How to Boost Racial, Ethnic and Gender Diversity in Clinical Research

Why All Stakeholders Must OWN The Mission
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Introduction

Healthcare transformations take time—and the time lag has consequences.

It has been 25 years since Congress passed the National Institutes of Health Revitalization Act requiring federally funded clinical research programs to prioritize inclusion of women and minorities. Since then, both the NIH and the Food and Drug Administration have mounted numerous initiatives, including regulatory guidance aimed at shoring up the law’s intent.

Despite parallel efforts by biopharmaceutical innovators, the demographics of clinical trials today still do not reflect the racial, ethnic or gender diversity of target patient populations around the world. This is true for trial subjects, of whom an estimated 83 percent are white. And it’s true for the race/ethnicity/gender representation of investigators at many trial sites as well.

As advanced health systems around the world enter an era of genomic and precision medicine, lack of diversity across the clinical research landscape is a daunting obstacle.

As of 2018, some 78 percent of individuals included in genome-wide association studies were of European descent, while those of African or Hispanic ancestry made up just 2 percent and 1 percent, respectively, according to a report in the journal *Cell*. The bias in the data harms our understanding of genetic and environmental causes of disease and impedes both individualized and population-wide efforts in prevention and treatment.

Many experts worry that population trends will magnify the negative impact of racial/ethnic imbalances in clinical research. After all, in the U.S., the percentage of minority participants in studies rarely exceeds low double digits at a time when racial and ethnic minorities make up nearly 40 percent of the population overall. The picture will be more complex as we move beyond the year 2045, a crossover point when Caucasians will comprise just less than half (49.7 percent) of the U.S. population.

“Future population shifts will magnify the negative impact of disparity in our clinical research—with grave implications for precision medicine,” says Syneos Health Behavioral Scientist Kathleen Starr, who, in June 2019, chaired a panel exploring both the causes and potential corrective approaches to research disparities at the BIO International Convention in Philadelphia. In short, the panel warned that translational relevance of biomedical research will shrink over time unless societies address intrinsic bias issues as results are generalized from a white European subject base.

There is, however, good news: Even as the challenges persist, education and outreach efforts by agencies, industry organizations, patient groups and private companies are accelerating. The strong consensus among all these stakeholders is that, by tackling these issues today, we can build for the 21st century.

The report that follows will describe some of the strategies different stakeholders employ to address a diversity deficit, along with their insights and experiences on the front lines of this endeavor.
DIVERSITY DEFICIT BY THE NUMBERS

Disparities have dire implications for precision medicine as we approach a crossover point in 2045 when non-Caucasians will outnumber Caucasians in the U.S.

To Make Precision Medicine “Precise,” We Need Clinical Trials That Look Like ALL of Us

LATINOS
- represent nearly 18% of the U.S. population,
- yet <5% participate in clinical trials
- and together comprise just 1% of clinical trial participants

<5% PARTICIPATION WITH 14% HIGHER RISK

Black participants made up <5% of the trials for 24 of the 31 cancer drugs approved since 2015, yet a 2019 report from the American Cancer Society suggests that black people experience a 14% higher relative risk of dying from cancer

In 1997, 92% of participants in clinical trials for treatments targeting cancer, CNS diseases and heart disease were white. By 2014, that percentage only dropped six points to 86%

DIVERSITY DEFICIT BY THE NUMBERS

Individuals included in genome-wide association studies as of 2016

European 81%
Asian 14%
African 3%
Other ~1.5%
Hispanic & Latin American .5%
Government Engagement

The model for U.S. government leadership is an NIH initiative called “All of Us.” It aims to enroll one million American volunteers in the equivalent of a crowd-sourced biomedical data repository.

“All of Us,” which has enrolled nearly 200,000 people since kicking off in May 2018, will pool information from electronic health records (EHR), blood samples, data on environmental exposures, and cultural and behavior patterns to create the first-ever research database that truly reflects the nation’s race, age, gender and socioeconomic diversity. With assistance from 100 organizations, including companies, community groups and academic medical centers, the NIH has designed this database to deliberately “oversample” minority communities that, until now, have been underrepresented in biomedical research.

Those groups make up 80 percent of the first 143,000 who have completed the initial steps—specifically, surveys and an agreement to share electronic health records and provide blood and urine samples. This spring, NIH announced the beta release of an interactive data browser that participants, researchers and other members of the public can use to learn more about the participant community and explore summary data.

The FDA, meanwhile, continues to urge trial sponsors to broaden eligibility criteria wherever appropriate, scientifically and clinically, to increase enrollment of underrepresented populations. Regulators in June released fresh guidance on how industry might achieve greater balance in trial participation. Among other highlights, the FDA zoomed in on unique challenges in increasing diverse trial enrollment for rare diseases with geographically dispersed patient populations. “Special efforts may be necessary to enroll and retain these participants” to ensure minority ethnic/racial representation, the guidance declares. Regulators advise sponsors to work closely with patient advocacy groups to accomplish this objective.

Dismantling barriers rooted in culture, however, is never quick or efficient. Consider the persistent, pernicious case of gender biases in research.

For years, research communities in the U.S. and Europe saw no harm in deriving diagnosis and treatment recommendations from drug trials with no female subjects. For example, the famous Physicians Health Study assessing cardiovascular benefits of low-dose aspirin included 22,000 men and no women at all. The final report on that study appeared in July 1989—in other words, well into the era we think of as modern medicine.
Thanks to three decades of government, societal and peer pressure, researchers are much more vigilant now than in 1989. A 2015 U.S. Government Accountability Office (GAO) report cited NIH data showing that more women than men were enrolled in NIH-funded clinical research for fiscal years 2005–2014. Yet, the report also noted the NIH does not make all enrollment data available to people wishing to crunch the numbers. More importantly, GAO stated that “even when women are included in clinical trials, the results of analyses are often not reported by sex.” That omission “limits the ability of researchers to identify potentially important sex differences that may ultimately affect patient care.”

**Minding the Gaps**

Before examining stakeholder initiatives to bolster research diversity, it’s useful to examine the kinds of gaps in clinical trial design and recruitment that motivate these efforts.

Consider the relatively low engagement of Hispanics and Latinos, who may soon make up one-fifth of the U.S. population, yet comprise less than 1 percent of clinical trial participants. This is profoundly troubling to many doctors and scientists—including those working with patients who have nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

NAFLD and NASH can lead to cirrhosis and liver cancer and also increase the risk of death from cardiovascular disease. Currently, there is no effective treatment for NASH, which affects more than 16 million people in the U.S. today and may affect 27 million by 2030. Hopes are riding on new treatments for these and other hepatic conditions, as reflected in mergers-and-acquisitions activity in the commercial marketplace. Despite clinical trial setbacks in recent months, buyers in M&A deals continue to express strong interest in hepatic drugs, according to Syneos Health's 2019 Dealmakers' Intentions Study.

In other words, new treatments for these conditions will continue to emerge from research pipelines. From a methodological standpoint, however, the challenges persist. Recent data reveal that conditions which predispose individuals to NAFLD and NASH are more common in Hispanic communities. Some 43 percent of Hispanics suffer from obesity, 35 percent have metabolic syndrome, and a high proportion have a gene variation called PNPLA3—all of which can be predictive of these illnesses.

While Hispanics have the highest prevalence of NAFLD among racial/ethnic groups in the U.S. and, as a group, are not averse to participating in clinical trials, researchers continue to be stymied in minority recruitment efforts. Furthermore, it’s not clear whether researchers are employing methodologies that will yield clinically meaningful insights about how to diagnose and treat diverse populations.
Even when it comes to tests as basic as A1C, used to diagnose and monitor type 1 and type 2 diabetes and prediabetes, failure to take stock of racial/ethnic variances in test populations can skew the data. That’s because many people of African, Mediterranean or Southeast Asian descent have inherited hemoglobin variants (hemoglobinopathies, including sickle cell trait) that render A1C unreliable.

At least with regard to NASH and other illnesses that disproportionately affect minority and socioeconomically disadvantaged communities, some policy prescriptions are clear, according to Fabian Sandoval, CEO and Research Director of the Emerson Clinical Research Institute and an advocate for research diversity. The onus is on biopharmaceutical companies to initiate more sophisticated recruitment strategies that lead to better treatment guidelines. At the same time, he adds, it’s important that all stakeholders work together. Community outreach that builds trust will be a key factor, Sandoval explains.

“Trial sponsors have to start giving Hispanic physicians a chance to lead studies,” says Sandoval, who also notes that diverse communities must become more engaged and self-motivated. “The biggest challenge to boosting Hispanic participation in trials is awareness—letting patients know there is something out there and that there’s a benefit to participating. Together, we have to overcome the knowledge gap.”

**Bringing Research Awareness to Communities**

While health officials and regulatory bodies debate the best ways to make research more inclusive, Fabian Sandoval is taking the message to the people. The CEO and Research Director of the Emerson Clinical Research Institute speaks at churches, health fairs and other community events. And every Sunday, he hosts a medical show on Telemundo titled *Tu Salud Tu Familia* (*Your Family Your Health*) that draws as many as 200,000 viewers in the Washington D.C. area. The show’s 30-minute segments have zoomed in on everything from childhood obesity and PTSD in the military to treatment advances of breast cancer and colon cancer. And, in several 30-minute segments, Sandoval has focused on the treatment opportunities available to patients who participate in clinical trials. Sandoval urges trial sponsors to take this same message into their local communities, working with church groups and other organizations. “Okay, maybe you won’t get to star in your own TV show like I do,” Sandoval says with a smile. “But you can work locally and build a lot of trust. It’s easier than you may think.”
Shades of Gray in Race/Ethnicity Identification

Itemizing the challenges to building an inclusive research ecosystem is easy. Indeed, some patient advocates complain that the industry is still “admiring the problem” of low diversity rather than solving it.

In reality, significant hurdles arise the moment researchers attempt to specify detailed inclusion targets in a study. And the subtle shades of gray have implications for every phase of drug development, from clinical trial design and recruitment through patient monitoring and drug label optimization.

From the program’s outset, researchers encounter obstacles such as how to define or measure race and ethnicity versus ancestry, heritage and learned culture in a quantifiable, scientifically rigorous fashion. Does it advance a genomic or precision-medicine agenda if trial subjects with faint traces of African ancestry are classed as “black”? And how does it help the mission if researchers are aware that certain Spanish-speaking subjects of European ancestry choose, in census bureau surveys, to self-identify as Hispanic?

In some instances, “the convenience and routine nature of census categories [seems] to lead scientists to infer that the reasons for differences among groups were self-evident and required no additional exploration,” according to a recent Policy Forum in *Science Magazine*, with Columbia University bioethicist Sandra Soo-Jin Lee and colleagues. “The ripple effects of initial study design decisions go beyond issues of recruitment to shape other facets of research across the life course of a project, from community engagement and the return of results to the interpretation of study findings for human health.” Adding to the confusion, different funding agencies and regulatory bodies might employ different definitions of diversity, along with different metrics and benchmarks for inclusion.

In the Forum article, Lee and her co-authors offer an example of how such ambiguities affect research conclusions. Researchers in their case study, from University of Florida, looked at two different classifications for “race” in an investigation of hypertension demographics in Puerto Rico. One gauge was skin color—a local, culturally defined characterization—and the other was genetic ancestry. In this study, the former, non-genetic portrayal proved more meaningful as a predictor of disease.

Going forward, Lee and her coauthors call on researchers interested in clinical trial diversity to embrace “practices that allow for a diversity of measurement approaches.” This step, the authors write, must be accompanied by transparency as to why one approach was selected over the other. By empirically “studying the studies,” scientists can build a culture of openness and increase public trust in science.
Combating Cancer Disparities

In oncology, the track record for minority recruitment in clinical trials is scarcely any better than in hepatic illnesses. This has drawn attention at a time when cancer immunotherapies are bringing life-saving benefits to some patients, but not to others. A review published by the American Society for Clinical Oncology (ASCO) this spring showed that black participants made up less than 4 percent of patients in trials for checkpoint inhibitors targeting lung cancer. Looking more broadly at 230 trials leading to FDA oncology drug approvals over the past decade, authors of an August 2019 study in *JAMA Oncology* found that blacks represented just 3.1 percent of trial participants.

This can perpetuate outcome disparities, the authors of the ASCO study noted, because “the unique biology of the host and [of] the tumors from this subpopulation is not accounted for as new treatment algorithms to guide optimal use of immunotherapy are developed for use in the real world.”

Financial Toxicity: Finding Voices that Resonate

Cancer survivors often face dire economic consequences. Roughly a quarter say they have trouble paying medical bills, according to the Centers for Disease Control, with financial hardship concentrated among patients aged 18-64 years old. Examining the financial status of 9.5 million cancer patients diagnosed between 2000 and 2012, a 2018 study in the *American Journal of Medicine* found that 42.4 percent had depleted their entire life’s assets within three years of learning they were sick. The CDC, the National Cancer Institute and the American Cancer Society say providers, practices and payers must adopt sustainable strategies to lower out-of-pocket costs for survivors. But advocacy organizations, including Lazarex and the Pink Fund, say patients can’t wait for change. After facing financial devastation while battling breast cancer, Molly MacDonald founded the Pink Fund in 2006. The public charity helps breast cancer survivors meet basic needs while they focus on healing. In April, MacDonald won an eyeforpharma “Champion Award” for helping patients find a voice that resonates in boardrooms, in Congress and in hospital corridors.

Often, challenges to trial participation come down to something patient advocate Dana Dornsife identifies as financial toxicity. As Chairman of the Board and founder of Lazarex Cancer Foundation in Danville, California, she has encountered many patients from disadvantaged communities who struggle every day with unforgiving logistics. As Dornsife frames it: “Do I pay to park my car at an investigational site in San Francisco, or do I put food on the table for my family?” Lazarex is helping patients and families deal with this obstacle, she said. But what if the trial site is 50 miles—or 500 miles—from the patient’s home, and he or she is in no condition to manage the travel? For a cancer patient who may be battling a terminal illness, “being able to bring a loved one to the trial is important for physical, emotional and spiritual support,” Dornsife says. “We provide financial assistance for a travel companion.”
Seeking Leadership

Because the promise of precision medicine rests on effective engagement of subjects with diverse backgrounds, an inclusive research strategy is a priority for companies of all sizes. That said, larger firms have greater wherewithal and may be called on to show leadership in designing inclusive trials.

“We know the populations that industry is recruiting into clinical research are not representative of the patients that will receive our medicines, and there’s real urgency around this,” says Nicole Richie, Global Head of Health Equity Science and Strategy, Clinical Development at Genentech Roche. “That’s why we’re focused on identifying patients from diverse populations, helping them gain access to genomic testing, and making it easier for them to participate in clinical research.”

Indeed, wherever small biotechnology ventures are expanding the boundaries of science, there’s a growing sense that they and their larger pharmaceutical partners should be strategizing around inclusive trial design and recruitment.

Consider the closely watched area of microbiome science. Some experts predict this gestational research field could blossom into a commercial market worth nearly $900 million over the next six years. Since 2015, well-heeled companies have spent more than $5.4 billion on partnerships and acquisitions in the therapeutic microbiome space, according to a recent analysis by Syneos Health. A few large pharmaceutical companies are at the forefront—notably, Janssen Pharmaceuticals and Takeda. The need for research diversity is paramount, as emerging therapeutics are likely to be highly personalized. “Advancing microbiome-based therapeutics will require taking into account differences in the baseline composition and function of the microbiome across populations with different ancestry and socioeconomic makeup,” Nature Medicine noted in a June 2019 editorial.

Blueprints for Racial/Ethnic Inclusion

The NIH maintains a Scientific Workforce Diversity website with toolkits to improve recruitment of talented researchers from minority racial/ethnic communities. Until this disparity is resolved, efforts to invite more minority patients into trials are unlikely to bear fruit.

The American Society for Clinical Oncology (ASCO) also would like to see more diversity among clinical trial investigators. Noting that only 2 percent and 3 percent of all practicing oncologists in the U.S. are black and Hispanic, respectively, the organization has launched funding and mentoring programs aimed at medical students from underrepresented groups. Other associations have started similar programs.

Would you like to know if study results pertain to people similar to you? Through the FDA’s Drug Trials Snapshots program—a consumer-facing website—visitors can download summaries showing percentages of race/ethnicity/gender representation in clinical trials for every new FDA-approved drug in a given year. Now, you can find out if researchers uncovered any differences in safety or efficacy among demographic subgroups.

Patient organizations such as African Americans Against Alzheimer’s and the Lazarex Cancer Foundation are tackling the diversity challenge from multiple angles—educating minority communities on the benefits of trial participation, helping cover travel and other costs, and working with companies to upgrade education and outreach materials.
Social Media Catalyst

Geographic and cultural barriers present obstacles to research inclusiveness today. But these walls may gradually crumble as researchers increasingly leverage social media, mobile technology and other boundary-busting tools to engage patients close to their homes.

Genes for Good, a large, ongoing study of health, genetic and behavior information, recently published U.S.-based data showing the equalizing role social media might play in increasing trial diversity. Epidemiologist Katharine Brieger and colleagues at the University of Michigan engaged more than 80,000 people from all 50 states to share their health histories in surveys administered through a Facebook app. Of those, more than 27,000 submitted “spit kits” enabling genomic analysis.

Predictably, participation was skewed toward a younger age group than the population at large, and had a higher percentage of females than in many traditional clinical trials. The study also reflects a greater diversity of ancestral backgrounds, consistent with usage of social media among diverse groups in the U.S. The investigators reasoned that the unusual study design would “help us reach populations that might not typically participate in genetic studies,” according to the detailed analysis published in the *American Journal of Human Genetics*.

“Potential advantages of social media-based study designs include the ability to reach diverse populations and the ability to engage participants in research over time,” the authors note.

High participation rates among mostly young women, especially, will be welcome news to stakeholders concerned about persistent gender-related distortions in the analysis of clinical research.

How Mapping Tools Help Address Research Disparities

By Stephanie Monroe, Executive Director, African Americans Against Alzheimer’s

From our perspective, patients’ voices really need to become part of the conversation around research practices. In one sense, it’s about who controls clinical recruitment, who controls trial design, advocacy, awareness, and implementation. **It’s also about treating research subjects as citizen scientists, recognizing they are vital members of the teams we put together to investigate innovative treatments and mechanisms.**

My organization is looking at ways to leverage 21st century tools to examine Alzheimer’s and other dementias, and comorbidities that make it more likely an individual will suffer cognitive decline. Among other things, we are developing a mapping tool that will show every person in a community who has been diagnosed with Alzheimer’s disease or another form of dementia. It will also show where the clinical trials are, how far patients are from trials, the bus lines, barriers to participation and other logistics.

We can see the hot pockets where there are high densities of comorbidities, like diabetes and vascular disease, that are predictive elements. With ZIP code-based mapping, we’ll know where people are, and we can apply emerging toolkits related to Big Data. And, once we understand the needs, we can better help patients with the logistics.
Conclusion

Leading biopharmaceutical companies are fully conscious of disparities that persist in both publicly and privately funded research and their implications for medical progress.

“Without understanding all the factors and intricacies in the genome that bear on diversity, as well as social determinants of health, we will be incredibly limited in designing precision medicine for all populations,” warns Genentech Roche’s Nicole Richie. “In fact, we run the risk of perpetuating and advancing the very disparities we need to address.”

The issues raised in oncology, hepatology and microbiome studies speak broadly to diversity-related challenges for precision medicine as a whole. Nonetheless many researchers are hopeful. They point to committed initiatives by biopharma companies, advocacy groups and government agencies that include:

- Working more closely with community organizations to educate minority populations on the potential benefits of trial participation
- Collaboratively preparing clinical trial outreach and education materials that speak to individuals of diverse backgrounds
- Activating populations to feel a sense of pride when participating in research that benefits others who share the same ancestry, cultural experiences or socioeconomic struggles

With robust federal and privately funded initiatives in place, transparency on official channels such as FDA’s Drug Trials Snapshots, a burgeoning research ecosystem on social media and collaborative education and outreach programs on the ground, it should be possible to build trust among demographic subgroups that are chronically underrepresented in clinical research. Trust, after all, is the gateway to the healthcare transformation everyone desires.
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Thank you to our contributors:

Dana Dornsife
Founder and Chairman of the Board, Lazarex Cancer Foundation

Stephanie Monroe
Executive Director, African Americans Against Alzheimer’s

Nicole Richie
Global Head of Health Equity Science and Strategy, Clinical Development at Genentech Roche

Fabian Sandoval
CEO and Research Director, Emerson Clinical Resource Institute (ECRI)

Syneos Health contacts:

Claudine Brisard
Senior Vice President, Global Head CNS, claudine.brisard@syneoshealth.com

Keri McDonough
Advocacy Specialist, keri.mcdonough@syneoshealth.com

Nicholas Kenny
Chief Scientific Officer, nicholas.kenny@syneoshealth.com

Kathleen Starr
Managing Director, Behavioral Science, kathleen.starr@syneoshealth.com

Contact us:
Phone: +1 919 876 9300
Fax: +1 919 876 9360
Toll-Free: +1 866 462 7373

syneoshealth.com