Causes and consequences of dilated cardiomyopathy

VALORIZATION

This chapter discusses the future valorization of the findings presented in this thesis. The valorization of knowledge is the *relevance* for *social and/or economical purposes* and to translate it into *products*, *processes* and *innovations*. The valorization of this thesis can be divided in the proposed three parts: [1] clinical consequences of genetics, [2] redefining disease diagnostics and therapeutics, and [3] screening of asymptomatic family members.

Relevance

The prevalence and incidence of chronic heart failure (HF) is likely to increase in the following decades due to ageing of the population. At present, over 240.000 people suffer from HF in the Netherlands of which over one-third has non-ischemic dilated cardiomyopathy (DCM). There are over 30.000 hospitalizations and 7.500 deaths every year due to HF in the Netherlands. Despite the improvements in therapy these past decades, the 5-year survival rate is still close to 50%, which is similar to many forms of cancer. Together, the costs of health care associated with HF was 817 million euros in the Netherlands in 2017.

Current treatment strategies are primarily aimed at treating the signs and symptoms of a patient, which are in general similar among all HF patients. However, not all DCM patients show the desired improvement to the general HF therapy, and therefore this group of HF patients may benefit from alternative, additional treatment options.

Genetic testing has become a routine diagnostic tool in the clinical care of DCM patients. Although the possibilities and quality of genetic testing has improved, the subsequent clinical consequences of specific gene variants often remain uncertain, thereby limiting the clinical utility of genetics. Re-evaluating the genetic testing platform in DCM, and associating the results to clinical phenotype and outcome is crucial information to go towards an (cost-)efficient genetic-first approach.

Target groups

The results presented in this thesis are relevant for patients, their relatives and for physicians, in particular cardiologists and geneticists. Increasing knowledge of genotype-phenotype associations, will make the prediction of the disease course of a specific patient more accurate, and provide possibilities for earlier intervention.

The genetic features of DCM are characterized by variable disease expression and penetrance, even within families. This leaves uncertainty for relatives who carry the pathogenic familial DCM variant, but also for the counselor which carries the responsibility for providing the best possible advise.

Unraveling the underlying pathophysiological mechanisms in various (genetic) subgroups of DCM patients will be relevant for companies interested in targeted therapies and non-invasive profiling. Although there are no targeted therapies for genetic cardiac diseases on the market yet, there is one ongoing phase 3 clinical trial investigating a therapy which is specific for *LMNA* carriers (NCT03439514) and myosin inhibitors have been investigated in several phase 1 and phase 2 trials for the treatment of genetic hypertrophic cardiomyopathy (HCM) patients. The increasing number of trials focusing on targeted treatment in genetic cardiomyopathies highlights the need for novel treatments for this patient group, and the willingness and commitment of research groups and companies to invest in the development. Other specific gene-related cardiomyopathies (*e.g. TTN, FLNC*) are likely to be future target groups for gene-directed specific therapy.

Products, processes and innovation

The results presented in this thesis provide the opportunity to be translated in utilities. The critical re-evaluation of genes included on diagnostic screening panels and subsequent variant classification is direct knowledge which can be translated in the diagnostic process of genetic centers. Decreasing the number of genes tested, and enhancing the clarity of variant classification will limit time spent on analyzing genetic data and provide more clear test results. This will have a direct impact on the clinical work of cardiologists and geneticists, and decrease the number of false-positive genetic test results in patients.

The described research strategies and published bio-informatic analytic tools can be applied interdisciplinary. The generated transcriptomic dataset gathered from sequencing RNA isolated from cardiac samples of DCM patients, is currently one of the largest datasets in well-phenotyped DCM patients. This data was made available in the Gene Expression Omnibus (GEO) repository and is an important contribution to the research field of DCM.

This thesis presented pathophysiological differences among DCM patient subgroups. The distinct pathophysiological pathways associated with clinical phenotypes provide novel treatment targets or repurposing of existing drugs. We explored the potential of recognizing these DCM subgroups within an outpatient DCM population. In a proof-of-principle study, we generated a clinical classifier which could place every patient in one of the four unique subgroups with moderate accuracy. Such classifier based on easy accessible clinical variables carries great potential as the utility and subsequent clinical implementation has a low threshold, which will be further discussed below.

The application of speckle tracking to analyze cardiac images in more depth was an innovative approach to detect subclinical cardiac abnormalities. This additional information could help redefine the serial screening frequency in the process of cardiac screening for relatives of DCM patients, finetuning the current position statement of the European and American cardiology associations.

Planning, realization and implementation

The proposed re-evaluation of gene panels should be organized (inter)nationally to establish new position statements on a diagnostic DCM-specific gene panel. International efforts such as the Clinical Genome Resource (ClinGen) consortium and the DCM Precision Medicine Study are much needed to curate gene-disease validity, variant pathogenicity, and clinical actionability. The Dutch Society of Clinical Genetic Lab Diagnostics (VKGL) is organizing these efforts on a national scale. Re-establishing the gene-disease validity will allow us to analyze genotype-phenotype associations within large cohorts, eventually leading to gene-specific treatment plans in the guidelines for the cardiologist.

As showed in this thesis, many etiology-directed trials have been performed in the past years, although only a few had positive results with subsequent guideline implementation. These trials were conducted parallel to the ongoing unraveling of the complexity of DCM. New insights in pathophysiology and subsequent post-hoc studies of the trials show that the included patients were often too heterogeneous and might therefore not respond in the same manner to the investigated intervention. In this thesis, we provided a novel outlook towards patient selection which includes the DCM complexity. The next step is to train and validate our clinical classifier in order to place patients in specific subgroups with high accuracy. Afterwards, there are two consecutive steps to improve patient treatment: [1] investigate and enhance response to current treatment regimens and [2] uncover new treatment targets and subsequent develop novel targeted therapies.

To specify screening recommendations for relatives of DCM patients we need to [1] investigate the disease penetrance and expression per specific gene, and [2] to determine the accuracy of speckle tracking in detecting early disease. These points should be addressed in separate studies, which will envisage large cohorts of asymptomatic carriers and long-term follow-up. Afterwards, the 'window' of early treatment should be explored, to see whether this approach can prevent (overt) DCM development.

All data is generated from observatory studies; randomized clinical trials (RCT) are necessary before treatment regimens will be adapted. Research presented in this thesis forms the basis towards basic clinical research and RCT establishing causality and optimal timing for intervention.