Racial differences in the dermatological manifestations of tuberous sclerosis complex and the potential effects on diagnosis and care

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Abstract

Background: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder of non-malignant tumor growths throughout major organ systems and neurological, neuropsychiatric, renal, and pulmonary co-morbidities. Skin manifestations are readily visible, often develop early in life, and are major features that contribute to TSC diagnosis. Medical photographs of such manifestations are commonly shown as examples from White individuals creating a potential barrier to accurately identifying these features in darker skinned individuals.
Objectives: The aim of this report is to raise awareness of dermatological manifestations associated with TSC, compare their appearance by race, and consider how recognition of these features could impact diagnosis and treatment of TSC.
Design and Methods: We conducted a retrospective chart review at the TSC Center of Excellence (TSCOE) at the Kennedy Krieger Institute, which included all patients in the center from 2009 (inception) through the end of the calendar year 2015 and analyzed data from the TSC Alliance Natural History Database (NHD).
Results: Among TSCOE patients, 50% of Black patients were diagnosed before the age of 1 year, compared with 70% of White patients. NHD data corroborated this trend showing a significant difference with only 38% of Blacks as compared with 50% of Whites were diagnosed at age ≤1 year. A significant difference was observed where White participants had higher odds of having received genetic testing in both data sets. While no differences in the total number of TSC features was observed in either data set, shagreen patches and cephalic fibrous plaques were more frequently recorded in the NHD for Black individuals.
Conclusion: We highlight a disparity in the representation of Black participants within the NHD, TSCOE, and TSC trials, in addition to differences in utilization of molecular testing and topical mechanistic target of rapamycin (mTOR) inhibitor therapy between Black and White individuals. We show a trend toward later diagnosis age in Black individuals. These differences between races warrant further study across additional clinical sites and other minority groups.

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Plain Language Summary

Differences in skin manifestations between races in individuals with tuberous sclerosis complex and the potential effects of these differences on diagnosis and care

Background: To our knowledge, tuberous sclerosis complex (TSC) does not affect races at different frequencies; however, observations in clinical settings anecdotally, and results from research studies, suggest a disparity in the representation and diagnosis of

Black individuals with TSC. Historically, it has been noted that TSC facial features, such as angiofibromas, present differently in individuals with darker skin tones and are often misdiagnosed leading to delays in TSC diagnosis and treatment.

Objectives: The aim of this publication is to identify differences in TSC skin features between Black and White individuals to raise awareness in the clinics and community. In addition, we provide insight into how these differences can affect the timing of TSC diagnosis and subsequent treatment regimens. We aim to highlight these potential disparities to ensure improved timing in diagnosis and treatment regimens for all affected by TSC in the future.

Design and Methods: Differences between Black and White individuals with TSC were observed looking at historical medical data collected at a TSC Center of Excellence (TSCOE) on all patients seen in the center from 2009 through the end of 2015 and in the TSC Alliance Natural History Database (NHD) that has been collecting clinical data on individuals with TSC since 2006.

Results: We observed that Black individuals are less likely to be diagnosed at ≤1 year of age as compared with White individuals within the NHD. Data from the TSCOE support these findings but were not statistically significant. We observed a difference in NHD participation with only 150 Black individuals participating, representing 6% of total NHD participants. Our data indicate a difference between Black and White individuals both in the TSCOE and NHD showing that Black individuals are less likely to receive genetic testing, utilize topical mTOR therapy, and participate in TSC clinical trials.

Conclusion: Given the observed trends, outreach and education to clinicians and other healthcare providers is needed to inform of these differences. Given that skin manifestations play an essential role in early recognition of TSC and timely referral to TSC specialists, we hope these data lead to improvement in the recognition of TSC in darker skinned individuals at earlier ages, thus improving clinical outcomes associated with TSC manifestations by optimizing treatment early in life.

Introduction

Tuberous sclerosis complex (TSC) is a neurocutaneous, genetic condition diagnosed in approximately 1 in 6000 live births that results from an autosomal dominant or spontaneous mutation in either the *TSC1* or *TSC2* genes.[1,2] Clinical diagnosis of TSC is based on the presence of a specific combination of major and minor features, of which four major and one minor are dermatological manifestations (Table 1).[3] Skin manifestations are readily visible and often develop early in life.[4] Hypomelanotic macules, also called ash-leaf spots, are the most common dermatologic feature of TSC in patients under the age of 1 year (Figure 1).[5] A complete skin examination utilizing a wood's lamp is recommended in those with lighter skin complexions to visualize these findings. They are often present on the limbs, trunk, and buttocks, but can be identified throughout the body. Later in childhood, facial angiofibromas, also referred as adenoma sebaceum, are a hallmark feature of TSC (Figure 2).[6] Other common skin lesions in TSC include ungual fibromas, shagreen patches, and cephalic fibrous plaques.[4] Examples of hypomelanotic macules, facial angiofibromas, cephalic fibrous plaques, and shagreen patches in both Black and White individuals are shown in Figures 1–4, respectively. Dermatological features of TSC are typically non-life threatening and are less severe than other TSC features; however, early recognition in combination with other features can help expedite a clinical diagnosis to promote early intervention strategies that are shown to improve cognitive outcomes.[3,7] In some cases, the dermatological examination alone is sufficient to establish a definite diagnosis of TSC.[8]

Table 1. Clinical diagnostic criteria for tuberous sclerosis complex [reprinted under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND) from the study by Northrup *et al.*].[3]

| Major criteria	Minor criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	'Confetti' skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM[a]	
Angiomyolipomas (≥2)[a]	

LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.
Definite TSC: two major features or one major feature with two minor features. Possible TSC: either one major feature or more than two minor features. Genetic diagnosis: A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production). Some variants compatible with protein production (e.g. some missense changes) are well-established as disease-causing; other variant types should be considered with caution.
[a]A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

Furthermore, cutaneous manifestations are often the only visual manifestation of TSC for individuals with mild to moderate phenotypes of TSC. These features can negatively impact one's body image, self-acceptance, and quality of life.[9]

Facial angiofibromas occur in up to 75% of patients and become more prominent with age.[3] Facial angiofibromas often appear erythematous, raised, and in a butterfly-shaped appearance across the nasolabial folds; however, in Black individuals, they are typically hyperpigmented (Figure 2). In Black individuals, facial angiofibromas may be confused for seborrheic keratoses or other benign epidermal growths or even other neurocutaneous disorders.[10] To date, medical photographs of facial angiofibromas and other TSC skin manifestations are commonly shown as examples from White or other individuals with lighter skin tones, creating a barrier for clinicians to accurately compare in Black or other individuals with darker skin tones. There is an evident lack of published resources for individuals with darker skin. Recent case studies of Black individuals emphasize the importance of early diagnosis, wherein a late diagnosis at the age of 37 in a Black patient led to complications including hemodialysis and a complete bilateral nephrectomy and complications involving the central nervous, renal, and respiratory systems in a 24-year-old, respectively.[11,12]

Recognizing that skin manifestations of TSC may have implications for diagnosis and treatment, this study seeks to provide examples of how these manifestations present by comparing Black and White individuals from a TSC Center of Excellence (TSCOE) and from participants in the TSC Alliance Natural History Database (NHD) on TSC.
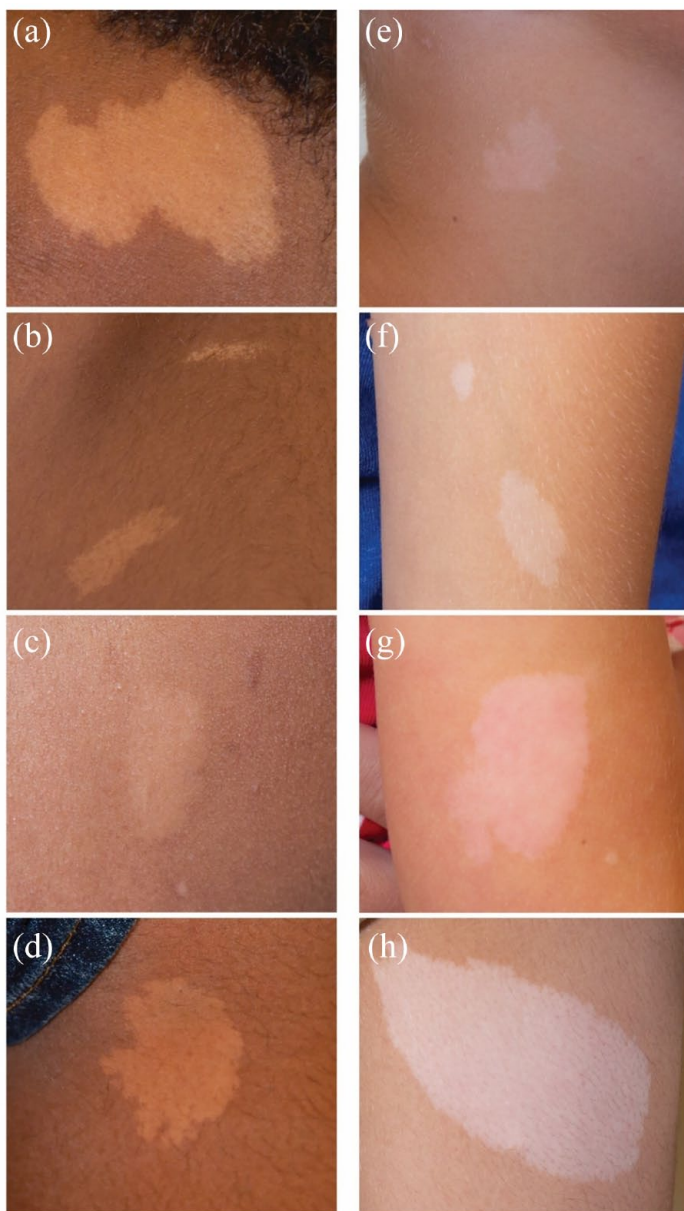
Figure 1. Hypomelanotic macules in Black and White individuals with TSC. (a–d) Black individuals with hypomelanotic macules. (a) Age 11 male, on forehead. (b) Age 11 male, on back. (c) Age 14 male, on cheek. (d) Age 14 male, on leg. (e–h) White individuals with hypomelanotic macules. (e) Age 8 male, on neck. (f) Age 7 female, on arm. (g) Age 4 female, on arm. (h) Age 15 male, on leg.

Methods

Study design and ethics approval

We conducted a retrospective chart review of patients from the TSCOE at the Kennedy Krieger Institute to extract the age at diagnosis of TSC by a medical professional, the number and type of clinical features of TSC, and the individual's race. The Johns Hopkins Institutional Review Board (IRB) approved protocol NA 00076475 Interdisciplinary Protocol for Patients with TSC allowing use of de-identified data from the Kennedy Krieger Institute clinical database for research purposes. Data on skin manifestations, race, genetic testing, and topical treatments from the TSC Alliance NHD were obtained with permission from the NHD and Biosample Repository Steering Committee. The TSC Alliance has IRB approval from Ethical and Independent Review Services for the NHD study (Protocol 15039-08) that permits use of de-identified clinical data for TSC research. STROBE guidelines were followed when preparing the article.

Settings

Data were obtained *via* retrospective chart review from the TSCOE and data exports from the TSC Alliance NHD. The Tuberous Sclerosis Clinic at Kennedy Krieger Institute is dedicated specifically to the care of individuals affected by TSC and their families. The TSC NHD was implemented in 2006 and captures clinical data to document the impact of the disease on a person's health over his or her lifetime. More than 2000 people with TSC are enrolled in the project among 18 US-based clinical sites and the TSC Alliance site. The TSC Alliance provides funding to participating clinics to perform data entry, monitors the integrity of the database, and makes data available to investigators to answer specific research questions and identify potential participants for clinical trials and studies. The TSC Alliance utilizes Studytrax as their platform to store and monitor natural history data. Race was obtained from clinic sites *via* recorded race in the medical record, self-report by participant or participant's family, or provider observation of skin color. Race obtained from participants consented *via* the TSC Alliance was obtained *via* self-report by participant or participant's family or recorded race in the medical record. Patient or parental consent *via* a signed photo release was obtained to use images collected from individuals with TSC. All images were captured by the same photographer and camera at a TSC Alliance event.

Participants and data sources

Data from the TSCOE at the Kennedy Krieger Institute from 2009 to 2015 were utilized in these

analyses. For the TSCOE cohort, patients with a confirmed clinical diagnosis of TSC and a recorded age at diagnosis were utilized for analysis. Diagnostic criteria can be found in Table 1. Out of 41 patients, 18 were Black, 21 were White, and 2 were classified as other for race (1 Asian, 1 Middle Eastern). Given the limited number of participants in the other category, we restricted our analyses to individuals who were recorded as Black or White. Data collected since 2006 were utilized in an export from the NHD on January 5, 2022. For all NHD data analyses, blank entries were excluded. For the NHD, data from 1966 participants with a confirmed clinical diagnosis of TSC and race recorded as either Black or White out of a total of 2375 participants were utilized in this analysis. Where relevant, the total number of participants used in each comparison is noted. In the NHD, 77% (1,816) of total participants were White and 6% (150) were Black. At the time of analysis, the NHD was underrepresented for Black participants and overrepresented for White individuals as compared with US Census calculations.[13] We selected Black and White participants with a recorded TSC diagnosis date in the NHD (*n* = 1487; 107 Black and 1380 White) for further analyses. Study size was not previously determined using power analysis but was limited by availability of data within the clinic cohort and the NHD.

Bias

Selection bias was addressed by incorporating analysis of the TSC Alliance NHD to our research question as we recognize that analysis of a single clinic cohort introduces potential bias for

Figure 2. Facial angiofibromas in Black and White individuals with TSC. (a–d) Black individuals with facial angiofibromas, ages 11, 14, 16, and 28, respectively. (e–h) White individuals with facial angiofibromas, ages 13, 37, 39, and 28, respectively.
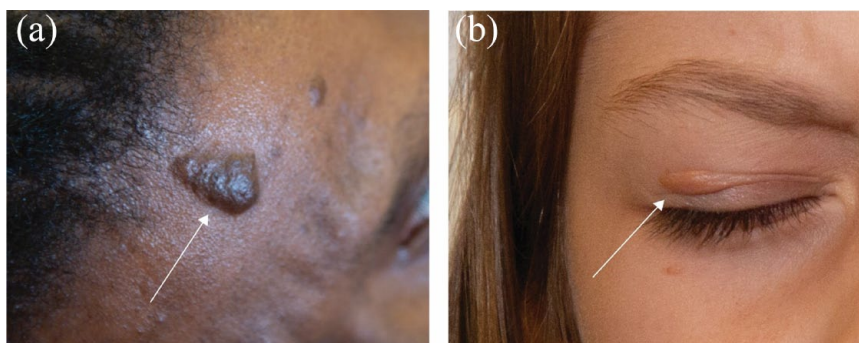
Figure 3. Cephalic fibrous plaques (CFPs) in Black and White individuals with TSC. (a) A 28-year-old Black female and (b) a 7-year-old White female with cephalic fibrous plaques (CFPs) on the forehead and eyelid, respectively. White arrows indicate location of CFPs.
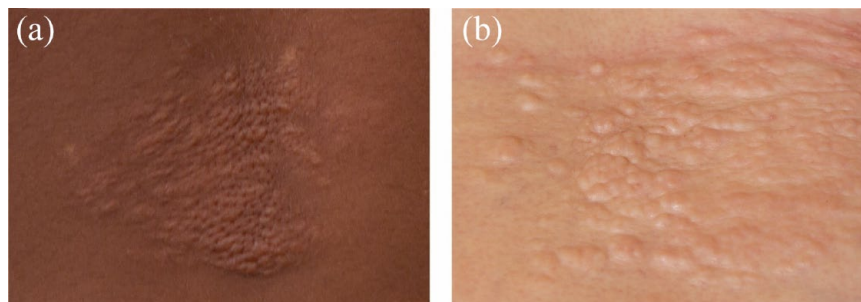
Figure 4. Shagreen patches in a Black and White individual with TSC. (a) An 11-year-old Black male with a shagreen patch on the back and (b) a 37-year-old White female with a shagreen patch on the back.

geographic location, socioeconomic status, or other variables. We did observe that the number of Black participants in the NHD was underrepresented as compared with the US census; however, due to the retrospective study design, we were limited to enrolled participants at the time of data export.

Statistical analyses

For TSCOE data, statistical analyses were conducted using GraphPad Prism 9 software and reviewed *via* consultation with the Biostatistics, Epidemiology, and Research Design Unit at The University of Tennessee Health Science Center. No power analyses were conducted, and eligibility included any TSC patient at the TSCOE from 2009 to 2015 with race identified as Black or White. A Fisher's exact test for the hypotheses of independence between the variables of race and age at diagnosis, race and number of features identified, race and molecular testing, and race and identification of specific features (e.g. facial angiofibromas, hypopigmented macules, and cephalic plaques) was conducted. We further fitted a logistic regression model in which the outcome was being diagnosed at the age of $\leqslant 1$ year *versus* age of $\geqslant 2$ years, and the predictor variables were sex, race, and number of features identified.

For NHD data, statistical analyses were conducted using GraphPad Prism 9 software and reviewed *via* consultation with an independent statistical consultant. No power analyses were conducted, and the full NHD cohort was considered (outlined in Figure 5). Specific tests used are noted in corresponding figure legends. For all NHD data analyses, blank entries were excluded, and the number of records included in each analysis is noted in the figure legends. A Fisher's exact test for the

hypotheses of independence between the variables of race and presence of specific skin manifestations, molecular testing, treatment between races, participation in clinical trials, and age at diagnosis when comparing groups at age $\leqslant 1$ year with age $\geqslant 2$ years. Unpaired *t*-tests with Welch's correction were utilized to compare average age at diagnosis and count of TSC features between races.

Results

Participants and descriptive data

The study population from the TSCOE included 41 individuals with a median age of 13 years at time of the study with 44% (18 out of 41) identified as Black and 56% were White (23 out of 44; Table 2). The distribution of age at diagnosis by race in the TSCOE cohort is provided in Table 3. The process of selecting NHD participant records for analysis is shown in Figure 5.

Main results

A trend was observed showing that Black patients were less likely to be diagnosed at an earlier age, with 50% (9 out of 18) diagnosed at $\leqslant 1$ year compared with 70% (16 out of 23) of White patients in the TSCOE cohort, although this finding was not statistically significant ($p = 0.33$). We did not have recorded diagnosis dates specific to the dermatological manifestations to assess which features may have been present in the group diagnosed with TSC at age $\leqslant 1$ year *versus* those diagnosed $\geqslant 2$ years to support the early diagnosis. The distribution of the number of major TSC features by race at TSCOE is shown in Table 4. A Fisher's exact test for independence found no evidence of an association between the number of major TSC features and race ($p = 0.76$). The tests for
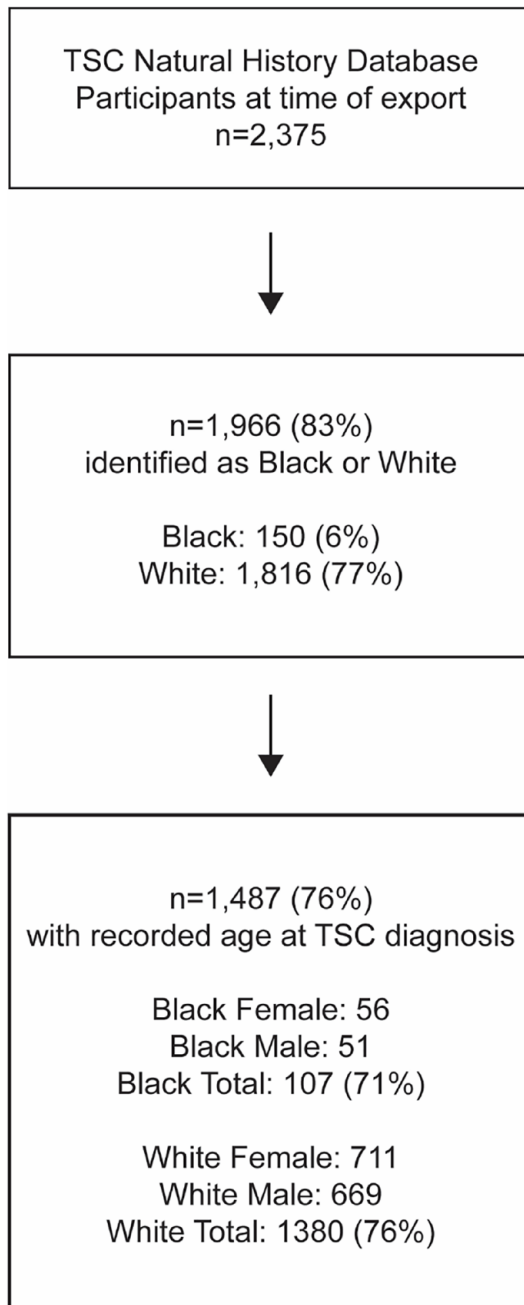
Figure 5. TSC participant selection from the NHD. We restricted our analyses to records of Black and White individuals in the NHD. Analyses not requiring an age at TSC diagnosis utilized Box 2 (*n* = 1966) as the data source, whereas analyses focused on age at diagnosis utilized Box 3 (*n* = 1487) as the data source. Total counts for each analysis are located in the respective figure legends.

independence between race and the presence of each of three specific dermatological features – facial angiofibromas, hypopigmented macules, and cephalic fibrous plaques – indicated that race was

independent of whether these features were identified ($p > 0.05$ for all; Supplementary Figure 1).

A multiple logistic regression model in which the outcome was age at diagnosis (≤1 year *versus* ≥2 years) was fitted for the TSCOE cohort. For this model, the predictor variables were race, sex, and number of major features. The results from this model indicate that White individuals had higher odds of being diagnosed by age 1 year; however, this association was non-significant ($p = 0.10$; Table 5). In addition, we found that a higher number of major features was associated with a significantly increased probability of having been diagnosed earlier: with each increase of one feature, the probability of having been diagnosed at ≤1 year was increased by a factor of ~1.5 ($p = 0.045$).

For participants that had a recorded TSC diagnosis date in the NHD ($n = 107$ Black, 1380 White), the average age of TSC diagnosis was similar between White (5.7 years) and Black (5.4 years) individuals (Figure 6). To further compare with the cohort data from the TSCOE, we investigated the proportion of Black and White individuals diagnosed at age ≤1 year *versus* ≥2 years in the NHD. We found a statistically significant difference ($p = 0.03$) with 38% of Black participants diagnosed at age ≤1 year compared with 50% of White participants (Figure 7). Furthermore, broadly comparing all Black and White individuals in the NHD, we found no evidence that the number of major or minor TSC features differed between the groups, with both Black and White participants having on average five major and less than one minor features (Figure 8). Looking specifically at TSC dermatological manifestations, we assessed the number of participants with a record of having facial angiofibromas in the NHD. Similar proportions of Black (64%) and White (69%) individuals had facial angiofibromas, and a similar diagnosis age was observed with the average age at facial angiofibroma diagnosis as 11.3 years for Black and 10.7 years for White participants (Figure 9). Further analysis showed that Black participants had a significantly increased probability of having shagreen patches ($p < 0.0001$) and cephalic fibrous plaques ($p = 0.014$) as compared with White participants in the NHD (Figure 10). No significant differences were observed for the hypomelanotic macule, ungual fibroma, nor confetti lesion manifestations (Supplementary Table 1). We did not have data on the ungual fibroma nor confetti lesion manifestations from the TSCOE cohort to compare these features further.

Table 2. Patient demographics and characteristics at TSCOE.

Variable	N = 41
Age at data capture in years, median (IQR)	13 (6.5–30)
Sex, *n* (%)	
Female	17 (42)
Male	24 (58)
Race, *n* (%)	
Black	18 (44)
White	23 (56)

IQR, interquartile range; TSC, tuberous sclerosis complex; TSCOE, TSC Center of Excellence.

Table 3. Distribution of age at diagnosis in TSCOE by race.

Age at diagnosis	Black, *n* (%)	White, *n* (%)	Total, *n* (%)
≤1 year	9 (50)	16 (70)	25 (61)
≥2 years	9 (50)	7 (30)	16 (39)
Total	18 (100)	23 (100)	41 (100)

TSC, tuberous sclerosis complex; TSCOE, TSC Center of Excellence.

A Fisher's exact test yielded a non-significant difference ($p = 0.33$) in the age of diagnosis between Black and White individuals seen in this cohort at the TSCOE.

Table 4. Distribution of number of major features by race in TSCOE cohort.

Number of major features	Black, *n* (%)	White, *n* (%)	Total, *n* (%)
1–4	9 (50)	13 (57)	22 (54)
5–8	9 (50)	10 (43)	19 (46)
Total	18 (100)	23 (100)	41 (100)

TSC, tuberous sclerosis complex; TSCOE, TSC Center of Excellence.
A Fisher's exact test yielded a non-significant difference ($p = 0.76$) in the number of major TSC features between Black and White individuals seen in this cohort at the TSCOE.

Overall, these findings highlight potential differences in the presentation of dermatological symptoms in TSC between Black and White individuals that warrants further exploration clinically.

We further investigated the use of a topical mechanistic target of rapamycin inhibitor (mTORi) for facial angiofibromas in the NHD cohort. Analysis

showed a greater percentage of White participants utilized a topical mTORi as compared with Black participants (26% *versus* 13%, respectively; Figure 11). A potential variable within this data set was the lack of FDA approval for the topical mTORi rapamycin to treat facial angiofibroma at the time of data entry in the NHD. Another potential contributing variable was participation in clinical trials for mTORi among NHD participants. To address this, we analyzed NHD participants enrolled in the 'Topical Rapamycin to Erase Angiofibromas in TSC (Treatment)' (NCT01526356) clinical trial and observed that 43 White individuals and only 2 Black individuals in the NHD were recorded as participants. Since this trial first published results in 2018, it is possible that there was reluctance to utilize topical mTORi prior to the publication of trial results.[14] To further investigate, we analyzed use of topical mTORi between Black and White participants diagnosed with facial angiofibromas in year 2018 or later. Unfortunately, we only found 1 Black participant with a recorded facial angiofibroma diagnosis date ≥ 2018 *versus* 27 White individuals. Of these, 41% (11 out of 27) of White participants and the single Black participant were recorded to be taking a topical mTORi. Further analysis is needed to assess prescription patterns of topical mTORi in Black and White individuals across multiple TSC clinic sites, especially given the recent FDA approval of Hyftor sirolimus topical gel in 2022.[15]

Although systemic mTORi therapies are not currently approved for facial angiofibromas, reduction in the appearance of facial angiofibromas has been noted in patients taking them for other major features of TSC.[16] We assessed the use of systemic mTORi across Black and White participants with a facial angiofibroma diagnosis and found 8 Black participants (8 out of 92, 9%) and 86 White individuals (86 out of 1166, 7%) that were prescribed a systemic mTORi for SEGA (subependymal giant cell astrocytomas), and 9 Black participants (9 out of 92, 10%) and 107 White participants (107 out of 1166, 9%) treated with a systemic mTORi for renal angiomyolipoma, suggesting the disparity we observed in mTORi utilization was specific to topical mTORi use. Further analysis is needed to investigate this finding in a clinical setting. Given the small number of recorded Black participants in the topical rapamycin trial, we further investigated research participation recorded in the NHD. Participation of NHD participants is recorded for 17 distinct clinical trials (Supplementary Table 2). While 217 (217 out of

Table 5. Multiple logistic regression model for being diagnosed before or at age 1 year *versus* after age 1 year in TSCOE cohort.

Predictor	Odds ratio	*p* value	95% confidence interval
Sex (male as reference)	0.45	0.29	0.09029–1.872
Race (White as reference)	3.5	0.10	0.8519–17.10
Number of major features (continuous variable)	1.5	0.05*	1.038–2.285

TSC, tuberous sclerosis complex; TSCOE, TSC Center of Excellence.
A multiple logistic regression model in which the outcome was age at diagnosis was fitted with the predictor variables of race, sex, and number of major TSC features. The association between sex was not significant. The association between race showed a non-significant trend that White individuals had higher odds of being diagnosed by age 1 year. The number of TSC features did show a significant association, wherein an increased number of features was associated with an increased likelihood of diagnosis at age at ≤1 year.
*denotes statistical significance

1816, 11.9%) White individuals had participated in at least one clinical trial recorded in the NHD, only 8 (8 out of 150, 5.3%) of Black individuals had, illustrating a significant difference in clinical trial participation (*p* = 0.01; Table 6). We observed a similar trend looking at participation in the TSC Alliance's Biosample Repository project, wherein only 22 Black (22 out of 150, 14.7%) *versus* 516 White (516 out of 1816, 28.4%) individuals were participating at the time of analysis. This result could be due to lack of representation in the NHD as it is a research study itself or for other reasons as further highlighted in the discussion.

Since genetic testing is one route of obtaining a TSC diagnosis, we further investigated the frequency of molecular testing for the *TSC1* or *TSC2* genes and found a significant difference (*p* = 0.009) between Black and White participants. A total of 145 Black participants and 1692 White participants had a recorded answer for molecular testing, with 79 Black (79 out of 145, 54.5%) and 1108 White (1108 out of 1692, 65.5%) having confirmed molecular testing related to TSC recorded in the NHD (Figure 12). This finding was also observed in the TSCOE cohort with a significant difference noted (*p* = 0.049), wherein only 44% of Black *versus* 78% of White participants had molecular testing noted in their medical records (Figure 13). Further analysis is warranted to assess why this discrepancy exists specifically in the context of genetic testing for TSC.

Discussion

A late diagnosis of TSC can delay appropriate treatment and lead to unnecessary and sometimes devastating consequences. For example, subependymal giant cell astrocytomas carry the risk of growing large enough to obstruct ventricular flow in the brain, leading to hydrocephalus and death without emergent surgical intervention.[17] Renal angiomyolipomas, which contribute to renal disease are the most common cause of mortality in TSC[18] and can encroach on normal renal tissue, leading to end-stage renal disease.[19] Growing renal angiomyolipomas also carry the risk of causing aneurysms and life-threatening hemorrhages.[19] Lymphangioleiomyomatosis (LAM), which occurs primarily in women with TSC, can lead to progressive decline in lung function.[10] It is important to note that systemic and topical therapies in the form of mTORi are available and recommended by the 2021 TSC consensus guidelines to treat specific manifestations of TSC.[20] Early treatment of epilepsy in TSC also has implications for neurodevelopmental outcomes in TSC-associated neuropsychiatric disorders (TAND), including intellectual disability and autism spectrum disorder. Results from the TSC Autism Center of Excellence Network (TACERN) study determined that infants with TSC who develop seizures early in life are more likely to exhibit global developmental deficits by 24 months of age than infants with TSC that do not experience early seizures.[21,22] Although dermatological features are not life threatening and can manifest at different points across the lifespan, the dermatological features that present in the early years of life are important indicators of a TSC clinical diagnosis. As a result, prompt diagnosis is critical to optimize neurocognitive outcomes, minimize life-threatening complications, and improve the quality of life for those with TSC.[23]
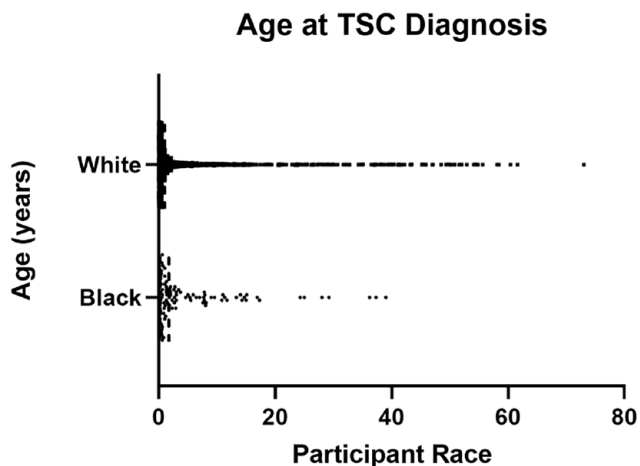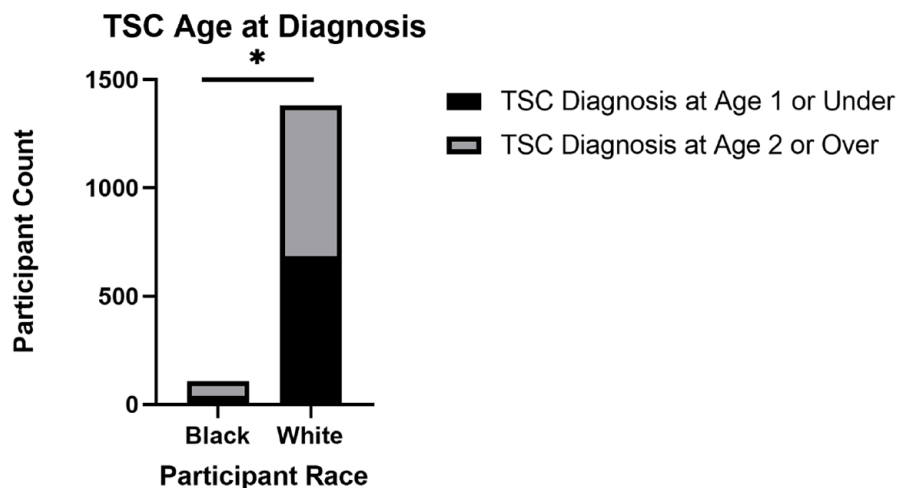
Figure 6. Age at TSC diagnosis for Black and White participants in the TSC natural history database.
Scatterplot showing a total of 107 Black and 1380 White participants that had an age of diagnosis recorded in the NHD. An unpaired *t*-test with Welch's correction was conducted determining a non-significant difference in the variances of age at TSC diagnosis ($p = 0.7264$) between Black (average age 5.4) and White (average age 5.7) individuals.

Skin lesions are the most readily visible manifestations of TSC and provide an opportunity to identify the disease without invasive medical tests. However, we observed that facial angiofibromas, which are recognizable even without a complete skin exam, may appear differently (Figure 2). Other skin manifestations such as hypomelanotic macules, cephalic fibrous plaques, and shagreen patches may also appear differently across skin tones (Figures 1, 3, 4) and can present at different frequencies across races (Figure 10). While we recognize that our observed differences in diagnosis frequencies at age ≤1 were likely not due to the appearance of facial angiofibromas as they most often appear later in childhood, the other skin manifestations may play a role and warrant further exploration in other clinic data sets. We did not have sufficient data on diagnosis dates for these features to analyze at the time of data export.

Therefore, we hope this publication increases recognition of these features and leads to improved early identification of this disorder to provide proactive intervention and avoid irreversible and catastrophic outcomes. Regarding our finding from NHD data related to underutilization of topical mTORi in Blacks relative to Whites, other potential barriers exist that could contribute including economic status (e.g. not able to afford the medication and/or lack of insurance or insurance coverage), access issues (e.g. no compounding pharmacies nearby to make the topical cream, living far away from a clinical trial site), and potential mistrust by minority groups of the medical or research community for treatments that are not yet FDA approved.[24,25] The latter point has been observed in many cancer


Figure 7. Comparison of age at TSC diagnosis for Black and White participants in the TSC natural history database.
A total of 107 Black and 1380 White participants had an age of diagnosis recorded in the NHD. A Fisher's exact test was used to compare how many participants were diagnosed at age ≤1 year as compared with age ≥2 years. A significant difference ($p = 0.027$) was observed with 38% of Black participants diagnosed at age 1 or under, while 50% of White participants were diagnosed at age 1 or under.
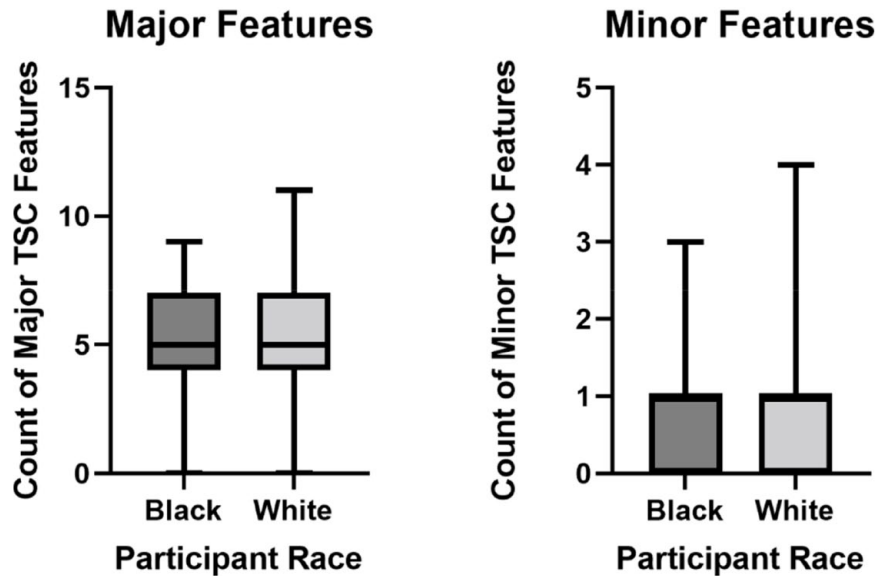
Figure 8. Count of major and minor TSC features in Black and White participants in the TSC natural history database.

This analysis was completed on the 150 Black and 1816 White participants in the NHD regardless of a recorded age at diagnosis. Box and whiskers plots (line at median) illustrating the variation in the presence of major and minor features in Black and White participants. An unpaired *t*-test with Welch's correction was conducted showing a non-significant difference ($p = 0.28$) in the number of major TSC features between Black (mean 5.2) and White participants (mean 5.0). The same analysis was conducted for minor TSC features illustrating a non-significant difference ($p = 0.29$) in the number of minor TSC features between Black (mean 0.7) and White participants (mean 0.7).
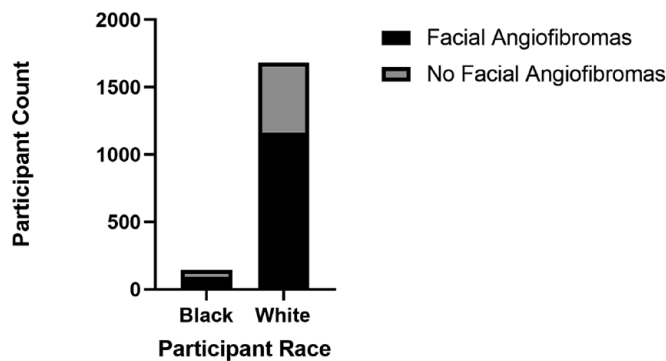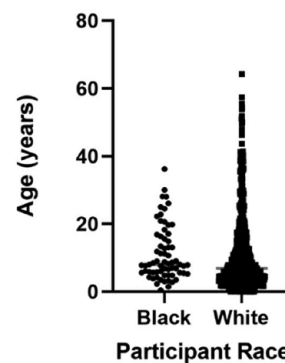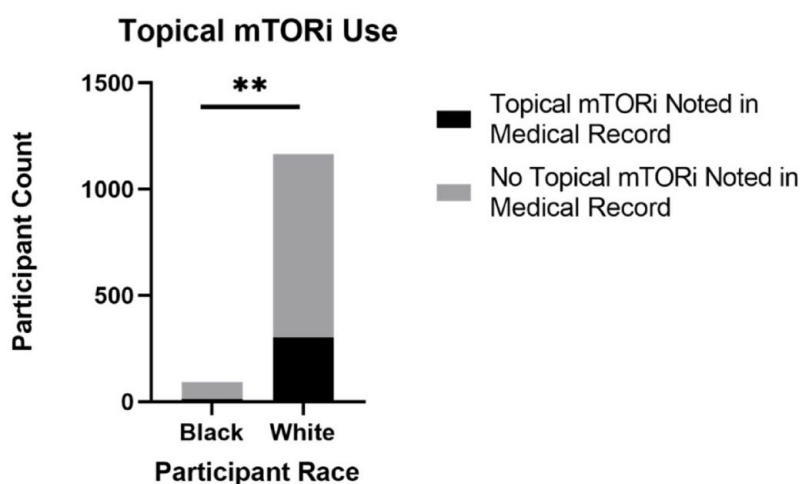

Figure 9. Facial angiofibromas in Black and White participants in the TSC natural history database.
(a) Count of Black and White individuals with or without facial angiofibromas. Out of 144 Black individuals with a recorded response, a total of 92 (64%) were reported to have facial angiofibromas. Out of a total of 1682 White individuals with a recorded response, a total of 1166 (66%) were reported to have facial angiofibromas. A Fisher's exact text showed a non-significant difference ($p = 0.189$) in the percentages of Black and White individuals with facial angiofibroma. (b) A total of 67 Black participants and 791 White participants had a date recorded for the age at angiofibroma diagnosis. An unpaired *t*-test with Welch's correction was conducted determining a non-significant difference in the age at facial angiofibroma diagnosis ($p = 0.6198$) between Black (average age 11.25 years) and White (average age 10.72 years) participants. Mean illustrated by red lines in (b).
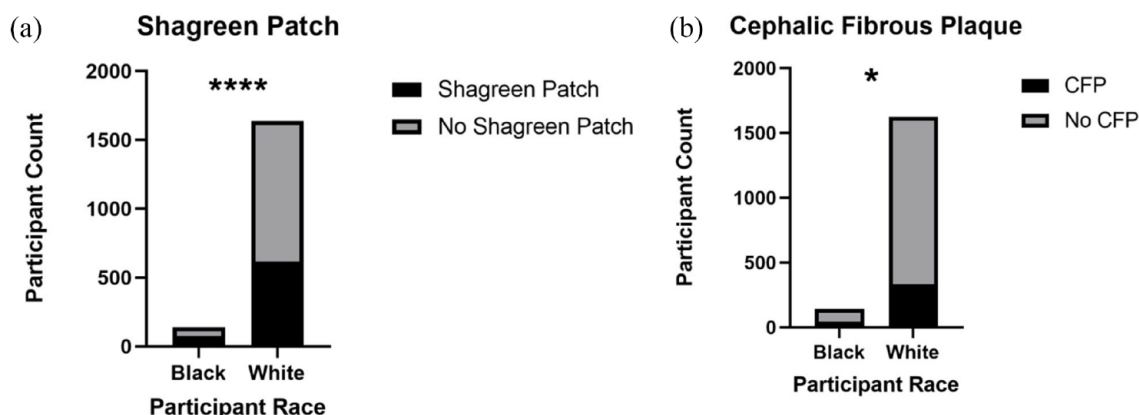
Figure 10. Presence of dermatological features in Black and White Participants in the TSC Natural History Database. (a) A total of 141 Black participants and 1639 White participants had a recorded answer for the presence or absence of shagreen patch. A Fisher's exact test showed a significant difference ($p < 0.0001$) in the presence of shagreen patch between Black and White Participants, with 55.3% of Black and 37.6% of White individuals noted to have a shagreen patch. Odds ratio of 2.051 (95% CI: 1.457–2.919) indicates that Black individuals have an increased probability of having a shagreen patch. (b) A total of 142 Black participants and 1626 White participants had a recorded answer for the presence or absence of cephalic fibrous plaque. A Fisher's exact test showed a significant difference ($p = 0.0139$) in the presence of cephalic fibrous plaque between Black and White participants, with 29.6% of Black and 20.5% of White individuals noted to have a shagreen patch. Odds ratio of 1.625 (95% CI: 1.105–2.358) indicates that Black individuals have an increased probability of having a shagreen patch.

Figure 11. Use of topical rapamycin for facial angiofibroma in Black and White participants in the TSC natural history database.
A total of 92 Black participants and 1166 White participants had a recorded answer for the use of the topical mTORi rapamycin. A Fisher's exact test yielded a significant ($p = 0.006$) difference in the frequency of topical rapamycin use to treat facial angiofibroma in Black and White participants in the NHD cohort.

clinical trials, with Black patients constituting less than 4% of all patients enrolled across multiple trials.[26] Not only does this perpetuate underrepresentation of minority groups, but also has the potential to expand outcome disparities due to the possibility of unique biological differences inherent to different racial groups. We noted a similar trend in our data showing that White individuals were twice as likely than Black individuals to participate in a clinical trial looking at 17 different TSC trials in the NHD. We observed a comparable trend when assessing participation in the TSC Alliance's Biosample Repository project, wherein Black individuals were participating at a lower rate than White individuals. Similarly, genetic testing in data sets from both the TSCOE and NHD illustrated that Black individuals were less likely to receive genetic testing than White individuals (Figures 12 and 13). This result may be due to lower awareness of genetic testing as suggested by Canedo *et al.*,[27] concerns about trust, privacy, and the benefits of genomic studies,[28] or other factors not considered here. While we understand some of the barriers to clinical trial participation[29] and medication use, further analysis of specific barriers to participation is warranted in the context of TSC. In summary, these data highlight that racial disparities are not limited to common diseases such as cancer, but that they also exist in the rare disease space. It may be difficult for diseases that are rarer than TSC to obtain sufficient numbers of patients to conduct similar analyses.[30,31]

Table 6. Participation of Black and White participants in the TSC natural history database in recorded TSC clinical trials.

Black or African American	
0 clinical trials	142 (94.7%)
1 clinical trial	8 (5.3%)
White	
0 clinical trials	1599 (88.0%)
1 clinical trial	192 (10.6%)
2 clinical trials	22 (1.2%)
3 clinical trials	3 (0.2%)

TSC, tuberous sclerosis complex.
A total 217 (11.9%) White participants have participated in at least one clinical trial recorded in the TSC Natural History Database *versus* only 8 (5.3%) Black participants. Clinical trials reported in the NHD shown in Supplementary Table 2. A Fisher's exact test shows a significant difference ($p = 0.01$) between Black and White participation in TSC clinical trials. Odds ratio 2.4 (95% CI: 1.187–5.028).

Limitations

While we aim to bring awareness to racial disparities in the context of TSC, our analyses are limited. A limitation to the NHD data analysis is that we do not know if our data set is a representative sample size. Total numbers differ across figures due to several blank (i.e., unknown) responses regarding the feature being analyzed. For each feature, analysis was limited to records with a recorded value, further restricting our sample size for each comparison. Where applicable, the number of records is included in the text or figure legend. In addition, the NHD was underrepresented for Black individuals and overrepresented for White individuals as compared with the US census at the time of data export. Increased participation in research by minority groups is crucial to properly analyze disparities and potentially discover relevant differences to approach treatment based on race. Another major limitation was the cohort size at the TSCOE ($n = 41$). Replication across additional TSC clinics would be helpful to expand on these analyses.

Conclusion

There is limited understanding about how racial and ethnic disparities impact patient care outcomes
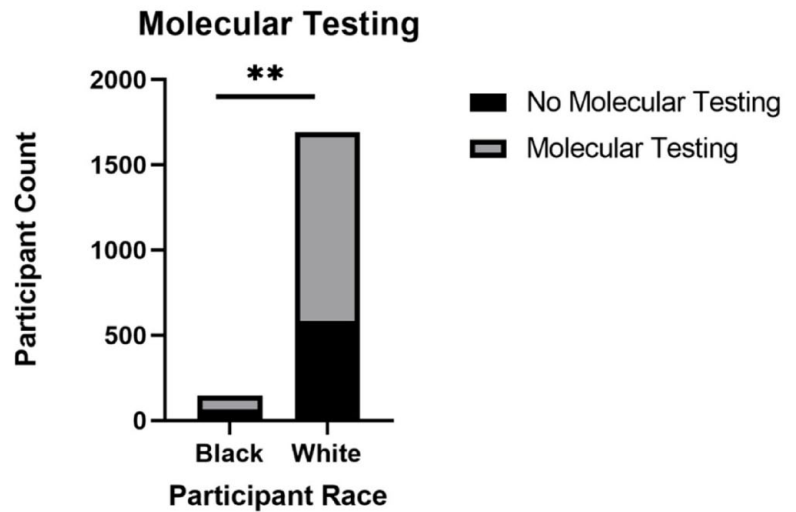
Figure 12. Molecular testing in Black and White participants in the TSC natural history database.
A total of 145 Black participants and 1692 White participants had a recorded answer for molecular testing. A Fisher's exact test yielded a significant difference ($p = 0.009$) in the frequency of molecular testing between Black and White participants, with 54.5% of Black participants and 65.5% of White participants receiving molecular testing, respectively. Odds ratio 1.589 (95% CI: 1.129–2.251).
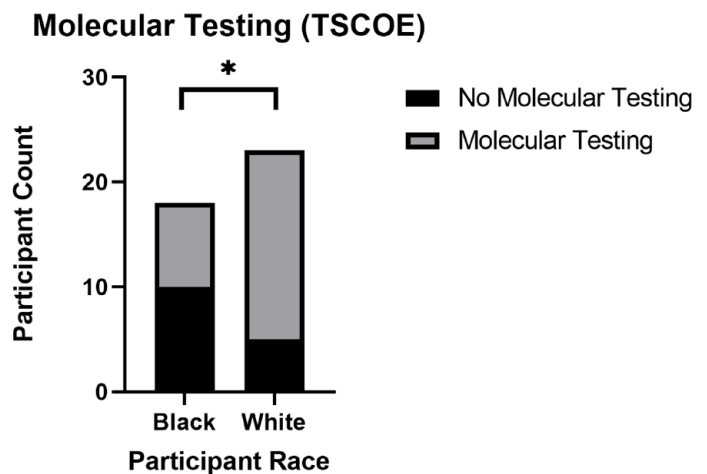
Figure 13. Molecular testing in Black and White participants in the TSCOE.
Out of the 41 participants in the TSCOE cohort, only 8 Black participants had molecular testing noted in the medical record (44%) *versus* 18 White participants (78%). A Fisher's exact test yielded a significant difference ($p = 0.049$) in the frequency of molecular testing between Black and White participants. Odds ratio 4.5 (95% CI: 1.188–17.83).

in the TSC community. In this publication, we highlight a disparity between Black and White individuals with TSC specifically in the underrepresentation of Black patients in research studies and clinical trials, age at TSC diagnosis, differences in the utilization of topical mTORi therapy and

molecular testing, and appearances of skin symptoms that are major features for diagnosis. Identifying these disparities and their potential as barriers to care is the first step to implementing evidence-based practices to optimize patient-centered clinical outcomes. These differences warrant further study across additional clinic sites and other races in the future.

Declarations

Ethics approval and consent to participate
The Johns Hopkins Institutional Review Board approved protocol NA 00076475 Interdisciplinary Protocol for Patients with TSC allowing use of de-identified data from the Kennedy Krieger Institute clinical database for research purposes. The TSC Alliance has IRB approval from Ethical and Independent Review Services for the Natural History Database study (Protocol 15039-08) that permits use of de-identified clinical data for TSC research.

Consent for publication
Written patient or parental consent *via* a photo release form was obtained to use images collected from individuals with TSC.

Author contributions
Ashley J. Pounders: Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

Gabrielle V. Rushing: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

Sonal Mahida: Conceptualization; Data curation; Methodology; Resources; Writing – original draft.

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Emily A. Thomas: Data curation; Resources.

Rabiah Sundus Tameez: Formal analysis; Project administration; Resources; Validation; Visualization; Writing – review & editing.

Tanjala T. Gipson: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft.

Competing interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AJP and GVR are employees of the TSC Alliance, a non-profit organization, which reports revenue from individual donors and corporations including BridgeBio, Chemistry Rx, DiRx, Jazz Pharmaceuticals, LivaNova, Marinus, MassMutual, Neurelis, Nobelpharma America, Noema, Ovid, TotalCare Rx, UCB, and Upsher-Smith. The views expressed in this article are those of the authors and do not necessarily reflect the opinion of the TSC Alliance. TTG served as a principal site investigator for a Novartis study (EXIST-3); funding was provided to her institution only.

Availability of data and materials
All raw data used in this analysis will be made freely available to others by request to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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