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ORIGINAL ARTICLE

Ethnic origin in cancer clinical trials: overrated or understated? A comprehensive analysis of cancer clinical trials leading to FDA and EMA approvals between 2020 and 2022

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Background: Ethnic diversity in cancer clinical trials is essential to ensure that therapeutic advances are equitable and broadly applicable in multicultural societies. Yet, missing consensus on the documentation of ethnic origin, partially based on the complexity of the terminology and fear of discrimination, leads to suboptimal patient management of minority populations. Additionally, eligibility criteria, such as stringent laboratory cut-offs, often fail to account for variations across ethnic groups, potentially excluding patients without evidence-based justification.

Patients and methods: This analysis addresses this issue by investigating ethnic diversity in clinical trials that led to European Medicines Agency (EMA) and Food and Drug Administration (FDA) approvals between 2020 and 2022. Trials were identified from FDA and EMA databases, and available protocols and full-text publications were reviewed for documentation of ethnic background and eligibility criteria for organ function (bone marrow, liver, and renal). Descriptive statistics were applied to summarize the findings.

Results: Of the 56 trials analyzed, only two-thirds of primary result publications included information on ethnic origin. Caucasian and Asian groups were documented in most of those trials and also had the highest percentages of participants across trials, while other ethnic subgroups were less frequently documented and only made up a small proportion of trial participants. Eligibility criteria often set strict organ function cut-offs that did not consider variations among ethnic groups, potentially excluding minorities. The Cockcroft—Gault formula was frequently used to assess kidney function, despite its known limitations for multiethnic cohorts.

Conclusions: Ethnic homogenous participants and eligibility criteria that favor majority groups limit the applicability of findings in diverse populations, leading to inadequate patient management. While United States guidelines encourage inclusivity, similar recommendations are lacking in Europe. Thus European regulatory authorities, research organizations, and patient advocates should establish guidelines to improve ethnic diversity in cancer clinical trials, aligning research practices with the increasingly multicultural composition of European societies.

Key words: ethnic origin, ethnicity, race, clinical trials

INTRODUCTION

Background

The importance of ethnic origin in cancer treatment and research with respect to trial accessibility, differences concerning drug efficacy, and implementation of new therapeutic concepts in clinical routine has already been recognized decades ago.[1] Stringent inclusion criteria, such as strict laboratory values for the determination of bone marrow; liver and kidney organ function, which can vary significantly across ethnic subgroups; and social barriers, often limit access to clinical trials for ethnic minorities.[2,3] In addition, differences in drug tolerance, metabolism, and response to treatment underscore the need for inclusive trial designs.[4,5]

Moreover, incidence and mortality rates for malignant diseases of immigrants may shift with migration and lifestyle adaptation, but often do not change completely on these grounds.[6,7] This suggests that while environmental factors strongly influence cancer risk and outcome, they do not entirely override genetic differences, thus reinforcing

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the need for inclusivity of diverse ethnic backgrounds in trial design.[8-14]

As a result, clinical trial findings based on homogeneous patient populations may not be fully transferable to a multicultural society, thereby limiting the generalizability and equity of therapeutic advancements. Clinical trials should include patients with diverse ethnic backgrounds to minimize the risk that therapies are tailored exclusively to majority populations, which could unintentionally disadvantage minorities. However, global documentation of racial and ethnic background is diverse in academic research as consensus on the definition of race, ethnicity, ancestry, and migrational background is largely lacking. Although often used synonymously, these terms draw on different societal and scientific concepts and discourses. On the one hand, these terms want to draw attention to biological diversities between individuals. On the other hand, they also try to reflect sociocultural conditions, thereby leading to disregard of biological factors. Depending on the concrete subject, either the genetic or the socioeconomic and cultural aspects of this concept play a more prominent role; however, these factors influence each other, and therefore cannot be strictly dissociated. Yet, clear definitions of these terms are not provided by healthcare authorities. Even guidelines addressing the issue of missing diversity in clinical trials often do not specify the terms they are using.[15,16] In this paper, we use the term 'ethnic origin' to primarily reflect the role of biological and genetic aspects, yet we want to emphasize that terminology is complex and that we do not claim exclusiveness for this term. In the end, no single term or category is sufficient to describe the complexity embedded in biological as well as sociocultural origin and belonging, which is highly personal and sensitive.

These challenges contribute to considerable ambiguity and uncertainty regarding which data should be collected and the methodologies most appropriate for accurate and consistent documentation. In addition, fear of discrimination further prevents the documentation.[17] Thus insufficient classification and documentation of ethnic origin in everyday routine is frequent.[18-20] Although ethnic origin recording has improved over the last decades, data on ethnic subgroups concerning malignant diseases remain scarce. Even data collection in clinical trials is inconsistent.[21,22] Thus the Food and Drug Administration (FDA) issued a guideline in 2016[16] and the Multiregional Clinical Trials Center team addressed the challenges of diversity, inclusion, and equity in clinical research in a guidance document in 2020.[15] Moreover, ClinicalTrials.gov began requiring the reporting of ethnic origin information (if collected) during result submission for trials in 2017.[23] In addition, the American Society of Clinical Oncology (ASCO) and Association of Community Cancer Centers published a statement to achieve more ethnic diversity in cancer clinical trials.[24] However, European data and guidance on this issue are scarce with lacking guidance from the European Medicines Agency (EMA) and the EudraCT clinical trials database.

This paper addresses this issue by investigating ethnic diversity in clinical trials, that led to EMA and FDA approvals between 2020 and 2022, and delving into the underlying challenges and complexities associated with this crucial topic. It aims to promote heightened awareness by providing a succinct overview of the landscape of ethnic diversity in modern cancer trials and elaborating on common complexities that exacerbate this issue.

METHODS

This manuscript has a closer look at ethnic diversity in cancer clinical trials, which led to FDA and EMA drug approvals for novel therapeutic strategies in patients with cancer between 2020 and 2022. After identifying these trials through official approval information on the FDA website,[25] the medicine's approval status was verified based on the respective trial on the EMA website.[26] If both authorities had granted their approval between 1 January 2020 and 31 December 2022, the cancer clinical trial was included in this analysis. We then scanned the full-text publications and, if available, also the clinical trial protocols for the documentation of ethnic background, laboratory eligibility criteria associated with ethnic origin (bone marrow function, liver function, and kidney function), and information on pharmacodynamic or pharmacokinetics with respect to ethnic origin.

In accordance with the United States National Cancer Institute, we adopted the classification of five primary racial/ethnic groups as provided in the Annual Report to the Nation on the Status of Cancer ('non-Hispanic white', 'non-Hispanic black', 'non-Hispanic American Indian/Alaska Natives', 'non-Hispanic Asian/Pacific Islanders', and 'Hispanics').[27]

Descriptive statistics were used to summarize the characteristics of the included clinical trials, focusing on the inclusion of ethnic subgroups, and on the distribution of laboratory eligibility criteria for organ function assessment. Categorical data were reported as frequencies and percentages. Data visualizations with boxplots, bar charts, and pie charts were utilized to illustrate trends and disparities in racial and ethnic subgroups across trials.

Afterward, a literature review was conducted to identify possible factors that influence the documentation and diversity of ethnic origin in clinical trials.

RESULTS

Characteristics of trials evaluated in this manuscript and detailed information on each trial are displayed in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2024.104093. In addition, a flow diagram of the respective clinical trial selection is available in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.104093.

For four clinical trials, no study protocol was available.

Although most clinical trials included in this manuscript mentioned the documentation of ethnic origin in their

protocol analysis plans (47 trials), only two-thirds of the primary result publications contained this information about the patient population (37/56 trials). These findings emphasize that, despite recommendations from regulatory bodies such as the FDA and professional organizations such as ASCO, the routine publication of ethnic origin remains an elusive and underutilized practice within academic research.

The inclusion of ethnic subgroups in these 37 trials is visualized in Figure 1. Caucasian and Asian groups are included in 94.6% of the trials, reflecting a high level of participation in the clinical research landscape. Black patients were included in only 29.7% of trials, highlighting a significant gap in the inclusion of this demographic. Hispanic and American Indian/Alaska natives were mentioned only in a small portion of trials. Around half of the trials had categories labeled 'other' and/or 'missing', which reflects the complexity of gathering this highly sensitive information.

Moreover, 27/37 of these cancer clinical trials, show a predominantly Caucasian patient population of >50%. In 12 trials, the Caucasian population was ≥75%. There is a very low participation of Black, Hispanic, and Native American populations across most trials that included these subgroups, often <5%. The distribution of ethnic origin in percentages is visualized with boxplots in Figure 2 and available for each trial separately in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.104093.

Concerning laboratory values to assess organ function for eligibility, Table 1 shows laboratory assessment of bone marrow function according to trial protocols. Hemoglobin levels of 9.0 g/dl (40 trials), platelet levels of 100 g/l (40 trials), and absolute neutrophile count (ANC) levels of 1.5 g/l (47 trials) were the most commonly used cut-offs. White blood cell count and lymphocyte count were only mentioned in the eligibility criteria of 11 and 3 trials, respectively. One trial (FIGHT-202) did not specify concrete values for hematological eligibility assessment in the available protocol.

Liver function was evaluated with aspartate transaminase/alanine transaminase, bilirubin, coagulation parameters, and albumin and is available in Table 2. The most frequently used cut-off levels for aspartate transaminase/alanine transaminase were 2.5 × upper limit of normal (ULN; 26 trials) and for total bilirubin 1.5 × ULN (45 trials). Alkaline phosphatase, coagulation parameters, and albumin were only used for eligibility in 9, 18, and 7 trial protocols, respectively.

Kidney function evaluation criteria are available in Table 3. Creatinine serum levels were the primary eligibility criterion for renal function in 34 trial protocols, 29 of which had a cut-off level of 1.5 × ULN. Only four trials had a cut-off level of 2.0 × ULN and one trial had a cut-off level of 1.25 × ULN. Creatinine clearance (CrCl) and glomerular filtration rate (GFR) were recommended for eligibility assessment in 47 trials. Concerning the methods applied, the Cockcroft—Gault method (27 trials) and per institutional standards (13 trials) or either the Cockcroft—Gault method or per institutional standards (1 trial) were the most commonly used. In five trial protocols, the method was not specified and only one trial recommended Modification of Diet in Renal Disease (MDRD). Only in 18 trial protocols, the evaluation of renal function was solely based on CrCl or GFR without evaluation of serum creatinine levels. In scope of the cut-off levels of CrCl/GFR, 60 ml/min was used in 11, 50 ml/min in 17, 45 ml/min in 3, 40 ml/min in 3, 35 ml/min in 1, and 30 ml/min in 12 trial protocols, respectively.

None of the reviewed protocols or publications addressed differences in pharmacokinetics or pharmacodynamics due to ethnic origin.

DISCUSSION

Documentation of ethnic origin

Details about racial/ethnic background were missing in one-third of investigated clinical trials. The prevalence of ambiguity regarding the terminology might contribute to this high percentage. The lack of consensus may hinder standardized practices and widespread adoption in reporting.

In addition, different national and cultural contexts influence classifications and might result in disparities between the use of certain terms. A systemic literature review and subsequent quantitative content analysis of life science papers from German research institutes showed that the term race is used comparatively rarely by German authors. This is most probably associated with the history of German scientific racism and the persecution and extermination policies pursued under National Socialism, which German-speaking authors want to distance themselves from.[28]

Another bias concerning diversity in research manuscripts is that clinical trials are often limited to geographical regions based on study sites. However, human migration and mobility are global phenomena with possible repercussions on the recruitment of patient populations into clinical trials. While specific data on the percentages of racial/ethnic subgroups in Europe are lacking, European society is becoming increasingly diverse. The United Nations globally estimated that in 2020 there were ∼281 million international migrants, which equates to 3.6% of the global population.[29] Although the coronavirus disease 2019 (COVID-19) pandemic has slowed down global migration, the scale is constantly increasing. In recent years, Europe has become the prime destination for international migrants, reaching 87 million, corresponding to 30.9% of the international migrant population in 2020,[29] whereas the Annual Report on Migration and Asylum 2021 by the European Migration Network stated that there is an up to 14% share of third-country nationals in the European Union and Norway.[30] In addition, there has been a diversification in origin countries of emigrants leading to an expanding ethnic diversity in high-income countries.[29] Therefore the indication of geographical regions based on study sites is not equivalent to ethnic background.

Furthermore, predefined racial/ethnic subgroups in clinical trials are often insufficient and not transferable between regions. In the United States, documentation of

Figure 1. Inclusion of ethnic subgroups across clinical trials. The pie charts present how various ethnic groups were represented in the 37 clinical trials that led to drug approvals by the European Medicines Agency and the Food and Drug Administration between 1 January 2020 and 31 December 2022 and provided information about ethnic origin. Each chart represents a specific ethnic group, showing the proportion of trials that represented (green) or did not represent (purple) participants from that group.
AI Native, Alaska Natives; Am Indian, American Indian.

'non-Hispanic white', 'non-Hispanic black', 'non-Hispanic American Indian/Alaska Natives', 'non-Hispanic Asian/Pacific Islanders', and 'Hispanics' is provided by the National Cancer Institute, which tries to combine racial and ethnic aspects.[27]

In contrast, there is currently no European consensus on how to refer to ethnic origin in clinical trials. Yet, American guidelines cannot be transferred to other regions of the world due to differences in biological as well as sociocultural backgrounds. The complexity of nontransferability between the United States and Europe is emphasized by an estimation of >80 ethnic subgroups in Europe alone.[31] Whether all of these subgroups must be clearly distinguished or could be more broadly grouped in clinical trials remains unclear, as data on the association of different ethnic backgrounds and study outcomes are lacking. However, it is evident that

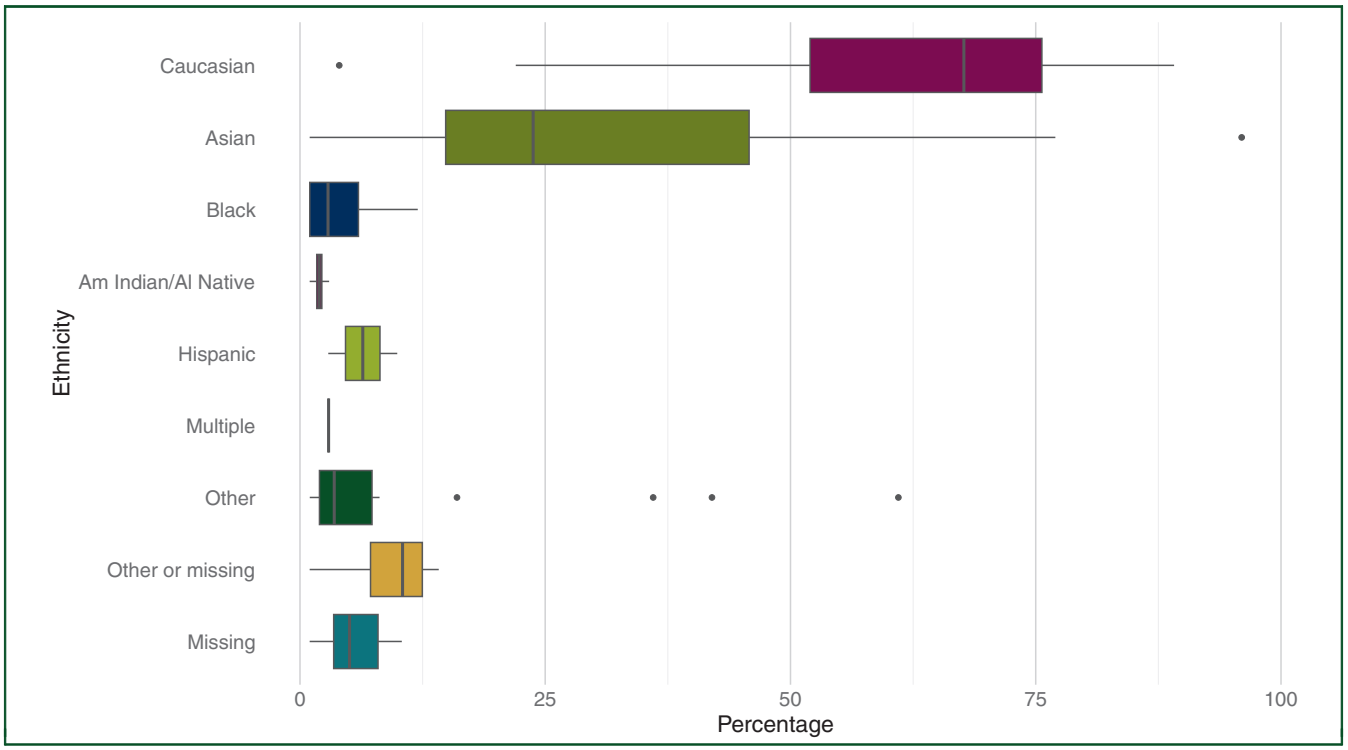

Figure 2. Distribution of ethnic subgroups across clinical trials. These boxplots visualize the distribution of various ethnic subgroups in percentages across 37 clinical trials as mentioned in the respective results section [Caucasian (35 trials), Asian (35 trials), Black (26 trials), American Indian (Am Indian)/Alaska native (AI Native; 4 trials), Hispanic (2 trials), multiple (2 trials), other (20 trials), other or missing (8 trials), and missing (18 trials)]. Each ethnic category is represented as a distinct box.

European recommendations must be implemented to improve documentation and thereby gather information on the influence of genetic backgrounds on cancer clinical trials. The results from these trials may then provide guidance to further improve accuracy of ethnic origin documentation.

Laboratory parameters

Reference intervals for clinical laboratory analyses are usually developed in majority populations and frequently overlook differences across ethnic groups. Thus misinterpretation of laboratory organ function tests for non-Caucasian sections of the population presents common difficulties in patient care.[2,3] Yet, laboratory assessments, including evaluations of bone marrow, liver, and kidney function, are a major cornerstone for determining eligibility in clinical trials. These cost-effective tests provide key insights into a patient's overall health and ability to tolerate treatment. Stringent cut-off levels for these functions are often established to ensure patient safety and to optimize the likelihood of trial success by minimizing adverse effects. However, these strict criteria are not adapted for diverse ethnic origins and, thus, might lead to disadvantages for minorities.[32]

Hemoglobin, white blood cell, platelet counts, and serum bilirubin levels have been known to be lower in black individuals compared with whites for decades.[33-35] Especially, differences in ANC and benign neutropenia might lead to systemic exclusion of ethnic subgroups. Yet, the important determination is not how many neutrophils are present in the peripheral blood, but whether the bone marrow can produce enough normally functioning cells when needed and, thus, patients with benign neutropenia show no evidence of increased susceptibility to infection or any other adverse effect.[36] Although over the past decades, more and more evidence has been gathered, that genetic polymorphisms lead to these increased ANC without any clinically significant disadvantage,[37-39] eligibility criteria still include strict levels independent of ethnic background (Table 1). Characterizing common phenotypes in non-white populations as abnormal due to their rareness in patients of European descent contributes to systemic racism and has to be overcome in everyday clinical care and in clinical trials.[40] Yet, recommendations to lower thresholds are lacking.

Furthermore, it has been shown that patients were discriminated regarding their participation in clinical trials due to kidney function tests[41]: For >20 years, it has been known that creatinine levels differ depending on sex, age, muscle mass, diet, and ethnic origin.[42] Yet, strict creatinine cut-off levels are still a frequently used tool in eligibility criteria for cancer clinical trials to assure patient safety. In recent years, estimated GFRs based on CrCl have gained ground in trial designs as they provide more accurate surrogate parameters for kidney function than creatinine values themselves. However, depending on the calculation, estimations can differ vastly, especially among ethnic subgroups.

Table 1. Laboratory eligibility criteria on bone marrow function of clinical trials leading to drug approvals by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) between 1 January 2020 and 31 December 2022[a]

Characteristic	*N* = 56
Hemoglobin (g/dl)	
≥10.0	8 (15.4)
>9.0	3 (5.8)
≥9.0	37 (71.2)
≥8.5	1 (1.9)
≥8.0	2 (3.8)
Not required	1 (1.9)
No protocol available	4
Platelets (g/l)	
>150	1 (1.9)
≥150	1 (1.9)
≥100	40 (76.9)
≥90	1 (1.9)
≥75	8 (15.4)
Not required	1 (1.9)
No protocol available	4
White blood cells (g/l)	
≥3.0	1 (1.9)
≥2.5	1 (1.9)
≥2.0	9 (17.3)
Not required	41 (78.8)
No protocol available	4
Absolute neutrophil count (g/l)	
>2.0	1 (1.9)
≥1.5	47 (90.4)
≥1.0	3 (5.8)
Not required	1 (1.9)
No protocol available	4
Lymphocyte count (g/l)	
≥0.5	3 (5.8)
Not required	49 (94.2)
No protocol available	4

[a]Values are presented as *n* or *n* (%).

Table 2. Laboratory eligibility criteria on liver function of clinical trials leading to drug approvals by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) between 1 January 2020 and 31 December 2022[a]

Characteristic	*N* = 56
Aspartate transaminase/glutamic-oxaloacetic transaminase and alanine transaminase/glutamic-oxaloacetic transaminase (× ULN)	
≤1.0	1 (1.9)
≤1.5	1 (1.9)
<2.5	1 (1.9)
≤2.5	25 (48.1)
≤3.0	22 (42.3)
≤5.0	2 (3.8)
Not required	0 (0.0)
No protocol available	4
Alkaline phosphatase (×ULN)	
<2.0	1 (1.9)
≤2.5	4 (7.7)
≤3.0	2 (3.8)
≤5.0	2 (3.8)
Not required	43 (82.7)
No protocol available	4
Bilirubin (×ULN)	
≤1.0	5 (9.6)
≤1.5	45 (86.5)
≤2.0	1 (1.9)
≤3.0	1 (1.9)
Not required	0 (0.0)
No protocol available	4
Coagulation (×ULN)	
INR and aPTT ≤1.5	2 (3.8)
INR or PT and aPTT ≤1.5	12 (23.1)
INR or PT ≤1.5	1 (1.9)
INR or PT and aPTT or PTT ≤1.5	1 (1.9)
INR ≤1.5	1 (1.9)
INR or aPTT ≤2.0	1 (1.9)
Not required	34 (65.4)
No protocol available	4
Albumin (g/dl)	
≥2.5	1 (1.9)
≥2.8	1 (1.9)
≥3.0	4 (7.7)
>3.0	1 (1.9)
Not required	45 (86.5)
No protocol available	4

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; ULN, upper limit of normal.
[a]Values are presented as *n* or *n* (%).

This analysis of available clinical trial protocols underlines that the Cockcroft—Gault—formula is still the most common calculation (Table 3), although it is proven to have major disadvantages compared with MDRD or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[43-46] While age and gender are included in all three calculations, only MDRD and an older version of the CKD-EPI (2009 CKD-EPI) incorporate black ethnicities in their estimations. However, several study results emphasize the importance of such differentiations based on ethnic origin.[47-49]

Thus the National Kidney Foundation recently endorsed the 2021 CKD-EPI equation without a coefficient for ethnic origin to improve accuracy throughout the general multi-ethnic population, feasibility, and discrimination of other ethnic subgroups.[50] Yet, the novel calculation led to lower creatinine-based estimated GFR values for black persons and higher values for 'non-black' persons.[51] Consequently, the former are potentially excluded from participation in clinical trials.[52]

It must be highlighted, however, that the recommendation of the 2021 CKD-EPI is not to use the creatinine-based but the creatinine and cystatin C-based equations to improve GFR estimations across ethnic subgroups, which did not increase population estimates of chronic kidney disease prevalence among blacks.[50] The combination of creatinine and cystatin C in the 2021 CKD-EPI equation estimated measured GFR more accurately than CKD-EPI equations with either the creatinine or cystatin C level alone and led to smaller differences from measured GFR between ethnic groups.[50,53]

In addition, the implementation of the novel 2021 CKD-EPI, which is based on data from the United States, in European patients raised the question of whether estimations are transferable between multicultural populations. Delanaye et al.[54,55] showed that the novel 2021 CKD-EPI might be suboptimal for the management of European patients.

An equation based on European patients is the full-age spectrum European Kidney Function Consortium (EKFC) equation. It showed more accuracy across different age groups than MDRD or 2009 CKD-EPI. However, no black patients were included in the cross-sectional analysis.[56]

Table 3. Laboratory eligibility criteria on kidney function of clinical trials leading to drug approvals by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) between 1 January 2020 and 31 December 2022[a]

Characteristic	*N* = 56
Serum creatinine (mg/dl)	
≤1.25	1 (1.9)
<1.5	1 (1.9)
≤1.5	28 (53.8)
≤2.0	4 (7.7)
Not required	18 (34.6)
No protocol available	4
CrCl/glomerular filtration rate (ml/min)	
≥30	10 (19.2)
>30	2 (3.8)
≥35	0 (0.0)
>35	1 (1.9)
≥40	3 (5.8)
≥45	1 (1.9)
>45	2 (3.8)
≥50	12 (23.1)
>50	4 (7.7)
≥51	1 (1.9)
≥60	9 (17.3)
>60	2 (3.8)
Not required	5 (9.6)
No protocol available	4
Method	
Cockcroft–Gault	27 (51.9)
Institutional standard	13 (25.0)
Institutional standard or Cockcroft–Gault	1 (1.9)
Modification of Diet in Renal Disease	1 (1.9)
Not specified	5 (9.6)
Not required	5 (9.6)
No protocol available	4

[a]Values are presented as *n* or *n* (%).

A follow-up study investigating the EKFC formula with cystatin instead of creatinine assessed the calculation in multicultural cohorts from Europe, the United States, and Africa. It showed that this equation improved the accuracy of GFR assessment over that of the creatinine-based 2009 CKD-EPI and the 2021 creatinine-based, cystatin-based, creatinine- and cystatin-based CKD-EPI equations.[57]

Yet, cystatin C is still not routinely used in daily clinical practice or clinical trials, due to increased costs with little improvement of kidney disease diagnosis and risk prediction.[58] Thus although the exclusion of ethnic origin in the cystatin- and creatinine-based version of the score seems feasible, there is an ongoing scientific discussion about whether the exclusion of ethnic origin in the widely used creatinine-based version of the equation was appropriate.[59]

Large clinical trials investigating several different kidney function tests in multiethnic patients with cancer have not yet been published. As different calculations might influence the estimated GFR, especially concerning ethnic subgroups, but often do not lead to a clinically significant paradigm change in chronic kidney disease treatment for most patients, funding is hard to receive.[58] Therefore recommendations on kidney function tests for cancer clinical trials concerning ethnic disparities are still lacking. However, as different estimated GFR equations might change the eligibility for patients with diverse ethnic backgrounds, this issue is important for clinical trials themselves and for the transferability of results to multiethnic real-world cohorts. Further investigation is needed to reduce discrimination of specific ethnic subgroups while assuring patient safety in clinical trials.

Pharmacokinetics, pharmacodynamics, and pharmacogenetics

Ethnic origin in the sense of genetic background can have substantial impact on pharmacokinetics of drugs.[60] Pharmacokinetic factors which can be expected to potentially exhibit ethnic differences are often based on hepatic metabolism, renal tubular secretion, and protein binding, as well as first pass metabolism.[4,61] Genetic variations are surmised to be responsible for these disparities,[62] which can be further amplified by socioeconomic background, diet, and environment.[63] However, data on the association of changes in pharmacokinetics and differences in pharmacodynamics, drug response, and adverse events remain scarce as clinical trial populations often lack ethnic diversity.[64] Hence patient management might be compromised by an inadequate understanding of drug safety and efficacy in ethnic minorities.

Ethnic origin and patient management in clinical trials

Reporting of ethnic origin, although recommended by FDA and ASCO, is often not routinely carried out in cancer clinical trials. Reasons for nonreporting are unclear, yet might include missing definitions of terminology, lack of documentation standardization, personal data protection, patient privacy, and fear of discrimination.[65,66] As awareness of data protection and privacy rights has been raised in recent years, patients might be skeptic about sharing personal data.[67] In addition, discrimination in healthcare is not only an appalling and mournful part of history, but also an ongoing problem, which lacks sufficient measurements[68] and consequences. As a result of personal data protection and discrimination, ethics committees often seem reluctant to address the issue of insufficient reporting of ethnic origin. Besides the recommendations from the FDA and ASCO, further statements by authorities or ethics committees are scarce. The lack of recommendations promotes patients' reluctance to provide data on ethnic origin and healthcare workers' reluctance to ask about ethnic origin, which may lead to insufficient reporting in clinical trials.

When reported, patient populations of clinical trials often do not represent the ethnic diversity of real-world cohorts. Based on the demographic data provided by the 2023 Census as reported by the Census Bureau, the distribution of racial background in the United States is 75.3% white [58.4% white (non-Hispanic)], 13.7% black or African American, 6.4% Asian, 1.3% American Indian and Alaska Native, 0.3% Native Hawaiian and Other Pacific Islander, and 3.1% reported multiple races. In addition, 19.5% identified as Hispanic or Latino regardless of race.[69] Yet, a substantial proportion of clinical trials in our analysis did not even document these racial subgroups (Figure 1), which may

skew the applicability of study results. By contrast, a diverse participant pool ensures that clinical findings and drug safety data are relevant and effective across all populations.

Although Europe has become the largest destination for international migrants, approvals of EMA are largely based on trial data from mostly Caucasian cohorts predominantly recruited in the United States. Despite cancer risk profiles of immigrants who adapt to their new home region, there is significant evidence from multiple world regions and diverse cancer entities that not only recently immigrated people, but also long-term established ethnic subgroups within societies are affected by disparities in cancer incidence, mortality, and tumor biology.[6,7,10,70-72] Thus these inequities need to be highlighted and addressed. Lack of diversity in clinical trials may lead to inadequate assumptions about the efficacy of cancer drugs for minorities and consequently to inferior patient management.

Yet, eligibility criteria including strict laboratory cut-offs in neglect of ethnic differences might strengthen further exclusion of minorities. In particular, stringent ANC cut-off levels are known to exclude large section of non-Caucasian patients and, thus, should not be used to evaluate bone marrow organ function.[37] Furthermore, kidney function tests are widely known to be influenced by ethnic origin and efforts to improve GFR calculations for multiethnic societies have been established.[50,56] So far, cystatin C-based estimations seem to be the most adequate independent of ethnic background.[50] However, evaluation of cystatin C is not routinely carried out due to cost—benefit ratios in connection with chronic kidney disease classification and treatment.[58] Therefore GFR calculations based on creatinine are still widely used. Concerning practice-changing clinical trials of the past few years, the most frequently used equations are the Cockcroft—Gault formula or equations as per institutional standard. Both options pose major disadvantages, as the Cockcroft—Gault calculation has been proven to be inferior compared with MDRD and CKD-EPI and the use of different calculations within the same trial might lead to biases with less comparability between patients.[43-46] Despite discussions about whether MDRD, EKFC, 2009 CKD-EPI with ethnic origin coefficient, or 2021 CKD-EPI is the most accurate creatinine-based equation for multiethnic societies, it is evident that each of them is superior to using the Cockcroft—Gault method or multiple calculations in a cancer clinical trial. Depending on the ethnic structure of trial populations, careful evaluation of the most appropriate kidney function test should be carried out. Moreover, overly strict cut-off levels for organ functions, which are not based on patient safety data concerning the investigational medicinal product, should be avoided to minimize discrimination of ethnic subgroups and improve transferability to real-world cohorts. Thus overcoming strict eligibility criteria, where patient safety allows it, may lead to greater ethnic variety and consequently improve patient management.

Conclusion

Missing documentation and lack of ethnic diversity in cancer clinical trials lead to inadequate translation of study results to everyday patient care in ever-diversified societies. To improve patient management in increasingly multicultural Europe, clinical trials need to be more inclusive of ethnic minorities and reporting needs to be improved. In addition, stringent eligibility criteria that favor majority populations need to be addressed.

It has to be highlighted that recommendations from European authorities concerning ethnic diversity in clinical trials are lacking. Although there are efforts to address this topic in some United States guidelines, these cannot be adopted for European cohorts as ethnic subgroups differ vastly between continents. Thus it is of utmost importance that European regulatory authorities, cancer research organizations, and patient representatives join efforts to establish recommendations concerning ethnic diversity for clinical trials carried out in Europe.

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