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Socio-economic impact and HTA Report

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0. Executive Summary

Context

The "Model-Driven Paediatric European Digital Repository - MD-PAEDIGREE)" project validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases. This deliverable reports on final work relating to Task 19.3 "Benefit-cost scenario for clinical impact assessment" of WP 19 "Exploitation, HTA, and Medical Device Conformity". It benefited from work undertaken in WPs 2, 8 and others on cardiac disease modelling, here particularly cardiomyopathy including heart failure. Cardiomyopathy is a summary term for a set of chronic and often progressive diseases in which the heart muscle (myocardium) is abnormally enlarged, thickened and/or stiffened

The overall goal of the tasks in WP 19 Exploitation, HTA, and Medical Device Conformity was to contribute from a socio-economic perspective towards making VPH models and clinical decision support tools readily available both to researchers for further development and to health professionals as decision support at the point of care.

Objectives

Given this overall context, these specific objectives are pursued:

- Apply the generic benefit-cost scenario for clinical impact assessment developed
- Review, adapt and validate the clinical pathway model for three disease states – mild, moderate and severe cardiomyopathy
- Relate the disease states and pathways developed to status-quo clinical interventions and their respective costs per year of treatment
- Estimate from real data the respective transition and absorption state probabilities for a cohort of patients moving over a ten-year cycle through different states of cardiomyopathy
- Populate the Markov Chain analysis tool with concrete cost data and outcome estimates from the hospital as well as from the literature
- Similarly, based on expert estimates, analyse the impact of MD Paedigree decision support tools on pathways, treatment decisions and accordingly adjusted transition and absorption state probabilities as well as costs
- Estimate and compare benefits (cost saved; QoL improved) between status-quo clinical care and healthcare supported by MD Paedigree tools

Methods

As a first step, to identify core elements, structures and actors on which data had to be collected, an explorative scenario approach is applied. Given the *extreme complexity* of (national) health systems, the number of actors involved in even relatively simple healthcare delivery processes, the political sensitivity of any health-related policy issue, and the mix of powerful stakeholder groups lobbying in this field, scenario analysis was preferred to other more formalised methods of analysis.

Next, to prepare for the concrete health technology impact assessment of MD Paedigree tools, a decision analytic modelling process is used. To reduce the overall complexity of the daily reality in a hospital when treating cardiomyopathy children, an operational clinical pathway model is developed. This then will be applied to estimate potential benefits from the new technology, i.e. the incremental health gains expected from the new decision support tools which MD Paedigree is developing, as well as changes in costs related to the new process. A mathematical probabilistic model, Markov process analysis, was chosen to integrate all of these data. This reflects reality in healthcare service provision, where outcomes of a decision are dependent on earlier events, and where there are usually several possible outcomes, not only two (like the toss of a con versus of a dice). Such processes in which the outcome of an event is dependent on the outcome of the previous event or process step are commonly known as Markov processes or chains.

Results

In the operational process model for treating cardiomyopathy, in line with clinical practice, three disease states a child may be in when entering the hospital are identified:

- mild cardiomyopathy/heart failure
- moderate cardiomyopathy/heart failure
- severe cardiomyopathy/heart failure

On average about 60% of children being presented for an initial diagnosis are classified into the mild heart failure state, 20% to the intermediate state, and roughly 20% to the severe state.

The three transition states had to be complemented by two absorption states:

- Mechanical cardiac support/transplant
- Death

Because the presently available MD Paedigree decision support tools do not provide information for the treatment of mechanical cardiac support/transplant patients, this state is defined as an absorption state.

The cardiomyopathy clinical pathway model is then translated into a Markov-chain model for estimating health (technology) impact. Estimates of the present costs of the three clinical sub-pathways for a given cohort of children will be collected: the costs of the diagnostic and treatment interventions per typical patient, and the percentage number of patients in each arm. Furthermore, estimates of the transition probabilities of a patient moving from one state to another are obtained.

Clinical data indicated that on average a child is 8 years old when being presented for the first time for diagnosis and treatment. Because these patients will need clinical attention for the rest of their lives, it is assumed that on average patients stay within the paediatric hospital treatment system for 10 years, till the age of 18. This then leads to 10 (annual) analysis cycles.

Based on all these data, the overall treatment costs for a cohort of 100 patients over a ten-year cycle are estimated.

The same analysis process is applied for a cohort of patients entering a new MD Paedigree–supported care pathway. Based on clinical expertise, improvements are to be expected with respect to:

- Improved risk stratification of patients
- Better Diagnostic decisions and predicting the progression of the disease
- Better therapeutic decisions.

These are translated into estimates of slightly changed transition probabilities, e.g. a minor reduction in the probability of a mild HF child moving to the moderate subset of patients. And it is anticipated that fewer interventions – resulting in lower treatment costs – will result.

Finally, to obtain a first rough assessment of the overall impact to be expected, the results for the present standard-of-care pathway and the new MD-Paedigree-supported care pathway are compared. The resource savings to be expected are calculated by comparing the overall costs for each pathway for 100 patients per cycle over ten years. When on average 100 new patients are presented at the hospital every year, and when these patients are, on average, being treated for a period of ten years, then the hospital is faced with an annual cardiomyopathy patient population of almost 1,000 children. For such a scenario, the savings are estimated at almost € 3.5 million. Comparing these savings with the overall costs for the old pathway of almost € 19,5 million, a reduction by around 18% results. The following table summarises these results:

Estimates of benefits from resource savings

	Cost in € (state cost per cycle x probability)				
	Mild HF	**Moderate HF**	**Severe HF**	**Sum**	**Cost for 100 patients over 10 years**
Sums Present St. of Care	8,080	47,213	139,553	194,846	19,484,619
Sums MD Paedigree Tool based	5,978	31,939	122,396	160,312	16,031,247
Difference (Savings)	**2,103**	**15,274**	**17,157**	**34,534**	**3,453,372**

The new pathway is expected to positively impact also on the prevalence of the severity of the disease states of patients. To take these benefits equally into account, the intangible benefits related to improvements in the quality of life of patients respectively death avoided are also assessed in monetary terms. Three major impacts are considered:

- Changed prevalence of moderate HF
- Changed prevalence of severe HF

- Deaths avoided

Improvements in the quality of life are commonly measured in quality-adjusted life years (QALYs). To measure them, one multiplies the utility value associated with a given state of health by the years lived in that state. It is assumed that moving from the moderate to mild HF state can be measured by a utility value of 0.2, and from the severe to moderate state by a value of 0.5. For the value of a statistical life year (VSL) an amount of € 50,000 is applied.

Combining the values of positive changes in years spent in a given health or disease state respectively the years of death avoided with these estimates for QALYs and VSLs, and remembering that overall the calculations are based on a cohort of 100 patients per year or around 1,000 patients overall under treatment at any point in time, then these estimates can be combined into a single value for the intangible benefits. The following table summarises these results:

Estimates of intangible benefits from reduced prevalence of moderate and severe HF as well as from deaths avoided

State	Savings in life years in that state (Markov analysis)	For 100 patients, over 10 years	Utility value for improved QALY	Sum of QALYs for all patients under treatment	Total Value (per full QALY: € 50k)
Moderate HF	0.630	63.047	0.2	12.61	630,474
Severe HF	0.150	14.974	0.5	7.49	374,360
Death	0.182	18.185	1	18.18	909,243
Sum				**38.28**	**1,914,077**

This leads to a further benefit estimate, albeit of intangible benefits accruing mostly to the children and their parents, of almost € 2 million.

Discussion

The monetary benefits estimated result from freed, re-deployable resources, not from direct cash savings for the hospital. Another aspect is that the costs applied in the estimates are based on average costs, not on marginal ones. Nevertheless, the benefits expected are large enough to surely justify the effort – not to mention the substantial intangible benefits for children and their parents.

However, an adequate interpretation of the benefits estimated will very much depend on the concrete context of a given hospital, its relationships and contracts with health insurances and patients in a Bismarck system, or in a national health system on its funding mechanisms, as well as on the overall regulatory environment, the role and power of its owners and stakeholders, and other factors. On the one hand,

'society' may want to regulate that the resources liberated – both cash and re-deployable ones – cannot be deployed for other activities by hospitals and other providers. In this case, the real benefits may become allocated not to hospitals which would lose income, but to tax payers respectively those employers and employees who have to pay for health and social care insurance in the end.

On the other hand, hospital management may decide that the liberated resources, particularly bed days, should be allocated to new activities responding to demand so far not yet met, or to new demand created by new offerings which become possible based on the redeployable resources.

No empirical evidence, not even theoretical discussions on such policy issues have been published, but one may expect that in reality a mixed result may occur.

Further research should feed the above explored analytical models with more robust data from concrete pilot applications in semi-routine clinical practice as well as from extended clinical trials, thereby ultimately illustrating how the transformation of MD Paedigree bio-computational modelling and VPH simulation technologies into clinical decision support tools will supplement and improve the current management of specific diseases targeted by MD-Paedigree. The goal of this clinical and socio-economic assessment perspective is to support the testing of clinical application scenarios and deliver empirical evidence for health system actors and decision makers, for exploitation planning and business modelling.

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1. Nature of the Deliverable

This deliverable reports on final work relating to Task 19.3 “Benefit-cost scenario for clinical impact assessment” of WP 19 “Exploitation, HTA, and Medical Device Conformity” of the MD-Paedigree Project, and it also relates to work undertaken in WPs 2, 8 and others. The benefit-cost scenario for clinical impact assessment (as developed in D 19.4) is applied, with the ultimate goal to generate economic and market evidence for true translational medicine. The benefit-cost scenario is tested and initially validated with preliminary, exploratory data derived from patient data files and presently implemented workflows as well as, for comparative purposes, from estimates exploring the future patient-centred workflows which will be based on the digital repository as well as the MD Paedigree clinical decision support tools and its infostructure.

This deliverable also contributes to MS4 “Final Data Collection and Prototypes, Clinical Validation, and Deployment.”

2. Background, goal and objective

This introductory chapter briefly explores the overriding goal of the work to be presented, and states concrete objectives of the task performed.

2.1. Background and goal

The overall goal of the tasks in WP 19 Exploitation, HTA, and Medical Device Conformity is to contribute from a socio-economic and commercial perspective towards making VPH models and simulations readily available both to researchers and to health professionals as decision support at the point of care.1 This involves preparing an appropriate analytical evaluation framework and undertaking groundwork for exploring market access, including meeting regulatory requirements of medical products. This also includes exploring business opportunities.

Here, we are concerned with Health Technology Assessment (HTA), which is a multi-disciplinary field of policy analysis that examines the medical, economic, social, and ethical implications of the incremental value, diffusion, and use of a medical technology in healthcare.2 As VPH technologies usually do not constitute an incremental, often marginal improvement of health technologies, but rather a leap forward towards more predictive, personalized, integrative, and efficient healthcare provision, a critical reflection of HTA approaches was undertaken in D 19.1. It included reviewing and developing a VPH-focused evaluation approach and meaningful indicator development.

D 19.4 then contributed a high-level, generic benefit-cost scenario for clinical impact assessment, including a detailed analysis of the disease types of cardiomyopathy/heart failure and presently available treatment options. An initial clinical pathway model was developed for the identified disease stages, and preliminary cost data and outcome estimates collected.

To render this deliverable a stand-alone document, some principles and approaches described in earlier deliverables will be succinctly summarised to allow for easier grasp of the work to be reported.

2.2. Objectives

For the third task and this deliverable – to be seen in the overall context of the goal and objectives of the MD Paedigree project, these specific objectives were pursued:

- Apply the generic benefit-cost scenario for clinical impact assessment developed
- Review, adapt and validate the clinical pathway model for three disease states – mild, moderate and severe cardiomyopathy

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[1] Hunter, P. et al. (2012), A Vision and Strategy for the VPH: 2012 update. Theme issue "The virtual physiological human: integrative approaches to computational biomedicine", Interface Focus (Royal Society), 06 April 2013, Volume 3 Number 2. 1. Rainer Thiel, Karl A. Stroetmann, Veli N. Stroetmann and Marco Viceconti (2009). Designing a Socio-Economic Assessment Method for Integrative Biomedical Research: The Osteoporotic Virtual Physiological Human Project. In: Studies in Health Technology and Informatics, Volume 150: Medical Informatics in a United and Healthy Europe - Proceedings of MIE 2009. Amsterdam: IOS Press, 2009, pp. 876 – 883.

[2] Neumann, P. J., Drummond, M. F., Jönsson, B., Luce, B. R., Schwartz, J. S., Siebert, U., & Sullivan, S. D. (2010). Are Key Principles for improved health technology assessment supported and used by health technology assessment organizations?. International journal of technology assessment in health care, 26(1), 71. Drummond, M. F., Schwartz, J. S., Jönsson, B., Luce, B. R., Neumann, P. J., Siebert, U., & Sullivan, S. D. (2008). Key principles for the improved conduct of health technology assessments for resource allocation decisions. International journal of technology assessment in health care, 24(03), 244-258. Philips, Z., Bojke, L., Sculpher, M., Claxton, K., & Golder, S. (2006). Good practice guidelines for decision-analytic modelling in health technology assessment. Pharmacoeconomics, 24(4), 355-371.

- Relate the disease states and pathways developed to status-quo clinical interventions and their respective costs per year of treatment
- Estimate from real data the respective transition and absorption state probabilities for a cohort of patients moving over a ten-year cycle through different states of cardiomyopathy
- Populate the Markov Chain analysis tool with concrete cost data and outcome estimates from the hospital as well as from the literature
- Similarly, based on expert estimates, analyse the impact of MD Paedigree decision support tools on pathways, treatment decisions and accordingly adjusted transition and absorption state probabilities as well as costs
- Estimate and compare benefits (cost saved; QoL improved) between status-quo clinical care and healthcare supported by MD Paedigree tools.

This then provides us with a high-level assessment of the benefits and costs to be expected from the application of the models developed respectively under development for this disease once they are indeed ready for clinical usage.

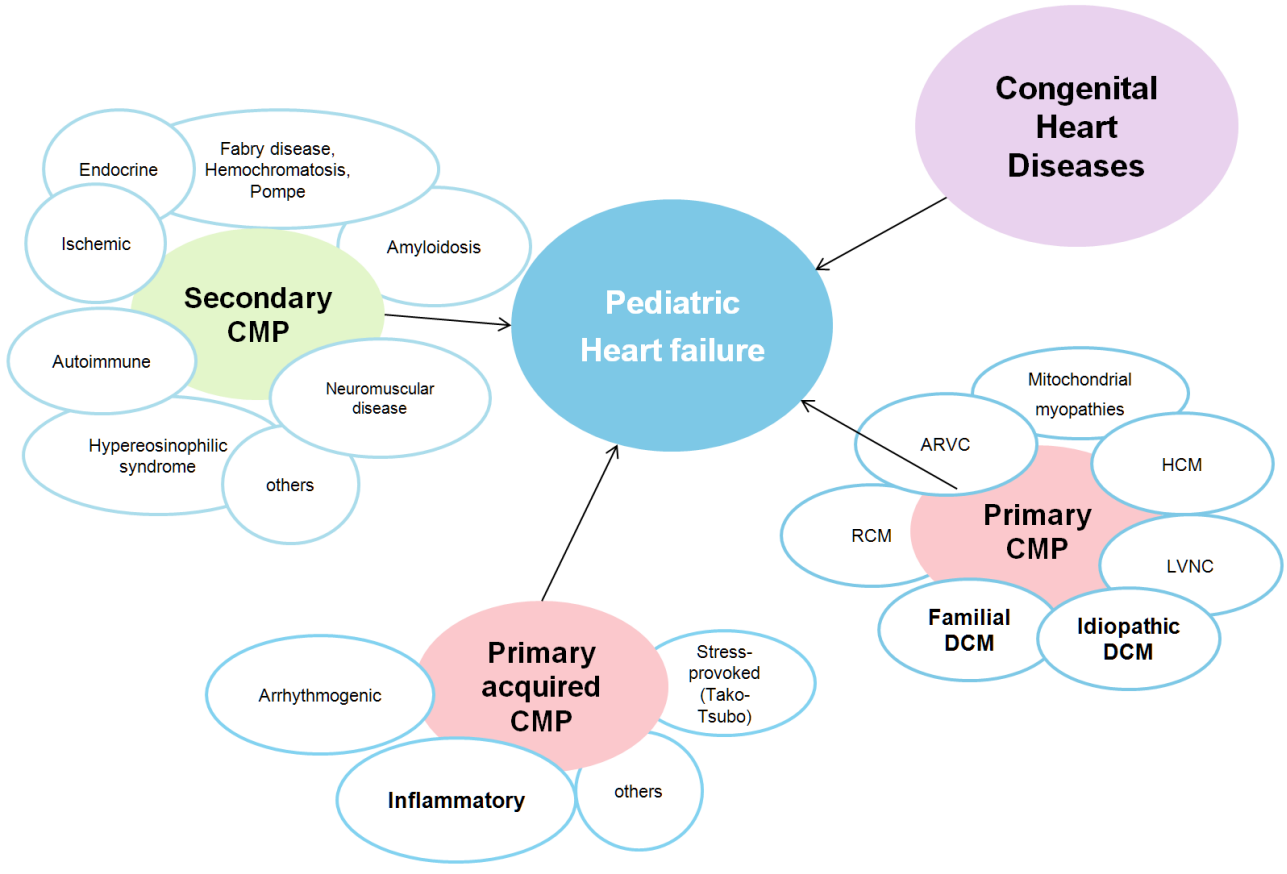
3. Clinical context and VPH background

This chapter briefly explores the types of cardiomyopathy diseases and their treatment options, the "Virtual physiological human - VPH" vision on which MD Paedigree builds, and the "Model-Driven Paediatric European Digital Repository - MD-PAEDIGREE" approach applied here, which has as its core goal to validate and bring to maturity patient-specific computer-based predictive models of various paediatric diseases.

3.1. Cardiomyopathy diseases and treatment options

What follows is mostly concerned with and develops on one of the disease domains of MD Paedigree, Cardiomyopathy (CMP), including Heart Failure (HF) in children.[3] Cardiomyopathy is a rare life-threatening disease leading to chronic cardio-active therapy, or even to mechanical support (artificial heart), heart transplantation or death. Cardiomyopathy is a summary term for a set of chronic and often progressive diseases in which the heart muscle (myocardium) is abnormally enlarged, thickened and/or stiffened. The condition typically begins in the walls of the heart's lower chambers (ventricles), and in more severe cases also affects the walls of the upper chambers (atria). The actual muscle cells as well as the surrounding tissues of the heart become damaged. Eventually, the weakened heart loses the ability to pump blood effectively and various types of severity of heart failure, or also irregular heartbeats (arrhythmias) may occur. Figure 1 illustrates the many varieties commonly identified in cardiology for this set of diseases.

FIGURE 1: TYPES OF HEART FAILURE AND CARDIOMYOPATHY IN CHILDREN



[3] [9] http://www.childrenscardiomyopathy.org/site/description.php.

Source: Franziska Degener, DHZB, 2017

Unfortunately, there is no current cure or treatment that can return the heart to normal or guarantee long term survival. If detected in the earlier stages, cardiomyopathy may be sometimes well controlled with long-term drug therapy, and perhaps placement of a pacemaker/defibrillator. This may allow the children concerned an almost normal life for a long period.[4] However, at stable conditions it is very difficult to predict which outcome a specific patient will have.

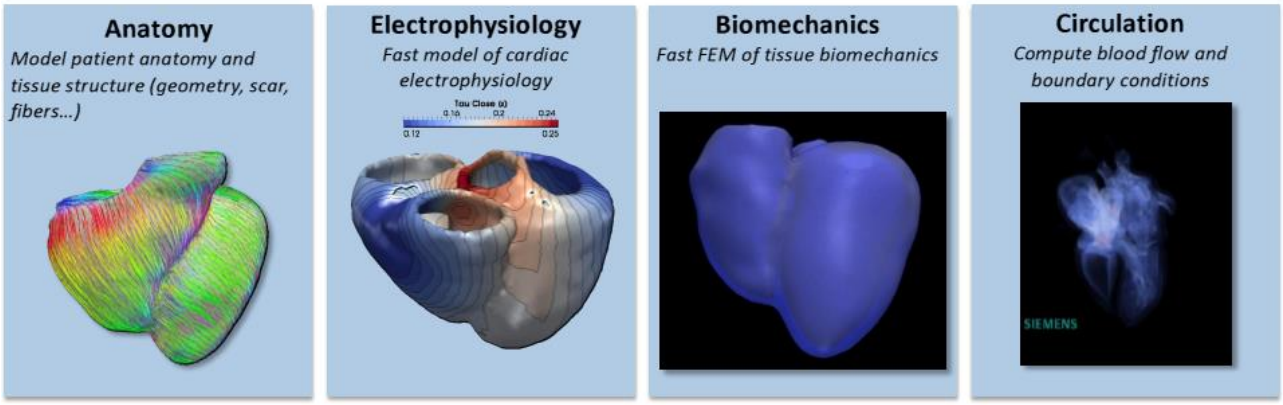
On the other hand, if the disease is diagnosed at an advanced stage or a severe deterioration occurs, critically ill patients may require immediate lifesaving measures such as placement of a breathing tube (mechanical ventilator) and administration of medications intravenously to improve blood pressure and heart function. Once the patient has stabilized, therapy involving oral medication, implantable devices, surgery or heart transplantation will be considered.

3.2. VPH background

The MD Paedigree project builds upon the "Virtual physiological human - VPH" vision,[5] which grew from the global "Physiome project".[6] The concept of a Virtual Physiological Human (VPH)[7] as a sophisticated computer modelling tool in healthcare is one of the foci of European Union eHealth research support.[8]

For more than fifty years by now,[9] computational models of the heart and later blood vessels have been developed to better understand and model the functioning (anatomy, electrophysiology, biomechanics/heart motion, haemodynamic conditions/blood flow) of the cardiovascular system[10] - see Figure 2.

FIGURE 2 THE HEART MODELLING PIPELINE

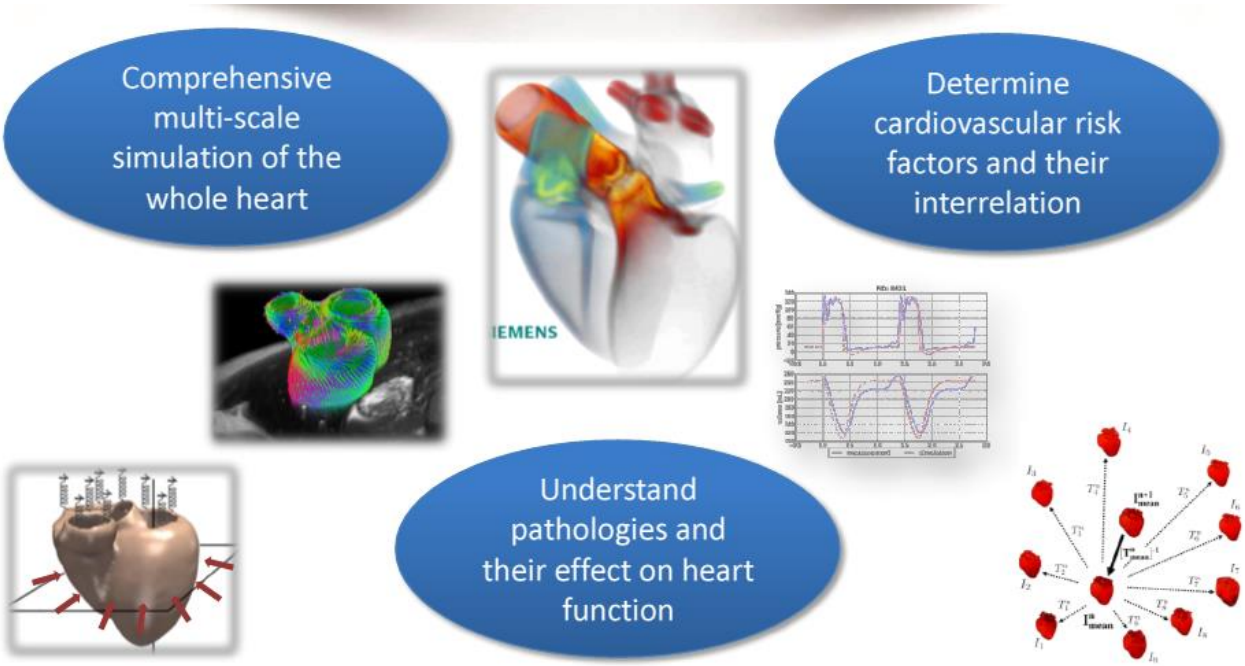


[4] Ibidem
[5] Fenner, J. W., et al. (2008). The EuroPhysiome, STEP and a roadmap for the virtual physiological human. Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences, 366(1878), 2979-2999.
[6] James B. Bassingthwaighte. The Physiome Project: The Macroethics of Engineering toward Health. V32-3: Engineering Ethics (Fall 2002). KAJIYA FUMIHIKO. Cardiovascular Physiome, Proceedings of the Symposium on Biological and Physiological Engineering, VOL. 18; 149-152 (2003
[7] Peter Hunter et al. A vision and strategy for the virtual physiological human in 2010 and beyond. Philos Trans A Math Phys Eng Sci . 2010 Jun 13, 368(1920):2595–614
[8] https://ec.europa.eu/digital-single-market/en/virtual-physiological-human; http://www.vph-institute.org/
[9] Denis Nobel. The Music of Life – Biology Beyond Genes. Oxford University Press, 2006
[10] KIM, H. J., et al. Patient-specific modeling of blood flow and pressure in human coronary arteries. Annals of biomedical engineering, 2010, 38. Jg., Nr. 10, S. 3195-3209.

Source: Tobias Heimann, Siemens Healthineers, 2017

Such models are by now equally employed to model and better understand a wide range of cardiovascular diseases (cf. Figure 3),[11] and they are also used for device design.[12] In order to enable and facilitate predictive, personalised (also termed precision) medicine,[13,14] sophisticated simulation models allowing for

FIGURE 3 OBJECTIVES IN CARDIAC MODELLING



Source: Tobias Heimann, Siemens Healthineers, 2017

the input of patient specific data is needed. Such computational tools may combine and integrate input and results from clinical radiology, image processing, finite element and fluid-dynamics analyses. As some results reported in the literature indicate, it is to be expected that the resulting clinical decision support (CDS) tools will facilitate the development of novel interventions and treatments.[15]

Such personalised treatment approaches are particularly relevant in the context of paediatric heart diseases. Other than adults with acquired diseases, children who were born with cardiovascular defects often show a wide range of different anatomies and conditions which are sometimes unique and very complex.[16] In addition, as the number of medical coronary devices available increases, the selection of an optimal

[11] Charles A. Taylor, C. Alberto Figueroa. Patient-specific Modeling of Cardiovascular Mechanics. Annual Revue of Biomedical Engineering, 2009;11:109–34

[12] Silvia Schievano et al. First-in-man implantation of a novel percutaneous valve: A new approach to medical device development. EuroIntervention: Journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology, 2010, 5 (6), 745-750

[13] Alla Katsnelson. Momentum grows to make 'personalized' medicine more 'precise'. Nature Medicine 19,249(2013) doi:10.1038/nm0313-249

[14] Francis S. Collins, Harold Varmus. A new initiative on precision medicine. New England Journal of Medicine 2015;372(9):793–5

[15] Zahra Keshavarz-Motamed, J. Garcia, L. Kadem. Mathematical, numerical and experimental study in the human aorta with coexisting models of bicuspid aortic stenosis and coarctation of the aorta. In: Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE. 2011. p. 182–5

[16] A. L. Marsden, J. A. Feinstein. Computational modeling and engineering in pediatric and congenital heart disease. Current Opinion in Pediatrics. 2015;27(5): 587.

treatment is not always straightforward. It seems highly likely that the availability of VPH-based CDS tools will greatly improve clinical decision making and thereby the treatment of such children.

However, as also the experience of the MD Paedigree project has shown, translation of VPH technologies into clinical practice remains a major challenge for both the clinical and the modelling community.[17] What is still direly missing are larger clinical studies which validate such in-silico models in comprehensive clinical trials. Sometimes modelling in congenital heart disease is still more of an art than a science.[18] This will only change if comprehensive, longer-term funding becomes available. As a consequence of this state of affairs, the use of patient-specific models is still far from constituting an established standard of care.

3.3. MD Paedigree approach

The "Model-Driven Paediatric European Digital Repository - MD-PAEDIGREE" project validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases.[19] In the cardiology domain, it built upon and further advanced models developed in the earlier Health-e-Child and Sim-e-Child projects and extended them to cardiomyopathies. The objective was to capture the main features of the cardiovascular system, including the heart, arteries and peripheral circulation, to predict cardiomyopathy progression and plan therapies like heart transplant and ventricular assist devices. Investigative data provided by imaging, blood pressure monitoring, and various other clinical observations were used to build these models and to validate them, by comparing model prediction with actual outcome. By merging all scattered information obtained from different diagnostic tools in clinical practice, and obtaining a generative model of heart function in children, these models will eventually provide decision support for clinicians at the point of care.[20] They can be accessed and used through an innovative infostructure integrating multimodal paediatric health data.

Particularly in paediatric cardiovascular disease, such modelling of disease stage and progression is of great benefit. Predicting how patients will respond to treatments, which treatments to use, and when to treat can be difficult to decide due to small patient numbers and limited outcome data. When children are presented with cardiomyopathy or new onset heart failure, there are - in principle - five possible outcomes:[21]

- full recovery,
- dilated cardiomyopathy (DCM) requiring drug therapy,
- DCM requiring transplantation or mechanical support,
- another diagnosis (other forms of cardiomyopathy, metabolic disease), or
- death.[22]

[17] Miguel S. Vieira et al. Patient-specific image-based computational modeling in congenital heart disease: a clinician perspective. Journal of Cardiology and Therapy 2.6 (2015): 436-448.
[18] G. Giannakoulas, K. Dimopoulos, X. Y. Xu. Modelling in Congenital Heart Disease. Art or Science? International Journal of Cardiology, 2009;133(2):141–4.
[19] http://www.md-paedigree.eu/about/
[20] Hunter, P. et al. (2012), A Vision and Strategy for the VPH: 2012 update. Theme issue "The virtual physiological human: integrative approaches to computational biomedicine", Interface Focus (Royal Society), 06 April 2013, Volume 3 Number 2. 1.
[21] Towbin, Jeffrey A., et al. "Incidence, causes, and outcomes of dilated cardiomyopathy in children." Jama 296.15 (2006): 1867-1876
[22] http://www.md-paedigree.eu/cardiomyopathies/

At presentation of the child, however, it is very difficult to predict which group any patient will end up in. Data suggests that good systolic function and younger age are good prognostic indicators for survival,[23] but better prognosticators are necessary.

It is here where the major impact of MD Paedigree modelling is expected. The main issue for modelling of patients suffering from cardiomyopathy regards both the understanding of the complex interactions between heart size, geometry and shape, cardiac workload, heart rate and heart pump function as well as the ability to provide better insight into prognosis and impact of treatment on cardiomyopathies.

As a base for the assessment to follow, comprehensive data on the disease types of paediatric cardiomyopathy/heart failure, treatment options, incidence and prevalence, prognoses for different outcomes to be expected were collected. Based on this knowledge, a detailed clinical pathway model was developed and validated against the clinical workflow in the paediatric care hospitals participating.

[23] Andrews, Rachel E. et al. British Congenital Cardiac Association: New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. Circulation, 2008; 117(1):79-84

4. Health Technology Assessment approach to MD Paedigree models

The goal of our impact assessment is to develop and estimate a high-level generic benefit-cost scenario for exploring the potential clinical (and socio-economic) impact of exemplary MD-Paedigree applications.

Analysing the socio-economic and commercial perspectives of research outcomes has become an integral part of European funding support.[24] In the medical domain, health technology assessment (HTA)[25] in its various forms is usually applied. As VPH technologies do not constitute an incremental, often marginal improvement of health technologies, but rather a leap forward towards more predictive, personalized, integrative, and efficient healthcare provision, a VPH-focused evaluation approach was developed and presented in an earlier deliverable.[26]

4.1. VPH-related methodological challenges

Because conventional HTA methods

- look mostly at existing, "mature" technology applications,
- provide information on consequences and implications of their use (and are accordingly not used as an aid in research guidance, or the development of new products or services),

they are, as a consequence, not sufficient for assessing complex multiscale simulation technologies.

This contrasts with the potential impact of simulation models and computer aided medicine on clinical decision making and practice. They may be far reaching, causing organisational, management, cultural – disruptive – impacts which have a potential to

- revolutionize prevention and diagnosis
- predict disease progression and outcomes related to treatment options
- generate new knowledge from patient and other health data (learning, adaptive decision support systems, which are different from conventional, static decision-support systems).

4.2. MD Paedigree dimensions for HTA

Any HTA will serve a distinct purpose, which usually is decision support in the context of a specific health policy issue. This requires clarifying at which *impact (or policy) level* the specific HTA under consideration may be applied. Concerning the health system or health services, these major players and stakeholders can be distinguished:

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[24] http://ec.europa.eu/health/health_policies/impact/assessment__tool/index_en.htm. Boehler, Ch. et al. (2015).Development of a web-based tool for the assessment of health and economic outcomes of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). BMC Medical Informatics and Decision Making 2015, 15(Suppl 3):S4; http://is.jrc.ec.europa.eu/pages/TFS/MAFEIP.html

[25] Neumann, P. J., Drummond, M. F., Jönsson, B., Luce, B. R., Schwartz, J. S., Siebert, U., & Sullivan, S. D. (2010). Are Key Principles for improved health technology assessment supported and used by health technology assessment organizations?. International journal of technology assessment in health care, 26(1), 71. Drummond, M. F., Schwartz, J. S., Jönsson, B., Luce, B. R., Neumann, P. J., Siebert, U., & Sullivan, S. D. (2008). Key principles for the improved conduct of health technology assessments for resource allocation decisions. International journal of technology assessment in health care, 24(03), 244-258. Philips, Z., Bojke, L., Sculpher, M., Claxton, K., & Golder, S. (2006). Good practice guidelines for decision-analytic modelling in health technology assessment. Pharmacoeconomics, 24(4), 355-371.

[26] Rainer Thiel et al. (2009). Designing a Socio-Economic Assessment Method for Integrative Biomedical Research: The Osteoporotic Virtual Physiological Human Project. In: Studies in Health Technology and Informatics, Volume 150: Medical Informatics in a United and Healthy Europe - Proceedings of MIE 2009. Amsterdam: IOS Press, 2009, pp. 876 – 883.

a) Health service delivery

- individual person
- groups of persons/populations
- healthcare provider organisations (primary, secondary, tertiary level)

b) Health system and public health

c) Society

Whether only one or several of these impact levels will be considered in any specific HTA will have to depend on the context and objectives pursued. When implemented, HTA-based decisions, however, will always influence health services and health outcomes through health practice, i.e. through the health system. In what follows the major focus will be on two groups – the patient population of children suffering from cardiomyopathy including their informal carers (parents, relatives, etc.), and hospitals servicing their needs, because they are the main addressees of the decision tools developed by the VPH community.

Concerning the *time line*, we will look only at children while in the paediatric hospital system. In a formal sense, paediatrics is concerned with children up to the age of around 18 years. Given that the average age of children being presented to a hospital with the (preliminary) diagnosis of cardiomyopathy is around 8 years, the time line applied will be 10 years, a medium-term perspective. Once this diagnosis has been confirmed, most children will stay within the healthcare system for the rest of their life, but move to adult service facilities in due time.

4.3. Identifying clinical benefits and costs

Clinical impact and health-related outcomes may refer to factors and variables such as:

- Primary and secondary endpoints of medical and clinical trials, for example, changes in mortality (death rate) or morbidity (disease rate), length of stay in hospital, visits to physicians/outpatient clinics or hospitals avoided, quality of life of patients, etc.

Other benefits may include

- Reduced period of bed-rest at home for patients, reduced readmission rates due to the avoidance of complications and side effects, fewer drugs to take, less care to be provided by community nurses, family carers and neighbours, fewer side-effects experienced, etc.

Further clinical impacts may relate to

- Organisational and change management aspects
- Human resource implications, knowledge & education needs
- Efforts for application (convenience/ease of use; costs for introduction of new technology)

In our estimation of clinical impacts of MD Paedigree models the focus is predominantly on factors and measurements related to the first two bullet points above because, in a longer-term, uncertain context they are regarded as of primary interest and relevance. Only if clear benefits in terms of factors of direct impact on the health and well-being of patients are to be expected, then do further factors important for the successful implementation and diffusion at the organisation/healthcare provider level of such new approaches become relevant.

When analysing potential future impacts in the clinical domain, one should consider the status-quo of care: presently, at presentation of a child at the hospital and when undertaking diagnostic work, it is very difficult to predict which group any patient will end up in. Data suggests that good systolic function and younger age are good prognostic indicators for survival[27], but better prognosticators are urgently needed.

It is here where the major longer-term impact of MD Paedigree decision support tools is to be expected. The main issue for the modelling of patients suffering from cardiomyopathy regards both the understanding of the complex interactions between heart size, geometry and shape, cardiac workload, heart rate and heart pump function as well as the ability to provide better insight into prognosis and impact of treatment of cardiomyopathies. Patient management will be considerably improved through:

- Modelling of complex interactions

  This concerns the modelling of interactions between the different components of the heart and cardiac performance in dilated cardiomyopathy (mechanical modelling, haemodynamic modelling, fluid-structure interaction).

- Predicting the effect of time and intervention

  Predicting evolution of the disease and identifying possible predictors of outcome and impact of changes in cardiac performance by changing heart rate and cardiac load using specific medications

From the workflow as developed in WP2 it can be derived that the models can significantly impact the care of the patients affected by cardiomyopathy by:

- ✓ Identifying patients at higher risk of outcome
- ✓ Predicting of the timing from the onset of heart failure to the need of transplant/mechanical support
- ✓ Guiding medical/therapeutic decision on most efficient regimens for each specific patient (or 'patient type')

Beyond this, assessing whether a certain scenario may indeed constitute a likely business case for a healthcare provider organisation or society at large, i.e. whether it can be expected to indeed eventually reach the clinical workflow level, also requires at the very least a ball-park assessment of costs for implementing the workflow, infrastructure- and organisation-related costs; and, where feasible, the implied organisational burden of changing current standard of care pathways. Here updated data (as outlined in detail in D 9.4) will be applied.

4.4. Using an explorative healthcare delivery scenario

Here we apply an explorative scenario approach. Such scenarios are characterised by the openness to several possible future developments and encompass an external and strategic mode. *External scenarios* focus on external factors beyond the control of the relevant actors. They are typically used to inform strategy development of a planning entity and provide a framework for the development and assessment of policies and strategies. The external scenarios can then help the user to develop robust strategies, i.e. strategies that will survive several kinds of external development.[28]

[27] Andrews RE et al., Andrews RE, Fenton MJ, Ridout DA, Burch M; British Congenital Cardiac Association. New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. Circulation, 2008; 117(1):79-84

Given the *extreme complexity* of (national) health systems, the number of actors involved in even relatively simple healthcare delivery processes, the political sensitivity of any health-related policy issues, and the mix of powerful stakeholder groups lobbying in this field, scenario analysis is indeed preferred to other more formalised methods of analysis. Scenarios permit a rethinking of the structure and boundaries of healthcare systems, as well as the nature and role of these stakeholders in the pursuit of sustainable health systems.[29]

4.5. Applying a Markov chain approach to clinical impact modelling

Finally, to prepare for the concrete assessment to be presented in the next chapter of this paper, the general socio-economic model structure to be applied as part of the MD Paedigree clinical impact assessment will be described. Such models can be used to assess health technology impact in MD Paedigree using decision analytic modelling (DAM).[30] This provides the base for the mathematical Markov chain (or process) approach which will be applied to estimate overall benefits and costs.[31]

When applying decision analytic modelling (DAM) to the health field, the overriding question is essentially what treatment decision a healthcare professional makes based on all the information which is currently available and accessible about a particular patient [32] The basic idea is that a decision cannot be avoided even if the information to support this decision is scarce, meaning that such decisions need to be taken under conditions of uncertainty. The basic strategy is to "synthesise all available information from multiple sources and to apply mathematical techniques to assess the impact (costs and outcomes) of health interventions".[33] The essential data inputs are probabilities for clinical events, and the impact of such events on a) costs (resources valued in monetary units) and b) values or utilities for health outcomes. The appeal of this approach in general is the fact that DAM "pulls together the many needed pieces of information from multiple sources and then stitches them together into a (hopefully) cohesive whole".[34]

When treating a patient over several years, many of such decision points will arise, each decision taken having an impact on the further (clinical) pathway and quality of life of the patient concerned. Looking not only at an individual patient, but at a whole patient population, like here children suffering from cardiomyopathy, a highly complex network of decision points interconnected by treatment episodes will unfold. An individual patient will enter the network when presented for initial diagnosis at a hospital, will stay for the rest of its life within such treatment networks, or exit the network due to full recovery or death.

To reduce the overall complexity of the daily reality in a hospital when treating such patients, a clinical pathway model may be developed. This then is applied to estimate potential benefits from the new technology, i.e. the incremental health gains expected from the new decision support tools which MD Paedigree is developing, as well as changes in costs related to the new process. Making use of mathematical probabilistic models is an obvious choice for such computations.

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[30] Weinstein, Milton C., et al. "Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies." Value in health 6.1 (2003): 9-17.
[31] Springer, Clifford H. et al. Probabilistic Models – Vol. 4 of the Mathematics for Management Series. Homewood, Ill.: Richard D. Irwin, 1968
[32] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL (2005). Methods for economic health evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press
[33] O'Brien (1996). Economic evaluation of Pharmaceuticals – Frankenstein's Monster or Vampire of Trials. Medical Care, vol. 34, No. 12, suppl. Pp.DS99-DS108
[34] Ibid.

However, these are not simple stochastic processes where the outcome of a particular event is in no way influenced by any other event either past or future. Rather, here the outcomes of a decision are dependent on earlier events, and in healthcare there are usually several possible outcomes, not only two (like the toss of a con versus of a dice). Processes in which the outcome of an event is dependent on the outcome of the previous event or process step are commonly known as Markov processes or chains.[35] When introducing the assumption that a given event is only dependent on the previous event, but not on events before that previous event, then a mathematical solution for the probability of events after n steps, or whether the overall process converges to an equilibrium state of the system, i.e. whether it becomes stable, can be calculated.

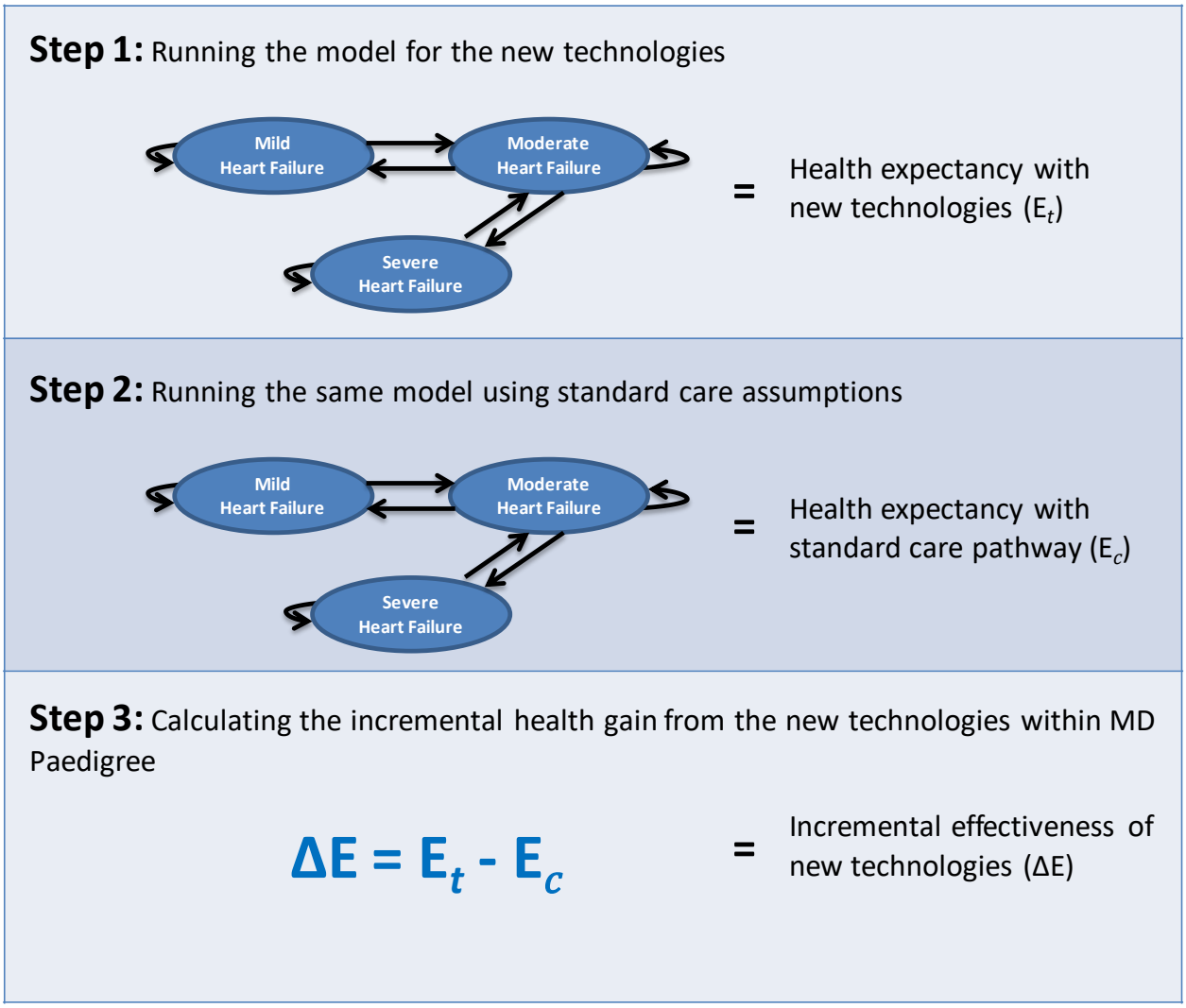
Note that a key assumption when applying a Markov process analysis is that such a process is 'memoryless' – once a transition from one state to another one has been made, the population subset in a particular health state is considered homogeneous regardless of where the patients have come from, and when.

For our objectives, it is necessary to develop clinical pathways both for status-quo treatment and treatment options after introduction of simulation-tool supported decision making, and to obtain probability estimates for each event in the respective process network. For each event benefit-cost estimates have to be derived, once with data on the standard care pathway, and once with data on the new pathway with new technologies. Based on a very basic Markov process model, this is illustrated in Figure 4. The incremental gain resulting from moving from the old to the new pathway (ΔE) is than calculated as $\Delta E = E_t - E$[36], where E_t is the health impact expectancy with the new intervention and E_c is the health impact expectancy with the standard care pathway.

[35] https://en.wikipedia.org/wiki/Markov_model

[36] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL (2005). Methods for economic health evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press

FIGURE 4 BASIC MARKOV PROCESS MODEL FOR ESTIMATING HEALTH IMPACTS (BENEFITS AND COSTS)



Source: empirica/MD Paedigree 2017

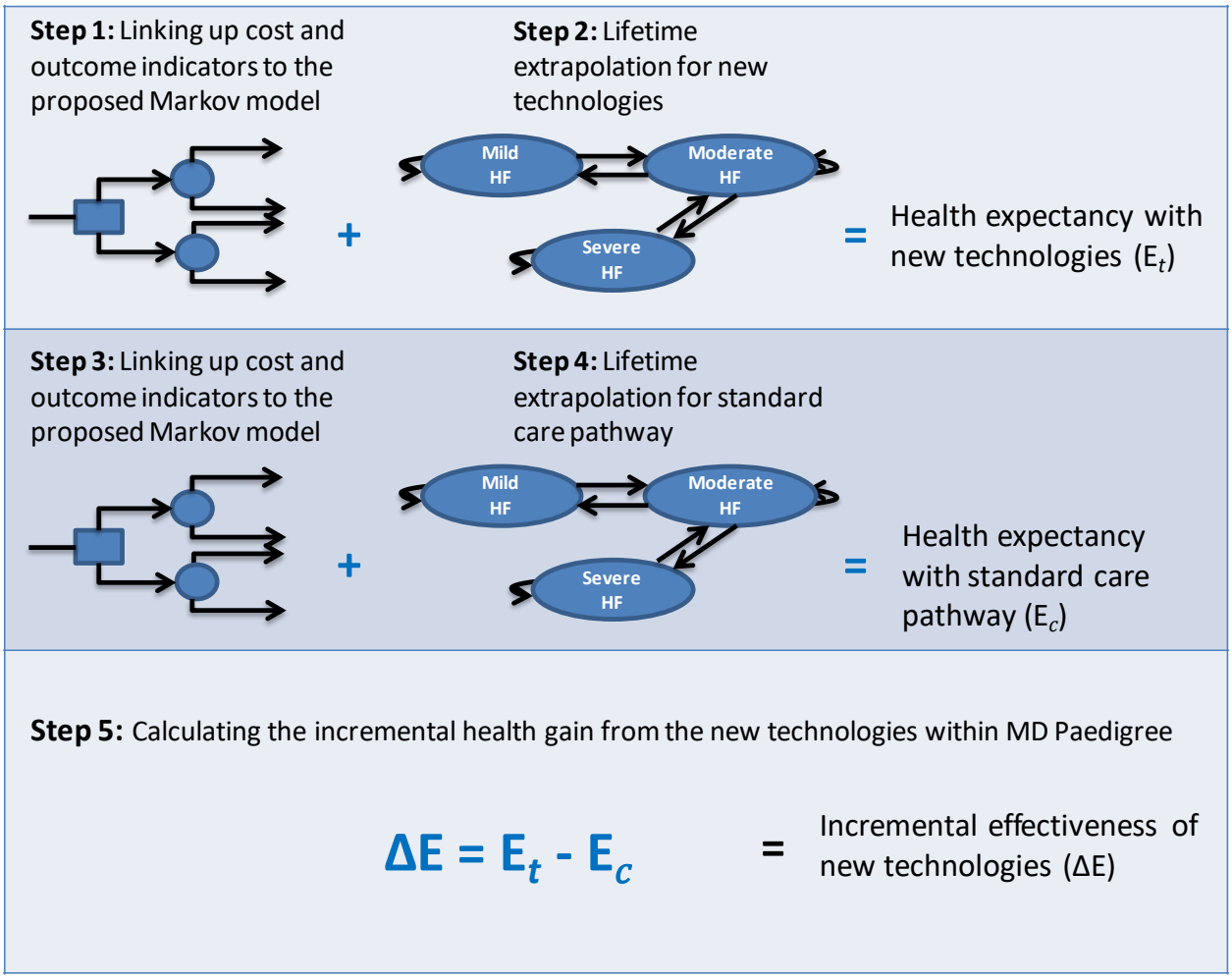
The impact model developed allows drawing from data related to each "event" - benefits and costs related to each individual process step as well as primary and secondary outcome measures. It rests on three "ideal type" health states: mild, moderate and severe cardiomyopathy/health failure.

This basic model can be linked and adapted to extrapolate the MD Paedigree impact model to a more complex set of assumptions. E.g., to link secondary outcome indicators to the model, more has to be done than calculating the basic three-stage Markov model illustrated in Figure 4. Combining a decision tree to the Markov model is one way to achieve this[37], as seen in Figure 5. Although a Markov process model differs in various aspects from a standard decision tree, it can be seen as "a form of recursive decision tree".[37]In the present context, we use the decision tree (or Markov decision process)[38] model to model and identify the outcomes of diagnosis, treatment, mechanical device/transplant in each of the care pathways over an

[37] Briggs, A, Claxton, K, Sculpher, M (2006). Decision modelling for health economic evaluation. Oxford University Press, Oxford, UK
[38] Markov decision processes (MDPs) provide a mathematical framework for modeling decision making in situations where outcomes are partly random and partly under the control of a decision maker: https://en.wikipedia.org/wiki/Markov_decision_process

extended period of time - with and without the new technologies. This will subsequently impact the respective proportion (probability) of a patient ending up in each state of the Markov model at a given stage (time interval) and influence the cost composition in the care scenarios.

FIGURE 5: EXTENDING THE BASIC MARKOV PROCESS MODEL TOWARDS A MARKOV DECISION PROCESS MODEL



Source: empirica/MD Paedigree 2017

5. Clinical impact assessment of MD Paedigree cardiomyopathy decision support tools

5.1.Introduction

In the following sections, first the presently performed clinical pathways will be outlined. They describe, as an operational model, the state-of-the-art diagnostic and intervention processes for the advanced treatment of cardiomyopathy/heart failure for babies and children in a tertiary care hospital. Three disease states – mild, moderate, severe – are distinguished. Next the annual costs for each disease state and the probabilities for staying in or changing a disease state are determined. This then serves as input for a Markov process analysis in order to calculate over 10 annual cycles the overall costs for a cohort of 100 patients. By comparing the present state-of-the-art (SOTA) processes with the estimates for the MD Paedigree-based processes we obtain initial estimates of the socio-economic impact of the new tools.

5.2. Modelling the clinical pathway for treating cardiomyopathy

The modelling of the clinical pathway to treat the set of Cardiomyopathy diseases is undertaken in three steps: Firstly, three standard states of the disease are defined by applying a severity scale used by clinicians to stratify patients. This is then applied to draft a model pathway system or network based on these three states. It is represented as a graphical operational model to illustrate the processes used to create socio-economic impact or value, applied to healthcare service delivery. Finally, this will be translated into a graphical model of the Marcov decision process for both the present and the new, future pathways, as basis for the Markov analysis to estimate the expected benefits and costs from improving both diagnosis and treatment through the modelling services developed by the MD Paedigree project.

5.2.1. Disease states

When defining a process model for treating cardiomyopathy, three arms of a clinical pathway can be distinguished, one for each of the following disease states a child may be in when entering the hospital: a patient may be suffering from

- mild cardiomyopathy/heart failure
- moderate cardiomyopathy/heart failure
- severe cardiomyopathy/heart failure

Patients are usually referred by their GP, paediatrician, or also an emergency service, and they enter the hospital either via the emergency room or the outpatient clinic. After primary diagnostics have been performed, they are assigned to one of the three arms based on both quantitative diagnostic measures and a qualitative assessment of the attending cardiologist.

The following Figure 6 Cardiomyopathy clinical pathway depicts these arms and their respective diagnostic and treatment components, which will subsequently be outlined (percentages given in that figure are based on all patients at that stage of the pathway in in the respective arm of the pathway).

This presently implemented standard of care pathway will serve as the central comparator with the future MD Paedigree facilitated clinical pathways. All assumptions underlying our impact assessment are based on approximations of incidence, prevalence, outcome and other data taken from current literature and epidemiological data, as well as on interviews with clinical experts from project partners. It lies within the

nature of social scientific comparisons and evaluations that, in order to methodologically handle complexity and uncertainty of data input, parsimonious, i.e. simplified, models need to be applied.

Mild heart failure

Those patients that are diagnosed with mild heart failure are serviced by the outpatient clinic. Each visit to the outpatient clinic involves:

- Consultations with a HF cardiologist
- Diagnostics procedures including cardiac MRI, secondary screening, echocardiography, stress testing, and 24-hour blood pressure and heart rate monitoring
- Review and, if deemed necessary, (adjustment of) medicinal therapy

Depending on the outcome, the patient is then (re-)classified according to its diagnosed clinical condition. A sufficiently improved condition would point to further care that can happen in their home region by local specialists and the GP; however, in reality, all of these patients return regularly for examination and treatment to the hospital. Patients that exhibit a stable condition are scheduled for monthly or bi-monthly recurring visits to the hospital's outpatient clinic. Patients that experience a worsened condition are moved to the hospital ward where they enter the moderate, or in rare cases even the severe HF arm.

Moderate heart failure

Moderate heart failure patients are admitted to the hospital ward. During their stay, they are treated as follows:

- Consultation with the cardiology team
- Diagnostics procedures including cardiac MRI, secondary screening, echocardiography, stress testing, and 24-hour Blood Pressure and Heart Rate Monitoring
- Medicinal therapy

During their stay, the patient's clinical condition is constantly monitored. If the condition improves, it will be transferred to the mild heart failure arm (*i.e.* they are checked out of the hospital ward and are instructed to participate in recurring visits to the hospital).

Here a stable condition indicates that the patient would stay in the ward and continues medical therapy, and a worsened condition would transfer the patient to the severe heart failure pathway (described below).

Severe heart failure

Patients who are diagnosed with severe heart failure are placed in the cardiology intensive care unit (ICU). This pathway involves the following:

- A consultation with an anaesthesiologist, ICU cardiologist, and heart surgeon
- Diagnostic procedures including a cardiac catheter, secondary screening, and echocardiography
- A clinical conference that results in the decision of whether to (a) put the patient under (further) medication, (b) put the patient on mechanical support, or (c) forward the patient directly to the transplant list.

Those placed under medication are monitored for their clinical condition whereas those who improve are moved to the hospital ward for medical therapy (under the moderate heart failure pathway), those who have

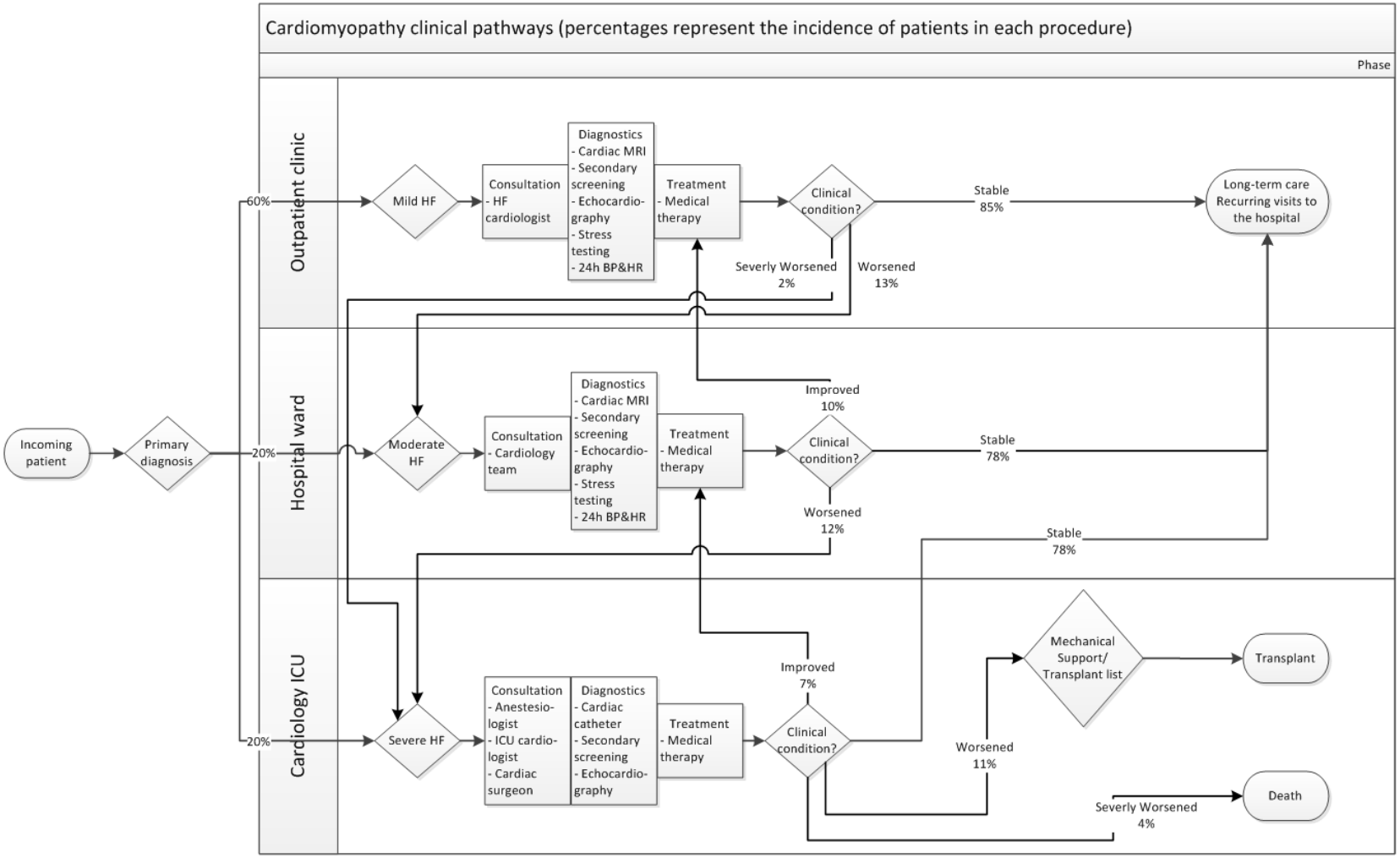
a stable condition maintain their current medication, and those whose condition has worsened are given mechanical support.

Outcomes for children on the transplant list depend on the waiting time (among other factors) they are still able to survive; for some receiving a mechanical circulatory support device will extent this timespan by a few to up to 12 months.

5.2.2. Operational pathway model

All of these considerations and information are translated in “Figure 6 Cardiomyopathy clinical pathway” into a model of the clinical pathway for treating cardiomyopathy. Percentages given in that figure at the entry stage (“cycle zero”) reflect that on average about 60% of children being presented for an initial diagnosis are classified into the mild heart failure state, 20% to the intermediate state, and roughly 20% to the severe state. Once allocated to one of the three states, the percentages given in the figure relate to all patients in that arm of the pathway:

FIGURE 6 CARDIOMYOPATHY CLINICAL PATHWAY MODEL



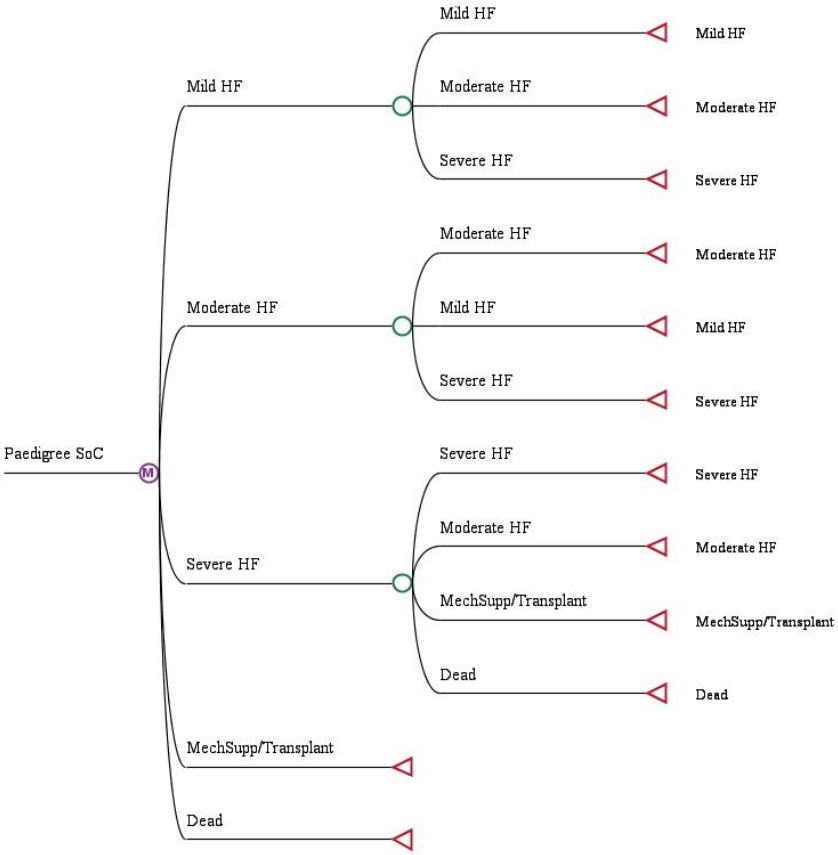
Source: (c) empirica/MD Paedigree 2017

5.2.3. Cardiomyopathy Markov model

As discussed earlier in section "4.5 Applying a Markov chain approach to clinical impact modelling", a Markov process model will be used as the basis to derive realistic, representative cost estimates for a cohort of cardiomyopathy patients. This will be necessary for both the old and the new pathway. Here "the standard care scenario should generally reflect routine practice, hence, reporting health outcomes of the most common care strategy that would be replaced by the intervention in question."[39] A similar definition has been adopted in many national guidelines for the economic evaluation of healthcare technologies[40,41].

In the following Figure 7, the cardiomyopathy clinical pathway model presented above in Figure 6 has been translated into a Markov-chain model for estimating health (technology) impact.[42]

FIGURE 7: TRANSLATING THE CARDIOMYOPATHY CLINICAL PATHWAY MODEL INTO A MARKOV-CHAIN MODEL FOR ESTIMATING HEALTH IMPACT



Source: empirica/MD Paedigree 2017

[39] Abadie, F., & Boehler, C. (2015). Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing (MAFEIP)-Conceptual description of the Monitoring and Assessment Framework for the EIP on AHA (No. JRC96205). Institute for Prospective and Technological Studies, Joint Research Centre.

[40] Eldessouki R, Smith MD (2012). Health Care System Information Sharing: A Step Toward Better Health Globally. Value Health Regional Issues; 1:118-129

[41] International Society for Pharmacoeconomics and Outcomes Research (ISPOR). ISPOR Pharmacoeconomic Guidelines Around The World. Available at: http://www.ispor.org/PEguidelines/index.asp. [July, 067 2014].

[42] For the Markov analysis and to generate the figures presented on this, the TreeAge Pro Markov cohort model module of the TreeAge Pro Helthcare 2017, R1 Release, software was applied. For more details, see https://www.treeage.com/

As can be seen from this graph, we will have to deal – in Markov parlance – with five "disease" states. We identified three *transition* states, from which a patient may move on to the same or another state:

1. Mild HF
2. Moderate HF
3. Severe HF

Furthermore, two *absorption* states need to be introduced; these are states which are final states from which a patient will not move on to another disease state:

4. Mechanical support/transplant
5. Death

Of course, the state 'mechanical support/transplant' will eventually lead also to death, but in our context it is defined as an absorption state because those patients will, on average, life for more than 10 to 15 years, or even sometimes many more years,[43] which is beyond our time horizon of 10 cycles (= years) for the analyses to follow. Furthermore, for cost considerations, these patients are not a subset of the set of patients for which the MD Paedigree tools may lead to improved treatment and care – these patients are outside of the domain of present research efforts.

5.3.Clinical impact assessment - standard of care

5.3.1. Treatment cost – standard of care

To estimate the overall costs of the three clinical sub-pathways for a given cohort of children over the 10-year cycle, the approximate costs of the diagnostic and treatment interventions per typical patient and the percentage number of patients in each arm are required.[44] The percentages (or probabilities) of patients moving from one pathway to the other and receiving treatment and interventions there, moreover, are basic input for the overall cost-effectiveness analysis further below.

The costs of standard of care pathway are associated with those of the baseline clinical protocol for cardiomyopathy in children as agreed with WP2 and across the clinical specialists in the project, which reflects current practice in the diagnosis and treatment of cardiomyopathy. The actual cost estimates reported in D 19.4 have been critically reviewed and validated, with only minimal modifications. For the standard-of-care pathway, they are summarised in Table 1. They are reported for the initial (start) cycle or year one, for cycle two, and for cycles 3 to 10. They are, on average, assumed to be more or less stable, independent of the age of the child and the duration of the treatment received for the three disease states.

The absorption state 'mechanical support/transplant' is for modelling purposes assumed to be one single state, whereas in reality a child in need of a transplant may receive, as an intermediary step, a mechanical circulatory or cardiac support device for up to one year to bridge the time till an appropriate graft becomes available. To account for this, and as about every 5th child may receive mechanical support before transplant, the cost for cycle one is a combined estimate of both interventions. A child with a transplant requires still considerable attention and treatment in the hospital in year two – with the associated costs. However, once

[43] Copeland, Hannah, et al. "Pediatric recipient survival beyond 15 post-heart transplant years: a single-center experience." The Annals of thoracic surgery 98.6 (2014): 2145-2151.

[44] See also NICE 2008: Developing costing tools methods guide, http://www.nice.org.uk/media/F3E/57/DevelopingCostingToolsMethodsGuide.pdf.

the overall health situation has been stabilised, the treatment costs for cycles 3 ff are even lower than for moderate HF children.

TABLE 1 ESTIMATES OF COST DATA PER CYCLE - STANDARD OF CARE

States / Cycles	1. Death	2. Mild HF	3. Moderate HF	4. Severe HF	5. Mechanical Support/Transplant
1. Start cycle (year)	0.00	2,000	17,300	72,500	95.000
2. Cycle2	0.00	2,000	17,300	72.500	27,700
3. Cycles 3 ff	0.00	2,000	17,300	72.500	7,100

5.3.2. Transition matrix – standard of care

As reported earlier, after initial presentation in the hospital and having undergone an initial diagnostic process, children are allocated to one of three disease severity subsets: mild, medium, severe by applying a severity scale used by clinicians to stratify patients.

Following the logic of a Markov process, which closely mirrors clinical observations, patients may stay in cycle two either in their entry state – the probabilities for which are reported in the diagonal of Table 2 – or move to another state. These distinct cycles of disease states are attributed probabilities relating to the transition between these states. For modelling purposes, it is assumed that the duration of these cycles are annual intervals. The probabilities for them are also given in that table. In summary, the probabilities for each starting state ("from") have to add up to 100%. These estimates are based on and derived from patient data for a cohort of patients in Ospedale Pediatrico Bambino Gesù (OPBG), Rome.

This transition matrix for the standard of care pathway is presented in Table 2 below. Here, the factor "time" is explicitly associated with the probability of a patient moving through certain states in a series of discrete periods of time.

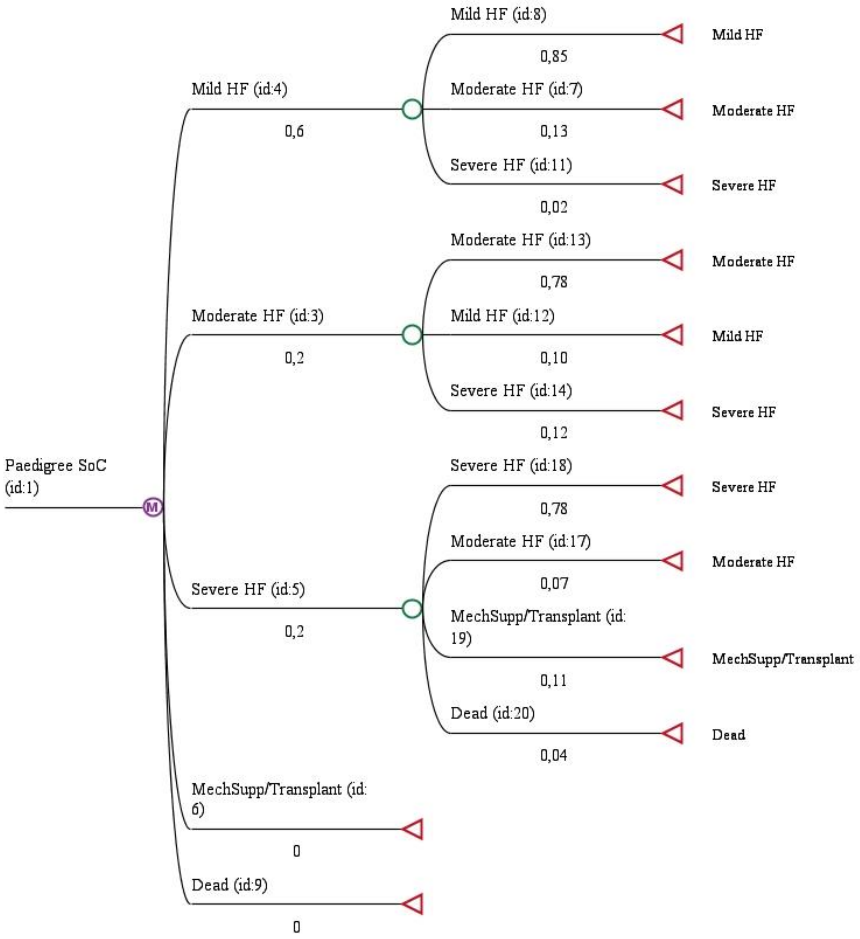
TABLE 2: TRANSITION (PER CYCLE = ONE YEAR) AND ABSORPTION PROBABILITIES - STANDARD OF CARE

To state / From state	1. Mild HF	2. Moderate HF	3. Severe HF	4. Mechanical Support/Transplant	5. Death
1. Mild HF	**0.85**	0.13	0.02		
2. Moderate HF	0.10	**0.78**	0.12		
3. Severe HF		0.07	**0.78**	0.11	0.04
4. Mechanical support/transplant (absorption state)				**1.00**	
5. Death (absorption state)					**1.00**

Both death and mechanical support/transplant show up only as a final arm/exit from severe HF.

This transition matrix is then transformed into the Markov chain graph in Figure 8, which illustrates how a patient may move over time through disease states, with the relevant probabilities from the above matrix attached to each arm.

FIGURE 8 MARKOV-CHAIN TRANSITION PROBABILITIES FOR PRESENT STANDARD OF CARE



Source: empirica/MD Paedigree 2017

5.3.3. Results – standard of care

Next the results obtained when undertaking a Markov process analysis for the standard of care pathways are presented. However, first we have to clarify over how many cycles – in healthcare conventionally measured in years – the analysis should be run.

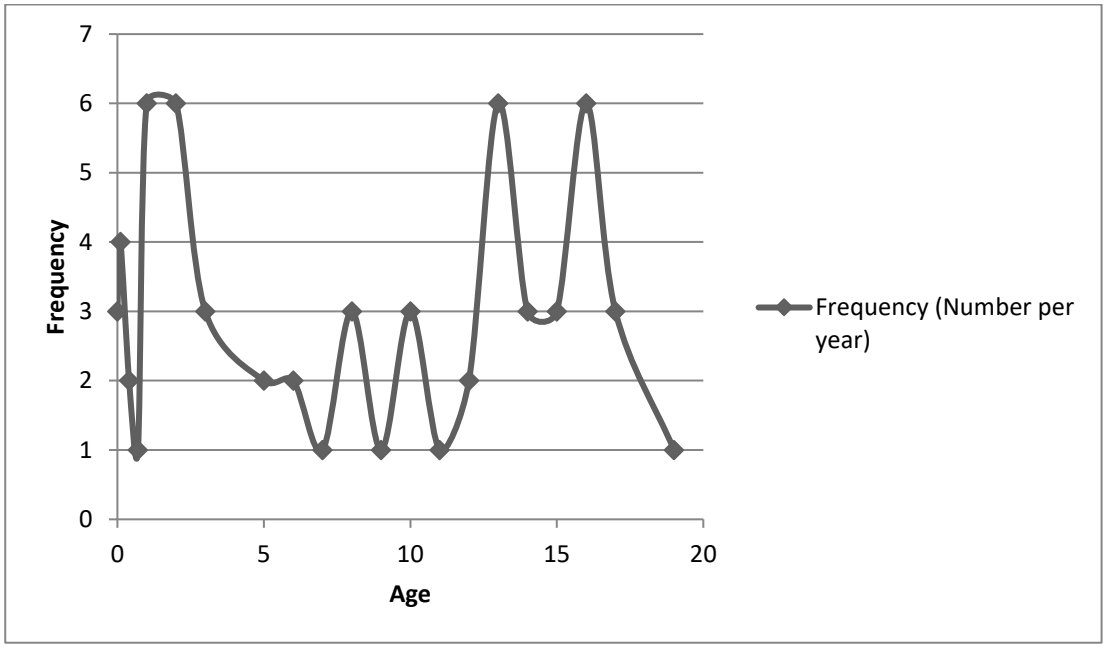
Time horizon and cycles

As briefly mentioned earlier, paediatrics is usually concerned with treating children of the age zero up to 18. Depending on the country, this may differ slightly. Also, sometimes children/young adults older than 18 are nevertheless still treated e.g. in a paediatric hospital because they prefer this due to their sometimes-long-term relationship with staff there.

The following Figure 9 is based on a small sample of HF patients at OPBG. It shows two typical bumps around the ages of 1 – 2 and 13 – 16, i.e. symptoms of cardiomyopathy show a certain tendency to appear very early

or around puberty. Taken together, the average age of this patient sample is about 7.85 years. For our purposes, we therefore assume that on average patients in our analysis cohort stay within the paediatric hospital treatment system for 10 years, till the age of 18. This then leads to 10 (annual) analysis cycles.

FIGURE 9 NUMBER OF CHILDREN PER AGE PER YEAR



Probabilities per cycle and state

When performing the Markov analysis based on the transition probabilities matrix presented earlier in "Table 2: Transition (per cycle = one year) and absorption probabilities - Standard of care", the values as reported in the following Table 3 result:

TABLE 3 MARKOV CHAIN PROBABILITIES FOR10 CYCLES AND FIVE STATES – STANDARD OF CARE

Stage/Cycle	% Mild HF	% Moderate HF	% Severe HF	% MechSupp/ Transplant	% Dead
1	0.600	0.200	0.200	0.000	0.000
2	0.530	0.248	0.192	0.022	0.008
3	0.475	0.276	0.190	0.043	0.016
4	0.432	0.290	0.191	0.064	0.023
5	0.396	0.296	0.192	0.085	0.031
6	0.366	0.296	0.193	0.106	0.039
7	0.341	0.292	0.194	0.127	0.046
8	0.319	0.285	0.193	0.149	0.054
9	0.300	0.278	0.191	0.170	0.062
10	0.282	0.269	0.188	0.191	0.069
Average	**0.404**	**0.273**	**0.192**	**0.096**	**0.035**

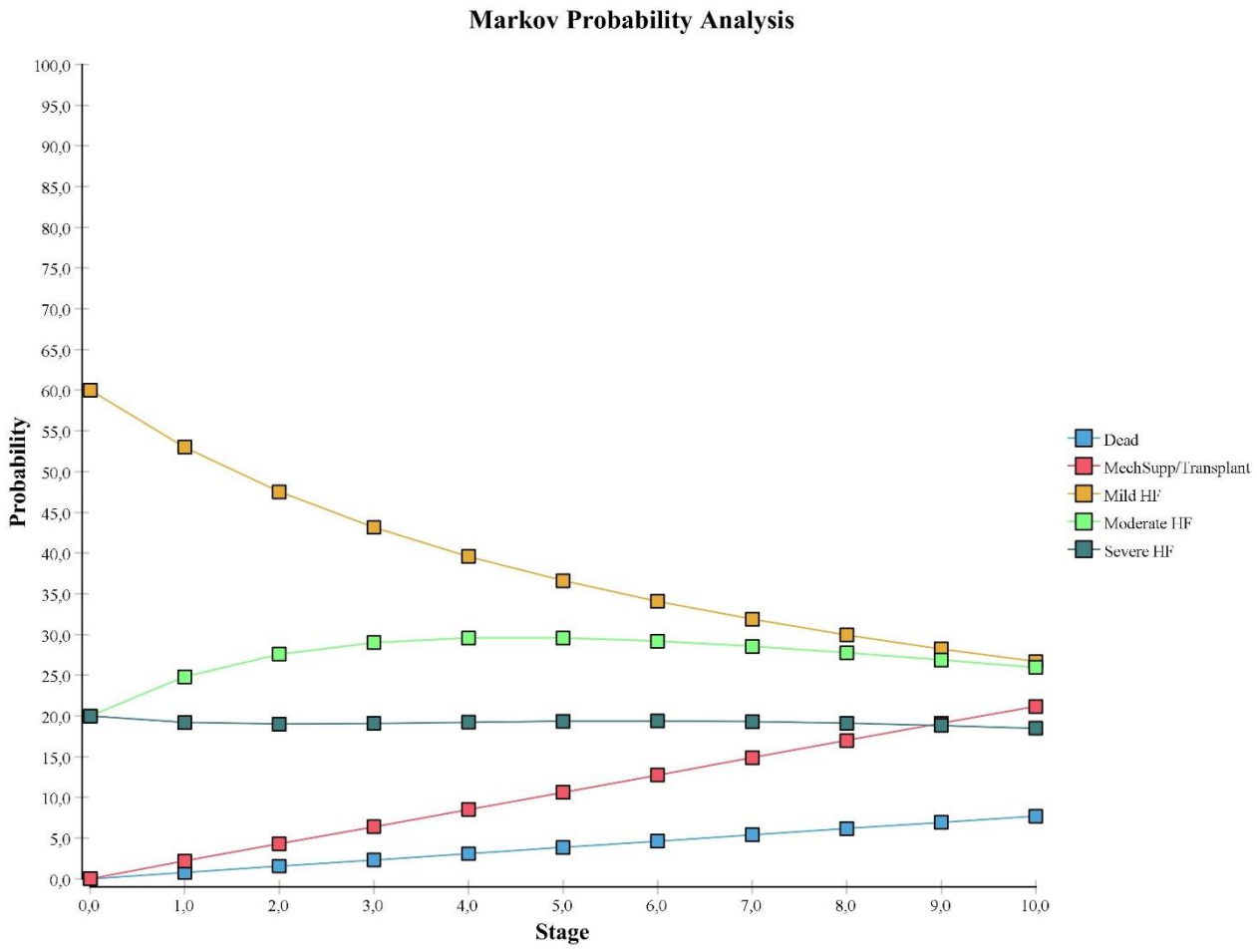
These values indicate – in our model environment and under the assumptions made earlier, particularly with respect to the Markov approach – with which probability an individual patient presented at the hospital for initial diagnosis may end up in which year in which state of the disease. On average after year ten, it is assumed that surviving patients move into the adult arm of health system services.

In a static environment, where every year the same number of patients enters the healthcare system of the cardiac unit of the hospital and where no changes in treatment lead to different outcomes, this matrix provides a full model of the state of paediatric patients under treatment during a particular year. When e.g. assuming that on average each year 100 new patients are presented at the hospital, then the total patient population under treatment would be around *10 years x 100 patients equal to 1,000 patients.*

At year-end, this number will be somewhat lower, minus those patients which have died in the meantime. As the data in Table 3 indicate, the overall (average) probability of death for all patients in this cohort is 0.035 or 3.5%, i.e. it is expected that of the 1,000 patients 35 will have died, implying that in any year, on average, 965 patients are surviving.

In Figure 10 these values are translated into a graphical presentation:

FIGURE 10 MARKOV CHAIN PROBABILITIES FOR10 CYCLES AND FIVE STATES – STANDARD OF CARE



Source: empirica/MD Paedigree 2017

It illustrates that the assumptions made – the transition probabilities – imply that the number of mild HF children in a given cohort decreases over time continuously (due to moving into more severe states), the

cohort of moderate HF patients increases somewhat during early years, but is relatively stable; stability also holds for the severe HF patients. And, as is to be expected, the number of children requiring a transplant or intermittently mechanical support rises. The same holds for the number of deaths, but at a much lower level.

Cost per cycle and state

Based on the estimated treatment cost per state and cycle as reported in "Table 1 Estimates of cost data per cycle - Standard of care" and the probabilities reported in "Table 3 Markov chain probabilities for10 cycles and five states – Standard of care" we calculated the expected cost for each disease state and each cycle/year by multiplying the two values. This provides us with the data reported in "Table 4 Cost in € per cycle and state – Standard of care." Note that these data cover only the three transition states defined earlier for cardiomyopathy, and not the absorption states mechanical support/transplant and death. This is so because the MD Paedigree decision support tools will, at least at present, not support or lead to improved treatment of patients with a transplant or mechanical device.

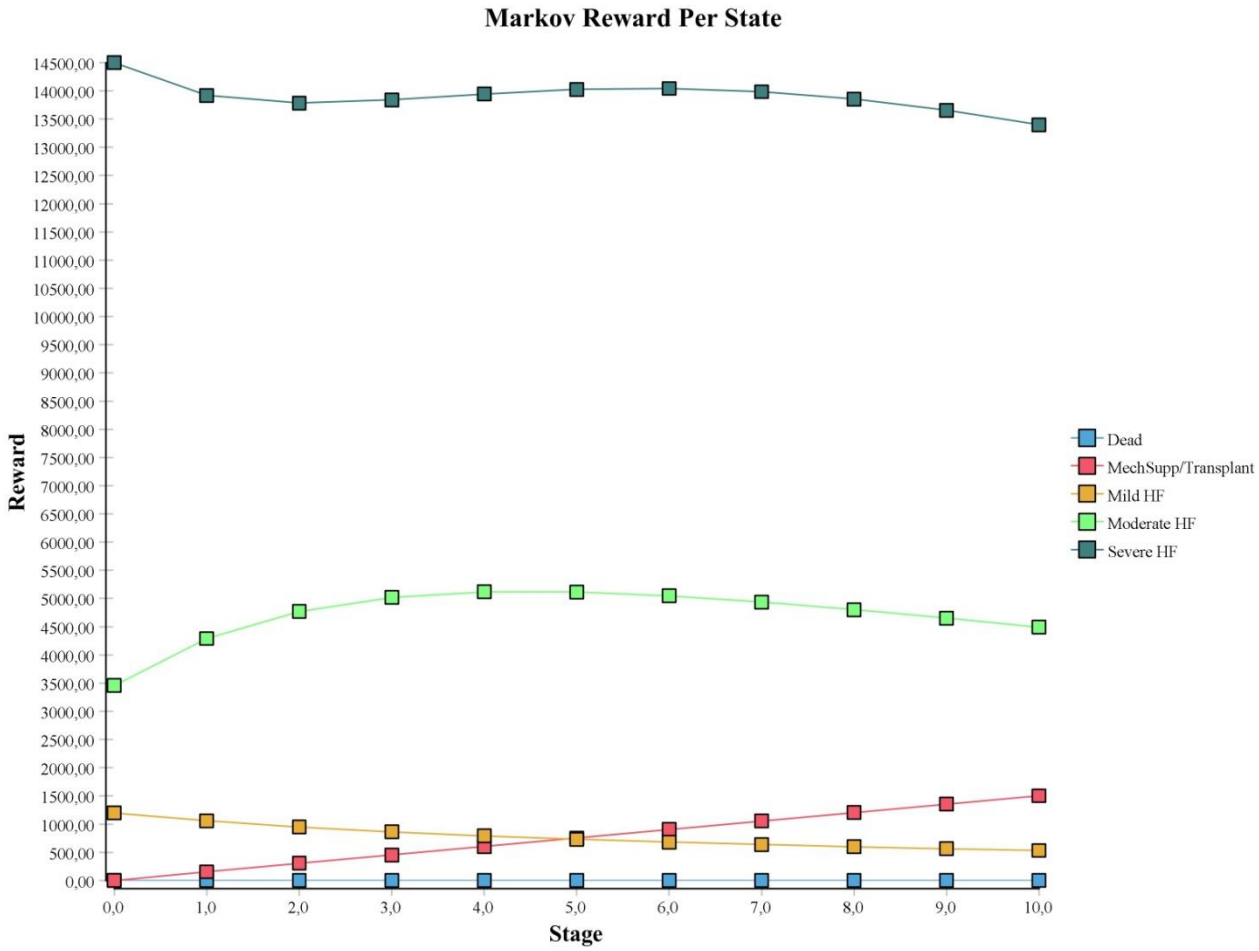
To arrive at the concrete costs to be expected per cycle, they need to be multiplied by the overall number of patients entering the treatment system during a given year. This then allows us to obtain realistic, representative cost estimates for a cohort of cardiomyopathy patients.

TABLE 4 COST IN € PER CYCLE AND STATE – STANDARD OF CARE

	Cost in € (state cost per cycle x probability)			
Stage/ Cycle	**Mild HF**	**Moderate HF**	**Severe HF**	**Sum**
1	1,200	3,460	14,500	19,160
2	1,060	4,290	13,920	19,270
3	951	4,771	13,784	19,505
4	863	5,021	13,840	19,723
5	792	5,118	13,946	19,855
6	732	5,115	14,025	19,873
7	681	5,047	14,043	19,772
8	638	4,938	13,986	19,561
9	599	4,802	13,854	19,255
10	565	4,651	13,656	18,871
Sum	**8,080**	**47,213**	**139,553**	**194,846**

In Figure 11 these values are translated into a graphical presentation (Note that "reward" – as inserted by the software – in our context refers to costs). By far the highest cost results from treating severe HF patients, followed by cost of treating moderate HF patients. "Death" is assumed, for our purposes, to carry no cost, and "Mechanical support/transplant" cost do not enter our further considerations for the reasons explained earlier.

FIGURE 11 COST IN € PER CYCLE AND STATE – STANDARD OF CARE



Source: empirica/MD Paedigree 2017

5.4.Clinical impact assessment - New MD Paedigree–supported care pathway

Next, we undertake the same analysis as above for new cardiomyopathy pathways support by MD Paedigree tools. Firstly, however we briefly discuss the benefits expected and predicted based on initial experience and assessment by clinicians of such tools for the future treatment of patients suffering from this disease.

5.4.1. Benefits expected from cardiomyopathy pathways support by MD Paedigree tools

Benefits are predicted for three areas:

Risk stratification of patients

The application of the new CDS tool(s) may allow paediatricians to better allocate children presented for examination and diagnosis to one of the three initial clinical pathway arms. The expected impact is an

a) Increase in the number/percentage of children allocated to the mild or moderate HF arm – the number of children allocated precautionary into the severe HF arm can be reduced because the risk of misallocation is reduced
b) This leads to a reduction in overall treatment effort and cost

c) It may also result in a release of resources to better focus on the most severely sick patients with the highest risk, thereby reducing their probability to need a transplant and perhaps an intermediary mechanical support device.

Diagnostic decisions and predicting the progression of the disease

The application of the new tools allows paediatricians to better predict the progression of the disease for an individual child within the three clinical pathways. The expected impact is

a) A reduction in diagnostic interventions: those children with a rather stable outlook can be identified, and the number and type of (costly) diagnostic tests (like echocardiography, MRIs...) which may be applied routinely may be reduced or even omitted.
b) Those children at a higher than up to now anticipated risk can undergo better timed and focused *diagnostic* interventions, thereby reducing their probability to suffer from a worsening of the disease (with resulting savings in the associated costs of change in pathway, or interventions like being treated in the ICU)

Therapeutic decisions

The application of the new tools allows paediatricians to make better therapeutic decisions. The expected impact is on

a) The *treatment* costs: due to better targeted drugs and other treatments, more costly interventions like ICU or hospital stay can be reduced because patients will be treated more timely and appropriately thereby also avoiding a worsening (or a slower worsening than up to now) of the progression of the disease (with the associated avoidance of transition to a costlier treatment path, or a later transition thereto than up to now)
b) Better therapeutic decisions will reduce the probability of a child moving from the moderate into the severe pathway, and the probability of a child in the severe pathway becoming in need of a transplant (and perhaps also an intermittently applied mechanical support device).

For our purposes, the expectations are translated into to impact classes – treatment costs and transition probabilities.

5.4.2. Treatment cost – New MD Paedigree–supported care pathway

The treatment cost estimates as presented in “Table 1 Estimates of cost data per cycle - Standard of care” were kept identical for year one of the cycle. As was discussed in detail in D 19.4 (cf. also D 19.7 Final exploitation plan), applying the new tool(s) will come with a considerable cost, which may be anywhere between € 300 and € 600 per patient, depending on the final functionality and user interface of the tool, the business model of how to deliver these services (e.g. as an external service provided for a fee per patient, or as an application within a hospital, etc.), the annual number of patients undergoing diagnosis and treatment etc. Therefore, to cover these costs, we assume that, in spite of considerable savings expected already during year one of treatment, that actually the cost per state and year one will stay the same as reported in Table 1.

However, as of year two, considerable savings are anticipated (see Table 5): For mild HF, annual cost may decrease to € 1,000 (from 2,000), for moderate HF to € 15,000 (from 17,300), and for severe HF to € 68,500 (from 72,500).

TABLE 5 ESTIMATES OF COST DATA PER CYCLE - INNOVATIVE (CDS-BASED) CARE

States / Cycles	1. Death	2. Mild HF	3. Moderate HF	4. Severe HF	5. Mechanical Support/Transplant
1. Start cycle (year)	0.00	2,000	17,300	72,500	95.000
2. Cycle 2	0.00	1,000	15,000	68,500	27,700
3. Cycles 3 ff	0.00	1,000	15,000	68,500	7,100

Table 6 summarises the estimated *changes* in cost per state and cycle:

TABLE 6 ESTIMATES OF CHANGES OF COST (IN €) DATA – FROM STANDARD OF CARE TO INNOVATIVE (CDS BASED) CARE

States / Cycles	1. Death	2. Mild HF	3. Moderate HF	4. Severe HF	5. Mechanical Support/Transplant
1. Start cycle (year)					
2. Cycle 2		- 1,000	- 2,300	- 4,000	
2. Cycles 3 ff		- 1,000	- 2,300	- 4,000	- 2,300

5.4.3. Transition matrix - New MD Paedigree–supported care pathway

When implementing a new standard of care based on MD Paedigree CDS tools, the earlier in "Table 2: Transition (per cycle = one year) and absorption probabilities - Standard of care" reported probabilities will change. Based on the above explored expectations regarding future benefits, the probabilities of patients moving from their initial pathway into another one, and/or of becoming in need of mechanical support or a transplant, or suffering the endpoint death will probably improve. In Table 7 the newly estimated probabilities are presented. They are based on very moderate expectations, assumed to rather represent the lower end of the expected improvements. In the same spirit, the entry probabilities are not (yet) changed to also avoid overestimation.

TABLE 7 TRANSITION (PER CYCLE = YEAR) AND ABSORPTION PROBABILITIES – INNOVATIVE (CDS BASED) CARE

To state / From state	1. Mild HF	2. Moderate HF	3. Severe HF	4. Mechanical Support/Transplant	5. Death
1. Mild HF	**0.90**	0.08	0.02		
2. Moderate HF	0.20	0**.71**	0.09		
3. Severe HF		0.10	**0.81**	0.07	0.02
4. Mechanical support/transplant - not modelled (absorption state)				**1.00**	
5. Death (absorption state)					**1.00**

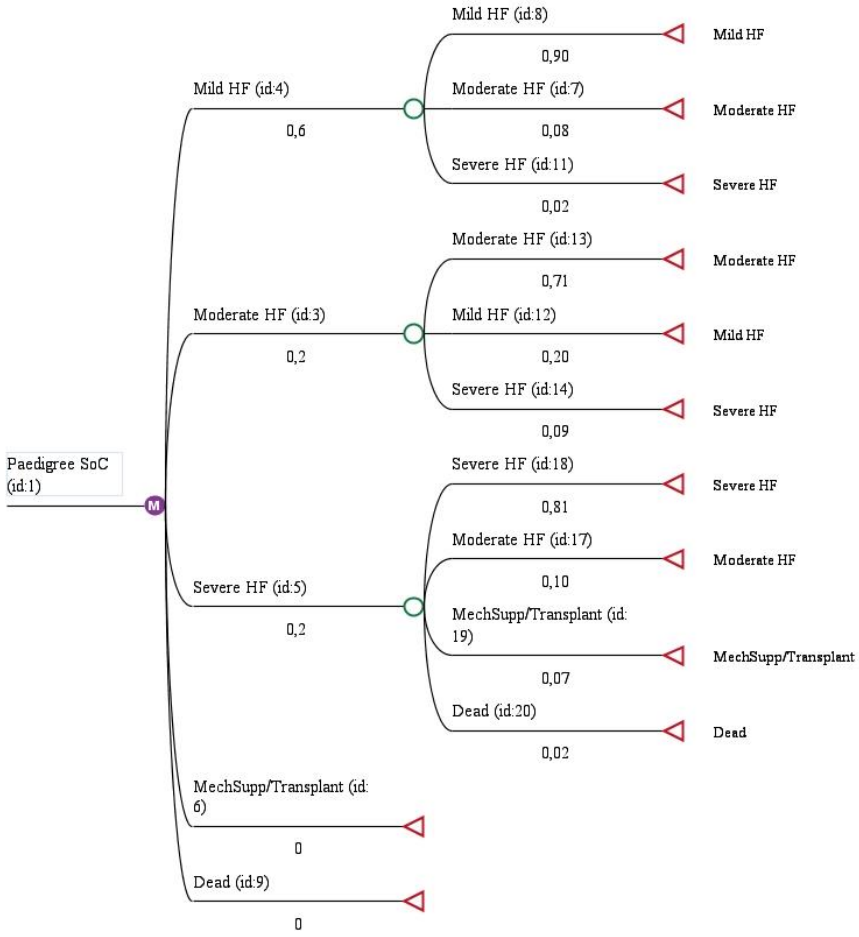
Table 8 summarises the estimated *changes* in transition and absorption probabilities per state and cycle when moving from standard of care to innovative, MD-Paedigree CDS tool-based care. There are only minor changes in probabilities asserted, with the largest ones relating to a change from moderate HF to mild by 0.10 – this more or less implying a reduction of the probability for staying in the moderate state, plus a slight improvement in probabilities for patients staying in the severe HF arm – rather than moving onwards to mechanical support/transplant or death – and a 0.03 increase in moving from a severe to moderate state.

TABLE 8 ESTIMATES OF CHANGES OF PROBABILITIES – FROM STANDARD OF CARE TO INNOVATIVE (CDS BASED) CARE

To state / From state	1. Mild HF	2. Moderate HF	3. Severe HF	4. Mechanical Support/Transplant	5. Death
1. Mild HF	**+ 0.05**	- 0.05			
2. Moderate HF	+ 0.10	**- 0.07**	- 0.03		
3. Severe HF		+ 0.03	**+ 0.03**	- 0.04	- 0.02
4. Mechanical support/transplant - not modelled (absorption state)				**0.00**	
5. Death (absorption state)					**0.00**

In Figure the new probability values are translated into a Markov chain model:

FIGURE 12 MARKOV-CHAIN TRANSITION PROBABILITIES FOR MD PAEDIGREE CDS TOOL-BASED CARE



Source: empirica/MD Paedigree 2017

5.4.4. Results - New MD Paedigree–supported care pathway

Next the results obtained when undertaking a Markov process analysis for the new MD Paedigree–supported care pathways are presented.

Probabilities per cycle and state

When performing the Markov analysis based on the transition probabilities matrix presented earlier in "Table 7 Transition (per cycle = year) and absorption probabilities – Innovative (CDS based) care", the values as reported in the following Table 9 result:

TABLE 9 MARKOV CHAIN PROBABILITIES FOR10 CYCLES AND FIVE STATES - NEW MD PAEDIGREE–SUPPORTED CARE

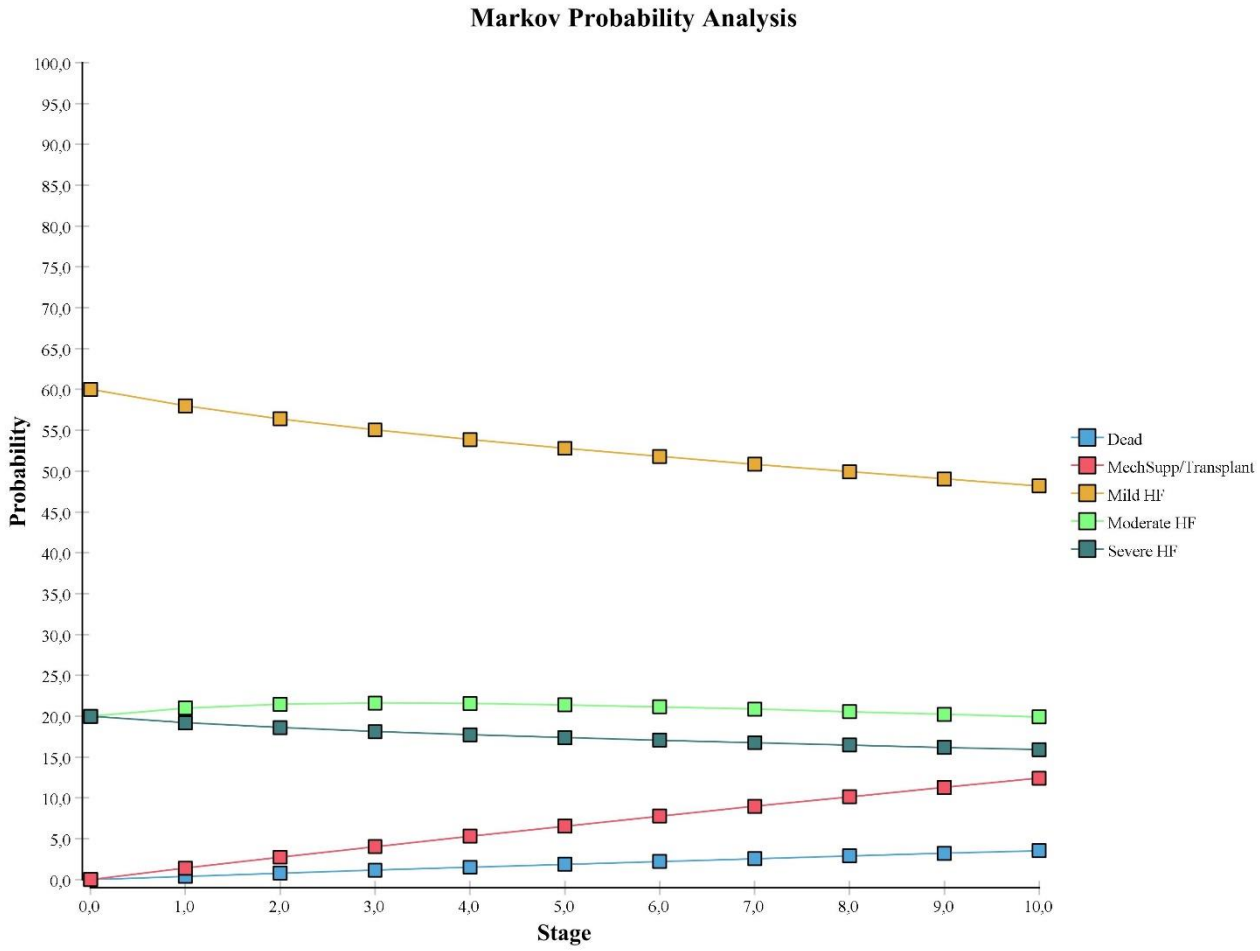
Stage/Cycle	Probabilities				
	Mild HF	**Moderate HF**	**Severe HF**	**MechSupp/ Transplant**	**Dead**
1	0.600	0.200	0.200	0.000	0.000
2	0.580	0.210	0.192	0.014	0.004
3	0.564	0.215	0.186	0.027	0.008
4	0.551	0.216	0.181	0.040	0.012
5	0.539	0.216	0.177	0.053	0.015
6	0.528	0.214	0.174	0.066	0.019
7	0.518	0.212	0.171	0.078	0.022
8	0.508	0.209	0.168	0.090	0.026
9	0.499	0.206	0.165	0.101	0.029
10	0.491	0.202	0.162	0.113	0.032
Average	**0.538**	**0.210**	**0.178**	**0.058**	**0.017**

Again, these values indicate, albeit for the new MD Paedigree–supported care pathway, with which probability an individual patient presented at the hospital for initial diagnosis may end up in which year in which state of the disease. On average after year ten, it is assumed that surviving patients move into the adult arm of health system services.

In a static environment, this matrix again provides a full model of the state of paediatric patients under treatment during a particular year as well as for the total patient population. From a theoretical perspective, this is a necessary assumption to allow for a mathematical solution to the Markov chain analysis. In reality, of course, treatment interventions are continuously improved; new medicinal products are introduced into the market, the characteristics of the patient population change. Noting these constraints, a Markov process analysis nevertheless provides highly relevant decision support information for healthcare policy makers as well as for healthcare providers and professionals, because it allows for more precise and well-argued insights into the development of a given patient population as it moves over the years through the healthcare system, and to prepare for such developments, including allocating the required resources. And a comparative analysis based on two different scenarios as undertaken in this deliverable adds a dynamic component to such analyses by investigating two different states-of-affairs providing well-reasoned insights into what the future may hold.

In Figure 10 the above probability values are translated into a graphical presentation:

FIGURE 13 MARKOV CHAIN PROBABILITIES FOR10 CYCLES AND FIVE STATES – NEW MD PAEDIGREE–SUPPORTED CARE



Source: empirica/MD Paedigree 2017

Comparing the MD Paedigree-based scenario with the present-state scenario, we see that the small improvements expected from the new process translate over a ten-year period into quite remarkable betterments. The percentage of patients in the mild HF arm decreases at a much lower rate, the moderate HF population remains almost stable rather than increasing quite a bit, and the prevalence of severe HF decreases continuously at a small rate rather than being more or less stable. The need for mechanical support/transplants increases at a much lower rate over the ten-year cycle, and the overall probability for death will be halved.

Cost per cycle and state

Based on the estimated treatment cost per state and cycle as reported in "Table 5 Estimates of cost data per cycle - Innovative (CDS-based) careTable 1 Estimates of cost data per cycle - Standard of care" and the probabilities reported in "Table 7 Transition (per cycle = year) and absorption probabilities – Innovative (CDS based) care" we again calculated the expected cost for each disease state and each cycle/year by multiplying the two values. This provides us with the data reported in "Table 4 Cost in € per cycle and state – Standard of care." Note that these data cover also here only the three transition states defined earlier for cardiomyopathy, and not the absorption states mechanical support/transplant and death.

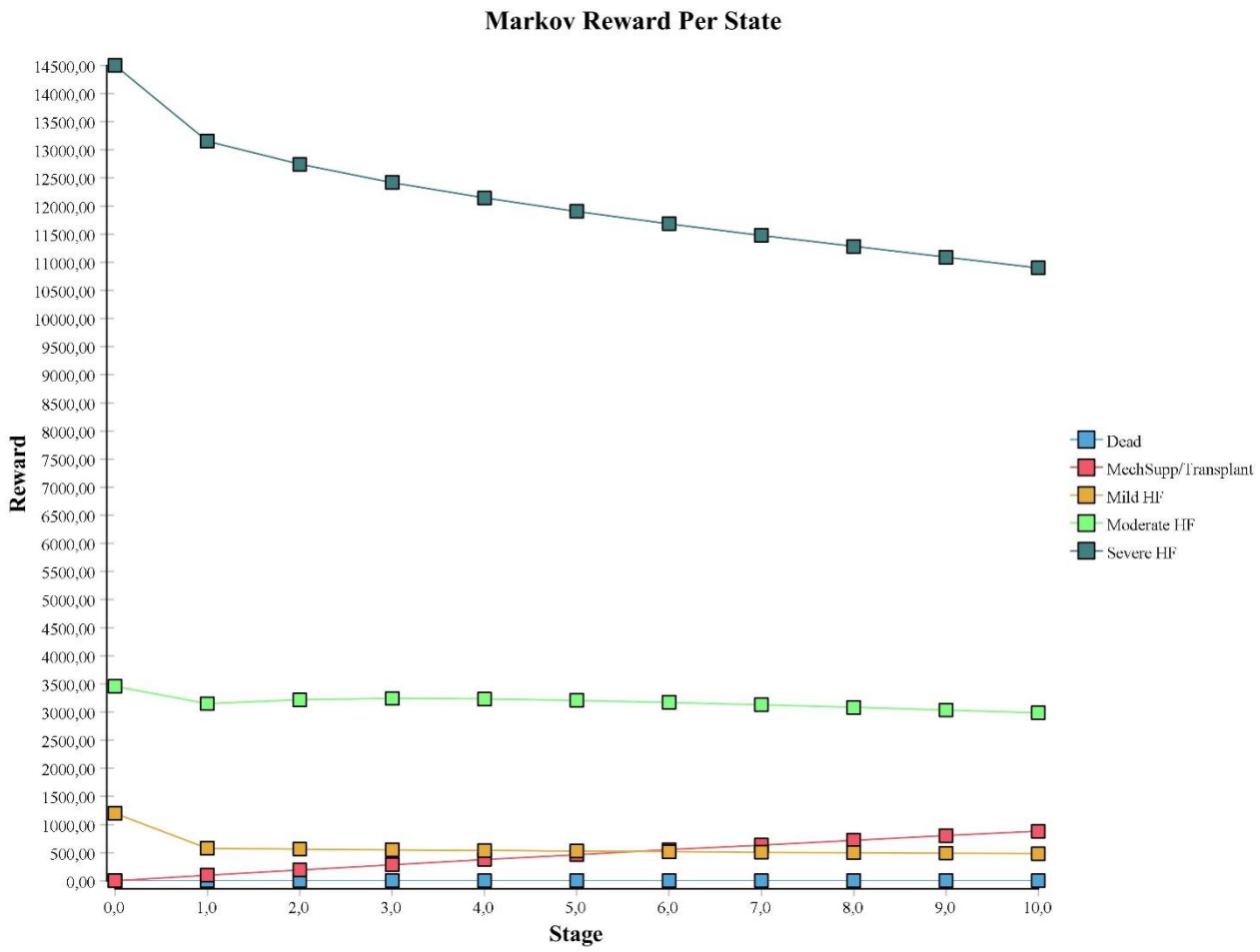
To arrive at the concrete costs to be expected per cycle, they need to be multiplied by the overall number of patients entering the treatment system during a given year. This then allows to obtain realistic, representative cost estimates for a cohort of cardiomyopathy patients treated under the new regime.

TABLE 10 COST IN € PER CYCLE AND STATE – NEW MD PAEDIGREE–SUPPORTED CARE

	Cost in € (state cost per cycle x probability)			
Stage/Cycle	**Mild HF**	**Moderate HF**	**Severe HF**	**Sum**
1	1,200	3,460	14,500	19,160
2	580	3,150	13,152	16,882
3	564	3,221	12,742	16,527
4	551	3,242	12,418	16,211
5	539	3,235	12,145	15,919
6	528	3,209	11,905	15,642
7	518	3,173	11,685	15,376
8	508	3,130	11,479	15,117
9	499	3,084	11,281	14,864
10	491	3,036	11,089	14,615
Sum	**5,978**	**31,939**	**122,396**	**160,312**

In Figure 11 these values are again translated into a graphical presentation. (Note that "reward" in our context refers to cost). Here, too, by far the highest cost results from treating severe HF patients, albeit at a somewhat decreasing rate over the ten-year period. The cost of treating moderate HF patients remains more or less stable rather than that it increases moderately. The cost for mild HF patients – which anyhow is comparably low - also here decreases at a continuous rate.

FIGURE 14 COST IN € PER CYCLE AND STATE – NEW MD-PAEDIGREE–SUPPORTED CARE



Source: empirica/MD Paedigree 2017

5.5.Estimating the benefits and costs of the new MD Paedigree-based pathway

In this pre-final section of the present chapter, the benefits to be expected from the new MD-Paedigree-tool-based pathways are calculated. They are based on the estimates presented so far. Firstly, we estimate benefits from cost and resource savings, and then intangible benefits related to improvements in the quality of life of patients respectively death avoided.

5.5.1. Resource saving benefits

The resource savings to be expected are calculated by comparing the overall costs for each pathway for 100 patients per cycle over ten years. Table 11 summarises the sums of the results presented earlier in "Table 4 Cost in € per cycle and state – Standard of care" and those from "Table 10 Cost in € per cycle and state – new MD Paedigree–supported care." To translate these data in estimates for a cohort of 100 patients over ten years, they have to be multiplied by 100. Calculating the difference in costs estimated for treatment of patients following the old and the new pathways, the expected savings are calculated. For 100 patients over ten years, or an annual cardiomyopathy patient population of almost 1,000 children, the savings are estimated at almost € 3.5 million. Comparing these savings with the overall costs for the old pathway of almost € 19,5 million, a reduction by around 18% results.

TABLE 11 ESTIMATES OF BENEFITS FROM RESOURCE SAVINGS

	Cost in € (state cost per cycle x probability)				
	Mild HF	**Moderate HF**	**Severe HF**	**Sum**	**Cost for 100 patients over 10 years**
Sums Present St. of Care	8,080	47,213	139,553	194,846	19,484,619
Sums MD Paedigree Tool based	5,978	31,939	122,396	160,312	16,031,247
Difference (Savings)	**2,103**	**15,274**	**17,157**	**34,534**	**3,453,372**

It needs to be noted that these are 'only' savings in resources, not necessarily financial or cash savings. Wither the estimated savings can indeed become translated into real cash savings or resources applied elsewhere in a manner 'profitable' for the hospital will depend on several factors. On the one hand it will depend on the type of resources set free by the new pathway, e.g. whether they can indeed be just deleted from the list of resources to be acquired without any impact elsewhere in the hospital, or usefully employed in another context to generate income, and on the other hand whether the reduced amount of services delivered to patients due to the improved decision making by healthcare professionals will have an equivalent impact on income or not; this may depend on the reimbursement system, whether it is a hospital in an national health service or a private hospital operating in a "fee for service" context, and other factors. These issues will be briefly discussed in the next chapter.

5.5.2. Intangible benefits - Improvements in QALYs and death avoided

As was noticed earlier, the new pathway is expected to positively impact also on the prevalence of the severity of the disease states of patients. To take these benefits equally into account, the intangible benefits related to improvements in the quality of life of patients respectively death avoided will be measured in monetary terms. To do this, we concentrate on three major impacts:

- Changed prevalence of moderate HF
- Changed prevalence of severe HF
- Deaths avoided

As a first step Table 12 compares the estimates of the probabilities for a patient ending up in the *moderate* HF population during each of the 10 cycles for both pathways (cf. "Table 3 Markov chain probabilities for10 cycles and five states – Standard of care" and "Table 9 Markov chain probabilities for10 cycles and five states - New MD Paedigree–supported care"), and calculates the difference. Over all 10 cycles, the positive change, a reduction, sums up to 0.63 or, when considering a cohort of 100 patients over 10 years, to about 63 life years not spend in the moderate HF state, but rather only in the mild state.

TABLE 12 ESTIMATES OF CHANGED PREVALENCE OF MODERATE HF

Stage/Cycle	Present St. of Care	MD Paed Tool	Difference
1	0.200	0.200	0.000
2	0.248	0.210	0.038
3	0.276	0.215	0.061
4	0.290	0.216	0.074
5	0.296	0.216	0.080
6	0.296	0.214	0.082
7	0.292	0.212	0.080
8	0.285	0.209	0.077
9	0.278	0.206	0.072
10	0.269	0.202	0.066
Sum	**2.729**	**2.099**	**0.630**

In the same manner, Table 13 compares the estimates of the probabilities for a patient ending up in the *severe* HF population during each of the 10 cycles for both pathways, and calculates the difference as well. Here the reduction sums up to 0.15 or, when considering a cohort of 100 patients over 10 years, to about 15 life years not spend in the severe HF state, but rather only in the moderate state.

TABLE 13 ESTIMATES OF CHANGED PREVALENCE OF SEVERE HF

Stage/Cycle	Present St. of Care	MD Paed Tool	Difference
1	0.200	0.200	0.000
2	0.192	0.192	0.000
3	0.190	0.186	0.004
4	0.191	0.181	0.010
5	0.192	0.177	0.015
6	0.193	0.174	0.020
7	0.194	0.171	0.023
8	0.193	0.168	0.025
9	0.191	0.165	0.026
10	0.188	0.162	0.026
Sum	**1.925**	**1.775**	**0.150**

Finally, as the last calculation of the first step of the procedure, Table 14 provides an identical calculation of a rough estimate of the number of life years which may be saved due to applying the new pathway process. The value obtained is 0.18 which provides with an estimate of 18 life years saved.

TABLE 14 ESTIMATES OF LIFE YEARS SAVED

Stage/Cycle	Present St. of Care	MD Paed Tool	Difference
1	0.000	0.000	0.000
2	0.008	0.004	0.004
3	0.016	0.008	0.008
4	0.023	0.012	0.012
5	0.031	0.015	0.016
6	0.039	0.019	0.020
7	0.046	0.022	0.024
8	0.054	0.026	0.028
9	0.062	0.029	0.033
10	0.069	0.032	0.037
Sum	**0.348**	**0.166**	**0.182**

In order to attach a quantitative value, measured in monetary terms (€) to these summary estimates, a second step is necessary. It requires first to determine a monetary value per year for a so-called statistical life ("VSL"). This value can then be applied to value a healthy life saved, which we will set in what follows equal to death avoided. Clearly, a life saved in our context is not necessarily a life in unabated health, but given the wide margins of our estimates this should be sufficient to provide an initial ballpark figure.

Next, when considering the improvement in the disease state, we need a rough estimate of what is commonly called an improvement in the quality of life, measured in quality-adjusted life years (QALYs).[45] This has been commonly agreed in health economics as a measure of the value of health outcomes. It assumes that health is a function of length of life and quality of life, and combines these values into a single index number.[46] To measure such QALYs, one multiplies the utility value associated with a given state of health by the years lived in that state. A year of life lived in perfect health is worth 1 QALY (1 year of life × 1 utility value). A year of life lived in a state of less than perfect health is worth less than 1 QALY. In what follows it is assumed that moving from the moderate to mild HF state can be measured by a utility value of 0.2, and from the severe to moderate state by a value of 0.5. These are subjective values open to individual assessment; there does not exist an objective measurement scale, despite numerous attempts to generate such a scale.[47] To arrive at economic values of QALYs, they must be multiplied with a monetary value estimated or agreed upon for the VSL.

To attach an economic value to a statistical life *per annum* is also an elusive, subjective exercise. Nevertheless, various methods and values have been discussed in the literature,[48] and WHO guidelines suggest that countries should aim to spend between one and three times their Gross Domestic Product (GDP) per capita for one of their citizens per QALY gained from a health-related treatment. This puts the value of a life in Luxembourg between $111,162 – $333,486, the value in Mexico between $10,307 – $30,921 etc.[49] For

[45] Miyamoto, John M., and Stephen A. Eraker. "Parameter estimates for a QALY utility model." Medical Decision Making 5.2 (1985): 191-213.

[46] Cf. https://en.wikipedia.org/wiki/Quality-adjusted_life_year

[47] See, e.g., Bleichrodt, Han, Enrico Diecidue, and John Quiggin. "Equity weights in the allocation of health care: the rank-dependent QALY model." Journal of health economics 23.1 (2004): 157-171.

[48] See Adlard, N., Kinghorn, P., & Frew, E. (2014). Is the UK NICE "Reference Case" influencing the practice of pediatric quality-adjusted life-year measurement within economic evaluations? Value in Health, 17(4), 454-461; Molinari, N. A. M., Ortega-Sanchez, I. R., Messonnier, M. L., Thompson, W. W., Wortley, P. M., Weintraub, E., & Bridges, C. B. (2007). The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine, 25(27), 5086-5096; Alex Mayyasi (2016). How Children Went from Worthless to Priceless. http://priceonomics.com/the-price-of-a-child/ and the literature mentioned in these references.

[49] Ashenfelter, O. (2006). Measuring the value of a statistical life: problems and prospects. The Economic Journal, 116(510), C10-C23

our purposes, we use € 50,000 as the value of a statistical life, because it is an "international standard most private and government-run health insurance plans worldwide use to determine whether to cover a new medical procedure."[50]

Combining the previously calculated values of positive changes in years spent in a given health or disease state respectively the years of death avoided with the above estimates for QALYs and VSLs, and remembering that overall our calculations are based on a cohort of 100 patients per year or around 1,000 patients overall under treatment at any point in time, then these estimates can be combined into a single value for the intangible benefits (expressed in monetary terms) predicted as shown in Table 15.

TABLE 15 ESTIMATES OF INTANGIBLE BENEFITS FROM REDUCED PREVALENCE OF MODERATE AND SEVERE HF AS WELL AS FROM DEATHS AVOIDED

State	Savings in life years in that state (Markov analysis)	For 100 patients, over 10 years	Utility value for improved QALY	Sum of QALYs for all patients under treatment	Total Value (per full QALY: € 50k)
Moderate HF	0.630	63.047	0.2	12.61	630,474
Severe HF	0.150	14.974	0.5	7.49	374,360
Death	0.182	18.185	1	18.18	909,243
Sum				**38.28**	**1,914,077**

In summary, this leads to a further benefit estimate, albeit of intangible benefits accruing mostly to the children and their parents, of almost € 2 million.

5.5.3. Return on investment considerations

We will not present any return on investment (RoI) estimates here. As discussed earlier, it is not yet clear what business model may be followed by those who will further develop MD Paedigree and other VPH simulation tools intended to improve medical decision making by clinicians and other healthcare professionals. And it is also not clear whether present and future investments, like urgently needed further quite costly clinical trials, may be regarded as sunk cost because the funding was/will be provided by public sources, or whether private investors expecting a high return on their risky investment will require an adequate return. Indirectly, a contribution to a return on investment has been included in the above estimations by assuming that in cycle year one a fee per patient of between € 300 and € 600 may be charged by a service provider of the MD Paedigree clinical decision support tools.

We abstained from discounting future benefits, because given the present capital market environment for more and more (public) debts virtually no interest is charged.[51]

[50] https://en.wikipedia.org/wiki/Value_of_life

[51] http://www.bbc.com/news/business-32284393: "Interest rates are now negative, below zero, for a growing number of borrowers, mainly in the financial markets. It means in effect they are being paid to borrow someone else's money."

6. Summary and conclusions

This final chapter briefly summarises the major results of this report, discusses the policy and management perspective when reflecting on the relevance and implications of the benefits identified, and finally points towards further research urgently needed to validate, extent and complement the work initiated by MD Paedigree in the field of technology and impact assessment of newly developed VPH decision support tools.

6.1.Summary

Context

The "Model-Driven Paediatric European Digital Repository - MD-PAEDIGREE)" project validates and brings to maturity patient-specific computer-based predictive models of various paediatric diseases. This deliverable reported on final work relating to Task 19.3 "Benefit-cost scenario for clinical impact assessment" of WP 19 "Exploitation, HTA, and Medical Device Conformity". It benefited from work undertaken in WPs 2, 8 and others on cardiac disease modelling, here particularly cardiomyopathy including heart failure. Cardiomyopathy is a summary term for a set of chronic and often progressive diseases in which the heart muscle (myocardium) is abnormally enlarged, thickened and/or stiffened

The overall goal of the tasks in WP 19 Exploitation, HTA, and Medical Device Conformity was to contribute from a socio-economic perspective towards making VPH models and clinical decision support tools readily available both to researchers for further development and to health professionals as decision support at the point of care.

Objectives

Given this overall context, these specific objectives were pursued:

- Apply the generic benefit-cost scenario for clinical impact assessment developed
- Review, adapt and validate the clinical pathway model for three disease states – mild, moderate and severe cardiomyopathy
- Relate the disease states and pathways developed to status-quo clinical interventions and their respective costs per year of treatment
- Estimate from real data the respective transition and absorption state probabilities for a cohort of patients moving over a ten-year cycle through different states of cardiomyopathy
- Populate the Markov Chain analysis tool with concrete cost data and outcome estimates from the hospital as well as from the literature
- Similarly, based on expert estimates, analyse the impact of MD Paedigree decision support tools on pathways, treatment decisions and accordingly adjusted transition and absorption state probabilities as well as costs
- Estimate and compare benefits (cost saved; QoL improved) between status-quo clinical care and healthcare supported by MD Paedigree tools

Methods

As a first step, to identify core elements, structures and actors on which data had to be collected, an explorative scenario approach was applied. Given the *extreme complexity* of (national) health systems, the number of actors involved in even relatively simple healthcare delivery processes, the political sensitivity of any health-related policy issue, and the mix of powerful stakeholder groups lobbying in this field, scenario analysis was preferred to other more formalised methods of analysis.

Next, to prepare for the concrete health technology impact assessment of MD Paedigree tools, a decision analytic modelling process was used. To reduce the overall complexity of the daily reality in a hospital when treating cardiomyopathy children, an operational clinical pathway model was developed. This then was applied to estimate potential benefits from the new technology, i.e. the incremental health gains expected from the new decision support tools which MD Paedigree is developing, as well as changes in costs related to the new process. A mathematical probabilistic model, Markov process analysis, was chosen to integrate these data. This reflects reality in healthcare service provision, where outcomes of a decision are dependent on earlier events, and where there are usually several possible outcomes, not only two (like the toss of a con versus of a dice). Such processes in which the outcome of an event is dependent on the outcome of the previous event or process step are commonly known as Markov processes or chains.

Results

In the operational process model for treating cardiomyopathy, in line with clinical practice, three disease states a child may be in when entering the hospital were identified:

- mild cardiomyopathy/heart failure
- moderate cardiomyopathy/heart failure
- severe cardiomyopathy/heart failure

On average about 60% of children being presented for an initial diagnosis are classified into the mild heart failure state, 20% to the intermediate state, and roughly 20% to the severe state.

The three transition states had to be complemented by two absorption states:

- Mechanical cardiac support/transplant
- Death

Because the presently available MD Paedigree decision support tools do not provide information for the treatment of mechanical cardiac support/transplant patients, this state was defined as an absorption state.

The cardiomyopathy clinical pathway model was then translated into a Markov-chain model for estimating health (technology) impact. Estimates of the present costs of the three clinical sub-pathways for a given cohort of children were collected: the costs of the diagnostic and treatment interventions per typical patient, and the percentage number of patients in each arm. Furthermore, estimates of the transition probabilities of a patient moving from one state to another were obtained.

Clinical data indicated that on average a child is 8 years old when being presented for the first time for diagnosis and treatment. Because these patients will need clinical attention for the rest of their lives, it was assumed that on average patients stay within the paediatric hospital treatment system for 10 years, till the age of 18. This then led to 10 (annual) analysis cycles.

Based on all these data, the overall treatment costs for a cohort of 100 patients over a ten-year cycle were estimated.

The same analysis process was applied for a cohort of patients entering a new MD Paedigree–supported care pathway. Based on clinical expertise, improvements are to be expected with respect to:

- Improved risk stratification of patients
- Better Diagnostic decisions and predicting the progression of the disease
- Better therapeutic decisions.

These were translated into estimates of slightly changed transition probabilities, e.g. a minor reduction in the probability of a mild HF child moving to the moderate subset of patients. And it is anticipated that fewer interventions – resulting in lower treatment costs – will result.

Finally, to obtain a first rough assessment of the overall impact to be expected, the results for the present standard-of-care pathway and the new MD-Paedigree-supported care pathway were compared. The resource savings to be expected were calculated by comparing the overall costs for each pathway for 100 patients per cycle over ten years. When on average 100 new patients are presented at the hospital every year, and when these patients ae, on average, being treated for a period of ten years, then the hospital is faced with an annual cardiomyopathy patient population of almost 1,000 children. For such a scenario, the savings are estimated at almost € 3.5 million. Comparing these savings with the overall costs for the old pathway of almost € 19,5 million, a reduction by around 18% results. The following table, a repetition of "Table 11 Estimates of benefits from resource savings" summarises these results:

ESTIMATES OF BENEFITS FROM RESOURCE SAVINGS

	Cost in € (state cost per cycle x probability)				
	Mild HF	**Moderate HF**	**Severe HF**	**Sum**	**Cost for 100 patients over 10 years**
Sums Present St. of Care	8,080	47,213	139,553	194,846	19,484,619
Sums MD Paedigree Tool based	5,978	31,939	122,396	160,312	16,031,247
Difference (Savings)	**2,103**	**15,274**	**17,157**	**34,534**	**3,453,372**

The new pathway is expected to positively impact also on the prevalence of the severity of the disease states of patients. To take these benefits equally into account, the intangible benefits related to improvements in the quality of life of patients respectively death avoided were also assessed in monetary terms. Three major impacts were considered:

- Changed prevalence of moderate HF
- Changed prevalence of severe HF
- Deaths avoided

Improvements in the quality of life are commonly measured in quality-adjusted life years (QALYs). To measure them, one multiplies the utility value associated with a given state of health by the years lived in that state. It was assumed that moving from the moderate to mild HF state can be measured by a utility value of 0.2, and from the severe to moderate state by a value of 0.5. For the value of a statistical life year (VSL) an amount of € 50,000 was applied.

Combining the values of positive changes in years spent in a given health or disease state respectively the years of death avoided with these estimates for QALYs and VSLs, and remembering that overall the calculations are based on a cohort of 100 patients per year or around 1,000 patients overall under treatment at any point in time, then these estimates can be combined into a single value for the intangible benefits. The following table, a repetition of "Table 15 Estimates of intangible benefits from reduced prevalence of moderate and severe HF as well as from deaths avoided" summarises these results:

Estimates of intangible benefits from reduced prevalence of moderate and severe HF as well as from deaths avoided

State	Savings in life years in that state (Markov analysis)	For 100 patients, over 10 years	Utility value for improved QALY	Sum of QALYs for all patients under treatment	Total Value (per full QALY: € 50k)
Moderate HF	0.630	63.047	0.2	12.61	630,474
Severe HF	0.150	14.974	0.5	7.49	374,360
Death	0.182	18.185	1	18.18	909,243
Sum				**38.28**	**1,914,077**

This leads to a further benefit estimate, albeit of intangible benefits accruing mostly to the children and their parents, of almost € 2 million.

6.2. Health policy and hospital management perspective

Most of the monetary benefits estimated result from freed, re-deployable resources, not from direct cash savings for the hospital. E.g., when an intervention needs no longer to be performed, the healthcare professional(s) will not lose their job, and a medical apparatus used a few times less during a day will not be discarded. Another aspect is that the costs applied in the estimates are based on average costs, not on marginal ones. For example, the absolute number of beds released may be relatively small compared to overall bed capacity – a fact which would make benefit realisation demanding. However, the benefits expected are large enough to surely justify the effort – not to mention the substantial intangible benefits for children and their parents.

However, such considerations illustrate that an adequate interpretation of the benefits estimated is not easy and will very much depend on the concrete context of a given hospital, its relationships and contracts with health insurances and patients in a Bismarck system, or in a national health system on its funding mechanisms, as well as on the overall national – and perhaps also regional - regulatory environment, the role and power of its owners and stakeholders, and other factors.

Whether and to what extent indeed the final payers (health insurances or national health systems/the taxpayer) will benefit from VPH tools like those developed by MD Paedigree is not obvious. It will depend very much on the regulatory environment, and the strategy hospital management and medical officials will follow when introducing such new technologies. On the one hand, 'society' may want to regulate that the resources liberated – both cash and re-deployable ones – cannot be deployed for other activities by hospitals and other providers. In this case, the real benefits may become allocated not to hospitals which would lose income, but to tax payers respectively those employers and employees who have to pay for health and social care insurance in the end.

On the other hand, without such a regulatory framework or interventions by 'higher powers', hospital management may decide that the liberated resources, particularly bed days, should be allocated to new activities responding to demand so far not yet met, or to new demand created by new offerings which become possible based on the redeployable resources.

No empirical evidence, not even theoretical discussions on such policy issues have been published, but one may expect that in reality a mixed result may occur. Hospitals, e.g., will as a first step not fire employees or reduce bed capacity, but rather go for improvements in service quality and an expansion of services if possible. But increasing competition, more transparency on quality of outcomes achieved, regulatory and fiscal pressure may indeed lead to some hospitals leaving the market for good in the longer term. But this may not hold for highly specialised hospitals active at the tertiary service level, like those treating the kind of cardiomyopathy patients on which the benefit-cost impact analysis was based.

In spite of their temporal dimension, the results obtained reflect a static status-quo ante and post comparison and cannot reflect all the options which in reality exist and may impact the results which may be seen 10 years after initial implementation and diffusion of new technologies. Considering longer-term impacts, key issues directly influencing the financial impact on hospitals, the healthcare system and others would be whether hospitals will

- reduce their resource input, particularly bed capacity, accordingly over time and thereby indeed save
- redeploy these resources for other purposes (like lab capacity, cafeteria, ...) without expanding the quantity of health-related services
- reconfigure bed capacity and attract additional patients which would otherwise not be treated
- better compete with other HCPs for clients, a strategy which may lead, e.g., other hospitals having to close down.

Another aspect to be considered is the reimbursement regime prevailing. As the benefits arise from hospital related treatments, the situation is similar for hospitals being paid by lump-sum DRG (diagnosis related groups) fees, or those operating under a payment regime by bed-days. However, unless they see other business opportunities, none of them has an initial incentive to reduce the number of patients or the intervals for a visit, because this reduces their income.

On the other hand, depending on the health system and reimbursement context payers are another category of beneficiaries with may, without investments, reap substantial returns. This alludes to a dilemma of such eHealth investments in general, which will require policy interventions and changes in reimbursement to indeed realise the potential value added at societal level: in health systems the costs of re-engineering delivery processes and of related organisational change are often borne by different organisations and professionals from those who will benefit in terms of greater economic efficiency and better quality. This is close to a set-piece guarantee of permanently impeded progress, as there is no incentive for those in the key position to innovate, and no lever for the potential beneficiaries.[52]

6.3. Further research

The research plan for years to come should be feeding the above explored and further improved analytical models with more robust data from concrete pilot applications in semi-routine clinical practice as well as extended clinical trials, thereby ultimately illustrating how the transformation of MD Paedigree bio-computational modelling and VPH simulation technologies into clinical decision support tools will supplement and improve the current management of specific diseases targeted by MD-Paedigree. The goal behind this clinical and socio-economic assessment perspective is to support the testing of clinical application scenarios and deliver empirical evidence for health system actors and decision makers, for exploitation planning and business modelling.

These steps should include an improved modelling of health states and outcomes, and reflect in more detail the presently applied and in future expected clinical treatment processes. The benefits of improved health states, better stratification of high risk patients, improved predicting of the process from the onset of heart failure to the need of mechanical support would become transparent in more detail. In order to reliably assess and validate the results obtained by MD Paedigree, more detailed and focused analyses akin to and undertaken with the methodological rigour used in clinical trials will be necessary.

As the benefits estimated indicate, there exists a clear business case for MD Paedigree clinical decision support tools. However, they will only be transformed into an innovation, i.e. a new product or service in the market, and will only diffuse, i.e. gain a sizeable impact on the future diagnosis and treatment of paediatric diseases, if they indeed not only meet a clear market demand and have a well-defined value added for the intended customers, but if first of all an organisation or individual entrepreneur is interested in and prepared to further explore the remaining technical, commercial, and health system challenges.

[52] Stroetmann, K.A. "Achieving the integrated and smart health and wellbeing paradigm: a call for policy research and action on governance and business models." International Journal of Medical Informatics 82(4), e29-e37, April 2013