Racial and Ethnic Diversity in Studies Funded Under the Best Pharmaceuticals for Children Act

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abstract

BACKGROUND AND OBJECTIVES: The Best Pharmaceuticals for Children Act (BPCA) incentivizes the study of on-patent medicines in children and mandates that the National Institutes of Health sponsor research on off-patent drugs important to pediatric therapeutics. Failing to enroll cohorts that reflect the pediatric population at large restricts the generalizability of such studies. In this investigation, we evaluate racial and ethnic minority representation among participants enrolled in BPCA-sponsored studies.

METHODS: Data were obtained for all participants enrolled in 33 federally funded studies of drugs and devices conducted from 2008 through June 2020. Observed racial and ethnic distributions were compared with expected distributions by sampling Census data at the same geographic frequency as in the studies. Racial and ethnic enrollment was examined by demography, geography, study type, study burden, and expected bias. Standard descriptive statistics, χ^2, generalized linear models, and linear regression were applied.

RESULTS: A total of 10 918 participants (51% male, 6.6 $\pm$ 8.2 years) were enrolled across 46 US states and 4 countries. Studies ranged from treatment outcome reviews to randomized, placebo-controlled trials. Minority enrollment was comparable to, or higher than, expected ($+0.1\%$ to $+2.6\%$) for all groups except Asian Americans (-3.7%, $P < .001$). American Indian and Alaskan Native and multiracial enrollment significantly increased over the evaluation period ($P < .01$). There were no significant differences in racial distribution as a function of age or sex, although differences were observed on the basis of geography, study type, and study burden.

CONCLUSIONS AND RELEVANCE: This study revealed no evidence of racial and ethnic bias in enrollment for pediatric studies conducted with funding from BPCA, fulfilling the legislation's expectation to ensure adequate representation of all children.

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Dr Abdel-Rahman conceived of and designed the study, acquired, analyzed, and interpreted the data, and drafted the initial manuscript; Drs Paul, Hornik, Sullivan, Wade, and Zimmerman and Ms Delmore participated in study design, data analysis and interpretation, and critical revision of the draft manuscript for important intellectual content; Dr Sharma contributed to acquisition and analysis of the data, and critical revision of the draft manuscript for important intellectual content; Dr Benjamin participated in data acquisition and interpretation, and critical revision of the draft manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: The federal government has purposefully investigated the impact of legislation on the inclusion of children in studies of on-patent drugs and reported on racial and ethnic inclusion. However, representation in legislatively mandated, federally funded studies of off-patent medications is yet undescribed.

WHAT THIS STUDY ADDS: In this study, we highlight the extent to which pediatric investigators, overseeing drug and device trials, ensure balanced ethnic and racial representation among study participants. To our knowledge, similar findings have not been reported for other large Government-sponsored pediatric trial programs.

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Since the mid-1970s, federal regulations have underscored the need for data on the safety and efficacy of medicines in children.[1–4] However, it took a 1990 workshop, convened by the Institute of Medicine, the National Institutes of Health (NIH), the American Academy of Pediatrics, the US Food and Drug Administration (FDA), and representatives from the pharmaceutical industry, to spotlight prioritizing these efforts.[5] Pioneering legislation passed in 1997 by the US Congress (FDA Modernization Act) and supplemented in 2002 (Pediatric Research Equity Act; Best Pharmaceuticals for Children Act [BPCA]) incentivized this activity and was successful enough to prompt 3 successive reauthorizations under the FDA Amendments Act, the FDA Safety and Innovation Act, and the FDA Reauthorization Act.[6–10] Although no commercial or economic incentives were put in place to study underrepresented minorities, BPCA did highlight that studies should "take into account adequate representation of children of ethnic and racial minorities" and ordered the Comptroller General to examine "the extent to which members of ethnic and racial minorities are underrepresented."[7] This recommendation underscored the importance of ensuring that studies of drugs and devices, for which there is equal access across the general population, should enroll cohorts that mirror the population at large. Failure to balance racial and ethnic distribution in these studies severely restricts the generalizability of their findings and serves as a missed opportunity to identify groups of individuals in whom safety or efficacy may be compromised.[11–14]

Under BPCA, drug companies can receive an additional 6 months of patent exclusivity for conducting studies in children. A 2003 General Accounting Office report revealed that 23 medicines benefited from this legislation, having performed studies in a combined 6952 children. However, only 7% of those children enrolled were Black, 5% were Hispanic, and 1% were Asian American.[15] By 2016, >42 000 children had been enrolled by the private drug-development sector in studies of medicines under this legislation, and gains were seen across all underrepresented groups, although some minority populations still fell short of the proportions observed in the general population.[16]

Also nested within BPCA is a mandate for the NIH to sponsor research that generates data to guide the appropriate use of medicines in children for off-patent drugs important to pediatric therapeutics in which there is no financial incentive for the pharmaceutical industry to fund the study. These studies, largely designed and conducted in the academic sector, are supported through the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), which is subject to the NIH Revitalization Act of 1993 that addresses diversity and inclusion in federally funded clinical research.[17] In this article, we explored the representation of racial and ethnic minority participants enrolled in BPCA-funded pediatric studies sponsored by NICHD.

METHODS

The study population reflected all participants enrolled in completed or ongoing BPCA-funded studies occurring from 2008 through June 2020 whose data are maintained with the BPCA data coordinating center. No study had inclusion and exclusion criteria that explicitly referenced race or ethnicity. The data extracted included age, race, ethnicity, study site, study protocol, and the month and year of enrollment. Studies enrolling mother–infant dyads were retained in the analysis, but those enrolling adults only were excluded. The geographic site of enrollment was identified for each participant along with reference census data for the general population in that city as derived from the US Census Bureau, World population review, Statistics Canada, United Kingdom Office for National Statistics, Israeli local council data, and Department of Statistics Singapore.[18–23] All participating study sites, irrespective of country, were required to record race and ethnicity according to the standards laid out by the Office of Management and Budget as used by the US Census Bureau.[24] The observed racial and ethnic enrollment distribution across all studies was compared with the expected racial and ethnic enrollment distribution determined by sampling the general population at the same geographic frequency as in the BPCA-funded studies.

Racial and ethnic enrollment was examined categorically by age, sex, and geographic region, whereas trends in minority enrollment were estimated over the entire evaluation period. Enrollment diversity in each state was explored by calculating the Simpson's diversity index according to $D = 1 - [(\Sigma\, n^*(n-1))/(N^*(N-1))]$, where n represents the total number of children for each racial or ethnic subgroup and N represents the total number of children for all groups.[25] The subgroups combine each of 7 racial groups (American Indian or Alaskan Native, Asian American, Black, Hawaiian or Pacific Islander, multiracial, not reported or unknown, white) with two ethnic groups (Hispanic, non-Hispanic) for a total of 14 groupings as recorded in each of the studies. The calculated index "D" ranges from 0 to 1 and represents the probability that two randomly selected individuals, from the same area, belong to a different racial or ethnic group. Converted to percent, 0 represents no diversity and 100 suggests maximal diversity.

The studies from which the participants were drawn were subclassified to investigate comparisons of minority enrollment by study characteristic. Study "type" was categorized as interventional or noninterventional. The perceived burden of participating in the study for any participant (ie, study burden) was classified as none, low, medium, or high: a rating reflecting the composite assignment of 3 pediatric clinician researchers, selected in a block randomized fashion from 6 in total. Raters evaluated each study according to their view on the burden of participation taking into consideration duration of participation, frequency of travel required for study visits, risks associated with study participation (ie, physical, emotional, social), invasive nature of study procedures, and prospect for direct benefit. Discrepancies between raters were adjudicated by a seventh independent clinician researcher. Raters were also asked to classify (yes or no) whether they expected to see racial or ethnic biases in participant diversity for each study (ie, study bias). Classification category was assigned by consensus of all raters on the basis of peer-reviewed literature, publicly available reports, and disease-focused Web sites (eg, Centers for Disease Control and Prevention, March of Dimes, NIH) that address racial and ethnic differences in disease epidemiology, health care use patterns, medication use, access to care, and prescriber treatment bias for the diseases under investigation.

Standard descriptive statistics were used to describe the study population. Comparison of proportions between observed and expected enrollment was accomplished by using a χ^2 test or z test. Generalized linear models were used to explore differences by sex, study type, and study burden. Linear regression was used to examine trends in enrollment over time. All statistical analyses were performed in SPSS v.23 (IBM, SPSS Statistics, IBM Corporation).

RESULTS

Data from 34 studies were available, representing 11 045 participants. Enrollment occurred at 164 clinical study sites distributed across 46 US states along with sites in Canada, England, Israel, and Singapore. One study in which researchers enrolled pediatric critical care providers (eg, physicians, nurses, and emergency medical technicians; n = 127) was excluded from the analyses, leaving a final data set constituted by 33 studies (Supplemental Table 7) enrolling 10 918 participants (United States: 10 483, international: 435). Studies ranged from retrospective reviews of treatment outcomes to prospective, randomized, placebo-controlled investigations. Thirty studies represented investigations of drugs, whereas the remaining 3 represented medical devices. The overall age of participants in these studies averaged 6.6 ± 8.2 years (range: 0–45 years) and was evenly distributed among male and female individuals (51% male versus 49% female). However, when mothers from studies enrolling mother–baby dyads were removed (n = 439), the participant age lowered to 5.5 ± 6.1 years (0–28 years, Fig 1).

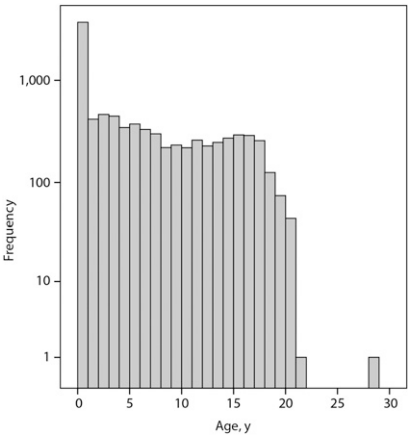

FIGURE 1
Distribution of pediatric participants in BPCA-funded studies by age (the single 28-year-old reflects a neurology patient being managed at 1 institution).

Enrollment across all studies paralleled the expected enrollment based on estimates from the general population (Table 1). Although minimal with respect to percentage points, significantly higher-than-expected enrollment was observed in white, multiracial, American Indian, Hawaiian, and Hispanic children, ranging in absolute increases over expected from +0.2% to +2.6% ($P <$ .05). Asian American children enrolled in lower absolute proportions than expected (−3.7%, $P <$ .001), whereas essentially no difference between observed and expected enrollment was found for Black children (24.6% vs 24.5%, P = .864). There were no significant differences in racial distribution as a function of sex (P = .214), nor were any significant differences observed between the largest of the enrolled populations (infants <3 months, n = 3139) and children >3 months of age (P = .769).

Not surprisingly, enrollment in the United States varied widely by Census region and division (Table 2). A comparison with the expected racial and ethnic distribution by geographic region, when sampled at the same frequency from the same locations as the study participants, reveal a net neutral balance for most population groups. However, absolute percentage deviations of >5% and 10% were observed in 7 of 9 and 4 of 9 census divisions, respectively. Only the West North Central Midwest and the West South Central South saw enrollment parallel the general population, with deviation <5% across all racial and ethnic groups. The 1 exception to otherwise balanced enrollment across the United States was observed for the Asian American population. As illustrated in Table 2, statistically fewer Asian American children were enrolled in all but 1 Census division,

TABLE 1 Observed Versus Expected Enrollment by Race and Ethnicity for 33 BPCA-Funded Studies Conducted From 2008 to 2020

Race or Ethnicity	Expected (n = 10 918), %	Observed (n = 10 918), %	Difference, %	95% CI	P
White	61.5	63.1	+1.60	0.31 to 2.88	.015
Black or African American	24.5	24.6	+0.10	−1.04 to 1.24	.864
Multiracial, not specified	3.2	3.7	+0.50	0.02 to 0.99	.043
Asian American	6.0	2.3	−3.70	−3.18 to −4.23	<.001
American Indian or Alaskan native	0.5	0.8	+0.30	0.09 to 0.52	.006
Hawaiian or Pacific Islander	0.1	0.3	+0.20	0.08 to 0.33	.001
Not reported or unknown	4.2	5.2	+1.00	0.44 to 1.56	.001
Hispanic or Latino	13.2	15.8	+2.60	1.67 to 3.53	<.001

and this was most pronounced in Western divisions where a higher overall proportion of the population originates from Asian ancestry.

A more granular look at enrollment diversity by state, as represented by the diversity index, is presented in Fig 2. The shading cutoffs employed in this figure reflect those that have been used, by others, to describe population diversity in counties across the United States.[26] In non-US study settings, the diversity was far less varied (Table 3), although wholly aligned with expectations for those regions. Calculated diversity index (converted to %) was highest in Canada (D = 54.0, n = 386), followed by England (D = 32.4, n = 21), with essentially no diversity in Israel (D = 0.0, n = 13) and Singapore (D = 0.0, n = 15).

When examining trends in racial and ethnic enrollment across the 13-year time frame, we observed wide fluctuation from year to year, although the rank order between racial and ethnic groups stayed relatively consistent (Table 4). In 5 racial groups (Asian American, Black, Hawaiian or Pacific Islander, not reported or unknown, white), there was no significant trend in enrollment over time, as evidenced by confidence intervals for the slope that span zero (Table 4). Similarly, there was no trend in enrollment among Hispanic participants. By contrast, enrollment among American Indian and Alaskan Native and multiracial children significantly increased during this time frame at rates of 0.17% and 0.36% per year, respectively ($P < .01$). Nevertheless, the absolute numbers enrolled for these population subgroups remain modest.

When explored by study type, the only significant racial and ethnic differences observed were lower enrollment for American Indian and Alaskan Natives and higher enrollment for Hispanic individuals in the interventional studies ($P < .05$, Table 5). More differences in racial and ethnic distribution were observed by study burden; however, these were largely influenced by the higher proportion of participants in the "zero" burden studies in which information on race and ethnicity was incompletely captured (Table 6). When focusing on the studies with some degree of participant burden (ie, those scored in the range of 1–3), white children were represented to a lower extent in moderate burden studies, whereas the inverse was observed for Black children. A higher proportion of multiracial children were enrolled in high burden studies (versus low or moderate burden) and a higher proportion of American Indian children were enrolled in moderate versus low burden studies.

Finally, we explored whether observed enrollment tracked with the over- or underrepresentation bias that we predicted on the basis of reported epidemiological, sociodemographic, and health care use patterns. For studies of conditions in which we expected higher enrollment in the Black population (eg, prematurity, obesity, sickle cell disease), we observed that the proportion of Black children enrolled was nearly 10 percentage points higher than seen in studies in which no bias between Black and non-Black children was expected (33% vs 24.3%, $P < .001$). In contrast, assumptions for studies in which we expected disproportionate enrollment in white (eg, mental health, infantile hemangioma) or Hispanic (eg, status epilepticus, renal transplant, obesity) children proved largely incorrect. For example, in studies in which a higher proportion of white children were expected, enrollment percentages were nearly 6 points lower than in studies in which no bias in white representation was expected (58.2 vs 63.9%, $P < .001$). Similarly, studies in which we predicted lower Hispanic enrollment demonstrated a near doubling in the opposite direction as compared with studies in which bias was not expected (29.8% vs 15.3%, $P < .001$).

DISCUSSION

This study reveals that the pediatric investigators responsible for executing federally funded drug and device studies under BPCA have ensured ethnic and racial representation among study participants. The minority enrollment observed in these studies was comparable to, or greater than, what

TABLE 2 Racial and Ethnic Distribution in Enrollment by US Census Region and Division for BPCA-Funded Studies From 2008 to 2020

	Northeast, %			Midwest, %			South, %				West, %		
	New England (n = 187)	Mid-Atlantic (n = 1348)	Overall (n = 1535)	East North Central (n = 2095)	West North Central (n = 1763)	Overall (n = 3858)	South Atlantic (n = 2598)	East South Central (n = 318)	West South Central (n = 984)	Overall (n = 3900)	Mountain (n = 346)	Pacific (n = 889)	Overall (n = 1235)
White	68.8	65.8	66.1	70.9	66.0	68.7	47.6	69.6	58.4	52.1	76.9	73.4	74.4
Black or African American	12.9	22.8	21.6	19.7	26.1	22.6	38.8	24.7	31.2	35.7	5.3	4.4	4.7
Multiracial, not specified	9.7	3.9	4.6	3.0	3.4	3.2	3.4	3.5	3.8	3.5	3.6	5.8	5.2
Asian American	2.2	3.9	3.7	1.5	2.0	1.7	1.2	0.0	1.5	1.2	0.0	5.3	3.9
American Indian or Alaskan native	0.5	0.5	0.5	0.1	0.2	0.2	0.7	0.3	1.3	0.8	5.3	1.4	2.5
Hawaiian or Pacific Islander	0.0	0.1	0.1	0.2	0.4	0.2	0.0	0.0	0.2	0.1	1.5	1.5	1.5
Not reported or unknown	5.9	3.0	3.3	4.5	2.0	3.3	8.5	1.9	3.5	6.7	7.4	8.2	8.0
Hispanic	19.4	10.8	11.9	26.2	16.4	21.7	7.4	3.8	18.9	10.0	22.8	24.2	23.8
Absolute difference (% observed − % expected)													
White	9.3	−7.9[a]	-5.9[c]	20.4[a]	−0.4	10.9[a]	−10.4[a]	10.3[b]	1.9	-5.6[a]	6.5	4.7[c]	5.2[b]
Black or African American	−3.1	7.6[a]	6.3[a]	−14.3[a]	3.5[c]	-6.2[a]	8.0[a]	−10.2[b]	−1.3	4.1[a]	−0.9	−1.6	-1.4
Multiracial, not specified	5.7[c]	1.7[c]	2.2[a]	−0.2	−0.6	-0.3	0.7	1.2	1.0	0.8[c]	−0.5	−0.4	-0.5
Asian American	−7.4[b]	−1.9[c]	-2.5[b]	−3.3[a]	−0.5	-2.1[a]	−4.6[a]	−2.2[b]	−2.4[b]	-3.8[a]	−5.1[a]	−9.5[a]	-8.2[a]
American Indian or Alaskan Native	−0.1	0.3	0.3	−0.2	−0.4	-0.3[c]	0.4[c]	0.1	0.7	0.5[b]	3.5[c]	0.8	1.6[b]
Hawaiian or Pacific Islander	−0.1	0.1	0.1	0.2[c]	0.3	0.1	0.0	−0.1	0.1	0.1[c]	0.6	0.8	0.7
Not reported or unknown	−4.3	0.0	-0.6	−2.7[a]	−1.8[b]	-2.3[a]	6.1[a]	0.9	−0.2	4.1[a]	−4.1	5.2[a]	2.6[c]
Hispanic	−6.4	2.9[b]	1.8	7.0[a]	4.6[a]	5.9[a]	−2.6[a]	−1.3	0.7	-1.7[c]	−4.8	10.3[a]	6.1[b]

[a] $P < .001$.
[b] $P < .01$.
[c] $P < .05$.

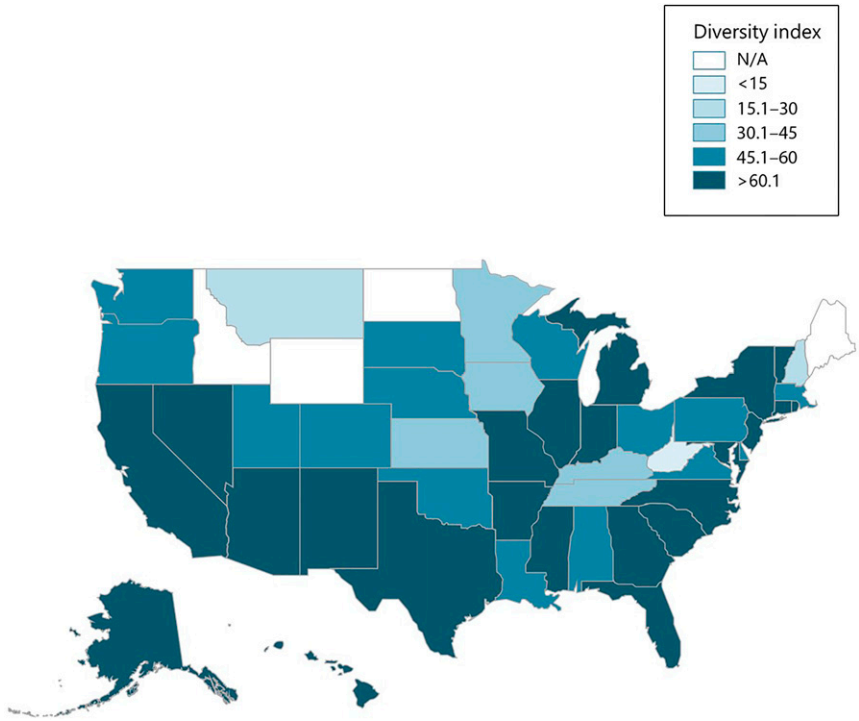

FIGURE 2
Enrollment diversity by US state. N/A, not applicable.

would be expected on the basis of estimates from the general population. Thus, although the legislation never required prespecified racial and ethnic representation in pediatric studies, legislators may be reassured that racial and ethnic minorities are appropriately represented in trials supported by the off-patent component of BPCA, which is required by law to be reviewed and renewed by the US Congress every 5 years.

It is possible that the equity observed in this study arose because federally funded investigators are attuned to NIH initiatives surrounding race and ethnicity. However, the wide range of minority representation reflected in the most recent triennial inclusion reports for the various NIH institutes argues that this is unlikely the sole reason for our findings.[27] It is also possible that pediatric-trained clinician-investigators feel a greater sense of responsibility to ensure that broad enrollment is sought from all eligible participants and families for whom they care. However, this remains speculative because, to our knowledge, this has not been documented quantitatively for other large NIH-sponsored pediatric clinical trial programs. Another possibility is that multidisciplinary, pediatric, clinician-investigator teams that are experienced in the conduct of drug and device trials approach trial design with an eye toward simplifying inclusion and exclusion criteria, eliminating undue emotional distress, and minimizing participation burden wherever possible. However, we would be remiss not to acknowledge that the findings might simply reflect the balance of children presenting to the participant

TABLE 3 Racial and Ethnic Distribution in Enrollment by Non-US Country for BPCA-Funded Studies From 2008 to 2020

	Canada (n = 386), %	England (n = 21), %	Israel (n = 13), %	Singapore (n = 15), %
White	71.2	81	100	0
Black or African American	10.4	0	0	0
Multiracial, not specified	3.6	0	0	0
Asian American	5.4	0	0	100
American Indian or Alaskan native	2.1	0	0	0
Hawaiian or Pacific Islander	0.0	0	0	0
Not reported or unknown	7.3	19	0	0
Hispanic	6.2	0	0	0
Absolute difference (% observed − % expected)				
White	−0.6	−7.8	3.3	0.0
Black or African American	2.1	−1.9	0.0	0.0
Multiracial, not specified	3.2[a]	−2.1	−3.3	0.0
Asian American	−8.7[b]	−6.0	0.0	3.3
American Indian or Alaskan native	0.8	0.0	0.0	0.0
Hawaiian or Pacific Islander	0.0	0.0	0.0	0.0
Not reported or unknown	3.2	17.9	0.0	−3.3
Hispanic	2.8	0.0	0.0	0.0

[a] $P < .01$.
[b] $P < .001$.

TABLE 4 Trends in Racial and Ethnic Pediatric Study Enrollment Over Time for BPCA-Funded Studies

	AI/NA	Asian American	Black	HI/PI	Multiracial	NR	White	Hispanic
Year, %								
2008	0.8	3.4	29.7	2.5	2.5	4.2	56.8	19.5
2009	0.0	0.7	28.3	0.3	1.7	5.3	63.7	16.0
2010	0.0	5.3	17.1	0.3	2.6	6.6	68.1	22.7
2011	0.6	1.7	29.4	0.6	2.3	6.2	59.3	20.9
2012	0.0	1.9	22.9	0.2	2.4	3.9	68.7	13.0
2013	0.5	1.6	18.0	0.5	1.9	3.7	73.8	14.0
2014	0.7	1.4	38.1	0.2	1.5	9.2	48.8	10.5
2015	0.4	2.1	27.2	0.4	3.2	3.9	62.9	18.5
2016	1.1	2.6	15.3	0.3	4.2	8.2	68.3	14.4
2017	1.0	2.7	19.5	0.1	7.1	3.7	66.0	18.1
2018	0.9	1.7	16.3	0.1	4.9	7.0	69.1	12.9
2019	1.8	3.5	25.0	0.2	5.6	5.0	58.9	15.6
2020	3.2	2.7	18.6	0.9	5.4	2.7	66.5	18.1
Min, %	0.0	0.7	15.3	0.1	1.5	2.7	48.8	10.5
Max, %	3.2	5.3	38.1	2.5	7.1	9.2	73.8	22.7
Slope, %	0.17	0.00	−0.67	−0.07	0.36	−0.04	0.26	−0.28
Lower CI, %	0.07	−0.20	−1.74	−0.17	0.17	−0.37	−0.85	−0.85
Upper CI, %	0.27	0.20	0.40	0.03	0.55	0.29	1.37	0.29
P	.003	.986	.196	.161	.001	.787	.622	.306

AI/NA, American Indian or Native Alaskan; CI, 95% confidence limit; HI/PI, Hawaiian or Pacific Islander, NR, not reported.

institutions. If this latter explanation were proven to be the case, it would underscore the need to purposefully select study sites that serve a broad cross-section of the population.

The one exception in these studies was children of Asian ancestry, who were represented at significantly lower proportions than the census would have suggested. Reasons for this finding remain unclear. With no significant disparity in overall rates of medically uninsured among Asian Americans, economic factors may not serve as the primary explanation.[28] It is well described that cultural norms influence health care seeking behaviors in the Asian American community, resulting in lower health care use,[29–33] and this appears to extend to Asian American children as well.[34,35] However, without the demographic distribution of patients receiving care at each of the 164 participating study sites, this theory cannot be confirmed. It is also possible that limited English proficiency, coupled with a lower likelihood of permission or assent and consent forms being translated into Asian languages versus more prevalent languages (eg, Spanish), could have played a role. Unfortunately, we did not have access to the permission or assent and consent forms created for these studies to explore this theory.

We observed no discernible trends in participation by study burden across the entire cohort, although unique differences were noted within populations. However, the conclusions that can be drawn from these findings are limited by the fact that our views of research burden (ie, the views of clinical investigators with extensive clinical trials experience) may be different from those of participants. Where medical and economic risks to clinical study participation are objectively easy to identify, psychological burdens are perhaps less so.[36] In the context of pediatric research, it is unclear whether concerns of the parent or guardian are projected onto the child. On a separate note, the overrepresentation of unknown or unreported participants in the zero burden studies, which largely reflects retrospective chart reviews, speaks to the inherent limitations of research conducted by using Electronic Health Record systems in which race and ethnicity are incompletely captured.

Interestingly, our predictions of enrollment bias, as informed by the medical literature, were largely incorrect. Although we did see higher Black participant enrollment in studies in which bias in favor of Black participation was expected, this was

TABLE 5 Racial and Ethnic Distribution in Enrollment by Study Type for BPCA-Funded Studies From 2008 to 2020

Race or Ethnicity	Noninterventional, %	Interventional, %
White	63.3	61.9
Black or African American	24.4	26.1
Multirace, not specified	3.8	3.4
Asian American	2.4	1.9
American Indian or Alaskan native*	0.8	0.3
Hawaiian or Pacific Islander	0.3	0.4
Not reported or unknown	5.1	6.1
Hispanic or Latino*	15.3	18.2

* $P < .05$.

TABLE 6 Racial and Ethnic Distribution in Enrollment by Study Burden for BPCA-Funded Studies From 2008 to 2020

Race or Ethnicity	No burden (0), %	Low burden (1), %	Moderate burden (2), %	High burden (3), %
White	44.8[a]	67.1[b]	55.4[c]	64.6
Black or African American	40.7[a]	21.3[b]	30.8[c]	21.4
Multiracial, not specified	1.1[a]	3.8[d]	3.1[c]	9.6
Asian	2.3	2.3	2.7	1.6
American Indian or Alaskan native	0.7	0.7[b]	1.3	0.8
Hawaiian or Pacific Islander	0.0[e]	0.4	0.2	0.0
Not reported or unknown	10.4[a]	4.4[f]	6.6[c]	2.0
Hispanic or Latino	10.0[a]	16.6	15.3	16.3
Not reported/unknown	15.5[a]	2.5	3.3[c]	1.4

[a] Difference between 0 vs 1/2/3, $P < .05$.
[b] Difference between 1 vs 2, $P < .05$.
[c] Difference between 2 vs 3, $P < .05$.
[d] Difference between 1 vs 3, $P < .05$.
[e] Difference between 0 vs 1, $P < .05$.
[f] Difference between 1 vs 2/3, $P < .05$.

not reproduced for the white and Hispanic populations. A posteriori examination of our miscalculations for expected bias in white participants appeared to be influenced by the inclusion of studies dealing with pregnancy and lactation in which our perceptions were driven by reported racial differences related to adequate prenatal care. However, we were unable to account for the composition of the population served by the enrolling centers. When these studies were removed from the analysis, we did observe bias in the predicted direction (69.1% vs 63.9%, $P = .009$), albeit moderate. Our findings in the Hispanic population, in which lower estimates of enrollment were expected, may also be driven by patient demographics at the enrolling centers. However, it is more likely that our predictions reflect an incomplete understanding of the factors that influence the rate and extent to which patients present for care.

Despite perpetuated myths about minority participation in clinical research,[37] our data do not indicate that underrepresented pediatric populations are less likely to participate in clinical research. However, we cannot discriminate between the rate at which families from racial and ethnic minorities were approached for participation in these studies and the proportion that elected to participate. Nevertheless, these data reassure us that minority children have not been overlooked in the pediatric studies conducted with funding from BPCA.

On the basis of the nature of this investigation, we were unable to identify whether the individual studies were powered to explore the impact of race and ethnicity on study outcomes and whether such analyses were undertaken. However, ensuring balance in the acquisition of knowledge and the generation of evidence will be an important initiative as we look to refine our understanding of drug and device response as it shapes the risk/benefit balance for these interventions in children of different racial and ethnic backgrounds. Failure to do so will only serve to exacerbate the health disparities that exist among racial and ethnic minorities.[38]

CONCLUSIONS

Historically, the biomedical research community has done an inadequate job of ensuring the broad and balanced enrollment of underrepresented minorities in drug and device trials.[39–44] This study revealed no evidence of racial or ethnic bias in pediatric clinical trial enrollment for investigator-initiated studies conducted with funding from the BPCA: a reassuring finding in light of the racial and ethnic disparities that persist in health care. However, these findings are not reflective of all contexts wherein pediatric clinical research takes place. In clinical research settings where similar findings have not been observed, or in settings where clinical trial planning is ongoing and adequate racial representation is paramount (eg, coronavirus disease therapeutic trials), collaborative discussions between stakeholders may offer solutions to resolve these disparities.

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ABBREVIATIONS

BPCA: Best Pharmaceuticals for Children Act
FDA: US Food and Drug Administration
NICHD: *Eunice Kennedy Shriver* National Institute for Child Health and Human Development
NIH: National Institutes of Health
PTN: Pediatric Trials Network

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