The policy of public health genomics in Italy

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\textbf{A B S T R A C T}

Italy has a monitoring system for genetic testing, consisting in a periodic census of clinical and laboratory activities performed in the country. The experience is limited, however, concerning the translation of genomic testing for complex diseases into clinical practice. For the first time the Italian Ministry of Health has introduced a policy strategic plan on genomics and predictive medicine within the 2010–2012 National Prevention Plan. This achievement was supported by the Italian Network for Public Health Genomics (GENISAP) and will likely contribute to the integration of public health genomics into health care in the country. Our experience might be of interest not only in Italy, but in other high-income countries, struggling to keep a healthy economy and healthy citizens.

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1. Background

Italy has a population of 60.6 million. It has been ranked the world’s twenty-fourth most-developed country in 2010 [1], and its quality of life index, gross domestic product (GDP), nominal GDP per capita and standard of living are among the highest in the world [2–4]. Once a country of mass emigration, Italy is today home to over 4 million foreign national residents registered with authorities, 7.1% of the country’s population [1].

1.1. Health system

Since 1978 Italy has had a public healthcare system based on principles of universalism, comprehensiveness and solidarity in funding. In 2008 healthcare expenditure amounted to 9.5% of the national GDP; the health system is highly evolved and ranks 2nd worldwide, with the 3rd best healthcare performance [1]. Most of the public health care current expenditure is still dedicated to the hospital sector, which accounts for approximately 46% of the overall healthcare budget. Although some progress has been made in the past years, prevention only absorbs 4% of the overall healthcare expenditure [1,5].

Healthcare today is provided by a mixed public-private system and is administered on a regional basis. The de- volution of powers and competences at a sub-national level, which was started with the reform of “Title V” of the Italian Constitution in 2001, required the establishment of solid links between national and regional institutions. The role of central government is conceived as to set the so-called “essential levels of care” (Livelli Essenziali di Assistenza, LEAs), which must be guaranteed to all residents [6].

2. Current scenario on genetic and genomic testing in Italy

2.1. Clinical and prenatal genetics

To our knowledge, Italy is the only country in Europe and one of the very few in the world where a monitoring system for the use of genetic tests was implemented since the mid-80s. The Italian Society of Human Genetics (SIGU, Società Italiana di Genetica Umana) has been carrying out a periodic census of clinical and laboratory activities performed in the country. The last census, in 2007, covered 217 molecular genetic laboratories, 171 cytogenetic laboratories and 102 clinical genetic services throughout the country (total: 490). Data were collected from 278 responding centres (respondence rate: 57%). Only 28% of the responding centres were certified according to quality standards. About 560,000 genetic tests, including 311,069 cytogenetic and 248,691 molecular analyses of 556 genes, were recorded. The foetal karyotype was examined on either chorionic villi or amniocytes in about one of every 4.4 at term pregnancies. Only the 11.5% of cytogenetic analyses and the 13.5% of molecular tests were accompanied by genetic counselling. Low congruity was found between clinical diagnoses and laboratory results, suggesting that the request of genetic tests may not be appropriate in several instances [7].

2.2. Complex diseases

Predictive genetics have currently few applications in clinical practice. Predictive tests have raised some interest in public health only in the case of high-penetrance genetic variants associated with common types of cancer (breast/ovarian and colorectal cancer syndromes) and, to a lesser extent, the maturity onset diabetes of the young (MODY).

Testing for low-penetrance polymorphisms is still fragmentary, and a structured and organic experience in Italy is still missing.

The Institute of Hygiene of Università Cattolica in Rome has partnered the Public Health Genomics European Network (PHGEN) in 2006 and founded in 2007 the Italian Network for Public Health Genetics, later named GENISAP Network, with the objectives of generating knowledge, monitoring the predictive genetic testing activities in Italy, assessing their appropriateness, performing cost-effectiveness analyses and contributing to the development of evidence-based recommendations and guidelines on the translation of genomic technologies in clinical settings [8,9]. The GENISAP Network, four years later, counts around 50 experts from different backgrounds.

Recent results produced by some of the members of the GENISAP Network have shown that molecular laboratories testing for hereditary breast/ovarian and colorectal cancers in four Italian Regions (Abruzzi, Liguria, Tuscany, Latium) are not coordinated, as there are no regional (and national) guidelines or plans for the delivery of these tests, and quality is not monitored in a systematic way. Furthermore, there is a very wide inter-laboratory heterogeneity in terms of procedures, costs and turnaround times. Lastly, genetic tests for well-established hereditary syndromes (namely, BRCA-related breast/ovarian cancers and Lynch syndrome) appear markedly under-prescribed compared to population estimates of their incidence [10].

A more systematic approach to care of women at risk of breast cancer has recently been undertaken by Emilia-Romagna Region which has organised a network, based on a “hub and spoke” model, involving genetic and senology units in integrated activities [11]. This model includes quality monitoring of clinical variables (e.g. referral appropriateness and efficacy of clinical pathways) and establishes genetic testing management strategies.

Another study promoted by the GENISAP Network focused on the use of genetic tests for the assessment of the risk of developing thromboembolic events [methyleneetrahydrololate reductase (MTHFR) C677T polymorphism, Factor V Leiden, prothrombin G20210A]. The conclusion was that these tests are highly prescribed, although scientific evidence does not support their use for assessing the individual thromboembolic risk [12]. This is particularly true with regard to the MTHFR gene: although current literature is concordant that MTHFR polymorphic variants do not affect significantly the risk of thrombosis, it is prescribed within the panel of thrombophilia genes, which is by large the most frequently prescribed susceptibility test in Italy [7].

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In Italy two key documents define a governance planning for predictive medicine based on genomics, namely the 2010–2012 National Prevention Plan (NPP) [13] and the 2011–2013 Technical Document for the reduction of the burden of cancer diseases [14].

The NPP is ordinarily published every two years, since 2005, by a concerted action of Ministry of Health and Regions and addresses the preventive actions within the public health system in Italy.

The 2010–2012 NPP is structured into four main areas listed below:

1. Collective prevention, targeted to the most common risks, including surveillance and control of infectious diseases and interventions to promote a healthy lifestyle and working environment;
2. Prevention in high-risk groups, including vaccination coverage for individuals exposed to certain pathogens, oncologic screenings, individual risk assessments and counselling delivery;
3. Prevention of complications and recurrences of chronic diseases, especially among the elderly;
4. Predictive medicine: the detection of potential risk factors for the occurrence of diseases in healthy individuals (the cardinal points of genomic predictive strategies are identified in: tailored clinical pathways, active involvement of individuals, defined cost-effectiveness profiles and explicit evaluation criteria).

According to the organisation of the Italian health system, all stakeholders at all levels should be involved in decision making and organisational strategies necessary for the implementation of the plan, following the stewardship management framework proposed by the Ministry of Health [13].

The 2011–2013 Technical Document for the reduction of the burden of cancer disease is a part of the national oncologic planning [14]. It emphasizes the importance of genomics in cancer prevention, research, innovation and care fields. The document aims to develop tools and processes to use genomic-based knowledge in the decision-making, and to put the PHG in all policies. In that direction it also provides the drawing up of a specific plan for PHG in Italy.

Based on both the 2010–2012 NPP and the 2011–2013 Technical Document, a dedicated National Plan for Public Health Genomics (PHG-NP) [15] has been drafted by the Public Health and Innovation Department of the Ministry of Health, with the scientific support of the Institute of Hygiene of Università Cattolica and with the advisory of the members of the GENISAP Network. To our knowledge, this is the first example in Europe where a national prevention strategy plan foresees a specific policy plan on PHG.

The formal approval of the PHG-NP is currently under discussion and it is in charge of the Italian Ministry of Health. After its publication, additional contents defined within the so called ‘PHG protocol’ will further complete the central framework defined within the PHG-NP, detailing programming tools at the regional level the implementation of all action lines and tools relevant to genomics.

As for the contents of the PHG-NP, the plan addresses in depth how to translate the genomics knowledge into public health for the benefits of population health, by defining the actions to be taken at central level in order to implement a stewardship governance model to best translate genomics in clinical practice (Table 1). It also suggests the institution of a steering board for PHG within the Italian Centre for Disease Prevention and Control (CCM), which should act as a technical advisor for all the genome related technologies with a potential health related application.

The plan focuses on five main strategic objectives [15], including:

1. the definition of areas of intervention of PHG;
2. the collection of evidence on current PHG experience in the country;
3. the definition of the best instruments for the promotion of genome-based knowledge among health professionals and citizens;

<table>
<thead>
<tr>
<th>Stewardship domain</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed actions</td>
<td>• Institution of a registered network of all the structures and laboratories, with defined standards and requirements, delivering genetic tests • Definition of a standard surveillance system. The data produced by the system can be used to evaluate appropriateness of genetic test prescription and delivery Proposal of policies for an appropriate use of resources for research</td>
</tr>
<tr>
<td>Tools to support actions</td>
<td>• Promotion of best practices in genomics and development of guidelines and clinical and health care pathways • Systems for health technology assessment of genomic technologies and appropriate prescription of genetic tests • Capacity building and strengthening • Professional education and definition of a core curriculum of “basic” skills for trainers and medical prescribers of genetic tests • Definition of a network of centres, involving research experts and regional representatives • Networks and partnerships with existing associations of patients and volunteers • GENISAP Network role on addressing governance issues</td>
</tr>
<tr>
<td>Accountability</td>
<td>• Communication plan with the citizens • Implementation of programmes for the empowerment of citizens</td>
</tr>
<tr>
<td>Knowledge-based management</td>
<td>• Development and assessment of an integrated informative system providing genomics standardised data (comparable both at national and European level) • Definition of new competences for regional centres in the analysis and processing of genome-based data</td>
</tr>
</tbody>
</table>

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4. Implementation of the policy of public health genomics through dedicated projects

In order to start implementing the PHG-NP, even before its publication, the CCM has financed two different lines of executive projects.

The first project [17] involves six regions (Latium, Veneto, Tuscany, Liguria, Emilia Romagna and Lombardy) and it is finalised to achieve a more appropriate and rational use of predictive genetic and genomic tests for complex diseases based on three strategic lines:

1. To create a national registry of all public and private laboratories where predictive genomic tests are delivered. This will be achieved extending and integrating the already existing registries in the country;
2. To build a portal for such registry, available on the website of the CCM. Such portal will report not only which predictive tests are available and where, but will also contain indications on appropriateness, utility and costs of the tests;
3. To institute, in the Italian regions directly involved in the project, accredited training courses, workshop and seminars (held by specialists in public health, genetics, molecular biology, oncology, gynaecology and neurology). These activities will be aimed at the potential prescribers of genomic tests, such as general practitioners, public health specialists of the community prevention services, oncologists, gynaecologists and neurologists [18].

The second project aims to evaluate the economic impact on the National health system of genomic tests, using a sample of regions recruited on voluntary basis. Three strategic lines are defined:

1. Economic assessment of the health care pathways, in the Italian regions directly involved in the project, relatively to the most commonly prescribed predictive genetic and susceptibility tests. The assessment will focus both on predictive tests of proven effectiveness and cost-effectiveness (such as BRCA1 and BRCA2 for breast and ovarian cancer syndrome, or APC for hereditary colorectal cancer syndrome), and on tests with scarce effectiveness and/or cost-effectiveness (such as thrombophilia susceptibility genes).
3. Analysis of the European scenario on health policies in PHG, to be achieved via two surveys: (a) PHG health policies currently implemented in European countries; and (b) evaluation of training courses on PHG in postgraduate medical residency programmes of Public Health and/or Community medicine in Italy.

5. Conclusions

As of today, it is difficult to predict the full potential of predictive testing for complex traits and diseases. It is plausible that in the forthcoming future disease prevention and treatment plans will be devised for single patients or groups of patients according to their genetic characteristics, and will be conducted by identifying early medical surveillance systems, changing lifestyles and diet, or by implementing targeted drug therapies. We strongly support the notion that is it worthwhile exploring the intriguing field of PHG with a scientific approach and an unbiased mind. Evidence base in genomics is difficult to gather, and ethical, legal and social issues can prove challenging [19].

A first step for the introduction of a solid genome-based prevention system can only pass through a phase of intense research on the field. This is where we are in Italy now. Investments, like those provided within the National Prevention Plan, are necessary to fund studies able to assess the potential applications of genome knowledge into clinical practice by the public and private healthcare: the
Conflict of interest

All authors declare no conflict of interest.

Role of the funding source

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