales, Wilson; Supervision: Gonzales, Wilson

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