THE EVALUATION AND THE IMPLEMENTATION OF GENETIC/GENOMIC APPLICATIONS: AN HEALTH TECHNOLOGY ASSEMENT EXERCISE?

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Domain 2
Economic evaluation of predictive genomic applications

Domain 5
Identification of organizational models for the provision of predictive genomic applications

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

**PRECeDI Recommendations**

**Domain 2**
R.2. A comprehensive evaluation of the value (outcomes/cost) of genetic and genomic applications should also include evidence on the social aspects, and context-related dimensions 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.

**Domain 5**
R.5. The integration of genomics 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.

**PRECeDI Recommendations**

**Domain 2**
**EVALUATION**

**Domain 5**
**IMPLEMENTATION**

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

HTA is the systematic evaluation of properties, effects and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology [WHO].

"The main purpose of conducting an assessment is to inform a policy decision making"

Genetic tests are becoming increasingly available and the assessment of their actual benefits has become crucial for clinical and public health practice. Despite different evaluation models have been developed to guide their implementation, none of them reached a generalized consensus: the evaluation of genetic tests for use in clinical and public health practice remains a challenging process.

OLD BOTTLE WITH A NEW LABEL?
The Health Technology Assessment process

FROM THE EVALUATION TO THE EVALUATION FOR MANAGEMENT AND DELIVERY

[...] HTA has evolved through three distinct phases: the machine, the clinical outcomes, and the delivery models, with the third of these still under way. As the focus has shifted from a single machine to choosing among interventions for specific disease conditions to service delivery approaches, HTA has drawn on research and modes of discourse from a growing variety of disciplines [...]
The path from basic science discovery to improved population health outcomes involves several overlapping and nonlinear phases of translational research.

**RESEARCH STEPS IN PUBLIC HEALTH GENOMICS AND PERSONALIZED MEDICINE**

**TRANSLATIONAL RESEARCH**

<table>
<thead>
<tr>
<th>TRANSLATION RESEARCH PHASE</th>
<th>NOTATION</th>
<th>TYPES OF RESEARCH</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Gene and other discoveries</td>
<td>Genome-wide association studies, candidate gene studies</td>
<td>Discovering new genomic variants or biomarkers</td>
</tr>
<tr>
<td>T1</td>
<td>Discovery to candidate health application</td>
<td>Phases I and II clinical trials; observational studies to characterize genes and gene-environment interaction; pharmacogenomics</td>
<td>Evaluating gene–environment interactions or evaluating the function of genomic variants</td>
</tr>
<tr>
<td>T2</td>
<td>Health application to evidence-based practice guidelines</td>
<td>Phase III clinical trials; observational studies; evidence synthesis and guidelines development</td>
<td>Assessing whether a genomic application performs better than the standard of care in improving health outcomes or developing evidence from the clinical setting to informed evidence-based guidelines</td>
</tr>
<tr>
<td>T3</td>
<td>Practice guidelines to health practice</td>
<td>Dissemination research; implementation research; diffusion research; phase IV clinical trials</td>
<td>Evaluating the implementation of genomic applications in community-based centers</td>
</tr>
<tr>
<td>T4</td>
<td>Practice to population health impact</td>
<td>Outcomes research; population monitoring of morbidity, mortality, benefits and risks</td>
<td>Performing nationwide surveillance to evaluate how the implementation of a particular genomic test has affected population health</td>
</tr>
</tbody>
</table>

Adapted from Schully 2010 and Schully 2014
GENOMICS IMPACT ON PUBLIC HEALTH: OPTIMISTIC POINTS OF VIEW

The completion of the human genome project will allow for ‘…the development of rational strategies for minimizing or preventing diseases…’

Collins. NEJM 1999

‘I predict that comprehensive, genomics-based health care will become the norm with individualized preventive medicine and early detection of illness’

Zerhouni, J Investig Med 2006

GENOMICS IMPACT ON PUBLIC HEALTH: PH EXPERTS POINT OF VIEW

“Many see genetic screening as the hope of the future of disease prevention. But caution is essential. …. While this type of screening can certainly help to evaluate risk and may be appropriate in certain high-risk groups if nothing can be done to alter the finding, the need for, and use of, such information must be very carefully considered. Is it useful to diagnose without being able to treat? The main purpose of genetic screening at present is to prevent rather than to treat disease. But it must not be allowed to neglect the basic principles and criteria of screening. Information cannot be regarded as worthwhile, regardless of the outcome”

Walter Holland, 2006
GENOMICS IMPACT ON PUBLIC HEALTH: THE HEALTH ECONOMISTS’ POINT OF VIEW

‘How much will the expanded use of genetic information further escalate the cost of healthcare, and who will pay for that?’
Varmus, 2002

‘Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health’
Willett W, 2002

‘...in this era of increasing concern about healthcare costs, it will be impossible to consider the implication of genomic medicine without considering the economic implications.’
Phillips KA, 2004
SCREENING TEST OUTCOMES ARE DESCRIBED BY THE 2×2 TABLE

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Test</strong></td>
<td>Group (a) True Positive</td>
<td>Group (b) False Positive</td>
</tr>
<tr>
<td><strong>Negative Test</strong></td>
<td>Group (c) False Negative</td>
<td>Group (d) True Negative</td>
</tr>
</tbody>
</table>

**Positive Predictive Value (PPV):**
\[ \frac{a}{a+b} \]

**Negative Predictive Value (NPV):**
\[ \frac{d}{c+d} \]

**FACTORS THAT INFLUENCE PREDICTIVE VALUES:**
- Sensitivity of the test \((a/(a+c))\)
- Specificity of the test \((d/(b+d))\)
- Prevalence of the disease

THE IMPORTANCE OF THE PRE-TEST PROBABILITY OF DISEASE (PREVALENCE OF THE DISEASE)

**Sensitivity = 99%; Specificity = 95%**

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Disease Present</th>
<th>Disease No</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence = 1%</strong></td>
<td>99</td>
<td>495</td>
<td>17%</td>
</tr>
<tr>
<td>Positive result</td>
<td>495</td>
<td>475</td>
<td>51%</td>
</tr>
<tr>
<td>Negative result</td>
<td>5</td>
<td>9025</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>9500</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence = 5%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive result</td>
<td>495</td>
<td>475</td>
<td>51%</td>
</tr>
<tr>
<td>Negative result</td>
<td>5</td>
<td>9025</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>9500</td>
<td></td>
</tr>
</tbody>
</table>
CAN WE REASON IN THE SAME WAY FOR GENETIC TESTING?

Continuum of genetic risk

Most common diseases
Examples: Alzheimer disease, asthma, diabetes, most cancers, most cardiovascular disease

Infectious diseases
Example: Chicken pox

Caused mostly by genetic change

Caused by genes and environment

Group (a)
True Positive

Group (b)
False Positive

Group (c)
False Negative

Group (d)
True Negative

Burke, 2004

TWO 2X2 TABLES
(AND SIX PROBABILITIES TO TAKE INTO ACCOUNT)

Genotype +
Test +
Group (a)
True Positive

Group (b)
False Positive

Sensitivity

Genotype -
Test -
Group (c)
False Negative

Group (d)
True Negative

Prevalence of genotype

Genotype +
Test -
Group (a)
True Positive

Group (b)
False Positive

Genotype -
Test +
Group (c)
False Negative

Group (d)
True Negative

Lifetime risk of disease

Relative risk

Disease +
Group (a)
True Positive

Group (b)
False Positive

Disease -
Group (c)
False Negative

Group (d)
True Negative

Analytic validity

Clinical validity
WHICH KIND OF INFORMATION DO PATIENTS (AND CLINICIANS AND POLICY-MAKERS) WANT FROM A GENETIC TEST?

- Probability of getting the disease given a positive test result (clinical positive predictive value)
- Probability of no getting the disease given a negative test result (clinical negative predictive value)
- Is an effective and acceptable treatment available given a positive test result (clinical utility)?

CLINICAL POSITIVE PREDICTIVE VALUE

THE IMPORTANCE OF THE RELATIVE RISK

<table>
<thead>
<tr>
<th>Frequency of Susceptibility-Confering Genotype (%)</th>
<th>1.0</th>
<th>2.0</th>
<th>5.0</th>
<th>10.0</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>7.5</td>
<td>10.0</td>
<td>24.9</td>
<td>49.6</td>
<td>98.1</td>
</tr>
<tr>
<td>0.5</td>
<td>7.5</td>
<td>10.0</td>
<td>24.5</td>
<td>47.8</td>
<td>91.3</td>
</tr>
<tr>
<td>1.0</td>
<td>7.5</td>
<td>9.9</td>
<td>24.0</td>
<td>45.9</td>
<td>84.0</td>
</tr>
<tr>
<td>10.0</td>
<td>7.1</td>
<td>9.1</td>
<td>17.9</td>
<td>26.3</td>
<td>34.5</td>
</tr>
<tr>
<td>30.0</td>
<td>6.5</td>
<td>7.7</td>
<td>11.4</td>
<td>13.5</td>
<td>14.9</td>
</tr>
</tbody>
</table>

*The positive predictive value can be calculated with use of the following formula: \[ \frac{R(D) \times 100}{G(R-1)+1} \], where \( R \) is the relative risk, \( D \) is the incidence of a disease (in this case 0.04), and \( G \) is the frequency of a susceptibility-conferring genotype.

Holtzman & Marteau, 2000
HOW TO INCREASE THE RELATIVE RISK? I

Table 1. Positive Predictive Value of Tests for
Sensitivity-Conferring Genotypes in the Presence of
an Interacting Covariate, According to the Frequency
of the Covariate and Relative Risk Associated with It,
for a Genetic Relative Risk of 2 and a Disease
with a Lifetime Risk of 5 Percent.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive Predictive Value in Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (frequency, 1%)</td>
</tr>
<tr>
<td></td>
<td>frequency, %</td>
</tr>
<tr>
<td></td>
<td>With factor disagreed</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
</tr>
</tbody>
</table>

*The positive predictive value of the test is a function of the frequency
of the covariate (f) and the positive predictive values in the absence of the
covariate (PPV) and in the presence of the covariate (PPV_c), where WR is the relative risk of disease associated with the covariate
among persons with the genotype PPV_c [H22] = WR / [1 + (1 - WR) / PPV].
Phase 1 can be rearranged to solve for PPV_c: in phase 1: PPV_c [H22] = PPV / (f + PPV / (1 - f) / [1 + (1 - WR) / PPV]). The above follows the model of type 4 interaction
described in Khoury and Wagoner. More complex models that lead to higher
positive predictive values.

Khouri, 2000

HOW TO INCREASE THE RELATIVE RISK? II

Yang et al, 2003
HOW TO INCREASE THE RELATIVE RISK? II

<table>
<thead>
<tr>
<th>Inserted Thrombophilia</th>
<th>No. of Healthy Subjects</th>
<th>No. of Patients</th>
<th>POSTORIOR Probability of Developing Disease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden:</td>
<td>+</td>
<td>775</td>
<td>3.9 (1.4-6.6)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>15,175</td>
<td>2.6 (2.2-3.1)</td>
</tr>
<tr>
<td>G20210A prothrombin gene mutation:</td>
<td>+</td>
<td>11,610</td>
<td>12.3 (8.5-17.8)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>322</td>
<td>126.8</td>
</tr>
<tr>
<td>Protein C deficiency:</td>
<td>+</td>
<td>45</td>
<td>.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1,937</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Combined tests

Yang et al, 2003

WHO CRITERIA FOR SCREENING

1. The condition should be an important problem
2. There should be an acceptable (and effective) treatment
3. Facilities for diagnosis and treatment should be available
4. There should be a recognized pre-symptomatic stage
5. The natural history of the condition should be well understood
6. There should be an acceptable test
7. The test should be acceptable to the population
8. There should be an agreed policy about whom to treat
9. The cost should be economically acceptable

Wilson & Jungner, 1968
WHICH KIND OF EVIDENCE DO WE NEED ABOUT GENETIC TESTS?

THE “IDEAL” RCT

- Study population
  - Inclusion criteria
  - Informed consent
- Study participants
- Randomization
- Genetic testing and appropriate intervention in case of positive test result
- Usual surveillance strategy and traditional interventions
- Long-term mortality
- Long-term mortality

WHICH KIND OF EVIDENCE DO WE NEED ABOUT GENETIC TESTS?

A “MORE REALISTIC” FRAMEWORK

<table>
<thead>
<tr>
<th>Domain</th>
<th>Evidence about ...</th>
<th>Types of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytic validity</td>
<td>Sensitivity and specificity of the test in relation to genotype</td>
<td>Laboratory studies comparing test results with gold standard</td>
</tr>
</tbody>
</table>
| Clinical validity    | • Prevalence of the genotype  
                      | • Lifetime risk of disease  
                      | • Gene-disease association  
                      | • Gene-gene interactions  
                      | • Gene-exposures interactions | • Cross-sectional studies  
                      | • Cohort studies  
                      | • Case-control studies |
| Clinical utility     | Benefits and harms of interventions accruing from both positive and negative tests | • RCTs  
                      | • Observational studies  
                      | • Systematic reviews and meta-analysis |

+ Ethical, Legal and Social Implications
GENOMICS IN PUBLIC HEALTH

“A multidisciplinary field concerned with the effective and responsible translation of genome-based knowledge and technologies to improve population health” (Bellagio Statement, 2006)

As genome-based research generates new ideas for healthcare innovation, there is a critical need for an evaluation process, based in ongoing integration of knowledge within and across multiple disciplines (including ELSI) to determine the outcomes, both health-related and social, of new genome based applications. In the absence of a robust evaluation strategy, a trial-and-error process of innovation occurs. Resulting commercial incentives tend to promote the value of genetic tests based on the intuitive appeal of risk knowledge in the absence of proven benefit. This approach is already evident in direct-to-consumer and -physician marketing of genetic tests, and represents a potential drain on healthcare resources.

There is also a risk that effective innovations will not be implemented, or implemented haphazardly

Burke, 2006

THE INTRODUCTION OF A GENETIC TEST INTO THE PUBLIC HEALTH AND CLINICAL PRACTICE

The “ideal” world

The development and validation of a genetic test leads to understanding the clinical context, which includes the prevalence of disease and inheritance, the accuracy and clinical sensitivity and specificity, the availability and efficacy of prevention/interventions, the costs of screening, follow-up, diagnosis, and treatment. This is followed by cost-effectiveness analysis and the development of professional recommendations/practice guidelines. These recommendations then lead to clinical practice.

The “real” world

The development and validation of a genetic test is followed by understanding the clinical context, which includes the prevalence of disease and inheritance, the accuracy and clinical sensitivity and specificity, the availability and efficacy of prevention/interventions, the costs of screening, follow-up, diagnosis, and treatment. This is followed by cost-effectiveness analysis, the development of professional recommendations/practice guidelines, and finally, clinical practice.

Col, 2003
INAPPROPRIATE USE vs CITIZENS’ RIGHTS

GENETIC/GENOMIC APPLICATIONS SHOULD BE EVALUATED RIGOROUSLY BEFORE ENTERING INTO CLINICAL AND PUBLIC HEALTH PRACTICE

GENETIC/GENOMIC APPLICATIONS WITH PROVED EFFICACY AND COST-EFFECTIVENESS SHOULD BECOME CITIZENS’ RIGHTS

IMPLEMENTATION ISSUES
PHARMACOGENETICS vs PREDICTIVE GENETIC TESTS

PREDICTIVE GENETIC TESTS

- Health promotion
- Preventive measures
- Public health services

PHARMACOGENETICS

- Treatments

• PHYSICIANS AND OTHER PHG PROFESSIONALS
• TRAINING
• GUIDELINES
• LABS
• HEALTH CARE INTERVENTIONS
HTA has evolved through three distinct phases: the machine, the clinical outcomes, and the delivery models, with the third of these still under way. As the focus has shifted from a single machine to choosing among interventions for specific disease conditions to service delivery approaches, HTA has drawn on research and modes of discourse from a growing variety of disciplines [...]

Battista, 2006

29 tools published between 2000 and 2017 (USA n.12, Canada n.4, Europe n.9, Australia n.2, International n.2).

They are mostly based on the ACCE model (n.13 tools) and on the HTA model (n.6 tools) or both (n.2 tools).

17 tools address all types of genetic test, while the others take into account a specific type of genetic test (newborn screening, predictive genetic tests, genetic susceptibility tests).
RESULTS - Evaluation components and methodological aspects

Most used evaluation criteria are analytic and clinical validity, clinical utility and ethical, legal and social implications.

The economic dimension is always considered even if in little detail.

Attention for delivery models, organizational aspects and consumer’s point of view is often lacking.

Only few models highlight research priorities or criteria to recommend the use of the test.

GENETIC TESTS EVALUATION FRAMEWORK

Overall structure

Section I – The genetic test
Overview of the test and the clinical condition
Analytic validity
Clinical validity
Clinical utility
Personal utility

Section II – Delivery of the genetic test
Overview of the delivery programs
Organizational aspects
Economic evaluation
Ethical, legal and social implications
Patient’s/individual’s point of view

Section III – Research priorities

Section IV – Criteria to establish recommendations on the use of the genetic test
Net benefit of the delivery program
Cost-effectiveness of the delivery program
Organizational and feasibility aspects
GENETIC TESTS EVALUATION FRAMEWORK

Section I - The genetic test
Overview of the test and the clinical condition
• Name of the genetic test and of the clinical condition
• Clinical condition (clinical and pathophysiological description, genetic background, public health impact)
• Test (general features, technical features, clinical context)
Analytic validity
Analytic sensitivity and specificity, assay robustness, accuracy, precision, quality control
Clinical validity
Scientific validity, test performance (clinical sensitivity and specificity, positive and negative clinical predictive value, influencing factors)
Clinical utility
Available interventions, efficacy and effectiveness, health risk, net benefit
Personal utility

GENETIC TEST vs GENETIC TEST PROGRAM

Genetic test program = Health care program including the genetic test
GENETIC TESTING PROGRAMS

Section II - Delivery of the genetic test

Overview of the programs and the delivery models for the genetic test

- Healthcare programs
- Delivery models

Organizational aspects

- Expected demand
- Resources needed
- Education of professionals, patients, and citizens
- Information dissemination to professionals, patients, and citizens
- Cooperation, communication, and coordination
- Quality assurance, monitoring, and control
- Barriers to implementation

Economic evaluation

Ethical, legal and social implications

Patient's/Individual's point of view
Section III - Research priorities

Evidence gaps, Research questions and Priorities
The existing evidence gaps should be formulated in research questions and classified by importance to define the research priorities

<table>
<thead>
<tr>
<th>Evaluation criteria</th>
<th>Evidence (present/present in part/ lacking)</th>
<th>Research questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytic validity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Validity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical utility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal utility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organizational aspects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethical, legal and social implications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s individual’s point of view</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Section IV - Criteria to establish recommendations on the use of the genetic test

Recommendations are based on the following criteria:

- Net benefit of the delivery program
- Cost-effectiveness of the delivery program
- Organizational and feasibility aspects

<table>
<thead>
<tr>
<th>Rating</th>
<th>Characterization</th>
<th>Available scientific evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High probability that the implementation of the health care program including the genetic test brings to a positive net benefit</td>
<td>Analytic validity, clinical validity, clinical utility, ELSI, patient’s individual’s point of view</td>
</tr>
<tr>
<td>B</td>
<td>Moderate probability that the implementation of the health care program including the genetic test brings to a positive net benefit</td>
<td>Analytic validity, clinical validity, clinical utility</td>
</tr>
<tr>
<td>C</td>
<td>High or moderate probability that the implementation of the health care program including the genetic test brings to a low or null net benefit</td>
<td>Analytic validity, clinical validity, clinical utility</td>
</tr>
<tr>
<td>D</td>
<td>High or moderate probability that the implementation of the health care program including the genetic test brings to a negative net benefit</td>
<td>(Analytic validity)</td>
</tr>
</tbody>
</table>

* Referring to the dimension that most individually demonstrates positive net benefit in Class D; analytical validity can be proven or not but there is scientific evidence to the detriment of other dimensions such as the clinical utility.
Section IV - Criteria to establish recommendations on the use of the genetic test

<table>
<thead>
<tr>
<th>Rating</th>
<th>Characterization</th>
<th>Estimate of cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Delivery program of the genetic test highly cost-effective</td>
<td>Less costly and more effective than the comparator (cost-saving)</td>
</tr>
<tr>
<td>B</td>
<td>Delivery program of the genetic test cost-effective</td>
<td>More costly and more effective than the comparator (ICER below the considered threshold)</td>
</tr>
<tr>
<td>C</td>
<td>Delivery program of the genetic test questionable cost-effective</td>
<td>More costly and more effective than the comparator (ICER exceeding the threshold)</td>
</tr>
<tr>
<td>D</td>
<td>Delivery program of the genetic test not cost-effective</td>
<td>More costly and less effective than the comparator (dominated)</td>
</tr>
</tbody>
</table>

*Referring to the interpretation of the incremental cost-effectiveness ratio (ICER).

<table>
<thead>
<tr>
<th>Rating</th>
<th>Characterization</th>
<th>Estimate of feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Delivery program implementable in the reference scenario</td>
<td>Easy overcoming of barriers to implementation</td>
</tr>
<tr>
<td>II</td>
<td>Delivery program potentially implementable in the reference scenario</td>
<td>Possible overcoming of barriers to implementation</td>
</tr>
<tr>
<td>III</td>
<td>Delivery program not implementable in the reference scenario</td>
<td>Impossible overcoming of barriers to implementation</td>
</tr>
<tr>
<td>NA</td>
<td>Available information not sufficient to establish feasibility of the delivery program</td>
<td>Further data are required to provide a final recommendation</td>
</tr>
</tbody>
</table>

*Referring to the analysis of economic resources, coordination and cooperation, personnel training, information for staff and citizens, quality assurance, monitoring and control.

SYSTEMATIC REVIEWS OF PRIMARY ECONOMIC EVALUATIONS OF GENETIC/GENOMIC TESTS: A FUNDAMENTAL STEP
GENETIC TESTING FOR BRCA 1/2 EVIDENCE OF COST-EFFECTIVENESS

D’Andrea et al. 2016

DELIVERY MODELS

Definition

THE BROAD CONTEXT WITHIN THE PHG FRAMEWORK IN WHICH GENETIC SERVICES ARE OFFERED TO INDIVIDUALS AND FAMILIES WITH OR AT RISK OF GENETIC DISORDERS

In other words, a genetic delivery model is a combination of personal healthcare services provided by healthcare professionals to individuals and families (i.e., diagnosis, treatment/management, and information) and PH services and functions (i.e., population screening, financing, policy development, workforce education, information/citizen empowerment, service evaluation, and research).
DELIVERY MODELS FOR GENETIC TESTS (I)

DELIVERY MODELS FOR GENETIC TESTS (II)

Unleashing the power of human genetic variation knowledge: New Zealand stakeholder perspectives

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Purpose: This study aimed to address the challenges in using genetic information in health care and to identify opportunities for improvement.

Methods: With a grounded theory approach, semi-structured interviews were conducted with 48 participants to collect multiple stakeholders perspectives on genetic services in New Zealand. Results: Three themes emerged from the data: (1) access to service delivery models; (2) barriers to sharing and using genetic information; and (3) a need for more comprehensive education. Conclusions: Addressing the issues of genetic information and knowledge management is crucial for improving genetic services. Key Words: genetic service, genetic testing, grounded theory, information technology, stakeholder involvement.
DELIVERY MODELS CLASSIFICATIONS

BATTISTA ET AL.
Focus on the role of the healthcare professional
- Multidisciplinary specialist clinics and coordinated services in rare genetic disorders led by geneticists
- Genetic services integrated in other medical specialties (e.g., oncogenetics, neurogenetics, cardiogenetics)
- Genetic services integrated into primary care
- Genetic services provided in screening programs (e.g., prenatal and newborn screening)

GU ET AL.
Focus on the patients’ pathway
- The Patient–Doctor–Counselor Model;
- The Patient–Doctor–Lab Model;
- The Patient–Counselor–Lab Model; and
- The Patient–Lab (Commercial) Model (i.e., direct-to-consumer genetic testing).
OUR CLASSIFICATION

DELIVERY MODELS IDENTIFIED IN THE LITERATURE

BRCA1/2  Lynch syndrome  Familial hypercholesterolemia

Model I: Genetic services led by geneticists  Model II: Primary care model  Model III: Medical specialists model  Model IV: Genetic services integrated into population screening programs  Model V: Direct-to-consumer (DTC) model
BARRIERS TO IMPLEMENTATION: THE EUPHA SURVEY

Why this survey?

• 2003 Human Genome Project debate on the utility of genomic science for public health purposes

• Public health genomics (PHG): diverting resources or providing useful prevention opportunities?

Aim of the survey

To assess the attitudes of European Public Health (PH) professionals belonging to EUPHA network regarding their role in the implementation of PHG, and their knowledge and attitudes regarding genetic testing and the delivery of genetic services.

RESPONDENTS

(4 October 2017)

493 Respondents
382 Completed the survey

+44 non EU
RESULTS - KNOWLEDGE

Correctly identified all applications of genetic testing which are based (and not) on evidence of effectiveness 1.6% (6/387)

Correctly identified all clinical conditions for which there is (and not) strong evidence supporting the use of a genetic test (CDC tier-1) 12.4% (48/387)

Correctly identified which health professionals may be involved in the delivery of genetic testing 50.0% (191/382)

Knew that genetic testing should necessarily be associated with genetic counseling 90.8% (346/381)

RESULTS - ATTITUDES ON GENETIC TESTING AND ON GENETIC SERVICES

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is more important to invest in the social and environmental causes of ill health than in the implementation of genetic testing</td>
<td>110 (28.8%)</td>
<td>120 (31.4%)</td>
<td>105 (26.4%)</td>
<td>45 (12.0%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Susceptibility (or predisposition) tests should be introduced in the clinical and public health practice even without health interventions with proven efficacy.</td>
<td>8 (2.1%)</td>
<td>55 (13.3%)</td>
<td>38 (10.0%)</td>
<td>162 (42.4%)</td>
<td>123 (32.2%)</td>
</tr>
<tr>
<td>Susceptibility (or predisposition) tests should be introduced in the clinical and public health practice only if economic evaluations show cost-effectiveness ratios favorable compared with alternative health interventions</td>
<td>46 (12.1%)</td>
<td>172 (45.1%)</td>
<td>69 (18.3%)</td>
<td>80 (21.0%)</td>
<td>34 (9.1%)</td>
</tr>
<tr>
<td>Genetic tests for diseases who could have a fatal outcome (e.g. BRCA testing for breast and ovarian cancer) should be provided free at the point of delivery to people who could benefit from them.</td>
<td>99 (25.9%)</td>
<td>155 (40.5%)</td>
<td>48 (12.6%)</td>
<td>60 (15.7%)</td>
<td>20 (5.2%)</td>
</tr>
</tbody>
</table>
### RESULTS - ATTITUDES ON THE ROLE OF PH PROFESSIONALS ON PHG

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health thinking should consider that risk factors can affect subsets of the population differently based on genetic susceptibility.</td>
<td>99 (26.9%)</td>
<td>227 (61.9%)</td>
<td>26 (7.1%)</td>
<td>10 (2.7%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Public health professionals should be involved in the continuous assessment of the utility and validity of emerging genomic applications.</td>
<td>143 (18.9%)</td>
<td>181 (49.1%)</td>
<td>36 (9.8%)</td>
<td>6 (1.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Public health programs should actively implement genomic applications that are evidence-based (e.g. BRCA testing for relatives of known mutation carriers).</td>
<td>96 (26.2%)</td>
<td>187 (51.0%)</td>
<td>69 (18.8%)</td>
<td>14 (3.8%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Public health professionals should measure the utilization of genetic services in order to assess unmet needs and inequalities of access to services.</td>
<td>110 (10.0%)</td>
<td>186 (50.9%)</td>
<td>57 (15.6%)</td>
<td>6 (1.6%)</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Public health professionals should measure in practice outcomes, process indicators and value added of genomic applications.</td>
<td>126 (34.3%)</td>
<td>178 (48.5%)</td>
<td>54 (14.7%)</td>
<td>5 (1.4%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>I think that in the future public health programmes (e.g. cancer screening, chronic diseases prevention programmes) will make a stronger use of genetic information.</td>
<td>109 (29.7%)</td>
<td>199 (54.2%)</td>
<td>50 (13.6%)</td>
<td>8 (2.2%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

### DETERMINANTS OF ATTITUDES

#### MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Attitudes on genetic testing and delivery of genetic services (0= score ≤ 2, 1= score 3-4)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge score (0= score ≤ 2, 1= score 3-4)</td>
<td>2.44</td>
<td>1.44-4.13</td>
<td>0.001</td>
</tr>
<tr>
<td>PHG professional (0= not involved in PHG, 1= involved in PHG)</td>
<td>1.40</td>
<td>0.80-2.42</td>
<td>0.236</td>
</tr>
<tr>
<td>PHG main area of work (0=no, 1=yes)</td>
<td>1.87</td>
<td>0.67-5.20</td>
<td>0.230</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attitudes on the role of PH professionals in PHG (0= score ≤ 2, 1= score 3-6)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge score (0= score ≤ 2, 1= score 3-6)</td>
<td>1.41</td>
<td>0.93-2.40</td>
<td>0.205</td>
</tr>
<tr>
<td>PHG professional (0= not involved in PHG, 1= involved in PHG)</td>
<td>1.72</td>
<td>1.02-2.86</td>
<td>0.038</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1=25-40 [omitted]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1=41-55</td>
<td>0.78</td>
<td>0.46-1.39</td>
<td>0.320</td>
</tr>
<tr>
<td>2=56-75</td>
<td>0.47</td>
<td>0.27-0.81</td>
<td>0.007</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- The analysis shows a low level of knowledge on PHG among EUPHA members, while attitudes on the use of genetic testing and genetic services and on the possible roles of PH professionals in PHG are generally positive.
- Positive attitudes are associated with higher level of knowledge and younger age.
- *Initiatives to increase culture on PHG among EUPHA members may contribute to fostering the incorporation of genomic applications in PH activities.*

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CONCLUSIONS

- Genetic/genomic applications: inappropriate use vs citizens’ rights
- Need of an Health Technology Assessment approach
- Systematic reviews of economic evaluations are important
- Culture and training are strategic