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ARTICLE

Committing to genomic answers for all kids: Evaluating inequity in genomic research enrollment

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ABSTRACT

Purpose: Persistent inequities in genomic medicine and research contribute to health disparities. This analysis uses a context-specific and equity-focused strategy to evaluate enrollment patterns for Genomic Answers for Kids (GA4K), a large, metropolitan-wide genomic study on children.
Methods: Electronic health records for 2247 GA4K study participants were used to evaluate the distribution of individuals by demographics (race, ethnicity, and payor type) and location (residential address). Addresses were geocoded to produce point density and 3-digit zip code maps showing local and regional enrollment patterns. Health system reports and census data were used to compare participant characteristics with reference populations at different spatial scales.
Results: Racial and ethnic minoritized and populations with low-income were underrepresented in the GA4K study cohort. Geographic variation demonstrates inequity in enrollment and participation among children from historically segregated and socially disadvantaged communities.
Conclusion: Our findings illustrate inequity in enrollment related to both GA4K study design and structural inequalities, which we suspect may exist for similar US-based studies. Our methods provide a scalable framework for continually evaluating and improving study design to ensure equitable participation in and benefits from genomic research and medicine. The use of high-resolution, place-based data represents a novel and practical means of identifying and characterizing inequities and targeting community engagement.

Introduction

The Genomic Answers for Kids (GA4K) study is a large-scale, ongoing initiative with the goal of collecting genomic and health data for 30,000 pediatric patients and their families. The GA4K study is building a data repository to improve diagnostic capabilities for genetic disorders and to facilitate research, including applications of PacBio HiFi long-read genome sequencing.[1] GA4K is led by Children's Mercy Hospital in Kansas City, which lies at the border of Kansas (KS) and Missouri (MO) and is unique in both its scope and structure. Data are continuously made publicly available,

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providing a valuable resource for improving diagnoses and outcomes for children, especially among those with rare disorders. Early efforts contributed to a diagnosis for 13% of previously undiagnosed children after earlier negative genetic testing. Although these results are promising, previous publications and study documentation have not addressed diversity in enrollment or plans for continual evaluation of enrollment patterns over time, potentially limiting the capacity of the GA4K program to benefit all children.

There is growing evidence of racial, ethnic, and socioeconomic inequities in enrollment for genomic medicine and research, with clinical, ethical, and practical implications.[2] Despite calls for greater focus on race and ethnicity in genetics research, it is still uncommon for pediatric genetic research to measure or evaluate racial diversity among participants; essential steps to identifying and eliminating health disparities. Similarly, socioeconomic factors and geographic context are particularly unlikely to be evaluated, potentially excluding socially disadvantaged children and communities from the benefits of genetic research. Furthermore, this potential bias in enrollment can limit future research on the relationship among social needs, environmental exposure, social determinants, and genetics. Current health disparities related to inequity in access to genomic medicine and research are likely to grow if studies do not prioritize equity, inclusion, and justice.[3] In response to these challenges, initiatives such as the Clinical Sequencing Evidence-Generating Research consortium engage underserved populations to understand barriers to accessing genomic medicine or participating in research.[4] Findings from Clinical Sequencing Evidence-Generating Research consortium highlight the nuanced relationship between access to research and access to care, emphasizing the importance of equity in research enrollment and the need for participatory research and engagement. These inequities affect not only the well-being of excluded patients but also the quality and future utility of genomic research databases. Diversity in research is important to the search for DNA variants associated with rare diseases or subtle contributions to complex diseases.[5] For example, pharmacogenomic analyses may have limited value for diverse ancestral populations when genotyping panels emphasize variants prevalent in patients of European descent, given that the frequency of some DNA variants associated with drug metabolism vary by ancestry.[6,7] Similarly, underrepresentation in population-wide databases also complicates analyses because certain variants may initially appear to be ultrarare in a nonheterogeneous cohort but turn out to be common in an ancestral group that was not studied or included in reference databases.[8] Genetics databases, such as gnomAD, that form the cornerstone for medical genetic interpretation are predominated by participants of European ancestry, which creates an artificially exaggerated rare variant burden among underrepresented ancestry groups.[9] This results in a cycle in which less representation leads to less accurate interpretation of results, including increased variants of uncertain significance and lower diagnostic rates, consequently, delaying personalized care.[10]

There are a several reasons why these disparities exist, including structural inequalities in access to genetic services and high-quality health care in general, lack of awareness or bias among referring physicians and health care providers, limited access to study recruitment, ineffective design and content of study materials and educational resources for providers and patients, and valid historic mistrust of health care and research among racial and ethnic minoritized groups.[11] Disparities in access to genetic services not only excludes patients from preventative and diagnostic clinical care but can also affect the ability for genomic studies to recruit diverse patient samples.[12] Complicating matters further is structural bias in the process for funding rare disease research through an advocacy-based model that often overlooks less privileged communities.[13]

In this study, we applied an equity-focused evaluation strategy to the GA4K study to identify disparities in enrollment patterns. Using study participant data and electronic health records (EHR), we investigated enrollment in terms of demographics and location, providing insight into inequitable enrollment and avenues for continual evaluation and improvement.

Materials and Methods

Data

The GA4K study is based in the main hospital of Children's Mercy Kansas City (CMKC), which acts as the primary source of participant recruitment. This facility is in the center of Kansas City, MO (KCMO) near the border between MO and KS. The Total Service Area (TSA) is the primary network area for CMKC, which includes Wyandotte and Johnson counties in Kansas, and Jackson and Clay counties in Missouri. Children residing in this 4-county region within the Kansas City Metropolitan Area account for 69.7% of all encounters at CMKC.[14]

Research and data collection for this study is covered by the Health Equity Analytics and Research Data Repository protocol (Study #1981), which meets the criteria for exempt determination according to the CMKC institutional review board. GA4K uses PhenoTips to store information about enrolled participants in a protected manner.[15] We extracted the medical record number from PhenoTips for all proband participants—affected children—enrolled between June 6, 2011 and December 31, 2020. GA4K probands are registered in the CMKC EHR (Oracle Cerner). Medical record numbers were used to query CMKC EHR data stored in a Business Objects (SAP Corporation) data repository, pulling current records of participant address, demographics, and payor information. Data from related family members were excluded from this study, given inconsistent inclusion in the EHR and limited information about their demographics. Data collection and processing was performed using R and RStudio.[16,17]

Descriptive statistics

The GA4K study participant sample was summarized by race, ethnicity, and payor type. The distribution of participants within census tracts identified as rural areas by the Federal Office of Rural Health Policy[18] and by location within or outside CMKC's TSA counties was also summarized. Population race and ethnicity for the CMKC patient population, TSA, and nation were included for comparison with the GA4K sample. The CMKC patient population demographics were pulled from recent public reporting on diversity and equity within the institution.[19] Population demographics for the general population within the TSA and nationwide were collected from the 2010 US Decennial Census[20] using the TidyCensus package in R.[21]

Geographic analysis

Residential addresses were geocoded using ArcGIS Pro v. 2.1.8 to map study participants. The 3-digit zip code geography (zip3) was used to create a prevalence rate estimate of GA4K participants per the total population in 2010 to investigate the scope of GA4K enrollment throughout MO and KS. The Point Density tool in ArcGIS Pro was used to generate an estimate of the density of participants per square mile to examine the distribution of participants within the TSA. Census tracts were overlaid on the point density map for comparison with 2 demographic and socioeconomic indicators mapped at the census tract geography for the TSA: the percent of the population living below 200% of the national poverty level (population with low income) and the percent of the population identified as a racial and/or ethnic minority (the total population excluding non-Hispanic White individuals).[22] Given the region's historical context, the historic line of racial residential segregation in KCMO, Troost Ave.,[23] was added to each TSA map as a point of reference. Communities west of Troost Ave. are predominantly White and have higher incomes, whereas segregated communities to the east of Troost Ave. are historically Black and have lower incomes.

All maps were generated using the Viridis color palette, which is accessible to colorblind audiences.[24] Low values on the map are associated with darker colors, and higher values are associated with lighter colors. The zip3 map was symbolized using equal interval class breaks, the census tract maps used natural (Jenk's) breaks, and the point density map was symbolized using a continuous color classification.

Results

Descriptive statistics

A total of 2427 proband participants were enrolled in GA4K between 2011 and 2020. Table 1 summarizes cohort demographics, payor type, and areas of residence. Table 1 suggests children of some racial and ethnic minoritized groups are underrepresented in the GA4K cohort relative to the local and CMKC patient population makeup, especially Black or African American children. For example, approximately 14% of both the general population in the TSA and the CMKC patient population identify as Black or African American (non-Hispanic/Latino), whereas only 5% of the GA4K participants identify as Black or African American (non-Hispanic/Latino).

Only 7% of the sample is reported as Hispanic or Latino (any race). In contrast, 16% of the total population in the United States, 9.4% of the TSA, and 11% of patients at CMKC were identified as Hispanic or Latino. No other individual demographic group accounted for more than 2% of the study population. Consequently, White (non-Hispanic/Latino) participants are overrepresented; 77.8% of study participants identified as White (non-Hispanic), substantially higher than the CMKC health system (58.0%), the TSA (70.6%), or the United States overall (63.7%). The EHR indicates that 21.9% of patients were covered by both commercial and Medicaid insurance at some point during their care within the CMKC network and 31.7% of study participants had Medicaid insurance alone. In comparison, CMKC reports that approximately 50% of its patients are Medicaid insured, though it is unknown whether this figure includes patients who have a record of both commercial and Medicaid insurance.[25]

Table 1 also shows the distribution of participants by location in rural census tracts as well as the distribution of participants by county within and outside of the TSA. In terms of rural status, 25.8% of GA4K participants live in rural census tracts, compared with only 19.7% of the general population in the US. Only 1 census tract in the TSA—less than 0.01% of the total population in the TSA—officially qualifies as rural according to the Federal Office of Rural Health Policy, which means the rural participants mostly live outside the TSA. This is reflected in the distribution of GA4K participants by location, where GA4K enrollment was lower in the TSA (44%) relative to the total volume of encounters for patients seen at CMKC (69.3%).

Geographic analysis

Of the 2427 GA4K participants evaluated, 2363 had valid addresses, of which 96.9% were matched in the geocoding process. Unmatched addresses were because of invalid or erroneous address entries. The count of participants by zip3 normalized against 2010 Census population estimates in Figure 1A shows enrollment for participants living in Missouri, Kansas and in limited areas in Nebraska, Iowa, Oklahoma, and Arkansas, though enrollment is concentrated in areas around the TSA.

Figure 1A suggests that, as a percent of the total population by zip3, GA4K enrollment was higher in relatively wealthy, suburban, and rural areas outside of Wyandotte County, KS (WYCO), and KCMO. This is supported by

Table 1 Descriptive statistics for the GA4K participant sample

GA4K Participants, December 2020	$N = 2427$	Demographic Comparison Groups		
Race/Ethnicity[a]		CMKC[b]	TSA	United States
White	1888 (77.8%)	130,438 (58%)	1,127,399 (70.6%)	196,817,552 (63.7%)
Black or African American	122 (5.0%)	31,485 (14%)	232,736 (14.6%)	37,685,848 (12.2%)
Hispanic or Latino	176 (7.3%)	24,738 (11%)	150,117 (9.4%)	50,477,594 (16.3%)
Asian	35 (1.4%)		41,608 (2.6%)	14,465,124 (4.7%)
Native Hawaiian or Pacific Islander	5 (0.2%)		2447 (0.2%)	481,576 (0.2%)
American Indian or Alaska Native	14 (0.6%)		6115 (0.4%)	2,247,098 (0.7%)
Other or multiracial	95 (3.9%)		37,359 (2.3%)	6,570,746 (2.1%)
Unknown	92 (3.8%)	6747 (3%)		
Medical coverage				
Commercial	1028 (42.4%)			
Medicaid	769 (31.7%)			
Medicaid and Commercial	532 (21.9%)			
Other	10 (0.4%)			
Self-Pay	24 (1.0%)			
Unknown	64 (2.6%)			
Location in FORHP eligible census tracts				
Rural	626 (25.8%)		102 (0.01%)	60,758,275 (19.7%)
Urban/suburban	1663 (68.5%)		1,597,679 (99.9%)	247,987,263 (80.3%)
Unknown	138 (5.7%)			
Address within CMKC Total Service Area counties				
Jackson County, MO	400 (16.5%)			
Clay County, MO	167 (6.9%)			
Wyandotte County, KS	60 (2.5%)			
Johnson County, KS	442 (18.2%)			
Outside TSA	1294 (53.3%)			
Unknown	64 (2.6%)			

CMKC, Children's Mercy Kansas City; *FORHP*, Federal Office of Rural Health Policy; *GA4K*, Genomic Answers for Kids; *KS*, Kansas; *MO*, Missouri; *TSA*, Total Service Area.

[a]The category for "Hispanic or Latino" includes participants of any race. All other categories represent race alone and include only non-Hispanic participants.

[b]CMKC reporting on race groups Asian, Native Hawaiian or Pacific Islander, American Indian and Alaska Native, and other patients together in a single category, amounting to 8% of the patient population according to 2021 reporting, whereas multiracial patients account for 6% of the patient population.

Figure 1B, which shows the point density of GA4K participants per square mile in the TSA, demonstrating substantial local variation in enrollment within and between different communities. Patterns show a concentration of participants residing in higher-income, less diverse, and lower-density suburbs of Johnson County, KS and eastern Jackson County, and MO, but relatively low enrollment from historically segregated, socially disadvantaged neighborhoods in the heart of KCMO or WYCO. Patterns of racial residential segregation and uneven development in the TSA are illustrated in the census tract low-income and demographics maps in Figure 1C and D.

Discussion

We used PhenoTips and EHR data from GA4K study participants to evaluate patterns in enrollment in terms of participant characteristics and geographic context. The results show a gap in study participation among socially disadvantaged children and communities, especially among Black or African American children. The methods used in this study, including geographic analysis of participants, present a scalable means of evaluating enrollment for clinical research, including nongenomic studies. Additionally, these methods can be used to inform continual improvement and community engagement strategies that ensure diverse and inclusive research participation over time—place-based health data can be used to identify underserved communities, helping to plan engagement and participatory research in specific neighborhoods, which is important for learning more about possible causes of inequitable recruitment and for improving participation among children and families from these areas.

We compared participant characteristics—race, ethnicity, payor type, and location within the region—to relevant benchmarks, including the CMKC health system, the primary CMKC network area (the TSA), and national estimates. In addition to inequity in enrollment in terms of race and ethnicity, the results suggest a gap in enrollment in terms of both rural status and location within the TSA. Although enrollment is generally concentrated in and around the TSA, as indicated by the regional zip3 map in Figure 1A, a substantial number of participants are in

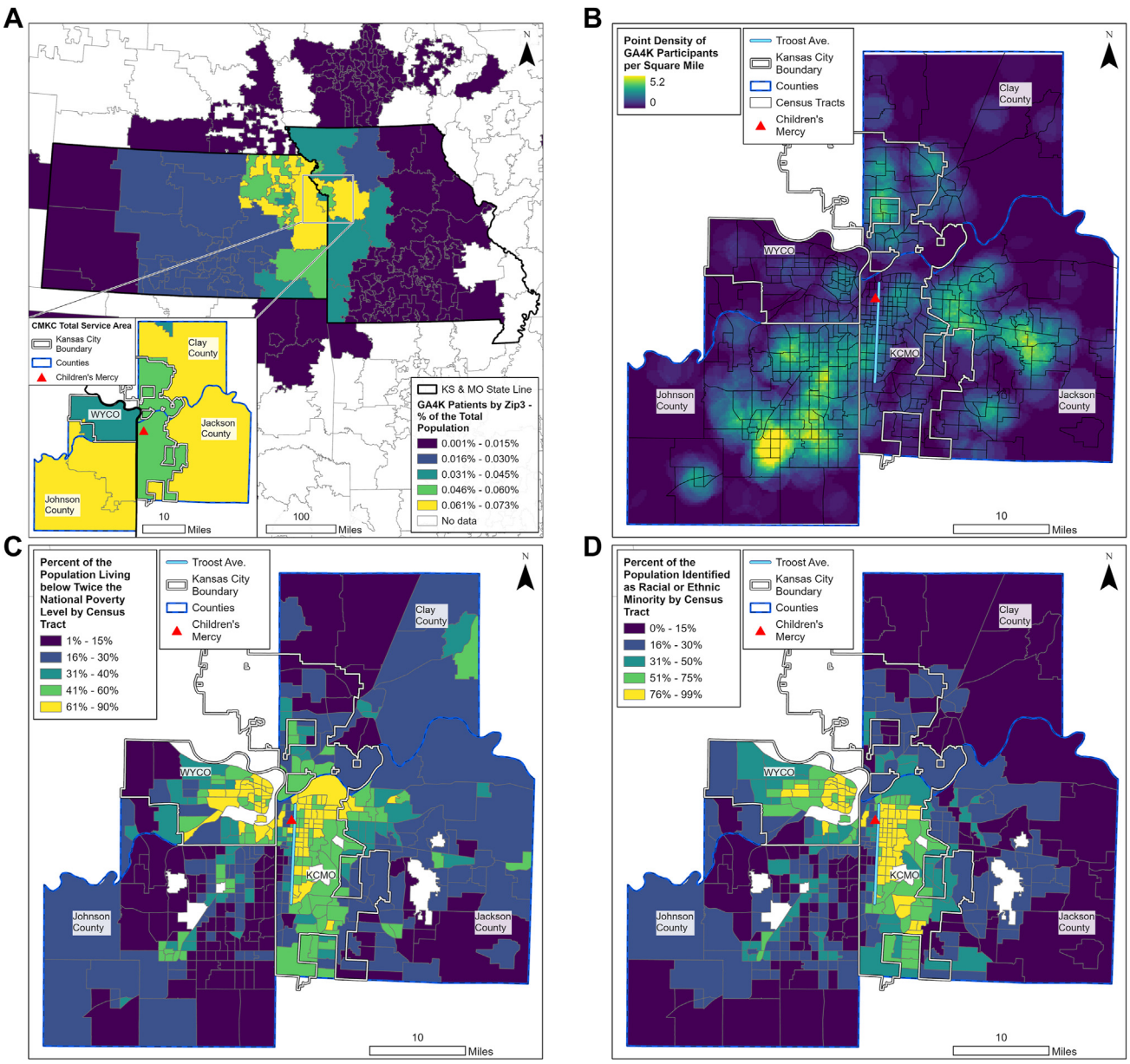

Figure 1 **Geographic analysis results**. A. Rate of GA4K participant enrollment by 3-digit zip code. B. Point density of GA4K participants per square mile. C. Percent living below twice the national poverty level (population with low income) by census tract. D. Percent racial-ethnic minority population by census tract. GA4K, Genomic Answers for Kids; KCMO, Kansas City, Missouri.

southeast KS, east-central KS, southwest MO, and northwest MO. This may be explained by the location of CMKC health system facilities in Wichita and Topeka in KS, and Joplin and St. Joseph in MO. Recruitment and enrollment location, however, are not recorded in PhenoTips.

Although improvements in all areas of metadata tracking for individuals is needed, place-based information provides valuable context for the GA4K study participants and can reveal patterns in enrollment that may signal systemic bias in recruiting patterns. In Kansas City, as in many other US metropolitan areas, the demographic, socioeconomic, and environmental contexts of communities were shaped by historic racial residential segregation, resulting in an inequitable and unjust distribution of health risks and outcomes.[26] These historic patterns of uneven development are reflected in the geographic analysis of GA4K participants. Furthermore, as shown in Figures 1C and D, the primary CMKC facility is located near historically segregated communities east of Troost Ave. in KCMO. Despite this proximity, our analysis shows that enrollment patterns favored children residing further away in relatively advantaged, less diverse areas of the TSA (Figure 1B). These findings are consistent with recent research, which suggests a relationship among referral outcomes, diagnoses, and neighborhood opportunity.[27]

Genomic research initiatives such as GA4K represent important resources for families seeking answers to complex medical conditions. A clear diagnosis can provide not only psychological benefits but also reduce the burden of

unnecessary testing or inappropriate treatments.[2,28] Inequity in enrollment in terms of socioeconomic status represents the exclusion of patients who may benefit from research-based testing and limits the quality of data resources for future research investigating the relationship among health, socioeconomic status, social needs, and genetics.[8] There is a substantial gap between GA4K participants insured exclusively by Medicaid (31.7%) and the reported 50% of all CMKC patients, which may indicate socioeconomically disadvantaged children are underrepresented in the study. However, an additional 21.9% of the cohort has a record of being covered by both Medicaid and commercial insurance, making it difficult to interpret payor status as an indication of socioeconomic status of the GA4K cohort, or to evaluate representativeness in the GA4K cohort compared with major benchmarks. Future research should verify whether CMKC reporting captures individuals with a history of both types of coverage and investigate patterns in changes to payor type over time to better refine an indicator of socioeconomic status for use in equity-focused work.

The summary of GA4K participants by race, ethnicity, payor type, and region illustrate potential inequity in study opportunity and recruitment. Context, however, plays a central role in defining what constitutes equitable recruitment and access to care. Framing GA4K participant enrollment in the context of CMKC's patient population and network area demonstrates a starting point for appropriately monitoring equity in study participation compared with low-resolution, aggregate population estimates at the state and national levels.[29] Furthermore, using address-geocoded data for participants enabled us to aggregate and analyze spatial data at multiple geographies. The zip3 geography is useful for reviewing deidentified geographic trends at the state level,[30] but it is not a standard health geography and can obscure important regional and local variation.[31] In contrast, the point density map was created to investigate the local distribution of participants while maintaining deidentification. Our work demonstrates that large regional studies can use geospatial analysis of participants in the context of community knowledge and demographic patterns to ensure a more representative cohort.[32]

Recruitment location within the CMKC health system may affect diversity in the GA4K cohort. One solution to improve diversity in participation for GA4K may be to recruit from primary care providers, who often serve a relatively diverse patient population. Although recruitment from the primary care setting may help to engage underrepresented and underserved populations in genomic medicine, there are several likely barriers. These include time and resource constraints, limited training on genetic diagnosis, health care provider bias, and other systemic barriers.[33-35] We suggest the GA4K study team actively engage primary health care venues in reaching underserved patients, helping to mitigate barriers and challenges faced by providers.

There are several limitations to this study and opportunities for future research and data collection. GA4K was unable to capture accurate details about referrals to the study, preventing deeper analysis of organizational factors influencing enrollment patterns. This is partly due to many participants being enrolled after serial referrals from different providers, making it difficult to identify the original point of care. Additional research should be done to define efficient, accurate, and appropriate data collection strategies for studies, such as GA4K. This could provide insight into early recruitment and enrollment practices and outcomes and provide reliable alternatives to the EHR for documenting characteristics, such as race and ethnicity. This is particularly important, given evidence that Black or African American patients, for example, may be very willing to participate in research but are approached less often for recruitment.[36]

Future research could expand on this analysis to explore more relevant benchmarks using CMKC EHR data, including demographics and measures of social disadvantage, referring department and subspecialty, and by location within the region. These insights would inform more strategic recruitment and outreach by the GA4K study team. Additional indicators related to equity should be included in future analyses, including non-English speaking participants, who remain underrepresented in pediatric research generally,[37] and participant sex. Investigating the distribution of participants by CMKC facility, possible recruitment location, and residential address could help to inform relevant goals for recruitment from rural populations as well. This will be important to ensure that low-income and racial and ethnic minoritized rural participants are included more frequently in the study. Finally, this study used available data to evaluate equity in recruitment. These methods and results can help to inform interventions, community engagement in underserved neighborhoods, and continual improvement over time. It does not, however, investigate the specific enrollment and recruitment practices of GA4K that may contribute to inequity in participation.

In conclusion, reducing inequities in genomic medicine and related health disparities, as in other areas of health research, will require an antiracist[11] and equity-focused approach[38]; one that embraces and prioritizes cultural awareness and the unique needs of different populations and communities.[39,40] Central to this strategy is evaluation—using available data to identify unique populations within a study, engaging communities in participatory research to understand the problem and establish meaningful outcomes, and monitoring disparities to ensure that research helps to alleviate the burden of inequities rather than contribute to them.[41] Furthermore, engagement with racial and ethnic minoritized and socioeconomically disadvantaged communities is a practical means of creating relationships, building trust, and recruiting and retaining participants from underrepresented communities.[42]

Underrepresentation and inequitable participation among socially disadvantaged populations is common across genomic and clinical research generally. Recognizing this problem, the GA4K team launched this study to actively audit GA4K as a first step in their continual commitment to

equity in enrollment. GA4K is in a strong position to adapt, given the ongoing nature of the study and the findings of this research, to ensure the success of the initiative over time for all children. The methods used in this work are readily extensible to all other clinical research involving recruitment from a large region.

Data Availability

The data sets used to create the data summaries and visualizations in this article are identified, and the subsequent indicators and spatial data created from participant information are also protected. Publicly available demographics and other geographic indicators used in this study are cited in the text and are free to download. The GA4K repository itself is publicly available. More information on how to access GA4K data is available in the earlier GA4K publication (PMID: 35305867).

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Ethics Declaration

Research and data collection for this study is covered by the Health Equity Analytics and Research Data (HEARD) Repository protocol (Study #1981), which meets the criteria for exempt determination according to the CMKC institutional review board.

Conflict of Interest

The authors declare no conflicts of interest.

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