Executive summary

Health Council of the Netherlands. Next generation sequencing in diagnosis. The Hague: Health Council of the Netherlands, 2015; publication no. 2015/01.

What is next-generation sequencing?

The term “next generation sequencing” (NGS) covers a range of techniques that are designed to map a person’s entire genetic code quickly and relatively cheaply. This horizon-scanning report explores the benefits and issues associated with the use of these techniques in diagnosis.

There are various levels of sequencing. One level is represented by gene panels consisting of a limited number of genes associated with specific disorders, such as cardiomyopathies. At another level, all of the protein-coding sections of the DNA (the exons) are sequenced. This is referred to as whole exome sequencing (WES). WES is used in cases where a disorder (such as severe intellectual disability) is suspected of having a genetic cause, but where the defect involved has not yet been traced to a specific gene (or genes). Alternatively, the entire genome – including all coding and non-coding sections – can be sequenced. This is referred to as “whole genome sequencing” (WGS) and is still primarily used for scientific research. Both WES and WGS can be used to analyse just a part of the sequenced code, similar to a gene panel. Accordingly, sequencing and the analysis of sequences are not necessarily the same thing.

Advantages

NGS offers a range of advantages. One major advantage is that NGS makes it possible to perform a rapid, comprehensive genetic diagnosis. Whereas, in the past, genes could only be sequenced one at a time, it is now possible to sequence a large number of genes simultaneously. This saves time when it comes to making (or ruling out) a diagnosis and instigating a course of treatment. In addition, there are other ways of determining whether a disorder has a genetic cause, even when the exact nature of the disorder in question is not entirely clear.

Another advantage of NGS techniques is that they can enhance the direction and speed of treatment. In the area of oncology, for instance, NGS is already being widely used to identify the properties of tumours. Treatment can then be specifically tailored to the type of tumour involved.

Over the longer term, the use of NGS is expected to prevent, limit, or replace other tests. For instance, once the different types of biomarkers and the significance of genetic variants are better understood, there will be less need (if any) for extensive laboratory testing, for imaging examinations, or for pathological examinations. The potential of NGS for screening, such as broad prenatal or neonatal screening, is increasingly being discussed. However, this involves far-reaching epidemio-logical, technical, quality and ethical aspects that need to be investigated properly before such screening can be implemented.

Points of special interest

As with any new medical technique, there are a number of issues with regard to NGS. One is that a better understanding of the significance of genetic variations is needed. Another major issue is the quality of sequencing. The level of accuracy obtained depends on the “depth” (how often a section of DNA is sequenced) and on the exact technique used. While the professional groups involved have reached quality agreements in this regard, it is important not to lose sight of this issue. The quality of the interpretation of mapped sequences is, if possible, an even more important concern. To this end, use is being made of emerging databases that are not always entirely up to date, which occasionally means that outdated and incorrect information is used. There are also many gaps in our knowledge. Data sharing is an important means of expanding knowledge. Another issue in this context is that the composition of gene panels occasionally

varies from one centre to another. Professional groups are increasingly calling for greater harmonisation in this area.

There are two issues with regard to the processing and storage of data. One involves the capacity required for processing and storage. Although this is currently very expensive, advances in IT technology are expected to resolve this issue in time. Another aspect is privacy. Who is authorised to save what data, and for how long can they retain it? And who is authorised to access these data?

Other privacy-related issues involve dealing with incidental findings, and the provision of information to patients and participants in scientific studies. What should/shouldn't/can/can not be reported? By whom, and when? The blurring boundaries between diagnosis and research (when increasing use is made of WGS) and between diagnosis and screening (when tests for a number of genes become a standard part of genetic diagnosis) will not make these decisions any easier. In this connection, it is important that medical professionals and the general public develop a better understanding of genetics. Disease is not determined by genes alone, but results instead from an interplay of genetic and environmental factors. Accordingly, it is important to be wary of placing too much reliance on genetic knowledge.

Recommendations

The Standing Committee on Genetics concludes that NGS is already in common use in Dutch clinical genetics departments and in university medical centre laboratories. It recommends that efforts be made to improve the quality of sequencing and interpretation, and to enhance our understanding of genetic variation. Similarly, medical professionals' knowledge of genetics and NGS also needs to be improved. Professional groups have an important part to play in this regard. The Standing Committee also recommends that incentives be provided to encourage the study and implementation of new consent forms. Increasing the level of knowledge among the general public is also important. The Erfocentrum (the Dutch knowledge and information centre for genetics) can play an important part here. Finally, the government can get involved by coordinating the debates surrounding issues such as the advisability of expanding the further use and scope of NGS techniques in diagnosis and screening.