PRECeDI
Personalized PREvention of Chronic DIseases

How to integrate Personalized Medicine into Prevention?

Recommendations from the Personalized pREvention of Chronic Diseases (PRECeDI) consortium

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Introduction

The Promise of Personalised Prevention

Personalisation of healthcare is a driver of innovation in research, healthcare systems and industry. Policy makers, healthcare professionals, citizens, and private companies need proper advice to realize its potential. The Personalized pREvention of Chronic DIseases consortium (PRECeDI) is a Marie Skłodowska Curie Action (MSCA) project funded within the Research and Innovation Staff Exchange (RISE) scheme that aimed at providing high-quality, multidisciplinary knowledge through training and research in Personalized Medicine (PM), with specific reference to personalized prevention of chronic diseases. PM approaches are already being implemented especially in the fields of disease diagnosis and treatment with the use of biomarkers, however, development and implementation of such approaches for chronic disease prevention needs further investigation and concerted efforts for proper implementation in healthcare systems.

We must be explicit about the new potential benefits that disease prevention can bring in the context of PM. Technological advances jointly with current demographic trends and the expectations of citizens, have the potential to widen the gap between available resources and the requirements for health care. As highlighted by the European Steering Group on Sustainable Healthcare, the implementation of sustainable healthcare requires a shift from treatment of established disease to disease prevention and early diagnosis, and it relies on the need to engage citizens to take greater responsibility for their health in order to establish a more participatory healthcare model [1]. Despite the tremendous increase in life expectancy in Europe in the last 50 years, the latest Eurostat reports that the average number of years of life lived with some disability in Europe is 19.4 for females and 17.7 for males [2]. Although it is acknowledged that prevention in health care can improve the quality of life at a very reasonable price by reducing the years of life spent with disability, only 2.8% of health expenditure is for prevention activities [3]. Personalized prevention approaches bring the promise of being even more effective and cost-effective by using the latest advancements in life sciences and (digital) technologies to stratify healthy individuals based on individual and environmental factors, in order to target precise primary, secondary and tertiary prevention interventions. Such approach is supported by a highly cited 2008 editorial in NEJM, which reported that "...if preventive care could be provided only to those who are going to get the illness, it would be more cost-effective" [4].

PRECeDI Laying the Foundation for Making Personalised Prevention a Reality

The PRECeDI consortium consists of 8 beneficiaries and 3 partners, of which 7 are academic institutions and 4 non-academic, including 2 SMEs, and it received funding from the Horizon2020 (H2020) European Union's Eight Framework Programme for research [5, 6]. During four years (2014-2018), 28 early stage researchers and 22 experienced researchers were seconded for an average of 3 months from academic to non-academic institutions and vice-versa, for training in research projects related to personalized prevention of chronic diseases including cancer, cardiovascular diseases and Alzheimer's disease.

Different projects were carried out, from basic research to economic evaluations, from health service organization issues to physician education, including ethical, social, and policy issues in PM, supported by a team of leading EU scientists. The consortium is embedded in existing cooperative structures, such as the CSAs IC PerMed [7] and TO-REACH [8], the IMPACT-HTA project funded from the H2020 programme [9], and the JA iPAAC funded by the Third EU Health programme [10].

How PRECeDI contributes to the integration of Personalised Medicine in the Prevention of Chronic Diseases

Based on the results of the research carried out by the PRECeDI consortium, a set of recommendations for policy-makers, scientists and industry has been drawn up, with the main goal to foster the integration of PM approaches in the field of chronic disease prevention. As a reflection of the work carried out during the project, most of the recommendations fall in the "translational phase of research in genomics" as defined by M. Khoury [11] in "T1 (seeks to move a basic genome-based discovery into a candidate health application)" and "T3 (attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research)".

In particular these **recommendations fall within the five research domains of PRECeDI** [6]: *"Identification of biomarkers for the prevention of chronic diseases; Economic evaluation of predictive genomic applications; Ethico-legal and policy issues surrounding personalized medicine; Sociotechnical analysis of the pros and cons of informing healthy individuals on their genome; Identification of organizational models for the provision of predictive genetic testing"*.

In addition, when formulating the recommendations, the PRECeDI consortium considered two main additional documents: the Strategic Research and Innovation Agenda (SRIA) published in 2016 by the PerMed Consortium [12] and the report published in 2017 from the PHG Foundation [13, 14]. PerMed SRIA reported five challenges for further implementation of PM in Europe, namely: *"Developing Awareness and Empowerment; Integrating Big Data and ICT Solutions; Translating Basic to Clinical Research and Beyond; Bringing Innovation to the Market; Shaping Sustainable Healthcare"*. The 2017 PHG Foundation Report, as recalled by Ricciardi and Boccia [14] incorporated a public health perspective and reported six prerequisites to implement the future of personalized healthcare: *"Achieving better genetic literacy for professionals and for the public; engaging citizens in the discourse; improved governance, consent and trust in healthcare; feeding and harnessing the data–knowledge cycle for better health; adopting and adapting the Health Technology Assessment framework for the evaluation of the new technologies; and retaining humanity and community in health and care"*.

Taking into account that personalized prevention can only be successfully implemented when handled as a truly cross-sectoral topic, our recommendations integrate the perspective of experts across the entire healthcare value chain that are represented in the PRECeDI consortium.
As a matter of fact, this document is also the result of the discussions of the one-day PRECeDI workshop "Policy development in Personalized Medicine" held in Amsterdam on 15th March 2018 [15] that convened experts and representatives of relevant stakeholders in the field of PM. The experts participating fully endorsed this document.

These recommendations are formulated as a direct output of the research results and the scientific publications produced by the PRECeDI Consortium. This direct link between the scientific evidence and each recommendation is highlighted in this document.

The implementation of the recommendations will benefit citizens, patients, healthcare professionals, healthcare authorities and industry and ultimately seek to contribute to better health for Europe's citizens.

In order to be fully shared and endorsed by relevant authorities and decision makers, this document will be published and open to a public consultation via the PRECeDI website [5].

This document contains **recommendations** that are based on the results of the projects carried out **within the five research domains of PRECeDI** that integrates the two sets of aforementioned recommendations [12, 14].

	PRECeDI Domains	PRECeDI Recommendations
	**Domain 1:** Identification of biomarkers for the prevention of chronic disease.	**R1.** Personalized interventions for the prevention of chronic diseases require robust evidence of efficacy and/or effectiveness of the new technology when implemented in health care.
	**Domain 2:** Economic evaluation of predictive genomic applications.	**R2.** In addition to what reported in R1, a comprehensive evaluation of the value (outcomes/cost) of the new technology should also include evidence on the social aspects, and context-related dimensions to better support the clinical decision-making process. Genetic or genomic applications with evidence of efficacy, effectiveness and cost-effectiveness should be implemented in clinical and public health practice.
	**Domain 3:** Ethico-legal and policy issues surrounding personalized medicine.	**R3.** The era of genomics requires that we clarify and validate the obligations and responsibilities of the research community, research participants, and the general public including patients through collaboration and dissemination of high-quality ethical, policy and legal analysis.
	**Domain 4:** Sociotechnical analysis of the pros-and cons of informing healthy individuals on their genome.	**R4.** A dedicated effort is necessary to stimulate further implementation of evidence-based interventions in health care, such as testing of family members in cases of hereditary cancers or cardiovascular diseases.
	**Domain 5:** Identification of organizational models for the provision of predictive genomic applications.	**R5.** The integration of genomic sciences in other medical specialties should be promoted through new delivery models involving different healthcare professionals and new professional roles, in order to guarantee the use and sustainability of existing and new genomic applications in practice.

Recommendation n. 1

*Recommendation 1 is based on the **"Identification of biomarkers for the prevention of chronic diseases"** research domain.*

Biomarkers have the potential to stratify populations because they can help to indicate an individual's risk or resistance to disease as well as the potential response the individual may have to different treatments. There is also an expectation that this may lead to better targeting of preventive interventions by defining the disease and targeting the treatment based on a person's molecular pathology.

R.1. Personalized interventions for the prevention of chronic diseases require robust evidence of efficacy and/or effectiveness of the new technology when implemented in health care.
In particular: large trials evaluating the efficacy of disease risk communication based on broad range newly discovered biomarkers (versus risk communication based on the solely traditional risk factors) on behavioral change among healthy subjects at increased risk are required for targeted evidence-based primary preventive interventions.
For biomarkers that allow discriminating high-risk subjects, large trials evaluating the efficacy of medical interventions are required among such high-risk subjects for targeted evidence-based primary and secondary preventive interventions.
Where intervention studies cannot be performed, however, the use of large datasets, Big Data from collaborative research projects, should be considered for the evidence of effectiveness. In order to ensure timely results for the use of such predictive biomarkers, the collection of such evidence by action research should be foreseen in the course of implementation and accompanied by collection of genetic data to allow for state-of-the Mendelian Randomization studies to mimic conventional trials.
In these situations, a clear commitment to hypothesis to be tested in advance is needed as is the case with (the registration of) classical trials.
For tertiary prevention, the adoption of accurate biomarkers for precise monitoring and early prediction of disease progression should be encouraged.

This recommendation is based on the results of the biomarkers identified (and validated) for the prevention of Diabetes [16]*, Alzheimer's disease* [17]*, and Head and Neck cancer* [18-21]*.*

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A Mendelian Randomization Study of Metabolite Profiles, Fasting Glucose, and Type 2 Diabetes.

Liu J, van Klinken JB, Semiz S, van Dijk KW, Verhoeven A, Hankemeier T, Harms AC, Sijbrands E, Sheehan NA, van Duijn CM, Demirkan A.

Diabetes. 2017 Nov;66(11):2915-2926. doi: 10.2337/db17-0199. Epub 2017 Aug 28.

Type 2 diabetes is a progressive metabolic disease characterized by hyperglycemia, and associated with dyslipidemia. Several circulating molecules have previously been shown to be dysregulated in type 2 diabetes. However, the causal paths between these metabolites and glucose/type 2 diabetes in humans remain unclear from observational studies and require randomized controlled trials that are difficult to conduct.
To explore potentially causal metabolic paths that underlie the observed associations, the current study used genetic predictors from published metabolite GWAS, and performed a mendelian randomization analysis (MR) between selected metabolic markers and glucose/type 2 diabetes.
The study analyzed 2,776 participants from the prospective family-based study of the southwest of the Netherlands (Erasmus Rucphen Family study) in whom targeted metabolomics measurements were performed by either nuclear magnetic resonance spectroscopy or mass spectroscopy.
The study selected 124 metabolites that are correlated with glucose in the population without diabetes, and using MR, tested whether this metabolic profile points to any causal paths involved in glucose level or type 2 diabetes. Combining metabolomics and MR, the authors detected 14 candidate causal associations: 10 metabolites influencing fasting glucose, 1 influencing type 2 diabetes, and 3 influenced by type 2 diabetes.
The study provides evidence for potentially causal metabolic paths of glucose homeostasis and type 2 diabetes. The results indicate that an increase of large HDL particles might have a decreasing effect on glucose, while an increase of small HDL particles might have an increasing effect. The study further found evidence that type 2 diabetes may alter levels of alkyl-acyl phosphatidylcholines and alanine, which also here can be translated into prevention of disease complications and prognosis.

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Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies.

Sven J. van der Lee, Cornelia M. van Duijn et al.

Alzheimer's & Dementia: The Journal of the Alzheimer's Association , Volume 14 , Issue 6 , 707 – 722. doi: 10.1016/j.jalz.2017.11.012. Epub 2018 Jan 6.

Cognitive function is an important determinant of health and well-being and a key component of the dementia spectrum, including Alzheimer's disease (AD), the most common cause of dementia. Vascular dysfunction and metabolic dysregulation contribute to impairment in cognitive performance, and the recent decrease in incidence of dementia in longitudinal studies has been attributed to improved control of vascular and metabolic factors.
These findings have fueled speculation that discovery of other circulating metabolites influencing cognition and future dementia may not only improve our understanding of the determinants of cognition but may also facilitate prevention through interventions on lifestyle factors and dedicated medication. Previous studies have shown circulating metabolites in blood to be associated with cognitive function and conversion from normal cognition to dementia or AD. However, these studies were relatively small and findings have not been replicated, emphasizing the need for studies in large well-characterized populations.
This study performed a comprehensive metabolic analysis (299 metabolites) using two large population-based studies in the Netherlands—the Rotterdam Study (RS) and the Erasmus Rucphen Family (ERF) study. The authors determined whether the associations were independent of known vascular and metabolic risk factors. Metabolites independently associated with cognition were replicated in independent cohort studies, and their relation to the risk of dementia and AD was validated in eight cohort studies. Finally, they assessed whether lifestyle factors, including dietary fish intake, smoking, and physical activity, were associated with the identified metabolites.
They discovered and replicated 15 metabolites associated with general cognitive ability. This metabolic profile includes subfractions of HDL, DHA, ornithine, glutamine, and glycoprotein acetyls. We show that metabolites in the profile are independent of classical cardiometabolic blood correlates of cognitive function. Six of the cognition-associated metabolites were related to the risk of dementia and three of these also with AD. Furthermore, the results show that lifestyle factors, such as diet, smoking, and physical activity, have strong effects on metabolites in the profile.

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Plasma miRNAs as Prognostic Biomarkers for Head and Neck Cancer.

Pastorino R, Giraldi L, Cadoni G, Amore R, Arzani D, Boccia S.

Manuscript in preparation.

Cancers of the head and neck (HNC) are currently the seventh most common cancer worldwide, with a 5-year overall survival (OS) rate around 55%. Over 50% of HNCs develop local recurrences, and 15% develop second primary malignancies, both associated with poorer survival. Cigarette smoking, alcohol consumption, HPV infection for oropharynx cancers, and family history of HNC affects not only the risk of first HNC, but also the risk of recurrence and survival. Additionally, a major clinical challenge to date lies in development of validated biomarkers to predict clinical outcomes. MiRNA have been suggested as potential biomarkers for HNC, but so far specific miRNA signatures for the prognosis of HNC have not been identified.
The authors profiled the expression levels of 233 miRNAs in plasma samples of 90 HNC cases (screening phase). RNA extraction was conducted by Nucleo Spin miRNA Plasma kit (Macherey Nagel) and the TaqMan® Array Human MicroRNA Card Set v3.0 was utilized. The criteria to select significantly deregulated miRNAs were P<0.05 and FCR (Fold Change Ratio)<0.25; miRNA not correlated with the hemolysis miRNA miR-451; miRNA that have not been indicated previously in the literature to be affected by haemolysis. The findings were validated in an independent cohort of 150 HNC cases (validation phase).
Five deregulated miRNAs were identified after the screening phase (hsa-miR-338-5P-002658; hsa-miR-30e-3p-000422; hsa-miR-28-3p-002446; hsa-miR-485-3p-001277; hsa-miR-363-001271). In detail, the plasma levels of all the five miRNA were significantly associated with poor prognosis. Of the 5 miRNA, miR338 and miR30 displayed a significant different expression level in plasma of death patients compared with alive patients without recurrence. The plasma levels of miR-30, miR-28, and miR-363 were significantly altered in patients with local recurrence compared to patients without recurrence. The validation phase is terminated and the statistical analysis is ongoing.

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Alcohol and cigarette consumption predict mortality in patients with head and neck cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.

Giraldi L, Leoncini E, Pastorino R, Wünsch-Filho V, de Carvalho M, Lopez R, Cadoni G, Arzani D, Petrelli L, Matsuo K, Bosetti C, La Vecchia C, Garavello W, Polesel J, Serraino D, Simonato L, Canova C, Richiardi L, Boffetta P, Hashibe M, Lee YCA, Boccia S.

Ann Oncol. 2017 Nov 1;28(11):2843-2851. doi: 10.1093/annonc/mdx486.

Squamous cell carcinoma of the head and neck (HNC) is the seventh common cancer worldwide, and is the eighth leading cause of cancer death. HNC includes different types of cancers, of which the most frequent are cancers of the oral cavity, oropharynx, hypopharynx and larynx. The overall survival (OS) rate for these neoplasm has improved over the last decades, but still differs depending on the HNC subsite. To date, very few large studies have examined the role of prognostic factors for HNC on survival from these neoplasms. The aims of this study are to investigate the OS and cancer-specific survival in a large cohort of HNC patients within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, and to identify independent prognostic factors for HNC subsites. The authors conducted a pooled analysis, including 4759 HNC patients from five studies within the INHANCE Consortium. Cox proportional hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated including terms reported significantly associated with the survival in the univariate analysis.
Five-year OS was 51.4% for all HNC sites combined: 50.3% for oral cavity, 41.1% for oropharynx, 35.0% for hypopharynx and 63.9% for larynx. When we considered HNC-specific survival, 5-year survival rates were 57.4% for all HNC combined: 54.6% for oral cavity, 45.4% for oropharynx, 37.1% for hypopharynx and 72.3% for larynx. Older ages at diagnosis and advanced tumour staging were unfavourable predictors of OS and HNC-specific survival. In laryngeal cancer, low educational level was an unfavourable prognostic factor for OS (HR=2.54, 95% CI 1.01-6.38, for high school or lower versus college graduate), and status and intensity of alcohol drinking were prognostic factors both of the OS (current drinkers HR=1.73, 95% CI 1.16-2.58) and HNC-specific survival (current drinkers HR=2.11, 95% CI 1.22-3.66). In oropharyngeal cancer, smoking status was an independent prognostic factors for OS. Smoking intensity (>20cigarettes/day HR=1.41, 95% CI 1.03-1.92) was also an independent prognostic factor for OS in patients with cancer of the oral cavity. OS and HNC-specific survival differ among HNC sites. Pre-diagnosis cigarette smoking is a prognostic factor of the OS for patients with cancer of the oral cavity and oropharynx, whereas pre-diagnosis alcohol drinking is a prognostic factor of OS and HNC-specific survival for patients with cancer of the larynx. Low educational level is an unfavourable prognostic factor for OS in laryngeal cancer patients.

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Tumour stage and gender predict recurrence and second primary malignancies in head and neck cancer: a multicentre study within the INHANCE consortium.

Leoncini E, Vukovic V, Cadoni G, Giraldi L, Pastorino R, Arzani D, Petrelli L, Wünsch-Filho V, Toporcov TN, Moyses RA, Matsuo K, Bosetti C, La Vecchia C, Serraino D, Simonato L, Merletti F, Boffetta P, Hashibe M, Lee YA, Boccia.

Eur J Epidemiol. 2018 May 19. doi: 10.1007/s10654-018-0409-5.

Recurrent disease and second primary cancer (SPC) continue to represent the major obstacles to long-term survival in head and neck cancer (HNC). Despite advances in the treatment of HNC, it is currently well established that the percentage of patients who will develop recurrent disease can be as high as 50%. HNC survivors also have an increased risk of developing SPC compared to the overall population, with frequent SPC of the head and neck, oesophagus, and lung, which are tobacco- and alcohol-related cancers.
So far, a few large studies evaluated whether established demographics and lifestyle-related risk factors for HNC influence recurrence, and development of SPC in HNC patients. To explore these issues, the authors conducted a multicentre study by using data from studies conducted in Brazil, Italy, and Japan, which are members of the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, totalling 4005 HNC cases.
Multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for recurrence and SPC. During follow-up, 1161 (29%) patients had recurrence and 343 (8.6%) developed SPC. Advanced tumour stage was associated with increased risk of recurrence in HNC overall (HR=1.76, 95% CI 1.41–2.19). Women with laryngeal cancer had a reduced risk of recurrence compared to men (HR=0.39, 95% CI: 0.24–0.74). Concerning predictors of SPC, advanced age (HR=1.02; 95% CI: 1.00–1.04) and alcohol consumption (>1 drink per day, HR=2.11; 95% CI: 1.13–3.94) increased the risk of SPC among patients with laryngeal cancer. Additionally, women were at higher risk of SPC, in HNC overall group (HR=1.68; 95% CI: 1.13–2.51) and oropharyngeal cancer group (HR=1.74; 95% CI: 1.02–2.98). Tumour stage and male gender (larynx only) were positive predictors of cancer recurrence in HNC patients. Predictors of SPC were advanced age and alcohol use among laryngeal cancer cases, and female gender for oropharyngeal and HNC overall.

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Application of Single-Nucleotide Polymorphism-Related Risk Estimates in Identification of Increased Genetic Susceptibility to Cardiovascular Diseases: A Literature Review.

Fiatal S, Ádány R.

Front Public Health. 2018 Jan 31;5:358. doi: 10.3389/fpubh.2017.00358.

Although largely preventable, cardiovascular diseases (CVDs) are the biggest cause of death worldwide. Common complex cardiovascular disorders (e.g., coronary heart disease, hypertonia, or thrombophilia) result from a combination of genetic alterations and environmental factors. Recent advances in the genomics of CVDs have fostered huge expectations about future use of susceptibility variants for prevention, diagnosis, and treatment. Our aim was to summarize the latest developments in the field from a public health perspective focusing on the applicability of data on single-nucleotide polymorphisms (SNPs), through a systematic review of studies from the last decade on genetic risk estimating for common CVDs. Several keywords were used for searching the PubMed, Embase, CINAHL, and Web of Science databases. Recent advances were summarized and structured according to the main public health domains (prevention, early detection, and treatment) using a framework suggested recently for translational research. This framework includes four recommended phases: "T1. From gene discovery to candidate health applications; T2. From health application to evidence-based practice guidelines; T3. From evidence-based practice guidelines to health practice; and T4. From practice to population health impacts." The majority of translation research belongs to the T1 phase "translation of basic genetic/genomic research into health application"; there are only a few population-based impacts estimated. The studies suggest that an SNP is a poor estimator of individual risk, whereas an individual's genetic profile combined with non-genetic risk factors may better predict CVD risk among certain patient subgroups. Further research is needed to validate whether these genomic profiles can prospectively identify individuals at risk to develop CVDs. Several research gaps were identified: little information is available on studies suggesting "Health application to evidence-based practice guidelines"; no study is available on "Guidelines to health practice." It was not possible to identify studies that incorporate environmental or lifestyle factors in the risk estimation. Currently, identifying populations having a larger risk of developing common CVDs may result in personalized prevention programs by reducing people's risk of onset or disease progression. However, limited evidence is available on the application of genomic results in health and public health practice.

Recommendation 2

*Recommendation 2 is based on the "**Economic evaluation of predictive genomic applications**" research domain.*

The growing availability of genomic technologies is contributing to the shift of the medical approach towards personalized medicine, where medical decisions are based on an individual's characteristics, including the genomic profile. This has made the assessment of the performance of genomic tests crucial for clinical and public health practice. In fact, in order to maximize population health benefits, it is essential to distinguish genomic tests with proven efficacy and/or effectiveness and cost-effectiveness and support their implementation.

R.2. A comprehensive evaluation of the value (outcomes/cost) of genetic and genomic applications should include evidence on the efficacy and/or effectiveness of the new technology (i.e., analytic validity, clinical validity, clinical utility), social aspects (ethical, legal and social implications, and personal utility), and context-related dimensions (e.g., economic evaluation, delivery models, organizational aspects, and consumer viewpoint) to better support the decision-making process.

Genetic or genomic applications with evidence of efficacy, effectiveness and cost-effectiveness should be implemented in clinical and public health practice (i.e. programs that include tools for identifying affected women at higher risk for inherited breast and ovarian cancers or familial history-based screening for *BRCA1/2;* universal or <70 years of age-targeted colorectal cancer-based Lynch Syndrome screening; cascade screening of familial hypercholesterolemia). The genomic or genetic testing programs and their implementation should be developed and pursued based on the characteristics of target populations and health-care systems to ensure an appropriate translation of evidence into the "real-world."

The implementation of a genetic or genomic application should be continuously assessed, measuring the population health impact and relative value of new technologies.

Adherence to the programs should be monitored and the education and training of clinical and public health professionals should be promoted with the aim of reducing inappropriate use in health care.

This recommendation is based on the results of: a systematic review for the identification of the domains for an appropriate evaluation of genetic/genomic technologies [22,23]*; systematic reviews on the cost-effectiveness of genomic applications* [24-26]*; a perspective on the main characteristics to consider for an appropriate implementation* [27,28]*; two surveys on (i) patient experience throughout the delivery pathways and (ii) knowledge and attitudes of European public health professionals on the delivery of genetic services and a systematic review on patient management* [29-31].

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How is genetic testing evaluated? A systematic review of the literature.

Pitini E, De Vito C, Marzuillo C, D'Andrea E, Rosso A, Federici A, Di Maria E, Villari P.

Eur J Hum Genet. 2018 May;26(5):605-615. doi: 10.1038/s41431-018-0095-5.

The increased availability of genetic tests has made the assessment of their performance crucial for clinical and public health practice.
Several frameworks have been proposed for the evaluation of genetic tests, but it is unclear how and in what respect they differ. The importance of a well-planned evaluation strategy is twofold. On the one hand, it would avoid the uncontrolled implementation of technologies without proven benefits, which can lead to inappropriate management of patients and detrimental effects on patient health, as well as a waste of resources and loss of public confidence in the medical profession. On the other hand a reliable evaluation strategy would support the implementation of those currently available tests that have proven effectiveness and cost effectiveness. To guide the appropriate translation of genomics into clinical practice, Italy developed a National Plan for Public Health Genomics. It has various strategic objectives including the development of a well-planned evaluation strategy for genetic tests. This systematic review was conducted to implement this plan and aims to identify and compare the existing evaluation frameworks for genetic tests, taking into account their methodology and evaluation criteria.
The authors searched PUBMED, SCOPUS, ISI Web of Knowledge, Google Scholar, Google, and gray literature sources for any documents describing such frameworks. They identified 29 evaluation frameworks published between 2000 and 2017.
The majority are based on the ACCE Framework (whose name derives from the evaluation components used: analytic validity, clinical validity, clinical utility, ethical, legal and social implications) (n=13), on the Health Technology Assessment (HTA) process (n=6), or both (n=2). The remaining frameworks refer to the Wilson and Jungner screening criteria (n=3), or to a mixture of different criteria (n=5).
Due to the widespread use of the ACCE Framework, the most frequently used evaluation criteria are analytic and clinical validity, clinical utility and ethical, legal and social implications. Less attention is given to the context of implementation. An economic dimension is always considered, but not in great detail. Consideration of delivery models, organizational aspects, and consumer viewpoint is often lacking. Since decision makers are the main audience of the evaluation process, the lack of attention to the context-related evaluation components and to the recommendation-making process are arguably the main limitations of the retrieved frameworks.
The study suggests the adoption of a broader HTA approach, including the assessment of the context-related evaluation dimensions (delivery models, economic evaluation, and organizational aspects). This approach would maximize population health benefits, facilitate decision-making and address the main challenges of the implementation of genetic tests, particularly in universal health care systems, where economic sustainability is a major issue.

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A Systematic Review on the Existing Screening Pathways for Lynch Syndrome Identification.

Tognetto A, Michelazzo MB, Calabró GE, Unim B, Di Marco M, Ricciardi W, Pastorino R, Boccia S.

Front Public Health. 2017 Sep 12;5:243. doi: 10.3389/fpubh.2017.00243.

Lynch syndrome (LS) is the most common cause of inherited colorectal cancer (CRC), accounting for about 3% of newly diagnosed cases, and results from a mutation in one of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). As LS is associated with an increased risk of colorectal, endometrial, and other cancers, it is important to identify both the probands and their family members. Early detection of individuals with LS is relevant, since they can take advantage of life-saving intensive care surveillance. The debate regarding the best screening policy, however, is far from being concluded.
The authors performed a systematic search of MEDLINE, ISI Web of Science, and SCOPUS online databases for the existing screening pathways for LS. The eligibility criteria for inclusion in this review required that the studies evaluated a structured and permanent screening pathway for the identification of LS carriers. The effectiveness of the pathways was analyzed in terms of LS detection rate.
They identified five eligible studies. All the LS screening pathways started from CRC cases, of which three followed a universal screening approach. Concerning the laboratory procedures, the pathways used immunohistochemistry and/or microsatellite instability testing. If the responses of the tests indicated a risk for LS, the genetic counseling, performed by a geneticist or a genetic counselor, was mandatory to undergo DNA genetic testing. The overall LS detection rate ranged from 0 to 5.2%.
This systematic review reported different existing pathways for the identification of LS patients. Although current clinical guidelines suggest to test all the CRC cases to identify LS cases, the actual implementation of pathways for LS identification has not been realized. Large-scale screening programs for LS have the potential to reduce morbidity and mortality for CRC, but coordinated efforts in educating all key stakeholders and addressing public needs are still required.

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Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations.

D'Andrea E, Marzuillo C, De Vito C, Di Marco M, Pitini E, Vacchio MR, Villari P.

Genet Med. 2016 Dec;18(12):1171-1180. doi: 10.1038/gim.2016.29.

There is considerable evidence regarding the efficacy and effectiveness of BRCA genetic testing programs, but whether they represent good use of financial resources is not clear.
This study has two purposes. The first is to identify the BRCA genetic testing programs whose cost-effectiveness has been analyzed in published economic evaluations. The second is to provide an overview of which BRCA testing programs are potentially ready for implementation on the basis of their cost-effectiveness, structure, and main assumptions, together with a discussion of the difficulties of transferring context-specific tools such as economic evaluations to other settings This review was conducted according to the Center for Reviews and Dissemination guidance on undertaking systematic reviews of economic evaluations and the Cochrane Handbook for systematic reviews of interventions. Nine economic evaluations were included, and four main categories of BRCA testing programs were identified: (i) population-based genetic screening of individuals without cancer, either comprehensive or targeted based on ancestry; (ii) family history (FH)-based genetic screening, i.e., testing individuals without cancer but with FH suggestive of BRCA mutation; (iii) familial mutation (FM)-based genetic screening, i.e., testing individuals without cancer but with known familial BRCA mutation; and (iv) cancer-based genetic screening, i.e., testing individuals with BRCA-related cancers.
Currently BRCA1/2 population-based screening represents good value for the money among Ashkenazi Jews only. FH-based screening is potentially very cost-effective, although further studies that include costs of identifying high-risk women are needed.
The results of this systematic review indicate that, although BRCA1/2 population-based screening is currently an inefficient use of health-care resources, population-based screening of the Ashkenazi Jews community appears to be a good value for the money. Furthermore, it is highly likely that FH-based screening is potentially very cost-effective, although further studies that include costs of identifying high-risk women are needed. This point is crucial because counseling strategies to detect at-risk individuals could involve primary-care physicians, and currently physicians seem to be not yet adequately prepared about hereditary breast cancer and BRCA1/2 testing.
There is no evidence of cost-effectiveness for BRCA screening of all newly diagnosed cases of breast/ovarian cancers followed by cascade testing of relatives, but programs that include tools for identifying affected women at higher risk for inherited forms are promising. In any case, the price of BRCA1/2 testing is of paramount importance in determining the cost-effectiveness of BRCA1/2 testing programs. If the cost of testing falls significantly, then all BRCA1/2 testing strategies analyzed in this review-perhaps including population-based screening-are likely to become highly cost-effective interventions.

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The Cost-effectiveness of Genetic Screening for Familial Hypercholesterolemia: a Systematic Review.

Rosso A, Pitini E, D'Andrea E, Massimi A, De Vito C, Marzuillo C, Villari P.

Ann Ig. 2017 Sep-Oct;29(5):464-480 . doi: 10.7416/ai.2017.2178.

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism that leads to elevated plasma LDL-cholesterol levels and premature coronary heart disease (CHD). An understanding of the mutations responsible for FH and the effectiveness of statins in lowering the risk of CHD in FH patients has increased interest in genetic screening strategies to improve FH diagnosis. In this study, the aim is to evaluate the cost-effectiveness of the genetic approach to screening for FH.
The review was conducted according to the centre for Reviews and Dissemination gyuidance on undertaking systematic reviews of economic evaluations.
The authors used relevant search terms to investigate Medline, Scopus, Web of Science, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database. The key features of the included studies were summarized in a narrative synthesis.
Seven economic evaluations that assessed the cost-effectiveness of genetic screening for FH, published mainly in Europe between 2002 and 2015, were included in the systematic review. Most studies had a no-screening strategy as a comparator, focused on relatives of index cases with genetic or clinical diagnosis of FH (cascade screening), considered a lifetime horizon and adopted a health care payer viewpoint. Cascade screening, based on genetic testing of relatives of an index case with confirmed clinical or genetic diagnosis of FH, was shown to be cost-effective in most settings.
The review shows that cascade screening based on genetic testing of relatives of an index case with confirmed clinical or genetic diagnosis of FH is cost-effective in most setting
Further research may be needed to assess the cost-effectiveness of cascade screening following the introduction of newly recommended therapeutic regimes and next-generation sequencing.

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Which Lynch syndrome screening programs could be implemented in the "real world"? A systematic review of economic evaluations.

Di Marco M, D'Andrea E, Panic N, Baccolini V, Migliara G, Marzuillo C, De Vito C, Pastorino R, Boccia S, Villari P.

Genet Med. 2018 Jan 4. doi: 10.1038/gim.2017.244.

In 2009, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing for LS in individuals with newly diagnosed CRC.
Although genomic information has the potential to improve the delivery of patient-centered care through tailored preventive, diagnostic, and treatment strategies, there is a considerable gap between discoveries in genomics research and the translation of these findings into genetic services that benefit patients. Therefore, the widespread implementation of a successful LS screening program will require a strongly integrated multidisciplinary public health approach, including a careful evaluation of the appropriate use of available economic resources.
In this systematic review, the authors have carried out a comprehensive assessment of LS screening programs whose cost-effectiveness has been subject to an economic evaluation. The aim was to identify cost-effective LS screening programs that can be implemented in the "real world." Overall, 20 studies were included in the systematic review. Based on the study populations, they identified six categories of LS screening program: colorectal cancer (CRC)–based, endometrial cancer–based, general population–based, LS family registry–based, cascade testing–based, and genetics clinic–based screening programs. They performed an in-depth analysis of CRC-based LS programs, classifying them into three additional subcategories: universal (i.e., screening of all newly diagnosed CRC patients, without performing a preliminary selection in terms of age or clinical criteria), age-targeted (i.e., screening of only those newly diagnosed CRC patients who fall below specific age cutoffs such as 50, 60, or 70 years), and selective (i.e., screening of only those newly diagnosed CRC patients who meet clinical criteria such as the Amsterdam II criteria or the Revised Bethesda Guidelines (RBG) criteria). In five studies, universal programs based on immunohistochemistry, either alone or in combination with the BRAF test, were cost-effective compared with no screening, while in two studies age-targeted programs with a cutoff of 70 years were cost-effective when compared with age-targeted programs with lower age thresholds.
From a health-care perspective, the cost-effectiveness of both universal and age-targeted CRC-based LS screening is acceptable in terms of willingness-to-pay for health gains. Therefore, as recommended by most US and European guidelines, universal or <70 years age-targeted CRC-based LS screening programs should be implemented in health practice. However, both the design of the screening program and the implementation process will need to be tailored to the characteristics of target populations and health-care systems to ensure the translation of cost-effectiveness evidence into the "real-world."

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Universal screening of Lynch syndrome is ready for implementation.

Di Marco M, D'Andrea E, Villari P.

Genet Med. 2018 May 8. doi: 10.1038/s41436-018-0027-3

Letter about the reults of "Which Lynch syndrome screening programs could be implemented in the "real world"? A systematic review of economic evaluations".

Universal screening is good value for money and, together with near-universal screening (age-targeted screening for individuals <70 years), it should be proposed to decision-makers as a potential LS screening program. They agree that context matters, and this is why each individual health system should select the most suitable model and adapt it for its own requirements. The challenges of LS screening will be to reach all CRC patients affected by LS, inform and test as many relatives as possible, offer effective surveillance interventions to reduce cancer morbidity and mortality among mutation carriers, and thus effectively maximize the health status of the population with the available resources.

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Screening Programs for Lynch Syndrome in Italy: State of the Art and Future Challenges.

Pastorino R, Tognetto A, Boccia S.

Epidemiology Biostatistics and Public Health. 2017, Volume 14, Number 2. doi: 10.2427/12615.

The Italian Ministry of Health is strengthening the efforts to implement adequate diagnosis and management programs of the highly penetrant hereditary forms of cancers within the National Prevention Plan 2014-2018. In order to support decision-makers with a feasible approach toward setting health priorities, the authors are currently revising the published diagnostic pathways for Lynch Syndrome (LS) performed internationally and assessing the cost-effectiveness of different testing strategies to identify LS from the Italian National Health Service perspective. To date, no organized screening pathways are in place in Italy to identify LS, nor economic evaluations in the Italian context have been reported.
The cost-effectiveness analysis is ongoing, but the preliminary results revealed that universal testing for all newly diagnosed CRC patients versus no testing is cost effective.

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Patient experience and utility of genetic information: a cross-sectional study among patients tested for cancer susceptibility and thrombophilia.

D'Andrea E, Lagerberg T, De Vito C, Pitini E, Marzuillo C, Massimi A, Vacchio MR, Grammatico P, Villari P.

Eur J Hum Genet. 2018 Apr;26(4):518-526. doi: 10.1038/s41431-017-0083-1.

Over the last decade, researchers and policy makers have made measuring and improving the patient experience of genetic health-care services a high priority. Evidences suggest that high performance in these measures is associated with high performance in other aspects of health-care quality, such as clinical processes, patient adherence to prevention and treatment measures, and even health outcomes, particularly of chronic conditions. Consequently patient satisfaction and perception of their health-care experiences are expected to be increasingly used as a measure of performance in public reporting and programmes related to genetic testing.
This study evaluated whether genetic tests with evidence of clinical and personal utility are associated with higher satisfaction and a more positive perception of the care experience than genetic tests with undefined utility. As genetic tests with well-defined utility, they included testing for dominant germline variants in the adenomatous polyposis coli (APC) gene, which have almost 100% penetrance and cause about 1% of all colorectal cancers, and testing for dominant variants in one of the breast/ovarian cancer susceptibility genes (BRCA1, BRCA2), which have 40–70% penetrance and are responsible for 2–7% of breast cancers and 10–15% of ovarian cancers. Genetic testing for two variants (Factor V Leiden and/or FIIG20210A) of inherited thrombophilia, which is associated with low-risk susceptibility to venous thromboembolism (VTE), was selected as a genetic test with undefined utility. Three aspects of patient satisfaction and experience were assessed: effective communication through pre- and post-test genetic counselling; collaboration between health-care providers on the management of patient care; and impact of genetic testing on quality of life.
A cross-sectional survey was performed through telephone interviews to patients tested for deleterious variants in APC or BRCA1/2 genes, or for inherited thrombophilia (FV Leiden and/or FIIG20210A) in the genetic service of the San Camillo-Forlanini Hospital (Rome, Italy) during a 5-year period (2008–2012).
Overall 237 patients had telephone interviews. Multivariate logistic regression analyses showed that patients tested for APC or BRCA1/2 variants were more likely to be satisfied with both pre- and post-test counselling than those tested for inherited thrombophilia (APC vs. thrombophilia, p=0.039 and 0.005; BRCA1/2 vs. thrombophilia, p=0.030 and <0.001). Patients tested for APC were more likely to report an improvement in quality of life than those for thrombophilia (OR=2.97, 95%CI 1.14, 7.72; p=0.025). A positive association was observed between patients who underwent BRCA1/2 testing, and self-perceived improvement in quality of life (OR=1.41, 95%CI 0.74, 2.69; p=0.294). Tests of undefined clinical and personal utility are associated with a lower degree of patient satisfaction with genetic counselling and no clear opinions on changes in quality of life compared with those with well-defined utility.
In conclusion, the assessment of patient experience helps to define the performance of a genetic service. The results show that patient experience depends, at least partially, on the type of genetic test carried out, with the overall utility of the test apparently being an important factor. In line with international recommendations, genetic tests should be offered only once their utility has been demonstrated, as in the case of APC and BRCA1/2 testing. Successful models for functional integration of genetics with other clinical specialties can improve patient experience, reducing inappropriate referrals.

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European survey on knowledge and attitudes of public health professionals on public health genomics: Pilot study.

Rosso A, D'Andrea E, Di Marco M, Pitini E, Unim B, De Vito C, Marzuillo C, Villari P.

EBPH 2017; 14(3):e12531-1-e12531-4.

During the past decade a debate has arisen on the possible utility of genomic science for public health purposes. In view of fostering the integration of public health genomics (PHG) into public health practice in Europe, a survey will be conducted on a sample of European public health professionals belonging to the network of the European Public Health Association (EUPHA) to assess their knowledge and attitudes regarding PHG. The aim of this paper is to describe the pilot phase of the survey conducted with the aim to assess to ensure practicability, validity of the survey questionnaire and interpretation of answers.
A specific questionnaire was developed to assess knowledge and attitudes of European public health professionals on PHG, consisting of 33 items grouped into five sections: A. Professional details (4 questions); B. Professional activity (7 questions); C. Knowledge on genetic testing and delivery of genetic services (8 questions); D. Attitudes on genetic testing and delivery of genetic services (8 questions); E. Attitudes on the role of public health professionals in PHG (6 questions).
Thirty-four participants responded to the questionnaire, mostly medical doctors (61.8%). With regards to knowledge, no respondent could correctly identify all applications that are currently based on an evidence of effectiveness
In terms of attitudes, more than one third of respondents agreed that it would be more important to invest resources in the social and environmental causes of ill health than in implementing genetic testing.
Nearly 70% of respondents thought that genetic testing should be introduced in clinical practice only with evidence of efficacy. The rate of agreement with the proposed roles of PH professionals in PHG was very high.
The sample of this pilot study showed a very positive attitude towards PHG, but is arisen the need to improve knowledge on the appropriateness of genetic testing and on delivery models of genetic services. Some deficiencies in knowledge were also found among professionals involved in PHG activities.

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Familial Hypercholesterolemia: A Systematic Review of Guidelines on Genetic Testing and Patient Management.

Migliara G, Baccolini V, Rosso A, D'Andrea E, Massimi A, Villari P, De Vito C.

Front Public Health. 2017 Sep 25;5:252. doi: 10.3389/fpubh.2017.00252.

Familial hypercholesterolemia (FH) is an autosomal-dominant hereditary disorder of lipid metabolism that causes lifelong exposure to increased LDL levels resulting in premature coronary heart disease and, if untreated, death. If left untreated, men and women with heterozygous FH typically develop CHD before age of 55 and 60years, respectively, while individuals with homozygous FH typically develop CHD before they are 20years old and do not survive beyond age 30.
Identification of FH patients can be achieved by clinical diagnosis, by examination of personal and family history, or by genetic testing. Genetic testing can confirm a clinical diagnosis or assist in identifying individuals whose close relatives will subsequently require screening. Several types of genetic test are available, which adopt different approaches. The most rapid tests aim to identify a specific mutation in the LDLR, APOB, or PCSK9 genes that has already been identified in another family member. At the opposite, extreme are tests that check for all known and possible mutations in recognized disease genes [i.e., next-generation sequencing (NGS) for comprehensive mutation detection or in specific loci of interest]. Therefore, this systematic review of guidelines aims to evaluate the role and importance of genetic testing in the screening, diagnosis, and management of FH patients and summarizes related health-care pathways.
The authors performed a systematic review of the literature; inclusion criteria were English or Italian guidelines focusing on genetic testing. The guidelines were included and evaluated for their content and development process using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. Ten guidelines were considered eligible, and all were judged to be of good quality. Although they were judged to be adequate in their clarity of the purpose and in the exposition of the recommendations, major concerns surround the poor description of the methodology used to produce the recommendations in most of the guidelines and the lack of information about the funding received and the conflicts of interest. The most common indications for performing genetic tests were high levels of cholesterol, or physical findings consistent with lipid disorder, in the subject or in the family history. Subsequent screening of family members was indicated when a mutation had been identified in the index patient. Regarding patient management, the various guidelines agreed that intensive treatment with lipid-lowering medications should begin as quickly as possible and that lifestyle modifications should be an integral part of the therapy. This study highlights the importance of DNA testing for the identification of FH patients and their carrier status at the earliest opportunity, which has significant benefits and implications with respect to mortality and morbidity. Currently, the best approach to ensure an effective patients' management may be represented by a combined strategy of genetic testing and clinical approach to achieve the highest level of accuracy in the FH case identification. In addition, once a mutation causative of FH has been found in the index patient, the cascade genetic screening using DNA analysis is an excellent tool to obtain an efficient detection of affected relatives. Indeed, while FH is a significant risk factor for CVD, it is also a treatable disorder whose inherited nature makes finding FH cases among family members of an index case essential.

Recommendation 3

*Recommendation 3 is based on the "**Ethico-legal and policy issues surrounding personalized medicine**" research domain.*

There is an increasing need for a co-ordinated effort to foster the development and further harmonization of dedicated policies to integrate genomics policies into existing health systems in a responsible manner. Introducing a common ethically and legally validated policy framework could represent one of the drivers needed to manage a future with increasingly personalized healthcare and a shift in the use of genomic approaches from disease treatment to prevention.

R.3. The era of genomics requires that we clarify and validate the obligations and responsibilities of the research community, research participants, and the general public. This can be achieved through collaboration and dissemination of high-quality ethical, policy and legal analysis. Legal interoperability is necessary to ensure complementarity of goals between researchers in different jurisdictions.

In order to be at the forefront of the currently shifting research landscape, we need to draw on multiple levels of expertise (e.g. law, ethics, medicine, bioinformatics, IT) in an array of multi disciplinary, jurisdictional, and institutional settings.

Finally, a metric assessing the impact of policy development or lack thereof is a fundamental tool to fine-tune guidance to multiple stakeholders.

This recommendation is based on the results of a survey performed among the Europeans Chief Medical Officers on the genomics policies in healthcare [32].

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

Mazzucco W, Pastorino R, Lagerberg T, Colotto M, d'Andrea E, Marotta C, Marzuillo C, Villari P, Federici A, Ricciardi W, Boccia S.

Eur J Public Health. 2017 Oct 1;27(5):931-937. doi: 10.1093/eurpub/ckw155.

A need for a governance of genomics in healthcare among European Union (EU) countries arose during an international meeting of experts on public health genomics (PHG). The authors conducted a survey on existing national genomic policies in healthcare among Chief Medical Officers (CMOs) of the 28 EU member states, plus Norway.
A questionnaire with 7 sections was sent to CMOs after a meeting on the policy implications of PHG held during the Italian presidency of the Council of EU in 2014. Section A asks about the presence, and extent, of any policy on genomics in healthcare and related financial support. Section B examines research in support of genomics policy in healthcare. Section C examines progress in developing genomics in healthcare. Section D asks about health technology assessment while Sections E, F and G exploring ethical and legal issues, education and training, and public engagement, respectively.
The response rate was 65.5% (19/29 of the CMOs).
Twelve (63.2%) countries (Austria, Belgium, Estonia, France, Hungary, Italy, Latvia, Norway, Poland, Spain, The Netherlands and the UK) reported having a policy on genomics in healthcare in place. Fifteen (78.9%) countries reported having dedicated funding for development of policies on genomics in healthcare. Thirteen (68.4%) of the countries reported having public research facilities devoted to development of policy or services in genomics.
Nine countries (50.0%) reported that national reports on progress in public health genomics were published.
Fifteen (83.3%) countries reported that there were national working groups on the development of policies and/or services related to genomics in the healthcare, of which half worked under the umbrella of the National Ministries of Health. Additionally, 38.9% of the countries reported working groups on the development of genomic policies in healthcare at the regional level.
Sixteen (88.9%) countries reported having departments or agencies dealing with ethical issues related to the use of genomics in public health.
Twelve (66.7%) and fourteen (77.8%) countries reported the presence of pre-graduate and postgraduate, respectively, university courses on genomics in healthcare. Thirteen (72.2%) states reported having training courses for health professionals on the appropriate use of genetic testing for susceptibility to complex disorders.
The majority of the responding countries (55.6%) reported a lack of specific information campaigns addressed to citizens (by use of advertisements on billboards, TV or radio, etc.) on genetic tests of susceptibility for complex diseases.
In conclusion, Belgium, France, Italy, Spain and UK documented the presence of a policy on genomics in healthcare. While many caveats are necessary because of the methodology, results suggest a need for a co-ordinated effort to foster development and harmonization of dedicated policies across EU to responsibly integrate genomics policies into existing health systems.

Recommendation 4

*Recommendation 4 is based on the "**Sociotechnical analysis of the pros and cons of informing healthy individuals on their genome**" research domain.*

Genetic testing of family members of patients affected with hereditary cancers or cardiovascular diseases allows for personalized prevention and it is paramount to find and inform these family members in a timely manner. Several countries are building cascade screening programs and they are discussing how family members can be traced and informed in an ethically responsible and efficient manner. In conditions where genetic testing offers a substantial and quantifiable risk estimate and prevention is available, preventive services should be prioritized. More government involvement is needed as a formally organized screening program could standardize support and information, and lead to more equitable healthcare**.**

R.4. A dedicated effort is necessary to stimulate further ethically responsible implementation of evidence-based interventions in health care, such as testing of family members in cases of hereditary cancers or cardiovascular diseases. Where guidelines for such genetic testing exist, collaboration between genetic and non-genetic health care professionals needs to be facilitated to improve implementation, education opportunities must be provided and roles and responsibilities towards informing family members must be reconsidered so we can achieve a truly multidisciplinary approach that can realize the potential of personalized medicine.

This recommendation is based on the results of a sociotechnical analysis for familial hypercholesterolemia [33].

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Stakeholder views on active cascade screening for familial hypercholesterolemia.

Van El CG, Baccolini V, Píko P, Cornel MC.

Healthcare 2018 Aug 31;6(3). pii: E108. doi: 10.3390/healthcare6030108.

In familial hypercholesterolemia (FH) carriers profit from presymptomatic diagnosis and early treatment. Due to the autosomal dominant pattern of inheritance, first degree relatives of patients are at 50% risk. A program to identify healthy relatives at risk of premature cardiovascular problems, funded by the Netherlands government till 2014, raised questions on privacy and autonomy in view of the chosen active approach of family members. Several countries are building cascade screening programs inspired by Dutch experience, but meanwhile the Netherlands' screening program itself is in transition. Insight in stakeholders' views on approaching family members is lacking. Literature and policy documents were studied and stakeholders were interviewed on pros and cons of actively approaching healthy relatives. Sociotechnical analysis explored new roles and responsibilities, with privacy, autonomy, psychological burden, resources and awareness as relevant themes. Stakeholders agree on the importance of early diagnosis and informing the family. Dutch health care typically focuses on cure rather than prevention. Barriers to cascade screening are paying an own financial contribution, limited resources for informing relatives and privacy regulation. To benefit from predictive, personalized and preventive medicine roles and responsibilities of stakeholders in genetic testing as preventive strategy and informing family members need to be carefully realigned.

Recommendation 5

*Recommendation 5 is based on the **"Identification of organizational models for the provision of predictive genetic testing"** research domain.*

The identification and evaluation of existing genetic service delivery models are important steps towards the enhancement and standardization of genetic service provision. Integration of genetics in all medical specialties, collaboration among different healthcare professionals, and redistribution of professional roles are fundamental elements for the organization of these models. Furthermore, their implementation must hinge on professional education, adequate funding, and public awareness in the field of genomic medicine.

R.5. The integration of genetics in other medical specialties should be promoted through new delivery models involving different healthcare professionals (medical specialists, nurses, technicians, etc.) and new professional roles (i.e. genetic counsellors, genetic associates, genetic nurses), in order to guarantee the use and sustainability of existing and new genomic applications in practice.

Roles and responsibilities (e.g. risk assessment, genetic counseling, genetic testing) should be redistributed among different health professionals to enhance work performance and the standard of care.

It is advisable to define the appropriate model for genetic service provision in a specific setting according to the type of healthcare system and the genetic test provided.

Professional education/training in genomics medicine, laboratory quality standards, and public awareness are essential factors for the successful implementation of genomic applications in practice.

This recommendation is based on the results of: a systematic review focusing on existing genetic service delivery models **[34, 35]***; a perspective on the main characteristics to consider for an appropriate implementation* **[27, 36, 37]** *and three surveys on (i) patient experience throughout the delivery pathways, (ii) genetic services' delivery models in European Countries, and (iii) knowledge and attitudes of European public health professionals on the delivery of genetic services* **[30, 38]**.

For References 27 and 30 please refer to Recommendation n.2 .

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Identification of Delivery Models for the Provision of Predictive Genetic Testing in Europe: Protocol for a Multicentre Qualitative Study and a Systematic Review of the Literature.

Unim B, Lagerberg T, Pitini E, De Vito C, Vacchio MR, Adamo G, Rosso A, D'Andrea E, Marzuillo C, Villari P.

Front Public Health. 2017 Aug 22;5:223. doi: 10.3389/fpubh.2017.00223.

The appropriate application of genomic technologies in healthcare is sur- rounded by many concerns. In particular, there is a lack of evidence on what constitutes an optimal genetic service delivery model, which depends on the type of genetic test and healthcare context considered.
The present project aims to identify genetic service delivery models for the provision of predictive genetic testing in the European context, and to classify, and evaluate them. The genetic service delivery models will be compared between European and extra-European (Anglophone) countries (Canada, USA, Australia, or New Zealand). The project also aims to assess knowledge and attitudes of European public health (PH) professionals regarding the delivery of genetic services, and to obtain a picture of European PH community's readiness to incorporate PHG into their practice.
The protocols describes as the project will be carried out through a multidimensional approach, which includes (i) a preliminary (non-systematic) literature search to define genetic services and genetic delivery models; (ii) a systematic review of published literature on existing genetic service delivery models and selected country websites for policy documents; (iii) structured interviews with health experts on genetic service delivery models, policies governing the use of genomics medicine, and evaluation of genetic testing and related services in their respective countries; and (iv) a survey of European Public Health Association (EUPHA) members' knowledge and attitudes regarding the use of genomic applications in clinical practice.
The transfer of genomic technologies from research to clinical application is influenced not only by several factors inherent to research goals and delivery of healthcare but also by external and commercial interests that may cause the premature introduction of genetic tests in the public and private sectors. Furthermore, current genetic services are delivered without a standardized set of process and outcome measures, which makes the evaluation of healthcare services difficult. The present study will identify and classify delivery models and, subsequently, establish which are appropriate for the provision of predictive genetic testing in Europe by comparing sets of process and outcome measures. The current project will identify possible points of improvement for currently implemented genetic services delivery models in Europe and provide recommendations to decision makers involved in the financing, delivery, and consumption of genetic services.

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Delivery models for predictive genetic testing: preliminary results of a systematic review.

Unim B, Lagerberg T, Adamo G, Pitini E, D'Andrea E, Vacchio MR, De Vito C, Villari P.

Eur J Public Health 2016, 26(suppl_1):ckw169.043, https://doi.org/10.1093/eurpub/ckw169.043.

Research on the integration of genomic knowledge into clinical practice and public health is in an early phase, and many concerns remain. The aim of this study is to identify, classify, and evaluate delivery models for the provision of predictive genetic testing in Europe vs. extra-European (Anglophone) countries.
A systematic review of the literature was conducted to identify existing genetic delivery models. Inclusion criteria were that articles be: published 2000-2015; in English or Italian; and from European or non-European countries (Canada, USA, Australia or New Zealand). Additional policy documents were retrieved from represented countries' government-affiliated websites (non-systematic search).
A total of 117 records were included, reporting on 148 genetic programmes. The programmes integrated into healthcare systems were 99 (64.9%), 49 (33.1%) were pilot programmes and 4 (2.7%) were direct-to-consumer genetic services. Most programmes were delivered in the United Kingdom (58, 39.2%), USA (35, 23.6%) or Australia (16, 10.8%). Tests for hereditary breast and ovarian cancer and Lynch syndrome were most commonly offered (39.9% and 12.8% of programmes, respectively). Many of the genetic tests offered have insufficient clinical validity or utility. The identified genetic programmes can be classified into five basic genetic service models based on which type of healthcare professional has the most prominent role in test referral: I) the geneticists model; II) the primary care model; III) the medical specialists model; IV) the population screening programmes model; V) and the direct-to-consumer model. Rudimentary evaluation of the identified programmes will be made based on outcomes and process measures of the models.
This review, as part of an European multicenter study, facilitates the identification of appropriate models, outcome and process measures for the provision of predictive genetic testing in Europe.

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Barriers and Facilitating Factors for Implementation of Genetic Services: A Public Health Perspective.

Cornel MC, van El CG.

Frontiers in Public Health. 2017;5:195. doi:10.3389/fpubh.2017.00195.

The aim of this study is to discuss how public health can benefit from promising examples of genetic testing, such as in cases of hereditary forms of breast and colorectal cancer, and what barriers and facilitating factors should be addressed for a successful implementation.

The first barrier is the lack of genetic knowledge and competences. If physicians working in public health are to take a role in the development and delivery of genetic services and in identifying family members at risk, a lack of genetic knowledge relevant for every day care is a major problem. Curricula may focus on scientific aspects of human genetics.

A second barrier for implementation is the lack of health technology assessment for the application of genetics. Randomized clinical trials may not be appropriate for persons with rare conditions often caused by different mutations that may have different risk profiles. Both the evaluation of a specific treatment for a rare gene variant and the evaluation of the clinical utility of testing may demand new study designs. If personalized medicine is the future, analytical considerations such as Bayesian analysis and use of biomarkers as surrogate outcomes may be considered.

A third barrier is the lack of translational research in terms of translation “from bench to bedside” unlike translational research “from mice to man.” No more than 3% of published genomics research focuses on research beyond the first phase of translation. The higher phases of translation include assessment of the value of a genomic application for health practice, evidence-based guidelines delivery, dissemination and diffusion research, and evaluation of health outcomes of a genomic application in practice.

A fourth barrier relates to the slow pace of translation, which in turn led to commercial offers direct-to-consumers of tests, often with low predictive value.

Furthermore, the lack of availability of resources and access to these resources, including laboratories and personnel, may limit the application of genetics. Ethical issues and lack of approval of innovative testing strategies may also be barriers.

Serious diseases where positive testing results would have a high positive predictive value and where interventions are available are the first for which genetic services should be implemented. Interventions can be both at the level of secondary prevention (colonoscopy to remove polyps and thus prevent colorectal cancer) or primary prevention (chemoprevention by aspirin).

Public awareness is a facilitating factor. It can be increased by a famous person such as Angelina Jolie who found herself in the position of being at risk of hereditary breast and ovarian cancers.

Furthermore, initiatives to train relevant health care professionals including public health genetics can open doors.

In conclusion, in cancer screening, genetic education, and (economic) evaluations, much work needs to be done for both the public health and genetics communities to address barriers and make use of promising developments to further a successful and responsible implementation of genetic services in public health.

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Creating a common language: defining individualized, personalized and precision prevention in public health

K. Bíró, V. Dombrádi, A. Jani , K. Boruzs , M. Gray.

Journal of Public Health | pp. 1–8 | doi:10.1093/pubmed/fdy066.

Because of the limited success of population-based prevention methods and due to developments in genomic screening, public health professionals and health policy makers are increasingly interested in more individualized prevention strategies. However, the terminology applied in this field is still ambiguous and thus has the potential to create misunderstandings.
This paper sets out to fulfill three objectives: (i) to identify how the terms individualized, personalized and precision prevention are used in both the grey and white literature thus far, (ii) to create definitions of these terms by using the same wording and by considering how they are related to each other and (iii) to understand how these terms fit into the existing paradigms of preventions within public health.
According to the literature search on the topic of individual-based prevention, the authors determined that while there are a few definitions of 'precision prevention', both 'individualized prevention' and 'personalized prevention' are used inter-changeably and haphazardly. Essentially, both terms can be used to describe any form of prevention which is not population-based, whether or not genomic-based is included.
Concerning the various types of individual-based prevention, the authors defined:
1) **Individualized prevention** a form of prevention in public health, in which health professionals consider the characteristics, lifestyle, family history, anamnesis, risk status and medication of the client when making proposals to maintain or improve the individual's quality of life.
2) **Personalized prevention** a form of prevention in public health, which includes the activities of individualized prevention and in which health professionals also consider biological information and biomarkers at the level of molecular disease pathways, genetics, transcriptomics, proteomics and metabolomics of the client when making proposals to maintain or improve the individual's quality of life.
3) **Precision prevention** a form of prevention in public health, which includes the activities of personalized prevention and in which health professionals also consider the socioeconomic status or the opportunities offered by psychological and behavioral data of the client when making proposals to maintain or improve the individual's quality of life
Creating a common language in any field of science is necessity, and individual-based prevention in public health is no exception. By defining these three key terms for different types of individual-based prevention both researchers and health policy makers can differentiate and use them in their proper context.

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Interim results of EUPHA network members' s survey on Public Health Genomics.

Rosso A, D'Andrea E, Di Marco M, Pitini E, Unim B, Baccolini V, De Vito C, Marzuillo C, Vacchio MR, Barnhoorn F, Zeegers D, Villari P.

Eur J Public Health 2017, 27 (suppl_3)ckx187.327, https://doi.org/10.1093/eurpub/ckx187.327.

Despite the continuous emergence of new genomic applications that could be integrated in public health (PH) activities little is known about PH professionals' preparedness to incorporate genomics in their practice. A survey is currently on-going to assess EUPHA network members' attitudes regarding their role in the implementation of public health genomics (PHG), and their knowledge and attitudes regarding genetic testing and the delivery of genetic services.
Invitation to take part in an on-line survey was included in EUPHA February 2017's newsletter and was sent to the members of some of EUPHA thematic sections. An interim descriptive analysis of knowledge and attitudes was conducted, along with a univariate and multivariate analysis of their determinants.
176 people completed the questionnaire by April 2017; 12.2% of respondents were involved in PHG activities, while PHG was one of the main areas of work for 7.4% of them. Only 15.9% correctly identified all medical conditions for which there is (and there is not) evidence for implementing genetic testing, with higher rates among professionals involved in PHG activities (P = 0.001). Professionals not involved in PHG agreed to higher rates that investing in genomics may divert efforts and resources from addressing social and environ- mental causes of ill health (93.7% vs 62.1%, P = 0.000). Respectively 60.3% and 78.9% of respondents agreed that PHG needs to be grounded on evidence of effectiveness and cost- effectiveness. The 62.5% of the sample agreed with all the proposed roles for PH professionals in putting PHG into practice.
This interim analysis shows a quite positive attitude but the need to increase knowledge of European PH professionals on PHG. Those directly involved in PHG activities tend to have a more positive attitude and a better knowledge; however, gaps are also evident in this group, suggesting the need for a stronger knowledge exchange among professionals.

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