nederlandse vereniging voor Humane Genetica

NVHG Najaarssymposium 2017
21 & 22 september, Veldhoven

Volledig programma op www.nvhg-nav.nl

VKGL, donderdag 21 september 2017

Symposium 1B : VKGL
14:00-14:40 uur

VKGL

Pharmacogenetics in clinical care: a 15 year experience

Ron H.N. van Schaik

International Expert Center and IFCC Reference Center for Pharmacogenetics, Department Clinical Chemistry, Erasmus MC University Medical Hospital, The Netherlands

Adverse drug reactions (ADRs) are a severe complication in treating patients, and are responsible for 5-7% of hospitalizations. In addition, only 25-60% of drugs prove to be effective. The problem is partially caused by interindividual variation in drug metabolism. Whereas we pay a lot of attention to prescribing exactly the right dose, the variability between individuals to metabolize drugs, did not receive a lot of attention in clinical practice yet.

Predicting how patients metabolize drugs based on their DNA (pharmacogenetics) addresses genetic polymorphisms in drug metabolizing enzymes and drug transporters. With 5,000 articles/year being published on genomic markers to guide drug therapy, there is a huge potential to improve therapy, yet, the challenge is to select those with sufficient impact for clinical care. The cytochrome P450 enzymes are responsible for the metabolism of 80% of all drugs. For CYP2D6 (involved in the metabolism of 25% of all drugs), 5-10% of the population is deficient. due to inheritance of two inactive CYP2D6 variant alleles. Such a deficiency can be tested upfront, and drug therapy can be adjusted based on the outcome. Evidence-based dosing guidelines are in fact already available for this in every pharmacy in the Netherlands.

Our 15 year experience in implementing pharmacogenetics in the Netherlands will be illustrated. Successes as well as unexpected challenges will be addressed. European initiatives such as the European Pharmacogenetics Implementation Consortium (www.eu-pic.net) and the European Society for Pharmacogenomics and Personalized Therapy (ESPT) (www.esptnet.eu) will be highlighted.

P +31-10-7033119
E r.vanschaik@erasmusmc.nl
W www.erasmusmc.nl/farmacogenetica, www.farmacogenetica.nl, www.eu-pic.net, www.esptnet.eu

Symposium 1B : VKGL
14:40-15:20 uur

The concept of "one-genetic-test-fits-all-diseases": a genetic and cost-effectiveness perspective

Lisenka E.L.M. Vissers[1] & Geert W.J. Frederix[2]

[1] Department of Human Genetics, Radboudumc Nijmegen & [2] Department of Genetics and Julius Center, UMC Utrecht, The Netherlands

The field of clinical genetic diagnostic testing has experienced many changes over the last decades. In the early 2000s, genomic microarrays found their way into clinical practice, for the first time allowing an unbiased high-resolution analysis of genome wide copy number variation explaining disease in approximately 15% of patients with neurodevelopment disorders. More recently, next generation sequencing technologies, such as whole exome sequencing (WES), have allowed an unprecedented view at all protein-coding sequence at single base pair resolution, providing a genetic diagnosis in another 30% of patients with clinically and genetically heterogeneous disorders.

The implementation of these novel technologies have mostly been driven by technological advances, and promises to increase diagnostic yield. Whereas this – without a doubt – has been the case for microarrays and WES – these technologies are mainly employed as an add-on test rather than replacement of others. This raises the questions to what is the most efficient approach to diagnose a patient? Which strategy is most cost-effective? And what is the impact of a genetic diagnosis on other medical diagnostic pathways?

In this presentation, we will show results of clinical utility studies comparing WES and conventional diagnostic testing, as well as a health technology assessment taking into account the costs to our health care system. Moreover, the data presented serves as a stepping stone to introduce the national project operated by the RADICON-NL consortium to evaluate Whole Genome Sequencing as first tier - and only - test to diagnose patients with a rare genetic disorder.

Symposium 1B : VKGL
15:20-16:00 uur

Translational metabolism: key to the future of inherited metabolic diseases

Ronald J.A. Wanders

Departments Clinical Chemistry and Pediatrics, Emma Children's Hospital, Laboratory Genetic Metabolic Diseases, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands

Until recently, the diagnostic process in any patient suspected to suffer from an inborn error of metabolism (IEM), would start with the analysis of metabolites in a blood, urine and/or CSF sample followed by enzymatic studies in fibroblasts and molecular analyses. Although this classical approach has proven its great value over the years and has led to the identification of many new IEMs, this approach also has its limitations, especially in milder affected patients showing only minimal metabolite abnormalities or none at all, and also in patients with atypical phenotypes. Importantly, technological advances, notably in the field of DNA sequencing, have led to a paradigm shift in the diagnostic process with whole exome/whole genome sequencing (WES/WGS) taking over from metabolite analysis as the first step in the diagnostic process, at least in several centers. Although many successes have been reported, including the identification of new defects and new phenocopies of known disorders, interpretation of WES and/or WGS sequencing results is often not trivial and can best be done in a team effort involving physicians, geneticists, bioinformaticians, metabolic and enzymatic experts and ideally basic researchers knowing about metabolism, model organisms, genetics and systems biology. Such a set-up is required to translate data coming from WGS and/or WES but also other omics techniques into functional consequences for metabolism in any patient investigated. This approach which we call translational metabolism may start with the identification of a VUS which requires analysis of its functional consequences for the protein involved. If the protein has enzymatic activity, expert knowledge on enzymology comes in, followed by investigations aimed to resolve the functional consequences for the metabolic pathway involved which requires whole cell flux studies in vitro in patients' cells and ideally also in vivo in patients. Such a multidisciplinary approach in which all information comes together is probably also the best setting to think of therapeutic options for each patient based on the expert knowledge gathered. The application of this translational metabolism approach will be illustrated.