Oncology Central

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Addressing disparities in cancer care

Contents

Editorial

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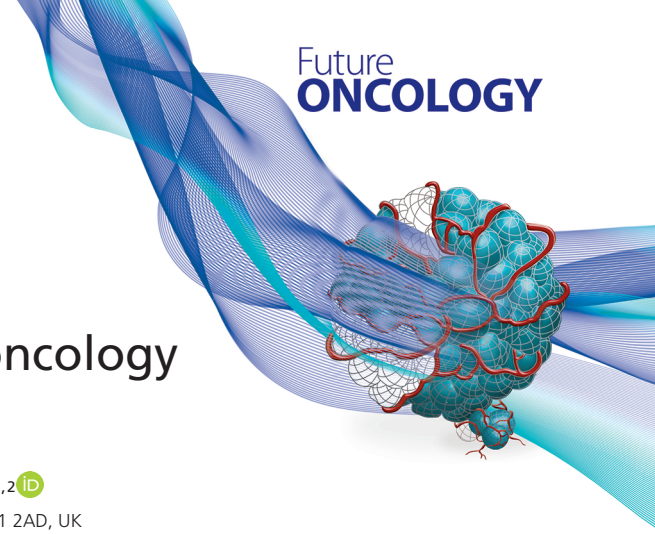

Telemedicine health disparities in oncology care

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> "Even if access to appropriate devices and an internet connection is secured, telemedicine necessitates a technologically adept population that is capable of using internet-based technologies to a satisfactory degree so their medical care does not suffer."

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Health inequities in medicine have been recognized for centuries; they occur between countries as well as within them. As the incidence of global cancer increases, most cases are predicted to occur in low-income countries, increasing healthcare divisions [1]. In low-income countries, including many countries of Latin America, cancer is the second leading cause of death among children [2]. The COVID-19 pandemic has exacerbated pre-existing health inequalities while there has also been a rapid shift to telemedicine.

Telemedicine has been extensively used during the COVID-19 pandemic to decrease the need for face-to-face consultations [3]. Teleoncology, which describes remote oncology care via telemedicine, has protected vulnerable immunosuppressed cancer patients from contracting COVID-19 by reducing unnecessary clinical exposure [4]. Although teleoncology holds promise for the future and may alleviate healthcare divisions, its technological requirements are neither available nor affordable to all. Thus, the impacts of teleoncology on pre-existing health disparities must be considered.

Addressing social disparities

Teleoncology, originally aimed at decreasing inequities between rural or remote regions and urban areas as well as resource-rich and resource-poor centers within high-income countries [5], provides an improved and easy way to communicate between healthcare professionals and patients, facilitating fruitful collaborations and effective delivery of care [6]. Increased distance from medical centers has been found to be the cause of health disparity. Travel burden, defined as travel time or distance, can affect cancer diagnosis and management, and those living further away from their designated hospital tend to present with a more advanced stage of cancer at the time of diagnosis [7,8]. It is essential for oncologists to recognize this burden among patients and to realize that teleoncology can overcome these barriers.

Video consultations offer life-changing potential for patients with hearing impairments. Yet the rapid shift toward telemedicine has caused an upsurge in telephone-based clinics that disadvantage patients who are hard of hearing and those with complete deafness. In pre-pandemic times, adults with deafness since birth or early childhood were less likely to see a doctor and faced increased difficulty accessing primary care services [9]. Video consulting could erase these injustices by allowing patients to lip-read and communicate via sign language. Moreover, video conferencing platforms such as Attend Anywhere, which is now widely used within the UK National Health Service (NHS), offer chat functions that can help clarify important aspects of the consultation. Video conferencing is also a great alternative for individuals who find medical appointments and sitting in waiting rooms distressing, such as those with agoraphobia.

A novel use of teleoncology has been effective in supportive or palliative treatments as well as hospice care by allowing video assessment of patients suffering from radiotherapy- or chemotherapy-induced side effects, which require appropriate management [10,11]. Telemonitoring or remote patient monitoring offers great potential for improving early diagnosis and for home-based management of cancer treatment sequelae, such as dehydration from nausea and vomiting, infections in immunosuppressed individuals and pain [10]. In addition, telemedicine could facilitate remote delivery of cognitive behavioral therapy, online group therapy, mindfulness training, yoga and personalized exercise plans for cancer patients, who, beyond the physical suffering, often experience chronic stress years after completing their treatment [12].

Exacerbating social disparities

Although telemedicine can decrease inequalities in oncology care, it may also exacerbate these in certain circumstances. Telemedicine requires that both patient and provider have access to compatible internet-enabled devices as well as a stable broadband connection. In the USA, although 80% of adults have access to a smartphone, only 75% have access to a broadband connection at home, and these figures decrease further among individuals with lower income and educational attainment [13,14]. Katzow *et al.* report that only two-thirds of patients registered at their practice provided an e-mail address [15]. Limited availability of internet-enabled devices within households – for instance, in the case of a shared family computer – may require a sacrifice of remote work or educational activities to complete the medical appointment. This sacrifice may further increase the educational and financial inequalities of these households. Moreover, in low-income countries, such as those in the region of Sub-Saharan Africa, access to electronic internet-enabled devices and the provision of a broadband connection are significantly poorer, rendering effective teleconsultations difficult. Additionally, a poor-quality microphone and video camera may restrict diagnostic accuracy in teleconsultations.

Even if access to appropriate devices and an internet connection is secured, telemedicine necessitates a technologically adept population that is capable of using internet-based technologies to a satisfactory degree so their medical care does not suffer [3]. Digital literacy is influenced by previous experience and skill. Low-income families and those with poorer educational attainment may struggle with installing and using unfamiliar applications to facilitate teleconsultations, needing more hands-on support in preparation for their appointment [15]. Trust in technology, but also in health care in general, can be lacking in lower socioeconomic groups, impacting telemedicine uptake. One study showed that patient education was the only factor that was significantly associated with the favourability of telemedicine utilization [16]. Digital literacy must be considered even more in the case of cancer patients, who are predominantly older individuals and may struggle to use telemedicine systems. Older patients may also reside in remote areas where telemedicine is difficult to carry out for practical reasons. In these circumstances, the presence of a carer, another family member or a close friend with greater digital literacy may be necessary to carry out the teleconsultation. Otherwise, poor teleclinic attendance and decreased quality of care are to be expected for elderly patients, perpetuating ageist inequalities in medicine.

Finally, teleoncology may accentuate communication barriers in vulnerable patient populations, such as those from ethnic minority backgrounds and those with impaired hearing, vision or cognition [3]. Practitioners must ensure these patients are not intimidated by the technology or pressured into its use, suggesting that otherwise they will not receive the care they need, as this would lead to overt discrimination against this group of people, which has already been seen during the pandemic [3,17,18]. Limited English proficiency and the need for trained medical interpreters, although theoretically possible by adding a third party to the call, require planning, additional resources and time [15]. Setting up a teleconsultation with a sign language interpreter to aid communication with a deaf patient may be resource-intensive because of the technological restrictions of connecting the video through a specific application available only on certain devices.

Strategies ensuring fair telemedicine

Although not a new invention, the rapid implementation of telemedicine across health care because of the COVID-19 pandemic may have well changed the face of medicine forever [19,20]. Unfortunately, this has not come without a price, and strategies for addressing arising health disparities are paramount to ensure telemedicine is predominantly beneficial.

First, a large public health campaign is essential to educate individuals who are less familiar with telemedicine or technology in general. Social outreach and diversification of staff may be effective at improving telemedicine uptake at the community level [15]. A systemic effort is also required from governments, regulatory bodies as well

as public and private organizations to develop user-friendly software that could be adapted to a simpler version for less technology-literate patients.

Moreover, in collaboration with contracted technology companies, a national scheme should be established, ensuring that every household has access to a simple tablet or smartphone compatible with the software utilized for NHS appointments. The implementation and distribution side of this scheme could be facilitated by general practice surgeries, which would ensure the timely delivery of devices with preinstalled software to registered patients. Additionally, a helpline for those encountering difficulties while using the software could be a valuable strategy for ensuring that, despite occasional technological complications, patients' experience with telemedicine is positive overall.

Conclusion

Telemedicine offers many advantages and has the potential to alleviate socioeconomic disparities in certain settings. However, caution should be advised in its widespread adoption, as telemedicine poses a risk of increasing social inequalities due to innate barriers associated with its use. With emerging data indicating that COVID-19 disproportionately impacts low-income families and communities of colour [2], it is of paramount importance that healthcare providers innovate solutions to actively diminish systemic social injustice.

Author contributions

Writing, reviewing and editing: AM Wozniak and KS Rallis. Conceptualisation, writing, reviewing and editing: R Elkaddoum.

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No writing assistance was utilized in the production of this manuscript.

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Systematic Review

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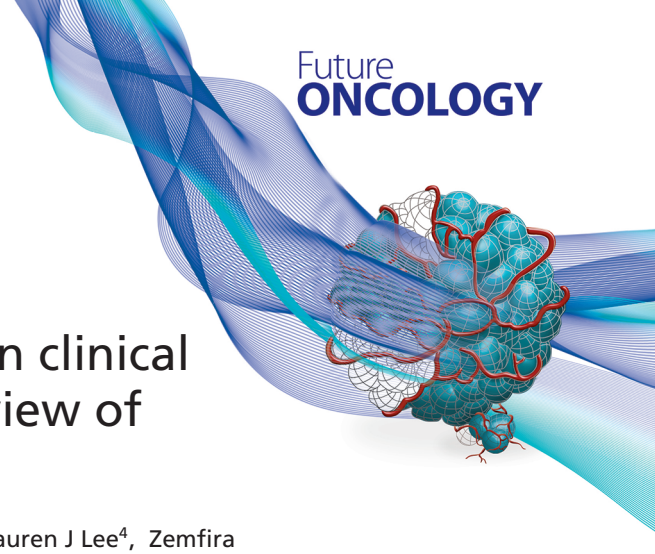

Race and ethnicity representation in clinical trials: findings from a literature review of Phase I oncology trials

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Aim: To provide an assessment of published literature on the demographic representation in Phase I trials of biopharmaceutical oncology agents. **Materials & methods:** We conducted a rapid evidence assessment to identify demographic representation reported in Phase I clinical trials for biopharmaceutical oncology agents published in 2019. **Results:** Globally, the population was predominantly White/Caucasian (62.2%). In the USA, the distribution was heavily skewed toward White/Caucasian (84.2%), with minimal representation of Blacks/African–Americans (7.3%), Asians (3.4%), Hispanics/Latinos (2.8%) or other race/ethnicity groups. **Conclusion:** Our data highlight that Phase I oncology trials do not reflect the population at large, which may perpetuate health disparities. Further research is needed to understand and address barriers to participation, particularly among under-represented groups

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Keywords: clinical trial • disparities • ethnicity • oncology • Phase I • race

Clinical trials provide answers to scientific questions that enable global regulatory agencies (i.e., the US FDA and the EMA) to evaluate the safety and efficacy of novel therapeutics, inform medical professionals on the use of new therapeutic agents, and make approval decisions. Clinical trial participation provides benefits both for participants and for informing drug development to improve treatment options for patients. It is important that clinical trials provide evidence regarding pharmacokinetics/pharmacodynamics, safety and efficacy of investigational treatments across different demographic populations. An important consideration in drug development is addressing health disparities (defined by Healthy People 2020 as 'a particular type of health difference that is closely linked with social, economic and/or environmental disadvantage') [1] which exist among racial or ethnic minority groups. These disparities can include health outcomes influenced by unequal access to health insurance, as well as differences in the incidence [2] and survival rates [3] for people with cancer. For example, there is a disproportionately higher incidence of multiple myeloma, colorectal cancer, triple negative breast cancer and prostate cancer in African–Americans, gastric cancer in Asians and Pacific Islanders, and cervical cancer in Hispanic and American–Indian/Alaska Native women [2]. Hence, there is a compelling need for clinical trials including oncology trials, to have an equitable representation of diverse racial and ethnic groups rather than the current over-representation of non-Hispanic White individuals.

A study published in 2018 reported on the racial/ethnic composition of individuals participating in biobanks, genomic studies and clinical trials [4]. Of patient-provided oncological samples, data on the donor's race/ethnicity

was not reported (NR) for 48.3% of samples, and remaining specimens were from White (37.5%), Asian (10.0%), African–American (3.8%) and Hispanic (0.4%) donors. Of particular note is that among 416 cancer-related genome-wide association studies including more than 6.3 million samples, 92% of the samples were obtained from people of European descent [4]. This trend calls into question whether the effectiveness and safety of investigational drugs are tested in a broader percentage of the population that will eventually use the approved drug.

The FDA Safety and Innovation Act of 2012 (FDASIA) [5] directs the FDA to investigate the demographic representation (sex, age, race and ethnicity) of applications for medical products for both inclusion in clinical trials and for subgroup-specific safety and effectiveness data. Section 907 of the Act focused 27 actionable items into three priorities, which aim to increase the completeness and quality of demographic subgroup data, improve the public availability of demographic subgroup data, identify barriers to subgroup enrollment in clinical trials, and employ strategies to encourage greater participation. Additionally, in June 2019, under Section 610(a)(3) of the FDA 26 Reauthorization Act of 2017 (FDARA) (21 U.S.C. 360bbb note) [6], the FDA issued draft guidance to broaden eligibility criteria in clinical trials for drugs intended to treat rare diseases or conditions so as to avoid unnecessary population exclusions from clinical trials, develop eligibility criteria and improve clinical trial recruitment [7]. The overall aim of these measures is for participants enrolled in clinical trials to better reflect the population most likely to use the drug, if approved, while maintaining safety and effectiveness standards.

Although guidance has been introduced to increase the inclusion of racial/ethnic minorities in clinical trials, participation in oncology trials by individuals with these demographics remains low. For example, in 2019, 3593 patients participated in clinical trials used to generate evidence for FDA submissions for oncology drugs, resulting in the approvals of 11 new oncology therapeutics. Of these, the majority of participants were male (62%) and White (73%), as compared with Asian (18%), Black or African–American (4%), and Hispanic (5%). Just over half of participants (59%) were ≥65 years and approximately one quarter (24%) of participants were from US-based enrollment sites [8].

Eligible participants in Phase I oncology trials generally have advanced disease, with limited or no evidence-based treatments available [9], and inclusion in such trials is of benefit to a wide patient demography. Better representation of the population at large in Phase I trials should allow assessment of drug candidates in populations that are likely to receive the drug when marketed.

Objective

This manuscript reports a summary from a rapid evidence assessment (REA) of recently published Phase I clinical trials in clinical oncology. The primary objective of the REA was to conduct a descriptive assessment of published literature on the demographic representation in Phase I clinical trials of biopharmaceutical oncology agents.

Materials & methods

Search strategy

This REA was guided according to the principles of the Interim Guidance from the Cochrane Rapid Reviews Methods Group [10] and guidance from the University of York Centre for Reviews and Dissemination [11]. The REA employed a standardized, systematic and transparent approach to identify, describe, report and interpret published evidence in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines and as described in an *a priori* study protocol (unpublished). The search strategy was designed to identify current literature (published between January and December 2019) that reported the demographic representation of individuals recruited for Phase I clinical trials for biopharmaceutical oncology agents. Searches were run on 18 December 2019 in the following literature databases, for publications in English: Embase® via Ovid, MEDLINE® (including in-process citations, etc.) via Ovid and PubMed. The full search strategy and number of identified hits for each database are presented in Supplementary Appendix 1.

Selection criteria & screening

The population, intervention, comparator, outcomes and study types included in the REA are described in Table 1. Publications that met the criteria described in Supplementary Appendix 2 were excluded. These included non-English publications, congress abstracts, studies of benign hematologic disorders, and reviews or meta-analyses.

One reviewer (K Smoyer) screened the titles and abstracts (level 1) of the references identified in the database searches against study inclusion/exclusion criteria; a second reviewer (C Rolland) conducted a 20% cross-check to

Table 1. Inclusion criteria.

PICOS criteria	Inclusion criteria
Population	Patients ≥18 years of age, with any solid tumor or hematological malignancy or healthy volunteers
Intervention	Any biopharmaceutical agent investigated for the treatment of cancer
Comparator	Any or none
Outcomes	Any
Study design	Phase I, Ia or Ib prospective interventional studies
Time period	Published in the peer-reviewed literature between 1 January and 31 December 2019

PICOS: Population, intervention, comparator, outcomes and study type.

validate the screening. The same process was applied for the full-text (level 2) screen of the papers identified in level 1, including a 20% validation by a separate reviewer (C Rolland). Disagreements were discussed until consensus, or a third reviewer (I Jacobs, LJ Lee or J McGinnis) was consulted to make the final inclusion/exclusion decision.

Data extraction & reporting

One reviewer (G Bowden) extracted the data from the included manuscripts into a prespecified data extraction form, and a second reviewer (K Smoyer) validated 100% of the extractions. Discrepancies were resolved by consulting the original manuscript. Missing data were coded as 'not reported'. Data are reported as a whole for all trials and stratified by three main regions as follows: the USA only, mixed (USA + ≥1 other country) and USA-excluded (any country other than the USA). Due to a relatively homogeneous population (90% or more Asian ethnic groups, or classified as 'homogenous' according to the CIA Factbook) [12], all participants in trials from the following single countries were classified as Asian if not otherwise specified: China, Japan, South Korea, Taiwan and Vietnam. Details of the data extraction and classification into regions are provided in Supplementary Appendix 3.

Patient counts for each demographic group were summed across the included Phase I trials and for the three regions. Data were tabulated for all participants, patients only and healthy volunteers, and are reported at the clinical trial level as well as the population level. The results presented here, however, mainly focus on those from clinical trials conducted in patients in the USA, in order to assess demographic representation in accordance with FDA guidance [5].

Results

Clinical trial characteristics

Out of 1431 references identified from the literature searches and undergoing title/abstract screening, 381 were retained for full-text screening, and 1050 were excluded. After full-text screen of 381 papers, 374 papers were included with a combined total of 16,763 participants. A complete list of included papers is provided in Supplementary Appendix 4. A summary of results from the database searches and publication selection process is presented in Figure 1. Characteristics of the included trials are summarized below (Table 2).

The proportion of males and females across all trials was balanced (48.7 and 47.7%, respectively). Gender was NR or not available in 13 (3.5%) studies, comprising 613 participants. Race or ethnicity was identified in 220 (58.8%) of the 374 Phase I oncology clinical trials assessed in this review, encompassing a total of 9972 participants. Among the 220 clinical trials with demographic data, the population was predominantly White/Caucasian (62.2%) (Table 3). Asian participants (29.9%) were predominantly from studies conducted in Asian countries (all participants classified as Asian). Black participants (3.9%) and Hispanic/Latino participants (1.2%) were under-represented.

US-only trials

A total of 139 trials was conducted in the USA only; 137 of these were in patients and two trials were in healthy subjects. Of the subset of Phase I oncology trials conducted in US patients, 64.2% reported race/ethnicity, representing 3197 patients. The distribution of patients in US trials was heavily skewed toward Whites (84.2%), with minimal representation of Blacks/African–Americans (7.3%), Asians (3.4%), Hispanics/Latinos (2.8%) or other race/ethnicity groups among the trials that reported race or ethnicity data (Table 4). Blacks and Hispanics, who account for an estimated 13.4 and 18.3% of the total US population, respectively, were under-represented in the clinical trials identified in this study, even though age-adjusted cancer rates are comparable to Whites.

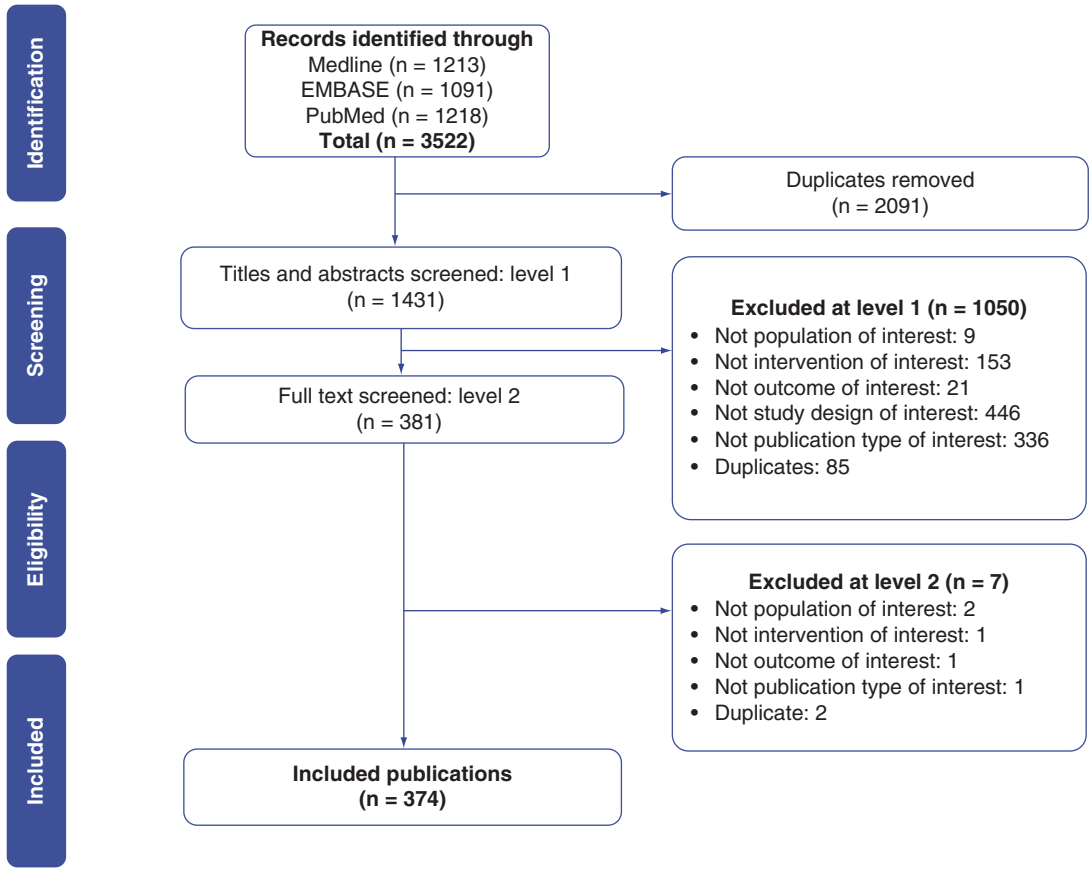

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of publication selection process.

Table 2. Characteristics of Phase I oncology trials.

Trial characteristic	Studies (n = 374), n (%)
Phase I studies	374 (100.0)
– Studies in patients	367 (98.1)
– Studies in healthy subjects	7 (1.9)
First in human studies	89 (23.8)
Demographic characteristics	
– Race/ethnicity reported	220 (58.8)
– Gender reported	361 (96.5)
Geography of trials	
– US population only	139 (37.2)
– Ex-US population only	150 (40.1)
– Mixed US and ex-US population	79 (21.1)
– Unable to determine	6 (1.6)
Cancer type	
– Solid malignancies	297 (79.4)
– Hematological malignancies	58 (15.5)
– Solid + hematological malignancies	12 (3.2)
– Conducted in healthy subjects	7 (1.9)

Solid malignancies: e.g., breast, lung colorectal, prostate, gastric and so on. Hematological malignancies: e.g., multiple myeloma, lymphomas, leukemias and so on.
Ex-US: the USA-excluded.

Table 3. Race/ethnicity of participants in Phase I clinical trials in oncology: all regions globally.

Race/ethnicity	All participants (n = 9972), n (%)	Patients (n = 9550), n (%)
Total with race or ethnicity reported	9972 (100.0)	9550 (100.0)
White/Caucasian	6198 (62.2)	6056 (63.4)
Black/African–American	388 (3.9)	371 (3.9)
Asian	2986 (29.9)	2734 (28.6)
Native Hawaiian/Pacific Islander	8 (0.1)	5 (0.1)
American–Indian/Native Alaskan	11 (0.1)	10 (0.1)
More than one race	11 (0.1)	4 (<0.1)
Other/unknown	321 (3.2)	321 (3.4)
Hispanic/Latino†	115 (1.2)	113 (1.2)

†Some studies reported Hispanic/Latino as a race category and some as an ethnicity; as a result the sum of participants by race/ethnicity category is greater than the total number of participants.

Table 4. Race/ethnicity of US patients in Phase I clinical trials in oncology compared with US demographics and cancer incidence.

Race/ethnicity	US patients (%)	US Census† (%)	SEER data‡: 2013–2017 age-adjusted cancer incidence per 100,000
White/Caucasian	84.2	76.5	452.1
Black/African–American	7.3	13.4	440.4
Asian	3.4	5.9	302.0§
Native Hawaiian/Pacific Islander	0.1	0.2	NR§
American–Indian/Native Alaskan	0.1	1.3	310.1
More than one race	0.0	2.7	NR
Other/unknown	3.7	–	NR
Hispanic/Latino	2.8	18.3	348.4

†Source: US Census Bureau. Population Estimates, July 2019 (https://www.census.gov/quickfacts/fact/table/US).
‡Source: Surveillance, Epidemiology and End Results (SEER) Program. 5-Year age-adjusted incidence rates, 2013–2017 for all cancers (https://seer.cancer.gov/explorer/).
§Hawaiian/Pacific Islander included with Asian.
NR: Not reported; SEER: Surveillance, Epidemiology and End Result.

Participation of Native Hawaiian/Pacific Islander and American–Indian/Native Alaskan patients was extremely low.

Discussion

Our review of the literature published in 2019 found the demographic composition of the 220 Phase I oncology clinical trials (n = 9972), for which race or ethnicity was identifiable, to be predominantly White/Caucasian (62.2%), followed by Asian (29.9%). For clinical trials conducted in the USA only, and the main focus for this report, the distribution was heavily skewed toward Whites (84.2%), with minimal representation of Blacks/African–Americans (7.3%), Asians (3.4%), Hispanics/Latinos (2.8%) or other race/ethnicity groups among the trials that reported race or ethnicity data. Despite the introduction of FDA guidance to increase enrollment of under-represented groups in clinical trials, the results of this REA indicate that participation in recent Phase I oncology trials by individuals with these demographics remains low. Because patients in Phase I trials may potentially experience therapeutic benefits [13], inclusion of a broader patient population in Phase I trials can help ensure that diverse groups, regardless of race or ethnicity, benefit from new treatment options.

This review of Phase I trials published in 2019 further showed that the imbalance in racial representation in oncology trials observed at later phases continues to exist in earlier phase trials. This can lead to Phase I oncology trials that are not representative of the population most likely to benefit from new cancer treatments. The demographic findings of the current study are similar to a study by Ramamoorthy *et al.* of Phase I–III pivotal trials of drugs approved by the FDA between 2008 and 2013 for breast, colorectal, lung or prostate cancer [14]. In those trials, 79.7% of patients were White, 12.4% Asian and 3.8% Black/African–American; Hispanic/Latinos comprised 3.6% of patients in the included trials [14]. Our findings are also similar to those of a recent study by Loree *et al.* of clinical trials leading to FDA approvals for cancer drugs between 2008 and 2018, which reported

that 63% provided data on at least one racial group, with Whites representing 76.3%, Asians 18.3%, Blacks 3.1% and Hispanics 6.1% of clinical trial participants [15].

An analysis of 358 oncology trials comparing those sponsored by pharmaceutical companies versus the National Cancer Institute's National Clinical Trial's Network reported that the proportion of Black patients was 2.9% for pharmaceutical company-sponsored trials and 9.0% for National Clinical Trial's Network trials, significantly lower than their calculation that estimated that 12.1% of the US cancer population are Black (the calculation was based on an adjusted analysis of Surveillance, Epidemiology and End Results data to reflect the US cancer population by weighting estimates based on national distributions of age, sex and race using US Census data). The findings were generally consistent across individual cancer types [16].

The lack of racial representation may perpetuate health disparities due to the disproportionately higher incidence of certain cancers among non-White, non-Hispanic populations. African–American males develop cancer 25% more frequently than White males and have a 43% higher mortality rate compared with White men for all cancers combined [17]. Furthermore, according to the CDC, African–American men "have more cancers of the lung, prostate, colon and rectum than do White men. Overall, African–American men have more malignant tumors and are less likely to survive cancer than the general population" [17], further highlighting the importance for higher inclusion of African–Americans and other demographic groups in Phase I oncology trials to better reflect the populations that are most likely to benefit from a drug. Our REA provides an initial broad look at demographic representation across recently published Phase I oncology trials within defined parameters. Future analyses could include additional considerations such as reporting on the number of studies that request biomarker or targeted mutation analyses for preselection, and if this varies by race for example.

Race/ethnicity was NR in over 40% of the Phase I oncology trial publications included in our analysis; without this information, it was not possible to assess demographic representation in those trials. A lack of reporting impedes efforts to increase diversity and serves to perpetuate the status quo. When collecting race/ethnicity data, the use of a standardized method should be encouraged, and ideally self-reported versus investigator assessed (also see Standards for maintaining, collecting, and presenting federal data on race and ethnicity) [18]. Publications should be more explicit and conscientious when reporting race and other useful demographic data. Equitable demographic representation is particularly important in clinical trials of cancers with racial/ethnicity differences in incidence and/or survival; however, sizable disparities in participation persist. All-cause cancer rates in the USA are high for African–Americans and are only slightly lower than for Whites [19]. A greater presence of African–Americans in oncology trials is needed to identify whether novel therapeutics show efficacy in this population, as well as to assess their safety profiles.

A lack of racial representation in oncology trials is an issue that has persisted for many years. In 2006 [20] a review of 163 Phase I participants from five major cancer centers in the USA reported that most participants were White (88%), had health insurance (96%) and many (66%) were financially secure (household income ≥$50,000). Only 3% were African–American and 4% were uninsured. The sociodemographic characteristics of the patients were similar to the characteristics of participants from other Phase I trials, but did not reflect those of the community. For example, at the time of the analysis, 12.3% of the US population was African–American according to the 2000 US Census [21]. Part of the reason underlying the disparities in representation, in addition to health insurance coverage/restrictions, could be due to barriers to participation in Phase I trials such as a lack of information due to the types of institutions where patients receive care, physicians not recommending participation or not spending enough time with patients, or patient mistrust. Also, Phase I trials, by definition, require more intensive visits, and thus access to a higher level of medical care. In a study using focus groups and interviews of US patients and community members in Louisiana, Davis *et al.* reported that although most were aware of clinical trials, they did not know about specific trials or where to find more information [22]. Recruitment of patients is often through an encounter with a participating physician or treatment center, which differs from healthy subject recruitment.

A qualitative study from the USA of patient visits to oncologists found that physicians spent less time with African–American than White patients and recommended that oncologists make an effort to discuss clinical trial participation, purpose and risks with patients, particularly African–Americans [23]. Another factor to consider is that Medicaid is not required by federal law to provide coverage for the routine care costs for patients participating in a clinical trial [24]. Since patients covered by Medicaid tend to be ethnic and racial minorities, women, children and rural populations, the lack of coverage for Medicaid enrollees in clinical trials may exacerbate under-representation of these groups in clinical trials.

In high-risk prostate cancer, multiple randomized clinical trials have shown that definitive therapy improves overall survival among patients. However, a recent publication reported that many patients do not receive definitive therapy because of sociodemographic and health-related factors [25]. In an analysis of factors associated with the receipt of nondefinitive therapy and survival among patients with high-risk prostate cancer, it was found that compared with White patients, Black and Hispanic patients were more likely to receive only systemic therapy, or not be treated at all. The most significant factors associated with receiving nondefinitive therapy were insurance status, race/ethnicity, median household income, and health- and disease-related factors, including tumor stage and medical comorbidity score [25]. In an analysis of the role of sociodemographic factors in treatment decisions for non-small-cell lung cancer, however, socioeconomic factors rather than race/ethnicity appeared to influence the refusal of cancer treatment in patients with stage IV non-small-cell lung cancer [26]. Various other reports have highlighted racial or ethnic disparities in cancer incidence, treatment and outcomes, across a broad range of cancer types [27–33].

Further research and dissemination of data highlighting the under-representation of ethnic minorities in Phase I clinical trials should help increase awareness. In this respect, the American Society of Clinical Oncology convened a working group, which resulted in a series of recommendations and position statement to increase participation in Phase I trials [13,34]. The key goals of these recommendations were: improve payers' coverage of routine patient costs in Phase I trials, improve patients' and clinicians' understanding of goals of Phase I trials, increase the number of patients who enroll in Phase I trials, increase researcher and trial sponsor compliance with best practices for Phase I trials and increase biopharmaceutical industry support of pediatric Phase I trials. Recommendation 2 suggested that the educational efforts of professional societies should target improving the ability of clinicians and researchers to explain the goals of Phase I cancer trials, including how to discuss the purposes and risk-benefit assessment to potential patient participants [13]. Recommendation 3 advised that professional societies should enhance educational materials for clinicians and researchers to help overcome challenges to Phase I trial enrollment, such as incomplete understanding of insurance coverage and attitudes that Phase I trials should be considered only after other treatment options fails [13]. There is also a need for more clinicians and researchers from under-represented groups, which may help build trust and confidence in trial participation. A recent report highlighted that although progress is being made in this respect, much work remains to be done in increasing the number of under-represented racial/ethnic groups in medical schools and faculty rosters [35].

This current review of Phase I trials that were published in 2019 reveals that the imbalance in racial representation seen in later phase oncology clinical trials is also present in earlier phase trials. This period was chosen given that it represented the most recent publications available at the time the REA was performed. Current barriers to participation may arise due to the types of institutions where patients receive care, physicians not recommending trials or not spending enough time with patients, health insurance coverage/restrictions, certain social determinants of health, or patient mistrust of clinical trials. As a result, many Phase I oncology trials are not representative of the general population, and this may perpetuate health disparities [36]. When taking the COVID-19 pandemic into account, which has disproportionately impacted communities of color and limited access to some trials, there is the potential for this imbalance to worsen. Conscious efforts are paramount to resolve these disparities in participation in Phase I oncology trials, which can provide access to novel therapeutics.

There are some limitations to our analyses: for example, by observing data from trials published over just 1 year, we were unable to track any longitudinal effects on disparities, although several other studies already discussed corroborate our findings. The unavailability of precise information on race/ethnicity in trials conducted in Asian countries is another limitation of this analysis and may over-represent the percentage of trials reporting race and the percentage of Asian subjects in clinical trials globally in this region. However, this did not affect the dataset from the USA.

Conclusion

Recruitment and retention of under-represented groups in Phase I oncology clinical trials is essential to ensure the demographics of participants reflect the wider population at large. A targeted strategy to recruit representative populations is needed, and further research is required in order to understand, and thus reduce, the barriers to participation, particularly among under-represented groups.

Future perspective

It is clear that an imbalance in racial or ethnic representation in Phase I oncology trials has been an issue for many years, and still persists today. Further research and publication of data highlighting this under-representation would help increase awareness. The recommendations and guidance from bodies such as American Society of Clinical Oncology, the FDA and other organizations, along with educational materials for clinicians and researchers should help overcome challenges to Phase I trial enrollment. Patients may also become more aware of available options through greater interaction with clinicians and researchers from under-represented groups, which may help build trust and confidence in trial participation.

Summary points

- Clinical trials provide answers on the safety and efficacy of novel therapeutics, inform medical professionals on the use of new therapeutic agents, and enable global regulatory agencies to make approval decisions.
- Clinical trials should enroll patients that are representative of the demographics of the population to be treated. However, the literature reports disparities in trial participation, particularly in the inclusion of racial and ethnic minorities.
- This study investigated demographic representation in Phase I oncology clinical trials of biopharmaceutical oncology agents published during 2019, with a particular focus on US-based trials.
- We employed a standardized approach to identify, describe, report and interpret published evidence in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines.
- Globally, race or ethnicity was identified in 220 (58.8%) of 374 Phase I oncology clinical trials assessed in this review, with a total of 9972 participants.
- Among the 220 clinical trials with demographic data, the population was predominantly White/Caucasian (62.2%), followed by Asian (29.9%), Black (3.9%) and Hispanic/Latino participants (1.2%) were under-represented.
- The distribution of patients in US trials was heavily skewed toward White/Caucasian (84.2%), with minimal representation of Blacks/African–Americans (7.3%), Asians (3.4%) and Hispanics/Latinos (2.8%).
- Many current barriers to participation may contribute to this disparity, such as the types of institutions where patients receive care, health insurance coverage/restrictions and certain social determinants of health. As a result, Phase I oncology trials are not always representative of the general population, and this may perpetuate health disparities.
- Recruitment and retention of under-represented groups in Phase I oncology clinical trials is essential to ensure the demographics of participants reflect the wider population at large. Focused strategies to recruit representative populations are needed, and further research is required in order to understand any barriers to participation.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-1262

Author contributions

I Jacobs, LJ Lee, J McGinnis and KE Smoyer contributed to the design, planning and conception of the study, as well as data interpretation and manuscript development. DR Camidge, H Park, Z Askerova and Y Zakharia contributed to data interpretation and manuscript development. All authors reviewed manuscript drafts and have reviewed and approved the final version for submission.

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Merck, Pfizer, Phosplatin, Psioxus, Rain, Roche/Genentech, Seattle Genetics, Symphogen, Takeda and Tolero. H Park has received funding paid to institution as PI for company sponsored trials from Ambrx, Amgen, Aprea Therapeutics AB, Array BioPharma, Bayer, BeiGene, BJ Bioscience, Bristol-Myers Squibb, Daiichi Pharmaceutical, Eli Lilly, EMD Serono, Five Prime Therapeutics, Genentech, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Hoffman-LaRoche, ImmuneOncia Therapeutics, Immunomedics, Incyte, Jounce Therapeutics, Mabspace Biosciences, MacroGenics, Medimmune, Medivation, MERCK, Mirati Therapeutics, Novartis Pharmaceuticals, Oncologie, Pfizer, PsiOxus Therapeutics, Puma Biotechnology, Regeneron Pharmaceuticals, Seattle Genetics, Synermore Biologics, Taiho Pharmaceutical, TopAlliance Biosciences, Turning Point Therapeutics, Vedanta Biosciences, Vertex Pharmaceuticals and Xencor, Inc. K Smoyer is an employee and shareholder of Envision Pharma Group, which was paid by Pfizer to conduct this study. I Jacobs, LJ Lee and Z Askerova are employees of and own stock in Pfizer, Inc. J McGinnis was a Pfizer, Inc. employee and stockholder at the time this study was conducted. Y Zakharia has served on advisory boards for Amgen, Roche Diagnostics, Novartis, Janssen, Eisai, Exelixis, Castle Bioscience, Array, Bayer, Pfizer, Clovis and EMD Serono; has received grant/research funding for Institution Investigator Initiated clinical trials from Pfizer, Exelixis, Eisai and DSMC: Janssen Research and Development; and received consultant honorarium as a consultant for Pfizer and Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Review

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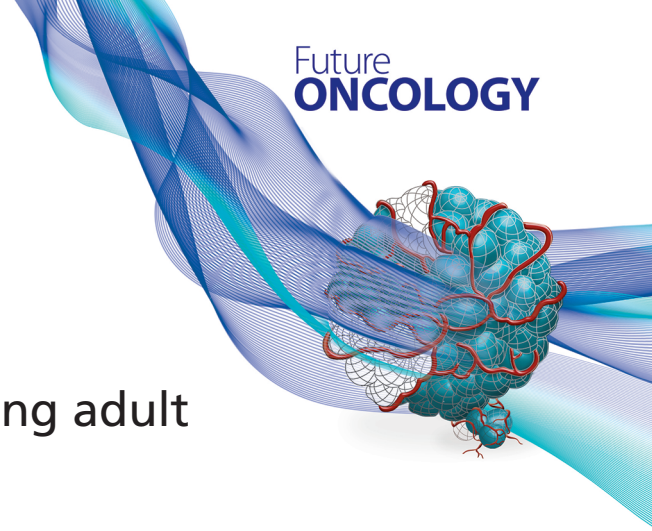

A call to action: Antiracist patient engagement in adolescent and young adult oncology research and advocacy

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Amidst the concurrent global crises of coronavirus disease 2019 (COVID-19), uprisings against Anti-Black racism and police brutality, as well as anti-Asian racism and violence, the field of medicine found itself simultaneously called upon to respond as essential workers in the public health devastation of COVID-19, and as representatives of healthcare institutions wrought with the impacts of systemic racism. Clinicians, researchers, and advocates in adolescent and young adult (AYA) oncology, must come together in authentic activism to begin the work of creating structural change to advance antiracist approaches to patient engagement in AYA oncology research and advocacy. Critical review of existing practices is needed to ensure that ethical and effective research methods are employed when engaging with racial and ethnic minority AYA patients with cancer, who may be particularly vulnerable and exploited in the current context.

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On the evening of Monday, 25 May 2020, amidst a surging coronavirus disease 2019 (COVID-19) pandemic, George Floyd, an unarmed 46-year-old Black man, was murdered. Mr Floyd was murdered by police, while in their custody for allegedly attempting to use a counterfeit US$20 bill to purchase a pack of cigarettes. The viral video of the murder prompted mass protests and uprisings worldwide. Across every industry sector, organizations declared that Black Lives Matter in their respective missions.

These concurrent global crises exposed long-standing power structures that have benefitted white citizens, while imposing a greater burden of disease, mortality, and psychosocial harm on racial/ethnic minorities. Racial consciousness among non-Black people was raised to such a compelling level that predominantly white institutions responded to the negative impacts of persistent racism and health disparities suffered by our Black citizens. Following Mr Floyd's murder, heightened global interest in the problem of racism and police brutality retrospectively amplified other recent murders of unarmed African–Americans. On a Sunday afternoon, 3 months earlier (23 February 2020), Ahmaud Arbery, a 25-year-old Black man, was jogging in a residential neighborhood when he was fatally gunned down by two white vigilantes who racially profiled and pursued him. In the dead of night on Friday,13 March

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2020, 2 months prior to Mr Floyd's murder, Breonna Taylor, a 26-year-old Black healthcare worker, was murdered in her own home during a police raid by two white plainclothed officers.

As the COVID-19 outbreak drastically altered our social world, vast misinformation fueled public fears, xenophobia, and a sharp increase in violence and racism against Asian people and their communities across the globe. According to the Center for the Study of Hate Crime and Extremism, anti-Asian hate crimes in the United States' major cities increased by 145% between 2019 and 2020, despite an overall decrease of 6% for the general population [1]. Meanwhile, the Stop AAPI (Asian American and Pacific Islander) Hate reporting center received 3,795 reports of anti-Asian incidents during the one-year period from March 19, 2020 to 28 February 2021, noting that these data represent only a fraction of the actual number of anti-Asian incidents [2]. In the early evening of Tuesday, 16 March 2021, against this backdrop of increasing anti-Asian sentiment over the preceding year, a series of related mass shootings occurred at three spas in Atlanta (GA, USA). A white gunman killed eight people, six of whom were Asian women: Soon Chung Park, Hyun Jung Grant, Sun Cha Kim, Yong Ae Yue, Delaina Ashley Yaun, Paul Andre Michels, Xiaojie Tan and Daoyou Feng. One person was left severely wounded: Elcias Hernandez-Ortiz [3].

In effect, practitioners in the field of medicine became active stakeholders in two simultaneous sociopolitical disasters, as front-line essential workers in the public health devastation of COVID-19, and as representatives of healthcare institutions wrought by the impacts of perpetuating a long history of systemic racism. To date, responses from the medical community have included calls to action for antiracist approaches that support greater accountability for racial and ethnic disparities in the provision of healthcare [4,5] and the conduct of healthcare research [6,7]. The authors advise healthcare institutions on how to dismantle and replace existing systems rooted in white supremacy, thereby moving beyond insufficient traditions of mere awareness and acknowledgement on issues of racial and ethnic inequity [4–7].

In 2020, there were an estimated 89,500 new incidences of cancer among adolescents and young adults (AYA) between ages 15–39 years in the USA, which is consistent with the overall increasing trend in cancer incidence for AYAs during the recent decade (2007–2016) [8,9]. Five-year survival rates for all cancer types among AYAs have seen gradual improvements since the 1970s [8]. When disaggregated, however, racial and ethnic minority AYAs have not seen these improvements, and actually experience lower five-year survival rates for all cancer types. This worsening trend is especially observed among non-Hispanic and Black individuals, who comprise 75% of racial and ethnic minority AYAs [8,10,11].

Like the overall healthcare research sector, AYA oncology researchers have made slow progress on critical issues of health equity, including the lack of racial and ethnic diversity among principal investigators of NIH-funded studies [12–15], persistent gaps in knowledge about racial and ethnic minority AYA patients [16], and long-established racial and ethnic disparities in AYA health outcomes that have seen little or no improvement [16,17]. Even as they cope with the devastation of cancer, AYAs are still-developing patients, whose growth depends upon social interactions for firsthand experiences to meet their two primary developmental challenges: (1) learning to resolve intrapersonal conflicts between autonomy and dependence, and (2) establishing intimate interpersonal relationships [18–22]. As a consequence, AYAs may be particularly vulnerable to discrimination and exploitation by self-interested organizations. To genuinely advance antiracist AYA cancer care and research, our methods cannot continue to be rooted in racism and white supremacy. For example, BIPOC (Black, indigenous, or people of color) AYAs are commonly tokenized by predominantly white-led and white-serving organizations, who call upon individual BIPOC patients to serve as performative representatives of cancer disparities experienced by their racial group, regardless of whether that particular BIPOC AYA individual has actually experienced the disparities of interest. On research projects, racial and ethnic minority AYA patient advocates commonly find themselves utilized as token afterthoughts – asked to formally acknowledge support for research studies that they had no part in developing, and often, with implications they may not comprehend [23].

As clinicians, researchers, and advocates in AYA oncology, we come together to begin the work of creating structural change to improve patient engagement in the conduct of research in partnership with racial and ethnic minority AYA patient advocates. In a demonstration of authentic activism, we present this review and discussion of current practices in AYA oncology research and advocacy, and offer recommendations to advance an antiracist future for patient engagement. Critical review of existing research practices is needed to ensure that ethical and effective methods are employed when engaging with vulnerable racial and ethnic minority AYA patients.

Figure 1. Four domains of research according to Patient-Centered Outcomes Research Institute.
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Antiracism & engaging AYAs in the conduct of research

BIPOC patients in healthcare settings have experienced vast mistreatment in the name of research [24], from historical malicious disregard (e.g., the Tuskegee syphilis study [25]) to more recent exploitation and/or exclusion, such as disproportionately low COVID vaccine inoculation rates among Latino Americans despite their overrepresentation as essential workers during the pandemic [4]. To avoid these discriminatory practices and mitigate inherent power differentials within the research process, employing a conscious *antiracist* lens is critical for valid research focused on racial and ethnic minorities [26]. The antiracism scholar, Ibram X. Kendi, defines *racism* as a policy or idea that creates and perpetuates inequality between people of different races [27]. In contrast, *antiracism* is defined as a policy or idea that creates an equitable society for all races. Kendi poignantly asserts that, across American history, the heartbeat of racism has been denial, and the sound of that heartbeat is "I'm not a racist" [27]. He further explains that there is no such thing as a policy being *not racist* [27]. Policies are either *antiracist:* creating an equitable society; or *racist*: contributing to inequities [27]. Antiracism calls upon AYA oncology to depersonalize reactions to racism, acknowledge mistakes, and take corrective actions in a timely manner.

It is important to distinguish antiracism from *liberal multiculturalism.* Often, AYA oncology is given credit for antiracist action, when their efforts to promote cultural diversity and inclusion are, in fact, not expressions of antiracism, but rather liberal multiculturalism. Liberal multiculturalism suggests that the primary social justice issues between different cultural groups are a lack of recognition of positive contributions, misunderstandings, miscommunication, and prejudice of individuals as the root causes [26]. Refuting this oversimplification, antiracism prioritizes systemic injustice and other forms of societal oppression as the causes of inequities [27].

Given the dynamic nature of AYAs' evolving psychosocial context, inclusion of racial and ethnic minority AYAs in the conduct of research on their own terms is necessary, and must be approached with both antiracism and developmental appropriateness. Developmental psychologists acknowledge that the experience of discrimination related to being a racial or ethnic minority is an expanded adverse childhood experience (ACE), a psychological trauma associated with individual- and community-level stressors that AYAs are challenged to learn to cope with while they make passage from childhood to adulthood [28]. It follows that AYAs from racial and ethnic minority groups may be particularly susceptible to exploitation during periods of individual and societal upheaval, such as the current climate defined by COVID-19 and racial unrest [29].

PCORI framework for patient engagement

The Patient-Centered Outcomes Research Institute (PCORI) was authorized in 2010 under the Patient Protection and Affordable Care Act, and charged with generating scientific evidence to inform health decisions by engaging with patients, clinicians, payers, and other healthcare stakeholders in the research process [29]. The *PCORI Framework for Patient Engagement* is the gold standard for patient engagement in research, and organizes all activities in the research process into four domains (Figure 1) and six core principles (Table 1) [30]. Transparency-honesty-trust are

Table 1. Patient-Centered Outcomes Research Instituteengagement core principles and potential strategies.

Reciprocal Relationships
• Include patient and stakeholder partners as key personnel
• Collaboratively define clearly stated roles and inclusive decision making
Partnerships
• Request reasonable time commitments and appreciate contributions
• Demonstrate commitment to diversity and cultural humility
Colearning
• Ensure patients and other stakeholders understand the research process
• Prioritize patient-centeredness and stakeholder education
Transparency-Honesty-Trust
• Implement open and honest communication that supports inclusive decision making
• Employ transparent research processes by disseminating results to stakeholders

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presented together because they share common strategies and are dependent on one another. According to PCORI, patient engagement is defined as the involvement of patients and other stakeholders throughout the planning, conduct, and dissemination of the proposed projects. Employing an antiracist and developmentally-appropriate lens, the authors review current patient engagement practices in AYA oncology, and utilize the four domains of research according to PCORI as an organizing structure to discuss current strengths and unmet needs, while also offering recommendations to promote greater inclusion of racial and ethnic minority AYA patient perspectives.

Token versus genuine patient engagement

The current review is centered on a shared value for genuine (as opposed to token) engagement with AYA patient advocates across the research process to generate scientific evidence that responds to the highest-priority issues of relevance to AYAs following a diagnosis of cancer. Token engagement (or tokenism) in research efforts is defined as the practice of making perfunctory or symbolic efforts to include patients simply for the sake of appearance (e.g., failing to give patients any decision-making authority while touting their involvement in publications or at conferences). In contrast, genuine engagement equips patients with real power to affect outcomes [24]. Hahn and colleagues' qualitative study (n = 50) examined conversations among key stakeholders in healthcare research (patient advocates, community clinicians, and academic researchers) in response to the question, "How do we move beyond tokenism in patient engagement?" Content analysis of participants' responses produced examples of genuine and token engagement that were subsequently categorized into three domains: (1) methods/structure of engagement, (2) intent, and (3) relationship building [24]. The authors also suggest that examples within each domain of engagement can be graded along a genuine–token continuum, with relative ratings of either more genuine or more token engagement that can in turn guide researchers interested in implementing real engagement with patients and community partners. Specifically, within the patient engagement domain of *relationship building*, one example of more genuine engagement to build trust and rapport is the presence of mutual benefits (Table 1), whereas more token engagement occurs when the benefit is not mutual [24].

Existing strengths in AYA patient engagement

One area where AYA patient engagement has achieved notable success is in the utilization of Internet-based social support networks and social media. Patient networks are effective mechanisms for the delivery of research outcomes while also ensuring that research-related communications, such as study recruitment flyers and informed consent language, are relevant to the stakeholders most impacted [32–34]. Within oncology, AYA patients are characterized by the greatest social media savvy compared with other patient care populations, which has made social media an effective medium for raising awareness about clinical trials among these so-called "digital natives" [34,35]. What's more, the COVID-19 pandemic has ignited rapid uptake of telemedicine among AYA oncology patients and providers, pointing to great potential for ever-expanding innovation in cancer care [35], and holding much promise for optimizing patient engagement at each stage of the research process [36].

A second area of strength in AYA patient engagement is the employment of cancer patients on research teams as *embodied researchers*, who hold lived experiences of the phenomena of interest while they lead its empirical investigation [37–40]. In Dei and colleagues' examination of critical issues in antiracist research methodologies, the authors emphasize the importance of *embodied knowledge* that can only be obtained through lived experience [26]. Embodied knowledge is defined as "personal feelings, emotional and spiritual connectedness, and a deep passion

Table 2. Recommendations for antiracist patient engagement in research†.

Topic selection and research prioritization
Extend timing of patient engagement Patient engagement must begin with the discussion of potential research topics, and extend to the highest levels of strategic planning.
Identify racial and ethnic disparities in research area of interest In all research, it must be incumbent on researchers to first identify if there are racial/ethnic disparities that exist in the area of study.
Increase sociodemographic diversity among AYA patient advocates Issues of recruitment and access must be examined and addressed to improve the persistent lack of sociodemographic diversity among AYA patients who serve as advisors and who provide patient-reported input.
Proposal review: design and conduct of research
Provide education and honest disclosure to AYA patient advocates Investigators must fully educate and inform patients so they can make meaningful contributions; make honest and complete disclosure to AYAs about the costs and benefits of being a patient who engages with the oncology research process.
Prioritize responsiveness to BIPOC AYAs' developmental challenges Racial and ethnic discrimination is an expanded ACE that researchers must consider, as it may influence what is developmentally appropriate for BIPOC AYAs.
Address between-group power dynamics Acknowledgement and responsiveness to power differentials between and within sociodemographic groups must be incorporated to enable true partnership.
Dissemination and implementation of results
Avoid persistent tokenism of the same AYAs AYA oncology is culpable for token use of the same patient advocates repeatedly in representation of patient perspectives in the dissemination and implementation processes.
Establish new incentives in academic research New incentives in academia are needed to ensure that research results are disseminated to the communities who will benefit from the findings, and BIPOC-embodied researchers can be instrumental to this process.
Invest additional resources and support for hard-to-reach communities Regardless of whether embodied researchers are employed, dissemination of study results to particularly hard-to-reach communities typically demands additional resources and support.
Evaluation
Rectify overrepresentation of sociodemographic privilege Participation in evaluation often requires high engagement from patient advocates at a professional level that is usually not conducive to still-developing AYAs' availability and capacity.
Optimize virtual access to evaluation events COVID-19 has demonstrated that the US healthcare system can quickly restructure itself in response to vast changes brought about by a global pandemic, which holds great promise for urgently dismantling racism, and supplanting with structures that support antiracist practices.

†Recommendations are organized according to PCORI Framework for Patient Engagement's four domains of research.
ACE: Adverse childhood experience; AYA: Adolescent and young adult; BIPOC: Black, indigenous, or person of color.

and commitment to seek knowledge and use these things to transform existing conditions as a noble cause that emanates from within the self." Patient perspective becomes an integral part at every stage of research, and can be especially valuable when patients work in research contexts investigating cancers they have had. Following the leadership of patient-turned-scientists and survivor-scientists can also inform research questions that are especially pertinent to various facets of AYA life after a cancer diagnosis and treatment [38,39]. There is increasing evidence that elevated levels of patient engagement are associated with better adherence and health outcomes, including better clinical indicators, more healthy behaviors, greater use of women's preventive screening tests, and a decrease in medical-related financial burden [41,42]. Such patient engagement can help to better examine how factors such as health disparities and cancer care delivery options affect cancer patients' survivorship and risk of recurrence [43].

Recommendations for topic selection & research prioritization

Timing of patient engagement

Patient engagement must begin with the discussion of potential research topics and extend to the highest levels of strategic planning within health systems and academic institutions (Table 2). The preponderance of current research engages patient advocates at a point where the subject matter and direction for research has already been decided [43]. This practice introduces the patient to the research process at a point where they must apply their knowledge and experience to someone else's research priorities and agenda. This conundrum likely leads to more token use of patient advocates in the validation of research topics and priorities. The most critical area for positive change to defeat this type of tokenism in research topic selection and prioritization is to have patients involved in the strategic planning of research at the highest level in health systems and academic institutions, and in doing so,

inform research priorities for grant funding at the national level [24,44]. Early and foundational engagement can transform research perspectives and significantly increase patient influence and empowerment.

Identification of existing racial and ethnic disparities

In all research, it is incumbent on researchers to first identify if there are racial or ethnic disparities that exist in the area of study (Table 2). These may be systemic or institutional barriers, clinical outcomes, social barriers, psychological challenges and so on, depending on what research is being undertaken. One of the very first questions in the selection of a research topic relevant to racial and ethnic minority AYA patients with cancer should be whether the research can have a positive impact on reducing health-related inequities. Research questions should be shaped by the answers to these questions from the outset [28].

Socioeconomic diversity among AYA patient advocates

Issues of recruitment and access must be examined and addressed to improve the persistent lack of socioeconomic diversity among AYA patients who serve as advisors and provide patient-reported input (Table 2). The majority of patient advocates who advise on research studies tend to be white, higher socioeconomic status, well educated, and well connected to supportive care [26]. Consequently, AYAs are commonly described as a monolithic body, despite encompassing a wide range of chronological ages, developmental stages, and life experiences. Patient advocates engaged with the research process are often a reflection of those who have participated in clinical trial studies, and data shows that the preponderance of AYA enrollees in oncology cooperative group clinical trials are male and white [45]. Per the National Cancer Institute's (NCI) SWOG (formerly the Southwest Oncology Group) Cancer Research Network's experience from 1993 to 2017, SWOG AYA patients were less female (44.7% vs 48.8%, $p < 0.0001$), Black (10.4% vs 11.8%, $p = 0.0001$), and Hispanic (8.0% vs 12.4%, $p < 0.0001$) than AYA patients in the United States cancer population [46]. Thus, there is under-representation of BIPOC in both the available data and in the representation of advocates who participate in guiding research agendas.

Recommendations for proposal review: design & conduct of research

Education & honest disclosure to AYA patient advocates

To truly engage racial and ethnic minority AYA patients in designing and conducting research, investigators must be sure to fully educate and inform patients so they can make meaningful contributions (Table 2). Much research in both scientific and health services is clouded by the language and mystique of the specialist area [47,48]. Researchers may have had a lifetime of education and engagement in their chosen research area. To create true equality in patient engagement, these still-developing patients must come to fully understand the purpose, design, and conduct of the research [24,49]. If the investigators make independent decisions on study procedures, and subsequently convene the community advisory group to simply approve what is already decided, then genuine patient engagement has not been achieved.

Furthermore, honest and complete disclosure to AYAs about the costs and benefits of being a patient with cancer who engages with the oncology research process is necessary (Table 2). There is too much conversation about resiliency and grit and not enough about the physical and emotional costs of patient advocacy work. For racial and ethnic minority AYA patients with cancer, this cost is especially notable [50]. When engaging with racial and ethnic minority AYA patient advocates, a trauma-informed approach should be part of antiracist research methods [28].

Genuine education and disclosure to AYA patient advocates means using the preferred natural language of the patient (e.g., plain English) in dialogue and written materials [51,52], giving space and time for understanding [24], and encouraging and supporting advocacy to instill confidence to challenge, question, and debate [24]. At a structural level, researchers and their teams should be expected to demonstrate genuine patient engagement to their institutions [53], and show evidence of patient satisfaction in study design and conduct [51]. Institutions and research systems must modify their own policies and practices to enable and support researchers to deliver genuine patient engagement [53]. Genuine patient engagement should be acknowledged and valued by academia, in line with publications that are the *de facto* currency of academic success and productivity. The process of engagement itself—establishing genuine relations with patient advocates who share the same ultimate goal to improve real-world health challenges—is as valuable as the research outcomes [51].

Responding to BIPOC AYAs' developmental challenges

Racial and ethnic discrimination is an expanded ACE that researchers must consider, as it may influence what is developmentally appropriate for BIPOC AYAs (Table 2). BIPOC AYAs are at greater risk of experiencing trauma because of societal treatment based on their status as racial or ethnic minorities, potentially resulting in unique developmental issues [28]. Expanding the body of research that is inclusive of BIPOC AYAs, and acknowledges the distinct developmental challenges of adolescence (identity formation) and young adulthood (engagement in personal and professional relationships), is essential [26,54,55]. Current programs supporting academic, career, financial, and personal needs of AYAs ensure that good medical outcomes do not come at the cost of failure in these developmental domains. When BIPOC AYAs are represented in research, and not only singled out for isolated studies, AYA oncology will be better-equipped to generate a nuanced understanding of the impact of a cancer diagnosis across the various stages of psychosocial development (identity, independence, relationships, goal setting, and self-sufficiency) that captures sociodemographic influences for the entirety of the AYA population.

Awareness & responsiveness to between-group power dynamics

Acknowledgement and responsiveness to power differentials between and within sociodemographic groups must be incorporated to enable true partnership in research (Table 2). In the current discussion around racism and the intersectionality of multiple sociodemographic identities, we are missing much-needed dialogue about what group membership means, and the power that comes with membership or nonmembership in a certain group [28,56] What that discussion is missing is recognition of power hierarchies across groups. For example, higher socioeconomic status influences one's intersectional experience of other aspects of identity, such as race and gender [56]. Similarly, there have not been enough conversations about how these groups come together, and the power differentials that may compromise a true partnership [53,56,57].

Recommendations for dissemination & implementation of results

Persistent tokenism of the same AYAs

AYA oncology is culpable for repeated token use of the same patient advocates in representation of patient perspectives in the dissemination and implementation processes (Table 2). Consequently, oncology researchers are not connecting with hard-to-reach AYAs who may be in great need of, but remain excluded from, participation in such research activities [58]. These communities are not as hard to reach as we think. We simply need to include stakeholders with meaningful ties to racial and ethnic minority communities to lead and champion—not just participate symbolically—in dissemination and implementation [24,26]. Representation of various patient perspectives helps limit the erasure, omission, and misconstruing of diverse BIPOC experiences, moving away from a Eurocentric paradigm [16].

Tokenizing the same AYAs is akin to research bias from convenience sampling, which produces results that are not representative of the entire population of interest. In this case, the bias swings toward the dominant culture and those AYAs who are well connected to the healthcare system, receiving adequate cancer care, and have their medical and psychosocial needs met. To prevent such bias, AYA oncology researchers should adopt a community-based participatory research (CBPR) approach for building authentic relations with hard-to-reach populations, as has proven successful in public health settings [59–61]. Following long-established best practices for outreach to socially disadvantaged groups, such as planning for higher resourcing and operating costs via community partnerships, is critical to securing representation from racial and ethnic minority AYAs, who are more likely to face issues of access and barriers to care [62].

New incentives in academia & BIPOC-embodied researchers

New incentives in academia are needed to ensure that research results are disseminated to the communities that will benefit from these findings, and BIPOC-embodied researchers can be instrumental to this process (Table 2). PCORI focuses on the dissemination and implementation phase so heavily because it is evident that genuine patient engagement at this stage of research is lacking [30,63]. Academic researchers are incentivized and evaluated based on research grants and peer-reviewed publications [64]. Thinking beyond that sphere into real-world contexts can be challenging. It takes time for research to get from bench to bedside, and then to community [65], and that's if it even makes it into the community. Some social scientists in AYA oncology believe their job ends with journal publication [66].

Additionally, it is problematic that the field of oncology research only considers certain types of people – those without lived experience of the research topics – to have the capacity for scientific objectivity. BIPOC researchers and patients are commonly assumed not to be objective [67]; "It's '*me*-search,' not research." Critics erroneously believe that their embodiment of lived experiences is synonymous with investigator bias and at odds with rigor, as BIPOC researchers choose to focus on research topics of pertinence to their own communities. But all researchers will always have their own theories – implicit or explicit – about what they are attempting to investigate, regardless of whether they have embodied experiences similar to their study participants. BIPOC embodied researchers may be uniquely equipped to pursue inquiries on topics and in ways that might not otherwise be derived. They are necessary contributors to the scientific knowledge base, who may also have exclusive access to BIPOC stakeholders and communities that directly benefit from the results of their research [37–40].

Additional resources & support for hard-to-reach communities

Regardless of whether embodied researchers are employed, dissemination of study results to particularly hard-to-reach communities typically demands additional resources and operational support (Table 2) [26]. For example, research where the outcomes suggest that some form of information and education campaign is needed to change health behaviors must ensure that these findings are presented to the appropriate community leaders and decision makers, who can respond and support further dissemination and implementation of findings. Research should not be undertaken unless there is a clear plan for sharing the study results with the relevant communities [24,26]. Publication of findings should never be the only goal of research. Publication is only dissemination within the scientific community, especially when articles are located behind cost-prohibitive paywalls; therefore, it must be accompanied by a plan to inform change where change is needed [68].

Recommendations for evaluation

Overrepresentation of sociodemographic privilege

Participation in evaluation often requires high engagement from patient advocates at a professional level that is usually not conducive to still-developing AYAs' availability and capacity (Table 2). It must almost become the patient advocate's full-time job to stay engaged with late-breaking research [43]. This can prove a burden for the average patient [53], and may be particularly burdensome for racial and ethnic minority AYAs, who might have limited resources and face additional barriers to engagement. Given these practical hurdles, patients who are engaged in advocacy tend to be of higher socioeconomic status, often retirees, who have available time and resources to withstand the structures of reimbursement for expenses such as travel [53]. Organizational structures for inclusion of patient engagement are not friendly to patients who are not part of an overwhelmingly white, select, often socially elite, and culturally dominant group [53].

Virtual access to evaluation events

COVID-19 has demonstrated that the United States healthcare system can quickly restructure itself in response to tremendous changes brought about by a global pandemic. This holds great promise for urgently dismantling racism, and supplanting with structures that support antiracist practices, if we so choose (Table 2). For example, before COVID-19 put limits on research conferences and travel, evaluation often required in-person attendance at conferences, with potentially prohibitive travel expenses and less-than-hospitable or unclear organization of group meetings. When research conferences moved to virtual platforms, patient advocates were given opportunities to participate without incurring high costs. Due to the multiplicity of potentially confounding factors, it may be difficult to determine whether increased participation in oncology meetings among racial and ethnic minority participants has been observed during the COVID-19 pandemic, and whether this increase is associated with the greater accessibility of a digital platform. The proliferation of digital technologies spurred by COVID-19 may be positive encouragement for further examination of digital dissemination and evaluation approaches aimed at improving access to presentations of late-breaking research for at least a subset of racial and ethnic minority AYA patient advocates.

PCORI's Core Principles of Patient Engagement

Across the aforementioned four domains of research activities, *transparency-honesty-trust* is the most salient patient engagement principle when engaging with racial and ethnic minority AYA patients with cancer. Table 1 shows PCORI's six principles of patient engagement, with transparency-honesty-trust presented in combination

as principles four through six. For racial and ethnic minorities, who have historically been marginalized, lied to, experimented on, oppressed, ignored, and traumatized by healthcare systems, this principle is especially critical [50]. Transparency-honesty-trust is the only successful route from information to implementation. Without the belief that the benefit is ultimately the patient's, there can never be buy-in, especially in a population that bears skepticism as necessary armor.

As clinicians, service providers, researchers and advocates in health settings, we bring this systemic track record to our patient encounters. Healthcare institutions must create relationships where racial and ethnic minority AYA cancer patients will not (re-)experience historical discrimination or trauma [69]. In order to do that, enacting durable structural changes that enable relationships based on a solid foundation of transparency-honesty-trust is paramount (Table 1); we must start there to get to the other principles of engagement–reciprocal relationships, partnerships, and colearning [70]. Genuine, not token, engagement begins there.

One major challenge to upholding the principle of transparency-honesty-trust is the lack of BIPOC in leadership roles within research and advocacy that have the resources, available time, and power to create meaningful change. Less than 2.4% of the National Institutes of Health (NIH) grant application reviewers are Black or African American [71], and only 1.5% of R01 grant applications received by NIH are from Black or African American investigators [72]. Hoppe and colleagues' study of NIH grant application review and award trends between 2011 and 2015, found that relative to white investigators, Black or African-American investigators tend to propose research topics with low award rates, such as research at the community and population level, as opposed to more basic science-oriented and mechanistic investigations that achieve higher award rates [71]. To reverse this trend, the funding priorities of grant makers, the majority of whom are white, should be informed by the work of Black investigators and their communities, rather than vice-versa. In order for predominantly white leadership to build systems of research to ensure transparency-honesty-trust for racial and ethnic minority patients, it must be demanded by funding criteria, rather than relying on intrinsic motivation. Additionally, genuine patient engagement may require AYA oncology leaders to accept that research structures themselves might need to change and adapt to accommodate diversity [24,26,56]. Academic and institutional policies that support structural racism must be removed and/or rewritten to fix systems that perpetuate inequities among racial and ethnic minorities. For example, the R01 Transformative Research Award is the highest research grant offered by NIH. Current criteria for membership on NIH R01 proposal review committees requires that these select reviewers must themselves be a previously-funded principal investigator of an NIH R01 award. BIPOC researchers remain sharply underrepresented among NIH-funded principal investigators [12–14]. Thus, such a policy perpetuates a long history of underinvestment in projects driven by the needs and perspectives of BIPOC researchers and their communities [13].

Furthermore, AYA oncology researchers must approach patient engagement with racial and ethnic minority AYAs with openness and adaptability to ensure that trust and engagement centers on addressing patient advocates' experiences of power differences, rather than researchers' tolerance of racial and ethnic diversity [24,26]. In this authentic process, researchers must prioritize a readiness to move out of their comfort zones and away from traditions of maladaptive strategies to truly accommodate difference [56]. In order to advance antiracist transformation, researchers and their institutions must commit to continuous personal and institutional practices of unlearning, re-evaluating, and responding to implicit biases, thereby cultivating *cultural humility* in an environment that facilitates growth [73].

Compensation for patient advocates should be compulsory. Financial compensation for contributions to research projects is especially necessary for BIPOC AYA patient advocates, given that participation may be particularly burdensome due to their transitional life stage, high risk of financial hardship resulting from the disruption of cancer on their work lives, and often, lack of generational wealth [74,75]. PCORI provides a model for addressing fair compensation for engaged research partners that organizes patient engagement into four levels from lowest to highest contribution of effort: inform, consult, collaborate, and stakeholder directed (Table 3) [76]. According to PCORI's framework for financial compensation, corresponding levels of compensation at each level of contribution may vary. This framework can benefit from further details on the amount and process of financial compensation. For example, naming a timeframe for compensation within which patient advocates can anticipate the balance due to them and providing a validated formula (e.g., based in comparable industry standards such as market rate for similar consultation and federal per diem rates) that researchers can use to calculate a fair and equitable amount of compensation at each level of patient engagement in a given research study.

Table 3. Sample model addressing fair compensation for engaged research partners.

Engagement activity levels		Varying compensation levels
I. Inform	Simply informing	Communicating plans to the patient community
II. Consult	Consulting on decision	Offering opinions, advice, feedback
III. Collaborate	Deciding together, acting together	Joint decisions solicited, taking actions jointly
IV. Stakeholder directed	Encouraging independent initiatives	Leading to patient/caregiver/organization-generated research

Conclusion

Although structural racism and white supremacy in patient engagement may be a seemingly intractable challenge, we have begun the conversation by employing an antiracist and developmentally-appropriate lens to critique current patient engagement practices in AYA oncology research and advocacy. We utilized the PCORI framework of patient engagement as an organizing structure to present our review and recommendations, aimed at advancing greater inclusivity of racial and ethnic minority AYAs and genuine approaches to patient engagement toward this goal. The PCORI principles of patient engagement ground the discussion in shared values for bolstering transparency-honesty-trust with patients across the research process.

Future perspective

The first decade-and-a-half of AYA oncology brought greater research attention and increased empirical knowledge of the lack of improvement in survival rates and constellation of unique psychosocial challenges for patients diagnosed between ages 15–39 years. In the next phase of growth for AYA oncology, we challenge the field to pursue its research questions with structural reinforcements to prevent unnecessary harm to racial and ethnic minority patients engaged in the conduct of research. We are optimistic that the interprofessional community of AYA oncology can sustain positive progress with antiracist approaches to patient engagement by working together in authentic activism to erect durable structures that encourage, support and incentivize genuine efforts.

Future research should investigate the perspectives of racial and ethnic minority AYA patients and their responses to the recommendations proposed in our current discussion among AYA oncology professionals. Such an endeavor would produce scientific evidence on antiracist patient engagement that is validated by AYAs themselves, through meaningful collaboration between researchers and key stakeholders. Authentic activism from AYA oncology professionals and greater representation of racial and ethnic minority AYA patients in the development of patient engagement strategies are essential to effectively inform genuine antiracist and developmentally-appropriate patient engagement in AYA oncology.

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Executive summary

- Amidst concurrent global crises of COVID-19, uprisings against anti-Black racism and police brutality, as well as anti-Asian racism and violence, the field of medicine found itself simultaneously called to respond as both essential workers and representatives of healthcare institutions wrestling with systemic racism.
- COVID-19 is proof-positive that massive structural changes in healthcare are possible with sufficient impetus to adapt to a crisis.

Antiracism & engaging AYAs in the conduct of research

- Antiracist patient engagement in the conduct of adolescent and young adult (AYA) oncology research requires approaches that value both antiracism and developmental appropriateness, given Black, indigenous, and people of color (BIPOC) AYAs' dynamic psychosocial context, and their unique experience of expanded adverse childhood experiences (ACE) associated with racial and ethnic discrimination.

PCORI framework for patient engagement

- By employing an antiracist and developmentally-appropriate lens, we review current patient engagement practices in AYA oncology, and utilize the *PCORI Framework for Patient Engagement* as an organizing structure to discuss current strengths and unmet needs, and offer recommendations to promote greater inclusion of racial and ethnic minority AYA patient perspectives.

Token versus genuine patient engagement

- This review is centered on a shared value for genuine (as opposed to token) engagement with AYA patients across the cancer-research process, which requires shared values for both antiracism and developmental appropriateness given the dynamic nature of AYAs' evolving psychosocial context.

Recommendations for topic selection & research prioritization

- Patient engagement must begin with the discussion of potential research topics, and extend to the highest levels of strategic planning within health systems and academic institutions.
- In all research, it must be incumbent on researchers to first identify whether there are racial or ethnic disparities that exist in the area of study.
- Issues of recruitment and access must be examined and addressed to improve the persistent lack of sociodemographic diversity among AYA patients who serve as advisors, and who provide patient-reported input.

Recommendations for proposal review: Design & conduct of research

- To truly engage racial and ethnic minority AYA patients in designing and conducting research, investigators must fully educate and inform patients so they can make meaningful contributions.
- Honest and complete disclosure to AYAs about the costs and benefits of being a patient with cancer engaged with the oncology research process is necessary.
- Racial and ethnic discrimination is an expanded adverse childhood experience (ACE) that researchers must consider, as it may influence what is developmentally appropriate for BIPOC AYAs.
- Acknowledgement and responsiveness to power differentials between and within sociodemographic groups must be incorporated to enable true partnership in research.
- AYA oncology is culpable for token use of the same patient advocates repeatedly in representation of patient perspectives in the dissemination and implementation processes, which is akin to research bias from convenience sampling and produces results that are not representative of the entire population of interest.
- New incentives in academia are needed to ensure that research results are disseminated to the communities that will benefit from the findings, and BIPOC-embodied researchers can be instrumental to this process.

Recommendations for dissemination & implementation of results

- Dissemination of study results to particularly hard-to-reach communities typically demands additional resources and operational support.

Recommendations for evaluation

- Participation in evaluation often requires high engagement from patient advocates at a professional level that is usually not conducive to still-developing AYAs' availability and capacity.

PCORI's core principles of patient engagement

- Transparency-honesty-trust is the key principle for advancing genuine patient engagement over tokenism.

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SPECIAL FOCUS ISSUE | Patient Engagement in Cancer Research

Commentary

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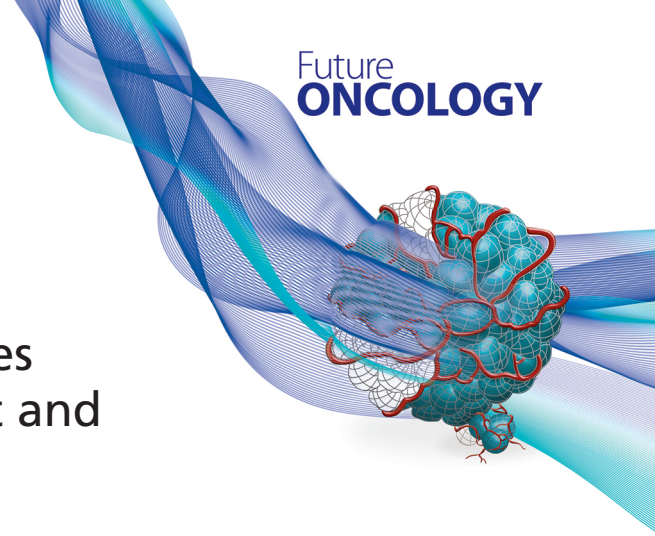

The future of oncology care requires integration of patient engagement and equity into practice

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> "As oncology professionals, we have the capacity *right now* to critically evaluate our operations for equity, to intentionally address medical, social and economic conditions and to bring patient-level precision into precision medicine for cancer. Now is the moment for each of us involved in oncology, individual and organization alike, to take the next step."

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Cancer is a global and national public health challenge, taking an estimated 10 million lives and costing more than US$1 trillion annually [1]. Cancer is also a case study in health disparities – the burden of who gets sick, who gets treated and who survives is distributed unevenly, with the greatest suffering experienced by low- and middle-income countries worldwide [1] and by communities of color in the USA [2].

Structural racism has its roots in the trans-Atlantic slave trade and spreads its branches into every aspect of daily living for black communities in the USA, including health care [3]. 'Structural racism' as a term describes how societal practices reinforce racial discrimination through 'mutually reinforcing systems,' with the consequence of systemically proliferating 'discriminatory beliefs, values, and distribution of resources' [4]. Recognition of its impact is not new. In 1946, President Harry Truman signed the Hill–Burton Act into law, which was a monumental step forward in addressing unequal care and treatment in the USA [5]. In 2003, the Institute of Medicine report 'Unequal Treatment – Confronting Racial and Ethnic Disparities in Health Care' highlighted that legacy of racism in healthcare in the USA by cataloging how racial and ethnic minorities are less likely to receive preventive medical care than whites – and receive lower-quality care once diagnosed [6].

Systemic transformation in equitable cancer care requires an acknowledgment of structural racism as a root cause of disparities [3] through embedded structures that determine eligibility and that route people to a given course of care, such as cancer risk assessment models, screening guidelines, treatment center locations, instrument calibration formulas, outcome measures and endpoints. A shared vision for equitable, high-quality care integrates patient engagement practices and antiracism strategies with health information technologies to correct these structural inequities and address cancer risk factors related to biology, patient behavior and timely access to care across populations. Further, systemic transformation requires that individuals and institutions alike accept accountability for our role in the system and commit to driving change through personal actions.

This article describes these opportunities and the actions that we can all take right now to begin dismantling structural racism in cancer and to reimagine a system that delivers equitable quality care that results in better outcomes across populations. Although our discussion describes structural disparities specific to the US black experience, we hope that the perspectives and approaches offered may also inform ways to better serve other marginalized populations living with cancer, including LGBTQ communities and people with disabilities.

Future Medicine

Five priorities for transforming equitable cancer care over the next 10 years

The Cancer Continuum of Care extends through screening, diagnosis, treatment (including clinical research participation) and survivorship; there are opportunities within and across these domains to transform care for the populations experiencing the poorest outcomes [7].

Accelerate 'stage shift' by developing & adopting emerging early detection technologies & corresponding treatment options in early-stage cancer clinical care and research

Only five cancer types have established and recommended screenings: breast, cervical, colorectal, prostate and lung cancer [8]. For cancer types without screening modalities, such as esophageal, pancreatic, kidney, ovarian and stomach, emerging technologies for multicancer early detection (MCED) offer the promise of earlier detection, diagnosis and treatment. Via a blood draw, these tests can detect multiple types of cancers before individuals become symptomatic. Racial and ethnic minorities in the US are among those diagnosed with unscreened cancers at later stages compared to non-Hispanic whites. Continued development, adoption and access to these technologies may lead to better and more equitable cancer outcomes for these populations.

There are no guarantees, however. Risk assessment models, such as the GAIL model for metastatic breast cancer, need continuous improvement to end exclusion of nonwhite populations [9] from screening and care pathways. Incentives are needed to promote the continued development of early detection technologies [8] as well as to measure the impact of early detection and screening for diverse populations [10]. Relevant clinical guidelines, recommendations, new treatment options and payer coverage must keep pace with MCED technology development, with particular focus on the needs of minority communities [8]. Trusted patient and community advocates can help in the cocreation of health literate and culturally competent community outreach and education materials about cancer risk, prevention and early detection [2,8].

Integrate community oncology settings in clinical trials networks

Community oncology practices offer a multidisciplinary team approach to treat cancer patients locally; these practices are not typically part of a larger hospital system or academic research center and are located in urban as well as rural geographies. Approximately 55% of cancer patients in the US are cared for in community oncology practices [11].

Engaging community oncology practices in cancer clinical research can be part of a strategy to improve care outcomes as measured by guideline adherence [12]. Oncology experts and regulatory officials increasingly recognize the role that community oncology can play in ensuring that cancer research participant populations represent the diversity of the patient population and generate generalizable data. US FDA drug development director Janet Woodcock advocates for integrating community oncology into a 'national clinical trial capacity stockpile,' a strategy that would make clinical trials available to patients regardless of their proximity to the academic medical centers where most clinical research is conducted [13].

In parallel, the American Society of Clinical Oncology (ASCO) is partnering with the Association of Community Cancer Centers (ACCC) to help community cancer centers assess and build their capacity to offer clinical trial options to patient populations who are traditionally underrepresented in research. The initial ASCO–ACCC initiative begins with a pilot project testing tools such as a diversity site assessment tool and implicit bias training to determine the outcomes related to 'structural and procedural factors' at a site that may influence clinical trial screening and participation rates [14].

Adopt, study & publish impact of expanding eligibility criteria in clinical trials

In 2016, ASCO and Friends of Cancer Research (FOCR) began a joint effort to expand inclusion criteria for cancer clinical trials, recognizing that existing exclusion criteria may be disproportionately leaving out cancer patients of color, women and the elderly (75+) and inhibiting the development of representative data [15]. Facilitating multistakeholder working groups including clinicians, patient advocates, drug development manufacturers and researchers, ASCO-FOCR issued consensus recommendations and guidance documents related to multiple topics in cancer protocol development: brain metastases, virus infections (HIV/AIDS, hepatitis B, hepatitis C), organ dysfunction and prior and concurrent malignancies, and minimum age for enrollment. Subsequent recommendations now include washout periods and concomitant medications, performance status, prior therapies, laboratory reference ranges and testing intervals [15].

The collaboration encourages researchers to study and publish the impact of adopting these guidelines on participation demographics and patient access to research options through real-world analysis. In one study of non-small-cell lung cancer (NSCLC), researchers found that adopting the new criteria in three areas – brain metastases, no other malignancies and creatinine clearance – nearly doubled the pool of eligible participants compared with traditional criteria, in particular allowing more women and elderly patients to participate as well as those with stage IV NSCLC [16].

Adopt digital endpoints to accelerate decentralized clinical trials

The onset of COVID-19 has jump-started interest in and innovation for decentralized clinical trials. Decentralized clinical trials allow for some study-related activities and monitoring to take place remotely, away from the investigator site, through the use of 'administrative and technological support; virtual platforms (including telemedicine), and (patient) in-home services' [17]. Since March 2020, the FDA has issued guidance allowing the use of 'alternative methods' to replace on-site study visits for safety assessments to ensure the safety of clinical trial participants and staff during the conduct of a clinical trial [18].

By reducing access burdens for patients and enabling more clinicians to participate, decentralized clinical trials offer promise in expanding and diversifying clinical research participation [17]. The development and adoption of digital clinical measures and endpoints is necessary for decentralized clinical trials to achieve this promise [19]. Digital clinical measures and endpoints are achieved when digital sensors are used to transmit signals from patients on factors related to their clinical care, such as monitoring performance status or vital signs. The Digital Medicine Society (DiME), a professional organization for experts in digital medicine, reports that there are no digital measures or endpoints being used in industry-sponsored clinical trials for oncology medical products among the 166 unique digital endpoints contained in its library, or among the seven under evaluation by the FDA [20].

Consensus-defined best practices in clinical care, technology development and operations exist to support the development of digital endpoints to enable safe and equitable delivery of quality oncology care outside of the clinic or investigator site [20]. The opportunity is now for sponsors to invest in the development of these endpoints and implement them in oncology clinical trials [19].

Focus institutions on inclusion in the workplace, professional associations & in operational practices

The personal bond between patients and their providers is an essential element to individual patient engagement [21]. Research suggests that people experience better care when they share a race, ethnicity and/or cultural identity with their providers [22]. In 2020, a team of researchers from Penn Medicine published results of a large survey concluding that patients who shared the same racial or ethnic background as their physician were more likely to give the maximum patient rating score [23].

Oncology institutions, including medical practices, health systems, professional associations, advocacy organizations and the medical products industry, have expressed a commitment to equity, particularly over the past year in the US, where the disparities associated with COVID-19 and the deadly consequences of overpolicing have become impossible to overlook and accept.

Oncology institutions have work to do when it comes to representation among the professional ranks in the USA. In 2019, Dr. Robert Winn of the Massey Cancer Center at Virginia Commonwealth University became only the second Black director of one of the National Cancer Institute's 71 federally designated cancer centers since the program began 50 years ago [24]. Other statistics confirm this disparity: studies suggest that nearly 60% of the oncology workforce is white [25]; female physicians of color are less represented than white males in oncology practice and in academic leadership positions [26] and in cancer research grants [27].

A vision for patient-centered, antiracist cancer care

An antiracist, patient-centered system for cancer care relies on the interdependence of the patient engagement, antiracism and health information technology (health IT) across four patient population levels: Patient, Practice (Organization), Population and Public. Activities related to patient engagement and inclusion at each level facilitate and mutually reinforce interventions to support the collection, analysis and use of cancer care and research data to inform guidelines, influence policies and ultimately improve care and outcomes, as illustrated in the health IT interoperability roadmap (Figure 1) [28].

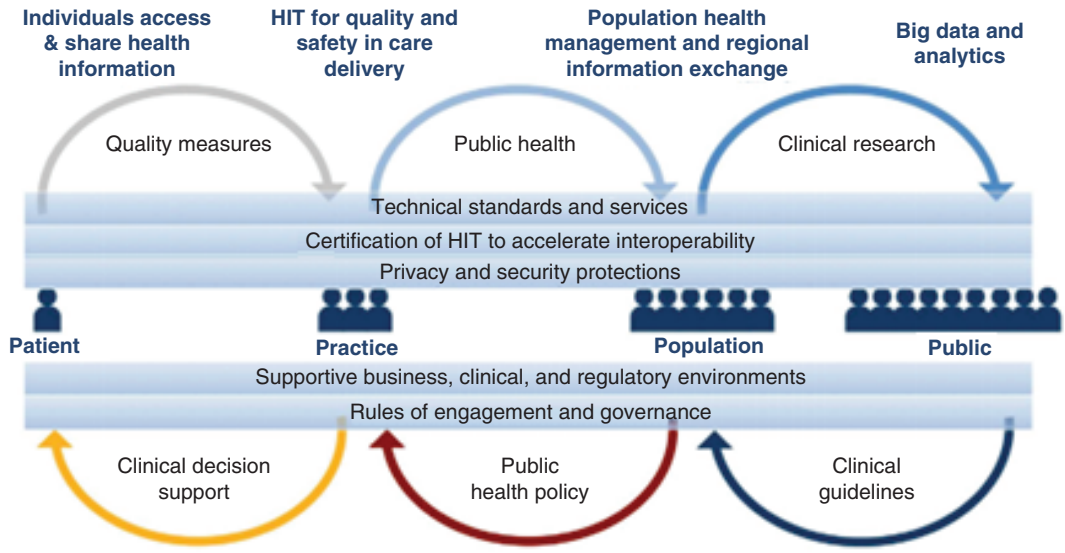

Figure 1. Interoperability across the health information technology ecosystem and different levels of care.
HIT: Health information technology.
Reprinted from [28].

Patient

Activities at the patient level revolve around strategies and tools to empower an individual patient, support individual behavior modification, elicit preferences, surface implicit bias and facilitate shared decision-making and document this information in the electronic patient record. Decision support materials are an example of an intervention at this level. Researchers may redesign traditional clinical trial recruitment materials to offer decision support to a patient during informed consent. These materials contain essential information specified by individual patients to help them decide with their providers if a given trial option is right for them [29].

Practice (organization)

This level relates to an individual practice or other health care organization. Strategies and tools at this level support organizational culture and operational practices, particularly as they relate to patient care coordination and health system referrals. They may also include nonmedical business functions that affect a community's social determinants of health, such as workforce hiring and compensation, budgeting, facilities placement and operations and procurement practices. An organization may establish a community and/or patient advisory council to inform the organization's protocols, policies and procedures for developing and delivering care. Cancer care success factors include investment in facilities or collaborations that allow accuracy in molecular profiling and precision diagnostics [7,21] as well as in interoperable health IT systems, such as electronic medical records synced with clinical trial management systems, combined with opt-in features in the patient portal for patients to indicate preferences [21]. Further operational success factors include mechanisms for collecting and reporting data on the patient race and ethnicity when assessing patient engagement initiatives [21] and employing staff and community volunteers as patient navigators [21].

Population

Stakeholders identify the cancer patient population by disease, geography and demographic factors. Data are collected and analyzed to see the population in terms of aggregated disease status and health outcomes, comorbidities and health care utilization of treatments and services, including health care setting and health insurance. The disparate, negative consequences of structural racism and policies, such as neighborhood red-lining, on community health become apparent.

Interventions at this level relate to engaging patients and caregivers in cancer disease registries, clinical trials and in technology use, such as telemedicine and wearables, to deliver comprehensive care. Specific success factors include the development, dissemination and implementation of operational tools cocreated by multistakeholder groups

with patient representation, such as ASCO–FOCR joint guidelines to expand cancer research eligibility criteria. Similarly, Centers of Excellence programs, such as GO2 Foundation for Lung Cancer's Care Continuum Centers of Excellence Networks for screening and care continuum coordination, promote the application of patient-directed treatment paradigms for comprehensive cancer care [30].

Public

The public level refers to the overall health care environment that applies to the general public. This is the level of 'Big Data' systems, which includes codification schemes, such as International Classification of Diseases – 10th revision codes, aggregated insurance claims data and data related to lifestyles, environments and human biology as collected in programs such as the NIH's All of Us Research platform [31].

At this level, diverse patients may engage in establishing global and national research priorities, determining public health policies, and designing public awareness and disease prevention campaigns, such as cancer screening drives. National policies and programs support the 'development of pipeline training programs for health care professionals representing the ethno-cultural and linguistic diversity' of the public [3].

Call to action

We can take action today to reimagine equitable cancer care. As individuals, we can educate ourselves about the legacy of racism in health care as well as about principles and practices of patient engagement. We can advocate within our organizations for the adoption of tools, toolkits and training programs that have been cocreated with patients and community stakeholders. Following are five action areas for individuals and organizations. See Supplementary Resources for examples of specific programs and recommended reading.

Five action areas & next steps for individuals & organizations

1. **Educate yourself** in patient engagement, antiracism, implicit bias, legacy of racism in medicine and related topics. **Individual:** Sign up for courses and set personal development goals. **Organization:** Offer or require these programs in workforce curricula and performance objectives. Sponsor the development of new training related to the health effects of structural racism [32].
2. **Advocate for and use cocreated tools and toolkits** to support patient engagement and diversity in operational practices, such as clinical trial protocol design and site selection. **Individual:** Seek out tools/toolkits to use in teams and functional roles. **Organization:** Integrate cocreated tools and toolkits into practices and standard operating procedures.
3. **Align antiracist, patient engagement and health IT approaches** along the patient population levels to address the areas of priority for equitable cancer care: early detection, community cancer centers, eligibility criteria, digital endpoints and workforce diversity. **Individuals:** Learn the specific issues and initiatives related to each area. **Organizations:** Develop measures and standards for assessing the impact of interventions and policies on patient access, diagnosis, care and outcomes.
4. **Publish results** of interventions, with specific emphasis on impacts for minority communities. **Individuals:** Participate in and recommend colleagues for diverse publication teams for abstracts, manuscripts, speaker panels. **Organizations:** Collect data related to race/ethnicity of clinical trial participants. Set a policy of transparency for publishing and otherwise disseminating race and ethnicity data in manuscripts for medical science journals [33].
5. **Mentor and be mentored. Individuals:** Schedule dates for listening and/or speaking on topics related to cancer care equity and your role in oncology at internal and external meetings among staff, colleagues, young professionals and students. Facilitate research, mentoring and speaking opportunities for colleagues and new professionals from underrepresented populations [33]. **Organizations:** Develop a representative workforce/membership through internal programs for hiring, research and mentoring. Support managers and staff with regular check-ins and conversations about the internal atmosphere for inclusion. Conduct regular assessments of compensation scales and packages for equity [33].

Conclusion

A moment of reckoning for racial justice is upon us. Dollars and other resources from philanthropies, government and industry are being directed *en masse* to health equity efforts – cancer care among them. At the same time, patient engagement practices and tools along with health care technologies have evolved to a point where we can intentionally apply them to reimagine and implement a more equitable, patient-centered, data-driven system to

support cancer prevention, diagnosis and quality care serving all populations. As a society, we have the resources available *right now* to take action to drive systemic changes to cancer care policies, treatment practice and research infrastructure. As oncology professionals, we have the capacity *right now* to critically evaluate our operations for equity, to intentionally address medical, social and economic conditions and to bring patient-level precision into precision medicine for cancer. Now is the moment for each of us involved in oncology, individual and organization alike, to take the next step.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0912

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Tools for adapting cancer trials during the COVID-19 pandemic: an interview with Harish Dave

Harish Dave has more than 35 years of experience in basic science, academia and industry and has conducted over 100 studies with a focus on hematology, oncology and transplantation. He also has had extensive interactions with the US FDA and submitted multiple IND's. Dave served on a number of NIH (National Institutes of Health) committees, as well as chairing two Brain Disorders and Neurosciences Review committees. He is the Co-Founder & Chief Medical Officer of AUM Biosciences (Singapore) where he provides scientific and medical guidance ensuring that the company maintains sharp focus on developing cancer medications that address unmet medical needs for the benefit of cancer patients. Dave holds an MB, ChB from the University of Sheffield (UK) and an MBA from the TRIUM program (jointly awarded by New York University, New York, London School of Economics, UK and HEC, Paris, France). He is also a Member of the Royal College of Physicians (UK) and is ABIM board certified in internal medicine, hematology and medical oncology.

Harish Dave

In this interview with Harish Dave (AUM Biosciences, Singapore) we explore how the COVID-19 pandemic has led to the adaptation of cancer clinical trials including how decentralizing clinical trials can expedite oncology research and drug development. We also speak about what's in store for the oncology industry against the COVID-19 backdrop.

Q) How can decentralizing clinical trials expedite oncology research and drug development?

Over the past decade, the conventional centralized, "big pharma" innovation model has resulted in more than a 100% increase in the cost of developing new drugs, despite a 10 times reduction in the Internal Rate of Return (IRR) and a more than 20% reduction in commercial Return on Investment (ROI).

This is clearly a broken model and is unsustainable. This traditional centralized pharma model is getting increasingly replaced by "decentralized innovation", wherein pharmaceutical companies explore collaborative and externally facing innovation models.

Smaller companies are generally more cost efficient, as they are acutely aware that failure of their drug often means failure of their company. They are therefore highly incentivized to drive for success, instead of in larger pharma companies where there is less pressure of failure.

Q) What other tactics do you think could reshape the drug development landscape in oncology?

The deeper understanding of cancer biology that was ushered in by the development of molecular biology has enabled us to move from thinking of cancer at an organ level to a cellular level. We can appreciate alterations at cellular, sub-cellular and genetic level that gives us insights into the aberration(s) associated with cancer and to develop medicines that target those abnormalities. This is akin to finding a key for the lock to open it as opposed to using a crowbar to try to break the lock.

The deeper understanding of cancer biology that was ushered in by the development of molecular biology has enabled us to move from thinking of cancer at an organ level to a cellular level.

For example, we are now thinking of cancer as a large number of disease sub-sets, each with an individual and unique solution. Therapy is then targeted at what defines each subset, taking advantage of molecule medicine and rational drug design. Also, our prior lack of a deep understanding of cancer meant we generally relied on toxic chemicals to kill tumors. That was the art of killing the cancer cells just a little faster

than killing the patient, not a very desirable state of affairs. The current paradigm is to understand the biology of the cancer, which means we are slicing and dicing cancer into a thousand plus orphan indications, developing customized treatments for these sub-sets.

Another tactic would be the increased focus on long-term durable disease control. While the goal of therapy is certainly finding a cure eventually, we have increasingly come to recognize that turning cancer into a chronic disease in the interim is a realistic solution, so long as the side-effects of our treatments are tolerable and allow the individual to function in society. The idea of cancer becoming like hypertension or diabetes has some merit, and we are seeing that in a number of areas.

For example, breast cancer can, in many instances, be seen as a chronic disease with different therapies given over time, with occasional treatment free intervals, leading to patients having a longer and productive life.

Q) What impact has COVID-19 had on cancer care?

The COVID-19 pandemic has resulted in some major challenges – our patients are reluctant to venture out due to risk infection in their immunocompromised state. Many clinics and hospitals are not allowing caregivers to enter the facility to minimize the risk of contagion. And several doctors stopped seeing patients or relied heavily on telemedicine, which may not be entirely satisfactory to the patient, and could lead to delayed diagnoses as well as poorer outcomes.

From the investigator and pharma perspective, clinic visits were disrupted with missing data and delayed imaging, and Clinical Research Associate's (CRA) inability to get on site (though this has been mitigated by remote access to Electronic Medical Records (EMR)). As the Omicron variant has demonstrated, we will continue to see newer and potentially more infectious variants emerging, making it difficult to go to the status quo.

Q) How have oncology healthcare systems in the US adapted throughout the pandemic and in your opinion, how can this be improved upon?

The COVID-19 pandemic has disrupted cancer care, causing delays in diagnoses and treatment. According to Nature Cancer, healthcare systems are rapidly reorganizing cancer services in response, to ensure that patients continue to receive essential care while minimizing exposure to SARS-CoV-2 infection.

However, the overwhelming demands placed on the medical system by needing to take care of COVID-19 patients has led to a reduction in availability of care to patients with other illnesses including cancer. There are delays in performing elective surgeries, even biopsies, to diagnose and manage earlier stage cancer when it is potentially surgically curable. Family members of patients or others in their support system are often prevented from coming to the clinic or hospital, leaving the ill and sometimes frail patient to navigate complex hospital systems by themselves. A number of academic institutions have been declining new oncology research protocols as their ethics committees and research staff are focused on COVID-19 related research, thus denying access to experimental oncology medicines to cancer patients.

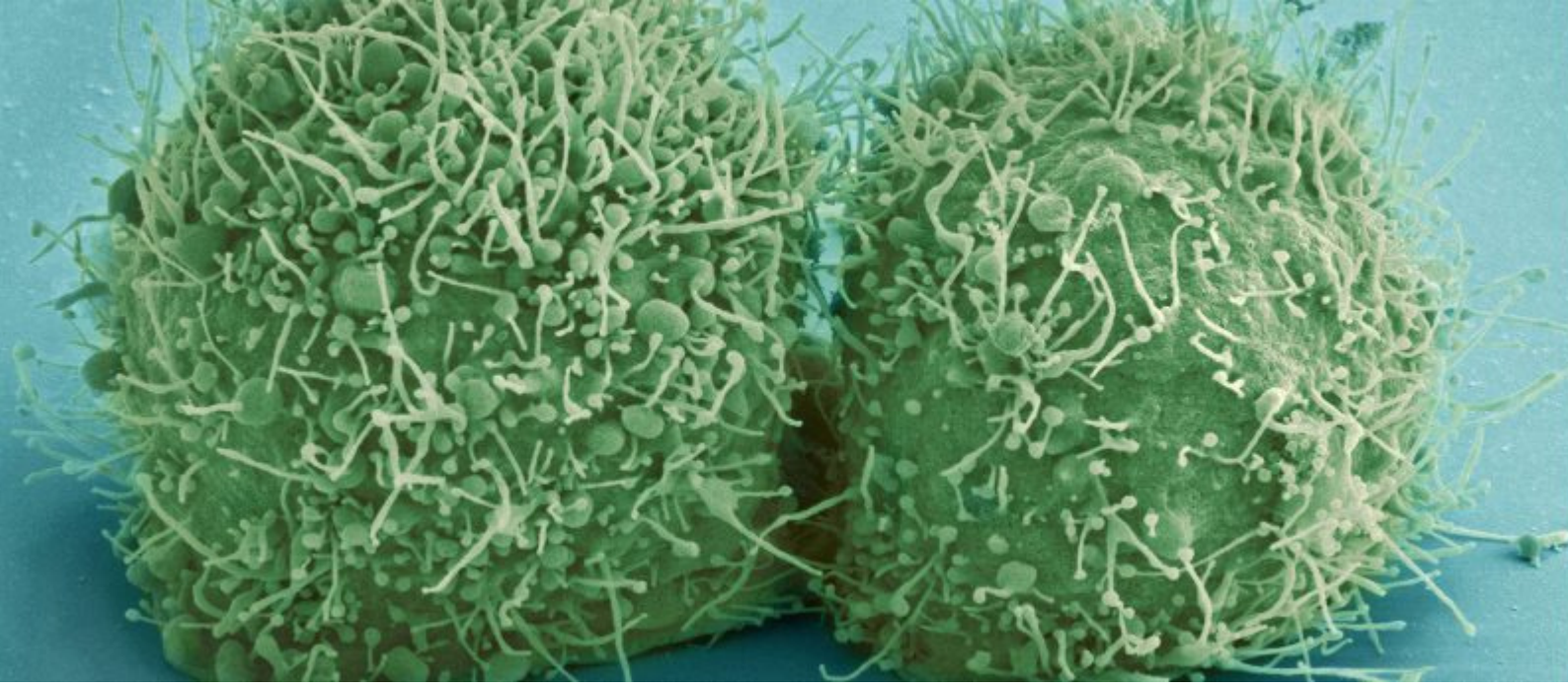
In time, no doubt, a new equilibrium will be established, and a balance reached between the needs of oncology patients versus those with other diseases. However, the ripple effects of COVID-19 related disruption will be felt for some time.

Q) Any closing comments?

Cancer is a major global health problem that is under-appreciated, cutting across all age groups but with a clear rise in incidence with age. The economic losses to the workforce from cancer are staggering yet little spoken about in comparison to heart disease or diabetes. Physicians have long dreamed of narrowly focused therapy for cancer, killing just the malignant cells and leaving alone the healthy cells. That dream is now coming close to reality as we develop a greater understanding on what goes wrong in a cell to make it cancerous.

Where we cannot cure cancer, we can surely hope for converting it to a chronic disease, learning to live and function with cancer supported by medicines with limited side-effects. We long to see this new reality come to pass. In so doing, we need to keep in mind the economic burdens that our medicines impose and strive to make them affordable to all.

The opinions expressed in this interview are those of the author and do not necessarily reflect the views of Oncology Central or Future Science Group.



AACR22: dramatically lower survival rates in pediatric cancer patients from low- and middle-income countries

A new study has revealed that pediatric cancer patients in low- and middle-income countries were at a dramatically higher risk of all-cause mortality than their counterparts in high-income countries in the first 9 months of the COVID-19 pandemic. The study authors warn that the COVID-19 pandemic has exacerbated existing global health disparities in childhood cancer treatment.

Pediatric cancers whilst rare still represent the second leading cause of non-communicable deaths in children around the world. Muhammed Elhadi, presenter of the study and medical doctor at the University of Tripoli (Libya), explains “childhood cancers are often curable, but without appropriate and timely diagnosis and treatment, they are too often fatal”. Researchers suspect that cancer services in low-income countries were hit disproportionately by the COVID-19 pandemic thus worsening outcomes for patients.

The study results were recently presented at the AACR Annual Meeting 2022 (8–13 April 2022, LA, USA) and published in BMJ Open. The study investigated the effect of the pandemic on worldwide pediatric cancer care.

You may also be interested in:

- AACR22: natural killer cells show promise as a possible lymphoma treatment
- AACR Annual Meeting 2022: what talks should you look out for?
- AACR22: CodeBreaK 100 trial data shows long-term clinical benefit of sotorasib for NSCLC

The team of researchers and healthcare professionals from The Global Health Research Group on Children's Non-Communicable Diseases Collaborative were led by Kokila Lakhoo and Noel Peter. Data from 91 hospitals and treatment centers around the world were collected from March to December 2020.

This included 1,660 cancer patients aged 18 or younger who were recently diagnosed or being treated for acute lymphoblastic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, Wilms tumor, sarcoma, retinoblastoma, gliomas, medullablastomas or neuroblastomas.

In total, 66.5% of patients were from low- and middle-income countries (LMICs) and 33.5% were from high-income countries (HICs).

At 1 month into the study:

- 45 patients died in LMICs compared to just two in HICs.
- All-cause mortality risk was 4.3% in LMICs but only 0.4% in the HICs.

At 3 months into the study:

- 66 deaths were reported in LMICs with just 5 deaths in HICs.
- 7% risk of all-cause mortality LMICs, compared to 0.9% risk in the HICs.

Other key findings include:

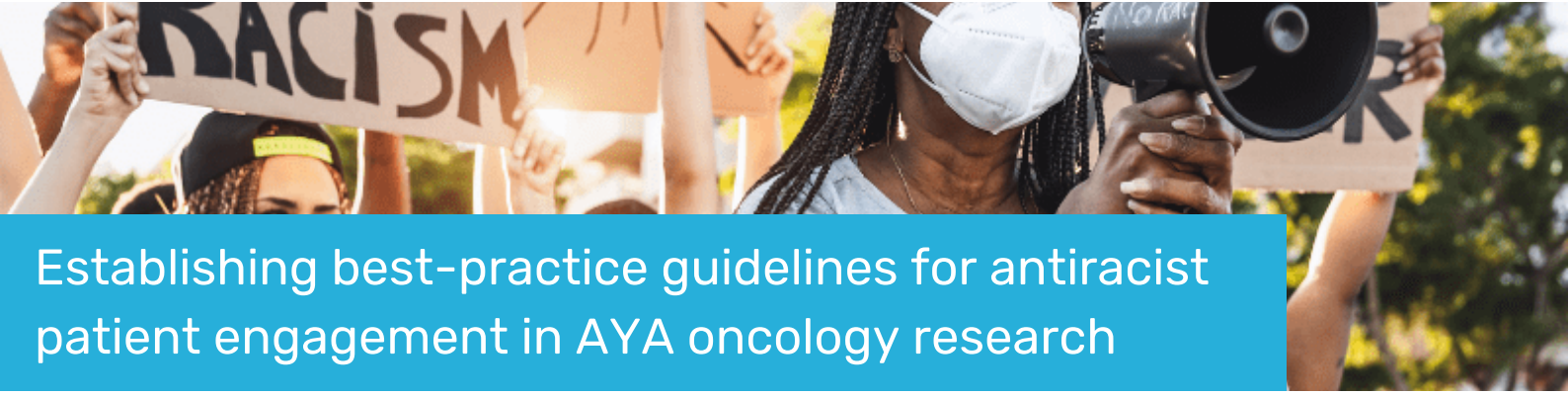
- Pediatric cancer patients in LMICs had a 35.7 times greater risk of all-cause mortality than children in HICs (after controlling for age, sex, weight, tumor grade and tumor stage).
- Overall, 219 children experienced delays, interrupted or changes to their treatment as a result of the pandemic.
- Researchers suggest that the pandemic led to many cancer cases going undiagnosed which may mean that the true burden is even greater than reported.

Researchers were unable to determine whether the deaths resulted from cancer, COVID-19 or other causes. The researchers are now collecting outcomes data from the first year of the pandemic to determine the causes of mortality.

Elhadi concludes, "more than 90% of pediatric cancer deaths occur in LMICs, due to factors including underdiagnosis and lack of access to effective therapies. This study illustrates the stark disparities that continue to exist in children's cancer care, and the multiple impacts that the COVID-19 pandemic has had on health care systems across the globe".

Regarding the pandemic, he argues that "understanding its true impact, taking on key lessons, and identifying vulnerabilities within health systems helps us develop solutions, which will also prove critical on our path toward equitable global pediatric oncology care".

Source: www.aacr.org/about-the-aacr/newsroom/news-releases/pediatric-cancer-patients-in-lower-and-middle-income-countries-faced-significantly-higher-mortality-risk-during-the-covid-19-pandemic/



Establishing best-practice guidelines for antiracist patient engagement in AYA oncology research

Christabel K. Cheung is a scholar, writer and self-proclaimed 'cancer gangster' who has twice-survived Hodgkin's lymphoma. Cheung is a tenure-track assistant professor at the University of Maryland School of Social Work and member of the University of Maryland Greenebaum Comprehensive Cancer Center (both MD, USA). Her research interests in psychosocial oncology are primarily focused on adolescent and young adult (AYA) cancer patients in the domains of financial hardship, social determinants of health, disparities, embodied research methods, and antiracist patient engagement in the conduct of research. In pursuit of these interests, she has led research projects as principal investigator and co-principal investigator, and contributed to numerous cancer care optimization, patient education, and advocacy initiatives aimed at improving health and behavioral health outcomes.

Christabel K. Cheung

In this interview we speak with Christabel Cheung about her current research focused on developing guidelines for patient engagement in in adolescent and young adult (AYA) oncology research and her hopes for engaging BIPOC (Black, indigenous, and people of color) AYAs in oncology research will improve over the next few years. If you would like to find out more about Christabel's research make sure to also check out the team's most recent Review paper, published in Future Oncology, here.

Q) Can you provide an overview of the Delphi study?

The purpose of the current Delphi study is to develop guidelines for best practices in antiracist patient engagement in AYA oncology research and advocacy to inform the development of effective strategies for collaborating with still-developing BIPOC AYAs in the conduct of research. Furthermore, findings will provide unique data with the potential to improve patient-centered programs, policies, and support for BIPOC AYA cancer patients.

In a preceding study, AYA oncology professional experts developed a review article describing their recommendations for antiracist patient engagement in AYA oncology research and advocacy by co-authoring a review article that has been submitted to a peer-reviewed journal for publication. The PCORI Framework for Patient Engagement provided the organizing structure for their review. Meanwhile, the PCORI Core Principles were discussed in terms of identifying the highest priority principle and explicating their rationale.

In the current study, a panel of BIPOC AYA cancer patient experts will participate in a Delphi study to present their own recommendations for antiracist patient engagement in AYA oncology research and advocacy. Additionally, they will respond to the recommendations from AYA oncology leaders resulting from the preceding study. Through this process, guidelines for best practices in antiracist patient engagement in research will be co-created and derived from the expertise of both BIPOC AYA cancer patients and AYA oncology experts by employing a consensus process that is informed by theories that advance antiracism.

Results of our Delphi study will be presented virtually at 4th Annual Global AYA Cancer Congress (London, UK, 1–2 December 2021). Afterwards, we will pursue publication in a peer-reviewed journal.

Q) Can you give us an overview of your research?

My psychosocial oncology research prioritizes scientific innovation that is inspired by the embodied knowledge of our ever diversifying and intersectional AYA patient care population in the domains of financial hardship, social determinants of health, disparities, and antiracist patient engagement. My ultimate goal is to eliminate unnecessary suffering.

Q) What prompted you to investigate this topic?

I was initially prompted to study AYA oncology by my own embodied knowledge as a BIPOC AYA patient scientist, who is a two-time survivor of Hodgkin's lymphoma and a bone marrow transplant beneficiary. I have since been compelled to respond to the huge gap in empirical knowledge on the minoritized and intersectional experiences of AYA patients, who are characterized by non-dominant racial/ethnic identities.

Q) Why do you think the results from this study are so important to the oncology field?

This study will innovatively fill a huge gap in knowledge on BIPOC AYAs by uniquely advancing best practice guidelines for oncology research that elucidate a genuine commitment to antiracism. Through a genuine, inclusive, and rigorous scientific process, guidelines for best practices in antiracist patient engagement in research will be co-created and derived from the expertise of both BIPOC AYA cancer patients and AYA oncology experts. Findings from this study will set a new standard for antiracist approaches to patient engagement in the conduct of research; it will be instructional for researchers and clinicians interested in implementing patient-centered methods.

Q) Why is this data so important for adolescent and young adult patients?

In these fraught sociopolitical times, AYA oncology researchers have an opportunity to seize this moment of racial awakening to implement lasting, structural changes that bring the expertise of BIPOC cancer patients to the fore at every stage of research prioritization, conduct, dissemination, and evaluation. The current climate of rapidly increasing diversity, equity, and inclusion (DEI) responses from white-led and predominantly white-serving oncology institutions in the name of "antiracism," often excludes BIPOC individuals and communities from the leadership of these efforts. What's more, the majority of these white leaders have little to no experience or track record for implementing successful antiracist strategies. This lack of BIPOC leadership perpetuates the long-standing problem of structural racism in oncology research and advocacy, and leaves AYA cancer patients acutely vulnerable to exploitation by mainstream organizations to serve in 'token' roles that do not hold true influence nor power to create change. Since BIPOC AYAs are still biologically and psychosocially developing into adulthood, such token participation has great potential to inflict harm. Guidelines for best practices that prioritize an antiracist lens and are responsive to the developmental needs of BIPOC AYA cancer patients in the conduct of AYA oncology research and advocacy are urgently needed to inform ethical and effective patient engagement, especially in our current sociopolitical environment.

The current climate of rapidly increasing diversity, equity, and inclusion (DEI) responses from white-led and predominantly white-serving oncology institutions in the name of "antiracism," often excludes BIPOC individuals and communities from the leadership of these efforts.

Q) How do you hope engaging BIPOC AYA patients will change in the next 5 years?

I hope to see more BIPOC leaders of AYA oncology institutions and initiatives who are being utilized and compensated appropriately for their contributions, and fewer AYA cancer initiatives that tokenize BIPOC AYAs. It is currently quite common to find token images of BIPOC AYAs on the websites of AYA cancer care programs, but no actual BIPOC representation among their program participants and/or leadership in real life. Genuine efforts aimed at promoting health equity require BIPOC leaders with strong track records of success to lead efforts that aimed at including BIPOC AYAs. It would seem absurd for a women's health initiative to have no women involved in its leadership; likewise, BIPOC initiatives need BIPOC leadership on efforts that address issues that originate from BIPOC AYAs themselves.

I also hope that one day, I will no longer hear disheartening stories about BIPOC AYA cancer patients, who felt fooled into thinking there would be other BIPOC participants at a cancer support program based on photos in marketing materials, but subsequently discovering zero BIPOC participants

when they joined.

The suffering created by the tokenization and exclusion of BIPOC patients in AYA oncology is unnecessary and can be eliminated. We offer guidelines to begin this urgent process of dismantling legacies of racism and erecting new structures that will secure an antiracist future.

I also hope that one day, I will no longer hear disheartening stories about BIPOC AYA cancer patients, who felt fooled into thinking there would be other BIPOC participants at a cancer support program based on photos in marketing materials, but subsequently discovering zero BIPOC participants when they joined.

The opinions expressed in this interview are those of the speakers and do not necessarily reflect the views of Oncology Central or Future Science Group.

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Review

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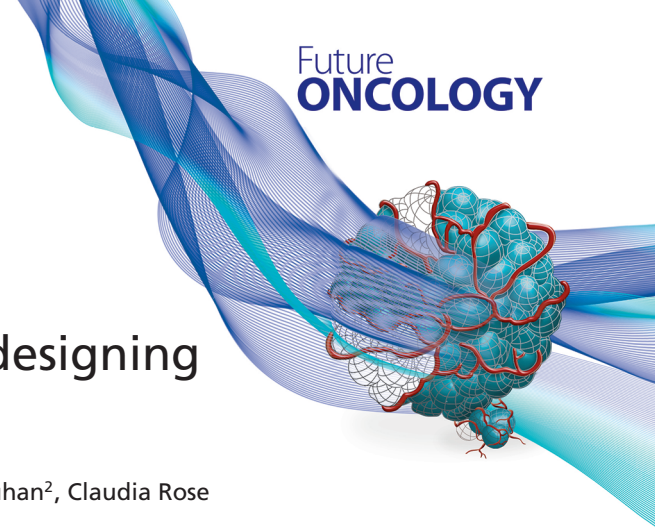

Pragmatic patient engagement in designing pragmatic oncology clinical trials

Bernard Bright Davies-Teye[1,2], Michelle Medeiros[1,2], Cynthia Chauhan[2], Claudia Rose Baquet[1,2] & C Daniel Mullins*[,1,2]

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Oncology trials are the cornerstone of effective and safe therapeutic discoveries. However, there is increasing demand for pragmatism and patient engagement in the design, implementation and dissemination of oncology trials. Many researchers are uncertain about making trials more practical and even less knowledgeable about how to meaningfully engage patients without compromising scientific rigor to meet regulatory requirements. The present work provides practical guidance for addressing both pragmaticism and meaningful patient engagement. Applying evidence-based approaches like PRECIS-2-tool and the 10-Step Engagement Framework offer practical guidance to make future trials in oncology truly pragmatic and patient-centered. Consequently, such patient-centered trials have improved participation, faster recruitment and greater retention, and uptake of innovative technologies in community-based care.

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Advances in oncology therapeutics and personalized medicine have extended life and improved the quality of life for cancer survivors. As cancer treatment choices increase, so has demand for innovation in designing and conducting pragmatic clinical trials while maintaining scientific rigor [7–10]. How best to assure that pragmatic clinical trials in oncology are patient-centered and exactly how to incorporate patient engagement throughout the process remains elusive for many who design trials. There is a misperception that patient engagement is limited to patients who enroll in the trial as participants rather than understanding that patients can serve as advisors or co-developers [11–13]. For some, the idea of engaging patients – also termed patient involvement in other jurisdictions – in trials raises concerns about compromising the scientific integrity of the trial design.

On the contrary, patients engaged as co-developers, like any member of the trial design team, provide specific perspectives that add synergies but do not replace the expertise of other members. Oncology patients bring a lived experience perspective which, when involved at an early stage of trial development, can foster bidirectional learning with scientists and researchers so that oncology trials are meaningful, feasible and most beneficial [14–17]. The present work is designed to provide guidance on enhancing patient engagement and addressing diversity in pragmatic cancer trials.

Beyond improving the scientific rigor of oncology trials and making trials relevant and feasible for cancer patients, patients' participation in research funding decision-making has also progressed. It is an increasingly significant criterion to secure research funding from organizations, such as the Patient-Centered Outcomes Research Institute (PCORI) [18,19]. Research funding organizations involve patients in strategic decision-making on a shared research plan, call and receipt of research proposals and funding decisions [18]. For example, to qualify for funding, PCORI in the USA requires investigators to provide a mandatory letter of recommendation from patients as evidence of early and continued patient engagement in the research protocol development [19]. Similarly, close to twenty research funding organizations in the Netherlands have patient participation advisory teams who participate in the research agenda setting, calls for proposals and eventual research funding decisions[18]. With the growing discovery

Future Medicine

of genetic diversities in cancer types due to advances in diagnostic technology, more adaptive oncology trials are needed to discover and develop effective medicines for diverse oncology patients. The next generation of adaptive oncology trials require timely access to funding and underscores the need for meaningful patient engagement in these trials [20].

The practical approach to pragmatic trial design engages patients to enhance the interest of oncology patients in enrolling and completing study requirements. This real-world approach supports higher participant retention. Therefore, patients and their community providers bring pragmatism regarding the ability to comply from a participant perspective so patient participation can meet regulatory requirements. There are areas where pragmatic design and current best practices for patient engagement provide the evidence needed by stakeholders (patients and their healthcare providers and regulators). For example, there is evidence that adopting a pragmatic trial design and best practices in patient engagement may improve diverse populations' participation in trials and address barriers encountered during trials. Adopting patient engagement best practices may inform a personalized approach to oncology trial conduct and provide valid and generalizable results to the targeted oncology patient population. Consequently, this can facilitates early uptake of new drugs or technologies that may improve the quality of life of cancer survivors [21–26].

Pragmatic clinical trials in oncology

Pragmatism in clinical trials is meant to address concerns that many trials do not adequately inform real-world clinical practice outside a unique set of healthcare settings, such as academic medical centers [27]. Pragmatic trials are often simple, large, and designed to minimize trial procedures and data collection requirements to reflect real-world clinical care settings. At the same time, patient-centered pragmatic oncology trials assess symptoms and other outcomes such as aspects of health-related quality of life that are meaningful to patients and influence patients and their community healthcare providers' decisions about treatment options.

Pragmatic trials generally include patients who are representative of the diversity of patients who would receive the intervention in clinical care and across broader healthcare delivery systems than the traditional explanatory trial designs [22]. In some cases, pragmatic trials may permit less obtrusive follow-up and measurement of trial outcomes by linking trial data to electronic health records or intervention-specific registries. This approach reduces the burden on patient participation and allows the capture of long-term follow-up data [23,24]. For example, during the trial, measurement of patient-reported outcomes (PROs), which reflect patients' symptoms or quality of life, may be assessed using online self-reporting tools, such as tablet computers or mobile phone applications, without a clinician or anyone else's interpretation. This approach may enhance the real-world nature of data collection within the clinical trial and require less intense follow-up visits to trial centers [28,29]. Because some elements of pragmatic trials, such as unblinding of participants to study drugs, could bias the study outcome measurement and compromise the scientific integrity of the trial design or data capture, it is valuable to incorporate patient input along with clinical, biostatistical and other scientific expertise to identify practical ways to reduce bias in assessing outcomes [30].

In the context of pragmatic oncology trials where more than one active intervention is compared, the authors posit that researchers should purposefully integrate unblinding into the trial design to assure participants' safety in the case of life-threatening adverse events. This viewpoint is consistent with the current US FDA's guidance on blinded oncology trials [31]. In pragmatic oncology trials, unblinding can be particularly important to assure participants' safety or based on overwhelming evidence of treatment benefit in interim analyses. At the same time, unblinding can also be a source of bias in outcome assessment [31,32]. For example, in a blinded oncology trial involving an immunotherapy group and an active control group, if a participant in the control group develops adverse events, they could be unjustifiably treated with high-dose immune suppression treatments [33]. Such high-dose immunosuppressants could harm the patient if the trial clinician managing this patient remains blind to the treatment allocation.

On the other hand, unblinding may occur inadvertently in trials involving study drugs delivered through different routes of administration that may reveal treatment allocation [32,34,35]. In such situations, trialists must adopt measures to minimize bias in the measured outcome. Trialists may use independent adjudicators, where clinical events identified as potential outcomes are sent to a panel of independent experts to assess the study outcome to minimize bias [32,36]. Where data collectors or independent adjudicators cannot be blinded, oncology researchers may choose objective end points relevant to patients [34,35]. The requirement for patient-centered study outcomes in the context of unblinding underscores the need for meaningful patient engagement. Alternatively, when possible, investigators can use duplicate assessments of outcomes and then report the level of agreement the

assessors achieved. Irrespective of the approach researchers adopt to minimize bias in an unblinded study, they must be transparent and discuss the potential bias unblinding might have introduced [34,35,37]. In any case, unblinding is fundamental to pragmatic trials, as it preserves the ecology of routine in which clinicians know what they are prescribing, and patients understand what they are receiving [34].

Trialists often wish to inform real-world decisions; however, they typically end up designing more explanatory trials than pragmatic ones [1,10]. Using validated pragmatic trial design tools and approaches, such as the PRECIS-2 tool and sustained stakeholder engagement, provide a more practical approach to achieving pragmatism in oncology trials [1,38]. For example, the PRECIS-2 tool has nine modifiable trial design domains, which are scored from 1 (very explanatory) to 5 (very pragmatic) to facilitate domain discussion and consensus among the engaged stakeholders. The domains include eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome and primary analysis [1]. In this regard, the PRECIS-2 tool provides patients a realistic means to assess the pragmatism of the trial design and gives valuable input to make it even more patient-centered. For example, if the study design is such that potential costs of participation, the time involved, or the general sense of feeling unwell may impede participation in an oncology trial, patients or advocates could meaningfully address these barriers during robust PRECIS-2 domain discussions [39]. In addition to drugs and technologies, oncology trials may evaluate surgeries, therapies and aspects of healthcare service delivery [40]. That both participants and investigators may be unblinded in oncology surgical trials reflects real-world practice. However, oncology surgical trial design aspects (e.g., setting, trial outcomes) must be adapted to embrace pragmatism [32,40]. For example, in a trial that evaluates specialized surgical procedures, the PRECIS-2 setting domain may receive higher scores, making it less pragmatic. In this context, meaningfully engaging patients and stakeholders may provide practical solutions to make these trials pragmatic and patient-centered [40]. Thus, patient engagement assures that all relevant expertise, including the lived experiences of patients, is part of the design and implementation of oncology trials [41]. Patient engagement can offer solutions to barriers to trial participation, such as lack of access to trial sites, nonavailability of trials, oncologists unwillingness to propose trials to patients and lack of patient involvement [42,43]. Patient engagement is complementary to innovation in oncology trial design.

Applying a 10-Step Engagement Framework to pragmatic oncology trials

Engaging patients, patient advocates and their healthcare providers in a continuous and meaningful way gives them a level of ownership of the research enterprise. As a result, the engaged patient advocates and their healthcare providers actively support the research agenda setting, recruitment and participation. For example, the James Lind Alliance Priority Setting Partnership in the United Kingdom has been a truly collaborative effort that has engaged patients, their caregivers and clinicians to spearhead oncology research agenda setting [44]. Despite this example, patients and patient advocates often are engaged late in the planning of research activities, when the general aspects of the study protocol have been finalized [2–4]. Continuously engaging patients with cancer and advocates throughout the research continuum engenders trust and results in patient-centered research questions, study design and clinical end points meaningful to patients' disease-specific experiences [5,45]. Patient-centered study procedures improve patients' comprehension of the research, support faster recruitment and higher retention, and help to avoid or mitigate challenging data collection issues [46]. In their systematic review and meta-analysis, Crocker and colleagues concluded that a clinical trial is likely to improve participant enrollment if it engages patients and stakeholders [47]. Meaningful patient involvement from study conceptualization enhances the subsequent study implementation and sharing of the resulting patient-centered evidence. Continuous patient engagement mitigates real-world obstacles to performing oncology clinical trials and the application of research findings.

A 10-Step Engagement Framework developed by Mullins and colleagues provides methodological guidance to engaging patients throughout the research process, ensuring bidirectional learning while maintaining research design and implementation integrity [5,6]. The 10-Step Engagement Framework, presented in Figure 1, includes engaging patients from topic solicitation and prioritization to study conduct, interpretation, translation, and dissemination of results. Topic solicitation refers to seeking patients' input in identifying research topics. Topic solicitation generates various topics that are then prioritized with end points that are important to patients and aligned with those of stakeholders. Patients assist in framing the research questions to ensure that the final research question is practical and relevant to them. A critical area of patient engagement is to review informed consent. A review of the extent to which patients comprehend the informed consent they grant before participating in trials showed that only a tiny minority of patients understand the concepts of a placebo, randomization, safety, risk and adverse effects [48].

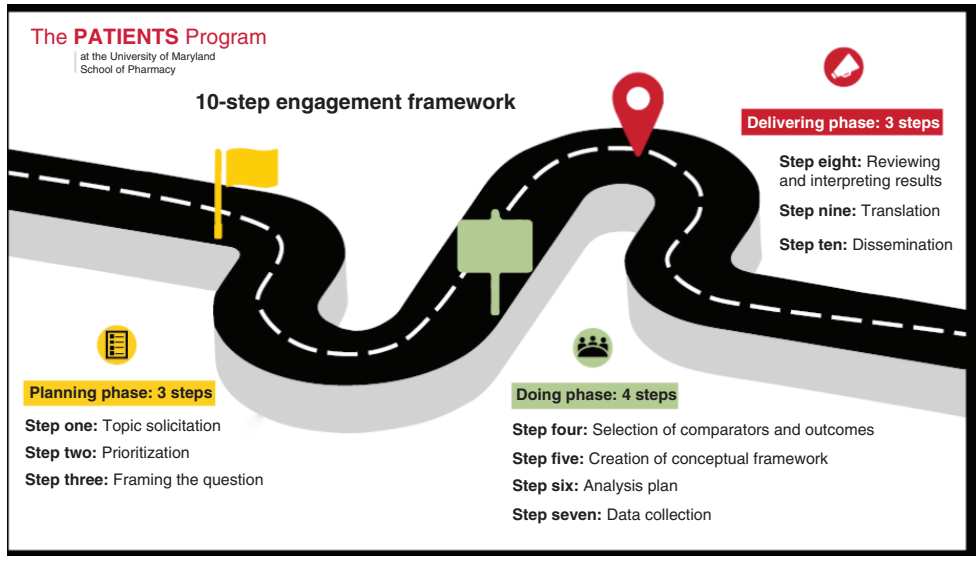

Figure 1. The 10-Step Stakeholder Engagement Framework.

Informed consent requires documents to be in plain language that oncology patients can understand. Engaging patients in the examination of these documents from their perspective allows them to propose changes where appropriate and provide valuable feedback [5].

When designing a potential framework for a specific oncology trial question, patients may propose a framework that reflects their individual experiences. Patients' input may help determine best practices for data collection. For example, patients can provide information about the proposed content of the data collection tool and participate in a pilot evaluation of the data collection items. Patient input is infrequently considered during the development of the analysis plan. However, the authors advocate that patients can help to define or categorize variables even if they do not have training in research methods. When reviewing and interpreting study results, patients can reflect on whether results are plausible and believable. They can suggest other factors that should be considered and how results may vary across subgroups of patients. In the translation phase, patients can identify which results are easy or difficult to understand and suggest the best way to explain study findings to other patients. Patients can help determine the best dissemination strategies, provide dissemination channels and craft specific plain language messages targeted to patients who will benefit most [5]. To further facilitate dissemination, patients can assist in developing a one or two-page patient summary of the trial to provide trial highlights of patients' accounts and impressions – in patient speak – of the trial.

At each engagement step, the engagement approach to adopt should be the best choice to elicit the patient's perspective. During the initial stages of an oncology trial, such as topic solicitation, engaging patients through telephone conversation and teleconferencing may be most beneficial. As the trial progresses, more in-depth information and patient input may be required. Engagement methods such as stakeholder meetings, in-person meetings, focus groups and individual patient interviews may provide robust discussion regarding population to include, treatment to compare and outcomes to assess [6,49]. These engagements must be evaluated using evidence-based patient and public engagement reporting tools and adequately documented to quantify and assure the quality of patient engagement. Using engagement evaluation tools like the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) long and short forms will ensure that patient engagement is based on the best evidence and its evaluation is also standardized [38,50]. This continuous and meaningful patient engagement in oncology trials may help ensure that trials are genuinely patient-centered and measure outcomes relevant to patients who are the ultimate consumers of the technologies or services evaluated.

Diversity in participation in oncology trials

Despite the progressive investment and efforts to create equitable access to cancer clinical trials, participation has remained disproportionately low for racial and ethnic minorities, older adults and females [51]. For example, in the United States, African Americans only constitute 1.3 percent of the overall enrollment in cancer clinical trials,

yet they continue to have the highest incidence rates for many cancers [52]. Trial participants are also significantly younger than the population of patients with diseases. This age disparity has widened over time and is particularly evident in industry-funded trials and trials testing targeted therapies [53]. Eliminating these persistent disparities means technological innovations from oncology trials are generalizable, accelerating progress in cancer treatment outcomes. The American Society of Clinical Oncology (ASCO) recently prioritized increasing equitable access to cancer clinical trials in its 2020 and beyond research agenda. Similarly, the National Institute for Health Research (NIHR) established the Innovations in Clinical Trial Design and Delivery for the Underserved (INCLUDE) to improve equitable access to clinical trials among underserved groups in the United Kingdom. Recognizing patient engagement as a best practice to understand and address patient and community practices that impede trial participation, ASCO and INCLUDE independently recommended a significant paradigm shift to engage patients and communities to close the gap [21]. Patient engagement should be continuous and reflect the diversity of patients who could benefit from the trials' treatments. Diversity in trial participation helps assess whether treatments work across the spectrum of oncology patients, identifies treatment effect heterogeneity and ultimately helps achieve health equity [54].

Diversity in oncology trial participation varies widely both within and across institutions, including those that participate in cooperative groups as well as across pharmaceutical companies and countries. Funding for oncology trials comes from two primary sources: public cooperative groups and for-profit organizations, often the biopharmaceutical industry. In the United States, an estimated 70 percent of clinical trials are funded by industry. However, Hakoum and colleagues found that 58 percent of published trials were publicly funded [55–57].

Society needs public and industry-led oncology trials to generate new evidence, develop new interventions and improve cancer care. Yet, different forces drive trials funded by these sources. The desire to launch new drugs, benefit from patent protection and remain profitable in business guides industry-led trials. On the other hand, academic-led trials are designed to address questions pertinent to patients and society [55–57]. Their respective driving forces have characterized the nature of patient engagement in these trials. Cooperative groups such as NCI and PCORI have established a policy requiring oncology researchers to provide evidence of patient engagement in the trial design to secure their funding [58,59]. However, in the industry-led trials, contract research organizations (CROs) who manage the trial conduct are the drivers of the patient engagement plan but are not obliged to engage patients meaningfully to secure funding [60]. Although 75 percent of pharmaceutical companies agree that the patient is at the heart of clinical trials, patient engagement remains a fanciful idea with no robust framework to practically integrate it into industry-led trials [60]. Further, there is limited published information on the extent to which industry-led oncology trials meaningfully engage patients.

The authors posit that the difference in the driving forces of cooperative group-funded versus industry-funded trials will be reflected in the approach to patient engagement. Research to critically examine the approach to patient engagement in cooperative group-funded versus industry-led trials will provide valuable information to promote patient-centered oncology trials.

Informing a personalized approach to oncology clinical trials

Investments made in oncology trials have engineered a greater understanding of cancer molecular biology, advanced detection methods, diagnosis and new drug innovations [61]. At the same time, the extensive understanding of cancer genetics has occasioned an unprecedented increase in the development of immune-oncology therapies, the number of treatments entering drug development, and the number of regulatory-approved innovative therapies with promising activities based on evidence from phase 1/2 trials [62–66]. The traditional drug development trial sequence, where drugs are evaluated in phase 1 for safety, assessed for early efficacy in phase 2, and evaluated versus standard therapy in phase 3, has given way to the emergence of adaptive trials with basket and umbrella designs [63].

While adaptive trials aim to enhance pragmatism by allowing for study protocol modifications as data accrue, the umbrella and basket designs enhance trial flexibility and broaden eligibility for oncology trial participation, respectively, to reflect real-world practice [63,65]. For example, the adaptive design may accommodate patient-recommended changes of study eligibility criteria, sample size, outcome variables, doses of study drugs, or addition or substitution of study drugs based on interim success or failure. These unique features provide the flexibility to accommodate randomization, incorporate patients' recommended changes and enhance eligibility for oncology trial participation, to assure scientific rigor and to reflect real-world practice [63,65].

Alongside this increasing complexity of oncology trial designs, a new framework was established for more robust and faster collaboration among stakeholders (clinicians, pharmaceutical companies and regulatory agencies) in

drug development [63,65,67]. Oncology patients, who are the ultimate beneficiaries of the developed therapies, must be engaged in any discourse relating to implementing these emerging, complex oncology trials. Patients considering participation in these trials with more significant uncertainty need understandable information about objectives, study processes, procedure, potential benefit, risk, as well as the anticipated modifications, including their preferred surrogate end points [67]. Patients and patient advocates may provide valuable input to informed consent and preference for the potential improvements that may ensue during the trial implementation. Innovative clinical trial design and continuous patient engagement in trial implementation are germane to leveraging emerging advancements and meeting regulatory requirements to bring innovative technologies to widespread implementation.

Survivorship & health-related quality of life

The five-year relative cancer survival rate for most cancers has improved over the past 20 years. In the United States, the number of cancer survivors continues to increase annually. In January 2019, an estimated 16.9 million individuals with a history of cancer lived in the United States, which is estimated to grow to more than 22.1 million by January 2030. This trend of improved survival is mainly due to advances in cancer diagnostic technology and therapeutics resulting from cancer science and trials [68]. Similar to trends in survivorship, clinical trials on survivorship have also increased during the past two decades [69–73]. Yet, only 5 percent of cancer survivors were engaged in these trials, although 26 percent of survivors reported willingness to be involved [70]. Most of these trials used a conventional approach, emphasizing investigator-identified priorities rather than a patient-centered approach [74,75]. In a systematic review that examined older adults – who comprise 60 percent of cancer survivors – participating in oncology trials showed that older cancer survivors preferred PROs compared with survival and response rate. In particular, older cancer survivors chose broader end points relevant to the elderly, such as tolerability, treatment efficacy and overall treatment utility [76–82]. This review revealed preferred outcomes that could inform oncology trials that meaningfully engage cancer survivors and make trials more pragmatic.

Health-related quality of life (HRQoL) has become an important outcome measure of survivorship alongside improved survival. It reflects patient satisfaction and the perceived benefits of a treatment strategy that other end points, such as overall survival (OS) or progression-free survival (PFS), do not capture in oncology trials [32,83,84]. Many survivors, particularly older adults or those living with incurable cancer who experience significant disability and long-term treatment adverse effects, may value HRQoL as a more meaningful outcome to assess in oncology trials [83–85]. HRQoL is multidimensional in construct, comprising a cancer survivor's physical, social, functional and psychological or emotional well-being. These varied domains provide avenues to capture specific PROs that reflect the treatment goals for cancer types, clinical stages and patients, similar to clinical practice settings, and therefore make such trials more pragmatic in terms of outcome measurement. The Consolidated Standards of Reporting Clinical Trials–PRO (CONSORT-PRO) extension statement provides oncology researchers a rigorous scientific framework to incorporate PRO or HRQoL measures into clinical trials design as primary or secondary end points [86]. In particular, the CONSORT-PRO stipulates that trials that select PROs as primary or secondary end points must provide evidence that PRO instruments used to capture data are valid and reliable to ensure scientific rigor. Such validated questionnaires for oncology trials, including EORTC QLQ-C30 and EORTC ELD 15/ELD 14, assess overall HRQoL, which, alongside survival, contribute to determining Quality-Adjusted Life Years (QALYs), making such trials both patient-centered and pragmatic [84]. The selected instrument(s) must be sufficient to give meaningful data and short enough to alleviate the patient participation burden. The questionnaires should be included in the trial calendar so that they are part of the patient's understanding of the trial requirements from the start.

Survivorship & the benefits of engaging patient advocates

Paradoxically, during the same period of limited survivor engagement in oncology trials, there has been an increasing number of cancer survivors involved in cancer research advocacy and the formation of solid advocacy groups. Advocacy groups constitute an infrastructure that serves as a strong voice for cancer patients and survivors [87]. Some examples are the American Cancer Society (ACS), National Breast Cancer Coalition (NBCC), Breast Cancer Research Foundation (BCRF), National Foundation for Cancer Research (NFCR) and Prostate Health Education Network (PHEN) [68,87,88]. Most of these advocacy organizations have existed for the past twenty years and have chalked up significant success in advocating for improved healthcare service delivery for cancer patients and survivors. However, the remaining part of this section will discuss their contribution in supporting patient-centered oncology trials and the need for academic researchers to leverage the resourcefulness of advocacy groups to extend

the frontiers of pragmatic oncology trials. The authors also offer some guidance to encourage oncology trialists to engage survivors continuously.

Cancer survivors organizations have been pivotal in securing funding to support research [87]. In the United States, ACS, and NFCR advocate for increased Federal and State funding for oncology research [89]. For example, in 2017, ACS advocacy contributed to the US Congress increasing medical research funding by $2 billion, including $475 million for NCI [90]. Cancer advocacy groups are significant stakeholders and have become an integral part of research funding decision-making committees within funding organizations like PCORI and NIH [59].

In parallel, these advocacy groups can be helpful to researchers in engaging patients and survivors to participate in clinical trials. When they are engaged by oncology researchers, throughout the oncology research continuum, they can serve on trial advisory committees, identify research priorities and advise on making the research more patient-centered. They can also help researchers find solutions to the barriers to participation in oncology trials, leverage their network of cancer patients to help improve cancer patient participation, publicize and disseminate study findings [5].

These advocacy groups are willing to help improve patient engagement and participation in oncology trials; however, the extent to which these organizations participate in a particular trial depends on the researchers spearheading the engagement process. PCORIs' policy requiring researchers to provide evidence of patient engagement through protocol development before providing funding for their research is an exemplar of encouraging oncology trialists to improve sustained patient engagement [59]. Similarly, requiring evidence of meaningful patient engagement in oncology trials as part of the criteria for marketing authorization, health technology, and value assessments for reimbursement and formulary decision-making may invigorate trialists to meaningfully engage oncology patients [91]. While these interventions can be enforced at varying degrees based on country-specific context, there must be a concerted effort internationally to make meaningful patient engagement mandatory, particularly for oncology trials. In the United States and Europe, there is a range of frameworks to facilitate patient involvement in the regulatory process. The Prescription Drug User Fee Act (PDUFA) in the United States aims to improve patient participation in the drug development and approval process. The FDA's Patient-Focused Drug Development initiative is committed to obtaining patients' input on specific disease areas and their conditions, impact on daily life and available therapies [92].

Given the increasing role of cancer advocacy groups in the oncology trial economy, academic oncology researchers' ability to continuously engage cancer survivor advocacy groups has the potential to define the future of financial resource mobilization for oncology trials and ensure improved survivor participation in cancer research.

Barriers to participation in oncology clinical trials

Patients with cancer face significant challenges in participating in clinical trials. Some of these include the costs of participation, time spent, conflicting work and family obligations, feeling unwell while willing to participate and lack of trial information [93]. Trial participants have been documented to have a higher costs compared with non-trial participants with incremental treatment cost due to trial participation ranging from 6.5% to 17% [94]. The additional cost burden is derived from travel, lodging and sustenance. Most National Cancer Institute (NCI)-designated comprehensive cancer centers are situated in major cities. A review of geographic accessibility to clinical trials sites for advanced cancer in the USA showed that between 30% and 50% of advanced cancer patients drive more than 60 minutes one way to access the clinical trial site [25]. This data is consistent with the fact that trial participants living far from these centers require enormous travel time to make trial-related visits [95,96]. Sometimes, patients need to lodge in hotels overnight and, for that reason, incur hotel and food costs. These costs are sometimes significantly higher than the reimbursement patients receive for participation in the trial. This additional costs burden can impede enrollment and participation in oncology clinical trials and exacerbate disparities [97].

In contrast, a pragmatic oncology trial that includes oncology centers in smaller cities and towns may provide patients with cancer living nearer to these centers geographic access to clinical trials than trials conducted at NCI-designated comprehensive cancer centers. Geographic access could significantly reduce travel time to trial sites, time spent on follow-up visits and costs associated with participation. At the same time, embracing innovation with continuous patient engagement throughout the research continuum may identify patient-centered solutions to time and cost barriers. For example, in a situation where specialized treatment such as organ transplants are part of the treatment, these may be available only at specialized centers and may be associated with higher costs and travel time. Therefore, when study design is discussed during planning and prioritization engagement sessions, a pragmatic

reimbursement amount that meets patients' needs and does not violate regulatory concerns of inducement could be selected.

Positive influence on the uptake of new drugs and technologies into practice

Successful dissemination of new drugs and technologies is crucial for patients, pharmaceutical companies, healthcare providers and trial sponsors [26]. For a new oncology technology to be translated into medical practice, it must be beneficial to the patients and acceptable to physicians [5]. Beyond the safety and benefit–risk assessments that influence marketing authorization, new health technologies must be sufficiently valuable to be reimbursed within the national health insurance package or be enlisted in formularies [98]. Increasingly, agencies, such as the Institute for Clinical and Economic Review in the United States and the National Institute for Health and Care Excellence (NICE) in the United Kingdom, that assess the value of health technologies to make reimbursement or formulary decisions are requesting patient-based evidence to make these decisions [91,98,99]. The patient-based evidence must show the impact of technologies on real-world outcomes that reflect patient experience not usually captured in more explanatory randomized control trials [98]. In this context, a pragmatic trial that incorporates meaningful and sustained patient engagement may generate more acceptable evidence for reimbursement or formulary decisions to enhance uptake into clinical practice. At the same time, translating a new surgical technique into broader practice requires that the evidence of the technique's effectiveness and safety is established via improved patients participation in the surgical trials [100].

Following a favorable reimbursement or formulary decision, physicians must accept innovative technologies to foster prescription and uptake [26]. For example, Lublóy and colleagues, in their systematic review of the factors that determined early uptake of a new drug, found that meaningfully engaging physicians in trials foster early uptake of new medicines. An engaged physician may be knowledgeable of drug efficacy and scientifically committed to prescribing the drug when indicated. In addition, an involved physician may be willing to communicate with colleagues about the medicine, which may significantly influence uptake [26].

The authors argue that meaningfully engaging oncology patients, physicians and other stakeholders throughout the trial continuum may foster bidirectional learning and help improve oncology patients' participation in trials. The improved participation of stakeholders in trials may contribute to producing valid results that are generalizable to the targeted oncology patient population, and at the same time, keeping physicians updated on new evidence [5]. Further, during the conduct of such an innovative trial that reflects a real-world oncology practice setting, meaningfully engaged oncology physicians may find beneficial results more acceptable, and be more scientifically committed to adopting and advocating for the new drug among colleagues [5,9,26,101].

Beyond the positive healthcare provider influence, the trust built among stakeholders (patients, patient advocates, the community, researchers and funders) may facilitate dissemination [5] of findings and support patients and community willingness to accept new drugs or technologies developed from such patient-centered oncology clinical trials [5,26,102]. To facilitate dissemination of findings, patients could assist in framing the message, creating plain language summaries, targeting audiences for dissemination efforts, and providing platforms (like ASCO annual conferences) for dissemination of findings [5,103].

Conclusion

Patient engagement and pragmatism in oncology trial design lead to innovations in evaluating drugs and other oncology technologies to inform their use in clinical practice. At the same time, it is crucial to understand and assure that patient engagement is about adding a unique, valid perspective to the expertise of clinicians, scientists and biostatisticians. Including patients within the trial design team helps to harness emerging innovations to optimize cancer patients' participation in trials because patient-centered trials have faster recruitment and better retention [5,46,104]. Patient engagement does not compromise scientific or regulatory integrity. Implementing novel ways to address these critical aspects of oncology research simultaneously will position patient-centered, pragmatic oncology trials to optimally energize and benefit from the unprecedented emerging advances in the sciences of trial design and patient engagement. Given the projected increase in cancer incidence, particularly for breast, melanoma and obesity-related cancers (pancreas, liver, and colorectal cancers), and genetic subtypes in the next decade, the investments and advancements in technology provide unparalleled opportunity to develop preventive, diagnostic and therapeutic technologies, or surgical procedures to meet preventive, diagnostic and treatment needs [105–108]. Demand will increase for innovative trial designs to determine these technologies' effectiveness or efficacy and safety. The demanded innovation will require that oncology trials be pragmatic to reflect routine care

settings, but also adaptive to identify treatment effect heterogeneity for varied genetic subtypes to realize the promise the of personalized medicine (molecular targeted agents and immunotherapies) paradigm in oncology [63,109,110]. It will be particularly impactful for future oncology trials to fully incorporate continuous and meaningful patient and stakeholder engagement in a manner that can be scientifically evaluated to help address the barriers to trial participation to improve diversity and participation in trials [5,38,50]. An improved continuous and meaningful engagement of oncology patients as both participants and advisors will not only ensure that the next-generation oncology trials are truly patient-centered, but that public funding becomes accessible to make oncology trials feasible [5,87,111]. Only then can oncology trials remain the cornerstone to identifying technologies that are genuinely beneficial to patients and improve societal welfare.

Executive summary

Patient engagement

- How best to assure that pragmatic clinical trials in oncology are patient-centered and exactly how to incorporate patient engagement throughout the process remains elusive for many trialists who design oncology trials.
- Increasingly public research funding agencies, like PCORI, demand evidence of meaningful patient engagement to fund research.

Pragmatic clinical trials in oncology

- Patient-centered pragmatic oncology trials often include more diverse patients, representative of patients who would receive the intervention in clinical care settings, and assess outcomes, such as health-related quality of life, that are meaningful to patients.
- The authors recommend using validated pragmatic trial design tools and approaches, such as the PRECIS-2 tool, and sustained stakeholder engagement to provide a more practical approach to achieving pragmatism and assuring scientific rigor in oncology trials.
- The PRECIS-2 tool has nine modifiable trial design domains scored from 1 (very explanatory) to 5 (very pragmatic) to facilitate domain discussion and consensus among the engaged stakeholders [1].
- The domains include eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome and primary analysis.

Applying a 10-Step Engagement Framework to pragmatic oncology trials

- Engaging patients, patient advocates and their healthcare providers in a continuous and meaningful way engenders trust, provides a level of ownership of the research enterprise, and actively supports oncology trial design, recruitment and participation.
- Despite the benefits of patient engagement, patients and patient advocates often are engaged late in planning research activities in a tokenistic manner [2–4].
- The 10-Step Engagement Framework developed by Mullins *et al.* provides methodological guidance for engaging patients throughout the research process, ensuring bidirectional learning while assuring research design and implementation integrity [5,6].
- Methods of engagement to adopt at each engagement step should be the best choice to elicit the patient's perspective.

Diversity in participation in oncology trials

- Despite the investment and efforts to create equitable access to cancer clinical trials, participation has still been disproportionately low for racial and ethnic minorities, older adults and females.
- Applying validated practical trial design tools and sustained stakeholder engagement approaches, such as PRECIS-2 tool and the 10-Step Engagement Framework, respectively, provide superior means to eliminate the persistent racial, age and gender disparities among oncology trial participants.

Informing a personalized approach to oncology clinical trial

- Investments made in oncology trials have engineered a greater understanding of cancer molecular biology, advanced detection methods, diagnosis and new drug innovations.
- Innovative trial designs must be flexible to accommodate patient-recommended modifications to study protocol, and to add or substitute targeted study therapies on interim data analyses.

Survivorship & health-related quality of life

- Advances in cancer diagnostic technology and therapeutics resulting from cancer science and trials have improved cancer survivorship.
- Health-related quality of life is valuable to patients and survivors as it captures patient-reported outcomes and plays a role in determining quality-adjusted life years (QALYs).

Survivorship & the benefits of engaging patient advocates

- Most cancer survivors are rarely engaged meaningfully in oncology trials to make the trials more patient-centered.

- The authors posit that researchers' ability to continuously engage cancer survivor advocacy groups has the potential to define the future of financial resource mobilization for oncology trials and ensure improved survivor participation in cancer research.

Barriers to participation in oncology clinical trials

- Patients with cancer face significant challenges – cost of participation, time spent, conflicting work and family obligations, feeling unwell while willing to participate and lack of trial information – to participating in clinical trials.
- Embracing innovative, pragmatic trial designs with continuous cancer patient engagement may help identify patient-centered solutions to these barriers and improve patient participation.

Positive influence on the uptake of new drugs or technologies into practice

- For a new oncology therapy to be translated into medical practice, it must be beneficial to the patients and acceptable to physicians.
- Meaningfully engaging stakeholders throughout the pragmatic trial continuum may produce valid results generalizable to the targeted oncology patient population and keep physicians updated on the new evidence [5].

Conclusion

- Patient engagement and pragmatism in oncology trial design lead to innovations in evaluating drugs and other oncology technologies to inform their use in clinical practice.
- Patient engagement does not compromise scientific or regulatory integrity.
- Implementing novel ways to address these critical aspects of oncology research simultaneously will position patient-centered, pragmatic oncology trials to optimally energize and benefit from the unprecedented emerging advances in the sciences of trial design and patient engagement.

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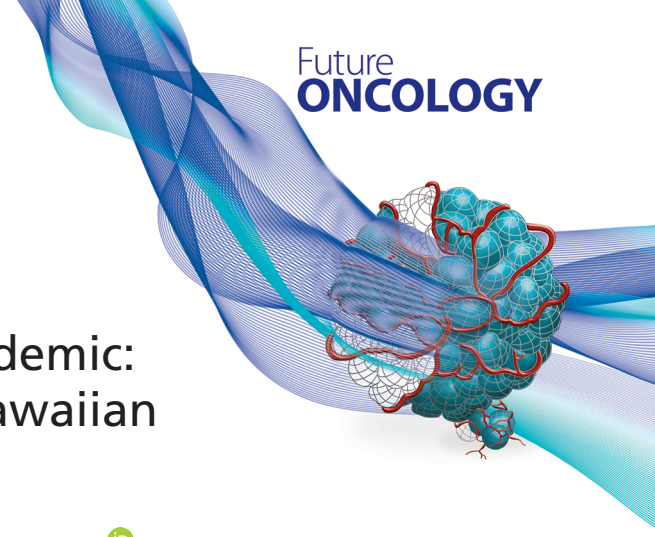

Telehealth amid the COVID-19 pandemic: perception among Asian, Native Hawaiian and Pacific Islander cancer patients

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Aim: To assess the perception of telehealth visits among a multiracial cancer population during the coronavirus disease 2019 pandemic. **Methods:** This cross-sectional study was conducted at outpatient cancer clinics in Hawaii between March and August 2020. Patients were invited to participate in the survey either by phone or email. **Results:** Of the 212 survey respondents, 61.3% were Asian, 23.6% were White and 15.1% were Native Hawaiians or Pacific Islanders. Asians, Native Hawaiians and Pacific Islanders were less likely to desire future telehealth visits compared with Whites. Predictors with regard to preferring future telehealth visits included lower income and hematopoietic cancers. **Conclusion:** The authors found racial differences in preference for telehealth. Future studies aimed at overcoming these racial disparities are needed to provide equitable oncology care.

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Keywords: COVID-19 • health disparity • pandemic • patient satisfaction • race • telehealth • telemedicine • teleoncology

The impact of the COVID-19 pandemic has accelerated the development of new models of care in oncology practice. Individuals with cancer are at an increased risk of mortality from COVID-19, leading to a greater need for precautions, such as social distancing [1,2]. In an attempt to decrease in-person office visits, oncology clinics have altered treatment schedules by increasing intervals between treatments [3,4]. The American Society of Clinical Oncology recommended adoption of telemedicine for patients not requiring a physical exam, treatment or in-office diagnostic testing [5]. Furthermore, the Department of Health and Human Services lifted restrictions, allowing wider adoption of telehealth visits as a substitution for in-person visits without diminishing reimbursements [6]. As a result, oncologists have rapidly adopted the use of telehealth in place of the traditional office visit to decrease the risk of transmitting the virus among patients and providers [7,8].

In general, telehealth refers to the use of telemedicine (defined by the Centers for Medicare and Medicaid Services as real-time interactive audio and video telecommunication) and/or telephone visits [9]. As a modality of provider-to-patient interaction, telehealth is relatively young, existing since only the early 1990s. Prior to the COVID-19 pandemic, telehealth was traditionally used for the delivery of healthcare services where distance was a critical factor. At present, the majority of patients are being converted to telehealth visits because of COVID-19 directives rather than distance. Recent teleoncology studies have demonstrated high rates of satisfaction with telehealth during the COVID-19 pandemic [10–12]. However, teleoncology has not been extensively studied in Asian and indigenous Pacific Islander populations, such as Native Hawaiians, who may have different experiences with the modality [13]. This study aimed to assess the perception of telehealth visits among a multiracial cancer population for whom in-person visits were the standard of care prior to COVID-19.

Future Medicine

Methods

Participants & eligibility criteria

This study was conducted at outpatient cancer clinics in Hawaii affiliated with the Queen's Health Systems and Hawaii Pacific Health. Together, these clinics care for about 70% of all cancer patients in the state. Patients who completed a telehealth visit between March and August 2020 were eligible to participate. Adults aged 18 years and older, with any cancer type and treatment intent, were eligible. Participants needed to be literate in English.

Data collection & measurement

Participants were approached sequentially in the survey time frame. Patients were invited to participate in the survey either by phone or email. All surveys were completed anonymously, and no personal health information or personally identifiable information was collected.

Demographic data collected included sex, age, education level, income, insurance type, race, type of cancer and stage of cancer. The authors developed a survey using Likert-type scales to evaluate patients' telehealth experience. Patients also rated their telehealth visit in comparison with a traditional face-to-face office visit (office visit is better, telehealth visit is better or no difference). Survey questions were adapted from a study by Donelan *et al.*, who published their assessment of the Massachusetts General Hospital telehealth experience [14]. A final open-ended question allowed participants to offer feedback on issues not covered in the survey.

Age was categorized as younger than 60, 60–79 and 80 and older. Education level was grouped into three categories: up to some college but no formal degree, associate or bachelor's degree and master's or doctoral degree. Categories for income included prefer not to say, <$30,000 per year, $30,000–89,999 per year and $90,000 or more per year. Insurance was categorized as private insurance; Medicare with a supplement; and other insurance, which included Medicaid and Medicare without a supplement. Patients self-identified their race and were grouped as either White or Native Hawaiian or Pacific Islander or Asian. Cancer type was grouped as gastrointestinal, hematopoietic (acute myeloid leukemia, myelodysplastic syndrome, lymphoma or myeloma), genitourinary, breast and lung or other. Cancer stage was grouped as 'I do not remember,' stage 0–2 and stage 3–4.

The primary end point of the study was the determination of a patient's perception of the overall quality of her or his telehealth visit. The secondary end point was establishment of the preference for future visits to be via telehealth compared with the traditional office visit. This study was also designed to determine the degree to which patient demographics and cancer type impacted these outcomes.

Statistical methods

Nonparametric descriptive statistics were used to evaluate characteristics of standard demographic data, tabulated by method of telehealth visit. A $p < 0.05$ was considered statistically significant. Overall quality was analyzed by comparing patients who preferred telehealth or found no difference between telehealth and office visits with patients who preferred office visits. Analysis of the desire for future visits compared patients who agreed with having future visits via telehealth with those who were neutral or disagreed with having future telehealth visits. Logistic regression models for quality of the telehealth visit and desire for future telehealth visits were built to obtain odds ratio (OR) and 95% CI. Multivariate models were adjusted for age, sex, race, insurance status, education level, distance from the oncology office, income, cancer type and stage and inclusion of video. Statistical analyses were performed with SPSS Statistics 27.0 (IBM Corporation, NY, USA).

Ethics

Approval for this study was granted by the Queen's Medical Center Research and Institutional Review Committee, the Hawaii Pacific Health Institutional Review Board and the Western Institutional Review Board. In addition, informed consent was obtained from the participants involved.

Results

A total of 450 patients were contacted, and 224 patients completed the survey, for a response rate of 49.8%. Patients were excluded from analysis if they stated 'prefer not to say' for the following demographics: race, age and distance. In addition, patients (n = 5) were excluded if their race could not be categorized as White, Native Hawaiian or Pacific Islander or Asian. A total of 212 patient surveys were included in the final analysis.

Of the 212 survey respondents, 138 (65.1%) were female and 74 (34.9%) were male (Table 1). The majority of participants were Asian (130; 61.3%), followed by White (50; 23.6%) and Native Hawaiian or Pacific Islander (32;

Table 1. Patient characteristics.

Characteristic	All patients		Audio only		Audio and video		p-value
	n	%	n	%	n	%	
Overall	212	100	73	34.4	139	65.6	
Sex							0.09
Female	138	65.1	42	57.5	96	69.1	
Male	74	34.9	31	42.5	43	30.9	
Age, years							0.23
<60	62	29.2	16	21.9	46	33.1	
60–79	128	60.4	49	67.1	79	56.8	
≥80	22	10.4	8	11.0	14	10.1	
Education							0.95
Less than associate	76	35.8	27	37.0	49	35.3	
Associate or bachelor's	105	49.5	36	49.3	69	49.6	
Master's or doctorate	31	14.6	10	13.7	21	15.1	
Income							**0.03**
Prefer not to say	40	18.9	12	16.4	28	20.1	
<$30,000	35	16.5	18	24.7	17	12.2	
$30,000–89,999	70	33.0	27	37.0	43	30.9	
≥$90,000	67	31.6	16	21.9	51	36.7	
Insurance							0.91
Medicare without a supplement, Medicaid, other	38	17.9	12	16.4	26	18.7	
Medicare with a supplement	73	34.4	26	35.6	47	33.8	
Private	101	47.6	35	47.9	66	47.5	
Ethnicity/race							0.14
Asian	130	61.3	51	69.9	79	56.8	
Native Hawaiian or Pacific Islander	32	15.1	7	9.6	25	18.0	
White	50	23.6	15	20.5	35	25.2	
Distance							0.06
15-min drive or less	63	29.7	26	35.6	37	26.6	
16–30-min drive	80	37.7	32	43.8	48	34.5	
More than 30-min drive	39	18.4	8	11.0	31	22.3	
Flight	30	14.2	7	9.6	23	16.5	
Cancer type							**0.045**
Gastrointestinal	49	23.1	23	31.5	26	18.7	
Hematopoietic	28	13.2	5	6.8	23	16.5	
Genitourinary	20	9.4	10	13.7	10	7.2	
Lung and other	23	10.8	7	9.6	16	11.5	
Breast	92	43.4	28	38.4	64	46.0	
Cancer stage							0.54
I do not remember	45	21.2	18	24.7	27	19.4	
Stage 0–2	97	45.8	34	46.6	63	45.3	
Stage 3–4	70	33.0	21	28.8	49	35.3	
Overall quality							**0.007**
Telehealth is better or no difference	139	65.6	39	53.4	100	71.9	
Office visit is better	73	34.4	34	46.6	39	28.1	
Preference for future telehealth visits							0.28
Agree	121	57.1	38	52.1	83	59.7	
Neutral or disagree	91	42.9	35	47.9	56	40.3	

Bold values denote statistical significance at the $p < 0.05$ level.

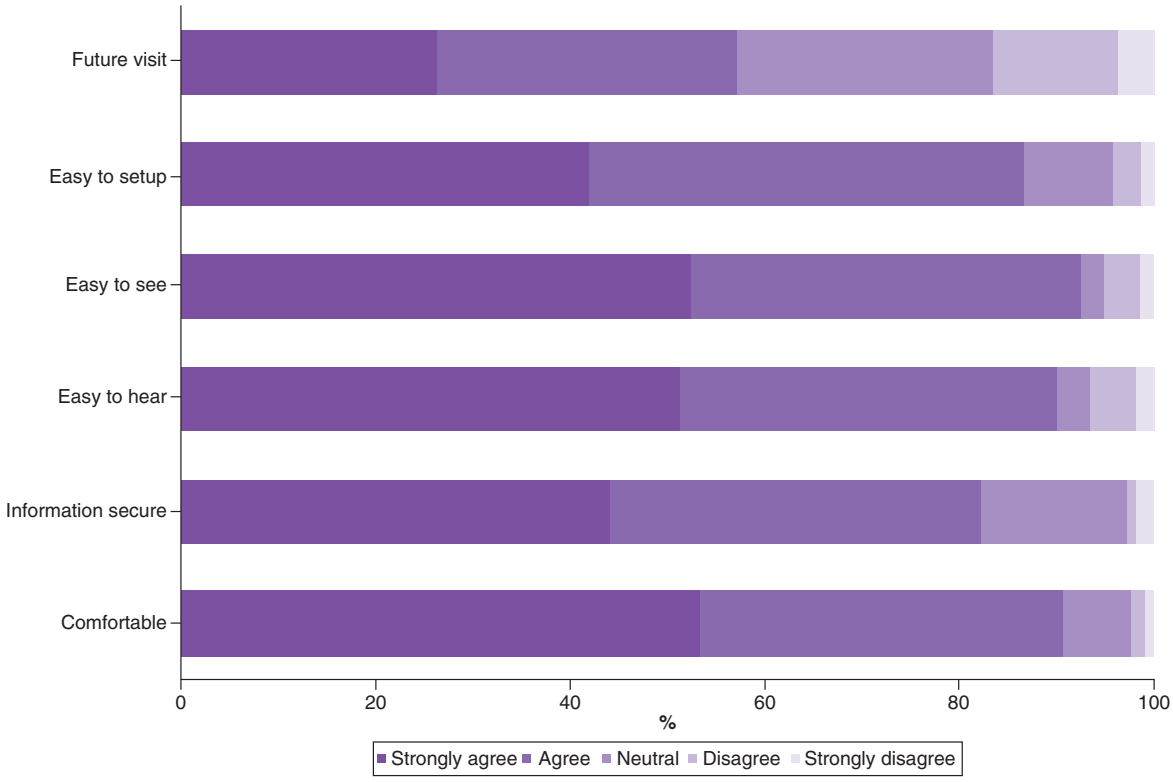

Figure 1. Patient experiences of the telehealth visit.

15.1%). The most common cancer type was breast cancer (43.4%), followed by gastrointestinal cancer (23.1%) and hematopoietic cancer (13.2%). Most telehealth visits included video (65.5%). Of the video platforms used, the most common was FaceTime (33.7%), followed by MyChart (28.3%), Zoom (24.1%), Doximity (12.7%) and Webex (1.1%). A large fraction of the patients did not remember which platform was used (27.8%).

Characteristics were similar between patients who had telehealth visits that included video and those who had audio-only visits; however, patients with higher income were more likely to have a visit that included video ($p = 0.03$). Patients who experienced video visits perceived the telehealth visit as being better or no different from the traditional office visit more often than patients with audio-only visits ($p = 0.007$).

Based on Likert scale questions, patients' experiences with telehealth were mostly positive (Figure 1). Over 90% of patients were comfortable with the telehealth visit and had no difficulties seeing or hearing the physician. The majority of patients were satisfied with the technology aspect of the visit, with 86.8% agreeing or strongly agreeing that it was easy to set up the telehealth visit and 82.1% agreeing or strongly agreeing that their information was securely transmitted. However, when asked if they would like future visits to be telehealth, only 57.1% of respondents agreed or strongly agreed, whereas 26.4% were neutral and the remaining 16.5% disagreed or strongly disagreed.

The items were asked in the survey as followed – future visit: 'I would like some of my future visits to be telehealth visits rather than face-to-face visits'; easy to set up: 'it was easy to set up my telehealth visit using my phone/computer/tablet'; easy to see: 'it was easy to see my doctor during the telehealth visit (video visit only)'; easy to hear: 'it was easy to hear my doctor during the telehealth visit'; information secure: 'my information was securely transmitted during my telehealth visit'; comfortable: 'I felt very comfortable with my telehealth visit'.

Most patients felt that the overall quality of the telehealth visit was the same as that experienced with an office visit (55.2%) or better (10.4%). Conversely, 34.4% of patients felt that the overall quality of office visits was better (Figure 2). Patients favored telehealth or felt a telehealth visit was similar to an office visit with regard to time spent with the provider (72.2%), wait time (89.2%) and finding a convenient time for the visit (85.8%). However, when asked about the personal connection they felt with their provider, half (50.0%) of the patients found the personal connection in office visits to be better.

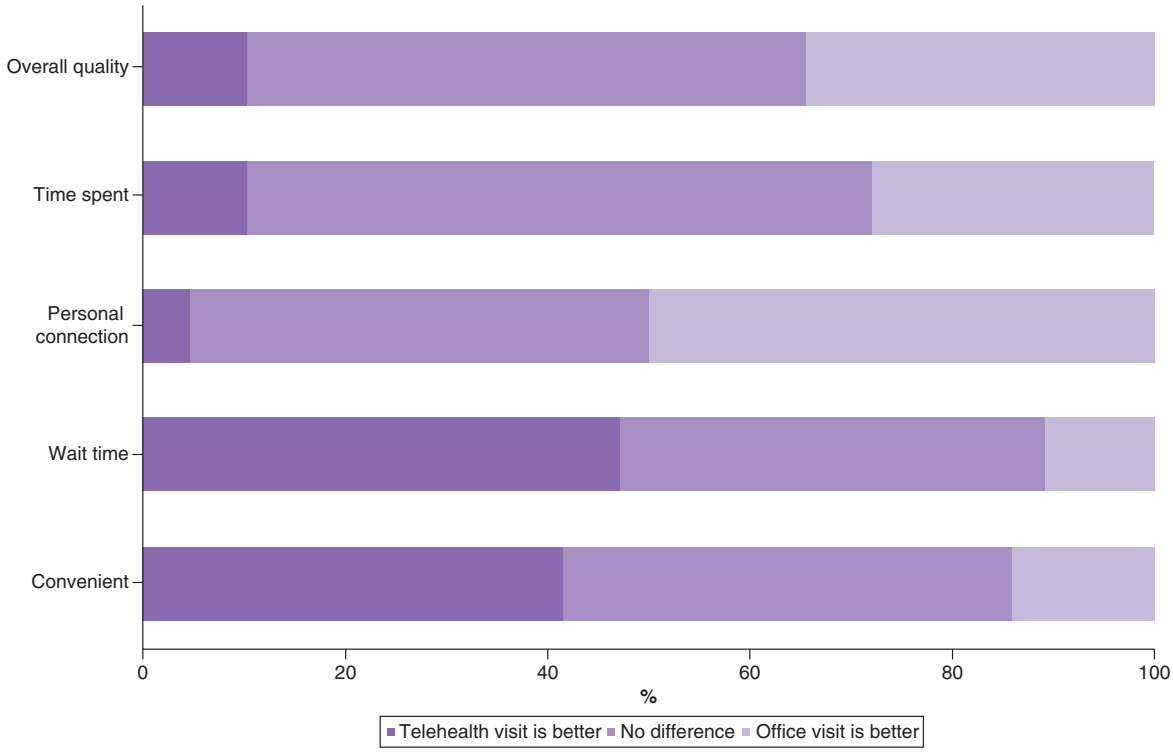

Figure 2. Patient-reported preferences for telehealth visits compared with office visits.

The items were asked in the survey as followed - Overall quality: 'overall quality of the visit'; time spent: 'amount of time I spent with the doctor'; personal connection: 'personal connection I feel with the doctor during the visit'; wait time: 'amount of time I wait for the doctor'; convenient: 'finding a convenient time for the visit'.

Logistic regression models were created to identify predictors of overall quality of the telehealth visit and the desire to have future telehealth visits. The only predictor of visit quality was the inclusion of video, which was significantly associated in both univariate (OR: 2.24; 95% CI: 1.24–4.03) and multivariate (OR: 2.22; 95% CI: 1.12–4.38) analyses. No other predictors of visit quality were identified.

There were several significant predictors of the desire for future telehealth visits (Table 2). On univariate analysis, patients with hematopoietic cancers (OR: 2.87; 95% CI: 1.11–7.41) and those who favorably rated the quality of the visit (OR: 8.74; 95% CI: 4.55–16.81) were more likely to want a future telehealth visit. Conversely, Asians (OR: 0.34; 95% CI: 0.16–0.70) and Native Hawaiians and Pacific islanders (OR: 0.32; 95% CI: 0.12–0.82) were less likely to desire future telehealth visits compared with Whites. These factors remained significant on multivariate analysis. In addition, lower income of $30,000–89,999 was associated with the desire for future telehealth visits compared with income ≥$90,000 (OR: 3.85; 95% CI: 1.44–10.30). Video during the telehealth visit was not a significant variable with regard to wanting future visits to be telehealth.

Discussion

In the authors' study, the majority of patients (65.6%) found the overall quality of their telehealth visit to be equivalent to or better than office visits. Satisfaction with telehealth was even higher among patients whose visit included video (71.9%). This acceptance of telehealth visits is similar to that seen in a study by Donelan *et al.* performed prior to the pandemic, which showed that 75.2% of patients found the quality of the video visit to be equivalent to or better than a face-to-face visit [14].

Preference for wanting some future visits to be telehealth was seen in only 57.1% of patients, a stark difference from that seen in studies reported prior to the pandemic. Among radiation oncology patients, Hamilton *et al.* found that 89.6% of survey respondents wanted all or some of their visits to take place via telehealth [15]. In a non-oncology setting, Polinski *et al.* reported an even stronger desire for future telehealth visits, with 98% of patients stating that they would definitely or probably use telehealth again [16]. Although these studies were performed in different

Table 2. Univariate and multivariate linear regression for variables predicting preference for future telehealth visits.

Factor	Univariate		Multivariate	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Female sex	0.73 (0.41–1.29)	0.27	0.69 (0.24–1.92)	0.47
Age, years, <60 as reference				
60–79	0.90 (0.48–1.66)	0.73	0.38 (0.09–1.61)	0.19
≥80	0.68 (0.25–1.80)	0.43	0.78 (0.33–1.85)	0.57
Education, master's or doctorate as reference				
Less than associate	0.76 (0.32–1.80)	0.53	0.52 (0.15–1.83)	0.31
Associate or bachelor's	0.65 (0.29–1.50)	0.31	0.63 (0.18–2.16)	0.46
Income, ≥$90,000 as reference				
Prefer not to say	0.78 (0.36–1.71)	0.53	0.81 (0.29–2.28)	0.68
<$30,000	1.29 (0.56–2.96)	0.55	2.63 (0.79–8.72)	0.12
$30,000–89,999	1.55 (0.78–3.08)	0.21	**3.85 (1.44–10.30)**	**0.007**
Insurance, private as reference				
Medicare without a supplement, Medicaid, other	1.03 (0.49–2.19)	0.93	0.77 (0.26–2.31)	0.65
Medicare with a supplement	1.34 (0.73–2.48)	0.34	1.16 (0.49–2.71)	0.74
Ethnicity, White as reference				
Asian	**0.34 (0.16–0.70)**	**0.004**	**0.26 (0.10–0.71)**	**0.01**
Native Hawaiian or Pacific Islander	**0.32 (0.12–0.82)**	**0.02**	**0.19 (0.05–0.66)**	**0.01**
Distance, 15-min drive or less as reference				
16–30-min drive	0.87 (0.45–1.70)	0.69	0.69 (0.29–1.67)	0.42
>30-min drive	1.08 (0.48–2.42)	0.86	0.63 (0.20–2.03)	0.44
Flight	1.30 (0.53–3.17)	0.57	0.39 (0.11–1.38)	0.15
Cancer type, breast as reference				
Gastrointestinal	0.92 (0.46–1.84)	0.81	0.90 (0.27–3.05)	0.87
Hematopoietic	**2.87 (1.11–7.41)**	**0.03**	**4.99 (1.13–22.08)**	**0.03**
Genitourinary	1.78 (0.65–4.86)	0.26	1.38 (0.24–7.83)	0.72
Lung and other	2.19 (0.82–5.82)	0.12	2.61 (0.65–10.54)	0.18
Cancer stage, 0–2 as reference				
Stage 3–4	1.25 (0.67–2.32)	0.49	1.14 (0.45–2.91)	0.78
I do not remember	1.14 (0.56–2.32)	0.73	0.74 (0.23–2.33)	0.61
Video included	1.37 (0.77–2.42)	0.29	2.09 (0.48–2.46)	0.84
Overall quality	**8.74 (4.55–16.81)**	**<0.001**	**13.96 (6.10–31.99)**	**<0.001**

Bold values denote statistical significance at the $p < 0.05$ level.
OR: Odds ratio.

medical specialties, this discrepancy in preference for future telehealth visits may be in part due to the abrupt shift to telehealth in the authors' patient population compared with the cohorts studied by Hamilton *et al.* and Polinski *et al.*, for which telehealth was an accepted practice.

Asian and Native Hawaiian patients were less likely to desire future telehealth visits than White patients. This racial difference persisted even after adjusting for other sociodemographic factors. However, the authors did not identify an association between race and the perceived quality of the telehealth visit compared with traditional office visits. In a study conducted on face-to-face visits, Palmer *et al.* demonstrated that Asian and Pacific Islander cancer patients report worse communication with their providers and lower quality of care and self-efficacy than Whites [17]. These racial disparities likely carry over into telehealth visits and may be magnified by the additional challenges that come with virtual visits. In addition, when interviewed about their telehealth perceptions, Native Hawaiians highlighted the importance of nonverbal communication and the need to develop the patient–physician relationship to overcome differences in culture and ways of conceptualizing health [13]. The abrupt adoption of telehealth visits as a result of the COVID-19 pandemic may have resulted in encounters with practitioners who were not adept at addressing the cultural needs of Native Hawaiian patients over virtual visits.

In this study, the authors observed a large loss in patient–provider personal connection in telehealth visits. Only a small proportion (4.7%) of patients rated their personal connection with their oncology provider via telehealth as better than that seen during an office visit, whereas exactly half of the patients felt that office visits were better. This loss in personal connection persisted when restricting the analysis to only patients with video visits (47.5%) or patients who identified as White (44.0%). Donelan *et al.* showed a better personal connection among their patients, with only 32.7% of patients feeling that office visits were better than video visits [14]. Of note, there are significant differences between our patient populations. Donelan *et al.* surveyed predominantly White patients who presented to psychiatry, neurology and cardiology appointments. The authors' population was racially heterogeneous and made up exclusively of cancer patients. It is conceivable that oncology patients may create high levels of expectation for their relationship with the oncology provider [18]. This personal connection may be diminished when the visit is conducted digitally. Furthermore, the loss of expected personal connection may disproportionately affect the preference for telehealth in Asian and Native Hawaiian and Pacific Islander cancer patients, who represented a large part of the authors' study population. The authors' findings support the hypothesis that the preference for telehealth in culturally diverse groups may be dependent on whether it can nurture the patient–provider relationship despite its potential for improving the access to and quality of health care [13].

The authors found that income level impacted the inclusion of video as part of the telehealth visit and the desire for future telehealth visits. Patients who had audio-only visits were more often of lower income and may not have had the resources required for video visits. Although video enhances the quality of the visit, audio-only visits remain an important option for patients with lower income or poor digital literacy. A multivariate analysis demonstrated that patients with lower income ($30,000–89,999) were more likely to want future telehealth visits compared with patients with an income ≥$90,000. This finding is in contrast to recent research in which patients with the lowest income were less likely to use telehealth during the pandemic [19,20]; the authors' study showed an increased preference for telehealth in only the middle income bracket. This may highlight the ability of telehealth to overcome barriers to healthcare access that working people in a lower income group more often face, such as transportation challenges, gaining approval for time off work and finding childcare.

Of the study population, 85.8% lived on Oahu and likely did not experience telehealth prior to the pandemic. Furthermore, 34.6% of the patients on Oahu lived within a 15-min drive of the provider's office, a situation in which the convenience of telehealth may be less pronounced. Although the patients lived in varying proximity to their provider, the authors' study demonstrated that distance was not a significant factor in patient satisfaction or preference for telehealth. By contrast, a study conducted on spine patients in Texas and Pennsylvania during the pandemic found any distance greater than 10 miles to be a significant predictor of a preference for telehealth [21]. This may reflect differences in patient demographics, disease type and geographical preferences for telehealth during the pandemic.

The authors' study was focused on oncology patients and revealed that patients with hematopoietic cancers were significantly more likely to prefer future telehealth visits than breast cancer patients. Hematopoietic cancer patients are often reviewing laboratory test results during visits and may not have significant findings on physical exam. Breast cancer patients, however, regularly receive breast examinations during their visits and would be missing a more notable part of their normal doctor visit if the visit occurred via telehealth. Many patients expressed this concern in the free text response, stating that they preferred office visits specifically for the breast examination. Laboratory and imaging studies for the patients in this study were done on an outpatient basis, usually at locations convenient for the patient, demonstrating the utility of telehealth beyond the COVID-19 pandemic to provide remote follow-up care. Others have similarly found that telehealth visits often suffice in meeting cancer patient needs without further in-person care [22,23]. Although the authors' study found that certain cancer patients were more or less likely to prefer telehealth, it is imperative that providers accommodate patient preferences while continuing to provide appropriate clinical care.

Limitations

This study is limited by its relatively small number of participants. Furthermore, all subjects receive their care in cancer clinics in Hawaii, which could limit the generalizability of the authors' findings. However, selecting this cohort of patients provided the authors the ability to analyze a multiracial cancer population with a large number of Native Hawaiians and Pacific Islanders. Similar to other patient survey studies, the authors' findings are subject to recall bias, if patients did not accurately recall their telehealth experience, as well as social desirability bias, as patients often provide answers they think their physician would like to hear.

Conclusion & future perspective

The perceived quality of the telehealth visits and the desire for future telehealth visits were not uniform across different patient populations. Asian and Native Hawaiian and Pacific Islander patients were less likely to desire future telehealth visits in comparison with Whites. During the time frame of this study, distance was not the main driving factor for the use of telehealth, and our study demonstrated that distance did not significantly influence telehealth satisfaction in oncology patients. On the contrary, patients with lower income or hematopoietic cancers, in which the physical exam was less pertinent to care, were more likely to prefer future telehealth visits. The inclusion of video significantly enhanced the quality of the visit. Telehealth is a powerful tool in expanding care to oncology patients, and our results may guide both oncology providers and policymakers in better implementing telehealth during and after the COVID-19 pandemic. The preference for telehealth will continue to grow as telehealth visits become more normalized in future generations. Further studies and interventions are needed to overcome racial disparities in telehealth.

Summary points

- The COVID-19 pandemic has rapidly accelerated the use of telehealth in oncology practice.
- This study aimed to assess the perception of telehealth visits among a multiracial cancer population for whom in-person visits were the standard of care prior to coronavirus disease 2019.
- Asian and Native Hawaiian and Pacific Islander patients were less likely to desire future telehealth visits in comparison with Whites.
- Patients with lower income or hematopoietic cancers were more likely to prefer future telehealth visits.
- The inclusion of video significantly enhanced the quality of the visit.
- Future studies aimed at overcoming these racial disparities are needed to provide equitable oncology care through telehealth.

Author contributions

Data analysis and writing of the manuscript: M Meno, J Abe, J Fukui, C Braun-Inglis, I Pagano and J Acoba. Study design: J Fukui, C Braun-Inglis and J Acoba. Statistical analysis: I Pagano.

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Disclaimer

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Epigenomics

A transdisciplinary approach to understand the epigenetic basis of race/ethnicity health disparities

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Health disparities correspond to differences in disease burden and mortality among socially defined population groups. Such disparities may emerge according to race/ethnicity, socioeconomic status and a variety of other social contexts, and are documented for a wide range of diseases. Here, we provide a transdisciplinary perspective on the contribution of epigenetics to the understanding of health disparities, with a special emphasis on disparities across socially defined racial/ethnic groups. Scientists in the fields of biological anthropology, bioinformatics and molecular epidemiology provide a summary of theoretical, statistical and practical considerations for conducting epigenetic health disparities research, and provide examples of successful applications from cancer research using this approach.

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The goal of this manuscript is to provide a transdisciplinary perspective on the contribution of epigenetics to the understanding of health disparities among socially defined racial/ethnic groups, drawing on expertise from scientists in the fields of biological anthropology, bioinformatics and molecular epidemiology. Herein, we summarize theoretical, statistical and practical elements of investigating racial/ethnic health disparities using epigenetics and provide examples of successful applications from cancer research using this approach. This work will aid in shaping how researchers understand and therefore approach problems of health disparities when incorporating epigenetic data.

What is epigenetics?

Epigenetics is the study of heritable phenotypic variations that do not involve changes in the DNA sequence, often involving control for gene activity and expression [1,2]. Examples that produce such changes are histone and chromatin modification, and DNA methylation. DNA methylation is the best-studied type of epigenetic modification in humans, playing a critical role in the regulation of gene expression. This primarily occurs by reducing the transcription of genes at the promoter and enhancer regions, although more complex regulatory mechanisms have been described in other gene contexts [109 3,4]. DNA methylation is one of the key players in cellular differentiation, providing cell identity [5]. Genetic variation and environmental factors can affect the cell subpopulation selection through epigenetic adaptation, and under extreme pressures, can alter cell differentiation

Future Medicine

and lead to abnormal phenotypes, including cancer cells [6–8]. This plasticity makes epigenetic processes lie at the interface of the environment and transcriptional control.

Using epigenetics to understand the development of health disparities

Health disparities are differences in disease risk between populations groups, and oftentimes, are accompanied by a higher than expected mortality burden. Health disparities are common across a variety of social contexts and are documented for a wide range of morbidities that occur across the life course. Such disparities may emerge according to race. Race is defined here as the social construct of human variability based on perceptions of biological differences (e.g., skin color or other aspects of physical appearance). While race categories do not reflect genetically distinct groups, experiences of racism and structural violence can adversely impact the biology and health of racialized minorities. Similarly, health disparities may also emerge according to ethnicity. Ethnicity, according to Mersha *et al.*, refers to a 'multidimensional construct reflecting biological factors, geographical origins, historical influences, as well as shared customs, beliefs, and traditions among populations that may or may not have a common genetic origin' [9]. As such, each 'race' or 'ethnicity' may include multiple subgroups (e.g., Hispanic/Latinx are comprised of Cubans, Panamanians, Ecuadorians, Argentinians, etc.).

Given that racial/ethnic groups are social categories that do not necessarily align with underlying patterns of genetic variation [10], genetic factors alone are insufficient to explain how racial/ethnic health disparities emerge. It is therefore critical to evaluate how differences in experience and environment shape health outcomes. In fact, it is now becoming clear that environmental differences are important in shaping more complex phenotypes that are of interest in public health regarding racial/ethnic inequalities, such as low birth weight, preterm birth, asthma, cancer and cardiovascular disease. Epigenetic studies may help to understand how differences in environmental experience translate into differences in phenotype. Although a limited number of studies have directly connected DNA methylation to health disparities, a few studies have reported intriguing results. Socioeconomic status [11], as well as factors that vary according to socioeconomic statuses such as psychosocial stress exposure [12,13] and diet [14,15], have been associated with variation in DNA methylation.

Early life experiences may be particularly important for shaping health disparities. The Developmental Origins of Health and Disease hypothesis suggests that a mother's experience during her life and her pregnancy may shape the epigenome and future health trajectory of her infant [16,17]. Moreover, different environmental exposures during pregnancy (maternal lifestyles, diseases and exposures to environmental toxicants) have been associated with alterations in DNA methylation in the placenta or the umbilical cord blood of the newborn [18–21]. However, there has been criticism of the overemphasis on maternal effects relative to paternal effects in predicting health outcomes via epigenetic mechanisms [22]. While it has been less frequently investigated, growing evidence suggests that paternal environmental experience can also affect offspring through epigenetic processes. For example, paternal obesity in the peripartum period is associated with significant differences in offspring methylation at imprinted genes important for regulating growth and development [23]. These findings suggest that socially patterned exposure to stressors in both parents could potentially affect offspring health via changes in the offspring epigenome.

Among historically marginalized communities, the ancestral experience of trauma (i.e., historical trauma) shapes disparities in later health generations [24–26]. In addition to being related to the intergenerational effects described above, the health impacts of historical trauma likely also reflects within-generation epigenetic impacts of environmental conditions shaped by ancestral experience [27,28]. For example, forced displacement of ancestors increases the likelihood that members of the contemporary generation experience poverty and therefore associated health sequelae. Likewise, the parental experience of trauma could shape both the intrauterine environment and patterns of parental care, both of which affect the developing epigenome of offspring [27,29]. Therefore, historical trauma should be considered as an additional conceptual model for explaining observed health disparities.

Statistical methodology for studying the epigenetic basis of health disparities

Studies investigating the DNA methylation basis of health disparities have generally employed global DNA methylation, targeted gene methylation, single variant methylation or network-based analysis [30–32]. With the rapid development of high-throughput technologies in recent years, population-based epigenome-wide association studies at a single-nucleotide resolution became a popular approach utilized in epigenetic studies. The common supervised selection strategy is to select CpG sites affecting phenotypic differences, noted as differentially methylated cytosines [33]. Differentially methylated cytosines can be selected based on the absolute difference in mean beta values or test statistics from a t-test, Wilcoxon test or multivariable regression model. Another selection approach is

to consider differential variance in methylation between two traits, noted as differentially variable cytosines, using, for instance, the Bartlett test or the Levene's test [34,35]. In genomics, variance-based selection of SNPs approaches could be used to prioritize those SNPs for subsequent gene–gene and gene–environment testing [36]. Although some tools have been developed for this goal [37], epigenome-wide approaches for epigenome–environment and genome–epigenome interactions are infrequently studied beyond locus-specific interactions due to computational burden and concerns over model assumptions when using untargeted approaches. On the other hand, the unsupervised selection procedure is to rank and filter CpG sites by variance, aiming for the selection of the most variably methylated cytosines [38]. The most variably methylated cytosines generally represent various levels of DNA methylation and may contain those driven by SNPs or cell heterogeneity (e.g., different immune cell populations in blood/saliva or immune-cell infiltration in solid tissues). Studies have also employed the most variably methylated cytosines approach to filter CpGs before single variant methylation tests to reduce the burden of multiple hypothesis testing.

Differences at any individual site may be small; however, if these differences are persistent across a region or a certain group of genes, statistical power to detect them may be greater. Several methods have been developed to identify sets of neighboring CpGs sites that are correlated with each other, known as differentially methylated regions, and link them with traits of interest, including DMRcate [39], bump hunting [40] and the A-clustering method [41]. Other methods aiming to build gene co-methylation networks have also been proposed. For example, weighted gene co-methylation network analysis aims to describe the correlation patterns among genes across microarray samples, find clusters of highly correlated genes, and relate such clusters to a phenotype of interest via enrichment analysis or network eigengenes (the top principal component of genes in the cluster) [42].

Challenges & opportunities in statistical methodology

Although advances in epigenetic studies are expected to help understand racial/ethnic health disparities, there are notable challenges and limitations to consider. Epigenetic studies are potentially impacted by a range of confounding factors, including but not limited to population genetic patterns, cell-type, environmental confounders related to ethnicity and sample processing batch [43]. Population stratification is another critical source of confounding for studies including heterogeneous populations. DNA methylation signatures of target tissue (e.g., saliva, whole blood, placenta, adipose and tumors) are an average of cell type-specific methylation levels. Hence, the cell-type proportion is generally related to the measured DNA methylation levels, and in many cases, is also associated with race/ethnicity [44] and traits of interest [45]. Various statistical methods have been proposed to adjust for this potential bias. Statistical models for cell-type deconvolution are classified into three categories called reference-based [46], reference-free [47] and semi-reference-free [48–51], the last of which alleviates some of the problems of both reference-based and reference-free methods. The choice of the appropriate method for cell-type deconvolution mainly depends on the availability of a proper reference database for DNA methylation of the cell types involved [52–54]. Some other methods developed specifically for methylation data, or for general purposes, can be used to control for all unmeasured confounding, including; surrogate variable analysis (SVA) [55], independent SVA [56], smartSVA [57], remove unwanted variation [58,59] and principal component analysis [60]. Several of these methods have been used to adapt reference-free approaches and semi-reference-free approaches and have been reviewed and compared elsewhere [2,61]. However, residual confounding may still be possible after adjustment. In statistical genetics, genomic inflation represents the excess of false positives in genomic analyses. In epigenome-wide association studies, the genomic inflation factor calculation and the quantile-quantile plots have been used to quantify the excess inflation in statistics, however, in most of these analyses, genomic inflation is not corrected. The application of genomic control correction has shown to be ineffective due to the small differences detected in epigenome-wide association studies, with only a few methods that have been adapted specifically for DNA methylation analyses but are still not widely used in the field [62]. Finally, several biomarkers derived from DNA methylation information have been developed which could offer global measures of epigenetic drift related to various phenotypic variations of interest. Among those, we have age acceleration using the DNA methylation age measures [63,64], fetal cell of origin [65], inference of multiple retrotransposons using epigenome-wide information [66] or global methylation changes [67]. The selection of specific methods should be adapted to the specific hypothesis being tested.

Insights & applications from cancer research

Locus specific changes and differentially methylated cytosines related to race/ethnicity have been identified among cancer biologists interested in health disparities and have been extensively reviewed in the past [30,68–70]. Beyond the locus-specific promoter changes, epigenome-wide association studies have continuously reported variation in

DNA methylation patterns between different populations such as Europeans, Hispanics, Africans and Asians [71]. Determining how these race/ethnicity variations are associated with disease outcomes will further help to understand health disparities. Another approach is to describe demographic and environmental factor-associated and disease-associated differentially methylated cytosines in different race/ethnicity groups.

Cancer health disparities research in the USA is largely focused on race/ethnicity, where cancer incidence is highest among African–Americans or Blacks, followed by non-Hispanic Whites, Hispanics and Asian/Pacific Islanders [72]. Generally, African–Americans also have the highest mortality rates and worse survival outcomes in comparison with all other race/ethnicity groups. The disparity gap between whites and African–Americans for cancer incidence and mortality has narrowed over time, but there is still a notable 14% difference in the mortality rate [72]. While African–Americans are disproportionately affected overall, other race/ethnicity groups (e.g., Hispanics, Asian/Pacific Islanders) have a greater cancer burden or worse survival for certain cancers. For example, Hispanics have a higher incidence of infection-associated cancers (e.g., liver, stomach and cervical cancer) [73]. Cancer is also more prevalent among socially, economically or environmentally disadvantaged populations. Higher cancer incidence and mortality rates, as well as lower survival, are experienced by cancer patients with low educational attainment or residents of impoverished neighborhoods compared with more educated individuals and residents of affluent areas [74]. As the socioeconomic status and race/ethnicity are inextricably linked to one another, it is often difficult to disentangle their independent effects on cancer disparities.

The underlying causes of cancer health disparities are complex and multifactorial. While a portion of the disease burden is due to the marginalization of minority populations, disease susceptibility is a combination of population isolation, genetic burden and selection of specific phenotypes that are advantageous for certain environments [75]. One example is the trends in cancer subtype susceptibility for certain race/ethnicity groups. Skin cancer distributions differ across race/ethnicity as the risk of squamous cell carcinoma is higher in Eurasian descendants and anecdotally in African populations with albinism [76]. Triple-negative breast cancer and aggressive prostate cancer are much more frequent in African–Americans compared with other racial/ethnic groups in the USA. Even after accounting for healthcare access and other social factors, African–Americans with these subtypes have a worse prognosis compared with white–Americans. Interestingly, Hispanic cancer patients have better outcomes than African–Americans despite similar sociodemographic characteristics, also known as the 'Hispanic paradox' [77], while at the same time, this group is still adversely affected by other health outcomes, such as infectious diseases, disabilities and diabetes compared with non-Hispanic whites. As neighborhood socioeconomic status has been shown to contribute to survival disparities in Black and Hispanic cancer patients, but not Asian/Pacific Islanders [78], neighborhood socioeconomic status does not represent the only source of variability contributing to health disparities for these groups.

Considerable strides have been made in cancer research to investigate the link between DNA methylation and cancer health disparities, primarily for the most common cancers. In breast cancer, several studies have identified differentially methylated loci when comparing tumors from African–American and European–American women [79–84], with the most differences observed in women with estrogen receptor (ER) negative tumors and younger women. Another study uncovered seven genes hypermethylated in Korean versus European women, which again, was particularly seen among ER and progesterone receptor (PR) negative tumors and women aged $\leq$50 years [85]. Similarly, work in prostate cancer found several CpG sites that are differentially methylated among tumors from Black versus white men [86–90], with studies consistently implicating *CD44* and *GSTP1* [86,87,90]. Besides breast and prostate cancer, the literature investigating the epigenetic basis of race/ethnicity disparities in other cancer types is fairly sparse [91–97], especially for rare cancers where challenges arise due to the limited number of cases in existing studies, particularly within minority or underserved populations. Many additional studies in the literature investigate DNA methylation of cancer patients within a specific race/ethnicity but do not compare with other race/ethnicity groups. While these studies uncover the unique epigenetic alterations within different populations, they do not provide a comparison group to elucidate a potential racial/ethnic disparity and are not discussed herein.

Challenges in epigenetic health disparities research

Race/ethnicity is the most common disparity investigated in cancer epigenetics as well as other disease disparities, with the majority of studies comparing African–American/Black and European–American/White populations. Little emphasis has been placed on other race/ethnicity groups (e.g., Hispanics, Asian/Pacific Islanders, American–Indians/Alaskan Natives), although these under-represented groups have notable disparities for many chronic and

acute diseases and are a growing proportion of the U.S. population. Moreover, any racial/ethnic categorization encompasses very heterogeneous populations. For instance, Hispanics and Asian/Pacific Islanders represent a variety of ethnic subgroups (e.g., Cuban, Mexican, Filipino and Chinese) that have different experiences and risk profiles. These racial/ethnic groups are often understudied due to inadequate sample sizes or the under-representation of these populations within any one study. Adding to this challenge, there is typically a lack of studies with available biospecimens to conduct epigenetic disparities research.

Promoter methylation of candidate genes or a preselected panel of genes has been the approach used most often to measure DNA methylation. The array-based methodology offers an agnostic approach to move beyond a single gene or gene promoter. However, the majority of studies using arrays to quantify DNA methylation levels have used the Illumina 27 or 450K array. Both are now obsolete after the introduction of the MethylationEPIC (or 850K) array, which provides comprehensive genome-wide coverage and captures additional enhancer and intergenic regions of the genome that were not included on the older versions of the array. As genome-wide association studies note the importance of noncoding regions of the genome in disease susceptibility, the EPIC array will be able to shed light on whether this is also true for epigenetic alterations. DNA methylation sequencing (e.g., reduced representation bisulphite sequencing or whole genome bisulphite sequencing) has been used in a few health disparities studies [98], however, this technology cost is higher than the microarrays and depending on the biospecimen, the genome coverage may not be consistent.

Conclusion

Epigenetic markers have shown several interesting associations that could be driving health disparities from a biological perspective. When investigating the association between racially/ethnically different epigenetic variations and disease outcomes in cross-sectional settings, determining causality is challenging [99]. Prospective follow-up studies among racially/ethnically heterogeneous populations would allow researchers to identify methylation changes involved in different pathways preceding disease onset. Using a Mendelian randomization approach to integrate genotype and epigenetic data may also prove useful in determining causality [100]. However, there are several limitations of this approach including but not limited to low statistical power, population stratification generating spurious genetic variants, re-introduced confounding through pleiotropy and linkage disequilibrium with multiple causal genetic variants of the epigenetic variation [100].

The use of machine learning is of great interest in disease prediction and classification. For example, the elastic net, a penalized regression model, has been applied in predicting human age with DNA methylation data in the USA [63], Chinese and multiracial/multiethnic populations [101,102]. Integrating the epigenome with other types of -omics data such as the genome, transcriptome, proteome, metabolome and the microbiome has the potential to unlock the 'black box' in health disparities. Although current technologies are still facing challenges, researchers have found intriguing results [103,104]. Future enhanced bioinformatics and analytical tools [105] will enable a more comprehensive analysis of human observational and interventional studies in a systematic way.

Future perspective

Some studies have devised an integrative approach including a comprehensive analysis of the social and environmental exposures of specific race/ethnicity associated epigenetic changes [32,106]. Newer longitudinal cohorts are trying to recruit more diverse populations representing minorities that were not included in traditional cohort studies [107]. Transdisciplinary approaches to understand the roots of health disparities are required to improve the outcomes of minorities and marginalized populations. From the genetic point of view, researchers are moving beyond self-reported race/ethnicity to the use of ancestry informative genetic markers. In highly admixed populations, such as Latin–Americans or African–American populations, ancestry informative genetic markers reveal a different layer of information about population migration and in some cases, clusters of disease susceptibility that may not be associated when using only self-reported race/ethnicity [9]. Ancestry information will provide broad geographically relevant population information (population migration and inbreeding); however, so far, the utility of genetic markers has been limited for interventions [108]. Epigenetics, on the other hand, provide a unique opportunity to fully integrate the genetic, social and environmental contributors to health disparities, while offering a potential for intervention.

Executive summary

Using epigenetics to understand the development of health disparities

- Health disparities reflect differences in morbidity and mortality among socially defined categories, including racial/ethnic groups.
- Experiences of racism and structural violence can adversely impact the biology and health of racialized minorities.
- Early life trauma and historical trauma are disproportionately experienced by socially disadvantaged groups and could contribute to health disparities via epigenetic changes.

Statistical methodology for studying the epigenetic basis of health disparities

- Studies investigating the DNA methylation basis of health disparities have generally employed methods at different resolutions. Population-based epigenome-wide association studies analyzing single-nucleotides became a popular approach.
- Other techniques employing differential variability or differentially methylated regions are being more widely used.
- Epigenetic studies are potentially impacted by a range of confounding factors, including but not limited to population genetic patterns, cell-type, environmental confounders related to ethnicity, and sample processing batch.

Insights & applications from cancer research

- Considerable strides have been made in cancer research to investigate the link between DNA methylation and cancer health disparities, primarily for the most common cancers (breast and prostate cancer) in US African–American populations.
- There is still limited information available for other race/ethnic groups in the US, with very heterogeneous populations.
- Determining causality in cross-sectional settings is challenging. Prospective follow-up studies among racially/ethnically heterogeneous populations and techniques as mendelian randomization will identify methylation changes involved in different pathways preceding disease onset.

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