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Participant Diversity by Race, Ethnicity, and Sex in Rare Disease Clinical Trials: A Case Study of Eight Rare Cancers

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KEY POINTS

- Rare cancer clinical trials appear to enroll less diverse participants than clinical trials more broadly and therefore may require additional considerations or unique solutions to diversify participant recruitment. These differences persisted within both NIH and non-NIH funded trials. The rare cancer clinical trials in this study were completed between 2004 and 2023.
- People from non-White racial and ethnic backgrounds tend to be underrepresented in the rare disease clinical trials we examined relative to the incidence rates for these groups.
- An increasing share of new oncology clinical trials are aimed at rare cancers or small subsets of more common cancers. Lack of diversity in these clinical trials will inhibit health equity for a growing number of patients, with underrepresented groups less likely to benefit from experimental treatments and health systems lacking information about the efficacy of treatments in diverse populations.
- Further federal engagement and coordination is needed to understand and overcome challenges to enrolling diverse populations in rare cancer clinical trials.

BACKGROUND

Over the past few decades, cancer drug development has led to major strides in novel therapeutics, such as immunotherapies and precision medicines, that have increased survival rates.[1] Cancer clinical trials with diverse populations allow researchers to assess the differential efficacy, safety, and tolerability of tested interventions, as well as analyze biological predictors of clinical outcomes.[1,2] Diversity of participants in clinical trials is important for the equitable advancement of health research. There are many important dimensions of diversity in health research, including race, ethnicity, sex, sexual orientation, gender identity, age, disability status, income, and others, but much of the existing literature primarily examines race and ethnicity. Inadequate representation may lead to clinically relevant gaps that contribute to worse health outcomes, including lower survival rates, for the population group that is excluded from the clinical trials.[1,3] Multiple studies have investigated this relationship. For example, Valbuena and colleagues[4] showed that unrepresentative clinical trials can lead to ineffective medical products. Additionally, Alsan and colleagues[5] reported reduced willingness of physicians to prescribe new medication to Black patients when the clinical trial is not representative of the group that is being treated, which could further stymie equitable diffusion of innovative therapeutics.

U.S. Department of Health and Human Services (HHS) agencies have made strides in addressing disparities in clinical research generally and cancer clinical trials specifically (see Appendix B). For example, the National Institutes of Health (NIH) Revitalization Act of 1993 mandated the inclusion of underrepresented racial and ethnic groups and women in all NIH-funded research.[6] The Food and Drug Administration (FDA) Amendments Act of 2007[7] (effective beginning in 2017) requires sponsors to report participant race and ethnicity to Clinicaltrials.gov, when collected, within 12 months of a trial's conclusion.[8] Several other Departmental guidance documents and policies, including NIH's 2016 policy on sex as a biological variable, and FDA's 2020 guidance on *Enhancing the Diversity of Clinical Trial Populations*, have shaped best practices for increasing participation by underrepresented populations.

While all HHS Divisions are actively engaged in addressing questions of equity, NIH is particularly focused on efforts related to clinical research due to its role as the largest public funder of biomedical research.[9] Within NIH, the National Cancer Institute (NCI) is focused on cancer research. NCI's National Clinical Trial Network (NCTN) and NCI Community Oncology Research Program (NCORP) are actively working toward increasing diversity in cancer clinical trials, with underrepresented racial and ethnic group accrual within the two programs increasing from 14% during 1999-2001 to 25% during 2017-2019.[10] NCORP, which supplies many NCTN clinical trial participants, has 14 sites designated as "Minority/Underserved Community Sites", wherein at least 30% of the patient population belong to an underrepresented racial or ethnic group, or are rural residents.[11]

Despite these policies and programs and the gradual improvement in clinical trial diversity, clinical trials in the United States still tend to overrepresent White populations and males, while other racial and ethnic groups and females are underrepresented,[12-14] suggesting additional opportunities for HHS initiatives to reach more diverse populations.

For this issue brief, we focus on rare cancer clinical trials, which we hypothesize might present particular challenges for improving diversity.[i] By definition, rare cancers have low incidence, which can make it difficult to accrue appropriate sample sizes for studies.[15] Rare cancer clinical trials are often conducted at major cancer centers that have large patient populations.[16] Despite the advantages large cancer centers can offer, not all patients have access to treatment at these facilities, so recruitment at these sites may not accurately reflect the diversity of the affected population. Additionally, rare cancers are more likely to be diagnosed at later stages of disease progression,[3] with underrepresented groups often more likely to experience delayed diagnosis,[17,18] meaning that timely treatment or clinical trial enrollment may be less likely.[19] Underrepresented racial and ethnic groups tend to have slightly higher rates of rare cancer diagnosis, potentially contributing to overall worse cancer outcomes compared to non-Hispanic White populations.[3,15] Patients diagnosed with rare diseases are also likely to face higher individual medical costs than patients with non-rare diseases.[20] Although the Affordable Care Act required insurers to cover routine care costs for clinical trials beginning in 2014,[21] other costs of participating in clinical trials, such as travel and childcare, may still be prohibitive to some patients.[12]

Studying rare cancers presents important opportunities to learn about cancer and health disparities more broadly. Despite their individual rarity, rare cancers collectively present a significant heath burden, accounting for one in five cancer diagnoses in the United States.[3] As additional cancer subtypes are identified in the post-genomics era, the challenges inherent to rare cancer clinical trials, such as small patient populations, are likely to become more common.[22] These challenges have been recognized in the reignited Cancer Moonshot initiative, which aims to reduce cancer mortality by 50% over the next 25 years.[23] The challenges around rare

[i] For the purposes of this report, we focus on sex, race, and ethnicity.

cancer clinical trials likely make them particularly under-representative, but few studies have measured representation in these trials.

Our brief contributes to ongoing efforts across HHS to advance health equity by identifying significant underrepresentation of non-White racial and ethnic groups in rare cancer clinical trials. While our analysis focuses on rare cancers, it is important to note that many of the trends observed in rare cancers are likely to extend to other disease areas as the field moves toward identifying treatments that target more specific disease subtypes. In part, this is due to our increasing understanding of and investment in the genetic and mechanistic underpinnings of disease that are foundational to precision medicine. As precision medicine allows for more diseases to be distinguished into different subtypes, it is likely that this will result in differing treatment approaches, leading to a larger share of clinical trials experiencing the same barriers as rare cancers. Therefore, addressing participant diversity in rare cancer trials is likely to provide useful insights into future challenges and opportunities in enhancing participant diversity for the clinical research enterprise as a whole.

METHODS

Rare Cancer Criteria

We defined rare cancers as those that affect fewer than 200,000 people[ii] in the United States and used the Genetic and Rare Diseases (GARD) database from the National Center for Advancing Translational Science (NCATS)[24] to identify these cancers. We considered only those diseases with at least one FDA-approved treatment that received orphan drug designation[25,26] and had at least one clinical trial listed in ClinicalTrials.gov. This allowed us to focus on drugs most likely to be currently in use specifically for rare cancers. We eliminated any cancers that did not have epidemiological information inclusive of sex, race, and ethnicity available in National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)*Explorer application.[27] We selected eight rare cancers that met these criteria and ensured tractability of data collection and sufficient numbers of observations (i.e., clinical trials within each condition) for statistical comparisons (Table 1). Although we considered additional cancers, such as pancreatic and brain, many of these cancers were excluded because they had few clinical trials that met our criteria.

Clinical Trial Data

For each condition-drug pair[iii], we obtained baseline participant demographic information using individual clinical trial results from Clinicaltrials.gov. We excluded trials that did not report results, had predominantly pediatric populations[iv], or had any trial sites outside the United States. For each trial in our search, we manually collected data on sex (male, female), ethnicity (Hispanic/Latino, non-Hispanic or Latino, unknown), and race (American Indian and Alaska Native (AIAN), Asian, African American or Black, Native Hawaiian or Pacific Islander (NHPI), White, Multiple, Other, Unknown), when available. Trial reporting of demographic descriptors was varied, and many trials reported a subset of the demographic variables we indexed. In the rare cases where trials reported more demographic descriptors than we collected, we aggregated them under the most similar descriptor (e.g., East Asian and Southeast Asian were aggregated under Asian). A small number of trials listed Hispanic/Latino as a race instead of an ethnicity, which we addressed by moving these counts from race to ethnicity. In these cases, we considered race to be not reported.

[ii] This definition is based on the Orphan Drug Act: "… the term "rare disease or condition" means any disease or condition which (A) affects less than 200,000 persons in the United States". 21 USC 360bb Sec. 526 (a) (2).

[iii] Condition-drug pair is defined as a specific condition matched with a single intervention tested for that condition in clinical trials.

[iv] Pediatric clinical trials may be subject to additional oversight and have different inclusion criteria, and pediatric drug development may be subject to different incentives than drug development for adults. As a result, the demographics of pediatric clinical trials could vary substantially from adult clinical trials.

In addition to collecting demographic data on clinical trials, we also collected information on whether NIH funded (i.e., provided the funds used to conduct a clinical trial but did not collect or analyze the data) or sponsored (i.e., both funded as well as collected and analyzed the data, or holds an investigational new drug application or investigational device exemption) the clinical trials and whether clinical trials were associated with NIH programs that have improved participant diversity in clinical trials. We identified trials as being NIH funded if they appeared in NIH's ExPORTER clinical studies data.[v] The ExPORTER database was provided by the Clinical Trials Transformation Initiative (CTTI).[28] Using the CTTI database, we divided trials into sponsored by NIH, co-sponsored by NIH, and not sponsored by NIH. Finally, we specifically pulled out clinical trials that were associated with the National Clinical Trials Network (NCTN). NCTN derives approximately 30-35% of its patients from the NCORP, which is focused on reducing disparities in clinical trials.[29] We associated clinical trials from our dataset with NCTN by first identifying all the requests for applications (RFAs) associated with NCTN as recorded in grants.nih.gov. We used the RFA numbers to search for clinical trials in RePORTER's clinical studies data, which we then used to sort the clinical trials in our dataset into NCTN and non-NCTN sets.

Table 1. Rare Cancers Used for Analysis

GARD Condition[1]	SEER Condition[2]	Drugs[3]	Total Clinical Trials[4]	Total Enrollees
Acute Lymphoblastic Leukemia	Acute Lymphocytic Leukemia	Mercaptopurine, pegaspargase, dasatinib, imatinib, asparaginase, vincristine sulfate liposome injection, clofarabine, ponatinib	32	2,045
Acute Myeloid Leukemia	Acute Myeloid Leukemia	Filgrastim, sargramostim, idarubicin, mitoxantrone	67	5,062
Malignant Mesothelioma	Mesothelioma	Pemetrexed	9	548
Mantle Cell Lymphoma	Non-Hodgkin Lymphoma	Bortezomib, lenalidomide, ibrutinib	33	2,430
Multiple Myeloma	Myeloma	Melphalan, doxorubicin, lenalidomide, bortezomib, carfilzomib, pomalidomide, thalidomide, panobinostat, ixazomib, elotuzumab, daratumumab	221	17,508
Osteosarcoma	Bones and Joints	Leucovorin	1	20
Soft Tissue Sarcoma	Soft Tissue including Heart	Mesylate, trabectedin, pazopanib, olaratumab	23	1,259
Stomach Cancer	Stomach	Trastuzumab, ramucirumab	5	446
Total	---	---	**391**	**29,318**

Notes: [1]Condition names from the GARD list. [2]Condition names in SEER matched to conditions from the GARD list. [3]Interventions used in clinical trials for the specified condition. All interventions are FDA orphan drugs approved for the specified condition. [4]Clinical trials were included for analysis if at least one of the conditions being treated was the specified condition and at least one of the interventions was the among the specified interventions.

[v] Clinical trials are represented using a clinical trial identification number. This number is indexed in NIH funding data and clincialtrials.gov, allowing for high fidelity linkage of the two datasets. NIH. ExPORTER. Accessed at: https://reporter.nih.gov/exporter/clinicalstudies

Rare Cancer Epidemiology Data

We used SEER*Explorer to extract incidence rates by sex, race, and ethnicity for each of our eight conditions. These incidence rates were then normalized to 2010 Census population numbers as described in Aldrighett, *et al* (2021).[33] Where possible, we used exact disease matches. However, because the conditions we analyzed are rare, it was not always possible to find exact matches in SEER*Explorer. In these cases, we used data available for a less specific subset of cancer (for instance, we used bone and joint cancer incidence to approximate the incidence of osteosarcoma). A list of SEER*Explorer terms matched to our selected diseases can be found in Table 1. We used a range of data (2000-2019) to account for variation in incidence over time. The SEER*Explorer data reported a combined Asian and NHPI incidence rate, so we aggregated these descriptors in clinical trial data when comparing to incidence data.

Demographic Analysis

For each rare cancer, we measured over- or underrepresentation of every demographic group based on race, ethnicity, and sex in clinical trials relative to that demographic's rare cancer disease burden. To measure representation, we created a distribution for each demographic group's total share of participants in clinical trials for each of our eight conditions. Similarly, we created a distribution of each demographic group's share of incidence for each condition in each year from 2000-2019, normalized to Census standard populations. We examined whether these distributions were statistically different by observing how frequently the difference in the median values of two random combinations of those distributions ("representation difference") was greater than that observed between the original distributions (i.e., a permutation test). We performed this random combination and comparison process 10,000 times to generate p-values for the statistical significance (p-value < 0.05) of the difference between the original distributions. We also generated confidence intervals for representation difference by resampling the original distributions with replacement and recomputing representation difference 10,000 times (i.e., a bootstrap confidence interval).

In addition to our disease burden-based representation analysis, we also compared clinical trial representation in our set of rare cancers to clinical trial representation as a whole, as determined through FDA Snapshots data for 2015-2019.[30] We calculated percent representation for each demographic group across all our rare cancer clinical trial participants. We then calculated the percent difference between representation in our data set and representation in the FDA Snapshots data set by subtracting percent representation in our dataset from percent representation in the FDA Snapshots cohort.

Limitations

A primary limitation is the generalizability of this study, due to data selection and availability. We focused exclusively on trials conducted in the United States to understand the current context and effect of HHS programs. Although conducting successful clinical trials for rare cancers may require international collaboration to increase sample size,[31] we excluded trials with international sites because results were typically not disaggregated by country and it was not possible to break out only participants from U.S. trial sites. Although clinical trials results from other countries may be used for U.S. drug approvals, it can be difficult to assess how representative these trials are of populations in the United States. Guidance for trial sponsors to stratify baseline demographics by country could help increase our understanding of the level of diversity in rare cancer clinical trials and determine to what extent policy can help with diverse recruitment in the United States. In order to further concentrate our focus, we selected FDA-approved treatments that had received orphan drug designation. Although this helped to focus on only those drugs potentially in use by patients and that are most likely to be used for rare diseases, it also limits generalizability to studies that did not result in FDA approval or non-orphan drugs used for rare diseases. Within our selected studies, not all trials defined race and ethnicity consistently and appropriately, which introduced ambiguity where we needed to aggregate

or collapse these demographic factors for analysis. We use FDA Snapshots as a means to compare to a more general clinical trial population; however, it should be noted that this data has limits as well. Notably, the FDA Snapshots data available did not cover the exact period of time covered by our analysis, and Snapshots data reports only on clinical trials leading to the initial approval of a new drug.

Additionally, our use of a case study approach may limit the generalizability of the results to other cancer or diseases. However, a case study approach was needed because demographic data from Clinicaltrials.gov is formatted inconsistently, making it difficult to conduct large-scale, automated data collection. A future iteration of Clinicaltrials.gov could address these issues and make it easier for researchers to collect higher-volume data. Promisingly, the CTTI has taken a step in this direction through their Aggregate Analysis of ClinicalTrials.gov database, which is a relational database of all protocol and results data from clinicatrials.gov.[28] Despite the limited number of rare cancer case studies we used, a strength of this study is the large number of clinical trial participants overall. Because of the smaller number of case studies, we are also able to report results for each rare cancer type in addition to reporting aggregate numbers.

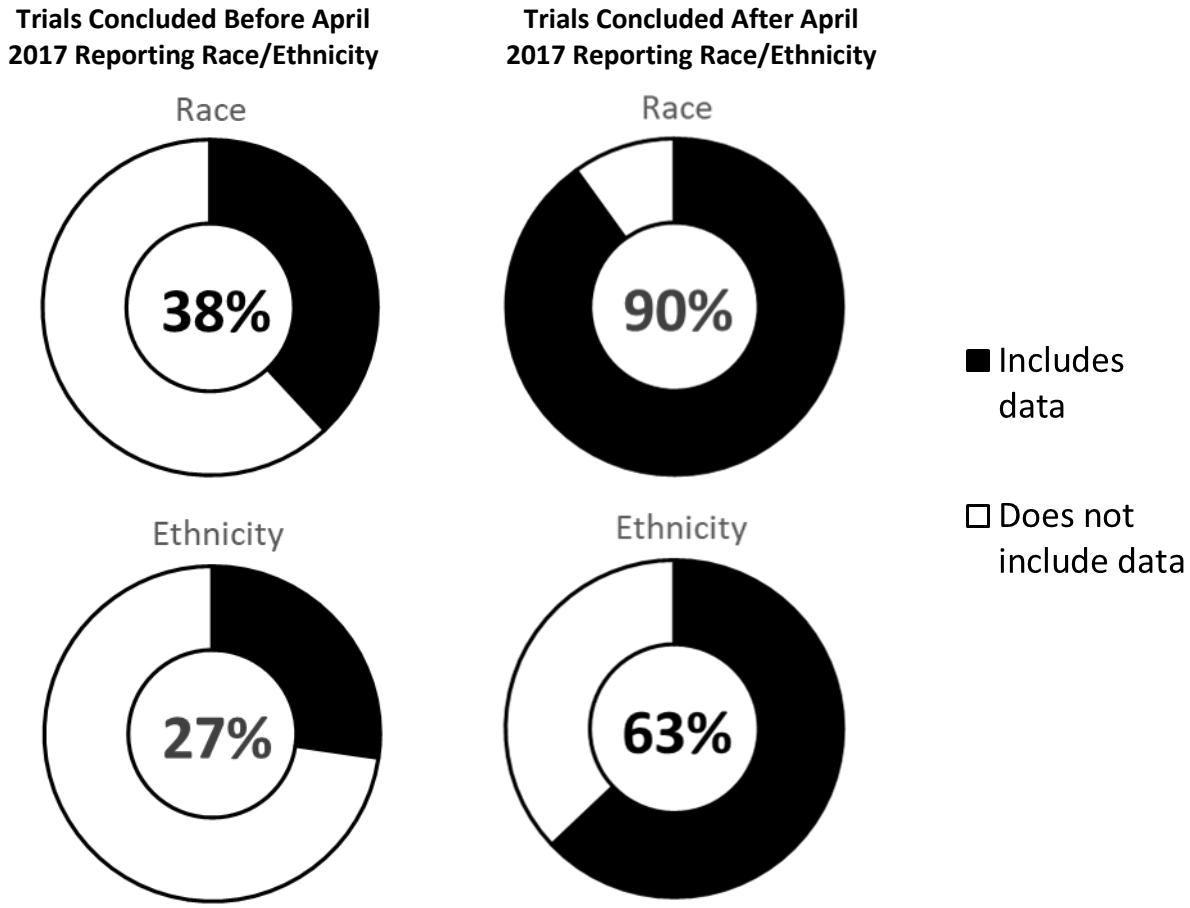
RESULTS

Search Results and Data Completeness

A total of 29,318 participants were represented across 391 clinical trials for eight rare cancers (Table 1). 100% of the trials we analyzed reported sex (male or female) as a variable. Approximately half (55%) of all trials reported race, and 39% reported ethnicity. For clinical trials concluding before April 2017,[vi] 38% reported race and 27% reported ethnicity (Figure 1). For trials concluding in or after April 2017, 90% reported race, though only 63% reported ethnicity. Primary completion dates ranged from 2004 to 2023.

[vi] Reporting rates for these variables increased steeply in April 2017 because FDA began requiring clinical trial sponsors to report race and ethnicity data in Clinicaltrials.gov, if collected.

Figure 1. Percent of Clinical Trials Concluded Before/After April 2017 Reporting Race and Ethnicity

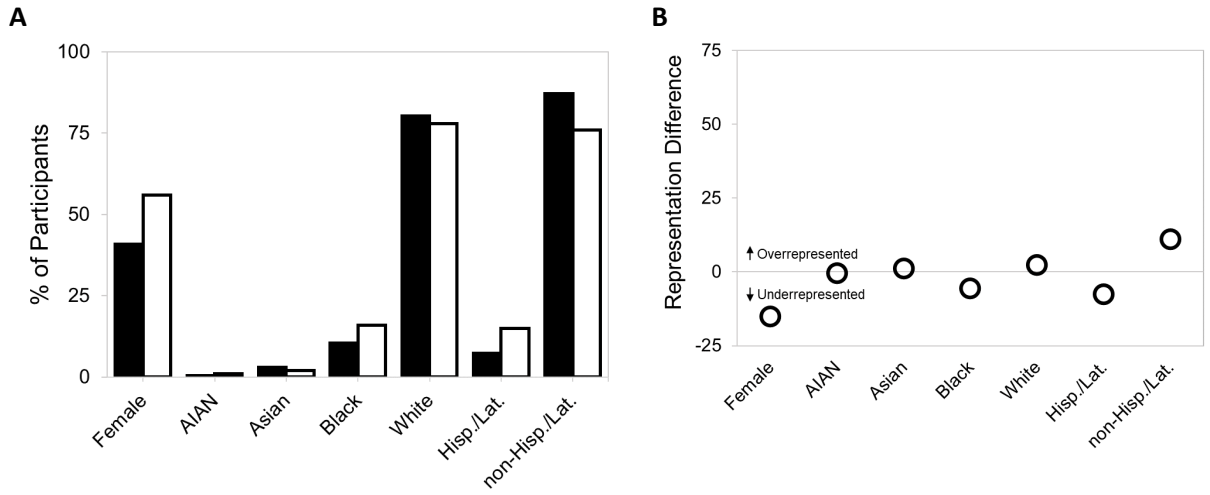


Notes: In clinical trials (Clinicaltrials.gov, all available years) with a primary completion date prior to April 2017, only 38% on race, and 27% reported on ethnicity. For trials that concluded after April 2017, when Clinicaltrials.gov began requiring reporting of race and ethnicity data if collected, 90% of trials reported race, while only 63% reported ethnicity. Of all clinical trials analyzed in this study, 55% include data on race and 39% include data on ethnicity.

Comparison to FDA Snapshots data

We compared these rare disease clinical trial demographics to clinical trial demographics more broadly using FDA Snapshots 2015-2019 aggregate clinical trials data. Figure 2(A) shows a comparison between rare disease data and FDA Snapshots data for sex, race, and ethnicity. Figure 2(B) shows the percent difference between these two data points, with negative numbers reflecting lower representation and positive numbers reflecting higher representation in our rare disease data. Participation rates for females were lower in our set of rare diseases, as were rates for American Indian/Alaska Native, Black, and Hispanic/Latino groups. Asian people, while still participating at below-Census levels, had slightly higher participation rates in our data compared to Snapshots data. Non-Hispanic/Latino participants as a whole were overrepresented among the rare cancer clinical trial participants as compared with the Snapshots data.

Figure 2. Aggregate Participation Statistics for Rare Cancers and All Clinical Trials



Notes: A. Comparison of participation demographics for the rare cancers in our study (black; data collected from Clinicaltrials.gov for all available years) and all clinical trials (white; data collected from FDA Snapshots for 2015-2019). **B.** Representation difference from A for each demographic category. Points represent the difference between the black and white bars in A (e.g., Representation Difference for Female = black bar – white bar for female in plot A), with overrepresentation implying greater participation in all rare cancer clinical trials than in all clinical trials. The y-axis is scaled to match that for Figure 3 below. Abbrev: American Indian/Alaska Native (AIAN), Hispanic or Latino (Hisp./Lat.).

Clinical Trial Participation and Disease Incidence Rate

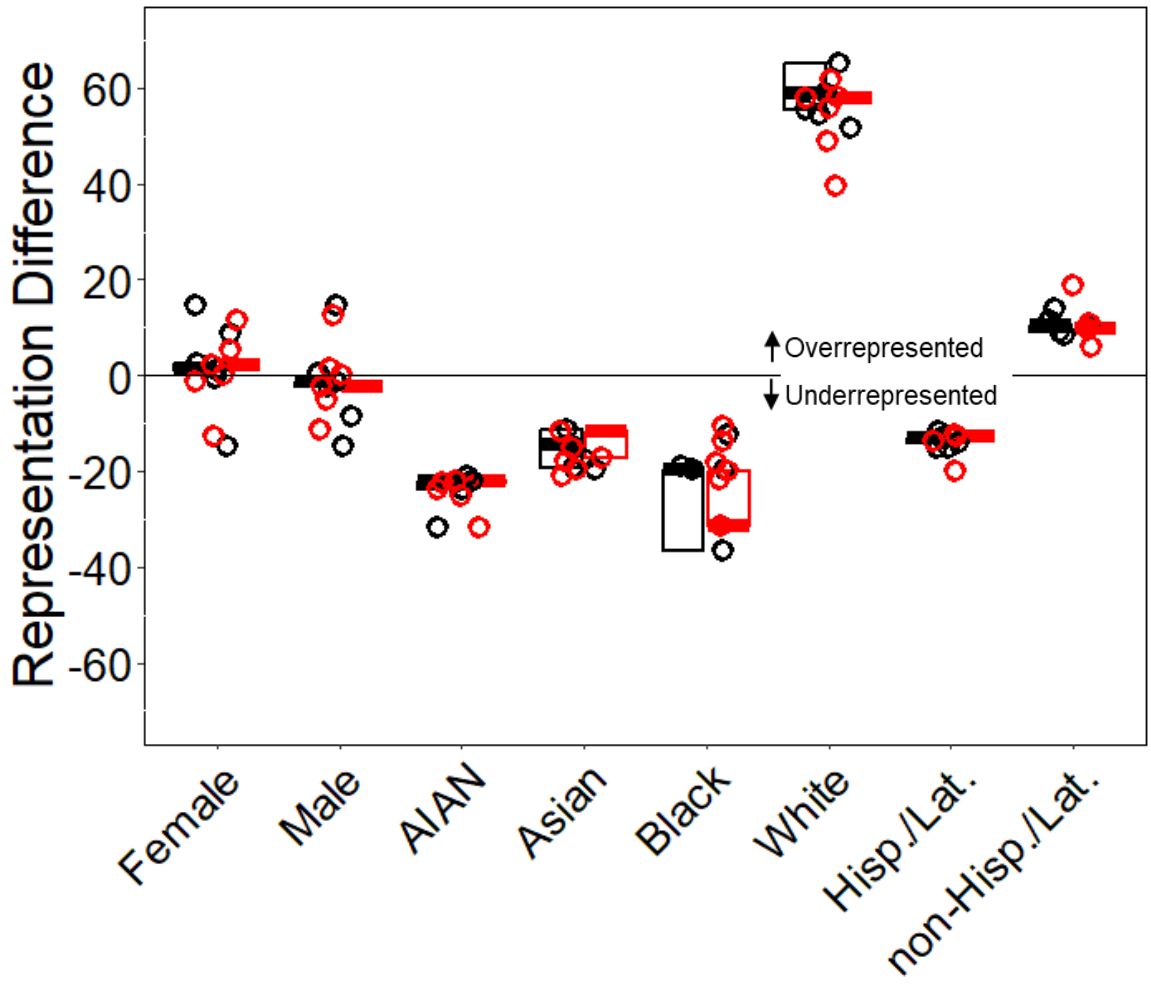
Figure 3 shows the demographic representation difference between the rare disease clinical trials and the incidence of each rare cancer condition within each demographic dimension we measured. There was no consistent deviation between sex representation in rare cancer clinical trials and incidence by sex across conditions, but most race and ethnicity variables showed statistically significant representation differences where statistical tests were possible (Supplemental Table 1). In nearly all of these cases, significant differences in representation manifested as overrepresentation of the White and non-Hispanic/Latino groups and underrepresentation of other racial groups and Hispanic/Latino groups.[vii]

These trends hold for both NIH-funded and non-NIH funded clinical trials (compare red and black points/boxes in Figure 3). Of the 673 rare cancer clinical trials funded through an NCTN RFA,[viii] only 11 were also associated with the rare cancer clinical trials in our dataset. As a result, statistical analysis was only possible for sex and ethnicity demographic variables, and no statistically significant differences were observed between NCTN and non-NCTN clinical trial participant demographics.

[vii] For some conditions, Asian populations were not significantly underrepresented or were slightly overrepresented.

[viii] None of the 128 clinical trials associated with NCORP were associated with our rare cancer clinical trials, but this result was expected given NCORP's focus on different aspects of cancer care than what we use in this study.

Figure 3. Differences in Clinical Trial Demographic Representation and Disease Incidence for Rare Cancers, by Funding Source



Notes: The difference in a demographic group's representation (representation difference) in clinical trials funded by NIH (black) or not funded by NIH (red) and incidence at the level of individual conditions (points). Representation difference is the median share of clinical trial enrollment minus the median share of condition incidence (percent difference between disease incidence and share of clinical trial enrollment), with overrepresentation implying greater participation in clinical trials than would be expected from the incidence data (see Methods). Boxes identify the interquartile range and median (thick line) weighted by the number of clinical trials. Demographic variables may have different numbers of points because the clinical trials within a condition/group do not always report all listed variables (see Supplemental Table 2). Abbrev: American Indian/Alaska Native (AIAN), Hispanic or Latino (Hisp./Lat.). Data for clinical trial enrollment collected from Clinicaltrials.gov for all available years; data for condition incidence collected from SEER for 2000-2019.

DISCUSSION

Already, more than half of all new oncology clinical trials are for rare cancers.[32] As the field of oncology shifts toward precision therapies, more new drugs are likely to target specific subsets of common cancers, and trials for these drugs may face challenges similar to rare cancer clinical trials due to their smaller patient size.[22] Lack of diversity in clinical trials can mean that underrepresented populations have reduced access to experimental medications; it may also mean that clinicians have less information about the efficacy of a treatment in diverse populations. In order to ensure that future oncology treatments meet the needs of the American public and

the end users of each treatment, it is increasingly important to understand the unique challenges involved in achieving diverse participation within these trials.

Although clinical trial reporting of race and ethnicity within our sample improved from 55% to 90% and 39% to 63%, respectively, since the Food and Drug Administration Amendments Act of 2007 became effective in 2017, there is still room for improvement. Ethnicity reporting, in particular, remains low, and we found that race and ethnicity identifiers were not always consistent between studies. Consistent with previous studies that have investigated clinical trials of more common cancers,[15,33] our results show under-representation of all other racial and ethnic populations compared to non-Hispanic and White populations in rare cancer clinical trials. Across all other racial and ethnic groups, clinical trial enrollment in our set of rare disease clinical trials was lower than would be predicted by the incidence rate of each disease. Moreover, our study found that female, AI/AN, Black, and Hispanic groups had lower representation, ranging from less than one (AI/AN) to 15 (female) percentage points difference, for our set of rare cancer clinical trials than for clinical trials more broadly.[ix] In addition, clinical trial participation in our set of rare cancers was lower across non-White racial and ethnic groups than would be expected compared with each group's rare disease incidence rate in the general population. Together, this suggests that representation disparities in clinical trials for rare cancers may be larger than those for oncology clinical trials more generally.

This finding of disparities in rare cancer trials for both NIH- and non-NIH-funded trials is despite efforts by NIH and other agencies to boost research participant diversity. Our findings suggest that outreach alone may be insufficient to address disparities in participation in rare cancer clinical trials, which has important implications for programs' strategies to increase representation in clinical research more broadly. As we previously described, there are sizable barriers in rare cancer clinical trials – for example, later diagnosis,[3] difficulty accruing participants due to low patient numbers,[15] and higher out-of-pocket medical costs[20]. These unique barriers make it challenging to apply approaches to increase diversity that have been successful in other types of trials. Geospatial analysis of this sample of rare cancer clinical trials to assess potential regional differences in participant diversity was beyond the scope of this study but presents another opportunity to investigate health inequities. Similarly, pediatric and US trials paired with international sites were not included in this analysis, highlighting further gaps in the understanding of the extent to which diversity is an issue in rare cancer clinical trials.

Our results indicate that current HHS policies have not fully ameliorated this issue and additional federal engagement may be needed to overcome the unique challenges that face rare disease clinical trial diversity. One avenue to address this may be utilizing the unique coordinating abilities of the Cancer Moonshot. The Cancer Moonshot brings together a broad spectrum of federal stakeholders, each with specific investments and expertise in recruitment, access, and diagnosis, which could be used as leverage to provide additional federal coordination on this issue. [23]

Innovations during the COVID-19 pandemic could also be leveraged and adapted to increase the representation of non -White populations in clinical trials for rare cancers. For example, utilizing telehealth for intake and follow-up could help reduce time and cost burdens for patients. Other strategies, such as community engagement, remote monitoring, digital health, and point-of-care technologies, that were employed to improve the racial diversity of clinical trials for COVID-19 diagnostics, vaccines, and therapeutics, could also be leveraged to improve representation in rare cancer clinical trials.[34] Some of these strategies are already being employed at HHS; for example, NCI has awarded several projects focused on community

[ix] We note that the representation difference for females disappears when comparing clinical trial representation to disease incidence; the cancers in our analysis tend to occur more frequently in males than females (see Supplemental Table 1).

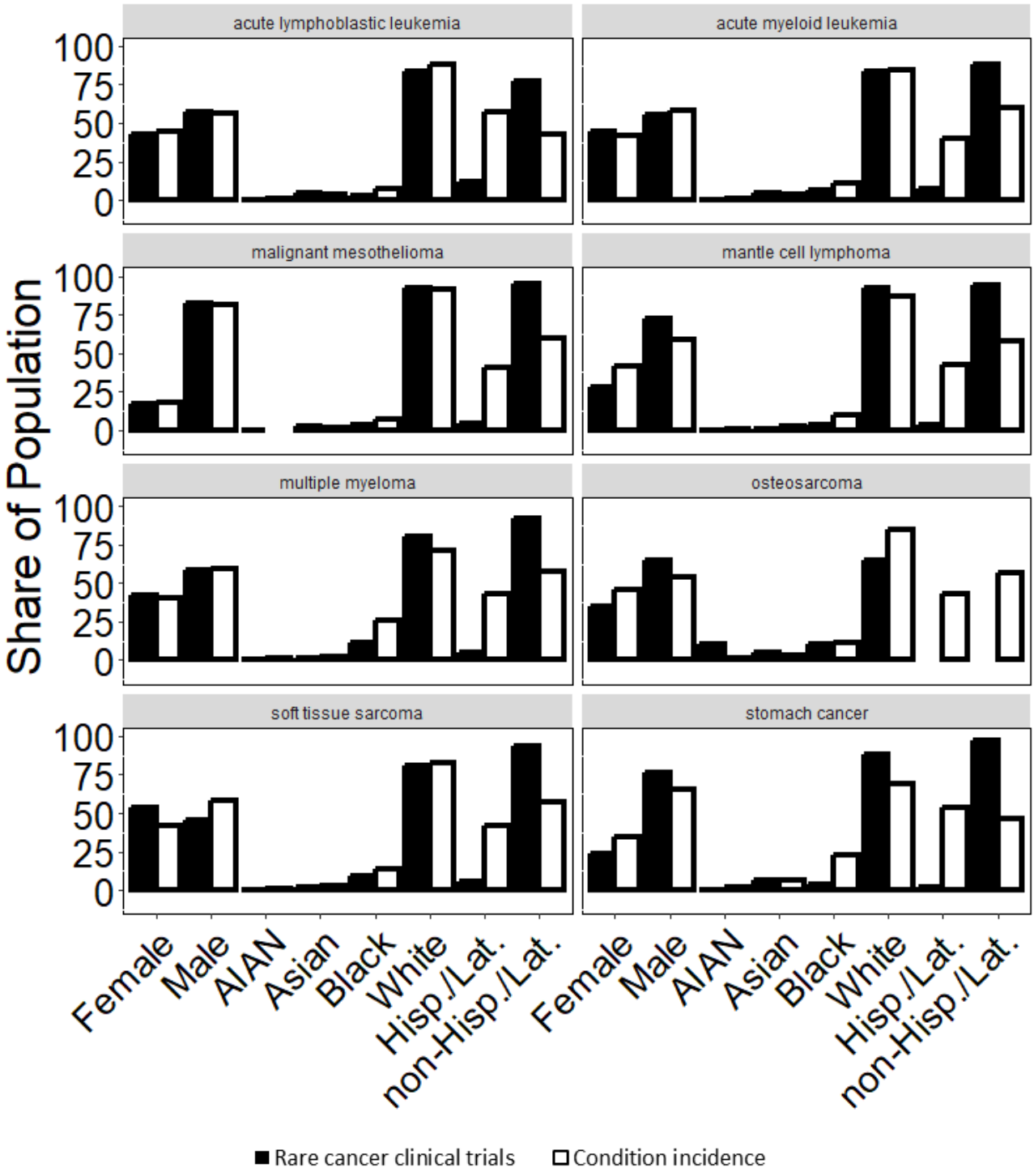
engagement and aligned with the Cancer Moonshot goal of establishing a network for direct patient engagement.[35]

CONCLUSIONS

Rare cancer clinical trials now comprise the majority of new oncology trials,[32] making it critically important to understand the challenges and opportunities surrounding rare cancer clinical trial diversity. This study finds that non-White racial and ethnic groups are underrepresented in clinical trials, to an even greater degree than for clinical trials at large. This information can be used by policymakers to determine research priorities at the intersection of rare cancers and health equity, particularly with respect to initiatives like the Cancer Moonshot, which is well positioned to lead cooperation on this critical issue.

APPENDIX A. INDIVIDUAL CLINICAL TRIAL DEMOGRAPHICS

Supplemental Figure 1. Comparison of rare cancer clinical trial participation against condition incidence



Notes: Grouped bar chart showing the differences between clinical trial participation (Clinicaltrials.gov data, all available years) and condition incidence (SEER*Explorer, 2000-2019) across sex, race, and ethnicity. Bar heights represent the median percentage of a group's participation or incidence from the distribution of clinical trials or years, respectively. Rare cancer clinical trials are in black; condition incidence is in white.

Supplemental Table 1. Disparities in clinical trial participation by condition

Condition	Demographic Variable	Median % Clinical Trial Participants (low, high)	Median % Condition Incidence (low, high)	Median Difference (low, high)	p-value*
Acute Lymphoblastic Leukemia	Female	43 (35 , 50)	44 (44 , 45)	-1 (-5 , 4)	5.12E-02
	Male	57 (50 , 65)	56 (55 , 56)	1 (-4 , 5)	5.12E-02
	Black	3 (0 , 6)	7 (7 , 8)	-4 (-7 , -2)	4.00E-04
	Asian	5 (3 , 7)	3 (3 , 3)	2 (0 , 3)	4.00E-04
	AI/AN	0 (0 , 0)	1 (1 , 1)	-1 (-1 , -1)	1.70E-03
	White	84 (79 , 88)	88 (88 , 88)	-4 (-6 , -1)	3.00E-04
	Hisp./Lat.	12 (10 , 25)	57 (56 , 57)	-45 (-47 , -32)	0.00E+00
	Not Hisp./Lat.	77 (72 , 90)	43 (43 , 44)	34 (28 , 47)	0.00E+00
Acute Myeloid Leukemia	Female	44 (38 , 51)	41 (41 , 42)	3 (1 , 5)	1.06E-01
	Male	56 (49 , 63)	59 (58 , 59)	-3 (-5 , -1)	1.06E-01
	Black	6 (3 , 13)	11 (11 , 11)	-5 (-7 , -1)	6.60E-03
	Asian	4 (1 , 7)	3 (3 , 3)	1 (-1 , 3)	1.59E-02
	AI/AN	0 (0 , 0)	1 (1 , 1)	-1 (-1 , -1)	4.00E-04
	White	84 (76 , 89)	85 (85 , 85)	-1 (-6 , 2)	1.99E-02
	Hisp./Lat.	7 (4 , 10)	40 (40 , 40)	-33 (-35 , -30)	0.00E+00
	Not Hisp./Lat.	88 (77 , 94)	60 (60 , 60)	28 (23 , 31)	0.00E+00
Multiple Myeloma	Female	42 (36 , 47)	41 (40 , 41)	1 (0 , 2)	3.72E-01
	Male	58 (53 , 64)	59 (59 , 60)	-1 (-2 , 0)	3.72E-01
	Black	11 (6 , 20)	25 (25 , 26)	-14 (-16 , -12)	0.00E+00
	Asian	1 (0 , 4)	2 (2 , 2)	-1 (-2 , 0)	2.96E-01
	AI/AN	0 (0 , 0)	1 (1 , 1)	-1 (-1 , -1)	0.00E+00
	White	80 (71 , 88)	71 (71 , 72)	9 (6 , 11)	1.13E-02
	Hisp./Lat.	5 (0 , 9)	43 (42 , 43)	-38 (-39 , -36)	0.00E+00
	Not Hisp./Lat.	92 (86 , 97)	57 (57 , 58)	35 (33 , 37)	0.00E+00
Mantle Cell Lymphoma	Female	28 (23 , 32)	42 (42 , 42)	-14 (-17 , -12)	5.20E-03
	Male	72 (68 , 77)	58 (58 , 58)	14 (12 , 17)	5.20E-03
	Black	3 (2 , 4)	10 (10 , 10)	-7 (-8 , -6)	0.00E+00
	Asian	1 (0 , 4)	3 (3 , 3)	-2 (-3 , 0)	1.00E-04
	AI/AN	0 (0 , 0)	1 (1 , 1)	-1 (-1 , -1)	1.40E-03
	White	92 (86 , 96)	86 (86 , 87)	6 (2 , 8)	0.00E+00
	Hisp./Lat.	3 (2 , 7)	42 (42 , 43)	-39 (-41 , -35)	0.00E+00
	Not Hisp./Lat.	94 (87 , 97)	58 (57 , 58)	36 (29 , 39)	0.00E+00
Soft Tissue Sarcoma	Female	54 (38 , 58)	42 (42 , 42)	12 (2 , 14)	2.00E-04
	Male	46 (42 , 62)	58 (58 , 58)	-12 (-14 , -2)	2.00E-04
	Black	9 (7 , 12)	13 (13 , 14)	-5 (-7 , -1)	1.00E-04
	Asian	2 (2 , 6)	3 (3 , 3)	-1 (-1 , 3)	2.00E-04
	AI/AN	0 (0 , 3)	1 (1 , 1)	-1 (-1 , 2)	4.00E-04
	White	81 (75 , 86)	83 (82 , 83)	-2 (-8 , 3)	2.00E-04
	Hisp./Lat.	5 (5 , 6)	42 (42 , 43)	-37 (-38 -36)	0.00E+00
	Not Hisp./Lat.	93 (87 , 95)	58 (57 58)	36 (29 37)	0.00E+00

Condition	Demographic Variable	Median % Clinical Trial Participants	Median % Condition Incidence (low, high)	Median Difference (low, high)	p-value*
Malignant Mesothelioma	Female	17 (15 , 27)	18 (17 , 21)	-1 (-3 , 9)	4.04E-01
	Male	83 (73 , 85)	82 (79 83)	1 (-9 , 3)	4.04E-01
	Black	3 (3 , 4)	7 (7 7)	-3 (-5 , -2)	0.00E+00
	Asian	3 (1 , 4)	1 (1 2)	1 (-1 , 2)	0.00E+00
	AI/AN	0 (0 , 0)			
	White	92 (88 , 95)	92 (91 , 92)	0 (-4 , 5)	2.92E-01
	Hisp./Lat.	4 (2 , 6)	41 (39 , 41)	-37 (-39 , -33)	0.00E+00
	Not Hisp./Lat.	95 (92 , 98)	59 (59 , 61)	36 (31 , 39)	0.00E+00
Stomach Cancer	Female	23 (16 , 26)	35 (34 , 36)	-11 (-26 , 34)	8.00E-04
	Male	77 (74 , 84)	65 (64 , 66)	11 (-34 , 26)	8.00E-04
	Black	4 (3 , 4)	22 (22 , 23)	-19 (-20 , -17)	0.00E+00
	Asian	6 (4 , 12)	7 (6 , 7)	-1 (-5 , 20)	2.74E-01
	AI/AN	0 (0 , 0)	2 (2 , 2)	-2 (-2 , -1)	0.00E+00
	White	88 (81 , 92)	69 (68 , 70)	19 (2 , 24)	0.00E+00
	Hisp./Lat.	2 (1 , 5)	54 (54 , 55)	-52 (-54 , -46)	0.00E+00
	Not Hisp./Lat.	98 (95 , 99)	46 (45 , 46)	52 (46 , 54)	0.00E+00
Osteosarcoma	Female	35 (35 , 35)	46 (45 , 46)		
	Male	65 (65 , 65)	54 (54 , 55)		
	Black	10 (10 , 10)	11 (10 , 11)		
	Asian	5 (5 , 5)	3 (3 , 3)		
	AI/AN	10 (10 , 10)	1 (1 , 1)		
	White	65 (65 , 65)	85 (85 , 86)		
	Hisp./Lat.		43 (41 , 43)		
	Not Hisp./Lat.		57 (57 , 59)		

Notes: *Significant values are highlighted. **Because only one clinical trial is included for osteosarcoma, we were not able to run statistical tests.

APPENDIX B. REGULATIONS, POLICIES, AND PRACTICES SUPPORTING CLINICAL TRIAL DIVERSITY

Several pieces of legislation address clinical trial participation generally. In response to the under-representation of some U.S. populations in clinical trials, Congress enacted the National Institutes of Health (NIH) Revitalization Act of 1993, which mandated the appropriate inclusion of women and underrepresented racial and ethnic groups in all NIH-funded clinical research.[6] However, the mandate does not extend to industry entities that sponsor the majority of clinical trials for drug approvals.[36] Several analyses in the decades since the NIH Revitalization Act was passed have found that certain racial and ethnic groups remain significantly underrepresented, although reporting of racial, ethnic, and sex variables for NIH-funded trials has improved.[12,37] Legislation has also addressed the role of the Food and Drug Administration (FDA) as a regulator of the clinical research enterprise. Section 801 of the Food and Drug Administration Amendments Act of 2007[7] (effective beginning in 2017) established reporting guidelines for a subset of U.S. phase 2-4 trials in Clinicaltrials.gov. It requires sponsors to report race and ethnicity, when collected, within 12 months of a trial's conclusion.[8] More recently, the Consolidated Appropriations Act of 2023 required clinical trial sponsors to submit a "diversity action plan" that includes trial participant enrollment goals, the rationale behind those goals, and an explanation of how they will be met.[38] HHS is also directed to issue guidance regarding the content and form of the plans.

Departmental policies and guidance documents have also attempted to address inadequate diversity in clinical trials. NIH policy requires that awardees include a plan for inclusion of women and underrepresented groups in their funding proposals.[39] In addition, Phase III clinical trials must provide plans for analysis by sex/gender, race, and ethnicity "unless there is clear evidence" that there is unlikely to be clinically important differences among these groups. NIH also issued policy on sex as a biological variable in 2016, which requires applicants to factor sex into their research design and provide "strong justification… for applications proposing to study only one sex." In 2020, FDA issued guidance on *Enhancing the Diversity of Clinical Trial Populations*, which includes among its recommendations broadening eligibility criteria and recruiting trial participants that reflect the end user demographics of a drug.[40] FDA has also issued guidance to clinical trial sponsors on collection and reporting of demographic data, which recommends use of standard demographic descriptors consistent with the Office of Management and Budget (OMB) categories.[41]

The ODA established economic incentives for industry to develop drugs for rare diseases, such as rare cancers, that have "no reasonable expectation that the cost of developing… will be recovered."[42] As of 2021, there were 552 approved orphan-designated small molecules and biologics on the market.[43] Between 1990 and 2022, 491 novel orphan drugs were approved, and approximately two-thirds of those were designated for a single rare disease.[44]

Policies specific to cancer include the 21st Century Cures Act, which funded the Cancer Moonshot initiative at $1.8 billion over seven years starting in 2017 to accelerate progress in cancer research.[45] In 2022, the Biden Administration announced a new phase of the Cancer Moonshot and identified rare cancers as one of seven priorities of the initiative.[23] Rare cancer-related projects include the My Pediatric and Adult Rare Tumor Network (MyPART), the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium, and the NCI Comprehensive Oncology Network Evaluating Rare Central Nervous System Tumors (NCI-CONNECT). In total, $216 million were allocated to the Cancer Moonshot through NCI for fiscal year 2023.[46]

In addition to the programs mentioned in the main body of the paper, another notable initiative is the Rare Disease Clinical Research Network, a collection of consortia that collects, analyzes, and shares data to help diagnose and treat rare diseases.[47] Congress and HHS, recognizing the importance of clinical trial representation to improving health outcomes, have taken numerous actions to improve representation. A

recent example is the FY23 Omnibus Appropriations Bill, which includes requirements for sponsors to submit diversity plans to FDA prior to receiving FDA authorization to use an investigational drug or device in humans.[38] FDA has also issued guidance on inclusion of underrepresented groups and how demographic data should be reported to better evaluate the participation of underrepresented groups in clinical trials.[40,48-50] NIH plays a crucial role in funding clinical trials and has established policies and guidelines requiring the inclusion of underrepresented groups and women for all NIH-funded research.[39,51,52]

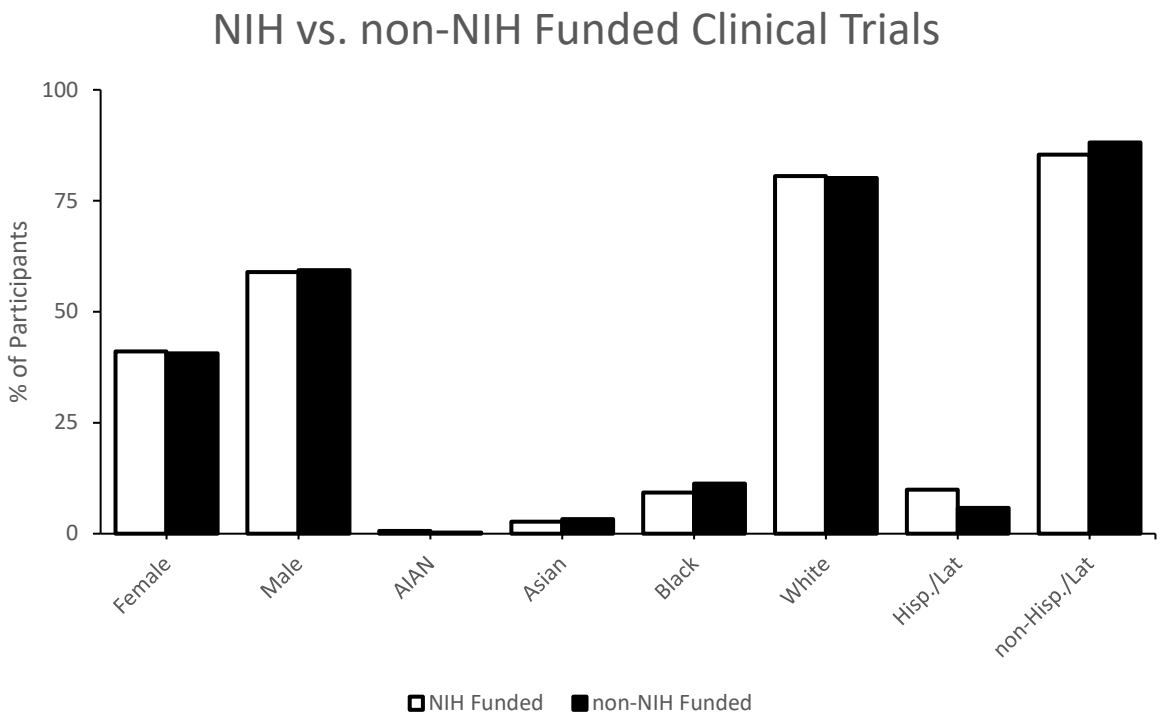
In addition to regulations and policies, HHS Divisions, most prominently NIH, have also launched programs aimed at improving diversity in clinical trials.[53] The National Cancer Institute (NCI) funds several diversity-focused programs, including the NCI Community Oncology Research Program (NCORP), which is aimed at leveraging communities to improve clinical trial representation. NCORP provides 30-35% of the recruits for the NCI Clinical Trial Network (NCTN), which supports a large number of clinical trials investigating oncologic drugs, including those for rare cancers.[29] NCI also leads efforts related to the Cancer Moonshot, which provides additional stimulus to developing new cancer treatments and diagnostics for rare cancers. As part of its Cancer Moonshot efforts, NCI has also proposed an initiative to increase the speed of clinical trials by improving both the rate and representation of participant recruitment.[54]

APPENDIX C. SUMMARY STATISTICS FOR NIH VS. NON-NIH FUNDED CLINICAL TRIALS

We separated the clinical trials in our data set based on whether NIH was listed as a sponsor and calculated percent representation for each demographic group across both of these categories.

There were no large differences for any of our demographic groups based on NIH funding. This result is striking because NIH has made some strong efforts at improving clinical trial diversity as a whole, including through programs like NCORP and NCTN. This lack of a clear difference may point to the need to use different strategies to address underrepresentation in rare cancer clinical trials than the strategies used elsewhere.

Supplemental Figure 2. Comparison of NIH (black) and non-NIH (white) Funded Clinical Trials



Notes: Grouped bar chart showing the difference between clinical trial representation by sex, race, and ethnicity in clinical trials that received NIH funding and those that did not receive NIH funding. NIH funded clinical trials are in black; non-NIH funded clinical trials are in white. Bar heights represent the percent of participants across all clinical trials analyzed for the eight rare cancers in this study. Data collected from Clinicaltrials.gov for all available years.

Supplemental Table 2. Number of Conditions Included for Each Variable for Figure 3

Variable	Number of Conditions represented	
	NIH	non-NIH
Female	6	6
Male	6	6
AIAN	5	5
Asian	5	6
Black	5	6
White	5	6
Hisp./Lat.	5	4
non-Hisp./Lat.	5	4

Notes: In order to be included in Figure 3, each condition within a group (NIH or non-NIH) needed to have at least three clinical trials with at least 10 enrollees each. Some clinical trials did not include all variables, so the number of conditions represented differs between groups/conditions.

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