FINAL REPORT

Feasibility study for the development of business cooperation, management organisation and evaluation methodology for personalised medicine pilot project

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### Acronyms

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<th>Description</th>
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<tbody>
<tr>
<td>CCHT</td>
<td>Competence Centre of Heath Technologies</td>
</tr>
<tr>
<td>CDSS</td>
<td>Clinical decision support system</td>
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<tr>
<td>CIO</td>
<td>Chief Innovation Officer</td>
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<td>CPH</td>
<td>Copenhagen</td>
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<tr>
<td>CPOE</td>
<td>Clinical Physician Order Entry</td>
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<tr>
<td>CRO</td>
<td>Clinical Research Organisation</td>
</tr>
<tr>
<td>DDSS</td>
<td>Digital Decision Support Systems</td>
</tr>
<tr>
<td>eMERGE</td>
<td>Electronic Medical Records and Genomics</td>
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<tr>
<td>EBMeDS</td>
<td>Evidence-Based Medicine electronic Decision Support</td>
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<tr>
<td>EGCUT</td>
<td>Estonian Genome Center of the University of Tartu</td>
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<tr>
<td>EHIF</td>
<td>Estonian Health Insurance Fund</td>
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<tr>
<td>EIF</td>
<td>European Investment Fund</td>
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<tr>
<td>EMR</td>
<td>Electronic medical record</td>
</tr>
<tr>
<td>EPMPP, PP</td>
<td>Estonian Personalised Medicine Pilot Project</td>
</tr>
<tr>
<td>ETRIKS</td>
<td>European Translational Information and Knowledge Management Service</td>
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<tr>
<td>FDI</td>
<td>Foreign direct investments</td>
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<tr>
<td>FIMM</td>
<td>Institute for Molecular Medicine Finland</td>
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<tr>
<td>GE</td>
<td>Genomics England</td>
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<tr>
<td>GP</td>
<td>General Practice</td>
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<tr>
<td>GeCIP</td>
<td>Genomics England Clinical Interpretation Partnership</td>
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<td>GMCs</td>
<td>Genomic Medicine Centres</td>
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<tr>
<td>GP</td>
<td>General Partner</td>
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<tr>
<td>HEE</td>
<td>Health Education England</td>
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<tr>
<td>HIE</td>
<td>Health Information Exchange Platform</td>
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<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
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<tr>
<td>ICT</td>
<td>Information and communications technology</td>
</tr>
<tr>
<td>IPO</td>
<td>Initial Public Offering</td>
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<tr>
<td>IPR</td>
<td>Intellectual Property Rights</td>
</tr>
<tr>
<td>LP</td>
<td>Limited Partner</td>
</tr>
<tr>
<td>MSA</td>
<td>Ministry of Social Affairs</td>
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<tr>
<td>NCTCR</td>
<td>National Centre for Translational and Clinical Research</td>
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<tr>
<td>NGO</td>
<td>non-governmental organisation</td>
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<tr>
<td>NHGRI</td>
<td>National Human Genome Research Institute</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>NHSE</td>
<td>National Health Service England</td>
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<tr>
<td>PE</td>
<td>Private Equity</td>
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<tr>
<td>OECO</td>
<td>Organisation for Economic Co-operation and Development</td>
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<td>PHE</td>
<td>Public Health England</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>PM</td>
<td>Personalised Medicine</td>
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<tr>
<td>RoI</td>
<td>Return on Investment</td>
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<tr>
<td>R&amp;D&amp;I</td>
<td>Research &amp; Development &amp; Innovation</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trials</td>
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<tr>
<td>SDLC</td>
<td>System development life-cycle</td>
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<td>SiSu</td>
<td>Sequencing Initiative Suomi</td>
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<tr>
<td>SME</td>
<td>Small and medium-sized enterprises</td>
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<tr>
<td>STO</td>
<td>Stockholm</td>
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<tr>
<td>TAI</td>
<td>National Institute of Health Development</td>
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<td>UT</td>
<td>University of Tartu</td>
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Executive summary

The past few years have led personalised medicine from being a futuristic vision to an actual and widely accepted innovative approach to healthcare. In October 2013, the European Commission published a document on “-omics” technologies in personalised medicine that outlines several specific perspectives for personalised medicine: ability to make better-informed decisions; increase in the probability of achieving desired results due to more precise medical approach; decrease in the probability of the use of contraindicative medicines; focus on prevention and prediction instead of responding to illnesses; faster intervention in pathogenesis compared to the current situation; and better control over expenses in healthcare.

Still, the present solutions available in personalised medicine account for only a fraction of what could be achieved if the full potential of personalised medicine is unleashed. The uniqueness of the opportunity for all stakeholders lies in the notion that so far there is no existing and validated model of personalised medicine (also known as personal or precision medicine) in wide clinical practice, which makes the quest for a working “prototype” desirable for showing the benefits, outcomes, risks and implications of personalised medicine. A successful breakthrough assumes strategic and well-organised cooperation between four fields: clinical practise, research and development, business and healthcare informatics (E-health).

Estonia has been a pioneering actor in the global society of personalised medicine from the early days of the development of the concept. The establishment of clear and transparent legal environment and organisational structures led to the creation of a globally competitive initiative for collecting genomic and health data. Thus, Estonia has been among the forerunners of the personalised medicine league. In addition, Estonia has taken bold steps in implementing digital technologies for authentication and handling public data, which has resulted in a globally unique secure public data exchange platform. Public support to health and genomic data collection and scientific research has also created a beneficial environment for personalised medicine development and implementation in Estonia.

In December 2014 the government made a principal decision to actively pursue further steps in creating competitive personalised medicine infrastructure. For this end the Estonian Personalised Medicine Pilot Project (EPMPP) was planned. According to the concept paper approved by the Ministry of Social and Affairs 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 in the area of personalised medicine.

More specifically there are three target areas defined as aims of personalised medicine development:
• 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;
• to implement an ecosystem of research, development and innovation to support the transfer of knowledge about PM to universities and companies.

To prepare the EPMPP a feasibility study was procured by the Ministry of Social Affairs of Estonia. The current report is addressing the study component on central governance structure of EPMPP, the business opportunities that EPMPP can create and how to evaluate the implementation process.

It is well-known fact that the majority of new innovations and initiatives fail because of weak governance and management of implementation, including lack of co-ordination. Personalised medicine is not just a research and innovation project with a huge amount of health related data, but also should be made possible with a well-established organisation and management of new knowledge and competencies, resources and, last but not least, the trust in society.

As there are several and often confusing interpretations of the notion of personalised medicine a consensus definition was developed by the project steering committee. For sake of this study the following definition was agreed and used:

*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.*

To map the current landscape semi-structured interviews as input for a stakeholder analysis were performed, covering all relevant parties involved in PM field. Vast majority of stakeholders indicated clear support to PM development. However, majority of stakeholders underlined that PM concept, definition and the purpose should be well described before the start of the project. Also, importance of central coordination and leadership was emphasised: be it for database solution or other major activities of the project. The need for a sufficiently fast initiation speed and the critical mass of actors involved was another important element underlined.

A full implementation of in every-day health care practices must be preceded by a well-coordinated and managed pilot project, which has to cover several aspects: (1) legal regulation for entire PM landscape, including data access and protection, rights and responsibilities in relation to treatment and research; (2) the value chain and system of risk assessment and diagnostics, counselling and preventive treatment; (3) financing of PM services; (4) training and competency development support for professionals; (5) comprehensive (public) communication and public education before and during the pilot project; (6) systematic handling of ethical issues; (7) and last but not least, transparency in additional resource needs, sources of funding and advantages of PM compared to the current approach.
An overview of most often cited international PM initiatives and the global PM market as a set of different sub-markets with their own dynamics, customers and development drivers was conducted in correspondence with the Estonian strengths and opportunities in the field. Estonia, having already a well-regulated comprehensive biobank and advanced e-health data infrastructure, has some specific advantages on the global arena. Three key industry sectors can give an opportunity to position Estonia as an attractive and important partner in the global PM value chain: (1) Drug discovery & clinical trials sector; (2) Diagnostics sector including the development of both, software and hardware solutions; and (3) Decision support applications sector (ICT solutions, big data analysis, interfaces, secure data processing, etc.). However, the advantages that Estonia has is temporary, taking into account the major efforts planned by a number of countries and the window of opportunity for Estonia is probably open only for the next years.

As already mentioned, the organisational and governance model is the key for balancing stakeholder interests and providing value to the society. The choice of management and co-ordination model of the EPMPP will also have a crucial role in attracting foreign investments and developing the research network to secure the feasibility of the project. For the successful outcome of the EPMPP implementation process the working group suggests to use a combination of two legal structures under private law as the most optimal strategy: (1) a special purpose non-profit foundation set up by the government with the task to coordinate all activities in the field of PM in Estonia; and (2) a for-profit entity founded by the non-profit foundation for global commercial activities. The latter is proposed to be a concerted action between the government, academic partners and investors. As for implementation depth, two basic scenarios of EPMPP are proposed: (1) optimal, where most of the projected activities will be implemented and, hence, also most of the set goals can be anticipated to be fulfilled; (2) minimal, where only basic or very little of planned activities can probably be accomplished.

Depending on PM pilot project scope and specific set-up, an approach that allows to monitor and evaluate the entire value chain of the project and to balance short-term and long-term evaluation needs has to be defined in the very beginning of the pilot project, however, with respect that during the development it has to be adjusted according to specific needs and learned experience. The EPMPP evaluation framework, developed during the feasibility study, 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. The 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. 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 rollout 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.

Thus the next steps for wider personalised medicine implementation were outlined in the feasibility study and should provide the necessary input for building the initial organisational structure, involving stakeholders and learning from the experience as a whole society, which facing the challenges and opportunities of future healthcare.

Executive summary

Rahvusvaheline Inimgenoomi Projekti lõppemisel 15 aastat tagasi olid kõrged ootused personaalmeditsiini (PM) koheseks rakendamiseks tervishoius. Tegelikkus osutas märksa keeruliseid ning alles viimastel aastatel on personaalmeditsiini teenused ja ravimeetodid hakanud kanda kinnitama igapäevase teadmispõhise tervishoiu arsenalis. 2013. a. oktoobris avaldas Euroopa Komisjon dokumendi personaalmeditsiini “omics” –tehnoloogiatest tuues välja mitmed spetsiifilised arenguvõimalused tervishoius: võime teha teadlikumaid otsuseid diagnostika- ja raviprotsessis; suurendada tõenäosust saavutada soovitud tulemusi; vähendada ravimite kõrvalnäht; keskenduda juba tekinud haiguste ravimise asemel nende prognoosimisele ja ennetusele; vahetumalt ja kiiremini mõjutada haiguste patogeneesi ning, köike eelnevat arvesse võttes, ohjata järjest kasvavaid tervishoiukulutusi.

Tänased praktilised personaalmeditsiinilised lahendused võimaldavad ära kasutada vaid murdosa köigest sellest, mida personaalmeditsiini rakendamine võiks potentsiaalselt pakkuda. Hetkel ei ole olemas valideeritud mudelit personaalmeditsiini laiemaks liikumiseks rakendamiseks ja seetõttu on üheks peamiseks globaaliseks tervishoiualaseks järgmiseks väljakutseks sellekohase prototüübi loomine. Kriitiliseks on strateegiline ja hästi organiseeritud koostöö neljas valdkonnas: kliiniline praktika, teadusarendustegevus, ettevõtlus/äriarendus ja tervishoiu informatika (E-tervis).

Eesti on olnud personaalmeditsiini globaalse kogukonna pioneeride hulgast nüüd kasutada võimalikuid tõhusaid eesliikumisi: digitaalsete tehniliste eesliikumiste kasutamine, tervishoiuplaanide, ettevalmistuse ja digitaalse tervishoius, võidakse kasutada digitaalsete tehnoloogiate rakendamisel eesliikumisest kasulikud. Lisaks on Eesti astunud olnud personaalmeditsiini kogukonnas kasutada võimalikuid võimalusi, mis võimaldavad suurendada digitaalsete tehnoloogiate rakendamisest kasulikuks ning hea organisatsiooniline suutlikkus on võimaldanud luua rahvusvaheliselt konkurentsivõimalise genoomika- ja terviseandmete kogu, mis omakorda on tõstnud Eesti personaalmeditsiini eesliikumise hulk. Lisaks on Eesti astunud oluliselt samme digitaalsete tehnoloogiate rakendamisel riigi tasandil andmete kasutamiseks ja autentimiseks. Selle tulemuseks on unikaalne ja turvaline andmetehnikas, mis loob
võimalused tõsta avaliku halduse suutlikkust ja efektiivsust. Märkimisväärne avalik toetus tervise- ja geneeniandmete kogumiseks ja teadusuuringute läbiviimiseks aitab samuti kaasa soodsa keskkonna loomiseks personaalmeditsiini arendamisel ja rakendamisel.

Detsembris 2014 tegi Eesti valitsus otsuse alustada aktiivset tegevust konkurentsivõimalise personaalmeditsiini infrastruktuuri loomiseks, mille esimeseks sammaks planeeriti Eesti Personaalmeditsiini Piloottprojekti (EPMPP) läbiviimine. Vastavalt Sotsiaalministeeriumi poolt heaks kiidetud kontseptsioonidokumendile on pilootprojekti eesmärgiks luua aktiivsete ja koordineeritud tegevuste abil võimalused personaalmeditsiini arendamiseks, juurutamiseks ning sellega seotud tervishoiu teenuste ja ettevõtluse arendamiseks, kasutades ära ning võimendades juba saavutatut.

Personaalmeditsiini pilootprojekti vahtuteks eesmärkideks on:
- valideerida personaalmeditsiini rakendatavust ja efektiivsust kliinilises patsiendikäsitluses vähemalt kolmes valdkonnas;
- arendada välja informatika- ja andmehallustaristus personaalseeritud lähenemiseks haiguste ennetamiseks ja ravis;
- juurutada teadus-arendustegevuse ja innovatsiooni ökosüsteem personaalmeditsiini ajaluse teadmussiridte toetuseks ülikoolidele ning ettevõtetele.


On tõsias, et uued innovatsioonid ja ettevõtmised ebaõnnestuvad sageli kesise valitsemise, juhtimise ja/või ebapiisava koostöö tõttu. Personaalmeditsiini rakendamiseks ei piisa lihtsalt teadus- ja arendustegevusest suurandmete valdkonnas. Õnnestumiseks on tähtis ühiskonna poolne usaldus ja võimekus korraldus ning juhtimine.

Personaalmeditsiini mõiste selgitamiseks on kasutatud erinevaid, sageli segadust tekitavaid, sõnastusi ning seetõttu alustati käs olevalt hakati prosessi osalejatele ühtselt arusaadava definitiiooni kokku leppimisega, mille tulemusena kinnitati töötati juhtühma poolt välja EPMPP kontekstis kasutatav personaalmeditsiini definitsioon:

*Personaalmeditsiin tähistab individuaalsete geno- ja fenotüübi andmete põhjal arvutusliku analüüsi, mille tees analüüsiga leitud indivi dussete riskide tõenäosustele ning otsustet olgu on teatud, diagnoosimist ja ravi. Personaalmeditsiini rakendamine panustab preventiivse, prognoosiva ja inimesi kaasava lähenemise ulatuslikumasse juurutamisesse tervisesüsteemis.*

Personaalmeditsiini maastiku kaardistamiseks analüüsiti valdkonnaga seotud osapoolte seisukohti kasutades pool-struktureeritud intervjuusid. Enamus küsitletutest väljendas selget poolehoiu PM arendustele, tuues välja vajaduse kirjeldada enne pilootprojekti käivitamist üheselt ja erinevatele osapoolte arusaadavalt PM kontseptsiooni, tähendust ja eesmärke.
Tõsteti esile ka projekti keskse koordineerimise ja eestvedamise olulisust nii andmebaaside kui ka muude suuremate rakenduste arendusega seonduvalt. Läbiviimise kiirust ja kriitilise osalejate hulga saavutamist peeti samuti olulisteks tingimusteks projekti õnnestumisel.

PM kontseptsiooni laiemaks rakendamiseks on oluline viia läbi hästi koordineeritud ja juhitud pilootprojekt, mis hõlmaks vähemalt järgnevaid komponente: (1) PM rakendamisega seonduv optimaalne õiguslik regulatsioon sh. ligipääs andmetele ja andmekaitse, kliinilise tegevuse ja teadusuuringutega kaasnevad osapoolte õigused ja kohustused; (2) haigusriikide määramise ja haiguste diagnostika, nõustamise ja ennetava ravi valdkonna väärtusahel (ja süsteem); (3) PM teenuste finantseerimine; (4) osalavate spetsialistide koolitus ja kompetentsid; (5) laiastulatukõhine biopank ja E-tervise infrastruktuur annavad meie teatud rahvusvahelise eelise ja võimaluse kiireteks edasisteks arendusteks. Viib välja tuua kolm põhilist valdkonda, kus Eesti võiks globaalses PM väärtusahelas eda saavutada: (1) ravimiarendus ja kliinilised uuringud; (2) Diagnostikasektor koos riist- ja tarkvaaraarendusega; (3) digitaalsed otsusetoe rakendused (IKT lahendused, suuremahulised andmeanalüüsid, kasutajaliidesed, turvaline andmevahetus jne.). Seejuures on oluline märkida, et võttes arvesse mitmete riikide üha kasvatav aktiivsus personaalmeditsiinis, on edumaa ajutine ja kestab tõenäoliselt vaid järgnevad 1-2 aastat.

Nagu ülal juba mainitud on organisatsiooni- ja juhtimismudel võtmeteguriks osapoolte huvide tasakaalustamisel ja eelduseks projekti eesmärke saavutamisel. EPMPP juhtimis- ja koordinatsionimudel kannab otsustavat rolli ka välisinvesteeringute ligitõmbamises ja teadusalase võrgustiku arendamisel. Et saavutada EPMPP edukas läbiviimine, soovitab uuringu tööruhm optimaalseima võimalusena kahe ERAJoshigusliku struktuuri kombinatsiooni: (1) valitsuse poolt spetsialiselt, kõikide Eesti PM tegevuste koordineerimiseks, loodud sihtasutus; ja (2) eeltoodud sihtasutuse poolt asutatud äriühing. Äriühingu loomine peaks rajanema valitsuse, akadeemiliste partnerite ja investorite koostöol, mis on seega ka enamus seedet eesmärke täidetakse; (2) minimaalne, mille puhul rakendatakse vaid mõned peamised või väike osa planeeritud tegevustest.

Pilootprojekti läbiviimiseks ning üli- ja pikaajaliste eesmärkide täitmise jälgimiseks on oluline EPMPP tegevuste süsteemne hindamine ja kogemusest õppimine. See eeldab piisavas mahus hindamistegevusi, samuti selget hindamisraamistikku, metodikat ning organisatsioonilist
struktuuri hindamise läbiviimiseks. Käesolevas töös 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 pakuti välja peamised hindamismõõdud ja -küsimused, et pilootprojekti tulemuslikkust hinnata koos selgituse ning hindamise eest vastutavate organisatsoonidega.
Introduction

The past few years have led personalised medicine from being a futuristic vision to an actual and widely accepted innovative approach to healthcare. In October 2013, the European Commission published a document on “-omics” technologies in personalised medicine that outlines several specific perspectives: ability to make better-informed decisions; increase in the probability of achieving desired results due to more precise medical approach; decrease in the probability of the use of contraindicative medicines; focus on prevention and prediction instead of responding to illnesses; faster intervention in pathogenesis compared to the current situation; and better control over expenses in healthcare.

Still, the present solutions available in personalised medicine account for only a fraction of what could be achieved if the full potential of personalised medicine is unleashed. The uniqueness of the opportunity for all stakeholders lies in the notion that so far there is no existing and validated model of “personal/precision medicine” in wide clinical practice, which makes the quest for a working “prototype” desirable. Critical aspects for a successful breakthrough assume strategic and well-organised cooperation between four fields: clinical practice, research and development, business and healthcare informatics (E-health).

Estonia has been pioneering actor in the global society of personalised medicine from the early days of the development of the field. By establishing clear and transparent legal environment and initiating organisational capacity that has lead to creation a globally competitive collection of genomic and health data has Estonia been among the forerunners of the personalised medicine league. In addition, Estonia has taken bold steps in implementing digital technologies for public data handling and digital authentication, which has resulted in an unique public secure data exchange platform. Public support to health and genomics data collection and scientific research is also creating a beneficial environment for personal medicine development and implementation in Estonia.

In December 2014 the government made a principal decision to pursue actively further steps in creating competitive personalised medicine infrastructure. For this end the Estonian Personalised Medicine Pilot Project (EPMPP) was planned. According to conception paper approved by the Ministry of Social and Affairs 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 in the area of personalised medicine.

More specifically there are three target areas defined as priority components of PM development:
• to validate the possibility of the implementation and the efficiency of clinical treatment of patients in at least three areas;
• to develop computing and data management infrastructure for a PM approach;
• to implement an ecosystem of research, development and innovation to support the transfer of knowledge about PM to universities and companies.

It is well-known fact that many of new innovations and initiatives fail because of the weak management, governance and lack of co-ordinated implementation. Personalised medicine is not just research and innovation with huge amount of health related data, but also well established organisation and management of new knowledge and competencies, resources and last but not least the trust in society.

A feasibility study to prepare lay the basis for EPMPP was procured by the government and is commissioned by the Ministry of Social Affairs in Feb 2015. The research was carried out by the Tartu Biotechnology Park and Praxis Centre for Policy Studies from March to July. The project was supported by the European Union Structural Funds via the programme TerVE implemented by the Estonian Research Council.

As there are several and often confusing interpretations of the notion of personalised medicine, a consensus definition was developed by the project steering committee. For sake of this study the following definition was agreed and used:

*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 current report is addressing the study component on central governance structure of EPMPP, the business opportunities that EPMPP can create and how to evaluate the implementation process.

Chapter one gives an overview of PM developments in Estonia, referring to existing projects, practices and also defining some of the strengths and weaknesses of PM development so far. It also provides an insight to the stakeholders’ world concluding that balancing the interests and roles of the main stakeholders in short-, medium- and long term proves to be a key for EPMPP success. Chapter one provides also an overview on specific developments in business sector in Estonia in relation to the PM.

Chapter two provides an overview of most often cited international PM initiatives and the global PM market as a set of different sub markets with their own dynamics, customers and development drivers. The chapter also outlines the PM market sectors that are most relevant for Estonia with respect to the market size, growth and correspondence with Estonian strengths to illustrate the size of the opportunity. The chapter concludes with the discussion about the current status of the market development and the Estonian strengths, opportunities and key stakeholders for the development of the EPMPP. The section concludes that 3 key industry sectors can create an opportunity to develop Estonia as an attractive and
important partner in the global PM value chain: (1) Drug discovery & clinical trials sector; (2) Diagnostics sector including both hard and software solutions development; and (3) Decision support applications sector (ICT solutions, big data analysis, interfaces, secure data processing, etc.). Having already a well regulated comprehensive biobank and advanced E-health data infrastructure in place gives Estonia some advantage over most same size competitors on global arena. However, the advantage is only temporary, taking into account the major efforts planned by a number of countries. This means the window of opportunity for Estonia to be open for the next 1-2 years only.

Chapter three focuses on organisation and governance models, providing comparative analyses of different options and gives recommendations for future development. As mentioned earlier organisational and governance model lay as a key how to balance stakeholder interests and yet provide value to society. The choice of management and coordination model of the EPMPP will have a crucial role in attracting foreign investments and developing the research network to secure the project’s feasibility. The chapter is concluding the work of previous chapters by summarising the work of the task group in suggesting actual solutions for the governance structure that possibly could pave the way to successful and sustainable implementation of EPMPP. Solutions for two scenarios of EPMPP are proposed: (1) optimal, where most of the projected activities will be implemented and, hence, also most of the set goals can be anticipated to be fulfilled; (2) minimal, where only basic or very little of planned activities can probably to be accomplished. For the successful outcome of the EPMPP implementation process it will be most optimal to harness a combination of two legal structures under private law: a special purpose non-profit foundation set up by the government with the task to coordinate all activities in the field of PM in Estonia; and a for-profit entity founded by the non-profit foundation for commercial activities. The latter is proposed to be a concerted action between the government, academic partners and investors.

Chapter four discuss about different evaluation approaches and suggests input – process – output – outcome measurement approach. Given approach allows to monitor and evaluate entire value chain and to balance short-term and long-term measurement needs. Depending on pilot project scope and specific set-up, an evaluation model has to be defined in the very beginning of the pilot project, however with respect that during the development it has to be adjusted according to specific needs and learned experience. 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 rollout 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.

The first three chapters of the report have been prepared by the team lead by Tartu Biotechnology Park (Tartu, Estonia). Tartu Biotechnology Park was also the general coordinator of the study component. The project team consisted several experts: Dr Jaanus Pikani, Dr Andres Rannamäe, Dr Krista Kruuv-Käo, Mr Rauno Vinni, Ms Katriin Antonov and Mrs Margit Ilves; Mr Seppo Mäkinen and Mrs Kadri Vunder Fontana were adding a valuable contribution as international business experts. The fourth chapter of the report on evaluation methodology was lead by the Health Policy Programme at Praxis Centre for Policy Studies (Tallinn, Estonia). The core research team involved Mr Priit Kruus, Mrs Gerli Paat-Ahi, Dr Andres Rannamäe, and Dr Noel Carrol.

This feasibility study has combined a variety of methodologies from extensive literature reviews up to interviews, expert group work and systematic analysis. Foreign expertise was used to focus the literature reviews, to develop the prototypes, and to formulate the recommendations. More detailed description of used methodology is introduced at the beginning of each paragraph.
1. Overview of the current personalised medicine environment in Estonia

1.1. Current experience in implementation of personalised medicine and genomic data projects in Estonia

This chapter outlines the inter-organisational cooperation cases in implementation of personalised medicine and genomic data projects and services. Although there are only few examples that correspond fully to the definition of personalised medicine used in this study, some cases demonstrated are well illustrating the strengths and readiness for inter-organisational collaboration in implementation of EPMPP.

The chapter is defined into three sections. The first section gives overview of project and organisations related to implementation of personalised medicine R&D projects. The second one introduces collaboration in provision of clinical services that are funded by Estonian Health Insurance Fund. The third section contains examples of private companies developing and/or offering PM services.

The methodology used was semi-structured interviews conducted by the project team. The interviewed managers of the organisations were proposed to describe their current experience in collaboration in implementing the projects related to the analyses of gene data and/or personalised medicine (counselling) services. The questions asked included the aims and purposes of the collaboration and collaborative mechanisms, and the manner in which they have been employed and regulated. (The list of interviewed organisations and their representatives is given in Appendix 3).

For the last 15 years or so the notion of personalised medicine has been used in Estonia differs in some ways from the PM definition used for this feasibility study and has been connected mainly with the use of genomic data in evidence-based preventive, prognostic and engaging approach for preventing and treating diseases adjusted for personal risks. Major and pioneering role in the field relies with the Estonian Genome Center of the University of Tartu (EGCUT) which can be considered a ground-breaking initiative in the field of personalised medicine not only in Estonia but also globally. On the other hand Estonia exceeds most countries by advanced e-governance infrastructure X-road with e-health system being part of the infrastructure. The e-health component of the X-road platform has been developed and maintained by a public not-for-profit company the Estonian E-Health Foundation. Although the project team tried to have as comprehensive as possible coverage of the Estonian PM landscape there might be some examples that have been not addressed in this overview. In particular it can true for academic research projects or small commercial developments that have been published or reached the market. Taking into account the component of “computational decision support analysis of person’s phenotype and genotype data” of
definition of personalised medicine used for this study, not too many examples will match the criteria.

The general state of development of the personal medicine and genetic consulting service in Estonia is similar and in some respect even more advanced compared to other countries that have decided to move toward implementation of personalised medicine. For example, Estonia shares several strengths that Maarja-Liisa Voipio-Pulkki - the Minister of Social Affairs and Health in Finland – outlined in her presentation at the GetPersonalised Summit 2015\(^1\):

- Strong tradition in genetic and molecular medicine research,
- Active research in the field of personalised medicine,
- Strong IT management capabilities,
- Nationwide electronic patient data repository,
- Reliable registries and population databases.

In addition to that, Finland emphasises its vital research and innovation environment, which is expected to facilitate collaboration and attract investments. Still, having already a well regulated comprehensive biobank and advanced E-health data infrastructure in place gives Estonia some advantage over most same size competitors on global arena. In Estonia, good examples of cooperation are the R&D&I projects implemented by the Estonian Genome Center of the University of Tartu, Institute of Computer Science of the University and eMed Lab of Technomedicum of Tallinn Technical University, Competence Centre on Health Technologies and the Software Technology and Applications Competence Centre.

One of the aspects of the Estonian innovation environment that can be improved is the cooperation between academia and businesses. This issue has been raised in several documents (e.g. the strategic Teadmistepõhine Eesti 2007-2013, 2014-2020) as well as by influential scientists, entrepreneurs and during public debates.

A research paper published by M.Vadi and T.Haldma from the two largest Estonian Universities (University of Tartu and Tallinn University of Technology) is pointing out that the factors influencing cooperation between universities and industry are often influenced by external factors, including social demand and request, statutory framework, proper research funding etc. as well as by a number of internal institutional factors, like organisational and management culture, nature of academic work are influencing knowledge transfer \(^2\). Competent and active individuals have an important role in initiating and completing such projects.

1. **Project and organisations related to implementation of personalised medicine**

**R&D projects**

\(^1\) http://www.slideshare.net/SitraHyvinvointi/voipiopulkki-nettiin

• **Estonian Genome Center of the University of Tartu (EGCUT)** is a research institute at the University of Tartu that aims to promote development of human genetic research, and to collect information on health issues and genetics of the Estonian population. The activities of EGCUT are focused on using results of the latest genomic research to improve public health and on acting as forerunner of personalised medicine in Estonia. EGCUT has extensive experience in collaborating with government organisations, large hospitals, universities, primary care providers and patients. EGCUT is also a founding member and a scientific partner in CCHT. The international collaboration of EGCUT with relevant institutions is excellent. The collaboration is mostly carried out in the form of research projects with more than one international partner.

EGCUT has the most advanced knowledge in personalised medicine among Estonian organisations. With its state-of-art biological sample handling and storage, genotyping and research infrastructure, and extensive international network EGCUT has definitely the largest socio-economic impact among the organisations covered by the overview. The research delivered by EGCUT can be a valuable input for new products and services for developed by biotech and pharma industry as well as health care providers. Some of these examples are included below.

• **Institute of Computer Science of the University has established the Bioinformatics, Algorithmics, and Data Mining research group BIIT** which is a joint research group between the Department of Computer Science of the University of Tartu, bio-IT company Quretec and the Estonian Biocenter. BIIT’s main research topics and capabilities include gene regulation, gene expression data analysis, biological data mining, systems biology, combinatorial pattern matching, developing software for biomedical research databases, as well as partnering in stem cell and cancer related projects. The Institute is a partner in the Estonian Center of Excellence in Computer Science and the Software Technology and Applications Competence Centre. The Institute is also a regional coordinator of European life-science infrastructure development project ELIXIR. The aim of the project is to build a sustainable European infrastructure for biological information, supporting life science research and its translation to medicine.

• **The eMed Lab of Technomedicum of Tallinn Technical University** is active in research on health technologies, digital health records, health informatics and development of e-health services. eMed Lab personnel played an essential role in creating Estonian nationwide Health Information Exchange (HIE) platform which opened up new dimensions in research of shared databases and modern shared workflows in healthcare. Starting in autumn 2015, the eMed Lab is a consortium partner of CCHT for implementation of experimental research and development of decision support systems for prevention and treatment of common complex diseases.

• **Reproductive medicine projects developed under Competence Centre on Health Technologies (CCHT)** are focused on novel approaches for human infertility diagnostics and treatment, and human assisted reproductive technologies. Projects started five years ago will enter the industrial research and thereafter product development phase later this year and are planned to be ready for clinical implementation in three to six years. This autumn two personalised medicine projects for common complex diseases and cancer
will be started. CCHT is a consortium consisting of academia, leading biotechnology enterprises and clinics (in total 13 partners). Through collaborative synergy among its partners CCHT aims to establish a platform for innovative technologies’ development and commercialisation. The main funding comes from Enterprise Estonia matched by consortium partners own financing. Research out implementation and intellectual property sharing are regulated by a consortium agreement signed by all partners involved.

- **National Centre for Translational and Clinical Research (NCTCR)** is a national research infrastructure formed by the University of Tartu, Estonian University of Life Sciences and Tartu University Hospital with the aim to improve quality and innovation in health research in Estonia. NCTCR brings together researchers and competencies from diverse areas of medical research. **Happy Pregnancy Study** is an example of translational medicine collaboration between NCTCR and Quattromed HTI Laborid OY (Synlab) with the objective to develop novel non-invasive biomarkers in order to achieve fertility and healthy pregnancy and to develop together with the private partner a multi-marker test of these biomarkers for routine clinical practice. The three-year project started in 2012 and was funded by European Regional Fund. The collaboration activities were conducted in the form of educational and training activities and research sub-projects.

- **Software Technology and Applications Competence Centre (STACC)** is a research and development organisation to conduct high-priority industrial research. STACC conducts industrial research in data mining and software engineering. One of the STACC's research projects is Biomedical Data Integration and Mining. The research team behind this project is developing new tools (prototypes) for health data collection, analysis and presentation by using real data from electronic health records. STACC is a joint initiative between the University of Tartu and Tallinn Technical University, eHealth Foundation and leading IT companies like Cybernetica, Regio, Nortal, Quretec, Browserbite, Skype Technologies, ZeroTurnaround and Massi Miliano. Several additional partners - including EGCUT, EHIF, and the North Estonia Medical Centre etc. - will join STACC for development of predictive genetic models of diseases and decision support systems this autumn.

2. **Collaboration in clinical services already implemented in practice**

- **Genetics Centre of Tartu University Hospital** was created by merging two departments – medical genetics and molecular diagnostics – of the laboratories that offered genetic services. The Genetics Centre offers services in most areas of genetics (including clinical genetics, prenatal diagnostics, molecular diagnostics and oncogenetics). The services are provided throughout Estonia. The main focus of the centre is rare diseases. All services provided are financed by the Estonian Health Insurance Fund. Prenatal diagnostic services of hereditary diseases and disorders are offered in cooperation with general practitioners and gynaecologist. Occasionally there are also patients seeing geneticist directly. The guidelines for prenatal diagnostics are approved by the Estonian Society of Human Genetics, the Estonian Society of Laboratory Medicine and the Estonian Perinatal Society. The lab tests are done in house (by Central Lab of Tartu University Clinics) or ordered from private companies like Asper Biotech. For the clinical genetics services some of lab analyses
are made abroad. The centre is already providing consultation for hereditary ovarian and breast cancer to predict, prevent and improve treatment of the disease, while implementing the test for evaluating the risks for colorectal non-polypous cancer is still under development. These activities are conducted in cooperation with oncology clinics. The Genetics Centre is running a neonatal screening program for detecting hypothyreose and 19 metabolic diseases with therapy available, which is provided routinely by women's clinics in the whole Estonia.

- **Clinic of Haematology and Oncology Of the Tartu University Hospital** offers internationally acknowledged quality standard precision oncology services. The clinic is active in clinical research incl. clinical trials for developing new drugs in PM sponsored by pharmaceutical companies. The Clinic has extensive collaboration with laboratories carrying out genetic testing, both within the hospital as well outside (e.g. Asper Biotech, iGen, Caris Life Sciences, NewOncology).

These collaborations are regulated by contracts, conditions of which are agreed upon during the negotiations. The main problem for the Clinic is financing of the novel treatment modalities as many personalised medicine drugs are still not reimbursed by EHIF.

### 3. Private companies developing and/or offering PM services

- **Asper Biotech**, is a biotechnology company offering wide range of validated genetic tests as well as customised development services and training. The company has a number of collaborative activities both domestic and international in product development and in marketing and sales. The main client for the company are health-care providers. Collaboration is mostly contract-based, the ownership of the results can vary. In case of joint developments proportional sharing is one of the most common solutions. Asper Biotech participates in number of academic research projects. The lists of research partnerships include reputable universities and research institutions both in the U.S.A and in Europe. The projects have been co-financed by EU or Enterprise Estonia. The clinical services offered through doctors are financed by EHIF (in Estonia) or directly by the client in the case of international services. It has to be said that company has good reputation among specialists internationally as a high-level eye disease genetics company. The company is also providing some direct to consumer marketed wellness genetic tests, like physical capabilities testing.

- **Quattromed HTI Laborid OÜ (Synalb)** is the largest private medical laboratory in Estonia with more than 20 years of experience. Since 2013 it belongs to Synlab Group. The company is the clinical laboratory service provider for more than 50% of family doctors in the country. Along it core business of business to business laboratory services it also offers personalised heath assessment packages for private persons. Access to and communication on the service is mainly via web based Patient Portal but also physical consultation is available.

- **IB Genetics (iGen)** is a private company offering genetic testing services to medical and wellness sector. The company has expertise in genetic testing and offers mainly oncogenetic and pharmacogenetic testing with expert interpretation. It also performs
assay development and genotyping services for clinical laboratories, research groups and genetic tests distributors. The most prominent partners in research include the Competence Centre for Cancer Research, the North Estonia Medical Centre and Tartu University Hospital. The **Gene Test Laboratory of IB Genetics** offers a list of consumer genetic tests incl. tests for losing weight, evaluation of the vitamin deficiency risk etc.

- **Sports Gene Llc.** is specialised in personalised medicine consumer wellness testing. The company has elaborated a methodology for assessing individual genetic predispositions to engage in certain sports. It offers two genetic tests – one to determine athletic abilities and one for weight management.

- There are some companies developing or already providing health and wellness products or services that contain some components of personalised medicine like **Cognuse, Fibrotex, BIEX, WellBiome, DietBooster, LabToWellness**.

### 1.2. Mapping of EPMPP stakeholder interest. Overview of the EPMPP’s partners and their potential roles

Current chapter gives an overview of stakeholders of EPMPP and their interest and roles in regard to PM development. The first part of the chapter gives an introduction to the definition of the EPMPP stakeholder and provides background of the interviews performed with representatives of all stakeholder groups. Detailed reflection of stakeholder interviews is presented in Annex 3.

The second part of the chapter provides more specific description of stakeholders’ roles and discussion of potential conflicting interests between stakeholder groups. At the end of the chapter there is provided summary of main findings and issues of concern.

#### 1.2.1. Stakeholders of EPMPP

Stakeholders related to personalised medicine are actors (persons or organisations) with a vested interest in the policy or concept being promoted. Stakeholders may be any person, group or organisation who can be positively or negatively impacted by, or cause an impact on, the actions or activities proposed.

During the current stakeholder analysis we defined ten major stakeholder groups and through interviewing their representatives gathered and analysed qualitative information to determine the interests and expectations that should be taken into account when developing and/or implementing a personalised medicine policy, including the pilot project. The following key stakeholder groups were defined and interviewed:

1. Patients and patient groups.
2. Clinicians.
3. Medical and biotech researchers.
4. Medical and pharma industry.
5. Hospital and outpatient clinic managers.
6. Professional partner organisations.
7. Regulatory authorities.
8. Payer organisation.
10. Investors.

**Stakeholder interviews and used methodology**

The data collection was done by semi-structured interviews. Main focus of the interviews considered the key implications and opportunities what the development of PM can bring to different stakeholders and what roles different stakeholders will carry on, including such stakeholder characteristics as knowledge of the PM policy, interests related to the policy, position for or against the policy, potential alliances with other stakeholders, and the ability to affect the policy process (through power and/or leadership).

Stakeholders were asked the following questions

- Please define the main expectations and positive challenges the development of Personalised Medicine may provide?
- Which changes in the behaviour of the main stakeholders may be forecasted with the development of PM?
- Can you see any potential risks and threats the development of PM may bring along?
- Which requirements and conditions you consider a “must” in order to safely develop the concept and services of PM?
- Would you and your organisation be ready actively to take part in the pilot project – in case one will be initiated?

In total approximately 50 personal semi-structured interviews were conducted with the representatives of the defined stakeholder groups. Interviews were structured with open-ended questions to identify the main interests and expectations of the stakeholder regarding PM in general and towards EPMPP in particular. Attention was also paid to define main concerns and threats in relation to PM development seen by the stakeholders. Based on the received information the overall situation was analysed and observations made to define potential conflicting interests between different stakeholders.

Current analysis presents the views of the stakeholders through the prism of questions referred above. The statements made by stakeholders having similar character are consolidated, grouped and not repeated. In addition, there are included specific comments made by the stakeholders addressing specific concerns or expectations. More detailed analyses and summary of stakeholder interviews is attached in Annex 3.

**1.2.2. Stakeholder analyses**

Based of interviews and gathered information it can be stated that vast majority of the stakeholders have positive attitude towards PM initiatives. Despite an overall vague
knowledge about the PM concept among stakeholders, there is a dominantly positive expectation towards innovation and knowledge enhancement the PM development may provide. Understandably, the majority of stakeholder representatives mentioned the need for a good definition of PM and comprehensive communication with all involved parties, and within the community in general. As the result of PM development many challenging scenarios can be forecast in the future, for instance such as affordability of the new treatment possibilities, competition for being financed and, last but not least, emerging new ethical dimensions. The interviewees expressed the need to address actively these challenges rather than ignoring or avoiding them. The majority of the stakeholder representatives also expressed their support to the pilot project initiative and willingness to participate actively in the pilot project should such a chance evolve.

The following table provides an aggregate of the main stakeholder roles and how they can contribute to the advancement of EPMPP.

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Main roles and contribution to the success of PM</th>
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| Patients                            | • Transparent and true information sharing to earn patients trust  
|                                     | • Active participation in new PM service initiatives                                                                                                                               |
| Clinicians                          | • Learn and develop competencies relevant to PM approach  
|                                     | • Build trusted relationship with patients                                                                                                                                            |
| Medical and Biotech Research        | • Opening new dimensions and the understanding of PM approach  
|                                     | • Developing decision support tools and providing support to healthcare providers  
|                                     | • Linking segment between evident based PM research and society, attracting people to actively participate                                       |
| Medical and Pharma Industry         | • Development of new tests and drugs based on PM generated data  
|                                     | • Support to healthcare providers introducing new testing and treatment routines  
|                                     | • Financial incentives to get access to health data and share positive outcomes with drug development                          |
| Hospital and Outpatient Clinic      | • Smooth introduction of PM services and securing supportive environment for clinical advancement, including clinical research                                             |
| Managers                            |                                                                                                                                                                                   |
| Professional Partner Organisations  | • Broaden the scope of their activities using own competencies to support PM initiatives                                                                                             |
| Regulatory Authorities              | • Secure regulatory framework to safeguard patient safety                                                                                                                             |
Table 1.2.2.1. Stakeholder roles

<table>
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<tr>
<th>Stakeholder</th>
<th>Role</th>
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<tbody>
<tr>
<td>Payer Organisation</td>
<td>• Develop competitive and transparent environment that support scientific and clinical progress, including research</td>
</tr>
<tr>
<td>Politicians</td>
<td>• Learning PM development and developing new payment mechanisms</td>
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<tr>
<td></td>
<td>• Provide legal environment to regulate stakeholders roles</td>
</tr>
<tr>
<td></td>
<td>• Identification of PM role and priority, balancing with other healthcare fields</td>
</tr>
<tr>
<td></td>
<td>• Public consultations and getting public acceptance to PM approach</td>
</tr>
<tr>
<td>Investors</td>
<td>• Secure funding of PM initiatives in pilot phase</td>
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<tr>
<td></td>
<td>• Government to balance investors interest and incentives</td>
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The following description provides broader discussion of stakeholder roles and evidence gathered during the interviews.

1. Patients

It has been suggested that patients in new era with unlimited access to the internet and all health related information, including diseases and treatment, know more and more about her or his disease and health condition. Potential implication is that patients or patient groups are prepared to challenge health care professionals in decision making process and over the time more pressure by various patient groups can be exercised on decision makers at various levels in the health care system. Increased public awareness about opportunities created by PM may force policymakers to allocate resources to the health care.

Patients will play crucial role in developing PM service, namely their active participation in new service initiatives is of key importance. No doubt patients expectation is that new delicate information created during the PM service delivery is handled with care and trust of people should be earned in very early phase of service development.

However, it is difficult to assess what influence PM will have on patient behaviour. An example may serve a fact that genotyping of patients will exclude a number of patients from treatment, which may create a feeling of inequalities but serves also as positive example of avoiding unnecessary treatment and cost-efficiency on the other hand. PM in its initial development phase may create a conflict with reality, where too much hope for any new treatment option cannot be realised and new dimensions of treatment and patient-physician relationship can be forecasted.
2. Clinicians

The ultimate goal of any physician is to cure the patient and to find the optimal treatment regimens. PM with the promise of being able to determine which patients will respond to a particular therapy is a major advance for clinical practice to tailor treatment regimens for the benefit of individual patients. We may also assume that clinicians are eager to learn and understand more about the benefits from novel and presumably more efficient drugs and treatment methods being developed by the industry using the PM approach.

One of the warning patterns in the future may be increasing “consumerism” by patients what clinicians can face. Patients could visit the clinicians with a firm opinion on their disease risk, after having purchased a gene/DNA analyses as a consumer product, which can unbiased relationship between clinician and patient.

As an opposite to the first mentioned positive pattern of clinician’s behaviour, there is also possible to foresee a potential conflict of interests where clinicians must follow new established clinical procedures and handle additional amount of work related with record management. Clinician role is crucial whether new PM initiatives are introduced smoothly and it would be recommended to be prepared for moderate opposition and to provide extensive training and other needed programmes to secure clinician’s supportive attitude.

3. Medical and biotech researchers

We can see a great role for medical and biotech researches, both in academia as well in industry, to open new dimensions of hypotheses and understanding of the causes of human disease using PM methods and approach. They are probably the single category in the life science sector that will benefit the most from the use of PM methods, and this is valid for basic research and just as much as clinical research. Researches will be valuable resource for setting up pilot project in initial phase for data collection and interpreting the data in value creation process.

However, in addition researches have significant role to play in developing decision support tools and applications and providing support for further integration into electronic health records management.

Academic research people are potentially also involved in further curricula development to undergraduate training and providing support for developing continuous professional skills for clinicians. And last but not least they play significant role earning patients trust in regard to PM development and can provide evidence based value creation and attracting people to actively participate in PM initiatives.

4. Medical and pharma industry

It can be foreseen that PM initiatives become the key interest areas for pharma companies, the entire process of product development and marketing will be affected. Pharma companies
will benefit from the access to gene sequencing and other relevant information from patient
data banks to increase the opportunities to define new treatment paradigms. It is estimated
that selecting genetically supported targets could double the success rate in clinical
development and using the growing wealth of human genetic data to select the best targets
and indications should have a measurable impact on the successful development of new drugs.

In addition the genetically predetermined selection of the clinical trial groups can further
improve efficiency of the clinical development process.4

If new products reach the market the Pharma will face new challenges, like entering the
market and pricing issues with regulatory and payer organisations. The trend to introduce
payment mechanisms on evidence based treatment and cost (risk) sharing mechanisms will
be part of PM concept as well. Another issue is good collaboration between the drug
companies and healthcare providers in order to support introduction of new unfamiliar
clinical routines. Potential conflict of needs and resources available can be foreseen, where
specifically targeted drugs for smaller target groups should have fair pricing strategy in order
to make efforts mutually worthwhile.

On the other hand, small country like Estonia can mutually benefit with pharma companies
from PM initiatives, if financial incentives are agreed and well balanced. Namely the access to
information has its cost and that money can be used for developing the healthcare
infrastructure and PM services. Also ideas about potential royalties and rights to have drugs
with bargain price available for the country can be issues to be considered.

Key stakeholder of pharma industry in Estonia can potentially be the Association of
Pharmaceutical Manufacturers that has shown readiness for innovative initiatives and has
initiated pricing strategy developments in regard to cost-sharing mechanisms.

5. Hospital and outpatient clinic managers

Managers of outpatient clinics and hospitals can be considered as separate stakeholder group
than clinicians. Introducing new clinical routines and services will have more complex and
economic meaning for them. The pricing issues of new services, securing high qualifications
of personnel to provide new services and last but not least notable investments into
technological infrastructure should be considered. Smooth introduction of new services is
always a challenge and change management needs good ownership and leadership by
managers.

All major hospital and outpatient clinic managers (see the list of interviewees) indicated their
readiness to participate actively in pilot project of PM and further on. One, but very important
precondition was addressed by them, that clear definition of PM, the scope and goal setting
has to be made before the launch of pilot project.

3 http://www.nature.com/ng/journal/vaop/ncurrent/full/ng.3314.html
4 Communication during the visit by pharma industry representatives to Estonia on June 16, 2015 (see Appendix 5)
6. **Professional partner organisations in medical field**

We considered also professional partner organisations as stakeholders who can contribute to the development of PM. Hereby we refer only to most influential partner organisations.

National Institute for Health Development plays important role to establish and share health related knowledge in society, as well as to influence health behaviour and determinants of health to increase the wellbeing of the people in Estonia. Currently they act on population based intervention initiatives mostly, but it would be wise to use their competence also for development of personalised counselling services based on health data.

Health Board is primarily responsible to perform surveillance and enforcement activities in the field of health care, communicable diseases, environmental health, chemical safety and medical devices. After the launch of new services under PM development these services have to be monitored as well as issues of licencing, quality control and patient complaints are to be handled by Health Board.

7. **Regulatory authorities**

Introduction of PM concept will create also new dimensions to the relationship between industry, healthcare service and regulatory authorities. Presumably that would lead to a revised regulatory framework as well. There are two main regulatory authorities in Estonia – Ministry of Social Affairs and Agency of Medicines. They both have to ensure that regulatory frameworks are in place to safeguard patient safety and at the same time launching new innovative services and that scientific progress is not hampered.

8. **Payer organisation for health services**

We can foresee increasing tensions and conflicting interests if medical companies introduce products with higher safety and efficacy as a consequence of the PM approach, and yet perceive that they are not being properly compensated for the technology level their products represent.

Estonian Health Insurance Fund fully shares a view that there is a need for new innovative drugs and payment mechanisms relevantly. Thus, it may take time and require learning for payers to appreciate and accept that higher sophistication levels that motivate new reimbursement criteria are built into products as a result of the PM approach. Still, we may assume conflicting interest will increase where payers are motivated to pay as low as possible and have to act in circumstances of limited resources.

9. **Politicians**

The political system has to face entire complexity of PM approach. It has to regulate the allocation of resources to healthcare, and how these resources are distributed between different fields. From experience we may say that sooner or later any proven new medical
technology will become a part of healthcare provision. PM approach is hardly exceptional, even though they may require new resources as well as organisational change. Therefore, we should understand that politicians may try to hinder the implementation of PM.

Health economics will play more and more significant role to support political decision making on investments required to implement the PM. Issues related to costs of infrastructure (biobanks, genome sequencing, bioinformatics, etc.) and the concept of higher costs for more effective treatment will become to the political agenda.

No doubt important issue in politician’s agenda is privacy regulation and public consultation on PM implementation, including “opt in/opt out” strategies for research participation.

We assume politicians overall guiding interest is to obtain the maximum return for society and citizens through investment in PM.

10. Investors

It is difficult to assume that PM development in Estonia may take place without significant capital investments. Government in current situation is expected to design appropriate framework to attract private investments. Investments may come from different sources – from Venture Capital firms, from strategic stakeholders (Big Pharma), from private investors (Business Angels) and last but not least from Government.

Different investor categories have different interests and different investment horizons. While strategic investors may see long-term investment attractive, then VC and Angels may look for exit strategies in 3-4 year period. However, the business model would excel if all investors can find the role in PM development, inclusive Government participation to indicate commitment and leadership.

In summary. As a result of an analyses the following requirements and conditions were considered by stakeholders as “must” in order to safely develop the concept and services of PM. The stakeholders addressed the following issues:

- The whole PM concept and definition should be well described before the start of any initiative, the purpose should be defined;
- The development of PM services and related issues should be coordinated by a central leadership organisation;
- The access to data should be well regulated and protected, all rights and responsibilities in relation to treatment or research purposes inclusive. Data protection should not be achieved with the cost of losing flexibility in the system;
- Most of interviewees were in favour of central solutions for database and other major application development, mentioning also that the success of implementation will depend on the speed of developments and the critical mass of service providers and other relevant parties involved. Recent history has shown that voluntary participation and fragmented infrastructure and data management may hurt or block good initiative;
The need for a well coordinated and managed pilot project, good preparation for further phases for going live;

The entire value chain and system to be thoroughly thought through – from risk assessment and diagnostics, counselling and preventive treatment to treatment and financing of the whole package of services;

Comprehensive training and other competency development support for service providers and clinicians. There is, potentially a need for well developed counselling service and infrastructure;

Comprehensive media coverage and public education initiatives before and during the pilot project, systematic handling of issues of potential ethical concern;

There should be transparent understanding of additional resource needs to introduce PM services, sources for financing and the advantages of PM compared to other services;

More detailed analyses and summary of stakeholder interviews is attached in Annex 3.

1.3. State governance in the light of large innovation projects

This chapter focuses on the impact of the current situation and the potential developments in the state governance on the EPMPP. The goal of this chapter is to make recommendations on EPMPP organisation and management within the authority of executive power (i.e. horizontal coordination between the governmental authorities and vertical coordination within the area of government of a ministry). This section does not cover the corporate governance of EPMPP. The brief analysis provided here rests on a larger review of academic literature and research reports (e.g. Impact assessment report on Estonian Biotechnology program), as well as on interviews conducted with Estonian (top) civil servants (Appendix 3).

EPMPP can be characterised as a ‘wicked’ problem from a public policy point of view – not because it is ‘evil’, but because it is a very complex issue. The greater the complexity, the uncertainty and the divergence of policy issues, the more ‘wicked’ the problems are. Increasing wickedness is commonly associated with growing barriers in terms of coordination (Sarapuu and Lember 2015). Wicked problems challenge governance structures, skills bases and organisational capacity (Kickbusch and Gleicher 2012: 93) and therefore organising the EPMPP is an important coordination challenge for the Estonian government.

The challenges of the Estonian governance system

Estonia is considered to be a state with a relatively strong command and control regime where rules and regulations are considered an important coordination instrument and where

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8 In a public sector context, coordination represents a purposeful alignment of tasks and efforts of public sector units, generally to create greater coherence in policy and to reduce redundancy, lacunae, and contradictions within and between policies. The intention is to make better use of scarce resources, create synergies by bringing together different stakeholders (see http://www.pa-knowledge.org/focus/focus-coordination-in-the-public-sector).
relations between units and layers are top-down and mechanistic. At the same time, Estonia can be characterised as a state with market driven tradition – there is a strong belief that market driven incentives generate more effective, more efficient and more innovative services (Bekkers, Tummers and Voorberg 2013; based on Loughlin & Peters 1997; Pollitt & Bouckaert 2011).

The latest OECD Public Governance Review (2015\textsuperscript{10}) reveals that despite some positive developments in recent years, the main difficulties of the Estonian governance system remain the same – Estonia has to address the issues of siloed administrations, gaps in strategic leadership and the lack of flexible resources to help strengthen the government’s coherence and ability to strategic decision-making.

The 2015 OECD report recommends that the Government of Estonia should institutionalise co-ordination mechanisms to achieve whole-of-government policy coherence; enhance cross-ministry co-ordination in strategy-setting and implementation, e.g. by mandating Cabinet Committees with the decision-making authority, including spending authority, to oversee the implementation of strategic multi-sector policy initiatives; and by ensuring that these committees or reference groups report regularly to full Cabinet. Estonia has to invest in the capacity to transform information into knowledge, e.g. by building analytical capacity within ministries and through the opening up of data, tap into external communities to expand its available analytical capacity and gather new policy insights, etc.

Estonian politicians have understood the need for public administration reform. The new coalition, formed in April 2015, agreed to develop horizontal cooperation between ministries; review the rules of creating and operating government agencies, so that agencies could be more effective and flexible; specify the status role and responsibilities of ministers who are the political leaders of a policy area\textsuperscript{11}.

**EPMPP and state governance**

On the basis of literature overview, one can argue that, as a large innovation project, EPMPP should be organised around the principles of network-type coordination\textsuperscript{12}. On the other hand, hierarchy and market type coordination mechanisms have been popular in Estonia (which, along with other factors, has led to a fragmented governance organisation). The result is that the current governance system does not ‘actively’ support the implementation of EPMPP, as one interviewed official put it. But on the positive side, there is no direct contradiction between the current governance tradition and the needs of the future – hierarchy, market and network type coordination mechanisms can co-exist. State governance structure should combine the best features of each coordination mechanism to support effective management of EPMPP. This means that the state can and should take an active role in organising EPMPP.

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\textsuperscript{11} See the coalition agreement at https://valitsus.ee/sites/default/files/content-editors/failid/re-sde-arl-valitsusliidu-lepe-2015.pdf.

\textsuperscript{12} See Sarapuu, K. and Lember, V. (2015) for a brief description of basic coordination mechanisms.
An active state is not automatically an over-bureaucratic state; it means that an active state is purposively and systematically involved in building coherence between various stakeholders and creating a favourable (regulative, operational) environment for such a large innovation project.

In addition, several officials interviewed argued that the problems of the existing governance system could be effectively solved if there is clear leadership. The current legal environment makes it harder, but not impossible, to implement large scale innovative initiatives. If EPMPP is a priority for the government and there is a strong (political) will, the problems of weak cooperation culture can be bridged. The fact that the government in power has plans to address the problems of present governance organisation gives ground to (moderate) optimism that conditions can only get better in the future. In fact, EPMPP could serve as an example or blueprint in the forthcoming governance reform.

A distinctive feature of Estonian governance system is that its effectiveness is often dependent on the effectiveness of the personal leadership/networks (see for example OECD 2015 Public Governance Review\(^\text{13}\)). Personal networks support sound governance if there is a clear leader (or leaders) and the relations between important stakeholders are good. The system built on personal networks does not work in case the innovation champions change and/or relations turn bad. Drawing on OECD’s recommendation, the Estonian government has to rely more on formal coordination mechanisms to complement the existing interpersonal networks. The lesson in the context of EPMPP is that there is a need for both aspects of good governance – clear leadership and division of responsibilities between politicians and officials (on different governance levels) have to be in balance with supportive institutions/formal coordination arrangements in the executive branch of the government.

Estonia is a small state with limited (human) resources. This has to be taken into account when creating the institutional arrangements to steer the implementation of EPMPP. The coordination of EMPP in the executive branch should be built on the existing institutional structures (for example current/upcoming R&D coordination instruments) as much as possible. On the other hand, as a complex policy problem, PM needs flexibility in management and organisation. Therefore, the decision-makers need to acknowledge that monitoring the results, change and adaptation should be built into the management of EPMPP from the start. In relation to that, the Government of the Republic Act presently does not support quick and flexible formation, reorganisation and termination of governmental authorities (it has to be done pursuant to law, which is a complicated and lengthy procedure). Consequently, the implementation of EPMPP should be organised using institutional solutions other than governmental authority\(^\text{14}\). The latter has the role of ‘steering’ (in section 7, it is referred to as stewardship), the ‘rowing’ should take place in a body governed by private law.

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\(^{14}\) According to the Government of the Republic Act (§ 39), governmental authorities are authorities which are financed from the state budget and which main function assigned by law or pursuant to law is to exercise executive power. Governmental authorities are ministries, the Estonian Defence Forces, the Government Office and county governments as well as executive agencies and inspectorates and their local authorities with authority to exercise executive power. Other governmental authorities may also be prescribed by law.
There are two other factors that have to be taken into account when choosing the best governance structure/organisational type:

1) An organisation funded mainly from state budget (and perhaps form EU structural funds) has to follow rather strict budgetary and financial reporting rules that is not in lines with the need for flexibility of any large innovation project;

2) A successful innovation project needs a great deal of autonomy in its (operational) decision making processes and the decisions have to rest on the best knowledge available at a specific moment; this means that the EPMPP organisation should encourage the involvement of the best experts both as employees and as members of the governance and management system (see section 7 for the explanation of these terms) level.

Recommendations

The proposals are derived from literature, interviews and the discussion above and between the authors of the report. At first sight some of the recommendations might seem obvious, but they are brought out as part of a whole system.

- **Top level politicians have the task of overall policy guidance and steering. There should be a government level committee (a standing body) that has the task to coordinate PM across various government institutions.**

At present, there is a task force of e-Health that is jointly managed by the Ministry of Social Affairs and the State Chancellery. This is a temporary body with the task to create e-Health strategy for the year 2020. The task force is an advisory body of experts, officials and relevant stakeholders. There is also the Research and Development Council that could serve as a ‘substitute’ for a creation of a new government level PM committee. The work of the Council is supported by **two permanent committees** that focus on the research and development policy and innovation policy. Ad hoc committees can be established to elaborate on specific tasks.

The advantages of using Research and Development Council as a high level (political) forum of discussing strategic issues in PM are:
- The council is chaired by prime minister;
- Includes high level stakeholders with various backgrounds (Minister of Health and Labour is not a member at present and has to be appointed to be a member in the future);
- Personal medicine committee could be a third permanent committee chaired by Minister of Health and Labour; but it could also be an ad hoc committee in the beginning.

- The minister responsible for health area should have a clear responsibility to offer political guidance to civil servants in the areas of PM and overall health R&D&I.

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In addition to a high level (political) committee, the civil servants of the Ministry of Social Affairs (MSA) need a mandated political frontrunner that can provide day-to-day political leadership and make political decisions in a wider framework accepted by other political figures. The minister has the task of translating the decisions of the cabinet into political guidelines. In addition, PM as a complex political issue assumes that the minister is actively involved in cabinet level collaboration and negotiations with his or her colleagues in cabinet. In previous and current coalition government, the policy area of Ministry of Social Affairs has been divided between two political leaders. If that practice continues, it should be absolutely clear which minister is responsible for EPMPP.

- **There has to be a clear responsibility for PM policy in the civil service; top managers in MSA should agree on who coordinates what and with whom (bearing in mind the forthcoming changes in state strategic management and budgeting system in Estonia)**

The Health system R&D&I strategy\(^{16}\) calls for a clear leader in civil service responsible for health R&D&I, it proposed a position of Chief Innovation Officer (CIO) which has been introduced by now. The Health System R&D&I strategy describes the relevant competencies and tasks of CIO. The following question arises – will PM be a responsibility of CIO or the deputy general who manages health area in MSA?

A simple answer to these choices would be that it all depends on the priorities of EPMPP – are the goals and strategy of EPMPP more related to clinical issues or is R&D more important? An option is to say that secretary general should take the role of leading and managing the EPMPP. The problem might be that secretary generals are overloaded with all kinds of (other) questions. Taking into account the fact that PM is a horizontal issue, working arrangements in MSA can be built up in a way that the question of who plays the first violin in the orchestra is of secondary importance. Horizontal cooperation and the fact that secretary general and deputy secretary general(s) all have a responsibility to coordinate (PM related) policy issues with higher officials from other ministries, is more important than the internal coordination system between top MSA managers (were the number of players is smaller).

A lesson from previous large scale innovation projects (see for example the Impact assessment report of Estonian Biotechnology program) is that there is a need for clear goals. Every stakeholder has to understand its role in the overall system. An important task here for policymakers is to formulate and communicate incentives for cooperation!

Another lesson is that weak coordination between ministries and unclear motivation to collaborate leads to fragmented and ineffective financing system. Ministry of Research and Education will pilot a new system of program based budgeting starting from 2016. In the light of new strategic management and budgeting system, MSA, Ministry of Finance, Ministry of Research and Education and Ministry of Economic Affairs and Communications have to agree on whether or not PM could be a separate program (in the sense of new State Budgeting Law) with its own resources. The new budgeting and reporting system could be helpful in dividing

\(^{16}\) Available at: [http://www.tervishoiuak.edicy.co/](http://www.tervishoiuak.edicy.co/)
the tasks and responsibilities between all relevant parties. On the basis of interviews one could argue that MSA should take a lead in managing PM as a separate (and separately financed) program.

- **MSA needs a PM advisory body in order to have a forum where societal groups and experts meet with each other and civil servants.** The main role of such a body is to agree on main goals and strategy of PM and share information on the outcomes. The advisory body should be part of the existing R&D&I governance system.

The OECD 2015 Public Governance Review recommends that Estonia should analyse the use of mirror committees on political level by creating such committees of high-level officials. This option could be useful if ‘conventional’ coordination instruments (from personal network to regular meetings of secretary generals, etc.) do not work. At the moment there are lots of committees and task forces in the field on R&D&I, health, entrepreneurship, smart specialisation, etc. There is also a temporary task force of e-health managed jointly by State Chancellery and MSA. The creation of another committee might lead to further fragmentation of (human) resources and duplication of tasks. The first choice could be to use the existing coordination instruments which have to be complemented by personal leadership of MSA top civil servants (see previous recommendation).

MSA is planning to set up a permanent high level R&D board in health area (see the Health System R&D&I strategy). The body will be led by the minister responsible for health. It will be co-chaired by the head of the standing committee on medical science and health strategy (Estonian Academy of Sciences). The R&D board will engage representatives of health related R&D institutions and enterprises, NGO’s dealing with advocacy in the field.

The board will discuss strategic R&D issues and innovative policy initiatives in health; it will be a forum where priorities and criteria of funding R&D in health will be agreed upon; the board makes recommendations to overall R&D policy in Estonia. The board will also have the right to engage various experts into the activities and to form (temporary) task forces. The board is also planned to play the role of several other organs described in other strategy documents. It is a field expert body of national health strategy; a field board of overall R&D&I policy (i.e. a third committee affiliated to Research and Development Council). It also has the role of health technologies growth area subcommittee.

The same body could serve as an advisory board for PM policy. The focus of health R&D is wider than PM, but this is an advantage on a ministerial level since it creates an opportunity to discuss PM policy in a wider health and R&D policy context and with more varied stakeholders. Also, since the pool of experts and policymakers in Estonia is small, there is a good chance that the persons engaged would be to a great extent the same as when creating a separate organ for PM policy. Since the R&D board has the right to create task forces, PM could be a good example of using such an option.

- **There have to be lower level officials in MSA who will serve as liaison officers between all the boards, committees, political and administrative leaders, stakeholders, etc. But**
their main role would be to oversee the implementation of PM strategy in EPMPP implementation unit on daily basis and mediate the issues that arise from implementation level.

The project of EPMPP drafted by MSA (2014) foresaw\(^{17}\) that there will be two employees who will act as executive management board inside MSA. There is indeed a necessity for officials who will communicate between policymaking and implementation levels of EPMPP. These officials will ensure that communication is effective, the materials needed for decision-making will be prepared, the meetings will be organised, etc. In short, these persons are not policy level decision-makers, but they are important parts of the system in order to prepare necessary inputs to policymaking and implementation; gather necessary feedback and solve running problems in a timely manner.

- **There should be yet another link between ministry and implementation unit. There are examples that can serve as models of coordination between ministry and PM implementation unit.**\(^{18}\)

In spite of the obvious need for clear leadership on higher management levels and the conclusion that there is a need for lower level officials (facilitators), there could be yet another link between ministry and implementation unit. There are examples (e.g. in Ministry of Economic Affairs and Communications / Enterprise Estonia) where high level officials, facilitators, and managers of implementation units meet in order to ensure efficient coordination.

The managers of EPMPP do not have to be official members of MSA’s R&D advisory board. Therefore a forum (management committee) for regular discussions on progress in implementing EPMPP strategy and reviewing results, discussing tactical problems etc. might be necessary. This organ could consist of deputy secretary general responsible for PM, facilitators from MSA, and managers of EPMPP. It could also engage representatives (e.g. secretary generals or department heads) from other ministries that have vested interests in EPMPP.

This kind on cooperation organ does not have a regulatory base in Estonian laws. The steering/management system between Ministry of Economic Affairs and Communications and Enterprise Estonia is an example of an informal solution that can be used as a coordination instrument to ensure flexibility in implementing PM initiative(s) or correcting the strategy of EPMPP.

**To summarise** this section – the complex nature of PM presupposes the need to use a flexible organisational model. The role of the state is to provide strategic guidance and create a supportive environment (i.e. steering, stewardship; but also engaging societal stakeholders to

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\(^{18}\) An important remark: the recommendation might not add value in all circumstances. If the (advisory) board of future EMPP organisation itself consists of really competent professionals – which is recommended by this report, the need for an intermediate body or so-called link, is considerably smaller.
policy making processes). EPMPP itself as a large pilot project should be managed as an “island of excellence” where highly motivated people have freedom of action. This means that governance/management of EPMPP has to make full use of expert knowledge and therefore professionals, not politicians, have to be in charge on EPMPP’s advisory board as well as on the executive board. Therefore, implementation of EPMPP should stay in a body regulated by private law. The experts of public administration and public law interviewed during the preparation of the report argued that – form the viewpoint of governance and government – clear goals and strategy of developing EPMPP are far more important than the specific judicial form of the implementation unit provided that the implementation stays outside government authorities. The state should clearly define the (public) tasks related to PM to be further fulfilled by a private body. The choice of organisational model/judicial form is dependent on other contextual factors than the pure logic of the governance system.

1.4. Engagement of Estonian innovative companies in EPMPP

As a subgroup of stakeholders’ interviews we arranged dozens of semi-structured interviews also with entrepreneurs and/or general managers of different companies. These companies are either related to health/medical research, clinical treatment and/or services or IT-systems development (gene-, immunome tests, decision support-, diagnostic systems, help systems for medical treatment, IT-systems development, etc.). The selection is not absolute but gives an overview of the main trends, understandings, threats and expectations among entrepreneurs.

We prepared slides and made an introduction of EPMPP for interviews as well as for further implementation of personalised medicine. Every person received slides and questions in advance. Typically, the interview took slightly more than 60 minutes. The companies interviewed so far: IB Genetics OÜ, Asper Biotech AS, LabToWellness OÜ, Sportsgene OÜ, Terviseagentuur OÜ, Protobios OÜ, ELIKO Tehnoloogia Arenduskeskus OÜ, Tarkvara Tehnoloogia Arenduskeskus OÜ, Tervisetehnoloogiate Arenduskeskus AS, Cognuse OÜ, Nova Vita Kliinik AS, DietBooster, UPITEC, Fitnessteam OÜ. Several companies proposed for interview found themselves not related with PM by their management. (Please see the list of representatives of interviewed organisations in Appendix 3).

The main findings:

1. Available information about personal medicine, its role and connections between different institutions is clearly very limited among different stakeholders. The confusion starts already with the meaning of the term PM itself. There is a clear need for information that would clarify the terms, roles of PM stakeholders, expectations and aims, the specified to be carried by state and so on.

2. The companies that have been involved with services or products for medical sector are better informed and have more ideas or visions regarding the further process. A number of companies hoped to face new opportunities related to the project and were ready to provide various services. However, some companies are focused on
their daily business related aspects and considered EPMPP a nice idea rather than a real project to follow. At the same time a number of the companies emphasized the importance of the long-term vision and agreements and “one step only” was found useless.

3. The state should make great efforts to motivate the crucial element in PM – the medical system (all layers, incl. hospital, doctor, etc.) to cooperate. All technical aspects, regulations and policies should not be underestimated; they may need significant resources but the outcome depends on the ability of the medical system to collaborate. Notwithstanding the status of EPMPP, the medical system has to maintain a high quality of daily treatment offered to patients.

4. The PM know-how has two very different sides that have to be combined: on the one hand IT, and on the other hand health (medical). The problem is that IT-specialists don’t understand medicine and vice versa, but combined efforts for the development process are inevitable.

5. Personal relations between stakeholders’ key persons were found to be an important factor to act as a barrier to better cooperation between various stakeholders. At the same time one should not forget the competition for patients between the hospital and a new invention (Everyone is afraid of losing business).

6. Expectations, inevitable requirements, risks and threats as well as limitations and constraints were grouped separately.

The main expectations were that the development of Personalised Medicine will create the infrastructure for the development of different (incl. diagnostic) services. As a process it shall change the mental attitude that “a Holter monitor” (a specific measurement device) is given and then again taken back. Rather, we have entered a new era where a different type of monitoring as such is going on systematically (continuously and during a long period of time) and that is a part of present-day normality. There is a large group of people who monitor their physical activities, food consumption etc. on a daily basis and are clearly interested (they pay for the service) in getting an analysis of their performance; at the same time they are interested in receiving more extensive health-related information. That is a good platform for early prevention programmes and more generally for the modernisation of medicine that is more inclusive and instigates people to take responsibility and follow a reasonable lifestyle & healthy behaviour. At the same time it defines the important role of data mining, analytics and algorithms development. The scientific knowledge how this works in interaction with different counterparts should also be created. At the end of the day one part of the solution may lay in proper electronic data systematisation that is a crucial basis for creating new knowledge.

Three aspects were considered inevitable requirements for the safe development of the concept and services of PM: access (health data, linkage between databases as well as permits to exchange the data); demand to strict validation (evidence based) in terms of new
diagnostic and theranostics tools as well as the motivation of the medical system (all layers, incl. hospital, doctor etc.) to cooperate.

A long list of potential risks and threats, limitations and constraints related to the development of PM were identified. Typical of entrepreneurs, many were cautious of the risk of investing into something that might not have future.

More specifically the following was pointed out:

- Shortcomings from the legal framework as well as regulations change that may terminate any possibility for data mining or data exchange. In some countries the regulations are rather strict. Non-health institutions cannot get access data from the e-Health system, rights for data analysis are given for a limited period only etc.;
- Significant and various types of resources need to be allocated to teaching the stakeholders, including updating the courses for medical students as well as teaching the new aspects to the medical professionals. Simultaneously, the system has to keep a high standard of daily treatment offered to patients;
- The role of bioinformatics as well as the timeline might be underestimated. Creating knowledge out of PM related data mining; analysis and algorithms may take far more time than expected;
- “Over-the-boarder questions”
  - How to transfer the same system (solutions or services developed in Estonia) cross-border in order to scale up the developed system where tools for identification specific for Estonia, like X-road & ID-card, are not in use or accessible?
  - The need to have an initiative and expertise in standardization? On occasion solutions or services developed in Estonia should work in a larger scale than only Estonia, “The Estonian team” has to be confident in different market regulation systems (world scale - ISO, US scale - ASTM, EU scale - CEN). Standardisation as such (regulations system) is a very important background factor for business. Totally new developments that don’t exist in medicine yet may need new regulative acts as well.
  - Market regulations and compliance (HIPAA, FDA, EMA etc.)?
- Ethical aspects, too high expectations to PM versus traditional medicine, as well as problems related to the risk of getting lost in translation.

Main recommendations for potential business models
The companies were mostly ready to offer some sort of service. These proposals were not qualified as descriptions of a new business model. A company that handles thousands of customers in their loyal customer base offered some useful recommendations. The new solution has to be naively simple because people may not follow too complicated things.

The main potential of the PM project lies in amplifying the effect increasing with every new layer, every new counterpart’s contribution. As soon as the accessible connected databases are created the first and primary layer is set. The health data adds the second layer, the gene and genome data another, behaviour data the next, telemedicine another, and so on. Further
business should come already as a natural process from different stakeholders’ interactions. One solution may be an interaction platform for others. The content providers who have a validated information base are always welcome to join other platforms because the summarized data is better and the outcome suggestion better balanced. In the current development phase, it may happen that several similar platforms start to compete with each other offering an opportunity to link other support-decision parts and the best platform will be the one that has implemented more different tools.

The quality of data is of utmost importance. In terms of potential business a lot depends on the quality of the health data (Lab analysis data, imaging etc.). Conservative medical system by default uses health data to verify every new tool applicability. Accordingly, that plays an important role for creating new business.

**Main recommendations for cooperation mechanisms**
The state should make an effort to motivate the crucial element in PM – the medical system (all layers, incl. hospitals, doctors etc.) to cooperate. All technical aspects, regulations and policies should not be underestimated. This may require significant resources but the outcome depends on the cooperation of the medical system.

The project needs significant resources to be allocated for teaching various stakeholders, as well as for training the current medical system people. Simultaneously, the system has to maintain a high standard of daily treatment offered to patients.

Entrepreneurs expect that cooperation between private and public sector will be transparent. Different clustering and networking initiatives potential should be used to amplify the cooperation.

**Main recommendations for IP rights management**
Open access to state or private-capital owned databases would be mostly preferred. However, taking into consideration the costs of the maintenance of databases, the access can be regulated by imposing reasonable access fees. A database as such does not mean that there is IP. Hence, IP belongs to the person or organisation who has developed the data mining algorithms, interpreting algorithms etc. The state should initiate a system to access and motivate all counterparts to make the data available for research and product development.

**How to engage Estonian innovative companies in EPMPP?**
In order to engage Estonian companies in EPMPP several types of actions are required. First, a proper information campaign should be arranged to introduce the basic terms, the roles of PM stakeholders, expectations and aims, the role to be carried by the state and so on. The second part is sharing technical information (such as product/service information) about the available data, its form, used programmes, etc. The third part could be finding a liaison organisation(s) whose duty is to sign preliminary agreements with interested companies and to arrange a set of small pilots. On the one hand that would help to test the entrepreneur’s ideas and the usability of them in small scale without interfering with the health system, and at the same time would prepare EPMPP for similar actions with over-the-border partners. The
candidates for the appropriate liaisons could be health- & IT-related Competence Centres. Business support organisations, such as Enterprise Estonia, should develop strategy and measures for supporting the appearance and rapid development of new businesses in the Personalised Medicine area. Business accelerators and incubators have an important role to play supporting newcomers - from early start-ups to established organisations.
2. Examples of global initiatives in personalised medicine. Financing, commercialisation and business opportunities

This chapter provides an overview of most often cited international PM initiatives and the global PM market as a set of different sub markets with their own dynamics, customers and development drivers. The chapter also outlines the PM market sectors that are most relevant for Estonia with respect to the market size, growth and correspondence with Estonian strengths to illustrate the size of the opportunity. The chapter concludes with the discussion about the current status of the market development and the Estonian strengths, opportunities and key stakeholders for the development of the EPMPP.

2.1. Comparative overview and analysis of governance setup and principles of the existing personalised medicine and genomic dataset projects and their practical implementation globally

Globally, many if not most developed countries are currently in the process of formulating large-scale personalised medicine projects, although the majority of such projects is in the development phase today and only a few have reached practical outcomes. These ground-breaking personalised medicine implementation programs are built on advances in high-throughput genomic technologies coupled with a growing number of genomic results potentially useful in clinical care.

In January 2014, the Symposium convened by the National Human Genome Research Institute (NHGRI, U.S.) brought together 25 groups developing personalised medicine projects from around the world to describe and compare projects, examine the current state of implementation and desired near-term capabilities, and to identify the opportunities for collaboration to promote the responsible implementation of genomic medicine. According to the information gathered during the symposium, mainly three approaches are used to enhance the development of personalised medicine - population-wide genomic sequencing and electronic medical record (EMR) integration, coordinated nationwide genomic medicine research programs, and localized efforts focusing on unique capabilities. The most common implementation efforts among participants involve cancer genomics, large-scale exome or whole-genome sequencing, and pharmacogenomics, while several current projects focus on particular national priorities (Please see Table 2.1.1).
Table 2.1.1 Examples of specialized PM implementation projects globally\textsuperscript{19}.

<table>
<thead>
<tr>
<th>Country</th>
<th>(Name of Project)</th>
<th>Goals of Specialized Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Country Efforts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td>Develop national framework for translating –omics discoveries into clinical research and practice, including advice on return of results from genomics research and clinical testing</td>
</tr>
<tr>
<td>Belgium</td>
<td>(Belgian Medical Genomics Initiative, BeMGI)</td>
<td>Create national framework for clinical exome sequencing, share variant frequency data, incorporate into international initiatives, train the next generation of researchers and clinicians [<a href="http://www.bemgi.be/">http://www.bemgi.be/</a>]</td>
</tr>
<tr>
<td>Canada</td>
<td>(Genomics and Personalised Health Competition)</td>
<td>Assess benefits (including economic benefits) of genomic technology to patients and expand capacity for clinical and translational research in 17 diverse projects [<a href="http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx">http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx</a>]</td>
</tr>
<tr>
<td>Estonia</td>
<td>(Estonian Program for Personal Medicine)</td>
<td>Sequence 5K individuals, develop Estonian genotyping array, pilot of 50K Estonian Biobank members, offer to all 35-65 yo (~500K) and link to EMR</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td>Create national network of molecular genetics laboratories, clinical cancer genetics centres, and inter-regional sequencing platforms</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td>Develop infrastructure for genomic medicine implementation including disease susceptibility assessment across ethnic groups, fetal risk prediction and anomaly diagnosis, and cancer genomics</td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td>Use genomics in cancer treatment, push de-identified family history data into EMR of relatives</td>
</tr>
<tr>
<td>Japan</td>
<td>(Implementation of Genomic Medicine Project, IGMP)</td>
<td>Use genomics for optimized diagnosis, treatment and prevention</td>
</tr>
<tr>
<td>Korea</td>
<td>(Genome Technology to Business Translation Program)</td>
<td>Use genomics to develop early diagnosis and treatment approaches for personalised and preventive medicine</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>(Centre for Systems Biomedicine)</td>
<td>National Centre of Excellence in Early Diagnosis and Stratification of Parkinson’s Disease</td>
</tr>
<tr>
<td>Singapore</td>
<td>(POLARIS)</td>
<td>Pilot TGFB\textsuperscript{I} testing for disease diagnosis and family risk assessment in stromal corneal dystrophies, then implement 90-gene panel for gastrointestinal cancers</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td></td>
<td>Use SNP genotyping to identify thalassemia carriers and genetic modifiers to convert thalassemia to manageable, chronic illness</td>
</tr>
</tbody>
</table>

\textsuperscript{19} January 2014, the Symposium convened by the National Human Genome Research Institute (NHGRI, U.S.) in press.
<table>
<thead>
<tr>
<th>Region</th>
<th>Initiative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>Implement PGx card to identify risk for top ten drugs with risk for Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), integrated with nationwide pharmacovigilance program</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Sequence 100K whole genomes and link to National Health Service records to treat individual patients and better understand cancer, rare and infectious diseases [<a href="http://www.genomicsengland.co.uk/">http://www.genomicsengland.co.uk/</a>]</td>
</tr>
<tr>
<td>Multi-National Efforts</td>
<td>Build collaborative efforts between developed and developing/low-income countries, genotype pharmacogenomically relevant variants in developing nations, develop national/ethnic genetic databases using a data warehouse approach, engage in public health genomics projects</td>
</tr>
<tr>
<td>Gulf States (Genatak)</td>
<td>Laboratory network for pre-marital, pre-natal and post-natal detection of recessive diseases, genetic counseling, personalised cancer treatment, chronic disease risk</td>
</tr>
</tbody>
</table>

National efforts to build the infrastructure for genome sequencing and other genomic and information technologies were underway in nearly all represented countries at the meeting. One of the largest such effort is the UK project that aims to sequence 100,000 whole genomes by 2017 through the creation of Genomics England. The Estonian Pilot Project for Personalised Medicine was also introduced at the time as a program involving the sequencing of 5,000 Estonians and development of an Estonian-specific genotyping array, coupled with automated decision support and training of physicians to use the results in everyday practice.

Another on-going project is the Electronic Medical Records and Genomics (eMERGE) Network in the U.S. connecting infrastructures of 18 medical research institutions in the U.S. Medicine Initiative project "ETRIKS," funded jointly by the European Union and industry (16 consortium partners), aims to create and run an open, sustainable research informatics and analytics platform for sharing data and supporting translational research in personalised medicine.21

In addition to information outlined by the NHGRI Symposium we have mapped information from other large-scale personalised medicine initiatives directed at collecting, researching and implementing genetic and health data, including deCode Genetics (Island), Study of Health in Pomerania – SHIP (Germany, SiSu Project, FiMM (Finland) and Healthbank (Switzerland). There were also some initiatives developing Digital Decision Support Systems (DDSS) under observation. Two of them, Duodecim (Finland) and Syapse (U.S.) are described in p. 2.1.1

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21 [http://www.etriks.org/]
Considering the ultimate goal of the work, which is to come up with the best-fitting solution for Pilot Project governance setup and principles, we gathered information in a way to bring forth the scope and aims, current status and future prospects, organisational setup and management, access to samples and data, stakeholders, collaboration mechanisms, IP regulation, form of consent, budget and financing, business model and commercialization strategies used in most of the projects (Appendix 1).

2.1.1 Examples and discussion on PM initiatives globally. Financing and commercialisation models

Two initiatives were selected for more detailed inspection: Genomics England and Healthbank. Both initiatives are launched lately and their organisational setup is developed taking into account the need to involve private funding. Genomics England, established in 2013, was chosen because of the large cohort size, the specially developed and implemented public-private partnership management structure with a goal to integrate the genomics-based information into clinical services, and drug development. Healthbank, founded in 2014, is one of the newest initiatives that was established using approaches that are relatively novel in the context of PM and health care industry in general.

**GENOMICS ENGLAND**

Scope and aims
Genomics England (GE) was established in 2013 with an aim to prepare and implement the 100,000 Genomes Project in the UK that is the sequencing of 100,000 personal DNA codes of patients in years 2015-2017, leading to more personalised health-care. Combining clinical and whole genome sequencing data started with rare diseases, common cancer, and infections. The aims of the project include patient benefit, an ethical and transparent program based on consent, new scientific insights and discovery, accelerating the uptake of genomic medicine in the National Health Service (NHS), stimulating and enhancing UK industry and investments, and increasing public knowledge and support for genomic medicine.

Stakeholders and collaboration
GE provides leadership and management to the Project. GE is working with NHS England (NHSE), Public Health England (PHE), Health Education England (HEE), and NHS Trusts. This is to ensure that the project is fully aligned with NHS transformation and sits within a program of related initiatives in clinical and laboratory genetics, molecular pathology, service innovation, disease registration, clinical audit, training, and technology funding. NHS England is the major delivery partner for the project and is principally responsible for securing a sufficient quantity and quality of samples from consenting patients.

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"http://www.genomicsengland.co.uk"
Organisational setup and management

The Department of Health has established Genomics England as a wholly owned limited company to deliver the project. The company was established as a part of the UK Government’s Life Sciences Strategy. To identify and enrol participants, the NHS Genomics Medicine Centres (GMCs) were created. NHS England commissioned a number of these centres to harness the capability and capacity of the NHS across England to contribute to the Project between 2015 and 2017. To maximize the value of this programme, GE created the Genomics England Clinical Interpretation Partnership (GeCIP)\(^{23}\), which brings funders, researchers, NHS teams, trainees and potentially industrial partners together to enhance the value of this dataset for healthcare benefit. The Genomics England Chief Scientist’s Team was responsible for establishing and delivering GeCIP. During the Project, GE will support and provide GeCIP members with an informatics platform and datasets as released from the Project. In partnership with the Wellcome Trust, the Wellcome Trust Sanger Institute and Illumina, the NHS Genomics Medicine Sequencing Centre in Hinxton will be created which will undertake whole genome sequencing (WGS) for the main programme. GE is working with industry from the start and making the most of companies’ expertise in developing new diagnostics and treatments. In March 2015 ten pharma companies created the Genomics Expert Network for Enterprises (GENE) Consortium\(^{24}\) to oversee a yearlong Industry Trial involving a selection of WGS across cancer and rare diseases. GE also collaborates with companies that specialize in data analysis, so that the project can benefit from cutting-edge advances in handling Big Data. The Trial aims to identify the most effective and secure way of bringing industry expertise into the Project in order to realize the potential benefits for patients but also for collaborating companies. A consortium works in the pre-competitive environment alongside GeCIP members with the goal of accelerating diagnostic, analytical and therapeutic advances for healthcare benefit. The models for these commercial interactions are still being worked upon. Work will be done in open innovation space and GE will own the clinical and sequence data and any results derived from these data. Intellectual property will be licensed back to academics, clinicians and commercial partners if appropriate. More detailed information about consortia is given in A Framework for Industry Engagement – Genomics Enterprises Prospectum\(^{25}\).

Funding of the 100,000 Genomes Project in the UK is £100M over the next 5 years; £7M funding was delivered to GMC-s to improve their infrastructure.

\(^{23}\) http://bit.ly/1AfOhNB
\(^{24}\) http://bit.ly/1HZpeGC
\(^{25}\) http://bit.ly/1bTCSOa
Figure 2.1.1.1 Organisational structure of 100,000 Genomes Project in UK. Source: internal team

HEALTHBANK

Scope and aims
Healthbank is building the world’s first citizen-owned health data integration and transaction platform connecting data sources from all facets of the healthcare ecosystem and rewarding participants for sharing their data for research purposes. Healthbank will leverage the advantages of Swiss neutrality, trust, and data privacy to enable citizen users, researchers, and organisations with large data sets, to utilize the value of health and medical data on an independent, global transaction platform. Healthbank empowers users to store, manage, share and benefit from their personal health information according to each user’s individual needs. Healthbank aims to engage 1M users in 18 months.

Stakeholders and collaboration
Healthbank is defined as platform for buying and selling health related data by the various stakeholders: patients as sellers, pharma companies, diagnostics companies, hospitals, clinical research organisations, researchers in academia, wearable health systems developers and market research companies as buyers. Users/patients manage and control their own data, and they alone decide case by case whether to share their data with health care providers, family members, researchers and others. On the basis of functionality and collaboration mechanisms the platform may be divided into four units: research platform, user platform, business-to-business platform (see picture below to illustrate the projects with business partners), data mining platform (requires a large user base so not immediately possible after launch).

26 https://www.healthbank.ch/
Organisational setup and management
Healthbank is a Swiss cooperative established in 2014, owned and governed by its members. Everybody can join the cooperative by paying a one-time membership fee of CHF 100. As a member, he/she can participate in General Meetings and be eligible to receive any dividends approved by and distributed to all members. The voting rights of Cooperative members are equal, and no member has more than one vote. The ownership/governance structure was designed by leading experts in the area of Swiss cooperatives, a common business form for large Swiss companies such as banks and grocery store chains (e.g. Raiffeisen, Migros, etc.). The Healthbank cooperative established the for-profit company Healthbank Innovation AG, the majority of which is always owned by the cooperative.

Figure 2.1.1.2 Investment structure of Healthbank Innovation AG. Source: internal team.

General considerations
By comparing the governance setup and principles of personalised medicine and genomic dataset projects in different countries, the following circumstances of importance for fulfilling the task can be outlined:

- Today, similarly to the situation of 15 or so years ago when the first initiatives were started, majority of the projects are initiated, coordinated and controlled by the public sector. However, the first major project in the field of population genetics (can be viewed as a predecessor of PM) launched in Island in 1996 by neuroscientist Kari Stefansson was initiated as a private endeavour in the form of a for-profit company, deCode Genetics. Likewise, the Healthbank cooperative established just last year is a private initiative. Both population based biobanks, UK Biobank and Estonian Biobank, established in 2001, were initiated by public sector. UK Biobank Ltd. as a for-profit company. The Estonian Genome Center (Estonian Genome Project Foundation) was founded as a public non-profit organisation, although it had already in the very early phase a private-public component included. The EGP Foundation started as a private arm registered in the US and was able to raise US $4.5M private investments to
prepare infrastructure and conduct pilot phase. The way the patients/donors were attracted could be considered one of the key factors determining sustainability. The UK Biobank itself that did not use a model of broad consent enabling to re-contact the participants has turned out to be a project with isolated and out-dated data in silo. Today, there are the samples of more than 500,000 people in UK Biobank and they are utilized merely as an academic research infrastructure. However, the skills and knowledge gained in developing UK Biobank are now being put to use with the establishment of UK Biocentre, a wholly-owned UK Biobank subsidiary geared to helping other pioneering health studies. UK Biobank has become one of the world-leaders in biological sample management and is in collaboration to Genomics England storing biological samples collected in 100,000 Genomes Project. The deCode was one of the first biobanks that implemented a broad informed consent. The company was publicly listed at Nasdaq, has undergone bankruptcy and several changes of ownership. Today it is an affiliate of Amgen working in close collaboration with a number of life science companies and in 2013 launched a diagnostics-focused spinout. The Estonian Genome Center, that started off as a government-established foundation and that was initially financed on a PPP principle, is now a research institute at the University of Tartu and is financed mostly by public funding from the Estonian government and EU funds, but has also been able to start attracting private funding through collaborative research projects.

- Since the competence and interest for developing this novel area has so far been mainly in academic organisations, and the majority of large-scale actions have been publicly funded, this has also had an impact on the governance setup and principles. Genomics England is also largely funded from public sources. However, by today the stage has been reached where in order to put the large amount of collected genomic data into practical use, integration with health data is required but that in turn necessitates large investments into infrastructure. The increasing awareness and need to integrate genome and health data into a single data resource has attracted pharma- and biotech industry willingness to invest in developing the infrastructure. GE is a great and transparent example of how pharmaceutical companies have formed consortia to conduct industrial trials and implement the results in drug development. In case of GE, the collaboration with private partners runs in two stages – the precompetitive stage that includes joint developments, and the competitive stage, where the most common approach is the right to study anonymous data according to individual business interests and to use the outcomes for product development. The structures of project organisations have been created in a way, which allows attracting financial resources from various sources, both public and private.

- The use of intellectual property has been regulated in various ways. Looking at projects where a special management organisation has been created, the same organisation is also the sole owner of the created IP which will then be out-licensed; or the IP is owned by an external company that created the IP and that will pay royalties to the project organisation when the IP is realized.
Since the next large global task is to provide clinical evidence for new knowledge, collaboration with academic research institutions and health-care service providers (mainly university hospitals) is inevitable. For example, in the case of GE, NHS has included 11 university hospitals as partners who will recruit patients, conduct clinical trials and in the future will also provide counselling. This means the project has been structured in a way that makes it possible to later integrate services in the health-care system and thus assures the sustainability of the project.

As a large number of people need to be involved in order to put the projects into practice, the social aspect of the enterprise and a positive attitude of the public have been considered important. The corporate structure of the projects has been created in a way to inspire confidence (public sector/state) and to make for safer collection and processing of data. GE has created a clear advantage for researchers from the UK to participate in conducting studies.

Healthbank, on the contrary, is an extreme example of private initiative tapping into the Swiss practice of public engagement, where each person as a shareholder of the cooperative decides who and for what purpose can use his or her data.

**Initiatives developing Digital Decision Support Systems (DDSS)**

Among the initiatives observed, there are also companies developing e-health information systems enabling the translation of clinical, pharmacological and in one case also molecular information into routine clinical workflow. The Palo Alto, USA based company **Syapse** provides clinical software applications (IT platform) that enable healthcare providers to deploy precision medicine programs. Another one, **Duodecim Medical Publication Ltd** owned by the Finnish Medical Society Duodecim, which is the scientific society for Finnish doctors, has developed a system called Evidence-Based Medicine electronic Decision Support (EBMeDS). The EBMeDS rules are developed and maintained using a web-based collaboration tool, the EBMeDS Script Description Editor (ESDE), which is open for use for trained end-users of the system. **EBMeDS** develops and provides a decision support system that receives structured patient data from electronic health records (EHRs) and returns reminders, therapeutic suggestions and diagnosis-specific links to guidelines.

**SYAPSE**

Syapse enables healthcare providers to deliver actionable insights from genomic and molecular data at point of care. Through an intuitive web interface, clinicians see a comprehensive view of a patient’s clinical history integrated with molecular profiles from internal or external labs. Clinical decision support based on institutional guidelines and knowledge improves the accuracy of diagnoses and treatment decisions. With Syapse software, clinicians seamlessly order tests, initiate drug procurement, enrol patients in molecularly matched trials, and capture outcomes. Syapse oncology and pharmacogenomics applications use the rules engine of the Syapse Precision Medicine Platform™.

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27 www.syapse.com
Syapse is a private company established in 2011 in California, USA. The company is backed by angel investments and two venture capital funds, $14.6M in total. Currently, it has about 40 employees.

Academic and community healthcare providers like the Stanford University School of Medicine, the Roswell Park Cancer Institute, the Intermountain Healthcare, the Sarah Cannon and Swedish Cancer Institute use the Syapse Precision Medicine Platform.

**DUODECIM MEDICAL PUBLICATIONS – EBMeDS**

EBMeDS is an evidence-based medicine decision support system that receives structured patient data from electronic health records (EHRs) and returns reminders, therapeutic suggestions and diagnosis-specific links to guidelines. 45% of therapeutic suggestions are generated according to country-specific treatment suggestions; the remaining 55% are global. It can also be used to automatically prefill forms and calculators with patient-specific data. In addition to real-time use, the EBMeDS decision support rules can also be run in patient populations ("virtual health checks"). EBMeDS is a platform-independent service, which can be integrated into any EHR containing structured patient data. In Finland physicians and nurses open articles about 625 times per person and totally 40 million times in a year.

EBMeDS is developed by [Duodecim Medical Publications Ltd](http://www.ebmeds.org/web/guest/home?lang=en), a Finnish company owned by the Finnish Medical Society Duodecim, which is the scientific society for Finnish doctors. Both the association and the company have a long-standing collaborative relationship with the Cochrane Collaboration, the GRADE Working Group, the Guidelines International Network (G-I-N) and the publishing company Wiley-Blackwell. The process for creating the EBMeDS clinical decision support content has got NHS accreditation.

The database is regularly upgraded four times a year. Duodecim has employed 20 medical doctors for upgrading the content but about 2000 physicians have taken part in the development voluntarily for a symbolic fee of 100 €. Healthcare providers are paying for the service in Finland.

All end-users of the EBMeDS service can contribute to the development of new scripts. The simplest way of contribution is to send a suggestion of a script idea to the EBMeDS editorial team. End-users are also offered free access to the EBMeDS Script Description Editor (ESDE), a web-based editing tool for collaborative development of evidence-based decision support rules. The use of ESDE requires registration.

In addition to Finland, the system is incorporated into health care systems in a greater or lesser extent in Belgium, Great Britain, Denmark and the United States of America. Its module RenBase for renal failure and dosage of drugs is used in Sweden, Finland, Austria, Poland and Italy.

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29 [accreditation report](http://bit.ly/1GOglOw)
In Belgium, the construction of a national electronic point-of-care information service, EBMPracticeNet, was initiated in 2011 to optimize quality of care by promoting evidence-based decision making. The system is financed by the state and was developed in collaboration with the government, health care providers, evidence based medicine (EBM) partners, and vendors of EHR. All Belgian health care professionals get free access to an up-to-date database of validated Belgian and nearly 1000 international guidelines, incorporated in a portal that also provides EBM information from other sources than guidelines, including computerized clinical decision support that is integrated in the EHRs. A project leader, an editor-in-chief, five editors, and a secretary, all working part time on this project and representing two fulltime equivalents, coordinate the building and management of EBMPracticeNet. The processes are being implemented in collaboration with the Belgian EBM producers, technical experts, and volunteers. Finding competent volunteers that are motivated to participate in these processes is a key factor in the sustainability of this project. The use of volunteers can include taking on the responsibility for one or several guidelines to ensure that the recommendations and their updates are in accordance with the Belgian context.

In Estonia, Duodecim EBMeDS is partly available from 2014. The service is implemented in North Estonia Medical Centre, Hospitals using ESTER health information system and pharmacies working with Hansasoft software. Medicum, Nortal and LIISA software users will be joining during 2015. The eHealth Foundation is a partner of the company. The distributor in Estonia is Celsius Healthcare. In May 2015, Celsius Healthcare in cooperation with The Estonian Association of General Practitioners made a proposal to the Health Insurance Fund to establish a consortium (similarly to Belgium) in Estonia for implementing the system in a larger scale.

2.2 Business environment in personalised medicine

This chapter is defined into two sections. The first section defines the PM market through the PM value chain and describes the key market segments providing info also on some key trends and key customer needs. The PM market as such is not a homogeneous market with one type of customers and drivers but it is rather a set of different sub markets with their own dynamics, customers and development drivers. For this reason, a value chain model has been developed in order to illustrate the market dynamics of the various submarkets and highlight the key market sectors most interesting from the Estonian perspective.

The second section outlines the PM market sectors that are most relevant for Estonia with respect to the market size, growth and correspondence with Estonian strengths to illustrate the size of the opportunity. The section concludes with the discussion about the current status of the market development and the Estonian strengths, opportunities and key stakeholders for the development of the EPMPP.

The market analysis has been based on the literature analysis as referred to in the text and

http://www.researchprotocols.org/2013/2/e23/
expert interviews and analysis by Ms Kadri Vunder based on the internal knowledge of international venture capital and market research companies of Travis AG, bms AG and LSVenture GmbH/LSVenture OÜ.

2.2.1 Personalised medicine value chain and business models

Business model is a concept that can be used in many ways by the business thinkers. As an example, Peter Drucker defined the term - “assumptions about what a company gets paid for” - which is part of Ducker’s “theory of the business.” In addition to what a company is paid for, “these assumptions are about markets. They are about identifying customers and competitors, their values and behaviour. They are about technology and its dynamics, about a company’s strengths and weaknesses.” A good business model answers Peter Ducker’s age-old questions, ‘Who is the customer? And what does the customer value?’ It also answers the fundamental questions every manager must ask: How do we make money in this business? What is the underlying economic logic that explains how we can deliver value to customers at an appropriate cost?32

For simplification purposes, the current study has focused only on the product aspect of the business model definition, i.e. what the companies get paid for.

Personalised medicine ecosystem is a complex of very diverse public and private entities as well as diverse business and operating models. In order for the ecosystem to function, all its individual consistent parts have to be operational, aligned and co-functioning. For this reason, it is easiest to describe the PM ecosystem in terms of a value chain as shown in the illustration below (See Fig. 2.2.1.). Each box represents an individual actor in the value chain that has unique services/products to sell and is interdependent on the preceding and following value chain parts having a service level interaction in between. The variety of business models in the value chain is very large. Many existing businesses in the described value chain are backward or forward integrated. Sophia Genetics, for example, provides a drug response decision support system (both diagnostic kits including an assay as well as cloud based interface for the results interpretation) to hospitals33. Their revenue is generated based on the treated patients and their solution is developed by integrating the value chain parts 4, 5, and 6 for selling to customers in value chain part 11.

Such integration is mostly due to industry evolutionary reasons – the industry is relatively young and not all the value chain parts have been historically available, so the companies have built up parts themselves, or due to differentiation reasons, i.e. in case a specific integration model would provide a competitive advantage.

Moreover, the described value chain is a generic value chain and does not need to have all its parts fulfilled for all services offered. As an example, the repositories store samples and data and might have a direct interface with end customers, e.g. for blood cord samples storage, only value chain parts 1, 4 are needed to serve the customers in the value chain part 14.

33 Sophia Genetics: www.sophiagenetics.com, accessed on 21.06.2015
Figure 2.2.1.1 Personalised Medicine value chain illustration with examples of end product output in each of the value chain parts. Source: internal team analysis.

Each of the value chain parts, i.e. businesses, has different challenges to face. As an example of the challenges for the value chain part no. 4, Data processing and security systems, the challenges are associated with the integration of various forms of data such as text (clinical information), numeric values (laboratory data, age), categorical (staging, grading, scoring), image (histology, x-ray, magnetic resonance), array (genomic data), composite (DNA signatures, mutations, variants, transcription factor interactions) and/or hierarchic (pedigrees). Moreover, there exist a number of data security and confidentiality concerns related to the exchange of sensitive patient data. 34

As an example of a decision support systems developer who is developing novel algorithms for biomarker prediction is a company called Data4Cure 35. This company is backward integrated covering value chain parts 4 and 5. Their business model is built up on a service, delivering biomarker proposals based on proprietary algorithms linking genetic patterns to diseases. In this space, there are many different types of companies delivering the same service with different set up (e.g. access to data, algorithms, cohort, disease focus, data mining algorithms, machine learning protocols, etc.). One of the key success factors for such companies is the clinical validation of the developed biomarkers and therefore cooperation with academia and CROs.

35 Data4Cure: http://www.data4cure.com, accessed on 21.06.2015
Another example in the same value chain part is Qointa who is developing a platform for clinical trial design and execution. Qointa will be a compliant and validated platform where patients can be monitored and coached (automated) independently from the device they are using (ehealth). The platform is built in such a way that patients can be directly randomized in (adaptive) clinical trials. The platform can also acquire and use the data sitting in hospital electronic medical records (structured and unstructured) without being typed over (eSource). The platform contains all the features to perform high standard clinical trials (randomization, patient diaries, education etc.). The key success to the business model of Qointa is the seamless interaction of value chain parts 5, 8 and 12.

Pharma companies, as depicted in the value chain part 7, are focused on new drug discovery and development. Their key interests in genomics are threefold:\footnote{Discussion about the insights into pharma industry needs, due diligence visit to Estonia of Merck, BioGen, Bayer Pharma on 16th and 17th of June 2015.}

Identification of the most promising targets, e.g. through whole genome sequencing (WGS) or exome sequencing in selected families and enriched populations, and through genome wide association studies (GWAS) and rare variant weighted aggregate statistics (RWAS) to pinpoint disease associated genes and loci;

- validation of targets through providing evidence for functional significance through experiments (e.g. expression/eQTL studies) or through establishing “allelic series” (genetics-based function-phenotype curve) through linking genotypes with phenotypes and conducting systematic in vitro functional studies;
- prediction of efficacy and adverse events e.g. through Mendelian randomization (e.g. association with surrogate biomarkers); or through PheWAS (e.g. association with comorbidities available through EMRs).

Through genetics, the pharmaceutical companies aim to establish casual relationships between intermediate phenotypes and diseases with an aim to improve quality of drug targets that enter clinical trial phase and thus increase the efficiency of the whole drug development value chain. According pharma industry\footnote{Personal communication with Mr Robert Plenge (VP, Head of Translational Medicine, Merck Inc., Boston, USA)} app. 85% of all costs of developing new drugs are connected to clinical phases, which underlines the drive for getting better output from pre-clinical phase and predicts substantial savings in the later phases for the companies. The relevant studies that need to be performed in order to establish the latter include genetic association – biomarkers, genetic association – disease risk, functional characterization, molecular profiling and epidemiology.

There are various limitations to-date to using the full potential of genetics in drug discovery:
● Limitations in genetics – better understanding is needed of human genetic variation
  ○ Comprehensive catalogue of genetic variation in humans is needed
  ○ Understanding of which genes cause loss-/gain-of-function (LoF/GoF) in humans is needed
  ○ “allelic series” is needed for every possible target
  ○ the functions of all genes need to be assayable in a system suited for drug discovery

● Limitations in clinics – need to better understand genetic basis of human disease
  ○ What are the exact consequences of genetic variation on phenotype
  ○ How do the same/different human phenotypes relate to changes in the genome
  ○ Large, re-callable clinical cohorts are needed that are well characterized at the genetic (incl. WGS), biomarker and clinical level.

● There is a limited interconnection between genotypes and phenotypes and between pharma and academia.

In order to overcome these limitations, the pharma companies need multidirectional interfaces with data processing and security interfaces (value chain part 4), access to different data sources (1, 2, 3) requiring various correlation algorithms between genetic material, hereditary diseases, risk profiles and drug response, CROs (12) as service partners for clinical trials (incl. targeted clinical trials) and hospitals and clinics (11) for the treatment options. Last but not least, they need access to different patient cohorts (0).

Examples of companies and initiatives covering parts of the pharma needs in linking genetics with phenotypes in this value chain include Kaiser Permanente, Geisinger, NIH-AMP, Human Longevity, deCode Genetics, Genomics UK Biobank, Genomics, Interval, Lifandis Hunt, Finnish Founder Population, Singapore Biobank, Saudi Arabia Genome project, Maccabi, PROMIS, 23andme, Veteran’s Administration, Ancestry.com, The precision medicine initiative. The business models of Healthbank and Genomics England have been described in more detail above in this report.

**Conclusion:** in the PM space there is not one business model that fits all but a variety of business models depending on the value chain position and integration rationale. Each of the companies and business models has a unique set of challenges to face and key success factors to optimize.

The successful companies in the PM space have all had a few things in common – they have all had a very focused approach to a well defined customer segment and application and they have all had development partners from the industry early on to establish the proof of concept early on, attracting through that enough capital for the development of the products (examples include Data4Cure, BC Platforms, Sophia Genetics, deCode, etc.).

In order for the industry to start developing in any region, there are key enablers that need to be in place. In the context of Estonia, the enabler for the development of the industry on a large scale would be the speedy, integrated and key-application-oriented development until
proof-of-concept of the value chain parts 1, 2, and 4. This would enable the various industrial partners to start dedicated programs and other application developers to start to engage. The existing landscape in Estonia in these value chain parts as a total is rather scattered. Therefore, it is advisable to create a service company integrating these parts of the value chain via service level agreements to enable a controlled and focused approach to the development of certain key applications as well as provide a coordinated interface towards the various customers and other stakeholders. This should also be the scope and focus of the EPMPP and the platform development.

2.2.2 Personalised medicine market and application in Estonia
The PM market is relatively young and scattered across the value chain. Uniform data is not available and care needs to be taken when analysing the data as the definitions in various data sources have not been the same. A thorough market study needs to be performed in order to have a uniform and consistent set of market data. However, there is data available from various sources about some parts of the value chain.

Some trends and the most relevant parts for EPMPP have been outlined below.

Key trends

- Number of new drugs in decline;
- Rise in approval of drugs with companion diagnostics;
- 10% FDA approved drugs have Pharmacogenomic labelling;
- 50% of drugs in pipeline are biomarker-based;
- 1-3B samples banked and growing;
- >75% biobanks are disease specific;
- $>1B technology spend per year

Key Markets relevant for EPMPP are the following:

1. Healthcare data market. This is the pharma research market for establishing casual relationships between intermediate phenotypes and diseases. The market for health data analytics is young and will see a substantial growth in the next 5+ years. It is driven by new technologies (e.g. sensors) and transformational concepts in life science (e.g. personalised medicine). The indication for market size and customer need can be provide by:

2. The deals that have been realized between pharma and personalised medicine projects or funding deals like deCode and Amgen (value USD 415 M)\(^{39}\), Castlight Health (USD 178 M IPO at 2 b valuation)\(^{40}\), ims health applied (USD 1.3 B IPO)\(^{41}\), patientslikeme (Genentech 5-year data access agreement; Actelion: research initiative to create new patient reported outcomes tool for a type of T-cell Lymphoma), 23and me (Pfizer: research initiative involving Inflammatory Bowel Disease and Ulcerative Colitis/Chrohn’s Disease; 10 K Data sets sought from new users), Flatiron

\(^{38}\) Liberating the knowledge in your biospecimens, Mark A Collins Ph.D. Molecular Med Tricon 2013
\(^{40}\) http://www.imshealth.com/portal/site/imshealth/menuitem.c76283e8b8f1e98f53c753
\(^{41}\) http://www.imshealth.com/portal/site/imshealth/menuitem.c76283e8b8f1e98f53c753
(USD 130 M Series B round led by Google) \(^{42}\), Foundation Medicine (Strategic collaboration with Roche in the field of molecular information in Oncology (tender value USD 780 M)\(^{43}\). Estimated marketplace of USD 50 billion for Life Sciences and USD 25 billion for Payers and Providers in information and technology services\(^{44}\). Healthcare analytics estimated to reach USD 21 billion by 2020\(^{45}\). Decision Support Systems (DSS) – the market growth can be estimated based on:

a. Bioinformatics tools and data market (see details below)

b. Diagnostics and next generation sequencing services and tools markets (see details below)

**The bioinformatics tools and data market**\(^{46}\)

- The global bioinformatics market was nearly $3.2 billion in 2012 and is forecast to grow to nearly $7.5 billion by 2017. The U.S. accounts for 52.8% of global sales.
- The bioinformatics tools and database services segment of the bioinformatics market generated more than $1.5 billion in 2012 and is forecast to grow to $3.4 billion by 2017, with a 2012-2017 CAGR of 17.9%.
- The data analysis and software market generated more than $1.1 billion in 2012, and it is forecast to grow to nearly $2.9 billion by 2017, with a 2012-2017 CAGR of 20.3%.

**In Vitro Diagnostics (IVD) market**

An in vitro diagnostic is a method of performing a diagnostic test outside of a living body in an artificial environment, usually a laboratory. Everyday examples of in vitro testing include checking blood for signs of infections, or urine for the presence of glucose. Nowadays, IVDs provide much more than simple assays conducted in test tubes and examining glass dishes under microscopes. IVDs are used in large-scale population screening, such as for cervical cancer, as well as for predicting whether a specific medicine or treatment will work on a patient. Patients with diabetes use IVDs regularly to monitor their blood glucose. They are also used to make or confirm a medical diagnosis, from confirming a pregnancy to checking for infectious diseases such as hepatitis or HIV. At one end of the scale, IVDs can be sophisticated, automated systems capable of analysing large numbers of samples for multiple parameters; at the other end, they can be self-testing systems providing information directly to the individual performing the test.

The IVD industry produces reagents, analytical instruments, and accessory products that are needed to perform diagnostic laboratory tests.

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42 http://techcrunch.com/2014/05/07/google-ventures-leads-130m-series-b-in-cancer-data-startup-flatiron-health/ accessed on 25.06.2015
44 IMS SEC Filing, January 2014
46 BCC Research, MA, USA, 2013
- Reagents are solutions of highly specific biological or chemical substances that are able to react with target substances in the samples. This process will result in an outcome that can be measured or seen.
- The analytical instruments are the various machines and equipment that automate the process and are used to bring samples and reagents together. Analytical instruments measure the result or other qualities and parameters in the samples.
- Accessory products, such as the software programs used to run the instrumentation, and control solutions that check the performance of the systems are also produced by the IVD industry.

Together, reagents, instruments, and accessories are referred to as "in vitro diagnostic systems". In the below illustration, the market segmentation per competitors and per market segment are given. Of the market segments listed, relevant for PM and sequencing methodologies are all listed market segments but diabetes monitoring. The global market for IVD in 2013 was USD 52 billion with an annual CAGR of 5%.

![Market share and size](image)

**Figure 2.2.2.1** IVD Market size and segmentation by competitors and market segments

**Next Generation Sequencing (NGS) products and services**
A sub market of the IVD is the next generation sequencing market enabling the high speed of sample-to-data solutions. The key products in this sector are:
- Reagents and Next Generation Sequencing workflows optimized for various sample types;
- Predesigned, custom, and clinically validated gene panels (arrays);
- RNA and miRNA Next Generation Sequencing service with advanced analysis and data interpretation.

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48 Roche Diagnostics, 9th Swiss-Scandinavian Bio-Business 2015
The below illustration shows the next generation sequencing market development for its key segments – academia and diagnostics. The market is expected to grow to USD 7 Billion by 2022 with an annual CAGR of 45% for diagnostics segment and CAGR of 13% for the research segment.

Figure 2.2.2.2. Market forecast for NGS products and services

Predictive genome-based testing for some complex diseases has been available to consumers for a number of years already; however, these genomic-based tests have not yet reached the level of routine clinical use. The commercial tests have been blamed mainly for lacking clinical validity, which has mostly prevented their more widespread dissemination. Also missing is a problem-solution and clinical product/service fit for improved management of complex diseases, using the disease risk approach for behavioural changes to successfully avoid or postpone the onset of complex diseases. The key stakeholders influencing the outcome of the medical services – the physicians, are in need of tools to manage disease risks in health communication, intervention planning and patient motivation and empowerment. Due to the special and delicate attitude towards genetic information and the sophisticated nature of health-related research, the most genome-based personalised medicine projects are built as public academic undertakings, e.g. UK Biobank, Cart-aGene in Canada, Biobank of Finland, and many others. While the commercial projects, e.g. 23andMe, Pathway Genomics and CD Genomics, are facing criticism for lacking robust clinical validity in their practice. Although both of these approaches, public and private, are applying state-of-the-art computational tools to analyse the links between the robust genetic data and historical and dynamic health data, there are still major shortcomings to overcome. For example, the existing solutions are strongly criticised because of the difficulties in bringing together enough health, medical and

49 Leerink Swann LCC
genome data, which are stored in different health-care institutions (databases) and stand-alone genome banks, preventing an integrated approach for data handling and analysis. There are several bottlenecks that globally hinder the application of the achievements of molecular medicine and info- and communication technology (ICT) in the interests of human health. Therefore, it is necessary to combine the recent key advances in medical and population genetics, bioinformatics, E-Health and ICT in general, to develop the preventive, diagnostic and treatment algorithms and decision-support systems for personalised medicine for common complex diseases and cancer.\textsuperscript{50}

Estonia has a unique potential for combining the genome, health and environmental data from various sources, as Estonia has the Estonian Biobank (population based genome bank), a nationwide Health Information System, database of the Estonian Health Insurance Fund, and several other health registries, which let Estonia be the first test-country worldwide for personalised medicine. This opportunity for Estonia was recently highlighted in the journal Nature, featuring Estonia as a pioneering country for genomic-based personalised medicine. Moreover, the Estonian Development Fund’s paper on smart specialization depicts ICT and health services and technologies as the key strengths and development sectors in Estonia.\textsuperscript{51}

During the study a due diligence visit by several global pharma players was conducted to the Estonian Genome Centre of the University of Tartu\textsuperscript{52}. The main feedback of the visit was that the representatives of companies participating saw great potential in Estonia. The companies would activities in some small scale due diligence and visibility studies (e.g. systematically analyse the existing genetic and phenotypic data, hire a couple of epidemiologists to start with the validations etc.) and in the background start to prepare a much more extensive collaboration around clinical data validation and whole cohort genotyping initiatives that would include – 1) to genotype all samples in the EGCUT biobank; 2) validate both EGCUT biobank and national data repositories; 3) develop software tools and make all registry data interlinkable through one engine; 4) perform a throughout phenotype-genotype analysis to evaluate the quality of clinical data 5) perform visibility studies among participants, doctors and general public about clinical studies and pharma engagement; 6) carry out some small scale genotype-driven clinical trials and 7) develop tools to effectively engage with public. In parallel, the companies underlined the need for expedient enlargement the existing biobank from current 50 000 participants to 200 000-500 000 scale. In addition, the establishment of Phase I “first in human” clinical trial capacity in Estonia was considered a must.

\textsuperscript{50} CCHT business plan 2015
\textsuperscript{51} Nutikas spetsialiseerumine - Kvalitatiivne analüüs, Eesti Arengufond, veeburar 2013
\textsuperscript{52} Representatives of Merck Inc., Bayer Pharma AG and Biogen Inc. Paid a visit to Estonia on June 16-17, 2015. The program of the visit and list of participants please see in Appendix 5.
Estonia could capitalize its strengths in the following key areas of personalised medicine:

1. Access to industrial and academic partners to large scale well established, integrated and dynamic health and -omics data platform that enables preclinical and clinical research
2. Development of genome-based tests for complex diseases to predict the risk for common diseases that cause health problems, such as heart disease and ischemic stroke, type 2 diabetes, cancer etc., and to provide pharmacogenomic-based recommendations for certain drugs.
3. Development and integration of digital decision-support tools to implement ever increasing bulk of evidence based clinical algorithms, -omics and big data derived knowledge in everyday medical practice and patient communication
4. Personalised cancer therapy to fully integrate the innovative clinical and translational oncology activities already underway at CCHT. It is necessary to build a referral system matching the patients with advanced cancer to the best treatment sites and clinical trials for their specific needs.
5. Development platforms for big data clinical genomics analytics and genomic profiling of tumour tissues for personalised cancer therapy

Examples of key stakeholders relevant for the above mentioned areas in EPMPP:
EGCUT with its current well-regulated genetic and health data collection would be a main actor for developing large scale health and -omics data platform. In addition, EGCUT can provide facilities and high-level expertise required to process and store the DNA samples as well as genomic technologies (including next-generation sequencing), genetic epidemiology, statistics and bioinformatics.
Analysis of data structure and quality in health related databases and development of common data exchange standards, standard profiles and taxonomies for integrated database query algorithms are in the scope of the eMedicine Laboratory (eMed Lab), Technomedical, and Tallinn University of Technology. Asper Biotech has competence and capacity for development and validation of genetic tests. LabToWellness business area is in patient-centred and user-friendly reports for clinicians and patients in personalised medicine.
HealMe is currently building a treatment access referral network for patients with advanced metastatic cancer. Interpretive Genomics has computing resources, skills and manpower to further enhance the analytical strengths and big data visualization capacities.
The Competence Centre on Health Technologies (CCHT), Software Technology and Applications Competence Centre (STACC) can play important role in coordinating university-industry collaboration in R&D activities needed for fulfilment of the aims set for EPMPP
Tartu University Hospital and North Estonia Medical Centre have modern facilities for providing high quality clinical trial infrastructure.
University of Tartu has a computing capacity that involves 300TB for data storage and a computing cluster for high-performance data processing. The computing laboratory will implement the ISO standards and accreditation in 2015.

Concluding, due to the lack of global industry proximity and scarce capital insensitivity, Estonia, has only limited capability to develop new technologies in drug development and diagnostics sectors. However, Estonia has a unique opportunity for being the pioneer in the
integrated approach for data handling and analysis due to its existing systems (databases and data with informed consent) and development strengths in ICT and health services and -technologies sectors. It will be important to consider the concerns and proposals articulated by the big pharma and take immediate action to address them. It will be also important to secure optimal financing to achieve the set goals. Therefore, realistic implementation plan has to be agreed. Estonian public funding sources are hardly able to cover the costs to implement the needed steps in developing the phenotype-genotype platform that enables to achieve set goals of establishing Estonia as a globally competitive PM industry hub. Therefore, coordinated actions from all parties are essential to secure private investors involvement. At the same time, the arrangement negotiated for private public partnership has to foresee ways to attract innovative companies, domestic and foreign, to join the activities in developing new tools and services to develop the platform as well as to implement PM concept in clinical practice. This could include at least two directions

1. the potential investors should commit to start a PM business incubator either independently or in cooperation with the government,
2. the government should enable supportive financing instruments through existing mechanism that will create addition motivation for these companies.

**In summary:** we can outline 3 key industry sectors that would create an opportunity to develop Estonia as an attractive and important partner in the global PM value chain with the initiation of the EPMPP and platform initiative:

1. **Drug discovery & clinical trials sector**
2. **Diagnostics sector including both hard and software solutions development**
3. **Decision support applications sector (ICT solutions, big data analysis, interfaces, secure data processing, etc.).**

The realisation of the opportunity, however, depends on the ability of the Government and the main stakeholders to plan and implement the actions proposed by potential commercial partners in an expedient and coordinated manner. Having already a well regulated comprehensive biobank and advanced E-health data infrastructure in place gives Estonia some advantage over most competitors on global arena. However, the advantage is only temporary, taking into account the major efforts planned by a number of countries. This means the window of opportunity to be open for the next 1-2 years only.
3. Development of central governance structure

This chapter is aimed to develop suggestions for the central governance structure of EPMPP. The chapter is divided into five sections. The first three sections are about the process of developing criteria for the central governance structure model (3.1), proposing potential alternatives for the structure (3.2) and selecting optimal options from the potential alternatives (3.3).

The last two sections of the chapter are devoted to specific suggestions for optimal and minimal alternative scenarios in EPMPP implementation and proposing specific roles of involved parties for two clinical interventional pilot studies worked out by the Clinical component subgroup of the pre-feasibility study.

The methodology to carry out the work was mainly task group brain storming, communication with other pre-feasibility study components’ team members as well as with the representatives of MoH, and desktop analysis. This subcomponent was conducted by Tartu Biotechnology Park team of Jaanus Pikani, Krista Kruuv-Käo and Andres Rannamäe.

3.1. Criteria to evaluate the EPMPP central governance structure.

The section analysis the capacities and functions that the central governance structure has to meet in order secure successful implementation of EPMPP. The analysis process built on previous chapters’ outcomes and input from other components of the pre-feasibility study. The section concludes of eight criteria (Sustainability and flexibility, Private business involvement, Financing and resources, Stakeholder involvement and partner cooperation, Social dimension and public acceptance, Implementation feasibility, Governance and management, Stewardship) that were basis for further process for selection of optimal alternatives for the governance model.

Based on the EPMPP preliminary plan and the call document the governance structure of the EPMPP has to enable and facilitate most importantly the implementation of the EPMPP in order 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, by taking advantage of and enhancing the existing strengths of Estonia in the area of personalised medicine.

More specifically, the planned governance structure has to:

- Secure practical implementation of the EPMPP plan and fulfilment of the set goals
- Secure development of relevant ITC, research and clinical material and organisational infrastructure in Estonia for PM
- Enable and motivate foreign academic as well as industry partners to join the efforts
• Enable engagement of various sources of financing – public and private – to secure achievement of the set goals
• Support application of PM in day-to-day health care practice after completion of the EPMPP
• Enhance Estonian R&D&I capacity in biomedical field in general and in PM in particular
• Support FDI into and export capability of Estonian economy
• Establish Estonia as a globally known and attractive test site for conducting research and new applications in PM

On a more technical level the governance structure has to create an organisation and legal/regulative system that will enable and facilitate to develop an environment that will support clinical research and eventual PM services implementation for the general population in diagnosing and treatment of diseases as well as for health risk management. In order to achieve this an infrastructure, which (1) links all existing health and other relevant databases in Estonia, (2) enables dynamic and renewable data enquiries to these self-standing datasets, and (3) provides a possibility for complex analysis supported by expert systems with predefined algorithms, is required.

In theory, there are several options to reach the goal. In practical terms it is obvious that some potential solutions will be more suitable and some, even legally and technically conceivable, might be unsuitable taking into account the complex nature of the endeavour and the need for smooth private-public partnership. Therefore, an appropriate instrument to appraise and assess the potential solutions is necessary.

Through brainstorming and mapping the existing relevant projects globally we have developed an original comprehensive, but still a simple enough tool for option appraisal of potential solutions. The task group ended up with seven main categories we consider to be most relevant and suitable for an efficient evaluation process.

Criteria for development and evaluation of potential solutions for the EMPP governance structure

1. Stewardship

The government’s role and commitment. Ability of proactive steering. Political support and acceptance. Horizontal political and public governance coordination.

2. Governance and management

Will the proposed structure enable efficient and flexible governance? How rigid are the procedures in personnel affairs, hiring and remuneration? How does the structure support the possibility to engage competent and well-motivated professionals? Complexity of the structure - centralized vs. decentralized decision-making. Accountability: how clear and transparent is the accountability system? How well can the reporting system be defined. Flexibility vs. stability.
3. **Implementation feasibility**

The complexity of the implementation process of setting up the EPMPP governance organisation: is there any need for legislative system update or change? What are the risks of facing strong opposition and failure to start the new governance structure? Can the whole structure be implemented stepwise without a major overhaul?

4. **Social dimension and public acceptance**

How well are public interests represented? Does the structure support socially fair decision-making and patient data privacy? How well can the project be perceived by the wider public? How does the structure protect a fair distribution of the outcomes of the project? How can it secure that there will be adequate access to the data and benefit resulting from the process? To what extent will Estonia benefit from the IP potentially created during the project? How is the private persons’ motivation to participate in EPMPP supported.

5. **Stakeholder involvement and partner cooperation**

Are all needed EPMPP stakeholders and partners optimally represented and empowered, their rights protected? How rigid is the process in regard to involving new stakeholders and partners? How transparent is the structure. How can the partners’ long term commitment be secured?

6. **Financing and resources**

- Public resources: How well does the structure support maximum recruitment of public resources? Do the structure and organisational set-up and philosophy provide a secure framework for public and private financing schemes?
- Private resources & investors: Does the organisation set-up and philosophy provide a secure framework for private financing schemes? Is it transparent and clear enough for private financing bodies and/or investors? Is it flexible enough to adjust to the ever-changing financing ecosystem?
- Will the structure and organisational set-up and philosophy enable to secure adequate financing to accomplish the set goals?

7. **Private business involvement**

- Does the structure support private business involvement? How does it motivate local and foreign SME-s to partner with the project? Will it motivate global companies to bring their business and investment to Estonia? How transparent and motivating is the access to the data? IPR rights. Will the participating companies have freedom to operate with respect to IP generated by the shared activities? Will the company or companies participating in EPMPP activities have ownership of IP created through their efforts? Will it be subject to right to use by the Estonian government within Estonia?
• How complicated is it to participate as a service provider? How rigid and sophisticated is the procurement process?

8. **Sustainability and flexibility**

Will the structure secure continuity in PM-related research and health care service implementation after completion of the PP? To what extent is the structure able to respond to potential changes in political, regulatory, investment or business environment in Estonia and globally?

3.2. **Alternatives for the EPMPP central governance structure**

In this section the process of working out all legally possible and theoretically feasible alternatives for the EPMPP central governance organisation. The task was work was performed by several brain storming sessions of the task group. The result of the sessions was two options governed by public law and four legal structures under private law. The outcome was one of the components for the next phase of the selection process described in the next section.

Based on the results of the already conducted analytical and descriptive tasks the project group formulated a list of theoretically possible options of legal structures for the EPMPP governance. The task was accomplished by a brainstorming session. Theoretically a variety of options can be suggested for the governance structure of the EPMPP, but in practice these may prove an unmanageable undertaking. Hence, the primary task of the group was to set some rules for the process.

After a lengthy discussion the group members unanimously decided on the following methodology for our brainstorming:

- we aim to look at all possible legally available alternatives
- our only limitation will be the existing good public governance practice in Estonia

Therefore, the range of possible solutions was considered for the options entirely governed by public law to various opportunities regulated under private law. There is also a number of mixed alternatives depending on the governance preferences and the extension of stakeholder involvement.

The task group was guided by the work of the previous tasks presented in the project call proposal under WP 1 in general and in particular by tasks “1.1.1. Global overview of large-scale personalised medicine projects” and “1.1.4. Current public governance practices of large scale innovative projects in Estonia” as well as by task “1.2.1 Criteria development to evaluate the EPMPP central governance structure”.

The result of the brainstorming session was a comprehensive or a “long list” of alternatives that can in theory be feasible for EPMPP governance:
1. **Solutions governed entirely under public law.** These are in principle various combinations of governmental institutions. The theoretical background and a more detailed substantiation on this option have been elaborated in the chapter above. Numerous models of public governance bodies can be foreseen as a solution. In practical terms, however, depending on the government structure housing the unit, two main possible alternatives can be considered feasible:

   - A structure in the Ministry of Social Affairs (MSA) itself
   - A public structural unit under the MSA (board, agency etc.)

Based on the explicit fact that the current pre-feasibility study has been initiated and overseen by the MSA, the task group excluded the options that would locate the general responsibility to other government structures (the Ministry of Education and Research, the Ministry of Economic Affairs and Communication or the Prime Minister’s Office) as practically not implementable.

2. **Solutions steered under public stewardship and thus under public control but managed by organisations governed by private law.**

   2.1. **Non-profit company (Foundation).** According to Estonian law a foundation is defined as a legal person in private law, which has no members and which is established to administer and use assets to achieve the objectives specified in its articles of association. Transformation of a foundation into a legal person of a different class is prohibited.\(^{53}\) Depending on the governance structure agreed upon by the founders, one can further contemplate several options that can have a rather different outcome when it comes to stakeholders’ involvement and empowerment.

      - **A foundation fully governed and controlled by government.** The government will found the foundation and the government will appoint all members of the supervisory board. There is practically no stakeholders’ involvement other than on the management level partnership or separate non-statutory consultation institutions.

      - **A foundation founded by government or jointly by government and stakeholders** but the articles of association stipulate **sharing the rights to appoint the members of the supervisory board** in order to secure dialogue between the government and the stakeholders.

      - **A foundation founded by government or jointly by government and stakeholders or solely by stakeholders** but the members of the supervisory board **will be appointed entirely by the stakeholders.**

   2.2. **Non-profit association.** A non-profit association is a voluntary association of persons the objective or main activity of which shall not be the earning of income from economic activity and may be founded by at least two persons. The founders may be

natural persons or legal persons. Transformation of a non-profit association into a legal person of a different class is prohibited.54

2.3. **For-profit company.** For foundations there are several options depending on who is going to control the activities. In addition to public surveillance accomplished by legislation the government can steer the process in a more pro-active manner by initiating business units or participating as a shareholder. Based on how actively the government is participating in the management of the project three main options can be suggested:

- A public limited company founded/controlled by stakeholders
- A public limited company founded/controlled by government
- A public limited company founded/controlled by government and stakeholders

Due to obvious major social impact and the nature of the project we do not foresee the option of running the EPMPP by a private limited company, nor do we suggest a general partnership as a legal structure for the EMPP governance body.

2.4. **Commercial association.** A commercial association (Kooperatiiv/Tulundusühing) can be another alternative that will enable to empower private persons and stakeholders in implementing the EPMPP. However, based on Swiss Healthbank example, it might be useful to have an additional private or public limited company attached to the association to facilitate efficient strategic and operational management.

3. **“Do nothing option”**

This option foresees relying on the existing structures (public and private) by allocating them specific functions in the implementation of the EPMPP, and will not foresee any new special-purpose legal bodies to be initiated.

3.3. **Central governance structure long list option appraisal**

In order to select the optimal legal structure options for the central governance structure, a classical option appraisal exercise by using a balanced scale with an equal number of positive and negative categories and consisting of enough points to extract the necessary information was conducted by the task group. The 5-point scale provides reasonable variation of categories, forces a sharper focus than is possible with the popular 1-to-10 scale, and provides more differentiation than only three-dimensional assessment. The latter has obvious disadvantage, tending to cluster toward the middle of the scales.

During the scoring process we compared all stimuli at the same time in accordance with the required appraisal criteria. This allows comparison of different organisational forms against

54 https://www.riigiteataja.ee/en/eli/529012015009/consolide
the same assessment criteria and their position on the positive and negative scale. After the assessment a simple counting of positive and negative valuations shows which legal forms are more suitable considering the complexity of the evaluation criteria.

The following is a summary of the evaluation matrix (see Table 3.3.1 below) for potential organisational forms with explanations and discussion of the majority of strategic criteria for different legal forms:

1. The most preferred organisational forms with equal scores are **Non-Profit Company (Foundation)** founded jointly by Government and main stakeholders, and **For Profit Company founded by Government and investors**.
   a. Both legal forms provide balanced protection of stakeholder/investor interest and public acceptance through active stewardship by Government. In case of For Profit Company public acceptance was evaluated neutral simply because the driving nature of the organisation is profit.
   b. Both forms allow the introduction of best management practices and provide reasonable freedom to operate the company, highly competent staff and a motivating environment. In order to secure transparency of company strategy, management and financial performance both legal options stipulate that stakeholders, including the Government, should establish good governance practice and governing structures.
   c. Strength of For Profit Company is the financing mechanism where moderate public financing can be leveraged with private stakeholder investments. Non-Profit Foundation is perhaps financially less attractive because of its non-profit nature and it would be a challenge to attract private investors and significant investments. Therefore, Non-Profit Foundation got a neutral score for the financial capacity.
   d. Both organisations got also high scores in sustainability where matching private and public interest may secure the stability in long-term development.

2. The next-ranking score goes to For-Profit Company established by Investors only. This option is supported by the freedom and motivation to get competent team on board and to establish good governance practice to guide private investment. Other strengths of this option are also sustainability and flexibility to manoeuvre should circumstances require. The weakness of this option was the fact that should it remain a private initiative only this may potentially leave the company without the Government support, and on the other hand, because of the profit-oriented nature, the public acceptance may not be as high as needed.

3. A somewhat lower score goes to Non-Profit Company established by Government only. The overall rankings were rather similar to the winning scenario, but all rankings got one grade less because of Government dominance and the missing private stakeholders’ and investors’ involvement.

4. The fourth position with equal score to Non-Profit Company was awarded to Commercial Association, but certain criteria of great importance such as the lack of potential Government stewardship and unclear financing mechanism left this option one position lower.
5. The remaining three legal forms – Structure or Function within the MSA, Unit under the MSA and Non-profit Association – got the weakest rankings. One way or another none of these options provide the security and confidence that the PM initiative can be managed within the interest of all parties. In a public service organisation or in Non-Profit Association with many members there are several weaknesses in a number of evaluation positions, and all these options have potential difficulties to achieve good governance practice. It will be difficult to attract other stakeholders, also financing prospects will be limited mostly to public sources. Due to direct exposure to political control and limited security for private investors a unit under the ministry status seems also unable to provide sustainability of the organisation.
<table>
<thead>
<tr>
<th>MSA</th>
<th>Unit under MSA</th>
<th>Non-profit (Foundation) Government only</th>
<th>company Government &amp; Stakeholders</th>
<th>Non-profit Association</th>
<th>For profit company founded by Government</th>
<th>Investors</th>
<th>Government &amp; Investors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Stewardship  
Governance & Management  
Implementation feasibility  
Social dimension & public acceptance  
Stakeholder involvement  
Financing  
Private business involvement  
Sustainability & flexibility

Table 3.3.1. A matrix table to evaluate the “Long List” of legal organisational options proposed in the Ch. 9 above
Rating scales used for assessment: “++” Excellent; “+” Above Average; “0” Average; “–” Below Average; “––” Poor
3.4. Suggestions for optimal alternative for the EPMPP central governance structure

This chapter is concluding the work of all previous chapters by summarising the work of the task group in suggesting actual solutions for the governance structure that possibly could pave the way to successful and sustainable implementation of EPMPP. Solutions for two scenarios of EPMPP were contemplated: (1) optimal, where most of the projected activities will be implemented and, hence, also most of the set goals can be anticipated to be fulfilled; (2) minimal, where only basic or very little of planned activities can probably to be accomplished.

The section finds that for the successful outcome of the EPMPP implementation process it will be most optimal to harness a combination of two legal structures under private law: (1) a special purpose non-profit foundation set up by the government with the task to coordinate all activities in the field of PM in Estonia; and (2) a for-profit entity founded by the non-profit foundation for commercial activities. The latter is proposed to be a concerted action between the government, academic partners (Broad Institute, University of Tartu) and investor(s).

Although legal structure creates a general framework for effective organisation management the actual outcome of the project will depend on the detailed governance structure and practice applied for both entities. Based on extensive in-depth discussions with various parties like relevant government officials, representatives of research organisations and investor community as well as other teams of the study components, some ideas for governance principles to pave the road for smooth implementation and sustainable operations of the EPMPP were outlined.

Depending on various internal and external factors to support practical implementation we present two possible alternatives to consider:

1. **Optimal** - needs some considerable amount of efforts, can give more outlook for success;
2. **Minimal** – needs little organisational development, obviously will not result with fulfilment substantial part of the goals set

**The Optimal Alternative**

The two options from the previous appraisal exercise above resulted to be equally preferred structure for central governance of the EPMPP: a **non-profit company (Foundation) jointly governed by the government and main stakeholders**, and a **for-profit limited company (Company) governed by the government and investors**. Both options prove to have good balance between enabling flexible governance of the organisation and secure sustainability, however each of them from the different perspective. While the Foundation proves to be the best solution to secure suitable structure to pursue the government’s strategic goals and stewardship by involving most important stakeholder groups, the Company, on the other hand, can offer the optimal environment for investors, and thus providing the tool for commercialisation and financing of EPMPP.
It is important to note that there are at least three important goals in implementation of EPMPP:

1. to develop the existing Health Information System (EHIS) to qualitatively new level by introducing disruptive solutions;
2. to improve comprehensiveness and quality of phenotype as well as genotype data that will be the basis for reliable and meaningful clinical support systems to be used;
3. to validate the PM concept in one or two clinical areas in clinical practice.

Any of these do not come for free and will need substantial financial resources that will be difficult to achieve by the existing public financing mechanisms alone.

In order accomplish the set goals obviously a substantial part, if not a majority of the financing, has to be raised by involvement of private partners. In addition, there are explicit expectations from the government to introduce Estonia internationally as a global hub for business development in PM field able to attract investment capital and new business ideas, start-ups as well as more matured companies to start activities in Estonia. All above-mentioned components are equally important in the planning task of the optimal and balanced governance structure.

It can be difficult to see how these two intrinsically opposing goals - public interest and private investors’ basic requirement for return of investment (RoI) - can be consolidated under one of these competing legal structures. Therefore, a combined approach with more complicated governance structure that embrace both forms legal persons – a foundation and a company – seems to be more relevant for successful implementation and sustainable operation of EPMPP.

The Foundation
According to our proposal the Government could start a special purpose non-profit entity to supervise, steer and coordinate PM activities in Estonia I with the specific functions of

- Coordination of PM activities in Estonia on national level
- Development, implementation and management of the EPMPP activities
- Evaluation of EPMPP implementation process and results
- Public communication regarding PM
- Coordination and implementation of educational efforts for stakeholders and health professionals in particular
- Coordination of professional stakeholders’ input to personalised medicine DDSS
- Coordinating data aggregation and normalisation with all relevant health, disease, environmental and self-reported data sources
- Coordinating and organising biological sample collection, processing and storage in collaboration with health care providers and EGCUT to enlarge the biobank from current 52,000 to the range hundreds of thousands participants in order to maintain global competitiveness of Estonia in the field.
• Provide feedback on personal risk profiles and lifestyle advice to the population
• Securing for proper regulatory environment and coordinating data access to the relevant databases
• Representing the government’s interest in the commercial activities of PM
• Dissemination information on Estonia as a global PM and digital health for-runner

Although the debate on the content of personal medicine in a broader sense is still on-going, it has been widely accepted that the involvement of various stakeholders will be crucial for a successful implementation of EPMPP. Hence, it will be of utmost importance to achieve true engagement of a critical number of the most important interest groups into coordination and decision making of the Foundation. According to the regulation on non-profit companies in Estonia the main decision-making body is the supervisory board of the foundation. To secure stakeholders’ engagement in the process in practice the terms of involvement of stakeholder groups on the board has to be determined already in the founding documents, i.e. articles of association. At the same time it is also important to enable efficient decision-making, in the case of complicated or emergency occasions in particular. Therefore it might be useful to foresee an arrangement the MSA representative has a permanent chairman position and also the right to veto decisions that might have substantial and long-lasting detrimental impact on personal data security. In any of those cases the veto right usage has to have detailed substantiation.

For the sake of efficient implementation it will be advisable for the government to found the entity as a sole founding party. The MSA as the leading government institution in EPMPP will steer the process and will also have the function to appoint the supervisory board members according to the following potential pattern:

**Supervisory board**

**The Stakeholders**
Stakeholders could have 6 members in a 12-member board. The following institutions could appoint these seats:

1. Tallinn University of Technology
2. University of Tartu
3. Representative of specialist doctors (Medical School of the University of Tartu will select one representative from the candidates nominated by various associations of specialty doctors. The exact selection mechanism has to be decided by the Medical School)
4. Representative of patients (joint proposal by the Estonian Patient Advocacy Association and disease based patient organisations)
5. Representative of GPs (Family Doctors’ Association)
6. Representative of Business community (joint proposal by the Estonian Chamber of Commerce, Employers Union and Chamber of Service Economy)
The Government
The government institutions will have the authority to appoint the other 6 seats

1. MSA (Chair, has extraordinary veto right, this right should be used only in extraordinary situations and has to be properly justified)
2. Ministry of Education and Research
3. Ministry of Economic Affairs and Communication
4. Health Development Institute (TAI)
5. Estonian Health Insurance Fund
6. Estonian Development Fund/ Enterprise Estonia (EAS)

Advisory Board
The supervisory board could be supported by an advisory board that will comprise of internationally acknowledged experts in the field of PM. The supervisory board and the management is obliged to actively ask the opinion of the advisory board in matters concerning overall development and research strategy, ethical issues, annual activity review and/or communication to the global specialty network.

Permanent working committee of professionals
An important function of the Foundation will be coordination the development, maintenance and implementation of activities on DDSS:
- Strategy development
- IT procurement
- Management procurement
- Continuous development

For this end a permanent team of people with relevant competencies have to be employed by the Foundation and a network involving health care professionals should be created. Practical way for active specialist doctors and GPs engagement is a permanent working committee embracing representatives of doctors associations.

The Company
A PPP structure in the form of for profit limited company can be set up by the Foundation to attract private capital to finance research activities in order to commercialise the existing genomic and e-health data infrastructure. The Company will support the vision and the mission EPMPP and advance personalised medicine, biotechnology products, and academic research in Estonia. Specifically, it can create a platform for (i) continued genetic and related research, (ii) investments in biopharmaceutical products and diagnostics, (iii) improved biotechnological services, (iv) gene therapeutics, (v) improvements to the Estonian and global

55 For example Duodecim example given earlier in this document has a group of 20 FTE specialists supported by 2000 volunteer active doctors to manage the development and maintainance of the DDSS product
health care industries, (vi) creation of employment opportunities in the health care and technology industries and (vii) improvements to the health of the population.

In addition, The Company can provide genotyping and genetic sequencing services to additional members of the population and help fulfil the government’s goal of converting biological samples into useful information for those individuals who have provided or seek to provide their data. It can also facilitate innovation and economic development by creating a special purpose incubator program in the field of PM in which the Company can provide seed funding and additional capital as well as access to the prepared and normalised information to entrepreneurs selected to participate in the program to promote the growth of new businesses. The ultimate goal of the Company shall be to become a global leader in genetic research, development and commercialisation of life-saving pharmaceutical products, other medical products and devices, and health care services by partnering with health care industry stakeholders and genetic research centres on terms acceptable to the Company and the Estonian government subject to the approval of the IP Board (see below).

To accomplish this and secure commercial competitive advantage in the market the Company has to be granted full, exclusive, and unrestricted access to existing and future genomic and health data collected into biobank for the purposes of creating information of commercial value, provided that nothing should limit the current holders of the databases from licensing them for non-commercial, basic academic research without charge. In the event that any publication or other release of such research into the public domain is intended, a prior approval of by an intellectual-property board (IP Board) that will be formed by the Company has to be obtained.

The aim for investment capital provided by investors could be targeted on the level €150-180 M disbursed in equal instalments through the first 2-3 years followed by the project financing from Pharma partners willing to get access to the data. It can be realistically expected the partnership model to create sustainable income and turn the business profitable after 3-5 years after the start.

The Minimal Alternative
In the case there will be not enough support and willingness to take the bold but potentially challenging steps a minimal arrangements that still can provide a structure to achieve at least some goals of EPMPP can be proposed. A minimal alternative can be to create at least a unit in the MSA that will take care at least of a basic set of the listed functions of the Foundation above. It will be evident that a unit in the MSA will have difficult to get to operational capacity and flexibility close to those of Foundation. In this case the ambitions in the EPMPP aims have to be realistically targeted lower, in particularly concerning ability to finance the program and therefore realize to the planned goals.

In summary, it can be concluded that optimal solution to secure smooth planning and implementation of EPMPP would consist of
3.5. Stakeholders’ involvement and roles in implementation the clinical interventional studies of EPMPP

In this section the task group is performing a function specific analysis of the key stakeholders’ roles in planning and conducting pilot studies suggested by the clinical component of the pre-feasibility study. The clinical component task group of the pre-feasibility study have proposed pilot interventional studies in two clinical areas: (1) cardiovascular disorders and (2) cancer prevention and early detection. The methodology of the task was bench top analytical work coupled with the work group discussions. For the sake of clarity the results are presented in a form of simple two-dimensional matrix table (see Tables 3.5.1 and 3.5.2). It is obvious that the main stakeholders in the both studies will be clinical partners (primarily three main hospitals in the country – Tartu University Hospital, North Estonian Regional Hospital, and East-Tallinn Central Hospital) and family doctors as the follow-up partners. The coordinating body of the study is supposed to be the newly non-profit entity that is proposed to be set up by the government for coordinating PM activities on the national level (see chapter above). In the case it will be decided not to start the special purpose entity or the founding process will be delayed, it can be envisage the pilot study process planning and start-up activities to be coordinated by the Estonian Institute for Health Development or by the Medical Faculty of the Tartu University. The financing of the studies has to be included into EPMPP general budget and taken care by the MSA. The part of the study activities that coincide with health care services that are covered by public health care financing can be financed by EHIF under existing health service provider’s contracts.

Table 3.5.1 Roles of the key stakeholders for personalised prediction and care of cardiovascular disorders and for cancer prevention and early detection studies

<table>
<thead>
<tr>
<th>Pilot activity/role</th>
<th>Organisation/ Stakeholder</th>
<th>Organisational principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project coordination</td>
<td>SA</td>
<td>(Contractual) assignment from MSA</td>
</tr>
<tr>
<td>Project coordination</td>
<td>TAI or UT</td>
<td>Contractual assignment from MSA</td>
</tr>
<tr>
<td>Study population recruitment and follow-up</td>
<td>Tartu University Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Study population recruitment and follow-up</td>
<td>North Estonian Regional Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Study population recruitment and follow-up</td>
<td>East-Tallinn Central Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Study population recruitment and follow-up</td>
<td>Family doctors</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Selection/development of CDSS</td>
<td>SA or E-Health Foundation</td>
<td>Contractual assignment from project coordinator</td>
</tr>
</tbody>
</table>

56 Newly formed non-profit foundation. In the case the government decide to set up a special purpose non-profit organisation for coordinating PM activities
57 National Institute of Health Development. In the case the government decides not to create a special structure for EPMPP governance or the decision to so will be delayed.
58 Tartu University. In the case the government decides not to create a special structure for EPMPP governance or the decision to so will be delayed.
<table>
<thead>
<tr>
<th>Implementation of CDSS</th>
<th>SA or E-Health Foundation</th>
<th>Contractual assignment from project coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data (EHR)</td>
<td>Tartu University Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Clinical data (EHR)</td>
<td>North Estonian Regional Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Clinical data (EHR)</td>
<td>East-Tallinn Central Hospital</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Clinical data (EHR)</td>
<td>Family doctors</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Data on health services and prescription medication</td>
<td>EHIF</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Clinical data</td>
<td>E-Health Foundation</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Data on mortality</td>
<td>TAI (Death registry)</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Genomic data and DNA sample processing</td>
<td>EGCUT</td>
<td>Contractual assignment from project coordinator</td>
</tr>
<tr>
<td>Study financing</td>
<td>MSA</td>
<td></td>
</tr>
<tr>
<td>Study health care service component financing</td>
<td>EHIF</td>
<td>Health service contract</td>
</tr>
<tr>
<td>Data analysis</td>
<td>UT/EGCUT</td>
<td>Contractual assignment from project coordinator</td>
</tr>
</tbody>
</table>

It has to be emphasised that the proposed roles and organisational arrangement are provisional and can vary substantially based on the detailed study protocols that are still to be prepared. Also, interventional clinical pilot study general governance and financing setup will depend on the overall national PM strategy and EPMPP detailed implementation plan.
4. Estonian Personalised Medicine Pilot Project evaluation methodology

Chapter 4 provides input for evaluating Estonian Personalised Medicine Pilot Project (EPMPP) and its components. It includes a summary of the evaluation methodology development, overview of previous evaluation experience relevant to EPMPP, overview of the proposed methodology, international experience regarding evaluation of the components of EPMPP and guidance for implementing the methodology in the Estonian context. Also initial intervention logic of the EPMPP is described and evaluation process outlined.

4.1 Evaluation methodology development

The following section 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 cooperation with Biopark AS (Tartu, Estonia) and Irish Centre of Excellence for Applied Connected Health Research (Dublin, Ireland). This was done in close cooperation with stakeholders implementing the EPMPP. The core research team involved Priit Kruus, MSc (e-health and health policy analyst), Gerli Paat-Ahi, MPH (health technology assessment analyst), Andres Rannamäe, MD (organisation evaluation expert), and Dr Noel Carroll, PhD (HIS evaluation expert), Riina Sikkut (health policy analyst).

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 chapter 1.
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 chapter 3.5).
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 (also referred to as result chain, logical framework or logical model).

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.

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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 companies. 

        can be measured as: number of new innovative services in different service/product development phases (e.g. technology readiness level 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).

![Figure 4.1.2. Stated goals of EPMPP](http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf)

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).

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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 3.1.5 below), which is a hierarchical framework that also illustrates moving from activities to the final goal using indicators.
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.

<table>
<thead>
<tr>
<th>Level</th>
<th>Indicators</th>
<th>Source of verification</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>If the OUTCOMES are achieved, then this should contribute to the overall objective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>If OUTPUTS are produced, then the OUTCOMES can be achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outputs</td>
<td>If the ACTIVITIES are conducted, then OUTPUTS can be produced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities</td>
<td>If adequate RESOURCES/INPUTS are provided, then the ACTIVITIES can be conducted</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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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. 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.

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) develop advocates for change to institutionalise the evaluation findings, and (d) supports funding the continuation or expansion of the project. Based on Rieker, 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)

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65 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 SMEs

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:

• 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

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

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Aspects to measure in evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stewardship</strong></td>
<td>• Political support</td>
</tr>
<tr>
<td></td>
<td>• Flexible organisational form (can adjust to changing circumstances and does not duplicate functions of other organisations)</td>
</tr>
<tr>
<td></td>
<td>• Existing legal framework</td>
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<tr>
<td><strong>Governance and management</strong></td>
<td>• Transparent reporting to the public and stakeholders on progress of EPMPP and organisational outcomes</td>
</tr>
<tr>
<td></td>
<td>• Capacity to involve stakeholders and well-motivated professionals</td>
</tr>
<tr>
<td></td>
<td>• Management success – goals of pilot project fulfilled</td>
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<tr>
<td><strong>Implementation efficiency</strong></td>
<td>• Cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>• Higher efficiency of using health care resources</td>
</tr>
<tr>
<td></td>
<td>• Decreasing bureaucracy in new service implementation</td>
</tr>
<tr>
<td><strong>Social and health dimension and public acceptance</strong></td>
<td>• Public perception of the PM governance organisation</td>
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<tr>
<td></td>
<td>• Readiness of public to be involved in personalised medicine initiatives (providing genetic information, sharing patient reported health data etc).</td>
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<tr>
<td></td>
<td>• Social/health impact measures, e.g:</td>
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<tr>
<td></td>
<td>o Quality of life of patients</td>
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<td></td>
<td>o Health levels of patients</td>
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<tr>
<td></td>
<td>o Work-capacity of patients.</td>
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<tr>
<td></td>
<td>o Patient empowerment.</td>
</tr>
<tr>
<td><strong>Stakeholder involvement and partner cooperation</strong></td>
<td>• Stakeholder satisfaction (fulfilment of expectations, empowerment, interest protection)</td>
</tr>
<tr>
<td></td>
<td>• New (international) stakeholder involvement</td>
</tr>
<tr>
<td></td>
<td>• Active involvement of stakeholders</td>
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<tr>
<td></td>
<td>• Data-sharing contracts</td>
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<tr>
<td></td>
<td>• Trainings conducted among stakeholders (incl healthcare workers)</td>
</tr>
<tr>
<td></td>
<td>• Number of clinics involved in the sub-projects</td>
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<tr>
<td><strong>Collaborative projects among universities/research centers, businesses and health care providers supporting personalised medicine service implementation</strong></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Financing and resources</strong></th>
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<tbody>
<tr>
<td>• Contributed public and private capital</td>
</tr>
<tr>
<td>• Capital growth (new companies with investments)</td>
</tr>
<tr>
<td>o Industrial partners</td>
</tr>
<tr>
<td>o Technology SMEs</td>
</tr>
<tr>
<td>o Private investors</td>
</tr>
<tr>
<td>• Sustainable financing model(s) developed in 4 years</td>
</tr>
<tr>
<td>• Sustainable business models for personalised medicine related services/products</td>
</tr>
<tr>
<td>• Regulatory changes supporting new business-model development</td>
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<table>
<thead>
<tr>
<th><strong>Private business involvement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Number of new service providers interoperable with Estonian health information system (EHIS)</td>
</tr>
<tr>
<td>• Decreased time from interoperability connection application to fully operational service using/sending data to EHIS</td>
</tr>
<tr>
<td>• University spin-offs</td>
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<tr>
<td>• Private investor contracts and investments</td>
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<table>
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<tr>
<th><strong>Sustainability</strong></th>
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<tbody>
<tr>
<td>• New research projects and publications validating and/or developing personalised medicine services</td>
</tr>
<tr>
<td>• Legal framework for new sustainable business models and validated new business models, supporting implementation of personalised medicine services</td>
</tr>
<tr>
<td>• Private financing sources in health care investments</td>
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<tr>
<th><strong>Quality, ethics and data protection</strong></th>
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</thead>
<tbody>
<tr>
<td>• Data breaches</td>
</tr>
<tr>
<td>• Ethical complaints</td>
</tr>
<tr>
<td>• Sufficient number of quality measures implemented and monitored by relevant stakeholders</td>
</tr>
</tbody>
</table>

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)\(^{67}\) 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

\(^{67}\) A separate review report was provided to the research team by Dr Noel Carroll (Ireland).
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](image)

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.

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) 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.

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

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?

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).

![Phases of evaluation](image)

**Figure 4.1.10. Phases of evaluation**

In order to synchronise the processes of different activities, an addition to the framework could be borrowed from Pulley et al.\(^\text{70}\) (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 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 an example of relevant dimensions of interdisciplinary personalised medicine implementation and evaluation.

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\(^{69}\) [http://meera.snre.umich.edu/planning-and-implementing-ee-evaluation](http://meera.snre.umich.edu/planning-and-implementing-ee-evaluation)

The framework by Pulley et al.\(^2\) 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 4.1.11. A framework for evaluating a personalised medicine pilot\(^71\)](image)

![Figure 4.1.12. Evaluating the goals of EPMPP and sub-projects of EPMPP](image)

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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 unintended 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. 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. Similar time and work-process measurement techniques could be used in the current evaluation process also, when implementing CDSS for GPs and other doctors.

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.

25 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.
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?

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.76

**Health technology assessment gaining momentum**

Until recently Estonia had also no systematic programme for health technology assessment (HTA)77, 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.78 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)79. 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 Medicines, Tallinn University of Technology, and University of Tartu. Health technologies are taken under evaluation, in case80:

- 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.

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77 **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.

78 [www.arth.ut/tth](http://www.arth.ut/tth)


80 **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.
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.81

**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)82 aspects regarding telemedicine evaluation in Estonia (Kruus et al 2014)83. Praxis has also led the evaluation methodology development practices for e-government services and conducted numerous

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81 For example in case of personalised cancer screenings the programme process in terms of overall rollout of the screening stays the same, but the personalisation of targe-group can have impact on the cost of the programme as well as behaviour.  
83 http://www.praxis.ee/tood/teleditsiini-laialdasem-rakendamine-eestis/
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).\textsuperscript{84}

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 institutions in Estonia, including Medical Faculty of University of Tartu, Estonian Institute for Health Development, also research centres and other health care institutions, 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\textsuperscript{85} 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 R&D 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 health 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

\textsuperscript{84} 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 realization, 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.

\textsuperscript{85} 7.03.2012 audittiaruanne „Riigi tegevus teadus- ja arendustegevuse võtmekaudkondade edendamisel“
conclusions should be kept in mind when developing the intervention logic for the Estonian Personalised Medicine Pilot Project.

Figure 4.-2.1 Estonian Health Programme intervention logic

Evaluation framework for innovation and enterprise support policies\(^6\) (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.

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.

---

47 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\(^6\) 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 startups 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 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.

9. Number of health technology and personalised medicine startups 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.

\(^6\) TRL 6 – technology demonstrated in industrially relevant environment

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.

![Diagram](image-url)

**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.

**Pilot project goals**

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.

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

<table>
<thead>
<tr>
<th>Measure on framework</th>
<th>Relevance, description and comments</th>
<th>Possible target level if applicable</th>
<th>Responsible evaluator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTPUTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data linkages between health databases completed</td>
<td>The number of databases integrated into the health system data management infrastructure. Protocols and standards developed for interoperability.</td>
<td>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.</td>
<td>MSA/CGO/E-health Foundation</td>
</tr>
<tr>
<td>Operational central decision support system developed</td>
<td>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.)</td>
<td>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</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td>Data management infrastructure with open connection protocols and standards developed (technology robustness)</td>
<td>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 organisational model for setting further development needs.</td>
<td>Qualitative evaluation – expert analysis. Validated expert report.</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Evaluation questions:</td>
<td>-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&amp;D&amp;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?</td>
<td>Qualitative data collection feedback from all of the stakeholders Increase (compared to current level, which should be</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td>-Ease of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>-flexibility</strong></td>
<td>Qualitative data collection feedback from all of the stakeholders (primary and secondary users).</td>
<td>Increase (compared to current level)</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-security</strong></td>
<td>Qualitative data collection feedback from all of the stakeholders (primary and secondary users).</td>
<td>Increase (compared to current level)</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-data relevance</strong></td>
<td>Qualitative data collection feedback from all of the stakeholders (primary and secondary users).</td>
<td>Increase (compared to current level)</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-data format</strong></td>
<td>Qualitative data collection feedback from all of the stakeholders (primary and secondary users).</td>
<td>Increase (compared to current level)</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-support service quality problem solving, response time</strong></td>
<td>Qualitative data collection feedback from all of the stakeholders (primary and secondary users), constant monitoring and documentation of support service provision.</td>
<td>Increase (compared to current level)</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-frequency of system use</strong></td>
<td>Quantitative monitoring data.</td>
<td>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</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
<tr>
<td><strong>-extent of system use</strong></td>
<td>Quantitative monitoring data with breakdown</td>
<td>-Extent of algorithm use (breakdown: personalised</td>
<td>MSA/E-health Foundation/ECGUT</td>
</tr>
</tbody>
</table>
with specific characteristics.

screenings / personalised consultations / pharmacogenomics counselling
- Needs for new algorithms acknowledged
- Time for new algorithm development

| 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?

| Quantitative evaluation:
Personalised medicine intervention increases the cost-effectiveness and medical efficacy compared to traditional services.
Qualitative evaluation:
(see questions in the box on the left) |

Clinical sub-project evaluation lead
<table>
<thead>
<tr>
<th>Personnel related barriers detected</th>
<th>Qualitative evaluation</th>
<th>Most relevant barriers described and specific recommendations drafted for changes in PM related personnel trainings, which would foster PM implementation and innovation</th>
<th>CGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvements made in training regarding PM (universities, training departments)</td>
<td>Expert validated improvements made in health care personnel policy at different levels in order to increase adoption of personalised medicine principles.</td>
<td>Qualitative evaluation – expert and stakeholder validation</td>
<td>CGO/Tartu University Medical Faculty/Hospitals</td>
</tr>
<tr>
<td>Legal/regulatory barriers detected</td>
<td>Qualitative evaluation</td>
<td>Most relevant barriers described and specific recommendations drafted for conducting regulatory changes fostering PM implementation and innovation</td>
<td>CGO</td>
</tr>
<tr>
<td>Regulatory changes made in order to decrease barriers for PM</td>
<td>Expert validated regulatory changes for decreasing barriers for PM medicine implementation and</td>
<td>Qualitative evaluation – expert and stakeholder validation</td>
<td>MSA/CGO</td>
</tr>
<tr>
<td>medicine implementation</td>
<td>increasing possibilities of R&amp;D&amp;I in personalised medicine field.</td>
<td>X number of different doctors involved (break-down in characteristics)</td>
<td>CGO/participating care providers</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Doctors and other specialist involved in EPMPP</td>
<td>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.</td>
<td>X number of patients (break-down in characteristics)</td>
<td>CGO/participating care providers</td>
</tr>
<tr>
<td>Patients involved in EPMPP</td>
<td>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.</td>
<td>X number of patients (break-down in characteristics)</td>
<td>CGO/participating care providers</td>
</tr>
<tr>
<td>Local level publications and communication on PM feasibility (output of EPMPP)</td>
<td>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,</td>
<td>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.</td>
<td>CGO/universities and research institutions</td>
</tr>
<tr>
<td>OUTCOMES</td>
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</tr>
<tr>
<td><strong>Public awareness of PM possibilities (user-acceptance)</strong></td>
<td>Survey among citizens of Estonia about the awareness of personalised medicine (conducted as part of pre-study)</td>
<td>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.</td>
<td>MSA/CGO</td>
</tr>
<tr>
<td><strong>Estonia known internationally as PM innovation hub</strong></td>
<td>Survey among experts and health technology business/industry communities regarding the perception of Estonia as a personalised medicine innovation hub.</td>
<td>Estonia known as personalised medicine innovation hub with R&amp;D&amp;I possibilities and business opportunities.</td>
<td>MSA/CGO/Ministry of Economic Affairs and Communications</td>
</tr>
<tr>
<td><strong>No of Master’s degrees in PM field</strong></td>
<td>Number of master’s degrees in personalised medicine related fields.</td>
<td>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.</td>
<td>Ministry of Education and Science</td>
</tr>
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</tr>
<tr>
<td><strong>No of PhD degrees in PM field</strong></td>
<td>Number of doctoral degrees in personalised medicine related fields.</td>
<td>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.</td>
<td>Ministry of Education and Science</td>
</tr>
<tr>
<td><strong>No of HTAs conducted on personalised medicine services (cost-effectiveness and clinical efficacy validated)</strong></td>
<td>Number of HTAs conducted (in the centre for Health Technology Assessment), which can have an input for the possible reimbursement of personalised medicine services.</td>
<td>Target measure depends on the selection criteria (outlined in chapter 3.2) - possibly 10 HTAs for personalised medicine could be conducted during the pilot project.</td>
<td>Centre for Health Technology Assessment/CGO</td>
</tr>
<tr>
<td><strong>Public health insurance financing of PM services</strong></td>
<td>New personalised medicine services in the reimbursement list of EHIF.</td>
<td>Target rate depends on the feasibility study and HTA’s conducted.</td>
<td>EHIF/CGO</td>
</tr>
<tr>
<td><strong>Companies with PM services/products (TRL +6)</strong></td>
<td>Three sub-measures: a) Number of health technology and</td>
<td>Target rate needs evaluation of current status of technology readiness level (TRL)</td>
<td>CGO, MSA, Ministry of Economic Affairs</td>
</tr>
</tbody>
</table>
### Three sub-measures:

<table>
<thead>
<tr>
<th>New internationally focused start-ups with PM services/products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a)</strong> 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).</td>
</tr>
<tr>
<td><strong>b)</strong> 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.</td>
</tr>
<tr>
<td><strong>c)</strong> Number of university spin-offs developing products/services in health technology and personalised medicine.</td>
</tr>
</tbody>
</table>

**Target rate needs**

- CGO: Mission of the personalised medicine innovation and Communications

**CGO, MSA, Ministry of Economic Affairs and Communications**
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.

c) 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).

<table>
<thead>
<tr>
<th>Private capital for PM development</th>
<th>a) Foreign private capital invested in health technology and personalised medicine companies.</th>
<th>PM should bring considerable numbers of foreign and local private capital into healthcare for investments in R&amp;D&amp;I. The proportion of private investments should rise considerably – specific target can be based on Estonian R&amp;D&amp;I strategy.</th>
<th>Ministry of Economic Affairs and Communications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b) Local private capital invested in health technology and personalised medicine companies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) Proportion of private R&amp;D investments of total R&amp;D investments in health technology and personalised medicine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved clinical information systems with decision support and data for personalised treatment</td>
<td>Improved clinical information systems which have developed integrations with renewed data management infrastructure and DSS and built user-accepted systems for personalised medicine treatment support.</td>
<td>100% of clinical information systems currently in use.</td>
<td>E-health Foundation monitoring, CGO</td>
</tr>
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</tr>
</tbody>
</table>
| 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 initiative (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, 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>
<thead>
<tr>
<th>Pilot project activity</th>
<th>Relevant evaluation process activity</th>
<th>Key evaluation step&lt;sup&gt;49&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drafting the EPMPP project plan</td>
<td>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.</td>
<td>Y</td>
</tr>
<tr>
<td>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.</td>
<td>Use benchmarking tool (see chapter 4.1) for aligning the input-process-output-outcome measures of clinical sub-projects with EPMPP.</td>
<td>Y</td>
</tr>
<tr>
<td>Developing the data infrastructure development plan with needs assessment for the clinical sub-projects.</td>
<td>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.</td>
<td>Y</td>
</tr>
</tbody>
</table>

<sup>49</sup> If Y, then it is a key evaluation activity and should be part of the minimal evaluation process.
| 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. | Y |
|---|---|---|
| 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. | Y |
| 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. | Y |
| 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 | Y |
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. | Y |
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</thead>
<tbody>
<tr>
<td>Regulatory changes made for data management infrastructure development.</td>
<td>Expert validation of regulatory changes for data management infrastructure development.</td>
<td>Y</td>
</tr>
<tr>
<td>Conducting data infrastructure development activities.</td>
<td>Constant monitoring, evaluation and unit testing according to set measures (above).</td>
<td></td>
</tr>
</tbody>
</table>
| 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 | Y |
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 chapter 3.5.2 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 chapter 3.5.2 for
<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
</tr>
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</table>
| 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 chapter 3.5.2 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 personalisation impact on:  
  - Lower NNS (number of needed to screen).  
  - Reduction in screening costs.  
  - Higher detection rate.  
  - Organisational development needs for conducting personalised/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 chapter 3.5.2 |
| 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).|

Involving international experts in conducting clinical studies.

more specific methodological approaches.)
<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
<th>Evaluation Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implications for educational institutions (e.g. universities for data science education).</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Communicate the modelling results at an early stage to relevant stakeholders for feedback and input for clinical study conduction.</td>
<td>Evaluate the reach and clarity of the results for different stakeholders.</td>
<td>Y</td>
</tr>
</tbody>
</table>
| 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 controversial opinions about the clinical efficacy and cost-effectiveness?  
- The extent of use and target groups in Estonia is not known. | Y                 |
| HTA conducted for personalised medicine intervention(s). | Evaluation conducted according to HTA rules set at the Centre of Health Technology Assessment (see chapter 3.2).  
HTA report results provided as an input for Health Insurance Fund reimbursement list addition process. | Y                 |
| 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). | Y                 |
| 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 | Y                 |
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 organisation for evaluating the success of EPMPP in reaching its goals (outcome measures provided in chapter 3.4)
– 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 feasibility 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 should 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 organisational 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 3.4) 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

4.5 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.\(^9\) 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\(^1\) 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.\(^2\)

An initial step towards evaluation is often through a pilot study. For example, Pulley et al.\(^3\) 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.

### 4.5.1 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\(^4\), thus personalise care. Therefore evaluation offers us the ability to

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learn from past and present performance with a view of improving process, care, economics and patient satisfaction for the future.

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 4.5.1.1.):

**Table 4.5.1.1. IS Evaluation Frameworks**

<table>
<thead>
<tr>
<th>Framework</th>
<th>Clinical</th>
<th>Technical</th>
<th>Economic</th>
<th>Human</th>
<th>Organisational</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Cs Model</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>CHEATS Model</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
</table>

96 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.
There have been some efforts to evaluate HIS including clinical decision support systems. For example, Yosof et al.\(^{102}\) 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,\(^{103,104}\) 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 3.5.1.1 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.\(^{105,106}\)

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.\(^{107,108}\) Another model which evaluates the use of ICT in health care includes the CHEATS framework.\(^{109}\) 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;

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4. **Administrative**: focusing on issues such as convenience, change and cost associated with health system;
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. 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 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 4.5.1.1):

- **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

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relevant stakeholders in each phase. Sub-dimensions: quality and safety, time and work-patterns, cost-effectiveness.

![Figure 4.5.1.1. IS Success Model](image)

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 through a number of important influential factors. Among these factors are (see Figure 4.5.1.2):

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

![Figure 4.5.1.2. Technology Acceptance Model](image)

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 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

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examining people’s acceptance of technology, it is limited in explanatory terms of technological ‘value’. Adopting a similar outlook on technology evaluation, Dixon presents a socio-technical evaluation model which examines the behavioural aspects of technology using the IT Adoption Model (ITAM).

ITAM (Figure 4.5.1.3) 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).

![IT Adoption Model (Dixon, 1999)](image)

**Figure 4.5.1.3. IT Adoption Model (Dixon, 1999)**

Related research also focuses on consumer health behaviours and their adoption of medical technologies. For example, Wilson and Lankton 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 4.5.1.4). 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

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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\textsuperscript{120} offers a simplified version of the SERVQUAL model\textsuperscript{121} using five key customer service issues (Table 4.5.1.2):

Table 4.5.1.2. Key Dimensions within the RATER Model

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

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...
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.\textsuperscript{122} examines the effect of relatively mature health information technology (HIT) systems on the quality and safety of health care and propose the 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 4.5.1.5) 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.

\textbf{Figure 4.5.1.5. The Triangle Evaluation Model}

As an Estonian example, Saluse et al.\textsuperscript{123} 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 user or fits with the organisation’s strategic aims (Total Cost ..., 2013, West and Daigle 2004)\textsuperscript{124125}, 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)\textsuperscript{126}, which is relevant in case of IS developments during the personalised medicine pilot project. For example, Stead et al. (1994)\textsuperscript{127} 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 4.5.1.6). 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.

\textsuperscript{123} Saluse, Janek; Aaviksoo, Ain; Ross, Peeter; Tilk, Madis; Parv, Ruth; Pohjonen, Hanna; Jakovlev, Ülle; Enni, Kaia (2010). Eesti terviseinfosüsteemi majandusmõju/puhastulu hindamine. TOF-DIGIMÕJU projekti lõpparuanne. Eesti Arst, 89(10), 659 - 696.
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.

4.5.2. 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 4.5.2.1.128

Figure 4.5.1.6. Esteves and Joseph eGovernment evaluation framework

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Figure 4.5.2.1. 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.¹²⁹

The CDC website¹³⁰ 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 4.5.2.2). 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 4.5.2.2. Evaluation process for screening

Principles of population screening as applied to genetic susceptibility to disease

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.
- 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.

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131 Ibid.
• 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 4.5.2.1 presents measures for evaluating screening programmes in quantitative terms.  

<table>
<thead>
<tr>
<th>Quantitative measures</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrance of a genetic variant</td>
<td>Probability that traits or characteristics associated with that variant will manifest (within a specified period of time)</td>
</tr>
<tr>
<td>Incidence</td>
<td>Number of new cases of disease occurring in a population (within a specified period of time)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Proportion of affected individuals in a population (at a given moment of time) incidence rate average duration of disease</td>
</tr>
<tr>
<td>Sensitivity or detection rate (DR)</td>
<td>Proportion of affected individuals (or those who become affected within a specified period of time) with a positive (unfavourable) screening test result</td>
</tr>
<tr>
<td>Specificity</td>
<td>Proportion of unaffected individuals with a negative screening test result</td>
</tr>
<tr>
<td>False-positive rate</td>
<td>Proportion of unaffected individuals with a positive screening test result specificity</td>
</tr>
<tr>
<td>DR5</td>
<td>Detection rate for a 5% false-positive rate</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>Risk of disease among individuals with risk factor (with positive screening test result) (clinical impact)</td>
</tr>
<tr>
<td>Population attributable fraction (PAF)</td>
<td>Proportion of cases that could be prevented if the risk factor was absent (the public health impact)</td>
</tr>
<tr>
<td>ROQ1_5</td>
<td>Relative odds of the highest fifth of the risk factor distribution compared with people in the lowest fifth</td>
</tr>
</tbody>
</table>

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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).

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 and the Crossroads 99 Group, a framework was created to assess susceptibility testing for breast, ovarian, and colorectal cancer.

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
- 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

**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

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141 Goel, ‘Appraising Organised Screening Programmes for Testing for Genetic Susceptibility to Cancer’.

142 Goel, ‘Appraising Organised Screening Programmes for Testing for Genetic Susceptibility to Cancer’.
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
- 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.

Pashayan et al. 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

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143 Ibid.
144 T. Dent et al., 'Stratified Screening for Cancer: Recommendations and Analysis from the COGS Project' (PHG Foundation: Collaborative Oncological Gene-environment Study, 2014).
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.\textsuperscript{146} 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.\textsuperscript{147} Women perceive high benefits of mammography screening\textsuperscript{148}, reflected in the high attendance rates (around 70%) across countries;\textsuperscript{149} although lower socioeconomic status and ethnic minority status have both been associated with lower participation rates.\textsuperscript{150} Perceived risk of breast cancer has been cited as encouraging some individuals to be screened, while deterring others;\textsuperscript{151} 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.\textsuperscript{152} 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.

\textsuperscript{147} J. Waller et al., ‘A Survey Study of Women’s Responses to Information about Overdiagnosis in Breast Cancer Screening in Britain’, \textit{British Journal of Cancer} 111, no. 9 (28 October 2014): 1831–35.
\textsuperscript{152} Susanne F. Meisel et al., ‘Adjusting the Frequency of Mammography Screening on the Basis of Genetic Risk: Attitudes among Women in the UK’, \textit{Breast (Edinburgh, Scotland)} 24, no. 3 (June 2015): 237–41.
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.153

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

Methods
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.\textsuperscript{154}

**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.\textsuperscript{155}

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 improvements or risk factor reduction and between intermediate health improvements and reductions in morbidity or mortality (see Figure 4.5.2.3).\textsuperscript{156}

\textsuperscript{154} 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.
\textsuperscript{156} Ibid.
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. 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

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157 Ibid.
communication (e.g., in the context of social norm feedback) either alone or in combination with other promising interventions (e.g., real-time wireless 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 (see Figure 4.5.2.4).

![Figure 4.5.2.4. Framework of possible constructs that may predict health behaviour change in the genomic setting](image)

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).  

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.  

The burden of managing costs of genomic technologies within the health care system loom large, and there

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159 Ibid.
is little consensus about how to effectively and efficiently incorporate genomics into health care.\textsuperscript{162}

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\textsuperscript{163} 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.\textsuperscript{164}

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.\textsuperscript{165} 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.\textsuperscript{166}

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.\textsuperscript{167}

\textsuperscript{165} McGowan et al., ‘Integrating Genomics into Clinical Oncology’.
\textsuperscript{166} F. Randy Vogenberg, Carol Isaacson Barash, and Michael Pursel, ‘Personalised Medicine’, \textit{Pharmacy and Therapeutics} 35, no. 11 (November 2010): 624–42.
5. Appendixes

Appendix 1

Attached as a separate Excel file

Appendix 2

Case study Companies

a. deCode Genetics, Inc

deCODE genetics, Inc. (Icelandic: Íslensk erfðagreining) was a biopharmaceutical company based in Reykjavík, Iceland. The company was founded in 1994 by Kári Stefansson, Ernir Kristjan Snorrason and Kristleifur Kristjansson to identify human genes associated with common diseases using population studies, and apply the knowledge gained to guide the development of candidate drugs. The company isolated genes believed to be involved in cardiovascular disease, cancer and schizophrenia, among other diseases (the company's research concerning the latter is said to represent the first time a gene has been identified by two independent studies to be associated with schizophrenia).

In the late 1990s deCODE proposed to create the world's first population-wide genomic biobank by collecting data from the entire population of Iceland, which numbered 270,000 at the time. The plan had these three major components: creating a genealogical database, collecting biobank specimens by means of which genotyping could be done, and creating a national electronic health record system to connect genetic data to each individual's phenotype.

In December 1998 with lobbying from deCODE, the Icelandic Parliament passed the Act on Health Sector Database which permitted public bidding for the right of a company to create this health database and use it for various purposes. The parliament shortly thereafter granted deCODE the right to create this database after the company made a successful bid to do so. Important factor influencing to the preliminary success of DeCode Genetics was the partnership with Roche bringing in about $200 Million for the business development.

deCODE's approach to identifying genes, and in particular its attempt to set up an Icelandic Health Sector Database (HSD) containing the medical records and genealogical and genetic data of all Icelanders, was very controversial, and prompted national and international criticism for its approach to the concepts of privacy and consent. A legal judgement from the Icelandic Supreme Court in November 2003 effectively killed off the HSD project. However, the company believed it could continue to identify disease-related genes without such a database.
b. Genizon Biosciences Inc., Canada

Genizon BioSciences Inc., founded in 1999, a Montreal genetics research firm headed by a London native, co-founded by Moroccan and U.S. scientists and largely funded by Europeans: They believed it hold the secrets to the most common hereditary diseases in the world.

Six million Quebecers can trace their roots to just 2,600 French settlers that arrived in the 17th century. Well into the 1900s, old-stock Quebecois, the so-called pure laine, largely stuck to their own -- French Catholic -- so the province has a limited gene pool.

The company and its networks was the only source for GeneMaps-comprehensive maps of genes, genetic markers, biochemical pathways and drug targets that are unequivocally involved in causing human disease-accelerating the development of safer, more effective medicines. GeneMaps also lead to the development of predictive diagnostics that facilitate personalised medicine.

Genizon's proprietary, automated gene discovery platform using genome-wide association studies involving thousands of members of the Quebec Founder Population provided unprecedented understanding of the genetic origins and mechanisms of common diseases, resulting in the best possible drug targets and genetic markers. The company's GeneMaps provided pharmaceutical partners with intellectual property that creates opportunities for leadership in many therapeutic areas by bringing to market better treatments that address the root causes of diseases. Genizon was conducting gene discovery programs in more than 25 common diseases. Genizon also provided high-throughput, high quality SNP genotyping, genetic analysis, gene expression and pharmacogenomics services to academic institutions, research organisations and the biopharmaceutical industry.

After many years and $60-million spent collecting blood from thousands of Quebecois Genizon claimed to have pinpointed up to 12 of the genes that cause Crohn's disease, an affliction of the bowels -- compared with the two genes that were previously discovered.

Armed with state-of-the-art machinery capable of doing 60 million DNA analyses a day, 300 computers to process the data Genizon hoped to rapidly expand that list of genetically mapped diseases.

In the past Genizon was hunting for the genes that cause attention deficit hyperactivity disorder, followed by endometriosis, a condition that causes pelvic pain and the formation of cysts. Schizophrenia, osteoarthritis and type II diabetes are next.

Genizon discovered genes, genetic biomarkers, biochemical pathways and drug targets that are involved in human disease susceptibility and drug response. These genetic insights allowed the development of predictive diagnostics that facilitate personalised medicine. Working with a network of over 1,000 clinical investigators, Genizon had recruited over 47,000 subjects in 25 common diseases, which were analysed in a unique, integrated high throughput
facility that was compliant with GCP and GLP guidelines. Discoveries were translated into clinical practice through collaborative research with academic and clinical leaders. Genizon also provided high throughput, high quality SNP genotyping, genetic analysis, gene expression and pharmacogenomics services to academic institutions, research organisations and the biopharmaceutical industry.

c. Jurilab Oy, Finland

Jurilab is a privately held company that was formed in 1985 with close ties to the Research Institute of Public Health at University of Kuopio, Finland. This relationship has allowed Jurilab, and now Nanogen, to have rights and access to the unique collection of DNA samples and phenotypic data from the East Finland founder population. Founder populations are excellent resources for genetic studies because their high degree of homogeneity makes them ideal for the discovery of disease-linked gene mutations. Based on the extent of data collected, and the prospective nature of the collection over 20 years, Jurilab's genetic discovery and validation not only address the underlying causes of common diseases, but also those factors which contribute to disease progression or disease complications. Jurilab's BlockMap(TM) genetic discovery platform utilizes and can potentially support programs in more than 30 disease indications. Jurilab applied its proprietary technologies, including Hierarchical Phenotype-Targeted Sequencing (HPTS(TM)), to mine this database and rapidly identify disease-relevant genetic variants. The novel biomarkers can then be used in Jurilab's testing services or licensed to diagnostic or pharmaceutical customers who may be interested in the markers as targets for the development of diagnostic tests or new drugs. The partnership with Nanogen provided Nanogen with a source of proprietary diagnostic markers for use in identifying the predisposition to disease and pharmacogenetic testing for related drug responses to secure access to important molecular targets for advancing the use of diagnostics and personalising healthcare.

Appendix 3

Stakeholders interviewed for completing following chapters of the Report:

4. Mapping of the EPMPP stakeholders' interest. Overview on the EPMPP’s partners and their potential roles.
5. Current experiences in implementation of personalised medicine and genomic data.
6. State governance in the light of large innovation projects
13. How to engage Estonian innovative companies to EPMPP? Suggestions for potential business models, cooperation mechanisms and IPR management.

Stakeholder interviews.

The stakeholders were asked the following questions

- Please define the main expectations and positive challenges the development of Personalised Medicine may provide?
- Which changes in the behaviour of the main stakeholders may be forecasted with the development of PM?
• Can you see any potential risks and threats the development of PM may bring along?
• Which requirements and conditions you consider a “must” in order to safely develop the concept and services of PM?
• Would you and your organisation be ready to actively take part in the pilot project – in case one will be initiated?

**Stakeholder’s feedback and observations**
Altogether close to 50 people representing various stakeholder groups were interviewed. The current analysis presents the views of stakeholders through the prism of questions referred to above. The statements made by stakeholders having similar character are consolidated, grouped and not repeated. In addition, we have included specific comments made by the stakeholders addressing specific concerns or expectations.

**General understanding of PM**
A vast majority of stakeholder representatives have positive expectations towards the development of PM. The positive attitude was expressed despite the fact that most of the stakeholders have a rather generic understanding of what the PM concept really is. It was recognized by stakeholders that there is little knowledge of PM in society in general, and even among specific stakeholder groups such as clinicians. Due to the insufficient knowledge of PM in general it was noted by the majority of stakeholders that at least two issues should be well defined before any formal development or launch of the PM pilot project:

• A sound definition of PM should be elaborated and communicated to stakeholders and in society more broadly;
• A clear goal statement for PM development and an understanding of which positive developments should be expected.

**Expectations and challenges of PM development**
A clear majority of stakeholder representatives noted positive challenges that the development of PM could bring to the society. Most commonly noted issues were:

• Significantly more data and a more systematic management of health related data will provide more knowledge to all parties involved in health care; there is already now a lot of data in health care but it is not used systematically and efficiently;
• More knowledge empowers people to take care of their own health risks and challenges them to make choices to stay healthy and promote health;
• More knowledge empowers the clinicians to give patients more competent and specific advice, to diagnose more accurately and provide better targeted treatment;
• Another potentially positive effect will be higher efficiency of using resources for treatment in health care as the treatment process is more targeted, more cause-effect driven and less random, and the number of treatments adding no real value will decrease;
• There is a potential for Estonia to participate and benefit in global development. All benefits may not be known yet today but being part of innovation is more challenging than taking a resistant or ignorant position;
The expectation that the clinicians will use the existing Gene Bank and E-Health services actively.

A number of more specific comments were given by a few health care (hospital and outpatient clinic managers, clinicians, professional partner organisations) stakeholder representatives, such as:

- Risk assessment and prevention of illness will get a new dimension;
- In treatment process it has become more and more obvious that the “one-size-fits-all solution is no any longer relevant;
- The development of new personalised drugs will not get cheaper, but new ICT technologies and applications may bring along cost-efficiency;
- Family practitioners may benefit from having a complex dashboard of patient health related data in order to understand their own patients better;
- For local investors and business angel community the development of PM does not seem to be that attractive, because it does not provide quick exit opportunities and demands high volumes of investment. Innovation and development of new applications in ICT field to serve PM seems to provide a more realistic interest.

Which changes maybe forecasted in doctor-patient relationship?
When asked which changes could be forecasted in doctor-patient relationship the majority of interviewees mentioned that potentially:

- General public and patients specifically will become more informed, knowledgeable and potentially more demanding towards service providers and clinicians, they will feel more empowered to make more informed choices and decisions about their own life;
- Over the time a shift of “power” in the traditional doctor–patient relationship may take place, moving more towards the patient (as mentioned by a few interviewees, the “doctor’s ego” will not be so high any more). The present dysbalance of power is caused by knowledge being on the clinicians’ side but in future the patients will be more knowledgeable;
- It was also mentioned that if knowledge is handled correctly and with care the increasing knowledge on both sides will create more trust and a better relationship in the treatment process;
- The development of PM will set definite needs and standards for doctors to meet the demands of counselling competencies, including how to motivate people to change their risk behaviour and how to handle communication in severe cases and sensitive situations;
- There will be an increasing pressure on doctors’ knowledge and competencies to handle a great amount of data, information and new ICT tools. The value can be generated if clinicians will be able to read and interpret information from sequencing;
- On behalf of service providers a more responsible behaviour can be predicted in treatment process s. Today’s examples of “cost-sharing and risk-sharing” mechanisms in treatment may serve as evidence how the pharma companies are involved and of the commitment to secure outcome oriented treatment;
• Virtual space around the person gets larger, more people and capacity involved.

More specific issues were addressed by service providers and payer stakeholder representatives:
• The development of PM may be accompanied with patients’ drive to “shop” around and demand more diagnostics, gene tests, risk assessment, etc. That may incur pressure on available public resources.
• Innovation and development of the quality of health service may create a higher motivation for younger doctors to find more challenging work and not to leave the country.

Several stakeholders identified additional dimensions of ethical nature which may arise when one has significantly better understanding of one’s own health conditions.
• What will ensue if we know there is an incurable disease? Which consequences may manifest on the patient’s side? Will psychological counselling be needed and available? Do we always want to know, and how to handle these situations?
• Risk assessment on genomics level will not provide expected value and outcome. It is much more cost efficient to handle population-based disease prevention and health promotion programmes to achieve change in risk behaviour.

Which potential risks and threats could be seen when developing PM?
Despite the fact that most stakeholders expressed their positive expectations towards the PM development we should also consider the risks and potential threats that could be faced during the pilot project as well as after the full PM implementation.
• Undertaking PM development not comprehensively and without clear commitment and effort will compromise good initiative (an example was the current e-Health initiative);
• Creating an expectation that PM and technology development will provide solutions for everything may fail and discredit itself. It is still very early to say that PM offers clear evidence based argumentation;
• As genetic risk assessment surveys are population-based, one should consider it very carefully before bringing outcomes and conclusions to individual level;
• The gene test to illustrate risk prevalence may be interpreted as a diagnostic test with relevant negative outcomes for patients;
• There is a potential threat that the development of PM will increase the workload and bureaucracy for clinicians and introducing new applications will not implicate more free time;
• Several interviewees expressed concern that PM as a new and “sexy” concept will get too much attention so that traditional medical service will remain “behind the scenes”;
• By nature, medical community is rather conservative and the current PM concept may not fall into fertile ground. Also, requirements for constant learning of new applications, technologies and acquiring new knowledge may create resistance;
• Superabundance of data may complicate the risk assessment and treatment process instead of making it easier;
• There is always the risk of misuse of personalised health data;
• There is a risk of knowing a lot but having little opportunity or resources to intervene, the risk of hurting people’s contentment;
• Another potential negative feature is that patients will start to “diagnose themselves” when there is a lot of information is available.

Specific concerns were expressed regarding the resource constraints and competition for being financed:
• Potential demand from the clinicians’ and patients’ side to use more diagnostic services and new costly treatment will put the payer under pressure;
• Competition for being financed may bring along typical “call for help” campaigns in media and putting public pressure on the payer;
• A weakness seen from the investors’ side, a reason why the Estonian technology start-ups have not succeeded so far, is a need to grow significantly beyond the country’s borders and to provide solid management, whereas there is low capacity to attract new round of investments;

Which requirements and conditions you consider a “must” in order to safely develop the concept and services of PM?
Based on the concerns and potential risk factors to be addressed in the early development stage, there are additional regulations, or other relevant systems to handle these risk situations. Stakeholders addressed the following issues:
• The whole PM concept and definition should be well described before the start of any initiative, the purpose should be defined;
• The development of PM services and related issues should be coordinated by a central leadership organisation;
• The access to data should be well regulated and protected, all rights and responsibilities in relation to treatment or research purposes inclusive. Data protection should not be achieved with the cost of losing flexibility in the system;
• Most of interviewees were in favour of central solutions for database and other major application development, mentioning also that the success of implementation will depend on the speed of developments and the critical mass of service providers and other relevant parties involved. Recent history has shown that voluntary participation and fragmented infrastructure and data management may hurt or block good initiative;
• The need for a well coordinated and managed pilot project, good preparation for further phases for going live;
• The entire value chain and system to be thoroughly thought through – from risk assessment and diagnostics, counselling and preventive treatment to treatment and financing of the whole package of services;
• Comprehensive training and other competency development support for service providers and clinicians. There is, potentially a need for well developed counselling service and infrastructure;
• Comprehensive media coverage and public education initiatives before and during the pilot project, systematic handling of issues of potential ethical concern;
• There should be transparent understanding of additional resource needs to introduce PM services, sources for financing and the advantages of PM compared to other services;

1. Patients groups
   a. Estonian Patients Advocacy – Kaido Kolk
   b. Estonian Society of Parents of Children with Cancer – Märt Avandi
   c. Cancer Society – Margot Kull

2. Clinicians
   a. Estonian Medical Society - Indrek Oro
   b. Estonian Society of Oncologists – Peeter Padrik
   c. Estonian Endocrine Society – Vallo Volke
   d. Estonian Society of Cardiology – Margus Viigimaa
   e. Estonian Society of Family Practitioners – Diana Ingerainen
   f. Estonian Society of Medical Genetics, Tartu University Clinics Genetics Centre – Katrin Öunap
   g. Terviseagentuur OÜ, Family Medicine Centre at Vormsi – Madis Tiik

3. Medical researchers
   a. Tartu University - Joel Starkopf
   b. Tallinn Technical University - Peeter Ross
   c. Estonian Genome Foundation - Andres Metspalu
   d. National Institute for Health Development – Toomas Veidebaum

4. Medical industry, Pharma Industry
   a. Association of Pharmaceutical Manufactures – Riho Tapfer
   b. Asper Biotech, LabToWellness - Indrek Kask
   c. Cognuse, - Andres Mellik
   d. FiguraGen, - Tarmo Kivi
   e. SportsGene, - Alar Meltsov
   f. Cybernetica - Oliver Väärtnõu
   g. Quretec - Tarmo Reisberg
   h. Opus online, DietBooster – Andre Lall
   i. OÜ Fitnessteam - Rene Poljakov
   j. Nova Vita Clinic – Merike Seer
   k. Protobios - Toomas Neuman, Kaia Palm

5. Hospitals
   a. Tartu University Clinic – Urmas Siigur
b. North Estonia Regional Hospital – Tõnis Allik  
c. East Tallinn Central Hospital – Ralf Allikvee  
d. Qvalitas – Tõnu Velt  
e. Ortokliinik - Ardo Reinsalu

6. Professional partners  
a. Estonian E-Health Foundation – Raul Mill  
b. National Institute for Health Development - Maris Jesse  
c. Tervise TAK, Andres Salumets  
d. Tarkvara TAK, Kalev Koppel, Sulev Reisberg  
e. Eliko TAK, Indrek Ruiso

7. Regulatory authority  
a. Ministry of Social Affairs – Ain Aaviksoo  
b. Ministry of Social Affairs - Ivi Normet  
c. Agency of Medicines – Kristin Raudsepp  
d. Data Protection Inspectorate – Kristiina Laanest  
e. Health Board - Tiiu Aro

8. Payers  
a. Estonian Health Insurance Fund – Tanel Ross , Mari Mathiesen

9. Politicians  

10. Investors  
a. Estonian Business Angels Network - Ivar Siimar

11. Civil servants  
a. Ministry of Justice, Public Law Division - Illimar Pärnamägi  
b. Government Office, Strategy Unit - Margus Sarapuu  
c. Ministry of Economic Affairs and Communications, Economic Development Department - Kaupo Reede  
d. Ministry of Social Affairs, Digital Capacity Development Department - Kitty Kubo

Appendix 4

Following questions were asked from representatives of enterprises:  
- Please define main expectations and positive challenges what development of Personalised Medicine may provide to your organisation?  
- What change in behaviour may demand from your organisation development of PM?  
- Can you see potential risks and threats what development of PM may bring along?
• What requirements and conditions you may define as “must” in order to safely develop the concept and services of PM?
• What measures would provide better understanding whether PM provides any benefit?
• Would you be able to define your organisation role in development and management of PM? Would your organisation be ready to take more actively part in Pilot Project?
• Can you foresee any specific strategic collaboration you need to make business in personalised medicine area?
• Can you describe collaborative mechanisms and the manner in which they may be employed to support entrepreneurship in PM related businesses?
• In your opinion, what are the barriers of deeper cooperation between various stakeholders (between businesses, state and other organisations)? How to overcome these barriers?
• Please define more specifically potential direct business benefits for your company?
• What limitations and constraints you can identify you may face?
• Would you be able to describe new business models as a result of access to the health and genome data of 50 000 persons. Who should own IP and how IP issues should be regulated?

Appendix 5

Pharma Due Diligence visit: June 16-17

Delegation

Merck
1. Robert Plenge (VP, Head of Translational Medicine, Boston, USA)
2. Heiko Runz (Dir., Head of Genetics, Boston, USA)
3. Edward Bortnichak (Exec. Dir., Pharmacoeconomics and Outcomes Research, Upper Gwynedd, USA)
4. Inge De Lepeleire (Sr. Princ. Scientist, Translational Pharmacology MSD Europe, Inc.)
5. Petri Lehto (Dir., Policy and Communications, Finland)

BioGen
1. Sally John (VP, Genomics and Computational Biology)
2. Tim Harris (SVP, Precision Medicine)
3. Aaron Day Williams (Assoc. Dir – Statistical Genetics)
4. Michael Sauter (Sr Dir – Digital Health Innovation)

Bayer Pharma AG
1. Kirsten Leineweber (Head, Global Drug Discovery-GTRG-CIPL-Disease Genomics)
2. Jörn Krätzschmar (Director Experimental Medicine, Bayer Pharmaceuticals)
3. Alfred Radlmaier (Bayer Pharmaceuticals)
Estonian
1. Jaanus Pikani (Chairman, Tartu Biotechnology Park)
2. Tõnu Esko (Deputy Director of Research, Estonian Genome Center, University of Tartu)

Agenda June 16-17
16.06 Tartu
Biobank repository tour
Session I – Genomic strategy & Estonian Biobank – Moderated by Andres Metspalu
“Vision for future drug discovery and the role of population biobanks” (Robert Plenge (Merck Inc); Sally John (BioGen Indec); Kirsten Leineweber (Bayer Pharma AG)
“Estonian Government vision for personalised medicine” (Dr Ain Aaviksoo, Undersecretary of e-health and Innovation, Ministry of Social affairs)
“Estonian Biobank – from past to future” (Prof Andres Metspalu, Director, Estonian Genome Center)
“Research – population structure and genetic discoveries” (Dr Tõnu Esko, Deputy Director of Research, Estonian Genome Center)
“Genetic profiling platforms and medical genetics” (Dr Lili Milani, Head of Sequencing and Genotyping Core Facility, Estonian Genome Center)
Tartu “Cohort profile – from baseline to electronic registries” (Dr Krista Fischer, Senior Research Fellow, Estonian Genome Center)

Session II – Comprehensive information exchange platform – X-road – Moderated by Peeter Ross
“X-road enabled electronic health registries” (Dr Peeter Ross, Head of e-Health Lab, Tallinn University of Technology)
“Estonian Biobank informatics strategy” (Erkki Leego, Managing Partner, Hansson, Leego & Partner)
“Mining the electronic repositories” (Prof Jaak Vilo, Bioinformatics Head of Institute of Computer Science, University of Tartu)

Session III – Clinical Trials landscape in Estonia – Moderated by Tõnu Esko
“Government regulations and state of trials in Estonia” (Dr Alar Irs, Chief Medical Officer, State Agency of Medicines)
“Phase I trials – competence and experience” (Prof Alexander Zharkovski, Head of the Department of Pharmacology at the Medical Faculty, University of Tartu)

17.06 - Tallinn
Wednesday 17th
e-Estonia Showroom, (Lõõtsa 2a, Ülemiste City, meet-up at 8:45 reception; taxi from hotel approx.5 min)
Session IV – e-Services enabled innovation in Estonia
“This Late Phase Clinical Trials in Estonia” (Dr Jaak Tälli, Head, Innomedica Ltd)
Presentation “e-Services enabled innovation in Estonia”

Session V – The Estonian Government Perspective
Parliament building (Mr Rannar Vassiljev, Minister of Health and Labour Ms Mailis Alt, Advisor to the Minister of Entrepreneurship, Ministry of Economic Affairs)