

Assessing Biocomputational Modelling in Transforming Clinical Guidelines for Osteoporosis Management

Rainer THIEL^{a,1}, Marco VICECONTI^b, Karl STROETMANN^a
^a*empirica Communication and Technology Research, Bonn, Germany*
^b*Istituto Ortopedico Rizzoli, Bologna, Italy*

Abstract. Biocomputational modelling as developed by the *European Virtual Physiological Human (VPH) Initiative* is the area of ICT most likely to revolutionise in the longer term the practice of medicine. Using the example of osteoporosis management, a socio-economic assessment framework is presented that captures how the transformation of clinical guidelines through VPH models can be evaluated. Applied to the *Osteoporotic Virtual Physiological Human Project*, a consequent benefit-cost analysis delivers promising results, both methodologically and substantially.

Keywords. Biocomputational modelling, VPH, clinical workflow, evaluation, impact assessment, osteoporosis

1. Introduction

There is a growing interest for computational technologies in the area of medicine. Whereas Information and Communication Technologies (ICT) already play a fundamental role in medical informatics and practice, bioinformatics, and telehealth, the use of ICT as support to prevention, screening, diagnosis, treatment, and monitoring remains limited. Yet it is by now evident that this is the area of medical technology most likely to revolutionise the practice of medicine in the longer term. Computer models that simulate physiopathological processes can be employed to take clinical decisions on the basis of “what-if” analyses (predictive medicine), to tailor the delivery of care to the specific needs of individual patients (personalised medicine), and to explore pathological scenarios for systemic interactions between multiple physiological processes (integrative medicine).

In Europe, the global framework of methods and technologies that will permit the delivery of a predictive, personalised, and integrative medicine has been developed under the name of *Virtual Physiological Human (VPH)*. This initiative has been marked by a demand for measurable evidence that such complex technology is actually worth the cost. The aim of this paper is (1) to introduce a new evaluation framework as developed and applied to predictive computational models for osteoporosis

¹ Corresponding author: Rainer Thiel, empirica Communication and Technology Research GmbH, Oxfordstr. 2, 53111 Bonn, Germany; E-mail: rainer.thiel@empirica.com.

management during the *Osteoporotic Virtual Physiological Human Project* (VPHOP)², and (2) to present preliminary results of a cost-benefit assessment (CBA).

2. Method

With respect to the conventional definition of Health Technology Assessment (HTA) [1], its application to VPH technology needs to take into account two additional elements: a) the technology involves predictive computer models, which have the potential to revolutionise currently applied clinical guidelines; b) the purpose of the assessment is extended to RTD policymaking, i.e. decisions made during the development of the technology itself. The methodological challenge in comparison to commonly applied health technology assessments is based on two reasons: (1) inherent is the need to assess the technology ex-ante, in very early stages of development [2]; (2) the impact on clinical decision making and practice may be far reaching.

For the purposes of assessing biocomputational technologies, standard HTA is not sufficient. To expand on this dimension [3], we suggest considering the complete life cycle of a new or modified technology, ranging across development stages. Therefore, we introduced a particular (VPH) *technology readiness level* [4]. For the purpose of the VPHOP technology assessment, a new concept assigning fine grained technology readiness levels was introduced across the broader development phases of *basic research*, *experimental validation*, *pre-clinical validation*, *clinical validation*, and *operational usage*, providing an overview of the technologies' maturity at a given time.

3. Result

As this paper is of methodological nature, this result section foremost presents the assessment framework.

3.1. Fundamental Attributes of Predictive Computer Technologies

We propose that every health technology that includes a predictive model should be assessed with respect to these fundamental attributes:

- *Capability*: substantiation that a computerized model's reliably represents a conceptual model within specified limits of (inherent) accuracy. Capability assessment requires tightly controlled conditions like laboratory environments.
- *Clinical accuracy*: model accuracy needs to be assessed not only under controlled conditions, but also under operational conditions. Predictive accuracy can thus be truly assessed only in the clinical environment.
- *Efficacy*: efficacy indicates the capacity for beneficial change (or therapeutic effect) of a given intervention in an optimal context. Here the assessment focuses on how medically beneficial is the new clinical pathway for the patient that incorporates the predictive technology (incl. risk).
- *Impact*: for adoption, a health technology should not only be beneficial for the patient, but also present an impact upon the other stakeholders involved

² EU FP7 #223865, www.vphop.eu.

(medical professionals, healthcare providers, healthcare payers, policy makers, society at large) that they consider favourable or at least acceptable.

3.2. Central Assessment Framework: VPH Measurement Variables and Indicators

All available indicators for each of the four fundamental dimensions above are exhibited in Table 1. The table depicts which indicators can and should be used to assess the four fundamental variables of predictive technology during the four stages of its lifecycle. This matrix serves as the central methodological framework that guided the VPHOP technology assessment.

Table 1. Grid of indicators VPH technology assessment

Development Phase	Impact Variable			
	Capability	Accuracy	Efficacy	Impact Measure
Basic research	Verification, validation	Prediction uncertainty	Estimated accuracy- efficacy function	Projected cost/time based on simulation
Experimental verification & validation (inherent accuracy)		RMS, ROC, AUC	FP/FN accuracy- efficacy function	Projected cost/time/risk based on actual use on prototype
Pre-clinical verification & validation			Comparative outcome, QALY	Actual cost/time/risk measured
Clinical validation & assessment (clinical accuracy)				Indicators of impact upon patient, provider, payer, etc.
Operational	Ex-post assessment			

3.3. Overall Outcome Measures of Socio-Economic Impact Assessment

Before the more concrete developments and application approaches about how to measure the technologies’ capability, accuracy, efficacy and impact were performed, it is worthwhile reconnecting the entire assessment exercise to the ultimate objective of the socio-economic technology assessment task. We can distinguish between two aggregate, overall socio-economic impact outcomes that further guided the further development of measurement variables, indicators and tools: once clinically applied – the ultimate reference point –, the new technologies will affect a) care provider, i.e. the health system, and b) the patient’s health (see Figure 1).

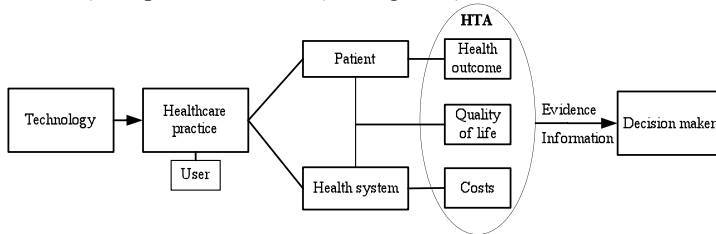


Figure 1. HTA based decision-making and influence of technology

Clinical impact, as the central avenue to approach the impact assessment, is constituted by two elements: (1) *clinical management* – i.e. the care pathway of the standard of care of the osteoporotic patient and, consequently, its change management; (2) *health impact* – the disease states and health of the patient (i.e. the expected consequences of fractures avoided) – scaled up to a macro/country level.

3.4. Efficacy and Definition of Clinical Pathways

While accuracy is a concept that can be associated to every technological component, the concept of efficacy can only be defined with respect to a specific clinical pathway, and its associated clinical scope. Once the new multiscale predictive technology has been validated in a clinical context, a new modified pathway will evolve. The comparison between the old and the new pathways represents the initial tool for estimating the expected overall impact of the new technology for the clinical guidelines and thus clinical management.

A *standard of care pathway* (SoC) served as the central comparator of current osteoporosis management with the future VPHOP clinical pathways. For the SoC, all assumptions are based on approximations of current literature and epidemiological data, and constitute a reduced version of the European Guidance algorithm [5]. For the VPHOP clinical pathways, a multi-layered pathways consisting of three levels with the respective technology components assigned was hypothesised for the deployment of the VPHOP technology.

3.5. Cost-Benefit Analysis VPHOP Clinical Pathway

Focussing on the outcome variables subsumed under *health impact*, a first preliminary and integrative cost benefit analyses was performed. The projected costs of the VPHOP clinical pathways (as based on an originally developed costing model robustly estimating costs of each deployable component) were set in relation to the expected benefits the increased inherent accuracy rates in comparison to the costs and predictive accuracy of the standard of care diagnostic pathway. At this early stage of the project, only the technical capability assessment served as the ground work for the consequent impact assessment. In sum, the final output of the dimension impact assessment forms the cost-benefit analysis.

The patient flow and output of the VPHOP and the SoC pathway with a hypothetical patient cohort of 5000 patients was comparatively simulated. Health impact was defined to encompass as outcome clinical management and health, formalised as fractures avoided. Each hip fracture amounts to life-time costs of €60.000 when diagnosed and treated in the SoC pathway (including costs of diagnosis, treatment, hospital stays, nursery facility costs, etc.) [6;7]. One of the causes for these enormous expenses is the low accuracy of the risk assessment of the current standard of care pathway. To reach an estimate of the health impact VPHOP technologies have on avoiding fractures and the derived amount of costs saved, the increased accuracy was multiplied with the costs of fractures. Further, in a conservative estimate, the average ten-year probability to suffer from a hip fracture is around 25%. We assume, furthermore, that the treatment efficacy is 50% in both pathways. For assessing the cost-benefit ratio of the VPHOP technologies, the benefits can be set equal as with the cost savings that derive from the *additional prevention of fractures the VPHOP prognosis pathway has achieved* in comparison to the standard of care. The costs, in sum, can be defined as the *extra costs of the VPHOP prognosis pathway* as compared to the costs of the SoC.

For the VPHOP clinical pathway, in a simplified manner, with $B = \text{Cost savings (fractures avoided)}$ and $C = \text{Extra costs}$, the benefit-cost ratio (BCR) can be calculated as:

$$Cost_{VPHOP} = Cost \text{ per entry cohort}_{VPHOP} - Cost \text{ per entry cohort}_{SoC}$$

$$BCR_{VPHOP} = \frac{B}{C} = \frac{Cost \text{ savings (fractures avoided)}}{Cost_{VPHOP}}$$

Alternating between conservative and relaxed assumption and data input, the calculated ratio indicated in nearly all instances a positive return. For the simulated patient cohort, and for the VPH technologies, to break even with the costs of the SoC, the number of additional fractures needed to prevent is within realistic reach, once the technology would be deployed in a clinical setting. The CBA exhibited clearly that the extra costs needed to implement the VPHOP pathways are by far offset through the large amount of costs savings that the improved fracture risk prognosis of VPHOP presents.

4. Discussion

Through newly developed clinical decision support and pathways, the transformation of biocomputational modelling and VPH technologies into future patient workflows are meant to ameliorate or even replace current clinical management processes, here of osteoporotic patients. The new (VPH) technology assessment framework developed forces many of the implicit assumptions behind such developments to lay bare. Since the assessment perspective is to develop concrete clinical scenarios, the further work, e.g. on VPHOP technologies, will clearly benefit from a much more focused alignment towards producing results that matter within the context of deployable, routine clinical applications. The cost-benefit analysis already at this early stage allowed highlighting some of the fundamental and, most importantly, clinical challenges VPHOP will have to overcome, thereby directing its further research into the clear direction of early clinical triability and later routine clinical deployment.

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