HEcoPerMed

Health Economics for Personalised Medicine

Deliverable
1.2

Report Information

Title:	Protocol for the Systematic Review of Model-Based Economic Evaluations of Personalised Medicine (including D1.2. Draft checklist to assess the methodological quality of model-based economic evaluations in personalised medicine)
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Version:	v0.1
Work package:	WP1
Date of publication:	31/05/2019
Dissemination level:	

Project Information

Project acronym:	HEcoPerMed
Project full title:	Health Economic Models for Personalised Medicine
Starting date:	01.01.2019
Duration:	36 months
Coordinator:	Dr Susanne Giesecke

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

History of changes			
Version	Date	Changes	Author

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1 HOW THIS DELIVERABLE LINKS TO OTHER DELIVERABLES

Deliverable 1.2 consists of a draft checklist to assess the methodological quality of cost-effectiveness studies that model personalised medicine interventions. The draft checklist gives an initial insight into the kind of issues encountered when modelling personalised medicine interventions and provides input into Deliverable 1.1, in which guidance on health economic modelling in personalised medicine will be developed. After finalisation of Deliverable 1.1, Deliverable 1.2 will be updated and finalised. Deliverable 1.1, in turn, provides input into Deliverable 2.2. In Deliverable 2.2 the three academic partners in the HEcoPerMed consortium will each build a model based on the developed guidance.

2 INTRODUCTION

This review is part of the H2020 HEcoPerMed (Health Economics for Personalised Medicine) consortium that aims to provide guidance on health economic modelling in personalised medicine, as well as on financing and payment strategies for personalised medicine. The European Council Conclusion on personalised medicine for patients (2015/C 421/03) defined personalised medicine as "a medical model using characterization of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". This definition is taken as the starting point of the HEcoPerMed project, though it may be iteratively adapted.

The systematic review aims to provide a comprehensive overview of recent model-based economic evaluations of personalised medicine published in scientific journals or submitted to Health Technology Assessment (HTA) bodies. Insight will be generated into the added value of personalised medicine by extracting results on incremental costs and health outcomes from the included studies. The studies will also be searched for promising methods for health economic modelling in personalised medicine.

Based on the promising modelling methods identified in the systematic review and on information gathered through interviews with relevant experts and end-users (i.e. those who use findings from HTA studies in decision-making), guidance for good health economic modelling practice in personalised medicine will be developed. The guidance will include a checklist that can be used to assess the methodological quality of model-based economic evaluations of personalised medicine. The current draft of this checklist is Deliverable D1.2.

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3 METHODS

3.1 Search strategy and study selection

This systematic review will be conducted according to PRISMA guidelines. On 13th March 2019 the Embase, Medline Ovid, Web of Science and Google Scholar databases were searched using search terms describing model-based economic evaluations and personalised medicine. See Appendix 1 for the search strategies. On 16th May 2019, an additional search was performed in the CRD (Centre for Reviews and Dissemination) Database, which is supplied with ongoing and completed health technology assessments by the 52 members of the International Network of Agencies for Health Technology Assessment (INAHTA) and by 20 other international HTA organisations. EconLit will be searched to identify additional grey literature. De-duplication will be done using the method described by Bramer et al. (2016).

Title and abstract screening will be performed in Rayyan. The reasons for exclusion will not be recorded at this stage. Subsequently, the records will be imported in EndNote in two folders: 'Inclusions' and 'Exclusions'. EndNote will be used for full-text screening of the studies that were included based on their title and abstract. In this step, several 'Exclusions' folders will be used, in order to categorise the excluded studies according to reason for exclusion.

At the stage of title/abstract screening, two independent reviewers will assess whether the first 30% of studies meets the inclusion criteria. After this, the results of the two reviewers are compared and discussed. If the differences in inclusion decisions are more than 5% of the assessed publications, another 10% of the articles will be independently screened by both reviewers. Subsequently, a similar assessment happens. If the discrepancy is more than 5% of the selected studies again, another 10% will be screened in duplicate. If more than 5% of the studies still does not overlap at 50% of the total amount of studies, the entire title/abstract screening will be done by two reviewers. A similar process will be used for the full-text screening, though here the initial batch will be 10%, to ensure comparison and discussion of the results of the two reviewers will be done early in the process. In the case of disagreement, consensus will be reached with the help of a third reviewer.

Cited references of selected papers and previous systematic reviews on the topic will be searched to identify other relevant studies. To assess the comprehensiveness of this systematic review, its included papers will be compared to the inclusions in previous systematic reviews.

3.2 In- and exclusion criteria

Publications are included if they report model-based economic evaluations considering costs and health outcomes of personalised medicine interventions (according to the EC definition described above). Studies will be excluded if: the intervention under consideration does not meet the EC definition of personalised medicine; no cost-effectiveness model was used to assess the intervention; final outcomes (expressed as life years (LYs) or quality-adjusted life years (QALYs)) are not included in the model; and/or the model does not extrapolate outcomes beyond the observed period or time horizon of the underlying clinical study. Systematic reviews of studies that meet our inclusion criteria will also be included and saved in a separate folder. Figure 1 illustrates the in- and exclusion criteria, which will be applied both at the title/abstract and full-text screening stages. The search was limited to studies published in English in or after 2009. A 10-year time frame (2009-2019) was chosen because the fields of health economic modelling and personalised medicine both advance swiftly and studies may become outdated relatively quickly.

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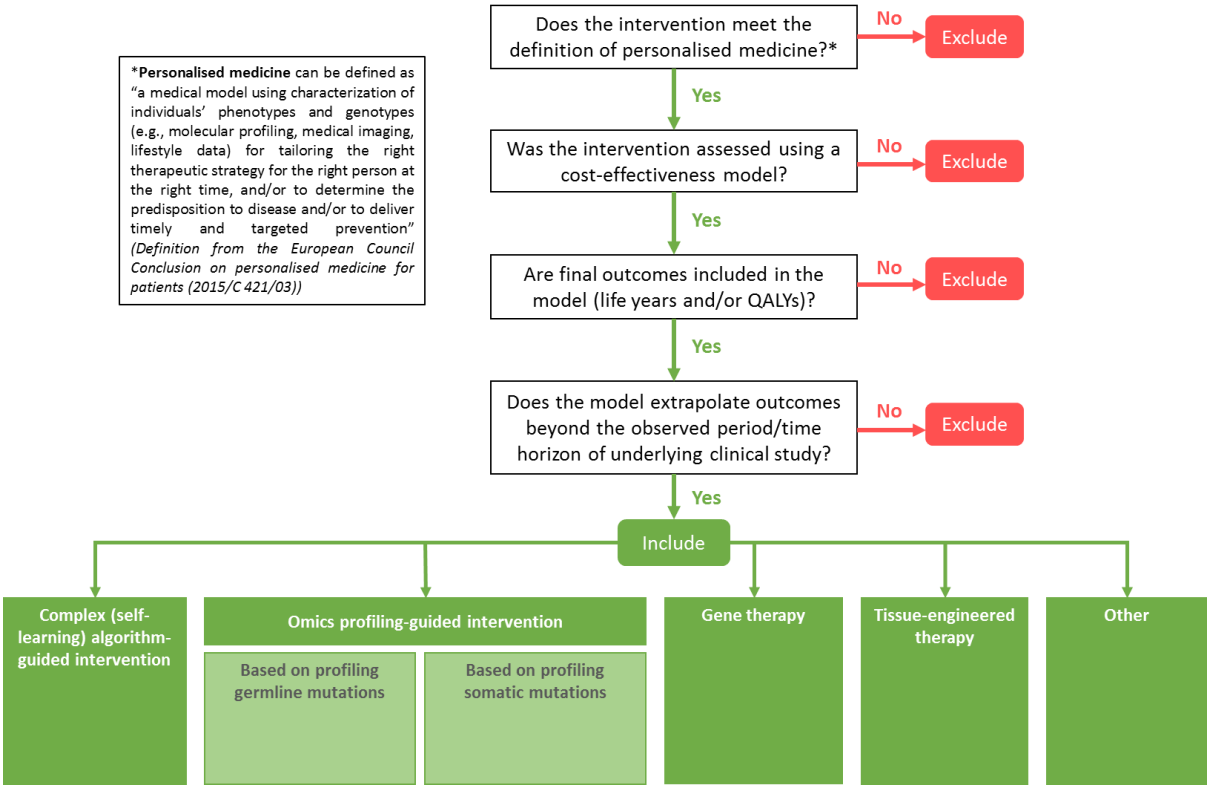
Figure 1 – Illustration inclusion criteria



After full-text screening, an additional selection will take place – in order to identify a subset of studies with modelling methods that may be interesting in light of the project's goal to develop guidance for health economic modelling in personalised medicine. A first draft of the identification list, which may be iteratively adapted, can be found in Appendix 2. The selection process will be illustrated in a flowchart, as per the PRISMA guideline.

Included studies will be subdivided in the following personalised medicine categories:

Table 1 – Categories personalised medicine interventions

Category	Explanation
1. Complex (self-learning) algorithm-guided intervention	Treatment pathway is based on multiple parameters that are combined in a systematic manner
2. Omics profiling-guided intervention	Treatment pathway is based on an omics test focusing on patients' molecular cell biology (as opposed to the molecular cell biology of disease-causing agents such as viruses). 'Omics' includes genomics, epigenomics, transcriptomics, proteomics, metabolomics, and others
a) Based on profiling germline mutations	Omics profiling is used to gain insight into germline, or constitutional, mutations
b) Based on profiling somatic mutations	Omics profiling is used to gain insight into somatic, or non-inherited, mutations – such as those found in tumour cells
3. Gene therapy	Treatment in which patients' genes are altered. While gene therapy is preceded by omics profiling, it is deemed a separate category from category 2 because both the determination of treatment and the treatment itself make use of omics medicine (as opposed to interventions from category 2, in which only the determination of treatment is done using omics techniques)

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4. Tissue-engineered therapy	Treatment in which existing tissue is stimulated or new living tissue is generated through materials development, cell culture and/or biochemical manipulations
5. Other	Other interventions that fall under the EC definition of personalised medicine but have not been captured in the categories above

3.3 Quality assessment of included studies

The quality of (a subset of) the included studies will be assessed using the draft HEcoPerMed checklist (Appendix 3), which is based on the Philips, AGREEDT and AdViSHE checklists but focuses on issues particular to personalised medicine. The draft checklist will be further refined after it has been applied to the included studies.

3.4 Data extraction

Data will be extracted using a data extraction form in Excel by one reviewer, whose work will be checked by a second reviewer. In case of disagreement, consensus will be reached together with a third reviewer. A comprehensive data extraction form is provided in Appendix 4. This data extraction form can be completed together with the HEcoPerMed checklist. Depending on the number of included studies after full-text screening, the final data extraction form to be applied may be limited to a subset of the items in Appendix 4.

3.5 Synthesis

For all studies that are included after full-text screening, study and model characteristics will be summarised in tables. Incremental differences in QALYs and costs will be reported in an aggregated manner. Reported incremental cost-effectiveness ratios (ICERs) will be compared to the thresholds used in the individual studies to evaluate in what percentage of studies personalised medicine interventions were considered cost-effective.

3.6 Meta-bias(es)

The Standards for Systematic Reviews by the Institute of Medicine spell out various forms of reporting bias that can occur in the academic literature and have to be considered by systematic reviewers. These include: publication bias; time-lag bias; location (i.e. journal in which article is published) bias; language bias; and multiple (duplicate) publication bias. The grey literature will be searched in addition to peer-reviewed publications, in order to address any time-lag or location bias. Although the search is restricted to articles published in English and might therefore cause language bias, the IOM document also states that there is no concluding evidence that excluding publications in languages other than English affects the findings of systematic reviews. Although initial de-duplication will be performed before screening starts, remaining duplicates or highly similar publications will be manually identified after full-text screening to mitigate multiple (duplicate) publication bias.

4 REFERENCES

Bramer, W., et al., *De-duplication of database search results for systematic reviews in EndNote*. Journal of the Medical Library Association, 2016. **104**(3): p. 240-243.

Institute of Medicine, “Finding What Works in Health Care: Standards for Systematic Reviews”. Morton, S., et al., (eds). National Academies Press, 2011.

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APPENDICES

A.1 – Search terms

	Total no. of hits	No. of hits remaining after de-duplication
Embase.com	2,648	2,594
Medline Ovid	2,482	1,026
Web of science	1,744	500
Google scholar	200	159
Total	7,074	4,279

Embase.com

('biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti)

AND ('economic model'/de OR 'simulation'/de OR (model/de AND (economics/exp OR 'economic aspect'/exp)) OR 'decision tree'/de OR (((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/6 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision NEAR/3 (analy* OR tree OR trees)) OR discrete-event* OR 'state transition' OR markov OR ((individual* OR patient-level*) NEAR/3 (sampl* OR simulation*)) OR (dynamic NEAR/3 transmission*) OR probabilistic* OR partition*-survival*):ab,ti)

AND ('personalized medicine'/de OR 'risk stratification'/de OR 'pharmacogenetics'/de OR 'genetic variation'/de OR 'genetic procedures'/exp OR 'genotype'/de OR 'biological marker'/de OR 'mobile application'/de OR 'personal digital assistant'/de OR 'mobile phone'/de OR 'gene therapy'/exp OR 'molecularly targeted therapy'/exp OR 'immunotherapy'/exp OR 'pharmacogenomics'/exp OR 'pharmacokinetics'/exp OR 'activity tracker'/de OR 'artificial intelligence'/de OR 'machine learning'/de OR (('algorithm'/de OR 'genetic algorithm'/de OR 'learning algorithm'/de OR 'classification algorithm'/de) AND (risk/exp OR therapy/exp)) OR 'omics'/exp OR 'pharmacogenetic testing'/de OR 'self monitoring'/de OR (((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR/6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) NEAR/3 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* NEAR/3 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR/3 (applicat* OR app OR apps)) OR wearable* OR (personal* NEAR/3 digital* NEAR/3 assistant*) OR (handheld NEAR/3 computer*) OR ((mobile OR cell*) NEXT/1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* NEAR/3 (genomic* OR genetic* OR kinetic*)) OR (digital NEAR/3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data NEAR/3 analytic*) OR (artificial* NEAR/3 intelligen*) OR (machine* NEAR/3 learning) OR ((remote OR self) NEAR/3 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* NEAR/3 (guide* OR base*) NEAR/3 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk NEAR/3 score*)):ab,ti)

NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) AND [English]/lim

Medline Ovid

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(Technology Assessment, Biomedical/ OR Cost-Benefit Analysis/ OR Quality-Adjusted Life Years/ OR ((technology ADJ3 assessment*) OR (economic* ADJ3 (evaluat* OR value)) OR ((cost OR costs) ADJ3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* ADJ3 adjust* ADJ3 (life-year* OR lifeyear*)) OR qaly*).ab,ti.)

AND (Models, Economic/ OR Decision Trees/ OR (((model OR modeling OR modelling OR simulation* OR microsimulation*) ADJ6 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision ADJ3 (analy* OR tree OR trees)) OR discrete-event* OR state transition OR markov OR ((individual* OR patient-level*) ADJ3 (sampl* OR simulation*)) OR (dynamic ADJ3 transmission*) OR probabilistic* OR partition*-survival*).ab,ti.)

AND (Precision Medicine/ OR exp Pharmacogenetics/ OR Genetic Variation/ OR Genotype/ OR Biomarkers/ OR Mobile Applications/ OR Computers, Handheld/ OR Cell Phone/ OR Genetic Therapy/ OR Molecular Targeted Therapy/ OR exp Immunotherapy/ OR exp Pharmacokinetics/ OR Fitness Trackers/ OR Artificial Intelligence/ OR Machine Learning/ OR ((Algorithms/) AND (Risk/ OR Therapeutics/)) OR omics/ OR Pharmacogenomic Testing/ OR (((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) ADJ6 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) ADJ3 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* ADJ3 marker*) OR biomarker* OR telemonitor* OR (mobile ADJ3 (applicat* OR app OR apps)) OR wearable* OR (personal* ADJ3 digital* ADJ3 assistant*) OR (handheld ADJ3 computer*) OR ((mobile OR cell*) ADJ phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* ADJ3 (genomic* OR genetic* OR kinetic*)) OR (digital ADJ3 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data ADJ3 analytic*) OR (artificial* ADJ3 intelligen*) OR (machine* ADJ3 learning) OR ((remote OR self) ADJ3 monitor*) OR pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* ADJ3 (guide* OR base*) ADJ3 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk ADJ3 score*)).ab,ti.)

NOT (exp animals/ NOT humans/) AND english.la.

Web of Science

TS=((((technology NEAR/2 assessment*) OR (economic* NEAR/2 (evaluat* OR value)) OR ((cost OR costs) NEAR/2 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/2 adjust* NEAR/2 (life-year* OR lifeyear*)) OR qaly*))

AND ((((model OR modeling OR modelling OR simulation* OR microsimulation*) NEAR/5 (econom* OR pharmacoeconom* OR cost OR costs)) OR (decision NEAR/2 (analy* OR tree OR trees)) OR discrete-event* OR "state transition" OR markov OR ((individual* OR patient-level*) NEAR/2 (sampl* OR simulation*)) OR (dynamic NEAR/2 transmission*) OR probabilistic* OR partition*-survival*))

AND ((((personalized OR personalised OR individualised OR individualized OR precision OR stratif* OR targeted* OR algorithm*) NEAR/5 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration OR decision*)) OR ((genetic* OR gene OR genom* OR molecular*) NEAR/2 (variation* OR technique* OR procedure* OR test OR testing OR therap* OR sequenc* OR profil*)) OR genotype* OR (biologic* NEAR/2 marker*) OR biomarker* OR telemonitor* OR (mobile NEAR/2 (applicat* OR app OR apps)) OR wearable* OR (personal* NEAR/2 digital* NEAR/2 assistant*) OR (handheld NEAR/2 computer*) OR ((mobile OR cell*) NEAR/1 phone*) OR smartphone* OR immunotherap* OR immunetherap* OR immun*-therap* OR pharmacogenomic* OR pharmacogenetic* OR pharmacokinetic* OR (pharmac* NEAR/2 (genomic* OR genetic* OR kinetic*)) OR (digital NEAR/2 (health OR medicine)) OR mHealth* OR eHealth* OR m-Health* OR e-Health* OR tracker* OR (data NEAR/2 analytic*) OR (artificial* NEAR/2 intelligen*) OR (machine* NEAR/2 learning) OR ((remote OR self) NEAR/2 monitor*) OR

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pharmacometabolom* OR metabolom* OR proteomic* OR pharmacoproteomic* OR lipidomic* OR pharmacolipidomic* OR omics OR (model* NEAR/2 (guide* OR base*) NEAR/2 (medicine* OR therap* OR treat* OR risk OR regimen* OR dosing* OR duration)) OR (risk NEAR/2 score*))) AND (medicine OR health* OR patient* OR hospital* OR therap* OR genetic* OR pharmac* OR virus* OR genotype* OR disease* OR diagnos* OR cancer*) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)))

AND DT=(article) AND LA=(english)

Google Scholar

"technology assessment"|"economic evaluation"|"cost|costs benefit|effectiveness" model|simulation|microsimulation economic|pharmacoeconomic|markov "personalized|personalised|individualised|individualized|precision medicine"

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A.2 – Draft identification list

Have the following aspects been addressed/incorporated in the analysis?

Topic	Aspect	Related questions on draft checklist (A.3)	Score (Y/N)
Decision problem and scope	Comparators that are non-PM interventions	2	
Conceptual model	Conditionality of test sequences and/or test outcomes	11-15	
	Time periods (i) from patient presenting until test and (ii) from test until initiation of patient management strategy	16	
	Patients' treatment adherence	19	
	Clinicians' adherence to protocols/guidelines	20	
	Potential bias in the extrapolation of outcomes for interventions aiming to cure	23-24	
Input data	Deviation from standard discount rates for reasons particularly relevant to PM interventions	25	
	Validity of using expert opinion	26	
	Potential bias in observational studies	29	
	Potential bias in studies with small patient population	30	
	Values beyond the QALY	34	
	Values beyond the current patient	35	
Equity	Equity issues particularly relevant to PM interventions	36-37	
Uncertainty	Uncertainty analysis particularly relevant to PM interventions	39-42	
Other	Other aspects particularly relevant to PM interventions		

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A.3 – Draft HEcoPerMed checklist

Topic	Subheading	#	HEcoPerMed checklist	Source
Decision problem and scope	***Personalisation approach***	1	Is described how the intervention was personalised (according to the EC definition of personalised medicine)?	*iv*
		2	Is the potential advantage of the personalised medicine approach over usual care considered?	
	Target population and a priori subgroups	3	Is the target population described?	*vii*
		4	Are a priori subgroups* described?	*ii*
	Details stratification/ personalisation	5	Are the biomarkers and other variables used for stratification/personalisation described?	
		6	Are the cut-off values of the biomarkers and other variables used for stratification/personalisation described and rationalised?	*ii*
		7	Is the purpose of stratification/personalisation described?	*ii, iii, iv*
		8	Are the patient management strategies described for all post-test/algorithm subgroups**?	*ii*
	Comparators	9	Are the comparator(s) included in the evaluation described for all post-test/algorithm subgroups?	*vii*
Conceptual model	***General***	10	Is the structure of the model consistent with the personalisation approach described in question 1?	*vii,viii*
	Test/algorithm	11	In case of multiple tests/algorithms, is described whether they were performed in parallel or in sequence?	*ii*
		12	Is considered whether test/algorithm sequences vary across a priori subgroups?	*ii*
		13	Is considered whether test/algorithm performance and cut-off value(s) vary across a priori subgroups?	*ii*
		14	Is considered whether test/algorithm sequences depend on previous test outcomes?	*ii*
		15	Is considered whether test/algorithm performance and cut-off value(s) depend on previous test outcomes?	*ii*
		16	Are the time periods from the patient presenting to test and from test to initiation patient management strategy considered?	*ii*
		17	Are adverse events caused by the test considered?	*ii*
	Adherence	18	Is patients' willingness to be tested considered?	
		19	Is patients' adherence to treatment considered?	*ii,vi*
		20	Is clinicians' adherence to protocols/guidelines considered?	*vi*
	Extrapolation	21	Are the methods used to extrapolate short-term results to final outcomes described and rationalised?	*vii*
		22	Is a definition of 'cured' clearly stated?	

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	Interventions aiming to cure	23	Is considered whether the extrapolation of outcome measures may be biased for interventions aiming to cure?	*v*
		24	Are specific statistical methods used to address potential bias in the extrapolation of outcomes for interventions aiming to cure?	*v*
Input data	***General***	25	If the discount rates used differ from those prescribed in relevant HTA guidelines, has this been rationalised?	*vii*
		26	Where expert opinion has been used, are the methods described and rationalised?	*vii*
	Algorithm/test	27	Are the sensitivity, specificity, negative predictive value (and its complement) and positive predictive value (and its complement) of the test described?	*ii*
	Treatment effect	28	Are treatment effects described for all post-test/algorithm subgroups, including false positives and false negatives?	*ii*
		29	Are methods used to compensate for potential bias in data from observational studies?	*vi,vii*
		30	Are methods used to compensate for potential bias in data from studies with a small patient population?	*vi, vii*
	Cost	31	Are costs described for all post-test/algorithm subgroups, including false positives and false negatives?	*ii*
		32	Are costs of the test included (including cost of retesting where relevant)?	*ii*
	Utility	33	Are utilities described for all post-test/algorithm subgroups, including false positives and false negatives?	*ii*
		34	Are values beyond the QALY (e.g. value of knowing, patient preferences regarding undergoing tests, the impact on caregivers) considered?	*ii*
		35	Are values beyond the current patient (e.g. value to relatives and descendants of discovering hereditary gene variants) considered?	*ii*
Equity		36	Is considered whether parameters used for stratification correlate with socioeconomic status, ethnic background, age, gender or other variables that could lead to inequity?	*vi*
		37	Is considered whether differential uptake of treatment correlates with socioeconomic status, ethnic background, age, gender or other variables that could lead to inequity?	*vi*
Outcome measures		38	Is the percentage of patients in which the disease-management strategy changes as a result of the intervention described?	
Uncertainty	***General***	39	Is considered whether uncertainty is expected to have increased/decreased as a result of the PM approach?	
	Parameter	40	Are parameter uncertainties that are of specific interest in PM addressed through sensitivity analysis?	*ii,vi,vii*
		41	Is probabilistic sensitivity included? If not, has this omission been rationalised?	*viii*

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	Structural	42	Are structural uncertainties related to PM addressed through sensitivity analysis?	*vii*
Validity	***Expert opinion***	43	Were experts asked to assess whether the model appropriately reflects the PM approach in question?	*i*
	Internal	44	Were internal validity checks performed?	*i*
	Cross-model	45	Was the model compared to other models of the PM approach in question?	*i*
	External data sources	46	Were model outcomes compared to outcomes of other models of a similar PM approach?	*i*

* A priori subgroups are a result of heterogeneity in the target population. They are determined before testing takes place and might be informed by patient characteristics for example.

* Post-test/algorithm subgroups are formed based on the test/algorithm results and are a result of the intervention's stratification approach.

References

i. Vemer, P., et al., *AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users.* Pharmacoeconomics, 2016. **34**(4): p. 349-361.
ii. Kip, M.M., et al., *Toward alignment in the reporting of economic evaluations of diagnostic tests and biomarkers: the AGREEDT checklist.* Medical decision making, 2018. **38**(7): p. 778-788.
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v. Jönsson, B., et al., *Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare.* The European Journal of Health Economics, 2018: p. 1-12.
vi. Love-Koh, J., et al., *The future of precision medicine: potential impacts for health technology assessment.* Pharmacoeconomics, 2018. **36**(12): p. 1439-1451.
vii. Philips, Z., et al., *Review of guidelines for good practice in decision-analytic modelling in health technology assessment*, in *NIHR Health Technology Assessment programme: Executive Summaries*. 2004, NIHR Journals Library.
viii. Yang, Y., et al., *Use of Decision Modelling in Economic Evaluations of Diagnostic Tests: An Appraisal and Review of Health Technology Assessments in the UK.* PharmacoEconomics-open, 2018: p. 1-11.

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A.4 – Data extraction form

Topic	Subheading	#	HEcoPerMed checklist	Data extraction
Decision problem and scope	***Personalisation approach***	1	Is described how the intervention was personalised (according to the EC definition of personalised medicine)?	Intervention PM category: a) complex algorithm-guided intervention b) omics profiling-guided therapy c) gene therapy d) tissue-engineered therapy e) other
		2	Is the potential advantage of the personalised medicine approach over usual care considered?	
	Target population and a priori subgroups	3	Is the target population described?	Target population (disease, mean age, proportion male/female, ethnic background, socioeconomic status)
		4	Are a priori subgroups* described?	A priori subgroups
	Details stratification/ personalisation	5	Are the biomarkers and other variables used for stratification/personalisation described?	Biomarkers and other variables used for stratification
		6	Are the cut-off values of the biomarkers and other variables used for stratification/personalisation described and rationalised?	
		7	Is the purpose of stratification/personalisation described?	Purpose of stratification: a) risk factor screening b) disease screening c) diagnosis d) prognosis e) decide on therapy f) response monitoring g) relapse surveillance
		8	Are the patient management strategies described for all post-test/algorithm subgroups**?	
	Comparators	9	Are the comparator(s) included in the evaluation described for all post-test/algorithm subgroups?	Comparator(s)

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	Perspective and country			Perspective (healthcare, healthcare payer, societal or provider) Country
Conceptual model	***General***	10	Is the structure of the model consistent with the personalisation approach described in question 1?	Type of model (decision tree, Markov model, patient-level simulation, DES, etc.)
	Test/algorithm	11	In case of multiple tests/algorithms, is described whether they were performed in parallel or in sequence?	
		12	Is considered whether test/algorithm sequences vary across a priori subgroups?	
		13	Is considered whether test/algorithm performance and cut-off value(s) vary across a priori subgroups?	
		14	Is considered whether test/algorithm sequences depend on previous test outcomes?	
		15	Is considered whether test/algorithm performance and cut-off value(s) depend on previous test outcomes?	
		16	Are the time periods from the patient presenting to test and from test to initiation patient management strategy considered?	
		17	Are adverse events caused by the test considered?	
	Adherence	18	Is patients' willingness to be tested considered?	Methods for incorporating patients' willingness to be tested
		19	Is patients' adherence to treatment considered?	Methods for incorporating patients' adherence
		20	Is clinicians' adherence to protocols/guidelines considered?	Methods for incorporating clinicians' adherence
	Extrapolation	21	Are the methods used to extrapolate short-term results to final outcomes described and rationalised?	Time horizon of analysis Time horizon of underlying clinical study
	Interventions aiming to cure	22	Is a definition of 'cured' clearly stated?	
		23	Is considered whether the extrapolation of outcome measures may be biased for interventions aiming to cure?	

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		24	Are specific statistical methods used to address potential bias in the extrapolation of outcomes for interventions aiming to cure?	Methods used
Input data	***General***	25	If the discount rates used differ from those prescribed in relevant HTA guidelines, has this been rationalised?	Discount rates Reason for specific discount rate
		26	Where expert opinion has been used, are the methods described and rationalised?	Methods for eliciting and incorporating expert opinion
	Algorithm/test	27	Are the sensitivity, specificity, negative predictive value (and its complement) and positive predictive value (and its complement) of the test described?	
	Treatment effect	28	Are treatment effects described for all post-test/algorithm subgroups, including false positives and false negatives?	
		29	Are methods used to compensate for potential bias in data from observational studies?	Methods used
		30	Are methods used to compensate for potential bias in data from studies with a small patient population?	Methods used
	Cost	31	Are costs described for all post-test/algorithm subgroups, including false positives and false negatives?	Cost categories included Year of reported costs and currency
		32	Are costs of the test included (including cost of retesting where relevant)?	
	Utility	33	Are utilities described for all post-test/algorithm subgroups, including false positives and false negatives?	Utility values by subgroup
		34	Are values beyond the QALY (e.g. value of knowing, patient preferences regarding undergoing tests, the impact on caregivers) considered?	Measure of value beyond QALY
		35	Are values beyond the current patient (e.g. value to relatives and descendants of discovering hereditary gene variants) considered?	Measures of value beyond current patient
Equity		36	Is considered whether parameters used for stratification correlate with socioeconomic status, ethnic background, age, gender or other variables that could lead to inequity?	Equity considerations

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		37	Is considered whether differential uptake of treatment correlates with socioeconomic status, ethnic background, age, gender or other variables that could lead to inequity?	Equity considerations
Outcome measures				Measure of health outcome Incremental costs, outcomes, and cost-effectiveness ratio
		38	Is the percentage of patients in which the disease-management strategy changes as a result of the intervention described?	% of patients in which patient-management strategy is different as result of intervention (vs comparator)
Uncertainty	***General***	39	Is considered whether uncertainty is expected to have increased/decreased as a result of the PM approach?	
	Parameter	40	Are parameter uncertainties that are of specific interest in PM addressed through sensitivity analysis?	Sensitivity analyses regarding parameters that are of specific interest in PM (e.g. allele frequency, test performance, cut-off values, unit cost test etc.)
		41	Is probabilistic sensitivity included? If not, has this omission been rationalised?	
	Structural	42	Are structural uncertainties related to PM addressed through sensitivity analysis?	Sensitivity analysis regarding structural uncertainties related to PM (e.g. test sequences, extrapolation long-term effects)
Validity	***Expert opinion***	43	Were experts asked to assess whether the model appropriately reflects the PM approach in question?	
	Internal	44	Were internal validity checks performed?	
	Cross-model	45	Was the model compared to other models of the PM approach in question?	Other models mentioned to justify results
	External data sources	46	Were model outcomes compared to outcomes of other models of a similar PM approach?	Other studies mentioned to justify results
Limitations				Mentioned study limitations particular to PM

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