Implications of Clinical Trials: A View of the Panorama

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The advances in basic and clinical research over the past two decades since the identification of mutations in the gene for most individuals with Rett syndrome (RTT) has been astonishing. Within the past few years, we have seen the number of clinical trials involving potential disease-modifying pharmaceutical agents expand quite dramatically, both in this country and abroad. We expect this number to increase in the future. We, also, have long recognized that approaches to replace the aberrant gene with a normal gene or to activate the normal gene silenced in most individuals with RTT offered the greatest potential for 'cure'. Indeed, we see recent results of important efforts to bring gene replacement to clinical trials. This is truly exciting.

However, we must realize that we should not put all of our eggs in one basket. We need to continue to identify promising pharmaceutical agents in parallel with gene replacement. We also need to remember the importance of new therapeutic habilitation approaches to the physical and cognitive issues experienced by individuals with RTT. We must be mindful that the results of gene therapy, as those of drug treatment, are possibly/probably going to depend on the age of the individual at the time it is employed. We know that the *MECP2* gene exerts important neurobiologic influences from a very early age. Therein lies the rub. The effect of this treatment in a one year-old could be very different from that in a five, ten, or twenty year-old. This is because the natural history of RTT provides an evolutionary pattern of changes in physical and cognitive abilities and medical issues. To the extent that these additional issues such as feeding, mobility, and scoliosis occur across the life spectrum, we must be aware that no single therapy is likely to have the same result for individuals of different age.

For this reason, we must be prepared to utilize multiple approaches including gene-based, pharmaceutical, and neuro-habilitation-based strategies. In fact, this is not a completely novel idea since combined behavioral and pharmacological treatments are being tested in autism, anxiety and other neuropsychiatric disorders. To do all of these, we need a multipronged approach with experts in various fields to develop, test, and guide us. Further, we will need the support of families affected by this neurodevelopmental disorder to be open to trying the different treatment approaches. Without this combined experience, we cannot expect to move forward on the broad front needed to effect true improvement.