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Special Article

Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias

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ABSTRACT

The COVID-19 pandemic is causing global morbidity and mortality, straining health systems, and disrupting society, putting individuals with Alzheimer's disease and related dementias (ADRD) at risk of significant harm. In this Special Article, we examine the current and expected impact of the pandemic on individuals with ADRD. We discuss and propose mitigation strategies for: the risk of COVID-19 infection and its associated morbidity and mortality for individuals with ADRD; the impact of COVID-19 on the diagnosis and clinical management of ADRD; consequences of societal responses to COVID-19 in different ADRD care settings; the effect of COVID-19 on caregivers and physicians of individuals with ADRD; mental hygiene, trauma, and stigma in the time of COVID-19; and the potential impact of COVID-19 on ADRD research.

Amid considerable uncertainty, we may be able to prevent or reduce the harm of the COVID-19 pandemic and its consequences for individuals with ADRD and their caregivers. (Am J Geriatr Psychiatry 2020; 28:712–721)

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected

in late 2019. It has been identified as the cause of COVID-19, a respiratory illness of varying severity. On March 11, 2020, with COVID-19 affecting 113 countries or territories, the World Health Organization declared

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COVID-19 to be a pandemic of “alarming levels of spread and severity.”¹

While the situation is rapidly evolving, this pandemic has already disrupted the world in three major ways: due to its direct health impact, its impact on the health care system, and the social and economic consequences of the response to the pandemic. During normal times, individuals with Alzheimer’s disease and related dementias (ADRD) are among the most vulnerable persons in society, depending on family or professional caregivers for their day to day survival. This pandemic further exacerbates their vulnerability, due to both the morbidity and mortality from COVID-19 and the indirect effects of the pandemic on the social supports and the health care system on which they depend.

An understanding and appreciation of the current and potential impact of the pandemic on individuals with ADRD can help in their care. These considerations can also influence the decisions of caregivers, health professionals, institutions, and policymakers. Thus, in the context of a rapidly evolving situation, this Special Article discusses and proposes mitigation strategies for six major issues: 1) why individuals with ADRD are at high risk for COVID-19 and its associated morbidity and mortality; 2) how COVID-19 will impact the diagnosis and clinical management of ADRD; 3) the impact of societal responses to COVID-19 in different ADRD care settings; 4) the impact of COVID-19 on caregivers and physicians of individuals with ADRD; 5) mental hygiene, trauma, and stigma in the time of COVID-19; and 6) how the potential impact of COVID-19 on ADRD research threatens the patients of tomorrow. (In this Special Article, we consider mild cognitive impairment [MCI] as the least severe form of ADRD.)

(1) Individuals with ADRD are at High Risk for COVID-19 and its Associated Morbidity and Mortality

Several features of ADRD may increase the risk of contracting COVID-19. Some individuals with ADRD may be unable to follow the recommendations from public health authorities to reduce the transmission of COVID-19: hand hygiene; covering one’s mouth and nose when coughing; monitoring for and reporting symptoms of COVID-19; maintaining physical distance from others; and self-isolating by remaining

alone at home.² Some with MCI or milder dementias may be unwilling or unable to comply due to apathy or depression. Those with more severe dementias will not be able to understand, appreciate, or remember most of these recommendations due to the severity of their short-term memory loss and overall cognitive impairment. Finally, behavioral and psychological symptoms of dementia (BPSD), such as motor agitation, intrusiveness, or wandering, may undermine efforts to maintain isolation.

Despite considerable uncertainty and variability in estimates of COVID-19 outcomes, age and comorbid medical conditions have consistently been the most significant factors associated with a poor prognosis including hospitalization and death.^{2–4} Age is the best established risk factor both for ADRD and for symptomatic and severe illness and mortality from COVID-19.⁴ This is illustrated by the situation in Italy where over a third of confirmed cases and approximately 9 of 10 deaths are occurring in individuals 70 years and older.³ Precise estimates of outcomes will only be known in time, but they seem to depend on local circumstances such as demographics and resources, in particular the ability of the health care system to cope.

Beyond age, increased morbidity and mortality is expected in patients with ADRD due to the association of ADRD with physical comorbidities and other features of ADRD. Individuals with dementia are more likely to have cardiovascular disease, diabetes, and pneumonia compared to individuals of the same age without dementia.⁵ These conditions have been associated with poorer outcomes including death, in individuals with COVID-19.⁶ Among 1,099 cases of laboratory-confirmed COVID-19 in China, pneumonia occurred in over 90% of cases.⁷ Absent the pandemic, mortality from pneumonia has been reported to be twice higher in individuals with dementia compared to those without dementia.⁸

(2) COVID-19 Will Impact the Diagnosis and Clinical Management of ADRD

A rapid increase in the number of COVID-19 cases is adversely affecting health systems and is causing a shortage of hospital beds and a strain on health care providers.⁹ Increased demand on health systems may also result in the diversion of resources away from patients with chronic diseases, including those with ADRD.

The suspension of elective and nonurgent care is occurring in many affected areas. The availability of urgent and intensive care resources becomes compromised when the prevalence of severe cases of COVID-19 exceeds local resources.¹⁰ Individuals with ADRD may suffer disproportionately from constraints in resources due to the chronic nature of their illness and their specific care needs.

Workup, Diagnosis, and Clinical Follow-up for ADRD

The workup and diagnosis of ADRD is vulnerable to disruption in several ways. As primary care providers and specialists are being redeployed to address medical emergencies, these physicians are not available to work up neurocognitive disorders. Attending a clinic for one or more appointments and visits for blood work and neuroimaging expose frail individuals to risks that may exceed the benefits of timely evaluation and regular monitoring.

In many jurisdictions, outpatient physicians have transitioned to providing virtual care, completing assessments and follow-ups by telephone or videoconferencing. These modalities may not be adequate to perform the physical and neurological examinations or some of the cognitive tests required when diagnosing MCI or dementia or monitoring their progression. In some cases, it may be possible to provide an initial visit in person and follow-ups remotely. Otherwise, diagnosis and care may have to be deferred or limited.

Medication Management of ADRD

The use of anticholinesterase inhibitors and memantine is common in patients with ADRD. Medications frequently used for the treatment of BPSD include antipsychotic, antidepressant, antiepileptic, and other psychotropic medications.¹¹ Patients who are stable on medications may be impacted if the supply of their medication is disrupted due to missed visits, disruption of pharmacy pickup or delivery, or supply chain problems.

Initiating a new medication during the pandemic may be associated with higher risk, particularly if components of routine screening are disrupted such as in-person clinical assessments, blood work, or electrocardiogram, or the ability to follow up on adverse events in a timely manner. Rare but serious adverse

events associated with medications used in the treatment of ADRD and BPSD—e.g., bradycardia, gastrointestinal symptoms, falls, fractures, cardiovascular events, or strokes—carry higher morbidity and mortality if access to urgent care is impeded. In the context of social isolation, individuals with ADRD who rely on family or health professionals for reminders or assistance with taking their medications are at risk for sudden discontinuation of medications. The risk-benefit ratio of some medications in dementia may shift towards harm if adequate prescribing and monitoring is not possible.

Nonpharmacologic Management

Common nonpharmacologic interventions for ADRD in general, and BPSD in particular, involve social and physical contact such as social groups, exercise groups, and pet therapy. A limitation on resources and a need for physical distancing will not merely suspend these interventions, it will also result in increased isolation, a lack of physical exercise, decreased social engagement, and a suspension of purposeful activity. While confined at home, many people are now using technology to socialize and even exercise in group; individuals with ADRD may not be able to use electronic tools and software (See below).

Medical Care Following the Pandemic

Resolution of the pandemic may be associated with an increased demand for care that was deferred. Individuals with ADRD and their family may also need assistance to resume care and address complications that arose from the lack of follow-up and monitoring or from the disruption in health-promoting interventions.

(3) Impact of Societal Responses to COVID-19 in Different ADRD Care Settings

The societal response to the pandemic includes travel restrictions and home confinement (“lockdowns”). People are encouraged or required to isolate socially and not to leave their home. Nonessential businesses are shut down. The extent and duration of these social distancing measures is uncertain, but it may be significant and prolonged in some jurisdictions. In this

context, many resources upon which patients with ADRD depend may become unavailable.

Depending on the severity of their illness, individuals with ADRD live in various settings and rely on the availability and accessibility of various resources. In the context of the COVID-19 pandemic, these settings may influence both the risk and impact of societal consequences of COVID-19.

Community

Most individuals with milder ADRD have minimal care needs and live in the community where they may have established robust supports. However, their ability to live in the community may be threatened if it depends on services that are disrupted by the pandemic. Delivery services such as Meals on Wheels may be delayed or disrupted due to increased demand, closures, or supply chain failures. Family or professional caregivers (e.g., home health care workers) providing in-home support for activities of daily living can also become unavailable due to increased demand, workers' illness, or required isolation due to exposure; some workers may also be prevented by their employer from working in multiple settings. Individuals with ADRD living in the community may be particularly vulnerable if they are unable to seek help should they fall ill. COVID-19 can be associated with a sudden deterioration of respiratory status and cardiac complications.¹² Thus, symptomatic patients require frequent check-ins, while maintaining physical distance.

Many individuals with ADRD who rely on personal savings and investments are also at risk of financial adversity due to the economic consequences of the pandemic. As other people, they may need to access government programs for financial support. Also, they are less likely to drive a personal vehicle,¹³ instead relying on mass transit or transportation services that increase their exposure and risk of infection. They may benefit from assistance in identifying safe means of transportation, and in reducing their need to leave home by facilitating deliveries and deferring nonessential travel.

Those living alone in the community may also suffer from loneliness due to increased isolation and disruption of group activities. Creative ideas to incorporate alternative social physical activities safely within the home are needed. Whereas people are

turning to technology to stay socially connected and access services including health care, some individuals with ADRD may have trouble using technology due to cognitive impairment. They may need instruction and support to use these tools.

As with any disaster, individuals with ADRD and their family need to make contingency plans for the provision of essential services. Families' and caregivers' awareness of the potential risks and disruptions described above for patients with ADRD living in the community may help mitigate their impact. Potential mitigation strategies include increased support in the form of more frequent contact by telephone or video chat, problem solving to maintain delivery and caregivers' services, planning for potential disruption, or temporarily moving to a location where the required supports can be provided. Paradoxically, some families may be able to temporarily provide support at home because they are unable to work due to lockdowns or other restrictions.

Group and Assisted Living

Many of the issues faced by individuals with ADRD in the community also apply to those living in group and assisted living environments. In some cases, the increased risk of infection associated with large groups may shift the risk-benefit ratio towards returning to one's home, if it is an option. However, many individuals with ADRD require a supportive living environment because of a decreased level of functioning. In these settings, physical touching and toileting, crowding and shared rooms, and staff working in multiple settings may further increase the risk of COVID-19 transmission. As discussed above, features of moderate to severe dementia such as severe memory impairment, and BPSD such as wandering, and agitation may thwart attempts to promote the actions recommended to reduce risk of transmission. In the other direction, imposition of increased hand hygiene, isolation, or restriction of visitors and activities may worsen cognitive symptoms or BPSD, increasing further care needs and risks.

Long-Term Care

Individuals with ADRD living in long-term care (LTC) ("nursing homes") face all the challenges of those in supportive living environments, and

additional risks. Their higher dependence on caregivers and health care providers eliminates the possibility of physical distancing. In these settings, personal protective equipment (PPE) may be rationed for confirmed or suspected cases or even become unavailable.⁹ When COVID-19 affects LTC homes, it can have a high attack rate and case fatality rate—for example, a case fatality rate of 33.7%—34 fatalities among 101 affected residents—has been reported in a Washington State LTC.¹⁴ This home also experienced a significant disruption to staffing, with 50 health care workers reported to be infected.¹⁴ Many staff of LTC work at multiple facilities or in private homes increasing the risk of transmission and disruption of care beyond an impacted facility.

Hospital

Patients with ADRD are hospitalized due to BPSD, comorbid illness, or inability to care for themselves and lack of access to supportive services or LTC.¹⁵ Hospitals present the same risks as LTC, with additional risks. Hospital staff and physicians are highly vulnerable to contracting COVID-19: of the first 48,548 confirmed cases in China (as of February 14, 2020), 1,716 (3.7%) were health care workers and professionals,² as were 2,026 (9.0%) of the first 22,512 confirmed cases in Italy (as of March 15, 2020).³ The risk of COVID-19 nosocomial infection is high due to high staff ratios and turnover, high patient volumes, crowded rooms, rapid inflow of detected and undetected cases of COVID-19, and constrained supply of PPE. For reasons discussed above (age, comorbidities, behavioral, and cognitive problems), individuals with ADRD are among those at highest risk of nosocomial infection.

In many communities affected by COVID-19, hospitals get strained or overwhelmed.⁹ Hospitalized individuals with ADRD may be particularly affected because they are less able to monitor their care or advocate for themselves. Decreased nursing time has been shown to be associated with increased medical errors and adverse events in dementia.¹⁶

The need for hospitalization implies a more severe illness. Patients with severe BPSD may be at even higher risk for the behaviours discussed above that elevate transmission of infection. On a South Korean psychiatric ward, 101 of 103 inpatients were infected and 7 died during a COVID-19 outbreak.¹⁷ Upon

admission, hospitals need to evaluate the risk to individuals with ADRD and the risk to others, in the context of potential, suspected, or confirmed cases of COVID-19. Planning for these situations is needed to clarify the ethical issues, local legal framework, and institutional policies that impact a decision with respect to the need for and use of locked seclusion, chemical and physical restraints, and end of life or palliative care in high risk situations.¹⁸ Regardless of choices made by patients with ADRD or their family members, health care interventions taken for granted may have to be rationed in some jurisdictions affected by the pandemic (see below).

Placement into Unexpected Settings

In addition to the usual settings in which patients with ADRD receive care, the pandemic will force some patients into unexpected and suboptimal environments with their own challenges. Hospitals dealing with or preparing for a surge in COVID-19 patients are discharging or diverting some patients with milder cases to hotels, convention centres, tents, and shipping containers.¹⁹ While the physical needs of some medically stable patients with ADRD may be met in these alternative settings, their cognitive and behavioral needs may not. During the pandemic, the perennial lack of availability of safe and adequate housing options for individuals with ADRD, combined with an unprecedented strain on medical and social resources, could create its own crisis, leading to unprecedented levels of morbidity and mortality in this frail population.

(4) Impact of COVID-19 on Caregivers and Physicians of Individuals with ADRD

As most patients with ADRD depend on caregivers, the impact of the pandemic on formal and informal caregivers need to be considered. In the best of time, the physical and mental health of some caregivers is precarious.²⁰ During this pandemic, some caregivers may become ill, they may need to isolate and be unavailable, or they may develop anxiety and other mental health issues. As discussed above, due to the sudden unavailability of established services, family members may have to become caregivers for a relative with ADRD. Grief and its consequences are likely in family caregivers who have lost a loved

one²¹ and in professional caregivers who have lost a patient.²² All of the above will lead to exhaustion and burnout.

As discussed above, specific aspects of caring for individuals with ADRD are incompatible with physical distancing. Inadequate or unavailable PPE or training related to its use sets the stage for viral transmission. Responding to agitation and threats of violence typically requires urgent interventions that impede proper PPE use and increase further the risk of viral exposure.²³

Many patients with ADRD have “do not resuscitate” status, including advanced directives not to transfer them to an acute medical floor. As a result, in some settings, if these patients develop COVID-19, neurologists, geriatricians, geriatric psychiatrists, or primary care providers will have to practice out of their scope and care, managing the symptoms and distress associated with pneumonia. However, this issue goes beyond COVID-19 and pneumonia. As discussed above, during this pandemic, many patients with ADRD who want to receive the full spectrum of care, including intensive care and intubation, may not be able to access optimal acute care for any medical issue, not just COVID-19. All physicians may have to treat a variety of medical issues that would have otherwise been treated by specialists. Preparatory discussions with patients and family members are needed to clarify the goals of care should these dire circumstances arise; they are particularly crucial if advance discussion of code status have not yet occurred or are not clearly documented.

Health care workers involved in ADRD care are already exposed to suffering and deaths.¹⁴ Their stress and anxiety may be further increased by the current risk to their own safety. The number of cases, deaths and societal impact of COVID-19 has already exceeded those observed during the 2003 epidemic of SARS. As following SARS, we need to be prepared to address the serious and long-term mental health effects of COVID-19 on health care workers, including post-traumatic stress disorder and depression.²⁴

(5) Mental Hygiene, Trauma, and Stigma in the Time of COVID-19

The COVID-19 pandemic threatens to disrupt not only the active care of individuals of ADRD, but also the basic routines that promote their mental health.

The pandemic and its social consequences may cause fear, anxiety, and anger. They will disrupt all forms of social interaction, possibly for a prolonged period of time. A lack of physical closeness may lead to increased loneliness and sadness. Exercise is recommended generally and specifically for individuals with ADRD, and confinement reduces access to exercise. Sleep disturbances is common in ADRD and sleep may be further disrupted due to anxiety and loss of social rhythms (“zeitgeists”).²⁵ In turn, lack of activities and sleep loss and stimulation may cause delirium in individuals with ADRD, contributing further to morbidity and mortality.²⁶

Like health care workers, individuals with ADRD may experience the loss of friends and family due to COVID-19. These losses may lead to grief, bereavement, or frank depression, a common feature of ADRD.²⁷ The pandemic and its consequences may also be experienced as a trauma, followed by post-traumatic stress disorder. In turn, stress and trauma can accelerate cognitive decline.²⁸ Age, illness, depression, trauma, and dementia are all risk factors for suicide.²⁹

During the pandemic, individuals with ADRD may be doubly stigmatized. Stigma is already a pervasive issue in ADRD.³⁰ Individuals with, or at risk of exposure to, COVID-19 have been stigmatized.³¹ Risks of stigma include ostracization and denial of health and social services,³¹ which comes at time of potential scarcity of resources to be allocated.³² Rationing raises triage issues beyond some of the logistical issues discussed above. Will older individuals with mild ADRD be able to access intensive care beds? If they are already on a ventilator, will they be taken off to reallocate these scarce resources to younger patients? How will these decisions be made ethically? What will be the psychological impact of triage on health professionals? A response to these complex questions is beyond the scope of this paper. However, some ethicists have proposed a framework to address these issues in the unprecedented context of the COVID-19 pandemic.³²

(6) Impact of COVID-19 on ADRD Research Threatens the Patients of Tomorrow

The discussion above has focused exclusively on the immediate risks and impact of the COVID-19

pandemic for individuals with ADRD, i.e., the patients of today. This pandemic also threatens the “patients of tomorrow.” Researchers have already sounded the alarm on how the COVID-19 pandemic may affect clinical research in unprecedented ways.^{33,34} The consequences may be even more dire for ADRD research. Over the past two decades, ADRD has become one of the most active areas of both basic and clinical research, attracting major industry, government, and philanthropic funding in the Western world. As of March 31, 2020, a search on *clinicaltrials.gov* using the key words “dementia” or “Alzheimer’s disease” reveals 592 active studies. A recent published study of the same registry identified 156 trials (including 42 phase-3 trials) investigating 132 agents for the treatment of ADRD, and another 33 trials of 15 different devices.³⁵ Abrupt interruption of all these research studies would not only jeopardize a crucial investment society has already made, but it could also have long lasting consequences for the field of ADRD research. At the same time, the COVID-19 pandemic could be a welcome catalyst to accelerate the adoption of innovative design and methods in clinical research,³³ fundamentally changing the way participants in trials for ADRD are recruited and assessed. The rest of this section discusses whether and how ADRD clinical research can continue during the pandemic.

Essential Versus Nonessential Research Activities During a Pandemic

As per the declaration of Helsinki, “concern for the interests of the subject must always prevail over the interest of science and society.”³⁶ Therefore, all research activities such as observational studies in which participants are exposed to a potentially lethal infection (e.g., through face-to-face contact with research staff) without the possibility of any direct benefit should be suspended unless they can be continued entirely remotely.³³ When participation in a study entails provision of essential medical care (e.g., an intervention that is only available through a research trial), continuation of the study should be considered with the maximum possible mitigation of the risk of infection.³⁴ The US Food and Drug Administration (FDA) has issued some guidance regarding continuation of research participation for intervention studies and how to mitigate the risks to participants

and to the integrity of the research studies during the pandemic.³⁷

Adapting and Protecting the Integrity of Research Activities During a Pandemic

Research activities have been and remain critical in advancing medical knowledge and alleviating the suffering for millions of future patients,³⁴ particularly in the field of ADRD, for which no new medication has been approved since 2003. Clinical investigators can explore creative ways to continue their studies while mitigating the risk of COVID-19 infection both for research participants and staff. This may require modification of study protocols to collect safety and endpoint assessments remotely. Some assessments (e.g., follow-up neuroimaging for a secondary outcome) may need to be deferred or missed. Challenges in terms of selective retention, measurement errors, data missing not at random, and other confounds will need to be addressed in the analyses and reporting of the results.

Change in Risk/Benefit Ratio of Research for Participants with ADRD During an Evolving Pandemic

When a study cannot be done entirely remotely because it requires in-person visits (e.g., a trial requiring regular monitoring of safety lab tests), the increased risk of participation associated with in-person visits needs to be discussed explicitly with participants or, in the cases of most studies involving participants with moderate to severe ADRD, their substitute decision maker (SDM). The established relationship between participants (or their SDMs) and the research staff will facilitate these discussions. Institutional Review Boards (IRBs) and Data and Safety Management Boards would also need to be involved in reassessing the risk and benefit ratio of continuing participation in these studies. A few clinical trials may consider not just to continue following and monitoring current participants, but also to recruit new participants. Except for some rare trials of purely psychosocial interventions, baseline assessments and safety lab tests would require in-person visits. Again, this would require the involvement of the Institutional Review Boards and Data and Safety Management Boards and careful discussion with

possible participants or their SDM and documentation of this consent process.

Lasting Impact of the COVID-19 Pandemic on ADRD Research Methods

As with any major crisis, the COVID-19 pandemic will have a lasting impact on the way all clinical research, including ADRD research, is carried out. The current challenging situation is forcing researchers to think how they could conduct most research procedures remotely. It will accelerate the adoption of technologies and tools that permit remote assessments.^{38–40}

In the field of ADRD research, we believe it will impact most the traditional neuropsychological and functional assessments on which most primary outcomes for ADRD interventions trials are based.⁴¹ In the long term, ADRD research will also benefit from these technological innovations because they should allow the recruitment and follow-up of much larger samples at reduced costs. Finally, the COVID-19 crisis may expedite the development of non-pharmacological interventions that can be delivered at the home of the participants, e.g., home-based cognitive training or physical exercise, or that use small portable devices that can be easily used in private homes, e.g., transcranial direct current stimulation and similar devices.⁴⁰

CONCLUSIONS

The COVID-19 pandemic is disrupting the world and its health care systems in unprecedented ways. This pandemic also threatens the integrity and viability of current and future ADRD research. Local impact will vary and evolve depending on specific factors, including the incidence of COVID-19, the associated death rates, the availability of resources, and the societal changes implemented to control the pandemic. These local variations combined with the heterogeneity of ADRD make simple generic recommendations ineffectual. However, awareness of this possible impact and mitigation strategies adapted to individual and local circumstances may prevent or reduce the harm of this pandemic and its consequences for persons with ADRD and their caregivers.

AUTHOR CONTRIBUTIONS

Eric Brown: Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be 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.

Sanjeev Kumar: Substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published

Bruce G. Pollock: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published.

Tark K. Rajji: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and final approval of the version to be published.

Benoit H. Mulsant: Substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be 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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