The ALS Challenge

Ed Rapp

Background: First medical descriptions of Amyotrophic Lateral Sclerosis (ALS) date back to the mid-1800s. ALS is a relentless progressive disease, robbing individuals of all voluntary movements – arms, legs, sitting, standing, walking, talking – and because it weakens the muscles for breathing, it is invariably and without exception fatal, usually within two to five years. Roughly 10 percent of ALS is genetic or familial while 90 percent is sporadic with no known cause or reason.

In spite of passionate physicians and scientists from around the world, to date only one drug, Riluzole (approved in 1995), has been FDA approved with only a modest effect at increasing patients' survival by, at best, three to five months. Since being approved more than 20 years ago, Riluzole has demonstrated no real effect at slowing the loss of any motor function; patients who take the drug live a bit longer, but not better.

Although relatively common (one in 500 men will die of ALS), unless people have been directly impacted by ALS, most are unaware of the disease. Awareness did increase to a certain degree with the social media excitement generated by the Ice Bucket Challenge. Ironically, the number of ALS diagnoses is just slightly below the incident rate for multiple sclerosis (MS); however, due to the fatal and fast-progressing nature of the disease, there is a relatively small population of people suffering from ALS at any one time, with an estimated 30,000 ALS sufferers in the United States today. The occurrence of ALS is the same worldwide, and men and women are similarly affected. Most individuals are diagnosed in middle age, but the disorder can strike a wide age range – from late teens to late 90s.

There have been considerable efforts and investments made in search of a therapy that can substantially retard the disease with the hope of finding a cure. The traditional model that has been deployed has generally been driven by someone who has been diagnosed with the disease and who then establishes a foundation, raises money and identifies a panel of scientific advisors who evaluate proposals from individual researchers seeking funding for specific ALS projects. This has led to an enormous amount of individual effort and a significant amount of money being raised, but to date, there is still no breakthrough for a substantially effective drug.

Development of the Mouse Models: In the late 1990s, with the establishment of foundations and fundraising gaining steam, a number of research projects were funded to develop mouse models of ALS. The putative value of these models was the ability to widely distribute this research tool, enabling more researchers to engage in the pursuit of a cure. The creation of these models was met initially with great enthusiasm and confidence that promising research applied to the mouse models would transfer into human trials. Unfortunately, to date, this has not been the case. It is not entirely clear why an ALS model using a mouse which develops a disease that substantially resembles the human disorder has failed to translate to human success. Many theories abound, including lack of proper human trial design following mouse drug trials, lack of reproducibility of the mouse drug trials, lack of proper design of mouse drug studies, lack of proper "biomarker" studies to prove the drug actually works at its biological target in humans. Finally, the ALS mouse models only apply to a very rare form of ALS and thus may not be applicable to the more common sporadic form of the disease. For these and other reasons, confidence in mouse studies or even the need for a mouse study in finding suitable drugs for humans has waned.

While progress has been made through the years, the net result of the efforts to date is that ALS remains a disease with a fatal diagnosis. Victims all end up in the same place with the only variation being their own timeline.

Evolving New Model – looking at the disease through a new lens. In business, doing the same things the same way and expecting different results is the definition of insanity. Fortunately, there are developments going on in the medical field, as well as related industries that could play a role in changing the rules of the game. Some of the recent developments that make a difference include

- Induced Pluripotent Stem Cells (iPS cells). The greatest limitation in ALS, Alzheimer's, Parkinson's and other neurological diseases is that the real diseased tissue, the brain/spinal cord, is not available to study directly. Having real human ALS brain tissue would be the best way to understand what is affecting patients and how to address the problem. In cancer and most other non-neurological diseases, great success has come from the simple fact that researchers can biopsy the cancer tissue to gain direct access to the disease. This cannot be done for brain or spinal cord tissue, but now the technology of iPS cells offers the ability to generate brain cells from patients' own blood or skin with their exact genetic foundation, which can be applied to ALS research. Research by the Robert Packard Center for ALS Research and others worldwide has shown that these patient-derived brain cells accurately replicate the human disease, providing an opportunity to understand why the disease starts and its biological mechanism, which can be used as a tool to screen for drugs and test against an individual's own motor neurons, leading to more patient-specific care. *The opportunity exists to target the right drug to the right patient.*

- Large Data computing and Analytics. Moore's Law describes the long-term trend in the computer hardware industry and involves the doubling of "compute power" every two years. The recent advancement in both computing power and storage capacity now allows genetic mapping of ALS patients and the integration of an enormous amount of the disparate data sets ranging from a patients clinical history to his/her entire genome makeup. As a result of these advancements, the cost per genome has dropped from $95M in September 2001 to less than $2,000 today. (Source: National Human Genome Research Institute.) *We can now amass massive amounts of data that provide insight that historically was not available.*

- Data analytics has rapidly progressed, allowing large amounts of data to be analyzed in search of algorithms and data trends. Having massive amounts of data is only one part of the equation; the data has to be translated into information. Today's machine learning allows for rapid analysis of complex data – a simple example of this is asking "Siri" what are the current weather or traffic updates – involving huge advances in machine learning to interpret voice and linking it to complex outcomes. Analytics is one of the mega trends in business, and the cognitive age is clearly upon us as indicated by more than $1 billion in venture capital funding for cognitive technologies in 2014 and 2015. Analysts project that overall market revenue for cognitive solutions will exceed $60 billion by 2025. (Source: Deloitte report on Analytics Evolution or Revolution.) *The power of analytics can for the first time play a role in solving a tough equation.*

- A strong collaborative mindset has continued to develop as multiple institutions and charitable organizations involved in the search for an ALS cure are openly collaborating and joining together in the pursuit of a common goal. Ironically, this has somewhat been facilitated by the larger

investments in research as each institution and the academic investigators have realized that they cannot achieve desired results on their own. *Solving tough problems is a team sport.*

Leveraging the tools and developments outlined above, meaningful steps have been made in advancing treatments for the genetic form of ALS, and some estimate that new drugs will be on the market in the next two to three years. This demonstrates what can be accomplished when there is biological certainty on the problem you are trying to solve. Understanding the mechanism of the disease is simply the most effective way to solve the problem and is the approach with the highest chance of success in the hopes of developing a disease therapy.

Answer ALS – a promising example of a concerted and collaborative effort to broaden the biological certainty of ALS. Answer ALS came about through the leadership from Team Gleason, which established the originating mission and identified great collaboration opportunities across the board. Johns Hopkins, Massachusetts General and Cedars-Sinai are co-leading the project, partnering with multiple businesses, sports and charitable organizations, such as Travelers, the Fishman Family and the Bari Lipp Foundation, Leandro P. Rizzuto Foundation, The Robert Packard Center for ALS Research, National Football League and Professional Golf Association.

The hypothesis that Answer ALS is focused on proving out has taken shape over the last decade of ALS clinical observation studies. The hypothesis is that there is not one form of sporadic ALS, but multiple variations of the disease. What we have learned about the familial form of ALS has played a key part in forming this hypothesis. We know that there are many different genes that cause familial (inherited) ALS and that clinically those patients are not distinguishable from the far more common sporadic ALS. Could the repeated clinical drug trial failures be due, in part, to "lumping" all sporadic ALS patients together? There are very informative lessons from cancer therapy where breakthroughs came by targeting a molecular subset of patients with drugs aimed at the proper disease mechanism, leading to far better outcomes.

To prove out the hypothesis, Answer ALS has launched and is working through four distinct and connected phases.

Part 1. This will be a comprehensive and longitudinal deep clinical data set collected from at least 1,000 ALS patients nationwide at six nationally distributed academic medical center clinics. Patients will be followed for approximately two years with "deep" clinical data repeatedly collected. In addition, bio fluids and tissue will be collected, e.g., blood, CSF (~10%), autopsy (~10%), along with DNA. Patients will wear a personal monitoring device and will also enter data at home via a smartphone app resulting in 24-hour, seven-day-a-week clinical data collection.

Part 2. Answer ALS will generate iPS cells from every patient: 1,000 different brain cell lines from the 1,000 patients. These cells will be converted into the patients' own motor neurons from the very cells at the heart of their disease.

Part 3. The real core of the program, and one that supersedes any prior study in any neurological disease, is the plan to perform comprehensive biological analytics using human brain cells—called *Multi-omics*. The plan is to study the brain cells for the DNA genome, comprehensive RNA Transcriptome, epigenome (environmental effect on DNA), proteome, metabolome and lipidome. In addition, the human brain cell will be robotically serially imaged for cell death and various growth characteristics.

Part 4. Overall, the Answer ALS program will result in a huge dataset from each patient over the two-three year observation period, ranging from their clinical progression to their genome to their brain proteins. No single computer program is capable of integrating all of this data to identify a single answer. However, newer methods of deep machine learning paradigms are remarkably effective at analyzing huge and disparate datasets. We are in discussions with Big Data firms on the best way to work through the large amount of data and apply machine learning. We are also exploring options to crowdsource the analytics to get fresh eyes on an old challenge.

If the above steps go as planned, hopeful outcomes would include the ability to divide patients into subgroups, identifying the underlying biological/molecular defects causing ALS, leading to a variety of drug target pathways in ALS, and ultimately, the ability to target the *right drug to the right patient*, leading to a cure. Additional outcomes of the data analysis include identifying biomarkers for future drug trials, which will result in better trial design, more informative trials and faster clinical trials.

Based on the current timeline, the 1,000-patient data base should be built by year end 2018, but data will be released as the Answer ALS database is being built. The answer to the hypothesis could be found before the complete data is finalized. While a lot of heavy lifting would remain if Answer ALS proves out the hypothesis, it could, for the first time, chart a course leading to a cure.