Gene-panel tests and mapping of all human genes with next-generation sequencing are now part of routine diagnostic practice. These are the primary tools of personalised medicine. Are Norwegian doctors ready to handle these developments?

Diagnostic success with pitfalls

With next-generation sequencing technology, a human genome can be sequenced in the course of a few days. Diagnostic tests based on this technology are now offered for roughly the same price as the cost of sequencing a single gene by traditional methods. In Norway too, next-generation sequencing is standard diagnostic practice in an increasing number of laboratories. In this issue of the Journal of the Norwegian Medical Association, a research group linked to Telemark Hospital presents two articles that demonstrate clearly the effectiveness of this technology for diagnosing rare hereditary disorders (1, 2). Such disorders, which are caused by serious defects in single genes, are challenging to diagnose because there are often many genes that can produce the same phenotype and because of the large overlap in their symptoms and signs. Causal mutations were detected in about 30 % of the subjects examined in the two studies. This is an impressively high diagnostic yield, in line with previous reports (3, 4). The clinical value of next-generation sequencing in routine diagnostics is well documented for this disease group (3, 5, 6), and there is no doubt that this technology will become a key tool in genetic diagnostics.

The two articles describe two different ways of using next-generation sequencing technology, and illustrate the advantages and disadvantages of each. In the article by Høyer et al. (1), a gene panel was used to diagnose hereditary peripheral neuropathy. The authors selected and sequenced 52 relevant genes; the remainder of the genome was not studied. This test has a technical accuracy of 99 %, i.e. approximately equal to the current gold standard – Sanger sequencing (99.999 %) (7). By contrast, Holla et al. used exome sequencing for the diagnosis of rare syndromes and intellectual disability (2). This method involves sequencing *all* exons; that is, the coding regions of our approximately 20,000 protein-coding genes (5). This technique does not have comparable technical accuracy because not all exons are sequenced as many times (i.e. as deeply) as might be desirable; coverage is variable. The reason why it still makes sense to use this method in diagnostics is that certain hereditary disorders may be due to genetic defects in one of very many genes (> 500 in the case of intellectual disability), while new disease genes are continually being identified (5). Only around half of the roughly 8,000 rare hereditary diseases described have a known genetic cause (8). A specific gene panel for a given disorder will thus quickly become outdated (1). Adding new genes to a specific panel test is labour-intensive.

There has been much concern over the fact that next-generation sequencing can also detect gene variants that increase the risk of other types of disease besides the one being tested for (9). In clinical practice, however, this is found to be a minor problem. In the 125 patients who underwent exome sequencing in Høyer's study, no such incidental risk variants were found. The incidence of incidental findings in the literature ranges from < 1 % to 8 % (4, 5). Incidental findings are nothing new in medical diagnostics. What is important is for patients to be counselled about the issue beforehand and to consent to the type of genetic risk information they would like to receive. It is also important that the patient is aware that those who analyse genomic data are not obliged to look for such incidental risk variants. Exome and genome sequencing are the most important tools of personalised medicine, i.e. «tailored» diagnostics and treatment. The Norwegian Directorate of Health is currently drawing up a strategy for introducing personalised medicine into the healthcare system. The success of this move will depend on our ability to extract the information we need from the genome in a targeted manner. An expectation, or requirement, for exome sequencing to provide information on all possible variants that could have implications for future disease will render diagnostics highly inefficient.

It is in general very difficult to interpret the significance of gene variants for disease. We each possess rare normal variants that no-one has described before, and for every pathogenic variant reported in a given gene, there are at least twice as many variants of unknown significance. Misinterpreting results will have consequences for the lives and health of patients; this is already happening because those who request the tests do not always understand the laboratory results. Good communication between the laboratory and the person ordering the test is crucial, and we should work together to establish common practices regarding who can request these tests, and for which indications. A plan of action to provide supplementary training in medical genetics to all of the country's doctors should be put in place as soon as possible. Failure to take this matter seriously will come at a high price in terms of misdiagnosis, incorrect treatment and misuse of resources. With ever increasing numbers of expensive tests and treatments on the market, there is also a compelling need for clear guidelines on prioritisation.

Within the field of medical genetics, expectations are high regarding the national strategy for personalised medicine currently being drawn up. There are many challenges that must be met if next-generation sequencing technology is to be used to the benefit of patients: Dealing with variants of unknown significance and incidental findings, active prioritisation, effective economic policies, not to mention further training of healthcare personnel – all of these are key factors that may dictate the success or failure of personalised medicine in the near future.

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