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This statement reflects the views of the Scientific and Clinical Advisory Team (SCAT) to the CdLS Foundation UK & Ireland.

The prospect of gene therapy is an exciting development in the medical field. There are many different types of gene therapy which aim to treat diseases caused by changes in the DNA that codes for a single gene. Some forms of gene therapy are in use now within the NHS to treat a very specific group of these genetic conditions, mostly severe blood and immunological disorders. One exciting development has been the introduction of gene replacement and splicing therapies for the severe neurological disorder that affects babies called spinal muscular atrophy. These have emerged from decades of work on gene defects in this disorder and our understanding of the cells in the spinal cord that are affected.

However, for the vast majority of severe genetic conditions it is not yet possible to deliver genetic therapies to the affected tissues without significant risk of causing more harm than good. The use of gene therapy in CdLS is a particularly complicated problem. Genes that are most commonly changed in the different forms of CdLS are very important to the function of the cell. The proteins that are produced by these genes control the activity of a very large number of other genes that are critical for normal development. In most cases of CdLS the amount of NIPBL protein is significantly reduced because a genetic change has inactivated one of the two copies of the *NIPBL* gene. We also know that having too much NIPBL causes a different neurodevelopmental problem. An exact amount of NIPBL is required and the only practical way of doing this is to correct the genetic change in each cell – this is called genome editing. This is possible to do for cells in a test tube but there is a very very large volume of work to do before we will know if this will be possible in the brain of a living animal. It will be at least ten years (possibly much longer) before the first research trials could start in a living human. One important point is that there are many genetic disorders that affect the brain which, similar to CdLS, have very active research communities. A breakthrough from one is likely to help all of these disorders. It is also fair to state that even if the therapy is successful in correcting the genetic changes in all cells this may not result in a "cure".

We all want to make life better for individuals with CdLS. Over the last 20 years we have seen the beneficial impact of many "non-genetic" therapies and we hope and expect more will arrive. New ideas and approaches to the management of CdLS are always welcome. We encourage any potential research activity to be openly discussed and, if appropriate then ethically and rigorously assessed using the null hypothesis. A null hypothesis is a hypothesis that says there is no statistically significant difference or relationship and is the hypothesis that we as researchers are trying to *disprove*. In other words, we must always begin with the premise that the intervention is not effective and change only when we have a statistically significant positive result that demonstrates that this premise is wrong.

Please contact the CdLS Foundation UK & Ireland if you have any questions or concerns.

Signed

The Scientific and Clinical Advisory Team to the CdLS Foundation UK & Ireland:

Professor David FitzPatrick
Dr Jo Moss
Dr Peter Gillett
Professor Chris Oliver
Dr Laura Groves
Dr Jenny Sloneem
Dr Penny Fallon
Ms Sara Peaford
Dr Jane Waite
Dr Hayley Crawford