Workshop 4

Successful PM approaches in Oncology and Rare Diseases

Why focus on rare diseases is worth.

A lot has been learned at molecular level.
➔ <u>Genomics</u> has indeed been disruptive.

However,
treatments are available only to a limited extent.
➔ <u>Genomics potential</u> far from being fully exploited.

Human genomes are regulated in a complex way, interdependently, interactively.

Discovery of coherent biological signatures needs to incorporate an increased complexity from which to predict phenotypic outcomes

However, predictive models are humans-mediated measures, prone to various biases, and including the inherent systemic stochastic uncertainties.

When clinical outcomes need modeling, comparisons among approaches and integration among omics critical to aid clinical decision making.

When multi-omics is not a possibility, cross-validating heterogeneous data from multiple cohorts is a necessity necessitating interoperability of the associated clinical and laboratory data.

Precision medicine is shifting this paradigm, as further benefit is seeked from other data types,

such as imaging and electronic medical records.

Clinical trials

Impacts from **re-phenotyping**, due to

❑ NGS-driven molecular profiling, together with clinical profiles

❑ Expansion by multiple omics dimensions of the etiology of oncogenesis and cancer progression

❑ Similar efforts should be done on chronic diseases

❑ Pharmacogenomics to tailor treatment

❑ Regulatory framework to provide PM research strategies and scientific advice

Rare vs common/multifactorial diseases

1. *Common perception of complementarity, but space for transferring of knowledge between them.*

2. *Common diseases or side effects becoming - once deconvoluted - similar to rare diseases as we learn more from the molecular etiology*

3. *Rare diseases expected to be subject to re-assessment in light of the Big Data.*

The challenges are:

➢ **Clinical intervention level**: in relatively fast time by enabling effective **translational research**.

➢ **Big data relevance:** both social and economic value

➢ Better use of **evidence-based data** to foster the utility of **Clinical Decision Support Systems**

Bottlenecks toward PM

- Generation of cost-effective high-throughput data
- Different regulatory framework for oncology drug development versus rare diseases
- Lack of EU harmonization with regard to reimboursement criteria
- Hybrid education and multidisciplinary teams
- Safe and sustained Data storage, integration, processing and interpretation
- Respect of privacy and rights of the individuals
- Making meaningful clinical use of biomarkers (ex liquid biopsy could add significant value due to rapid and economical evaluation)
- Individual and global economic relevance
- Pharma industry in support of research involving genetics

Engagement

Health Professionals ⟷ People

Missing links.

- Education to Personalized Medicine, Individualized Care, Targeted Therapies, etc. N-of-1 medicine

- Communication strategies, shared decision making

- Data Protection & share policies, Data consent, satisfaction scores, etc. **taking an active role**

- Quantified self and people-integrated data (the earlier the engagement the better)

    Standards for classification needed

Use Case 1

Implementation of WGS based diagnostics for rare inherited disorders into clinical routine at large scale

Academia and healthcare collab:

3 departments in the Karolinska university hospital (collab **SciLife lab**, at Karolinska and KTH universities)

Context: 15 different disease categories

(metabolic disorders, syndromes, primary immunodeficiencies, skeletal dysplasia, epilepsy, neuromuscular disorders, etc).

For each category, **cross-disciplinary teams** involved, including clinicians responsible for patient treatment.

Similar approaches, which at present pertain mostly to the diagnostic arena, are followed in other countries/institutions.

In most cases, the WGS based test is the first line diagnostic test. Basis for payment provided by the regional healthcare.

Measures of success

- Since start (Jan 2014) > 2500 samples analysed (WGS/WES), from about 2000 unique patient cases.

- Currently, 100-120 samples are received monthly

(annual volume of 1200-1500 cases).

- Analyses done in 5-20 days, (monthly average 10-14 days)

- 25-60% of patients receive a diagnosis. For example, metabolic disorders are about 35%, while certain epilepsies are >50%.

Generated Value

Workflow for <u>rapid processing of data</u> plus interfaces supporting <u>clinical decision making</u>.

➔ **Benefit for 30-60% of patients receiving a diagnosis**.

Ability to test also urgent clinical cases (e.g., neonatal intensive care unit cases) for the identification of disorders prone to early treatment.

Scalability of strategy toward other disease categories.

➔ **WGS-based rare disease diagnostics at national scale**

Discovery of new disease causing genes

Key challenges

- Initial funding to reach self-sustainability
- WGS data processing timely and reducing complexity to clinical tractability (minutes and hours rather than days)
- Recruitment of quant (bioinformatics) personnel
- Clinical interpretation.
- Reimbursement policies differ from country to country, sometimes even regionally
- VUS

Use Case 2

Entrectinib, an innovative drug as an example of PM approach

Nerviano Medical Sciences (NMS) (Italy): R&D focus, new oncological drugs

Ex: **entrectinib**, a potent selective <u>tyrosine kinase inhibitor</u> of the proteins encoded by the NTRK1,2 and 3, ROS1, and ALK genes, was discovered.

· The drug designed to target activating <u>alterations of these genes, which can be found in small subsets of different tumors.</u>

The tumor types include NSCLC, mCRC, salivary gland cancer, sarcoma, melanoma, thyroid cancer, glioblastoma, astrocytoma, cholangiocarcinoma, lymphoma, and others.

·

NMS developed etrectinib up to the **first Phase I trial** at Istituto Nazionale dei Tumori and Ospedale Niguarda Ca' Granda.

While ALK and ROS rearrangements were already known, the validation of TRK as a target in CRC resulted from a collab between NMS and Ospedale Niguarda Ca' Granda

This included the identification of a <u>novel LMNA–NTRK1 activating rearrangement in a patient</u> who was treated with entrectinib and achieved a partial response
➔ **first clinical evidence of efficacy for therapeutic inhibition of TrkA using a Trk inhibitor in a solid tumor.**
.
NMS licensed entrectinib to Ignyta, a Nasdaq-listed oncology Prec Med biotech, who is completing development of the drug

A Phase II basket trial with potential for registration is ongoing, enrolling patients with diverse tumors harboring alterations of the entrectinib targets.

Key Challenge:

Patient identification **based on target activation**, TRK or ROS rearrangements, across different tumor types

Value:

- *Novel target validation*: **One of the very few actionable molecular targets in colorectal cancer**, validated as a result of preclinical and clinical scientific collaboration

- *Paradigm shift*: **approach to registration in RK+ tumors** independently from tissue origin, one of the first examples of "**tissue agnostic**" drug development

- *Clinical value*: **Breakthrough therapy designation** obtained by **entrectinib** for use as a treatment for adult and pediatric patients with **NTRK-positive**, locally advanced or metastatic solid tumors , which is granted by FDA when "preliminary clinical evidence indicates the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints ". **>75% RR observed in ROS positive NSCLC**, including patients with brain metastases, with very tolerable safety profile

Use Case 3

EGFR inhibitor drug repositioning for the treatment of chordomas

The Istituto Nazionale dei Tumori (INT) is a reference center for the treatment of **chordomas**, a rare type of cancer arising along the axial skeleton, slowly growing but characterized by a high recurrence rate, extremely disabling and usually fatal for patients.

No standard therapy has been approved against chordomas not responsive to chemotherapy.

Within a scientific collaboration with INT, NMS **screened a panel of different chordoma cell lines with drugs already approved**, and therefore of immediate therapeutic potential for patients.
.

This effort led to the identification of an approved EGFR inhibitor as the only drug displaying potent and broad anti-proliferative activity in vitro and in vivo in different chordoma PDX models.

NGS data on the chordoma cell line panel are being used to identify predictive biomarkers of preferential sensitivity to the drug

These data provided the basis for an upcoming European phase II study supported by the Chordoma Foundation, the major patient advocacy group.

Use Case 4

Ongoing work to establish a multi-site cancer institute with ability to run clinical trials for oncology

Involved 6 comprehensive cancer centres in Europe (Cancer Core Europe) for carrying out clinical trials in a basket-of-basket based design.

Cancer Core Europe (http://www.cancercoreeurope.eu/)

discussions with pharma regarding funding

Key challenges and value

CH: Harmonise the diagnostic/testing workflows, including nucleic acid extractions, and data (generation - analysis – interpretation)

Value:

- Patients: Access to clinical trials (most partners have a too small population base)

- Healthcare: Ability to run clinical trials more efficiently, as well as to recruit patients into trials

- Pharma: Access to a strong partner that can recruit patients quickly as well as at lower cost compared to alternative strategies (e.g., screening cost can be shared between all companies)

Use Case 5
LKarge scale risk prediction of cardiovascular disease in (occupational) health care to motivate life style changes (ongoing project)

- Public-Private collaboration, seed funding from Finnish Funding Agency for Innovation
- Players: Institute for Molecular Medicine Finland (FIMM), Mehiläinen (private hospital), Finnish Red Cross Blood service, Carea (regional hospital)
- Aims: to test in large scale healthcare setting
1) whether a comprehensive risk assessment utilizing both traditional and genetic risk factors can motivate a long lasting change in lifestyle for improving health/disease prevention;
2) how do individuals participating in the project experience the use of genetic information;
3) development of web-based tools to communicate health risk
- 10,000 individuals to be engaged and followed up utilizing national health/hospital registries

Translating genomic risk into health care
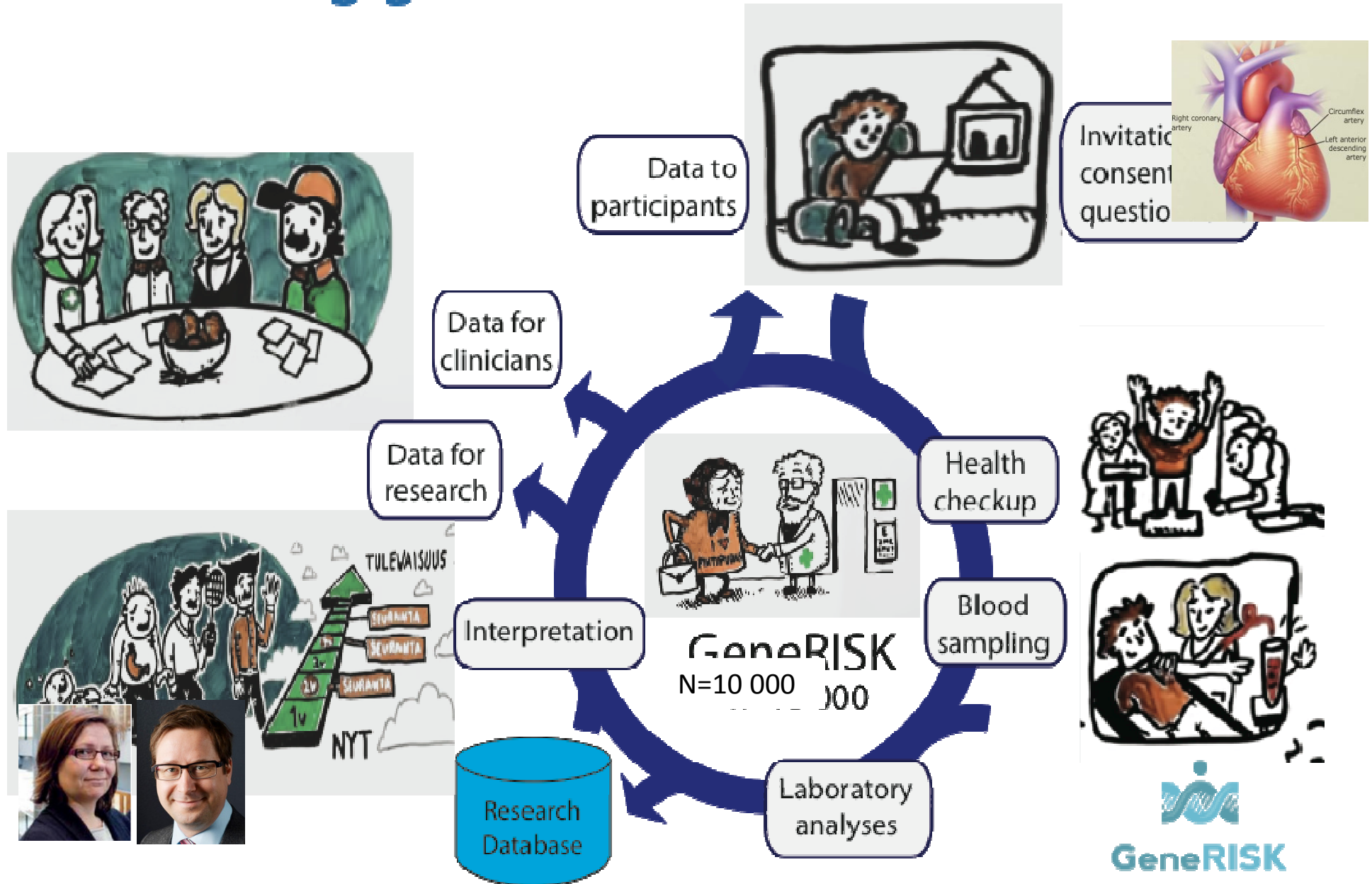
Measures of success

- First large scale proof-of-concept for utilizing complex disease genetic risk data in healthcare setting

- Since start (2015) > 6800 individuals recruited and samples analysed

- CHD risk estimation performed and returned for 5500 individuals

- Web tool to share risk information to participants

Example 6
Individual Systems Medicine (ISM) to impact on treatment of leukemia

- Ongoing national collaboration: FIMM and all university hospitals of Finland
- Aim: to improve treatment of hematological cancers by usage of systems medicine approach
- Systems analysis of patients diagnosed with AML (in vitro drug sensitivity and resistance analysis with 143 approved cancer drugs and 319 investigational drugs, genomics, transcriptomics, phospoprotein analysis) with a rapid return of the data to clinic to be utilized in treatment selection

Measures of success

- Rapid data return (4 days for drug sensitivity and resistance, 2 weeks for genomics profiling) to allow clinical utility
- Clinical translation was performed for 18 out of 52 relapsed and refractory AML patients (35%) based on drug testing
- 7/18 (39%) led to complete remission or morphologic leukemia-free state
- Set up described in more detail (see Pemovska *et al.*, Cancer Disc 3:1416-1429, 2013)
- Scalability of the strategy toward other haematological malignancies (> 200 multiple myeloma patients already screened)
- Set up allows testing of investigational drugs in primary patient cells (collaboration with drug companies)

Challenges

- Scalability of the strategy towards solid cancers ongoing but requires further development

- How to move forward to a clinical trial after successful proof-of-concept

Use Case 7
Data quality & standards

Pre-analytical errors account for about 70% of laboratory diagnostics errors, due to mishandling of samples during their collection, handling, preparing and storing.

BBMRI-ERIC last year gathered 89 experts from 18 Members States into 5 different quality working groups who completed joint intra-biobank and inter-biobank benchmarking against the CEN/TS Molecular in vitro diagnostics examinations – specifications for pre-examination processes.

This benchmarking effort resulted in improved samples handing procedures and documentation, motivating the practice of sample standardising and harmonising the processes in Europe.

Now published as Self-Assessment Surveys based on the 9 existing CEN/TS by which the biobanks are able to see if, and how well, their existing collections meet the CEN specifications, helping biobanks to implement their quality requirements and asses their performance.

Use Case 9:

Implementation of Personalized Medicine in Primary Care

Aim of the Pilot

- To evaluate patients' benefits, the process feasibility as well as the usability and acceptance of the PerforM - Perzonalized Information for Medication - report by the physicians.

Pilot description

- Participants
  - Practitioners of PNS (**P**raxisnetz **N**ürnberg **S**üd e.V. with 98 physicians)
  - 100 difficult to medicate polypharmacy patients
- Quality Control
  Automatically generated PerforM reports reviewed beforehand by a geriatrician and a clinical pharmacologist (UKSH, Kiel)
- Evaluation
- Pharmacogenetic data analysis by the Institute of Clinical Pharmacology, UKSH
- Evaluation of PerforM report acceptance, healthcare economy aspects and influence on the physician's medication decision by Wilhelm Löhe Hochschule, Fürth

Measures of Success

1.- To overcome the challenges practitioners ace in day-to-day work by means of digital pharmacogenetics

- Patients often take 5 or more drugs

- Patients frequently show ADRs

- Patients do not show therapeutic success

- Compliance problems. These patients show up frequently

- Most of them are elderly multi-morbid patients suffering from
e.g. coronary heart diseases, hypertension, diabetes, pain, depression

- Practitioners either have the time nor want to become experts in pharmacogenetics. However they would like to apply this knowhow to their patients

2.- To provide the information practitioners need to individually optimise the treatment:
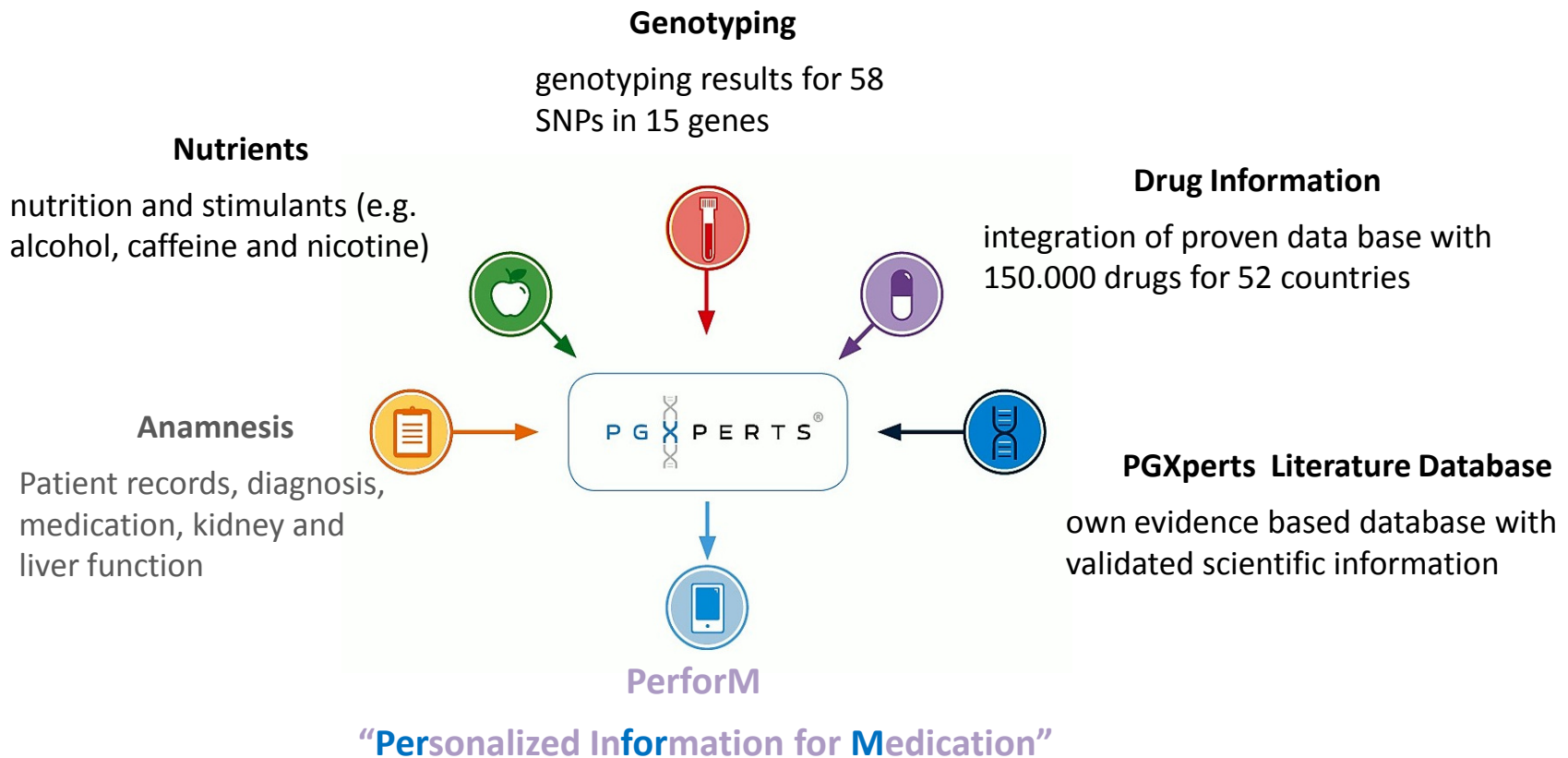
- The **pharmacogenetic patient profile** (PGx-profile) and **its clinical consequences**

- A drug interaction (DI) check for the prescribed medication

- Drug alternatives considering diagnosis, PGx-profile and DI

- All information in one personalised report:
  o Easy to read and understand
  o Well structured
  o Self-contained
  o Evidenced based
  o State-of-the art information

3.- To achieve a turnaround time of total max. 3 days as a result of fast interpretation algorithms bring genetics to family doctors

Generated value

A highly sophisticated expert system (PGXperts platform) has been developed and validated for routine clinical work as well as executing clinical studies.

PGXperts **interprets** the genotyping results, **checks** drug interactions and **correlates** all of them with additional data from the patient's health record and life style, enabling the physician to optimise the medication individually.

Genotyping

genotyping results for 58 SNPs in 15 genes

Nutrients

nutrition and stimulants (e.g. alcohol, caffeine and nicotine)

Drug Information

integration of proven data base with 150.000 drugs for 52 countries

Anamnesis

Patient records, diagnosis, medication, kidney and liver function

PGXPERTS®

PGXperts Literature Database

own evidence based database with validated scientific information

PerforM

"**Pe**rsonalized **Infor**mation for **M**edication"

www. hmg-systems-engineering.com & www.pgxperts.com

Key challenges

1.- Reimbursement

2.- Acceptance from Physicians at the clinics

3.- Standardization on the interpretation

4.- European on level of evidence required to provide information as required to optimize medication

5.- Cooperation in order to join efforts

Economic value of personalized tests (future disease onset, response to treatment, …)

Define/redefine a business model needed to guide investments and policy decisions

1. Need to have a robust system, harmonization needed at many levels

   (say, reimbursement system is key, but fragmented)

2. Expand the networks and integrate public, private sectors, HTA, regulators.

3. Specialized subjects might need more data/evidence exchange

   - relevance of validating in pan cancers
   - catalogs of success stories and curated DBs