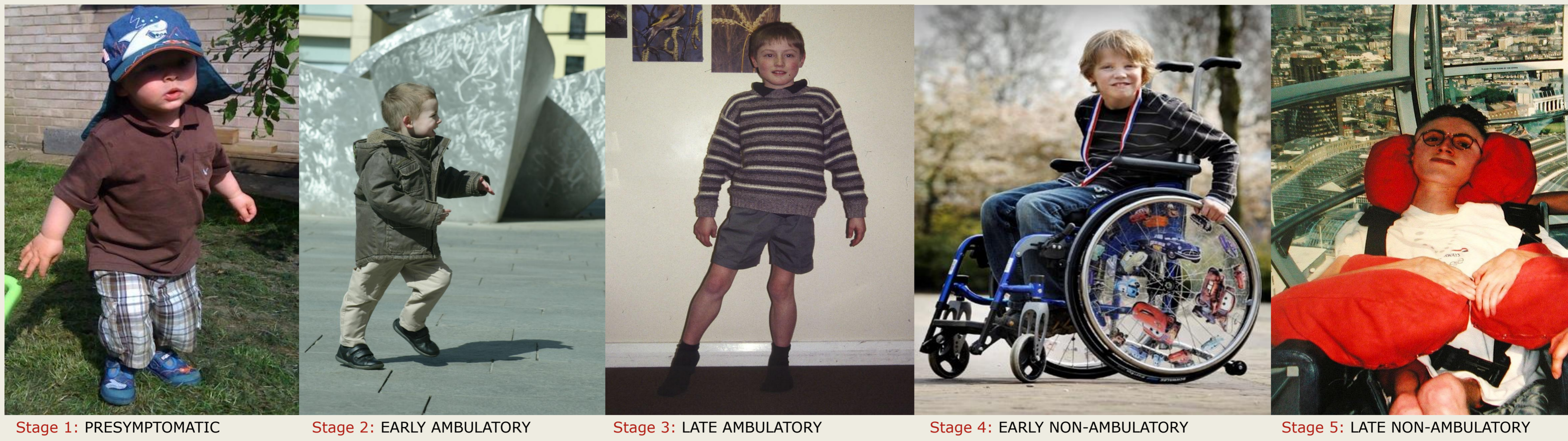


Cell therapies for Duchenne muscular dystrophy (DMD): some ethical issues for personalised medicines

Pauline McCormack, Policy, Ethics & Life Science, Newcastle University
 pauline.mccormack@ncl.ac.uk



DMD and personalised medicine

The definition of personalised medicine should not be confined to identifying sub-populations whose response to a particular drug or treatment can be determined by their genotype but can also be taken to mean the tailoring of a medicine for sub-sets of patients with certain genetic characteristics, as discussed in this poster.

Duchenne muscular dystrophy (DMD)

- An incurable rare disease
- One of the most common childhood genetic disorders, affecting boys primarily
- A fatal and devastating, progressive, muscle wasting disease
- Death from heart failure or respiratory problems typically in the twenties
- Social and emotional effects of the disease for families can be very burdensome

Gene mutation

DMD is caused by mutations in the gene that encodes for dystrophin – the protein that builds muscle. Dystrophin is the largest gene in the body, containing 79 exons and most mutations consist of a deletion of one or more of these exons. One of the most promising therapies in development is exon skipping where treatment is targeted to a specific exon and each different mutation requires a different chemical 'patch' to treat the disease.

There would need to be 30 different exon skipping chemistries to treat the majority of patients. Exons for the most common mutations will be tested first and trials for two exons are in progress or planned.

Top 10 exons in DMD (1)

Exon number	Approximate % of patients
51	13.0%
45	8.1%
53	7.7%
44	6.2%
46	4.3%
52	4.1%
50	4.0%
43	3.8%
6 & 7	3.0%
8	2.3%

“the community feels fragmented based on mutations, as if, for some boys, there is less hope than for others”

Pat Furlong, patient/parent representative

Ethical issues

The success of trials with exon skipping will bring the possibility of personalised medicine aimed at small sub-sets of boys with DMD.

Harm by omission

Within current regulations each exon would be considered a new drug which must undergo rigorous testing. This would not be cost effective and raises the possibility of those children with rarer exons being denied a potentially lifesaving treatment (2).

Children with DMD are disadvantaged due to the rarity of their condition, its life-limiting nature and from the lack of effective therapies. The precautionary approach to research this vulnerability requires can also be a further disadvantage. The protection afforded to these children needs to be balanced against the disadvantage of delaying research leading to effective treatment thereby harming by omission.

Boundaries between clinical care and experiment

- If therapies are developed for the rarer mutations the number of patients available to test a certain mutation become fewer
- A single person may be his own control in a trial
- Boundaries between experiment and therapy become blurred
- Therapy in such cases should be considered as empirical treatment rather than experimental trial

Some points to note with research in small populations

- Any deviation from randomised controlled trials should be rigorously justified
- Patients should be made fully aware of the increased uncertainty and the risk/benefit balance
- Power of the study should be maximised by using a range of methodologies and exploiting historical data
- Good science is the basis of good ethics

Reimbursement and non-abandonment

Exon skipping is likely to be an expensive therapy. Although the EC has introduced orphan drugs legislation designed to assure that 'patients suffering from rare conditions should be entitled to the same quality of treatment as other patients', orphan drug availability varies from country to country (3, 4).

Most would uphold the idea that the community has a moral obligation not to abandon those born with rarer mutations. We can see that orphan drugs incentives have been successful in helping to develop new therapies and the regulatory authorities are open to exploring new ways of regulating personalised medicines. To have significant resources assigned to a therapy which will be available to some patients within a single disease and not to others appears to be unjust.

References

- 1 Aartsma-Rus et al, 2009, Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations
- 2 Muntoni et al, 2010, The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy
- 3 Eurordis, <http://www.eurordis.org/IMG/pdf/2007ODsurvey-eurordis.pdf>
- 4 EC regulation on orphan medicinal products, 141/2000