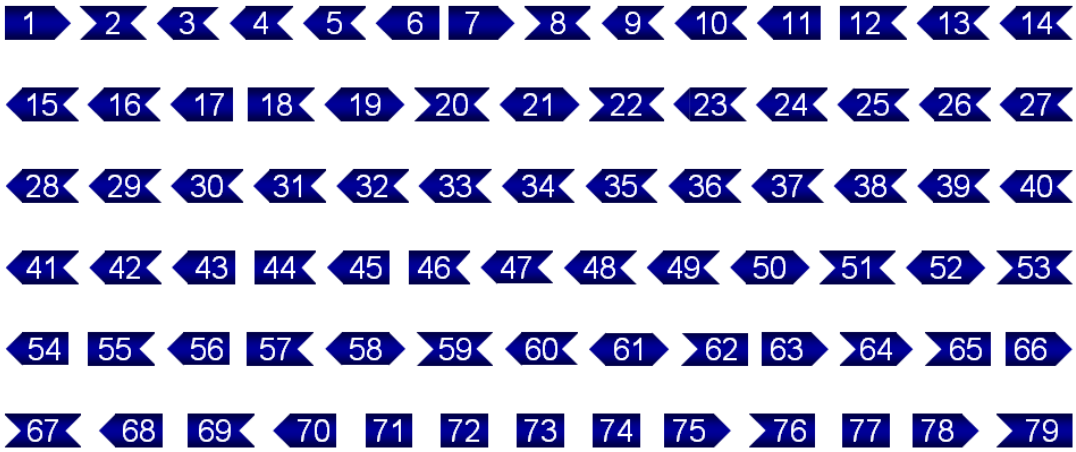
How to find which exon or exons to skip.

There is an easy way to find the exon or exons which have to be skipped for your son, if you know the mutation in his dystrophin gene – deletion, duplication, or premature stop. The arrangement of the 79 exons can be seen in the following picture which has been designed by Dr. Annemieke Aartsma-Rus and which I am showing here with her permission.

In this representation, the exons have different shapes because the border between them can be after the first or second genetic letter of the genetic words at the border or between entire words. As you can see, in this normal situation, the exons fit together smoothly. As a consequence of a mutation, one or more exons may be missing or are duplicated, and then the remaining ones may not fit anymore, meaning that the reading frame is shifted – it is *out-of-frame* – and Duchenne muscular dystrophy develops in most cases. If the exons still fit to each other after the mutation, the reading frame is not shifted –it is still *in-frame* –, but the dystrophin protein is shorter and this may lead in most cases to the slower developing Becker muscular dystrophy.



To find which exon to skip when the mutation is a deletion, cross out the deleted exon or exons and see whether the exon before or after the deletion must be taken out, *to be skipped*, so that the remaining exons fit to each other in one of the three "natural" ways.

For instance, a deletion of the 6 exons 45 – 50 means that the exons 44 before and 51 after the deletion do not fit together. But skipping exon 51 would produce a normal fit between the end of exon 44 and the beginning of exon 52. You will also see that the deletion of exons 44 – 50 could be repaired by skipping both flanking exons 43 and 51, so that exons 42 and 52 would fit to each other. You will also realize that a deletion, e.g. exon 44, that produces non-fitting exon borders mean a shifted reading frame leading to Duchenne dystrophy, while a deletion, e.g. 48 – 51, that produces fitting exons do not shift the reading frame, and that should mean Becker dystrophy. This procedure works also for duplications and premature stop codons.

If with these explanations you have found which exon or exons have to be skipped in the dystrophin mRNA of your son, it is important to understand that this does *not guarantee* that his severe Duchenne symptoms will be changed into the milder symptoms of Becker dystrophy, if he would be treated with his "personal" exon-skipping drug that makes the remaining exons *in-frame* again. All that can be said is that a particular skipping will change the reading frame of the genetic message on the mRNA from *out-of-frame* to *in-frame* again. It does not say that the in-frame genetic message will produce a "Becker"-dystrophin in every case, because the reading-frame rule has many exceptions, which are not completely understood in each case.

Thus, an exon skipping therapy will in many cases produce a protein that reduces the dystrophic symptoms, but *there might be surprises* which will only become apparent during an actual treatment.

For a detailed explanation of exon-skipping, please look at the report about this technique, updated in 2009, on my internet pages www.duchenne-informatiion.eu.