Introduction

Worldwide, lung cancer is the most common cancer and leading cause of cancer death (1). In 2018, 2.09 million people were diagnosed with lung cancer and there were 1.76 million deaths from lung cancer. Non-small cell lung carcinoma (NSCLC), divided into two major groups by histology: squamous and non-squamous, is the most common type of lung cancer, accounting for 84% of all lung cancer diagnosis (2).

Ethnicity may be defined as a group with a common ancestry, culture or history (3). However, in our review, we refer to it as a population with a shared ‘genetic ancestry’. It is now increasingly recognised that ethnicity does not just affect lung cancer epidemiology (3-10) but also the efficacy and toxicities of chemotherapeutics (11).

While tyrosine kinase inhibitors and immune checkpoint inhibitors have redefined treatment options in patients with advanced disease at presentation, the majority of patients will still require cytotoxic chemotherapy. Interindividual variability of pharmacokinetics, where different genetic polymorphisms affect drug metabolism, transport, and receptor binding may account for the ethnic differences (12-18). This is a major concern in the clinical setting as it influences outcomes and affect international harmonization of drug development. Efforts made to design prospective studies investigating ethnic specific determinants to systemic therapy and individualise lung cancer treatment based on genetic makeup of patient are important.

Treatment efficacy

Small cell lung cancer

A retrospective study of 3,428 patients from three Californian states with extensive stage small cell lung cancer
(ED-SCLC) showed that Asian ethnicity was a favourable prognostic factor in ED-SCLC (HR =0.785; P=0.0076) (19). A potential explanation is the ethnic variability in the genetic polymorphism of drug metabolizing genes (20,21).

The Japan Clinical Oncology Group (JCOG) 9511 and Southwest Oncology Group (SWOG) 0124 trial were two large phase three trials that demonstrated ethnic differences in chemotherapy response. This is despite similar eligibility criteria and treatment regimens between the two studies. The J9511 was done exclusively in Japanese patients which demonstrated a survival benefit for cisplatin/irinotecan over cisplatin/etoposide in patients with ED-SCLC. On the contrary, S0124+ trial was a large North American trial that failed to confirm a survival benefit of cisplatin/irinotecan. A combined analysis of these two trials demonstrated that the response rates (RR) were higher in Japanese patients compared to United States patients, with a RR of 68% vs. 57% (P=0.01) vs. 87% and 60% (P<0.001) for cisplatin/etoposide and cisplatin/irinotecan respectively. Overall survival (OS) was similar for Japanese and United States patients in the cisplatin/etoposide arm at 9.4 vs. 9.1 months (P=0.5), and superior in Japanese patients in the cisplatin/irinotecan arm at 12.8 and 9.9 months respectively (P<0.001) (22-24).

**Non-small cell lung cancer**

Several cancer registries have reported the association between survival and ethnicity in Asian patients with NSCLC. A retrospective population-based analysis of 15,185 Japanese and 13,332 Caucasians patients with NSCLC from the Japanese National Hospital Organization Study Group for Lung Cancer and Southern California Regional Cancer Registry between 1991 and 2001 revealed Japanese ethnicity to be an independent factor for OS (HR =0.937; 95% CI: 0.898–0.978, P=0.0028). When analysed according to stage, Japanese patients had improved OS for stage III (HR =0.830; 95% CI: 0.789–0.873, P<0.0001) and stage IV (HR =0.955; 95% CI: 0.915–0.997, P=0.0369) (25).

In another similar study comparing 4,622 Korean and 8,846 Caucasian patients between 1998 and 2005, Korean ethnicity was once again found to have a more favourable OS compared to Caucasians (HR =0.869; P<0.0001). The HR for OS in Korean patients compared with Caucasian patients on univariate analysis for stage I disease was 0.618 (95% CI: 0.543–0.705; P<0.001), stage II was 0.836 (95% CI: 0.867–1.016; P=0.0723), stage III was 0.772 (95% CI: 0.712–0.836; P<0.001) and stage IV was 0.846 (95% CI: 0.800–0.894; P<0.001). In this study, after the introduction of tyrosine kinase inhibitors in Korea in 2002, the Koreans had further improved OS advantage compared to the Caucasians (HR =0.889; P=0.0013 vs. HR =0.795; P=0.0001 in the pre and post tyrosine kinase inhibitor era respectively) (26).

Even among Asian patients living in United States, Ou and colleagues reported that Asian ethnicity is an independent prognostic factor regardless of smoking status. In their study of a total of 20,140 patients with NSCLC from three South California countries, Asian ethnicity has a favourable OS compared to non-Asians (HR =0.861; 95% CI: 0.808–0.918, P<0.0001), and the highest OS among the four major ethnicities (P<0.0001). This remained significant even after stratification by smoking status (HR =0.867; 95% CI: 0.807–0.931, P<0.0001 vs. HR =0.841; 95% CI: 0.728–0.971, P=0.0180 in smokers and never smokers respectively) (27).

In 1998, SWOG established a collaboration with Japanese investigators of lung cancer. The purpose was to facilitate standardization of clinical trials and to allow for collaboration (28). With the hypothesis that ethnic related pharmacogenomics could account for differences in clinical outcomes despite similar treatment regimes, SWOG prospectively designed three phase three trials—The Four-Arm Cooperative Study (FACS), LC00-03 and S0003 in advanced stage NSCLC, each with a common arm carboplatin/paclitaxel (29-31). In FACS, patients were randomly assigned to standard treatment in Japan (cisplatin/irinotecan) versus experimental arms of carboplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/vinorelbine (29). In LC00-03 which was conducted in Japan, patients were assigned to carboplatin/paclitaxel versus the non-platinum regime of sequential vinorelbine/gemcitabine followed by docetaxel (30). In S0003, patients were randomly assigned to carboplatin/paclitaxel with or without the cytotoxin tirapazamine (31).

A comparative analysis of the carboplatin/paclitaxel arm shows that the patients in LC000-3 had superior progression free survival (PFS) and median survival time compared to S0003 (32). Efficacy comparisons between all three trials were also reported. RR were similar between the trial trials and ranged from 32% to 36%. Median PFS was 4.5, 6 and 4 months in FACS, LC00-03 and S0003 respectively. Median survival times were numerically higher in the Japanese studies at 12 and 14 months in FACS and LC00-03 respectively compared to 9 months in S0003. One-year survival was higher at 51% and 57%
in FACS and LC00-03 respectively compared to 37% in S0003 (P=0.0004). This was despite numerically higher dose reductions (51% vs. 26% in LC00-03 and S0003 respectively, P=0.63) and more patients receiving the full six cycles of carboplatin/paclitaxel (29% vs. 36.5% in LC00-03 and S0003 respectively, P<0.0001). The dose reduction data from FACS was not available for comparison (28-33) (Table 1).

Genomic data was collected from patients in LC00-03 and S0003 and results analysed. Genotypic associations were observed between CYP3A4*1B for PFS (HR =0.36; 95% CI: 0.14–0.94, P=0.04) and ERCC2 K751Q for RR (HR =0.33; 95% CI: 0.13–0.83; P=0.02). Notably, there was a significant difference between Japanese and US patients in genotypic distribution for CYP3A4*1B (P=0.01) and ERCC2 K751Q (P=0.001) (33).

Docetaxel is used as a component of platinum-containing doublet regimens for previously untreated metastatic NSCLC (34). In addition, it has been approved in the second-line treatment of NSCLC (35-38). The efficacy of docetaxel across ethnic groups is likely to depend on the dosage administered, with an association between tumour RR and docetaxel dose. Docetaxel is approved for use at a dose of 75 mg/m² as a single agent or in combination regimens, and doses ranging from 75–100 mg/m² are frequently employed in global clinical trials (37-39). A lower dose of 60 mg/m² docetaxel has been widely used in previous Japanese studies, as originally recommended by a Japanese phase I clinical trial due to severe haematological toxicities in Japanese patients as compared to the patients in Europe/US (40). Hence, the results from Japanese trials cannot be directly compared with global trials. Several phase I/II studies of 60 mg/m² docetaxel in combination

| Outcomes                              | FACS       | LC00-03    | S0003     |
|---------------------------------------|------------|------------|-----------|
| Median PFS                            | 4.5 months | 6 months   | 4 months  |
| Median survival times                 | 12 months  | 14 months  | 9 months  |
| 1-year survival                       | 51%        | 57%        | 37%       |
| Dose reductions                       | NR         | 51%        | 26%       |
| Received 6 cycles of carboplatin/paclitaxel | NR      | 29%        | 36.5%     |
| Grade 3–4 neutropenia                 | 88%        | 70%        | 38%       |
| Febrile neutropenia                   | 18%        | 12%        | 2%        |
| Anemia                                | 15%        | 8%         | 7%        |

FACS, Four-Arm Cooperative Study; PFS, progression free survival; NR, not reported.
conducted in Singapore reported a higher RR of 50%, and a 34% RR based on intent-to-treat analysis in Asian patients with stage III inoperable NSCLC, albeit with a higher docetaxel dose of 100 mg/m\(^2\) every 3 weeks (48). This is comparable or higher than the reported docetaxel RRs (21–38%) in naïve or previously treated Western patients administered with the same dose of docetaxel monotherapy (49-52). In general, docetaxel as a single agent and combination therapy have shown better efficacy in Asian than Caucasian NSCLC patients. However, Japanese trials, which used lower docetaxel dose, have generally reported lower RRs as compared to other Asian NSCLC patients.

Multiple other studies of patients with advanced NSCLC reported in Asia had a numerically longer survival. Sekine et al. retrospectively compared platinum doublet phase III trials among Japan, European and American patients with advanced NSCLC. Doses of chemotherapy were generally lower in Japanese studies and survival better. In studies of cisplatin and gemcitabine, the median survival time of 14.8 months and 1-year survival of 60% in Japanese studies were numerically higher than 8.1–10.9 months and 33–44% respectively for Europe and US studies. The OS for carboplatin/paclitaxel were 12.3 vs. 7.8–11 months, cisplatin/vinorelbine 11.4 vs. 8.1–10.1 months for Japan and Europe/US studies respectively (53) (Table 2).

Differences in outcomes between Asian and Caucasian studies were observed in a meta-analysis of randomized trials of cytotoxic chemotherapy. The OS in Asian and Caucasian patients treated with chemotherapy was 10.1 and 8.0 months (P<0.001) and the overall RR was 32% and 26% (P<0.001), respectively. The differences in OS remained significant in studies pre-dating the use of EGFR TKI (54).

### Treatment toxicities

**Small cell lung cancer**

In the aforementioned J9511 and S0124 trial, enhanced hematologic toxicity was seen in Japanese patients as compared with United States patients, each receiving the exact same chemotherapy regimens. Grade 3 or more neutropenia was seen in 92% vs. 68% (P<0.001), and 65% vs. 34% (P<0.001) of Japanese and US patients receiving cisplatin/etoposide and cisplatin/irinotecan respectively (22-24).

Pharmacogenomic variability in single nucleotide polymorphisms (SNPs) may help explain interindividual differences and population-related differences in toxicity and outcome after chemotherapy. A pharmacogenomic analysis of S0124 showed significant associations between genotypic variants and toxicity levels. Variations of *ABCB1* was associated with an increased risk of irinotecan-associated grade 3 or worse diarrhea and, *UGT1A1* with increased risk of grade 3 or worse neutropenia (20,21). Multiple other studies also found pharmacogenetic information predicting for irinotecan toxicities. In one study, Fujita and Sasaki examined the effect of UGT genetic polymorphisms and found that the patients with *UGT 1A1* homozygosity had a higher incidence of neutropenia compared to patients with wild-type alleles. They also found that the *UGT1A1* allele is another polymorphism associated with defective glucuronidating function and severe neutropenia and is found almost exclusively in Asian individuals with a frequency as high as 20% (55). In another study, Innocenti et al. found that a TA indel genotype (*UGT1A1* variant) to be highly correlated to severe neutropenia (56). This finding was consistent with a retrospective analysis by Ando et al., in which the TA7 allele was a significant predictor of severe toxicity in patients receiving irinotecan containing regimens (57). This polymorphism is however significantly

| Regimen                      | Japan | Europe/UK studies |
|------------------------------|-------|-------------------|
| Carbo[paitaxel               | 32    | 17–46             |
| Response rate (%)            |       |                   |
| Median survival (months)     | 12.3  | 7.8–11            |
| 1-year survival (%)          | 51    | 32–43             |
| Cisplatin/docetaxel          | 37    | 17–32             |
| Response rate (%)            |       |                   |
| Median survival (months)     | 11.3  | 7.4–11.3          |
| 1-year survival (%)          | 48    | 31–46             |
| Cisplatin/gemcitabine        | 30    | 22–42             |
| Response rate (%)            |       |                   |
| Median survival (months)     | 14.8  | 8.1–10.9          |
| 1-year survival (%)          | 60    | 33–44             |
| Cisplatin/vinorelbine        | 33    | 25–39             |
| Response rate (%)            |       |                   |
| Median survival (months)     | 11.4  | 8.1–10.1          |
| 1-year survival (%)          | 48    | 36–42             |

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more common in Caucasians than in Asians (58).

Given the strong data linking the clinical association of irinotecan toxicities and interindividual genetic differences, the Food and Drug Administration (FDA) updated the safety label for irinotecan in 2005. They included pharmacogenetic information for a dose reduction of irinotecan if a patient is homozygous for UGT 1A1*28 allele. Molecular assays were developed to allow rapid detection of polymorphisms, allowing treatment to be individualised (59).

Non-small cell lung cancer

In a pooled analysis of hematological toxicities in Asian and non-Asian patients from 12 phase II and 38 phase III clinical trials, severe hematological toxicities were frequently observed in Asian patients compared with non-Asians in the treatment of chemotherapy for advanced NSCLC. Grade 3 or more neutropenia and anaemia were significantly higher in Asian than non-Asian patients when treated with cisplatin/gemcitabine, cisplatin/vinorelbine and cisplatin/paclitaxel. This difference was not observed for grade 3 or more thrombocytopenia (60) (Table 3). This difference in toxicities suggests that perhaps dose modification according to ethnicity should be considered.

Further evidence for differences in toxicities can be ascertained from the FACS, LC00-03 and S0003 trials. While survival rates favoured the Japanese patients, the toxicity profile were more favourable for the US patients. The rates of grade 3–4 neutropenia, febrile neutropenia and anaemia differed significantly in US patients but were comparable in the two Japanese studies. Rates of grade 3–4 neutropenia was 88%, 70% and 38%, febrile neutropenia 18%, 12% and 2%, anaemia 15%, 8% and 7% for FACS, LC00-03 and S0003 respectively (28-33) (Table 1). Similarly, Sekine et al. also reported 88% grade 3-4 neutropenia which was numerically higher than the 14–65% reported in Europe/US studies (53).

As previously mentioned, increased susceptibility towards docetaxel toxicity is observed in Japanese as compared to Western NSCLC patients, which justified a lower dosage of docetaxel being approved for NSCLC treatment in Japan (40). Similarly, an especially high rate of docetaxel treatment-related adverse side effects was observed in the first group of Asian patients in Singapore. Neutropenia is a major toxicity of docetaxel treatment in this study, with high grade neutropenia being reported in 69% of the patients, and febrile neutropenia in approximately 30% of patients during the first cycle of treatment (48). This finding of more frequent and severe docetaxel-induced neutropenia was corroborated by a multi-centre study in Australia and Singapore (45). Specifically, a significantly higher degree of this hematological toxicity was observed in Chinese and Indians as compared to Malays despite the absence

| Regimen          | Asian trials | Non-Asian trials | OR (95% CI)         | P value |
|------------------|--------------|------------------|---------------------|---------|
| Cisplatin/gemcitabine |             |                  |                     |         |
| Neutropenia (%)  | 53.9         | 25.3             | 3.45 (2.58–4.61)    | <0.001  |
| Anemia (%)       | 24.7         | 9.2              | 3.27 (2.30–4.56)    | <0.001  |
| Thrombocytopenia | 28           | 16.0             | 2.04 (1.48–2.82)    | <0.001  |
| Cisplatin/vinorelbine |         |                  |                     |         |
| Neutropenia (%)  | 78.8         | 45.6             | 4.43 (3.09–6.36)    | <0.001  |
| Anemia (%)       | 25.6         | 12.4             | 2.43 (1.67–3.54)    | <0.001  |
| Thrombocytopenia | 2.6          | 4.5              | 0.57 (0.57–1.59)    | 0.323   |
| Cisplatin/paclitaxel |         |                  |                     |         |
| Neutropenia (%)  | 70.9         | 33.7             | 4.79 (4.11–5.59)    | <0.001  |
| Anemia (%)       | 10.8         | 7.4              | 1.52 (1.20–1.91)    | <0.001  |
| Thrombocytopenia | 8.8          | 6.5              | 1.39 (0.94–2.06)    | 0.115   |

CI, confidence interval; OR, odds ratio.
of docetaxel pharmacokinetics among the different ethnic groups (61). In addition, the pharmacokinetics of docetaxel and the associated haematological toxicity were reported to be comparable in Caucasian and African black patients (62).

The possible mechanisms explaining the increased incidence and severity of docetaxel toxicities in Asian patients include pharmacogenetic differences in drug transporters and metabolizing enzymes (63–65). In a study performed by our group (66), a mean docetaxel clearance rate of 15.3±4.0 L/h/m² was reported which was lower than previous pharmacokinetic studies conducted in Europe and US (65). Correspondingly, neutrophil toxicity was common with a relatively high incidence of neutropenic fever at 29%. The genetic polymorphisms in CYP3A5 (*1/*3) and MDR1 (C3435T) genes involved in the metabolism and membrane transport of docetaxel respectively were examined in the cohort of patients and associated with the clearance rates of docetaxel and midazolam, which is a CYP3A substrate used as a probe to predict docetaxel clearance. It was observed that the CYP3A5*3 allele is more common as compared to the CYP3A5*1 allele. Although patients with at least one CYP3A5*1 allele tended to exhibit higher midazolam clearance rate, there was no evident trend in the docetaxel clearance among the genotype groups, as docetaxel clearance can be affected by various factors not limited to polymorphisms in CYP3A5 gene (66).

Another study reported that the presence of both CYP3A4*1B and CTP3A5*1A alleles were associated with marked increase in docetaxel clearance albeit the lack of association of individual polymorphisms in CYP3A4 and CYP3A5 on docetaxel pharmacokinetics (67). Furthermore, the C3435T polymorphism of the MDR1 gene is known to result in the production of P-glycoprotein with reduced substrate used like docetaxel. It was observed that T/T genotype of the MDR1 gene is observed in close to 30% of the patient cohort, being especially common in Malay patients. Although the T/T and C/T genotypes are associated with lower midazolam and docetaxel clearance as compared to the C/C genotype, the difference is not statistically significant. Nevertheless, the patient with the lowest docetaxel clearance had the T/T genotype, while that with the highest docetaxel clearance had the C/C genotype (66). The C3435T polymorphism of the MDR1 gene is also found to be common in a cohort of Caucasian NSCLC patients. Nevertheless, similar to the study by our group and others, this study did not find a significant association of this polymorphism with RR and OS in NSCLC patients treated with docetaxel (68). Furthermore, SNPs in drug transporters MDR2 and SLC01B3 were observed to be significantly associated with docetaxel-induced neutropenia in Japanese patients (69). Notably, among 28 SNPs which are significantly associated with docetaxel AUC, CYP39A1 (rs7761731) was the only SNP found to be significantly associated with high grade neutropenia in Japanese cancer patients (70). As variant alleles of these genes encoding drug transporters and metabolizing enzymes are common in specific ethnic groups, further studies of these polymorphisms in docetaxel pharmacokinetics are warranted (Table 4).

**Discussion**

This review articles demonstrates how interethnic and interindividual differences affect both the response and toxicities of chemotherapy. Identifying genetic variants has the potential to favourably impact cancer care. However, there are challenges involved in studying the pharmacoethnicity of cancer therapies. Firstly, understanding the underlying genetic mechanism of these differences often requires a diverse population with large trials and international collaboration. There are also often more than one gene affecting chemotherapy outcomes and toxicities, uncommon but potentially important polymorphisms and lastly, chemotherapy cannot be administered in healthy subjects (74).

Despite these limitations, the identification of the UGT1A1*28 allele in irinotecan metabolism is a successful and encouraging example of how these efforts can potentially translate into clinical practice and better outcomes for our patients. The FACS, LC00-03, and S0003 with a common arm of carboplatin and paclitaxel is also another feasible way of comparing pharmacogenomic results and evaluate population related differences in chemotherapy in a setting where joint clinical trials sponsored by the US National Cancer Institute were not possible.

Other than ethnic differences, treatment efficacy and outcomes are also explained by differences in diet and lifestyle, access to healthcare, cultural barriers and environmental exposure to carcinogens and pathogens (75). In the 1980s, about 70% of lung cancers occurs in the developed world. With the decline of tobacco use in the Western countries, the burden of lung cancer is shifting to the developing world with at least 50% of all lung cancers now occurring in the developing world (76). Another study demonstrated how black patients with early stage NSCLC...
Table 4 SNPs and effect on Docetaxel metabolism

| Gene      | Function                                                                 | Polymorphism                        | Ethnic group in study population | Associations                                                                 |
|-----------|---------------------------------------------------------------------------|-------------------------------------|---------------------------------|-----------------------------------------------------------------------------|
| CYP3A5    | Drug metabolism: group of heme-thiolate monoxygenases, involved in an NADPH-dependent electron transport pathway | *1, *3 (rs776746)                   | Asians (Singapore)              | No significance difference in docetaxel clearance among genotypes; CYP3A5*3 homozygotes tend to have lower midazolam clearance indicative of reduced CYP3A5 function (66) |
| CYP3A4    | Drug metabolism: group of heme-thiolate monoxygenases, involved in an NADPH-dependent electron transport pathway | *1B (rs2740574)                     | Caucasians (USA)                | Increased docetaxel clearance (67)                                         |
| CYP3A5    | Drug metabolism: group of heme-thiolate monoxygenases, involved in an NADPH-dependent electron transport pathway | *1A (rs776746)                      |                                  |                                                                              |
| CYP39A1   | Drug metabolism: converts 24-hydroxycholesterol into 7-alpha-hydroxylated product | 56503T > A (rs7761731)              | Japanese                        | Severe neutropenia (70)                                                    |
| ABCC10    | ATP binding cassette transporter/multidrug resistance protein ABCC10/MRP7 involved in transporting taxanes | rs2125739                          | Japanese                        | Severe neutropenia (71)                                                    |
| ABCB1     | ATP binding cassette transporter: Efflux pump, translocates drugs and phospholipids across membrane | 3435C > T                           | Asians (Singapore)              | No significant association between genotype and clearance of docetaxel was observed (66) |
| ABCB2     | ATP binding cassette transporter: Translocate drugs across membrane       | ABCC2 A > G (rs12762549)            | Caucasians (Europe)             | Better disease control and increased survival (68)                         |
| SLCO1B    | Drug metabolism: organic ion transporter                                 | SLCO1B A > G (rs11045585)           | Caucasian (USA)                 | No significant association between SLCO1B3 polymorphism and docetaxel clearance or neutropenia was observed (68) |
|           |                                                                          |                                     | Japanese                        | Neutropenia/leukopenia (69)                                                |
|           |                                                                          |                                     | Korean                          | Leukopenia (72)                                                            |
|           |                                                                          |                                     | Caucasians (USA)                | Reduced docetaxel clearance but not with neutropenia (73)                  |

have worse OS than white patients in the US. Firstly, black patients had significantly less invasive staging than white patients (OR =0.75; 95% CI: 0.67–0.83). Even when they had invasive staging, they were also far less likely than their white counterparts to have potentially curable surgery (OR =0.55; 95% CI, 0.47–0.64) (77). This study reflects how even in the same country, there is an ethnic difference in the willingness and ability of a patient to undergo treatment which affected outcomes. However, genetics still play an important role. For example, we previously discussed how Asians had more favourable RRs and OS compared to the Australians receiving the same treatment of carboplatin/docetaxel (45).

**Conclusions**

Ethnicity differences in treatment efficacy and toxicities exists in patients treated with chemotherapy. There are potential differences in trial designs, patient demographics and pharmacogenomics. Genomic diversity across racial
and ethnic groups pose unique but important challenges for therapeutic opportunities and personalised medicine. It is important to appreciate inter-ethnic differences in drug disposition as data is often extrapolated from landmark studies done in western countries to Asian populations for clinical use. Efforts made to individualise lung cancer treatment based on genetic makeup of patient is important in providing personalised care for patients.

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**Footnote**

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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