POLIITIKAUURINGUTE KESKUS

PRAXIS

Estonian Personalised Medicine Pilot Project evaluation methodology

SOTSIAALMINISTEERIUM

Eesti Teadusagentuur
Estonian Research Council

TerVE

Euroopa Liit
Euroopa
Regionaalarengu Fond

Eesti tuleviku heaks

2015

CENTER FOR POLICY STUDIES

This paper is an extraction from the "**Feasibility study for the development of business cooperation, management organisation and evaluation methodology for personalised medicine pilot project**". The paper includes chapter 4 of the study specifically focusing on the development of the Estonian Personalized Medicine Pilot Project evaluation methodology.

The developmental research project was commissioned by the Ministry of Social Affairs and carried out by Tartu Biotechnology Park and Praxis Centre for Policy Studies. The project is supported by the European Union Structural Funds via the programme TerVE implemented by the Estonian Research Council.

This paper includes the **chapter 4** of the overall feasibly study and summarises the approach for developing a **methodology for evaluating the EPMPP and its components**. The evaluation methodology was developed by the Health Policy Programme at Praxis Centre for Policy Studies (Tallinn, Estonia) in co-operation with Biopark AS (Tartu, Estonia). This was done in close co-operation with stakeholders implementing the EPMPP.

Team of authors and reviewers

Priit Kruus, MSc	E-health and health policy analyst at Praxis Centre for Policy Studies
Gerli Paat-Ahi, MPH	Health technology assessment analyst at Praxis Centre for Policy Studies
Andres Rannamäe, MD	Organisation evaluation expert
Riina Sikkut, MSc	Health policy analyst at Praxis Centre for Policy Studies
Dr Noel Carrol, PhD	Health information technology evaluation expert – reviewer of initial methodology, Irish Centre of Excellence for Applied Connected Health Research (Dublin, Ireland)

Praxis Center for Policy Studies is an independent non-profit think tank in Estonia that supports engagement and analyses-based policy making. Praxis has conducted policy research for more than ten years and are one of a kind in Estonia. The mission of Praxis is to improve and contribute to the policymaking cycle by conducting independent research and promoting public debates.

Praxis Center for Policy Studies
Tornimäe St 5
10145 Tallinn, Estonia
Ph +372 640 8000
www.praxis.ee

Contents

Estonian Personalised Medicine Pilot Project evaluation methodology

ABSTRACT

A framework was developed for evaluating the Estonian Personalised Medicine Pilot Project (EPMPP) and its relevant components. Based on international literature, stakeholder expectations, input from personalised medicine (PM) pre-studies, background material and expert advice, a methodology was worked out with the aim to support the planning and prioritisation of evaluation tasks of EPMPP.

The EPMPP evaluation framework is similar to performance evaluation, evaluating the entire value chain – inputs, processes, outputs and outcomes – in order to understand whether the expected goals were achieved. Methodology calls for differentiating immediate outputs and deliverables from long term outcomes. This is particularly important considering the rather short period of the pilot project and high expectations for PM development in the long run. An initial description of the intervention logic of the overall pilot project will help to support the evaluation exercise.

The framework allows combining quantitative data with stakeholder perceptions and other qualitative information. Methodology will also help to connect the measures of clinical studies and health information system development activities with the whole EPMPP – in order to secure the alignment of different activities of the project. The evaluation chapter also provides an initial organisational design for evaluation coordination, implementation and dissemination during the EPMPP, also the list of key output and outcome measures and guidance for carrying on with the evaluation procedure.

Further steps are needed for appraisal of the intervention logic provided and drafting the project plan for EPMPP – every sub-evaluation could also complement from specific evaluation procedure description and should be approached separately, while keeping an eye on the overall evaluation framework and outcome achievement. Stakeholder involvement is of critical importance in case of such broad health care programs and this should be acknowledged with the continuing dissemination of results of EPMPP evaluation activities. A good quality management system should be implemented with key quality control processes to ensure compliance with regulatory requirements, patient safety and health care quality standards. The roll-out of EPMPP should be iterative in order to build on the lessons learned, involve stakeholders and align EPMPP activities with the overall goals of Estonian health system.

Eesti personaalmeditsiini pilootprojekti hindamise raamistiku arendamine

LÜHITUTVUSTUS

2014. aasta lõpus otsustas valitsus toetada tervise- ja tööministri ettepanekut algatada personaalmeditsiini tervishoius rakendamise pilootprojekt aastateks 2015−2018. Personaalmeditsiin aitab leida igale inimesele võimalikult individuaalse ennetus- või raviplaani, analüüsides inimese geeniandmeid koos keskkonna-, tervisekäitumise ja tavapäraste haigusandmetega. Personaalmeditsiini projektis saavad kokku nii Eesti e-lahendused kui meditsiini innovatsioonid, et pakkuda uusi võimalusi haiguste raviks.

Personaalmeditsiini pilootprojekti vahetud eesmärgid on valideerida personaalmeditsiini rakendatavust ja efektiivsust, arendada välja informaatika- ja andmehaldustaristu personaliseeritud ehk individuaalsetel käitumise, tervise- ja geeniandmetel põhinevaks lähenemiseks ning juurutada teadus-arendustegevuse ja innovatsiooni ökosüsteem personaalmeditsiinialase teadmussiirde toetuseks ülikoolidele ning ettevõtetele

Käesoleva projekti raames töötati koostöös Eesti ning välismaiste ekspertidega välja metoodika Eesti personaalmeditsiini pilootprojekti hindamiseks.

Töö tulemusena kirjeldati metoodika väljatöötamise protsess ja sisendeid, toodi välja esialgne metoodiline raamistik, olulised küsimused sekkumisloogika loomiseks ja hindamise läbiviimiseks, samuti pilootprojekti alamprojektide sisendite-väljundite ühitamiseks pilootprojekti kui terviku ning laiemalt tervishoiu ja sotsiaalmajanduslike eesmärkidega. Analüüsi käigus loodi olemasoleva info põhjal esialgne sekkumisloogika, mis on hindamise aluseks ning pakutakse välja peamised hindamismõõdikud ja -küsimused, et pilootprojekti tulemuslikkust hinnata koos selgituse ning hindamise eest vastutavate organisatsoonidega. Tuuakse välja ka laiem hindamisprotsessi kirjeldus, mis sõltub pilootprojekti üldiste tegevuste kaardistusest.

Metoodika väljatöötamine toimus Personaalmeditsiini pilootprojekti juhtimise korralduse, ettevõtlusalase koostöö ning hindamismetoodika arendusuuringu raames, mis viidi läbi koostöös Aktsiaseltsiga Tartu Biotehnoloogia Park.

4.1 Evaluation methodology development

Evaluation framework development – aims and process

The **aim of the evaluation methodology** or framework is to provide a basis for evaluating the EPMPP in Estonia. Evaluation is often defined as a systematic and objective assessment of the design, implementation and results of a project compared to a set of explicit or implicit objectives, targets or standards. Evaluation often determines the **fulfilment of objectives, efficiency, effectiveness, impact, sustainability and relevance** of the project. Therefore, the framework should derive from the goals set by the project initiators, but also take into account the relevant value propositions, expectations and risks associated with the project. These perceptions can be derived from stakeholder interviews. It should also acknowledge the abundance of international literature regarding the evaluation of personalised medicine initiatives.

The **process** for developing the evaluation methodology:

1. Setting aim for the evaluation methodology development, based on goals and organisational design of EPMPP and stakeholder interviews described in main report.
2. Overview of international experience of evaluation approaches related to personalised medicine implementation, including evaluation of health information systems (HIS) and evaluation of personalised screenings and PM counselling (see Annexes).
3. Setting the focus of evaluation: starting from overall project organisation evaluation.
4. Developing an initial framework for evaluation.
5. Validating/reviewing initial evaluation framework (review and refinement proposals by experts).
6. Further developing the evaluation methodology – methodologically connecting the sub-project evaluation to overall project evaluation and overall health policy, R&D policy and economic policy goals.
7. Developing recommendations and guidance for the evaluation process, including roles, responsibilities, evaluation measures and questions.

The data sources and approach to evaluation framework development is described by the Figure 4.1.1. As a backbone for the framework development, the performance evaluation approach is used – covering the whole intervention value chain of input-process-output-outcome[12] (also referred to as result chain, logical framework or logical model).

[1] Gertler, P.J., S. Martinez, P. Premand, L B. Rawlings, C.M.J. Vermeersch (2011). Impact Evaluation in Practice.

The World Bank. [http://siteresources.worldbank.org/EXTHDOFFICE/Resources/5485726-1295455628620/Impact_Evaluation_in_Practice.pdf]

[2] EVALSED (2012) The resource for the evaluation of Socio-Economic Development. [http://ec.europa.eu/regional_policy/sources/docgener/evaluation/guide/guide_evalsed.pdf]

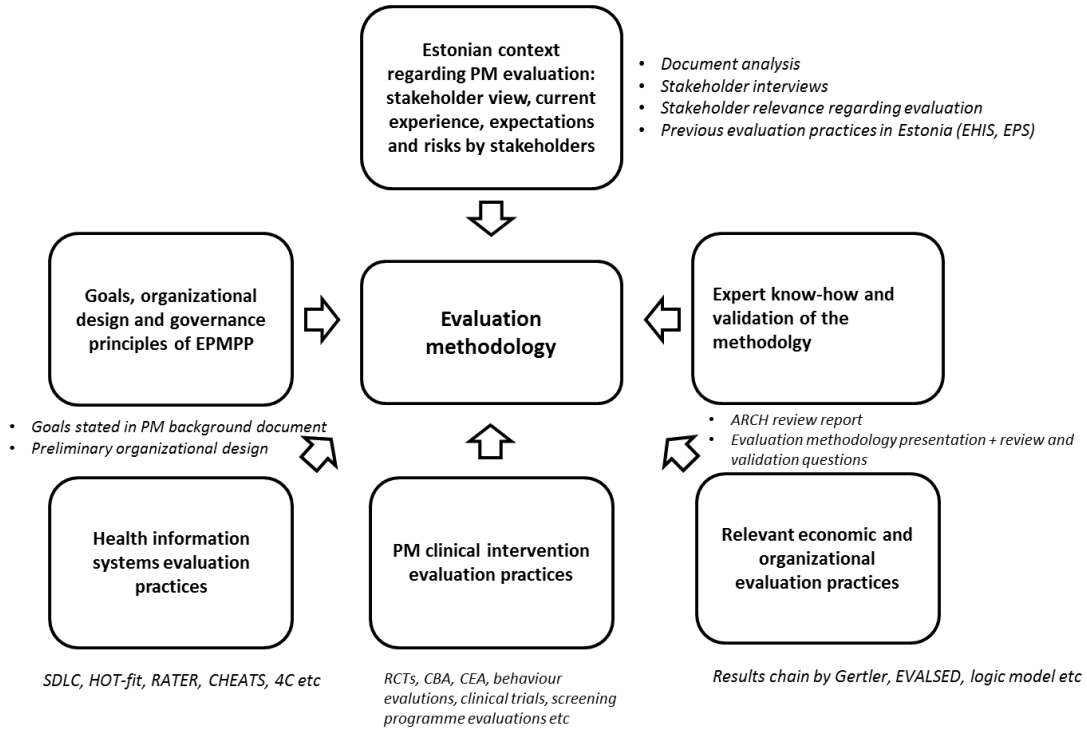


Figure 4.1.1. Evaluation methodology development approach

The primary aims/criteria of the evaluation methodology were defined. The evaluation methodology should:

1. Provide a **framework of relevant criteria and measures** (including input, process, and output and outcome measures).
2. Support a **planning exercise and prioritisation** of different evaluation tasks.
3. Enable to **evaluate the success of EPMPP in reaching its goals and overall Estonian health policy goals,** as well as support the evaluation of specific clinical interventions and logically connect the measures of both.
4. Allow the inclusion of the perspective **of different stakeholders**.
5. Allow the use of **different methods for evaluation**, including subjectivist, objectivist and mixed methods.

Starting point for evaluation – the goals of EPMPP

As stated in the background material of EPMPP, the objective of the pilot project is to create, via active and coordinated actions, opportunities for the development and implementation of personalised medicine as well as the development of associated health services and business enterprise by taking advantage of and enhancing the existing strengths of Estonia (country-wide e-health infrastructure and secure authentication, excellent biobank). Thus, in essence, the pilot project should provide an innovation boost for the Estonian health care ecosystem.

As a definition, personalised medicine refers to prevention, diagnosis and treatment of health disorders, based on individual risk-tailored approach using computational decision support analysis of person's phenotype and genotype data. The goal of personalised medicine is to contribute towards preventive, predictive and participatory health system.

The **direct goals** of the pilot project stated in the background document of EPMPP are:

- 'to **validate the possibility of the implementation** and the **efficiency** of personalised medicine in the clinical treatment of patients';

- 'to develop **computing and data management infrastructure** for a personal approach, i.e. one that is based on individual health, behaviour, genetic and other data in the prevention and treatment of illnesses';
- 'to **implement an ecosystem of research, development and innovation** to support the transfer of knowledge about personalised medicine (connections of genetic and molecular information with health and behavioural information for risk-based management of the health approach of people) to universities and companies'.

Thus, the evaluation framework should enable the assessment, whether such goals were reached using specific measures (initial examples of possible measures below):

1. **Feasibility of implementation of PM**
   can be measured as: overcoming barriers of implementation, context readiness, infrastructure readiness
2. **Efficiency of PM in clinical setting**
   can be measured as efficiency of different interventions: e.g using CDSS for more effective CVD prevention compared to current practices; implementing personalised and more precise cancer screening compared to current screening practices with regard to costs, detection rate etc.
3. **Development of data management infrastructure for personalised approach**
   can be measured with health information systems success measures (quality, use levels, user experience etc).
4. **Success in creating an ecosystem, which supports research, development and innovation, including successful knowledge transfer between universities and companie**s.
   can be measured as: number of new innovative services in different service/product development phases (e.g technology readiness level[3] measurement adjusted to Estonian health system context), number of new companies with sustainable business models in personalised medicine, number of scientific publications, number of new services etc).

Although the definition and goals provide an overall understanding of the purpose of the EPMPP initiative, they do not provide, in a sufficient manner, rigorous metrics for evaluating the whole EPMPP. The goals currently lack specificity and should be therefore supported by more specific measures. In the future it is also advisable to distinct the short-, medium- and long-term goals of EPMPP. Furthermore, it can be argued that the third goal is rather a process activity than a final result. Thus, in the framework this aspect should be acknowledged (see Figure 4.1.2 below).

[3] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf

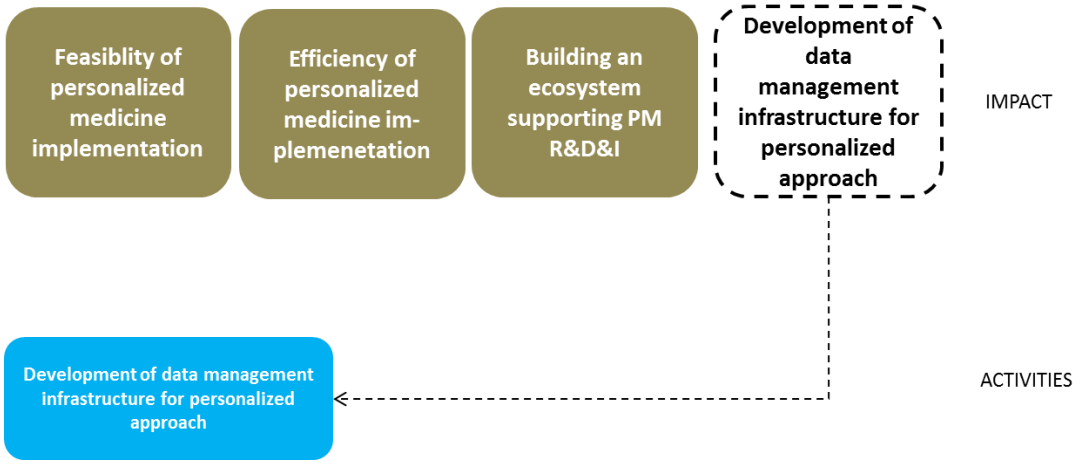


Figure 4.1.2. Stated goals of EPMPP

Interdependence of goals and activities of EPMPP

The goals are also **interconnected** – the feasibility of implementation can be validated with a good evaluation of personalised medicine context and barriers yet should be also **supported by the evaluation of the success and efficiency of piloted interventions**. The latter might require an input from the development of data management infrastructure. This logical dependency should be further explored in the preliminary evaluation exercise.

The EPMPP project plan should elaborate on the specific activities of EPMPP, **including clinical approach, decision support, information and data management infrastructure, communication and evaluation**. During the pre-study process, the decision was made to select **2 focus areas for piloting**: (a) breast cancer prevention, personalised screenings and counselling, (b) cardiovascular disease (CVD) prevention and treatment (including clinical decision support system (CDSS) supported personalised consultations).

The activities are interconnected, e.g. CDSS implementation can provide input to clinical interventions and overall communication activities, and vice-versa. This dependency supports the use of system development life-cycle (SDLC) or similar approach for evaluation to allow an interactive perspective to the evaluation.

Processes should be described for every broader activity. The evaluation framework should support this exercise. Activities and possible sub-projects of the pilot project are shown in general on the Figure 4.1.3.

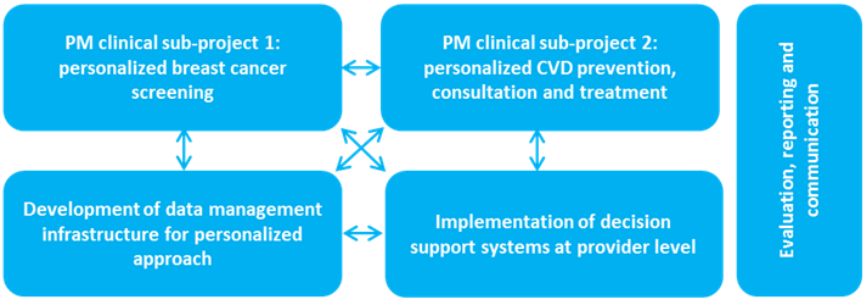


Figure 4.1.3. Activities and sub-projects of EPMPP

Models as an evaluation backbone

The evaluation methodology development strategy takes into account the EPMPP goals as well as stakeholder interviews and map the relevant measures on a simplified result chain. Result chain means describing the service from inputs to outcomes and impact as shown in Figure 4.1.4.

This graphic depiction should give an easy overview of how the impact is achieved – which inputs are transformed and activities used to attain the desired results. A similar approach is provided by the logical framework (logframe – see Figure 4.1.5 below), which is a hierarchical framework that also illustrates moving from activities to the final goal using indicators.

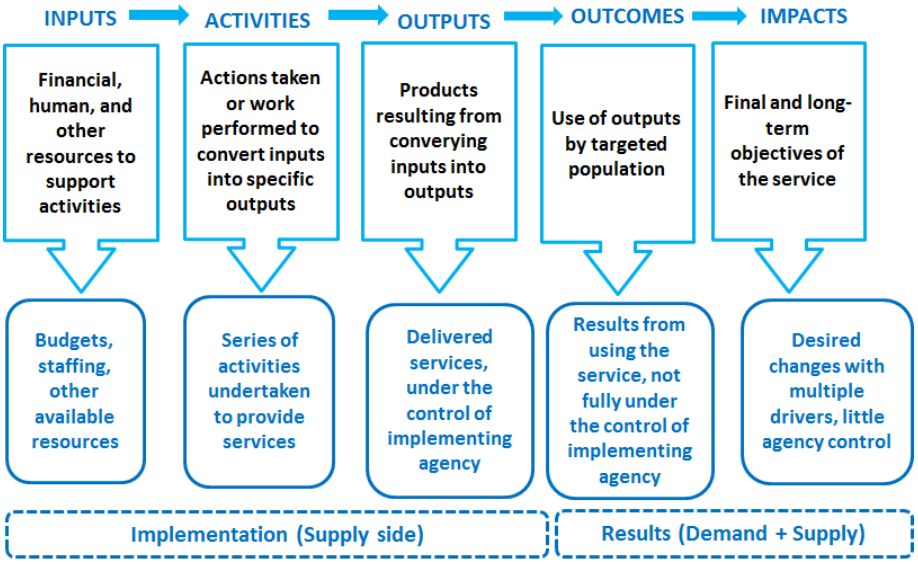
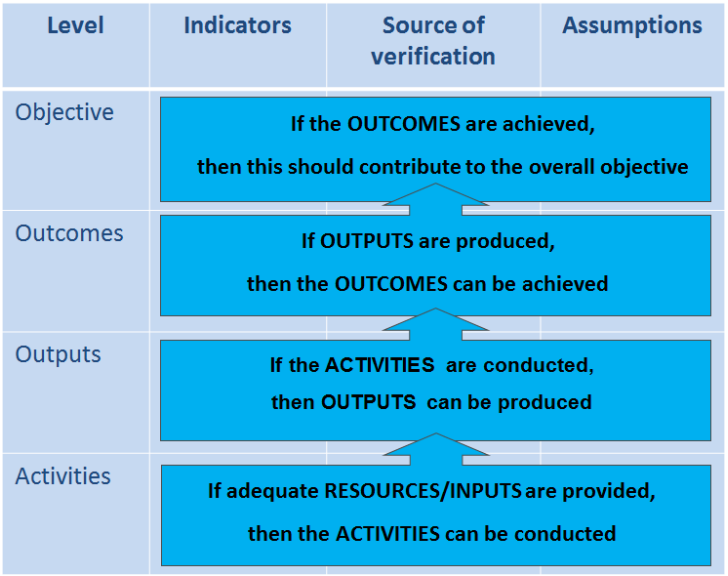


Figure 4.1.4. Result chain[4]

Logframe also demonstrates interdependence – outputs can be achieved only when actions are performed – higher level depends on the lower one. In addition, logframe enables describing the assumptions – what is needed or what conditions should be fulfilled in order to get the desired deliverables.



[4] Paul J. Gertler et al., *Impact Evaluation in Practice*, Pap/Psc edition (Washington, D.C: World Bank Publications, 2010).

Figure 4.1.5. Logframe

Such a performance evaluation approach is actively used in the implementation of health programmes. CHC Evaluation manual provides a similar approach for programme development (see Figure 4.1.6). It goes further with distinguishing outcomes with the possible time-line of producing an effect. This approach useful, as several activities in personalised medicine implementation cannot be reached in a few years, yet might produce results in 10 or more years.

Figure 4.1.6. Basic Program Logic Model by CDC evaluation guideline

Stakeholder interviews as input for evaluation

In order to map measures to each of the steps in the result chain, the initial list of evaluation measures/dimensions should be developed. Important sources for that are the **stakeholders**, whose perceptions in terms of expectations and fears are of high relevance. Thus, the conducted stakeholder interviews that are described in chapter 1 are used.

EPMPP can be **successful** when the expectations of different stakeholders as well as perceived risks and challenges of stakeholders are sufficiently taken into account and/or evaluated. Engagement of stakeholders into the evaluation process is important.[5] Often, operational challenges can be resolved within a particular stakeholder group, whereas poorly aligned stakeholder incentives (differing economic benefits to efficiency incentives) are more complex and more difficult to be resolved[6]

Stakeholder engagement is important to an evaluation because it (a) increases the credibility of the evaluation, (b) helps to implement the **interventions and activities** that are part of the project, (c) developc **advocates for change** to institutionalise the evaluation findings, and (d) supports funding the continuation or expansion of the project. Based on Rieker[7], steps for stakeholder involvement are the following:

1. Identify stakeholders.
2. Create a plan for stakeholder involvement and identify areas for stakeholder input.
3. Engage individual stakeholders or representatives of stakeholder organisations.
4. Target selected stakeholders for regular participation in key steps, including writing the project description, suggesting evaluation questions, choosing evaluation questions and disseminating evaluation results.

In terms of evaluating the EPMPP and taking into account the relevancy of stakeholders (criteria: implementers of PM, important data(base) owners, beneficiaries of EPMPP, financiers of EPMPP during pilot project, evaluators of EPMPP), a list of key-stakeholders can be provided:

- Patients
- Health professionals (clinicians)
- Health care providers (as institutions)

[5] Patricia A Deverka et al., 'Facilitating Comparative Effectiveness Research in Cancer Genomics: Evaluating Stakeholder Perceptions of the Engagement Process', *Journal of Comparative Effectiveness Research* 1, no. 4 (July 2012): 359–70, doi:10.2217/cer.12.36.
[6] Sairamesh Jakka and Michael Rossbach, 'An Economic Perspective on Personalised Medicine', *The HUGO Journal* 7, no. 1 (19 April 2013): 1.
[7] P Rieker, 'Partnership Evaluation Guidebook and Resources' (Centers for Disease Control and Prevention National Center for Chronic Disease Prevention and Health Promotion Division of Nutrition, Physical Activity, and Obesity, 2011).

- Family Doctors (as a critical stakeholder with preventive role, yet high work-load)
- Ministry of Social Affairs
- Estonian Genome Centre
- E-health Foundation
- Information Systems Authority
- Health Insurance Fund
- Universities (research, training and education)
- IT-vendors (IT-development)
- Pharmaceutical and medical technology industry international partners
- Health technology SME-s

The perspectives of stakeholders should be taken into account and specific organisational evaluation questions provided in the evaluation guideline (see chapter X).

The stakeholder interviews conducted during this study showed that there are certain **expectations towards personalised medicine:**[8]

- There will be more knowledge for all stakeholders of health system.
- People will be empowered in taking care of their health risks.
- PM will provide better targeted treatment.
- Higher efficiency of using resources.
- Active use of existing health data.
- Higher cost-efficiency of care.
- Better overview for GPs about patients' health.
- New businesses applying ICT in personalised medicine.
- Higher trust and better relationship in treatment process.
- Development of different new services (including diagnostic services).
- Improvement of treatment standards.

Stakeholder interviews also pointed out **perceived risks regarding PM implementation**:

- The possible lack of commitment.
- Too high expectations.
- Increase in work-load and bureaucracy.
- Other health system problems getting not enough attention.
- Abundance of information.
- Misuse of data.
- No access to relevant data for developing services.
- Rapid increase in demand for health services.
- Growing budgetary pressure for health insurance.
- Reducing affordability of health services.
- Lack of financial and human resources in health sector.
- Over-reliance on state investments (no interest from private sector).

These expectations and risks will be incorporated into the evaluation framework development exercise. As described in chapter 1, the governance structure for EPMPP has to create an organisation and **legal/regulative environment** that will enable and facilitate clinical research and PM services for general population in diagnosing and treatment of diseases as well as for health risk management. The EPMPP governing organisation needs to deal with mitigating the risks related to quality

[8] Expectations from the ongoing country-wide patient and doctor surveys regarding PM should be included in evaluation also.

management, ethics, legal aspects and data protection and sustainability. Therefore, the role of the governing organisation is high.

Initial framework development

Based on the agreed organisational dimensions of EPMPP, stakeholder interviews, expert discussions as well as international literature, the following initial list of aspects to measure in evaluation was produced (Table 4.1.1).

Table 4.1.1. Evaluation dimensions

Dimension	Aspects to measure in evaluation
Stewardship	• Political support • Flexible organisational form (can adjust to changing circumstances and does not duplicate functions of other organisations) • Existing legal framework
Governance and management	• Transparent reporting to the public and stakeholders on progress of EPMPP and organisational outcomes • Capacity to involve stakeholders and well-motivated professionals • Management success – goals of pilot project fulfilled
Implementation efficiency	• Cost-effectiveness • Higher efficiency of using health care resources • Decreasing bureaucracy in new service implementation

Social and health dimension and public acceptance	• Public perception of the PM governance organisation
	• Readiness of public to be involved in personalised medicine initiatives (providing genetic information, sharing patient reported health data etc).
	• Social/health impact measures, e.g:
	  ○ Quality of life of patients
	  ○ Health levels of patients
	  ○ Work-capacity of patients.
	  ○ Patient empowerment.

Stakeholder involvement and partner cooperation	• Stakeholder satisfaction (fulfilment of expectations, empowerment, interest protection) • New (international) stakeholder involvement • Active involvement of stakeholders • Data-sharing contracts • Trainings conducted among stakeholders (incl healthcare workers) • Number of clinics involved in the sub-projects • Collaborative projects among universities/research centers, businesses and health care providers supporting personalised medicine service implementation

Financing and resources	• Contributed public and private capital
	• Capital growth (new companies with investments)
	  ○ Industrial partners
	  ○ Technology SMEs
	  ○ Private investors
	• Sustainable financing model(s) developed in 4 years
	• Sustainable business models for personalised medicine related services/products
	• Regulatory changes supporting new business-model development

Private business involvement	• Number of new service providers interoperable with Estonian health information system (EHIS) • Decreased time from interoperability connection application to fully operational service using/sending data to EHIS • University spin-offs • Private investor contracts and investments
Sustainability	• New research projects and publications validating and/or developing personalised medicine services • Legal framework for new sustainable business models and validated new business models, supporting implementation of personalised medicine services • Private financing sources in health care investments

Quality, ethics and data protection	• Data breaches • Ethical complaints • Sufficient number of quality measures implemented and monitored by relevant stakeholders

These measures were modified, simplified and mapped into the logical model framework (see Figure 4.1.7 below) resulting an initial framework for EPMPP evaluation.

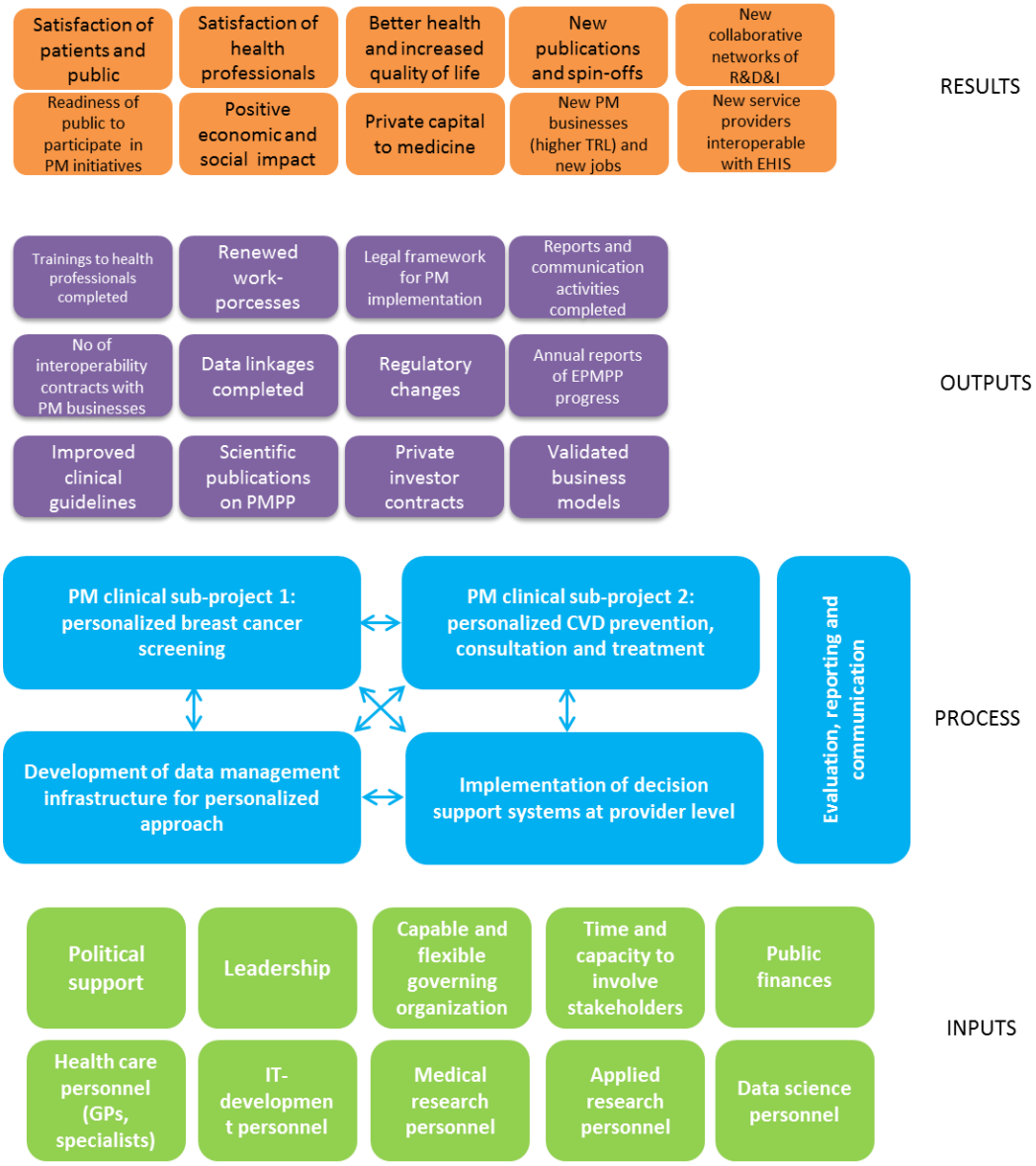


Figure 4.1.7. Initial framework for EPMPP

Revising the initial framework

Although this framework helps to capture the relevant measures for evaluating the EPMPP, it does not provide a good basis for prioritising evaluation tasks. Furthermore, the review and validation exercise proposed several adjustments to the initial evaluation framework. The review tasks

conducted by an international reviewer Dr Noel Carroll from Applied Research for Connected Health (ARCH)[9] stressed the importance of defining the goals of EPMPP more clearly, also the goals of EPMPP sub-projects.

Thus, the evaluation framework should be developed further to enable evaluation of the implementation process of EPMPP and provide evaluation questions for the evaluators. An operationalised evaluation process that includes key metrics measured throughout the various service development lifecycle stages (SDLC) should be developed – this is especially important for large HIS infrastructure projects – meaning the data management infrastructure development.

ARCH proposed an additional concept for the framework (see Figure 4.1.8), which would capture the different system development stages as well as derive from the value expectations of PM.

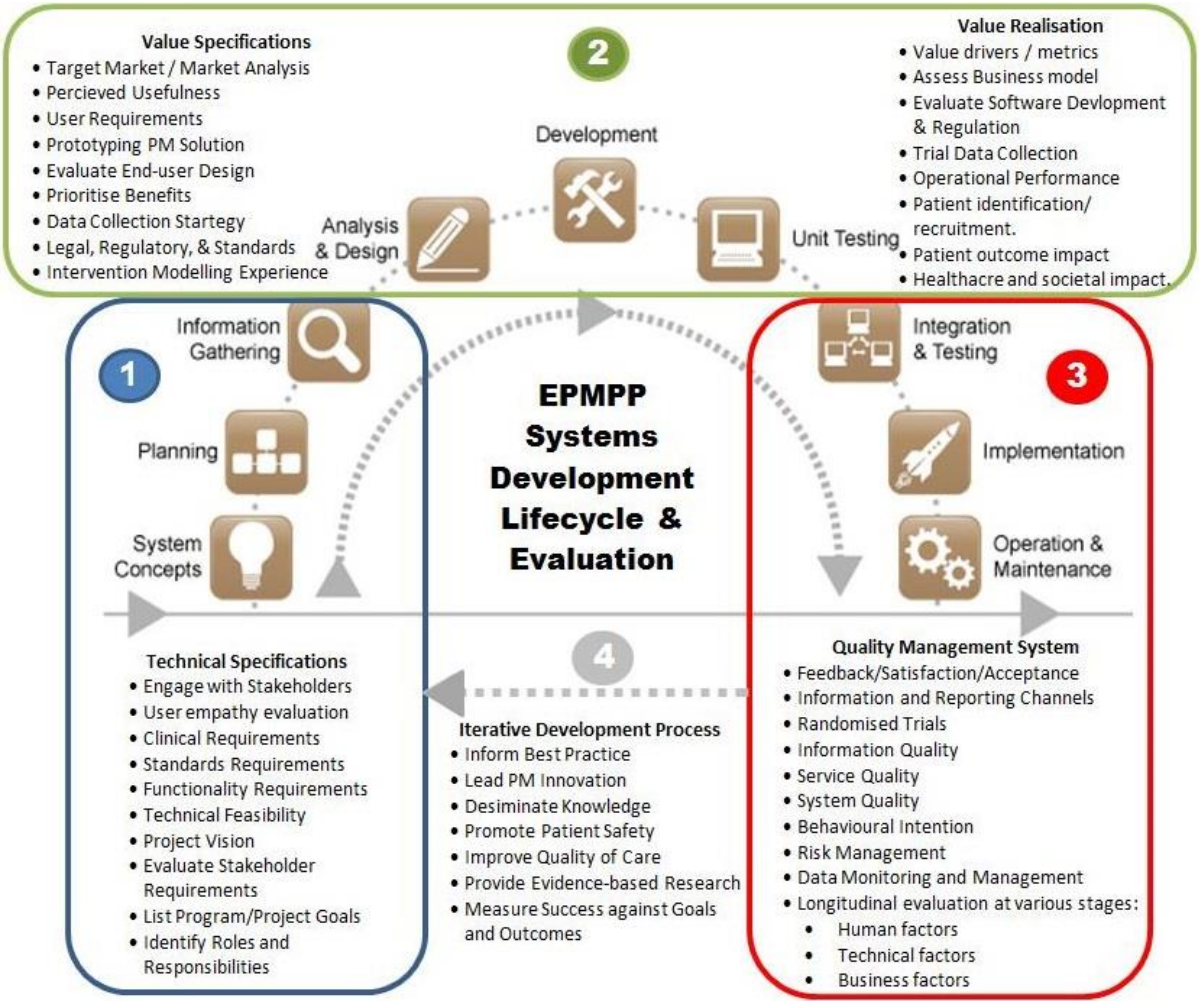


Figure 4.1.8. EPMPP systems development lifecycle and evaluation, by Dr Noel Carroll

The international reviewer report by ARCH stressed that there is a lack of longitudinal analysis to support the use of any particular evaluation framework in personalised medicine. Therefore, from an evaluation perspective, there is a clear need to adopt an iterative development within the project, i.e. breaking down the EPMPP development into smaller development pieces (or specific processes) while undergoing continuous development-testing-evaluation cycles.

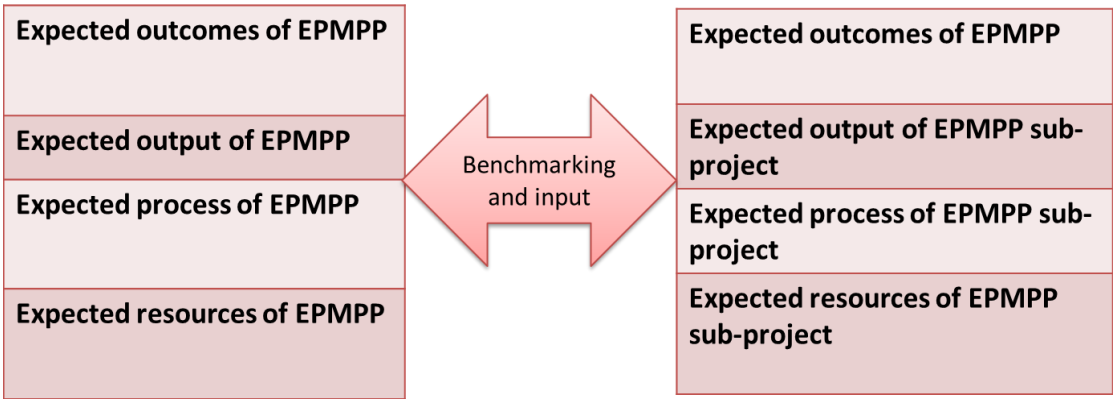
[9] A seperate review report was provided to the research team by Dr Noel Carroll (Ireland).

An SDLC approach would enable to undertake a capability maturity assessment of the current system, Estonian healthcare system's readiness to adopt EPMPP, examine various stakeholder analyses for each phase and identify specific metrics to report the value of the EPMPP. Adopting this methodology would enable the research team to tighten the focus of the project and focus on how it can improve **a specific element of health care system**, rather than the broad sweeping approach it currently adopts. Through various improvements in health care services, the EPMPP can develop through a **'lessons learned' approach** and grow through their evidence-based research using **iterative development**.

Aligning the evaluation of EPMPP and sub-projects

The feedback clearly demonstrated the **need for defining specifically the final goals and activities: sub-projects and their specific processes of EPMPP implementation**, while also taking into account scientific evaluation literature regarding those specific interventions, e.g country-wide HIS evaluation, specific CDSS evaluation, personalised medicine intervention evaluation (e.g personalising screenings, personalised counselling, genetic screening etc)[10] and accounting for the health policy goals of the Estonian health system.

In order to evaluate the EPMPP, the EPMPP sub-projects should comply with the overall project in terms of inputs, activities, outputs, outcomes and impact (contributing to each of the dimensions). For achieving that, a simple benchmarking exercise should be completed, where the **activities of suitable clinical intervention study mapped in a flow-diagram**, then the possible resource need evaluated and output and impact measures drafted.



Questions to be asked:

- *What are the specific processes of the subproject(s)?*
- *What resources are needed for implementing these processes?*
- *Are the resources available in the overall resource pool of EPMPP?*
- *Will the processes help to achieve the final goals of EPMPP?*
- *What are the outcome measures of the sub-project?*
- *Do the output and outcome measures of the sub-project coincide with or provide input to the overall project output and outcome measures?*
- *What output and outcome measures of EPMPP have not been covered as part of he sub-projects?*
- *Should the sub-project be adjusted in order to reach such goals?*

Figure 4.1.9. Aligning the measures of sub-projects and overall EPMPP

[10] Due to the ambiguous nature of the project details the specific selection of methods cannot be provided at this stage, but a through literature research can provide input for selecting the suitable methods (see chapter 3.3 for relevant input).

Next steps in evaluation of EPMPP

The phases of clinical sub-projects should contribute to defining the service and the specific objectives of the evaluation (the objectives of the evaluation should be derived from the overall goals of the EPMPP). The results of the sub-project evaluation can be an input for a second phase of the sub-project or for another sub-project (e.g input for public communication for fostering PM implementation and creating an ecosystem in Estonia as a whole). Help can be provided by a graphic depiction of the relevant phases of conducting a simple evaluation (see Figure 4.1.10).

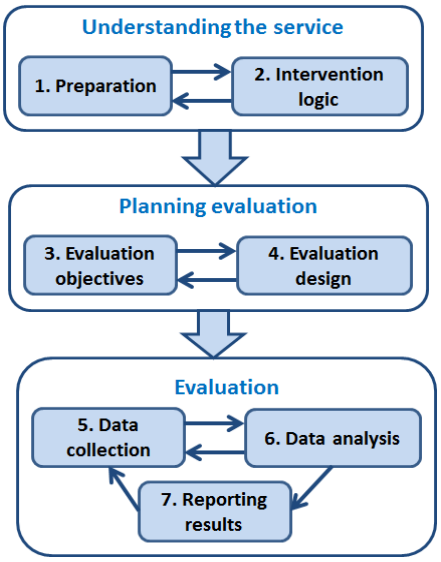


Figure 4.1.10. *Phases of evaluation*[11]

In order to synchronise the processes of different activities, an addition to the framework could be borrowed from Pulley et al[12] (2012), who described a personalised medicine project on operational implementation of prospective genotyping linked to advance CDSSs. Their approach shares some similarities with EPMPP, albeit at on a smaller scale. They used electronic medical record (EMR) and point-of-care decision support, which provided a first step towards implementing an evaluation strategy for personalised medicine. Their work highlights how health technology evaluation is a multidisciplinary process.
This framework (see Figure 4.1.11) provides and example of relevant dimensions of interdisciplinary personalised medicine implementation and evaluation.

[11] http://meera.snre.umich.edu/planning-and-implementing-ee-evaluation

[12] J. M. Pulley et al., 'Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project', *Clinical Pharmacology and Therapeutics* 92, no. 1 (July 2012): 87–95.

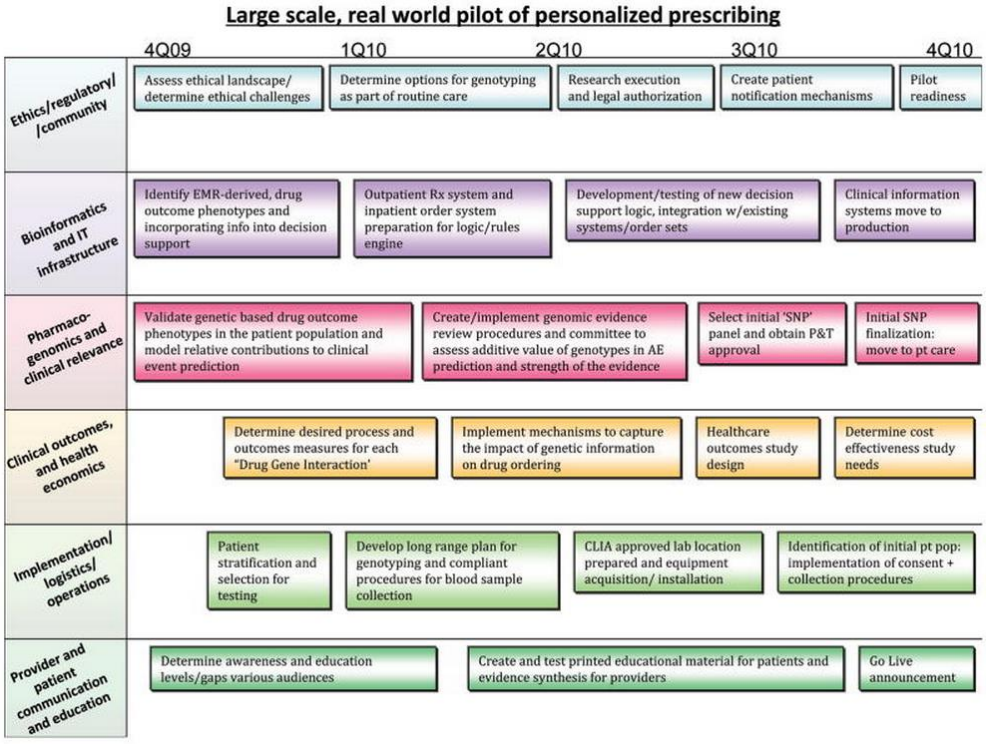


Figure 4.1.11. A framework for evaluating a personalised medicine pilot[13]

The framework by Pulley et al[12] suit the criteria set for EPMPP evaluation methodology and the recommendation by ARCH. Thus, similar approach can be taken in order to support the overall EPMPP evaluation.

On the other hand, the issue of aligning the EPMPP goals to the overall health system goals needs to be addressed. These are the main aspects that should be considered when evaluating the overall projects as well as when benchmarking the sub-project activities to the overall project (see Figure 4.1.12).

Figure 4.1.12. Evaluating the goals of EPMPP and sub-projects of EPMPP

[13] Pulley, J. M., Denny, J. C., Peterson, J. F., Bernard, G. R., Vnencak-Jones, C. L., Ramirez, A. H., ... & Roden, D. M. (2012). Operational implementation of prospective genotyping for personalised medicine: the design of the Vanderbilt PREDICT project. Clinical Pharmacology & Therapeutics, 92(1), 87-95.

The strategic goals of Estonian health system as well as R&D and economic development plans should be benchmarked to the goals of the EPMPP. The aim of PM is stated as to contribute towards preventive, predictive and participatory health system, yet the general health system goals of increasing quality, accessibility and cost-efficiency of care (stated in the Research, Development and Innovation Strategy for the Estonian Health Care System) should not be forgotten and preferably connected to the goals of EPMPP during the intervention logic development exercise. This should be supported by the thorough consideration of other dimensions such as relevance, efficiency, cost-effectiveness, sustainability, utility, equity, flexibility, institutional constraints, acceptance and quality. The supporting questions will be provided below, which should be answered when drafting the project plan for EPMPP. These questions will be used for developing the initial intervention logic of the project also.

Relevance

- Do the goals of EPMPP coincide with the overall strategic goals of the Estonian health system, R&D policy, economic policy and e-governance development plans?
- Are the goals understandable to all the stakeholders?
- Will the structure of EPMPP help to overcome barriers of implementing personalised approach in Estonian health care delivery?
- Will the EPMPP contribute towards preventive, predictive and participatory health system in Estonia?
- Would the same results be expected to emerge without the implementation of the EPMPP?

Effectiveness

- What are the main barriers for implementing EPMPP?
- What are the main motivators for implementing EPMPP?
- Ex post: has the EPMPP produced the expected effects in short term, medium term and long term?
- Ex post: to what extent have the objectives of EPMPP been achieved?

Efficiency

- Could better effects be obtained at the same cost?
- Ex post: Was the intervention cost-effective?

Sustainability

- To what extent will the results of the EPMPP be persistent?
- Can the results be maintained without public funding?
- Can the health system continue systematic PM implementation without EPMPP initiatives (after the EPMPP is over)?

Utility

- What are the possible unitented effects of EPMPP?
- Are the possible unintended effects acceptable from the point of view of direct or indirect beneficiaries?

Equity

- Who are the winners and losers of the EPMPP initiative?
- Does the intervention increase/decrease inequity regarding access to health care resources by patients, providers?
- Does the intervention increase/decrease inequity in terms of region, gender, age, income or other characteristics?

Flexibility

- How easy is the adjustment to the changed policy environment?
- Can the intervention produce results in changed environment?

Institutional constraints

- Does the EPMPP option fit the current law?
- What will be the necessary legal changes in order to implement EPMPP?
- Will there be sufficient administrative capabilities in the Ministry for conducting the legal changes?

- How much time will the necessary legal changes need for implementation?

Acceptance

- Do the stakeholders (people, entrepreneurs, government) accept the policy?
- Is there a steady measurement system developed for evaluating the acceptance of the policy?
- Do the stakeholders understand the EPMPP and its possible effect?
- Is there a plan for informing and surveying the stakeholders of the initiative?
- Are there sufficient capabilities and resources for conducting communication activities regarding the EPMPP?

Quality

- Does the EPMPP comply with quality management standards, e.g ISO9000:2005 quality management system?
- Is there a process for mitigating the development of relevant quality management indicators for sub-projects?

Patients and doctors – the frontline of personalised medicine

Patients are one of the **most important target groups expected to benefit from EPMPP**. They are also the payers for health services through a social-insurance health system and users of health services. Patients should be involved in testing the user-experience of the systems in several stages. Patients' perspectives have also been evaluated in broad terms (ongoing survey initiated by MoSA), but it is important to involve patients into the clinical sub-project studies as well.

The following questions are important in terms of patient involvement:

- What is the general perception of personalised medicine by the population?
- What is the readiness to participate in the implementation of personalised medicine?
- What will be the role of the patient organisations in the EPMPP?
- How will the patients benefit from the pilot project?
- How many patients will be involved in the pilot project and in each sub-project?
- Are the risks regarding patient health, data protection and ethics sufficiently managed?
- How will the patients be involved in the governance of the EPMPP?

Doctors and health care providers are **both implementers but also benefactors** of the EPMPP outputs, they serve also as the disseminators of the results of EPMPP success. Their perspective should be evaluated in case of every sub-project of EPMPP. The abundance of roles doctors have in the context of EPMPP is shown below (see Figure 4.1.13)

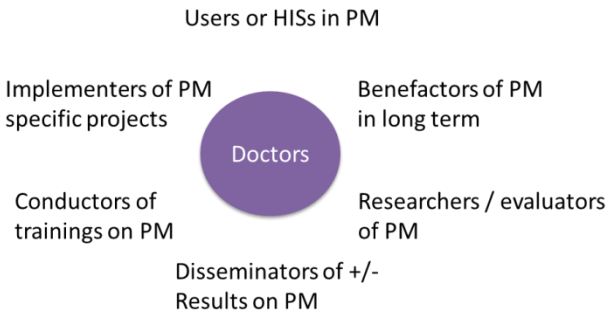


Figure 4.1.13. Roles of doctors in connection to PM implementation

Thus, several activities regarding the evaluation of EPMPP are done with close involvement of practicing doctors. Doctors will be key stakeholders in implementing personalised medicine clinical sub-projects.

As the focus of PM is on preventive medicine, then the **general practitioners** should also have an active role in the evaluation process (as feedback providers to other counterparts, but also as implementers, researchers, and disseminators of results to colleagues etc). As the time-management of GPs is of utmost importance and there is constant time-pressure on GPs, it is important that the evaluation puts sufficient focus on aspects regarding time and work-processes.

Several studies have observed the effect of HISs on time-usage and work patterns of professionals.[14][15][16] For example Murray et al measured the effect of computer-based outpatient prescription writing on pharmacist work patterns by using multidimensional work sampling method, seeking to find out the **percentage of time spent on different activities**, reasons for each activity ('function'), and people contacted. Recording these activities made it possible to describe pharmacists' work patterns **before and after** the implementation of computer-based outpatient prescription writing. Also an RCT with similar aims has been conducted to study the impact of CPOE implementation in primary care internal medicine practices using time-motion measurement technique[17]. Similar time and work-process measurement techniques could be used in the current evaluation process also, when implementing CDSS for GPs and other doctors.

The following questions are important in terms of doctor's involvement:

- What is the general perception of personalised medicine by doctors?
- What is the readiness to participate in the implementation of personalised medicine?
- What will be the role of the doctor organisations in the EPMPP?
- How will the doctors benefit from the pilot project?
- How many doctors will be involved in the pilot project and in each sub-project?
- How will the doctor's time be managed?
- How much training for doctors will be needed for initiating EPMPP?
- How will be the doctors involved in the governance of the EPMPP?
- How will the doctors be involved in HIS development?
- How much time will be needed for providing feedback for HIS deployment?
- How will the EPMPP impact the work-practices and work-processes of doctors?
- How will the doctors be involved in the evaluation and research of PM?

There are many other institutions whose perspective should be evaluated with regard to the EPMPP. These include institutions with relevant registries and databases, which will be integrated into the Estonian Health Information System combining phenome and genome data, but also institutions, which are responsible for funding of the project itself and the health system in general. With this regard, relevant evaluation questions include:

- How to take personalised medicine into account in the reimbursement procedures?
- What is the impact of EPMPP to HTA procedures – how will it affect HTA processes?
- How will EPMPP impact the publicly funded health system in terms of future demand for health services?
- What are the financing barriers for the new health technologies emerging from PM?
- Are the reimbursement systems relevant with regard to PM services?

[14] Murray, M.D., Loos, B., Tu, W., Eckert, G.J., Zhou, X.H., Tierney, W.M. (1998). Effects of computer-based prescribing on pharmacist work patterns. – *Journal of America Medical Informatics Association*, 5(6), 546-553. [WWW] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC61334/

[15] Overhage, J.M., Perkins, S., Tierney, W.M., McDonald, C.J. (2001). Controlled Trial of Direct Physician Order Entry Effects on Physicians' Time Utilization in Ambulatory Primary Care Internal Medicine Practices. – *Journal of American Medical Informatics Association*, 8 (4), 361-371. [WWW] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC130081/

[16] Stone, W.M., Smith, B.E., Shaft, J.D., Nelson, R.D., Money, S.R. (2009). Impact of a computerized physician order-entry system. – *American College of Surgeons*, 208(5), 960-967. [WWW] http://www.surgicalpatientsafety.facs.org/educate/stone0509.pdf

[17] For example time for activities such as 'calling to a patient' or 'writing an order' or looking a reference for a drug on computer was recorded.

These questions are used in drafting the intervention logic and the evaluation framework, but should be also given attention in the project plan writing phase. As the goals and overall evaluation approach have been presented above, the framework development process needs the description of intervention logic of the overall project followed by selecting the key evaluation measures and providing the framework for evaluation.

Figure 4.1.14. Phases of EPMPP evaluation framework development

The initial **intervention logic of EPMPP** will be presented in chapter 4.3 with the recommended evaluation methodology. The following chapter, though, will present the previous evaluation experience of relevant activities for EPMPP – the health information system evaluations, health technology evaluations, as well as broad R&D and economic policy evaluations.

4.2 Estonian evaluation experience and responsible organisations as input for EPMPP evaluation

HIS evaluation practices still low

Regarding the vast number of HIS projects, the evaluation experience in Estonia is rather low. An ex-ante evaluation of the **Estonian Health Information System (EHIS)** has been conducted by using PENG method and an evaluation framework for evaluating **Estonian Electronic Prescribing System** (EPS) has been developed ex-post.

There is lack of systematic evaluation in terms of broad HIS implementation activities in Estonia. For example, the developed EHIS evaluation method has not been adopted by the relevant institutions as a common practice. Even the most successful country-wide e-health implementation project, the Electronic Prescribing System, has not been sufficiently evaluated – there have been no key metrics set for EPS evaluation and no ex-ante evaluation was conducted – the actual impact of EPS has only been evaluated in terms of reduced costs for public administration, but insufficiently for user-experience, quality and time-usage.[18]

Health technology assessment gaining momentum

Until recently Estonia had also no systematic programme for health technology assessment (HTA)[19], but starting from 2011 considerable progress has been made in creating formal procedures for HTA and developing capacity in this field to support evidence-based decision-making in health care and public health.[20] The Centre for Health Technology Assessment was established in 2012 as part of the Department of Public Health at the **University of Tartu**. By May 2015 the center is expected to deliver 20 reports, those including also assessments of cancer screening programmes (in breast cancer, colorectal cancer)[21]. This experience is of high relevance in terms of implementing personalised screenings for cancer.

The topics of HTA reports are set by the Council of HTA, which coordinates the activities of the HTA Centre. The HTA Council includes representatives from the Estonian Health Insurance Fund, Ministry of Social Affairs, Estonian Hospitals Association, Union of General Practitioners, State Agency of

[18] http://www.ncbi.nlm.nih.gov/pubmed/25115948
[19] **Health Technology Assessment (HTA)** is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.
[20] www.arth.ut/tth
[21] http://rahvatervis.ut.ee/bitstream/1/5683/4/TTH05_mammograafia_veebruar2014.pdf

Medicines, Tallinn University of Technology, and University of Tartu. Health technologies are taken under evaluation, in case[22]:

- They are expected to have considerable beneficial effect on public health.
- Will use considerable resources from the health insurance and state budgets.
- There are controversial opinions about the clinical efficacy and cost-effectiveness.
- The extent of use and target groups in Estonia is not known.

Research questions to be addressed and answered in the report are described in the respective work description and verified by the HTA Council. The report is compiled by a team of 2 to 3 analysts together with 2 to 3 clinical experts. To start with, literature reviews on **medical efficacy and safety** as well as **cost-effectiveness** are compiled, and graduate and medical students are involved in this process. The **disease burden**, **treatment practices** and **costs** arising in Estonia are evaluated on the basis of epidemiological data and use of health care services. Specific models are constructed to evaluate the cost-effectiveness and **budget impact analyses** are conducted. The assessment team formulates conclusions of the HTA report and suggestions on organisational aspects, as applicable. Occasionally public consultations with interested parties (specialist medical societies and manufacturers) are carried out to discuss and **verify the methodology of the HTA report** and the conclusions drawn by the assessment team. The final report is submitted for review and approval by the HTA Council to ensure the quality of the report and the validity of the assessment process. The reports approved are published on the website of the HTA Centre and disseminated to all major health institutions and specialist medical societies in Estonia.

The HTA programme at University of Tartu is a **good organisational model** and basis for systematic evaluation of different personalised clinical interventions – the programme has necessary experience in conducting HTAs as well as active partnerships with relevant institutions. This is especially important in evaluating services, which have a rather traditional business model in the health care sector, yet the use of genetic and other data creates the need for especially evaluating the cost-effectiveness of the new service in Estonian context.[23]

Other institutions active in research and evaluation

Tallinn University of Technology (TUT) eHealth lab and Healthcare technology curriculum are leading the evaluation competence development in **e-health and HIS evaluation** – a number of articles have been published by the members of the lab and the Institute of Cardiovascular Medicine at TUT. The curriculum creates specialist with skills of **e-health innovation diffusion in health care organisations** – a competence needed in driving the change in e-health development and work-processes of healthcare organisations.

Estonian Genome Center of the University of Tartu (EGCUT) is a research institute at the University of Tartu that aims to promote the development of human genetic research, and to collect information on health issues and genetics of the Estonian population. EGCUT has considerable experience in personalised medicine, especially with regard to specific genetic research.

Praxis Centre for Policy studies has analysed the current practices of pharmaceutical health technology assessment procedures (Kruus, Sikkut, Aaviksoo 2012)[24] aspects regarding telemedicine

[22] **Health Technology Assessment (HTA)** is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.

[23] For example in case of personalized cancer screenings the programme process in terms of overal rollout of the screening stays the same, but the personalization of targe-group can have impact on the cost of the programme as well as behaviour.

[24] http://www.praxis.ee/tood/uute-ravimite-soodusnimekirja-lisamise-protsess-ravimi-ja-tervishoiupoliitika-kontekstis/

evaluation in Estonia (Kruus et al 2014)[25]. Praxis has also led the evaluation methodology development practices for e-government services and conducted numerous independent evaluations of screening programmes procured by the Estonian Health Insurance Fund (including projects such as osteoporosis, prevention of hereditary diseases, new-borns screening for phenylketonuria and hypothyroidism, new-born hearing screening, breast cancer, cervical cancer, reproductive health of young people).[26]

This was a preliminary list focusing on HTA, PM and HIS evaluation expertise, yet specific evaluation capabilities regarding medical research, big-data analysis, public health research can be found in other competent insitutions in Estonia, including **Medical Faculty of Universtiy of Tartu, Estonian Institute for Health Development**, also research centres and other health care insitutions, including the **Tartu University Hospital, North-Estonian Regional Hospital, East-Tallinn Central Hospital.**

Health R&D and innovation policy evaluation

As the project seeks to aim at the country's health policy, economic as well as R&D goals, it is important to acknowledge the previous evaluations regarding R&D and economic policy connected to the subject. The **Estonian State Audit Office** has evaluated[27] the Estonian R&D programmes and provided several critical conclusions, which should be kept in mind in case of EPMPP implementation:

1) Estonia has not been able to adjust RnD activities to the needs of Estonian society,
2) too broad R&D policy priorities are not feasible for Estonia,
3) R&D financial benefits and grants are not targeted enough for achieving the necessary goals.

The audit conducted by the State Audit office focuses on broader programmes and does not evaluate the specifics of different programmes. Nevertheless, during the process of **Estonian Health System R&D and Innovation Strategy** development, an evaluation of the Estonian Health Programme (specific sub-programme of Estonian R&D policy) was conducted. The evaluation of the intervention logic of that programme confirmed the 2nd and 3rd conclusion by the State Audit Office – in short, the priority activities were not sufficiently connected to the final goals and outcome measures of the programme (see Figure 4.2.1 below). The programme intervention logic lacked specific outcome measures to evaluate the success of different activities of the programme to public health or healty work and living environment. The more specific outcome measures were mostly focused on research outcomes (publications, PhD degrees, specialities covered with high level specialists) and very broad economic outcomes (rise in RnD investments by private sector and rise of the proportion of private investments in health care RnD).

No indicators were provided for evaluating the goals of innovative medicine technology development, also it was unclear how the results of different research and technology development will be transferred to services and products and how will they be funded and how will they result in better population health and economic goals. These specific conclusions should be kept in mind when developing the intervention logic for the Estonian Personalised Medicine Pilot Project.

[25] http://www.praxis.ee/tood/telemeditsiini-laialdasem-rakendamine-eestis/

[26] The evaluation process included the collection of materials about the best international practices for screenings, analyses of project documentation, project team interviews and evaluation of the project performance indicators. Furthermore, assessments of the satisfaction of target groups (surveys were conducted by the project managers) and the project's economic feasibility were carried out. The project evaluations considered the following criteria: planning of the project realisation, following and achievement of the objectives and performance indicators, satisfaction of the target group with the services, compliance of project activities with the expectations and preferences of the target group, engagement of different parties and movement of information, quality of the project management and sustainability of the project.

[27] 7.03.2012 auditiaruanne „Riigi tegevus teadus- ja arendustegevuse võtmevaldkondade edendamisel"

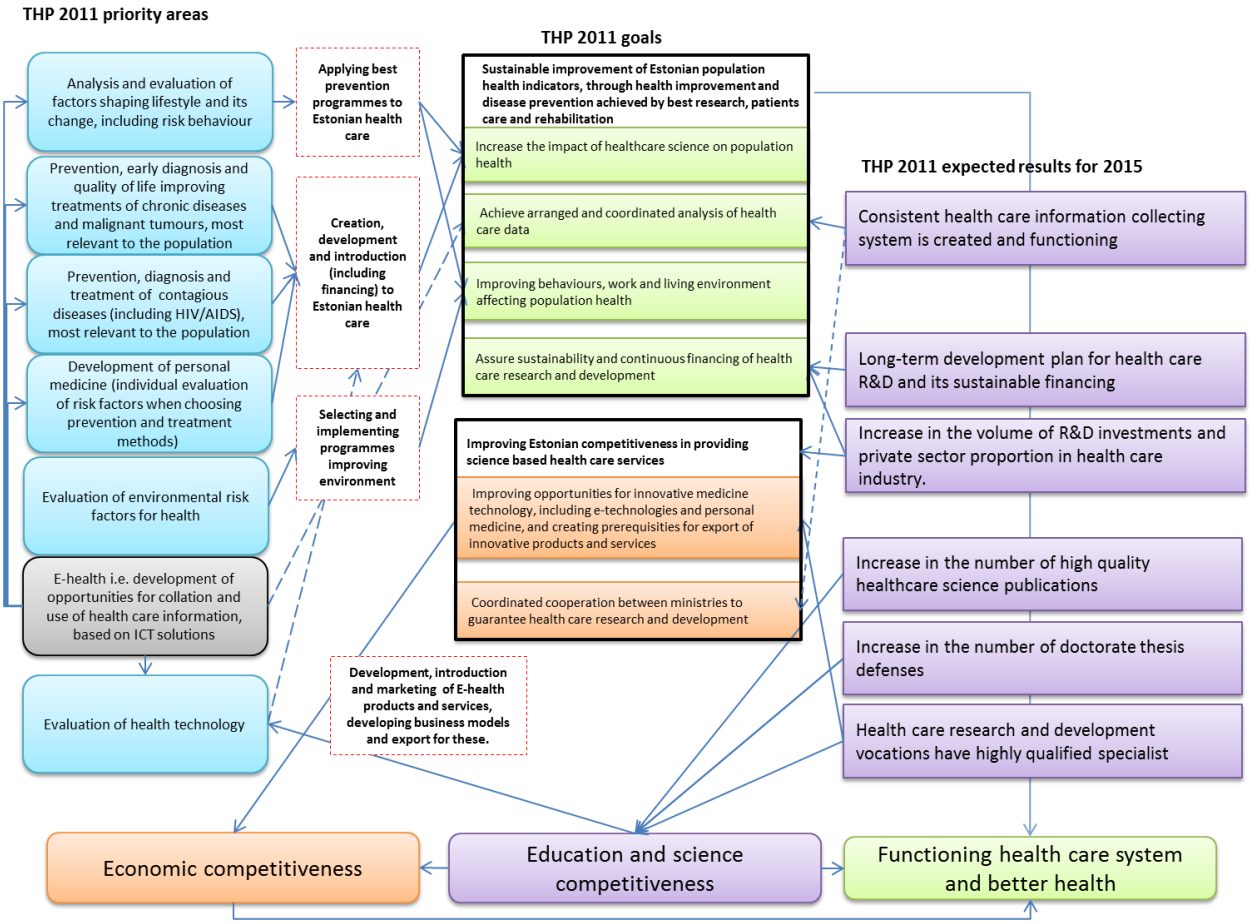


Figure 4.2.1 Estonian Health Programme intervention logic

Evaluation framework for innovation and enterprise support policies[28] (to the Ministry of Social Affairs of Estonia) could be helpful in defining the specific measures for evaluating the R&D and economic goals of the policy (currently lacking focus from the perspective of health system development). The report compiles different economic indicators to be used for evaluating the economic and innovation policy goals, including export indicators, employment in high tech sector, % of innovative enterprises, no of researchers, number of ISI/WoS publications etc.

[28] https://www.mkm.ee/sites/default/files/inno_17_24_11_2011.pdf

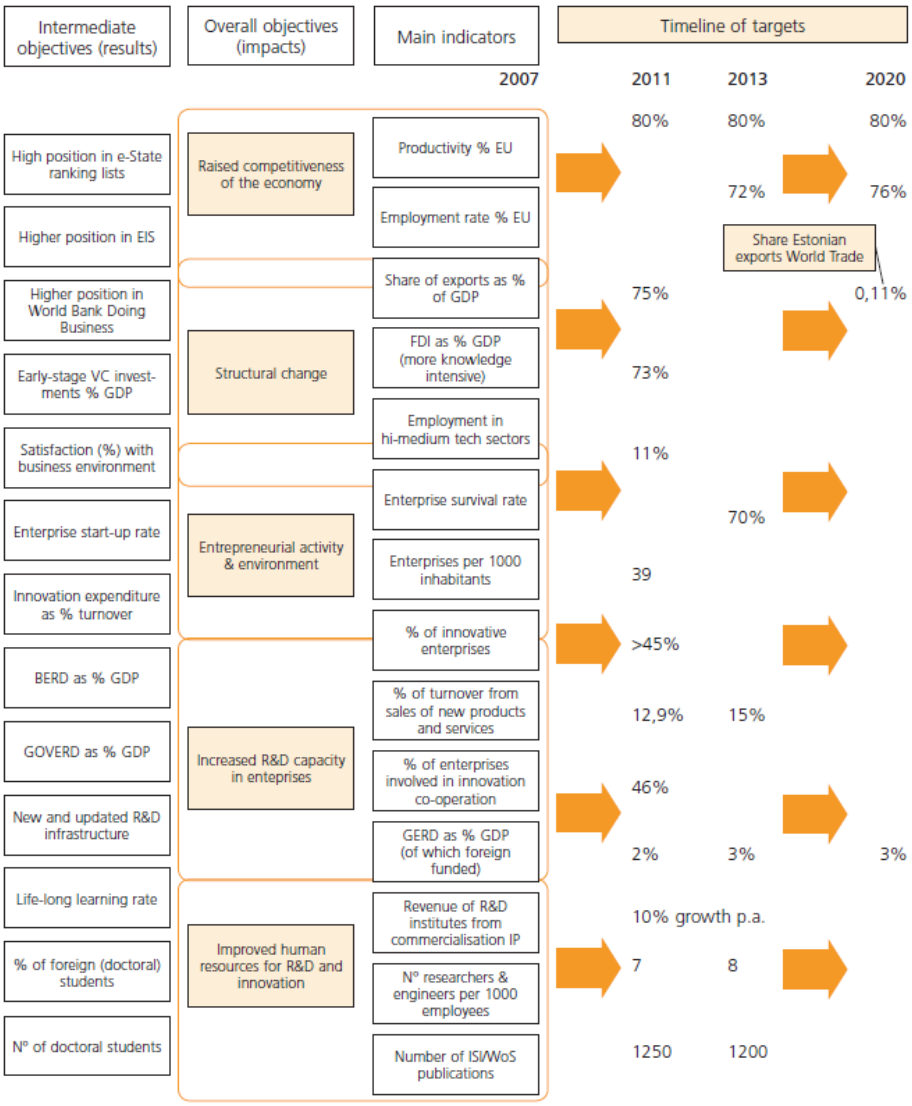


Figure 4.2.2. Evaluation framework for innovation and enterprise support policies[29]

The report also concluded that the current monitoring system provides a basis for evaluation at micro and meso levels but requires further refinement to appraise systemic impact and the focus should be first on assessing the intervention rationale in the overall policy. This is also specifically important in designing the evaluation methodology for the EPMPP.

Based on the indicator list provided for evaluating innovation and economic benefits and the problems, which arose from the Estonian Health Programme, a list of specific measures for evaluating the R&D and business results of the EPMPP can be provided with relevant target measures:

1. Number of high level publications on personalised medicine implementation.
2. Number of doctoral degrees in personalised medicine related fields.
3. Number of master's degrees in personalised medicine related fields.
4. Number of university spin-offs developing products/services in health technology and personalised medicine.

[29] *Evaluation framework for innovation and enterprise support policies (Männik et al 2011)*

5. Number of health technology and personalised medicine companies with new products/services with technology readiness level[30] of 6 and above (can be university spin-offs).
6. Proportion of health technology and personalised medicine companies with new products/services with technology readiness level of 6 and above of the overall number of health technology and personalised medicine companies with new products/services.
7. Number of health technology and personalised medicine start-ups with new products/services with technology readiness level of 6 and above (can be university spin-offs).
8. Proportion of health technology and personalised medicine start-ups with new products/services with technology readiness level of 6 and above of the overall number of health technology and personalised medicine start-ups with new products/services.
9. Number of health technology and personalised medicine start-ups with new products/services with technology readiness level of 6 and above (can be university spin-offs) with foreign owners (more than 50% of shares).
10. Foreign private capital invested in health technology and personalised medicine companies.
11. Local private capital invested in health technology and personalised medicine companies.
12. Proportion of private R&D investments of total R&D investments in health technology and personalised medicine.
13. R&D investments and implementations in personalised medicine in public hospitals.

To sum, it is important to implement the previous best practices of evaluating health technologies, health programmes, R&D and economic policies. Specific personalised health services evaluation should also be aligned with existing evaluation practices (HTA in Tartu University, E-health evaluation and healthcare technology innovation diffusion at TUT, genetic research at ECGUT) and the latter adjusted for personalised approach. A list of indicators can be derived from previous programme evaluations regarding healthcare technology R&D and innovation.

4.3 Recommended evaluation methodology to be used for evaluating the personalised medicine pilot project

An essential precondition for evaluation is defining the specific goals of EPMPP and describing the intervention logic of EPMPP in the context of Estonian health system. Without understanding the intervention logic is it complicated to evaluate the EPMPP. The general intervention logic is described in the Figure 4.3.1 below. It connects systematically the overall health system goals, economic and R&D goals and the EPMPP goals, as well as acknowledges the overall aims of personalised medicine and the sub-projects of the EPMPP.

The intervention logic follows the idea that developing an ecosystem of research, development and innovation to support the transfer of knowledge about personalised medicine to universities and companies has several preconditions: development of data management infrastructure and input from clinical sub-projects with regard to the feasibility and cost-effectiveness of personalised medicine implementation, also changes to regulatory and personnel policies in health care.

The outputs of the clinical sub-studies should serve as an input to the further development of data management infrastructure and central decision support system as well as for regulatory and legal framework changes supporting the implementation of personalised medicine. This supports the use of iterative approach of the HIS development activities of the EPMPP.

[30] TRL 6 – technology demonstrated in industrially relevant environment (http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf)

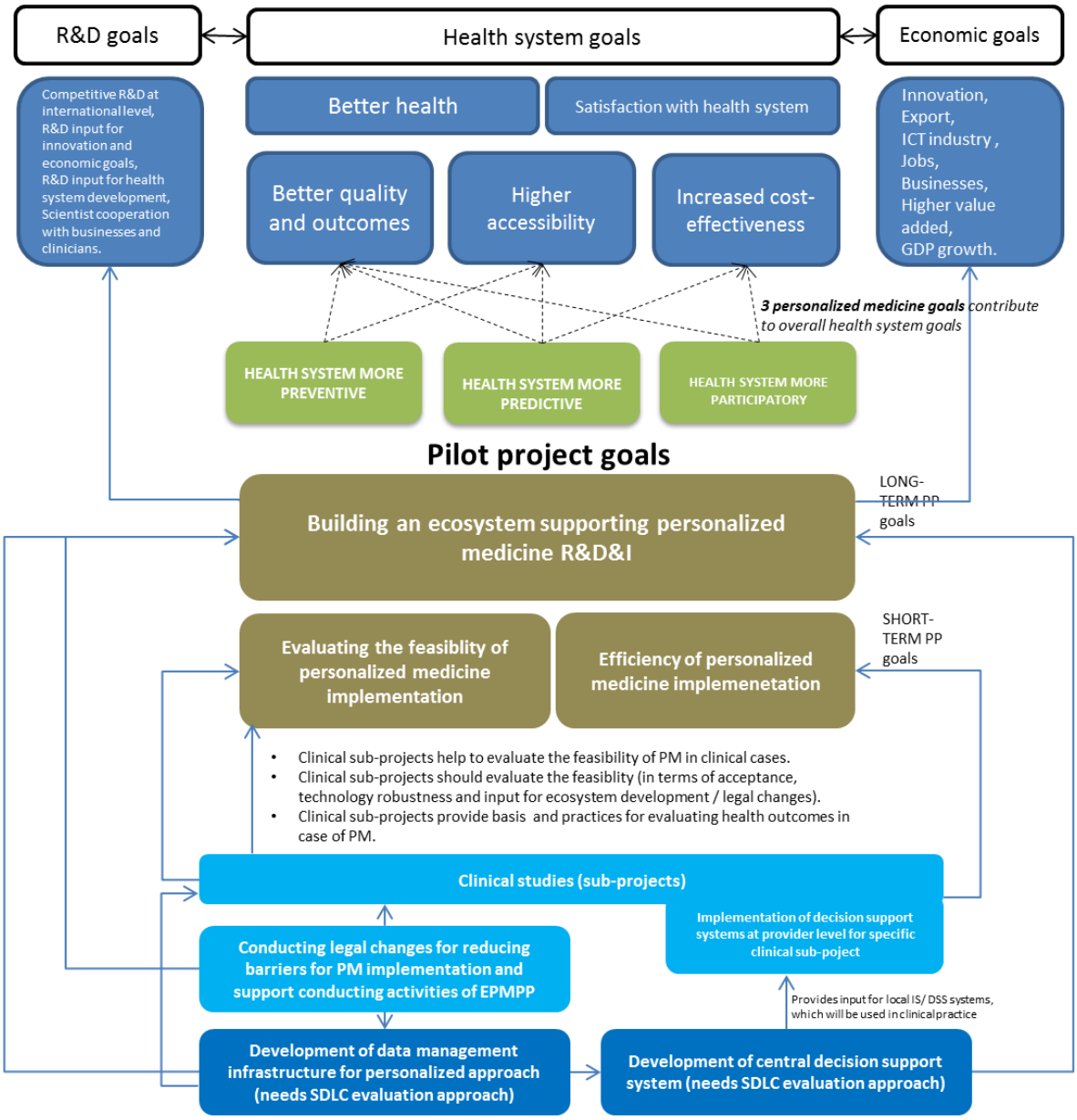


Figure 4.3.1. Initial intervention logic of EPMPP

This figure captures the goals and connects the final goals of EPMPP to the sub-projects of the EPMPP and overall goals of the Estonian health system. The following Figure 4.3.2 sums the necessary outcome and output measures for achieving the long-term goal of EPMPP.

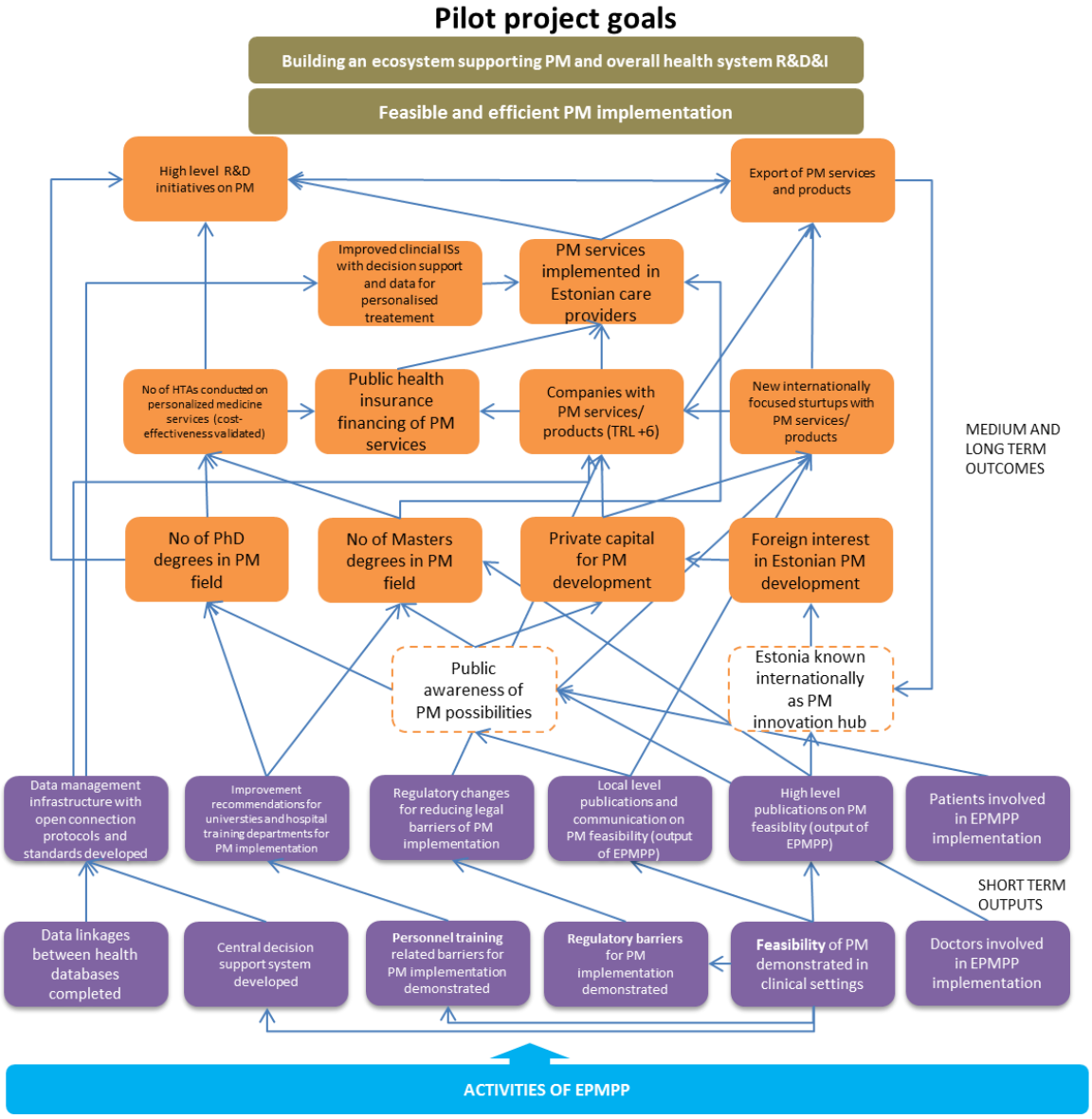


Figure 4.3.2. Outputs and outcomes of EPMPP for achieving the goals of EPMPP

This evaluation framework shows the importance of sub-projects in developing local and international awareness of EPMPP as well as providing an input to the personnel and regulatory policy changes. It also shows the relevance of transferring knowledge of EPMPP activities to everyday practice of the healthcare system – lessons learned (barriers detected) from smaller sub-projects for the overall health care system.

The specific process and measures of evaluation for the framework will be provided in the following chapter on guidance for evaluation. The following chapter also presents the governance organisation and aspects regarding the applicability (roles, data sources) of the selected framework.

4.4 Guidance for evaluation process – evaluation questions, stakeholder roles and recommendations

This chapter will present the outcome and output measures of the evaluation framework in a detailed manner with comments on relevance, targets and responsible evaluators. It also provides an initial organisation for evaluation and based on the information available, drafts the overall process of evaluation.

Key outcome and output evaluation measures, questions and evaluators

Table 4.4.1. Evaluation measures, questions and evaluators

Measure on framework	Relevance, description and comments	Possible target level if applicable	Responsible evaluator
OUTPUTS			
Data linkages between health databases completed	The number of databases integrated into the health system data management infrastructure. Protocols and standards developed for interoperability.	100% of the relevant databases integrated into the data management infrastructure. An organisational protocol / framework developed for linking person's genome, health and medical data and re-evaluating the need of possible additional data-sets to be added to the data management infrastructure.	MoSA/CGO/E-health Foundation
Operational central decision support system developed	Capability of providing decision support reports to local information systems and different users. Developed algorithms for the use of genome data (e.g. oncology, CVD, etc.)	Operational capacity to provide specific amount of reports from the central DSS to target groups during a specific time-frame. During the EPMPP, the minimum amount of reports is needed to conduct the clinical sub-projects.	MoSA/E-health Foundation/ECGUT
Data management infrastructure with open connection protocols and standards developed (technology robustness) ***see more specific measures listed below***	An organisational protocol / framework developed for linking person's genome, health and medical data – different databases and capability of providing decision support reports to local information systems and different users. Developed algorithms for the use of genome data and organizational model for setting further development needs. Evaluation questions: -Does the data management infrastructure serve as an input of personalised medicine innovation in healthcare (see outcome indicators)? -Does it increase the possibilities of R&D&I in personalised medicine field? -Does it make evaluation, new service development, new business development and management of health system easier and more flexible? -Does it help to validate PM services cost-efficiency and efficacy?	Qualitative evaluation – expert analysis. Validated expert report.	MoSA/E-health Foundation/ECGUT
-ease of use	Qualitative data collection feedback from all of the stakeholders (primary and secondary users).	Increase (compared to current level, which should be evaluated before the start of the EPMPP)	MoSA/E-health Foundation/ECGUT
-flexibility	Qualitative data collection feedback from	Increase (compared to	MoSA/E-health

	all of the stakeholders (primary and secondary users).	current level)	Foundation/ECGUT
-security	Qualitative data collection feedback from all of the stakeholders (primary and secondary users).	Increase (compared to current level)	MoSA/E-health Foundation/ECGUT
-data relevance	Qualitative data collection feedback from all of the stakeholders (primary and secondary users).	Increase (compared to current level)	MoSA/E-health Foundation/ECGUT
-data format	Qualitative data collection feedback from all of the stakeholders (primary and secondary users).	Increase (compared to current level)	MoSA/E-health Foundation/ECGUT
-support service quality problem solving, response time)	Qualitative data collection feedback from all of the stakeholders (primary and secondary users), constant monitoring and documentation of support service provision).	Increase (compared to current level)	MoSA/E-health Foundation/ECGUT
-frequency of system use	Quantitative monitoring data.	X no of DSS requests sent and processed X no of personalised health reports/data/risk scores viewed by doctors/patients X no of medical documents sent to renewed EHIS	MoSA/E-health Foundation/ECGUT
-extent of system use	Quantitative monitoring data with breakdown with specific characteristics.	-Extent of algorithm use (breakdown: personalised screenings / personalised consultations / pharmacogenomics counselling) -Needs for new algorithms acknowledged -Time for new algorithm development	MoSA/E-health Foundation/ECGUT
Feasibility of PM demonstrated in clinical setting	The feasibility analysis of PM should include the evaluation of what value PM implementation will bring in the specific case of implementation in terms of **cost-effectiveness** and **medical efficacy** and what would the impact be on safety, health care budget and treatment practices (time-usage) of doctors? Specific **evaluation questions** should include (qualitative evaluation): 1. To what extent can the results be generalised to other PM services in Estonia? 2. What are the barriers for achieving the full potential of the value of the service? 3. What should be changed in terms of training, education and health care personnel management in order to increase the value of the intervention? 4. What regulatory (legal, organisational) changes are needed for increasing the value of the personalised medical intervention?	Quantitative evaluation: Personalised medicine intervention increases the cost-effectiveness and medical efficiacy compared to traditional services. Qualitative evaluation: (see questions in the box on the left)	Clinical sub-project evaluation lead

	5. What are the specific requirements for the DSS in this clinical case? 6. Are the requirements for the DSS generalisable for other PM services/interventions?		
Personnel related barriers detected	Qualitative evaluation	Most relevant barriers described and specific recommendations drafted for changes in PM related personnel trainings, which would foster PM implementation and innovation	CGO
Improvements made in training regarding PM (universities, training departements)	Expert validated improvements made in health care personnel policy at different levels in order to increase adoption of personalised medicine principles.	Qualitative evaluation – expert and stakeholder validation	CGO/Tartu University Medical Faculty/Hospitals
Legal/regulatory barreirs detected	Qualitative evaluation	Most relevant barriers described and specific recommendations drafted for conducting regulatory changes fostering PM implementation and innovation	CGO
Regulatory changes made in order to decrease barriers for PM medicine implementation	Expert validated regulatory changes for decreasing barriers for PM medicine implementation and increasing possibilities of R&D&I in personalised medicine field.	Qualitative evaluation – expert and stakeholder validation	MoSA/CGO
Doctors and other specialist involved in EPMPP	An output measure for involvement of medical specialists in the pilot project. Has an impact on the overall awareness of PM in local and international settings and helps to diffuse the experience gathered during the project – doctors becoming advocates of change.	X number of different doctors involved (break-down in characteristics)	CGO/participating care providers
Patients involved in EPMPP	An output measure for involvement of patients in the pilot project and clinical-subjects. Has an impact on the overall awareness of PM in local and international settings and helps to diffuse the experience gathered during the project through public experience and knowledge.	X number of patients (break-down in characteristics)	CGO/participating care providers
Local level publications and communication on PM feasibility (output of EPMPP)	Local level publications (articles, conferences) are an important output of EPMPP to increase the awareness of the possibilities of PM as demonstrated during the pilot project. The publications should consistently cover the whole pilot project and capture the activities done on the whole innovation chain (clinical studies, organisational evaluations, health innovation policy, business opportunities in PM implementation etc).	X number of publications covering different aspects on the process of innovation diffusion in PM. X number of local level communication activities (conferences) for increasing awareness of PM.	CGO/universities and research institutions
High level	High level publications are an important	X number of new high level	CGO/universities

publications on PM feasiblity as part of EPMPP (output of EPMPP)	output of EPMPP to increase the awareness of Estonia as PM hub and innovator in personalised medicine. The publications should consistently cover the whole pilot project and capture the activities done on the whole innovation chain (clinical studies, organisational evaluations, health innovation policy, business opportunities in PM implementation etc).	publications covering different aspects on the process of innovation diffusion in PM. X number of publications presented in international conferences on PM field.	and research institutions
OUTCOMES			
Public awareness of PM possibilities (user-acceptance)	Survey among citizens of Estonia about the awareness of personalised medicine (conducted as part of pre-study)	Considerable increase in awareness and better understanding of the possibilities and risks of PM in the end of the pilot project. Repetition of the citizen survey conducted during pre-study phase at the end of the EPMPP and after 5 years of the end of EPMPP.	MoSA/CGO
Estonia known internationally as PM innovation hub	Survey among experts and health technology business/industry communities regarding the perception of Estonia as a personalised medicine innovation hub.	Estonia known as personalised medicine innovation hub with R&D&I possibilities and business opportunities.	MoSA/CGO/ Ministry of Economic Affairs and Communications
No of Master's degrees in PM field	Number of master's degrees in personalised medicine related fields.	Target rate needs evaluation of current status of number of master's degrees in the field and input from feasibility study and output measures regarding needs for improvements in training of specialists relevant for personalised medicine.	Ministry of Education and Science
No of PhD degrees in PM field	Number of doctoral degrees in personalised medicine related fields.	Target rate needs evaluation of current status of number of doctoral degrees in the field and input from feasibility study and output measures regarding needs for improvements in training of specialists relevant for personalised medicine.	Ministry of Education and Science
No of HTAs conducted on personalised medicine services (cost-effectiveness and clinical efficiacy validated)	Number of HTAs conducted (in the centre for Health Technology Assessment), which can have an input for the possible reimbursement of personalised medicine services.	Target measure depends on the selection criteria (outlined in chapter 4.2) - possibly 10 HTAs for personalised medicine could be conducted during the pilot project.	Centre for Health Technology Assessment/CGO
Public health insurance financing of PM services	New personalised medicine services in the reimbursement list of EHIF.	Target rate depends on the feasibility study and HTA-s conducted.	EHIF/CGO

Companies with PM services/ products (TRL +6)	Three sub-measures: a) Number of health technology and personalised medicine companies with new products/services with technology readiness level of 6 and above (can be universtiy spin-offs). b) Proportion of health technology and personalised medicine companies with new products/services with technology readiness level of 6 and above of the overall number of health technology and personalised medicine companies with new products/services. c) Number of university spin-offs developing products/services in health technology and personalised medicine.	Target rate needs evaluation of current status of technology readiness level (TRL) regarding PM companies. B) is a key metric showing the maturity of the personalized medicine innovation level.	CGO, MoSA, Ministry of Economic Affairs and Communications
New internationally focused start-ups with PM services/ products	Three sub-measures: a) Number of health technology and personalised medicine startups with new products/services with technology readiness level of 6 and above (can be universtiy spin-offs). b) Proportion of health technology and personalised medicine startups with new products/services with technology readiness level of 6 and above of the overall number of health technology and personalised medicine startups with new products/services. c) Number of health technology and personalised medicine startups with new products/services with technology readiness level of 6 and above (can be universtiy spin-offs) with foregin owners (more than 50% of shares).	Target rate needs evaluation of current status of technology readiness level (TRL) regarding PM startups. B) is a key metric showing the maturity of the personalized medicine innovation level.	CGO, MoSA, Ministry of Economic Affairs and Communications
Private capital for PM development	a) Foreign private capital invested in health technology and personalised medicine companies. b) Local private capital invested in health technology and personalised medicine companies. c) Proportion of private R&D investments of total R&D investments in health technology and personalised medicine.	PM should bring considerable numbers of foreign and local private capital into healthcare for investments in R&D&I. The proportion of private investments should rise considerably – specific target can be based on Estonian R&D&I strategy.	Ministry of Economic Affairs and Communications
Improved clinical information systems with decision support and data for personalised treatment	Improved clinical information systems which have developed integrations with renewed data management infrastructure and DSS and built user-accepted systems for personalized medicine treatment support.	100% of clinical information systems currently in use.	E-health Foundation monitoring, CGO

PM services implemented at Estonian care providers (incl hospitals, GPs)	a) New personalised medicine services part of care provider's work processes (reimbursed by EHIF). b) New personalised medicine services part of care provider's work processes (non-reimbursed by EHIF: OOPs or other financing mechanisms). c) R&D investments for implementation of personalised medicine services in public hospitals, GPs and care providers.	a) 100% of planned budget/contracts b) To be clarified – whether the private financing for such services should be more than public financing. c) Increase in R&D investments.	EHIF database, reports from care providers, CGO
High level R&D&I initiatives on PM	New R&D&I intiative (innovation projects) established after the conduction of EPMPP, based mostly on private capital. Public-private partnership initiatives. International initiatives.	3 new R&D&I initiatives / projects similar to EPMPP but on higher international level.	MoSA, CGO
Export of PM services and products	Rise in exports of PM services in terms of medical services export, product export, business-to-business service export, or other sub-characteristics.	Increase in exports/ proportion of exports	Ministry of Economic Affairs

Governance and coordination of evaluation

It is important that the overall organisational structure of evaluation is described, in-order to achieve a coordinated evaluation process and the aims of the evaluation, but also to use the time and energy of participating institutions, doctors and researchers as efficiently as possible. The following Figure 4.4.1 describes the organisational structure of the evaluation of the EPMPP.

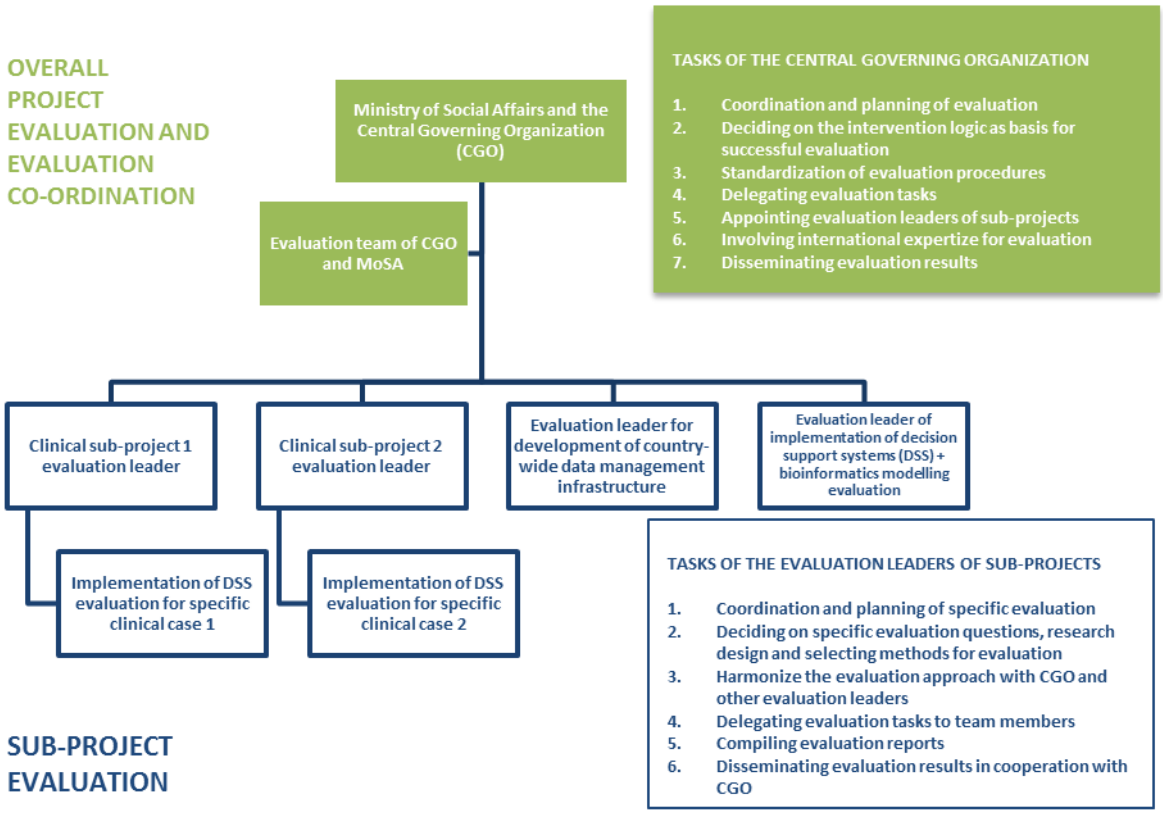


Figure 4.4.1. Organisational structure of EPMPP evaluation

The leader and coordinator of all the evaluation activities will be the organisation responsible for the overall EPMPP coordination, in this case the Central Governing Organisation (CGO). When delegating evaluation tasks to sub-project leaders, it is important to use the existing experience of health technology and HIS evaluation as sufficiently as possible, as described in chapter 4.2.

Evaluation process

The specific evaluation process is highly dependent of the overall EPMPP project plan. In order to provide the relevant evaluation process, the pilot project activities should be listed. In this section this is done based on the information available. It does not serve as a recommendation for a project plan, yet provides an overview of the evaluation process during the EPMPP.

Table 4.4.2. Evaluation process

Pilot project activity	Relevant evaluation process activity
Drafting the EPMPP project plan	Appraisal of the initial intervention logic provided (see relevant questions in chapter 4.1 and initial intervention logic in chapter 4.3). Evaluate the current goals of EPMPP in connection with the overall Estonian health system goals and stakeholder input.
Developing a detailed clinical sub-project plan and specific process descriptions. Setting the outputs of the clinical sub-projects for establishing the needs for input regarding data infrastructure development.	Use benchmarking tool (see chapter 4.1) for aligning the input-process-output-outcome measures of clinical sub-projects with EPMPP.
Developing the data infrastructure development plan with needs assessment for the clinical sub-projects.	Establishing key success indicators for evaluating the success of the data infrastructure development plan: • ease of use • flexibility • security • data relevance • data format • support service quality: problem solving, response time • frequency of system use • extent of system use • fit with organisation of EPMPP and relevant governing organisations Legislation and regulatory changes needed for data infrastructure implementation first steps.
Conducting an external independent audit of data collected in nation-wide and institutional health related and medical databases (EHIS, EGCUT, healthcare providers, etc.)	Cross-analysing of medical databases (including institutional information systems): • Analysis of structure of data • Relevance of data for specific uses • Assessing the needs for better structuring of the data • Assessing the readiness to participate and costs among the database owners • Agreeing on the sources of different data necessary for DSS algorithms • Developing input for system needs for DSS and concept formulation.
Piloting of Finnish EBMeDS (Duodecim Medical Publications Ltd.) Extraction of the genotype and phenotype data afterwards data harmonisation, consolidation.	Small-scale piloting and evaluation of EBMeDS. Input for systems needs and DSS concept formulation (lessons-learned) from piloting process and impact on barriers for implementation of DSS: ○ Legal/regulatory barriers ○ Organisational barriers ○ Technical barriers ○ Personnel related barriers • Evaluate impact on work-processes (time-usage and cost-effectiveness). • Develop key quality measures.
Formulation of system concept for the data management infrastructure development including: • DSS development • Linking the data stored in different medical databases	Information gathering from on-going clinical sub-projects, DSS pilot and conducted pre-studies. Introduce an iterative SDLC based development process and evaluation methodology in order to build on 'lessons learned' and achieve sufficient stakeholder

	involvement and unit testing.
Describing needs for data infrastructure DSS engine.	Needs description based on clinical sub-project activities and international literature. Needs should be described for different services: • personalised screenings • personalised counselling • pharmacogenomic counselling Evaluate, what kind and how many algorithms are feasible to be developed during the pilot project (in order to achieve results in sufficient time). Evaluate, the needs for integrating other information systems (local, off-the-shelf, mobile apps) to the central DS engine and evaluate the application requirements for individual and professional use.
Assessing the impact of data management infrastructure development to the organisations with relevant medical databases.	Ex-ante evaluation of: • Administrative burden (total cost of ownership) for stakeholders with medical databases. • Development and integration costs and possible time-span. • Readiness of top-management to be involved in the integration process.
Regulatory changes made for data management infrastructure development.	Expert validation of regulatory changes for data management infrastructure development.
Conducting data infrastructure development activities.	Constant monitoring, evaluation and unit testing according to set measures (above).
Setting the evaluation criteria for the clinical sub-projects	General evaluation measures that can be evaluated based on international literature. Key metrics should include: • Cost-efficiency • Clinical efficacy • Safety Qualitative organisational and financial evaluation measures are important for achieving the goals of EPMPP: • Impact on work-processes • Service delivery model generalisability to other specialties • Legal and regulatory barriers for implementation • Personnel related preconditions for implementation • Needs for health data and data management infrastructure
Planning of clinical study for high-level publication(s) in personalised medicine for clinical sub-projects.	Choosing a suitable evaluation design and methods for achieving the results of the specific sub-project and seeking accordance with international clinical study standards (see annexes for international experience for evaluating personalised screenings, personalised counselling). Evaluation questions in case of personalised interventions seeking behavioural change: • Do changes in patients' health behaviour improve

	health or reduce risk factors? • What is the relationship between duration of health behaviour change and health improvement (i.e., minimum duration, minimum level of change, and change–response relationship)? • What are the adverse effects of health behaviour change? • Does health behaviour change produce other positive outcomes (e.g., patient satisfaction, changes in other health care behaviours, improved function, and decreased use of health care resources)? • Is risk factor reduction or measured health improvement associated with reduced morbidity or mortality? • Is sustained health behaviour change related directly to reduced morbidity or mortality? • Are behavioural counselling interventions in clinical care related directly to improved health or risk factor reduction? • Are behavioural counselling interventions in clinical care related directly to reduced morbidity or mortality? (see annexes for more specific methodological approaches). Involving international experts in conducting clinical studies.

Select a clinical intervention modelling subject as part of clinical sub-project, with most potential for achieving broad benefits and clear understanding of benefits for different stakeholders (e.g see annexes on breast cancer screening personalisation impact on NNS).	Evaluate the selection of the clinical study based on the following criteria:
	• The results will be clearly understandable for policy makers, doctors and patients alike.
	• It is possible to model the impact on increased cost-effectiveness of the intervention. E.g modelling of breast cancer screening personalization impact on:
	  ○ Lower NNS (number of needed to screen).
	  ○ Reduction in screening costs.
	  ○ Higher detection rate.
	  ○ Organizational development needs for conducting personalized/genetic screenings and following counselling activities.
	  ○ Possible to evaluate the behavioural and communication risks of screening (readiness to participate, when higher risk communicated).
	  ○ Needs for data integrations for modelling and implementation (database connections)
	  ○ Other clinical criteria shown in annexes

Model the possible personalised intervention (data extracting, harmonising, linking, consolidating, mining).	Assess the possible costs associated with similar modelling and algorithm development for personalisation. • Time of modelling and algorithm development activities. • Personnel needs for modelling (specialists). • Implications for educational institutions (e.g universities for data science education).

Communicate the modelling results at an early stage to relevant stakeholders for feedback and input for clinical study conduction.	Evaluate the reach and clarity of the results for different stakeholders.
Selecting a list of clinical interventions as a possible reimbursed service after completion of initial evaluations and modelling.	Personalised intervention evaluated to the HTA evaluation criteria: • Is it expected to have considerable beneficial effect on public health? • Will it use considerable resources from the health insurance and state budgets? • Are are controversial opinions about the clinical efficacy and cost-effectiveness? • The extent of use and target groups in Estonia is not known.
HTA conducted for personalised medicine intervention(s).	Evaluation conducted according to HTA rules set at the Centre of Health Technology Assessment (see chapter 4.2). HTA report results provided as an input for Health Insurance Fund reimbursement list addition process.
Analysis regarding possible alternative financing models for piloted personalised medicine services.	Business model validation for personalised medicine services. Evaluating the barriers for scaling such business models in terms of: • Legal/regulatory barriers • Organisational barriers • Technical barriers • Personnel related barriers Evaluate the regulatory changes prioritization (expert validation).
Evaluation of the overall success of EPMPP	1. At the start of EPMPP: establishing outcome measurement framework for EPMPP. Responsibilities of different institutions for output and outcome measurements (see Table 4.4.1 for measures and responsible organisations). 2. At the end of EPMPP, evaluating the success of outputs of EPMPP and the process of achieving the overall outcomes of EPMPP (see Table 4.4.1). 3. 5 years after the end of EPMPP, evaluate the reaching of outcomes of EPMPP (see Table 4.4.1).
Communicating EPMPP results and evaluations	Conduct transparent communication activities during the EPMPP – evaluate the reach of communication activities according to following measures: • No of stakeholder representatives reached with communication activities (patients, doctors, researchers, businesses, students). • Level of engagement of stakeholders. • Feedback questionnaire from engagement activities (e.g conferences), which should be benchmarked with the overall intervention logic of the project. Distribute local and international publications of EPMPP and results of EPMPP to local and international communities.

The provided evaluation framework was developed before the official project plan of the EPMPP. Thus, the framework and guiding process descriptions need further appraisal from the stakeholders active in EPMPP project plan draft development. The initial intervention logic should be evaluated with relevant stakeholders and the more specific procedures described for the sub-projects. A selection of the optimal pilot project plan should be made.

Recommendations regarding important next steps of evaluation process

1. **Appraise the initial intervention logic of EPMPP in the context of Estonian health system strategic goals and EPMPP sub-project needs.**
2. **Establish outcome measurement framework and organization for evaluating the success of EPMPP in reaching its goals (outcome measures provided in chapter 4.4) – governing organisation should coordinate the evaluation in terms of standardisation, planning, delegation and dissemination.**
3. **Describe the specific sub-projects of EPMPP in terms of inputs, processes, outputs and outcomes as part of the pilot project plan – acknowledge the interdependence of different sub-project activities in terms of inputs-outputs and plan the evaluation activities of sub-projects in a way that sub-projects needing input from other evaluations get it in sufficient time.**
4. **Plan the evaluation of the feasibility of clinical personalised medicine services in terms of legal, organisational, technical and personnel related barriers – this short term output will provide important input for other activities of EPMPP: data infrastructure development and regulatory, legal, education/training policy changes to support R&D&I ecosystem development.**
5. **At the first phase of the EPMPP, the focus of clinical sub-project evaluation should be on defining the impact of PM services on work-processes and organisational feasiblity and demonstrating legal and regulatory barriers for implementation, personnel related preconditions for implementation and needs for data management infrastructure.**
6. **For the sub-projects involving HIS development an iterative SDLC based development process shoult be introduced in order to build on 'lessons learned' and achieve sufficient stakeholder involvement. Clinical sub-projects with DSS piloting should provide input to the data infrastructure development in terms of needs and barriers for implementation and open connection protocols for achieving interoperability.**
7. **Clinical outcome evaluation of personalised medicine services should be done in the second phase of the pilot project in the form of health technology assessment using the existing organizational framework and methods developed for that. This should also conclude in local and high level publications of personalised medicine implementation for increasing the awareness about personalised medicine in local and international communities.**
8. **Pilot project should include an activity for evaluating the possible alternative financing models for personalised medicine services in the Estonian context.**
9. **A sound evaluation organisation structure should be implemented with specific functions and roles for the overall evaluation coordinator and the evaluation leaders responsible for sub-project evaluations. An outcome measurement framework (example proposed in chapter 4.4) for evaluating EPMPP success in reaching its goals in 5 years after the project should be implemented during the early phases of the project.**
10. **Conduct transparent communication activities during the EPMPP – evaluate the reach of communication activities and seek for clarification of personalised medicine definition and concept among all the relevant stakeholders.**
11. **Develop a quality management system and implement key quality control processes to ensure compliance with regulatory requirements, patient safety and health care quality standards.**

A simplified conceptual framework of evaluation process is shown below in Figure 4.4.2.

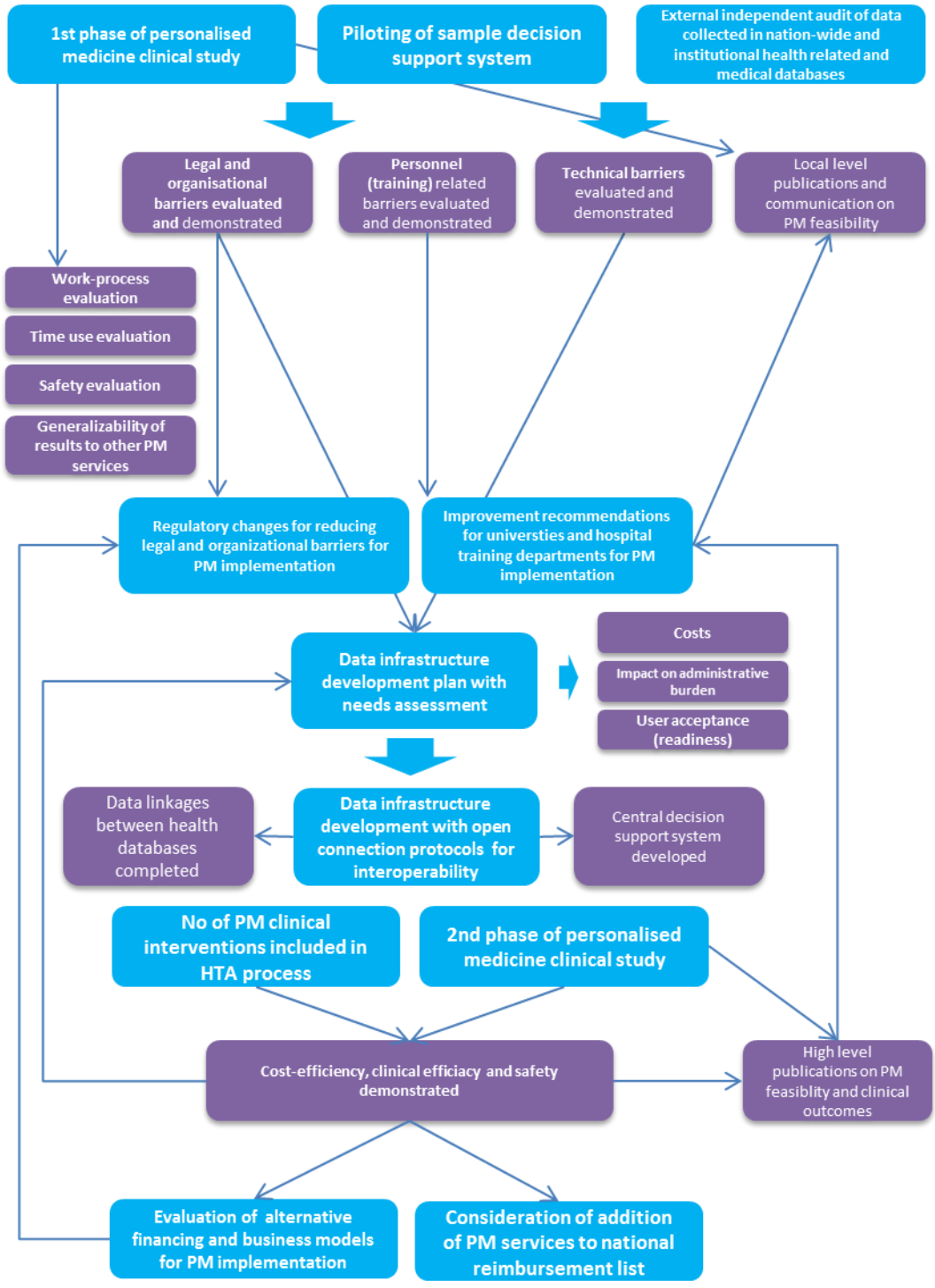


Figure 4.4.2. Simplified conceptual framework for evaluation process

Annex 1 – International literature regarding personalised medicine evaluation

This section will provide an overview of different evaluation approaches and methodologies for relevant components of personalised medicine implementation.

The international literature contains an abundance of articles of different **personalised medicine medical interventions** – personalised counselling, personalised screenings, pharmacogenomics, risk-scoring, personalised preventive approaches based on family history etc. Meanwhile, the governance structure of EPMPP entails principles common to e-governance interventions and broad government R&D programs. Therefore, the evaluation techniques regarding such initiatives should not be forgotten. The EPMPP could be also seen as a broad **health care information system implementation initiative** – various evaluation approaches have been developed for such systems as well. The aspects of ethics are of high relevance in terms of evaluation and should be given sufficient attention.

Bauer et al[31] remind us how technological advances have propelled the growth in personalised health care to cater for individual needs. Due to the unprecedented computational capabilities and high-throughput data collection methods the emergence of personalised, evidence-based health care to support genomic health management can become a realisation. While the technological potential is well documented and demonstrated, examining its 'success' within a health care context is a complex undertaking.

Newman and Freitag[32] explain that the level of clinical trial activity surrounding personalised medicine is growing and many efforts are being promoted to highlight the benefits of various projects. The personalised medicine landscape, however, is still evolving and requires more attention on the evaluation methods to demonstrate the value of personalised medicine projects and best practice in developing such health care initiatives. Personalised medicine has the potential to improve health outcomes and cost-effectiveness in a health care system but the actual economic assessment of this treatment approach is fraught with challenges. In theory, personalised medicine is promising from an economic perspective. Thus, from an evaluation perspective, the potential value of EPMPP should be validated pre-clinically for a highly selective therapy and proof-of-concept trials can be anticipated very early in the clinical development of the therapy. The current cost-effective analysis framework of using health gain to describe the value of complex health technology such as personalised cancer medicine is not likely to sufficiently capture all its benefits.[33]

An initial step towards evaluation is often through a pilot study. For example, Pulley et al[34] describe how they took advantage of the patient portal MyHealthAtVanderbilt.com, patient focus groups, and developed a better understanding of patient attitudes and their concerns (often related to privacy and management of data). In other studies, patient behaviour in response to a pilot test often informs the evaluation process and the quality-improvement program evaluation.

[31] Denis C. Bauer et al., 'Genomics and Personalised Whole-of-Life Healthcare', *Trends in Molecular Medicine* 20, no. 9 (1 September 2014): 479–86, doi:10.1016/j.molmed.2014.04.001.

[32] Newman, T. J., & Freitag, J. J. (2011). Personalised Medicine Development. Applied Clinical Trials, 20(7), 30.

[33] Katherine Payne and Lieven Annemans, 'Reflections on Market Access for Personalised Medicine: Recommendations for Europe', *Value in Health*, Personalised Medicine and the Role of Health Economics and Outcomes Research: Applications, Emerging Trends, and Future Research, 16, no. 6, Supplement (September 2013): S32–38.

[34] J. M. Pulley et al., 'Operational Implementation of Prospective Genotyping for Personalised Medicine: The Design of the Vanderbilt PREDICT Project', *Clinical Pharmacology and Therapeutics* 92, no. 1 (July 2012): 87–95, doi:10.1038/clpt.2011.371.

Annex 1.1 Relevant health information systems evaluation frameworks

Within a health care context, evaluating the impact of IS is important to understand the dynamic nature of technology and its ability to improve clinical performance, patient care, and service operations[35], thus personalise care. Therefore evaluation offers us the ability to learn from past and present performance[36] with a view of improving process, care,[37] economics[38][39] and patient satisfaction for the future.[40][41]

Identifying various methods of valuation throughout the IS literature enables us to build on the current knowledge and identify techniques to improve health care systems (Yusof et al. 2006) to support the emergence and evidence-base of personalised medicine innovation.

Various evaluation approaches on IS were developed with different outlooks, including technical, sociological, economic, human and organisational. A number of frameworks also explicitly focus on HIS evaluation. These perspectives can be summarised as follows:

- **Clinical:** medical practice, based on observation, interaction and treatment of patients;
- **Technical**: the application of hardware and software devices to connect health care service operations in a more efficient manner;
- **Human**: the evolution of social behaviour and development through the influence of both internal (e.g. attitudes, emotion, or health status) and external influences (e.g. service availability or economics of care) ; training, personnel attitudes, ergonomics and regulations affecting employment and patient experience in health care;
- **Economic**: understanding of the processes that govern the production, distribution and consumption of goods and services which impact on health care;
- **Organisational**: the nature of the healthcare organisation, its structure, culture and politics affect an evaluation;
- **Regulation**: a mechanism to sustain and focus control which is often exercised by a public agency over activities that are valued by the health care community and its stakeholders.

We some of these and The key factors in a number of HIS and IS evaluation models are examined and their primary focus summarised as follows (Table 1.):

[35] Michael Meltsner, 'A Patient's View of OpenNotes', *Annals of Internal Medicine* 157, no. 7 (2 October 2012): 523–24.
[36] Kathryn J. Hannah and Marion J. Ball, eds., *Evaluation Methods in Biomedical Informatics*, Health Informatics (New York: Springer-Verlag, 2006), http://link.springer.com/10.1007/0-387-30677-3.
[37] Suzanne G. Leveille et al., 'Evaluating the Impact of Patients' Online Access to Doctors' Visit Notes: Designing and Executing the OpenNotes Project', *BMC Medical Informatics and Decision Making* 12, no. 1 (13 April 2012): 32.
[38] María E. Dávalos et al., 'Economic Evaluation of Telemedicine: Review of the Literature and Research Guidelines for Benefit-Cost Analysis', *Telemedicine Journal and E-Health: The Official Journal of the American Telemedicine Association* 15, no. 10 (December 2009): 933–48.
[39] Jan Van Ooteghem et al., 'Economic Viability of eCare Solutions', in *Electronic Healthcare*, ed. Martin Szomszor and Patty Kostkova, Lecture Notes of the Institute for Computer Sciences, Social Informatics and Telecommunications Engineering 69 (Springer Berlin Heidelberg, 2011), 159–66, http://link.springer.com/chapter/10.1007/978-3-642-23635-8_20.
[40] K. A. Kuhn and D. A. Giuse, 'From Hospital Information Systems to Health Information Systems. Problems, Challenges, Perspectives', *Methods of Information in Medicine* 40, no. 4 (2001): 275–87.
[41] Bernd Blobel, *Contribution of Medical Informatics to Health: Integrated Clinical Data and Knowledge to Support Primary, Secondary, Tertiary and Home Care : Proceedings of the European Federation for Medical Informatics Special Topics Conference 2004 : Munich, June 13-16, 2004* (IOS Press, 2004).

Table 1. IS Evaluation Frameworks [42]

Framework	Clinical	Technical	Economic	Human	Organisational	Regulation
4Cs Model	✓	✖	✖	✓	✓	✖
CHEATS Model	✓	✓	✖	✓	✓	✖
TEAM	✖	✓	✖	✓	✓	✖
ITAM	✖	✓	✖	✓	✓	✖
IS Success Model	✖	✓	✓	✓	✓	✖
TAM	✖	✓	✖	✓	✖	✖
HOT-fit Model	✖	✓	✖	✓	✓	✖
Integrated Model	✓	✓	✖	✓	✖	✖
RATER Model	✖	✓	✖	✓	✓	✖

There have been some efforts to evaluate HIS including clinical decision support systems. For example, Yosof et al[43] proposed the HOT-fit framework (Human, Organisation and Technology-fit) that was developed from a literature review on HIS evaluation studies. A review of the literature revealed that specific instances of an evidence-based evaluation framework in personalised medicine is difficult to discover. This is similar for the field of Connected Health,[4445] there is no evidence of generic evaluation models which can be applied to Connected Health to provide a holistic view of its potential impact. Table 1 examines various factors which are considered in evaluation ranging from clinical, technical, economic, human, organisation and regulation. This indicates that there is a lack of wider evaluation approaches on health care which must be addressed in personalised medicine to deliver innovative and perhaps 'disruptive' solutions.[4647]

The 4Cs Evaluation Framework steers away from the technical issues of evaluation and, using a social interactionist perspective, it examines how human, organisational and social issues are important for service design, development and deployment. The 4Cs framework examines issues associated with *communication, care, control,* and *context* based on medical informatics.[4849] Another model which evaluates the use of ICT in health care includes the CHEATS framework.[50] It evaluates healthcare through six core areas:

1. **Clinical**: focusing on issues such as quality of care, diagnosis reliability, impact and continuity of care, technology acceptance, practice changes and cultural changes;
2. **Human and organisational**: focusing on issues such as the effects of change on the individual and on the organisation;
3. **Educational**: focusing on issues such as recruitment and retention of staff and training;
4. **Administrative**: focusing on issues such as convenience, change and cost associated with health system;

[42] Noel Carroll, 'In Search We Trust:: Exploring How Search Engines Are Shaping Society', *International Journal of Knowledge Society Research* 5, no. 1 (2014): 12–27, doi:10.4018/ijksr.2014010102.
[43] M.M. Yusof, R.J. Paul, and L.K. Stergioulas, 'Towards a Framework for Health Information Systems Evaluation', in *Proceedings of the 39th Annual Hawaii International Conference on System Sciences, 2006. HICSS '06*, vol. 5, 2006, 95a – 95a.
[44] Anshul Mathur, Joseph C. Kvedar, and Alice J. Watson, 'Connected Health: A New Framework for Evaluation of Communication Technology Use in Care Improvement Strategies for Type 2 Diabetes', *Current Diabetes Reviews* 3, no. 4 (November 2007): 229–34.
[45] Sonja A. O'Neill et al., 'Evaluation of Connected Health Technology', *Technology and Health Care: Official Journal of the European Society for Engineering and Medicine* 20, no. 3 (2012): 151–67.
[46] C. M. Christensen, R. Bohmer, and J. Kenagy, 'Will Disruptive Innovations Cure Health Care?', *Harvard Business Review* 78, no. 5 (October 2000): 102–12, 199.
[47] Lee H. Schwamm, 'Telehealth: Seven Strategies To Successfully Implement Disruptive Technology And Transform Health Care', *Health Affairs* 33, no. 2 (2 January 2014): 200–206.
[48] B. Kaplan, 'Addressing Organizational Issues into the Evaluation of Medical Systems', *Journal of the American Medical Informatics Association: JAMIA* 4, no. 2 (April 1997): 94–101.
[49] B. Kaplan, 'Evaluating Informatics Applications--Some Alternative Approaches: Theory, Social Interactionism, and Call for Methodological Pluralism', *International Journal of Medical Informatics* 64, no. 1 (November 2001): 39–56.
[50] Nicola T. Shaw, '"CHEATS": A Generic Information Communication Technology (ICT) Evaluation Framework', *Computers in Biology and Medicine* 32, no. 3 (May 2002): 209–20.

5. **Technical and social**: focusing on issues such as efficacy and effectiveness of new systems and the appropriateness of technology, usability, training and reliability of health care technology.

Another model which evaluates HIS includes the Total Evaluation and Acceptance Methodology (TEAM). This offers an approach based on systemic and model theories.[51] This framework identifies three key IS evaluation dimensions in biomedicine:

1. **Role**: evaluating IS from the designer, specialist user, end user and stakeholder perspective;
2. **Time**: identifies four main phases which provide relative stability of the IS;
3. **Structure**: distinguishes between strategic, tactical or organisational and operational levels.

From an IS perspective, there are also several well cited evaluation frameworks which were examined. For example, the IS Success Model[5253] examines the success of IS from a number of different perspectives and classifies them into six categories of success. The model adopts a multidimensional framework which measures dependencies between the various categories (Figure 1):

- System quality – The inherent features, such as user-interface and performance. Focuses on the questions of whether the system fits with user needs and work patterns, and is simple to use. Sub-dimensions: ease of use, flexibility, security.
- Information quality – The different information (e.g. prescription data or patient profiles) produced by the system by mostly using subjective methods. Sub-dimensions: relevance, format.
- Support service quality – The support provided by the provider of the technology (internal or external). Sub-dimensions: problem solving, response time.
- System use – The usage level (e.g. frequency) and extent of usage of the information system's different requests and functions. The dimension is also connected to the characteristics of the person who uses it (incl. computer skills, knowledge and acceptance/resistance). Sub-dimensions: frequency of use, extent of use.
- User satisfaction – A subjective measurement.
- Organisation structure – The characteristics of the various stakeholder organisations and the pilot project organisation.
- The environment – The external conditions surrounding the system including the legal, financing or political environment.
- Net benefits – The net benefits dimension characterises the balance of different types of positive and negative impacts (e.g. time, quality, and cost-efficiency) on all the relevant stakeholders in each phase. Sub-dimensions: quality and safety, time and work-patterns, cost-effectiveness.

[51] Andrew Grant, Ianik Plante, and Fréderic Leblanc, 'The TEAM Methodology for the Evaluation of Information Systems in Biomedicine', *Computers in Biology and Medicine* 32, no. 3 (1 May 2002): 195–207.
[52] William H. DeLone and Ephraim R. McLean, 'Information Systems Success: The Quest for the Dependent Variable', *Information Systems Research* 3, no. 1 (1 March 1992): 60–95.
[53] William H. Delone and Ephraim R. McLean, 'The DeLone and McLean Model of Information Systems Success: A Ten-Year Update', *J. Manage. Inf. Syst.* 19, no. 4 (April 2003): 9–30.

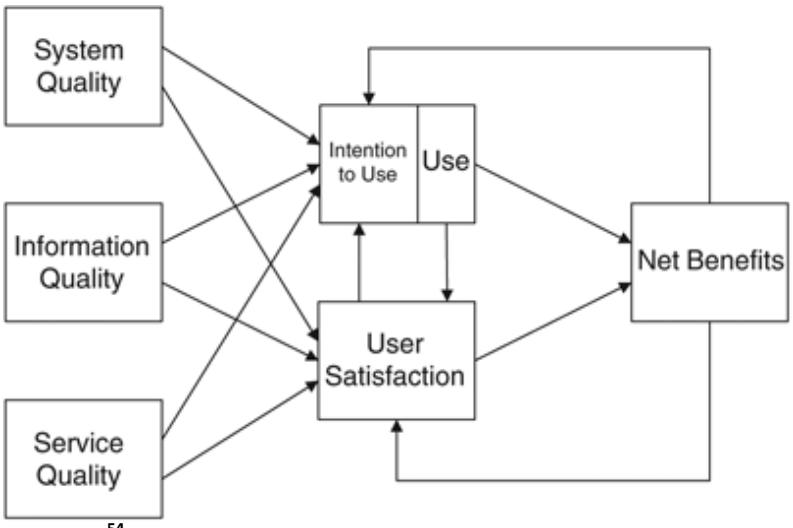


Figure 1. IS Success Model [54]

These dimensions suggest that there is a clear relationship between them which influences the success of the IS and whether certain net benefits can be achieved. The net benefits influence user satisfaction and use of the information system. In addition, the Technology Acceptance Model (TAM) examines how users accept the use of technology though a number of important influential factors. Among these factors are (see Figure 2):

1. The perceived usefulness (U) of the technology;
2. The perceived ease-of use (E) of the technology.

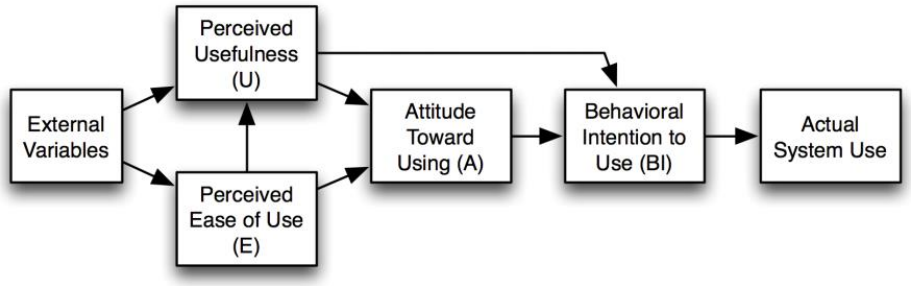


Figure 2. Technology Acceptance Model[55]

TAM suggests that these factors determine people's intention to use a technology. Through the integration of TAM and the Information Systems Success Model to justify and extend the Technology Acceptance Theory to health care information systems, Pai and Huang[56] demonstrate that system quality positively influences users' perceived ease of use which ultimately affects users' intention to use. While TAM provides an excellent approach to examining people's acceptance of technology, it is limited in explanatory terms[57] of technological 'value'. Adopting a similar outlook on technology

[54] DeLone and McLean, 'Information Systems Success'; Delone and McLean, 'The DeLone and McLean Model of Information Systems Success'.
[55] A Davis et al., 'A Critical Review of the Role of Neonatal Hearing Screening in the Detection of Congenital Hearing Impairment', *Health Technology Assessment (Winchester, England)* 1, no. 10 (1997): i – iv, 1–176.
[56] Fan-Yun Pai and Kai-I Huang, 'Applying the Technology Acceptance Model to the Introduction of Healthcare Information Systems', *Technological Forecasting and Social Change* 78, no. 4 (May 2011): 650–60, doi:10.1016/j.techfore.2010.11.007.
[57] Shirley Gregor, 'The Nature of Theory in Information Systems', *MIS Q.* 30, no. 3 (September 2006): 611–42.

evaluation, Dixon[58] presents a socio-technical evaluation model which examines the behavioural aspects of technology using the IT Adoption Model (ITAM).

ITAM (Figure 3) provides a framework for using implementation strategies and evaluation techniques from an end-user's perspective (i.e. fit for purpose, user perceptions of innovation usefulness and ease of use, and adoption and utilisation).

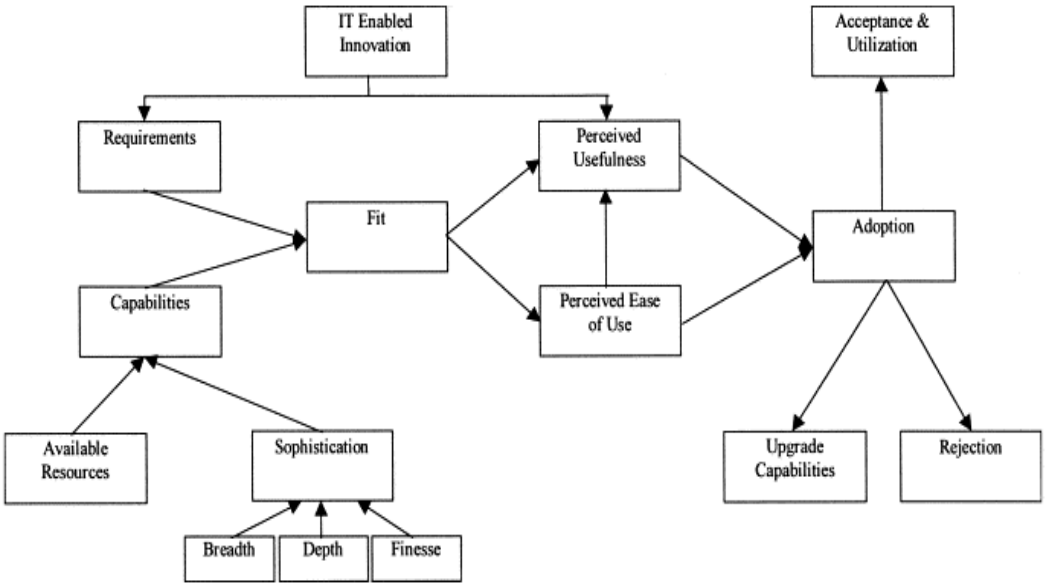


Figure 3. IT Adoption Model (Dixon, 1999)

Related research also focuses on consumer health behaviours and their adoption of medical technologies. For example, Wilson and Lankton[59] examine consumer acceptance of HIS to support patients in managing chronic disease. They integrated the use of TAM to extend the model which became known as the Integrated Model (Figure 4). Their Integrated Model merges perception of technology's usefulness (PU) with extrinsic motivation (EM) in a PU-EM scale and perception of a technology's ease of use (PEOU) scales. The key factors of this model evaluate healthcare technology by examining the:

1. Perception of a technology's usefulness (PU)
2. Perception of a technology's ease of use (PEOU)
3. Behavioural intention (BI) to use the technology
4. Intrinsic motivation (IM)
5. Extrinsic motivation (EM) to determine BI

[58] David R. Dixon, 'The Behavioral Side of Information Technology', *International Journal of Medical Informatics* 56, no. 1 (1 December 1999): 117–23, doi:10.1016/S1386-5056(99)00037-4.

[59] E. Vance Wilson and Nancy K. Lankton, 'Interdisciplinary Research and Publication Opportunites in Information Systems and Health Care', *Communications of the Association for Information Systems* 14, no. 1 (17 September 2004), http://aisel.aisnet.org/cais/vol14/iss1/17.

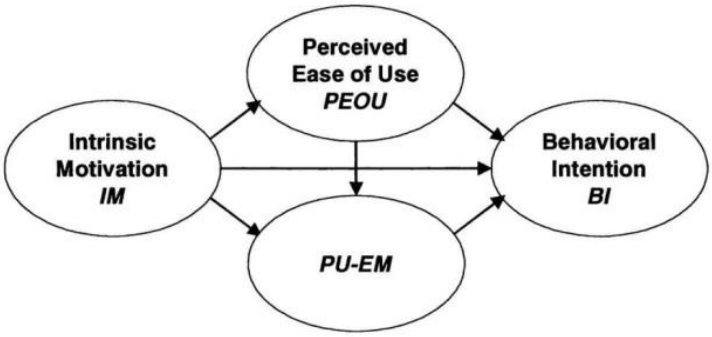


Figure 4. Integrated Model[60]

The five dimensions identified using the Integrated Model can also provide a useful lens to understand the impact of technology in personalised medicine, particularly the influential factors on IT-enabled innovation and the adoption of solutions. Identifying gaps in health service sectors is important to enhance the overall quality of the service delivery and identify how the EPMPP solution can address these gaps. There are a number of methods which evaluate the quality of services with a view of identifying areas to prioritise service improvements. For example, the RATER Model[61] offers a simplified version of the SERVQUAL model[62] using five key customer service issues (Table 2):

Table 2. Key Dimensions within the RATER Model

Dimension	Description
Reliability	Ability to provide dependable service, consistently, accurately, and on-time.
Assurance	The competence of staff to apply their expertise to inspire trust and confidence.
Tangibles	Physical appearance or public image of a service, including offices, equipment, employees, and the communication materials.
Empathy	Relationship between employees and customers and ability to provide a caring and personalised service.
Responsiveness	Willingness to provide a timely, high quality service to meet customers' needs.

By focusing on these five dimensions, we can begin to analyse and improve service offerings by the EPMPP. The five key dimensions can also support the development of a service plan to improve service delivery and are particularly apt in the EPMPP. Other initiatives which may support the evaluation of health technologies include the Intervention Mapping Framework (IMF). The IMF provides a systematic and rigorous approach that can be used to develop and promote health programmes. It achieves this through developing theory-based and evidence-based health promotion initiatives. These initiatives may be incorporated into the EPMPP evaluation, particularly from a patient-focused perspective.

A recent study carried out by Ancker et al[63] examines the effect of relatively mature health information technology (HIT) systems on the quality and safety of health care and propose the

[60] Ibid.
[61] Valarie A. Zeithaml, A. Parasuraman, and Leonard L. Berry, *Delivering Quality Service: Balancing Customer Perceptions and Expectations* (Simon and Schuster, 1990).
[62] A. Parasuraman, Valarie A. Zeithaml, and Leonard L. Berry, 'SERVQUAL: A Multiple-Item Scale for Measuring Consumer Perceptions of Service Quality', *Journal of Retailing* 64, no. 1 (1988): 12–40.
[63] Jessica S. Ancker et al., 'The Triangle Model for Evaluating the Effect of Health Information Technology on Healthcare Quality and Safety', *Journal of the American Medical Informatics Association: JAMIA* 19, no. 1 (February 2012): 61–65, doi:10.1136/amiajnl-2011-000385.

Triangle Model. This may align with the EPMPP since their focus was on quality and safety outcomes of health IT. This model identifies structure-level predictors, including characteristics of:

1. The technology itself
2. The provider using the technology
3. The organisational setting
4. The patient population

Their model can offer EPMPP a useful starting point since it broadly suggests the need for process predictors, including (1) usage of the technology, (2) organisational support for and customisation of the technology, and (3) organisational policies and procedures about quality and safety. More specifically, the Triangle Model provides the variables to be measured and offers some flexibility towards data (both qualitative and quantitative) gathering. The Triangle Model (Figure 5) proposes simultaneous measurement of structure, process, and outcome variables in all evaluations of the impact of health information technology on health care quality and safety.

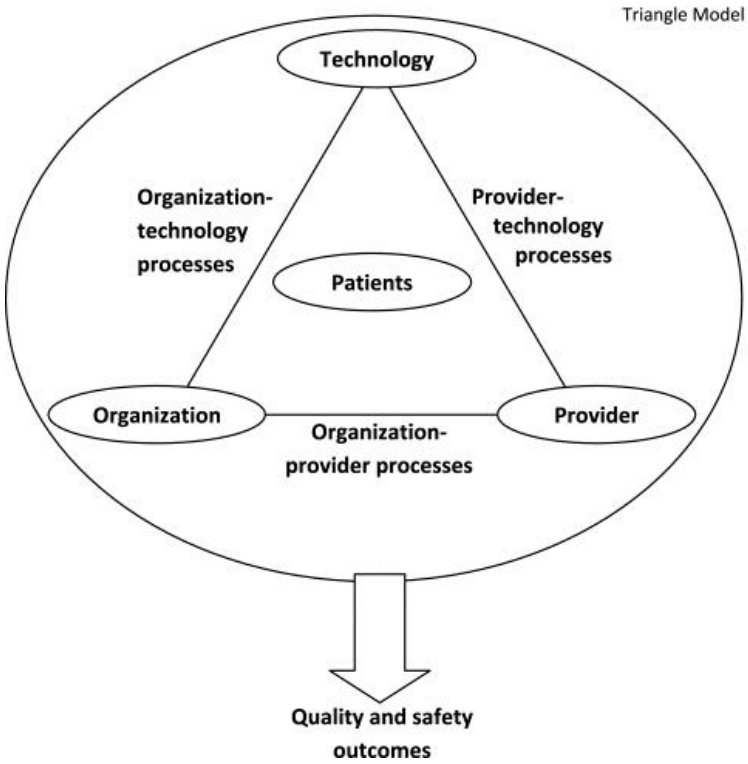


Figure 5. The Triangle Evaluation Model

As an Estonian example, Saluse et al[64] used an interdisciplinary approach (the PENG method) to analyse the costs and benefits of the implementation of an EHR by using both numerical and non-numerical data. The PENG approach made it possible to assess the financial, direct, indirect and immaterial benefits and costs by a mapping exercise, while taking into account the different stakeholders: patients, providers, society. Although due to its numerous dimensions the approach could be used as a broader framework for evaluation, the final result is the assessment of net benefits/economic impact and therefore the method is more suitable for investment evaluation. The PENG approach is similar to the Total Cost of Ownership method, which aims to quantify the short and long term (direct and indirect) costs of an information technology solution during the total life-cycle of the system, but TCO model does not usually assess how the system meets the needs of the

[64] Saluse, Janek; Aaviksoo, Ain; Ross, Peeter; Tiik, Madis; Parv, Liisa; Sepper, Ruth; Pohjonen, Hanna; Jakovlev, Ülle; Enni, Kaia (2010). Eesti terviseinfosüsteemi majandusmõju/puhastulu hindamine. TOF-DIGIMÕJU projekti lõpparuanne. Eesti Arst, 89(10), 659 - 696.

user or fits with the organisation's strategic aims (Total Cost …, 2013, West and Daigle 2004)[65][66], which can be seen as an significant limitation to the approach.

Several frameworks address the system development life-cycle in the framework (Currie 2005, 912)[67], which is relevant in case of IS developments during the personalised medicine pilot project. For example, Stead et al. (1994)[68] juxtaposed the system development level to the evaluation level, showing what should be the extent of evaluation during a specific stage of system development. They stress the importance of subjective evaluation techniques.

Meanwhile, the governance structure of EPMPP entails principles common to e-governance interventions and broad government R&D programs. For example Esteves and Joseph (2008) focused on ex-post evaluation of e-government using a three-dimensional framework for evaluation (Figure 6). The three dimensions were e-government maturity level, stakeholders, and assessment levels. This framework is also applicable to the current context, as the relevant dimensions can be used when drafting the initial EPMPP evaluation framework.

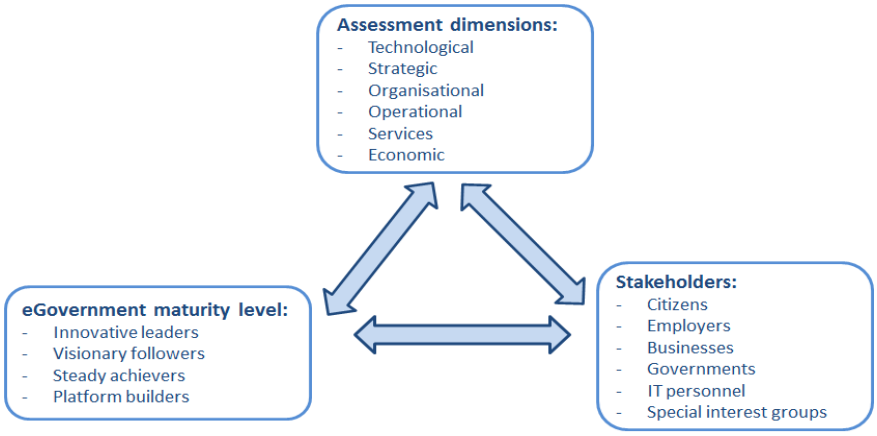


Figure 6. Esteves and Joseph eGovernment evaluation framework

As the new services in health care setting evolve, successive evaluation is necessary to determine if the goals are being met. One of the challenges in personalised medicine will be to create appropriate platforms in which innovations will be appropriately evaluated and subsequently linked with decision makers and technology assessors. To enable the infrastructure required to carry out personalised medicine, linkages with electronic health records will be necessary. Appropriate infrastructure is needed to collect large amounts of population data and link to biobanks and clinical data. Large cohorts that are appropriately sampled and phenotyped are critical, and research is therefore needed to address data sharing (biobanks, clinical data, health records, cohorts, etc.). The EPMPP evaluation combines numerous academic fields of evaluation (medicine, informatics, governance, social studies, innovation studies, epidemiology, bioinformatics etc). Thus, an overview of several personalised interventions is necessary for capturing the specific problems arising in PM clinical interventions.

[65] Total Cost of Ownership: Things to Consider. (2011). United Kingdom: Cabinet Office. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/78971/Total-Cost-of-Ownership-things-to-consider-v1.odt

[66] West, R., Daigle, S. L. (2004). Total Cost of Ownership: A Strategic Tool for ERP Planning and Implementation. – *Educase center for Applied Research*, 2004(1), 1-14. http://net.educause.edu/ir/library/pdf/ERB0401.pdf

[67] *Currie, L.M. (2005). Evaluation frameworks for nursing informatics. – International Journal of Medical Informatics. 74, 908-916.*

[68] Stead, W.W., Haynes, R.B., Fuller, S., Friedman, C.P., Travis, L.E., Beck, J.R., Fenichel, C.H., Chandrasekaran, B., Buchanan, B.G., Abola, E.E. (1994). Designing medical informatics research and library- resource projects to increase what is learned. - Journal of American Medical Informatics Association, 1(1), 28-3.

Annex 1.2. Evaluating personalised screenings and counselling services

Interventions that use a subject's clinical factors, gene expression profile, or perhaps other factors can also be considered as personalised medicine. In this overview attention is restricted to interventions that use genotype information as input for the intervention. Personalised medicine interventions may be evaluated using several different study designs (e.g targeted design, frequently used to evaluate genetic-based therapies, study eligibility may be restricted to a marker-positive subset of the population anticipated to benefit from therapy based on their genetic characteristics).

Evaluation framework for screenings

Should EPMPP implement personalised screenings, an evaluation framework with relevant modifications is necessary for evaluating the project. The six-step-evaluation process is commonly used in such occasions. Although the framework provides *steps* for screening program evaluation, the steps are not always linear; some can be completed concurrently. In some cases, it makes more sense to skip a step and come back to it. The important thing is that the steps are considered within the specific context of state. The steps are listed in following Figure 7.[69]

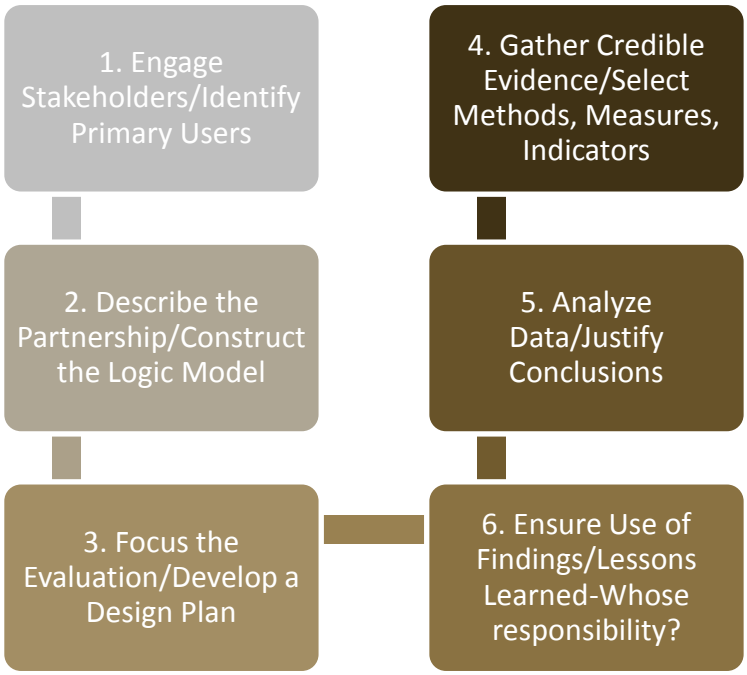


Figure 7. Six-Step Evaluation Process

When evaluating genetic tests or screenings, many uncertainties arise. Essential components of an assessment include the burden of suffering from a potentially increased disease risk, epidemiological measures (such as the frequency of disease-causing mutations in genes in different subgroups, and the contribution of genetic factors to the prevalence of disorders in populations), and the accuracy of the test, and the comparison with alternative methods of detection.[70]

[69] CDCP, 'Fundamentals of Evaluating Partnerships' (Centers for Disease Control and Prevention, 2008).

[70] Frauke Becker et al., 'Genetic Testing and Common Disorders in a Public Health Framework: How to Assess Relevance and Possibilities', *European Journal of Human Genetics* 19, no. S1 (April 2011): S6–44.

The CDC website[71] explains the evaluation components of analytic validity, clinical validity, clinical utility and ethical, legal and social implications. The **analytic validity** of a genetic test defines its ability to accurately and reliably measure the genotype of interest. This aspect of evaluation focuses on the laboratory component. The **clinical validity** of a genetic test defines its ability to detect or predict the associated disorder (phenotype). The **clinical utility** of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. **Ethical, legal, and social implications** surrounding a genetic test are represented by a penetrating pie slice, implying that the safeguards and impediments should be considered in the context of the other components.

The four eponymous components of the evaluation model (Analytic validity–Clinical validity–Clinical utility–Ethical, legal, and social implications) as well as their elements and relations to each other are displayed in the assessment wheel (Figure 8). At the hub of the evaluation wheel are the clinical disorders and the setting in which testing is done. The evaluation process begins only after the clinical disorder and setting have been clearly established.

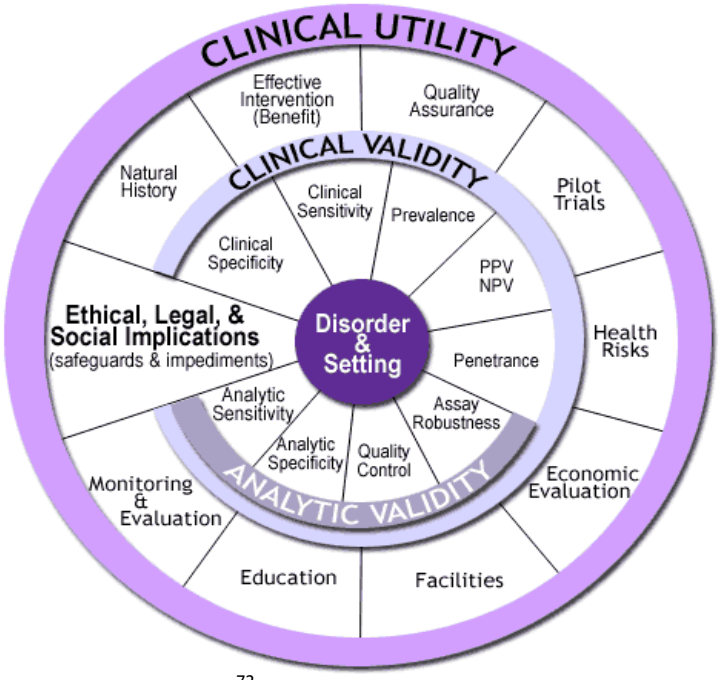


Figure 8. Evaluation process for screening[72]

Principles of population screening as applied to genetic susceptibility to disease [73][74]
Public health assessment

- The disease or condition should be an important public health burden to the target population in terms of illness, disability, and death.
- The prevalence of the genetic trait in the target population and the burden of disease attributable to it should be known.

[71] Public Health Genomics at CDC, 'Genomics|Genetic Testing|ACCE', accessed 5 June 2015.

[72] Ibid.

[73] Muin J. Khoury, Linda L. McCabe, and Edward R.B. McCabe, 'Population Screening in the Age of Genomic Medicine', *New England Journal of Medicine* 348, no. 1 (2 January 2003): 50–58, doi:10.1056/NEJMra013182.

[74] Becker et al., 'Genetic Testing and Common Disorders in a Public Health Framework'.

- The natural history of the condition, from susceptibility to latent disease to overt disease, should be adequately understood.

Evaluation of tests and interventions

- Data should be available on the positive and negative predictive values of the test with respect to a disease or condition in the target population.
- The safety and effectiveness of the test and accompanying interventions should be established.

Policy development and screening implementation

- Consensus regarding the appropriateness of screening and interventions for people with positive and negative test results should be based on scientific evidence.
- Screening should be acceptable to the target population.
- Facilities should be available for adequate surveillance, prevention, treatment, education, counselling, and social support.
- Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence.
- The cost effectiveness of screening should be established.
- Screening and interventions should be accessible to the target population.
- There should be safeguards to ensure that informed consent is obtained and the privacy of those tested is respected, that there is no coercion or manipulation, and that those tested are protected against stigmatisation and discrimination.

Measures to evaluate screening programmes

The following Table 2 presents measures for evaluating screening programmes in quantitative terms.[75][76][77][78]

[75] Alison Stewart et al., *Genetics, Health Care and Public Policy: An Introduction to Public Health Genetics*, 1 edition (Cambridge ; New York: Cambridge University Press, 2007).

[76] P. Vineis, P. Schulte, and A. J. McMichael, 'Misconceptions about the Use of Genetic Tests in Populations', *Lancet* 357, no. 9257 (3 March 2001): 709–12.

[77] M J Khoury and D K Wagener, 'Epidemiological Evaluation of the Use of Genetics to Improve the Predictive Value of Disease Risk Factors.', *American Journal of Human Genetics* 56, no. 4 (April 1995): 835–44.

[78] N. J. Wald, A. K. Hackshaw, and C. D. Frost, 'When Can a Risk Factor Be Used as a Worthwhile Screening Test?', *BMJ* 319, no. 7224 (11 December 1999): 1562–65.

Table 2. Quantitative measures for screening programme evaluation

Quantitative measures	***Characteristics***
Penetrance of a genetic variant	Probability that traits or characteristics associated with that variant will manifest (within a specified period of time)
Incidence	Number of new cases of disease occurring in a population (within a specified period of time)
Prevalence	Proportion of affected individuals in a population (at a given moment of time) incidence rate average duration of disease
Sensitivity or detection rate (DR)	Proportion of affected individuals (or those who become affected within a specified period of time) with a positive (unfavourable) screening test result
Specificity	Proportion of unaffected individuals with a negative screening test result
False-positive rate	Proportion of unaffected individuals with a positive screening test result specificity
DR5	Detection rate for a 5% false-positive rate
Positive predictive value (PPV)	Risk of disease among individuals with risk factor (with positive screening test result) (clinical impact)
Population attributable fraction (PAF)	Proportion of cases that could be prevented if the risk factor was absent (the public health impact)
ROQ1_5	Relative odds of the highest fifth of the risk factor distribution compared with people in the lowest fifth
Number needed to treat (NNT)	Number of people needed to treat for one success
Number needed to screen (NNS)	Number of individuals needed to screen to prevent one case of disease (measure to assess the performance of screening, combining penetrance and frequency with reduction in risk of disease) inverse of the frequency divided by the penetrance divided by the reduction in risk of disease.

It should be noted that similar measures have been established by the Estonian HTA programme in screening evaluations, which are an important input for the EPMPP.

Criteria for screening evaluation

The evaluation of genetic screening programmes has to include evaluation of the test characteristics, complemented by additional considerations regarding the screening context (ie, purpose, targeted groups).[79] Wilson and Jungner developed principles of population screening that can also be applied in the case of disorders with a genetic component. Based on the criteria by Wilson and Jungner[80] and

[79] Becker et al., 'Genetic Testing and Common Disorders in a Public Health Framework'.

[80] James Maxwell Glover Wilson, Gunnar Jungner, and World Health Organization, 'Principles and Practice of Screening for Disease', 1968, http://apps.who.int//iris/handle/10665/37650.

the Crossroads 99 Group, a framework was created to assess susceptibility testing for breast, ovarian, and colorectal cancer.[81] The Crossroads Criteria are based on a simple model of disease progression (see Potential screening pathways), which indicates that screening tests primarily detect genetic susceptibility to disease at a preclinical, asymptomatic phase.

Criteria for assessment of screening

Knowledge of population and disease

- Condition must be an important problem
- Recognisable latent or early symptomatic stage.
- Natural course of condition (including development from latent to declared disease) should be adequately understood [82]
- Burden of target disease should be important.
- Target population or population at risk identifiable
- Considerable level of risk or latent or preclinical phase
- Natural course (from susceptibility to precursor, early disease, and advanced disease) should be adequately understood [83]

Knowledge of test

- Suitable test or examination
- Test acceptable to the population
- Case finding should be a continuing process and not 'once and for all' project

Feasibility of screening procedures

- Entire screening procedure acceptable to the population
- Screening should be a continuing process and should encompass all elements of screening procedures

Treatment for disease

- Accepted treatment for patients with recognised disease
- Facilities for diagnosis and treatment available
- Agreed on policy concerning whom to treat as patients

Interventions and follow-up

- Interventions that have physical, psychological, and social net benefit available
- Facilities for adequate surveillance, prevention, treatment, education, counselling, and social support available
- Consensus on accepted management for those with positive test results

Cost considerations

- Costs of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditures on medical care as a whole

Societal and health system issues [84]

[81] Vivek Goel, 'Appraising Organised Screening Programmes for Testing for Genetic Susceptibility to Cancer', *BMJ : British Medical Journal* 322, no. 7295 (12 May 2001): 1174–78.

[82] Wilson, Jungner, and Organization, 'Principles and Practice of Screening for Disease'.

[83] Goel, 'Appraising Organised Screening Programmes for Testing for Genetic Susceptibility to Cancer'.

[84] Ibid.

- Costs should be balanced in economic, psychological, social, and medical terms and with health care expenditures as a whole
- Appropriate screening services accessible to the entire population, without adverse consequences for non-participants
- Appropriate confidentiality procedures and antidiscrimination provisions for participants and non-participants

Stratified screening

Screening programmes have made an important contribution to improvements in public health, but their value often depends on careful targeting. Stratification holds the prospect of achieving high rates of diagnosis and effective early treatment, while sparing lower risk, disease-free people from the risks and inconvenience of screening. It may also reduce overall costs. Using genomic information to improve this targeting is therefore attractive in principle and increasingly feasible.[85]

Pashayan et al[86] modelled the number of individuals eligible for screening and the number of cases potentially detectable by screening in a population undergoing screening based on age alone, as compared to a population undergoing personalised screening based on the 10-year absolute risk of being diagnosed with breast or prostate cancer. They calculated the conditional absolute risk taking into account age and polygenic risk profile. They set the risk threshold equivalent to the threshold for eligibility in the age-based screening programme.

For example Pashayan et al[87] modelled the efficiency of a personalised approach to screening for prostate and breast cancer based on age and polygenic risk-profile compared with the standard approach based on age alone. In a best-case scenario analysis, assuming all possible susceptibility variants for breast cancer were known, 28% of women 35–79 years would be at 2.5% risk and 76% of the cases would occur in this group. Compared with screening from age 47, 57% fewer women would be offered screening at a cost of detecting 10% fewer cases. To detect the same number of cases as screening from age 47, 39% (25 678 women eligible for screening per 100 000 population) fewer women would need to be screened.

Implementation of genomic risk-stratified breast cancer screening would require the support of the wider public. The public is generally very enthusiastic about screening.[88] Women perceive high benefits of mammography screening[89]; reflected in the high attendance rates (around 70%) across countries;[90] although lower socioeconomic status and ethnic minority status have both been

[85] T. Dent et al., 'Stratified Screening for Cancer: Recommendations and Analysis from the COGS Project' (PHG Foundation: Collaborative Oncological Gene-environment Study, 2014).

[86] N. Pashayan et al., 'Public Health Genomics and Personalised Prevention: Lessons from the COGS Project', *Journal of Internal Medicine* 274, no. 5 (1 November 2013): 451–56.

[87] N. Pashayan et al., 'Polygenic Susceptibility to Prostate and Breast Cancer: Implications for Personalised Screening', *British Journal of Cancer* 104, no. 10 (10 May 2011): 1656–63.

[88] J. Waller et al., 'A Survey Study of Women's Responses to Information about Overdiagnosis in Breast Cancer Screening in Britain', *British Journal of Cancer* 111, no. 9 (28 October 2014): 1831–35.

[89] Gianfranco Domenighetti et al., 'Women's Perception of the Benefits of Mammography Screening: Population-Based Survey in Four Countries', *International Journal of Epidemiology* 32, no. 5 (October 2003): 816–21.

[90] Philippe Autier et al., 'Breast Cancer Mortality in Neighbouring European Countries with Different Levels of Screening but Similar Access to Treatment: Trend Analysis of WHO Mortality Database', *BMJ (Clinical Research Ed.)* 343 (2011): d4411.

associated with lower participation rates.[91] Perceived risk of breast cancer has been cited as encouraging some individuals to be screened, while deterring others;[92] so predicting the impact of giving genetic risk information on screening uptake is difficult. There has also been attention to public perceptions of a 'right to be screened', which may militate against the acceptability of reducing breast screening frequency for those at the lowest risk.

Meisel et al[93] explored public attitudes towards modifying frequency of mammography screening based on genetic risk and found that women were positive about adjusting the frequency of mammography screening in line with personal genetic risk, but it will be important to develop effective communication materials to minimise resistance to reducing screening frequency for those at lower genetic risk. Over two-thirds of respondents (65.8%) supported the idea of varying screening frequency on the basis of genetic risk. The majority (85.4%) were willing to have more frequent breast screening if they were found to be at higher risk, but fewer (58.8%) were willing to have less frequent screening if at lower risk. This shows the importance of evaluating the public perception on stratifying screenings and also evaluating the communication tools for informing the public of screenings during the EPMPP.

Genetic counselling

Genetic counselling is the process through which knowledge about the genetic aspects of illnesses is shared by trained professionals with those who are at an increased risk or either having a heritable disorder or of passing it on to their unborn offspring. A genetic counsellor provides information on the inheritance of illnesses and their recurrence risks; addresses the concerns of patients, their families, and their health care providers; and supports patients and their families dealing with these illnesses. (WHO)

Genetic counselling, along with many other aspects of medicine and health care, must keep pace with radical new developments in biomedical research. Genetic counselling services serve several broader goals. Genetic counsellors facilitate knowledgeable decision making that supports patient autonomy. They promote meaningful informed consent based on an adequate understanding of the technical information and its implications for the individual and his or her family. They also foster effective adjustment to difficult situations in a manner that involves a realistic assessment of the positive and negative aspects of potential outcomes, promotes individual and family competence and mobilises social and professional support—all consistent with the family's beliefs, values and culture. Last but not least, genetic counsellors promote a relationship of trust that encourages continued utilisation of their services as well as those of other health care professionals.[94]

Examples from genetic counselling programme evaluations

Cuevas-Cuerda et al evaluated the cancer genetic counselling programme in Valencian Community using intermediate indicators.

Methods

[91] C. von Wagner et al., 'Psychosocial Determinants of Socioeconomic Inequalities in Cancer Screening Participation: A Conceptual Framework', *Epidemiologic Reviews* 33 (2011): 135–47.

[92] Maria C. Katapodi et al., 'Predictors of Perceived Breast Cancer Risk and the Relation between Perceived Risk and Breast Cancer Screening: A Meta-Analytic Review', *Preventive Medicine* 38, no. 4 (April 2004): 388–402,

[93] Susanne F. Meisel et al., 'Adjusting the Frequency of Mammography Screening on the Basis of Genetic Risk: Attitudes among Women in the UK', *Breast (Edinburgh, Scotland)* 24, no. 3 (June 2015): 237–41.

[94] Jon Weil, 'Genetic Counselling in the Era of Genomic Medicine', *EMBO Reports* 3, no. 7 (15 July 2002): 590–93.

It was a descriptive analysis of organisational and effectiveness indicators. Genetic testing was made in each family and carried out on the youngest individual who had been diagnosed with cancer. If the result showed a pathogenic mutation, the testing was offered to the rest of the relatives who were at risk. After this, the patients were informed of the test results. Consultations were carried out to inform each individual of the probability of developing a cancer, offering them recommendations on how to proceed or individualised treatment according to their level of risk. If the follow-up in a general hospital was required, patients were referred according to the syndrome diagnosed and their place of residence.

Evaluation design

The evaluation was designed to obtain the monitoring parameters of the sequential stages of the care process in the units, from the initial consultation up until the results of the genetic testing. The most relevant indicators were selected to obtain information about the organisation and effectiveness of the process.

Results

The authors found that it requires a huge management effort to coordinate and monitor laboratories and clinical services, to develop policies and regulations for the quality assurance and the management of resources, and to analyse the results. The results of the first 5 years confirm the appropriateness of this organisation, with facilities as part of an integrated health system, to identify families and individuals with genetic risk and to offer personalised counselling to them. To evaluate the impact of this programme on the health of the target population, a long term assessment is required to observe mortality and survival. Genetic testing enables healthy individuals to be ‘‘diagnosed’’ with an increased risk or predisposition to developing cancer. Then the expected benefits in terms of a lower incidence for the high-risk group or those diagnosed at an early stage can be analysed in the medium term. For this, it is important to evaluate this type of programme using intermediate process and result indicators. Other outcomes should be evaluated, such as the understanding of risks, satisfaction and psychological well-being.[95]

Behavioural counselling interventions

Health behaviours are an important determinant of many chronic diseases (including hearth diseases and cancer). Current knowledge suggests that behavioural patterns contribute more to premature death than genetic predisposition, social circumstances, environmental exposures, and health care errors. Behavioural counselling interventions are preventive services designed to help persons engage in healthy behaviours and limit unhealthy ones. Integration of behavioural counselling interventions with primary care delivery increases the reach of effective prevention strategies.[96]

Few behavioural counselling studies are designed to measure effects on health outcomes, such as death, disability, quality of life, or acute events, such as a stroke. Even the assessment of intermediate biometric risk factors, such as lipid level, blood pressure, and blood glucose level, is uncommon. In the absence of direct evidence for improvements in health outcomes, alternative indications through an indirect chain of evidence to epidemiologic and other types of studies can show that the target behaviour improves health outcomes. These associations are often represented in the analytic framework by dotted lines between changes in health behaviour and intermediate health

[95] Dolores Cuevas-Cuerda and Dolores Salas-Trejo, ‘Evaluation after Five Years of the Cancer Genetic Counselling Programme of Valencian Community (Eastern Spain)’, *Familial Cancer* 13, no. 2 (June 2014): 301–9.

[96] Susan J. Curry et al., ‘Behavioral Counseling Research and Evidence-Based Practice Recommendations: U.S. Preventive Services Task Force Perspectives’, *Annals of Internal Medicine* 160, no. 6 (18 March 2014): 407–13.

improvements or risk factor reduction and between intermediate health improvements and reductions in morbidity or mortality (see Figure 9).[97]

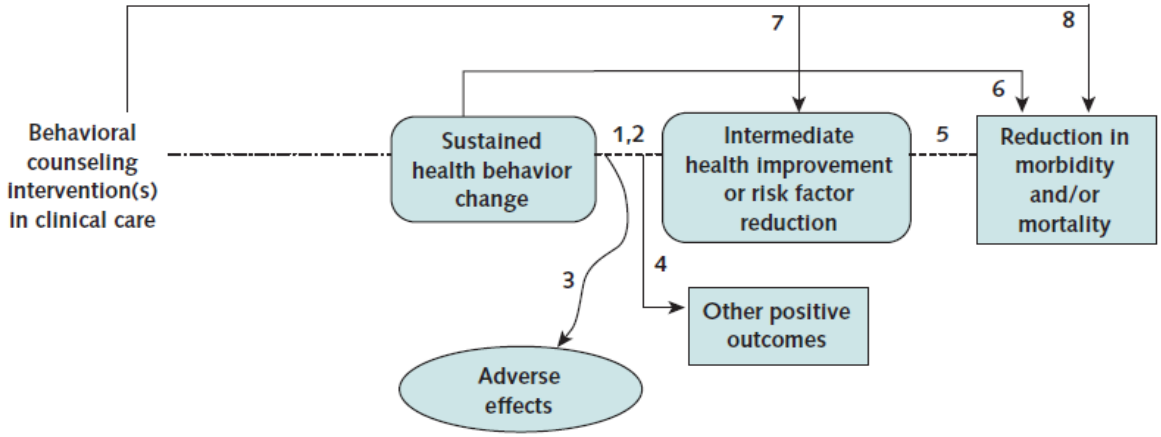


Figure 9. Analytic framework for behavioural counselling interventions[98]

Briefly, evaluation of these interventions focuses on two primary questions: do interventions in the clinical setting influence persons to change their behaviour, and does changing health behaviour improve health outcomes with minimal harms?

Key questions:

1. Do changes in patients' health behaviour improve health or reduce risk factors?
2. What is the relationship between duration of health behaviour change and health improvement (i.e., minimum duration, minimum level of change, and change–response relationship)?
3. What are the adverse effects of health behaviour change?
4. Does health behaviour change produce other positive outcomes (e.g., patient satisfaction, changes in other health care behaviours, improved function, and decreased use of health care resources)?
5. Is risk factor reduction or measured health improvement associated with reduced morbidity or mortality?
6. Is sustained health behaviour change related directly to reduced morbidity or mortality?
7. Are behavioural counselling interventions in clinical care related directly to improved health or risk factor reduction?
8. Are behavioural counselling interventions in clinical care related directly to reduced morbidity or mortality?

Bloss et al[99] reviewed the literature on lifestyle behavioural change in response to genetic testing for common disease susceptibility variants. They note that while simple communication of genomic information and disease susceptibility may be sufficient to catalyse lifestyle changes in some highly motivated groups of individuals, for others, additional strategies may be required to prompt changes, including more sophisticated means of risk communication (e.g., in the context of social norm feedback) either alone or in combination with other promising interventions (e.g., real-time wireless

[97] Ibid.

[98] Ibid.

[99] Cinnamon S. Bloss et al., 'Genomic Information as a Behavioral Health Intervention: Can It Work?', *Personalised Medicine* 8, no. 6 (November 2011): 659–67.

health monitoring devices). Genomic information may be more likely to motivate risk-reducing lifestyle behaviours when combined with other interventions, including interventions that provide real-time continuous feedback. In the context of models of behavioural change, this makes sense insofar as for a given behavioural change to occur, multiple needs may have to be addressed and multiple variables considered [100] (see Figure 10).

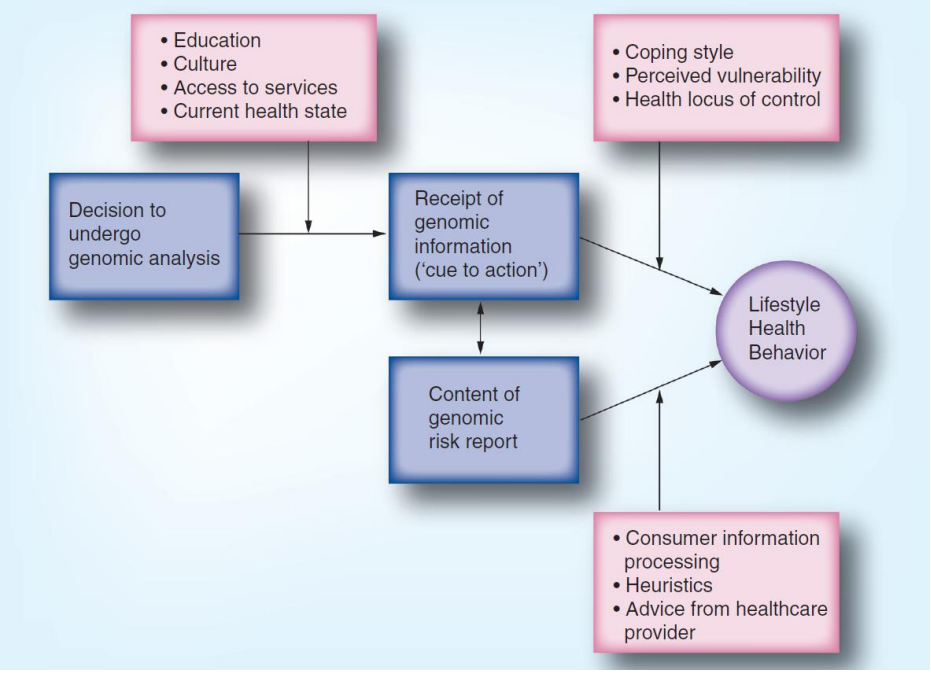


Figure 10. Framework of possible constructs that may predict health behaviour change in the genomic setting

Behavioural counselling interventions differ from screening interventions in several important ways that affect the ease and likelihood of their being delivered. Behavioural counselling interventions address complex behaviours that are integral to daily living; they vary in intensity and scope from patient to patient; they require repeated action by both patient and clinician, modified over time, to achieve health improvement; and they are strongly influenced by multiple contexts (family, peers, worksite, school, and community).[101]

Ethical and legal challenges as a critical evaluation aspect

Proponents of personalised medicine see several ethical and social challenges: meaningful and adequate informed consent for genetic testing, privacy and confidentiality of personal genomic information, differential access to health care resources for patients and clinicians, and the costs of integrating new technologies into the health care system.[102] The burden of managing costs of

[100] Ibid.

[101] Evelyn P Whitlock et al., 'Evaluating Primary Care Behavioral Counseling Interventions: An Evidence-Based Approach 1', *American Journal of Preventive Medicine* 22, no. 4 (May 2002): 267–84.

[102] Michelle L. McGowan et al., 'Integrating Genomics into Clinical Oncology: Ethical and Social Challenges from Proponents of Personalised Medicine', *Urologic Oncology* 32, no. 2 (February 2014): 187–9.

genomic technologies within the health care system loom large, and there is little consensus about how to effectively and efficiently incorporate genomics into health care.[103]

Weighing the social costs of expensive technologies and treatments is also a longstanding health care problem. Some guidance can therefore be found in deliberative democratic approaches to assessing the fair distribution of scarce health care resources[104] and in national health services' conditions for public health funding for targeted therapies on the basis of medical necessity, though proposed solutions are nonetheless fraught with practical and moral complexity.[105]

Ethical, legal, and social issues associated with the implementation of personalised medicine approaches need to be integrated throughout the translation of personalised medicine approaches into the healthcare system.[106] The societal impact of personalised medicine will need to be addressed as social perceptions, expectations, and values between stakeholders may be different and will have an impact on decision making. The difference in values between patients and practitioners must also be addressed. The commercialisation of personalised medicine tools will require research related to the ethical, legal, and social implication of these tools.[107]

Revision of the current evidence-based medicine model for assessing the clinical and cost-effectiveness of personalised therapies is, therefore, critically important, both for the design of ethical studies and the promotion of opportunities for personalised medicine in the future. This is especially important with regard to qualifying and quantifying the survival impact of treatments, which is critical to determining the cost-effectiveness of expensive new treatments, but hindered by most RCT designs. Understanding the overall survival impact and cost-effectiveness of new treatments will therefore require both new methodologies and new approaches to interpreting evidence.[108]

[103] Feero W, Wicklund C, and Veenstra DL, 'The Economics of Genomic Medicine: Insights from the Iom Roundtable on Translating Genomic-Based Research for Health', *JAMA* 309, no. 12 (27 March 2013): 1235–36, doi:10.1001/jama.2013.113.

[104] Leonard M. Fleck, 'Pharmacogenomics and Personalised Medicine: Wicked Problems, Ragged Edges and Ethical Precipices', *New Biotechnology*, Molecular Diagnostics & Personalised Medicine, 29, no. 6 (15 September 2012): 757–68, doi:10.1016/j.nbt.2012.03.002.

[105] Kelly A. McClellan et al., 'Personalised Medicine and Access to Health Care: Potential for Inequitable Access?', *European Journal of Human Genetics: EJHG* 21, no. 2 (February 2013): 143–47, doi:10.1038/ejhg.2012.149.

[106] McGowan et al., 'Integrating Genomics into Clinical Oncology'.

[107] F. Randy Vogenberg, Carol Isaacson Barash, and Michael Pursel, 'Personalised Medicine', *Pharmacy and Therapeutics* 35, no. 11 (November 2010): 624–42.

[108] Jan R. R. Lewis et al., 'The Economic Evaluation of Personalised Oncology Medicines: Ethical Challenges', *The Medical Journal of Australia* 199, no. 7 (7 October 2013): 471–73.