The Personalized PREvention of Chronic Diseases (PRECeDI) project

Supervisory Board
February, 20th, 2017

Supervisory Board- Agenda

• 14:00-14:15 General overview of the Project progress
• 14:15-14:30 First Interim Report
• 14:30-14:45 First Interim Financial report
• 14:45-15:15 The Secondment Plan (discussion and finalization of the secondment plan)
• 15:15-16:30 Overview of the Research Workpackages (discussion among partners)
• 16:30-16:40 Organization of the Plenary Meeting - Oxford
• 16:40-16:50 Next steps
• 16.50–17.00 Question and Answer
Supervisory Board

Supervisory Board Meeting n.2

The main tasks of the Supervisory Board are:

- Support the Project coordinator in the implementation of the actions, checking and providing advice in case of ethical, legal, economic issues raise from the project implementation;
- Monitor and report outputs for each of the 5 research domain;
- Ensure proper dissemination of on the work done by researchers and the research the research outputs.

GANTT Chart

We are in M26
**Round table in collaboration with the EUPHA section of Public Health Genomics**

«Bridging the gap between knowledge and practice in public health genomics»


16:40-17:40, 11th November 2016

**Programme:**

**Chairpersons:**
Róza Ádány (Section President), Hungary
and Stefania Boccia (Section Vice-President), Italy

- The evaluation of genetic tests: a HTA exercise?
  Prof. Paolo Villari, Italy

- Barriers and facilitating factors for implementation of genetic services
  Prof. Martina Cornel, the Netherlands

- Genetic/genomic testing to predict disease: ethical and legal implications
  Prof. Judit Sándor, Hungary

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**Dissemination - Seminar**

PHG in cancer - Meeting in Rome on 23 February

**“Public Health Genomics in cancer (and beyond)”**

*Marc Van den Bulcke*

**Agenda:**

- 10-11: Policy paper PHG in cancer
- 11-12: Marie curie initiative/ eupha taskforce
- 12-13: new JA on cancer
- Lunch break
- 14-15.30: videoconferencing
- 15.30-16.30: wrap up and next steps
Deliverables

<table>
<thead>
<tr>
<th>Deliverable Number</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>D8.2</td>
<td>Open Seminar (EUPHA 9-12, November 2016)</td>
</tr>
<tr>
<td>D1.14</td>
<td>Research Council Meeting n.2 (14 December 2016)</td>
</tr>
<tr>
<td>D1.10</td>
<td>Supervisory Board Meeting n.2 (20 February, 2017–today)</td>
</tr>
<tr>
<td>D1.7</td>
<td>Plenary Meeting n.2 (20-21 September, 2017)</td>
</tr>
<tr>
<td>D1.11</td>
<td>Supervisory Board Meeting n.3 (November, 2017)</td>
</tr>
</tbody>
</table>

All the scientific deliverables are scheduled for month 38 (February 2018)

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Periodic reports

The following reports will be submitted:

- Periodic technical report
- Periodic financial report

The reports must be drawn up using the forms and templates provided by the Agency in the electronic exchange system.

Periodic technical report

UCSC will prepare the technical report, also using the reports received from the WP leaders on the work performed from the beginning of the project and the main results achieved so far.

Please send us within March, 1:

- The list of articles, publication in conference proceeding, chapters in book, thesis..with the PRECeDI acknowledgement
- Type of dissemination and communication activities, and the type of audience reached
- Impact on SMEs
Periodic Financial Report

- Project Financial Report due by 28/02
- EC delay in issuing the reporting module → informal extension of deadline
- EC released the reporting module last week
- UCSC will send instructions to all partners → please inform your grant office
- Financial Report already pre-filled in by EC

Project Financial Report

Unit costs – number of Secondment Months pre-filled in. Check n. of SM, inform coordinator of discrepancies and send for FSIGN for signature.
Project Financial Report

- On the basis of the Financial Report → second installment
- Decision to take on 5% retention
- 45% of prefinancing retained has been used to cover reimbursement of travel costs to not funded partners + minor costs for common organisational meetings
- UCSC:
  - Suggest not to retain additional 5% from the second installment
  - Use the remaining funds to cover partner expenditures for workshop/seminar and final conference
  - Check savings or additional charge at payment of the balance at the end of the project.
  - Decision need to be taken officially by the Plenary.

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WP7: SECONDMENT MAP

- September 2015
  VUMC and BVHC renounced to 6 and 11 months, respectively

- On December 2016
  LINKCARE renounced to 12 months

An amendment of the Grant Agreement after the Supervisory Board has been requested by the PO

The amendment will impact on the project budget and potentially on the payment of the next installments.

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WP7: SECONDMENT MAP

February 2017

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
<th>MONTHS OF SECONDMENT (expected after re-shuffling)</th>
<th>MONTHS OF SECONDMENT (covered)</th>
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<tbody>
<tr>
<td>UCSC</td>
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<tr>
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<td>LINKCARE</td>
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<td>ERASMUS MC</td>
<td>27</td>
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<td>TOTAL</td>
<td>176</td>
<td>86.5</td>
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Please confirm to use the secondment months

Total number of researchers = 51
Researcher declaration

Each partner sending researcher in secondment was responsible for ensuring that a Researcher Declaration was filled in and sent via the Participant Portal for each researcher starting a secondment period.

After secondment – Knowledge return

The knowledge return in each organisation have to include at least lectures and training provided by the researchers after secondment.
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WPs

<table>
<thead>
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</thead>
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<td>1</td>
<td>48</td>
</tr>
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WP2- Research domain no.1: Identification of biomarkers for the prevention of chronic diseases

**Objectives**

- Advancing the exchanging staff with knowledge on aspects related to identification and implementation of the use of biomarkers for the prevention of CVD, AD, and HNC, through an active engagement in the research projects.
- Providing the staff with private sector perspectives on the commercialization of the –omics technologies.

**Work Package Leader : Erasmus MC**

**Task 2.1.** Identification of biomarkers for the primary prevention of CVD. (Task leader: ErasmusMC). The staff will be involved in the laboratory activities, data analysis, and data interpretation.

**Task 2.2.** Identification of biomarkers for the secondary prevention of AD (Task leader: ErasmusMC). The staff will be involved in the laboratory activities, data analysis, and data interpretation.

**Task 2.3.** Identification of biomarkers for the tertiary prevention of HNC (Task Leader: UCSC). The staff will be involved in the data analysis from the biological study and the epidemiological study, and data interpretation.
The task includes two objectives:

1) Identify specific microRNA signatures associated with the occurrence of recurrence, and overall survival (OS), within a multicentre biological study;

2) Evaluate the interaction between lifestyle factors and the resulting miRNA signatures from 1), on the occurrence of recurrence and OS.

### TASK 2.3 – Biological study

**MicroRNA profiles in Head and Neck Cancers**

(Task leader: UCSC)

Screening Phase RESULTS

- 5 prognostic miRNAs to be validated

Validation Phase

- 250 HNC cases

RNA extraction has been conducted by Nucleo Spin miRNA Plasma kit (Macherey Nagel). In the Screening Phase the TaqMan® Array Human MicroRNA Card Set v3.0 has been utilized. It is a two card set, specific for plasma/serum samples, containing a total of 384 TaqMan® MicroRNA Assays per card.
TASK 2.3- Epidemiological study
(Task leader: UCSC)

1) Impact of lifestyle habits on survival in head and neck cancer
2) Impact of lifestyle habits on recurrence and second primary cancer in patients with head and neck cancer

Data were collected from 5 different centers: Milan, Rome, Western Europe, Brazil and Japan

1) Impact of lifestyle habits on survival in head and neck cancer

Objective of the study was to evaluate whether demographics, pre-diagnosis lifestyle habits and clinical data are associated with the overall survival and head and neck cancer-specific survival in patients with head and neck cancer

Main Results

- Overall and HNC-specific survival differs among HNC sites
- Low educational level was an unfavourable prognostic factor for patients with laryngeal cancer
- Pre-diagnosis cigarette smoking was a prognostic factor of the overall survival for patients with oral and oropharyngeal cancer
- Pre-diagnosis alcohol drinking was a prognostic factor of the overall and HNC-specific survival for patients with laryngeal cancer
2) Impact of lifestyle habits on recurrence and second primary cancer in patients with head and neck cancer

Objective of the study was to evaluate whether demographics, pre-diagnosis lifestyle habits and clinical data are associated with the recurrence and second primary malignancies in patients with head and neck cancer.

Main Results

- Tumour stage (both oral cavity and oropharynx), low education (oral cavity only), and female gender (larynx only) were predictors of recurrence in HNC patients.
- Advanced age and high alcohol consumption were predictors for SPC only for patients with laryngeal cancer.

Next Step: Evaluate the interaction between lifestyle factors and the resulting miRNA signatures from the validation phase, on the occurrence of recurrence and OS.

HNC- Works ongoing at ICHAN

1. Markers of HPV infections and risk of cancer of subsites within the oral cavity

2. Interaction between oral HPV infection and Alcohol and Tobacco use in Head and Neck Cancer: a Systematic Review and Meta-Analysis
HNC- Works ongoing at UCSC

3. Genetic associations of second primary cancer occurrence among patients with primary head and neck cancers: a systematic literature review.


5. Second Primary Malignancy Risk in HN Cancer Survivors: a Systematic Review and Meta-Analysis

Biomarkers and their application in dermatology

Daniel Töröcsik
and
Marcello Paglione (Myriad Genetics)
Application of biomarkers in cancer

1. To help **diagnose** conditions, as in the case of identifying early stage cancers (Diagnostic)
2. To **forecast** how aggressive a condition is, as in the case of determining a patient’s ability to fare in the absence of treatment (Prognostic)
3. To **predict** how well a patient will respond to treatment (Predictive)
4. To initiate the development of future therapies (BCR-ABL - imatinib)

- AFP (Liver Cancer),
- BCR-ABL (Chronic Myeloid Leukemia),
- BRCA1 / BRCA2 (Breast/Ovarian Cancer),
- BRAF V600E (Melanoma/Colorectal Cancer),
- CA-125 (Ovarian Cancer),
- CA19.9 (Pancreatic Cancer),
- CEA (Colorectal Cancer),
- EGFR (Non-small-cell lung carcinoma),
- HER-2 (Breast Cancer),
- KIT (Gastrointestinal stromal tumor),
- PSA (Prostate Specific Antigen) (Prostate Cancer),
- S100 (Melanoma), and many others

Biomarkers in melanoma

The misdiagnosis of melanoma is the second most common reason for cancer malpractice claims in the US
Myriad myPath Melanoma –
to increase Diagnostic Confidence

Melanoma diagnosis –
translating mRNA changes to protein levels
Applying genetic tests is melanoma histopathology

Questionnaire on implementing genetic tools into melanoma diagnosis

1. For how long have you worked as a certified dermatologist/dermatopathologist?
   For decades, experts in dermatopathology

2. How many melanoma diagnosis do you have a month?
   From 4 to 25/month (depending on the center status of the place)

3. How many cases you have in a month where the melanoma diagnosis is not straightforward?
   About 5%

4. How many of these uncertain melanoma turns out to be a nevus?
   Answers are not representative

5. What are the histological markers you use to distinguish and confirm melanoma?
   Most common: HMB45, p16, SOX2, PAX8, Ki67

6. Do you detect genetic signatures from the specimens?
   If Yes,
   a. in all cases
   b. only when the diagnosis is uncertain
   c. only when administration of a possible drug requires it

7. What field you think genetic tools could be applied in melanoma diagnosis?
   a. Prediction
   b. Prognosis
   c. Therapy
Applying genetic tests is melanoma histopathology

Questionnaire on implementing genetic tools into melanoma diagnosis

8. How likely it is that you would add new genetic tools to your practice?
   a. absolutely, I’m open to anything that is new
   b. only if it’s convincingly useful
   c. not likely, I’m satisfied with the current diagnostic tools

9. Have you heard about the Myriad myPath Melanoma kit?
   a. No
   b. Yes, but never used it
   c. Yes, and it is integrated into our diagnostic tools

10. Looking at the link provided:
    https://mypathmelanoma.com/about-mypath-melanoma/understanding-the-mypath-melanoma-results/
    Would you find useful such scoring to help your decision in melanoma diagnosis?
    Yes

What we learnt from the questionnaire?

• About 5% of melanoma goes for consultations
• Greatest challenge is to diagnose Spitz naevi
• Trust their experience with long used markers (HMB45, S100, double staining: melanin + ki67)
• Work in teams to challenge questionable cases
• Needs the information from the clinician
• BRAF test costs 150-200 euro – too expensive
• Not clear what the price of a new kit would be acceptable (cost/benefit)
• Need to study the resistant tumors and identify more markers besides BRAF and also in connection with BRAF
• Non-invasive test to detect primary/metastatic tumor
• Application of new tools (microRNA, ctDNA, exosomes)
WP3

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<td>1</td>
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</tr>
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WP3-Research domain no.2 : Economic evaluation of predictive genomic applications

Objectives

- Estimating the economic impact of the health care pathways triggered by predictive genetic testing;
- Summarizing the scientific evidence on effectiveness and cost-effectiveness of selected predictive genetic and pharmacogenetic tests.

Work Package Leader : Università degli Studi di Roma LA SAPIENZA

Task 3.1 Evaluation of the costs of the health care pathways triggered by some predictive and pre-symptomatic genetic tests (task leader: Sapienza; participant: Myriad Genetics).
The staff will be involved in data extraction from current information systems, and data analysis from the surveys on experts, physicians and patients.

Task 3.2 Systematic review of the existing literature concerning the studies of effectiveness and the published full economic evaluations of predictive genetic tests and pharmacogenetic tests (Task leader: Sapienza; participant: ISMM).
The staff will be involved in bibliographic search, data extraction from relevant articles, and critical appraisal by using validated scales, of the literature retrieved.

WP3-Research domain no.2 : Economic evaluation of predictive genomic applications

Task 3.1 Evaluation of the costs of the health care pathways triggered by some predictive and pre-symptomatic genetic tests

STUDY PROTOCOL
The appropriateness of genetic testing. A proposal of a European multicenter study

1. Estimating the appropriate use of genetic tests
2. Evaluating knowledge and attitudes of public health professionals
3. Employing ICTs for genetic education and disease management
WP3-Research domain no.2 : Economic evaluation of predictive genomic applications

The appropriateness of genetic testing. A proposal of a European multicenter study

1. Estimating the appropriate use of genetic tests

General objective
To evaluate and describe the appropriate use of genetic testing in Europe, in order to obtain a snap-shot of actual process of integration of genetic tests into clinical practice

Intermediate objectives

✓ OBJECTIVE 1: To select the genetic tests as case-studies

✓ OBJECTIVE 2: To identify the European countries involved in the project and the project national referents

✓ OBJECTIVE 3: To perform systematic reviews of national and international guidelines to define the correct use of selected genetic tests and to estimate the recommended health care pathways

OBJECTIVE 4: To carry out on-line surveys to national experts, one for each selected genetic test

OBJECTIVE 5: To analyze, describe and discuss the main findings

National Referents – 28 EU Countries
Countries for which the PNRs the PNRs have provided a full list of experts (n. 10)
An on-line survey will be conducted on the network of the European Public Health Association (EUPHA)

A specific questionnaire was developed for this purpose, composed of the following 5 sections:

- Personal details (4 questions)
- Professional activity (7 questions)
- Knowledge on genetic testing and delivery of genetic services (8 questions)
- Attitudes on genetic testing and delivery of genetic services (9 questions)
- Attitudes on the role of public health professionals in PHG (9 questions)

Task 3.2 Systematic review of the existing literature concerning the studies of effectiveness and the published full economic evaluations of predictive genetic tests and pharmacogenetic tests.

WP3-Research domain no.2: Economic evaluation of predictive genomic applications

**ABSTRACT**

**Background**

Familial hypercholesterolemia (FH) is a genetic disorder that leads to elevated plasma LDL-cholesterol levels and premature coronary heart disease (CHD) disease. The new knowledge regarding mutations responsible for FH and the effectiveness of statins in lowering the risk of CHD in FH patients has raised interest in genetic screening strategies to increase the diagnosis of FH. We aimed to evaluate the cost-effectiveness of such strategies.


A systematic review on the cost-effectiveness of the genetic tests for Lynch syndrome is currently ongoing.

Economic evaluation of screening strategies for Lynch syndrome in Italy

Three research steps are taken to achieve this aim:

1) Three systematic reviews of international guidelines, existing screening pathways for LS, and economic evaluations

2) Semi-structured interviews with Italian experts to identify the diagnostic pathways actually performed in Italy

3) Cost-effectiveness analysis of the screening scenarios (ongoing).
Cost-effectiveness analysis of the screening scenarios

The aim is to assess the cost-effectiveness of different screening strategies for LS from the perspective of the NHS (Italy)

Focus: screening as instrument of prevention on the first-degree relatives

Screening Strategies for the Lynch Syndrome (Population with newly diagnosed colorectal cancer)

For the patients with germline mutation (LS mutation-positive), a site-specific germline testing is offered to relatives.

Management program for relatives with the LS (mutation-positive)

Economic evaluation

LYNCH SYNDROME

- Universal (all CRC cases)
- CRC < 70 years
Economic evaluation
LYNCH SYNDROME

Management program for persons with the Lynch syndrome (first-degree relatives)

WP4

<table>
<thead>
<tr>
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<th>Start</th>
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</tr>
</thead>
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WP4-Research domain no.3: Ethico-legal and policy issues surrounding personalized medicine

Objectives
❖ Introduce the staff to the ethical, legal and policy issues in genomics in both the research and clinical settings;
❖ Make the staff being familiar with social science research methodologies, especially international comparative analysis of normative policy and legal instruments.

Work Package Leader: McGill University

Task 4.1. Comparative analysis of national and international health policies, guidelines and legislation in public health genomics (Task leader: McGill)
The staff will pursue active research under the supervision of a mentor working in the Fellow’s area of interest. Specific areas of research at the Centre of Genomics and Policy include but are not limited to: biobanks, stem cells and reproductive technologies, newborn screening, breast cancer and risk assessment, rare diseases. They will be expected to conduct comparative legal analysis, write scholarly articles, present findings and develop research tools for harmonization and data integration.

Task 4.2. Analysis of the European scenario in terms of health policies developed or being developed at national level for public health genomics (PHG) (Task leader: UCSC; participant: EUPHA).
The staff will be involved in the data analysis of the interviews on PHG policies from the relevant stakeholders.

Task 4.2. Analysis of the European scenario in terms of health policies developed or being developed at national level for public health genomics (PHG) (Task leader: UCSC).

Current state of genomic policies in healthcare among EU member states: results of a survey of chief medical officers.

Padovan M1, Pastoretti A2, Leventides T3, Maiter D4, Kasteleit C5, Maurin C6, Van Rooyen A, Fortier F7, Bendigs M8, Borradori L9, Rocque S8.

Abstract
BACKGROUND: A need for a governance of genomics in healthcare among European Union (EU) countries arose during an international meeting of experts on public health genomics (PHG). We have conducted a survey on existing national genomic policies in healthcare among Chief Medical Officers (CMOs) of the 28 EU member states, plus Norway.

METHODS: A questionnaire was sent to CMOs after a meeting on the policy implications of PHG held during the Italian presidency of the Council of EU in 2014. The survey was closed in November 2015.

RESULTS: CMOS response rate was 65.5% (18/27). Twelve (63.2%) reported that their countries had a policy for genomics in healthcare in place, and 15 (78.9%) reported that public funding existed. Public research facilities for the development of such policies were documented in 13 (68.4%) countries, and 10 (55.6%) had working groups devoted to policy development. National agencies carrying out Health Technology Assessment of genomic-based technologies were present in nine countries (45%). Sixteen (88.9%) countries reported having agencies dealing with ethical issues related to genomic technologies. About 55% of countries disclosed the lack of information campaigns aimed at citizens, and 44% reported they had a legal framework for direct-to-consumer genetic tests.

CONCLUSION: Belgium, France, Italy, Spain and UK documented the presence of a policy on genomics in healthcare. While many caveats are necessary because of the methodology, results suggest a need for a co-ordinated effort to foster development and harmonization of dedicated policies across EU to responsibly integrate genomics policies into existing health systems.

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### WP5

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<tr>
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<td>Research domain no.1: Identification of biomarkers for the prevention of chronic diseases</td>
<td>4- Erasmus MC</td>
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<td>WP4</td>
<td>Research domain no. 3 : Ethical-legal and policy issues surrounding personalized medicine</td>
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<td>WP8</td>
<td>Dissemination</td>
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</tr>
</tbody>
</table>

### WP5- Research domain no.4: Sociotechnical analysis of the pros-and cons of informing healthy individuals on their genome

**Objectives**

This WP will describe (1) the arguments used and (2) the actors involved in decision making on new genomics technologies (such as whole genome sequencing and analysis).

**Work Package Leader**: VU

**Task 5.1** Responsible translation of new genomics technologies in the context of screening of healthy adults (Task Leader: VU). The staff will be involved in the literature study and interviews, as qualitative research instrument to carry out a sociotechnical analysis of the balancing of pros and cons of informing healthy individuals on genome.

**Task 5.2** Pathologist and Oncogenetics: test relevant tumors for microsatellite instability or panels of mutations (Task Leader: VU and McGill). The staff will be involved in small scale initiatives to inform high-risk carriers (e.g., interview, stakeholder meetings).
Role in the Project – Domain 4

- WP leader – Martina Cornel
  5.1 Task leader – Martina Cornel
  5.2 Task leader – Martina Cornel (together with Bartha Knoppers, McGill)

Tasks:
- 5.1. to make a sociotechnical analysis of how stakeholders balance pros and cons in informing healthy individuals on their genome (primary prevention healthy family members)
- 5.2. zoom in: to study and improve the current role of pathologists in (1) testing relevant tumors, and (2) organizing that the message reaches the family.
Domain 4: Secondeees

5.1 Sociotechnical analysis
• No secondee
• Help from Peter Piko (Debrecen University, Hungary) (seconded to EUPHA, September to March 4, 2017)

5.2 Role pathologist
• Secondee dr Anant Jani (BVHC) 1 month

In 2017: new secondments to EUPHA can assist in VUMC tasks: Annalisa Rosso, Alessia Tognetto, Valentina Baccolini, Jovana Stojanovic

Domain 4 - Work plan 5.1

5.1. Sociotechnical analysis:
- Study literature and guidelines on informing & testing (healthy) individuals on their genome,
  > Focus on FH
  > How active can doctors/counsellors trace & inform family members? (calls for restarting proactive population screening in NL; model for Europe?)

  Minister September 2016: Index patient responsible for informing family
  > Give information letters only? New media solutions?
  > Comparison oncology vs FH (Literature study 2016)

  - Identification stakeholders in cardiology and oncology (health care professionals; legal/ethical regulatory bodies; patients organizations)
    > 4-6 interviews and site visits (2017)
5.2. Role pathologist

>Focus on Lynch syndrome

UK: new guideline for routine use of pathology ‘genetic’ screening test IHC in patients under 50 years

NL: new guideline since 2016: routine IHC in patients under 70 years

>collaboration Bowel Cancer UK (meeting July 25, 2016)

- 10 hospitals UK selected:
  - 2 trusts that do routine testing via IHC
  - 2 trusts following pathway Multi Disc Team > IHC
  - 2 trusts following pathway MDT > Genetics referral > IHC
  - 2 trusts following pathway MDT > GP > Genetics referral > IHC
  - 2 trusts that did not implement routine testing

>Compare arguments (not) to implement routine screening for Lynch syndrome with 5 hospital teams in the Amsterdam region

Collaboration WP 6

- Assisting in writing Systems specifications* BVHC:
  - Breast Cancer; Lynch syndrome;
  - Familial Hypercholesterolaemia; Long QT Syndrome
  - Synergy secondments VUMC to LinkCare: Martina Cornel and Elisa Garcia

- Involving doctors VUMC/AMC hospitals Amsterdam in checking Systems specifications

- Abstract submitted to the European Society of Human Genetics, February 2017 for a Poster:

  High value genetic services through outcomes-based systems specifications

  A. Puggina¹, D. Vojinovic², A. Demirkan², R. Pastorino³, O. Damman³, P. Parente¹, T. Lagerberg⁴, C.G. van El¹, H. Meijers-Heijboer⁴, M. Cornel³, A. Jani³, M. Gray⁵;
  ¹Università Cattolica del Sacro Cuore, Rome, Italy, ²Erasmus Medical Center, Rotterdam, Netherlands, ³VU University Medical Center, Amsterdam, Netherlands, ⁴Better Value Healthcare Ltd, Oxford, United Kingdom, ⁵University of Oxford, Oxford, United Kingdom.
Collaboration WP 6

- Collaboration on surveys Sapienza:
  - EUPHA knowledge & attitudes
  - Services delivery models & appropriateness of health care pathways

Network meetings PRECeDI in Amsterdam, dissemination

- 19 January 2016 Kick off national network meeting value based genomic health care
  Lecture a.o. by Anant Jani, Martina Cornel (8 people)

- 18 April 2016 National Network meeting value-based genomic health care
  Lecture a.o. by Martina Cornel, Hanne Meijers Heijboer, Muir Gray, Danielle Timmermans (25 people)

- 29 April: Lecture Martina Cornel and Hanne Meijers Heijboer for Clinical Geneticists in Training VUMC/AMC hospitals (15 people)
  on value based genetic health care and mainstreaming

- 20 June 2016: Lecture by Elvira d’Andrea for Colloquium Community Genetics VUMC (10 people)
  An Introduction to the PRECeDI project

- 7 July 2016: Lecture by Martina Cornel for Clinical Geneticists VUMC/AMC hospitals (25 people) on value based health care and mainstreaming

- 25 October: Network meeting General practitioners and FH experts of AMC hospital on Better value FH care
  Lecture a.o. by Martina Cornel, Anant Jani (10 people)

- 18 April 2017: Meeting on mainstreaming cancer genetics for better value genetic health care for Clinical Genetics Departments VUMC/AMC
Initiatives for Articles BVHC

- Implementing the Systems Specification to improve outcomes in genetic health care: the case of hereditary breast cancer
- Implementing the Systems Specification to improve outcomes in genetic health care: the case of Lynch syndrome
- Implementing the Systems Specification to improve outcomes in genetic health care: the case of Familial Hypercholesterolaemia
- Implementing the Systems Specification to improve outcomes in genetic health care: the case of Long QT
- Assessing genomic screening of chronic diseases through the lens of the Triple Value Healthcare paradigm (Secondment Viktor Dombradi, Debrecen & Erica Pitini, Sapienza)

Secondment VUMC to Mc Gill

- Dalisa van den IJssel: 31 May-31 July 2017

Study the link between informed decision making and informed consent in relation to genetic screening. The focus will be on the development and definition of the concepts within different fields (e.g. legal-ethical domain versus psychology) and possible differences between countries (i.e. Europe versus North America; development of human rights perspective).
WP6

<table>
<thead>
<tr>
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</table>

WP6- Research domain no.5: Identification of organizational models for the provision of predictive genetic testing

Objectives

- To design healthcare systems for CVD, AD and HNC that integrate genomic information to deliver personalised care
- To create a means of normalising and benchmarking the performance of the healthcare systems run in the heterogenous contexts of our consortium partners
- To create a means of actively sharing learning and best practice amongst our consortium partners to boost the integration of genomic information within healthcare systems delivering personalised care.

Work Package Leader: Università degli Studi di Roma LA SAPIENZA

Task 6.1 Organizational models in place in EU (Task Leader: Sapienza; participant: LinkCare).
The deliverable is a report of the systematic review of organizational models for the provision of predictive genetic tests.
WP6-Research domain no.5: Identification of organizational models for the provision of predictive genetic testing

Task 6.1. Organizational models in place in EU

IDENTIFICATION OF DELIVERY MODELS FOR THE PROVISION OF PREDICTIVE GENETIC TESTING: PROPOSAL OF A EUROPEAN MULTICENTRE STUDY

GENERAL OBJECTIVE
To identify delivery models for the provision of predictive genetic testing in EU.

SPECIFIC OBJECTIVES

OBJECTIVE 1: Description of existing genetic delivery models in EU compared to extra-EU countries (USA, Canada, Australia and New Zealand)

OBJECTIVE 2: Identification of strengths and weaknesses of the delivery models

OBJECTIVE 3: Collection of process and outcome indicators from existing delivery models

OBJECTIVE 4: Identification of key points to address for an effective and efficient implementation of genetic testing in health care systems in EU

The identification of delivery models for the provision of predictive genetic testing is carried out through a multidimensional approach, which includes a systematic review of the literature and two cross-sectional studies that include experts’ interviews and a survey of public health professionals in Europe.

1. Systematic review of the literature
This approach allow us to collect information about:
- The study (i.e. authors, title of the study, etc.) and the genetic service (i.e. practice setting, financing mechanism, etc.) - GENERAL DESCRIPTION OF THE STUDY AND THE GENETIC SERVICE
- Patients and pathways to care (i.e. the characteristics of the target population of the genetic service and pathways to care, as well as cost-effectiveness and efficacy of the genetic service) - INFORMATION ON PATIENTS AND PATHWAYS TO CARE
- Type of genetic service delivery model, strengths and weaknesses of the model, as well as the genetic service capacity in terms of population and geographic area served, staff qualification, laboratory characteristics and outcome evaluation - GENETIC SERVICE EVALUATION
2. Experts’ interview on Genetic Services Delivery Models

The interview is constructed upon the results of the systematic review in order to:

i) encompass any genetic services delivery model that was not acquired with the literature search;

ii) enhance the collection of process and outcome indicators used for quality assessment of genetic services;

iii) collect opinions of expert panels about genetic services delivery models in their countries, in terms of strengths, weaknesses and possible improvements of the models.

Section C of the questionnaires includes a set of questions regarding delivery models

In this section, the experts are asked to answer 8 questions concerning genetic services delivery models for the provision of genetic testing and the associated patients’ pathways in their countries.
LINKCARE

OVERVIEW
# METHODOLOGY

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<tr>
<th>STAGE</th>
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<tr>
<td>DESIGN</td>
<td>• COLLECT EVIDENCE BASED INFORMATION&lt;br&gt;• DETERMINE THE NUMBER OF PROCEDURES&lt;br&gt;• DETERMINE AGENTS AND ELEGIBILITY CONDITIONS FOR EACH PROCEDURE&lt;br&gt;• DESIGN THE PROCEDURE</td>
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<td>IMPLEMENTATION</td>
<td>• DESIGN THE QUESTIONARIES IN THE CAREPEDIA&lt;br&gt;• CREATE THE DECISION SUPPORT ALGORITHMS (SCORINGS)</td>
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<tr>
<td>VALIDATE</td>
<td>• PERFORM FOCUS GROUPS TO CHECK THE SYSTEM</td>
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<tr>
<td>TEST</td>
<td>• DEPLOY TEST / PILOT SITES</td>
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<td>ADOPT</td>
<td>• DEPLOY AS HEALTH CARE TOOL</td>
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# PROGRAMS

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LYNCH SYNDROME PROGRAM

PROCEDURES

AGENT
- ONCOLOGIST
- PREVENTIVE MEDICINE

ELEGIBILITY
- COLON OR ENDOMETRIAL CANCER
- LS RELATIVE
- LS CARRIERS
- NO PREVIOUS SCREENING

PROCEDURE
- LS SCREENING
- LS CASCADE SCREENING
- LS CANCER PREVENTION
LYNCH SYNDROME SCREENING PROCEDURE

- LS SCREENING
  - INTERVIEW
  - ELEGIBILITY
  - FAMILY ANTECEDENTS
  - CLINICAL HISTORY
  - CLINICAL ASSESSMENT
  - SCORING
  - STRATIFICATION
  - CG
  - AMSTERDAM
  - BETHESDA
  - PREDICTION MODEL
  - TUMOR ASSESSMENT
  - MSI
  - IHC
  - BRAF
  - STRATIFICATION
  - DISCHARGE

- ELIGIBLE?
- POSITIVE SCORE?
- LS+?
- GENETIC TEST
- GENETIC COUNSELING
- DISCHARGE
- LS CASCADE SCREENING
- LS CANCER PREVENTION

FAMILIAL HYPERCHOLESTEROLEMIA PROGRAM

- AGENT
  - GENERAL PRACTITIONER OR CARDIOLOGIST
  - PREVENTIVE MEDICINE

- ELEGIBILITY
  - ELEVATED BLOOD CHOLESTEROL LEVELS
  - NO PREVIOUS SCREENING

- PROCEDURE
  - FAMILIAL HYPERCHOLESTEROLEMIA SCREENING
  - FH RELATIVES SCREENING
  - FH MANAGEMENT
FAMILIAL HYPERCHOLESTEROLEMIA SCREENING PROCEDURE

INTERVIEW & EXPLORATION
- ELEGIBILITY
- FAMILY ANTECEDENTS
- CLINICAL HISTORY
- LIFESTYLE HABITS
- MEDICATIONS
- PHYSICAL EXAMINATION

FH SCREENING
- REJECT
- TEST REVIEW
- LAB TEST PRESCRIPTION
- ELIGIBLE?
- OTHER CAUSES EXCLUDED?
- DISCHARGE

STRATIFICATION
- UNLIKELY
- DEFINITE
- POSSIBLE

DUTCH LIPID CLINIC NETWORK
- SIMON BROOME

GENETIC COUNSELING
- ASSESSMENT
- SCORING

GENETIC TEST

FH RELATIVES SCREENING
- FH MANAGEMENT

LONG QT SYNDROME PROGRAM

PROCEDURES

AGENT
- CARDIOLOGIST
- PREVENTIVE MEDICINE

ELEGIBILITY
- ECG ALTERATIONS ASSOCIATED TO LQTS
- NO PREVIOUS SCREENING

PROCEDURE
- LQTS SCREENING
- LQTS RELATIVES SCREENING
- LQTS TREATMENT & FOLLOW-UP

LQTS RELATIVES SCREENING
- LQTS CARRIERS

POSITIVE?
- DISCHARGE
LONG QT SYNDROME SCREENING PROCEDURE

- **INTERVIEW**:
  - Eligibility
  - Clinical History
  - Family Antecedents
  - Physical Examination
  - Symptoms
  - Medications

- **ADDITIONAL TEST**:
  - Schwartz Criteria
  - Holter ECG
  - Pharmacological Provocation ECG

- **GENETIC COUNSELING**

- **GENETIC TEST**

- **LAB TEST PRESCRIPTION**

- **CARDIAC US PRESCRIPTION**

- **ASSESSMENT**:
  - Scoring
  - Stratification

- **OTHER CAUSES EXCLUDED?**

- **DISCHARGE**

- **LQTS RELATIVES SCREENING**

- **LQTS TREATMENT & FOLLOW-UP**

BRCA-RELATED CANCERS PROGRAM

- **PROCESSES**
  - **PREVENTIVE MEDICINE**
    - General Practitioner
    - Cancer Relatives
    - No Previous Screening
    - No Cancer History
    - BRCA Screening
    - BRCA Cascade Screening
    - BRCA Cancer Prevention
  - **BRCA RELATIVE**
  - **BRCA CARRIERS**
  - **BRCA CANCER PREVENTION**

- **AGENT**
  - **GENERAL PRACTITIONER**
    - BRCA Screening
    - BRCA Cascade Screening
    - BRCA Cancer Prevention
BRCA-RELATED CANCERS SCREENING PROCEDURE

**BRCA SCREENING**

**INTERVIEW**
- ELEGIBILITY
- FAMILY ANTECEDENTS
- CLINICAL HISTORY

**REJECT**
- ELIGIBLE?

**ASSESSMENT**
- SCORING
- STRATIFICATION

**DISCHARGE**
- POSITIVE SCORE?

**GENETIC COUNSELING**
- GENETIC TEST

**DISCHARGE**
- BRCA+?

**Ontario Family History Assessment Tool**
**Manchester Scoring System**
**Referral Screening Tool**
**Pedigree Assessment Tool**
**FHS-7**

**BRCA CASCADE SCREENING**
**BRCA CANCER PREVENTION**

IMPLEMENTATION
ELIGIBILITY

Do you have Ashkenazi Jewish heritage?

No

Is there any history of breast, ovarian, pancreatic, prostate, pancreatic or colon cancer in your family?

Yes

Think about both your mother and father’s side of the family. Include yourself, parents, children, brothers/sisters, aunts/uncles, nieces/nephews, grandparents, and to first degree relatives.

Yes

Have you been tested for BRCA mutations before?

No

Have you a family member with a known potentially harmful mutation in the BRCA1 or BRCA2 genes?

No

FAMILY ANTECEDENTS

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<td>诸葛</td>
<td>Colon</td>
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<td>Great grandfather</td>
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<td>诸葛</td>
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</table>

FAMILY ANTECEDENT

FAMILY ANTECEDENT

FAMILY ANTECEDENT

FAMILY ANTECEDENT
•THANK YOU!

Jim Roldan
jimroldan@linkcare.es

The PRECeDI project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 645740.

Better Value Healthcare
Domain 5 - Work Package 6
Work Undertaken

The PRECeDI project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 645740.
BVHC’s expertise

Outcomes-based systems specifications

These define: Scope, Population, Aims, Objectives, Criteria for objectives.

• Aim: maximising value in healthcare
  – Allocative
  – Technical
  – Personal
• 2 types of outputs within WP6:
  – A) Reports (to assess possibility of introduction of technology)
  – B) Specifications (once A established)

BVHC has completed all planned outputs.

Outputs

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<th>Report topic</th>
<th>Secondee</th>
<th>Institution of Origin</th>
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<tr>
<td>Alzheimer’s Disease</td>
<td>Jun Liu</td>
<td>Erasmus mc</td>
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<tr>
<td>Head and Neck Cancer</td>
<td>Corrado De Vito,</td>
<td>Sapienza</td>
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<td></td>
<td>Roberta Pastorino</td>
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<td>Monogenic CVD</td>
<td>Anna Puggina</td>
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<td>Lynch Syndrome</td>
<td>Carla Van El,</td>
<td>VUmc, Erasmus mc</td>
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<td>Ayse Demirkan</td>
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<tr>
<td>Monogenic CVD</td>
<td>Dina Vojinovic</td>
<td>Erasmus mc</td>
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Reports (1)

Better value healthcare for Alzheimer’s disease in the genetic era

Main author: Jun Liu

- Currently established genetic biomarkers
  - Early-onset AD
  - Late-onset AD
- Emerging genetic biomarkers
  - Early-onset AD
  - Late-onset AD
- Potential for high-value genetic interventions against AD
  - Different scenarios for early- vs. late-onset AD

Bottom line:
Lack of effective treatment against AD makes it difficult to implement genetic biomarkers in treatment, even in the (rare) case of dominantly inherited AD.

Reports (2)

Head and Neck Cancer: Currently Established and Emerging Biomarkers

Main author: Corrado De Vito

- Genetic biomarkers: current and emerging
- Targeting oncogenic alterations in head and neck squamous cell carcinoma (HNSCC)
- Tumour suppression in HNSCC
- Alcohol consumption related to head and neck cancer

Bottom line:
At the moment, we mainly have prognostic biomarkers (HPV, EBV), but no predictive biomarkers.
Report + System Specification

Monogenic Cardiovascular Disease: Designing Systems to Deliver Personalized Care

Main author: Anna Puggina

Report
• Familial cardiomyopathies
• Inherited heart rhythm disturbances
• Connective tissues disorders of vessels
• Familial hypercholesterolemia

System specifications
• Long QT syndrome
• Familial hypercholesterolemia

Bottom line:
Genetic interventions have the greatest potential to be high value for long QT syndrome and familial hypercholesterolemia.

Specifications (1)

Breast Cancer and BRCA Mutations: Designing Systems to Deliver Personalized Care

Main author: Roberta Pastorino

Specifications for:
• Patients tested positive for BRCA
• Patients with a family history of breast cancer
Specifications (2)

Systems design for prevention of colorectal cancer in Lynch Syndrome

*Main author: Carla Van El*

Specific focus on: the population covered by the Thames Valley Network (~2.4 million) and the population covered by AMC, VUMC and NKI onco-genetic services from the province of North Holland, Netherlands (~2.7 million).

Specifications (3)

Monogenic Cardiovascular Disease: Designing Systems to Deliver Personalized Care

*Main author: Dina Vojinovic*

System specifications for:
- Long QTS syndrome: for
  - 1) individuals with known LQTS;
  - 2) family members of individuals with LQTS that have not themselves been identified as having it
- Familial hypercholesterolemia: for
  - 1) individuals with known FH;
  - 2) family members of individuals with FH that have not themselves been identified as having it
Core competences in genetics for physicians and other healthcare professionals

(Task leader: UCSC)

**Aim:** to identify the core competences in genetics for physicians not specialized in genetics and for graduated healthcare professionals other than physicians. For the latter category, we differentiated among those healthcare professionals working in genetic services, and all the others.

**Methods:** we performed a systematic review to identify potential items that might contribute to the competences, and subsequently we proposed such items for evaluation to a group of experts through a Delphi procedure

**Results:** three documents identified from the systematic review, starting from 217 articles.

- “Core Competences in Genetics for Health Professionals in Europe” – ESHG
- “Core Competencies in Genetics for Health Professionals” – NCHPEG
- “Learning outcomes in genetics and genomics for specialty trainees in non-genetic specialties” - UK NHS NGGEC

**Three curricula** produced, structured in four sections:

- Knowledge
- Attitudes
- Abilities
- Final competences

- Physicians (excluding geneticists)
- Healthcare professionals (not physicians) working in genetic services
- Other healthcare professionals
Participation of the University of Debrecen in PRECeDI
January 2015 - February 2017

Róza Ádány MD, PhD, DSc
Department of Preventive Medicine
Faculty of Public Health
University of Debrecen

Secondments (University of Debrecen)

<table>
<thead>
<tr>
<th>Name</th>
<th>Date (duration)</th>
<th>Seconded to Organisation (Short Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klára Bíró</td>
<td>August - October 2015 (3 months)</td>
<td>Better Value Healthcare Ltd (Oxford)</td>
</tr>
<tr>
<td>Viktor Dombrádi</td>
<td>September - November 2016 (3 months)</td>
<td>Better Value Healthcare Ltd (Oxford)</td>
</tr>
<tr>
<td>Péter Pikó</td>
<td>September 2016 – February 2017 (6 months)</td>
<td>EUPHA (Amsterdam)</td>
</tr>
<tr>
<td>Dániel Törőcsik</td>
<td>May - June 2017 (2 months)</td>
<td>Myriad Genetics Srl (Milan)</td>
</tr>
<tr>
<td>Gergely Fürjes</td>
<td>January - June 2017 (6 months)</td>
<td>LINKCARE (Barcelona)</td>
</tr>
</tbody>
</table>
Secondment – BVHC, Oxford

Participants: Klára Bíró, Viktor Dombrádi
Topics:
- Diabetes and personalized prevention
- Identifying the connection between the concept of value and genomics
Outcomes:
- Manuscript ready for submission
Title: Creating a common language: defining individualized, personalized, and precision prevention in public health
Authors: Klára Bíró, Viktor Dombrádi, Anant Jani, Tyra Lagerberg, Klára Boruzs, Muir Gray
- Manuscript in preparation
Title: Assessing genomic screenings of chronic diseases through the lens of the Triple Value Healthcare paradigm
Authors: Viktor Dombrádi, Erica Pitini, Carla G. van El, Anant Jani, Martina Cornel, Paolo Villari, Muir Gray, Klára Bíró

Secondment – EUPHA, Utrecht (VUMC, Amsterdam)

Participant: Péter Pikó
Topics:
- Preparation of EUPHA Factsheet on Personalized Medicine
- Overview of health policy implications of cluster screening of familial hypercholesterolaemia in the Netherlands;
- Qualitative research by interviewing key actors in public health and FH screening
Expected outcomes:
- EUPHA Factsheet published
- Sociotechnical report about the familial hypercholesterolemia entitled "How actively can you inform healthy family of index patient expected familial hypercholesterolemia?"
Secondment – Linkcare, Barcelona

Participant: Gergely Fürjes

*Topic:* IT support to screening colorectal cancer; investigation of usefulness of newly developed tools at the level of primary care

*Expected outcome:* report on adoption of IT tools at primary care level

Topic and expected outcome are on development.

Secondment – Myriad, Milan

Participant: Dániel Törőcsik

*Topic:* Biomarkers in diagnosis, prognosis and prediction of malignancies with a special focus on melanoma malignum

*Expected outcome:* publicly available overview on the recently identified biomarkers (pros and cons, limits and possibilities in the future development of personalized medicine and prevention)
Round table on „The impact of new and emerging technologies”
9th European Public Health Conference,
Vienna, 9-12 November 2016
13:50-14:50, 10th November 2016

Chairperson(s): Maaike de Vries - The Netherlands
Setting the scene: outcomes of a technology scan - Jacqueline Pot – The Netherlands

Panelists:

Róza Ádány – Public Health Genomics Section, EUPHA
Clayton Hamilton – WHO Regional Office for Europe
Nick Guldemond - Erasmus University, Rotterdam, The Netherlands
Supervisory Board - Agenda

- **14:00-14:15** General overview of the Project progress
- **14:15-14:30** First Interim Report
- **14:30-14:45** First Interim Financial report
- **14:45-15:15** The Secondment Plan (discussion and finalization of the secondment plan)
- **15:15-16:30** Overview of the Research Workpackages (discussion among partners)
- **16:30-16:40** Organization of the Plenary Meeting - Oxford
- **16:40-16:50** Next steps
- **16.50–17.00** Question and Answer

Plenary Meeting - Oxford

20-21 September 2017

20/09 from 2pm to 6 pm
21/09 from 9am to 1 pm

Supervisory Board Meeting and Internal Workshop at the same time
### Main Activities:
- Duration: 48 months
- Preliminary Training (T): M6
- Secondments (S): from M8 to M32
- Knowledge return: after secondment to M40
- Dissemination: ongoing + Seminar and Final Conference

### Supervisory Board Agenda
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- **16.50–17.00** Question and Answer
NEXT STEP

- **Plenary Meeting (BVHC – 20-21 September 2017)**
- **Organization of the second open seminar (M38)** - A 2-day practical multi-disciplinary seminar on “Policy Development in PM” will be held at M38- Feb 2018 at VUMC

Supervisory Board

THANKS FOR THE ATTENTION!