Policy Paper on Public Health Genomics in Cancer

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CONTENTS

1 Introduction

Genomics and molecular biology have developed rapidly over the last decade, and the pace of advances is set to accelerate in the future. However, claims and counterclaims about the role that genomics might play in improving population health abound. On the one hand, genomics is viewed as the harbinger of a brave new world in which healthcare is transformed by virtue of earlier diagnosis, more effective prevention programs and more precise targeting of therapies to more narrowly specified diseases. On the other hand, genomic medicine has also been said to promote a vision of healthcare that encourages individualism rather than collectivism, and that it may further fragment the risk pooling that underpins social solidarity, and increase the scope for stigmatization and discrimination. Amid these competing visions of the advances that genomic science might entail, there is a critical need for an appropriate policy response.

Healthcare around the world is at a crossroads, with financial pressures undermining the sustainability of health systems. As highlighted by a number of policy documents, such as those produced by the European Steering Group on Sustainable Healthcare and the World Economic Forum, sustainable healthcare requires a shift from treatment of established disease to early diagnosis and disease prevention. It also relies on the need to engage citizens in taking greater responsibility for their own health in order to establish a more participatory healthcare model. The three elements that are a consistent feature of reports seeking to address these issues are: placing the individual citizen at the centre of health systems; an increase in emphasis on early detection and risk reduction, i.e. prevention; and the reorganisation of service in which care is moved from the hospital to the community.

Although it is widely acknowledged that the application of genomics in healthcare has the potential to reduce the burden of disease and improve population health, none of the abovementioned reports explicitly discuss the role of genomics or the life sciences in contributing to solutions to these problems. In fact, the contribution of genomics to health in two main areas is clear: 1) in *personalised medicine*, where *omics* technologies may be used to diagnose disease, indicate the best treatments and monitor continuing disease activity or response, and 2) in *personalised prevention*, where new technologies help in the assessment of risk for disease and preventive medications that could reduce this risk, such as– in some cases– the use of aspirin in colorectal cancer.

It is time for policymakers, health authorities and other public organisations to promote and support resources that enable citizens- individually and cooperatively- to access, understand, interpret and make use of reliable information that supports application of genomics in healthcare. Policy should also help to define metrics to measure stakeholder participation, particularly among citizens and their communities, and to facilitate public dialogue on the value of personalised medicine and the necessary conditions for its success.

2 Aim

Cancer control is a major public health issue. Cancer is strongly driven by genetic modifications in the genome DNA. A new era in science has emerged in the last decade with the field of study of genomics, wherein the aim is to try to better understand health through integrating broad information on the genome with data on environmental factors such as nutrition, physical fitness and disease. When studied at the population level, this area is generally referred to as *public health genomics* (PHG).

This policy paper provides guidance on three important issues where PHG can substantially advance our understanding of cancer control as well as support policy makers, citizens and cancer patients in particular, in their common fight against cancer. These issues are: first, the importance of strictly regulating stratified screening by genetic testing of high-risk cancer patients; second, key issues to be addressed within the health system when implementing genomics in medical care; and third, how to address direct-to-consumer genetic testing (DTC-GT) within the health system.

3 General recommendations

Establish a framework on the ethical, legal and social requirements related to introducing the use of omics data into the health system.

Increase genetic and preventive literacy of healthcare professionals and citizens to promote responsible use of these novel options.

4 Theme 1: Personalised risk-assessment for stratified prevention (PeRaSP): Standards in genetic testing as a prerequisite for stratified screening and prevention of high-risk patients

Cancer screening (CS) aims to identify cancer at a pre-symptomatic stage in order to improve patient outcomes, i.e. to reduce mortality and morbidity and to improve quality of life. CS programmes implemented so far have been designed to test a target population which is mainly made up of people from the general population with an average risk to develop the disease in a specific age group. Therefore, the screening test being used is appropriate for the majority of individuals in this population.

Genetic screening (GS) is defined as genetic testing for medical purposes that is systematically offered to the entire population or specific segments of the population as a part of **personalised risk-assessment for stratified prevention (PeRaSP)**. Epidemiological studies suggest that about one third of the most frequent solid tumours, i.e. colon, breast and prostate cancer, are associated with inherited risk factors, although only a minor proportion of these factors have been identified so far.

For individuals known to be at higher risk for certain tumour diseases, general CS programmes might not be appropriate or might start too late in life. Therefore, these individuals could potentially benefit from PeRaSP. Using PeRaSP would thus reduce the incidence, morbidity and mortality associated with the disease, however this would require that individuals at risk be identified by GS. As an example, the identification of BRCA or HNPCC gene mutation carriers has already led to the offer of specific prevention programmes, including risk-adjusted screening for early detection and prophylactic surgery or preventive medicines, such as anti-estrogens for breast cancer and aspirin for colon cancer, for risk reduction (29).

Beyond the generally recognised principles for the implementation of CS programmes, additional requirements need to be fulfilled in order to justify PeRaSP. Specifically, any PeRaSP programme based on GS must include appropriate counselling both before and after genetic testing. Counselling should be target-group specific and non-directive, offering people appropriate information to empower them to take informed decisions. In particular, the *right not to know* must be respected, and discrimination and disadvantage must be prohibited. Also, counselling should

provide information regarding the phenotype, i.e. the typical clinical presentation linked to the genotype with respect to the natural disease course, subtype and treatment response.

Introducing PeRaSP programs requires careful streamlining with currently implemented population-based screening programs, when common cancer sites are targeted. Also, the cost of introducing PeRaSP programs will need to be evaluated in more detail.

5 Recommendations: Personalised risk-assessment for stratified prevention

Recommendation 1: Develop harmonised common entrance criteria for PeRaSP throughout Europe.

Recommendation 2: Establish and promote specific, multi-disciplinary professional structures for the indication, evaluation and provision of PeRaSP.

Recommendation 3: Increase genetic and preventive literacy of healthcare professionals (i.e. promote literacy on risk assessment, risk communication, clinical interpretation of genetic test results, and indication of preventive measures).

Recommendation 4: Increase genetic and preventive literacy of citizens to promote responsible use of preventive options for cancer and health system resources.

Recommendation 5: Establish new genotype/phenotype databases to enable prospective cohort studies and ensure that Quality Assurance is a prerequisite for the evaluation of effectiveness of PeRaSP (preferably linked to existing cancer registries).

Recommendation 6: Establish a harmonised framework on the ethical, legal and social requirements of PeRaSP in cancer.

6 Theme 2: Requirements and prerequisites for implementation of *omics* in routine molecular diagnosis in oncology

The implementation of genomics and other *omics* technology in somatic mutation profiling for targeted therapies or for linking prognosis to genetic markers such as BRCA 1&2 has become a reality in clinical diagnostics in oncology. Currently, targeted next-generation sequencing (NGS) gene panels are being used in routine diagnosis, and soon whole genome sequencing will become a standard asset. The novel approach represented by the extension of precision and personalised medicine- presumably linked to access to a wide range of (currently) non-reimbursed medicines- poses a great challenge for the sustainability of oncological care. Complex or rare cancers also require the co-evolution of research and care, which supposes the need for the establishment of a new operational framework in healthcare.

Multi-disciplinarity is a key element in the success of such a framework. It implies coordination in the concerted activities of many medical professionals (including oncologists, pathologists, surgeons, radiotherapists, clinical geneticists, and others) public health professionals, IT specialists,

biostatisticians, bioinformaticians, molecular/biomedical scientists, epidemiologists, and (population) geneticists.

This level of organisation does not currently exist in most European countries, although a few disparate activities at various levels are ongoing or in the process to being initiated. Considering the major impact the introduction of genomics may have on healthcare services and public health, it is essential that each country develop a system and infrastructure that ensures harmonisation in terms of quality, performance, interpretation and documentation of NGS, to facilitate and support the development and implementation of genomics in daily practice. All disciplines directly involved in the process as well as professionals, scientists, officials and patient/citizen representatives, should be included.

Two key elements of this novel paradigm in healthcare capacity building are: 1) the massive production, collection, storage and integration of different types of data, requiring broad computational capacities for analysis, i.e. big data, and 2) the integration of multi-disciplinary teams as part of a common vision for the 21st century organisation of public health and healthcare services aimed at long-term follow-up of cancer patients (by medical and health professionals, government, industry, and the general public).

In addition, it is clear that introducing this novel paradigm necessitates general acceptance by the European population. Therefore, it is important to maintain a culture of continuous open communication and debate. Raising awareness should take place broadly across society about the possibilities and limits of the approach: in education, from the high school level to highly specialised professional education programs in academic institutions and universities; in the healthcare, social and professional sectors; in the financial world (banking and insurance); in industry at large; and at the government level. Training and education at all levels of society will be the cornerstone in empowering people in their access to and choices regarding the potential benefits provided by these new opportunities.

7 Recommendations: *Omics* in the clinic

Recommendation 1: For each country, establish a system and infrastructure that oversees the rapid evolution of omics and the utility of molecular variants within oncological clinical use.

Recommendation 2: Develop an integrated outcome evaluation framework that links different healthcare information among registries and repositories. This framework should use standardised data formats and data transmission protocols to support development of clinical trials tailored to the personalised genome context.

Recommendation 3: Launch public debate on the limits and use of genomic information for improvement in public health and healthcare. Debate should include citizens, cancer patients, professionals, scientists, industry and government representatives.

8 Theme 3: Direct-to-consumer genetic testing

Since 2007, many companies have been promoting and selling genetic tests directly to consumers through the Internet (1), which have been referred to as direct-to-consumer genetic tests (DTC-GT).

DTC-GT are defined as genetic tests that are both marketed and sold directly to the public- including over the counter- without the supervision of a healthcare professional (18).

The use of DTC-GT has rapidly increased since their first commercialization in 2007 (2), and awareness of citizens on this issue has grown accordingly (3,4). Currently, many commercial tests are being offered in the form of multiplex genetic profiles (5-7).

Currently, three types of DTC-GT are available: 1) tests for one or a few specific conditions, 2) multiple single-nucleotide polymorphism risk assessment tests, and 3) whole human genome sequencing (8).

There is very little regulatory control over DTC-GT in most European countries and the United States (9). Since February 2015, the US FDA has allowed companies to market only limited DTC-GT (10), while in EU the situation varies widely. Regulatory and control mechanisms for DTC-GT in the EU vary among different member states. For instance, although Greece does not have explicit legal provisions for DTC genomics, several other laws, including soft law mechanisms, create the broader legal framework within which DTC genomic services may exist (11). In Belgium, Italy and the UK there is no specific legislation that forbids or regulates the provision of DTC genetic tests, while in France, Germany, Portugal, and Switzerland there is specific legislation that dictates that genetic tests can only be carried out by a medical doctor after the provision of sufficient information and appropriate genetic counselling (12, 13).

There has been debate about whether strict regulations regarding personal genetic services are likely to be enforced in European countries in the near future (14). The Human Genetics Commission (HGC) of the UK made recommendations in 2007, setting up a public consultation regarding DTC-GT in response to controversy over the matter, but the commission has not yet come up with specific regulations (14).

Although there is limited scientific evidence on the potential benefits of DTC-GT (15-17), these genetic tests also have the potential to be harmful as they lack professional counselling services that should accompany them (18). Moreover, the incidental finding of variants of unknown significance (VUS) may raise unnecessary concerns or even inappropriate interventions on the part of consumers. Other relevant issues have been reported, such as privacy protection of data storage, discrimination by employers and health insurers, and lack of delivery of genetic services in terms of diagnostic and/or preventive counselling due to the absence and/or ignorance of the healthcare workforce (19).

In some cases of DTC-GT, there is a lack of transparency about quality control, clinical validity (i.e. the strength of association that determines the test's ability to accurately and reliably identify or predict the disorder of interest) and clinical utility (i.e. the balance between benefit and harm when the test is used to influence patient management) (20).

Furthermore, social inequity and unnecessary follow-up, anxiety, and negative psychosocial consequences have been associated with the use of DTC-GT (21-24). In 2013 the European Parliament published the results of a survey on DTC-GT, reporting that a majority of service providers fail to offer sufficient information to consumers about the nature of DTC-GT, the interpretation of results, and the implications arising from the test itself (25).

In order to support decision making for policy at the European Union level, a systematic review of position statements, policies, guidelines, and recommendations produced by professional

organizations or other relevant bodies related to the use of DTC-GT was published (12). In all of the 17 included documents, the potential disadvantages of DTC-GT overweighed the potential benefits.

Concerning the field of cancer, DTC-GT often include only genetic variants with low or no clinical validity and no clinical utility. Consequently, people who are worried about cancer and undergo DTC-GT do not change their risk behaviour, but in fact may adopt unhealthy attitudes (26). Other literature also reports paradoxical behaviour with respect to cancer and dietary interventions (27).

As mentioned earlier, some DTC-GT provide information on known hereditary cancer genes (e.g. BRCA 1&2) (28), stressing the need for counselling. Indeed, people who undergo such DTC-GT might discover inheritance of a highly penetrant genetic variant and therefore have to deal with an incidental finding (29-32).

9 Recommendations: Direct-to-consumer genetic testing

Recommendation 1: In its current form, DTC-GT for cancer risk prediction is unlikely to have any positive impact on the health of citizens. Citizens' and healthcare professionals' awareness and education about DTC-GT is urgently needed.

Recommendation 2: Policy makers should regulate the offering of DTC-GT, with the understanding that legislation should balance consumer protection with freedom of opinion.

Recommendation 3: Each European citizen should have access to organised certified genetic counselling in his own country, provided by the national health system, taking into account the local context of organisation of services.

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