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WIDER PERSPECTIVES

Are we ignoring sex differences in haematological malignancies? A call for improved reporting

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Summary

There are clear sex-based differences in the incidence, risk factors and mortality of most haematologic malignancies (HM). Despite known differences in physiology, haematopoiesis, molecular profiles, drug pharmacokinetics, treatment-related toxicities and treatment experience, males and females receive standardized and identical treatment for most HMs. Previous published work has demonstrated disparities in female representation in cancer clinical trials and highlighted a paucity of information on differential treatment outcomes and toxicities by sex. We analysed references of 182 clinical trials which form the basis of recent treatment guidelines from the National Comprehensive Cancer Network and found a minority (17/9.3%) did not report the sex distribution of trial participants. However, a majority (165/90.6%) did not report sex-disaggregated outcomes. Of those that did, 36.5% showed outcome differences by sex. Academic leadership by women in the assessed trials as well as in guidelines committees was disproportionately lower than their representation in the profession. We call on all clinical trials leaders, consortia and guideline builders to include sex-disaggregated data in their analyses, reporting these in a transparent manner (as per regulations mandating such reporting), and for investigators to assess whether aetiological factors differ by sex. These actions will enhance personalized prevention, therapy and follow-up.

KEYWORDS

clinical trials reporting, gender, guidelines, leukaemia, lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative neoplasms, sex

INTRODUCTION

Biological factors such as age, renal and hepatic function, body surface area or weight and baseline blood counts are universally taken into account when designing and adjusting treatment for haematological malignancies (HM). However, despite increasingly recognized differences in disease risk, prognosis and treatment toxicity between males and females, sex and gender are rarely taken into account in treatment planning for these diseases. The influence of sex and sex hormones, as well as differential X-chromosome inactivation on stem cells, haematopoiesis and peripheral blood counts is widely accepted.[1] Sex-related differences in the epidemiology, presentation, molecular profile and prognosis of haematological malignancies are frequently reported, yet efforts towards understanding the mechanisms underlying these differences are limited.

Admittedly, there are areas in which sex and gender (see Box 1 for usage and definitions) have been recognized as making a difference in clinical practice. These include decision-making based on normal ranges of blood parameters, fertility issues, contraception and pregnancy. There are additional particular instances where sex-related clinical decisions come into play, such as in the choice of HLA-matched

BOX 1 Use of terms 'gender' and 'sex'

According to the World Health Organization (WHO), 'Gender refers to the characteristics of women, men, girls and boys that are socially constructed. This includes norms, behaviours and roles associated with being a woman, man, girl or boy, as well as relationships with each other' … 'Gender interacts with but is different from sex, which refers to the different biological and physiological characteristics of females, males and intersex persons, such as chromosomes, hormones and reproductive organs'.[81] Data on gender are particularly lacking in studies of cancer aetiology, treatment and prognosis. Furthermore, the science of cancer epidemiology, treatment and prognosis by sexual identity or orientation is in its infancy.[82]

In this paper, when discussing patient or participant characteristics we relate to two sexes, male and female, as binary, since the bulk of the medical literature refers only to two sexes. When referring to characteristics of investigators, authors, and guideline leaders, we refer to gender.

This is in keeping with the designation of sex/gender according to the NCCN Guidelines: 'NCCN Guidelines will continue to use the terms men, women, female and male when citing statistics, recommendations or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses'.[43]

bone marrow donors. It is recognized that not only the risk of graft-versus-host disease but also the graft-versus-leukaemia effect may be enhanced when using female donors to male recipients of allogeneic stem cell transplants[2,3] and this may play a role in decision-making. However, these examples are rare.

In 2018, the European Society of Medical Oncology (ESMO) sponsored the 'Gender Medicine Meets Oncology' Workshop and published its review and consensus statement in 2019.[4] The report dealt with differences in tumour biology, immune system activity, body composition and pharmacology of anticancer drugs, sex and gender differences of non-sex-dependent cancers and methodological challenges in the analyses of sex and gender differences in clinical trials in oncology. The group reviewed published basic and clinical data pointing to sex-related differences that may impact treatment choice and prognosis in the field of cancer. The report concluded with six consensus statements, comprising recommendations ranging from consideration of sex differences in the design, analysis and publication of clinical and preclinical studies, careful attention to pharmacokinetic and pharmacodynamic differences by sex during the process of drug development, inclusion of sex differences in drug pharmacokinetics and outcomes in oncology curricula and informing patients of sex-related differences in treatment outcomes or toxicities, among others. The ESMO consensus statement dealt mainly with solid tumours, with the exception of lymphoma, and was issued 5 years ago, and therefore warrants re-examination from the point of view of HM.

The attention to sex- and gender-related issues of ESMO, a large and important professional society, comes on the heels of policies and regulations, such as the National Institutes of Health directive to include sex as a basic biological variable (SABV) in clinical and preclinical studies.[5] This follows years in which basic and mechanistic medical research systematically relied on male biological models, despite the fact that even at the level of cell lines, the sex origin of the cell makes a difference.[6]

A considerable amount of basic and epidemiologic research effort has been devoted to the role of sex in the pathogenesis and outcome of HM. A non-time-limited PubMed search of keywords "sex or gender and leukaemia", "sex or gender and lymphoma", "sex or gender and multiple myeloma" in humans yielded 8523, 9541 and 1784 entries, respectively (though not all are specifically relevant to the core topic). Several review articles on gender issues have been published. And yet, it appears that sex, unlike age, has not entered the active consciousness of the practicing haematologist in day-to-day decision-making and is overlooked in the major sources of information for clinicians treating HM, including textbooks, clinical trial reports and practice guidelines. Bibliometric and systematic quantitative analyses of published clinical trials[7,8] and qualitative analyses of textbooks[9] demonstrate a dearth of sex-specific information regarding disease mechanisms, treatment effects and survival in oncology in general, and HM in particular.

With this lacuna in mind, in this perspective, we will briefly review some of the existing knowledge and knowledge gaps regarding sex differences in the incidence, mortality, aetiology, clinical presentation and prognosis of HM, as well as the toxicity of treatment and other sex-specific effects. We will then present a bibliometric analysis in which we examine the representation of women both as clinical trial participants and lead investigators in published trials which form the basis of treatment recommendations according to the National Comprehensive Cancer Network (NCCN) guidelines, while also assessing the gender profile of the leadership of these guideline committees. These guidelines are commonly used by oncology practitioners,[10] are considered by many to represent a standard of care and are frequently updated. The methods for this analysis are described below (Box 2). Finally, we offer some recommendations relating to

BOX 2 Bibliometric analysis of NCCN guidelines—methods

We evaluated the latest version of the NCCN guidelines[62] for 17 major HM entities, reported by 11 guideline committees.

Guideline-level assessment: We examined the gender make-up of the guideline committees including study chair and co-chair, number of members and proportion of women members. We determined whether there were sex-related recommendations in the body of the guideline using search terms 'sex' and 'gender' in each guideline.

Clinical trial-level assessment: We examined the references cited in the guidelines for clinical trials that formed the basis for treatment recommendations. At least 10 trials were chosen for review from each diagnostic category (except Burkitt lymphoma, where there were fewer recommended treatment options based on trials), representing a variety of therapeutic options. The selection of trials for review was made using either consecutive eligible references in a list of recommended therapies or alphabetical or numerical lists of references in the guideline. We focused on adult trials and those dealing with first-line treatments. We included only reports of clinical trials, excluding retrospective reviews or case series. We excluded reports that were based on abstracts only, as they rarely include a detailed description of participant characteristics. If the reference in the NCCN guideline was a late report of a previously published trial, we accessed the original report in order to examine the sex distribution of participants. The methods section of each trial was scanned for participant eligibility. Text and tables were scanned for the sex distribution of participants. Usually, only the number of male participants was reported, so the number and proportion of female participants was calculated from the total enrolled and percent of males. When the sex distribution was not shown in the body of the article, we scanned the supplement. We compared the ratio of males to females in the trial with the expected ratios for that disease based on population-based data from the Surveillance, Epidemiology and End Results (SEER) Registry for lymphoid malignancies,[15] ALL,[65] CML, AML and MDS[63]; and the French Registry for MPN (Myelofibrosis).[64]

We scanned the full text of the articles and their supplements for any other mention of sex-related results such as toxicities or differential treatment results using key words sex, gender, male or female. Finally, we noted whether the first author of the trial was a man or a woman via an assessment of names, a search of websites and social media data. Assessment of clinical trials was performed independently by two authors, and discrepancies were resolved by discussion. All raw data can be found in Table S1. The list of publications of reviewed trials can be found in Data S2.

gender and sex issues for educators, researchers and practitioners treating HM.

SEX DIFFERENCES—WHAT IS KNOWN?

Male to female ratios in incidence and mortality rates of haematological malignancies

Based on global data, substantial disparities exist in the incidence of most cancers, with a clear male predominance (except thyroid, breast and reproductive cancers[11]). Specific to HM, Cartwright and co-authors[12] reported male:female sex ratios above 1 for non-Hodgkin lymphoma, Hodgkin lymphoma, chronic lymphocytic leukaemia (CLL), acute lymphoblastic leukaemia (ALL) and multiple myeloma for nearly all age groups from incidence data collected between 1984 and 1993 in England and Wales. Similarly, using the Swedish Lymphoma Register database from 2000 to 2019, Radkiewicz et al.[13] reported that males represented over 50% of new cases in all non-Hodgkin lymphoma categories except marginal zone and primary mediastinal lymphoma. Subsequently, Zhang et al.[14] examined the global incidence of HM, reporting increased male:female incidence ratios at most ages except for the oldest-old. Furthermore, for some malignancies, namely leukaemia, myeloma and Hodgkin lymphoma, the ratio has increased over time (see Figure 1, panels A, C, E, G). Subtype-specific incidence data on lymphoid malignancies reveal that the male:female ratio may vary substantially by age.[15] A recent report providing data from 185 countries showed a male:female incidence ratio above 1 for ALL, acute myeloid leukaemia (AML), CLL and chronic myeloid leukaemia (CML) for all age groups, geographic regions and human development index (HDI) categories, which takes into account life expectancy, education and income.[16]

In both lymphomas[13] and leukaemia, the differences in blood cancer incidence also translate, in general, into parallel gaps in mortality (Figure 1, panels B, D, F, H[14]). Thus, females are deemed to be at a relative advantage regarding both the risk of these diseases and the mortality associated with them. Mortality-to-incidence ratios may reflect access to care, treatment intensity and response to treatment. For leukaemia, these ratios range from 0.4 to 0.76 depending on continent, region or HDI but are similar between males and females globally.[17]

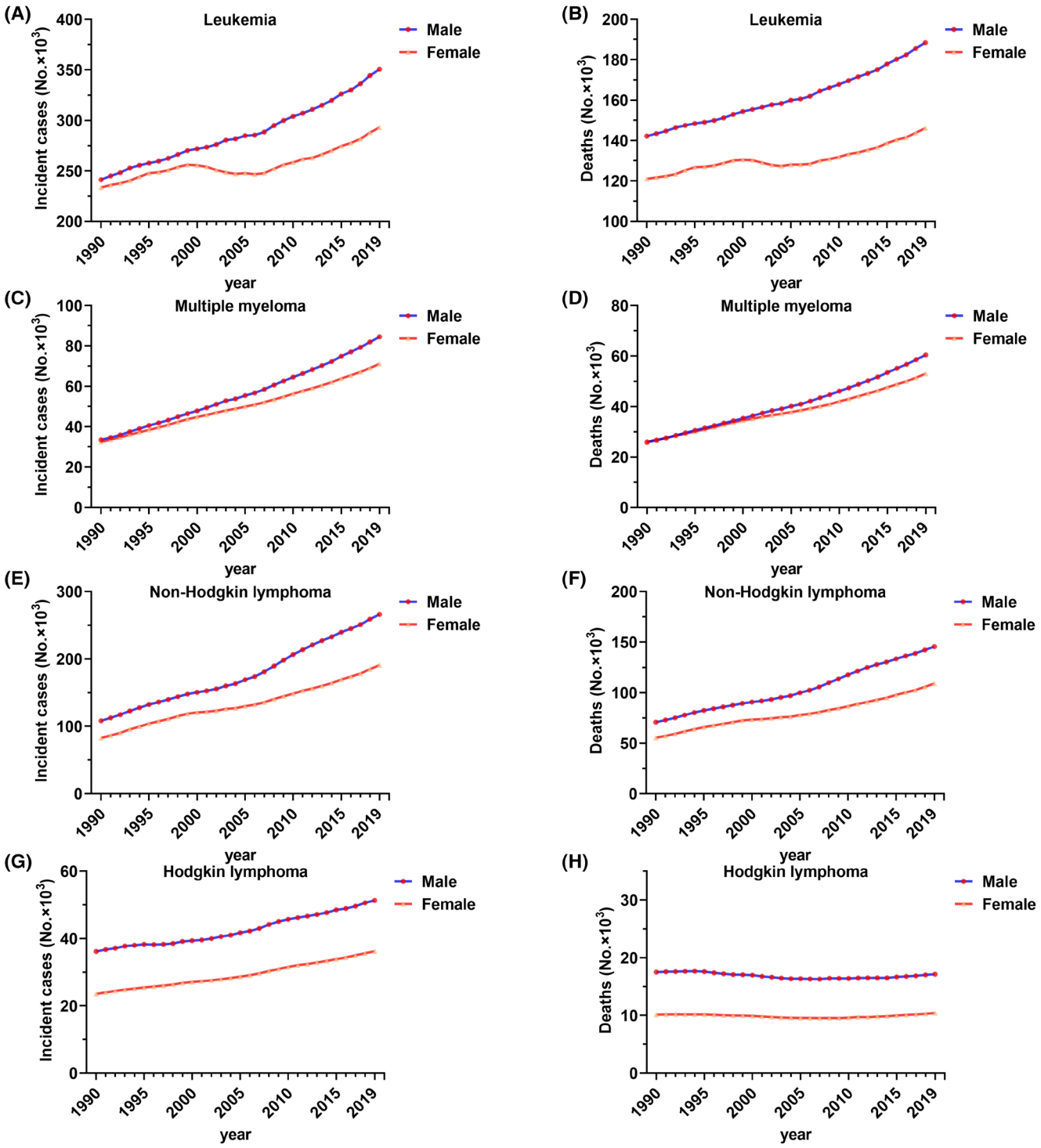

FIGURE 1 Global incidence and deaths of haematological malignancies by sex from 1990 to 2019, from Zhang et al.[14] (A, B) Sex differences in leukaemia. (C, D) Sex differences in multiple myeloma. (E, F) Sex differences in non-Hodgkin Lymphoma. (G, H) Sex differences in Hodgkin lymphoma. Reproduced under Open Access. This article is licensed under a Creative Commons Attribution 4.0 International Licence.

Risk factors

The reasons for the male excess in HM incidence are unclear. Relatively little attention has been paid to the differential effects of risk factors in the aetiology of HMs, and many epidemiological studies report sex as a risk factor but do not report differential exposure effects by sex. While gender-related gaps in smoking and alcohol consumption contribute to increased male mortality from diseases related to these exposures, including cancer, are recognized, occupational practices leading to heightened and repeated exposures to environmentally based carcinogens may also

be more common among men.[18] Furthermore, some of the differences in cancer risk may be mediated by height differences between males and females.[19]

The sexes may respond differently to the same toxic, environmental and hormonal exposures. For example, following exposure to benzene, a clearly leukaemogenic carcinogen, males and females may exhibit different blood toxin levels and degrees of perturbation of haematological parameters.[20] Differential cellular effects of benzene exposure by sex have been confirmed in preclinical studies.[21]

Wang et al.[22] reported a linear relationship between particulate matter (PM 2.5) exposure and leukaemia incidence in China in females but no such relationship among men. Conversely, in a large pooled analysis of European cohort studies, an association between nitrogen dioxide exposure in ambient air was associated with leukaemia in males only (hazard ratio (HR) = 1.33; 95% confidence interval (CI) 1.14–1.55).[23]

The molecular consequences of toxic exposures may also vary by sex. Solomon and colleagues,[24] in an analysis of over 8000 cord bloods of new-born boys and girls, reported differential methylation in nearly 47 000 CpG sites, most of which persisted into childhood. Differentially methylated sites were enriched in genes involved in cancer and other disease phenotypes showing male predominance. Male and female new-borns show differential effects in cord blood gene expression, following intrauterine exposure to carcinogens.[25]

The rates and mechanisms by which secondary HMs develop may also differ by sex. Among 984 patients treated for NHL, no differences in the incidence of clonal haematopoiesis were found between men and women.[26] However, the subsequent development of myeloid malignancies among patients who developed clonal haematopoiesis was more common in males than females (12.4% vs. 3.6%).[26]

Clinical presentation

Females with AML present at a younger age, with higher white blood cell counts than males.[27] Unlike other HMs, myeloproliferative neoplasms (MPN) are more common among females than among men.[28] However, the increased female:male ratio is driven by a preponderance of essential thrombocythaemia (ET), with a ratio of 2:1 for *JAK2-V617F*-positive ET. Conversely, presentation with myelofibrosis, high-risk disease, disease transformation, high burdens of *JAK2* mutations and additional somatic aberrations, including mutations, are more common among males, translating into a worse prognosis in MPN.[29]

In a UK study of diagnostic intervals (time from symptom onset to diagnosis), a consistent trend demonstrating longer median times to diagnosis was seen for females compared to males: 107 vs. 86 days for lymphomas, 155 vs. 143 days for multiple myeloma and 104 vs. 101 days for acute leukaemia.[30] In the case of lymphoma, these differences were statistically and clinically significant after adjusting for age and disease-specific symptoms (adjusted mean difference of 19.2 days, 95% CI 3.8–34.7, $p = 0.01$).[30]

In CLL, both incidence and mortality are increased for men. Interestingly, more women present in stage 0, and the prognosis for women presenting with low stage disease is better than for men.[31] However, women who present in stage 1–3 have identical prognoses to those of men in advanced disease stages.[31]

For both MPNs and CLL, an integrative review of studies showed an increased symptom burden for women as compared to men, although overall quality of life was not consistently different.[32] Regarding symptom burden in MPN, it is difficult to assess true gender-related differences since men participate in surveys, especially online surveys, at a lower rate than women, while women report higher symptom scores, raising the risk of significant reporting bias.[33]

Molecular and biological characterization of disease

Basic research has shown differential distributions of molecular subtypes of haematological diseases. The clinical implications of these differences are not always apparent; however, clinical follow-up may uncover that these are associated with survival differences or the risk of transformation to a more aggressive disease. For example, in a study of over 45 000 newly diagnosed patients with CML, gender differences in the type of *BCR:ABL1* fusion transcripts were noticed, and rare variants were more common among females than males.[34]

In patients with AML, there are substantial sex differences in the distribution of mutations in *DNMT3A* ($p < 0.001$), *NPM1* ($p < 0.001$) and WT1 ($p = 0.02$), *FLT3-ITD* ($p = 0.03$), and less often ASXL1 ($p < 0.001$), SRSF2 ($p < 0.001$), *U2AF1* ($p = 0.001$), and some differences in *RUNX1* ($p = 0.04$) and *KIT* ($p = 0.05$) between males and females.[27] Women were also less likely to have complex karyotypes. In primary myelofibrosis, *ASXL1* mutations predict more aggressive disease and are more common among males.[35] In myelodysplastic/myeloproliferative overlap syndromes, males were found to have higher proportions of somatic mutations, including high-risk *ASXL1* and *EZH2* mutations.[36] Other work has shown sex-related biological differences in molecular and cytogenetic features of CLL.[37,38] For example, in the LRF CLL4 trial, women were less likely to have unmutated *IGHV* genes as well as *TP53* mutations and/or deletions in chromosome 11q.[38] DNA methylation patterns also differ between males and females with CLL.[39] An early study showed that the multidrug resistance phenotype, assessed using rhodamine-123 dye exclusion or monoclonal antibodies, was much more common among males than females with CLL, even among those with early-stage disease.[40]

Response to treatment and survival by sex

Data from two large population-based data sources (the SEER and Multiple Myeloma Research Foundation (MMRF) CoMMpass datasets, $N = 78\,351$ and $N = 1143$ respectively) demonstrate an overall survival advantage for females with multiple myeloma (SEER: HR = 0.92, 95% CI 0.90–0.94, $p < 0.0001$; MMRF: HR = 0.66, 95% CI 0.51–0.85, $p < 0.0001$) compared with males, even after controlling for age, ISS, performance status and autologous stem cell transplant (ASCT).[41] An analysis of 28 473 patients with AML treated with chemotherapy from 2001 to 2018 demonstrated a survival advantage for females, both in terms of overall and relative survival, compared with males. The differences were statistically significant for all leukaemias except for subgroups with acute promyelocytic leukaemia, core-binding factor leukaemia and those with antecedent chemotherapy or conditions.[42]

In the era of novel agents, while some sex-specific differences have been reported for monoclonal antibodies (see below), none have been consistently shown for others. As yet, no study or guideline (see Table 2) identified a sex-related outcome leading to a suggested practice change such as modulation of dosage, frequency or formulation for the agents including Bruton tyrosine kinase inhibitors (BTKi's), immune modulating drugs (IMiDs) and proteasome inhibitors, and dosing remains standardized and uniform regardless of sex. While the NCCN CML guideline[43] mentions an increased recurrence rate among females discontinuing TKIs, this has not been borne out in a recent meta-analysis.[44]

Of the 89 221 oncology trials assessed by Kammula et al.,[8] only 472 (a striking 0.5%) reported at least one sex comparison, among which there were 278 reports of survival, outcome and response (SOR) differences by sex. For NHL, 33 trials compared SOR, of which 20 (60.6%) favoured females, 4 (12.1%) favoured males and 9 (27.3%) showed no difference between the sexes. For AML, trials reported better SORs for females, but the difference was not statistically significant.[8]

Pharmacokinetic differences by sex

Males and females differ in body composition, percentage of body fat, microbiome and hormonal exposures, among other features.[45] These differences, and others, may explain observed differences in drug metabolism, including elimination times, drug concentrations and toxicities.[46] In the treatment of ALL, sex differences in thiopurine metabolism and high-dose methotrexate toxicity may influence adherence and treatment results.[47,48]

In 2012, Carsten Müller and colleagues reported that rituximab clearance was reduced and elimination half-life prolonged in older (>60-year-old) women compared with men,[49] suggesting that this could account for superior results for women in trials incorporating rituximab. Further research, notably the SEXIE-R-CHOP trial, confirmed that higher doses of rituximab (500 vs. 375 mg/m^2) in males resulted in similar drug clearance as in females and appeared to abrogate the female advantage in progression-free survival.[50] An analysis of 13 clinical trials that used rituximab and reported sex-specific outcome differences found that 10 demonstrated survival outcomes that were better for women than men ($p = 0.005$ adjusting for multiple comparisons).[8]

These differences are not universal. For instance, pharmacokinetic differences between the sexes have been investigated and have not been shown in regard to antibody-drug conjugates such as gemtuzumab–ozogamicin (an anti-CD33 antibody covalently linked to calicheamicin)[51] and polatuzumab (anti-79a monoclonal antibody conjugated to monomethyl auristatin E (MMAE)).[49,52]

Treatment toxicity by sex

The published literature provides a mixed picture regarding the probability of sex differences in toxicity following chemotherapy or chemo-immunotherapy. A large study analysing severe (Grade ≥3) adverse events (SAEs) in Phase 2 and 3 trials carried out by the South West Oncology Group (SWOG), reported that overall, 64% of enrolled participants had SAEs, 68.6% of females and 62.2% of males, odds ratio [OR] 1.34; 95% CI, 1.27–1.42.[53] Symptomatic toxicity and objective haematotoxicity were more commonly observed in females than in males following all therapies, chemotherapy and immunotherapy (but not targeted therapies, specifically). The study comprised data from over 23 000 patients in 201 trials, derived from inspection of original case report forms and would not be transparent for readers of the published clinical trial reports. Despite regulations calling for sex-disaggregated outcome results, a review of 89 221 oncology trials using the digital Trialtrove platform revealed that only 44 (0.05%!) reported post-treatment side effects by sex.[8] In 22 of these 44 trials, males were reported to have fewer side effects; in 13 (29.5%) females had fewer, while in nine trials (20.5%), no sex difference was found. The paucity of toxicity reporting by sex underscores the need for more data.

Enhanced haematological toxicities may reflect higher drug levels and/or slower elimination times. Intriguingly, in an analysis of 4626 patients from the German Hodgkin Study group, females experienced more Grade 3 or 4 haematotoxicity but exhibited similar infection rates and an improvement in freedom from treatment failure compared to males.[54] Moreover, the development of Grade 3 or 4 haematotoxicity was associated with improved outcomes in *both* males and females, indicating that this toxicity may have reflected an enhanced treatment effect. Conversely, a study of 17 SEER sites in the United States showed that among 8088 patients with classic Hodgkin Lymphoma treated with chemotherapy, deaths from infection and from treatment-related toxicity were higher for females than for males.[55] Clearly, there is a price to pay for increased toxicity, and the role of clinical research is to clarify how to maximize benefit while minimizing treatment toxicity.

Other issues related to sex and gender relevant for those caring for HM

Therapy for HM has long-term consequences for employability, quality of life, secondary malignancies, immune dysfunction and other secondary morbidities, all of which may differ by sex. One aspect rarely referred to or even discussed with patients is sexual dysfunction after treatment for HM. A recent scoping review uncovered gaps in gender-specific research on sexual dysfunction after treatment for lymphoma.[56] Studies reported a high prevalence of erectile dysfunction among males, a lack of sexual interest or reduced libido, dyspareunia, vaginal dryness and pain among females but a paucity of gender-specific data and a lack of data relevant for LGBTQ and ethnic minorities.[56] Clinical trials do not generally report sexual dysfunction in their toxicity data. A small survey of participants in the German lymphoma suggested there were differences in sexual function after treatment with BEACOPP versus ABVD for Hodgkin lymphoma,[57] yet this toxicity is rarely if ever a consideration in treatment planning, unlike fertility preservation.

Furthermore, the relationship of disease and treatment of HM on the development of hypogonadism has been studied only rarely, and mainly in very small studies.[58] Patients may have questions about the impact of various treatments on hormone levels, such as testosterone levels and the efficacy and safety of replacement therapy after chemo-immune or radiotherapy, but robust studies are lacking.

PARTICIPATION OF MALES AND FEMALES IN CLINICAL TRIALS IN HAEMATOLOGIC MALIGNANCIES

The recent update of the Declaration of Helsinki states that 'Groups that are underrepresented in medical research should be provided appropriate access to participation in research'.[59] In the US following decades in which women of childbearing age were excluded from early phases of clinical research, the NIH Revitalization Act of 1993 (Public Law 103-43) entitled Women and Minorities as Subjects in Clinical Research mandated the inclusion of women and design and execution of clinical trials in such a way as to enable the analysis of the effects of studied variables in women.[60] Still, men continue to be over-represented in clinical trials of lymphoma in England, even after taking into account the higher incidence of the disease among males.[61] And in trials that inform the basis of FDA approval of new oncology drugs from 1998 to 2018, women are under-represented compared to their expected incidence of disease.[7]

We examined 182 trials which inform NCCN clinical guideline recommendations for HM (Table 1), of which almost half (48.4%) were Phase III trials, and the vast majority (86.8%) were multicentre. In all, 17 (9.3%) of the trials sampled and assessed did not report the sex distribution of participants, including 9 of 47 (19.1%) trials on the treatment of B-cell lymphomas, 6 of 31 (19.4%) trials in ALL, 1 of 10, and 1 of 15 trials in T-cell lymphoma and multiple myeloma respectively. In contrast, all assessed trials of AML, CML, MPN, and MDS reported the sex distribution. Females comprised 38.3% of trial participants, with proportions ranging from a minimum of 8.3% in one peripheral T-cell lymphoma trial and a maximum of 76% in one ALL trial, whereas the averages ranged from 22% to 53%. The sex ratios for participants summed over all the included trials were similar to the expected incidence ratios based on population-based data for many diagnostic categories, and where different, frequently fell within the reported 95% confidence interval for the population (Table 1). Exceptions were CLL, Burkitt and marginal zone lymphoma where males were over-represented, and MDS and CML where they were under-represented compared to their expected proportion in the population.

Toxicity data were not reported separately by sex in any of the trials assessed. Overall, of the 182 trials assessed, only 41 (22.5%) reported any kind of outcome (ranging from survival, relapse and reduction in spleen size, etc.) by sex, and of these, 15 (36.5%) reported differential outcomes. The guidelines themselves rarely provided sex-related data or recommendations (Table 2). Exceptions were advice to take into account male–female differences in haemoglobin values when assessing anaemia or cytopenia (in the MPN and MDS guidelines), the gender of the donor in allogeneic SCT (in the CML guidelines) and to consider sex when choosing chemoradiotherapy or the use of proton therapy in Hodgkin lymphoma (Table 2).

SCIENTIFIC/ACADEMIC LEADERSHIP OF WOMEN IN RESEARCH OF HAEMATOLOGIC MALIGNANCIES

Historically, medicine was a predominantly male profession. However, in recent years, the gender balance of the profession has improved, and this is also the case in medical specialties such as haematology. In the United States, 35% of haematologists/oncologists are women[66] In Australia, 40% in 2018 were women,[67] whereas in Israel, 54% of haematologists in 2022 were women.[68] Women are underrepresented in NIH funding,[69] receipt of awards,[70,71] as 'opinion leaders'[70] and investigators in clinical trials, including trials of novel therapies such as CAR T cell.[72]

In our review of NCCN guidelines and supporting references, we assessed the guideline committee composition, its leadership as well as the gender of first authors of the cited clinical trials (Table 2). Committee sizes ranged from 31 to 39, with women comprising 22.6%–45.4% of members. There were no (0%) women committee chairs, while 5 of 11 (45.5%) committees had women as vice-chairs. Of the 182 trials included in our review, only 38 (20.9%) had women as first authors (Table 1).

TABLE 1 Summary of trials assessed in each NCCN guideline[62]: Trial characteristics, gender of first author, participation and outcome reporting by sex.

Guideline name (haematological malignancy)	NCCN version, date issued month/ year	Number of trials assessed	Trial phase: *N*	Multi-centre trials, *N* (%)	Woman first author, *N* (%)	Participants per disease category, *N* [range per trial]	Female participants per disease category % [range of percentages per trial]	Male:female ratio of trial participants[a]	Male:female ratio in population-based published reports of the disease[b] (95% CI)	Trials not reporting sex of participants, *N*	Trials reporting results by sex-*N* [*N* with observed sex differences]	References of trials assessed (supplement S2)
Hodgkin lymphoma	3.2024 03/2024	12	II: 2 III: 10	12 (100)	2 (16.7)	8622 [44–1950]	46.8 [42–70.5]	1.20	1.16 (1.13–1.18)	0	3 [1]	1–12
B-cell lymphomas	3.2024 08/2024	47	I: 1 II: 25 III: 21	41 (87)	9 (19.1)	12 280 [14–1202]	40.8 [11.1–61]	1.45	NA	9	5 [2]	13–61
DLBCL		10	II: 4 III: 6	10	3	3907 [72–879]	45.7 [39.5–51.9]	1.23	1.20 (1.19–1.22)	3	1 [1]	13–23
Follicular		10	II: 2 III 8	9	0	4094 [36–1202]	50.3 [40–58]	1.05	1.03 (1.01–1.04)	2	1 [1]	24–34
Burkitt		7	II: 7	4	3	292 [14–113]	22.7 [11.1–42]	3.15	2.32 (2.17–2.47)	1	0	35–41
Marginal zone		10	II: 6 III: 4	9	3	1641 [39–401]	50.7 [39.5–61]	1.02	0.85 (0.83–0.88)	0	3 [0]	42–51
Mantle cell		10	I: 1 II: 6 III: 3	9	0	2346 [57–870]	26.5 [19–40]	2.68	2.43 (2.33–2.53)	3	0	52–61
Chronic Lymphocytic leukaemia	1.2025 10/2024	17	I: 1 II: 5 III: 11	15 (88)	4 (26.7)	5245 [28–817]	33.6 [20–40]	2.00	1.53 (1.51–1.55)	0	9 [2]	62–81
Waldenstrom macroglobulaemia	1.2025 09/2024	10	II: 8 III: 2	8 (80)	2 (20)	774 [26–202]	32.9 [16–47.8]	1.97	1.46 (1.40–1.52)	1	0	82–91
Multiple myeloma	1.2025 09/2024	15	I: 2 II: 9 III: 5	15 (100)	3 (20)	4001 [31–1085]	42.2 [26–54.8]	1.41	1.28 (1.26–1.29)	1	5 [1]	92–106
Peripheral T-cell lymphoma	2.2024 05/2024	10	I/II: 1 II: 7 III: 2	7 (70)	2 (20)	1110 [10–452]	32.8 [8.3–50]	1.62	1.45 (1.40–1.50)	0	2 [1]	107–117
Acute lymphoblastic leukaemia (ALL)	2.2024 07/2024	31	II: 23 III: 8	21 (68%)	9 (29)	6649 [20–1521]	41.5 [23–76]	1.89	1.29 (NA)	6	7 [3]	118–149
ALL PH+		10	II:10	5	3	533 [20–110]	41.5 [30–54]	1.13	1.21 (NA)	2	1 [1]	118–128
ALL PH-		10	II: 8 III: 2	7	2	2749 [46–1521]	44.3 [37–53]	1.48	1.29 (NA)	2	4 [1]	129–138
T-cell ALL		11	II: 5 III: 6	9	4	3367 [39–1031]	41.4 [23 –76]	2.33	2.38 (2.22–2.57)	2	2 [1]	139–149

TABLE 1 (Continued)

Guideline name (haematological malignancy)	NCCN version, date issued month/year	Number of trials assessed	Trial phase: *N*	Multi-centre trials, *N* (%)	Woman first author, *N* (%)	Participants per disease category, *N* [range per trial]	Female participants per disease category % [range of percentages per trial]	Male:female ratio of trial participants[a]	Male:female ratio in population-based published reports of the disease[b] (95% CI)	Trials not reporting sex of participants, *N*	Trials reporting results by sex-*N* [*N* with observed sex differences]	References of trials assessed (supplement S2)
Acute myeloid leukaemia	3.2024 05/2024	10	I/II: 1 III: 9	10 (100)	2 (20)	7199 [82–1942]	39.1 [35–55.5]	1.10	1.46 (NA)	0	2 [0]	150–159
MPN (myelofibrosis)	3.2024 072024	10	I: 1 II: 5 III: 4	9 (90)	3 (30)	3410 [30–2233]	44.6 [38.8–53.3]	1.69	1.83 (NA)	0	2 [2]	160–171
Myelodysplastic syndrome	2.2024 08/2024	10	I: 1 III: 9	10 (100)	2 (20)	1944 [88–358]	45.9 [29.9–76.3]	1.24	1.83 (NA)	0	4 [2]	172–181
Chronic myeloid leukaemia	1.2025 08/2024	10	I/II: 1 II: 2 III: 7	10 (100)	0 (0)	5625 [119–1538]	44.3 [36.6–55]	1.12	1.67 (NA)	0	2 [1]	182–196
Combined		182	Phase III: *N* = 88 (48.4%)	158 (86.8%)	38 (20.9%)	56 859	Total female participants, *N* = 21 755 (38.3%)	1.61	NA	17 (9.3%)	41 (22.5%) [15, *36.6% of those reporting outcomes by sex*]	

Abbreviations: CI, confidence interval; MPN, myeloproliferative neoplasm; *N*, number; NA, not available; Ph, Philadelphia chromosome.

[a]Includes only trials where sex distribution was reported.

[b]References [15,63–65]; most reports used age-standardized data.

TABLE 2 Summary of gender representation and mention of sex effects in national comprehensive cancer network guideline[62] committees for haematological malignancies.

Guideline name, version and date	Gender of chair/ vice-chair	Members, *N*	Women members, *N* (%)	Any reference to sex or gender in guideline?
Hodgkin lymphoma 3.2024 18 March 2024	M/W	37	16 (43.2)	Sex plays a role in choosing chemo- and photon therapy Survivorship guidelines for breast cancer screening
B-cell lymphomas 3.2024 August 2024	M/M	37	13 (35.1)	Male predominance in paediatric-type follicular lymphoma
Chronic lymphocytic leukaemia 1.2025 1 October 2024	M/W	35	11 (31.4)	Sex is part of prognostic index
Waldenstrom Macroglobulaemia 1.2025 13 September 2024	M/W	33	13 (39.4)	None
Multiple myeloma 1.2025 17 September 2024	M/W	33	12 (36.4)	None
Peripheral T-cell lymphoma 2.2024 28 May 2024	M/M	39	15 (38.5)	ATLL: males have poorer prognosis after allo transplant LGL: females worse prognosis
Acute lymphoblastic leukaemia 2.2024 19 July 2024	M/M	31	7 (22.6)	Sex differences in 6 MP bioavailability
Acute myeloid leukaemia 3.2024 17 May 2024	M/W	35	13 (37.1)	Males have more *RUNX1* mutations Males-increased risk of death in induction
Myelodysplastic syndrome (MDS) 2.2024 8 August 2024	M/M	38	17 (44.7)	Cytopenias defined by age, sex, altitude Females: decreased mortality in low-risk MDS with del (5q)
Myeloproliferative neoplasms 3.2024 25 July 2024	M/M	33	15 (45.4)	Definition of anaemia by sex, ET: decreased survival and increased calreticulin mutations in males
Chronic myeloid leukaemia 1.2025 8 August 2024	M/M	31	10 (32.2)	Difference in types of *BCR:ABL1* transcripts Sex of donor important in allo transplant Risk of recurrence higher after TKI discontinuation for females

Abbreviations: 6MP, 6-mercaptopurine; allo, allogeneic; ATLL, adult T-cell leukaemia/lymphoma; LGL, large granular lymphocytosis; M, man; TKI, tyrosine kinase inhibitor; W, woman.

TRAINING THE NEXT GENERATION OF HAEMATOLOGISTS TO BE GENDER-SENSITIVE AND AWARE OF SEX DIFFERENCES

As of now, professional organizations, while recognizing the need for gender equity, have not mandated training in sex differences in HM. The only mention of gender (not sex) in the European Hematology Association (EHA) curriculum states 'The trainee has received training in: Reference ranges of laboratory values, with relevance to gender, age and ethnicity'.[73] In Australia, the Royal College of Physicians has implemented new Curriculum Standards for Advanced Physician trainees which identified 10 domains of profession practice framework. While Cultural Safety is one of the professional domains, a specific reference to focus on sex or gender difference is not mandated as part of this. Likewise, within the specific knowledge guides, sex differences within core clinical haematology disease groups are not highlighted as key concepts in the curriculum. The Royal College of Pathologists of Australasia in its Haematology trainee manual[74] mentions sexual orientation and gender in the context of cultural competence but does not mention variation in disease presentation or outcome due to sex/gender differences. The joint Royal Colleges training board in Haematology in the United Kingdom mentions neither sex nor gender in its published curriculum.

TABLE 3 Recommendations for incorporating sex differences in training, research and practice.

I. Training	
Incorporate sex and gender in curriculum	• Include modules on how sex (biological differences) and gender (social, cultural factors) influence and treatment outcomes • Highlight examples from research showing significant sex-based differences in HM • Model sex- and gender-based patient care into daily practice
Case-based learning	• Use real-world case studies where sex and gender play a critical role in treatment decisions and outcomes to enhance critical thinking
Workshops and seminars	• Conduct workshops focusing on gender sensitivity and equity in research • Invite local/ international experts to discuss challenges, successes and recommendations in addressing sex differences in trials
Research ethics training	• Educate haematologists on ethical obligations to consider sex and gender during trial design, recruitment and data analysis
Interdisciplinary training	• Collaborate with epidemiologists, social scientists and public health experts to provide a comprehensive understanding of the sex-related differences in aetiology, disease characteristics and outcomes
II. Research	
Trial design	• Mandate sex-stratified analysis as part of trial design • Ensure recruitment commensurate with disease patterns including sex-specific variables—Collect data on biological sex, gender identity, hormone levels and reproductive history
Standardized reporting	• Mandate clinical trials to transparently report sex-disaggregated data to identify differences in response, side effects and outcomes • Report primary and secondary outcomes stratified by sex, such as overall survival, QOL, treatment-related toxicities • Implement and enforce existing guidelines
Preclinical research	• Use both male and female animal models and cell cultures in preclinical studies to understand sex differences
Biomarker studies	• Investigate biomarkers that may vary by sex and could predict treatment response or prognosis
Post-marketing surveillance	• Collect real-world data stratified by sex to monitor long-term outcomes and adverse effects
Technological solutions	• Using artificial intelligence (AI) and machine learning to identify sex-specific trends in large datasets
III. Professional organizations, advocacy, clinical practice	
Policy and advocacy	• Advocate for funding agencies and regulatory bodies to prioritize and incentivize research on sex differences in haematological malignancies
Clinical Awareness	• Raise awareness that sex differences may have clinical implications
Guidelines	• Insert sex differences and their implications into evidence-based guidelines

We would suggest that training strategies include curricular aspects which focus on sex and gender differences. In addition, clinical and translational research centres should implement modelling of sex differences in research design, analysis and reporting, and strongly consider future opportunities to implement this in post-research surveillance. Finally, guidelines should incorporate the accumulated knowledge in treatment recommendations. In Table 3 we have included recommendations for training, research, advocacy and professional organizations.

DISCUSSION

Our review has shown that much has already been discovered regarding the role sex plays in the development and pathogenesis of haematological malignancies, response to treatment and in specific short- and long-term toxicities. Yet most of these aspects are missing from textbooks, curricula and guidelines, which are major conduits of information which influence the clinical behaviour of clinicians. Our analysis has revealed major gaps between what is known and the translation of this knowledge into action.

As of 2025, the practical management of HMs is still 'gender blind'. Despite existing regulations,[60] sex-specific outcomes are not reported, limiting the clinician's ability to decide whether recommended treatments are appropriate for both males and females. Even among studies that examined the effect of sex on prognosis, that effect may be overlooked. A case in point is a study of dasatinib treatment as first- line therapy for Philadelphia chromosome-positive ALL.[75] The study showed an effect of sex on disease-free survival (HR for females vs. males, 2.501 (1.010–6.193), $p = 0.0476$) on multivariate analysis, yet reported in the text '*only BCR::ABL reduction correlated with DFS* (HR = 0.336, 95% CI, 0.126–0.895, $p = 0.02910$)'.

The method of reporting sex-specific effects is also problematic.[8] Of the studies that do relate to sex, most use a forest plot to depict whether treatment effects of the standard versus experimental arm are consistent in males and females, in a standard representation of planned or unplanned subgroup analyses. This form of presentation helps the reader discern

whether there is modification of the *relative* treatment effect by sex, but not whether there are *absolute* survival advantages for one sex or the other. It is rare to find multivariable analyses including sex as a prognostic variable and rare to see sex × treatment interaction analyses.[8]

When sex-related differences in treatment outcome are observed in clinical trials, the reader is often at a loss to explain them. Are these chance differences, that is, examples of type 1 error in subgroup analyses stemming from multiple comparisons, or are they true differences? A case in point is the POLARIX study[76] which demonstrated that polatuzumab combined with cyclophosphamide, rituximab and adriamycin (Pola-R-CHP) resulted in superior progression-free survival compared to the standard R-CHOP in intermediate and high-risk CD20+ diffuse large B-cell lymphoma. An 'exploratory' subgroup analysis, published in the supplementary data of the article but widely disseminated, appeared to demonstrate that the advantage of Pola-R-CHP was restricted to men (HR 0.7, 95% CI 0.5–0.7), while in women, the effect appeared to be null (HR = 0.9, 95% CI 0.6–1.4). This begs the question of differential treatment effects between men and women. In a study published in June 2024, 2.5 years after the publication of POLARIX, Deng et al. presented pharmacokinetic data on polatuzumab, demonstrating statistically nonsignificant differences in the antibody-conjugated (acMMAE)/unconjugated MMAE area under the concentration–time curve (AUC) between males and females.[52] Is it possible that the relative advantage of receiving polatuzumab for men and not for women in the POLARIX trial stems from the fact that men are in essence underdosed with rituximab, thus requiring further anti-B-cell immunotherapy, while for women, the standard rituximab dosing and response were adequate, with no further benefit to polatuzumab? This is a thought experiment, and obviously, the study was not designed to test this question. Yet it is a question worth raising, given published data on rituximab pharmacokinetics. Whether true sex differences in treatment effect exist remains unknown.

And more puzzling is the fact that when consistent data are available of a sex disadvantage for males in lymphoma trials which might be abrogated by giving higher doses to males, these data have not been incorporated into clinical practice or clinical trial design. Rituximab dosing has not been modified in a sex-specific manner in clinical trials or guidelines. Neither, to our knowledge, have the doses of any therapeutic agents which are calculated by weight or body surface area, despite known sex-related limitations in these parameters.

Why females experience increased toxicity and a greater number of side effects while enjoying a survival advantage in many HM is also a puzzle. However, in our opinion, the puzzle is not insoluble. Solving it requires concerted research focusing on similarities and differences in drug metabolism, distribution, dosing schedules, drug–drug interactions as well as a quantitative and qualitative investigations into the objective and subjective experience patients regarding the treatments they receive and their consequences.

Finally, it is widely acknowledged that males and females develop HM at different rates, and intriguing research has shown variable responses, by sex, to environmental and genetic stimuli. 'Precision prevention' would be served by understanding the differential effects of and sensitivities to exposures on males and females.

We have shown that sex-specific reporting of results is lacking in the very same trials that form the backbone of therapeutic guidelines which serve as important references for many clinicians in the field. Leadership of these guidelines is overwhelmingly by men, and the 'front people' who present and write up these trials, the first authors, are disproportionately male. This is surprising, given the gender make-up of the profession and multiple calls for gender equity.[70,71,77,78] It remains to be seen whether initiatives by women such as the 'Women in Lymphoma' advocacy group[79] will make a difference not just in promoting women in the profession but also in promoting greater awareness and explanations for sex-related differences in HM incidence and outcomes. This awareness would benefit not only women, but all patients.

Our analysis of the trials mentioned in NCCN guidelines has some limitations. We acknowledge that we assessed only a sample of the trials mentioned in the guidelines, and that there may be many trials which were not included that were led by women. The small sample sizes per diagnostic category precluded statistical analysis of sex-disaggregated reporting by trial characteristics, including whether lead authors were male or female. In general, we found that the sex distribution among participants in the trials reflects the reported incidence rates for males and females for most diseases. However, our comparison between observed ratios of males and females in the assessed trials with expected ratios as reported in population-based studies of the same diseases did not encompass all geographical settings, and did not take into account the age stratification in the trials themselves. In addition, our literature review, though wide in scope, was not exhaustive. Nevertheless, we have shown that while much is known, regrettable knowledge gaps exist. We have made some recommendations to address these gaps, addressing training, research and professional associations.

In conclusion, it is ironic that, in the era of personalized medicine, a basic personal characteristic—sex, has been given insufficient weight in decision-making. Clinicians and professional bodies must insist on seeing sex-disaggregated results in *all* reports of therapeutic trials of agents and regimens. These must be fully transparent and not hidden in supplementary data or preliminary reports. We will not know if sex matters unless we look. More data will enable us to judge whether, indeed, sex-based algorithms are necessary.[80] We believe the time has come to acknowledge that sex plays a role in why people become ill, how HMs manifest, but also how they should be treated, and what all sexes and genders can expect to experience during and after treatment. Where appropriate, this added knowledge may translate into more personalized guidelines.

AUTHOR CONTRIBUTIONS

Ora Paltiel designed the research study. Ora Paltiel, Sumita Ratnasingam and Hui-Peng Lee performed the research. Ora Paltiel analysed the data. Ora Paltiel wrote the first draft,

and all authors contributed to and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

All raw data are available in Table S1.

ETHICS APPROVAL STATEMENT

Not applicable—no patient data were accessed or reported.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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