Racial, Ethnic, Sex, and Age Disparities in CAR T-cell Clinical Trials

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Abstract

Health and healthcare disparities harm the sub-population groups who experience greater social and economic barriers to healthcare access. Historically based provider biases, patient culture and social beliefs, and healthcare system practices contribute to a continued disparity in care for many underrepresented groups based on race, ethnicity, gender, and age, with paralleled disparities in oncology treatments and clinical trial enrollment. Extrapolated data from clinical trials must contain a participant composition that reflects the disease population to generate reliable, safe, and efficacious results after treatment commercialization.

Objectives: This purpose of this study was to examine nationally registered immuno-oncology clinical trials, specifically CAR T-cell studies within the *ClinicalTrials.gov* database, for racial/ethnic, age, and gender disparities.

Methodology: The age, gender, racial, and ethnic breakdown of identified trials were compared to the US population-estimates derived from the Surveillance, Epidemiology, and End Results (SEER) Program. Analysis was performed for determining the mean age, gender composition, and race / ethnic proportions in trials compared to the US cancer population. Enrollment Incidence Ratios (EIR), Enrollment Incidence Disparities (EID), and $\chi 2$ tests were used to analyze the data.

Results and Conclusion: The results underline substantial gender, age, ethnicity, and race disparities in clinical trial participation across the five cancer types. The overrepresentation of male participants and members of the 18-65 age group, as well as the underrepresentation of Asian and Black communities, underscores the significance of diversifying representation to ensure a more comprehensive evaluation of CAR-T cell therapies for the spectrum of cancers.

Keywords: disparities, clinical trials, immunotherapy, CAR T-cell

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To my husband Greg—we can go back to co-parenting instead of me disappearing into my office. To Barry—thank you for checking on me every night before going to bed. To Gabe—thanks for hanging out in my office while I worked late, even though I suspect you were just stalling your bedtime. To Mack—thank you for herding me to bed when I started to fall asleep in front of my laptop. To Sarah and Neela—thanks for all the coffee. This project was completed through my entire family's patience and support.

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Table of Abbreviations

AA.....African American

ABM .....Andersen Behavioral Model

ACT.....Adoptive/Adaptive Cellular Therapy

ACTT .....Adoptive Cell Transfer Therapy

ADR .....Adverse Drug Reactions

AIAN.....American Indian and Alaska Native

ALL.....Acute Lymphoblastic Leukemia

AML.....Acute Myeloid Leukemia

ANBM.....Andersen and Newman Behavioural Model

ASCO.....American Society of Clinical Oncology

B-ALL.....B cell Acute Lymphoblastic Leukemia

CAR .....Chimeric Antigen Receptor

CAR T-cell.....Chimeric Antigen Receptor T cell (therapy)

CENTRAL .....Cochrane Central Register of Controlled Trials

CDC .....Centers for Disease Control and Prevention

CI.....Confidence Interval

CLL.....B-cell chronic lymphocytic leukemia

CRS.....Cytokine Research Syndrome

DET.....Data Extraction Table

DLBCL .....Diffuse Large B Cell Lymphoma

DLT.....Dose Limiting Toxicities

EID.....Enrollment Incidence Disparity

EIR .....Enrollment Incidence Ratio

EF .....Enrollment Fraction

FDA.....Food and Drug Administration

HHS.....U.S. Department of Health and Human Services

HLH .....Hemophagocytic Lymphohistiocytosis

ICI .....Immune Checkpoint Inhibitors

ICU.....Intensive Care Unit

FDASIA .....Food and Drug Administration Safety and Innovation Act

MAS .....Macrophage Activation Syndrome

MTD.....Maximum Tolerated Dose

MM .....Multiple Myeloma

NCI.....National Cancer Institute

NIH .....National Institute of Health

NH.....Non-Hispanic

NK.....Natural Killer cells

NWH .....Non-White Hispanic

OR .....Odds ratio

PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PRP .....Population Rate Prevalence

RP2D.....Recommended Phase II Dose

SDH.....Social Determinants of Health

SEER.....Surveillance, Epidemiology, and End Results Program

SES.....Socio-economic Status

SOC.....Standard of Care

TCR.....T Cell Receptor

U.S. .....United States

WHO.....World Health Organization

WOCBP .....Women of Childbearing Potential

Racial/Ethnic, Gender, and Age Disparities in CAR T-cell Clinical Trials

Chapter One: Introduction

The term "health disparities" is used in various ways by institutions, governing and reporting organizations, and groups such as the medical and surgical communities to describe the difference in disease burden experienced by sub-population groups (Centers for Disease Control and Prevention, 2013, 2017). Structural racism has resulted in continued racial inequalities between Caucasians, Hispanic groups, Asians, and African Americans in multiple social determinants of health (SDH), including income, wealth, and healthcare access, leading to racial disparities in health treatments and outcomes (Yearby, 2018). Patterns in healthcare access and use suggest that while significant progress has been made among some underrepresented groups, vulnerable racial/ethnic and gender groups remain highly disadvantaged as measured by metrics evaluating unmet needs (Manuel, 2018). Continued unmet need in the United States is evidenced, for example, through increases in emergency room visits for Black men and women compared to decreases in visits for their White counterparts, demonstrating differences in access to primary healthcare and health insurance, both indicators for long-term health, medical treatment, and health outcomes (Manuel, 2018; Sutton et al., 2020). Disparities are also seen in the field of oncology (Bulls et al., 2022) and in the clinical trials seeking to identify new treatments for oncology (Lee & Wen, 2020; Ludmir et al., 2019)

Demographic Disparities in Oncology

The documented differential in healthcare access and use has congruent differences in treatment and health outcomes for historically under-represented groups (Manuel, 2018; Yearby, 2018). Disparities in clinical treatment and outcomes associated with patient race/ethnicity, age, and gender have been well-established for several disciplines within the medical field. In the

United States, disparities in the incidence and outcomes related to age, race, and ethnicity have been established for several oncological areas, including urinary bladder (Wang et al., 2018), ovarian (Peres et al., 2018), breast (Zavala et al., 2021), prostate (Riaz et al., 2022), lung (Ludmir et al., 2019) and colon cancer (Zavala et al., 2021). In clinical care, including oncology, there are two concerns for gender bias: one for gender-equitable access to treatment and the other for gender equity in treatment outcomes regarding race/ethnicity (Horner-Johnson et al., 2021). There is a historical record of gender inequality in treatment access and treatment outcomes and an established disparity in care-based outcomes and mortality rates (Chinn et al., 2020) for women of under-represented groups (Sutton et al., 2020; Yearby, 2018).

Demographic Disparities in Clinical Trials

The disparities in treatment seen in most clinical disciplines are paralleled in clinical trial enrollment (Marshall et al., 2016; Riaz et al., 2022; Simon et al., 2014). Racial and ethnic disparities in treatment are often mirrored in the rates of patient enrollment in clinical research leading to a skewed representation in race, ethnicity, age, and gender (Steinberg et al., 2021) compared to the disease burden for these groups in the general population (Flores et al., 2021; Jan et al., 2022). Clinical trials are meant to have sample populations corresponding to the larger population's disease burden. A clinical trial’s objective is to extrapolate trial data, form conclusions that can be applied to the greater population, and ultimately produce accurate, generalizable results expected during post-authorization for marketed products (Masters et al., 2022). In 2018, the U.S. Food and Drug Administration (FDA) updated Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) to address data quality. The FDASIA update sought to improve the completeness of data for demographic subgroup analysis, increase subgroup participation, including the identification of enrollment barriers and

the employment of strategies to widen participation, reduce demographic disparities, and increase data transparency in order to make subgroup data available to the public (Food and Drug Administration, 2018a).

Demographic disparities in clinical trials may lead to incorrect conclusions regarding treatment reliability, efficacy, and safety. Underrepresentation of key subgroups, including race, ethnicity, gender, and age, can potentially affect health outcomes on a larger scale for marketed products (Syder & Elbuluk, 2023). While diverse representation is pivotal for accurate subgroup analyses, post-trial assessments still show disparities in a variety of medical specialties, including gastroenterology (Rabinowitz et al., 2022), ophthalmology (Berkowitz et al., 2021), rhinology (Spielman et al., 2021), dermatology (Syder & Elbuluk, 2023), cardiology (DiBartolomeo & Rowe, 2022), and vaccine trials (Flores et al., 2021). Clinical trials with diverse populations allow the discovery of the differential efficacy of drugs and treatments. The resulting therapeutic precision allows for the targeted delivery of approved medicines, thereby eliminating time and resources wasted on medical treatments with lower effectiveness for some populations. The diversity of clinical trials ensures reliable benefits to the larger population and is a barometer of societal equity and healthcare access (National Institute on Minority Health and Health Disparities, 2023).

Demographic Disparities in Oncology Clinical Trials

Oncology clinical trials are essential for approving novel therapeutic products and treatment modalities. Extensive studies regarding demographic disparities in oncological trials have found gaps in representation for multiple indications, including lymphoma (MacDougall et al., 2022), breast surgery (Fayanju et al., 2019), pancreatic (Fonseca et al., 2022; Zhao & Liu, 2020), prostate (Riaz et al., 2022), neurological (Fineberg et al., 2020), liver (Jan et al., 2022),

and bladder cancer (Wang et al., 2018). Lack of equitable representation has resulted in fewer cancer patients of color having the opportunity to access novel therapeutics and types of treatment only accessible to those participating in clinical trials. Under-representation in clinical trials not only decreases the quality of care available to minority patients but diminishes the global applicability of trial results used to measure the safety and efficacy of new therapies. Additional studies on demographic disparities regarding trial participants compared to the incident disease population have found age disparities prevalent and increasing across trials (Jan et al., 2022; Ludmir et al., 2019). Ludmir et al. (2019) found a significant variance between the median age of clinical trial participants and the median age of real-world patient rates for multiple indications. Given the rising geriatric population in cancer incidence rates throughout the United States (Sedrak et al., 2021), it is increasingly important that patients 65 years and older have proportionate representation in oncology clinical trials to establish the generalizability of trial outcomes.

Immunotherapy / CART-cell Therapy

Immunotherapy uses a patient's immune system to construct cancer-fighting cells that can be used to kill host-specific tumor cells (Abbott & Ustoyev, 2019). Forms of immunotherapy include immune checkpoint inhibitors, T-cell transfer therapy, and monoclonal antibodies. These types of immunotherapies are emergent treatments against advanced cancers and have been more effective in a broader population than traditional drug-based therapies (Abbott & Ustoyev, 2019). There is a potential for these treatments to be more impactful for sub-populations that already experience greater mortality rates and poorer outcomes. However, while studies suggest that innovative oncology treatments, such as chimeric antigen receptor (CAR) T-cell therapy, are showing improved survival rates, they also suggest that clinical trials for these treatments have

enrolled a lower proportion of Hispanic and Black patients, patients of a similar age range, and who were predominantly male (Grette et al., 2021; Nazha et al., 2019).

Problem Statement and Significance

While there were some preliminary studies (Al-Qurayshi et al., 2018; Nazha et al., 2019) conducted during the early development of immunology to discern if ongoing disparities seen in other clinical research are mirrored in the new field of cancer therapy, ongoing surveillance of potential bias and underrepresentation needs to be established for continued assessment as advances and new treatment modalities are created in this field. However, preliminary analysis of ongoing and completed immunotherapy trials for approved and non-approved checkpoint inhibitor products has shown racial disparities in trial recruitment and representation (Grette et al., 2021; Nazha et al., 2019). CAR T-cell therapy uses modified cancer antigens to target tumor cells and has been granted "breakthrough therapy" designation by the FDA. CAR T-cell products are, therefore, being fast-tracked through the FDA approval process, with six products already gaining approval for clinical use based on limited sample size clinical trials (Goldberg et al., 2018; Schneider et al., 2021). While many studies have analyzed the safety and efficacy of immunotherapy trials, an evaluation of their patient demographic representation compared to the larger oncology population needs to be assessed to ensure data reliability and validity.

Theoretical Framework

Health disparities directly impact those who experience systematic and substantial barriers in accessing healthcare services based on race/ethnicity, gender, and age. Additionally, studies have explored the intersection of disparities to ascertain how access differences within subgroups affect representation in others (Horner-Johnson et al., 2021). These disparities have been well-established in multiple disciplines of traditional clinical medicine, clinical trials, and

developing therapies. Andersen's Behavioral Model (ABM) has been applied as the primary theoretical framework in many healthcare access studies (Babitsch et al., 2012). Created in 1973, the original theoretical framework provided a lens to view health service utilization based on (1) the properties of available health delivery systems, (2) advances in medical practices and technology along with social patterns of acceptance of changes, (3) individual factors affecting utilization (Andersen & Newman, 1973). The Anderson and Newman Behavioral Model of Health Service Use (ANBM) is predicated on the ABM with an emphasis on healthcare usage. ANBM utilizes individual determinants, social determinants, and health services systems, incorporating contextual variables to establish predisposing, enabling, and need factors (Babitsch et al., 2012). ANBM posits that healthcare utilization depends on predisposing factors such as demographic and social beliefs, enabling factors such as healthcare access and income, and need factors such as the patient's illness severity and doctor's assessment of illness (Andersen & Newman, 1973).

The Purpose of this Study

This study aims to examine immunotherapy clinical trials, specifically CAR T-cell studies, for racial/ethnic, age, and gender disparities. As this type of therapy is being applied to multiple types of cancer and approved at an accelerated pace for universal application, it is important that the data used to prove its safety and efficacy represents the population that it will be used on for therapeutic purposes. This type of therapy is quickly being adapted to address other categories of disease, such as autoimmune and inflammatory diseases. Therefore, it is important to identify the root-cause factors that promote any discovered disparity in representation within oncologic-immunotherapy clinical trials. A secondary purpose is to

evaluate the impact that found disparities may have on the reliability and validity of trial outcomes as they pertain to the general population.

Research Questions and Hypotheses

Research Question 1: Is the racial/ethnic composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population being treated for that cancer?

Research Question 1_H: There is a significant disparity in the representation of racial/ethnic groups within the composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population being treated for that cancer.

Research Question 1_O: The representation of racial/ethnic groups within the composition of indication-specific CAR T-cell trials are proportional to the patient incident rate within the general population being treated for that cancer.

Research Question 2: Is the gender composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?

Research Question 2_H: There is a significant difference regarding gender enrollment in the composition of indication-specific CAR T-cell trials compared to the patient incident rate within the general population being treated for that cancer.

Research Question 2_O: The gender composition of indication-specific CAR T-cell trials are proportional to the patient incident rate within the general population being treated for that cancer.

Research Question 3: Is the patient age composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?

Research Question 3_H: The age composition of indication-specific CAR T-cell trials are not proportional to the patient incident rate within the general population for that cancer?

Research Question 3_O: Are the age composition of indication-specific CAR T-cell trials proportional to that seen in the patient incident rate within the general cancer population?

Chapter Two: Review of the Literature

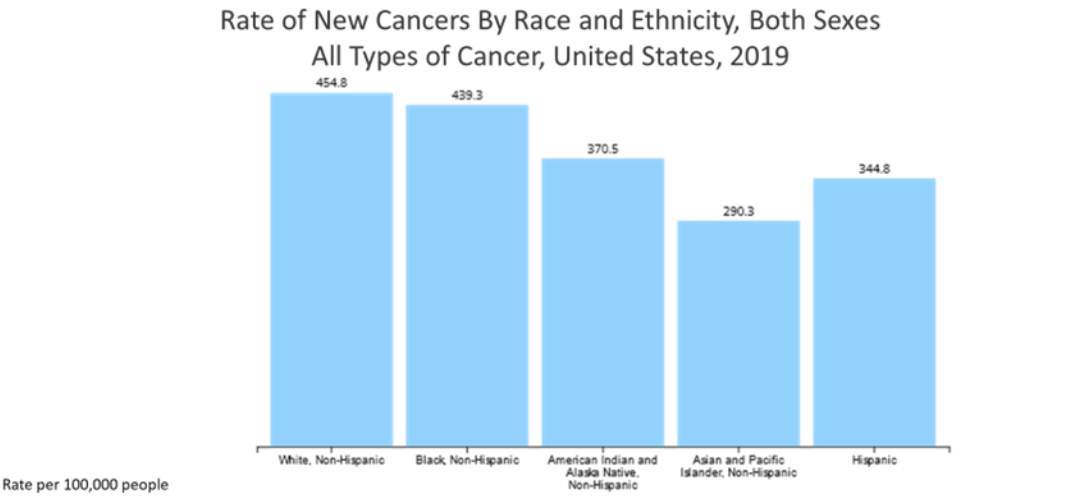
The treatment of cancer has evolved from chemotherapy, surgery, and radiation to targeted therapies that work by influencing the processes that control cell growth, division, and spread. Current studies focus on the development of immunotherapies that help a patient's immune systems destroy cancer cells and tumors. This review provides an overview of health and healthcare disparities characterized by gender, age, and experienced by racial and ethnic minority populations, in cancer care and clinical trial medicine. The review then looks at similar differential care occurring within immunotherapies, including emerging factors in CAR T-cell therapy. The review concludes with a look at gaps in the literature regarding disparities in CAR T-cell therapy clinical trials and the potential influence on cancer care.

Cancer Incidence and Treatment Disparities in Racial/Ethnic Minorities

Cancer is the second leading cause of death in the United States, with an estimated 1,752,735 new cancer cases reported in 2019 and 599,589 people dying of cancer that same year (Division of Cancer Prevention and Control, 2022). Projections based on incidence data from multiple registries and the National Center for Health Statistics estimate 609,820 people are expected to die from cancer in 2023, while approximately 1,958,310 new cancer cases are expected to be recorded during the same interval (Siegel et al., 2023). In contrast to the other leading causes of death, the overall cancer death rate in the United States has continued to decrease steadily, with a 1.5% decline from 2019 to 2020 (Siegel et al., 2023). However, despite declines in mortality for such cancers as lung cancer, liver cancer, and melanoma, there remains an increasing incidence for breast, uterine corpus cancers, and prostate cancer, three cancers with the largest racial disparity in mortality (U.S. Cancer Statistics Working Group, November 2022).

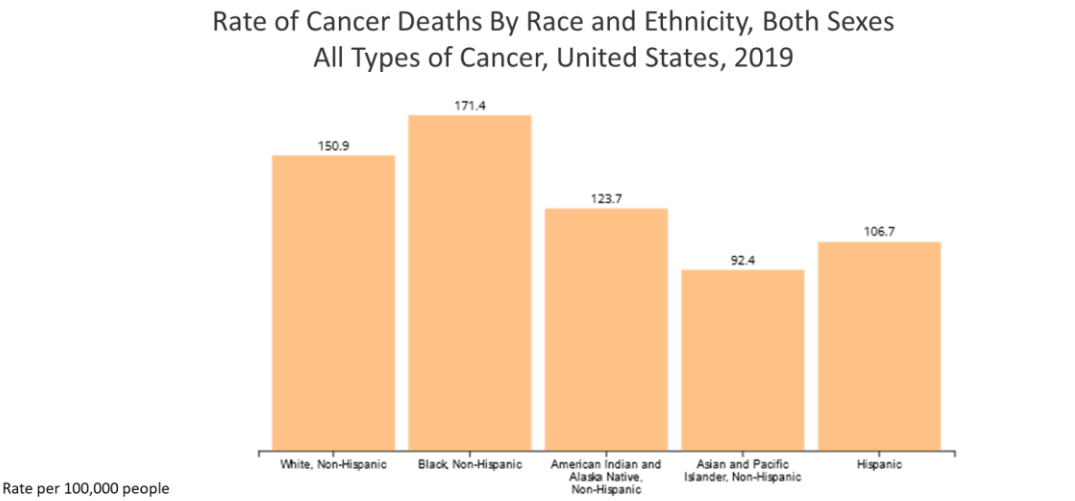
Cancer disparities occur when one subgroup in a given population bears a larger burden of disease and the associated effects more than others as measured through a difference in incidence, prevalence, morbidity, survivorship, or quality of life post-treatment (Bulls et al., 2022). African Americans comprise a disparate number of cancer patients while having the highest death rate and the lowest survival rates for cancer among all racial groups (DeSantis et al., 2019). When looking at the age-adjusted rate of cancer incidence per 100,000 people, Figure 1 indicates a statistically significant difference between N.H. Black and White people at the $p<0.05$ level.

Figure 1 Rate of New Cancers by Race and Ethnicity, All Types of Cancer, United States, 2019



Note: Persons of Hispanic origin may be of any race; other groups may include individuals reporting Hispanic ethnicity. Figure adapted from CDC's U.S. Cancer Statistics Data Visualization Tool 2019. (https://www.cdc.gov/cancer/uscs/dataviz/index.htm, released in November 2022). Rates are not presented for people whose race was not specified or who are members of other racial groups.

Figure 2 Rate of Cancer Deaths by Race and Ethnicity, All Types of Cancer, United States, 2019



Note: Figure adapted from CDC's U.S. Cancer Statistics Data Visualization Tool 2019. (https://www.cdc.gov/cancer/uscs/dataviz/index.htm, released in November 2022).

Non-Hispanic (N.H.) Blacks are the second largest racial/ethnic minority group in the United States, making up approximately 14.2% of the population (U.S. Census Bureau, n.d.). However, the proportion of Blacks living under the federal poverty level is almost twice that of non-Hispanic whites, with a similar disparity in the number of college-educated members of each group. The racial inequalities seen in cancer incidence and mortality rates are heavily influenced by socioeconomic status (SES) as it correlates to healthcare access and barriers (DeSantis et al., 2019; Zavala et al., 2021). Siegel et al. (2019) concluded that the documented strong correlation between low SES and reduced access to quality healthcare results in lower screening rates, delays in screening, diagnosis, and treatment results in cancer risks and outcomes inequalities. Notably, in its 2003 report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*, the Institute of Medicine stated that even when controlling for income and insurance status, racial and ethnic disparities persisted through a multitude of factors, including

language, geography, and cultural differences that influenced access to quality healthcare (Insitute of Medicine, 2003).

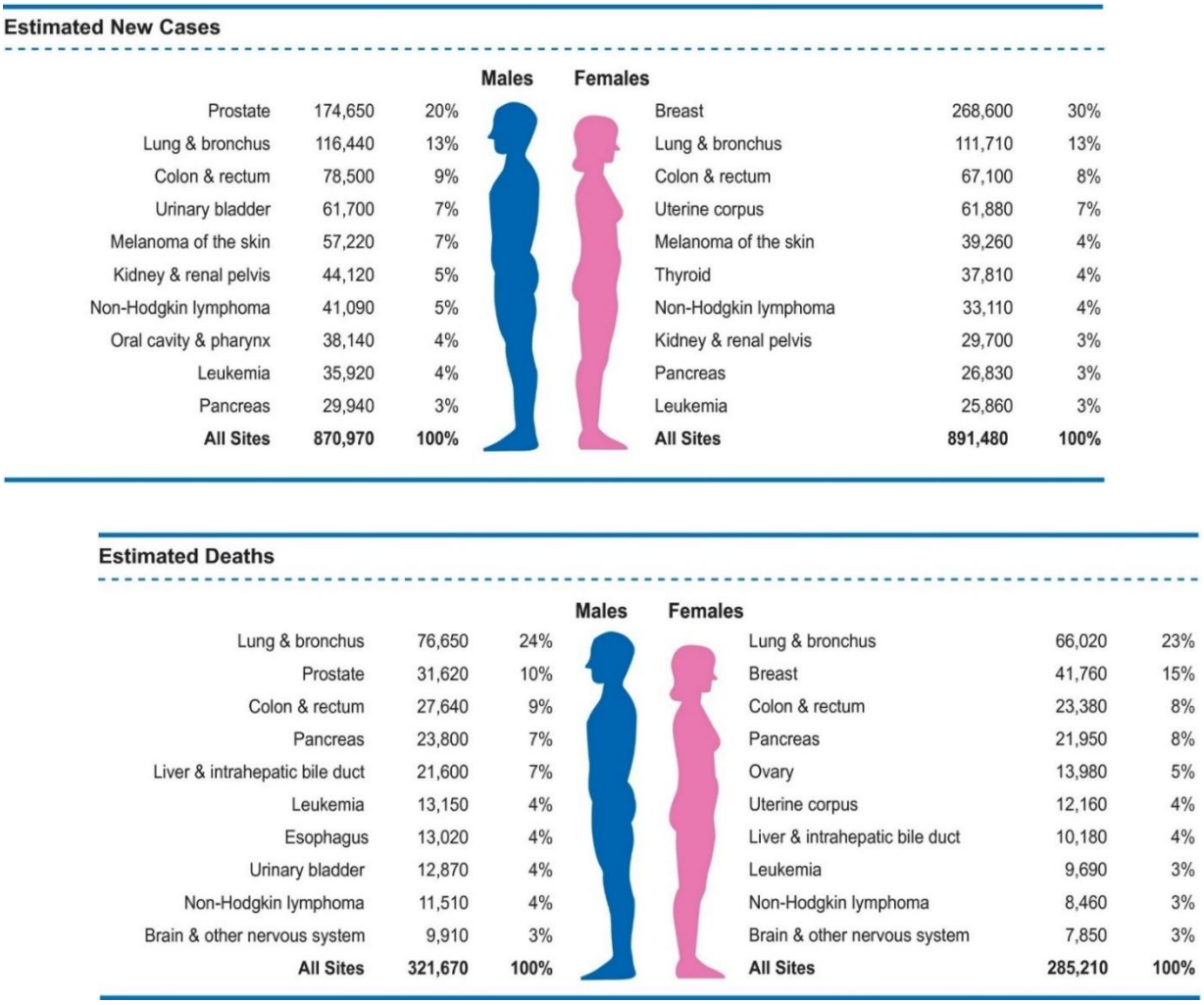
Decreased access to preventative medicine and treatment in conjunction with additional barriers related to socioeconomic disadvantages, such as medical insurance coverage, contribute to the overall unequal cancer burden among minority racial/ethnic groups. In an oncology study comparing the prohibitive effects of numerous possible factors regarding healthcare access for pancreatic cancer, Fonseca et al. (2022) found race to be a greater barrier to the expected standard of care than all other factors. In a systematic review of the delivery of cancer-directed therapy, several authors found that Black patients were less likely to receive surgical referrals and offered surgical resection or chemotherapy, the two curative options for localized pancreatic cancer (Fonseca et al., 2022). Beyond first- and second-line standard of care (SOC) treatments, cancer patients who have not experienced positive treatment outcomes, or have experienced cancer recurrence or relapse, are often referred to research institutions and high-volume centers to participate in clinical trials. Historically, participation in trials required referral from the primary physician. Recently, patients with higher health literacy and internet access have been able to find trials online and self-apply for screening to participate. However, a patient's trial participation still requires their primary physician to furnish medical records for trial enrollment and agree to serve in a primary capacity, thereby creating a gatekeeper role for the patient's doctor. Hispanic patients were less likely than white patients to be referred to high-volume centers and academic programs that offer novel therapy options (Sridhar et al., 2019). Fonseca et al. (2022) concluded that the referral disparity resulted from either from physician implicit bias or, even when referred, the patients' refusal due to negative physician-patient encounters

resulting from a combination of the physician lack of cultural competency and the patient poor health literacy.

Gender and Age-Disparities in Cancer Incidence and Treatment

Over the last two decades, a sex-specific difference in cancer incidence and mortality was recognized for various cancers (Figure 3). Cancer incidence patterns in males show rapid changes in prostate cancer incidence rates with an initial spike due to widespread prostate-specific antigen (PSA) testing of previously unscreened males, followed by a levelling-decrease with continued access and use to the PSA test (Siegel et al., 2019). For the past few decades, the overall cancer incidence rate in women has not changed significantly despite a slight yearly increase in breast, melanoma, thyroid, and pancreatic cancer incidence rates (Siegel et al., 2019). Excluding these two sex-specific cancers, lung cancer continues to have the highest incidence rate in both sexes and the overall highest mortality rate (Lee & Wen, 2020; Siegel et al., 2019). The overall incidence of lung cancer in the U.S. has continued to decline twice as fast in men than women projecting an increased incidence disparity between the sexes over the next decade (Barta et al., 2019; Hellyer & Patel, 2019).

Figure 3 Estimated New Cancer Cases and Deaths by Sex, United States, 2019



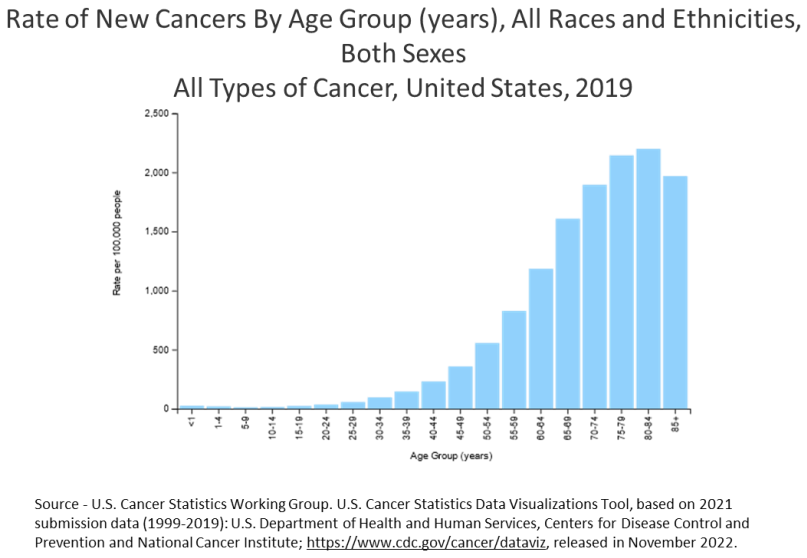
Note: Figure adapted from Siegel et. al., (2019) Cancer statistics, 2019. CA: A Cancer Journal for Clinicians, 69(1), 7-34. https://doi.org/https://doi.org/10.3322/caac.21551

Delays in cancer diagnosis, surgical treatment, and chemotherapy is seen in members of the female gender compared to their male counterparts (Manuel, 2018). There was one area where the gender disparity pendulum swung to the opposite position. Due to the increasing recognition of gender-biased data in oncology research, many clinical trials have enrolled equal male and female participants, thereby overrepresenting the female gender compared to the gender incidence in the real world (Steinberg et al., 2021). Siegel et al. (2023) documented a

gradual reduction in the sex gap between men and women's cancer incidence rate. Based on data gathered by the Surveillance, Epidemiology, and End Results (SEER) program, the male-to-female cancer incidence ratio decreased from 1.59 in 1992 to 1.14 in 2019, with a difference in gender-specific rates varying by age group (National Cancer Institute, 2022). For example, between the ages 20-49, women have an 80% higher incidence rate of cancer compared to men; however, at 75 years and older, males have a 50% higher incidence rate compared to their female counterparts (Rahib et al., 2021; Siegel et al., 2023).

Older adults, 65 years old and over, represent a growing population group with higher risk for cancer due to increased longevity (Ludmir et al., 2019). Age disparities in cancer rates (Figure 4) are not surprising given the many confounding factors including increased cumulative environmental and behavioral risk factors (Ludmir et al., 2019).

Figure 4 Rate of New Cancers by Age Group, All Types of Cancers, United States, 2019



Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2022.

Note: Figure adapted from CDC's U.S. Cancer Statistics Data Visualization Tool 2019. (https://www.cdc.gov/cancer/uscs/dataviz/index.htm, released in November 2022).

Age disparities are linked to factors such as frailty, comorbidities, polypharmacy, SES, and poor health literacy (Riaz et al., 2022; Sedrak et al., 2021). Although increased engagement with physicians for routine care is typical for this group, older-aged patients are less likely to receive cancer-directed therapies after an increased time before diagnosis (Fonseca et al., 2022). Studies on specific indications, such as pancreatic cancer, found referrals for surgical "curative" resection surgeries and chemotherapy has also been linked to older age (Zavala et al., 2021). Older age also impacted referrals to high-volume facilities and academic institutions, thereby decreasing participation in clinical trials and introduction to novel cancer therapies (Chang et al., 2009).

Disparities in Cancer Clinical Trial Participation

Cancer trials are essential for treatment development. While participation potentially benefits trial participants, the data gathered is crucial for developing future, universally available therapies. A clinical trial aims to explore a medication's efficacy while balancing patient safety (National Institute of Cancer, 2023). Safety is measured by balancing the potential benefits and harms. If a product is exceptionally efficacious in treating a disease, then a certain amount of toxicity can be endured. However, having a drug proven safe and effective for a group of patients is not particularly helpful to the larger population if those initial patients are demographically homogenous. For a drug or product to earn FDA approval, it must be proven that it will have the same benefits versus harm ratio in the general population as that seen in clinical research. In the United States, commercially marketed drugs are potentially available to members of the entire population; therefore, all drugs or products are expected to work equally well on all persons prescribed the medication. It is, therefore, a priority of the FDA, as a national regulatory body, to monitor the applicability of approved drugs by having trial participants represent the national

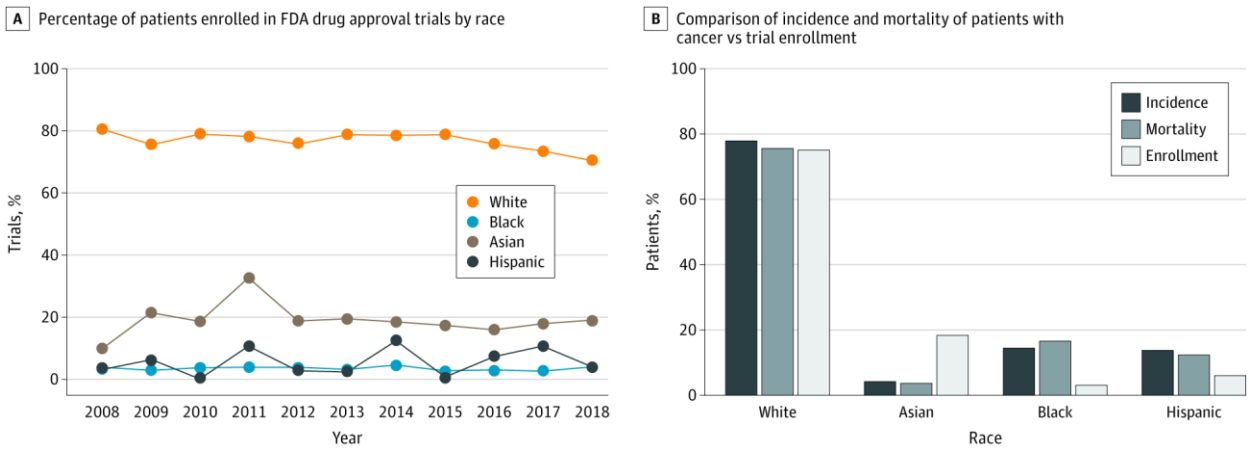
racial, gender, and age profile through regulations for trial diversity (Kozlov, 2023; Wechsler, 2022).

Racial/Ethnic Disparities in Patient Participants

Concerns regarding the underrepresentation of minority populations in research medicine for drug development led to the National Institutes of Health (NIH) Revitalization Act of 1993, which mandated the increased recruitment of women and racial and ethnic minorities into clinical trials. Prior to this Act, there was a countermovement to protect these groups from clinical research following unethical, and harmful behavior. Failing to gain appropriate informed consent and provide study risks, investigators conducted the highly discriminatory U.S. Public Health Service Syphilis Study at Tuskegee. Curative antibiotics were purposefully withheld from the African American men who participated in this study between 1932 and 1972 causing preventable illness, death, and a long-standing mistrust of the African American community towards clinical research (National Institute on Minority Health and Health Disparities, 2023). The Revitalization Act of 1993 allow the NIH to establish guidelines for the ethical inclusion of persons from racial and ethnic minorities in clinical research thereby promoting the inclusion of more diverse data in drug development (National Institute on Minority Health and Health Disparities, 2023). Over the past two decades, despite efforts to increase diversity, the composition of clinical trials has remained unchanged, with non-Hispanic white males making up most of the enrolled participants, even when racial/ethnic minorities are disproportionately affected by the disease being studied (Al Hadidi et al., 2020). Figure 5 represents the proportion of different races in trials submitted and receiving US Food and Drug Administration (FDA) approval from 2008 to 2018. Also depicted is the relative proportion of different races (pertaining to incidence and mortality) among patients with cancer in the United States

(estimated using the Surveillance, Epidemiology, and End Results database and compared with trial participants in FDA approval trials between July 2008 and June 2018). Notably, the representation of Black and Hispanic patients enrolled in pivotal FDA approval studies was low from 2008 to 2018 while Asian patients were over-represented compared to respective incidence and mortality rates (Loree et al., 2019).

Figure 5 Difference in Incidence, Mortality, and Enrollment in Clinical Trials Leading to FDA Oncology Drug Approvals vs US Population with Cancer



Note: Figure adapted from Loree et al., (2019) Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018. JAMA Oncology, 5(10), e191870. *https://doi.org/10.1001/jamaoncol.2019.1870*

Studies continue to cite several barriers to participation, particularly for Black populations, including access to healthcare, education, provider bias, historically based mistrust in clinical research, and patient studies using stratified demographic data. Using publicly available data, Al Hadidi et al. (2020) analyzed African American subject enrollment for trials leading to 75 cancer drug approvals during the four years between 2014 and 2018 to compare diverse enrolment and the study drug approvals. The proportion of African American subjects enrolled in identified trials, leading to the approvals being studied, was 7.44%. Using the

percentage of African American individuals among trial participants divided by the percentage of African American individuals among people with the disease (PRP), a 0.31 PRP ratio was determined for participation in clinical trials, leading to drug approval for all types of cancer collectively. Al Hadidi et al. (2020) further examined the data for key cancer subtypes that disproportionately impact African Americans, including breast, prostate, and lung cancer, calculating PRP of 0.29, 0.18, and 0.15, respectively.

Marginalized communities' distrust of the medical and scientific community has been well-studied and continues to be an ongoing source of racial disparity in clinical trials (Loree et al., 2019). This distrust is compounded by a lack of knowledge about clinical trials, unawares of federal regulations and institutional ethical protections in place for subgroup populations, language and cultural barriers related to a lack of provider cultural competence, and participant health literacy (Hughson et al., 2016; Otado et al., 2015). Wallington et al. (2016) proposed increasing minority and underserved populations' enrollment in cancer trials through community-embedded prevention programs and increased cultural knowledge about potential patients. These community programs would increase physician cultural competency, health literacy for patients, and overall participation in locally sponsored cancer trials.

A Latino-focused study emphasized physician awareness of trial benefits, attitudes toward participation, and behaviors toward enrollment as primary factors in clinical trial participation among Latino patients (Merz et al., 2022). Whether focused on clinical trials in general or perceived interest in participation, physician bias is still cited as an important factor in trial participation by underrepresented groups. Similar to studies citing a lack of communication on available trials from provider to patients for multiple conditions, Eggly et al. (2015) found racial bias, assumed mistrust in medical research, and perceived disinterest to influence oncology

trial participation, evidenced by less discussion and fewer mentions of these options. More recently, with the same issues of provider bias and stereotyping continuing to have an impact on trial enrolment, there is a renewed focus on designing inclusive interventional trials in built in strategies for patient diversity (Niranjan et al., 2020).

Gender-based Disparities in Clinical Trial Participation

Marginalization of women is a known source of health inequities, and research data lacking sex disaggregation may give rise to erroneous deductions regarding the generalizability of study conclusions. In an effort to make clinical research findings generalizable, the NIH Revitalization Act of 1993 also provides guidelines for the inclusion of women in an effort to have participant demographic data reflect the real-world population. Women have also been historically excluded from research as a group in need of special protections, particularly women of childbearing potential (WOCBP), that is: any woman or adolescent who has begun menstruation (Parekh et al., 2011). Specific incidences in drug history include the use of thalidomide as a morning sickness sedative resulting in birth defects and the use of diethylstilbestrol, also prescribed to pregnant women, for the prevention of miscarriages resulting in an increased risk of cervical and vaginal clear cell adenocarcinoma in their exposed daughters (Parekh et al., 2011). Female participants are currently underrepresented in trial medicine for several indications, with oncology clinical research having one of the lowest participation and, thereby the highest underrepresentation (Lee & Wen, 2020).

In contrast to interventional and curative studies, trials for preventative interventions have the highest female participation and equitable representation (Steinberg et al., 2021). Duma et al. (2017) established a 40% enrolment rate for women in clinical trials from 2003 to 2016, with African American, non-White Hispanic, and women less likely to be enrolled in oncology

clinical trials than other demographic groups. Jenei et al. (2021) analyzed female participation in oncology clinical trials from 2011 to 2020 compared to 2000 to 2010 finding a significant increase in female enrollment, 42%, compared to 40% (P<0.001). In an assessment of oncology trials that led to FDA approved treatments (Table 1), Dymanus et al. (2021) found women to have a 20% less enrollment rate overall and underrepresented in trials for cancer indications such as thyroid cancer and leukemia, while overrepresented in trials for liver and urinary bladder cancer. Perhaps more significant to future research, Jenei et al. (2021) observed that NIH-funded trials enrolled a greater proportion of women (48%) compared with industry-sponsored trials (41%) ($P < .001$). Levels of female participation was found to be concerning in multiple studies as female enrolment was lowest in Phase I and Phase II studies, during which data is used to determine dose tolerability (MTD), drug toxicity (DLT), and overall safety (Lee & Wen, 2020; Vidal et al., 2019).

Table 1 Relative Differences in Male and Female Enrollment in Clinical Trials and Incidence Rate by Specific Cancer Type

	Clinical Trials		Population-Based Incidence		
	Male (%)	Female (%)	Male (%)	Female (%)	EID
Colon and rectum	60.3	39.7	56.4	43.6	3.9
Digestive—stomach	72.1	27.9	64.4	35.6	7.7
Hodgkin lymphoma	57.0	43.0	55.4	44.6	1.6
Kidney cancer and renal pelvis	74.5	25.5	67.1	32.9	7.4
Leukemia	58.7	41.3	62.7	37.3	−4.0
Liver and intrahepatic bile duct	84.0	16.0	74.1	25.9	9.9
Lung and bronchus	59.1	40.9	55.8	44.2	3.2
Melanoma of the skin	56.4	43.6	62.1	37.9	−5.7
Myeloma	56.2	43.8	60.6	39.4	−4.3
Non-Hodgkin lymphoma	52.9	47.1	59.3	40.7	−6.4
Pancreas	56.8	43.2	56.0	44.0	0.8
Soft tissue including heart	33.2	66.8	59.3	40.7	−26.1
Thyroid	53.3	46.7	25.8	74.2	27.4
Urinary bladder	69.2	30.8	80.0	20.0	−10.8
Overall	60.3	39.7	55.4	44.6	4.9

Enrollment incidence disparity (EID) shows the gender disparity between clinical trials and US population by specific cancer type. Positive EID values indicate an overrepresentation of males (green color) in clinical trials when compared with incidence, whereas negative values indicate an underrepresentation of males (red color). Darker colors correlate to a stronger variation between the trials and the population.

Note: Adapted from Dymanus, K. A et. al., (2021) Assessment of gender representation in clinical trials leading to FDA approval for oncology therapeutics between 2014 and 2019: A systematic review-based cohort study. *Cancer, 127*(17), 3156-3162.

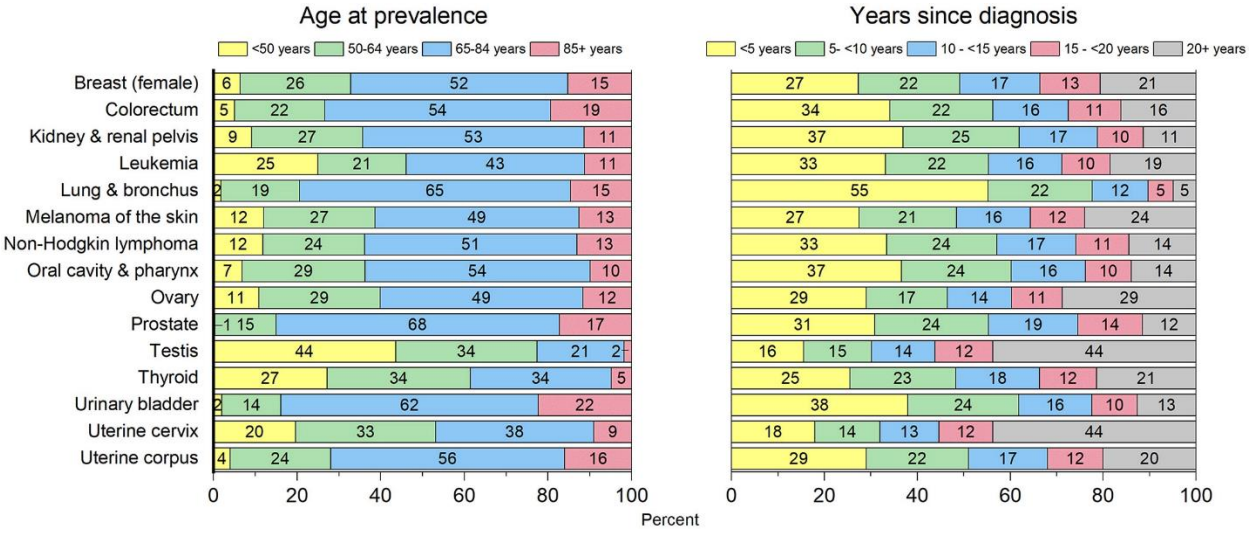
Age-based Disparities in Clinical Trial Participation

Pervasive age disparities in clinical trials have been increasing between the incidence of cancer and the participants of clinical trials. Despite constituting 42% of the overall cancer populace, registered U.S. trials show a 24% participation rate for patients 70 or older (Sedrak et al., 2021). Current projections estimates that by 2030, cancer diagnoses for patients 65 or older will make up 70% of all new oncologic cases, giving further importance for the inclusion of geriatric patients in oncologic clinical trials (Ludmir et al., 2019). When excluding age-defined trials, such as pediatric for general indications or pediatric-disease trials, elderly patients (65 years and older) were underrepresented in both all clinical trials (Duma et al., 2017) and oncology clinical trials (Jan et al., 2022). Using public data on *ClinicalTrials.gov*, Ludmir et al. (2019) found that U.S. based trials for the four most common cancer disease sites, breast, prostate, colorectal, and lung cancer, enrolled significantly younger participants (-6.49 years) compared to the population age of the disease indication. Industry-funded trials exhibited greater age disparities between enrolled participants and the disease population that appear to widen over time (Ludmir et al., 2019). Trial data regarding drug safety, including drug tolerance, drug interaction, and overall efficacy, can present risks unique to aging patients, who comprise a higher percentage of the disease population than those participating in therapeutic trials. While the average age of a colorectal patient in the United States is 72 years (U.S. Cancer Statistics Working Group, November 2022), only one-third of trial participants for this disease indication were over the age of 65 years (Ludmir et al., 2019).

Trial Protocol Inclusion and Exclusion Criteria.

Inclusion and exclusion criteria often narrow participation in clinical trials that do not represent the disease population. Criteria restricting comorbidities and ongoing medications are particularly restrictive for elderly patients who make up a significant portion of Americans with a history of cancer as in Figure 6 (Gresham et al., 2020; Jan et al., 2022; Miller et al., 2022).

Figure 6 Prevalence by Cancer Type, Years Since Diagnosis and Age at Prevalence as of Jan. 1, 2022, United States

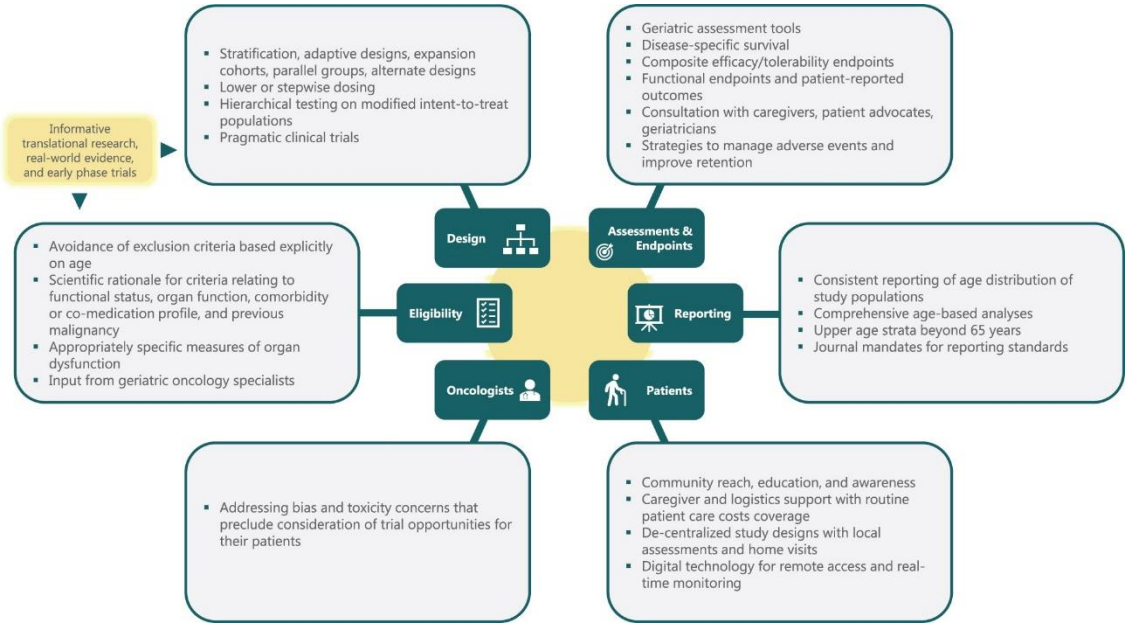


Note: Figure is adapted from Miller, K. D.et.al. (2022). Cancer treatment and survivorship statistics, 2022. *CA: A Cancer Journal for Clinicians, 72*(5), 409-436.

Patel et al. (2022) found a rise in the additional criterion for the exclusion for elderly patients through the exclusion of prior treatments for malignancies. Considering that most clinical trials target those that have received first and second-line treatment for their cancer for enrolment, it is almost antithetical for this to be an excluding factor for a subgroup of patients. Clinical trial participation is often predicated upon treatment failure and cancer recurrence with one of the most common trial protocol inclusion criteria being past therapies. However, post-

treatment patients, who have received first and second line SOC, have weakened immune systems, more concomitant medications due to side effects, more advanced-stage disease, and greater financial concerns making them less likely candidates for trial stability and completion (Jan et al., 2022; Ludmir et al., 2019). Trials designed to address specific concerns related to elder aged participants would allow for a greater understanding of treatment and dose tolerability, drug interaction, and quality of life issues pervasive in geriatric oncology (Habr et al., 2021; Sedrak et al., 2021). The use of strategies in trial design (Figure 7) to facilitate the inclusion of older adults would result in more generalizable data and treatment outcomes (Habr et al., 2021).

Figure 7 Strategies to Optimize Participation of Older Adults in Cancer Clinical Trials



Note: Adapted from Habr, D., McRoy, L., & Papadimitrakopoulou, V. A. (2021). Age Is Just a Number: Considerations for Older Adults in Cancer Clinical Trials. *JNCI: Journal of the National Cancer Institute, 113*(11), 1460-1464.

Role of FDA and Industry in Cancer Trial Disparities

The FDA is tasked with advancing the three ethical principles fundamental to biomedical research: respect for persons, beneficence, and justice (which attempts to balance who receives the benefits of research and bear its burdens) (Office for Human Research Protections, 2022). To aid in the advancement of the principle of justice, the FDA has a combination of statutes and policies that promotes the inclusion and range of demographic subgroups in clinical trials. However, through FDASIA, the FDA also has an expedited drug development tool it may bestow called "breakthrough therapy" designation. This status is designed to accelerate the development and review of US drugs that target serious or life-threatening conditions and show a substantial improvement of the already available therapies (Food and Drug Administration, 2018a). Once given this designation, a product still needs to demonstrate efficacy and safety, however it is also allowed more "efficient" trial design that requires fewer patients enrolled in clinical trials supporting marketing approval, thereby minimizing the potential for diversified patient populations (Fiorenza et al., 2020)

Additionally, over the past decade, the use of genetic variables in the development of treatments has allowed for a more targeted use of products (Food and Drug Administration, 2018b). A treatment that appears ineffectual in the larger population may be proven very effective in a smaller population with a specific genetic profile. Current trials use patient genetic profiles to tailor treatments that show higher efficacy in those with a specific gene, either present or deleted (Fountzilas et al., 2022). This move towards personalized medicine has shifted the emphasis away from trial enrollment diversity; however, when treatment is intended for wide population use, the inclusion of a diverse population remains necessary for real-world efficacy

and safety profiles, including the identification of differential improvement in racial/ethnic, gender, and age population-subgroups.

Research shows that cancer is a genomically centric disease, and alterations of the genomic and immune systems can yield increased response rates and therefore increased regulatory approvals (Fountzilas et al., 2022). However, cancer is part of a complex disease system, and targeting specific genomic sites or immune system cells cannot sufficiently respond and resolve adverse events and disease-mediated complications in a manner that determines patient health outcomes. Furthermore, gene-targeting treatments focused on specific genomic profiles inherently limit the scope of included patients. Treatments that involve the immune system pose a similar ethical question regarding the compressed inclusion criteria for clinical trials. Patients qualifying for immunotherapy trials must meet stringent inclusion and exclusion criteria, thereby introducing a bias in resulting predictive and treatment models.

Industry-sponsored clinical trials have the highest completion rate (69.2%), with increasing numbers of trials starting each year from 2000 to 2019 (Gresham et al., 2020). However, industry-sponsored trials have been found less likely to recruit non-Hispanic Black patients compared to NIH-sponsored, NCI-sponsored, or academic-funded trials. Similar recruitment patterns have been seen for Hispanic, Indian Americans/Alaskan Native, women, and elderly patient subgroup participation (Gresham et al., 2020).

Immunotherapy

"Immunotherapy" encapsulates treatments that utilize a person's immune system to fight a specific disease, such as cancer, or a medical condition, such as organ or tissue rejection post-transplant surgery. While traditional cancer therapies, mainly types of chemotherapy, utilize cytotoxic properties as the mechanism of action, immunotherapy uses the host immune system to

target tumor cells (Abbott & Ustoyev, 2019). Types of immunotherapies include adoptive cell transfer therapy (ACTT), immune checkpoint inhibitors (ICI), monoclonal antibodies, therapeutic (cancer) vaccines, and immune system modulators, each in various stages of development or commercial use (National Cancer Institute, n.a.). FDA approval and use of immune checkpoint inhibitors in the U.S. since 2011 has been credited for the sharp decline in cancer mortality (Siegel et al., 2019; Siegel et al., 2023) by changing standard-of-care options for over a dozen cancer indications (Xu et al., 2021). However, healthcare disparities can lessen the impact of novel therapies, especially for population subgroups that rely on provider referrals and insurance payments for the use of approved novel treatments.

Disparities in Immunotherapy

Yao et al. (2023) cite biological and psychosocial reasons for worsening racial disparities in ICI cancer treatments resulting in greater underrepresentation compared to standard treatments. Before FDA approval, access to immunotherapies was extended through clinical trials, compassionate use agreements, and the FDA's expanded access program (Ermer et al., 2022). Admission into clinical trials for checkpoint inhibitors, the first group of these novel treatments, was highly sought during the FDA approval period and retroactive studies on the demographic data for these trials and subsequent published literature for trends in population and access facilities characteristics (Ermer et al., 2022). Using data in the National Cancer Database, Ermer et al. (2022) completed the most comprehensive study of early immunotherapies for multiple disparity endpoints including differences in racial, ethnic, and gender access. Reported patient characteristics were evaluated in association with the receipt of immunotherapy during the 7 years (2012-2018) surrounding the approval of these cancer treatments. Among the patients included for evaluation, 55.9% were men and 44.1% were female with a race and ethnicity

composition of 11.8% Black, 3.9% Hispanic, 93.3% non-Hispanic, 83.4% White, and 4.1% identified as other races (Ermer et al., 2022). Study results showed Black participants were less likely to receive immunotherapy as their treatment arm compared to White participants and Hispanic participants were less likely to receive immunotherapy compared to non-Hispanic participants (Ermer et al., 2022).

Multiple factors impact enrollment and therapy assignment in unblinded trials. Hispanic and Non-Hispanic Black patients experience greater social and psychological stress due to negative SDH, increased adverse events due to a stronger immune response, and unequal response rates to treatment (Osarogiagbon et al., 2021) when compared to other racial/ethnic groups, which contribute to a unique immunity benefit-risk profile (Raez et al., 2020; Yao et al., 2023). As with many novel therapies, immunotherapy is expensive, and studies examining cancer registry data show a disproportionate benefit from ICI for non-Hispanic White patients compared to Non-Hispanic Black patients, thereby expanding the pre-existing survival gap (Osarogiagbon et al., 2021; Siegel et al., 2019). The causes for racial/ethnic disparities in immunotherapy clinical trial participation were the same as those seen for traditional cancer treatments and trials. Patient-level barriers included lower health literacy; provider-level barriers included the need for more education to decrease misconceptions associated with implicit bias; healthcare-level barriers included geographic local of clinical care (Ahn et al., 2022) and financial barriers (Sahara et al., 2020); and societal barriers included changes eligibility, inclusion, and exclusion criteria (Al-Qurayshi et al., 2018). There is an intersectionality between racial and gender disparities in clinical trial participation. Racial disparities are present in trials for gynecologic and breast cancers, including low recruitment of Black women (Grette et al., 2021). While it is well established that gender influences the immune system and its response to

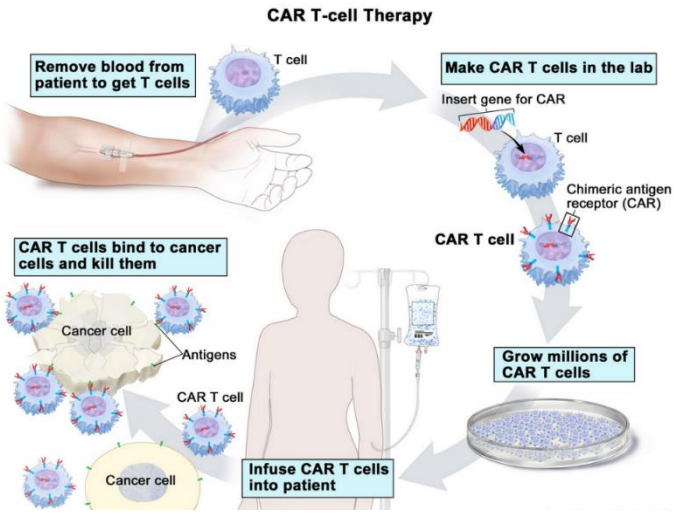
endogenous factors, there is a limited number of publications regarding the immune response and gender of patients (Irelli et al., 2020).

There is a need to interpret and understand the variations in treatment response, toxicity events, and therapy outcomes between the two traditionally established gender types. While older types of immunotherapies, such as the use of biologics, have shown greater efficacy and better outcomes for female patients, current immunotherapy that works by stimulating a patient's immune system has shown greater efficacy for males (Klein & Morgan, 2020) creating a possible loophole for the exclusion of female participants in future studies.

CAR T-cell Immunotherapy

One type of immunotherapy, chimeric antigen receptor T cells (CAR-T) therapy, is exceptionally effective against some types of blood cancers, including some types of multiple myeloma (MM), leukemia, and lymphomas (Abbott & Ustoyev, 2019). CAR T-cell therapy (Figure 8) requires collecting a patient's T-cells, genetically modifying them to have receptors that bind to cancer cells, and reintroducing the engineered T-cells to the patient allowing them to target cancer cells (National Cancer Institute, n.a.).

Figure 8 Illustration of CAR T-cell Therapy Process

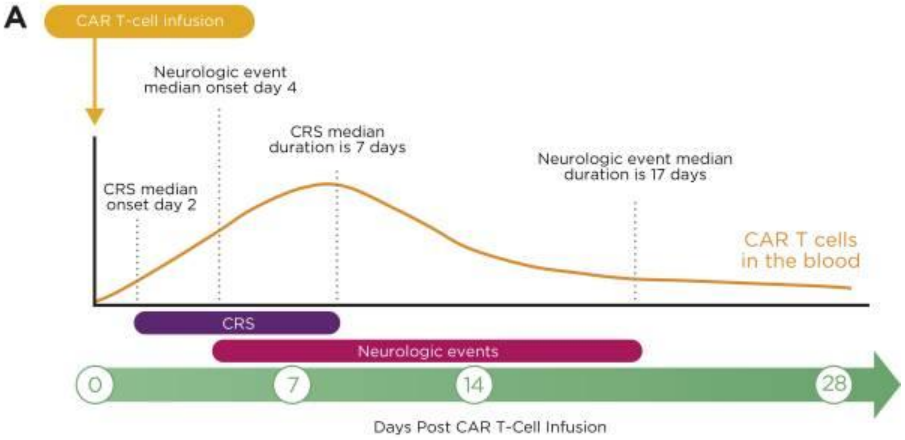


Note: Reprinted from NCI, 2023.

Clinical outcome data, first recorded in 2012, showed significant efficacy with a 90% response rate in both adult and pediatric B-cell acute lymphoblastic leukemia (ALL) patients and patients with aggressive non-Hodgkin's lymphoma (Abbott & Ustoyev, 2019). CAR T-cell patients often undergo “conditioning” chemotherapy, also called lymphodepletion, before being infused with their engineered T-cells making them more susceptible to infection pre- and post-infusion. The infusion of engineered T-cells is performed in the hospital setting, mostly in the intensive care unit (ICU), as patients often require high levels of care after their infusion. Maude et al. (2018) estimated that 77% of patients in CAR T-cell phase I and phase II trials experienced the most common serious adverse event (AE), cytokine release syndrome (CRS), while 47% of patients required ICU management of this systemic inflammatory response to increased cytokine levels prompted by the engineered T-cells. Equally severe and potentially fatal is the development of neurological symptoms associated with any immune effector cell therapy (ICANS), which requires prophylactic anti-seizure protocols, including a 4-week (in- or outpatient) observational period (Adkins, 2019).

Patients experiencing mild to severe CRS, or a closely related AE called macrophage activation syndrome (MAS), require additional care post-treatment after hospitalization, making a constantly available support system necessary for patients undergoing these therapies (Figure 9). Since the first approval, on 31 August 2017 for Kymriah, the FDA has approved 6 CAR T-cell therapies: Yescarta, Tecartus, Breyanzi, Abecma, and Carvykti (U.S. Food and Drug Administration, n.d.). In addition to the efforts to apply CAR T-cell treatment for solid tumor cancer indications, there are ongoing efforts to engineer T cells to attack other disease-related cells to treat autoimmune diseases and inflammatory diseases (Barros et al., 2022).

Figure 9 CRS and neurologic events symptoms. (A) Onset and resolution. (B) Common and serious symptoms.



B

CRS symptoms	
Common	*Serious*
• Fever • Hypotension • Tachycardia • Hypoxia • Chills	• Atrial fibrillation • Ventricular tachycardia • Cardiac arrest • Cardiac failure • Renal insufficiency • Capillary leak syndrome • Hypotension • Hypoxia • HLH/MAS

Neurologic event symptoms	
Common	*Serious*
• Encephalopathy • Tremor • Dizziness • Delirium • Confusion • Agitation	• Seizures • Leukoencephalopathy • Cerebral edema • Aphasia • Obtundation

Note: (A) Onset and resolution. (B) Common and serious symptoms. Adapted from Adkins, S. (2019). CAR T-Cell Therapy: Adverse Events and Management. Journal of the advanced practitioner in oncology, 10(Suppl 3), 21-28.

CAR T-cell Clinical Trials

Clinical trials for CAR T-cell therapies are very different from those involving "traditional" cancer drug therapies. Oncology drug trials usually involve four primary phases of research with decreasing numbers of treatments entering the subsequent phase for approval. Phase I trials, with 20-100 healthy volunteers or persons with the study disease, establish treatment safety and dosage (DLT, MDT, and adverse reactions (ADR)); Phase II trials may have up to a couple of hundreds patients with the disease or condition for the collection of safety and

efficacy data (AEs and clinical outcome data points) and last up to 2 years; Phase III trials can have 300 to 3000 participants over a larger geographic area and last up to 4 years; and Phase IV trials may have thousands of participants to monitor drug safety and efficacy (Gresham et al., 2020). Phase IV trials are often post-marketing trials, after regulatory approval, and part of the ongoing safety management of approved and commercialized products (National Institute of Cancer, 2023).

CAR T-cell clinical trials rarely involve repeated infusion of the engineered (expressing specific antigen receptors) cells as each manufacturing cycle (transforming and growing cells) costs approximately $500,000 per infusion (Gagelmann et al., 2022). CAR T-cell trials are primarily Phase I, non-blinded trials with no placebo and no healthy volunteers. These Phase I trials can consist of as little as10 patients to elucidate the appropriate Phase II recommended dose (RP2D) (Liu et al., 2020). Due to the breakthrough designation for this therapeutic product, Phase II studies can be the end phase for CAR T-cell therapies before approval providing they meet the requirement of greater efficacy and tolerable side effects (U.S. Food and Drug Administration, n.d.). The FDA has allowed these approvals with the provision that manufacturers conduct a five year post-marketing observational study involving the patient's treated (U.S. Food and Drug Administration, 2021). Khozin et al. (2017) observed that the 21st Century Cures Act gives the FDA the authority to accept real-world data for product approvals and utilizing aggregated data for already completed and ongoing CAR T-cell studies can further truncate the approval process for this line of therapy when applied to additional indications.

Current Status on Disparities Associated with CAR T-cell Therapy

In a study of US-based clinical trials using CAR T-cells to treat MM, Al-Qurayshi et al. (2018) found that 34% of the states analyzed had no clinical trial openings. Furthermore, in

states where trials were conducted, there was a lesser number of open sites for those states with the highest percentages of Black population, indicating inequitable geographic access for Black patients (Al-Qurayshi et al., 2018). Retroactive analysis of trials leading to the first two approved CAR T therapies (Table 2), both focused on MM, show participants enrolled in the CAR T group were 5.9% African American and 5.4% Hispanic compared to 10.4% and 7.4%, respectively, for those in non-CAR T group. Conversely, representation for other racial/ethnic groups in the CAR T group included 4.5% Asian, 6.1% White Hispanic, and 68.7% White compared to trial participants in the non-CAR T group who were 3.2% Asian, 4.7% White Hispanic, and 60.1% White (Ahmed et al., 2022; Emole et al., 2022). The same study found a similar disparity in income distribution, with 7.3% of participants from the CAR T arm from low-income neighborhoods compared to 11% in the non-CAR T group. Other disparities were found in the CAR T group insurance coverage; 48% of participants had private insurance, 37.4% had Medicare, 7.4% had Medicaid, and less than 1% for other payer groups (Ahmed et al., 2022).

Subsequent analysis of data leading to FDA-approved CAR T-cell therapies show similar disparities in pivotal trials for hematological malignant neoplasms, an indication that disproportionately affects Black participants (Al Hadidi et al., 2020; Al Hadidi et al., 2022). Since these studies, CAR T-cell therapies have gone through second, third, fourth, and fifth-generation iterations. Second-generation CARs have improved T-cell persistence and more robust anti-tumor efficacy. Third-generation CARs have increased potency. Fourth-generation CARs contain more transgenic and genetic modifications resulting in increased resistance to the tumor microenvironment, enhanced function and growth, and the ability to activate the native immune system's navigation to tumor sites (Branella & Spencer, 2021; Lindo et al., 2020; Vitale & Strati, 2020). Fifth generation CARs are currently being studied for solid tumor indications.

Table 2 Characteristics of CAR T-cell Therapy Patients with Lymphoma, MM, and ALL between 2018 and 2020

Characteristics		CAR T Group (N = 4396), n (%)	Non-CAR T Group (N = 2,600,505), n (%)	CAR T Cell Therapy per 100,000 Cases (Overall CAR T/100,000 Cases = 169)	CAR T over Non-CAR T Share (CAR T Percentage over Non-CAR T Cases)
Disease	DLBCL	2941 (66.9)	450,935 (17.3)	648	3.86
	MM	575 (13.1)	1,043,060 (40.1)	55	.33
	FL	149 (3.4)	175,011 (6.7)	85	.5
	MCL	153 (3.5)	104,579 (4)	146	.87
	ALL	350 (8)	355,212 (13.7)	98	.58
	Other B cell NHL*	228 (5.2)	468,708 (18.2)	48	.28
Sex	Male	2755 (62.7)	1,493,048(57.4)	184	1.09
	Female	1641 (37.3)	1,106,840 (42.6)	148	.88
	Unknown	—	617 (0.0)	-	
Age	<65 yr	2637 (60)	1,356,852 (52.2)	194	1.15
	≥65 yr	1759 (40)	1,243,653 (47.8)	141	.84
Income	<$40,000	321 (7.3)	284,913 (11)	113	.67
	≥$40,000	4075 (92.7)	2,315,592 (89)	176	1.04
Payer	Commercial	2134 (48.5)	1,105,224 (42.5)	193	1.14
	Medicaid	327 (7.4)	203,657 (7.8)	160	.95
	Medicare	1642 (37.4)	1,198,845 (46.1)	137	.81
	Other payer†	270 (6.1)	76,742 (3)	351	2.08
	Uninsured	23 (0.5)	16,037 (0.6)	143	.85
Race/ethnicity	White	3019 (68.7)	1,562,932 (60.1)	193	1.14
	White Hispanic	267 (6.1)	121,118 (4.7)	220	1.3
	NWH	218 (5)	115,416 (4.4)	189	1.12
	AA	259 (5.9)	270,350 (10.4)	96	.57
	Asian	197 (4.5)	84,450 (3.2)	233	1.38
	Other/unknown	436 (9.9)	446,239 (17.2)	98	.58
Driving time to treating facility	<30 min	1562 (35.5)	1,310,618 (50.4)	119	.71
	30-120 min	1559 (35.5)	880,816 (33.9)	177	1.05
	>120 min	1275 (29)	409,071 (15.7)	311	1.84

Note: Table extracted from Ahmed, N. et. al., (2022). Socioeconomic and Racial Disparity in Chimeric Antigen Receptor T Cell Therapy Access. Transplantation and Cellular Therapy, 28(7), 358-364.

Causes for CAR T-cell Access Disparities

There exist several significant barriers to accessing CAR T-cell therapies include cost, serious adverse effects, and cost-effectiveness analysis. The cost range for FDA-approved CAR T-cell therapies is between $373,000 to $475,000 per infusion, excluding additional costs such as post-infusion monitoring ranging from $79,466 to $85,267 per infusion (Choi et al., 2022; Kansagra et al., 2020). Treatment requires health coverage and the ability to pay uncovered

costs. This is in the face of lengthy employment leave for infusions and post-treatment effects, including numerous and potentially fatal serious adverse effects. The lack of cost-effectiveness data decreases the access to these therapies for patients that may have comparative effectiveness with the standard of care treatments (Fiorenza et al., 2020; Kansagra et al., 2020). The lack of data regarding patients' response to CAR T-cell regimens becomes a more significant issue when patients are part of an underrepresented group. Currently approved therapies were given Orphan Drug and Breakthrough Therapy designations by the FDA, thereby allowing fast-track status through their Phase I, Phase II, and Phase III clinical trials, and most of the already approved treatments were approved based on Phase I and Phase II data only (Choi et al., 2022; U.S. Food and Drug Administration, 2021). While these designations allow for expedited drug development for a serious disease where preliminary clinical data shows improvement in efficacy over available therapies, the resulting data does not meet patient diversity recommendations, nor is it subject to the breath of demographic subgroup analysis that would provide a sufficient comparative analysis to assure safe universal application.

Theoretical Models for Disparities in Healthcare

The most common theoretical model for disparities in cancer incidence, trial participation, and overall clinical care outcome is the Fundamental Cause Theory. This theory describes the relationship between SES and the health of communities or population subgroups. Fundamental Cause Theory posits that SES is the underlying reason for health inequities as it dictates access to fundamental resources needed for better healthcare, including education, employment, income, health insurance, etc. (Link & Phelan, 1995). Phelan et al. (2010) reported additional key findings supporting the theory while advocating for health policies that address medical advances and the equitable distribution of interventional treatments. However, while this

theory does explain some of the disparity seen in a clinical trial and immunotherapy access, it does not address the individual factors, including patient and provider bias, that influence accessing and utilization of healthcare resources.

The Anderson and Newman Behavioral Model of Health Service Use (ANBM) incorporates individual determinants, social determinants, and health services systems, incorporating contextual variables to establish predisposing, enabling, and need factors (Babitsch et al., 2012). ANBM posits that healthcare utilization depends on predisposing factors such as demographic and social beliefs, enabling factors such as healthcare access and income, and need factors such as the patient's illness severity and doctor's assessment of illness (Andersen & Newman, 1973). Based on the Andersen's Behavioral Model (ABM), the ANBM is a theoretical framework explaining healthcare access that takes into account (1) the properties of available health delivery systems, (2) advances in medical practices and technology along with social patterns of acceptance of changes, and (3) individual factors affecting utilization (Andersen & Newman, 1973).

Gaps in the Literature

While previous studies have looked at disparities in clinical data for CAR T-cell therapy trials, these were done for early, small, truncated trials that established Phase I and Phase II data for the now-approved treatments commercially available through FDA approval. Since then, CAR T-cell approved therapies have entered Phase IV observational surveillance status, consisting of larger patient populations, and being applied to more varied cancer indications being studied for commercialization. New clinical trials have been proposed, started, completed, or are in post-trial analysis for non-blood cancers. While the studied products in these trials have yet to be approved for commercial use, efforts towards these new therapies continue to be

focused on product and study design, treatment optimization, and AE mitigation and minimization. Studies focused on participant demographic diversity within the trial are still lacking despite the continued push for product expedited approval.

Summary

Demographic disparities in access are well documented for FDA approved and pre-approved cancer treatments in the United States. Commercially available immunotherapies and those still in clinical trials mirror these disparities in patient characteristics including race, ethnicity, age, and gender. Ongoing clinical trials for novel immunotherapy modalities, such as CAR T-cell therapy, may lack the generalizability needed for universal application despite ongoing FDA efforts to diversity among clinical trial participants. Current data suggests that early demographic disparities in immunotherapy may persist in current trials for solid tumor indications considering the treatment's positive benefit-to-risk ratio.

Chapter Three: Methodology

The focus of this study was the racial/ethnic, sex, and age composition of the trials as it relates to the disease population for the participants' oncology indication. The representation found in this study was used to infer the applicability of the clinical trial results and assumptions to the general population of the United States. This study's research questions guided the final determination of whether demographic representation in current CAR T-cell trials addresses their true purpose of investigating the safety and efficacy of the products for universal, commercial use after FDA approval. Primary questions being asked include:

1. Is the racial/ethnic composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population being treated for that cancer?
2. Is the gender composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?
3. Is the patient age composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?

Search Strategies

The primary point for inclusion in this analysis was registration on *ClinicalTrials.gov*; therefore, the analysis trials did not include trials not registered on this website. There is variability regarding the demographic patient data captured for each trial registered on *ClinicalTrial.gov*; therefore, additional data for selected trials was searched through research publications on those trials. Therefore, trials on the national registration website (*ClinicalTrials.gov*.) and publications pertaining to trials in the registries were used to gather patient data for analysis on representation.

The initial search on *ClinicalTrials.gov* used search terms “CAR,” “CAR T-cell,” “CAR-T,” and “chimeric antigen receptor,” along with selecting the United States of America for the “Country” and specifying studies “With Results”. The output was evaluated using the Data Extraction Table (Table 6). Two reviewers evaluated each resulting trial’s suitability and any corresponding articles from the publication search. Corresponding articles were gathered from four primary databases: CENTRAL, PubMed, Google Scholar, and *ClinicalTrials.gov*. The search for matching studies in PubMed, CENTRAL, Google Scholar, and Radford University’s McConnell Library search system utilized the terms listed in Table 1.

Table 3 Search strategy for PubMed, CENTRAL, Google Scholar, and Radford University’s McConnell Library

Databases:	PubMed, Google Scholar, Radford’s McConnell Library, CENTRAL
Keywords/ MeSH terms	“CAR T-cell therapy” OR “CAR” OR “chimeric antigen receptor” Oncology AND clinical trial AND cancer indication Study title OR sponsor name OR trial site

Trials in the *ClinicalTrials.gov* database were further selected based on their recruitment status. Trials with a "not yet recruiting” status were not included as they have been approved to but have not started enrolling patients for treatment. While studies that are “recruiting” and “enrolling by invitation” have started enrolling patients, the final demographic composition of patients at the end of enrollment is unknown and, therefore, represents an incomplete data set. Clinical trial studies were only included if they have enrolled patients’ demographic data available in a results analysis. The study data used included patients enrolled and assigned to a treatment arm. Trials that have a status of “suspended,” “withdrawn,” or “terminated” were included if study results were posted, including patient population characteristics. Reasons for

prematurely stopping a trial included loss of funding, unfavorable interim analysis regarding benefit-risk balance, failure to show efficacy beyond already available treatments, and low enrollment. Only trials of these statuses with completed study or interim study results and demographic data were included for analysis.

Trials listed as "active, not recruiting," and "completed" were also included in this study. Trials that are “active, not recruiting” are still ongoing but may have finished the enrollment and treatment processes with interim analysis data. These studies can be expanded in cohorts or become expansion studies until FDA approval is granted. Therefore, they contain enrolled patient demographic data. The search strategy to locate corresponding articles for the trials identified in *ClinicalTrials.gov* using the identified terms in Table 2 yielded demographic data already provided in the national registry. These data points were used to categorize the subgroups further and help identify trends in representation by disease indication.

Table 4 Search Strategy for *ClinicalTrials.gov*

Query		Select
Conditions or disease		Leave blank
Other terms		CAR, chimeric antigen receptor, CAR-T
Study type		All Studies
Study Results		All Studies
Status		Recruiting
		Enrolling by invitation
		Active, not recruiting
		Completed
		Suspended
		Terminated
		Withdrawn
		Unknown Status
Expanded Access		Leave blank
Eligibility criteria		
	Age	Leave blank
	Age group	Child
		Adult
		Older Adult
	Sex	All
Targeted Search		Leave blank
Locations		United States
Phase		Leave blank
Funder type		Leave blank
Study documents		Leave blank

All US-based oncology trials with results were assessed for 1) racial/ethical demographic analysis, 2) gender analysis, and 3) age analysis. Some studies reported only partial demographic data but were still used for the reported categories. For example, there was one “Child” only trial whose patients were not used for age analysis but included for racial/ethnic and gender analysis. Similarly, some studies reported gender, race, and age composition but lacked ethnic data. The reported data points were analyzed for age, racial, and gender composition compared to the disease population. Trials using cell types other than T lymphocytes, such as Natural Killer (NK) cells, were eliminated from inclusion. Table 2 contains the inclusion and exclusion criteria

applied to the studies in all databases. Using the term “CAR,” “CAR-T,” or “chimeric antigen receptor,” also resulted in trials with a patient pool of subjects that experienced disease recurrence or relapse after CAR T-cell therapy. Trials involving treatments for disease relapse post-CAR T-cell therapy were manually eliminated by the reviewers. Age was considered reported whether it is available as a binned or continuous variable. Race was considered reported if the United States Census main categories were reported, with other subgroups combined under “Other.” Ethnicity was considered reported if at least one category (of the two) was provided. The reviewers utilized Table 3 to determine the primary eligibility of search entries, and a third reviewer resolved all disputed entries.

Table 5 Inclusion and Exclusion Criteria for Studies / Articles

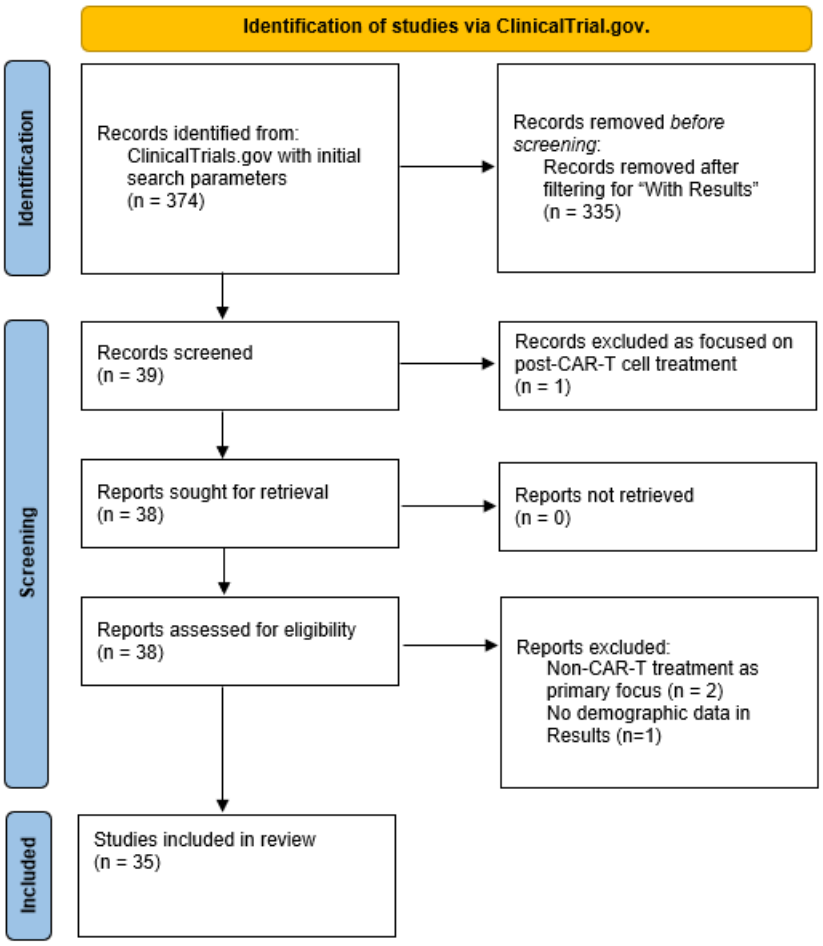
Inclusion	**Exclusion**
Studies published between Jan 2009 and December 2019	Studies published before the year 2009, after the year 2019 and duplicate articles
Study based in the United States	Studies with majority of sites outside of U.S.
Immunotherapy trials using T lymphocytes for product	Immunotherapy based on non-T lymphocytes, such as NK cell types
Studies where CAR T-cell is the interventional treatment	Studies for patients with failed CAR-T therapy and now receiving other drugs
Trials with full data on any specific demographic	Studies with an incomplete demographics for an individual data set (race/ethnicity, age, gender)
Active, not recruiting, completed, terminated, or suspended studies with final or interim data presented	Studies that are not yet recruiting, recruiting, or withdrawn

Studies with Results shown in *ClinicalTrials.gov* database	Studies without Results in *ClinicalTrials.gov* database

The general population information for the United States' cancer estimates was determined using the National Cancer Institute's Surveillance, Epidemiology, and End Results and the U.S. Census databases. After eliminating the above-excluded trials, the remaining trials were examined for demographic data via information reported on *ClinicalTrials.gov* and data published in PubMed, CENTRAL, Radford's McConnell Library advanced search or Google Scholar.

Relevant publications were individually evaluated to ensure they correspond to the trials resulting from the primary search. The study selection process followed the 2020 updated guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Matthew et al., 2021). Two data sets were combined for the final synthesis, primarily from *ClinicalTrials.gov* and secondarily from PubMed, CENTRAL, McConnell Library, and Google Scholar (Figure 10). Studies in *ClinicalTrials.gov* were identified by filtering the database using Table 4. Publications supporting the data for selected trials were attained through PubMed, CENTRAL, McConnell Library, and Google Scholar using Table 5. All publications identified as relevant through the inclusion and exclusion criteria listed in Table 5 were entered in the DET (Table 6). All studies and related publications identified and meeting all inclusion criteria were included in the final data synthesis.

Figure 10 PRISMA



Note: PRISMA flow diagram for new systematic reviews which included searches of databases, registers, and other sources. Adapted from "PRISMA Transparent Reporting of Systematic Reviews and Meta-Analysis" from PRISMA (http://prisma-statement.org/prismastatement/flowdiagram.aspx). Copyright 2020 by PRISMA.

Table 6 Data Extraction Table – Studies meeting inclusion and exclusion criteria

NCT Number	Study Title	Study Status	Study Results	Enrolment Date used for Population Comparison	Primary Oncologic Condition Studied	Sex / Gender	Age Group	Enrolled Patients (n=)	Type of Results
NCT00924326	CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma	C	YES	2009	Lymphoma	B	A; Eld	43	F
NCT01218867	CAR T Cell Receptor Immunotherapy Targeting VEGFR2 for Patients With Metastatic Cancer	T	YES	2010	Melanoma	B	A; Eld	24	F
NCT01626495	Phase I/IIA Study of CART19 Cells for Patients With Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma	C	YES	2011	Lymphoma	B	CP; A	73	F
NCT01583686	CAR T Cell Receptor Immunotherapy Targeting Mesothelin for Patients With Metastatic Cancer	T	YES	2012	Mesothelioma	B	A; Eld	15	F
NCT01454596	CAR T Cell Receptor Immunotherapy Targeting EGFRvIII for Patients With Malignant Gliomas Expressing EGFRvIII	C	YES	2012	Brain Cancer	B	A; Eld	18	F
NCT01593696	Anti-CD19 White Blood Cells for Children and Young Adults With B Cell Leukemia or Lymphoma	C	YES	2012	Lymphoma	B	CP; A	53	F
NCT01460901	Study of Donor Derived, Multi-virus-specific, Cytotoxic T-Lymphocytes for Relapsed/Refractory Neuroblastoma	C	YES	2012	Brain	B	CP	5	F
NCT01747486	Dose Optimization Trial of CD19 Redirected Autologous T Cells	C	YES	2013	Leukemia	B	A; Eld	42	F
NCT01865617	Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory CLL, Non-Hodgkin Lymphoma, or ALL	C	YES	2013	Lymphoma	B	A; Eld	204	F
NCT02028455	A Pediatric and Young Adult Trial of Genetically Modified T Cells Directed Against CD19 for Relapsed/Refractory CD19+ Leukemia	ANR	YES	2014	Leukemia	B	CP; A	167	I
NCT02030847	Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR and 4-1BB Signaling Domains in Patients With Chemotherapy Resistant or Refractory ALL	C	YES	2014	Leukemia	B	A; Eld	42	F
NCT02215967	Study of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma	C	YES	2014	Myeloma	B	A; Eld	30	F
NCT02348216	Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma	C	YES	2015	Lymphoma	B	A; Eld	307	F
NCT02535364	Study Evaluating the Efficacy and Safety of JCAR015 in Adult B-cell Acute Lymphoblastic Leukemia (B-ALL)	T	YES	2015	Leukemia	B	A; Eld	82	F
NCT02601313	Study of Brexucabtagene Autoleucel (KTE-X19) in Participants With Relapsed/Refractory Mantle Cell Lymphoma (Cohort 1 and Cohort 2)	ANR	YES	2015	Lymphoma	B	A; Eld	105	I
NCT02659943	T Cells Expressing a Fully-human AntiCD19 Chimeric Antigen Receptor for Treating B-cell Malignancies	C	YES	2016	Lymphoma	B	A; Eld	27	F
NCT02614066	A Study Evaluating the Safety and Efficacy of Brexucabtagene Autoleucel (KTE-X19) in Adult Subjects With Relapsed/Refractory B-precursor ALL (ZUMA-3)	ANR	YES	2016	Leukemia	B	A; Eld	125	I
NCT02706392	Genetically Modified T-Cell Therapy in Treating Patients With Advanced ROR1+ Malignancies	T	YES	2016	Leukemia	B	A; Eld	21	F
NCT02926833	Safety and Efficacy of KTE-C19 in Combination With Atezolizumab in Adults With Refractory Diffuse Large B-Cell Lymphoma (DLBCL)	C	YES	2016	Lymphoma	B	A; Eld	37	F
NCT02706405	JCAR014 and Durvalumab in Treating Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma	T	YES	2016	Lymphoma	B	A; Eld	30	F
NCT02794246	CART-19 Post-ASCT for Multiple Myeloma	T	YES	2016	Myeloma	B	A; Eld	6	F
NCT02935543	CART19 in Adult Patients With Minimal Residual Disease During Upfront Treatment for ALL	T	YES	2016	Leukemia	B	A; Eld	1	F
NCT02664363	EGFRvIII CAR T Cells for Newly-Diagnosed WHO Grade IV Malignant Glioma	T	YES	2017	Brain	B	A; Eld	3	F
NCT03049449	T Cells Expressing a Fully-Human Anti-CD30 Chimeric Antigen Receptor for Treating CD30-Expressing Lymphomas	C	YES	2017	Lymphoma	B	A; Eld	26	F
NCT03288493	P-BCMA-101 Tscm CAR-T Cells in the Treatment of Patients With Multiple Myeloma (MM)	T	YES	2017	Myeloma	B	A; Eld	105	F
NCT03019055	Study of CAR-20/19-T Cells in Patients With Relapsed Refractory B Cell	C	YES	2017	Lymphoma	B	A; Eld	26	F
NCT03318861	Study to Evaluate the Safety and Efficacy of KITE-585 in Participants With Relapsed/Refractory Multiple Myeloma	T	YES	2017	Myeloma	B	A; Eld	17	F
NCT03338972	Immunotherapy With BCMA CAR-T Cells in Treating Patients With BCMA Positive Relapsed or Refractory Multiple Myeloma	C	YES	2017	Myeloma	B	A; Eld	28	F
NCT03483103	Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006)	C	YES	2018	Lymphoma	B	A; Eld	74	F
NCT03602612	T Cells Expressing a Novel Fully-Human Anti-BCMA CAR for Treating Multiple Myeloma	ANR	YES	2018	Myeloma	B	A; Eld	35	I
NCT03568461	Efficacy and Safety of Tisagenlecleucel in Adult Patients With Refractory or Relapsed Follicular Lymphoma	ANR	YES	2018	Lymphoma	B	A; Eld	98	I
NCT03624036	Safety and Tolerability of Brexucabtagene Autoleucel (KTE-X19) in Adults With Relapsed/Refractory CLL and SLL	T	YES	2018	Leukemia	B	A; Eld	16	F
NCT03761056	Study to Evaluate the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma	ANR	YES	2019	Lymphoma	B	A; Eld	42	I
NCT03958656	T-cells Expressing an Anti-SLAMF7 CAR for Treating Multiple Myeloma	C	YES	2019	Myeloma	B	A; Eld	13	F
NCT04160195	T Cells Expressing Fully-human Anti-CD19 and Anti-CD20 Chimeric Antigen Receptors for Treating B-cell Malignancies and Hodgkin Lymphoma	T	YES	2019	Lymphoma	B	A; Eld	2	F

Note: All studies were approved by the two primary readers. Categories used:

Study Status: C = Completed; T = Terminated; ANR = Active_Not_Recruiting

Age group: CP = Child / Pediatric Study, A = Adult study, Eld = Elderly Study, All = All age groups

Sex: M = male only, F = female only, B = both male and female

Study Results Submitted: Yes / No

Type of Results: F = Final results; I = Interim results.

Statistical Analysis

The data analysis in this study encompassed several essential statistical methods to investigate and evaluate the enrollment disparities in CAR-T cell clinical trials across different cancer types. All study data points extracted were added to a Data Extraction Table (DET) for subgroup analysis. Table 4 represents the template for the DET. Race and ethnicity were classified as White, White Hispanic / Non-White Hispanic (NWH), African American (AA) / Non-Hispanic Black, Asian, and other/unknown. Mean and standard deviation were used to combine the trial age data. In this study, the term gender is being used as a categorical term and interchangeably with the biological variable sex. Therefore, gender was classified as male or female. While there are many distinctions for gender, clinical trial data use sex/gender at birth as the primary data point. For this study, sex/gender, as reported in the study information (by registry or publication), will be used. Age, racial, and ethnic breakdown of the U.S. population were estimated using the SEER dataset for each included cancer disease site.

Descriptive statistics were generated based on the data available from *ClinicalTrials.gov*. They were estimated using median and ranges to combine age data from trials where mean and standard deviation were missing (Wan et al., 2014). Age data reported solely as a binned variable

were excluded. For each included disease site, overall weighted mean age and standard deviation were aggregated over all trials with age data available. To measure enrollment disparity for age in absolute terms, the enrollment age disparity was calculated as the absolute difference between the mean age of patients among trial participants and the estimated mean age of the patients diagnosed with a specific cancer type among the US population. The proportion of trials reporting race and ethnicity data was calculated among all reporting trials. The proportion of patients of a specific race or ethnicity who participated in trials was calculated after removing trials that did not report information on race or ethnicity. In assessing the disparity in enrollment, two measures were employed: the Enrollment Incidence Disparity (EID) in absolute terms and the Enrollment Incident Ratio (EIR) in relative terms. The calculation of the EID involved determining the absolute difference between the proportion of trial participants identified with a specific race or ethnicity and the estimated proportion of individuals from the same racial or ethnic group diagnosed with a particular cancer type in the US population. Positive values reflected enrollment proportions exceeding those in the US population, while negative values indicated the opposite. On the other hand, the EIR, a relative measure, was obtained by dividing the weighted proportion of trial participants from a specific race or ethnicity by the estimated proportion of individuals from that group diagnosed with a specific cancer type in the US population. The Enrollment Incidence Ratios (EIR) and Enrollment Incidence Disparities (EID) calculation were executed using Microsoft Excel. Univariate statistical tests were subsequently performed to assess disparities within the study's diverse subgroups. Chi-square goodness-of-fit tests and Binomial tests were used to scrutinize the alignment between clinical trial participant data and the population-based SEER Incidence. IBM SPSS Statistics software (Version 26) was utilized for comprehensive statistical analyses.

Demographic comparisons for all participants were used to analyse variables within the CAR-T group and to compare the CAR-T and non-CAR-T groups. Group comparisons were performed using the t-test or $\chi 2$ test, as appropriate. P-values were 2-sided and considered statistically significant when ≤ 0.05. The combination of these statistical methods and software tools ensured that the investigation of CAR-T cell clinical trial participation was conducted with a high degree of precision, enabling the study to uncover and comprehend disparities across the various subgroups effectively. This comprehensive approach allowed for a more nuanced understanding of the differences in enrollment representation, which, in turn, informs strategies to promote equity and inclusivity in future clinical trials.

Use of the SEER database

The Surveillance, Epidemiology, and End Results (SEER) Program is a cancer statistics program of the National Cancer Institute (NCI), which is part of the National Institutes of Health (NIH) in the United States (National Cancer Institute, 2022). It collects and publishes cancer incidence and survival data from various cancer registries. SEER Cancer Statistics is a vital program that plays a key role in monitoring and reporting on cancer trends in the United States. SEER collects information on the incidence (new cases), prevalence, and survival rates of different types of cancer to provide a comprehensive view of cancer trends, patterns, and outcomes. Available data includes age, gender, race, ethnicity, tumor characteristics, treatment modalities, and outcomes. The SEER database is publicly accessible, making it an open resource for vital national statistics and trend data (Siegel et al., 2019).

Limitations and Delimitations

The most significant delimitating factor for this study was the selection of trials, particularly the status of the US-based trials selected, as this choice limited the scope of the

review. The conclusions of this study are not generalizable to other countries conducting similar clinical trials. Several limitations are recognized for this study. While the United States conducts the second-highest number of CAR T-cell therapy clinical trials, it is still a novel treatment method in oncology. Furthermore, eliminating clinical trials through the inclusion and exclusion criteria resulted in fewer studies for inclusion. Some literature showed conflicting information for demographic data in selected clinical trials. The data from *ClinicalTrials.gov* was considered the source for data over any conflicting information within articles sourced from PubMed, CENTRAL, and Google Scholar. For this study, no data was used from the literature not given in the primary database.

Chapter 4: Results

This section thoroughly examines CAR-T cell clinical trial participation across five distinct cancer types, as reported in *ClinicalTrials.gov*. The individual indication analyses focus on the Brain and other Nervous Systems, Leukemia, Melanoma, Mesothelioma, and Myeloma Cancers. Additionally, the study presents two comprehensive sections, which provide an amalgamated comparison of participant data from 35 specific clinical trials conducted between 2009 and 2019. These overarching sections offer a holistic viewpoint by contrasting the clinical trial participant data with SEER Incidence for the five individual cancer types and all cancers combined in the United States from 2009 to 2019. These meticulous analyses aim to uncover disparities in gender, age, ethnicity, and race representation within clinical trials, with the ultimate objective of identifying areas for enhancement, ensuring more equitable and efficacious assessments of CAR-T cell therapies across diverse patient cohorts.

Brain and Nervous System Cancer

Table 7 shows the representation of various subgroups in CAR-T cell clinical trials for Brain and Nervous System Cancer, compared to SEER Incidence Rates. Enrollment Incidence Ratios (EIR) with 95% confidence intervals (CI) provide insights into the alignment between clinical trial enrollment and population incidence. The gender distribution in these trials closely mirrors the general population. Male participants exhibit a statistically significant 18.5-fold higher enrollment (EIR = 1.33, 95% CI: 0.59 to 2.17), corresponding to a 1.33-fold higher enrollment than population rates. Conversely, female participants are 18.5-fold lower in enrollment (EIR = 0.57, 95% CI: 0.25 to 2.44), translating to a 0.57-fold lower enrollment compared to the general population. The chi-square test for gender reveals no significant disparity, χ^2 (1) = 1.67, p = .196. On the other hand, the age distribution shows that data for

participants aged <=18 years and >=65 years was unavailable. However, a prominent overrepresentation is observed within the 18-65 age group, with a 50.2-fold higher enrollment compared to what one would anticipate from the general population (EIR = 1.99, 95% *CI*: 0.51 to 3.59). While the ethnicity data shows a significant 18.8-fold overrepresentation of Hispanics (EIR = 2.30, 95% CI: 0.20 to 10.19), it does not reveal a significant disparity (p = .989). Finally, American Indian/Alaska Native and "Other" groups lacked available data for comparison. Asian and Black participants were notably underrepresented, with respective Enrollment Incidence Disparity (EID) of -7.0 and -7.5, signifying fewer participants than anticipated. In contrast, the White community had a 15.6-fold higher enrollment (EIR = 1.18, 95% CI: 0.51 to 2.26), indicating significant overrepresentation in the trials compared to their population proportion.

In summary, these findings suggest that gender representation closely aligns with population demographics, emphasizing an equitable approach in trial enrollment. However, the notable overrepresentation of the 18-65 age group highlights the need to address age diversity within these trials, as age is a crucial factor influencing treatment outcomes. Ethnicity data emphasizes the significance of fostering inclusivity, particularly for underrepresented groups. The racial disparities in enrollment call for strategies to enhance representation among Asian and Black communities to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies.

Table 7 Participation of All Subgroups in CAR T-cell Clinical Trials for Brain and Other Nervous System Cancer, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)	EID	EIR (95% CI)
Gender				
Male	9 (75.0)	36,278 (56.5)	18.5	1.33 (0.59 to 2.17)
Female	3 (25.0)	27,933 (43.5)	-18.5	0.57 (0.25 to 2.44)
Age				
<=18 years	-	7,003 (10.9)	-10.9	-
18-65 years	4 (100)	32,237 (50.2)	50.2	1.99 (0.51 to 3.59)
>=65 years	-	24,971 (38.9)	-38.9	-
Ethnicity				
Hispanic	1 (33.3)	93,22 (14.5)	18.8	2.30 (0.20 to 10.19)
Non-Hispanic	2 (66.6)	54,889 (85.5)	-18.8	0.78 (0.22 to 3.59)
Race				
AIAN	-	284 (0.5)	-0.5	-
Asian	-	3,853 (7.0)	-7	-
Black	-	4,123 (7.5)	-7.5	-
White	7 (100)	46,337 (84.4)	15.6	1.18 (0.51 to 2.26)
Other	-	292 (0.5)	-0.5	-

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Brain and other Nervous System cancers is based on three specific studies conducted in 2012 and 2017, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Brain and other Nervous System cancers from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, and “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit and Binomial tests were performed to compare population and clinical data for the “Gender” and “Ethnicity” subgroups. Due to small sample sizes, no comparisons were made for other subgroups.

Leukemia

Table 8 compares CAR-T cell clinical trial participation for Leukemia Cancer with SEER Incidence Rates, offering insights into the alignment between enrollment in clinical trials and population-based incidence. The gender distribution in these trials indicates a statistically significant 9.59-fold overrepresentation of male participants, with a corresponding Enrollment Incidence Ratio (EIR) of 1.17 (95% CI: 1.00 to 1.15), indicating a 1.17-fold higher enrollment compared to the general population. Conversely, female participants exhibit a 9.59-fold lower enrollment (EIR = 0.77, 95% CI: 0.81 to 0.99), translating to a 0.77-fold lower enrollment than the population. The chi-square test for gender reveals a highly significant disparity, χ^2 (1) = 43.23, $p < .001$. Participants aged 18-65 years show a considerable overrepresentation, with an EIR of 1.78 (95% CI: 1.17 to 1.40), signifying a 1.78-fold higher enrollment than anticipated based on population rates. The chi-square test for age distribution also indicates a significant disparity, χ^2 (1) = 198.05, $p < .001$. There is no significant disparity for ethnicity, with an EIR of 1.03 (95% CI: 0.85 to 1.20) for Hispanics and an EIR of 1.00 (95% CI: 0.93 to 1.07) for non-Hispanics. The chi-square test for ethnicity does not reveal a significant difference, χ^2 (1) = 0.11, $p = .739$. Regarding race, significant disparities are observed. American Indian/Alaska Native (AIAN) participants show a 2.62-fold overrepresentation (EIR = 2.62, 95% CI: 0.94 to 2.46). In contrast, Asian and Black participants are notably underrepresented, with EIR values of 0.68 (95% CI: 0.64 to 1.11) and 0.29 (95% CI: 0.41 to 0.84), respectively. White participants exhibit a 1.04-fold higher enrollment (EIR = 1.04, 95% CI: 0.95 to 1.08), indicating a slight overrepresentation. The "Other" racial group demonstrates a significant 4.23-fold overrepresentation (EIR = 4.23, 95% CI: 1.47 to 2.37). The chi-square test for race shows a highly significant disparity, χ^2 (4) = 240.63, $p < .001$.

In summary, the results for Leukemia Cancer trials reveal substantial disparities in gender, age, and race representation. While gender and age disparities are pronounced, ethnicity exhibits more equitable representation. The racial disparities highlight the need for strategies to enhance representation among underrepresented groups, particularly Asian and Black communities, to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies.

Table 8 Participation of All Subgroups in CAR-T cell Clinical Trials for Leukemia Cancer, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	767 (67.6)	88,548 (58.0)		9.59	1.17 (1.00 to 1.15)
Female	367 (32.4)	64,002 (42.0)		-9.59	0. 77 (0.81 to 0.99)
Age					
<=18 years	-	12,520 (8.2)		-8.2	-
18-65 years	486 (65.2)	56,018 (36.7)		28.51	1.78 (1.17 to 1.40)
>=65 years	259 (34.8)	84,012 (55.1)		-20.31	0.63 (0.72 to 0.93)
Ethnicity					
Hispanic	133 (14.0)	20,744 (13.6)		0.37	1.03 (0.85 to 1.20)
Non-Hispanic	819 (86.0)	131,806 (86.4)		-0.37	1.00 (0.93 to 1.07)
Race					
AIAN	17 (1.5)	754 (0.6)		0.93	2.62(0.94 to 2.46)
Asian	53 (4.7)	9,098 (6.9)		-2.23	0.68 (0.64 to 1.11)
Black	30 (2.6)	11,915 (9.0)		-6.39	0.29 (0.41 to 0.84)
White	964 (85.0)	108,114 (82.0)		2.98	1.04 (0.95 to 1.08)
Other	70 (6.2)	1,925 (1.5)		4.71	4.23 (1.47 to 2.37)

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Leukemia Cancer is based on twenty-three specific studies conducted in 2009 and from 2011 to 2019, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Leukemia Cancer from 2009 to

2020. “EID” signifies the Enrollment Incidence Disparity, and “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit was performed to compare population and clinical data for all subgroups.

Melanoma

Table 9 presents a comparative analysis of CAR-T cell clinical trial participation for Melanoma Cancer compared to SEER Incidence Rates, providing valuable insights into the concordance between clinical trial enrollment and population-based incidence. Gender distribution within these trials exhibited no significant disparity (p = .688). Male participants emerged overrepresented, showing a 7.58-fold higher enrollment (EIR = 1.13, 95% CI: 0.40 to 2.81) compared to the general population. Conversely, the available data did not suggest any significant difference for age distribution, with participants aged 18-65 years significantly overrepresented in the trials, demonstrating a 34.19-fold higher enrollment (EIR = 1.70, 95% CI: 0.52 to 3.02). However, it is important to note that data for participants aged 18 years and below and those aged 65 years and above remained unavailable, precluding a comprehensive age-based comparison. The results of the binomial test indicate no significant difference between population and clinical trial distribution for age (p = .219). Unfortunately, ethnicity data was not accessible for comparative analysis. However, among the available dataset, non-Hispanic participants exhibited a 3.23-fold higher enrollment in clinical trials compared to the anticipated population rates (EIR = 1.03, 95% CI: 0.46 to 2.23). Similarly, data related to race was unavailable for comparison; however, among the existing dataset, White participants surfaced as overrepresented in the trials, indicating a 5.97-fold higher enrollment compared to their population proportion (EIR = 1.06, 95% CI: 0.46 to 2.29).

In summary, the results for Melanoma Cancer clinical trials indicate that while gender representation is balanced, male participants are overrepresented. Additionally, the substantial overrepresentation of participants aged 18-65 underscores the need for more comprehensive age diversity in these trials. While ethnicity and race data availability limits detailed conclusions, these results underscore the importance of fostering inclusivity and enhancing representation among underrepresented groups to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies for Melanoma Cancer.

Table 9 Participation of All Subgroups in CAR-T cell Clinical Trials for Melanoma Cancer, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	4 (66.7)	151,329 (59.1)		7.58	1.13 (0.40 to 2.81)
Female	2 (33.3)	104,782 (40.9)		-7.58	0.81 (0.23 to 3.66)
Age					
<=18 years	-	750 (0.3)		-0.29	
18-65 years	5 (83.3)	12,5854 (49.1)		34.19	1.70 (0.52 to 3.02)
>=65 years	1 (16.7)	12,9507 (50.6)		-33.9	0.33 (0.09 to 4.38)
Ethnicity					
Hispanic	-	8,272 (3.2)		-3.23	
Non-Hispanic	6 (100)	247,839 (96.8)		3.23	1.03 (0.46 to 2.23)
Race					
AIAN	-	565 (0.2)		-0.23	
Asian	-	1,548 (0.6)		-0.62	
Black	-	1,031 (0.4)		-0.42	
White	6 (100)	233,052 (94.0)		5.97	1.06 (0.46 to 2.29)
Other	-	11,643 (4.7)		-4.7	

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Melanoma Cancer is based on one specific study conducted in 2010, with only

available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Melanoma Cancer from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, “EIR” indicates the Enrollment Incident Ratio. A Binomial test was performed to compare population and clinical data for the “Gender” and “Ethnicity” subgroups. Due to small sample sizes, no comparisons were made for other subgroups.

Mesothelioma

Table 10 compares CAR-T cell clinical trial participation for Mesothelioma Cancer with SEER Incidence Rates, providing insights into the alignment between enrollment in clinical trials and population-based incidence. The gender distribution in these trials shows a significant gender disparity, χ^2 (1) = 10.55, p = .001. Male participants were underrepresented with a 41.0-fold lower enrollment (EIR = 0.45, 95% CI: 0.26 to 1.88), indicating a 0.45-fold lower enrollment compared to the general population. In contrast, female participants exhibit a significant 41.0-fold higher enrollment (EIR = 2.60, 95% CI: 0.76 to 3.03), corresponding to a 2.60-fold higher enrollment than the population. For age distribution, data for participants aged 18 years and below and those aged 65 years were not available as these groups were not represented in trials. However, participants aged 18-65 years demonstrate a substantial overrepresentation in the trials, with a 77.36-fold higher enrollment (EIR = 4.42, 95% CI: 1.08 to 3.36), signifying a 4.42-fold higher enrollment compared to the population. In addition, Ethnicity data showed that non-Hispanic participants exhibited an 11.98-fold higher enrollment (EIR = 1.14, 95% CI: 0.60 to 1.86), indicating a 1.14-fold higher enrollment compared to the general population. Significant racial disparities were observed, χ^2 (2) = 6.92, p = .031. Asian participants show a significant 12.14-fold overrepresentation (EIR = 3.68, 95% CI: 0.44 to 7.07), while Black participants are notably overrepresented with an EIR of 2.83 (95% CI: 0.39 to 6.30).

White participants were underrepresented with a 22.21-fold lower enrollment (EIR = 0.75, 95% CI: 0.44 to 1.77), corresponding to a 0.75-fold lower enrollment compared to the general population.

In summary, the results for Mesothelioma Cancer trials reveal significant gender and age disparities. Compared to the national trend of incidence for this specific cancer, females were substantially overrepresented, while males were underrepresented in clinical trial participation. Significant racial disparities highlight the need for strategies to address underrepresentation among specific racial groups, particularly AIAN communities, to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies. The lack of representation of participants 65-years and older is notable as this age group makes up the majority of cases in the general cancer population.

Table 10 Participation of All Subgroups in CAR-T cell Clinical Trials for Mesothelioma Cancer, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	4 (33.3)	7,001 (74.3)		-41	0.45 (0.26 to 1.88)
Female	8 (66.7)	2,417 (25.7)		41	2.60 (0.76 to 3.03)
Age					
<=18 years	-	4 (0.04)		-0.04	-
18-65 years	12 (100)	2,132 (22.6)		77.36	4.42 (1.08 to 3.36)
>=65 years	-	7,282 (77.3)		-77.32	-
Ethnicity					
Hispanic	-	1,128 (12.0)		-11.98	-
Non-Hispanic	12 (100)	8,290 (88.0)		11.98	1.14 (0.60 to 1.86)
Race					
AIAN	-	39 (0.5)		-0.47	-
Asian	2 (16.7)	375 (4.5)		12.14	3.68 (0.44 to 7.07)
Black	2 (16.7)	489 (5.9)		10.77	2.83(0.39 to 6.30)
White	8 (66.7)	7,368 (88.9)		-22.21	0.75 (0.44 to 1.77)
Other	-	19 (0.2)		-0.23	-

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Mesothelioma Cancer is based on one specific study conducted in 2012, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Mesothelioma Cancer from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit was performed to compare population and clinical data for the “Gender” and “Race” subgroups. Due to small sample sizes, no comparisons were made for other subgroups.

Myeloma

Table 11 examines CAR-T cell clinical trial participation within the context of Myeloma Cancer, comparing it to SEER Incidence Rates. This analysis seeks to reveal the degree of concordance between clinical trial enrollment and population-based incidence.

In gender distribution, a statistically significant disparity is not evident, χ^2 (1) = 0.89, p = .345. Male participants are observed to exhibit a 3.48-fold higher enrollment (EIR = 1.06, 95% CI: 1.85 to 1.24), signifying an enrollment 1.06 times higher than the general population. The age distribution demonstrates considerable disparities, χ^2 (1) = 69.68, p < .001. Participants in the 18-65 age group exhibit significant overrepresentation, featuring a 30.9-fold higher enrollment (EIR = 1.85, 95% CI: 1.09 to 1.57), signifying an enrollment 1.85 times higher than the general population. Unfortunately, data regarding participants aged 18 years or younger is unavailable. The ethnicity subgroups also display disparities, χ^2 (1) = 5.88, p = .015. Hispanic participants reflect a 6.22-fold underrepresentation (EIR = 0.51, 95% CI: 0.41 to 1.35), indicating an enrollment at 0.51 times the general population's rate. In contrast, non-Hispanic participants are overrepresented by a factor of 6.22 (EIR = 1.07, 95% CI: 0.88 to 1.21), implying an enrollment at 1.07 times the general population's rate. Racial disparities are notably conspicuous, χ^2 (3) = 131.39, p < .001. Asian and Black participants are significantly underrepresented, with EIR values of 0.56 (95% CI: 0.37 to 1.63) and 0.84 (95% CI: 0.66 to 1.30), respectively. Conversely, White participants are virtually identically represented in the trials compared to their population proportion, with an EIR of 1.00 (95% CI: 0.84 to 1.19). The "Other" racial group presents a substantial overrepresentation at a magnitude of 10.84-fold (EIR = 10.84, 95% CI: 1.62 to 4.89), signifying an enrollment rate 10.84 times the general population's rate.

In summary, the outcomes explicate significant gender, age, ethnicity, and race disparities within clinical trial participation for Myeloma Cancer. Gender disparities are minimal, with both genders experiencing relatively balanced representation. Nevertheless, the notable overrepresentation of participants in the 18-65 age group underscores the necessity for diversifying age representation in these trials. Disparities related to ethnicity accentuate the demand for greater inclusivity, particularly within the Hispanic community. The evident racial disparities warrant strategies to amplify the representation of underrepresented groups, particularly Asian and Black communities, to ensure a more comprehensive assessment of and effectiveness of CAR-T cell therapies.

Table 11 Participation of All Subgroups in CAR-T cell Clinical Trials for Myeloma Cancer, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	109 (59.6)	42,601 (56.1)		3.48	1.06 (1.85 to 1.24)
Female	74 (40.4)	33,362 (43.9)		-3.48	0.92 (0.77 to 1.21)
Age					
<=18 years	-	14 (0.02)		-0.02	-
18-65 years	114 (67.5)	27,757 (36.5)		30.9	1.85 (1.09 to 1.57)
>=65 years	55 (32.5)	48,192 (63.4)		-30.9	0.51 (0.57 to 0.97)
Ethnicity					
Hispanic	11 (6.55)	9,695 (12.8)		-6.22	0.51 (0.41 to 1.35)
Non-Hispanic	157 (93.45)	66,268 (87.2)		6.22	1.07 (0.88 to 1.21)
Race					
AIAN	-	420 (0.6)		-0.63	-
Asian	7 (3.8)	4,518 (6.8)		-2.99	0.56 (0.37 to 1.63)
Black	34 (18.6)	14,516 (21.9)		-3.33	0.84 (0.66 to 1.30)
White	129 (70.5)	46,380 (70.0)		0.5	1.00 (0.84 to 1.19)
Other	13 (7.1)	434 (0.6)		6.45	10.84 (1.62 to 4.89)

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Myeloma Cancer is based on seven specific studies conducted in 2014 and from 2016 to 2019, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Myeloma Cancer from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit was performed to compare population and clinical data for all subgroups.

Comparing Clinical Trial Participation in Five Cancer Types to SEER Incidence Rates for Those Cancers

Table 12 shows an extensive analysis of CAR-T cell clinical trial participation across five different cancer types, drawing comparisons with SEER Incidence Rates. This evaluation seeks to unveil the degree of concordance between enrollment in clinical trials and the incidence rates within the general population. Gender disparities are discernible, as indicated by a highly significant chi-square test result χ^2 (1) = 34.56, $p < .001$. Male participants exhibit a substantial overrepresentation, with a 7.9-fold higher enrollment (EIR = 1.14, 95% CI: 0.99 to 1.13), suggesting an enrollment 1.14 times greater than the general population. Conversely, female participants are underrepresented, with a corresponding 0.81-fold lower enrollment (95% CI: 0.83 to 1.00), signifying an enrollment 7.9 times lower than the population. In addition, Age disparities are equally pronounced, with a chi-square test result indicating significant differences χ^2 (1) = 51.51, $p < .001$. Participants aged 18-65 years exhibit a marked overrepresentation, with a 13.7-fold higher enrollment (EIR = 0.77, 95% CI: 0.80 to 1.00) compared to population rates. Ethnicity data further underscores significant disparities, supported by the chi-square test result, χ^2 (1) = 21.71, $p < .001$. Hispanic participants exhibit a 3.9-fold overrepresentation (EIR = 1.44,

95% CI: 1.00 to 1.38), while non-Hispanic participants experience the opposite, with a 0.96-fold lower enrollment (95% CI: 0.92 to 1.04). Finally, examining racial disparities indicates notable differences, with a highly significant chi-square test result χ^2 (4) = 86.35, $p < .001$. American Indian/Alaska Native (AIAN) participants present a 0.9-fold overrepresentation (EIR = 3.10, 95% CI: 1.1 to 2.64). In contrast, Black participants exhibit underrepresentation, with EIR values of 0.88 (95% CI: 0.74 to 1.20). White participants show a 0.95-fold lower enrollment (95% CI: 0.92 to 1.04), indicating a slight underrepresentation. In contrast, the "Other" racial group demonstrates a 3.4-fold overrepresentation (EIR = 2.18, 95% CI: 1.13 to 1.74), signifying an enrollment 2.18 times greater than the general population.

Table 12 Participation of All Subgroups in CAR-T cell Clinical Trials for Five Cancers, Compared to SEER Incidence

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	893 (66.3)	325757 (58.4)		7.9	1.14 (0.99 to 1.13)
Female	454 (33.7)	232496 (41.6)		-7.9	0.81 (0.83 to 1.00)
Age					
<=18 years	-	20291 (3.6)		-3.6	1.26 (1.02 to 1.20)
18-65 years	621 (66.0)	293964 (52.7)		13.7	0.77 (0.80 to 1.00)
>=65 years	315 (33.5)	243998 (43.7)		-10.1	
Ethnicity					
Hispanic	145 (12.7)	49161 (8.8)		3.9	1.44 (1.00 to 1.38)
Non-Hispanic	996 (87.3)	509092 (91.2)		-3.9	0.96 (0.92 to 1.04)
Ethnicity					
AIAN	17 (1.3)	2062 (0.4)		0.9	3.10 (1.1 to 2.64)
Asian	62 (4.6)	19392 (3.8)		0.8	1.20 (0.84 to 1.39)
Black	66 (4.9)	28363 (5.6)		-0.7	0.88 (0.74 to 1.20)
White	1114 (83.0)	441251 (87.3)		-4.3	0.95 (0.92 to 1.04)
Other	83 (6.2)	14313 (2.8)		3.4	2.18 (1.13 to 1.74)

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Five (Brain and other Nervous System, Leukemia, Melanoma, Mesothelioma, and Myeloma) Cancers are based on thirty-five specific clinical studies conducted from 2009 to 2019, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for Five (Brain and other Nervous System, Leukemia, Melanoma, Mesothelioma, and Myeloma) Cancers from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit was performed to compare population and clinical data for all subgroups.

Comparing Clinical Trial Participation in Five Cancer Types to SEER Incidence Rates for All Cancers

Table 13 presents a comprehensive CAR-T cell clinical trial participation assessment across five cancer types in comparison to SEER Incidence Rates for all cancers. This examination is intended to elucidate the alignment between clinical trial enrollment and population-based incidence. Gender disparities are quite prominent, as evidenced by a highly significant chi-square test result, χ^2 (1) = 131.07, $p < .001$. Male participants exhibit a remarkable 15.62-fold overrepresentation (EIR = 1.31, 95% CI: 1.05 to 1.20), suggesting an enrollment 1.31 times higher than the general population. Conversely, female participants are underrepresented by a factor of 15.62 (EIR = 0.68, 95% CI: 0.77 to 0.93), signifying an enrollment 0.68 times lower than the population. Age disparities are equally significant, with a chi-square test result indicating a substantial divergence χ^2 (1) = 200.83, $p < .001$. Among participants aged 18-65 years, a noteworthy overrepresentation is observed, reflecting a 22.05-fold higher enrollment (EIR = 1.50, 95% CI: 1.10 to 1.29) compared to population rates.

The category of ethnicity does not manifest any significant disparity, as indicated by the chi-square test result χ^2 (1) = 1.37, p = .242. Hispanic and non-Hispanic participants exhibit relatively equitable enrollment compared to the population, with EIR values of 1.10 (95% CI: 0.89 to 1.23) and 0.99 (95% CI: 0.93 to 1.06), respectively. In terms of race, a profound disparity is evident, as indicated by a highly significant chi-square test result χ^2 (4) = 327.87, p < .001. American Indian/Alaska Native (AIAN) participants exhibit a 2.28-fold overrepresentation (EIR = 2.28, 95% CI: 0.89 to 2.30). In contrast, Asian and Black participants are notably underrepresented, with EIR values of 0.57 (95% CI: 0.61 to 1.00) and 0.43 (95% CI: 0.55 to 0.89), respectively. White participants, on the other hand, are virtually identically represented in the trials compared to their population proportion, with an EIR of 1.05 (95% CI: 0.97 to 1.09). The "Other" racial group demonstrates a significant 4.81-fold overrepresentation (EIR = 4.81, 95% CI: 1.60 to 2.45), signifying an enrollment 4.81 times the general population’s rate.

In summary, the results underline substantial gender and age disparities in clinical trial participation across the five cancer types. Male participants are notably overrepresented, emphasizing the need for a more balanced gender representation in these trials. Furthermore, the overrepresentation of the 18-65 age group highlights the significance of diversifying age representation. In contrast, ethnicity displays a relatively balanced representation. The disparities concerning race underscore the importance of implementing strategies to enhance the representation of underrepresented racial groups, particularly Asian and Black communities, to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies across the spectrum of cancers.

Table 13 Participation of All Subgroups in CAR-T cell Clinical Trials for Five Cancers, Compared to SEER Incidence for All Cancers

Characteristics	Trial Participants n (%)	SEER Incidence n (%)		EID	EIR (95% CI)
Gender					
Male	893 (66.3)	2527598 (50.7)		15.62	1.31 (1.05 to 1.20)
Female	454 (33.7)	2460673 (49.3)		-15.62	0.68 (0.77 to 0.93)
Age					
<=18 years	-	46713 (0.9)		-0.94	
18-65 years	621 (66.0)	2209606 (44.3)		22.05	1.50 (1.10 to 1.29)
>=65 years	315 (33.5)	2731952 (57.8)		-21.11	0.61 (0.72 to 0.90)
Ethnicity					
Hispanic	145 (12.7)	576754 (11.6)		1.15	1.10 (0.89 to 1.23)
Non-Hispanic	996 (87.3)	4411517 (88.4)		-1.15	0.99 (0.93 to 1.06)
Ethnicity					
AIAN	17 (1.3)	24520 (0.6)		0.71	2.28 (0.89 to 2.30)
Asian	62 (4.6)	358048 (8.1)		-3.5	0.57 (0.61 to 1.00)
Black	66 (4.9)	500399 (11.3)		-6.42	0.43 (0.55 to 0.89)
White	1114 (83.0)	3471871 (78.7)		4.31	1.05 (0.97 to 1.09)
Other	83 (6.2)	56679 (1.3)		4.9	4.81 (1.60 to 2.45)

Note: CAR-T cell clinical trial data is sourced from *ClinicalTrials.gov*. Data for clinical trials related to Five (Brain and other Nervous System, Leukemia, Melanoma, Mesothelioma, and Myeloma) Cancers are based on thirty-five specific clinical studies conducted from 2009 to 2019, with only available participant data included in the 'Trial Participants' column. SEER incidence rates provide population-based statistics for All Cancers from 2009 to 2020. “EID” signifies the Enrollment Incidence Disparity, “EIR” indicates the Enrollment Incident Ratio. Chi-squared goodness-of-fit was performed to compare population and clinical data for all subgroups.

Trend Analysis

Table 14 displays Spearman's correlation analysis between Clinical Trials and SEER incidence for various characteristics. These results offer valuable insights into the alignment between clinical trial participation and the broader population captured by SEER Incidence rates. First, in terms of gender, both males and females exhibit negligible negative correlations (Male: r (9) = -0.10, p = .759; Female: r (9) = -0.10, p = 0.759), indicating that gender distribution in clinical trials does not significantly mirror the SEER population. Regarding age, there is a significant positive correlation for individuals aged 65 and older, r (9) = 0.68, p = .021, suggesting that this age group is indeed well-represented within CAR-T cell clinical trials, following the trends. However, the 18-65 years age group shows a positive correlation, although it is not statistically significant, r (9) = 0.19, p = .573, implying a somewhat closer alignment with the SEER population.

In terms of ethnicity, the results indicate a lack of significant correlation. For Hispanic individuals r (9) = 0.23, p = .492, there is a positive correlation, though not statistically significant, suggesting a possible closer alignment with the SEER population. Conversely, for non-Hispanic individuals, the correlation is also not significant r (9) = -0.07, p = .832. This implies that there is no discernible correlation between non-Hispanic ethnicity and representation in CAR-T cell clinical trials. In the case of race, the correlations vary among different groups. Asian r (9) = 0.57, p = .042, Black r (9) = 0.52, p = .048, White r (9) = 0.66, p = .026, and Other r (9) = 0.72, p = 0.013 populations display significant positive correlations, suggesting a closer alignment with SEER Incidence. Conversely, the American Indian and Alaska Native (AIAN) population exhibits a notable negative correlation r (9) = -0.37, p = .258), indicating underrepresentation in clinical trials.

Table 14 Spearman's Correlation Analysis Between Clinical Trial and SEER Incidence for Demographic Characteristics

	Characteristics	
	SEER	*r*
	Incidence	
CAR-T cell Trial Participants	Gender	
	Male	-0.1
	Female	-0.1
	Age	
	18-65 years	0.19
	>=65 years	.68*
	Ethnicity	
	Hispanic	0.23
	Non-Hispanic	-0.07
	Race	
	AIAN	-0.37
	Asian	.57*
	Black	.52*
	White	.66*
	Other	.72*

Note. This table presents Spearman's correlation coefficients (r) to assess the relationships between clinical trial participation and SEER incidence rates for various demographic characteristics, including gender, age, ethnicity, and race. * $p < .05$ (two-tailed). ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed).

Figure 11 illustrates the shifting trends in gender distribution within CAR-T cell clinical trials compared to SEER population rates from 2009 to 2019. the line plot provides a clear visual representation of gender distribution trends within CAR-T cell clinical trials over an eleven-year period, highlighting persistent gender disparities. The plots illustrate that female representation in clinical trials was consistently lower than in the general population, while male participation

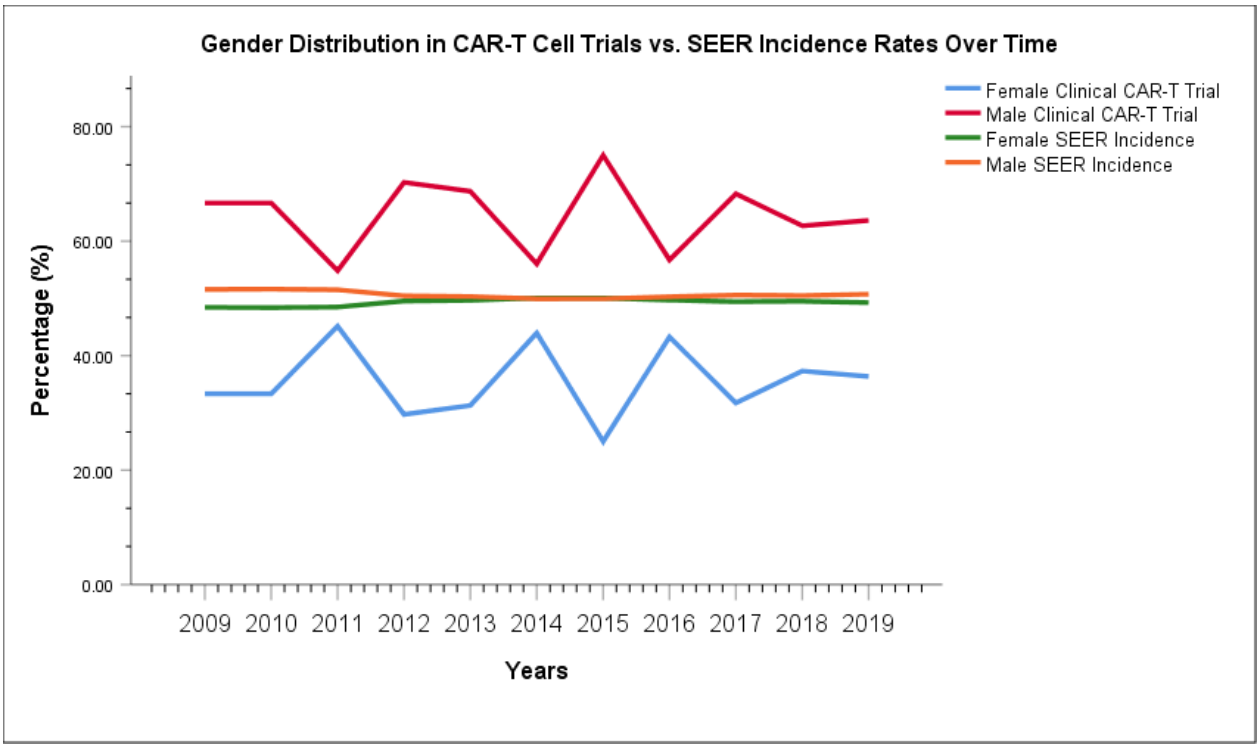
exceeded the corresponding SEER figures throughout the years. Over time, these disparities fluctuated but did not significantly diminish.

1. In 2009, male participants in clinical trials constituted 66.7%, significantly exceeding their representation in the SEER population (51.6%), while female participants were notably underrepresented in trials at 33.3% compared to 48.4% in SEER data.
2. In 2011, female representation in clinical trials increased to 45.2%, approaching the SEER incidence rate of 48.5%, whereas male participants decreased to 54.8%, a reversal from the previous year.
3. The trend continued to shift in subsequent years, with fluctuations in female and male participation. In 2014, the gap between clinical trials and SEER incidence was the widest, with 44.0% females and 56.0% males in clinical trials compared to 50.1% females and 49.9% males in SEER data.
4. The year 2015 saw female participation in clinical trials decrease to 25.0%, falling further behind the SEER incidence of 50.1%, while male participation increased to 75.0%.
5. Subsequently, the participation percentages converged, with male and female representation within clinical trials drawing closer to the SEER population. This trend continued until the end of the study in 2019.

The aggregated findings from the line plots across multiple cancer types suggest a consistent gender disparity in CAR-T cell clinical trial participation compared to SEER Incidence Rates. Males consistently exhibit higher representation, while females are underrepresented throughout the studied years. These trends imply a persistent gender gap that extends beyond specific cancer types and years, highlighting the need for strategies to ensure

more equitable gender representation in CAR-T cell clinical trials, fostering inclusivity and enhancing the generalizability of research outcomes.

Figure 11 Line Plot of Gender Distribution in CAR-T cell Clinical Trials vs SEER Incidence Rates Over Time



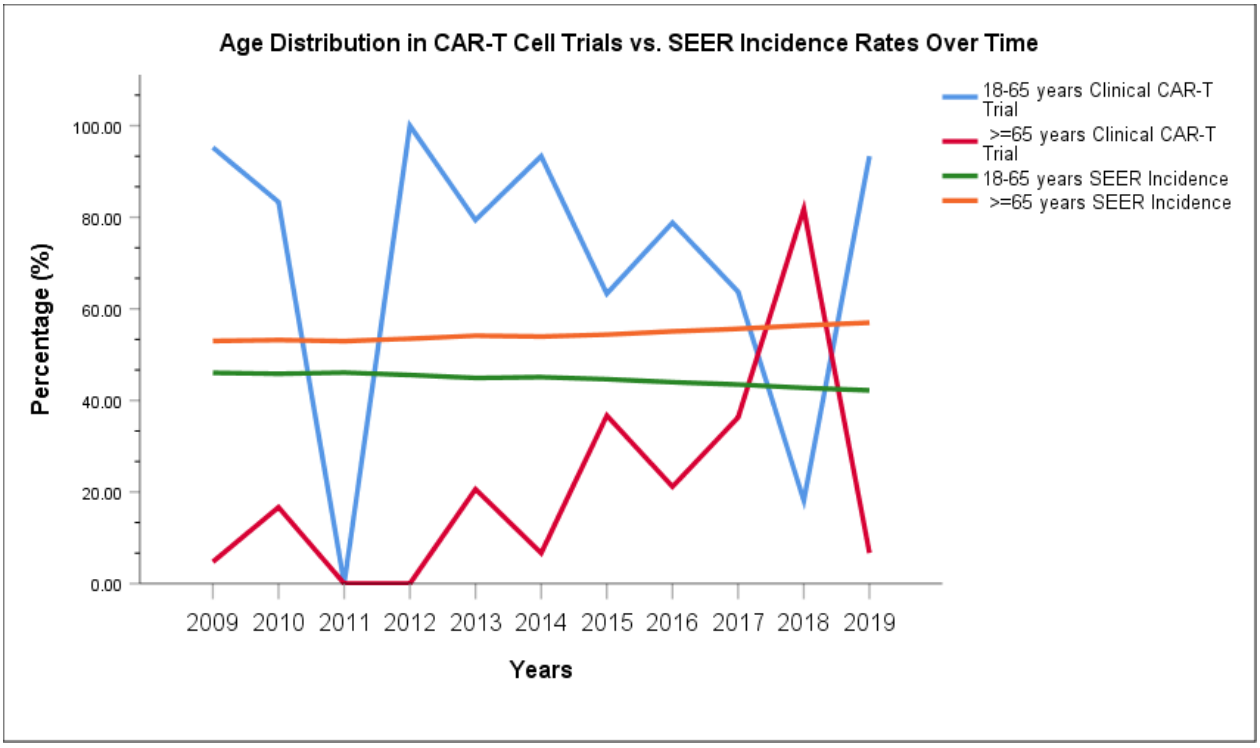
Note. This line plot illustrates the changing trends in gender distribution within CAR-T cell clinical trials for five specific cancer types over the 2009-2019 period, contrasted with SEER population rates. It emphasizes the consistent overrepresentation of males and underrepresentation of females in clinical trials.

Figure 12 illustrates the evolving trends in age distribution within CAR-T cell clinical trials compared to SEER population rates from 2009 to 2019. This line plot visually represents age distribution trends within CAR-T cell clinical trials over this eleven-year period. Notably, the age group below 18 years is excluded from the plot due to a lack of clinical trial participants in this category.

Throughout the study years, a persistent disparity in age distribution is observed between clinical trial participants and the general SEER population.

1. In 2009, participants aged 18-65 years accounted for 95.2% of clinical trial participants, markedly exceeding the 46.0% incidence in the SEER population. For those aged 65 years and above, the clinical trials included 4.8% of participants compared to 53.0% in SEER data.
2. 2010 saw a continued overrepresentation of the 18-65 years age group in clinical trials, with 83.3% participation versus 45.8% in SEER incidence. Conversely, only 16.7% of clinical trial participants were aged 65 years and above, in contrast to the 53.2% SEER rate.
3. In 2011, the age distribution within CAR-T cell clinical trials exhibited a unique characteristic. There were no participants in the 18-65 years age group in clinical trials. This absence was due to the availability of a clinical trial exclusively designed for children, resulting in no representation from the 18-65 years age group within the trials. Meanwhile, the SEER incidence data for this age category remained at 46.1%, reflecting the general population's composition in this particular year.
4. In 2018, the age distribution within CAR-T cell clinical trials demonstrated a notable difference from previous years. Participants aged 18-65 years constituted only 18.2% of the clinical trial population, markedly lower than the 42.7% incidence in the SEER population. In contrast, participants aged 65 years and above were significantly overrepresented, making up 81.8% of the clinical trial participants compared to 56.4% in SEER data.
5. From 2012 to 2019, the age distribution trends continued to fluctuate. In the clinical trials, the 18-65 years age group consistently exceeded the SEER incidence rates, with peaks and troughs observed except in 2018. The 65 years and above group’s participation in clinical trials varied but generally remained below the SEER incidence rate except in 2018.

Figure 12 Line Plot of Age Distribution in CAR cell Clinical Trials vs. SEER Incidence Rates Over Time

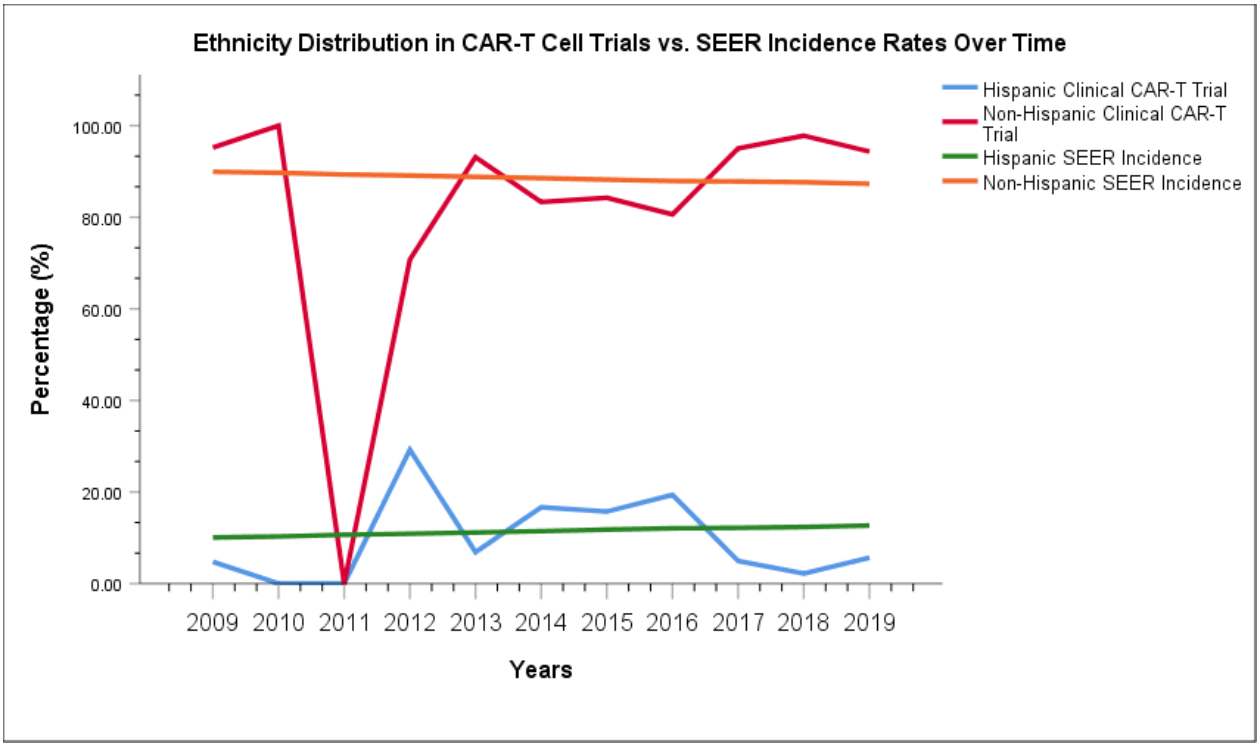


Note. This line plot illustrates the changing trends in age distribution within CAR-T cell clinical trials for five specific cancer types over the 2009-2019 period, contrasted with SEER population rates. Notably, the under-18 age group was excluded, revealing consistent disparities between clinical trials and SEER data.

Figure 13 illustrates the evolving trends in ethnicity distribution within CAR-T cell clinical trials compared to SEER Incidence Rates over the course of eleven years. The line plot visually represents these trends, highlighting the shifting patterns of ethnicity representation within clinical trials. Throughout the study period, a significant contrast is observed between Hispanic and non-Hispanic participants in clinical trials when compared to their respective SEER population rates. The trends within this line plot reveal the following key points:

1. In 2009, a notable disparity is evident. Hispanic participants comprised only 4.8% of clinical trial participants, considerably lower than the 10.1% incidence rate in the SEER population. Conversely, non-Hispanic participants dominated clinical trials at 95.2%, exceeding the 89.9% SEER incidence rate.
2. In 2010, the trend continued, with no Hispanic participants in clinical trials, while non-Hispanic participants comprised the entire clinical trial participation.
3. In 2012, a shift in trends was observed. Hispanic participants increased to 29.2% in clinical trials above the SEER incidence rate of 10.9%. Non-Hispanic participants decreased to 70.8%, below the SEER incidence rate of 89.1%.
4. Subsequent years saw fluctuations in Hispanic and non-Hispanic representation in clinical trials. In 2014, Hispanic participants in clinical trials increased to 16.7% higher than the 11.5% SEER incidence rate, while non-Hispanic clinical trial participants decreased to 83.3%, below the SEER incident rate.
5. By 2018, the representation of both groups began to draw closer. Hispanic participants increased to 5.7% in clinical trials, though still below the 12.7% SEER incidence rate, while non-Hispanic participants reached 94.3%, slightly above the 87.3% SEER incidence rate.

Figure 13 Line Plot of Ethnicity Distribution in CAR-T cell Clinical Trials vs SEER Incidence Rates Over Time



Note. This line plot illustrates the changing trends in ethnicity distribution within CAR-T cell clinical trials for five specific cancer types over the 2009-2019 period, contrasted with SEER population rates. It highlights disparities, including the underrepresentation of Hispanic individuals.

Figure 14 illustrates the evolving patterns in race distribution within CAR-T cell clinical trials compared to SEER population rates over an eleven-year period, spanning from 2009 to 2019. This line plot visually represents the trends in race distribution within CAR-T cell clinical trials for five specific cancer types.

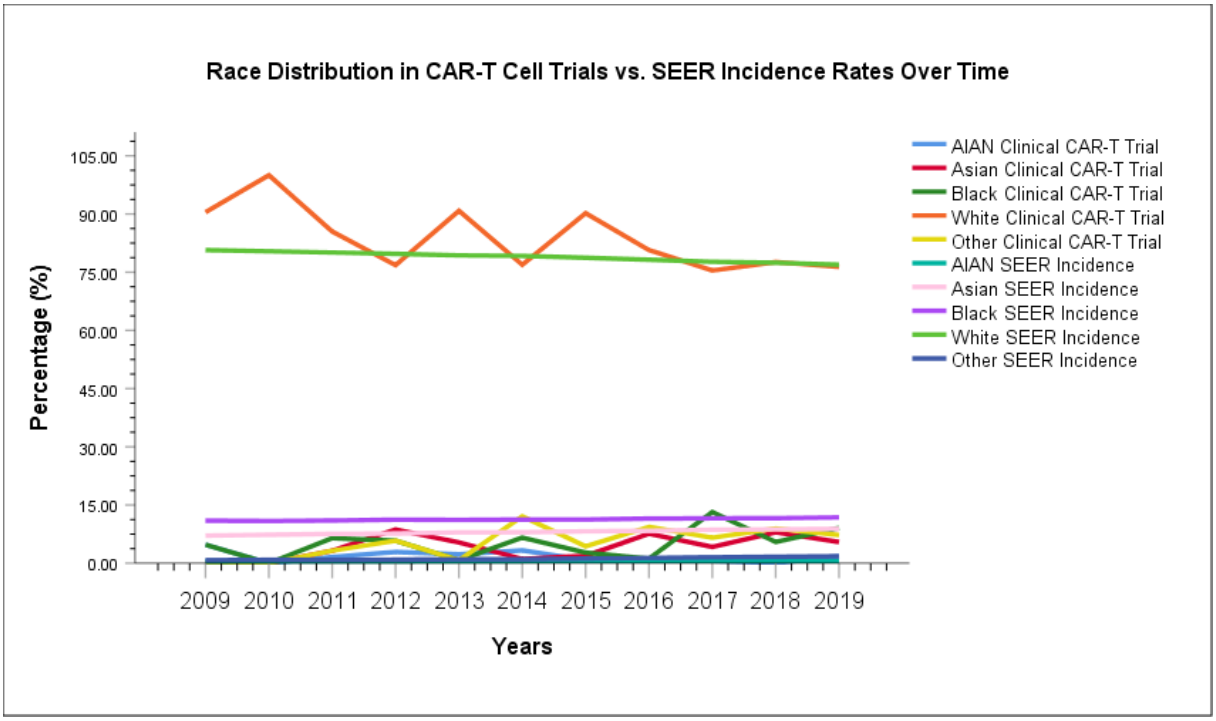
1. In 2009, the participation of American Indian/Alaska Native (AIAN) individuals in clinical trials was notably higher at 4.8% compared to the SEER population incidence of 0.5%. Similarly, Black participants constituted 4.8% of clinical trial enrollment, while the SEER

population exhibited 11.0% representation. White participants were prominently overrepresented in clinical trials, comprising 90.5% of participants compared to 80.7% in the SEER population. Asian participants, however, were scarcely represented in clinical trials but accounted for 7.1% of the SEER population.

2. Over the subsequent years, the trends in race distribution displayed variations. AIAN participation consistently remained higher in clinical trials compared to the SEER population. Asian representation gradually increased within clinical trials, albeit remaining below the corresponding SEER rates. The Black and White racial groups showed fluctuating trends, emphasizing disparities in clinical trial representation compared to SEER population rates.

The line plot underscores the disparities in race distribution within CAR-T cell clinical trials for the selected cancer types, particularly highlighting the overrepresentation of White individuals and the need for more inclusive strategies to enhance the representation of underrepresented racial groups.

Figure 14 Line Plot of Race Distribution in CAR-T cell Clinical Trials vs. SEER Incidence Rates Over Time



Note. This line plot illustrates the changing trends in race distribution within CAR-T cell clinical trials for five specific cancer types over the 2009-2019 period, contrasted with SEER population rates. It underscores disparities, including the consistent overrepresentation of White participants in clinical trials compared to SEER data.

Chapter 5: Discussion

This study examined immunotherapy clinical trials, specifically CAR T-cell studies, for racial/ethnic, age, and gender disparities using *ClinicalTrials.gov* (primary database of United States registered trials) and corresponding peer-reviewed literature. Data was collected and analyzed to assess CAR T-cell trials for significant differences in race, ethnic, gender, or age representation compared to the patient population in the United States, both for five specific cancer indications and an amalgamated comparison of participant data from 35 specific clinical trials conducted between 2009 and 2019. Trial and SEER data were compared, correlating with the year the study began enrollment. The generalizability of a clinical study's resulting assumptions depends on accurately representing all subgroup populations. Previously identified barriers to equitable healthcare access have been an ongoing focus for NIH - sponsored and commercial trials, particularly since the 1993 NIH Revitalization Act, calling for the just inclusion of underrepresented racial and ethnic groups. The assumptions of this study would be a continuation of disparities seen in previous clinical trials.

Discussion of the Results

Spearman's correlation analysis reveals distinct patterns in the representation of various demographic characteristics within CAR-T cell clinical trials when compared to SEER population rates. Notably, gender distribution in these trials shows minimal correlation with the general population, suggesting a persistent disparity between males and females. The age groups, on the other hand, exhibit varying degrees of alignment, with individuals aged 65 and older well-represented, while those between 18 and 65 years show a relatively closer match. However, ethnicity lacks significant correlation with clinical trial participation, whether Hispanic or non-Hispanic. The most pronounced trends are observed in race, with Asian, Black, White, and other

populations displaying positive correlations, indicating a closer alignment, while the American Indian and Alaska Native (AIAN) population shows a notable negative correlation, suggesting underrepresentation.

The results underline substantial gender, age, ethnicity, and race disparities in clinical trial participation across the five cancer types. The disparities concerning race highlight the need to implement measures that enhance the representation of underrepresented racial groups, particularly among Asian and Black communities, to ensure a more comprehensive evaluation and effectiveness of CAR-T cell therapies for the spectrum of cancers. Regarding ethnicity, disparities call for strategies to ensure more equitable enrollment. The collective findings across multiple cancer types suggest a prominent disparity in ethnicity representation in CAR-T cell clinical trial participation compared to SEER Incidence Rates. While non-Hispanic participants consistently dominate clinical trials, Hispanic representation displays notable variations over the years, albeit remaining below their SEER incidence counterparts. Participants aged 18-65 years consistently exhibit higher representation in clinical trials, while those aged 65 years and above are underrepresented over the study period. Furthermore, the overrepresentation of the 18-65 age group underscores the significance of diversifying age representation. The amalgamated data show a persistent age-based disparity in CAR-T cell clinical trial participation when contrasted with SEER Incidence Rates. The overrepresentation of male participants suggests the importance of achieving a more balanced gender representation in these trials.

Discussion on Research Questions and Outcomes:

The research questions for this study were answered using the measurements of the enrollment incident ratio (EIR) and the Enrollment Incidence Disparities (EID). Further assessment of the disparities within the study used the Chi-square goodness-of-fit tests and

Binomial tests to scrutinize the alignment between clinical trial participant data and the population-based SEER Incidence.

Research Question 1:

Research Question 1: Is the racial/ethnic composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population being treated for that cancer?

Research Question 1_H: There is a significant disparity in the representation of racial/ethnic groups within the composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population being treated for that cancer.

Research Question 1_O: The representation of racial/ethnic groups within the composition of indication-specific CAR T-cell trials are proportional to the patient incident rate within the general population being treated for that cancer.

While Hispanic and non-Hispanic participants exhibit relatively equitable Ethnic enrolment in comparison to the population, there is a profound disparity when races are examined. This disparity is evidenced by a highly significant chi-square test result χ^2 (4) = 327.87, $p < .001$. American Indian/Alaska Native (AIAN) participants exhibit a 2.28-fold overrepresentation (EIR = 2.28, 95% CI: 0.89 to 2.30). In contrast, both Asian and Black participants are notably underrepresented, with EIR values of 0.57 (95% CI: 0.61 to 1.00) and 0.43 (95% CI: 0.55 to 0.89), respectively. This allows for a rejection of the null hypothesis; even though ethnicity displays a relatively balanced representation, the disparities concerning race highlights needed change in race representation in CAR-T cell studies.

Research Question 2:

Research Question 2: Is the gender composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?

Research Question 2_H: There is a significant difference regarding gender enrollment in the composition of indication-specific CAR T-cell trials compared to the patient incident rate within the general population being treated for that cancer.

Research Question 2_O: The gender composition of indication-specific CAR T-cell trials are proportional to the patient incident rate within the general population being treated for that cancer.

This study found a substantial gender disparity in gender composition across the five cancer types studied in clinical trials meeting inclusion criteria. Male participants are notably overrepresented with a calculated EIR indicating an enrolment 1.31 times higher than that general populations. The study rejection of the null hypothesis is further supported by a highly significant chi-square test result, χ^2 (1) = 131.07, $p < .001$ emphasizing the need for a more balanced gender representation in these trials.

Research Question 3:

Research Question 3: Is the patient age composition of indication-specific CAR T-cell trials proportional to the patient incident rate within the general population treated for that cancer?

Research Question 3_H: The age composition of indication-specific CAR T-cell trials are not proportional to the patient incident rate within the general population for that cancer

Research Question 3_O: The age composition of indication-specific CAR T-cell trials are proportional to that seen in the patient incident rate within the general cancer population

This study underscores the need for changes in trials enrolment to reflect the age of patients affected by the indications studied. Age disparities were significant, with a chi-square test result indicating a substantial divergence χ^2 (1) = 201.17, $p < .001$. Among participants aged 18-65 years, a noteworthy overrepresentation is observed, reflecting a 23.1-fold higher enrolment (EIR = 1.52, 95% CI: 1.11 to 1.30) in comparison to population rates. This results in a rejection of the null hypothesis and highlights the need for new strategies the produce generalizable results applicable to the cancer population.

Recommendations for Future Research

Lack of diversity in clinical trials can lead to biased results, as different populations may respond differently to treatments due to genetic, physiological, and socio-cultural factors. To promote diversity and inclusivity in CAR-T cell trials, future studies should encompass a wider range of indication-specific oncologic population. In this study, only 35 studies met the inclusion criteria as having published demographics for studies with results posted. Further analysis should include a larger portion of studies with this information with multiple studies for each year. This would be feasible if inclusion criteria are applied to published data and verified with data available through multiple databases including but not limited to *ClinicalTrials.gov*. These studies would require greater time and effort to meet this increased scope, but would be useful to judge progress, or setbacks in diverse, inclusive, and equitable representation in clinical trials.

Another recommendation for future research would be an analysis of data for diversity in clinical trials based on sponsor categories. An examination of the racial, ethnic, gender, and age representation in clinical trials sponsored by industry (such as pharmaceutical companies and biotechnology groups) vs trials sponsored by the NIH vs trials sponsored by research hospitals could show a difference in compliance to federal guidance and stated diversity goals.

Conclusion

The significant disparity in the representation of racial and ethnic groups, imbalances in gender enrollment, and disproportions in age composition within the configuration of indication-specific CAR T-cell trials, as compared to the patient incident rate within the general population being treated for that cancer, reveals a profound inequity in the development and accessibility of cutting-edge cancer therapies. This imbalance not only highlights an unjust and systemic issue in our healthcare system but also underscores the urgent need for reform and inclusivity in clinical research. To address this critical disparity, it is essential for the medical and research communities to acknowledge the problem, proactively work towards recruiting more diverse trial participants, and ensure that the benefits of CAR T-cell therapy and other innovative treatments are accessible to all, regardless of their racial or ethnic background. Discrepancies in gender representation reflect not only a systemic issue within the healthcare system but also a failure to address gender-specific healthcare needs potentiating sub-optimal care and higher adverse outcomes. Achieving gender parity in clinical trials is not just a matter of justice but a step toward delivering the best possible care for all patients.

The age composition disparity observed in indication-specific CAR T-cell trials, as compared to the patient incident rate within the general population being treated for that cancer, signals a significant incongruity in the development and accessibility of advanced cancer therapies. It is vital for the medical and research communities to recognize the need for more representative age enrollment in clinical trials, ensuring that the benefits of CAR T-cell therapy and other innovative treatments are accessible to patients across all age groups, particularly those demonstrating the greatest statistical need. Failing to rectify this disparity not only disregards the principles of equitable healthcare but also impedes our collective progress in providing effective

and tailored treatments for all individuals, regardless of their age. Achieving age-appropriate representation in clinical trials is essential to advancing the field of oncology and improving patient outcomes

The evidence presented in this paper underscores the undeniable reality of racial, ethnic, gender, and age disparities in oncology clinical trials. The profound underrepresentation of diverse populations within these trials not only hinders the pursuit of equitable healthcare but also obstructs progress in the field of oncology. The disparities outlined in this paper are not merely a matter of statistics; they are indicative of systemic issues that persist within our healthcare system. To address these disparities, it is imperative that stakeholders across the healthcare continuum, from researchers and clinicians to policymakers and advocates, collaborate in a concerted effort to rectify this longstanding problem. Achieving inclusivity in oncology clinical trials is not just a matter of justice and fairness; it is a matter of saving lives, improving patient outcomes, and advancing the fight against cancer. Only through collective and persistent action can we ensure that every individual, regardless of race, ethnicity, gender, or age, has an equal opportunity to benefit from advancements in cancer research and treatment.

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