High-throughput sequencing data generation and the translation to medical practice

Ivo Gut

Centro Nacional de Analisis Genomico, Barcelona, Spain

2nd generation sequencing offers exquisite resolution of genetic features at an affordable cost. Whole human genomes can be sequenced for around 5000 Euros, focussing on the exomic regions of the human genome only costs less than 1000 Euros. However, many issues remain to be resolved before this supremely powerful technology can be taken into the clinic. Whole-genome sequencing is still fairly slow and can take even under optimal conditions close to one month. A further issue is that the sequence data interpretation requires dedicated informatics pipelines and a substantial number of cpu hours (computer time). Accelerated computational methods that preferably can run on a small commodity-type computer are required. No best practices for sequence data analysis exist and even systems in the hands of experts can lead to results that have less agreement with each other than one would desire. It is clear that substantial efforts by the community will be needed for standardisation of variant calling. Another problem that we face is that current clinical practice, in the treatment of cancer patients, disposes of roughly 100 molecular tests that look at somatic variants present in a tumour or the expression of specific surface markers by the tumour. Nearly all of these tests are related to a treatment decision. An exome sequence analysis of a tumour can easily show hundreds of somatic variants in a tumour and hardly any of these overlap with the commonly used tests and will have an accepted treatment associated with it. The question is how to deal with information that is clearly disease-specific, but for which we do not yet know a clinical action? Or an alternative is that we observe a clinically actionable variant that has an approved treatment for another form of cancer. Can a drug be repositioned? The next problem is that as treatments become more individualized and adapted to a patient profile, e.g. if a sample shows multiple actionable variants, can different drug-treatment regimes be combined. The corresponding clinical trial would not available and clinicians are moving on uncertain legal ground. These are just a few of the issues that will need to be resolved before high-resolution genome sequencing will be able to be integrated into clinical practice.