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Consensus core clinical data elements for meningiomas (v2021.1)

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Abstract

Background. With increasing molecular analyses of meningiomas, there is a need to harmonize language used to capture clinical data across centers to ensure that molecular alterations are appropriately linked to clinical variables of interest. Here the International Consortium on Meningiomas presents a set of core and supplemental meningioma-specific common data elements (CDEs) to facilitate comparative and pooled analyses.

Methods. The generation of CDEs followed the 4-phase process similar to other National Institute of Neurological Disorders and Stroke (NINDS) CDE projects: discovery, internal validation, external validation, and distribution.

Results. The CDEs were organized into patient- and tumor-level modules. In total, 17 core CDEs (10 patient level and 7 tumor level) as well as 14 supplemental CDEs (7 patient level and 7 tumor level) were defined and described. These CDEs are now made publicly available for dissemination and adoption.

Conclusions. CDEs provide a framework for discussion in the neuro-oncology community that will facilitate data-sharing for collaborative research projects and aid in developing a common language for comparative and pooled analyses. The meningioma-specific CDEs presented here are intended to be dynamic parameters that evolve with time and The Consortium welcomes international feedback for further refinement and implementation of these CDEs.

Keywords

clinical trials | consensus | core data elements | meningioma | retrospective studies

Molecular profiling of disease has redefined classification of other central nervous system tumors, like gliomas, and has opened the door for development of novel therapies targeting various genetic and epigenetic alterations.[1,2] This has stimulated a wave of recent research focused on the biological characterization of other brain tumors, including meningiomas, for which these studies were previously lacking. Meningiomas are the most common primary intracranial tumor and most behave in a benign manner and can be cured with surgery alone.[3] However, there is a less common subset of aggressive meningiomas with high risk for recurrence despite maximal therapy with surgery and radiation. These tumors are severely understudied, particularly given their poor prognosis. Most studies to date have focused on mutational assessment in meningioma. These studies have collectively demonstrated that meningiomas harbor *NF2* mutations or mutually exclusive non-*NF2* mutations in the so-called "TRAKLS" genes (*TRAF7*, *AKT1*, *KLF4*, *SMO*) as well as less common mutations in other genes such as POLR2A and DMD.[4–7] However, only a few mutations, such as those in *TERT* promoter, *BAP1*, and cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) have been associated with poor outcomes, which may in part be due to the limited number of aggressive meningiomas available for study at any given single center.[8–12] Cooperative groups such as the International Consortium on Meningiomas (ICOM) have been formed in order to pool samples across multiple centers around the world to have broader representation of aggressive meningiomas for molecular characterization and clinical study.

Pooling of data and resources from multiple centers introduces the challenge of variability in clinical definitions and reporting. Harmonizing the language used to capture clinical data across centers is critical to ensure that molecular alterations are appropriately linked to clinical variables of interest. Common data elements (CDEs), which are a combination of precisely defined variables linked with a specific set of questions common to different datasets and studies, have been used to this end in the clinical context of traumatic brain injury, epilepsy, oncology, and other diseases.[13–19] However, meningioma-specific CDEs, particularly for retrospective studies reporting on the molecular profiling of these tumors, have not been outlined. Without a common language, the maximum potential of clinico-molecular correlations cannot be realized, and in some cases, may lead to spurious findings.

To address this, ICOM has devised a set of CDEs for retrospective studies on meningiomas using expert consensus with subsequent field testing. Here, we present these CDEs for future implementation in order to facilitate consistent reporting of clinical data across different institutions and improved the development of a common language that will ultimately enable more appropriate comparisons and pooled analyses.

Methods

The generation of CDEs followed the 4-phase process similar to other National Institute of Neurological Disorders and Stroke (NINDS) CDE projects: discovery/development, internal validation, external validation, distribution (Figure 1).[15,19]

Development

To develop the Consortium CDEs, a clinical annotations committee was established and representatives from 29 institutions across 4 continents with expertise ranging across the fields of neurosurgery, neuropathology, neuro-oncology, neuro-radiology, radiation oncology, molecular/translational biology, bioinformatics, and biostatistics/epidemiology. These specific chosen fields were determined by consensus after discussion within ICOM and modeled after key personnel within a clinical multidisciplinary neuro-oncology team combined with translational research expertise. The final clinical annotations committee had focused representation with 20 members: 10 neurosurgeons, 1 neuropathologist, 3 neuro-oncologists, 1 radiation oncologist, 2 neuroradiologists, and 3 computational data scientists with representation from North America, Europe, and Australia. The subcommittee met regularly by teleconference as well as face-to-face. First, the committee reviewed clinical data elements reported from published meningioma trials as well as ongoing trials in meningiomas. Published trials were selected following a literature search on PubMed, EMBASE, Web of Science, and CINAHL using a combination of the keyword "meningioma" limited to "trials" in "human patients" from 2000 to 2019. Ongoing trials were screened on ClinicalTrials.gov, The European Union Clinical Trials Register (clinicaltrialsregister.eu), and other similar registries from Germany, the Netherlands, China, and India using the search term "meningioma" for "All Studies." Additional trials not captured with the above search methods were obtained from the citations of screened publications and through members of the clinical annotations committee. CDE forms for other diseases including, but not limited to, epilepsy, stroke, brain trauma, breast cancer, melanoma, and lung cancer from the NINDS, Minimal Common Oncology Data Elements (mCODE), American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and other registries of relatable diseases and treatment modalities were reviewed to develop a framework for the present study.[13–16,19–24] Clinical parameters relevant to studies reporting on the molecular profiling of meningiomas were listed and a data dictionary was generated by group consensus to define and standardize the reporting of each parameter not already defined in an adopted CDE dictionary. CDEs were chosen by all members of the clinical annotations committee on the predefined criteria of (1) high frequency of reporting in previously published studies and trials, (2) demonstrated prognostic value in terms of progression-free survival (PFS) and/or overall survival for meningiomas, and (3) clinical relevance as it pertains to the predisposition (eg, genetic conditions, childhood cranial radiation, etc.), development, treatment, and outcome of meningiomas. Disagreements regarding inclusion of a clinical parameter as a CDE were resolved by discussion and consensus when possible. In equivocal cases, a vote was carried out amongst the committee, and in instances of a tie, an independent neuro-oncologist not on the clinical annotations committee would make the final decision. Further open discussion then took place between committee members to categorize each parameter as either a core CDE (highly relevant clinical parameter that should be reported for all cases where possible) or supplemental

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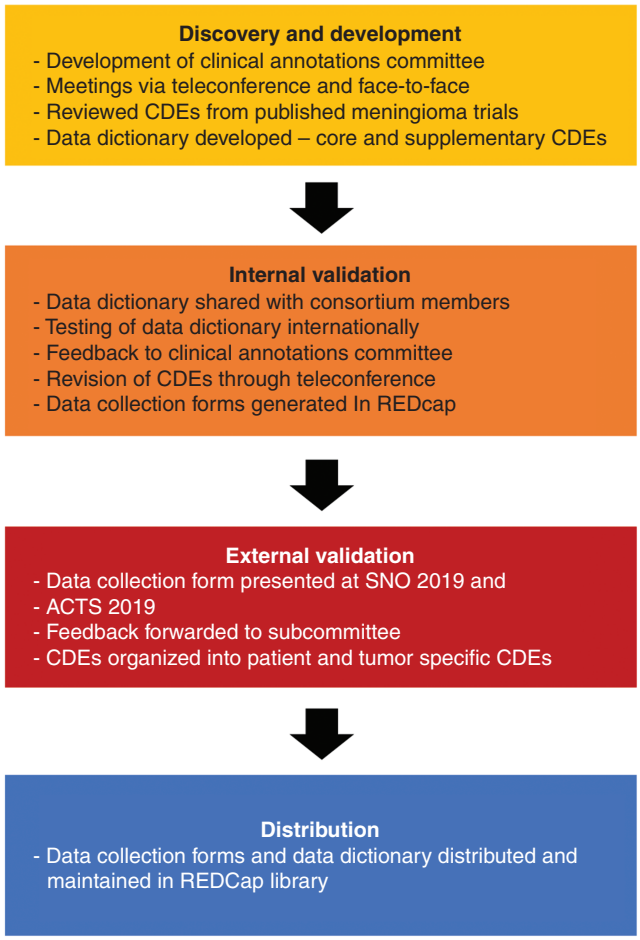

Fig. 1 Flowchart of 4-phase process for the development and validation of meningioma-specific CDEs.

CDE (relevant clinical parameter that would provide additive information but not detrimental if not reported), similar to other NINDS CDE projects.[13,15,19,25] Results from the previous discussion were presented, and discussed prior to a subsequent discussion whereby members were able to change their responses accordingly. Disagreements were resolved in a manner identical to what was described above for the initial discovery of the CDEs.

Internal Validation

The draft CDE data dictionary was shared with all 80 Consortium members and discussed via teleconference. One North American and One European site field tested the data dictionary independently by abstracting data from electronic health records for retrospective cases. Feedback was provided to the clinical annotations committee regarding (1) other pertinent parameters that should be added as CDEs, (2) removal of CDEs that were believed to have lesser clinical relevance or low levels of reporting, and (3) changes in the categorization of each parameter as a core or supplemental CDE. These changes were discussed within the Clinical Annotations Committee and the CDEs as well as their definitions were revised accordingly. Data collection forms to capture the selected elements were generated in the Research Data Capture (REDCap) data management platform.[26,27]

External Validation

The data collection form for the set of CDEs were presented at both clinical (Society for Neuro-Oncology, 2019) and epidemiological (Association of Clinical and Translation Statisticians, 2019) scientific meetings. Feedback was obtained at both meetings and provided to the subcommittee for further revisions. Based on feedback, the CDEs were further subcategorized into patient-specific and tumor-specific data elements.

Distribution

The data collection form for the set of CDEs, as well as the data dictionary are made available in Supplementary

Appendices 1 and 2. The forms will also be maintained at the REDCap Library (https://projectredcap.org/resources/library/). Following publication, the REDCap form, data dictionary, and feedback form will be made available on the ICOM's website (www.meningiomaconsortium.com).

Results

Given the complexities in relevant clinical parameters for surgically treated vs nonsurgically treated meningiomas and our objective of molecularly characterizing clinically aggressive meningiomas, the scope of this CDE has been focused to harmonize language for studies reporting on surgically treated meningiomas. Patients may harbor more than one meningioma, each with its own unique biology, clinical course and management, therefore, the defined CDEs were compiled into 2 modules: elements that would be applicable to the patient (ie, patient level) and more specific data elements that would be applicable to the management of a defined tumor (ie, tumor level). For patients with multiple tumors, although certain CDEs would remain unchanged for any given patient (eg, biological sex, race (racial/ethnic categories listed in accordance with OMB Directive 15), lifetime history of malignancy, receipt of prior radiotherapy (to meningioma or for alternative diagnosis), diagnosis of meningioma syndrome, etc.), a new set of data elements would be defined for each respective tumor from the patient level (eg, particularly age at index surgery, country of diagnosis and care, prior irradiation to that tumor, time to last follow-up, date of primary surgery, etc.), and particularly at the tumor level (all core and supplemental CDEs).[28] The complete list of CDEs as well as the data dictionary are provided in Supplementary Appendices 1 and 2, respectively. Overall, we identified 19 core CDEs that are highly clinically relevant and should be reported for all meningioma cases with molecular profiling and 16 CDEs as supplemental elements that have additive value but are not critical to report (Table 1).

Patient-Level Module

This module lists the CDEs that are collected and common for nearly all patients, even if patients have multiple tumors, as described above. To facilitate sharing of data across institutions while maintaining anonymity of samples, we felt it was critical to de-identify time-related clinical parameters by defining a tangible index date for each patient that could be used to calculate time-to-events. This way, specific dates would not need to be shared but rather could be converted to time-related events (ie, age of patient at surgery instead of providing both date of surgery and date of birth). Given that this CDE project focused on surgically treated meningiomas, the consensus was that the index date would be the date of first surgical resection for each patient. All time-to-CDEs were recorded as days before or days after this index date to anonymize the dataset. The patient-level CDEs that the Consortium defined as core elements were: age at index surgery, biological sex, country of diagnosis and care, diagnosis of neurofibromatosis 2, lifetime history of malignancy, receipt of prior chemotherapy, prior cranial radiation exposure (including irradiation to the head and neck, for example, scalp radiotherapy for tinea capitis, radiation for acne vulgaris, hematologic malignancies, head and neck cancers, etc.), prior irradiation to the meningioma, indication of whether the patient has multiple meningiomas, and time to last follow-up. Dosage of prior cranial irradiation was to be specified when known, as it pertains to the risk and latency of the development of radiation-induced meningiomas. Doses were stratified as very low (<10 Gy total), low (10-19 Gy) moderate (20-39 Gy total), and high (≥40 Gy total) dose in keeping with the historical nomenclature and a recent systematic review by Kok et al.[90,91,162]

Tumor-Level Module

For patients with multiple, separate tumors, the relevant surgical management and outcomes as well as histopathological and radiological information should be recorded independently. For each tumor, the timing of surgery (relative to the index date), location of the tumor, overall extent of resection at the time of surgery, histopathological grade according to the World Health Organization (WHO) classification, the year of the classification system, recurrence status, time to recurrence (from index surgery) were defined as the core elements.

Due in large part to the debatable and nuanced dural origins of meningiomas, several anatomical classification systems exist. The consensus anatomical definitions proposed by the Consortium take into consideration the commonly used anatomical nomenclature, the relevant locations that may impact surgical approach, and the embryological origins of meningeal development. The primary categories for location are: convexity, parasagittal, parafalcine, sphenoid wing, anterior midline, posterior fossa (anterior), posterior fossa (posterior), and tentorial, each with their respective subcategories, for example, anterior, posterior, lateral, medial, etc. (Supplementary Appendix 1).[163]

The extent of surgical resection of meningiomas is typically described according to the Simpson grade,[126] which necessitates reporting of the extent of soft-tissue and dural resection that is ultimately highly reliant on the surgeon's subjective description of the procedure.[119,120] The Consortium has therefore used a less granular but also less subjective and more clinically relevant definition for the extent of resection parameter as either gross total resection (Simpson grade 1-3) or subtotal resection (Simpson grade 4-5). This decision was, in part, influenced by the ability to objectively confirm this level of resection status using radiographic imaging postoperatively. Simpson grade, which cannot be objectively confirmed with neuroimaging alone, remains an additional supplementary data parameter for each case where available.[120]

Although tumor recurrence is the most clinically relevant outcome in meningiomas, there is no standard definition of recurrence. The Response Assessment in Neuro-Oncology (RANO) has proposed defining tumor progression/recurrence in prospective trials as an increase by ≥25% in the sum of the products of perpendicular diameters of the target lesion(s) compared to the smallest tumor measurement at baseline or a new lesion

Table 1 Core and Supplemental CDEs

Core CDEs	Supplemental CDEs
Patient-level module	
Age at index surgery[29–38]	Date of primary surgery[30,32,33,39,40]
Biological sex[41–46]	Race/ethnicity[41–44,47–49]
Country of diagnosis and care[50–55]	Hispanic race[47,48,56]
Diagnosis of neurofibromatosis 2[40,57–65]	Diagnosis of meningioma syndrome[64–70]
Lifetime history of malignancy[58,71]	Vital status[72–76]
Receipt of prior chemotherapy[77–87]	Cancer cause of death[72,74,88]
Prior cranial radiation exposure[87,89–98]	Death date
History of multiple meningiomas[66,99,100]	
Time to last follow-up	
Tumor-level module	
Timing of surgery (from index date)[101,102]	Presence of multiple lesions[66,99,103–106]
Location of tumor[107–112]	Tumor size[113–118]
Overall extent of resection[75,107,119,120]	Simpson grade[107,112,119–126]
Histopathological grade (WHO grade)[40,112,127–129]	Performance status at recurrence[30,34,76,130–134]
Year of WHO classification system[1,135,136]	Second intervention[137–143]
Recurrence status[133,144–146]	Second intervention date[137–142]
Time to recurrence (from index surgery)[127,143,147–151] Prior irradiation to tumor (meningioma)[40,129,152–155] Biospecimen availability MRI availability	Histopathologic subtype of recurrence[156–158] TERT promoter mutation[2,8,9,95,159] CDKN2A/B homozygous deletion[10,95,160,161]

Abbreviations: CDEs, common data elements; WHO, World Health Organization.

visible in axial, coronal and sagittal reconstructions of an enhanced MRI scan with ≤1.5-mm thick slices.[33] Typically, the size of meningiomas is recorded according to bidirectional measurements on gadolinium-enhanced magnetic resonance imaging with some centers performing volumetric analysis.[118,164] After surgery, some recurrent or residual meningiomas may exhibit a small degree of growth with a subsequent plateau, while others may exhibit the same initial growth but then go on to demonstrate continued or accelerated growth without a plateau. Although both of these tumors show an initial growth that could be considered a recurrence, the biology and clinical consequences of these 2 tumors are strikingly different and are not appropriately captured by simply denoting a date of recurrence (or time from surgery to recurrence/growth), and this has been noted as a particular challenge by the RANO subcommittee in meningiomas.[40,165] Whereas the above RANO definition of recurrence on a purely radiographic level may be better suited for prospective trials, where a decision in management needs to be made for patients based on imaging, the Consortium believes that retrospective biological studies may benefit from focusing their definition of recurrence to the more clinically relevant definition proposed: an increase in tumor size after surgical removal, as seen on gadolinium-enhanced magnetic resonance imaging (ideally, or on computed tomography in patients unable to receive MRI), that *necessitates a change in management*. By including reporting for both radiographic recurrence (Supplementary Appendix 1, 2.19) and recurrence requiring a change in management (change from continued observation to repeat surgery, radiotherapy, palliation, etc.; Supplementary Appendix 2, 2.21), we aim to better ascertain the utility of both these definitions of recurrence to see how they may be best applied for future reporting.

Lastly, several molecular alterations in meningiomas have been found to have prognostic value.[8–10,95] In particular, TERT promoter mutations, which have been found in 6%-10% of meningiomas, confer a higher risk of recurrence compared to their wild-type counterparts.[8,9,159] In addition, homozygous focal deletions of the CDKN2A/B, located at 9p21 has been frequently observed in anaplastic (WHO grade 3) meningiomas, and has been similarly associated with malignant progression and poorer prognosis.[10,95] Both of these molecular alterations are planned to be incorporated into the most recent update of the WHO classification for meningiomas, as stand-alone diagnostic criteria for anaplastic meningiomas. Therefore, we have included them as supplemental CDEs. Due to the lack of routine molecular testing currently available at the majority of sites worldwide, in order to facilitate the generation and sharing of molecular data, transfer of physical tumor and patient biospecimens may be required to sites that have the resources and expertise to process them appropriately in order to produce these data for sharing. Therefore, we have also included as a supplemental CDE, the availability of tumor tissue and plasma, that can be available for transfer between centers.

Discussion

Here we present the first expert-generated meningioma-specific CDE that can be applied for biological research. The CDEs have been generated and vetted through an international, multidisciplinary clinical and translational science expert consensus as well as subsequent field testing and are now made available for distribution. Adoption of these CDEs in studies that include surgically resected meningiomas will drive consistency in reporting and thereby facilitate comparison of results and more meaningful pooled analyses across different studies and between different research groups.

Nonoperative meningiomas such as those treated with radiotherapy alone represent a different population of tumors than those that are treated with surgery, with their own critical parameters that merit further discussion and consideration. Similarly, quality-of-life (QoL), patient experiences, and challenges associated with survivorship are gaining increasing attention in meningioma-related research and are critical given the often-long survival of these patients.[30,130–132] Although defining these parameters was outside the scope of this particular initiative, the modular format we have established with our CDEs for surgically managed meningiomas have closed some of this gap and will allow for expansion of our CDEs to accommodate these important parameters in the near future.

To facilitate widespread dissemination, we have generated data collection forms that adopt the CDEs presented here using the Research Data Capture (REDCap) data management platform. REDCap is a free, secure, web-based application designed to support data capture for research studies and has been widely used by academic, nonprofit, and governments to create secure online forms for data capture, management, and analysis with minimal dedicated training required.[26,27] It has been used recently by the American Association of Neurological Surgeons, Congress of Neurological Surgeons, and The Children's Brain Tumor Tissue Consortium for various surveys and data-sharing and provided an optimal platform for the dissemination of our forms and data libraries.[166,167]

The CDEs and their definitions designated in this study were selected to provide comprehensive annotation for meaningful clinical correlations but also to be efficient for data extraction. Decisions to include specific parameters were made by considering the time and resources needed for data collection with the importance of the data for clinical correlation. Feasibility of data collection as well as standardization approaches for collection are also important factors, as some parameters are not routinely reported in electronic health records in the format that would facilitate data extraction. For example, the bidimensional measurements of the tumor may not be routinely reported on magnetic resonance imaging at all institutions and therefore may require significant retrospective analysis of past imaging which may or may not be available. Additionally, for some tumor types, the bidimensional measurements are challenging to record given complexities in the shape of tumors that are not spherical or geometric (eg, en-plaque meningiomas, bilobed tumors). While this information can be useful, the limitations in the routine recording of this information as well as the time involved in reviewing each case retrospectively limit enthusiasm for setting these parameters as core elements. However, with advancements in machine learning protocols for data extraction and volumetric imaging analysis, it is possible that clinical parameters that were once considered resource-intensive for collection can become easily abstracted. For that reason, we intend the CDEs presented here to be dynamic tools and expect that they will evolve with time as the care of meningioma patients does as well.

The CDEs we present here obtain the majority of basic elements of the ASCO-mCODE.[168] In addition to these basic elements, we define disease-specific parameters that are highly relevant for meningioma research. A systematic review by Kaley et al attempted to define outcome benchmarks for patients with surgery- and radiation-refractory meningiomas for design of future clinical trials. They found that unsurprisingly, there was substantial heterogeneity in the study design and patient inclusion criteria of medical trials in meningioma which made interpretation of the literature and comparison of different trials and treatments challenging. They found that studies varied in their reporting of overall survival vs PFS, and at different intervals. The most consistent response metric across studies, and therefore the only outcome that was able to be summed across different studies, was PFS at 6 months.[82] Although our CDEs were designed for pooling of data from retrospective studies as opposed to prospective data collection for trial design, much of its content can also be utilized for the latter purpose as many of the same metrics are covered.

Lastly, although genomics research is gaining attention in meningioma, genomic testing of tissues is still not routinely performed at most institutions for the clinical care of meningioma, and therefore, molecular data are not included in our specific CDEs at the present moment. However, the clinical data covered by our CDEs are essential for ascertaining the clinical significance of novel molecular findings, as it pertains to patient outcomes, demographics, and tumor characteristics. Moreover, routine biochemical laboratory and test results, although important for the clinical care of patients, have not been robustly demonstrated to have relevance within translational meningioma studies and are therefore not included in our current set of CDEs. However, current platforms are being developed in neuroscience and bioinformatics for the sharing and analysis of multidimensional data including but not limited to imaging and molecular data. Increasing use of these platforms and integration of consensus molecular definitions into CDEs in the future for meningiomas and other brain tumors is inevitable and is the logical next step as we transition into molecular-based classifications of brain tumors that can reliably predict clinical behavior and anatomy. This will be particularly pertinent for the subsequent update in the WHO grading of meningiomas as TERT promoter mutation and CDKN2A/B homozygous deletion are listed as optional criteria for the diagnosis of WHO grade 3 meningioma. These molecular alterations have been included in our supplemental CDEs. In order to implement further molecular alterations that have prognostic

value in meningiomas, we intend to integrate molecular pathologists and basic scientists in the field of genomics in order to develop another set of more comprehensive, consensus molecular CDEs. The use of CDEs facilitates the pooled analysis required for molecular characterization of rare tumors, such as clinically aggressive meningioma, that we hope will usher in refined diagnostic and clinical paradigms seen in other diseases. The proposed CDEs for surgically resected meningioma are intended to harmonize with existing CDEs adopted across oncology and the neurosciences to enable a common language of scientific discovery.

Readers who are interested in providing feedback regarding these CDEs are encouraged to visit the website for the ICOM (www.meningiomaconsortium.com/contact/) for the updated data dictionary, REDCap data entry form, and feedback form. All feedback will be reviewed at our quarterly Clinical Annotations Committee meeting and considered for inclusion in subsequent iterations of our CDEs.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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Conflict of interest statement. None to disclose.

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