public health genomics
European Network

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European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies

PART II
European Best Practice Guidelines for Provision of Genome-based Information and Technologies

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1. Executive summary

Provision WP defines what, how and in what way (including general policy issues) genome-based services can be introduced in the system of healthcare developing Best Practice Guidelines for the Provision of Genome-based Information and Technologies.

The provision pillar established:
WHAT: which kind of genomic technology and genomic information can be transferred from the research setting to the system of health Care.

HOW: in order to introduce the genome-based information into Public Health it's important to validate technology in the diagnostic setting (HTA-Health Technology Assessment) and to establish a clear relationship between genomic information and contemporary methods of translation of medical research, including clinical utility and clinical validity.

IN WHAT WAY: The WP defines how to supply a good communication, the training requirements and competencies for the professionals to be involved in public health genomics-based interventions and technologies and also help decision makers to understand the genomic implications in decision making processes and to choose the "right health services for the right groups of patients and subpopulations".

WP also provides guidelines for decision makers to set up priorities in their acts by integrating both cost effectiveness and regional specific issues. WP revises the existing guidelines in order to fill any possible gap. To achieve these goals the WP considers the choice of stakeholders in different settings, both in health care systems and on markets; the main stakeholders are:

- Public policy makers/ decision-makers at European Union and National level
- Professional bodies and institutions in the health sector/Public Health Sector
- Patient organizations and lay people groups such as the European Organization for Rare Diseases (EURORDIS)
- Media companies and individual journalists
- Health products (e. g., in vitro diagnosis medical devices) industry
- Schools of Public Health
- Schools training Health Professionals
- Scientific/Professional/Civic organizations such as EUPHA, ASPHER, European Society of Human Genetics, European Science Foundation, European Public Health Alliance (EPHA) etc.

2. Specification of the pillar / working definition

2.1 General objective of the pillar: (perspective / definition)

The pillar is divided into tasks that cover the related fields such as:

Monitor health
Diagnose & Investigate
Inform, Educate, Empower
Mobilize Community Partnerships
Develop Policies
Enforce Laws
Link to/provide health care
Assure competent Workforce
Evaluate

Each task is dissected and discussed according to the followings:

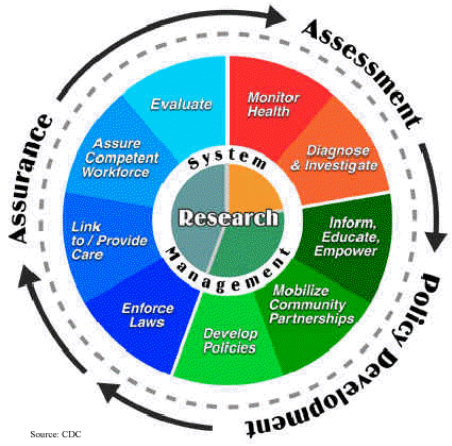
1. *State of the art (present practice)*

Description of the issue including short historical background. This part of the frame is targeted to give the necessary knowledge about the problem including the justification of its importance which should be supported by the incidence of the policy documents on the EU and, in case of necessity, national level.
The following subdivisions of the presentation of the recent practices in the area are proposed:
a. Present policy-related practices on the EU level (including legislative and regulative documents describing the state of affairs regarding the issue).
b. Present policy-related practices on the national levels (if applicable). The examples of policy actions as well as legislative acts (laws and regulations) can be provided in order to explain the present situation in the area and underline its importance.
c. Conclusions related to the field from former EU projects summarising the advances in the area based on the EU funded projects and its conclusions.

2. Focus points and policy-related priorities in the area
In this part the attention is paid to the general values held by the Institutions in the EU concerning the area.

3. Gaps identified (needs not reflected or not tackled properly by former policy guidelines)
This part of the framework draws conclusions from the previous chapters and points out the issues, linked to the area discussed, which in the present are missing guidance on the European level, but which are or will become increasingly important in the upcoming years.

4. Present proposal to the guideline (following the steps of the wheel)
This part presents the possible solutions on the meta-level for the gaps identified previously.



2.2. Specific objectives of the pillar (target audience)

What should be done for quality and successful monitoring of population health?

What should professionals do in order to diagnose and investigate?

What should professionals do to inform and educate?

What should professionals do to mobilize community partnerships?

How policies are developed? By whom? When?

How can professionals influence law enforcement? Which laws can protect their interests?

How professionals can provide health care?

What training should workforce get?

How should evaluation be done? Using which methods?

2.3. Working group members and task allocation

MEMBERS

Core WP Group Members

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  - Osteba, Basque Office for HTA. Dept. of Health and Consumer Affairs, Basque Government. Basque Country Spain

TASK ALLOCATION

Monitor health

What should be done for quality and successful monitoring of population health?

1. Professional Ethics
2. ELSI
3. Overview of health monitoring and health priority setting systems
4. ICD 11 considerations

Persons to be responsible:

- Ilona Koupil, Amal Khanolkar; Centre for Health Equity Studies (CHESS) Stockholm University/Karolinska Institutet
- Pal Moller; Norwegian Group on Inherited Cancer, Norway

Diagnose & Investigate

What should professionals do in order to diagnose and investigate?

1. Clinical guidelines on diagnostics
2. Genetic screening
3. Genetic screening of newborns
4. Priority setting

Persons to be responsible:

- Domenico Coviello, Elia Casati; Fondazione IRCCS, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Italy
- Henk van Kranen; RIMV, the Netherlands
- Bodo Lange; Max Planck Institute for Molecular Genetics, Germany

POLICY DEVELOPMENT

Inform, Educate, Empower

What should professionals do to inform and educate?

1. Genetic/Genomic counselling
2. Risk communication
3. Media communication
4. Class education/ school education/ improvement of curricula of relevant courses

5. Establishment of information campaigns
6. Role of professionals involved in GTg
7. The role of persons/citizens
8. Health literacy

Persons to be responsible:

- Pal Moller; Norwegian Group on Inherited Cancer, Norway
- Domenico Coviello, Elia Casati; Fondazione IRCCS, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Italy
- Iñaki Gutiérrez Ibarluzea; Osteba, Basque Office for HTA. Dept. of Health and Consumer Affairs, Basque Country Spain
- Stoyanka Popova, Klara Dokova; Medical University of Varna, Faculty of Public Health, Bulgaria

<u>Mobilize Community Partnerships</u>

What should professionals do to mobilize community partnerships?

1. Education of professionals in professional-public communication
2. Information campaigns on mobilisation issues
3. Support of the activities of the NGOs
4. PPP and incentives

Persons to be responsible:

- João Lavinha ; Instituto Nacional de Saude Dr Ricardo Jorge, Portugal
- Róza Ádány, Daniel Torocsik; University of Debrecen, Medical and Health Science Centre, Hungary
- Pal Moller; Norwegian Group on Inherited Cancer, Norway
- Domenico Coviello, Elia Casati; Fondazione IRCCS, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Italy

<u>Develop Policies</u>

How policies are developed? By whom? When?

1. Setting objectives
2. Allocation of funds
3. Establishment of necessary facilities
4. Introduction of new genome-based innovations to HC
5. Participation of medical professionals in policy development
6. Epigenetical influence on policy development

Persons to be responsible:

- Iñaki Gutiérrez Ibarluzea; Osteba, Basque Office for HTA. Dept. of Health and Consumer Affairs, Basque Country Spain
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- Elena Syurina; Institute for Public Health Genomics, University of Maastricht

ASSURANCE

Enforce Laws

How can professionals influence law enforcement? Which laws can protect their interests?

1. Protection of genetic information
2. Protection of rights of professionals
3. Intellectual property
4. Access to data

Persons to be responsible:

- *Maastricht group*
- Pal Moller; Norwegian Group on Inherited Cancer, Norway (just for consulting and making criticism on the product)

Link to/provide health care

How professionals can provide health care?

1. Clinical guidelines
2. Standards for provision of HC
3. Access to samples
4. Provision of facilities
5. Preventive interventions
6. Pharmocogenomics
7. Epigenomic effects on HC

Persons to be responsible:

- Bodo Lange, Max Planck Institute for Molecular Genetics, Germany;
- Wolfgang Hoeppner, BioGlobe GmBH, Germany

Assure competent Workforce

What training should workforce get?

1. Education of the medical and health professionals
2. Education of the decision makers at the meso and macro levels
3. Education of professionals involved in quality controlling and improvement
4. Education of professionals in health technology assessment

What kind of infrastructure and organization professionals should have?

Persons to be responsible:

- Róza Ádány, Daniel Torocsik; University of Debrecen, Medical and Health Science Centre, Hungary

Evaluate

How should evaluation be done? Using which methods?

1. Provision of monitoring services
2. Guidelines for professionals on monitoring and data use

Persons to be responsible:

- Róza Ádány, Daniel Torocsik; University of Debrecen, Medical and Health Science Centre, Hungary
- Ilona Koupil; Centre for Health Equity Studies (CHESS) Stockholm University/Karolinska Institutet

2.4. Background documentations

Monitor Health

Identified issue

We are addressing here the following identified issue:

The assessment work brought up the following useful findings

Background

3.1 Monitor Health

This function corresponds to the surveillance function in public health which can be viewed as (broad interpretation) applying to two objects:

a) health problems:
   - this corresponds to health needs assessment (epidemiology, burden of disease, users' perception of needs…)
   - guidance can help define what information should be collected and how…

b) emerging technologies:
   - this can be organised as a form of horizon scanning to scan for potential solutions/options to address health needs…
   - guidance on how to organise knowledge transfer from basic research and horizon scanning ….

There has been a long history and development of the monitoring function in public health in the European region that resulted into a variety of systems in different regions/countries today. Progress in standardising of the monitoring systems and a synchronised compilation of relevant and timely information for the whole region and beyond has been most marked in the area of communicable disease (ref to ECDC activities).

New developments in genomics together with the emerging evidence of life course and developmental origins of health and disease (DOHaD; Gluckman et al. 2008) and their application for improving population health in the European region pose new challenges to our existing routine monitoring systems.

The main challenges and opportunities for further development of our monitoring systems can be summarised as:

- need for monitoring of health and health needs for groups of individuals such as families with possible need for monitoring over more than two generations (for conditions that are partly or fully genetically determined or originate in exposures of previous generations)
- need for monitoring of exposure and health outcomes and possibility to link relevant data across the life course of individuals from in-utero till old age. Repeated measurements of e.g. linear growth, overweight and obesity are of particular importance in predicting and managing circulatory disease since a combination of low birth weight and later obesity has been shown to considerably increase risk of circulatory disease
- need for monitoring of health needs and health outcomes for social groups defined in terms of ethnicity, migration status, socioeconomic position, region of residence, gender, age etc. to address health inequalities and assure equitable access to new and old technologies and information
- need for monitoring of risks and health needs in a global perspective stretching beyond European boarders that are particularly relevant for issues like drug resistance or emerging infections
- we should consider introducing new monitoring systems for detecting problems and improving health of groups that had not been subjects to intensive screening before such as e.g. prospective parents and women of childbearing age (as a prevention of long term consequences of exposures acting around conception and in utero such as maternal diet)

A need for multiple ways of analysis of data from the monitoring system calls for a standardised methodology and a possibility for linkages of data from different sources that would allow easy comparisons across social groups, gender, geographical areas, ethnic groups with a possible identification of family links in the data (by e.g. combining data from biobanks, screening, social and health care use registers).

Genomic, life course and DOHaD research has identified numerous examples of “shared” causes of later health, social and behavioural problems (including criminality) and our approach to monitoring should reflect this by encouraging and allowing data sharing not only between different medical disciplines but also with other actors involved in health and social care.

Ongoing re-definition of disease categories that is particularly discussed in the area of psychiatric disease and behavioural problems poses yet another challenge in terms of a need for collecting information on specific symptoms and life histories.

It is very likely that further development of our monitoring systems (even with effort for collaboration and data sharing that can prevent excessive or unnecessary data collection) will results in large amounts of information being collected by on-going

monitoring. Timely and practical technical solutions for management of large amount of data, analysis of serial measurements and data clustered at family and other levels will be needed. Statistical data reduction techniques that make full use of the wealth of information we are collecting, will become very important for our analyses and evaluations.

It is important to promote use of data from the monitoring systems and assure access to information for many different actors in the public health system as well as allow this valuable information to be used for further research and advancing of our knowledge.

Best practice example: routine data from health and social registers have been used successfully and extensively in epidemiological and public health research and planning in Scandinavian countries (Koupil 2007).

The new monitoring system should make it possible to identify vulnerable individuals, relations, families, social groups without stigmatising them and without bringing about any negative consequences for their subsequent "life choices" (insurance, job, partner selection…).

The new monitoring system has to follow the ethical principles and rest on evaluation of potential risks (integrity of individuals, families and social groups; stigmatisation, potential negative impact on social career etc.) and benefits defined at a level of individual person as well as population groups.

Our ability to implement knowledge and new technologies in the genomics area is based on a long history of research, some of which made use of data from routine monitoring systems. Our responsibility in designing a new monitoring system is to allow ongoing evaluation and research that, in turn, will further enhance our ability to prevent and manage ill health in future generations.

We have to make sure that data from new monitoring schemes will be widely available to researchers and policy makers for continuing evaluations, quality assurance and research. We should indeed discuss and consider setting up of new research projects and evaluation efforts that would encompass several disciplines and combine different types of data (such as e.g. the success of Swedish epidemiological research based on combining data from registers with individually collected biological samples, questionnaires, tests etc. Koupil 2007; Koupil & Goodman 2011).

Evaluation of the impact on health equity has to be a core part of any evaluation scheme not only in the area of genomics but in any public health intervention generally.

Best practice example: Cochrane collaboration pays increasing attention to impact on equity and work on developing/standardising methods for evaluation of impact on equity (http://equity.cochrane.org/)

It is important to find out how far our current criteria for assessing efficacy, effectiveness and efficiency of interventions are also valid and sufficient for evaluation of interventions and policies based on developments in public health genomics. There has been a lot of development in the field of "causal inference" and the traditional epidemiological approaches to assessing causality have been revisited recently (Hernán 2004; Hernán & Robins 2006). The philosophy and the technical solutions form the causal inference research can be applied to our evaluation of new technologies and policies.

Together with a rigorous application of methods for detecting of causal effects, the apparent importance of individual and family histories in influencing the natural history of a disease seems to call for adaptation of our common designs and possible greater role of cross-over and/or innovative family designs, possibly extended to multigenerational approaches.

The success of collaborative efforts in evaluation of interventions by e.g. the Cochrane data base (Cochrane Collaboration, Cochrane Library) shows the potential of coordinated approach to evaluation of new technologies and to information sharing.

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3.2 Diagnose and Investigate

What should professional do in order to diagnose and investigate?

BACKGROUND

a) Clinical Guidelines on Diagnostics

By more than two decades, the diagnostic testing, presymptomatic testing and tests for the identification of healthy carriers of rare genetic diseases are used in medicine. The general guidelines for their use in clinical practice have been well-defined and shared internationally. The situation is different for complex diseases, because the development of knowledge on genetic factors obtained through genome-wide association studies has occurred in the last 4-5 years, and the results obtained to date are not easy to be interpreted in a health perspective, due to the modest influence of the polymorphisms so far identified with this approach (1).

Given that the use of tests of susceptibility to complex diseases is in a less advanced stage of testing for rare genetic diseases, for them it is necessary to identify the general principles and modalities for their future clinical application, including the development and promotion of targeted project activities to a transfer real clinical impact knowledge, as soon as they become available.

Certainly it is undeniable the value of genomic reserch as a basis for understanding complex disease mechanism, and the possibility that this would, in the longer term, lead to effective and useful clinical and public health interventions.

The study of contribution of different genetic variants to the phenotypic development of disease, together with other advances in post-genomic science (such as comparative genomics, systems biology and epigenetics), have the potential to elucidate how genes and environment interact and together contribute to disease. It is likely that this information will also have an impact on therapy because they will allow to identify new targets for drugs; furthermore, this information will allow to understand which individuals, according to their genetic characteristics, are more or less sensitive to the therapeutic and side effects of pharmacotherapy (pharmacogenetics and pharmacogenomics). Treatments should thus be more effective because used in a more selective and personalized way, and therefore have the potential to result in less frequent adverse drug reactions.

The research undertaken in recent years using large-scale association studies and systematic sequencing of the genome of large samples of cases and controls and studies expected in the coming years should help to identify a number of polymorphisms pathogenetically related to common complex diseases.

Consequently, it is reasonable to expect a significant increase in the number of genetic tests potentially available, provided that their predictive power is likely to achieve clinical relevance.

This increased demand will be fueled in part by requests from the medical community and the demand from citizens, resulting in the dissemination of knowledge through the media. It should also be given the opportunity to grow the direct offer of testing to consumers by commercial companies.

The introduction of predictive tests for cancer diseases (eg. BRCA genes for breast cancer) is relatively recent and, in some way, already contains the problems of susceptibility tests for complex diseases, because in these forms there is often no pathognomonic signs of the disease, in contrast to rare hereditary disorders. Therefore, the suspicion of an inherited condition refers to arbitrary thresholds of "probability of mutation," based on personal and family history.

During this evaluation process is not possible to provide a personalized risk, but only a personalized consultancy, by which the person receiving the consultancy is in the condition of consciously choose the most appropriate options, in terms of secondary prevention / risk reduction, including prophylactic surgery.

At present, susceptibility testing for complex diseases have relatively limited applications, especially when compared to the huge number of genetic tests that are likely to become available with the progress of scientific knowledge. These tests exhibit unique characteristics compared to those used for other medical purposes. In particular, genetic polymorphisms involved in complex diseases identified to date are relatively frequent in the general population (they are often present in> 5% of the population).

These gene variants, rather than independently determining the risk of disease, modulate the effect of exposure to environmental factors. Thus the real contribution to determine the risk of disease is highly variable depending on the lifestyles and individual exposures. Moreover, in most cases, people who have these polymorphisms are not affected. The predictive power is therefore limited clinical usefulness generally unproven.

The impact of genetics in the short and medium terms on medical applications has probably been overestimated. However, it is possible to imagine a future in which the disease prevention and treatment plans will be scheduled on the single patient or groups of patients according to their genetic characteristics, and will be conducted by identifying early medical surveillance systems, changing lifestyles and diet, or by implementing targeted drug therapies. The integration of Genomics into Public Health can offer many potential benefits.

As a matter of facts the predictive genomics has already found some applications in practice: for this reason it is logical to assume that the new technologies and scientific progress, together with the organization of networks of excellence, partnership, public programs of intervention, would determine a significant impact in medical practice and public health in the near future (2).

In short, one of the main aims of the study of genomics is to understand because under the same environmental conditions only some people develop a specific disease and other do not. This information can improve health, especially through prevention interventions targeted to the individual. The consistency of a plan of predictive medicine can not be separated from achieving full integration with the existing prevention and screening programs of proven effectiveness, which are addressed to the population. Moreover, to ensure that genomic knowledge is integrated into health care programs and prevention in an appropriate manner, we need robust, confirmed and validated scientific data (*Evidence Based Medicine,* EBM); before the introduction and correct application of new genomic tests, it will be important to provide citizens and professionals with clear evidence-based

information about the applications of predictive genomic tests, including the implications that such information could have on the health of the person.
It is necessary to differentiate between the truly useful tests and the less useful ones or even potentially harmful.
To adequately support the choices made by decision-makers concerning the health of citizens, we need to have the best scientific evidence, and it is therefore necessary to refer to sources of information validated in an international context. Currently there are two accredited sources of this type: the U.S. Preventive Services Task Force (USPSTF) and the Genomic Applications in Practice and Prevention Network (GAPPNet, Genomic Applications in Practice and Prevention Network), described below. The USPSTF (http://www.uspreventiveservicestaskforce.org/) is an independent organization to produce evidence-based recommendations on the issues of prevention (screening, counseling and preventive drugs). The recommendations made are considered the "gold standard" for clinical preventive services.
GAPPNet was founded in 2009 by OPHG (Office of Public Health Genomics; http://www.cdc.gov/genomics/); the Office of Public Health Genomics (OPHG) aims to integrate genetic knowledge in research, in the policies and public health programs, to improve preventive interventions.
GAPPNet activity is aimed to collect information on potential areas of application of genomics in four critical areas:

A. synthesis of knowledge, dissemination of existing and emerging technologies, and identify knowledge gaps;
B. development of an evidence-based process to elaborate specific recommendations (built on the activity of EGAPP);
C. translational research, to test the validity, utility and impact of genomic applications in the real world;
D. establishment of programs of integration of genomics to improve health care quality.

b) Genomic Screening & Screening on Newborns
By contrast to genetic testing, the term genetic screening is used primarily for testing a large number of populations or sub-populations of mainly asymptomatic individuals who are tested if they might or might not be at increased genetic risk of a particular condition.
As science advances it becomes increasingly possible to screen for susceptibility to common disorders.
Based on genetic profiling of multiple low-penetrance genes, personalised health care would become possible, as compared to a more global approach to disease prevention centred on primary prevention and health promotion strategies which attempt to address the social, behavioral and environmental determinants of health.
Public Health activities traditionally associated with genetics include newborn screening, or screening in other periods of life, reproductive health programs and services of clinical genetics.

Because of the revolution that genomics is bringing in healthcare, it is necessary that its practical applications are extended beyond the traditional fields of Mendelian genetics and embrace programs for chronic diseases, infectious diseases, environmental hygiene, epidemiology, the study of social inequalities, and so on.
The consistency of a plan of predictive medicine is not possible without full integration with the already existing programs of prevention and screening of proven effectiveness that address to the population.
This strategic obligatory choice has to be put into practice involving the results of genomic research in the campaigns against smoking and against the abuse of alcohol, in oncology and neonatal screening programs, in monitoring plans and in primary prevention for the population.
Rapid advances in genetics and genomics are outpacing the ability to adequately integrate new discoveries into health services and have led to a growing implementation gap between what is technologically possible, what exists in practice and what is acceptable and desirable or clearly justifiable. There is increasing pressure to introduce or expand genetic screening programs, although evidence of the clinical validity and utility of screening tests is often lagging behind (3).
New forms of screening can help people to live longer and healthier lives, and avoid the symptoms and consequences of conditions. There are several developments both in the early detection of conditions and in treatments that make neonatal screening a topic of great importance.
The potentially broadening goals of NBS (from identifying conditions where irreparable health damage can be avoided by early diagnosis to include reduction of diagnostic odyssey) should be subject to public debate. Neonatal screening programs and related interventions should be defined in a way that they are consistent with the overall health care strategies, capacities and the culture of a country. The opportunity offered by neonatal screening should also be assessed taking into consideration the possibility of screening at a later life stage, for those goals (reproductive choices) and disorders where preventive intervention is still timely, so that participation in screening can be decided directly by the subject.
The primary aim of NBS programs is to improve the health status of infants with treatable conditions. A case definition of a specific “treatable condition” or “important health problem” is needed for the assessment of the evidence on a specific test and treatment. For this reason, in the current age of high throughput technology, a relevant question is whether each of the conditions in a NBS program needs to fulfill the criterion “important health problem”. Alternatively, a technological development could define a group of disorders to be identified by one technology. There may be reasons to group conditions, especially cost-effectiveness, but this does not detract from any requirement for each individual condition to adhere to the prerequisites that there must be effective interventions as well as good test performance, few adverse effects on the unaffected population and adequate services to look after the children. A responsible evaluation per disease is thus needed.
A relevant issue related to NBS is related to the unintended findings that may derive from neonatal screening tests with information on mild phenotypes, late-onset disorders or carrier status. This may require adaptation of test and automatic data

processing, for instance by using filters that limit the reporting of results to certain specific metabolites, values outside certain thresholds, or specific gene mutations.

d) Priority setting

In order to make interventions and actions in the field of Public Health Genomics, more effective, efficient and shared, new paths must be developed to ensure proper application of new knowledge in clinical practice. This process must be developed within a program of capacity building and communication that includes the creation of networks of excellence and the establishment of partnerships among stakeholders. In the context of Public Health Genomics, we can define the term capacity building as the ability to promote quality of life and health of citizens by improving the quality of supply and demand of genetic testing, the opportunities for the health system, the productivity of public and private enterprises, by favoring a climate of trust between the actors.

The Capacity Building Program in Public Health Genomics must be based on public organizations able to provide and build service networks and infrastructures, ensuring quality standards in public services, evaluate and select the best design ideas, manage and monitor the implementation of interventions (4).

To ensure effective and efficient development will however require modification to the organization of health care services. In some clinical areas this may build on the considerable expertise in specialist genetics services, which will be well-placed to show substantial leadership. The role of new genomic technologies in clinical specialties must be explored including, in all cases, consideration of how the necessary massive expansion of bioinformatics support can be developed and sustained. Any strategy should explicitly address how clinical and laboratory personnel can be trained and employed, so to retain expertise and competence whilst enabling increases in capacity. This may involve reconfiguration of laboratories, clinical services and their supporting systems.

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	Category	Organisation	Title of Document	Publication date	Scope of action
1	Resolution	EU	Resolution on Future community action in the field of Public health	1999	EU
2	Statement	WHO	Statement of the WHO Expert consultation on new developments in human Genetics	2000	Int
3	Statement - Recommendation	Human Genome Organization (HUGO)	Statement on Benefit Sharing	2000	Int

4	Report/article	European Society of Human Genetics about Provision of genetic services in Europe	Provision of Genetic Service in Europe: current practice and issues.	2001	EU
5	Report	WHO	Genomics and World Health	2002	Int
6	Report	WHO	Report of Meeting on Collaboration in Medical Genetics	2002	Int
7	Working document	Council of Europe: working party on human genetics	Working document on the applications of genetics for health purposes	2003	EU
8	Report	Public Health Genetics Unit, Cambridge Genetics Knowledge Park	Addressing Genetics Delivering Health: A strategy for advancing the dissemination and application of genetics knowledge throughout our health professions	2003	Int
9	Report	UN	Genomics and Global health	2004	Int
10	Report	PricewaterhouseCoopers	Personalized Medicine: The Emerging Pharmacogenomics Revolution	2005	Int
11	Report	PHGEN I	Genome-based research and population health: Expert workshop held at the Rockefeller Foundation Study & Conference Centre, Bellagio Italy	2005	Int
12	Declaration	United Nations Educational, Scientific and Cultural Organization (UNESCO)	Universal Declaration on Bioethics and Human Rights	2005	Int
13	Recommendation	EuroGenTest	Draft Recommendations of the Minimal Criteria For Genetic Counselling	2006	EU

			Related To Genetic Testing		
14	Position statement	International Society of Nurses in Genetics (ISONG)	Provision of Quality Genetic Services and Care: Building a Multidisciplinary, Collaborative Approach among Genetic Nurses and Genetic Counsellors	2006	Int
15	Report	WHO	Public Health, Innovation and Intellectual Property Rights	2006	Int
16	Report	ETEPS NET	Consequences, opportunities and challenges of modern biotechnology for Europe (Bio4EU)	2007	EU
17	Statement - Recommendation	International Genetic Epidemiology Society (IGES)	Position Statement of the IGES in response to "Request for Information": Proposed Policy of Sharing of Data obtained in NIH supported or conducted Genome-Wide Association Studies (GWAS)"	2008	Int
18	Declaration	The World Medical Association	WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects	2008	int
	Report	PHGEN I	Key Issues in Public Health Genomics: WG3 Issues & Priorities for Timely and Correct Policy Development for Education and Training in Genomics for Health Services	2008	EU
21	Document	PHGEN I	PHGE Working Group VII: Policy Development for the Introduction of Genome-based Knowledge in Population Health	2008	EU
	Document	PHGEN I	Working Group 6:	2008	EU

22	Recommandation	European Society of Human Genetics (ESHG)	Draft Recommendations on Genetic Testing and Common Disorders	2009	EU
23	Recommendation	Organisation for Economic Co-operation and Development (OECD)	OECD Recommendation on Human Biobanks and Genetic Research Databases	2009	Int

3.3 Inform, Educate, Empower

- Knowledge transfer to macro, meso and micro level decision-makers to empower them with respect to decisions based on information regarding health problems and needs, adequacy of emerging technologies as solutions, limitations of technologies, gaps in the knowledge base, ELS issues…
- Guidance on knowledge transfer strategies, on information repositories, on information needs, on optimal presentation of information (on risks for instance), on issues of health literacy….

The main questions for the provision pillar related to the education/information of the public are:

- What should professionals do provide adequate class / school education and the improvement of curricula of relevant courses?
- What should professionals do to provide/assure the establishment adequate public information campaigns directed at the public?

3.3.1 Class/school education

Identified issue

What should professionals do in order to provide adequate class/school education related to genomics.

We are addressing here the following identified issue:

What is the current level of class/school education related to genomics?

The assessment work brought up the following useful findings

1. Quite unexpectedly there is a marked not only insufficiency but a lack of attention and activities in the field of class/school education related to genomics in Europe.

2. Non of the identified in PHGEN I guidelines and key documents is approaching that problem

3. There is a need for intensive and urgent collaborative activities in relation to the establishment of synchronyzed school education related to genomics in all levels and relevant science disciplines.

Background

School curricula often lags behind scientific research and genomic scientific advances are one such example.(1) Actually the low public awareness and the existing basic misconceptions among the public on genetic issues are a mirror of the insufficient genomic education in schools.

If an aim of public health and public health genomics is increased scientific (genomic) literacy of the public, then one of the most important target groups is school students from all levels of education.

A recent survey of 22 European countries indicates that systems biology is not explicitly mentioned in any science curriculum, in addition, the principles of bioinformatics—an important discipline with extremely valuable and necessary applications within the field of genomics—are mentioned in extremely few – partially in Germany and UK. Reference to molecular medicine approaches are mentioned in around 1 in 7 European curricula – (Finland, Greece and partially UK and Germany). Molecular evolution appears to be represented in at most 30% of European curricula.(2) Large intra-national differences in representation are often seen in countries with regionally defined curricula (e.g. Germany). (2)

Some countries have undertaken practical steps in this respect. Dutch genomics research centres have developed 'DNA labs on the road' to bridge the gap between modern genomics research practice and secondary-school curriculum in the Netherlands.(3) These mobile DNA labs offer knowledge to pupils within a context that they are familiar with, such as cancer or forensic research, after which the concept is further expanded upon. The DNA lab 'read the language of the tumor ' is considered a good, but still temporary example of relevant and up-to-date genomics education. It consists of 4 hour educational modules and a 2hour practical lab taught at the schools by university students with up-to-date genomics equipment and techniques.

In USA the NIH Office of science education has developed several supplement courses for high school students 9-12 grades related to genomics: cell biology and cancer; human genetic variation; using technology to study cellular and molecular biology.

In this respect the US is probably steps ahead of Europe, where a variety of public and private agencies provide funding and education in genomics. Both the Department of Energy (DOE) and the National Human Genome Research Institute (NHGRI) commit 3%–5% of funding for the HGP to the exploration of the ethical, legal, and social implications (ELSI) of its research, and basic education in genomics is funded through these ELSI programs. Industry and private organizations like the Howard Hughes Medical Institute (HHMI) are also major supporters.

Among the many international guidelines and documents on topics related to public health genomics there is not even one single document addressing the issue of school education in genomics!

.3.2 Establishment of adequate information campaigns on genomic issues

Identified issue

We are addressing here the following identified issue:

The assessment work brought up the following useful findings

Background

Two main issues are posed in the literature:

- What is desirable and 'adequate' knowledge, which individual members of the general public need in order to engage in proper decision-making regarding genomic issues.
- What is the level and content of public awareness/knowledge about genetics at the present moment.

The first question has been defined as important both for theoretical and for practical purposes (e.g. in the assessment of information campaigns the achieved level of knowledge among the public has to be compared with the desired or adequate aiming to be achieved; in principle to empower citizens when they have to take decisions on genomic issues that affect them personally or globally). We were not able to find in the literature an answer to that question and a definition of what exactly is a desired/adequate level of knowledge.

The second question has received more attention and a number of theoretical and empirical studies have been published. The first among all is a WHO report, (the only one) included in the PHGEN list of guidelines) which points out that alarming misconceptions about basic genetic terms that exist among the public, which may lead to incorrect processing of new specific genomic information, especially when individuals are unaware of their misconceptions (4).

It has been proposed that in relation to the study of people's knowledge about genomics, the Rogers' conceptualization of knowledge distinguishing between three types of knowledge with increasing complexity is applicable (5). These three types/levels are: "awareness knowledge"- the knowledge about the existence of e.g. genetic risk factors for common diseases with multiple causes; "how-to knowledge" -

practical knowledge concerning the proper use of an innovation; and “principles knowledge” – understanding of the underlying theoretical principles of the innovation.

With regards to the awareness knowledge:

A number of empirical studies have examined the question of whether the public is aware of genetic risk factors of different diseases. A review examining public awareness of the genetic risk factors of multifactorial diseases in a wide variety of countries(5) suggests that the general public is reasonably aware of the genetic risk factors of multifactorial diseases, with approximately 59% (range, 17.6–93.3%) of the sample being aware of the existence of genetic risk factors, although much lower and much higher proportions have also been observed.(5) For example 60% of the public were aware of genetic risk factors for breast cancer, while for cervical cancer these are only 20% (5).

A more recent study among 1,747 British adults reports that one third of the respondents identified genetic factors as influencing cancer (35%) and heart disease (36%) risk.(6) The authors suggest that people who recognize that genetics influence chronic disease risk appear more, not less, likely to recognize the role of lifestyles. This contradicts suggestions that the public takes an ‘either 'deterministic' view of the etiology or people believe that the disease risk is largely dependent on lifestyle and 'external' factors.

Another study explored the knowledge about genetic risk of disease, inheritance, biology, determinism among 1009 Western Australian citizens (7). The conclusion was that most members of the Western Australian community are aware of basic genetic concepts and the link between genes, inheritance, and risk of disease, but significantly fewer understand the biological mechanisms underlying these concepts and there was some misconception around the meaning of ‘increased genetic risk’.

A study on the causal beliefs about obesity among 3,534 individuals in the USA, reports that only 19% of the respondents indicated that inheritance has 'a lot' to do with causing obesity.(8) The rest 72% of respondents endorsed the belief that lifestyle behaviors have 'a lot' to do with causing obesity. A Japanese study on Public awareness of risk factors for cancer reports that 35% of all cancers are attributed to genetic risk factors (9).

Much more limited is the knowledge of the public in relation to the “how – to” knowledge - how genetic risk factors influence the risk of development a disease. One of the things which the general public seem to understand is that having a genetic predisposition implies heightened, but not absolute risk (5).

Information on the public’s “principles knowledge” referring to the knowledge of the underlying working mechanisms through which genetic risk factors affect disease development (e.g., knowing that certain polymorphisms create a genetic predisposition that interacts with other factors to develop the disease) is extremely scant. Only one study was identified in the cited review observing this most complex knowledge level.(5) It concludes that although participants recognized the increased

risk owing to genetic risk factors, their knowledge of the working mechanisms of genetic factors was (highly) inadequate, largely insufficient and superficial (5).

It seems also that individuals are only interested in the consequences of genetic risk factors and how to manage them, and are not at all interested in the underlying genetic principles (5). E.g the public has no need for detailed information on the working mechanism of DNA, but is interested in the signs of a genetic predisposition to cancer.

- *Effect of information on decision-making and engaging in preventive behaviour.*

Research examining the effects of mass media genetic health messages on preventive behaviour is also scarce. At the same time without such insight, genetic-based public health campaigns may 'do more harm than good'.

Smerecnik et al compared the effects of health messages communicating information about genetic risk factors for salt sensitivity and heightened cholesterol with general information without reference to genetic risk factors.(10) The results reveal that unaware participants who received a genetic health message reported lower perceived susceptibility associated with lowered intentions to engage in preventive behavior, compared to those who received a general health message. No such effects were observed for the participants who were aware of the existence of genetic risk factors. The authors conclude that alerting the public to the existence of genetic risk factors may not necessarily be beneficial to the public health (10).

Another study examined the potential behavioral consequences of genetic feedback on obesity risk in normal weight individuals. Individuals who were told they were at increased genetic risk for obesity showed higher overall intentions to eat a healthy diet. However, individuals with low external weight locus of control had significantly lower predicted intentions to eat a healthy diet when compared to those with high internal weight locus of control (11).

Other studies also prove that the provision of genomic information has an important influence on the audience. E.g. information about the population risk of inheriting a certain specific gene, substantially modifies the people's interest in genetic testing (12).

This suggests that researchers and educators should be very careful about the information provided to the public. Information on the existence of genetic risk factors should be accompanied by explanations for its meaning and consequences for the individual and his/her family. Information on the population risk of inheriting different genes when discussing the discovery of these genes with the media may also have variable effect on behavior.

- Existing genomic education for the public at the moment

The public at present has some access to information developed and provided by governmental organizations, academia, disease specific advocacy organizations, and the healthcare industry. Various organizations such as NIH, CDC, NLM (US National Library of Medicine) and academic institutions have websites and educational

materials on genomic issues at least for those who are interested. New entrants to the field include companies, particularly those looking to market tests and information directly to consumers. It is reported that sources from which the public receives most of its genomic/genetic information are internet, television, radio, magazines, and newspapers (13).

A study examining the accuracy and nature of media coverage of genetic research found that most newspaper articles accurately convey the results of and reflect the claims made in scientific journal articles.(14) However, the media do seem to overemphasize particular topics, such as behavioural genetics, underreports risks and puts an overemphasis on benefits. Such a trend may contribute to inflating the expectations of the general public and special interest groups such as patient groups and investors. . In this case, it is not just a question of informing people on the three dimensions, but informing mass media and information producers to make them aware of the consequences of the information they provide to the general public. An especial emphasis should also be made in the tailored difusion of the information and the different needs the people have in the three dimenssions and according to existing evidence.

As with the case of school education there is a gap in international genomic guidelines with regards to public education.

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3.4 Mobilize Community Partnerships

- This task can be viewed as a major role for the National Task Forces (bringing together genetics, public health, policy makers….) and is an extremely important input for policy development
- Guidance on new business models (health technology life cycle etc.) as well as guidance on stakeholder involvement, in the different phases that could discuss genomics technology provision, setting up of sustainable infrastructure for National Task Forces.

Identified issue

We are addressing here the following identified issue:

What should professionals do to mobilize community partnerships?

1. Education of professionals in professional-public communication
2. Information campaigns on mobilisation issues
3. Support of the activities of the NGOs
4. PPP and incentives

The assessment work brought up the following useful findings

Background

Principles

Medicine in a modern society should meet requirements of being predictive, preemptive, personalized and participatory (P4 medicine). Patients/consumers should be informed about the possibilities and advantages of the personalized medicine. Up to date tools of health literacy enhancement should be employed to support people in meeting the complex demands of health in modern society, personalized medicine in particular. Different stakeholders should work together to remove obstacles in integrating genomics and personalized medicine into routine clinical care. Policy makers at the EU and national levels should establish policies and procedures that create favorable environment for successful implementation of personalized medicine. Policies and procedures concerning personalized medicine should be based on wide public stakeholders' consultation and ensure a balanced representation of stakeholders interests, namely those related to ethical, legal and social issues - ELSI, e.g., ethical standards of human dignity, including autonomy; professional health care standards; social justice in health care resources allocation and use (1).

Practices

Establishing and maintaining community partnerships in the field of PHG depends on the mobilization of the relevant stakeholders, e.g., public policy/decision-makers (including funding agencies) at EU, national, regional and local level, health care providers, researchers, education and research institutions, scientific societies, health products industries, media, patient advocacy organizations, and lay people groups. Building upon the outputs from PHGEN I, namely the report on the development of stakeholder involvement (2), the following topics should be thoroughly considered:

1. Critical review and evaluation of recent successful (or failed) attempts of community stakeholder involvement and participation towards filling the wide knowledge gaps that exist between scientists, the public and different professional groups through an open and well-informed debate, using a wide range of communication tools (e.g., focus groups, public fora, citizen's juries, conventional and web-based media).
2. Provision of timely, personalized, culturally appropriate counselling to those being exposed to genome-based technologies (e. g., patients and their relatives, screened population segments, general population). Counselling activities will include scientific matters as well as ELSI, including the motivation for, and appropriateness of using direct-to-consumer clinically relevant genetic tests (3).
3. Organization of information campaigns (in the media, schools, health institutions, civic centres) that allow and encourage mutual communication to take place between professionals and non-professionals, recognizing the heterogeneity within the population (both lay and professional) concerning age, sex, social class, education, cultural/ethnic origin, geographic area of residence and religious persuasion and other values.
4. Support to the activities of the relevant NGO's (of, e g, patients, carers, service users, 'watchdog' groups, citizens) in order to stimulate an active participation of their membership, who own a special knowledge, experience and a unique perspective, to be complemented with improved health/genomic literacy. The latter could be achieved by translating findings from genomics, epigenomics and systems biomedicine to help understanding that individual biological pathways or networks are permanently interacting with environmental networks such as social networks (4).

As PHGEN I members nicely put it, we must recognise that our first steps with stakeholders will be to listen, learn and contribute public health and genomic expertise - for it is only through mature relationships involving collaboration, the building up of trust and the shared ownership of outcome that the future role of Public Health Genomics can be established (2).

As in other cases, these initiatives should be context-tailored and adopt the best feasible strategy top-down, bottom-up or converging. These models are mostly dependent on the characteristics of the systems where the stakeholders

involvement is required and especially in the cases in which decision makers involvement is lacking or there is scarce knowledge by health care professionals.

Public-private partnerships

The expression "public-private partnerships" (PPPs) covers a wide variety of ventures involving a diversity of arrangements, varying with regard to participants, legal status, governance, management, policy-setting prerogatives, contributions and operational roles. They range from small, single-product collaborations with industry (contractual or project PPPs) to formal legal entities run by proper corporate-governance mechanisms and jointly owned by public and private parties for the provision of public-health goods (institutional PPPs) (5).

Some so-called PPPs could be more accurately described as public sector programmes with private sector participation. PPPs for health should be distinguished from privatization. In the latter case, the public health policy goal and the rules under which for-profit entities operate are set and enforced solely by government agencies.

PPPs are closely scrutinized by a wide range of observers and some very different perceptions of their desirability and viability have emerged. In particular, concerns have also been raised inter alia about conflicts of interest over the role of industry partners. Others recognize that partnerships between public/governmental entities, private/commercial entities and civil society to meet common goals have a contribution to make in improving the health of the people by combining the different skills and resources of various organizations in innovative ways. Public agencies clearly benefit from working in collaboration with the private sector in areas where the public sector lacks expertise and experience, e g, in product development, production process development, manufacturing, marketing and distribution. On the other hand, there are areas where private sector could benefit from public sector expertise on reimbursement decisions and or health sector needs (public advice). However, there are areas, such as public health policy-making and regulatory approval, where the concept of partnership with for-profit enterprise is not appropriate. The purposes of partnerships should therefore be carefully considered and well articulated (6). In any case, the interactions should be also previously defined, transparent and accountable.

Major political and institutional actors at the central level [e. g., in Denmark] differ in their enthusiasm for the PPP concept, and the regulatory framework is somewhat uncertain. A number of general issues and concerns related to PPPs are also discussed. It is suggested that a risk-based framework can be useful for mapping the potential and challenges for both private and public partners. Such a framework can be used to feed into game theoretical models of pros and cons for PPP projects. In general terms, more empirical research is needed for the assessment of the various risk factors involved in using PPPs in health care. Most PPPs are still very young, and the evidence on performance and broader governance issues is only just emerging. Ideally, such assessments should include comparisons with a purely public alternative (7).

The "Innovative Medicines Initiative" (IMI) is a European PPP between the pharmaceutical industry (European Federation of Pharmaceutical Industry and Associations, EFPIA) and the European Commission (DG Research--health theme). Its architecture is based on the identification of the main bottlenecks to the development of innovative treatments (predictive pharmacology and toxicology, identification and validation of biomarkers, patients' recruitment, risk evaluation, and cooperation with the regulatory authorities). A follow-up exercise regarding the results of the first years of this PPP implementation is most needed.

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3.5 Develop Policies

- A broad interpretation can encompass under policies: laws and regulations, governmental policies, professional guidelines, quality assurance measures, different types of safeguards ...
- Guidance on existing forms of regulation, development and maintenance of specific forms of regulation, harmonisation issues, ...

Identified issue

We are addressing here the following identified issue:

The assessment work brought up the following useful findings

Background
'Biotechnology, genomics and informatics offer a growing range of approaches to help prevent monitor and detect, diagnose and treat infectious disease. Appropriate policies are however necessary to ensure that the right tools reach the right people at the right time.'
-Biotechnology and Sustainability: The fight against infectious disease, OECD[1].

The number of innovations in genomics leading to useful health applications is steadily growing. At this juncture, when this burgeoning field is still in its relatively early states, it is important for countries to develop strategies to ensure that these advances are harnessed to benefit the health of their citizens, and to undertake an appraisal of the potential of genomics for their citizens. This means taking careful account in the creation of policy of not only the scientific and technical aspects of genomics, but also of the not inconsiderable ethical and social implications its development and application may pose.

Genetic based technologies, usually highly specialized investigations, are being requested at an ever-increasing rate. At the same time, there is an exponential demand in assessing health technologies and including in the

[1] Biotechnology and sustainability. The fight against infectious disease. OECD. 2003. Available in: http://www.oecd.org/dataoecd/23/23/2508407.pdf

benefit package of the health care systems only those that provide value for money or an added value to their use and implementation. Parallel to this there are demands in many European countries to cut down the costs of health care to make them sustainable. The issue should be to include technologies with proven benefit in order to provide a better management to the individual patient and the society. All this has created a situation where professional guidelines for the provision of genetic services are needed (1). In the case of Europe and its complexity, the standardization of practices and the establishment of what belongs and to whom is especially necessary. Today, there is an increasing interest to develop policies centered in the patient or focus in the citizen and that could provide a common frame for public health services in a trans-border health care. In addition, reimbursement decisions may become more complex. When it comes to genetic-based diagnostic tests or therapies, subjectivity on a case-by-case basis may be required, calling for far greater collaboration among payers, providers, and the producers of drugs, diagnostics, medical devices, and therapeutics. Moreover, healthcare providers must also consider how this new concept of medicine will affect their technology capabilities and infrastructures. Today, a vast amount of healthcare information is already being collected, including patient histories, diagnostic reports, and clinical research findings. The increasing levels of adoption of electronic health records (EHRs) by hospitals and health care systems will ramp up the collection of health data exponentially over the next few years. And this is on top of a growing body of genomic data that ultimately will evolve into billions of data points on every individual, as powerful analytical tools are being developed.

The value of the genomic, proteomic, and other health data being collected becomes greater as it gets shared among research organizations and mined to become more predictive. How well providers manage, share, and make use of that data will be crucial to their ability to provide coordinated care and give broad-based clinical decision support for individualized patient management. Genomic medicine is a critical cornerstone of Integrated care for Patient Centered Health Systems. The investigation on how genetic information can be integrated in patient health records so that it can be used in care decisions and the interoperability among different health care providers and users. As genomic medicine becomes a reality, provider systems, payers, and the pharmaceutical and medical devices industry will be working together to create a new data architecture that will enable interoperability among information technology systems to facilitate the

linking and analysis of health data across not only the local health care systems but regional, national and European systems too.

In fact, there has been recently published by the EU a new directive on cross-border health care (2). This directive (Directive 2011/24/EU) on the application of patients' rights in cross-border healthcare has been published in the Official Journal of the European Union. The Directive applies to individual patients who decide to seek healthcare in a Member State other than the Member State of affiliation.

Two main articles of this directive although indirectly apply to genomic and genomic related technologies and issues: article 14 and article 15.

Article 14 defines that the Union shall support and facilitate cooperation and the exchange of information among Member States working within a voluntary network connecting national authorities responsible for eHealth designated by the Member States. This exchange of information and interoperability should be:
(a) work towards delivering sustainable economic and social benefits of European e-Health systems and services and interoperable applications, with a view to achieving a high level of trust and security, enhancing continuity of care and ensuring access to safe and high-quality healthcare;
(b) draw up guidelines on:
(i) a non-exhaustive list of data that are to be included in patients' summaries and that can be shared between health professionals to enable continuity of care and patient safety across borders; and
(ii) effective methods for enabling the use of medical information for public health and research;
(c) support Member States in developing common identification and authentication measures to facilitate transferability of data in cross-border healthcare.
The objectives referred to in points (b) and (c) shall be pursued in due observance of the principles of data protection as set out, in particular, in Directives 95/46/EC (3) and 2002/58/EC (4).

With regards to HTA, Article 15 of the Directive makes provisions for support of the collaboration activities of the voluntary network of HTA agencies. Member States must adopt the necessary laws, regulations and administrative provisions by 25 October 2013. This directive did not mention directly the situation of genomic technologies, their provision and

standardization, but nevertheless, in its paragraph 22 of its preamble generically expresses that: "*Systematic and continuous efforts should be made to ensure that quality and safety standards are improved in line with the Council Conclusions and taking into account advances in international medical science and generally recognized good medical practices as well as taking into account new health technologies*".

Cooperation in the evaluation of new health technologies can support Member States through economies of scale and avoid duplication of effort, and provide a better evidence base for optimal use of new technologies to ensure safe, high-quality and efficient healthcare. Such cooperation requires sustained structures involving all the relevant authorities of the Member States, building on existing pilot projects and consultation of a wide range of stakeholders. This Directive should therefore provide a basis for continued Union support for such cooperation.

Clear guidelines for best practice will ensure that the provision of genetic services develops in a way that is beneficial to its customers, be they health professionals or the public, especially since the coordination of clinical, laboratory and research perspectives within a single organizational structure permits a degree of coherence not often found in other specialties. It is time for a harmonization of capacities and its recognition and accreditation in all the countries of the EU (1). In each country, adherence to the organizational principles of prioritization, regionalization and integration into related health services will maximize the efficiency of genetic actions.

The development of policies should be based on the status of genomic technologies and their use that encompass everything from high-tech diagnostics to functional foods, to technologies that enable the storage, analysis, and linking of patient and scientific data.

On the other hand it should include the constant progress of medical science and health technologies presents both opportunities and challenges to the health systems. Harnessing genomics' benefits in the fullest sense therefore requires considering the entire process, from discovery, research and development, commercialization, and finally up to application—including mechanisms for financing each of these steps.

Great deal remains to be done to assure that genetic technologies, are integrated into health systems in an affordable, sustainable, and socially-appropriate way. Policy can have an enormous impact at each stages of this process. Careful and informed decision-making, which takes into account

local health needs, capacity, and customs, is essential to harnessing the full potential of genomics and its applications for improved health.

Fist of all, policies to be sustainable and effective, they need to be socially acceptable.
Following the considerations made by WHO (5, 6), we will consider 5 main areas: a) Public Education and Public Engagement; b) Research and Development; c) Regulation and Reimbursement of Genomic based technologies; d) Building Capacity; and e) ELSI.

a) Public Education and Public Engagement: The new paradigm There is therefore a need to educate citizens (not only patients) in a balanced manner about advances in the science, including the ethical legal and social implications they pose. Many encouraging examples of successful medical interventions that were preceded by public educational efforts exist today, as demonstrated by the example of genetic screening programs in the USA, Canada and Italy (Scriver et al., 1984 (8); Cao & Rosatelli, 1993 (9)). Mass media like the television, workshops and print campaigns have proved to be effective for raising public awareness. Others such as internet or social networks are to be explored. An ongoing analysis of public perception of genomics must be incorporated into policy making so that it truly addresses the areas of public concern, and constructively addresses the apprehensions of society towards genomics. Policies at the European level should follow other similar experiences in other environments or contexts such as the initiatives by the NIH or NLM in the US where Open Access and accurate information is publicly available to reduce misunderstandings and misbelieves on genomic based technologies and practices.
b) Research and Development: A further area of challenge for policy makers in the case of genomics and policy concerns the funding of research and development (R&D). The source of funding, be it the private or the public sector or a mixture of both, has implications for the affordability and accessibility of research findings, as well as their relevance to local needs. At present there is a great deal of private investment in genomic-based R&D, and new formulas have appear where public investment is included to ensure reversal to health care systems, what has been called Public Private Partnerships (PPPs) primarily due to the high costs involved. Universities and other not-for-profit institutions also engage in basic research in genomics, and even in the commercializing of its products and services. It is important to develop national policies that encourage an interplay among the different actors—government, universities, and industry—which

encourages innovation and strong research that is ultimately beneficial in addressing the socially relevant health needs. This interplay is part of a complex system that depends on several factors, including the technical capacity that exists within each sector. It is, so far, needed that the advancement is promoted, that the public policies invest in added value solutions and that the results are publicly available and the solutions implemented in the systems. Two main areas of work are included in this case, correct and focused investment and access to results and technologies. Public policies should, in this sense, ensure that public funds are invested in prioritized health technologies according to the needs of the population and health care systems and that the results are OA available in a reasonable period of time. In the US, all publicly funded projects should provide results in OA in a period not superior to 12 months. The NIH Public Access Policy ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication (10). No similar harmonized public policies are in place in Europe, not even detailed plans for coordinated investment public and/or PPPs in genomic technologies and solutions. Special focus should also be in place regarding the issue of intellectual property (11). There are now patents on diagnostic sequences. These amount to patents on the information that a specific gene sequence in a person has particular implications for the disease susceptibilities of that person or for the likelihood that a particular drug will be especially beneficial or harmful for that person. In a sense, they are patents on the information that there is a particular relation between a genotype and a phenotype. The patent confers control over use of this information as a diagnostic test — and this is very broad control. The number of patents of this character is likely to increase, because more and more data are being collected through micro-arrays during large-scale clinical trials. These micro-arrays provide genomic sequence information that can be correlated with participant physiology to provide new information about genetic markers of disease and of drug susceptibility. This fact has several economic consequences on the final price and costs for the systems of diagnostic and therapeutic genome based solutions.

c) Regulation and Reimbursement of Genomic based technologies: New legal and regulatory approaches need to be crafted in anticipation of or in

response to rapid developments in genomic research and genomic health care. These approaches will need to be sensitive to the ways in which new genomic technologies and information are integrated into society. They also will have to adapt to the challenges inherent in attempts to maintain confidentiality and privacy in a new era of genomic information coupled with revolutionary changes in information technology. In addition, policy-makers will need to revisit the issues of autonomy and ownership that are evolving as society changes. Research will be needed to explore the effects of existing policies and regulations and to provide data to inform the development of new policies and regulatory approaches (12). Current approaches of regulation to health technologies include genomic technologies, especially in the area of pharmaceuticals, nevertheless medical devices are under regulated and solely market authorization is required through CE mark. Coverage and reimbursement of genome based technologies should move toward an evidence and value-based approach using basic tools that are currently in practice for other health technologies such as technology assessment and appraisal. Value for genomic tests is as it is defined for other technologies, the intervention provides an overall benefit to the patient (including affordable organizational changes, social and personal acceptance) at an acceptable cost. This should be included in different policies. There are guidelines that cover the information required for the reimbursement of genomic based health technologies, based on evidence and the added value of those technologies to be included in the health benefit package (GEN guide (13); UK Genetic Testing Network Steering Group for the assessment of genetic tests within the UK National Health Service (14-16)). Another issue that should be taken into consideration is the disinvestment of existing technologies of low-added value and this issue is also applicable to genomic base technologies (17). So public policies might be directed to ensure the correct implementation and on time of added-value genomic based health technologies to ensure the efficient use of existing ones and to disinvest those that procure low or no added-value.

d) Building Capacity: Better training of health professionals in genomics and its ethical and social implications is essential for assuring that the potential of new technologies is realized for the full benefit of patients. Improving the training of medical researchers, clinical geneticists, genetic counselors and other core members of the health care team, will enable them to recommend the use of genomic-based applications and genetic services and counseling to their patients, increasing understanding of existing technologies, and ultimately improving their efficacy. This means including

science, including the rudiments of genomics, as part of the curriculum in elementary and secondary schools, and creating programs in genomics at the university level to equip researchers and clinicians with the necessary technical and analytic skills (18). Students across disciplines need to be sensitized to the ethical, legal, and social implications of genomics, with specific training for those pursuing a career in health policy, research, practice, or related field. It corresponds to public policies to ensure the best available training to professionals based on international standards and on levels of practice, to harmonize public policies on building capacities and to accredit and recognize competences at least, across Europe. For the performance of any professional work, there is a training and competences requirement and genetics is no exception. But in Europe there is no uniformity either in training or access to it. In a recent report of PHGEN (Working Group 6) this point became clear and stated the need to promote initiatives that favor the training of specialists in different areas and professional accreditation. In fact in most European countries there is a medical genetics as a recognized specialty but not in the whole Europe not even in the EU. Currently, there are professionals who have acquired skills and developed their daily work in genomics and do not have any accreditation to enable them to exercise those functions. Most professionals have acquired knowledge and skills in clinical genetics or genetic counseling graduate courses in different universities or promulgated by different societies. In this sense, there are different groups with initiatives that define common competencies to be acquired by health professionals involved in this field of knowledge. Perhaps the more developed proposal has been developed by the group EuroGentest and define the specific skills and specialty area (19). This proposal is available in its website (available at: http://www.eurogentest.org/web/info/public/unit6/documents.xhtml).
These core competences are endorsed by the European Society on Human Genetics.

e) ELSI: The Human Genome Project and related initiatives, have introduced powerful new methods to the study of genes. Genomics has laid the foundations for a new approaches to the diagnosis and treatment of human disease, and introduced new possibilities for reproductive choices. This progress is accompanied by important ethical and social issues. Although many of these issues are not unique to genomics (such as confidentiality, informed consent, discrimination and stigmatisation, etc.), they require focused consideration in the context of genomics. Genomics is special in that gene-based approaches introduce a new language of “probability” and

"susceptibility" to medical care, and furnish information about disorders; that often is of great interest to third parties – be they families, governments, insurance companies, law enforcement or scientific researchers. This is applicable to the directive 2011/24/EU on cross-border health care and the interoperability and transferability of human data. In this case the legal documents of reference are the Directives 95/46/EC (3) and 2002/58/EC (4) of the Committee of Ministers of the Council of Europe Member States on the Protection of Medical Data, and the International Declaration on Human Genetic Data UNESCO, 2003 (20). Finally it is needed to mention the Convention of Oviedo for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo, 4.IV.1997 (21).

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Assurance (Tasks 6-9: all three pillars)

3.6 Enforce Laws

- A broad interpretation is needed to encompass the application of the range of policies considered (e.g. Health in All Policies, …).
- Guidance on mechanisms to disseminate and to enforce laws, regulations, policies, quality assurance measures (accreditation, EQA …), means to protect and involve users (informed consent tools, …)

Identified issue

We are addressing here the following identified issue:

The interpretation of existing rules and the detection of gaps are of major importance for the current legal discourse on Public Health Genomics.

The assessment work brought up the following useful findings

A lot of regulatory frameworks and laws are already in place which provide opportunities for Public Health Genomics: e.g. Directive on Patient Rights in Cross-border Healthcare, Data Protection Directive 95/46/EC, Health in all Policies approach (HiAP), EU Regulations on Orphan Drugs and on Advanced Therapies, the Commission Communication and the Council Recommendation on Rare Diseases.

Background

There is high political commitment of the EU for initiatives such PHGEN including future developments such as personalized healthcare. Furthermore, the European policy-makers prepared already new frameworks enabling these future developments.

Examples are:

- The term “health information” includes all types and sources of information, which has been collected for health as well as other purposes. It covers data and information on the individual as well as on the population level. It includes genomic/biological as well as environmental data. Also, the “data clouds” of the virtual human is health information.

- On 28th of February 2011 the Council approved the European Parliament's amendments on a draft directive aimed at facilitating access to safe and high-quality cross-border healthcare and promoting cooperation on healthcare between Member States. In line with article 294 of the Lisbon Treaty the cross-
- border healthcare directive has now been adopted and Member States will have 30 months to transpose the directive's provision into national legislation. This opens up the possibility and a legal instrument, so that data can follow persons, which will be important for PHG.
- European reference networks (ERNs) for rare diseases will serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN will also reflect the need for services and expertise to be distributed across the EU. Since PHGEN interprets "rare diseases" not only in the traditional way of monogenic diseases, but also in the way of sub-entities of common complex diseases ("truly personalised medicine" based on the understanding of individual pathways), this initiative should be followed closely by PHGEN.
- The EU "Health in All Policies" (HiAP) concept acknowledges the importance of other policy areas for health and tries to influence decision-making in these policy areas such as in economics, social affairs, environment.
- The Health Technology Assessment (HTA) agencies have a central role for Public Health Genomics. Evidence can be interpreted not only in the classical way of RCTs (current golden standard), but also on individual level ("myself evidence"). Thus the person can have her/his own clinical trial ("personal trial"). Currently, new business models are developed (e.g. LAL model) promoting that Technology Transfer (TT) and HTA are not only closely working together, but also in parallel translating innovations effectively, efficiently and timely into the healthcare systems.

3.7 Link to / Provide Care

Identified issue

We are addressing here the following identified issue: The application of the combination of next genertion sequencing and systems biology modelling as for the development of new diagnostic and treatment approaches for cancer.

The assessment work brought up the following useful findings:

the application of personalized medicine in the field of systems biology and genome sequencing are close to providing new avenues for cancer diagnosis and treatment. However, further research, development and proof of concept are required to ensure real life application in the clinica and increased benefit for the patient. Ehtical issues such as the level of availability of genome type data to the public health sector and close monitoring of the benefit of the application of these techniques for the individual have to be monitored closely

Background

Progress in genomics technology such as next generation sequencing and systems biology modelling has opened up new fronts for the development of targeted approaches for personalised diagnostics and treatment. There are already good examples that the genetic background and mutational profile of a patient determine the outcome of treatment and survival (Roychowdhury et al. 2011). For examples the chemotherapeutic drug Erbitux (a monoclonal antibody against the EGFR receptor) will only be beneficial for treatment in the absence of KRAS mutations in colorectal cancer (Amado al. 2008, Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol; 26: 1626–1634.). However, we are still far away from routine application from genome sequencing and deriving reliable diagnostic predications for chemotherapeutic treatment base on such information. Nevertheless there is already a great demand to include such information into praxis and the clinic. This process is now a challenge in how and if patients should be referred to for genome analysis, best interpretation of results, best prescription of drugs, communication of risks and meaning of mutational profiles or genetic variations to the patient (Avard & Knoppers, 2009). The question is how this new praxis can be adopted and ensured to be efficient and be of real benefit to the patient and at the same time maintaining and protecting patients right

to their sequence information (Ginsburg, 2008). Hence for the provision of the best possible care for the patient it is critical to integrate new genome based knowledge and relevant technology into the praxis. It is therefore essential to establish best possible procedures and evaluation of/for:

a) Knowledge transfer to clinicians and application of practice guidelines

b) "Translation" of new practices into the required organisational changes (e.g. redefining roles and responsibilities of various professionals…) and implementation of these changes (e.g. planning adequate resources, negotiations…)

Clinical Guidelines and Standards for Provision of HC

Clinical guidelines must be implemented on several levels including clinics, clinical networks, regional county level, national and international level. These measures should include quality control, provide means of controlling where and how they are employed and ensuring that by applying them patient outcome is improved (Storme, Clinical practice guidelines in cancer: the European perspective, British Journal of Cancer 2001, 84 (Supplement 2), 6–7)[1]. It is conceivable that in order to avoid replication of work, already existing guidelines should be adopted, disseminate and integrate clinical guidelines that had already been generated. Such guidelines could be based on the US National Cancer Institute's comprehensive cancer data- base PDQ® (http://www.cancer.gov/cancertopics/pdq/cancerdatabase). In addition the Standards, Options & Recommendations (SOR) project was developed by the French National Federation of Cancer Centers (FNCLCC) (http://www.nature.com/bjc/journal/v89/n1s/full/6601094a.html) and the 20 French Comprehensive Cancer Centres (CRCC) in collaboration with specialists from French public universities, general hospitals, private clinics and scientific societies (Storme, 2001).

Comprehensive guidelines on a European Level were published (for example http://www.nature.com/bjc/journal/v89/n1s/index.html). However, there is now a need to implement newer genomics based information. It is encouraging that the demand for implementing genomic based information in decicion making progress for treatment and diagnostics have already been made on a political level. For example in the report of the German Parliament to the topic of Individualized Medicine and the health system (http://www.tab-beim-bundestag.de/en/news/20090303.html). In this report is has been proposed that "*Individualised medicine could penetrate medical practice from prevention to (early) diagnostics as well as therapy and after treatment monitoring. A multitude of scientific and technological developments contribute to this trend reaching from genome analysis, molecular imaging, cell therapies with the body's own cells to pharmacogenetics, nutrigenomics and the determination of patient-specific protein expression patterns.*"

In this context it becomes clear that a future emphasis will be the application and the assessment for the incorporation of biomarkers into clinical guidelines. Biomarkers, taking new genome and proteome based information into account, will change clinical practice that will be disseminated on multiple levels together with pharmaceutical and diagnostic companies, scientific societies and regulatory agencies. (Schmitt et al. 2004 (Identification, validation, and clinical implementation of tumor-associated biomarkers to improve therapy concepts, survival, and quality of life of cancer patients: tasks of the Receptor and Biomarker Group of the European Organization for Research and Treatment of Cancer. Int J Oncol. 2004, (5):1397-406.[2])

Biomarkers will be employed in a number of areas:

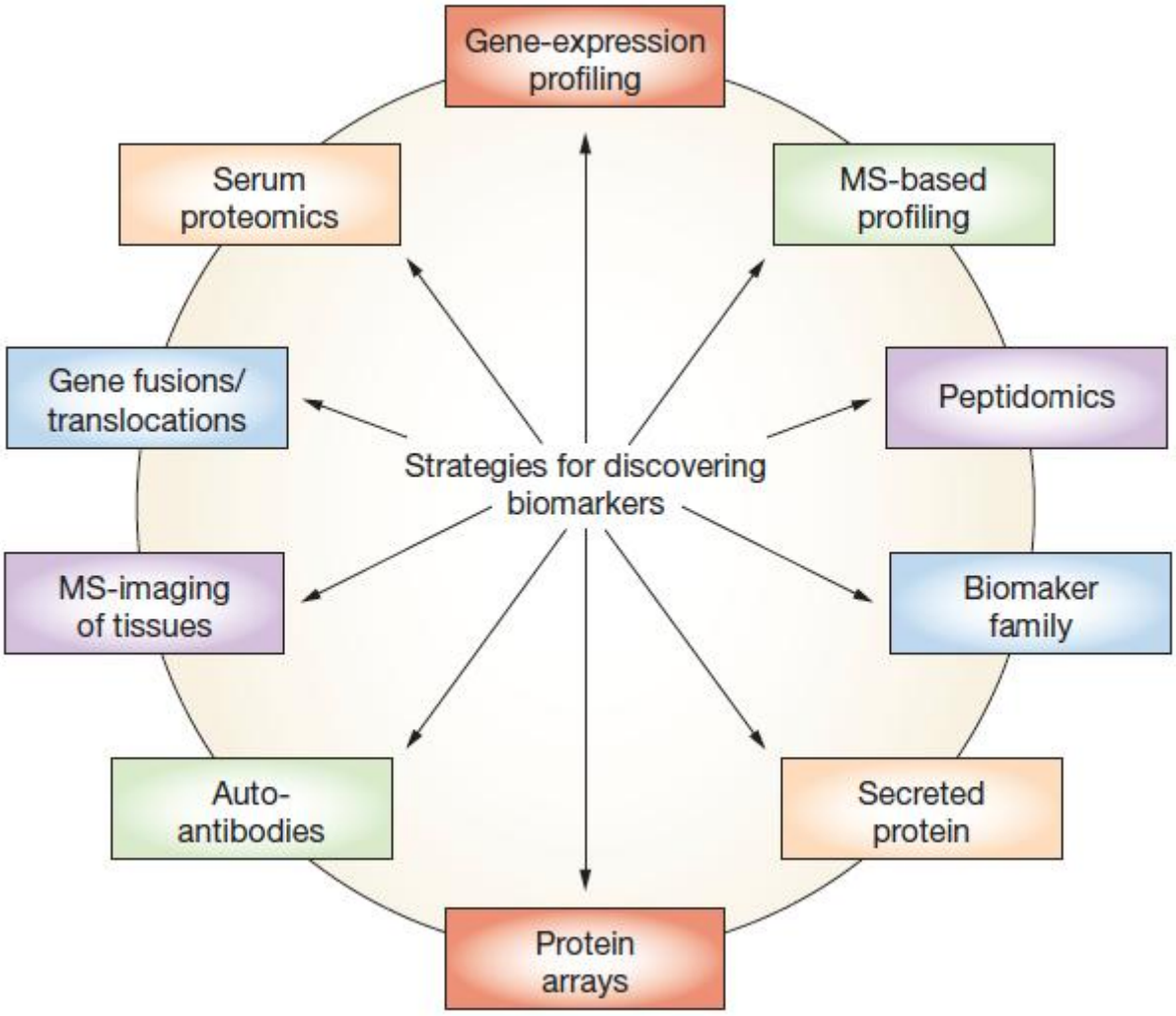
- diagnostic biomarker for early disease detection

- risk biomarker for predicting the risk of developing a disease

- prognostic biomarker for estimating the degree of aggressiveness of a disease

- predictive (stratifying) biomarker for estimating the response and toxicity of a particular treatment

Some of these biomarkers will help to stratify the patient group relevant for a particular treatment or for not treating them due to ineffectiveness of a certain drug or adverse reaction to it. The reasons for new developments and hopes in the field of biomarker discovery come from great technical advancements in the field of functional genomics and proteomics (summarized in the Figure "Biomarker discovery" from V. Kulasingam & E.P. Diamandis, Strategies for discovering novel cancer biomarkers through utilization of emerging technologies NATURE CLINICAL PRACTICE ONCOLOGY, VOL 5 NO 10: 588-599.[3]



On the European level there are a number of projects ongoing aiming at improving the discovery, evaluation and clinic implementation of biomarkers. The aims, bottlenecks and challenges for bringing biomarker into the clinic has been recently been summarized comprehensively in a document from the "Workshop to clarify the scope for stratification biomarkers and to identify bottlenecks in the discovery and the use of such biomarkers." European Commission, DG Research - Brussels, 10-11 June 2010". (http://ec.europa.eu/research/health/pdf/biomarkers-for-patient-stratification_en.pdf). Among some of the most critical problems and gaps identified were: (a) Pre-analytical and analytical procedures require gold standards, quality assurance schemes and standardisation of technical procedures, (b) needs for statistical and bioinformatics tools, (c) new clinical trials would be needed for the qualification of current biomarker candidates, (d) incentives are essential to allow stratified medicine becoming a reality, (e) a better understanding of disease mechanism and drug action is important, (f) development of stratification biomarkers is a vital concept to facilitate disease prevention and drug development (g) sensitivity of many biomarkers is limited and often restricted to later stages of the disease.

A major European project already aiming at the discovery and validation of biomarkers in the field of colon cancer is the IMI project OncoTrack (http://www.oncotrack.org/) (see also below). This project that started at the beginning of 2011 brings together academic, industry and partner from clinics to apply genomics technologies and Systems Biology modelling to achieving its goals of biomarker discovery and improving diagnostic and treatment approaches.

Part of these projects that will promote individualised medicine and stratified biomarker discovery will be heavily data and information technology driven. There will be a major challenge for IT - in terms of hardware, storage and communication. Bringing personalised medicine into action will therefore require fundamental advances both in the computational and biomedical sciences. A particular EU project that is currently in a preparatory phase is the IT Future of Medicine (ITFoM) (http://www.itfom.eu/) project that brings together research groups from across Europe and a series of non European partners from industry and academia. ITFoM is currently developing the concept for integrating and modelling molecular, physiological, anatomical and environmental data from individual patients. ITFoM will develop models of human pathways, tissues, diseases and ultimately of the human as a whole. Individualised models for each patient (the virtual patient) will be used to identify personalised prevention/therapy schedules and potential side effects of drug treatment.

2. Access to Samples and their Analysis

Access to clinical and patient samples is critical for a complete analysis of genome, proteome and metabolom data of patient tissues and body fluids that can help to diagnose the origin/type of disease and for potential optimisation of treatment regimes. This will become increasing important for the development of new concepts of individualized health care driven by the rapid advancement especially in the next generation sequencing technologies. There are clear examples that certain drugs (e.g. Erbitux) will be only beneficial in certain genetic or absence of mutational backgrounds for example in colorectal cancer treatment in the absence of KRAS mutations (Amado al. 2008, Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol; 26: 1626–1634.)[4]

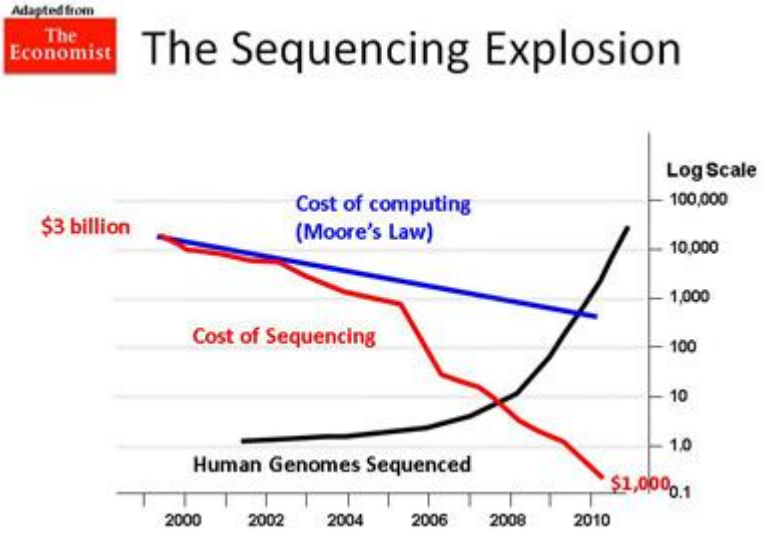
However, there are still many open questions on the functional relevance of certain mutations and their combined effect on for example cancer progression and patient survival rates. While mutational data from patients are deposited currently in large databases (e.g. COSMIC) driven by project such as the 1000 Genome project and others (http://www.1000genomes.org; http://www.icgc.org, http://cancergenome.nih.gov/dataportal/data/about) we are left with large datasets that require further characterisation and to discriminate between driver and passenger mutations. The Mutanom project (http://www.mutanom.org) and the IMI (Innovative Medicine project) OncoTrack Project http://www.oncotrack.org/) carry out systematic characterisation of such mutations found in cancer cells and is developing a systems biology approach that will in the future help to optimise diagnostics and treatment regimes.

The development of new drugs that target a broad spectrum of tumor types while providing reduced side effect for the patient has basically failed over the last decade; hence new diagnostic and therapeutic approaches have to be found. The reasons for this failure seem to lie in the complexity of the mutational profile of cancer tissues. Cancer and other multifactorial diseases are likely to be only exploited with a systems biology approach that takes into account the complex genetic background of the patients and additional contributing environmental factors (Hood et al. 2004; Systems Biology and New Technologies Enable Predictive and Preventative Medicine, Science, 306: 640-643[5]; Laubenbacher et al. 2009; A systems biology view of cancer, Bioch. Biophys. Act, 1796: 129-139[6]). Currently samples are collected for analysis of genomic data predominantly as academic exercises (as e.g. in the 1000 genome project) but will need to be expanded soon to individual patients for diagnostic purpose. A bottleneck is the systematic collection of e.g. cancer tissues in large Biobanks. Although currently being driven forward it is hampered by lack of standardisation of collection, conservation of samples and of lack of the clinical data that are relevant for the collected tissue (Riegman et al. 2008; Biobanking for better healthcare, Molecular Oncology, 2:213-222)[7]. On the other hand there are ethical issues that require strict control of who can access such samples and what analysis are permitted and should be made publically available.

3. Provision of facilities

Development of functional genomics technologies has advanced very much with respect to the information we can obtain now in a relatively short time (currently 7 to 10 days for whole genome information) at costs of roughly 1000 to 2000 Euro per genome. However, such facilities are not yet available to the general public health system but are carried out as research projects in large university departments, research institutes or by industry (for example at the Sanger Institute England; MPIMG in Berlin Germany).

Although examples are already published (Roychowdhury et al. 2011) routine diagnostic sequencing on a whole genome and/or transcritptome level is still something to be attained in the future. The reasons for this are several fold: (a) sequencing facilities that can provide such information are in the price range of several 100.000 to several Mio EURO (depending on the throughput and type of data to be obtained) (b) more efficient pipelines for sequencing data analysis have to be developed, (c) the relevance of the obtained data with respect to causative mutations or genomic variations has to be validated. As the sequencing efficiency and performance is increasing exponentially, sequencing costs are dropping (see Fig. A).



In addition improved algorithm for data analysis are developed by both commercial suppliers and by academics. However, the validation of which mutational background might lead in what individual patient to what disease is still our major challenge (Kahvejian et al 2008; What would you do if you could sequence everything?; Nature Biotechnology; 26: 1125-1133)[8]. Only a combined international effort will permit the unravelling of the consequence of the large variety of e.g. complex cancer genomes on a cellular and patient level to develop new diagnostic and therapeutic tools. This will provide then opportunities to integrate whole genome like sequencing as a true diagnostic tool in hospitals or doctor's praxis. We already see national or European projects such as Mutanom, Treat20 or OncoTrack that are trying to implement whole genome sequencing as diagnostic and predictive tools in close collaboration with the clinics, pharmaceutical industry and academic research institutes. Additional effort is required to avoid that certain population groups of patient groups are left behind (Need & Goldstein, 2009; Next Generation disparities in human genomics: concerns and remedies; Trends in Genetics; 25: 489-494[9]).

4. Preventive Interventions

There are currently two areas in medicine where true prevention is applied: vaccination and hygiene. Most other preventive measures aim for an early detection of upcoming symptoms of a disease to provide early treatment with better prognosis for cure or for slowing down the progress of disease. An efficient intervention that truly prevents a health problem would require good criteria to assess an individual's predisposition for a certain disease at young age. Preventive interventions are usually not evidence based, as it is difficult to perform long term studies without knowing who is at risk in advance. A tremendous amount of research has been conducted to identify genetic factors like SNPs or copy number variations that predispose to a certain disease. The negative or positive predictive value based on such genetic profiles is in most cases very low. Good algorithms to combine different genetic factors with biometric and lifestyle parameters for an integrated risk

assessment need to be developed. Systembiology may help in the future to explore the interactions between different internal pathways and nutritional, lifestyle and environmental factor and come up with risk prediction that reflects a holistic picture of an individual.

Table 1

- Intrinsic Risk Factors for AMD
  - **Genetics (polygenetic)**
  - **Age**
- Extrinsic Risk Factors
  - **Smoking**
  - Bright Sunlight
  - Hypertension
  - Oxidative Stress
  - Inflammation
  - Overweight
  - Malnutrition
  - ...others

A good example of risk assessment with combing a strong genetic component with biometric and life style parameters is the risk prediction for developing age related macular degeneration (AMD). This disease will have an increased impact on public health due to the demographic changes in western societies. During the world congress of the AMD alliance in Vienna 2010 the massive burden of visual impairment on the health care system and economies was reported. AMD contributes significantly to the economic burden with 20% of people at age of 65 having an early form and>5% at age >85 will suffer from end stage AMD. The genetic disposition can be tested with an assay characteristic comparable to the prediction of coronary heart disease according to the Framingham criteria, which is widely used and accepted in internal medicine. The international AMD alliance recommends: “Persons known to be at risk for AMD should take precautions that may help prevent development of AMD. They should have regular comprehensive dilated eye exams, not smoke, eat a healthy diet, exercise, maintain normal blood pressure and weight, and protect their eyes from the sun. Persons who have been diagnosed with dry AMD (which almost always precedes wet AMD) should have annual comprehensive dilated eye exams and take the AREDS formula if so advised by their physicians.” It is important to note that the genetic disposition contributes significantly to the development of AMD. But other factors have to be taken into account as well (table1). The role of psychosocial conditions, early forms of dementia may further deteriorate the condition of a patient. For an effective intervention all the problems listed in table 1 need to be addressed including the socioeconomic and psychosocial situation of the patient. Analysis of the genetic disposition is the earliest criteria to identify people at risk. Based on the degree of genetic disposition attention should be addressed to avoid the other risk factors which in part are lifestyle and/or nutrition related. A successful intervention requires well informed physicians, co-operation of the patient and his family and a health care system which supports those with the highest risk score to get access to formula recommended for prevention of AMD.

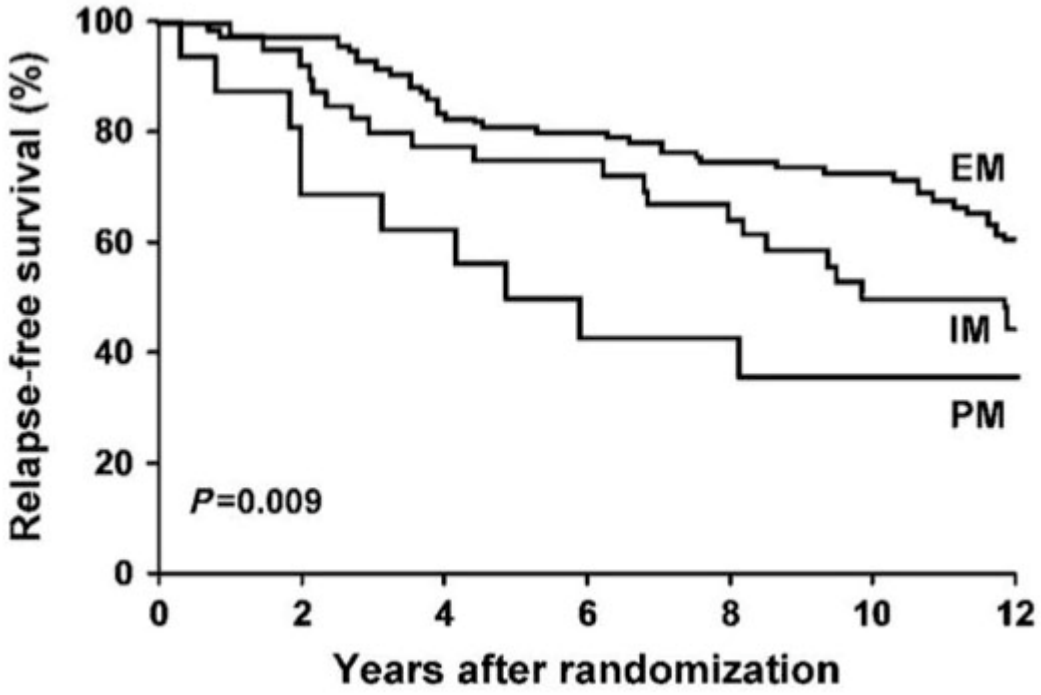
The lesson learned from AMD applies in similar way to other age related health problems like diabetes, osteoporosis and Alzheimer disease.

5. Pharmocogenomics

Pharmacogenomics deals with the genetic variations on drug response. Knowing the genetic make-up of a patient's drug metabolizing enzymes, drug transport proteins or drug target proteins can be the basis of an individualized selection of the appropriate drug and dosage. The hope is that efficacy of drug treatment can be improved, whereas the rate of non-responders can be reduced. Deleterious side effect can be avoided, if unfavorable alleles are excluded in advance.

There are two fields of applications for molecular diagnostic preceding a medication. Many modern drugs used in anti-cancer therapy target certain regulator proteins or components of its pathways (e.g. receptors, signal peptides) that have been activated by somatic mutations. An extensively discussed example is the treatment with herceptin (trastuzumab), a monoclonal antibody directed against the epidermal growth factor HER2/neu, in breast cancer patients. The receptor becomes activated by a gene amplification event. Treatment with herceptin is only ineffective and will not be reimbursed by the health insurance, if a diagnostic test fails to confirm this gene application in a tumor sample. A number of similar examples can be listed where a molecular diagnostic test can predict if a patient will profit from the treatment with a certain drug. This procedure is called companion diagnostic, because a medication and a diagnostic test accompany each other. As there is a straight forward link of the diagnostic test to the success of treatment, there is not much debate about this kind of genetic testing.

The second field of application looks at genetic differences inherited by variants in the germ line of a patient. Already when it comes to the use of anti-cancer drugs which are applied as pro-drugs, genetic variants of enzymes needed to activate the drug, are often not taken into account. Tamoxifen requires activation by the microsomal enzyme cytochrome P450 oxidase 2D6 (CYP2D6). Up to 20% of Caucasians have a reduced (poor metabolizer – PM) or increased activity (extensive metabolizer-EM) compared to the majority of the population (intermediate metabolizer – IM) of this enzyme. The response to treatment and the relapse free survival are related to the metobolizer status as published by Goetz et al. 2006 (Clin Pharmacol Ther. 2008 January; 83(1): 160–166.; see figure).



There is a controversial discussion in the literature and the scientific and medical community about the effectiveness of genetic testing for CYP2D6-genotypes even under medication with Tamoxifen and co-medication with drugs that inhibit CYP2D6 (e.g. certain anti-depressants). There is a lively discussion about what has to be rated higher: the cost effectiveness for the health system or the personal rights of a patient, who has an individual variant in his genome. This is currently one of the frontiers between personalized medicine and public health.

6. Epigenomic effects on HC

Epigentics has attracted a lot of attention during the last five years. There is increasing evidence that environmental factors have intermediate-term, long-term and even transgeneration effects on an individual's phenotype or the phenotype of offspring. Conditions, an embryo is facing in early gestation, may establish epigenetic patterns that persist throughout life and may expose the individual to disease risk. It has been shown in a Dutch population that individuals prenatally exposed to famine during the Dutch Hunger winter 1944-45 consistently displayed hypomethylation in the differentially methylated region of the IGF2-gene (DRM IGF2) (Heijmans et al. 2008, Proc Natl Acad Sci USA 105(44) 17046-17049). The first evidence for transgeneration inheritance in human came from the community Överkalix in Sweden. A demographic study revealed an association between exposure to food restriction about 100 years ago and the longevity in the grandchildren generation today. The transmission seems to be sex-specific from grandfather to grandson or grandmother to granddaughter (Bygren LO et al.2001, Biotheoretica 49:53-59). A similar correlation has been found between parental mid-childhood tobacco smoking and early growth in sons. It is suggested that these phenomenon may be due to

epigenetic marks passed on from one generation to the next. However the underlying mechanisms remain to be elucidated. Epigenetic mechanisms (in part) can explain incomplete penetrance and variable expressivity, which in the past posed questions for the inheritance of a number of diseases. Indeed for some rare genetic disorders, like Beckwith-Wiedemann syndrome, discordant methylation explains why monozygotic twins are discordant for the disease (Weksberg R et al 2002, Human Mol Genet 11:1317-1325). In the the aetiology for many complex diseases including cancer, psychosis, multiple sclerosis, epigenetic mechanisms play a pivotal role. The epigenome is affected by a number of environmental and lifestyle conditions. This includes exposure to stress, nutrition, tobacco smoking and exposure to other drugs. Also medications like 5-aza-2'deoxycytidine, valporate as well as sex hormones, vitamin D, methyl donors (folate, vitamin B12) leave marks in the epigenome with intermediate- and long-term implications. Probably this has to be considered as the tip of an iceberg. It can be expected that research will unravel more correlations between environmental, lifestyle factors and modulating effects mediated through epigenetic mechanisms. As these effects may be intermediate, long-term and transgeneration, it may be hard for public health professionals to identify epidemiological correlations and decide how and when intervention is necessary. Handel et al (Handel AE et al. 2009, Genetics 182: 1397-1398) discuss public health implication based on a model from Slatkin (Slatkin M 2009, Genetics 182: 845-850) with assumptions for the transgeneration rate of decay of epigentic marks. As no experimental data exist, the model can only present theoretical results. However, this demonstrates how urgent longitudinal studies are needed to understand the intermediate-, long-term and transgeneration implications of epigenetic on public health.

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3.8.1. ASSURING COMPETENT WORKFORCE

Identified issue

We are addressing here the following identified issue:

How the workforce mastering the skills of PHG could be developed?
What are the perspectives for this workforce?

The assessment work brought up the following useful findings

The training of the experts in PHG has to be improved and harmonized.

Background

The era of genomics ultimately called for a well-educated public health workforce that is capable of handling and implementing the genome based information. These experts should be able to recognize and give answers to the new challenges by synthesizing, integrating and applying the ample information of the fast developing field of genomics into public health thinking. Their task is also to apply this knowledge into already running public health actions as well as to develop new strategies that rely on and use the genomic information.

Workforce Competencies including knowledge- and skill competencies in the field of public health genomics for health professionals

- in clinical services evaluating individuals and families

- in epidemiology and data management

- in population-based health education,

- in laboratory sciences

- in environmental health

- as well as for leaders (managers) and administrators

should be defined as has been done partially by Center for Disease Control (CDC) (1). NCHPG (National Coalition for Health Professional Education (2)) also presented its Core Competencies in Genetics for Health Professionals: „health professionals master not only the knowledge base of their discipline, but also that they understand why, when, and how that knowledge should be applied to improve health outcomes for their patients". Although these documents contain generally useful information the EU requirements are partially different demanding its experts to be familiar with the demographic challenge, sociological, economical as well as regional issues that are specific for the EU and its regions.

3.8.2. TARGETS FOR PHG EDUCATION

Competencies can be obtained only in an education system when introducing PHG into public health thinking. Therefore it is sufficient to set up not just a program that includes the elements of PHG but provides guidelines for their education which can guarantee the knowledge and skills recognized throughout the EU. So far the involved fields for PHG experts are not clearly defined and such curriculum that is widely accepted and recognized does not exist.

3.8.3. TRAINING OF THE WORKFORCE

The aim of the PHG education is to include genomics as part of the checklist in training programs by not adding new competencies but inserting genomic aspects onto existing competencies. As it has to be delivered at different levels (MSc, BSc, PhD) therefore principles for the 'core course' and the basic learning outcomes have to be defined that satisfy the needs of a general education program. Depending on the level of education this knowledge could be further improved in each of its points.

3.8.4. ORGANIZATIONS RESPONSIBLE FOR THE EDUCATION

PHG covers a multidisciplinary field. As reflected in the proposed curriculum, to provide a coherent interdisciplinary core in the education, the participation of many different areas is required. Therefore competencies should be defined for the participating partners and the requirements that they should meet. Considering the

diversity of the curriculum it is reasonable to propose that the curriculum can be successfully delivered only by Universities and Schools of Public Healths that are able to provide the sufficient source of trained people from the involved fields.

Regarding the possibilities of inserting public health genomics into the curriculum of SPHs a questionnaire has been filled out by the heads of 31 member schools from Armenia, Austria, Belgium, Bulgaria, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Lithuania, Moldova, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Ukraine and United Kingdom of the Association of Schools of Public Health in the European Region (APSHER). On the basis of their answers the importance of PHG seems to be underestimated even by the leaders of the most relevant training sites. In the SPHs where PHG is already in the curriculum (12 out of 31), it is integrated such as “Genetic Epidemiology” or “Public Health Aspects of Human Genetics” modules into bachelor and/or master courses (7), while in few others it appears in traces as few lectures in the framework of a not clearly specified module. Great part of the responding schools has no PHG elements in the curriculum (19 out of 31), and the majority of them (15) declared that they do not intend to insert any PHG training into the curriculum in the future.

3.8.5. LEVELS OF TRAINING

Different forms and levels of trainings have to be launched to meet the levels and requirements of different professionals. Undergraduate (BSc) graduate (MSc) and postgraduate (PhD) levels are needed also in the field of PHG considering that the knowledge background and the future aims differ among the students. Education program should also represent a continuity that would allow continuing and upgrading education.

3.8.6. REFLECTING LOCAL LEVELS IN EDUCATION

Problems and aims recognized EU wide but at the same time reflecting the regional economic as well as the cultural differences faces a great challenge. With the aim to stick to the mainstream concepts and at the same time meet the local levels is an

important task. Identifying common problems and translating those into education has to be done. Coordination and monitoring of the activities should be done by the recommendations of the EU.

3.8.7. QUALITY CONTROL IN EDUCATION

Professionals all have different backgrounds of education as well as different roles in the service system therefore the training programs should be designed to target special needs. The success of the education greatly relies on the pre-education of the candidate students and the level of their knowledge. This requires a great attention and should be kept in mind that dealing with the rapidly improving field of genomics faces difficulties even in the populations that are trained at the highest level in genetics. Thurston et al. reported on a survey demonstrating that only 47% of U.S. and Canadian medical schools incorporate genetics into third- and fourth-year teaching (3), while Greb et al. pointed out that third-year medical students are largely incapable of applying genomic knowledge learned in their first year of training to clinical encounters (4). In line with these findings in our teaching experiences we also found that psychology students have troubles on defining genotype and phenotype, understanding modes of inheritance, the role of family history, genetic susceptibility, as well as genetic background of health behaviour. Keeping these in mind we should not promote a rote memorization of the roles genetics play but prepare the candidates to be able to incorporate the knowledge and methods of genomics into their practice, including sceptical and critical analysis.

3.8.8. ROLE OF E-LEARNING IN PHG EDUCATION

Developing an e-learning platform is a beneficial way of education providing quality and diversity. The success of the education relies on many pillars: people both as teachers as well as students are from a great variety of fields and many of them are to be participating in the frames of MSc programmes. Time and distance therefore call for a solution. On the other hand its limits should also be clarified like some parts of the curriculum have to reflect regional issues where personal connection between the partners is still essential.

3.9.1. PROVISION OF MONITORING SERVICES

Identified issue

We are addressing here the following identified issue:

PHG faces a challenge on how to implant currently available PH activities into its field.

The assessment work brought up the following useful findings

Currently available monitoring services are incapable of providing sufficient data for the needs of PHG.

Background

Monitoring and Evaluation plays a central role in gaining information about the success of a public health action and to define whether it is making positive contributions towards improving the population's health. The key questions to identify, what exactly to be monitored and evaluated and how this could be carried out, greatly differs in the public health genomics field from the 'classic' public health interventions as many 'traditional' indicators are not applicable to the field of PHG. The high amount of data from genomic research should be translated into health care objectives and its relation to public health should be addressed. Therefore PHG has to plan how to develop the set of relevant and available indicators and how to translate them into public health with the aim to make it informative over the health status and sensitive to changes over time. In order to overview and to follow up the recent advances in genetic disorders and diseases associated with genetic alterations the design of the monitoring systems should be revisited and improved making genetic background visible in the monitoring systems.

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3.9.2 PROBLEMS IN THE IDENTIFICATION OF TARGETS AND INDICATORS

Development of indicators that are relevant, reliable, useful, valid, applicable and feasible is crucial for the assessment of the present situation in the filed of PHG and also for the monitoring activity of health policies.

As the eleventh revision of WHO's ICD is due by 2015, public health monitoring services have to start building up their on evaluation system before the update of the ICD comes out representing the challenges that the field faces. In order to provide a useful database for public health actions, in the upcoming versions of IDC, public health specialists especially from the field of genetics – experts in public health genomics - should prepare for a major task in defining how data collection should be carried out and to define the aspects that should be represented in the new classifications in order to find common objectives with other users of the database. To extend the scope of public health monitoring services onto the filed of genetics proper databases should be developed with the necessary information for the experts to see clearly the problems that need actions.

WHO's International Statistical Classification of Diseases and Related Health Problems (ICD) *is the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use. These include the analysis of the general health situation of population groups and monitoring of the incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and circumstances of the individuals affected, reimbursement, resource allocation, quality and guidelines. It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and*

quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States (http://www.who.int/classifications/icd/en/). ICD is widely used as a catalog in which clinicians can search for a diagnosis to form study groups, and also essential for researchers to give them clinical descriptions to make sense of molecular information. The current ICD codes have two axes: morphological and topographical, which are not providing selected information on diseases with genetic background. To a geneticist, a tissue (endothel, skin, bone, connective tissue, and subclasses) are more meaningful entities than which part of these tissues are geographically located. As an example, the endometrium in the female uterus is from a tissue point of view close to identical with the endothel of the colon, and inherited colon cancer (MMR mutations) implies a close to equal risk for endometrial cancer as to colon cancer in females.

In the field of public health the information available through ICD based databases plays a pivotal role in health monitoring systems at local as well as at international levels, providing solid data for decision makers on mortality and morbidity. Unfortunately the expanding data on the genetic background of various diseases are not or under represented in the current ICD classifications: genetic disorders were given 32 categories in the sixth (in 1949), and 709 in the tenth revision that is still in use since 1992, before the human genome developments. It is needless to say that in the genome era the great number of evidence that genetic associations can be found and are behind many diseases have rapidly increased. Only in the field of dermatology about 90 such disorders were cataloged in 1991, that reached 580 by 2006 and is approximately 1.000 by 2011 (Moss C. JID, (2009) 129, 2543–2545). This rate of expansion can also be seen in other fields of medicine calling for a precise handling of the genome based information in the updating of ICD catalogs as well as for a change in the method of classification to provide useful databases that are compatible with the work of clinicians, researchers and policy makers in the fields of public health.

As genetics is about causes having consequences, it was immediately obvious that the ICD concepts were not applicable to understand genetics. McKusick made a list

of inherited syndromes, currently to be the universal catalogue systems for such (OMIM - http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim) . This is the agreed nomenclature for rare inherited disorders presenting themselves in early life, but it is not developed to have any useful meaning for inherited cancers. ORPHANET (http://www.orpha.net/consor/cgi-bin/index.php) basically builds on OMIM.

The agreed nomenclature for genetic variation is HGVS (see http://www.google.no/search?q=hgvs&ie=utf-8&oe=utf-8&aq=t&rls=org.mozilla:nb-NO:official&client=firefox-a). This is constantly developing. To have any idea about what genetic variation is, one will have to define a lot of parameters, including where the genes start and stop, what is the 'wild type' (= 'normal') and how to denote deviations. This is part of a large devloping body of international collobarative efforts. The VARIOME project (http://www.humanvariomeproject.org/) has the modest goal of compiling everything to everything, as to learn how any genetic variation correlates with any human phenotype.

To develop some European standards, EUROGENTEST was established some time ago (http://www.eurogentest.org/), but they are basically finished and the ongoing efforts are huge and to what degree they are competing in the future is unclear.

In the framework of the Health Monitoring Programme and the Community Public Health Programme 2003-2008 the EU began an integrated approach to establish European Community Health Indicators (ECHI). Activities toward the development of indicators cover five phases: analysis of data needs in their respective area; definition of indicators and quality assurance; technical support for national efforts; data collection at EU level; reporting and analysis; and promotion of the results. The ECHIM umbrella develop indicators for : Mental health (MINDFUL and WP on Mental Health); Cancer (Eurochip and CAMON); Diabetes (EUPID); cardiovascular diseases (Eurociss); lung diseases (IMCA); Musculoskeletal disorders (MSD); oral health (EGOHID); injuries (WP accidents/injuries); perinatal health (Peristat); Child health (CHILD); reproductive health (Reprostat); health in intellectually disabled (POMONA); lifestyle indicators connected to cardiovascular diseases, diabetes, other major diseases (EHRM); Nutrition (EFCOSUM, Dafne and Public Health Nutrition);

Environment and Health (ECOEHIS); Working Environment (Workhealth); health promotion (EUPHID).

3.9.3 PROBLEMS IN THE EXPECTED OUTCOMES

1. Probably the hardest task is to deal with problems that are specific to genetic diseases such as the fact that a single gene can cause more than one disease and, conversely, a single disease can be caused by different genes. Overlapping networks of genes responsible for the same clinical signs and the rapidly growing numbers of SNPs that have various levels of impact on disease development and progression should be clearly represented as well.

2. The way that clinical practice integrates research into everyday practice is also of high importance. The number of publications on SNPs and other genetic variations exceeds the limits of any possible monitoring services therefore protocols are needed to define what can be integrated into monitoring activities.

3. Besides identification of diseases with well characterized genetic backgrounds the confirmation of the underlying genetic variance is dependent on the financial as well as the facility background available. Therefore economic status of a health care system has to be taken into account when defining the needs of these improved databases.

4. When considering the effects of genetic susceptibility quantitative effects on gene expression, and qualitative effects on protein function, are also important. Most of the therapeutic approaches are not targeted against the genetic defect itself but against the encoded protein.

3.9.4 TRANSLATING OUTCOMES INTO OBJECTIVES

The properly identified indicators for PHG should enable experts to measure the impact of prevention, diagnosis/screening and care, allow policy makers to identify factors that are related to the ethiogenesis, and provide answers to differences due to geographical or ethnic differences. These can be achieved only with data from clear and reliable databases that are recognized and constantly harmonized.

3.9.5 DEFINING OBJECTIVES SUITABLE TO DETERMINE FUTURE GOALS

Member States of the EU all follow their own guides in collecting, processing and classifying data. Therefore some data might have been collected already but in different ways. Therefore making data comparable is a great challenge.
The goals can be classified into two major fields:

1. Conclusions regarding the current state of genetic related disorders in a population or in a region that allows to design actions and screening programs.

2. To define the role of the genetic background and susceptibility in the measures of other diseases which are not primarily related to genetic variations.

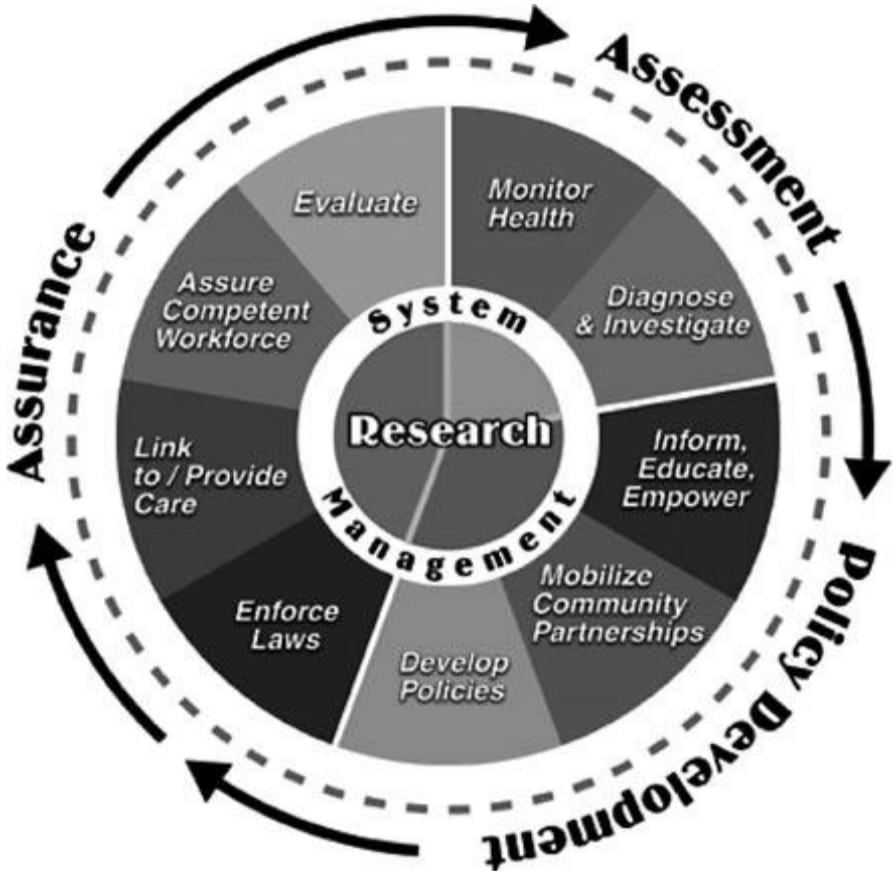
3.9.6 RISKS IN THE VALIDITY OF THE DATABASES

The purpose of these databases is not to monitor the health status of an individual but to see the whole population as one. Therefore these databases designed to collect data on the levels of individuals should be applicable to perform population wide searches without the loss or the false modification of the information. The

success of these databases highly depends on the data put in and the method it is used for data analyses.

At the present ICD codes are used widely for morbidity and mortality statistics, reimbursement systems, and automated decision support in medicine as well, therefore highly trained professionals are needed for the coding who also understand the driving force and the aspects of genetics in the coding.

3. The Guidelines (following the wheel per section of the wheel)



ACTION PRINCIPLES (10 Essential Pubic Health Tasks):

Research (Task 10: VU group)

3.10.1 Recommendations
a *(text here)*
b
c…

3.10.2 Best Practices
a *(text here)*
b
c…

3.1 Monitor Health

Recommendations:

- Adapt and expand current monitoring system to allow for monitoring of health and health needs across the life course for groups of individuals such as families, ethnic and migrant groups as well regions within country and socioeconomic groups.

- Design or adapt a routine monitoring system in a way that allows linkage of data from different sources including clinical notes, routine health and social registers and biobanks.

- Aim for standardisation of the methods for data collection and encourage data sharing for research and evaluation.

- Consider introducing new monitoring systems for detecting problems and improving health and life style of prospective parents.

- Adapt new emerging methods for causal inference to evaluation of interventions and policies based on genomics and explore designs for evaluation of interventions based on DOHaD and life course aetiology of health and disease.

- Preserve strong links to research and encourage collaboration and information sharing in evaluation efforts.

3.2 Diagnose and Investigate

In line with the above surveillance functions this assessment function can both (broad interpretation):

a) confirm and document the importance of health problems, and

b) evaluate whether the emerging technologies can be effectively/efficiently used and are appropriate to counter/solve health problems.

- The latter (b) thus combines the previous information and relies on (adapted) health technology assessment, including the ELSi (Ethical, Legal, and Social Implications) and organisational components. The ELSi and organisational components should lead to the definition of the optimal conditions of use for the emerging genome-based technologies and information (including safeguards). If projections are made of the likely consequences of use, a kind of a priori health impact assessment can be realised.

3.2.1 Recommendations

a) Clinical Guidelines on Diagnostics

1. Research should direct its effort towards the identification of universal criteria to prove the validity of genetic tests, considering sustainability and the potential risks related to the extended misuse of such tests.

2. The major challenge for public health genomics is to generate an evidence base, robust, confirmed and validated scientific data (Evidence Based Medicine, EBM), to demonstrate when use of genomic information in public health can improve health outcomes in a safe, effective and cost-effective manner.

3. The task of health professionals and politicians, over the next years, will be to clarify the conditions under which the 'genomic revolution', already underway in the medical field, will yield its benefits in the field of Public Health.

4. Despite the current scenario is characterized by a lack of strong evidence, it is necessary to start with a full assessment to allow the community to achieve a proper awareness about the use of predictive genetic tests.

5. Investments are necessary to fund studies able to assess the possible applications of genome knowledge into clinical practice by the public and private healthcare, and private companies.
6. For complex diseases should be considered not only the inherent characteristics of the test (specificity, sensitivity), but also the availability of effective and acceptable means of prevention and any possibility of harmful effects (clinical utility).

7. The offer of testing to the single patient should result from individualized clinical considerations, in particular the clinical utility, and not only from the a priori risk.

8. For complex diseases it may be useful to analyze the genetic profiles and consider, at the same time, the exposure to environmental risk factors, taking into account the mode of interaction between different elements, which can be very complex.

9. It is essential to stimulate scientific research to produce evidence not only of clinical efficacy but also of cost-effectiveness on tests that will become available through collaboration among public health professionals, geneticists, economists and policy makers.

10. To address the uncontrolled diffusion of direct to consumer tests, it is necessary to provide a correct information, scientifically supported by valid evidence.

b) Genomic Screening & Screening on Newborns

1. Presymptomatic testing in minors shall generally be limited to conditions where there is direct benefit, because early treatment can prevent irreparable damage.

2. NBS programs should avoid as much as possible unintended findings.

3. Screening goals and benefits should be assessed versus goals and benefits established/accepted for other clinical and public health interventions and strategies adopted in the country.

4. 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.

5. The quality of a screening program depends on the quality of each step in the chain of events, in which the involvement of several health care providers is essential.

c) Priority setting

1. The integration of Genomics into Public Health has the potential to:
    a. create more targeted and cost-effective public programs of prevention.
    b. to increase the impact of campaigns and messages of risk reduction.
    c. to promote communication and exchanges between the different areas of health care system.
2. In order to succeed in integrating genomics into public health it is necessary to set priorities, educate and motivate professionals and experts to develop appropriate communication strategies.
3. The complexity and the transversality of genomics require that, in the translational process, different areas of research and multidisciplinary teams of experts are involved.
4. It is necessary that professionals, who are involved in these programs at various levels, acquire the necessary skills; in the end, the potential user must be made aware of the potential of genomics.
5. It will be necessary identify and promote those fields of biomedical research, even in the industry who have a higher potential to bring benefits to improving the health and treatment of diseases.
6. It will be necessary to promote models that integrate research findings into policies and clinical practice of public health.
7. The Capacity Building Process in Public Health Genomics requires collaboration among all stakeholders at different levels: institution for the governance of genomics, network of researchers, technological consortia, multidisciplinary care networks, educational networks, communication network.

8. It is necessary to establish a working group, recognized by the major scientific societies, with the task of proposing guidelines for the governance of genomics information, that can optimize the resources and capacity, which has durability and will reduce the risks of self-referentiality. This group should produce shared documents information contained in them shall become operative across the country.

9. The establishment of an European network of excellence is important to coordinate a valuable collaboration among national networks.

10. At local level must be identified and strengthened the centers that will form the networks of excellence that must meet quality criteria well defined and certified at national and international level.

11. The process of implementation of genomics into public health will require the integration of new competencies, especially by clinicians, with knowledge of the pathophysiology and pathogenesis of diseases, genetics, genomics and bioinformatics.

12. With regard to health care professionals it will need to identify the skills required to be featuring the different professional figures:

    - physicians operating on the territory (General practitioners, paediatricians, internists)
    - Medical specialists not geneticists;
    - specialists in medical genetics;
    - laboratory technicians specializing in medical genetics;
    - professionals in the sector specifically trained (nurses, health care assistants);
    - laboratory technicians specializing in clinical biochemistry and molecular biology;
    - laboratory technicians specializing in clinical pathology;
    - other professionals involved (nurses, psychologists, social service workers, bioinformatics engineers, physicists, mathematicians etc.

13. At general practitioner level information and education in Genomics needs to be provided good enough only to identify patients at risk and refer them to the local clinical centers specific for the condition (for example thrombosis centres).

14. Laboratories performing the tests needs to be reorganized in order to be able to accept large number of samples from several clinical centers. Small laboratories need to be closed or incorporated in larger ones.

3.2.2 Best practices

a) Clinical Guidelines on Diagnostics

1. It is essential that the competent authorities take charge of disseminating the results of the first systematic assessments relating to predictive genomic tests available throughout the country, in terms of applications to the prevention and diagnosis.

2. Only tests of proven clinical utility and cost-effective should be implemented in clinical practice and offered within the National Health System (NHS), on the basis of principles of suitability and sustainability.

3. The evaluation of the clinical utility of genomic tests on common complex diseases should always be carried out before large scale application of the tests within the Public Health programs of evaluation.

4. It is necessary to develop and disseminate standardized processes based on the evidence of the overall assessment of the applicability of genetic testing before their introduction into clinical practice.

5. It is necessary to define specific paths for the clinical use of tests for complex diseases [*susceptibility testing for complex diseases*] with the help of all stakeholders and the development of research programs and assessment systems.

b) Genomic Screening & Screening on Newborns

1. Laboratories should be certified and participate in external quality assurance/control programs.

2. Facilities should be available for adequate surveillance, prevention, treatment, education, counselling, and social support.

3. Within a jurisdiction the number of laboratories should be limited.

4. Optimal quality performance and cost effectiveness requires a minimum number of samples handled, such as 30000-50000 samples per year.

c) Priority setting

1. Guidelines for best practices in genomics must be produced in order to assist European countries to integrate, in a responsible and prompt way, genomics in Public Health.

2. It is necessary to promote investments in dedicated infrastructures and networks and to support emerging initiatives, such as the creation of database that allow a systematic data collection and the constant supervising and updating of the same.

3. Appropriate policies should be developed at different levels: information, education and empowerment of physicians, patients and citizens.

4. A plan must be define to coordinate and suggest the basic levels of specialized training and the core competencies to the associations of the different health care professionals.

5. The education program needs to define the content of the training and the levels of application, to be discussed with the different health care professionals.

6. It is necessary to enable the partnerships at the community level between the different actors involved in the 'genomic revolution', that means a collaboration between stakeholders, networks of excellence, and an interaction with the political goals to develop appropriate policies for best practices.

7. It must be built a control system that ensures compliance with the regulations, allows transparent comparison of the various delivery systems of welfare benefits, ensure the presence of competent, trained professionals at every level, and that assess in a constructive manner way the quality of services provided.

8. The identification of pathways for each testing and the critical evaluation for the introduction in the NHS could be easily defined by a committee or a national working group that included representatives of all stakeholders, which should however be different from those involved in the organism of governance.

9. The indications provided by the network of excellence will have to find immediate applications to operational levels, in particular those of assistance and training.

10. At regional level, clinical centers for specific conditions need to be identified and they should be the only professional authorized to prescribe genomic tests.

11. Each clinical centers need to be linked with the nerwork of the specific pathology and needs to follow common admission criteria before prescribe the test.

12. It is important for the laboratories to achieve a very qualified experience performing a minimum number of test per year.

13. All the existing guideline for the laboratory of medical genetics are very important to be adopted (Quality system as ISO standards, 9001 and 15189; external quality assessment; ...)

14. An automation of all the process and implementation of the bioinformatics tools needs to be done in order to face the increasing numbers of test requested and maintain the quality and competence in the field.

As example of description of the process to apply genomic to clinical practice we reported the table below:

PHASES (1)	STAKEHOLDER (2)	REQUIRED SKILLS (3)	CAPACITY BUILDING PROCEDURES (4)
Application Health Technology Assessment report	Public heath expert, geneticists, policy makers, experts in organization, health economists; healthcare services management	Knowledge of the HTA methodology	Training Evaluation of the availability of resources, ethical, legal, social, political and organizational aspects
Test Supply	Geneticists and other clinicians (for individual supply)	Genetic basis of disease, patterns of gene-environment interactions in multifactorial diseases, applicability and limitations of genetic testing. Detailed knowledge of the clinical aspects and physiopathology of the disease concerned	Local training on the territory and upgrading of university curricula. Development of multidisciplinary networks between geneticists and other clinicians.
	Public health experts and geneticists (screening)		Information and proper communication to the population involved. Evaluation of organizational aspects. Development of multidisciplinary networks between Hygienists and other clinicians.
Informed Consent	Geneticists and other clinicians;	Ethical, legal, social and clinical implications	Structuring of an integrated system between the actors

(elaboration)	patients' associations, ethics committees	relevant to the user. Communication skills.	involved.
Test execution	Genetic laboratories	Presence of managers with expertise in medical genetics.	Biotechnologists Skills Quality control (laboratory) Quality certification. Professional accreditation.
Results interpretation	Laboratory geneticists; clinical geneticists and other clinicians	Knowledge of genome variability mechanisms and their role in disease processes, knowledge of the characteristics of the test.	Bioinformatics skills Quality control (laboratory) Local training on the territory and upgrading of university curricula. Close interaction between laboratories and clinicians.
Results Communication to the applicant	Clinicians: geneticists and other specialists; laboratory specialists; nurses, health assistants, psychologists, ethicists, sociologists	Knowledge of genome variability mechanisms and their role in disease processes, knowledge of the characteristics of the test, detailed knowledge of the clinical aspects and pathophysiology of the condition in question, and of the clinical options available. Ethical, legal, social and clinical implications relevant to the user. Communication skill	Quality certification. Professional accreditation. Development of multidisciplinary networks between geneticists and other clinicians. Information and proper communication to the population involved. Evaluation of organizational aspects. Development of networks between Hygienists and other operators.
Sensitive data protection	Policy maker, ethics committees, geneticists; computers	Legal, information technology and bioinformatics expertise.	Training of personnel dedicated to the creation and use of encrypted database. Organization of Bioinformatics networks

	experts; healthcare structure		
Definition of the clinical and supporting path on the basis of results and choices of the applicant	Clinicians; nurses, health assistants, psychologists, social service workers, patients' associations; Hygienists; bioethicists.	Knowledge of the clinical implications of the identified variations and methods useful for clinical monitoring, laboratory and instrumental, as well as possible preventive. Possible impact on reproductive choices. Organizational and managerial skills.	Development of diagnostic and therapeutic care paths with training of the operators involved; organization of multidisciplinary working groups
Family approach	clinical geneticists; psychologists, social service workers, bioethicists, sociologists, patients' associations, general pratictioner and pediatricians, policy maker	Ethical, legal, social and clinical implications relevant to the family. Communication skills	Organization of public information campaigns and local support networks.

3.3 Inform, Educate, Empower

- Knowledge transfer to macro, meso and micro level decision-makers to empower them with respect to decisions based on information regarding health problems and needs, adequacy of emerging technologies as solutions, limitations of technologies, gaps in the knowledge base, ELS issues…
- Guidance on knowledge transfer strategies, on information repositories, on information needs, on optimal presentation of information (on risks for instance), on issues of health literacy….

The main questions for the provision pillar related to the education/information of the public are:

- What should professionals do provide adequate class / school education and the improvement of curricula of relevant courses?
- What should professionals do to provide/assure the establishment adequate public information campaigns directed at the public?

- Table 1. Suggested nomenclature

Term	Includes
Professionals involved	Medical geneticists, treating physicians, other health care employees, media, government, school system.
Serious disease	Significantly reduced length of life and/or quality of life
Inherited disease	Serious disease with demonstrated genetic cause and penetrance more than 25%
Penetrance	Fraction of persons with genetic predisposition who are affected.
Age-related penetrance	Most inherited diseases are not present at birth and their penetrances are functions of age. If not otherwise mentioned, 'pentrance' means fraction who were affected at age 70 years
Familial disease	Disease aggregations in families without a demonstrated genetic causative defect. Examples: Familial breast or colorectal cancer

	without a demonstrated causative mutation in the family. Rheumatic disorders, diabetes or malignant melanomas caused by low penetrant genes in combination with environmental factors.
Genetic counseling	See www.eurogentest.org

- Table 2. Who is doing what?

Task	Delivered by	To whom
Genetic counselling	Medical geneticist (and collaborating genetic counsellers)	Persons with, at risk for, or having reasons to believe to be at risk for inherited disease
Information on inherited disease demonstrated	Examining/treating physician diagnosing/treating the disease in question.	Patients with demonstrated inherited diseases.
Information on familial disease	Treating physician / GP	Patients with familial diseases and their relatives
Information	All professionals and government	To population, if stratified on target groups, inherited disease in collaboration with medical geneticists. School included.
Media communication	All professionals and government	To population, if stratified on target groups, inherited disease in collaboration with medical geneticists.
Establishment of information campaigns	All professionals and government	To population, if stratified on target groups, inherited disease in collaboration with medical geneticists.

3.3.1 Class/school education

3.3.1.1 Recommendations

a The alarming lack of attention towards the need of genomic school education on European level needs urgent action.

b. Unified European science learning goals for all educational levels need to be developed.

c An intensive collaboration among EU members is not only necessary but compulsory, in order to synchronize such developments in school curricula and prevent major discrepancies between countries.

d To empower future citizens, school genomic education for all school ages should be established. It should promote the acquisition of life skills, such as being able to make informed decisions about practical life issues related to genomics, as well as understanding the implications of the new genomics knowledge for society.

e New concepts in the biology and in other science curricula, can be introduced.

f A process of preparing and motivating school teachers needs to be initiated. Forming networks of programmes for education of teachers in this field, both in less and more developed countries should be a priority.

3.3.1.2 Best Practices

a The *'DNA labs on the Road' a school based approach where students get the chance to try out the latest genomic technologies.*

b The "Public health genomics foundation" has developed educational materials directed at different target groups, including children below and above 8 years old: http://www.phgfoundation.org/pages/edu_resources.htm

3.3.2 Establishment of adequate information campaigns on genomic issues

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3.3.1.1 Recommendations

a. The provision of adequate information and education for the public is vital and this has to take place before communities are exposed to medical research involving genetic screening and testing, let alone the applications of genetic intervention for the prevention or management of disease.

b Before the introduction of genomic education to the public monitoring of public perceptions of different aspects of genomic research, especially as it relates to medical practice, will be of particular importance. Such surveys have an increasingly useful role in encouraging public debate on how far society should move in research and development relating to genomics while, at the same time, providing stimulation for the public to become better educated in the complex issues involved.

c In order to prevent and overcome the existing already discrepancy among European countries with regards to research on public genetic awareness and access of the public to educational information it is necessary for coordinated uniform policy and action plan to be developed for all member states.

d Experience suggests that the success of information campaigns depend on the media, particularly television. For this there is a need of well-informed body of science journalists and, here again, there are major opportunities for regional networking.

3.3.1.2 Best Practices

a In United Kingdom both government and charitable bodies have developed networks between scientists and the media such that the press and television industry can obtain expert advice as new scientific developments occur. Many research institutions run open days for the media and a variety of organizations are involved in furthering public understanding, awareness and appreciation of science.

b The UK Public Health genomic foundation

c. The Dutch centre for society and genomics which describes, analyses and improves the relationship between society and genomics research. By doing so, CSG improves the way in which genomics meets the expectations and needs of society.

d The activities of the office for Public health genomics at CDC.

3.4 Mobilize Community Partnerships

- This task can be viewed as a major role for the National Task Forces (bringing together genetics, public health, policy makers….) and is an extremely important input for policy development
- Guidance on new business models (health technology life cycle etc.) as well as guidance on stakeholder involvement, setting up of sustainable infrastructure for National Task Forces, ….

3.4.1 Recommendations

a. Provide genome-based information and technologies in line with the P4 medicine requirements of being predictive, preemptive, personalized and participatory.
b. Inform patients/consumers about the possibilities and limitations of genome-based information and technologies.
c. Base policies and procedures concerning personalized medicine on wide public stakeholders' consultation and ensure a balanced representation of stakeholders' interests, namely those related to ethical, legal and social issues (ELSI), e.g., ethical standards of human dignity, including autonomy; professional health care standards; social justice in health resource allocation and use.
d. Mobilize the relevant stakeholders, e. g., public policy decision-makers (including funding agencies), health care providers, researchers, education and research institutions, scientific societies, health products industries, media, patient advocacy organizations, and lay people groups.
e. Promote empirical research to assess the various risk factors involved in using PPPs in the provision of genome-based information and technologies. Most PPPs are still very young, and the evidence on performance and broader governance issues is only just emerging. Ideally, such assessments should include comparisons with a purely public alternative.

3.4.2 Best Practices

a. Set up national PHG Task Forces, bringing together public health practitioners, geneticists, HTA officials and public policy makers, to listen to, learn from, and contribute public health and genomic expertise to different stakeholders.
b. Offer technical advice to lay people and professionals on the provision of genome-based information and technologies
c. Apply up-to-date tools for health and genetic literacy enhancement to support people in negotiating the complex demands of health in modern society, and in personalized medicine in particular.

d. Involve and foster the participation of community stakeholders towards filling the wide knowledge gaps that exist between scientists, the public and different professional groups through an open and well-informed debate, using a wide range of communication tools (e.g., focus groups, public *fora*, citizen's juries, conventional and web-based media).
e. Provide timely, personalized, culturally appropriate counselling to those being exposed to genome-based information and technologies (e. g., patients and their relatives, screened population segments, general population). Counselling activities should include scientific matters as well as ELSI, including the motivation for, and appropriateness of using direct-to-consumer clinically relevant genetic tests.
f. Organize information campaigns (in the media, schools, health institutions, civic centres) that allow and encourage mutual communication to take place between professionals and non-professionals, recognizing the heterogeneity within the population (both lay and professional) concerning age, sex, social class, education, cultural/ethnic origin, geographic area of residence, and religious persuasion and other values.
g. Support the activities of the relevant NGO's (of, e. g., patients, carers, service users, 'watchdog' groups, citizens) in order to stimulate an active participation of their membership, who own a special knowledge, experience and a unique perspective, to be complemented with health/genomic literacy. The latter could be achieved by translating findings from genomics, epigenomics and systems biomedicine to help to understand that individual biological pathways or networks are permanently interacting with environmental networks such as social networks.

3.5 Develop Policies

- A broad interpretation can encompass under policies: laws and regulations, governmental policies, professional guidelines, quality assurance measures, different types of safeguards …
- Guidance on existing forms of regulation, development and maintenance of specific forms of regulation, harmonisation issues, …

3.5.1 Recommendations (according to the 5 main areas) a) Public Education and Public Engagement; b) Research and Development; c) Regulation and Reimbursement of Genomic based technologies; d) Building Capacity; and e) ELSI.

a. *Public Education and Public Engagement*
   - General and tailored information should be provided on genetics to the population and the media, to reduce uncertainty, minimize unnecessary queries and increase the collective knowledge in a sensitive area in the management of information and its interpretation.
   - Explore the use of internet and social networks to promote this interventions

b. Research and Development

• Genomic and its development, considered as an emerging technology, is closely linked to research. For this reason, it should be explicitly disassociated what is related to care services and which is included within research projects.

• Public policy should also defined what human and material resources are devoted to research and which are devoted to the health care as well as defining what is shared and how.

• Continuous improvement of organizations evolves in parallel to the development of innovative and complex techniques and the maintenance of the continuing education of professionals, so that the system should ensure that research in this area is driven properly, even in collaboration of health professionals with producers of innovation. Public policy should enable PPPs models but defining the role, duties and rights of each of the partners.

• Public policies should promote and finance projects as an appropriate action in this area and should define and prioritise areas of interest related to the current knowledge of the professionals. Areas of special interest are those that can be implemented in practice in a short to medium term.

• Public policies should be establish to ensure that the results of research and development with public participation are freely available (OA policies) and/or implemented in the health care systems as soon as possible (always taking into account the best standards to ensure the best quality services provision).

• Harmonize law on intellectual property to allow an affordable development of genomic based technologies and practices

c. Regulation and Reimbursement

• The incorporation of new technologies in the system should meet the standards referenced in this document or others based on evidence and accepted by the community.
• There should be a flexible mechanism to ensure the incorporation of relevant techniques without delay.
• The continuous assessment of existing technologies should be made to ensure its efficient use.
• Policies are to be put in place to ensure the disinvestment or delist of technologies with low or none-added value

d. Building Capacity

• Public policies should establish mechanisms to ensure the accredited training of professionals whose main scope is genomics, in order to ensure the quality of services provided.
• There is currently a shortage of professionals in this field that should be covered by professional training, after the definition of the competences to be developed.
• Promote dialogue with accreditation bodies in this biomedical field to ensure the provision of quality services and competent professionals.
• The knowledge of genetics should be incorporated, at least in the training of all clinicians that treat or may treat patients with diseases or conditions that required a genetic approach.

e. ELSI

• Public policies should be developed to ensure that the ethical, legal and social issues are considered in all cases and that that any use of genomic based technologies is in accordance with the principles of human rights, dignity and autonomy.
• Public policies should promote the empowerment of the patient and/or citizen and processes of shared decision-making.

3.5.2 Best Practices (see chapter on Policy development for the identification of best practices)

a. *Public Education and Public Engagement*
   - *NLM initiatives to provide accurate and scientifically correct information to the public and mass-media*
   - *CDC genomics http://www.cdc.gov/genomics/*
   - *WHO genomics http://www.who.int/genomics/en/*

b. Research and Development
   - OA policies of the NIH and NLM of the US.
   - Coverage with evidence agreements for PPPs

c. Regulation and Reimbursement
   - GEN guideline on the incorporation of genetic technologies
   - GuNFT guideline on the disinvestment of technologies of low or no-added value

- NHS. UK Genetic Testing Network. UK Genetic Testing Network Steering Group. Procedures and criteria for the evaluation of genetic tests for NHS Service.
- EUnetHTA core model (http://www.eunethta.net) for the assessment of existing technologies and
- DACEHTA model to elaborate mini HTAs (http://www.sst.dk/publ/Publ2005/CEMTV/Mini_MTV/Introduction_mini_HTA.pdf)

d. Building Capacity
   - EuroGenTest guidances on core competences

e. ELSI

Assurance (Tasks 6-9: all three pillars)

3.6 Enforce Laws

- A broad interpretation is needed to encompass the application of the range of policies considered (e.g. Health in All Policies…).
- Guidance on mechanisms to disseminate and to enforce laws, regulations, policies, quality assurance measures (accreditation, EQA …), means to protect and involve users (informed consent tools, …)

3.6.1 Recommendations

- The legal discourse in Public Health Genomics differs from the legal discourse in human genetics as it tries to set up an integrated approach towards both modifiable and non-modifiable health risks. Public Health Genomics focuses on the legal environment of common disorders with a low genetic risk, yet it must not neglect the needs of underserved patient groups in the field of orphan diseases.
- Health regulations require a solid evidence base: The legal discourse must be provided with this evidence by knowledge generating professions as it can only provide stakeholders with a secondary analysis of scientific findings.
- The "health in all policies" approach offers the opportunity to strive, in the long run for a consistent and coherent health regulation in fields other than traditional health law.
- Public Health Genomics Law also needs to focus on health systems regulation and medical law. The legally relevant interfaces of traditional health regulation and new concepts like "health in all policies" have not yet been fully explored.
- Law can serve as a tool and a platform for reasoning as it strives to integrate scientific knowledge, ethical and legal principles as well as modes of regulation. If the evidence is rightfully transposed into regulations, law is equipped to reach a concordance amongst the individual and collective rights at stake.
- Health regulation is a multi layer enterprise with a wide range of regulatory bodies, different modes/models of regulation applied. While some stakeholders will follow a certain professional or patient perspective, democratically legitimised regulators must aim to integrate and balance individual as well as collective rights and duties of professions and citizen.
- The interpretation of existing rules and the detection of gaps are of major importance for the current legal discourse on Public Health Genomics.

3.6.2 Best Practices

Please, see Use/User pillar (e.g. Directive on Patient Rights in Cross-border Healthcare, Data Protection Directive 95/46/EC, Health in all Policies approach (HiAP), EU Regulations on Orphan Drugs and on Advanced Therapies, the Commission Communication and the Council Recommendation on Rare Diseases)

3.7 Link to / Provide Care

Two aspects can be envisioned (broad interpretation) relating respectively to the practice and to the organisation of care:

a) Knowledge transfer to clinicians and application of practice guidelines

b) "Translation" of new practices into the required organisational changes (e.g. redefining roles and responsibilities of various professionals…) and implementation of these changes (e.g. planning adequate resources, negotiations…)

3.7.2 Best Practices

Currently best praxis in the application of genome based health information is difficult to define as the identification, analysis, application and validation of genome based technologies and information are not widespread. However following steps can be defined as critical for bringing new technology into the praxis:

a Dissemination and provision of training in genome based knowledge, diagnosis and technology through regular courses and on health care related conferences.

b Development and application of nonrandomized trials for identifying possibilities for targeted drug treatment and new combinatorial chemotherapeutic approaches based on genome information.

c Create new links between patients, doctors, stake holders and politicians through government and non government organisations for disseminating knowledge and application of such knowledge.

d Establishing and using digital health records including genome based patient data providing essential information on how to provide best diagnosis and treatment and carry out real life benefit analysis, providing feedback on the success and failure of treatment for own and other patients' benefit.

3.8.1. ASSURING COMPETENT WORKFORCE

3.8.1.2 Recommendations

1. For the successful realization of the goals defined by the PHGEN II project a competent workforce has to be developed.

2. Workforce should include Medical Doctors (with or without specialization in PH), Health Professionals and Public Health Professionals.

3. The competencies of the PH workforce in the field of public health genomics has to be defined at regional/subregional levels.

4. Knowledge and skills of the PH workforce should be provided by training.

3.8.3. TARGETS FOR PHG EDUCATION

3.8.2.2 Recommendations

In order to cover all fields that are dealing with Public Health Genomics proper and up to date knowledge should be introduced into the training of

- all public health workforce (public health, environmental health and health promotion specialists)
- medical and health professionals including primary care services
- health care managers
- policy professionals
- professionals involved in quality controlling and improvement
- professionals in health technology assessment
- specialists with advanced genetics

3.8.3. TRAINING OF THE WORKFORCE

3.8.3.2 Recommendations

In order to cover all the relevant aspects of public health genomics in the training programs, regardless of the level of training, we have developed a Curriculum Plan for the 'Core Course' that should give the basis for the general knowledge and therefore should be in all training programs.

1. The human genome and its variations *(The background and achievements of the Human Genome Project, eg. Number of genes, genetic variations and their role in population wide genome based analyses. The future of sequencing regarding the methods and related outcomes.*
2. Human biobanks for public health research *(Introducing already existing Biobanks - BBMRI. The importance of Biobanks in Health Care and Industry. Legal and ethical issues regarding the development and the handling of Biobanks.*
3. Methods to study genomic alterations *(Methods for identifying and verifying genetic variations eg. Polymerase chain reaction (PCR), high-throughput microarray, comparative genomic hybridization (CGH), Fluorescent in situ hybridization (FISH). Introduction of functional genome wide studies on tissues and cell cultures to identify agents that are affecting not the coding but the expression pattern of genes.)*
4. Molecular targets and tests for newborn screening *(Neonatal screening in practice eg. phenylketonuria, galactosaemia, congenital hypothyreosis, biotinidase deficiency, hemoglobinopathies). Disease that could be included in the population-wide newborn screening – the pros and contras, its limits and indications. Finding realistic goals in the genomic era and utopistic aims.*
5. Population-based genomic research focused on chronic non-communicable diseases: Malignancies, Cardiovascular diseases, Metabolic diseases *(eg. oncogenes and tumor suppressor genes in types of familial hereditary cancer, genetic susceptibility to breast cancer, genetic factors in cardiovascular diseases, genetic background of obesity and other metabolic syndromes)*
6. Genetic background of health behavior (smoking, alcoholism, nutrition, physical activity, etc) *(Genetic variations contributing to smoking, alcoholism*

and nutritional abnormalities. Genetic factors affecting sexual behavior. Genetic determinants of mental disorders.)

7. Genetic susceptibility to communicable diseases (influenza, tuberculosis, herpes virus and HIV infections, etc)
8. Ethical aspects of public health genomics *(genetic determinism, genetic reductionism, genetization of society, historical overview - eugenics, screening of thalassaemia in Cyprus)*
9. Legal aspects of public health genomics *(EU and regional laws and regulations. Legal aspects of genetic studies. Protection of individuals. Commercialization of genetics and genetic information.)*
10. European perspectives of legislation in connection with public health genomics
11. The European Public Health Genomic Network: its organization and functions

3.8.4. ORGANIZATIONS RESPONSIBLE FOR THE EDUCATION

3.8.4.2 Recommendations

1. In order to provide a complex curriculum institutions and organizations should be defined that are potential candidates for education.

2. The ethical, legal, sociological and economic aspects should be integrated into the curriculum.

3. To meet the needs of PHG as a multidiscipline course universities and Schools of Public Health should be the targets for education where available skilled staff that covering the involved fields is the most likely to be available.

4. Besides gaining the required knowledge guidelines should be set up regarding the criteria that one should meet to teach and to study in an academic environment. In other words what are the conflicts of interests that should be accepted and what are the excluding ones.

3.8.5. LEVELS OF TRAINING

3.8.5.2 Recommendations

In the development and the selection of the parts that should be included in all programs and the parts that should only be addressed to certain groups is a major challenge - the goal is to fulfill the needs of both medical training as well as the training of the above listed professionals. Therefore development of curricula suitable for the level of training should represent the knowledge and the requirements of each target group.

3.8.5.3 Best practices

1. Upgrading trainings for medical specialists and health professionals are already running.

2. New curriculum design for Public Health Professionals at undergraduate (BSc) and graduate (MSc) levels are under development.

3. PhD programs are devoted to supply qualified scientists that master the skills of PHG at the highest academic levels providing future policy makers.

3.8.6. REFLECTING LOCAL LEVELS IN EDUCATION

3.8.6.2 Recommendations

1. Education centers should maintain and provide staff with a common way of thinking and would be responsible for updating knowledge annually.

2. Establishing monitoring centers would be responsible for the training of the trainers who than would filter and integrate their knowledge depending on their experiences and skills related to the local levels.

3. EU should finance the training centers both at the EU as well as regional levels.

3.8.6.3 Best practices

1. In the annual upgrade the guidelines of the EU as well as WHO should be reflected.

2. Education centers responsible for the PHG training should be defined.

3.8.7. QUALITY CONTROL IN EDUCATION

3.8.7.2 Recommendations

1. The aim is to give the relevant information helping involved students not to get lost in the details.

2. Defining and assuring the criteria for the required knowledge is pivotal in guaranteeing the general concepts.

3. Besides performing guidelines on how to define and test the required basic knowledge, quality assurance and the compatibility of the education should also be covered between institutions.

4. Guidelines have to be developed for the examination processes and its requirements.

All points should be developed and accepted by the partners involved in education.

3.8.8. ROLE OF E-LEARNING IN PHG EDUCATION

3.8.8.2 Recommendations

1. Guidelines and proper planning with a focus on the benefits and limits are needed in order to introduce e learning into PHG education.

3.9 Evaluate

3.9.1. PROVISION OF MONITORING SERVICES

3.9.1.2 Recommendations

1. The following questions should be addressed when defining the role and the set up of the monitoring services related to public health genomics:

- What are the targets?
- What can be the indicators?
- What are the expected outcomes?
- Can the outcomes be translated into objectives?
- Are the gained objectives suitable to determine future goals?
- What are the risks?
- How could performance indicators be defined?

2. Monitoring systems should be designed by experts in public health genomics to identify both the achievements and the problems with its possible solutions both at the levels of planning and implication specific to the field of public health genomics.

3. Diseases that have a genetic background should be the target for the monitoring activity. Therefore reliable databases should be developed and used to meet the specific needs of Public Health Genomics.

4. Databases should include up to date information on the current status of diseases and their relation to genetic alterations.

6. Databases have to be designed to overview data population wide and to be accessible in respect of the legal and ethical issues.

3.9.2 PROBLEMS IN THE IDENTIFICATION OF TARGETS AND INDICATORS

3.9.2.2. Recommendations

1. Cornerstones for the development of describing and through that understanding the relations between genetic variations and phenotypes in man, and more specifically demand a specified purpose for future developments of ICD to make it more convenient to link ICD information with the databases build on genetic approaches.

2. ICD classifications should be upgraded and extended for PHG monitoring and for (public health) studies dealing with genome based data. To this aim, a working group has to be set up and recognized by the WHO in the ICD revision process.

3. Quality standards have to be defined for the databases.

4. To meet the needs of PHG, diseases should also be grouped and coordinated under the ECHIM umbrella from the aspect of genetic background that would allow the monitoring of indicators of PHG. ECHIM should be extended onto the field of PHG – for that a workgroup should be developed and maintained.

5. Clear definitions are needed to develop the set of indicators that are meaningful and realistic for monitoring in PHG.

3.9.2.3 Best practices

1. ICD classifications already realized the importance of representing the genetic background and started to form categories with codes designated for diseases with known genetic involvement.

2. All the mentioned standards/databases/organisations described in the "Background" part seem to agree that the only way to go is to go together, and at

the moment The VARIOME project is more or less basing their initiative on the joint forces of the BIC database (http://research.nhgri.nih.gov/bic/) (the BRCA variation international database kept by NCI), and the LOVD database (http://chromium.liacs.nl/LOVD2/colon_cancer/home.php?action=switch_db) which is becoming the central database for inherited colorectal cancers supported by INSIGHT (http://www.insight-group.org/) which is basically merging with The VARIOME project using the LOVD database as the example on how professionals could join forces in a non-commercial way. Simultanously, the LOVD database is a key player in developing the HGVS nomenclature system.

3. In the case of Rare Diseases (RD) a task force – Rare Diseases Task Force (RDTF) identified and developed indicators that can be used for RD from which many, listed below, could be and have to be implicated also in the field of PHG monitoring.

a) Contribution to morbidity and mortality

Prevalence, per disease and global

Incidence, per disease and global

Death rates (Mortality)

Hospital admissions

Contribution to mental/physical/neuro-sensory disabilities

Contribution to transplantation

b) Socio-economic impact

Impact on families (economic, social, psychological)

Annual budget to cover orphan drugs

Contribution of consanguinity

c) Availability of appropriate Health Services

Genetic testing: Laboratories certified/accredited

Availability of genetic counselling

Number of diseases for which there is biological testing

Prenatal diagnosis, Neonatal screenings

Age at diagnosis (diagnosis delay)

New orphan products

Availability/accessibility of orphan drugs

Number of Patients' Organizations and number of diseases covered

d) Information, research, technology development

Number of diseases with known genetic background with an ICD code

Diseases with genetic background for which good practice guidelines are available

Registries and databases, geographical coverage

Number of ongoing clinical trials

e) Monitoring of geographical differences in Europe

f) Surveillance of status/trends over time

3.9.3 PROBLEMS IN THE EXPECTED OUTCOMES

3.9.3.2 Recommendations

1. The collection of data should limit itself to already available data that are either available from running genetic tests - we refer to the other parts of the report such as newborn screening – or from research based studies.

2. Task force committees from the field of public health should be formed and be responsible for following and integrating research and its achievements into everyday health care and possible monitoring..

3. PHG experts should be able to make decisions on running and planned genetic tests as well as on the potential implications of scientific data to healthcare considering its impact on health and its cost benefit risk

4. Clinical and laboratory approaches all need to be applied and included in the databases in order to understand and apply the genetic indicators.

5. Databases should be designed to include functional data related to the altered gene expression.

6. European Commission should provide funding to establish and/or improve the facility of centers in the member countries.

3.9.4 TRANSLATING OUTCOMES INTO OBJECTIVES

3.9.4.2 Recommendations

1. Databases have to be prepared to perform data for PHG regarding the genetic background and its role as possible indicators of the diseases.

2. Pilot studies have to be preformed to test the relevance and availability of indicators for which sources of information are already available and accepted.

3.9.4.3 Best practices

1. A classification of the disease regarding its relation to genetic involvement should be represented in the classification: its relation to a single gene or to more than one gene.

2. The presence of SNPs with a known impact found during the diagnosis should also be put forward for discussion whether it has to be present in the classification or not.

3. A collaborative effort is needed including PHG Experts to improve these databases at the planning and at the implementation levels as well.

3.9.5 DEFINING OBJECTIVES SUITABLE TO DETERMINE FUTURE GOALS

3.9.5.2 Recommendations

1. To determine future goals a proper evaluation is needed with the involvement of policy makers from public health to governmental fields.

2. The differences in the practices of the Member States in the data collection and the processing phases should be harmonized. Common quality standards have to be developed and shared in the EU.

3. Already existing databases should be revised and made comparable.

3.9.6 RISKS IN THE VALIDITY OF THE DATABASES

3.9.6.2 Recommendations

1. Common collection methodologies are required.

2. Coding and classification of diseases with a genetic background should be created and upgraded.

3. Provide efficient and consistent reporting mechanisms that deal with the comparability of the data and the sensitivity of the indicators

3. Ethical and legal issues as discussed throughout the guidelines should be handled with an outmost care in these databases where anonymous data pools are supported from many aspects as public health actions focus on populations instead of exact individuals.

4. Technical Progress

4.1. Overview of activities for the period covered in the interim report
4.2 Involvement in the pilots
4.3. Scientific publications
4.4 Presentations

Lavinha J (2011) Human biobanking for public health. International workshop on Biobanking for Health Research, INSA, Lisboa.

4.5 Wiki-PHGEN contributions

http://wiki.phgen.eu/index.php/Mobilize_Community_Partnerships

5. Concluding Remarks

6. Annexes