Response to questions in Dr. Levine's letter to Drs. Stommel and Tandan, dated February 20, 2019:

Page 1, Paragraph 2: Do registries provide useful data for epidemiological research?

The significance of registries is well-known to clinicians, clinician researchers, epidemiologists, scientists and many other researchers studying diseases. Our responses below will address this question.

Contrary to the suggestion, our research is not inconclusive, as evidenced by multiple papers published in several peer-reviewed journals. It is incomplete in as much as is most contemporary research.

Page 1, Paragraph 3: The review of our research found many flaws.

What were these flaws? It will be educational for us to know so as to try and correct them in our ongoing collaborative research. As noted above, we have many papers published on our research in multiple peer-reviewed journals. We have a consortium of researchers all of whom are well known in their respective fields, including ALS specialist neurologists, epidemiologists, limnologists, toxicologists, ichthyologist, biologists, epidemiologists, statisticians and geo-tracking specialists. Cyanobacterial toxins synthesized by "blue green algae" are only one of many that may influence the development of ALS, including: nanoparticles (NPs), pesticides, heavy metals, persistent organic pollutants, etc..

We are not requesting a registry simply on the basis of our cyanobacterial toxin research. We want to ensure that all patients with ALS in Vermont are accounted for, and offered help to manage their disease. Data from the National ALS Association's 41 regional ALS Chapters suggests that there is under-reporting of ALS cases among 19 (46%) of the chapter regions, of which 42% are from rural parts of the US. Data from the Northern New England ALS Chapter, which is comprised of the predominantly rural states of Vermont, New Hampshire and Maine, indicates 14% under-reporting of ALS cases between January 2020 and January 2021. Thus, ALS patients that are not reported are denied specialty care and expertise, support and counseling, symptomatic treatment, opportunities to participate in clinical trials of new therapies, and the advantage of attending support and bereavement groups organized by chapter personnel.

Page 2, Paragraph 1: The burden of disease is less than that of a number of conditions ….

Just because ALS is a relatively rare disease, it does not negate the need for a registry. Although the physical burden of ALS is monumental on patients, the psychological and emotional stress on caregivers can be far greater than for patients. Patients not recognized as having ALS, due to incomplete or incorrect ascertainment, are thus at vastly increased risk of not having their emotional and physical well-being identified, discussed, and appropriately managed with appropriate therapies. Support and bereavement groups run by the Northern New England ALS Chapter in Vermont and across northern New England are helpful for not only patients, but also family members and children in families with ALS.

Page 2, Paragraph 2: The type of data collected in a registry is typically very basic demographics, and not necessarily data that allows for comprehensive hypothesis testing ….

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The content of information in registries depends on what the collected data is intended to achieve. The mandatory registry we would like to see implemented in Vermont would not only have demographic data, but also information on regions of domicile, environmental exposures, dietary habits, and genealogy. The National ALS Registry is not mandatory. In view of the higher proportion of cases throughout northern New England, the National ALS Registry has encouraged the identification of all ALS cases in regions and agreed to collaborate with ALS clinicians and researchers. The National ALS Registry will accept data from the Vermont Registry at no cost, and it is understood by its creators that this will strengthen the conclusions from its research. The National ALS Registry is encouraging states to set up mandatory registries to promote case ascertainment, such that appropriate services can reach all patients and families with the disease. The National ALS Registry is currently collaborating with the ALS Registry in the Commonwealth of Massachusetts (the only state in the US that currently has an ALS Registry) to further this objective.

Page 2, Paragraph 3: The costs are significant.

The cost of running the Vermont ALS Registry is anticipated to be minimal. It is expected that Drs. Stommel and Tandan have the infrastructure and finances to support this effort.

Does the Vermont Department of Health have an approximate cost of what it will cost to pay for a mandatory ALS registry? The ALS teams assembled by Drs. Stommel and Tandan have the experience and capacity to cover the management of ALS patients, and also the majority of the infrastructure and personnel expenses related to the registry. Data collected from patients can be inputted into RedCap and shared with the National ALS Registry, which supports creation of statewide registries. Data stored within the National ALS Registry is invaluable to help better and correctly identify ALS cases, and understand the genetic-environmental factors associated with the disease. If other states, especially large states, were to participate in this initiative, it would be a tremendous step forward in identifying all patients with ALS and allow better understanding of the risk factors associated with the disease.

Although ALS is relatively rare, it is a devastating disease for patients and families, thus making it imperative that all patients are accounted for and managed by experienced personnel and with the contemporary therapies available. It would be equally important to understand a disease that is potentially treatable. Intervention and support of the State of Vermont would be critical to making sure that these objectives are achieved.

Setting a precedence to better understand a lethal, potentially treatable disease at a trivial cost would seem to be a very reasonable endeavor for the State of Vermont. If this project is successful, Vermont would be only the second state in the nation to acknowledge the importance of better understanding ALS by creating an ALS Registry. If the cost of the registry is no more than minimal, why would the state not want to support such an effort?

Can we guarantee a cap on funds spent by the State? Drs.Tandan and Stommel will have no issues coming up with $25-30K to make the registry work.

There is really nothing to lose and a lot to gain by establishing an ALS Registry in the State of Vermont.

Outline of Letter:

ALS is a devastating, progressive neurodegenerative disease that usually leads to death in 2 to 3 years of diagnosis. It falls within a family of neurodegenerative diseases that includes Alzheimer's disease, Parkinson's disease and Huntington's disease. What makes ALS unique is that it is relatively easy to study and diagnose by experienced clinicians, whereas with a disease

like Alzheimer's disease it is more difficult to make a definitive diagnosis ante-mortem, and the sheer numbers of cases make it correspondingly difficult to manage. These neurodegenerative diseases share common mechanisms of disease causation, and hence understanding the causes of ALS almost certainly will shed light on these other diseases. Not only is ALS devastating to patients, but also to families, caregivers and children. ALS Centers of Excellence that run clinics and support groups are beneficial for all those involved, once patients are identified and referred to these facilities. Veterans of the wars in the Middle East have about a two-fold higher rate of ALS than the general population; often ALS patients are not aware of benefits that are available through the VA system. The ALS Centers of Excellence at the University of Vermont Medical Center and Dartmouth-Hitchcock Medical Center see the vast majority of Vermont ALS patients, but there are up to 15-20% of patients are not seeing ALS specialists for routine care and are thus denied such care.

Vermont has a history of ALS care and research. The first family found to have a genetic form of ALS was described in Vermont, the Farr family, from the St Johnsbury area. Both the UVMMC and Dartmouth ALS clinics follow patients from families where several members have come down with the disease. It would be very helpful to identify all cases of familial ALS in Vermont so as to be able to offer them new and exciting contemporary therapies that are now being studied. Currently, there is only one reportable/mandatory registry for ALS in the US, that being in Massachusetts. The registry in Massachusetts was set up in memory of Governor Cellucci, who died of ALS. It would be wonderful for Vermont to become the second state in the country to have a reportable ALS registry, and help familial and non-familial cases of the disease. It will reflect well on Vermont's desire to better understand neurodegenerative disease in general, and ALS in particular, that afflict so many of its residents. For example, a Registry will be able to answer several questions. Are all the residents in the state with the disease receiving expert care? Is the incidence of ALS increasing? Are there identifiable risk factors and clusters of ALS cases in Vermont? Are people getting ALS at an earlier age? Can Vermont identify genetic cases of ALS?

There is a National Registry for ALS but it is not mandatory to participate in, and thus it is not widely used for epidemiological studies as of yet. The Massachusetts registry cost approximately $250,000 to set up, but the Massachusetts population is approximately 10 times greater than that of Vermont. We have been in contact with the National Registry, and have worked in the past closely with that group. The National ALS Registry group is interested in serving as an infrastructure for any state that might be inclined to set up a mandatory registry and report its cases directly to the National Registry. In a state the size of Vermont, and with an infrastructure shared with the CDC/National Registry, we estimate that a budget of $25-$30,000 would suffice to set up a mandatory ALS registry in Vermont. There would be expenses such as forms, mailings, postage and potential legal help. We would envision using residents, medical students, and ALS team members at UVMMC and Dartmouth to help us with the 30-40 new cases of ALS expected each year.

How to enforce the reporting of ALS cases to the registry?

There are undoubtedly many ALS patients that do not participate in ALS Centers of Excellence clinics that exist both at UVM and at Dartmouth. There are regular support groups, and resources for patients and families, through the ALS Association all of which can be very helpful to patients and their families. There is also the issue of veterans with ALS not knowing that they are entitled to many services and benefits through the VA, which would otherwise be available to them through their insurances but with much paperwork and lag time.

What is the research being undertaken by the Dartmouth and UVM teams?

Our research has not been confined to cyanobacterial toxins. We are interested in any number of toxins such as persistent organic pollutants, air pollution/nanoparticles, pesticides, herbicides and heavy metals. We have identified a number of environmental factors related to ALS. Many of these toxins have been linked to veterans. We are examining gene/environment interactions to identify possible risk factors for ALS. We are also interested in the nutritional status of ALS patients and body mass index (BMI) as related to prognosis with patient's disease. This is an area that has been thoroughly researched by Dr. Tandan.

Location of Registry

We envision the UVMMC being the central location for the ALS Registry and Dartmouth being the main satellite location for running the Vermont ALS Registry. The majority of ALS patients in Vermont are shared by these two tertiary care academic medical centers and both are recognized National ALS Centers of Excellence.

How will data be entered into Registry?

Data from confirmed cases of ALS can be entered by primary care doctors' office staff, or be emailed or faxed to the UVMMC or Dartmouth ALS Centers to be entered into the registry. If necessary, and in appropriate cases, Drs. Stommel and Tandan will review the diagnostic workup data of patients to confirm the diagnosis of ALS, so as to avoid false positive diagnoses relating to ALS-mimic disorders.

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