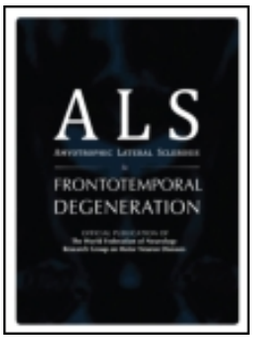

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Peer recommendations on how to improve clinical research, and Conference wrap-up

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Peer recommendations on how to improve clinical research, and Conference wrap-up

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Abstract

To promote clinical and patient oriented research, as part of the Second International ALS Conference in Tarrytown, NY, USA, seven pairs of clinicians and scientists were asked to lead discussions with meeting attendees on six major topics (one of which was discussed by two groups); each one the focus of a 90-min Breakout Session. Approximately 25 meeting attendees participated in each session. The Breakout Sessions considered six major themes: 1) Approaches to encourage clinicians to engage in more clinical research to discover the pathogenesis and cause of ALS; 2) Exploring avenues to build more effective partnerships between basic scientists and ALS physicians; 3) Increasing patient interest and commitment to participating in non-trial clinical research; 4) Brainstorming about factors that are most critical to the discovery of the pathogenesis and cause of ALS; 5) Finding ways to incorporate clinical research projects into clinical trials; and 6) Developing state-of-the-art epidemiological studies to solve the mystery of ALS. In this paper, we present the reports from each of the Breakout Sessions; and we provide a wrap-up of the entire conference.

Key words: *ALS, clinical research, peer recommendations*

Reports from the Breakout Sessions

How to encourage clinicians to engage in more clinical research to discover the pathogenesis and cause of ALS

First, we agreed that clinical research encompasses much more than performing clinical trials per se. We talked about how the core and spirit of clinical research resides in asking clinical questions, learning about the disease, encouraging collaboration between the scientist at the bench and the clinician at the bedside and, ultimately, discovering the cause(s) of ALS. Our view is that many clues to the puzzle of ALS pathogenesis will be found in the personal history, life experiences and clinical findings of each patient.

Secondly, we identified four obstacles and impediments to research: 1) Clinician-researchers find themselves with inadequate time to devote to research efforts; in general, there is a paucity of protected time. 2) There is a lack of funding for clinical

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research. 3) There is little reliable infrastructure or support network to provide the education in research methods to carry out clinical research. 4) Young clinicians entering the field of clinical research may experience difficulty finding a mentor – a seasoned investigator – who can help develop initial collaborations, and gather enough momentum to sustain a research project. Finally, there needs to be education about the importance of clinical research in order to change the overall attitudes of clinicians and researchers.

Thirdly, we discussed three possible solutions to these impediments: 1) Having novel ways to obtain funding for seed money – to support initial studies that might provide preliminary data – and for larger sums to move a promising project forward. 2) Having the infrastructure of an educational program along with mentoring by senior clinical researchers available to young investigators to teach them how to design and implement clinical research programs. 3) Creating networking opportunities to help build collaborative groups that include new investigators. 4) Making resources available to investigators for designing and implementing collaborative clinical research projects.

To move clinical research forward we believe it is critical to have an invested, engaged and interested patient population, and three additional components of the research endeavor that are central to the success of any clinical research project: 1) Funding agencies to provide support for clinical studies combining basic and clinical disciplines; seed money grants for pilot studies and research infrastructure, and financial support for ancillary studies during trials including proof of concept studies. 2) Collaborative research groups (ALS Research Group (ALSRG), European ALS (EURALS), Northeast ALS (NEALS), Western ALS (WALS) consortia, etc.) to stay their present course of allocating infrastructure that involves more than clinical trials per se. We feel that collaborative groups will need to act as 'matchmakers' and publicize research opportunities, bringing clinicians with clinical study ideas together with patients. There is a need for these groups to educate patients on the importance of clinical research, how hypotheses are generated and how studies are designed. Collaborative groups become stronger and more effective when they share their databases, statistical core and study methodologies. 3) Clinical investigators need to be active participants, understanding the importance of founding clinical trials and carrying out clinically based research and, most importantly, having a commitment to follow through with clinical research. There was consensus on the importance of continued encouragement and nurturing of the younger generation of clinical investigators so that a robust spirit of investigation is ensured for years to come.

How to build more effective partnership between basic scientists and ALS physicians

Participants in this group included pure scientists, clinician scientists and representatives of government and non-government organizations.

First, we framed the problem – recognizing that there were on the one hand barriers to partnership, to interaction and collaboration, and on the other, potential opportunities to bridge any perceived divide between pure scientists and clinicians engaged in ALS research. We identified several barriers and at least an equal number of strategies that work to bring the groups together.

We believe there is a knowledge gap between basic scientists and clinicians, that differences in training, experiences and approaches to problem-solving may have led us to conceptualize problems distinctively and use different 'languages' in our respective fields. We suggested that this barrier might be lowered if we could learn each others' language, and become more comfortable with the perspectives of our counterparts, trying to adapt our respective approaches to our modes of problem-solving. As an example of the added value of this approach, a pure scientist spoke of how he is collaborating with a neurologist, bringing a clinical diagnostic method (electromyography) into the laboratory to help in studies of the SOD1 mouse.

We identified geographical barriers, whereby even in the same institution there is often a physical distance (e.g. different buildings on a campus, different floors of a building) between the two groups. If not a tangible divide, then to the perception is one of inhabiting separate 'worlds' of problem formulation and problem-solving. We agreed that enhancing our abilities to communicate with one another would help remedy the situation; pure scientists and clinician scientists have been learning each others' language all week at this meeting in Tarrytown, so that national and international meetings offer a wonderful opportunity for a mingling of mind-sets.

We talked about the importance of the proactive attitude and approach; that, for example, the pure scientist might seek out opportunities to participate in some way in the clinical experience of patient care, perhaps by joining the clinician as they identify and manage patient problems that arise during visits to the ALS multidisciplinary centers. The clinician for their part might attend seminars and conferences hosted by the pure science community concerning the underlying biology relevant to understanding motor neuron diseases.

We spoke of the challenges facing clinician scientists wishing to undertake clinical research, among them the competing pressures of caring for patients, carrying out an educational mission, and fulfilling increasing administrative demands from regulatory agencies and Institutional Review Boards (IRBs). We

suggested that the partnering between clinician and pure scientist could begin in medical school and certainly in residency programs, especially if leadership in each realm collaborated in curriculum development to foster programs that help students and residents appreciate correlations between clinical findings and the basic sciences.

We discussed the impediments to transitioning from bench to bedside. A pure scientist might have a novel idea, find a compound or chemical that works on a certain pathway critical to motor neuron integrity, or results in some positive effect in an animal model. They may find that, before their clinician partner can initiate a clinical study, the specific drug or chemical agent must endure a complex process, including the manufacturing, mass production, packaging, and creation of a placebo. The National Institute of Health (NIH) is seeking ways of facilitating the transition from bench to bedside. In future, leadership and guidance in this process are going to be essential to foster breakthroughs in the treatment of ALS.

How to increase patient interest and commitment to participating in non-trial clinical research

In this session, we discussed ways to improve patient interest, recruitment and retention in non-clinical trials. (We believe a great deal of our discussion was also germane to clinical trials.)

First, we reviewed the current state of non-trial clinical research and noted that most ALS studies have slower than expected enrollment and delayed completions. The best estimate is that only 10% of patients with ALS enroll in studies, although data in this aspect of trial research are incomplete. It is estimated that, in general, enrollment in ALS studies approximates two patients per site per month, and that it is highly variable across published studies, from 0.1 to 8 patients per site per month (1). There is clearly a need for improved data collection regarding recruitment and enrollment, and more work is needed to answer several important questions, including: How often are patients being offered the chance to participate in studies? What is the ratio of eligible to ineligible patients for any given study? How many patients decline participation and why?

We identified three major issues regarding enrollment. First was the topic of study design. There does not seem to be a specific trial design factor that explains the variability in enrollment rate across previously published trials, and the variability in enrollment rate between sites with a given trial is often much greater that the variability between different trials. Secondly, we discussed the role of the site Principal Investigator (PI). We noted the challenges facing the PI – including limited resources of time and funding, possibly incomplete knowledge of and interest in a study, and a sense of nihilism that might prevail regarding outcomes – and yet how critically important it is for the PI to maintain a relationship with patients throughout a study. Thirdly, we focused on the perspective of the patient regarding clinical research. We noted that often patients do not know about ongoing studies although new websites such as clinicaltrials.gov and trial concierge services such as provided by the NEALS consortium are expected to mitigate this, as will the creation of 'Research Ambassador' teams of patient and caregiver who will help educate and advocate for research in a forum such as an annual Clinical Research Learning Institute. Once enrolled in a study, patients may face the burdens of losing time, draining of personal finances, stress of travel to research centers, perception and fear of being a 'guinea pig', concerns about possible risks inherent in a study, uncertainty regarding whether or not they might be assigned to a placebo group, and how they might not have perceived a message of hope. It is expected that developing home based outcome measures (being developed by NEALS) will help to ease some of the burdens of trial participation. On occasion, patients will have received misinformation and they might have magnified expectations regarding improvement. Patients expect continuity of care from the PI and instead feel disappointment when duties pertaining to a study are delegated entirely to someone else who does not possess a depth of understanding about them or their disease. Finally, patients may lose interest in a study if they think there is an effective alternative therapy.

We ended the session by considering a number of ways to enhance enrollment. It has been our experience that at the most successful sites, the PI takes the time to educate the patient about their disease, explains the study rationale, listens to the patient, and addresses common misconceptions. We feel that participation increases when patients are given supplemental information, including video material. Enrollment increases when study experts are made more accessible to patients, perhaps in chat rooms (for example, ALSRG), and by using national speaker programs. We discussed mechanisms to reduce the burdens experienced by patients who enroll in clinical studies, by providing a travel allowance, subsidizing a hotel stay, developing a home visit program when patients cannot come to the site, especially when they are in the later stages of ALS. It might be necessary to modify a study when appropriate, to be pragmatic and as flexible as possible and to debunk alternative therapies, using approaches such as 'ALSUntangled' (ALSU) (2). We spoke of the importance of keeping study patients fully informed during and after a study, convening a group of experts and patients for discussion of the study's highlights, and ideas and plans for future studies. Finally, we spoke of how we might honor the participation and commitment of patients who complete a study with what we might call 'ambassador status'.

What are the factors that are most critical to the discovery of the pathogenesis and cause of ALS?

We discussed the above topics in the two independent groups. We thought that if we could develop a better understanding of the evolution of the human disease, we would have a more solid grasp on the pathogenesis of ALS. We know little concerning the biological characteristics of the at-risk population and where risk begins during the course of human development and growth. Does risk actually begin at the moment of conception? Are there developmental factors that influence risk? In our current state of knowledge, it is as if there is a 'clinical horizon' over which patients appear unheralded, events before which are currently obscure. Alternatively, does ALS occur because an essentially pristine system goes suddenly wrong catastrophically later in life? We need to improve our ability to phenotype patients once they develop symptoms; and we believe that making tissue validation a priority is essential to helping advance the field.

Practical issues that need immediate attention are: 1) the issue of selectively vulnerability; and 2) a deeper understanding of neuronal inclusions. We felt a key question that needed to be answered before the community could gain greater understanding of the disease was: Why is the motor neuron selectively damaged in ALS? Although motor neurons are not the only cells that are targeted, it is quite evident that motor neurons are selectively involved in ALS. An answer to that question might well put us on the path to more productive research. It was equally important to gain a deeper understanding of neuronal inclusions. We acknowledged that they are often seen as part of this disease. We felt it was imperative to focus on whether they have a pathophysiological role and what therapeutic implications are suggested by their presence. If they are toxic, the goal would be to eliminate them; if, however, inclusions are beneficial – perhaps having a scavenging role for cellular debris within cells – then we would want to develop strategies to enhance their functions.

We tackled the question of what accounts for regional transmission in ALS (4). What are the factors that mediate or contribute to the apparent focal onset and then spread of motor neuron involvement from one region to another? Might a protein with deleterious effect be transmitted from cell to cell? Might there be a fall-off in the level of a neurotrophic factor? Acknowledging the prominent role of genetic factors in the pathogenesis of ALS, we noted that environmental factors too were clearly crucial to an understanding of the disease, and that epidemiological research – especially, based on large prospective, longitudinal studies, in the fashion of studies performed by Kaiser Permanente (a California based managed care system with more than nine million subscribers) – would continue to deepen understanding of the disease. We agreed upon the importance of evaluating clusters of ALS prevalence, such as cases on the Kii Peninsula in Japan, other foci within the U.S., perhaps affected by fish consumption.

At present, most ALS research is carried out with the SOD1 mouse model, and while helping to advance the field, we felt that, in general, ALS research has a paucity of appropriate models and that the development of new models – both animal and cell-line models – might potentially be fruitful. Furthermore, the connection between mutant genes and cell death is a fundamental issue that should be considered in modeling. We noted that the prevailing modeling paradigm has been genetic and that, in the future, studies might utilize environmental models (e.g. inspired by recent work regarding the potential role of BMAA (3)), or apply various environmental stressors on genetic models to investigate the environment-gene dynamic interaction. This will possibly further the influence of the phenomenon of epigenetics and must be incorporated. As an incentive for new model development, funding agencies might offer a prize for a novel idea in model development.

Next, we turned our attention to factors that are crucial to successful discovery of the pathogeneses and cause of ALS. We discussed the importance of developing an infrastructure to support the science around ALS. We felt that it would be helpful to model this development on other successful disease initiatives, e.g. the ADNI program of the Alzheimer's research group. We feel it would be most appropriate for the ALS community to model this program, and have a multicenter initiative with free access to the information derived from patient studies such as CSF analysis, neuroimaging findings, skin tissue, blood samples, as well as the results of neurophysiological assessments. Furthermore, we discussed the importance of engaging in discussion with our patients regarding tissue donation, especially since most patients – knowing there is a possibility that it may hold answers to the pathogenesis of ALS – express a deep interest in making an anatomical gift.

We agreed that collaboration is of the utmost importance to foster advances in the understanding of ALS. Should we act as silos, we will be inefficient and may not reach our goals, while a healthy collaboration between clinicians and basic scientists will help us in our quest to answer questions and solve problems regarding the puzzle of ALS. In this sense, we cannot overemphasize the importance of public-private partnerships and stress the worthiness of collaboration and cooperation so that all participants feel valued and rewarded.

We discussed the importance of developing new approaches to funding. We noted that advances in biological science often occur in step changes that come through allowing innovative, as well as incremental more established research, and the natural

serendipity of biological science. This may appear a high risk strategy for funding agencies, but it offers the best potential for seminal advances in the field.

We discussed the essentiality of heightening public awareness of neurological diseases and their symptoms; to instill in the public mind that our understanding of ALS and other disorders is still in evolution, and much still needs to be done; that, in some ways, neurodegeneration is a 'scientific emergency' that requires vision and resources to address effectively. Finally, we recognized the legacy effect, how crucially important it is for established, experienced, leaders in the field to pass the torch on to the cadre of young clinicians and scientists embarking on their quest to unravel the mysteries of ALS.

How can clinical research projects be incorporated into clinical trials?

We identified and discussed two principles and six barriers to carrying out clinical research in the context of clinical trials, and we sought ways of lowering the barriers.

The first principle – using an experimental medicine approach to each clinical trial – immediately found consensus. In the spirit of cutting edge clinical research we strive to innovate as much as possible and use the clinical study as an opportunity to advance clinical research. Principal goals in ALS research are biomarker development (utilizing CSF and blood, and findings from electrodiagnosis and neuroimaging), any thoughtful approach to clarifying disease mechanisms, and testing new trial designs and novel scales. Although somewhat controversial, some in our group felt that clinical trials provided opportunities to create minimum data sets, e.g. of a biological marker or a DNA sample. We also felt it was important to minimize regulation, to resist telling researchers how, for example, to create a data set, and rather take the approach of encouraging innovation on the part of investigators.

The second principle we identified was to establish prior agreements with companies sponsoring clinical trials, so as to cement partnerships at every stage of the study. When a clinical study is incorporated into a trial we recognize the importance of negotiating with the sponsor about publications, sharing results with patients before they are revealed to the public, agreeing upon intellectual property rights, and ensuring that the clinical research community has full access to data generated by the study.

We identified six barriers: first, we believe that clinical trials become more complicated for industry when clinical research projects are embedded within them. One attempt to solve this problem is by having discussions in the early planning phases of the study, seeking to manage expected increases in workload in a rational fashion, sorting out issues of authorship related to publications, deciding upon intellectual property rights, and ascertaining whether there will be a need for additional funding.

Secondly, if a trial becomes too complicated, patients may not be willing to become involved in the study, e.g. a biomarker project that requires multiple lumbar punctures during the course of the trial may reduce enrollment. Ensuring the interest of patients requires providing thorough explanations of a study's rationale, engaging the support of patient advocacy groups and training study recruiters to help with patient motivation.

A third potential barrier is being granted permission by IRBs, a process that is more problematic when a clinical research study is included in a clinical trial. This problem might effectively be addressed by having advocates familiar with rare diseases involved in these studies.

Fourthly, agreement from regulatory agencies may be more difficult to accomplish when studies are more complicated and might be countered by organizing yearly meetings to enhance or to improve dialogue between the agency and the PIs.

Fifthly, we need to be circumspect when considering whether to expand a clinical trial, since augmentation might not be in the financial interest of the sponsor. Therefore, to achieve the desired step-up in a study, there is a need for up-front and careful negotiation to secure funding, either on the public or private side, or with the help of public-private partnerships. Finally, we noted that when a complex study is going to be carried out at a small center, the infrastructure critical to the success of the study may not suffice; therefore, we immediately agreed upon how important it is to have in place large networks of study centers that would have the resources available to support even complex research studies in smaller centers.

How to develop state-of-the-art epidemiological studies to solve the mystery of ALS

With a daunting question posed to a diverse group of clinicians and scientists we chose to borrow a method from the social sciences, called the 'nominal group technique', based on a number of premises: 1) given time-constraints and numerous possibilities, to set priorities; 2) that all participants have equal opportunity to state their priorities and ideas, without undue influence; and 3) after all participants propose priorities and debrief their colleagues, to list and rank ideas, with everyone voting privately.

We generated 38 ideas including three top priorities for epidemiological research in ALS. The top priority was to develop well-characterized incident cohorts of ALS patients with appropriate controls for etiologic and prognostic studies, giving epidemiologists the opportunity for both case-control and nested case-control studies from these populations. The second priority was to develop population based

registries with good quality phenotypes, biological specimens and questionnaire data, emphasizing the importance of good quality and standardization of data collection criteria and the need for using standard operating procedures. The third of the top priorities was to look at cohort studies nested within non-diseased unbiased populations, e.g. as might be carried out in Iceland where there are very good registry data, with good ongoing collection of a great deal of data.

Our fourth priority was to educate funding agencies regarding the three top priorities in terms of obtaining support for potentially very expensive studies. We then discussed four additional priorities. The first of these was concerned with measurement issues in terms of validation of outcome and exposure data and knowing that we are measuring exactly what we think we are measuring. We agreed upon the importance of having consortiums to standardize data collection for comparative studies. Secondly, we discussed the potential value of carrying out studies in populations where ALS is endemic, e.g. in Guam, and parts of Japan. Prior studies of endemic areas have provided information that has inspired the formulation of compelling hypotheses and laid the groundwork for subsequent studies.

Thirdly, we discussed prospective studies of individuals at high risk for ALS, i.e. individuals who are obligate familial ALS gene carriers and what kind of environmental factors might actually increase the risk of disease in these already high-risk individuals. Studying high-risk populations has the potential benefit of providing for a very efficient epidemiologic design. Finally, there was much discussion of and enthusiasm for a special focus on understudied geographic regions and populations, attempting to increase our international base to include studies in Africa, in South America, perhaps in India and south-east Asia.

Throughout the entire session, three overall themes animated the discussion: the imperative of collaboration, the need for multidisciplinary approaches, and the biological complexity of ALS. Collaborative studies are critical to advancing the field in a rare disease such as ALS. Multidisciplinary approaches are essential to deepen understanding of the epidemiology. Awareness of the biological complexity of this disease compels clinical investigators to talk to and work with laboratory scientists in the most meaningful way and go beyond descriptive information to a point where epidemiology is used to test mechanistic hypotheses in human populations. Finally, we suggest the following: the dissemination of currently available tools and protocols to anyone who wants to study ALS epidemiology; sharing contact and resource information; and the establishment of gold standard protocols by a panel of experts.

Concluding remarks

At the ALS Conference held in Tarrytown, New York in September 2011, 69 papers were presented, and 150 clinicians and scientists participated in discussions dedicated to promoting clinical research in patients with ALS. The goals were to promote clinical research in patients with ALS, to identify the causes of ALS, and to understand the pathogenesis of this disease. The proceedings of the meeting are here summarized in six reviews of the current state of ALS research. Preliminary conclusions include the following:

- Delineating the various phenotypes of ALS and defining their natural history are fundamental to understanding the pathogenesis of ALS.
- Different neuronal systems are vulnerable to the pathological process that defines ALS.
- A fundamental defect underlying neuronal degeneration in ALS, influences phenotypic heterogeneity, begins focally and propagates, spreading contiguously outward over time.
- Frontotemporal dementia with inclusions of TAR DNA-binding protein 43 (TDP-43) and ALS are two ends of a spectrum of TDP-43 proteinopathies.
- In ALS, different sets of cortical neurons – not exclusively motor neurons – are affected: astrocytes may kill motor neurons by releasing a toxic soluble agent; oligodendrocytes and microglia may also have a role in pathogenesis.
- ALS is a systemic disease targeting predominantly motor neurons but affecting other organ systems, including non-motor brain functions and skin.
- Biomarkers include some associated with pathogenesis (e.g. oxidative stress and inflammation), some that help in diagnosis (skeletal muscle degeneration), and some that help to measure progression of disease (such as metabolomics (seeking metabolic differences between ALS and control subjects)).
- There may be a therapeutic role for human-induced pluripotent stem cells (iPSCs) derived from patients with sporadic or familial ALS to generate the blend of cell types – motor neurons, astroglia and oligodendroglia – that might create ‘ALS in a culture dish’ and allow for studies of disease modeling, biomarkers, screening for potential therapeutic agents or a source for cell therapy.
- Epidemiology will play a crucial role in identifying the causes of ALS and will depend upon large multicenter or population based studies aiming to identify environmental and genetic factors in diverse populations.
- Among enduring problems is the appearance and disappearance of numerous cases of ALS

among indigenous people on the island of Guam. Solving these problems may help the understanding of ALS elsewhere.

- Chronic traumatic encephalomyelopathy (CTEM) may involve a motor neuron disease resembling ALS, and is another unsolved problem.
- At the time of the conference in September 2011, 15 known genetic mutations had been identified as causing ALS. Just a few months before the conference, a novel ubiquilin-2 mutation was described (5), making it the first gene in a protein degradation pathway that leads to protein aggregation and neural degeneration. Only a month after the conference, another newly discovered gene mutation was reported (6,7) in *C9ORF72*, a repeat expansion mutation accounting for about 30% of familial ALS and perhaps up to 4% of sporadic ALS in North America.
- There is a rapidly growing interest in the field of epigenetics, and it is likely that one of the main regulating constituents of the epigenome – non-coding RNAs – may affect expression of protein coding genes and play a role in the pathogenesis of ALS; with a deeper understanding of abnormal RNA biology, innovative therapeutic strategies may emerge for ALS.
- As we consider the strong infrastructure and reliable resources that support ALS research today, we realize that we have come a long way over the past 30 years. However, an enormous task lies ahead, and a greater depth and breadth of infrastructure and resources will be necessary to understand and modify routes to ALS pathogenesis.
- Questions affect society. Are we attracting and supporting a sufficient number of ALS research neurologists? Can we foster harmonious relations among clinicians, research scientists, and advocacy agencies? Are we supporting sufficiently the funding of NINDS for ALS research?
- It is obvious that patient oriented clinical trials are the desired ultimate goal**.** It is true that we do not have effective therapy for sporadic ALS because we do not know the etiology or the pathogenesis. We know the etiology of familial ALS but we have not yet worked out the pathogenesis of these diseases.
- The field of human genetics has made great strides in understanding basic mechanisms of disease, but an enhanced understanding of pathophysiology has not yet been translated into effective therapies for many inherited diseases.
- In the meantime, there is unanimous agreement that we must continue to investigate ALS in our patients, using all of our intelligence, imagination and passion with state-of-the-art studies, to find the pathogenesis and causes of ALS and, ultimately, discover effective therapies.

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