Stellingen behorende bij het proefschrift

Pre-mRNA Splicing in Pompe Disease: Prospects for antisense therapy

1. Although splice prediction algorithms can be useful to predict the effects of gene variants on pre-mRNA splicing, systematic functional analysis should be performed to measure true pathogenic effects (*this thesis*).

2. Implementation of targeted long-read RNA sequencing in genetic diagnostics may provide a fast and reliable way to detect aberrant splicing (*this thesis*).

3. Aberrant splicing frequently occurs in genes even when no pathogenic variants are present, and thus provides potential targets for antisense therapy by enhancing expression of canonically spliced mRNA (*this thesis*).

4. Diagnostic screening for aberrant splicing in monogenic disease will almost certainly lead to the discovery of new targets for antisense therapy (*this thesis*).

5. Current advances in antisense based technology will likely lead to successful treatment of monogenic disorders like Pompe disease (*this thesis*).

6. Although exome and genome sequencing are often referred to 'whole' exome or genome sequencing, these services might better be called 'hole' exome and genome sequencing, as no approach today is comprehensive in its coverage of even those genic regions that are included in typical disease-targeted testing. (*Rehm, Nature Reviews Genetics, 2013*)

7. Conceptually, RNA-seq is shot-gun sequencing of the transcriptome, lending to both potential utility and considerable hurdles towards translating RNA to the clinic. (*Byron et al., Nature Reviews Genetics, 2016*)

8. The most important difference between genomic tests and clinical tests is that the medical establishment and the medical industrial infrastructure believe them to be very different. (*Kohane, Nature Reviews Genetics, 2012*)

9. The general physical examination comes closest to a genome or an exome in the breadth of what is being sought, what might arise 'incidentally' and the fact that it is difficult to consent a patient to the potential consequences of this evaluation. (*Biesecker, Nature Reviews Genetics, 2012*)

10. Oligonucleotide therapies appear to be inherently more conservative and will likely not be hampered by the safety issues that halted previous attempts at gene therapy. (*Fredericks, Biomolecules, 2015*)

11. To kill an error is as good a service as, and sometimes even better than, the establishing of a new truth or fact. (*Charles Darwin*)

Atze J. Bergsma
Rotterdam, September 20th, 2016