SAPIENZA
UNIVERSITÀ DI ROMA

IDENTIFICATION OF DELIVERY MODELS FOR THE PROVISION OF GENETIC TESTING, POLICIES GOVERNING THE USE OF GENOMIC APPLICATIONS AND EVALUATION OF GENETIC SERVICES: A MULTICENTRE STUDY

Doctoral Thesis

Ph.D. in Infectious Diseases, Microbiology and Public Health – XXXI cycle

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Academic year 2017/2018

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Abstract

The provision of genetic services, along with research in the fields of genomics and genetics, has evolved in recent years to meet the increasing demand of consumers interested in prediction of genomic diseases and various inherited traits (e.g. ability in sports, nutrigenomics, ancestry, etc.). Consumer demand and commercial interests have paved the way for the premature introduction, in the public and private healthcare sectors, of genetic tests with insufficient data on analytical and clinical validity, as well as clinical utility. There is also lack or insufficient evidence of cost-effectiveness of several genetic applications already introduced in clinical and public health practice. These concerns contribute to the lack of evidence on what constitutes an optimal genetic service delivery model, defined as the broad context within the Public Health Genomics framework in which genetic services are offered to individuals and families with or at risk of genetic disorders.

The aim of this dissertation is to identify existing genetic service delivery models, policies governing the use of genomic applications, and measures to evaluate genetic testing and related services in Europe and extra-European (Anglophone) countries (Canada, USA, Australia, or New Zealand). Two methodological approaches have been employed, a systematic review of the literature and a cross-sectional study addressing healthcare professionals with good knowledge and/or experience on the provision of BRCA1/2, Lynch syndrome, familial hypercholesterolemia, and inherited thrombophilia genetic testing, policies on genetic applications and evaluation of genetic services.

The identification and evaluation of existing genetic service delivery models are important steps towards the enhancement and standardization of genetic service provision. Current models of genetic services require the integration of genetics in all medical specialties, collaboration among different healthcare professionals, and redistribution of professional roles. Prior to implementation in clinical and public health practice, genetic tests should be evaluated based on available efficacy and cost-effectiveness data and offered to the citizens as right to benefit from innovative healthcare. The proper implementation of genomics application in mainstream medicine can be achieved through professional education, training, adequate funding, public policies, and public awareness of the field of genomic medicine.

Acknowledgements

First, I want to thank my supervisor Prof. Paolo Villari. I appreciate his contributions of time, ideas, and general guidance to make my Ph.D. experience successful. The joy and enthusiasm he has for research in the field of Public Health was contagious and motivational for me, even during tough times in the Ph.D. pursuit.

I would like to acknowledge the members of the Center of Genomics and Policy (CGP) that contributed to my personal and professional experience at McGill University (Montréal, QC, Canada) during my secondment as a research trainee. I am especially grateful to my secondment supervisor Prof. Bartha Knoppers for her time, interest, and helpful comments on the research project conducted in Quebec.

I received support for the research protocol and content of the questionnaires addressing healthcare professionals in Europe from the PRECeDI consortium. In particular, I would like to thank researchers from the Catholic University of the Sacred Heart (Rome, Italy); VU University (Amsterdam, Netherlands); Erasmus MC University (Rotterdam, Netherlands); European Public Health Association – EUPHA (Utrecht, Netherlands); Better Value Healthcare Ltd. (Oxford, UK); Linkcare Health Services (Barcelona, Spain); and Debrecen University (Debrecen, Hungary).

I also acknowledge the funding source that made my Ph.D. work possible. The research was funded by the PRECeDI project (Marie Skłodowska-Curie Research and Innovation Staff Exchange, RISE).

Glossary

Genetic services: specialized services offered to individuals and families with genetic conditions or at risk of developing or transmitting a genetic condition.

Genetic service delivery model: combination of personal healthcare services provided by healthcare professionals to individuals and families (i.e., diagnosis, treatment/management, and information) and public health services and functions (i.e., population screening, financing, policy development, workforce education, information/citizen empowerment, service evaluation, and research).

Patient pathway: patient flow through different professionals from the point of access to healthcare services to treatment of the genetic disorder and follow-up.

Genetic program: healthcare program providing a genetic test.

Genetic testing: type of medical test involving an analysis of human chromosomes, DNA, RNA, genes, and/or gene products (e.g. enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health.

Newborn screening: screening in infants shortly after birth for a list of genetic, endocrine, and metabolic disorders that are treatable, but not clinically evident in the newborn period.

Diagnostic testing: used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life but is not available for all genes or all genetic conditions.

Carrier testing: used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.

Prenatal testing: used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder.

Preimplantation testing or preimplantation genetic diagnosis (PGD): used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro

fertilization. Only embryos without genetic changes are implanted in the uterus to initiate a pregnancy.

Predictive and presymptomatic testing: used to detect gene mutations associated with disorders that appear after birth, often later in life. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis. Presymptomatic testing can determine whether a person will develop a genetic disorder before any signs or symptoms appear.

List of abbreviations

GWAS: Genome Wide Association Studies

SNP: Single Nucleotide Polymorphism

DTC: direct-to-consumer

FDA: Food, Drug, and Cosmetic Act

ELSI: ethical, legal, and social implications

PHAC: Public Health Agency of Canada

PHG: Public Health Genomics

CCMG: Canadian College of Medical Geneticists

CDC: Centers for Disease Control and Prevention

CF: cystic fibrosis

CLIA: Clinical Laboratory Improvement Act

MODY: maturity-onset diabetes of the young

GDNs: genetic diabetes nurses

PRECeDI: Personalized pREvention of Chronic DIseases consortium

MSCA: Marie Skłodowska Curie Action

RISE: Research and Innovation Staff Exchange

HBOC: hereditary breast and ovarian cancer

FH: familial hypercholesterolemia

IT: inherited thrombophilia

EUPHA: European public health association

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I. INTRODUCTION

1.1 Integration of genomic discoveries into clinical practice

The past decade has seen the emergence of Public Health Genomics (PHG), a multidisciplinary field that has established scientific and policy foundations for the appropriate translation of genomics research into health benefits for individuals and populations [Bowen et al. 2012]. Attempts to integrate genetic or genomic knowledge of common conditions into clinical practice are in the early stages, and the current state of this translation is surrounded by many questions [Scheuner et al. 2008]. The key component of translation research are evidence-based interventions, which can be defined as "The sequence of events in which a proven scientific discovery is successfully integrated into established practice and policy" [CDC 2007].

The continuum of multidisciplinary translation research in genomic medicine includes four phases, from T1 to T4 (Figure 1).

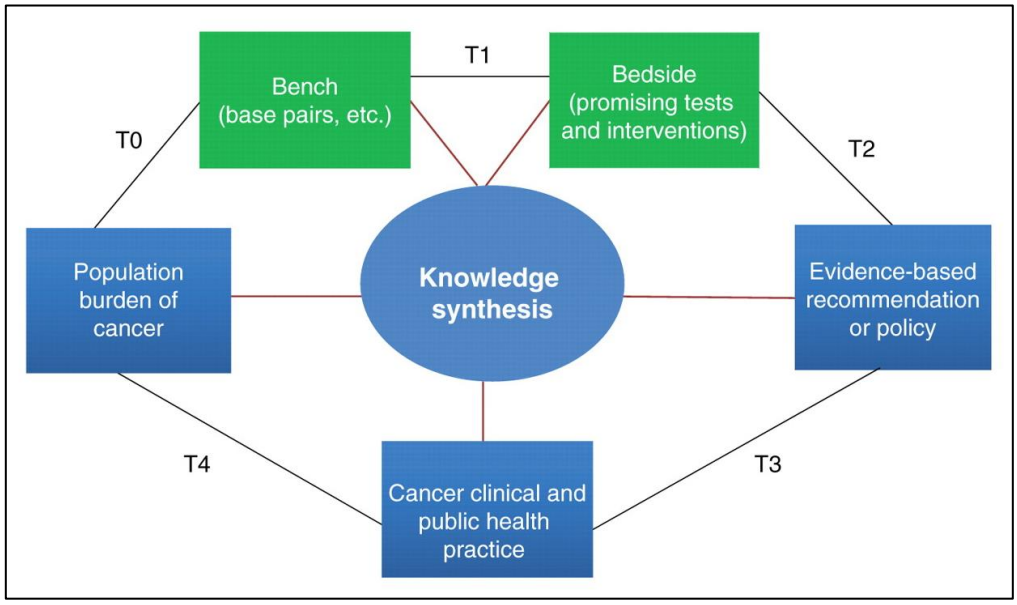

Figure 1. Phases of translational research. Source: Khoury et al. (2011)

The translation of a genetic test from research into practice starts with the identification of the disorder tested for, the specific test to be used, and the clinical scenario in which the test will be

used (T1). An important limitation of the T1 research is the tendency to reduce the genome to single genes or variants, potentially missing the value of looking across the genome. As a response to this issue, current approaches are including Genome Wide Association Studies (GWAS). This method searches the genome for Single Nucleotide Polymorphisms (SNPs) in any gene that occur more frequently in people with a particular disease compared to those without the disease. This approach has already identified SNPs related to several complex conditions including diabetes, heart abnormalities, Parkinson disease, and Crohn's disease [Yamada 2008].

Phase 2 translation research (T2) assesses the value of genomic application for health practice and leads to systematic reviews that will support the development of evidence-based practice guidelines. A test must be validated for each clinical application or intended use in terms of analytic validity, clinical validity, clinical utility, and ethical, legal, and social issues (ACCE components). Validation could be defined as "The procedure in which possible errors in the diagnostic process are identified, measured and evaluated to minimize the risk of an erroneous outcome of the test procedure, taking cost-effectiveness into account". Analytic validity refers to the technical performance of a test: how accurately and reliably the laboratory assay measures the variant in question [Teutsch et al. 2009]. Clinical validity refers to the ability of a test to accurately predict the trait or condition in question or stratify future disease risk or prognosis [Chowdhury et al. 2013]. Clinical utility relates to effectiveness in practice, compared with standard of care. The ultimate test of clinical utility is the impact on patient health outcomes, including changes in morbidity and mortality of the target condition, and also positive and negative psychosocial outcomes such as changes in personal risk perception, emotional impacts of risk information, and benefits from minimizing diagnostic delay, etc. [Burke et al. 2010].

The translation of evidence-based guidelines into practice (T3) is particularly challenging and may be influenced by factors inherent to research and delivery of healthcare, but also by external and commercial interests. A major concern regarding technology transfer in genetics is the premature introduction of tests in public and private health sectors with insufficient data on analytical and clinical validity, as well as clinical utility. There is also lack or insufficient evidence of cost-effectiveness of several genetic applications already introduced in clinical and public health practice [Scheuner et al. 2008, Khoury et al. 2007]. One of the challenges in the provision of genetic services is the effective coordination of the different components of the services while guaranteeing that genomic applications with proven efficacy and effectiveness are actually delivered to populations. The T3 research phase addresses such issues by increasing the spread of knowledge about evidence-

based interventions (dissemination research), integrating these interventions into existing programs and structures (implementation research), and promoting the adoption of these interventions by stakeholders (diffusion research) [CDC 2007, Khoury et al. 2007].

The last phase of translation research (T4) evaluates the impact of evidence-based recommendations and guidelines on population health outcomes. It focuses on clinical and public health outcomes and it is strongly associated to implementation processes of T3 research phase [Khoury et al. 2007].

1.2 Defining Genetic Services and Genetic Service Delivery Models

Although the terms “genetic(s) services” and “genetic delivery models” appear frequently in the peer-reviewed literature and in documents on genetics policy-related websites, they are usually not defined. Therefore, a literature search was carried out with the objectives to define the two terms and also to identify, describe and classify the genetic service delivery models. A common search strategy was used to identify articles from three electronic databases (PubMed, Google and Google scholar) with the following keywords: genetic(s) service, medical genetics, genetic service delivery, genetic(s) service delivery model, genomic service delivery. Only articles defining the two terms “genetic(s) services” and “genetic delivery models”, describing or classifying genetic service delivery models, and published in English or Italian languages were included. No period restrictions were applied. The search produced eight useful records.

The first record is the US Genetic Service Policy Project (GSPP) [Washington State Department of Health 2008] that was performed from 2004 to 2008. The aim of the work was to understand and report the current genetics healthcare delivery system in the US using existing data, compiling new data, and utilizing the expertise of many stakeholders. The GSPP defines genetic services as “genetic testing, diagnosis of genetic conditions, genetic counselling, and treatments for individuals with or at risk of genetic disorders”. The report also answered to a set of ten questions (Figure 2) while describing alternative models for service delivery and highlighting potential delivery gaps or issues. However, a specific definition of genetic services delivery models and their classification are not reported.

The provision of genetic services in the US occurs across five broad stages: preconception, prenatal, newborn, pediatric, and adult. Genetic service providers fall into two general categories: i) those who are specifically trained to provide genetic services and are certified by professional organizations (medical geneticists, genetic counsellors, genetic nurses, genetic technologists in the laboratory); and ii) those who perform genetic services but are licensed in another discipline and have received little or no formal training or certification in genetics, namely general practitioners (GPs) and other specialists (e.g. oncologists, neurologists, gynecologists, etc.); other professionals (e.g. nurse practitioners, midwives, physician assistants, and social workers).

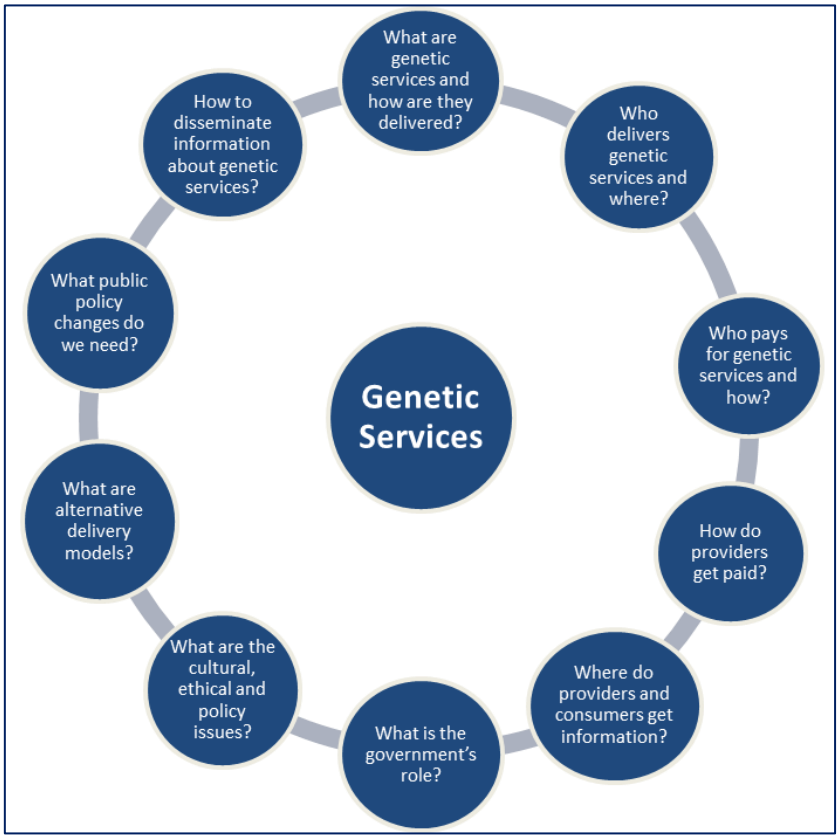

Figure 2. Ten questions of the US Genetic Service Policy Project (GSPP) Report.

In the US, genetic services are usually provided in clinical genetics clinics based in academic medical centers or tertiary referral centers. Laboratory providers work in public (including state) laboratories and commercial labs. In general, genetic services and consultations are more readily available in urban areas (such as academic medical centers) as opposed to rural areas.

States finance their genetic services activities through an array of public and private funding sources such as state general funds, Center for Disease Control and Prevention (CDC) and private grants, Medicaid, and consumers' out-of-pocket payments. Medicaid coverage is subject to state variation, but most state programs reimburse for "medically necessary" genetic services (e.g. amniocentesis, maternal-serum screening for neural tube defects and Down syndrome, chromosomal analysis from amniotic fluid). Private health insurance plans are financing a significant share of genetic services (e.g. genetic testing for chromosomal abnormalities, prenatal and neonatal diagnosis, and some pre-implantation genetic diagnosis services).

Regulation of genetic services includes government oversight of genetic testing, licensing of laboratories and their personnel, and quality assurance and control. At the federal level, the Clinical Laboratory Improvement Act (CLIA), the Food, Drug, and Cosmetic Act (FDA), and the Federal Policy for the Protection of Human Subjects regulate both the development and application of genetic tests. The CDC National Office of Public Health Genomics developed two projects that contribute to the regulation of genetic services: a) evaluation of Genomic Applications in Practice and Prevention (EGAPP); and b) evaluation of the analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications (ELSI) of genomic test data. In the private sector, professional societies and other organizations are involved in developing guidelines for genetic tests. These organizations include the Association of Public Health Laboratories, the American College of Medical Genetics, etc.

To enhance the coordination of different components of genetic services, which is a big issue in the US genetic service delivery system, interdisciplinary clinics with multidisciplinary teams providing care were developed (e.g. cancer genetics, cystic fibrosis - CF, neuromuscular diseases). Another important challenge is the current reimbursement practice that does not cover costs associated with the provision of genetic services. Furthermore, the number of clinical geneticists and other genetics health professionals is limited, and some areas have little or no access to genetic services.

The second record found was the article by Silvey et al. (2009). In 2006 and 2007, a working group of the Western States Genetics Services Collaborative (WSGSC) developed two tools: the "Defining Genetics Services Framework" and the "Genetics Services Outcomes Menu". The article by Silvey et al. was very useful for the definition of "genetics services" and for their contextualization within the Public Health framework. Consequently, the article contributed to the identification of a definition on genetic service, but a definition and classification of genetic service delivery models were not

provided. In developing the "Defining Genetics Services Framework" the work group decided that the first step was to define the term "genetics services", hence they conducted a peer reviewed literature and internet search. The definitions they found were based on the following criteria: i) who provides the service; ii) who receives the service; iii) the setting where the services are provided; iv) what healthcare services are included; v) whether only clinical services are addressed or if non-clinical public health services are included; and vi) the purpose of the definition. The working group adopted the definition of medical genetics services reported in the Specialized Services National Definition Set of the United Kingdom (2007): "medical genetic services are provided by specialist genetic centers and they include activities such as diagnostic laboratory services, education of healthcare professionals, participation in research and expert advice to policy makers". The definition is based upon the setting in which services are delivered and specifically excludes treatment or management of metabolic conditions because metabolic biochemistry is considered a separate specialty.

The "Defining Genetics Services Framework" is divided into three areas. The narrowest area of definition is *Personal Healthcare Services* provided by individuals trained in genetics, which encompasses services provided by different healthcare professionals (e.g. medical geneticists, genetic counsellors, nurses, and dieticians with specialty genetics training). These services are included in the intermediate level definition, *Genetics Healthcare Delivery System*, which is a combination of public health and personal healthcare activities (i.e. population screening, diagnosis, treatment/management, education, financing, and program evaluation). The intermediate area is in turn included in the broadest area, *Public Health Core Functions and Essential Services*, which is comprised of the core public health functions (i.e. assurance, assessment, and policy development) and the ten Essential Public Health Services (i.e. monitor population health, diagnose and investigate population health problems, enforce laws, inform, educate, empower, mobilize partnerships, policy development, link to or provide personal healthcare, workforce education, evaluation, and research).

The "Genetics Services Outcomes Menu" is a comprehensive list of outcomes that can be used to measure the impact of genetics services. The tool was developed through literature search and then peer reviewed by project collaborators. The working group achieved consensus on three important assumptions that could facilitate application of the outcomes tool. In particular, the outcomes should be: i) non-condition specific; ii) practical to measure; and iii) useful for users (e.g. clinicians, healthcare administrators, public health professionals, third party payers, legislators).

The third record found through the literature review was the article by Little et al. that describes genetic services available in Canada (2009). The article does not provide any definition of the terms "genetic service" and "genetic services delivery model", neither a classification of delivery models.
Canada has a publicly funded, universally accessible healthcare system delivered through provincial and territorial health insurance plans [Health Canada 2005]. The federal Public Health Agency of Canada (PHAC) provides strategic leadership in disease prevention and control and emergency response to communicable diseases, while provinces and territories directly deliver public health services. Most provinces and territories have decentralized resource allocation and healthcare delivery. About 70% of total spending on healthcare is met by governments at different levels, the rest being paid for by private health insurance schemes or healthcare consumers directly. There is no national approach to public health genomics in Canada. However, the PHAC has established an Office of Biotechnology, Genomics and Population Health to facilitate coordination of relevant activities [PHAC 2006]. In addition, the PHAC is providing the administrative hub of the Genome-based Research and Population Health International Network (GRaPHInt) [GRaPHInt 2008].
The following are Public Health Genomic related programs and services available in Canada. Family physicians, obstetricians, midwives, and nurses provide prenatal screening and congenital anomalies surveillance. Most provincial and territorial health insurance programs cover prenatal screening. Seven provinces and one territory have congenital anomaly surveillance systems, six of which capture information on pregnancies terminated following a prenatal diagnosis of fetal abnormality. Newborn screening is available since 1963 and is mandated by law in only two provinces (Saskatchewan and Quebec). Explicit informed consent for newborn screening is not required in any Canadian province. Most genetics services are located in academic centers, often providing outreach to smaller cities and rural areas. Concerning genetic testing, the most common are related to thrombophilia, hereditary hemochromatosis, and breast and ovarian cancer. Relatively to professional boards, the Canadian College of Medical Geneticists (CCMG) is one of the oldest genetics specialty organizations, credentialing clinical and laboratory geneticists since its inception in 1976. In 1986, the Royal College of Physicians and Surgeons of Canada (RCP) recognized medical genetics as a specialty.
Currently, few regulatory frameworks in Canada are directly relevant to genetic tests, services, or programs. Services provided by healthcare professionals are governed by pre-existing common law and civil law norms [Melzer et al. 2008].

The fourth record found was on genetic delivery services in Australia by Metcalfe et al. (2009). The definitions of the terms “genetic service” and “genetic services delivery model”, or a classification of the delivery models were not provided.

Australian federal system of government is democratic, based on states and territories, and there is a socialized healthcare system, in which public and private models operate in parallel. Clinical genetics services are publicly funded by State Departments of Health, with the model of service provision varying from state to state [Barlow-Stewart 2007]. In general, genetic services are typically multidisciplinary as they include a range of healthcare professionals (e.g. clinical geneticists, genetic counsellors, and social workers). In most states, the service is centralized, comprising clinics servicing the metropolitan community as well as regional and rural communities. Familial cancer service forms a substantial proportion of service delivery in inherited disease. There are very few clinical geneticists and genetic counsellors working in private practice.

A range of genetic tests is offered by publicly funded and private laboratories. These laboratories are generally attached to or affiliated with a public hospital or university. Private genetic testing or pathology laboratories also provide tests. In addition, a number of state government departments have laboratories that conduct genetic testing, while some tests are carried out in research laboratories, particularly those that are still in the research phase or for which there is little demand. Funding for genetic testing therefore varies, with a number of tests provided at no charge to the patient, while others require the patient to pay for the service partially or fully.

The current screening programs offered in a clinical setting in Australia are prenatal, newborn, carrier, and genetic susceptibility screening. Screening is provided during the prenatal and newborn periods for a number of conditions in every state and territory, although there is no single national approach yet. Carrier genetic screening is less common and genetic susceptibility screening is even more infrequent.

Regarding national agencies and professional boards, the National Health and Medical Research Council (NHMRC) serves as the central organization supporting health and medical research, and the Australian Health Ministers’ Advisory Council (AHMAC) provides advice on strategic coordination of health services across the nation. Both bodies are involved in the development of national genetics policy initiatives. The Human Genetics Advisory Committee (HGAC) was established in 2005 and has focused particular attention on four policy areas: i) privacy guidelines for health professionals; ii) genetic testing; iii) guidelines for biobanks and genetic registers covering

governance, privacy, and consent specific to the Australian research and clinical environments; and iv) genetics education addressing the general community and healthcare practitioners. The Human Genetics Society of Australasia is the main professional organization of genetic specialists and has an important role in informing practice and policy, and to date has published 24 guidelines and policy statements [HGSA 2009].

The fifth and sixth records retrieved were on the New Zealand (NZ) genetic service system [Gu et al. 2009, Gu et al. 2011]. Definitions of the terms "genetic service" and "genetic service delivery model" were not reported, but a useful classification of genetic service delivery models was provided. The researchers conducted structured interviews with forty-eight participants representing ten significant roles in NZ genetic services: patient and family members, GPs, medical specialists, clinical geneticists, genetic counsellors (genetic associates), genetic testing laboratory scientists, directors of health institutions who are directly involved in genetic services delivery, Information Technology (IT) experts, etc. The investigation focused on participants' operating procedures and their actual experience. Based on the responses, four genetic service delivery models were identified in NZ: i) Patient - Doctor - Counsellor Model; ii) Patient - Doctor - Lab Model; iii) Patient - Counsellor - Lab Model, and iv) Patient - Lab (Commercial) Model.

The *Patient-Doctor-Counsellor Model* is a basic NZ genetic services delivery pathway, involving patients, doctors, genetic counsellors, general medical labs, and genetic testing labs. The model starts when a patient presents with symptoms or concerns of a genetic disorder at a doctor's office (GP or specialist). The doctor might make a referral to a Regional Genetic Service office, where genetic counsellors evaluate and sort all referrals in a triage process. In a face-to-face meeting with the patient, a genetic counsellor or a clinical geneticist assesses the disease risk. If a genetic test is relevant and available, they suggest the testing to the patient and explain possible testing implications. If the patient consents to the test, genetic counsellors then arrange for testing. Sample collection (often a blood sample) is carried out in a general medical lab and sent to an accredited genetic testing lab according to a waiting list in the Regional Genetic Service office. Lab scientists perform the test and record any detected abnormality and its interpretation in a lab report. Based on this report, genetic counsellors write an explanatory letter suggesting surveillance recommendation and/or management intervention. After counselling the patient about implications of the test result, genetic counsellors store the doctor referral, family history, family tree, lab report, and explanatory letter into a family folder. This folder will be kept indefinitely in

the genetic service office as a reference for family members and future generations. Upon patient consent, copies of the lab report and explanatory letter can be sent to healthcare providers.

In the *Patient-Doctor-Lab Model* clinicians can order some tests directly from a genetic testing lab without routing through genetic services (e.g. HFE gene test for hemochromatosis). The physicians make direct contact with the genetic testing lab and arrange sample transfer, receive the lab report, explain result implications to patients, and file the lab report in medical notes. This process could change to a *Patient-Doctor-Counsellor Model* if the testing lab suggests that genetic counsellors should be involved, for example in prenatal testing or in pre-symptomatic testing of an incurable condition such as Huntington's disease.

The *Patient-Counsellor-Lab Model* bypasses the doctors. If a family folder already exists in a Regional Genetic Service office with information about a pathogenic mutation in the family, members of the family might call for a disease risk assessment and sometimes a subsequent genetic test. Although genetic counsellors prefer a doctor referral, self-referrals are sometimes accepted. In such cases, there would be no doctor data stored, and doctors would not be informed unless patients request it.

The *Patient-Lab (Commercial) Model* is based on direct-to-consumer (DTC) genetic testing by private companies typically through Internet advertisements. In this process, patients pay for the test, take their own sample at home, send it to the lab, and receive the report directly. Therefore, no documentation is stored for the health system.

Currently, genetic services delivery in NZ depends on a paper-based information storage and transfer mechanism. To achieve standardized documentation in all delivery models, the implementation of effective health IT tools is crucial. In addition, the lack of referral protocols and clinical guidelines to help clinicians to choose among these models and manage patients after genetic tests presents a major barrier to their use of the genetic services.

The seventh record retrieved reports on three examples of genetic service development in Europe [Rigter et al. 2014]. The article also provides a theoretical framework for implementation of genetic services into practice and describes a network of actors involved in transition processes in healthcare systems. However, definitions of the terms "genetic service" and "genetic services delivery model" are not reported, and no attempt is made to classify genetic services delivery models.

Detection and follow-up of maturity-onset diabetes of the young (MODY) in UK is the first example; it took place for the first time in Exeter, in 2000. A referral center for monogenic diabetes was initiated for the purpose and diabetes specialist nurses have been trained as genetic diabetes nurses (GDNs) in the UK since 2002 to raise awareness of monogenic diabetes. The center is focused on conducting research in monogenic diabetes and also in promoting the translation of these research findings into improvements in clinical care for patients (e.g. treatment outcomes for MODY patients). Furthermore, a website with information on monogenic diabetes is available for professionals and patients and an online MODY probability calculator has been developed. The center's activities have increase knowledge about MODY among diabetologists in the UK and more patients with monogenic diabetes are now diagnosed and treated accordingly. The majority of individuals are referred for genetic testing via the GDNs or diabetologists within secondary-care diabetes teams, with a small number from clinical geneticists or GPs. The main facilitating factor for the implementation of this service is related to diabetes specialist nurses who were already actively involved in diagnosis and follow-up of patients. Thus, minimal changes were required and only a relatively small group of nurses needed training as GDN. Some of the barriers to further broaden the current services are related to the research-funded aspect of the service and it is still difficult to convince some clinicians of the need for genetic testing. Organizing structural financing from regular healthcare budgets instead of research funding will be essential for the GDN project to become a fully integrated part of diabetes care in the UK.

The second example is the oncogenetics services in Catalonia, established in 1998. These services, offering genetic testing and counselling of people at increased risk for hereditary cancer, were initiated within the Catalan Institute of Oncology by a group of clinicians and geneticists at the Department of Prevention and Cancer Control. The oncogenetics services are currently organized as a Hereditary Cancer Program with three Cancer Genetic Counselling Units and one central Molecular Diagnostic Unit. Most referrals come from medical specialists, and since 1999, more than 1.000 carriers of highly penetrant cancer predisposing genes have been identified and are under surveillance by the multidisciplinary team (consisting of two oncogeneticists, four oncogenetics nurses, a psychooncologist, and a geneticist as coordinator). The service is paid for by the Catalan health system. Nowadays, similar services are available in other regions in Spain, and in Catalonia as well, without clear national guidance. Some of the regional governments, such as the Catalan Regional Government, however, have implemented clinical guidelines for cancer genetic counselling. Few comparable services are offered for other conditions than cancer and it seems hard

to convince other disciplines of the importance of cascade screening. In addition, private companies are increasingly offering testing, which could interfere with the use of the services offered in regular healthcare.

The third example is the cardiogenetic service in the Southern Swedish healthcare region that started from a case of sudden cardiac arrest of a young football player in 2005. Genetic counselling was necessary due to inheritable aspects of his previously undiagnosed heart condition. This incident initiated collaboration between cardiologists and clinical geneticists, who created a multidisciplinary network consisting of adult and pediatric cardiologists and clinical geneticists; pathologist and forensic specialists, are involved. They organize education for cardiologists in the 15 referring hospitals and developed and adopted regional guidelines and standardized notes of admission. Since the initiation, awareness for possible genetic causes and cascade testing of family members of cases of sudden cardiac arrest has increased in the southern region of Sweden. Costs for the services are provided by the regional healthcare system.

The eight record found through the preliminary literature review described and classified organizations of genetic services, which are essentially basic units of genetic services, integrated networks, and core professional resources [Battista et al. 2012]. The authors do not provide definitions of the terms “genetic service” and “genetic service delivery model”.

The core facilities or basic units are similar across various settings. They consist of genetic centers most often developed within a university or a hospital, generally offering both clinical and laboratory services.

Regarding the integrated networks, major genetic centers in Europe, North America, and Australia often coordinate their services with a number of specialized or general genetics clinics located in the community, in both urban and rural areas. This type of integrated network is generally referred to as a *hub and spoke structure*, where the core facility (hub) provides support and expertise to the peripheral units (spokes). Examples are the hub and spoke networks in Emilia Romagna Region (Italy) and in the UK, where each regional genetic center accepts referrals from clinics in district hospitals and community facilities, forming an integral part of the healthcare system. Within the networks, centers also established links with specialty clinics, such as oncology, and extended their reach to primary care providers.

The US has no nationwide network, with the exception of the recently created Regional Genetic and Newborn Screening Service Collaboratives for the coordination of screening programs. Each state

manages its own services in centers and outreach/specialty clinics. In Canada, the Ontario genetics program is based, as in the UK, on a regional network of services spread throughout its jurisdiction. There are nine genetic centers offering both clinical and laboratory services, ten outreach and nine cancer genetics clinics. In Australia, service provision varies from state to state. Two government organizations (Genetic Health Services of Victoria, Genetic Services of Western Australia) ensure coordination and delivery in their jurisdictions according to a hub-and-spoke structure.

The core professional resources delivering genetic services are substantially professionals in genetics (e.g. genetic counsellors, medical geneticists) and other healthcare professionals increasingly using genetics in routine care (e.g. GPs, medical specialists, nurses, psychologists, and social workers).

In Europe, 22 out of the 27 European Union countries now recognize genetics as a medical specialty. The UK did so in 1970, the Netherlands in 1987, Sweden in 1991, Germany in 1992, and France in 1995. In countries without official recognition yet, e.g. Belgium, physicians with a genetics background are in charge of centers for the diagnosis and treatment of genetic diseases. Canada recognized genetics as a medical specialty in 1986, while in the US it took place in 1991.

Battista et al. (2012), classified genetic services in Europe, North America, and Australia in four groups:

i) Multidisciplinary specialist clinics and coordinated services in rare genetic disorders led by geneticists;
ii) Genetic services integrated in other medical specialties (e.g. oncogenetics, neurogenetics, cardiogenetics);
iii) Genetic services integrated into primary care;
iv) Genetic services provided in screening programs (e.g. prenatal and newborn screening).

1.3 Operational definitions and preliminary considerations on Genetic Service Delivery Models

For the purpose of this dissertation, an operational definition of genetic service and genetic service delivery models was adopted considering the GSPP Report (2008), the article by Silvey et al. (2009) and the genetic service delivery models in extra-EU and EU countries retrieved through the preliminary literature search [Battista et al. 2012, Gu et al. 2009, Gu et al. 2011]. Particularly useful in developing the definition of genetic service delivery models were the ten questions of the GSPP Report (Figure 2), the two definitions of genetic services provided by the GSPP Report (2008) and Silvey et al. (2009), as well as the "Defining Genetics Services Framework" by Silvey et al. (2009). Genetic services are defined as specialized services offered to individuals and families with genetic conditions or at risk of developing or transmitting a genetic condition. A genetic service delivery model for the provision of genetic testing is defined as the broad context within the PHG framework in which genetic tests and related services are offered to individuals and families with or at risk of genetic disorders. In other words, a genetic service 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 public health services and functions (i.e., population screening, financing, policy development, workforce education, information/citizen empowerment, service evaluation, and research). Current models of service delivery are characterized by unique factors, such as:

i) practice setting and financial resources (public vs. private);
ii) service provider/patient access [geneticist vs. primary care/ other medical specialties (e.g. cardiac genetics, cancer genetic, neurogenetics, endocrine genetics, etc.)];
iii) policy regulation (national and local policies, clinical guidelines, protocols, and position statements);
iv) laboratory practice standards (quality control standards, qualified personnel, etc.);
v) information dissemination (methods of providing information about genetic services to patients and service providers).

These factors reflect the main aspects of phase three (T3) of translation research in genomic medicine and will be taken into account in order to describe genetic service delivery models identified through the research project and compare them across different contexts.

Out of the eight records retrieved through the literature search, the two articles by Gu et al. (2009, 2011) and the review by Battista et al. (2012) made an attempt to classify genetic services delivery models, while other records (The GSPP Report 2008, Silvey et al. 2009, Little et al. 2009, Metcalfe et al. 2009 and Rigter et al. 2014) only described genetic services available in different settings. Deep analysis and extensive group discussions regarding the aforementioned papers were carried out. The first step was to determine the grade of compatibility of the two classifications of genetic delivery models: Battista et al. (2012) vs. Gu et al. (2009, 2011). The research team proceeded by sorting out how many and which pathways described by Gu et al. (2009, 2011) could be part of the models described by Battista et al. (2012). This assessment was performed considering primarily the system of genetic service delivery in Italy that was compared with other European countries. In the second step, genetic delivery models of extra-EU countries (Canada, Australia, US) were taken into account to include any relevant model or pathway that were not yet considered.

The evaluation process highlighted that the main aspect emerging from the classification by Battista et al. (2012) is the prominent role of the healthcare professional involved in the provision of genetic services in each model. On the other hand, the classification provided by Gu et al. (2009, 2011) is mainly upon the patient pathway from the point of access to the genetic service to diagnosis and treatment of the genetic disorder. Furthermore, the genetic service delivery model related to screening programs was mentioned only in the review by Battista et al. (2012), while the direct-to-consumer (DTC) model was described only by Gu et al. (2009, 2011).

II. Objectives of the study

The present Ph.D. dissertation is part of a multicenter project coordinated by the Personalized pREvention of Chronic DIseases consortium (PRECeDI), which is a Marie Skłodowska Curie Action (MSCA) project funded within the Research and Innovation Staff Exchange (RISE) scheme. The PRECeDI consortium is a multidisciplinary group of institutions and consists of eight beneficiaries and three partners, of which seven are academic and four are non-academic institutions. The institutions work on different facets of personalized medicine, from basic research to economic evaluations, from health service organization issues to ELSI issues. For four years (2014-2018), 30 early stage researchers and 24 experienced researchers have been seconded from academic to non-academic institutions and vice-versa, for training in research projects related to personalized prevention of chronic diseases (i.e. cancer, cardiovascular diseases, Alzheimer's disease, diabetes, etc.). The ultimate goal of the PRECeDI consortium is to enable research staff to make informed decisions and appropriately serve healthcare systems, new biotech industries and policy makers at the dawn of the post-genomic era. As a senior researcher of the PRECeDI project, I conducted part of the Ph.D. research during my secondment, as a post-graduate trainee, for a period of ten months at the Center of Genomics and Policy, McGill University (Montreal, QC, Canada). The research focused on the delivery of genetic testing and related services, policies on the provision of genetic services, and evaluation of genetic services in the province of Quebec.

The first task of the PRECeDI consortium was to obtain consensus among the project partners on the most suitable genetic tests that could be employed in the multicenter project. Four genetic tests were selected during the preliminary meeting that took place in 2015 at Sapienza University of Rome (Italy). The selected genetic tests are for hereditary breast and ovarian cancer (HBOC), Lynch syndrome, Familial Hypercholesterolemia (FH) as examples of genetic tests of proven effectiveness and cost-effectiveness [CDC 2014] and Inherited Thrombophilia (IT) as an example of genetic test of not proven effectiveness and cost-effectiveness [Hickey et al. 2013, EGAPP 2011]. The second task of the consortium was to identify European countries that could participate in the multicenter project through EUPHA. The aim was to include as many countries as possible in order to obtain a more comprehensive picture of the provision of genetic testing and the implementation of genetic

service delivery models in Europe. Nineteen European countries willing to participate were individuated[1] in 2015.

The general objective of this dissertation is to identify current genetic service delivery models, policies governing the use of genomic applications and methods to evaluate genetic services in Europe and in selected (Anglophone) extra-European countries (the US, Canada, Australia, and New Zealand) that were identified through a preliminary literature search. The specific objectives are the following:

- OBJECTIVE 1: identification of genetic service delivery models for the provision of HBOC, Lynch syndrome, FH, and IT genetic tests in Europe and in the province of Quebec (Canada), in order to describe models of delivery for genetic tests of proven effectiveness and cost-effectiveness (BRCA1/2, Lynch syndrome, and FH) vs. genetic tests of not proven effectiveness and cost-effectiveness (IT).
- OBJECTIVE 2: identification of policies governing the use of genomic applications and methods of genetic service evaluation in Europe and in the province of Quebec
- OBJECTIVE 3: collection and classification of process and outcome indicators of the delivery models that will be used to define a minimum set of indicators necessary for the assessment of genetic services
- OBJECTIVE 4: assessment of European public health professionals' attitudes regarding their role in the implementation of PHG, and their knowledge and attitudes regarding genetic testing and the delivery of genetic services
- OBJECTIVE 5: Identification of key points to address for an effective and efficient implementation of genetic testing in European healthcare systems and in the province of Quebec

[1] Austria, Belgium, Croatia, Estonia, Finland, France, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, and UK

III. Materials and methods

3.1 The European context

The European study was carried out through a multidimensional approach, which includes: i) a systematic review of published literature on existing genetic service delivery models in European and extra-European (Anglophone) countries (USA, Canada, Australia, and New Zealand); ii) systematic review of the literature on policies governing the provision of genetic services in Europe and extra-European countries; iii) structured interviews addressing healthcare professionals on genetic service delivery models, policies governing the use of genomic applications, and evaluation of genetic testing and related services in their respective countries; and iv) a survey addressing public health professionals' knowledge and attitudes regarding the use of genomic applications in clinical practice. The research protocol is published in *Frontiers in Public Health,* volume 5, article 223 (Annex 1).

3.1.1 Systematic review of the literature on existing genetic service delivery models

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [Liberati et al. 2009]. Two investigators independently searched five medical electronic databases (PubMed, Scopus, ISI Web of Knowledge, Google, and Google Scholar) using the following search terms: genetic(s) services OR genetic(s) service provision OR genetic(s) service delivery OR genomic service delivery OR genetic(s) delivery models. A preliminary non-systematic search and a manual review of references from relevant systematic reviews were also performed. The inclusion criteria were: i) relevant articles and reports on pilot studies, best practices, and funded projects inherent to genetic service delivery; ii) provision of all types of genetic tests by genetic specialist teams and healthcare professionals practicing in primary or secondary care; iii) studies published in English and Italian languages between 2000 and 2015; and iv) interventions carried out in European and extra-European (Anglophone) countries (the USA, Canada, Australia, and New Zealand). The extra-European countries were used for comparison purposes. The exclusion criteria were: i) studies reporting only on genetic counselling services; ii)

descriptive studies where pathways to care were not well defined; and iii) studies not specifying the type of genetic test considered.

An ad-hoc data extraction form was developed to collect relevant information from the included studies and is composed of three sections (Annex 2):

- General description of the study and the genetic service. This section collects general information about the study (i.e. authors, title of the study, country/region where the genetic service is implemented, etc.), the genetic service and its programs (i.e. practice setting, financing mechanism, type of healthcare system in the country, existence of national or regional policies on genetic services, etc.);
- Information on patients and pathways to care. This section investigates the characteristics of the target population of the genetic programs offered (i.e. gender, age, ethnicity) and pathways to care, as well as cost-effectiveness and efficacy of the genetic program;
- Genetic service evaluation. This section investigates strengths and weaknesses of the genetic service and its programs in regard to cost-effectiveness and feasibility of the genetic programs, the genetic service capacity in terms of population and geographic area served, staff qualification, and laboratory standards.

Four members of the research team made an independent evaluation of each genetic service and the genetic programs offered using the data extraction form, followed by extensive group discussions. Eventual discrepancies were resolved after discussion with the coordinators of the project.

For the different types of genetic testing considered (i.e. prenatal, preimplantation, diagnostic, carrier, predictive, presymptomatic, newborn screening), the definitions of the National Institutes of Health (NIH) have been adopted [NIH 2018]. A patient pathway to care is considered throughout the dissertation as the patient flow through different professionals from the point of access to healthcare services to treatment of the genetic disorder and follow-up. The studies identified through the literature review were used for the classification of current genetic service delivery models and for the study on existing screening pathways for Lynch syndrome identification (Annex 3).

3.1.2 Systematic review of the literature on policies governing the provision of genetic services in European and extra-European countries

A systematic review of the literature was conducted to identify policies governing the delivery of genetic services in Europe and extra-European countries (i.e. USA, Canada, Australia and New Zealand) as an integration to the systematic review on genetic service delivery models for genetic testing.

Two investigators using electronic databases (Scopus, PubMed, and Google Scholar) with the following search term performed the review independently: (genetic* service* OR genetic* service provision OR genetic* service delivery OR genomic service delivery OR genetic delivery model OR genomic* delivery model*) AND (policy OR policies OR guideline* OR plan* OR national plan OR statement*). Additional policy documents were retrieved from represented countries' government-affiliated websites (Annexes 4 and 5).

The following key inclusion criteria were used: reports, guidelines, protocols, or position statements issued by national or international organizations, committees or scientific societies, and published in English or Italian from 2000 to 2015. Records were therefore excluded if they were editorials, conference proceedings or original research articles on genetic services. The review process, including search and study selection, was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [Liberati et al. 2009].

The following data that were not fully addressed in the systematic review on genetic services delivery models were extracted and summarized: a) informed consent; b) laboratory quality standards; and c) education, training and role of different healthcare professionals in the provision of genetic services. Genetic service delivery models were identified from the policy documents, where possible.

3.1.3 Structured interviews addressing healthcare professionals

Structured interviews with healthcare professionals on genetic service delivery models, policies governing the use of genomic applications, and evaluation of genetic testing and related services have been carried out to enhance the literature reviews.

Based on the systematic reviews, an ad hoc questionnaire was designed for each genetic test (BRCA1/2, Lynch syndrome, FH, IT). The questionnaires (Annexes 6-9) address healthcare

professionals (e.g. medical geneticists, other medical specialists, and genetic counsellors) working in genetic services with manager roles or in direct contact with patients requiring one of the four genetic tests. Each questionnaire is composed of the following sections: A. Demographic and personal information; B. Management of care pathways; C. Delivery models; and D. Clinical pathways. In section A, demographic and professional data of the national experts were recorded. Section B focused on the management of patients undergoing genetic testing, including information on access and referrals to genetic testing, genetic counselling, and follow-up. Section C focused on the delivery models for the provision of each genetic test, whilst the appropriate use of the genetic tests was assessed in section D.

The questionnaire on evaluation of genetic testing and related services (Annex 10) addresses health information management professionals who deal with health data collection and analysis at local (health facilities), regional (regional agencies), or national level (national institutes). The aim is to describe the flow of health information from each health facility to regional and national agencies where aggregate data are produced and used for planning activities. The related questionnaire is composed of the following sections: A. Demographic and professional information; B. Activity of genetic services; C. Quality of genetic services; D. Health outcomes of genetic services; E. Patient reported outcomes of genetic services; F. Coverage of genetic services; and G. Electronic records and genetic information. Section A collects demographic and professional data. The sections from B to G focus on evaluation of different aspects of genetic services (activity, quality, health outcomes, patient reported outcomes, coverage and electronic records).

The questionnaire on policy of genetic testing and related services (Annex 11) addresses experts in policy planning and policy research of genetic services employed in national institutes (e.g., National Health Institutes, ministries), universities or clinical research centres. The questionnaire is composed of the following sections: A. Demographic and professional information; B. Policy issues; C. Genetic services: access and availability; and D. Professional education and training. Section A collects demographic and professional data. The sections from B to D focus on policy of genetic testing and related services (i.e. access and availability of genetic testing and related services, education and training in genetics).

The first version of each questionnaire was piloted during the secondments of researchers from Sapienza University of Rome (Italy) to EUPHA, in collaboration with the partners from the VU Medical Centre in Amsterdam. The questionnaires were piloted through face-to-face administration to key experts in each clinical condition. Upon the pilot phase, the questionnaires were revised to improve clarity and to better meet the objectives of the study. Minor revisions were made to the questionnaires on BRCA1/2 and Lynch syndrome testing, while those on FH and IT required major revisions.

For the identification of European experts, National referents (NRs) were individuated for each EU country and Switzerland, through the PRECeDI consortium, with the aim to identify experts in each country who would fulfill the following criteria:

a) professionals with a good knowledge about the provision of one of the four selected genetic tests (BRCA1/2, Lynch syndrome, FH, and IT), i.e. medical geneticists or other medical specialists (experts could be the same for the different types of genetic testing);
b) the sample had to be representative, and the number of interviewed professionals per country was defined on the basis of the different realities of the country itself. The research team suggested a minimum of 20 experts in each country (i.e. 5 experts for BRCA1/2, 5 experts for Lynch syndrome, 5 experts for FH and 5 experts for IT).

Up to three reminders were sent to the NRs to compile a database of European experts for each clinical condition. Once the NRs provided their list, the experts were contacted via e-mail, outlining the objectives of the study, and requesting their support, and the experts subsequently received an invitation to participate in the survey. Up to three reminders were sent in order to increase the response rate to the surveys. Experts were required to answer the survey questions not basing on what they would recommend but on what the majority of physicians, or professionals involved in genetic testing would prescribe, suggest and/or recommend to their patients in their countries.

A quali-quantitative analysis of the survey results was performed. The healthcare professionals involved in patient pathways to care from access to genetic services to follow-up, as well as the organization of genetic laboratories and the identified models of genetic service delivery are summarized and presented according to EU countries.

3.1.4 Knowledge and attitudes of European public health professionals regarding PHG

Public health professionals may play different roles in the translation of genome-based knowledge and technologies into public health practice. They may use genomics tools to evaluate the impact of public health interventions on different subsets of the population [Bowen et al. 2012]. Although several surveys have been performed to evaluate knowledge, attitudes, and professional behaviours of physicians toward the integration of human genomic discoveries in clinical practice [Freedman et al. 2003, Bellcross et al. 2011, Nippert et al. 2011, Selkirk et al. 2013, Marzuillo et al. 2013, Petersen et al. 2014], only one study has been conducted for public health professionals. The study focused on knowledge, attitudes, and training needs of Italian public health professionals in the field of predictive genetic testing for chronic diseases [Marzuillo et al. 2014]. The study highlighted that public health professionals need additional training to increase their methodological skills.

The Sapienza research team designed a similar survey for a sample of European public health professionals who are also EUPHA members. EUPHA is composed of 71 organizations from 41 countries and has about 5.900 individual members. The online survey was carried out to obtain a picture of the European public health community readiness to incorporate PHG in their practice. It focused on attitudes and knowledge of public health professionals toward genomic applications in clinical practice, the delivery of genetic services, evaluation of genetic service delivery models, and the role of public health professionals in the implementation of PHG. The questionnaire is composed of the following five sections (Annex 12): A. Personal details; B. Professional activity; C. Knowledge of genetic testing and delivery of genetic services; D. Attitudes on genetic testing and the delivery of genetic services; and E. Attitudes regarding the roles of public health professionals in PHG.

The first draft of the questionnaire was shared with all PRECeDI project partners and with the participants in the Round Table organized by the EUPHA Section on PHG at the 8th European Public Health Conference (Milan, 14-17 October 2015), who were contacted via e-mail in April 2016 to access a first draft of the online survey. Following this first consultation, we decided to create a filter question that would give access to a reduced version of the questionnaire for some professional groups not involved in genomics. It was assumed, in fact, that EUPHA network members belong to one of the following categories: i) public health professionals involved in PHG activities; ii) public

health professionals not involved in PHG; iii) not public health professionals involved in PHG (e.g. geneticists); and iv) not public health professionals not involved in PHG (e.g. infectious diseases specialists). The filter question directed respondents not directly involved in PHG activities to a reduced version of the questionnaire.

A pilot phase was conducted on a sample of 61 staff members from the Department of Public Health and Infectious Diseases of Sapienza University in Rome and 10 members from the Department of Genetics from the Vrije University (VU) in Amsterdam. Staff members with different backgrounds were selected to guarantee the representativeness of the different profiles of EUPHA network members as outlined above. The pilot phase allowed testing clarity of language, practicability and interpretation of answers. The questionnaire was revised based on the results of the pilot study before distribution to the members of the EUPHA network. Regarding data analysis, attitudes of public health professionals was assessed through a three-point Likert scale ("agree," "uncertain," and "disagree"), while knowledge was assessed through a combination of multiple choice questions and three-point Likert scale answers. Internal consistency of all questionnaires was evaluated through Cronbach's alpha coefficients. The results of the pilot phase are published in *Epidemiology, Biostatistics and Public Health*, vol. 14(n.3) (Annex 13).

The online administration of the questionnaire was conducted from March 2017 to November 2017. An invitation to participate in the survey was included in EUPHA monthly newsletter of February 2017. Furthermore, the Presidents of five EUPHA sections (Public Health Genomics, Public Health Epidemiology, Public Health Monitoring and Reporting, Public health practice and policy, Chronic diseases) sent an invitation to their members to respond to the online survey. To increase the response rate, a reminder was also sent to all EUPHA members in September 2017. Other attempts to further increase the response rate were made by distributing hard copies of the survey questionnaire to participants during the 10th European Public Health Conference in Stockholm, (Sweden) and by sending another reminder via email to EUPHA members on January 2018.

3.2 The Quebec context

The Department of Public Health and Infectious Diseases of Sapienza University of Rome (Italy) coordinated the study, in partnership with the Centre of Genomics and Policy, Department of Human Genetics, McGill University. The research was conducted through an online survey addressing healthcare professionals, researchers and policy-makers with knowledge and/or practical experience in the provision of at least one of the four selected genetic tests (BRCA1/2, Lynch syndrome, FH, and IT), assessment of genetic service delivery models and policy planning of genetic services in the province of Quebec. Participants practicing in Quebec at the time of the study were eligible. The Quebec Network of Applied Medical Genetics and the Quebec Association of Genetic Counsellors forwarded the survey link to their members (approximately N=115 and N=45, respectively). The Faculty of Medicine Research Ethics Board approval was obtained prior to the recruitment of eligible participants who gave their consent through an online consent form (Annex 14).

The questionnaires were constructed to gain an in-depth understanding of genetic service organizational models, policies on the provision of genetic services and evaluation of genetic services in Quebec by acquiring information from qualified professionals in the field of clinical genetics. The survey was available in English and French.

The first part of the survey is on genetic service delivery models for the provision of the four selected genetic tests (BRCA1/2, Lynch syndrome, FH, and IT) and on the associated patient pathways to care (Annex 14). This part of the survey addresses healthcare professionals (e.g. medical geneticists, other medical specialists, and genetic counsellors) working in genetic services with manager roles or in direct contact with patients requiring one of the genetic tests. The questionnaire is composed of the following sections:

A. Demographic and professional information (5 questions: 4 multiple choice and 1 open-ended)
B. Genetic service delivery models for BRCA1/2, Lynch syndrome, FH, and IT genetic testing (21 questions: 18 multiple choice, 2 dichotomous and 1 optional open-ended)

The second part of the survey is on assessment of genetic service delivery models and addresses health information management professionals who deal with health data collection and analysis at local (health facilities) and provincial levels (provincial agencies responsible for health data collection and analysis from each health facility) (Annex 14). The related questionnaire is composed of six sections:

A. Evaluation of activity (8 questions: 1 dichotomous and 7 multiple choice)
B. Quality assessment (3 multiple choice questions)
C. Evaluation of health outcomes (2 multiple choice questions)
D. Electronic records and genetic information (3 multiple choice questions)
E. Genetic services and coverage (2 questions: 1 multiple choice and 1 optional open-ended)

The third part of the survey is on policies governing the provision of genetic services, it addresses experts in policy planning and/or policy research on genetic services employed in national institutes (e.g. National Health Institute, Ministry), universities or clinical research centers (Annex 14). The questionnaire is composed of the following sections:

A. Policy (9 questions: 4 dichotomous and 5 multiple choice)
B. Genetic services: access and availability (8 questions: 4 dichotomous, 3 multiple choice and 1 optional open-ended)
C. Professional education and training (2 questions: 1 dichotomous and 1 multiple choice)

The survey was available online from January to April 2017 after the initial invitation email sent by the associations. Participants were reminded through a second email notification two months following the initial email. Data were collected through an online platform (SurveyMonkey) [SurveyMonkey 1999-2018] and a quali-quantitative analysis was performed.

IV. Results

4.1 The European context

4.1.1 Systematic review of the literature on existing genetic service delivery models

Using five electronic resources, more than 16.000 records were retrieved (Figure 3). Most records were excluded during title and abstract evaluation and up to 150 articles did not meet the inclusion criteria regarding the description of the components of a genetic program (i.e. target population, genetic counselling, genetic testing, diagnosis of carrier status and the healthcare pathway based on the carrier status).

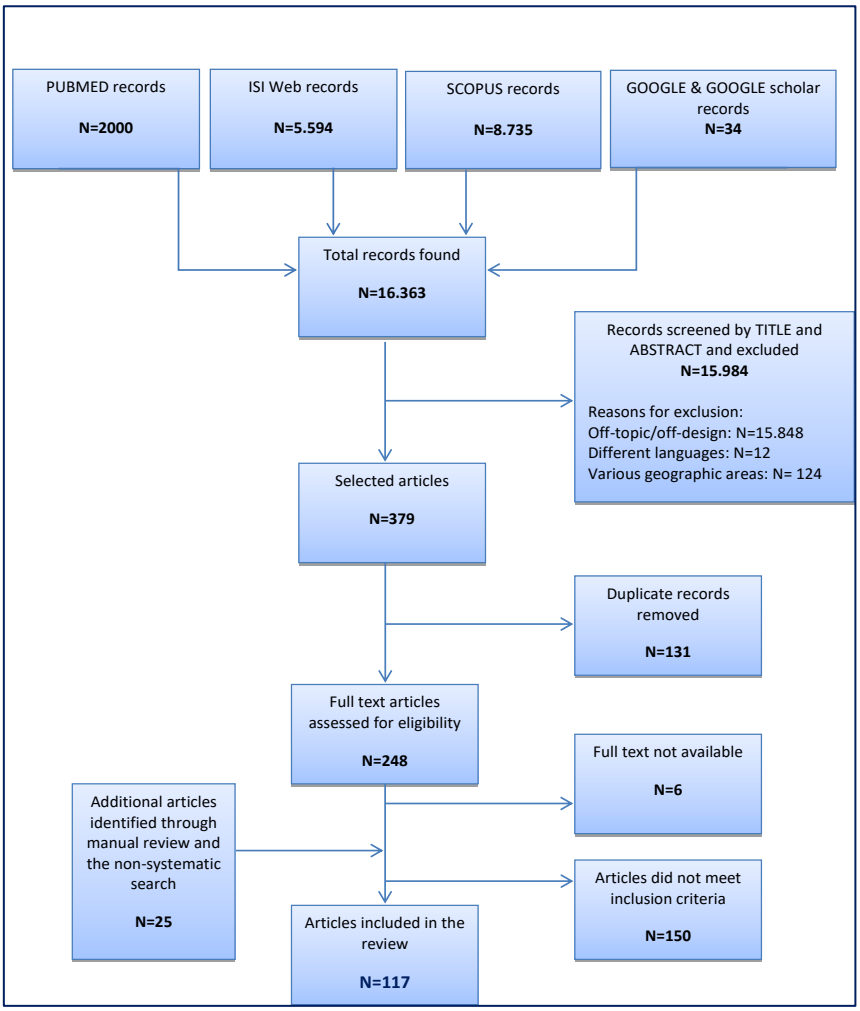

Figure 3. Flow diagram of the selection process

Most articles focused only on one of these components, mainly genetic counselling, and were therefore excluded. The systematic review consists of 117 records published from 2000 to 2015.

A total of 148 genetic programs, implemented between 1960 and 2012, were identified. The programs were delivered mostly in the UK (59; 39.86%); USA (35; 23.65%) or Australia (16; 10.81%) (Figure 4) and were available at national level (66; 44.59%), regional level (49; 33.11%) or only in urban areas (21; 14.19%).

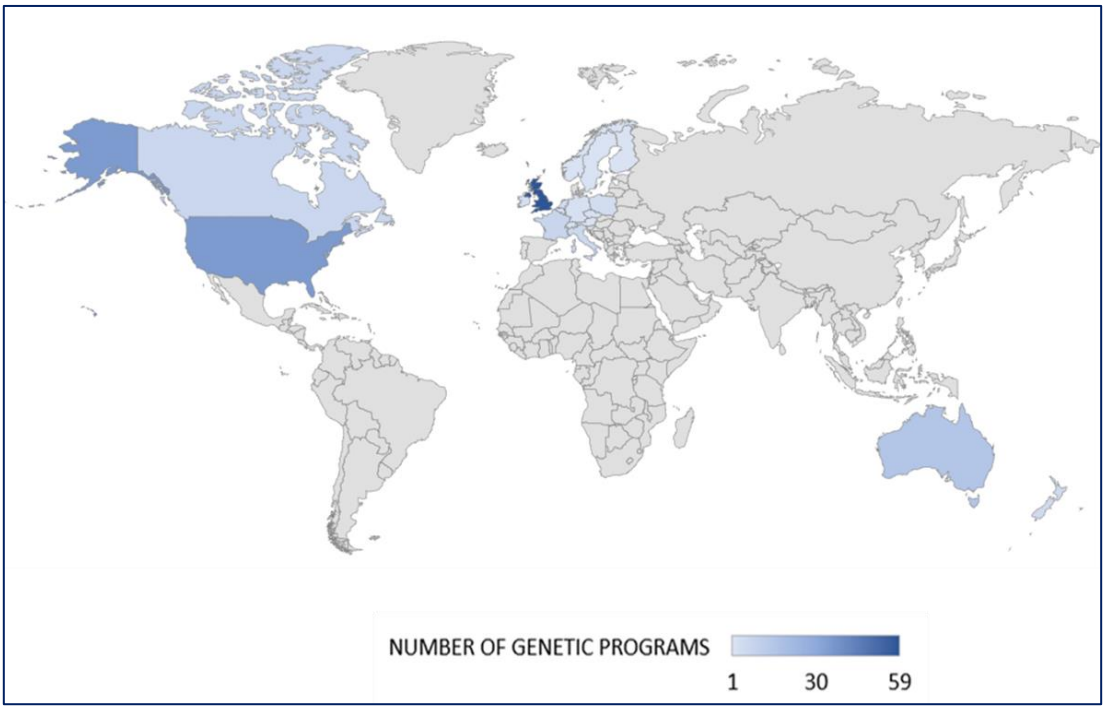

Figure 4. Geographical distribution of the genetic programs

A National Plan on PHG was reported only for the Italian setting (3 out of 6 programs) [Southern et al. 2007, Calzolari et al. 2005, Lucci et al. 2013], whilst regional or national guidelines on genetic services were reported for most genetic programs available worldwide. The programs were offered prevalently in the public sector, of which eight were academic-based [Lee et al. 2002, Hartenbach et al. 2002, Barlow-Stewart et al. 2003, Henriksson et al. 2004, Gozdzik et al. 2005, Brennan et al. 2007, Coffey et al. 2008, Mogayzel et al. 2014]. The main source of funding was public for over 90 programs and only private funds were used in eight programs, which were prevalently DTC services [Pichert et al. 2000, Hartenbach et al. 2002, Washington State Department of Health 2008, Kaye 2008, Smith et al. 2009, Gu et al. 2009, McGuire and Burke 2011, Gu et al. 2011].

Ninety-six (64.43%) genetic programs were integrated into healthcare systems, while 48(32.21%) were pilot programs and five (3.35%) were DTC genetic services. Genetic tests were offered in 145/148 genetic programs (Table 1) and the majority was for BRCA1/2 (59, 39.86%), Lynch syndrome (23; 15.54%) and newborn screening panel (18; 12.41%).

Table 1. Genetic tests and screening offered to individuals affected by or at risk of various genetic disorders

GENETIC SCREENING AND TESTING	N. PROGRAMS	COUNTRY (n. programs)	REFERENCES
BRCA 1/2	59	UK (29) USA (11) other (1-3)	Allen 2007, Anton-Culver 2003, Bennett 2007, Brain 2000, Brain 2002, Brennan 2007, Calzolari 2005, Campbell 2003, Donnai 2001, Drury 2007, Eble 2013, Eeles 2007, Eisinger 2008, Epplein 2005, Evans 2009, Evans 2012, Foretova 2006, Fry 2003, Gray 2000, Gronwald 2006, *GSPP 2008, Gulzar 2007, Hartenbach 2002, Henriksson 2004, Holloway 2004, Hopwood 2003, Koeneman 2014, Lee 2002, Little 2009, Mackay 2006, Menkiszak 2003, Mulsow 2009, Orlando 2013, Orlando 2014, Pichert 2000, Pujol 2013, Reis 2006, Ricker 2006, Rowland 2003, Slade 2015, Smith 2009, Speechley 2010, Srinivasa 2007, Tozer 2007, Westwood 2006, Williamson 2008, Wonderling 2001, Young 2006
Lynch syndrome	23	UK (6) other (1-3)	Bennett 2007, Eisinger 2008, Epplein 2005, Henriksson 2004, Hopwood 2003, Koeneman 2014, Mak 2007, Orlando 2014, Pichert 2000, Plunkett 2014, Pujol 2013, Schofield 2009, Schofield 2014, Williams 2007, Wonderling 2001
Disorders included in the Newborn screening panel	18	USA (9) other (1-3)	Basran 2005, Byck 2006, Calzolari 2005, Comeau 2004, GSPP 2008, Hanley 2005, Henry 2005, Little 2009, Massie 2000, Metcalfe 2009, Mogayzel 2014, Puryear 2006, Salbert 2003, Streetly 2009, Therrell 2006, Thuret 2010, Wisconsin Genetic Services Plan 2002
CF	17	USA (7) Australia (5) UK (4) other (1-2)	Barlow-Stewart 2003, Bickerstaff 2001, Blumenfeld 2012, Byck 2006, Currier 2012, Donnai 2001, Drury 2007, Ekstein 2001, Gozdzik 2005, GSPP 2008, Kornreich 2004, Long 2014, Massie 2000, Metcalfe 2009, Mogayzel 2014, Southern 2007, Speechley 2010

Hemoglobinopathies (alfa- and beta-thalassemia, HbS, HbC)	15	USA (3) other (1-2)	Amato 2014, Basran 2005, Bickerstaff 2001, Currier 2012, Hoppe 2011, Lena-Russo 2002, Streetly 2009, Long 2014, Kaufmann 2011, Metcalfe 2009, Speechley 2010, GSPP 2008, Thuret 2010
Familial hypercholesterolemia	11	Australia (5) UK (4) other (1)	Aarden 2011, Bell 2014, Bell 2015, Burton 2012, Heath 2001, Kirk 2014, Kirke 2014, Vickery 2014, Watts 2011
Chromosomal abnormalities (trisomy 21, 18 and 13, 22q11 deletions, translocations, fragile X syndrome)	10	USA (5) Other (1-2)	Bickerstaff 2001, Byck 2006, Currier 2012, Eble 2013, Little 2009, Long 2014, GSPP 2008, Metcalfe 2009, Salbert 2003, Speechley 2010
Tay-Sachs	8	Australia (4) USA (4) Other (1-2)	Bach 2001, Barlow-Stewart 2003, Bickerstaff 2001, Ekstein 2001, Gason 2003, Gason 2005, GSPP 2008, Wisconsin Genetic Services Plan 2002
Colorectal cancer	7	USA (3) other (1-2)	Anton-Culver 2003, Brennan 2007, Eble 2013, Gulzar 2007, Little 2009, Orlando 2013, Plunkett 2014
Diabetes 1 and 2 genetic testing, MODY	7	UK (4) USA (3)	Burton 2012, GSPP 2008, Shepherd 2001, Shepherd 2003, Shepherd 2014, Shields 2010, Orlando 2013
Hereditary cancer syndromes (von Hippel-Linda, neurofibromatosis, Wilms tumour, Li Fraumeni, Cowden, etc.)	6	USA (4) other (1)	Burton 2012, Epplein 2005, Henriksson 2004, Orlando 2013, Orlando 2014, Wonderling 2001
Adult onset diseases (Alzheimer, Huntington)	6	UK (4) other (1)	Bickerstaff 2001, Donnai 2001, Drury 2007, Harper 2000, Speechley 2010, Williamson 2008
Inherited cardiovascular conditions (arrhythmias, cardiomyopathies, inherited congenital heart disease, familial hyperlipidemia, etc.)	6	USA (3) other (1-2)	Burton 2010, Burton 2012, Charron 2002, Eble 2013, Kirk 2013, McCann 2009
Various disorders (thrombophilia, bowel cancer, cervical cancer, endometrial cancer, ovarian cancer, hereditary melanoma, hearing loss, developmental disabilities, surfactant dysfunction, mitochondrial diseases, carrier screening for genetic disorders in Ashkenazi Jews, etc.)	35	various settings (1-5)	Berkenstadt 2007, Bennett 2010, Bickerstaff 2001, Brennan 2007, Calzolari 2005, Coffey 2008, Donnai 2001, Drury 2007, Eble 2013, Ekstein 2001, Epplein 2005, GSPP 2008, Gu 2009, Gu 2011, Henriksson 2004, Henry 2005, Little 2009, Lucci 2014, Kaye 2008, Metcalfe 2009, McGuire 2010, O'Brien 2014, Rowland 2003, Ramsden 2013, Moeschler 2009, Nesbitt 2014, Pohjola 2012, Salbert 2003, Turcu 2013, Williamson 2008, Windmill 2006, Wisconsin Working Group 2002, Wonderling 2001

*GSPP 2008, Washington State Department of Health 2008: Final Report of Genetic Services Policy Project

Healthcare providers (HCPs) were informed about genetic services through professional boards, conferences, meetings, workshops, or scientific journals. Patients were informed about the availability of genetic services by HCPs, through service websites, and the media (e.g. advertisement on radio and TV, and in magazines). Information and Communications Technologies (ICTs; e.g. cellular phones, computer, satellite systems) were used for organization of medical records; videoconferencing; distance learning; various internet-based services including risk assessment programs, telemedicine, and appointment scheduling programs. Genetic services also used ICTs to communicate with patients and community HCPs.

Genetic services offered their employees training in genetic medicine consisting of continuing education programs, seminars, conferences, and workshops; provision of educational materials; interactive computer programs; referral guidelines; and staff supervision by geneticists or genetic counsellors. The training activities mostly addressed physicians and nurses, but also physicians' assistants, genetic counsellors, biologists, social workers, and midwives. Several studies reported that physicians form various specialties (e.g. obstetrician-gynecologists, oncologists, cardiologists, endocrinologists, etc.) and GPs had a specific background in genetics medicine. Medical geneticists and other medical specialists with genetic knowledge were more common than GPs. Among non-medical HCPs, genetic counsellors (73/148 programs), laboratory staff (73/148 programs) and nurses (49/148 programs) also had a good genetics background.
In 26 genetic programs, the quality of the laboratories corresponded to regional or national regulations. These laboratories are mostly affiliated with local or regional genetic services, academic centers, and some operated in the private sector.

Regarding access to genetic services, direct access (48 programs) was reported prevalently for BRCA1/2 testing, Lynch syndrome testing and newborn screening. Access was also mediated by a wide range of medical specialists (e.g. medical geneticists, surgeons, oncologists, pediatricians), as well as GPs. Non-medical HCPs involved in patient referrals were nurses, genetic counsellors, and midwives. Referrals to genetic services were also made by different categories of HCPs engaged in population screening programs. DTC services did not require referrals in most cases. One exception was a virtual clinic requiring referrals from GPs or other medical specialists [Washington State Department of Health 2008].

Medical geneticists, genetic counsellors, other medical specialists, and GPs provided pre- and post-test counselling. Nurses and other trained professionals were also involved in counselling sessions. Genetic programs where pre- and post-test counselling were performed mostly comprised those offering testing for BRCA1/2 (52/59 programs) and Lynch syndrome (19/23 programs).

Family history collection and risk assessment were provided prior to or during genetic counselling or medical examinations by medical geneticists, other medical specialists, and GPs. Non-medical HCPs such as genetic counsellors, genetic associates and other trained professionals were also involved. The trained professionals were nurses engaged in different medical specialties (i.e. cancer genetics, the genetics of diabetes, and the genetics of cardiac conditions); family history workers; health educators; social workers; and administrative staff of the screening services.

Risk assessment was performed largely through questionnaires, computer programs and face-to-face interviews. Family history collection and risk assessment were mostly performed in programs providing BRCA1/2 (52/59 programs), Lynch syndrome (21/23 programs) and CF testing (10/17 programs).

Mostly medical geneticists, other medical specialists (e.g. pediatricians, surgeons, clinicians engaged in screening programs, etc.) and GPs initiated genetic testing. It was also initiated by non-medical HCPs such as genetic counsellors, genetic specialist nurses, trained genetic service staff, and midwives. A consent form prior to genetic testing was explicitly required and reported in 43/148 genetic programs. A consent form was required mostly prior to testing for HBOC, Lynch syndrome, hemoglobinopathies, and newborn screening.

Cascade testing on relatives of index cases was performed in several genetic programs, mainly for BRCA1/2, Lynch syndrome, FH testing and newborn screening. The genetic services contacted relatives either directly, via a physician or through index cases who were asked to inform and suggest testing to their relatives. Follow-up services were provided in several programs and the period of surveillance ranged from 12 months to long term or lifetime.

The above analysis of genetic services, genetic programs and patient care pathways laid the groundwork for the identification and classification of genetic service delivery models. Delivery models for the provision of genetic testing are classified in five categories according to which healthcare professional plays the most prominent role in patient pathways to care: i) genetic services led by geneticists; ii) the primary care model; iii) the medical specialist model; iv) genetic

services integrated into population screening programs; and v) the DTC model (Table 2). The classification was obtained by matching each model provided by Battista et al. (2012) with all possible patient care pathways described by Gu et al. (2009, 2011) or identified in other literature records. A detailed description of the models is reported below.

Table 2. Genetic Service Delivery Models according to the roles of the healthcare professionals involved in patient pathways to care

PATHWAY	**Model I: Genetic services led by geneticists**	**Model II: Primary Care Model**	**Model III: Medical Specialist Model**	**Model IV: Genetic services integrated into population screening programs**	**Model V: Direct to consumer (DTC)**
I	Patient-(GP)-Medical specialist-Counsellor-Lab	Patient- (GP)-Counsellor-Lab	Patient-(GP)- Medical specialist-Lab	Patient-(GP)-Medical specialist-Counsellor-Lab	Patient- Lab
II	Patient-Counsellor -Lab	Patient- GP-Lab	Patient- Medical specialist- Counsellor-Lab	Patient-(GP)-Medical specialist-Lab	Patient-(GP)-Medical specialist-Counsellor-Lab (virtual clinic)
III				Patient-Counsellor-Lab	

GP, General Practitioner

Model I: Genetic services led by geneticists. In this model the professional team may include medical geneticists, genetic counsellors, and other healthcare professionals (e.g. genetic nurses). The professional team is responsible for risk assessment, counselling and testing of individuals or families affected or at risk of genetic disorders. Depending on the case, the genetic team collaborates with other medical specialists (e.g. oncologists, cardiologists, nephrologists, etc.) who could also be part of the genetic service (e.g. multidisciplinary genetic clinics). Classical examples of this model are genetic services for rare diseases. The access of patients to this model of genetic service may occur through two different pathways: a) Patient-GP or medical specialist-Counsellor-Lab, and b) Patient-Counsellor-Lab.

The first pathway (Ia) occurs when a patient seeks medical assistance from a GP or any specialist doctor who then makes a referral to the genetic service where a genetic counsellor or a medical geneticist can perform a risk assessment. If a genetic test is relevant and available, they may suggest

genetic testing to the patient; then samples are collected, and tests are performed in the laboratory. Based on the results of the test, genetic counsellors or medical geneticists recommend surveillance and/or management intervention. Clinical management of genetic conditions may involve various medical specialists, other than geneticists (e.g. oncologists, cardiologists, nephrologists, endocrinologists, etc.). The second pathway (Ib) occurs when a patient, without a medical referral, contacts a genetic service where a genetic counsellor or a medical geneticist can perform a risk assessment. Pathway Ib corresponds to pathway Ia from this point onward.

Model I was identified in 74 genetic programs and pathway Ia was the most frequent. The model is common in the UK and Australia. The main genetic tests offered under Model I are BRCA1/2 (43 programs), Lynch syndrome (16 programs) and newborn screening panel (9 programs) (Figure 5).

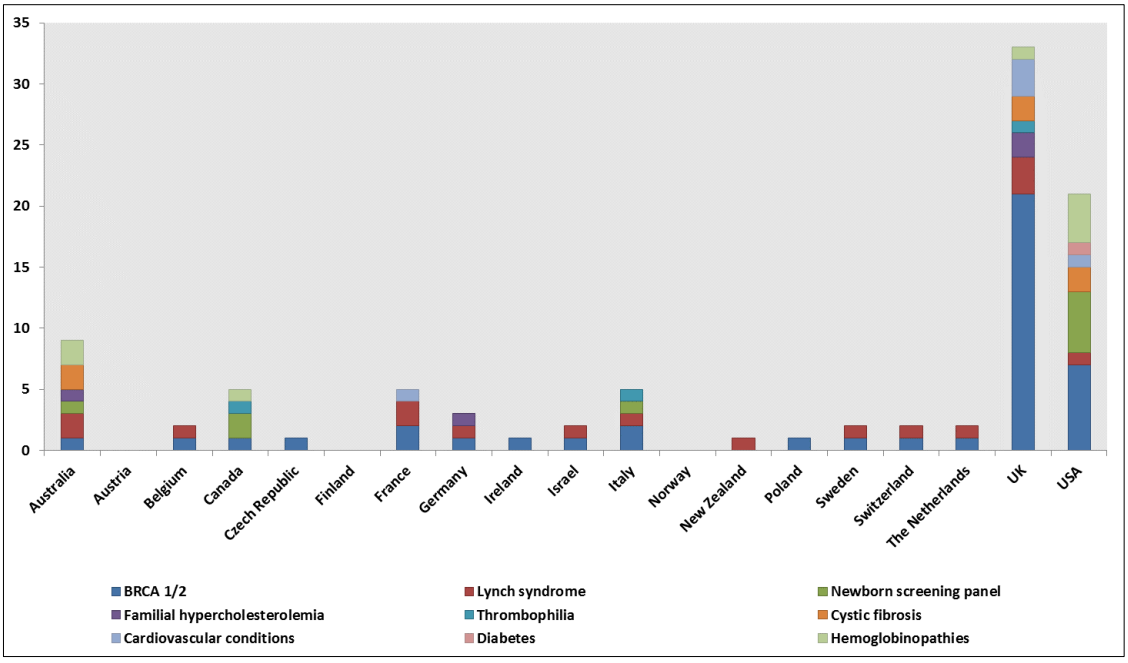

Figure 5. Geographical distribution of genetic tests under Model I: Genetic services led by geneticists

Model II: Primary care Model. In this model, primary care units in which GPs have specific genetic skills and can undertake an initial risk assessment, using standardized referral guidelines, play a prominent role. In some cases, GPs refer patients who are categorized as “high risk” to genetic services, while in other cases they can deliver genetic counselling, request genetic testing, and

interpret the results. Therefore, in this model, there are two possible patient pathways: a) Patient-GP-Counsellor-Lab; and b) Patient-GP-Lab.

Pathway IIa occurs when a patient contacts a GP who undertakes the initial risk assessment and then makes referrals to a genetic service, where a genetic counsellor or a medical geneticist can perform counselling and suggest genetic testing to the patient. A variation of pathway IIa was found in the GSPP Report 2008 [Washington State Department of Health 2008], in which only post-counselling was offered to patients. Thus, patients were seen by the genetic counsellor only after the genetic test: Patient-GP-Lab- Counsellor. Pathway IIb occurs when a patient contacts a GP who can perform the risk assessment, undertake counselling, and suggest genetic testing.

Model II, most frequently pathway IIa, was identified in 30 genetic programs. The model is prevalent in the UK and in the USA. The main genetic tests offered under Model II are BRCA1/2 (14 programs), Lynch syndrome, FH, and diabetes (four programs each) (Figure 6).

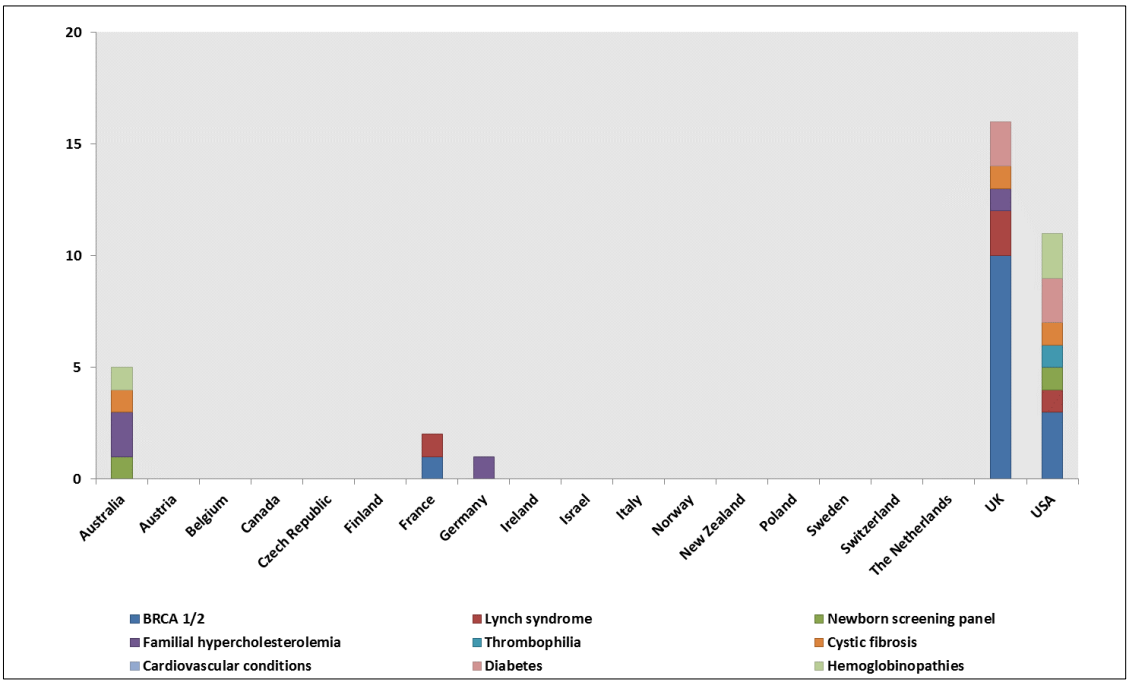

Figure 6. Geographical distribution of genetic tests under Model II: Primary care Model.

Model III: Medical specialist model. In this model, genetic tests can be requested directly by medical specialists (e.g. oncologists, cardiologists, neurologists, etc.) who may be able to manage

patients with genetic disorders without consulting medical geneticists. Thus, a medical specialist may request genetic testing, communicate genetic test results to patients and families and set up treatment with or without consulting a medical geneticist. There are two main patient pathways in Model III: a) Patient - (GP) - Medical specialist - Lab; and b) Patient - (GP) - Medical specialist - Counsellor - Lab.

Pathway IIIa occurs when a patient contacts (with or without a GP referral) a medical specialist (e.g. oncologists, cardiologists, neurologists, etc.) who performs a risk assessment, undertakes genetic counselling, and suggests genetic testing. Two variations of pathway IIIa have been identified in the studies of Shepherd et al. (2014) and Schofield et al. (2014). In Shepherd et al. (2014), patients were referred for maturity onset diabetes of the young (MODY; also known as monogenic diabetes) genetic testing by a genetic diabetic nurse (GDN) working in a diabetes clinical team. The GDN also guided the management and treatment of patients with monogenic diabetes and provided ongoing support to families and clinicians. The related pathway is: Patient-(GP)-Medical specialist/GDN-Lab. In the study by Schofield et al. (2014), medical specialists (i.e. oncologists, surgeons) requested Lynch syndrome screening tests for all newly diagnosed colorectal cancer patients and referred all patients with positive results to genetic services for counselling and possible germline testing. The related pathway is: Patient-Medical specialist- Lab (screening)-Counsellor-Lab (genetic testing). In pathway IIIb, a patient contacts (with or without a GP referral) a medical specialist who undertakes the initial risk assessment and then requests counselling, collaborating with the medical geneticist or genetic counsellor in the management of the patient.

Model III was identified in 54 genetic programs. The associated pathways IIIa and IIIb were equally distributed in the programs. The model is common in the UK, the US, Australia, and France. The main genetic tests offered under Model III are BRCA1/2 (15 programs), Lynch syndrome (10 programs) and FH (eight programs) (Figure 7).

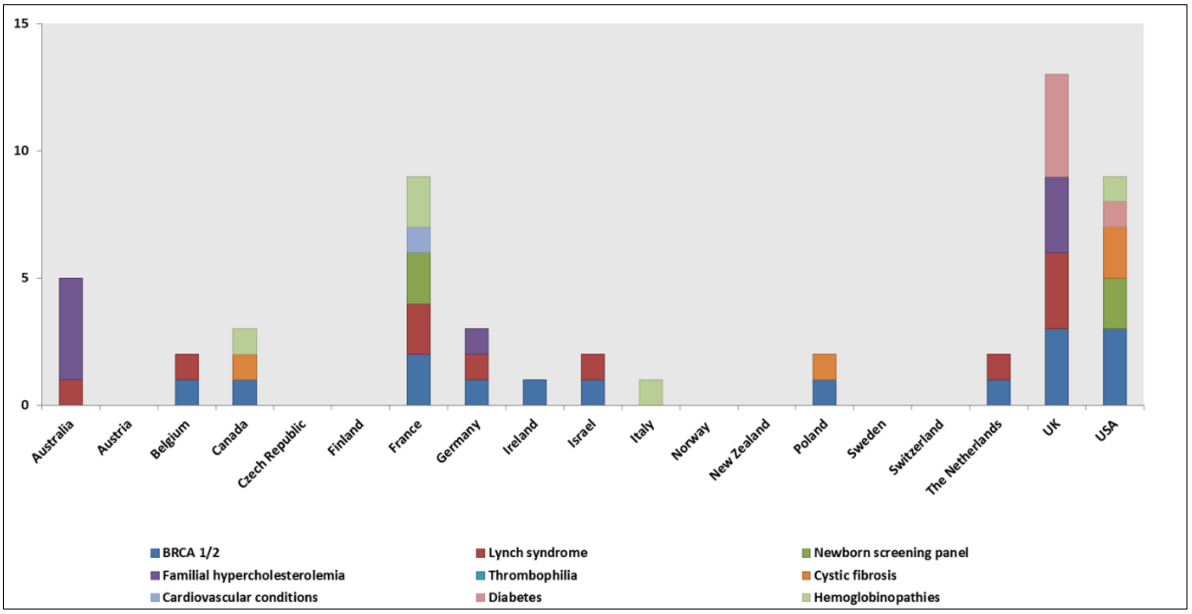

Figure 7. Geographical distribution of genetic tests under Model III: Medical specialist model

Model IV: Genetic services integrated into population screening programs. In this model, genetic services are provided within organized population screening programs (e.g. newborn screening, cervical cancer screening, HBOC screening, colorectal cancer screening, Ashkenazi Jewish genetic screening, etc.). There are three possible patient pathways in Model IV: a) Patient - GP/Medical specialist - Counsellor - Lab; b) Patient - GP/Medical specialist - Lab; and c) Patient - Counsellor - Lab. Pathway IVa occurs when a patient takes part in a population-based screening program; a physician (or another HCP) involved in the screening program can perform an initial risk assessment and refer the patient for genetic counselling. The genetic counsellor or medical geneticist can undertake counselling, suggest genetic testing and, based on the results of the test, recommend surveillance and/or management intervention. A variation of the IVa pathway was found in one record [Washington State Department of Health 2008], in which only post-test counselling was offered to patients (Patient - GP/Medical specialist - Lab - Counsellor). In pathway IVb, a patient takes part in a population-based screening program in which a physician (or another HCP) involved can perform risk assessment, undertake counselling, and suggest genetic testing. Based on the results of the test, the physician can recommend surveillance and/or management intervention. In pathway IVc, a patient contacts a genetic counsellor or a medical geneticist who can undertake counselling, suggest genetic testing and, based on the results of the test, can suggest surveillance through available population-based screening programs and/or intervention.

Model IV was identified in 44 genetic programs. The most frequent patient pathways were IVa and IVb. Model IV is common in the USA, Australia, and in the UK. The main genetic tests offered under Model IV are CF (22 programs), newborn screening panel (16 programs), and hemoglobinopathies screening (12 programs) (Figure 8).

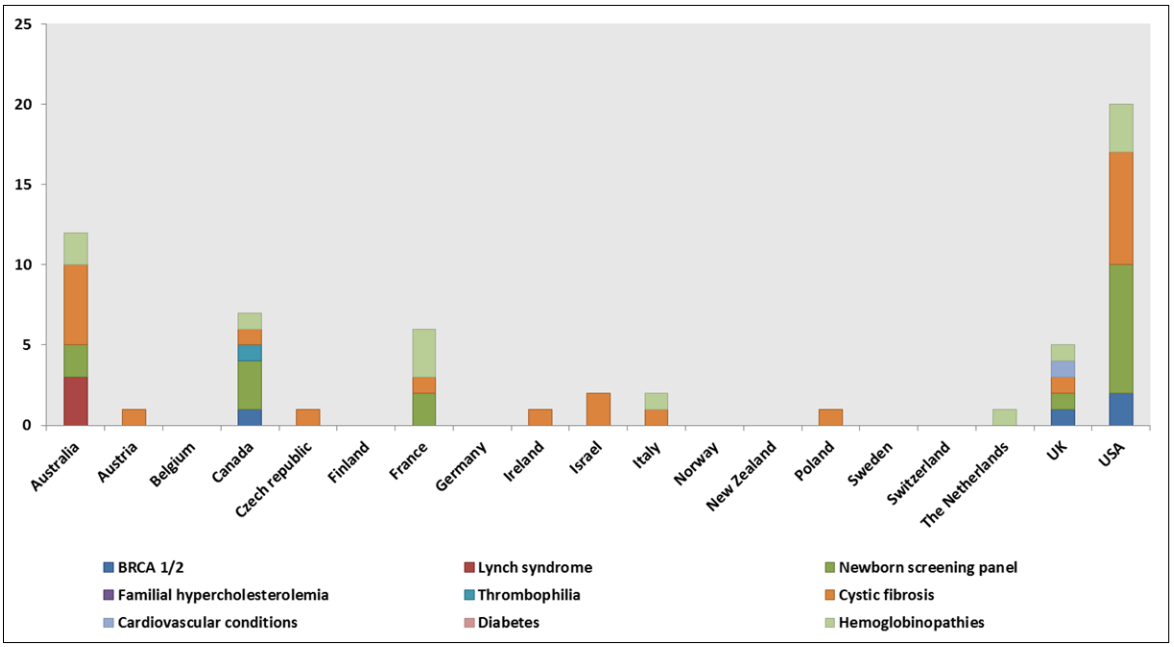

Figure 8. Geographical distribution of genetic tests under Model IV: Genetic services integrated into population screening programs

Model V: Direct to consumer (DTC). In this model, private companies offer genetic services, typically through websites. The pathways associated with Model V are: a) Patient-Lab-Counsellor; and b) Patient-GP/Medical specialist-Counsellor-Lab (virtual clinic). Healthcare professionals are usually not involved in the process and medical referrals are not required for genetic testing through DTC companies; thus, patients are self-referred. Furthermore, the companies usually do not offer risk assessment and genetic counselling. In pathway Va, patients purchase the test, take their own sample at home, send it to the lab, and receive the results directly. In contrast, a web-based virtual genetics clinic operating pathway Vb requires referrals from GPs or other medical specialists, offers risk assessment, pre- and post-test genetic counselling performed by genetic counsellors, and genetic testing that can be requested by genetic counsellors or medical specialists [Washington State Department of Health 2008]. Some DTC companies only offer post-test genetic counselling

[Kaye 2008, McGuire et al. 2011]. Model V was identified in five genetic programs available in the UK, the USA, and in New Zealand. The genetic tests offered under Model V were not well defined.

The evaluation of the identified genetic services highlighted that evidence of efficacy and effectiveness (i.e. guidelines and recommendations of scientific societies, health economic evaluations, feasibility studies) were reported for numerous genetic programs; the cost-effectiveness of the interventions was reported only for nine genetic programs. In addition, a feasibility analysis, intended as an evaluation of a proposed project to determine if it is technically and economically feasible, was reported for 11 programs.

The genetic conditions and the related tests identified in the review are presented as a three-tier classification, according to the CDC Office of Public Health Genomics (OPHG) evidence-based classification of genomic applications (Tables 3-5). Tier 1 encompasses genomic applications supported by evidence for implementation in practice. Tier 2 includes genetic applications with insufficient evidence supporting their routine implementation in practice but which may be useful for informed decision-making. Tier 3 comprises genetic applications lacking evidence or with irrelevant synthesized evidence, which are therefore not ready for routine implementation in practice, or have synthesized evidence that supports recommendations against or discourages use [CDC 2018].

According to the aforementioned criteria, most genetic programs identified in the review are included under Tier 1; specifically, these are genetic programs for HBOC, Lynch syndrome, FH, hypertrophic cardiomyopathy, and newborn screening (Table 3). Thirty-five genetic programs offering testing for various disorders, including Lynch syndrome testing under specific circumstances, are classified as Tier 2 (Table 4). Twenty-seven genetic programs offering not yet recommended genetic tests for various conditions (e.g. surfactant dysfunction, mitochondrial disease, cardiovascular conditions, type 2 diabetes) are reported as Tier 3 (Table 5). The tables with the three-tier classification (Table 3-5) do not comprise all genetic programs identified in the review as the circumstances under which some tests were provided and the genetic conditions were not well specified.

Table 3. Genetic tests identified in the literature studies and classified in Tier 1 according to the Center of Disease Control and Prevention (CDC)

DISEASE/DISORDER	TEST OR APPLICATION	INTENDED USE	N PROGRAMS	REFERENCES
BRCA-related cancer; hereditary breast and ovarian cancer	Family history of known breast/ ovarian cancer (1st or 2nd degree relative); personal history of any tumor type where profiling showed BRCA1/2 pathogenic mutation	Risk prediction for referral to further risk assessment, genetic counselling and possibly genetic testing	59	Allen 2007, Anton-Culver 2003, Bennett 2007, Brain 2000, Brain 2002, Brennan 2007, Calzolari 2005, Campbell 2003, Donnai 2001, Drury 2007, Eble 2013, Eeles 2007, Eisinger 2008, Epplein 2005, Evans 2009, Evans 2012, Foretova 2006, Fry 2003, Gray 2000, Gronwald 2006, GSPP* 2008, Gulzar 2007, Hartenbach 2002, Henriksson 2004, Holloway 2004, Hopwood 2003, Koeneman 2014, Lee 2002, Little 2009, Mackay 2006, Menkiszak 2003, Mulsow 2009, Orlando 2013, Orlando 2014, Pichert 2000, Pujol 2013, Reis 2006, Ricker 2006, Rowland 2003, Slade 2015, Smith 2009, Speechley 2010, Srinivasa 2007, Tozer 2007, Westwood 2006, Williamson 2008, Wonderling 2001, Young 2006
Lynch syndrome	Various strategies (i.e. family history of known cases of Lynch syndrome, newly diagnosed colorectal cancer)	Diagnostic, screening, and cascade testing of relatives	19	Bennett 2007, Eisinger 2008, Epplein 2005, Gulzar 2007, Hopwood 2003, Koeneman 2014, Mak 2007, Pichert 2000, Plunkett 2014, Pujol 2013, Schofield 2014, Wonderling 2001
Familial hypercholesterolemia (FH)	DNA testing and LDL-C concentration measurement	Cascade testing of relatives of people diagnosed with FH	11	Aarden 2011, Bell 2014, Bell 2015, Burton 2010, Burton 2012, Heath 2001, Kirk 2013, Vickery 2014, Watts 2011
Hypertrophic cardiomyopathy (HCM)- symptoms and signs of disease suggesting specific causes of HCM	Genetic testing	Confirm diagnosis of HCM	1	Charron 2002

*GSPP 2008, Washington State Department of Health 2008: Final Report of Genetic Services Policy Project

Table 3 continues

Newborn and children screening (e.g. CF, hemoglobinopathies, critical congenital heart disease, hearing loss, etc.)	Newborn screening panel for 31 conditions; screening in minors for other conditions	Screening	36	Amato 2014, Barlow-Stewart 2003, Basran 2005, Bickerstaff 2001, Byck 2006, Calzolari 2005, Comeau 2004, Donnai 2001, Drury 2007, Ekstein 2001, Gozdzik 2005, GSPP 2008, Hanley 2005, Henry 2005, Hoppe 2011, Kaufmann 2011, Kornreich 2004, Lena-Russo 2002, Long 2014, Little 2009, Lucci 2014, Massie 2000, Metcalfe 2009, Mogayzel 2014, Puryear 2006, Southern 2007, Speechley 2010, Streetly 2009, Therrell 2006, Thuret 2010, Windmill 2006, Wisconsin Genetic Services Plan 2002

Table 4. Genetic tests identified in the literature studies and classified in Tier 2 according to the Center of Disease Control and Prevention (CDC)

DISEASE/DISORDER	TEST OR APPLICATION	INTENDED USE	N PROGRAMS	REFERENCES
Lynch syndrome	Testing for Lynch syndrome based only on family history (patients meeting revised Bethesda guidelines or Amsterdam criteria)	Diagnostic, screening	3	Eisinger 2008, Henriksson 2004, Orlando 2014
Colorectal cancer in patient with 1st or 2nd degree relatives with Lynch syndrome related cancer at any age	Testing for Lynch syndrome	Diagnostic, screening	6	Anton-Culver 2003, Epplein 2005, Orlando 2013, Schofield 2009, Williams 2007
Single gene disorders and chromosomal abnormalities	Various genetic tests without formal evidence synthesis and reviews by evidence panels	Diagnosis, management, carrier testing	22	Amato 2014, Bach 2001, Barlow-Stewart 2003, Basran 2005, Berkenstadt 2007, Blumenfeld 2012, Burton 2012, Coffey 2008, Currier 2012, Ekstein 2001, Gason 2003, Gason 2005, GSPP* 2008, Hoppe 2011, Harper 2000, Little 2009, Metcalfe 2009, Morad 2007, Ramsden 2013, Salbert 2003, Speechley 2010, Williamson 2008
Lipid screening in infants, children, adolescents, or young adults (up to 20 years)	Family history relevant to dyslipidemia (otherwise undefined)	Risk prediction	1	Burton 2012
Skin cancer screening in adults	Family history of skin cancer	Risk prediction	1	Henriksson 2004
Prostate cancer	Tumor gene expression analysis	Risk prediction, management	2	Epplein 2005, Henriksson 2004

*GSPP 2008, Washington State Department of Health 2008: Final Report of Genetic Services Policy Project

Table 5. Genetic tests identified in the literature studies and classified in Tier 3 according to the Center of Disease Control and Prevention (CDC)

DISEASE/DISORDER	TEST OR APPLICATION	INTENDED USE	N PROGRAMS	REFERENCES
Common diseases (e.g. cardiovascular conditions, type 2 diabetes, hereditary hemochromatosis)	Test for various genetic risk factors	Risk assessment	20	Bennett 2010, Brennan 2007, Burton 2012, Calzolari 2005, Donnai 2001, Drury 2007, Epplein 2005, GSPP* 2008, Little 2009, Kirk 2014, Kirke 2015, Orlando 2013, Shepherd 2001, Shepherd 2003, Shepherd 2014, Shields 2010
Various conditions (e.g. Fanconi anaemia, surfactant dysfunction, mitochondrial diseases, intellectual disability, hereditary retinal diseases)	Panel of genes	Risk assessment, disease prevention	7	Ekstein 2001, Turcu 2013, Nesbitt 2014, O'Brien 2014, Moeschler 2009, Pohjola 2012, Salbert 2003, Hamblion 2012

4.1.2 Systematic review of the literature on policies governing the provision of genetic services in European and extra-European countries

A total of 80 records met the inclusion criteria (Figure 9); most documents were published between 2010 and 2015 in European countries (30/80), followed by USA (25/80), Australia and New Zealand (20/80). Two documents were related to Canada and three were issued by an International society.

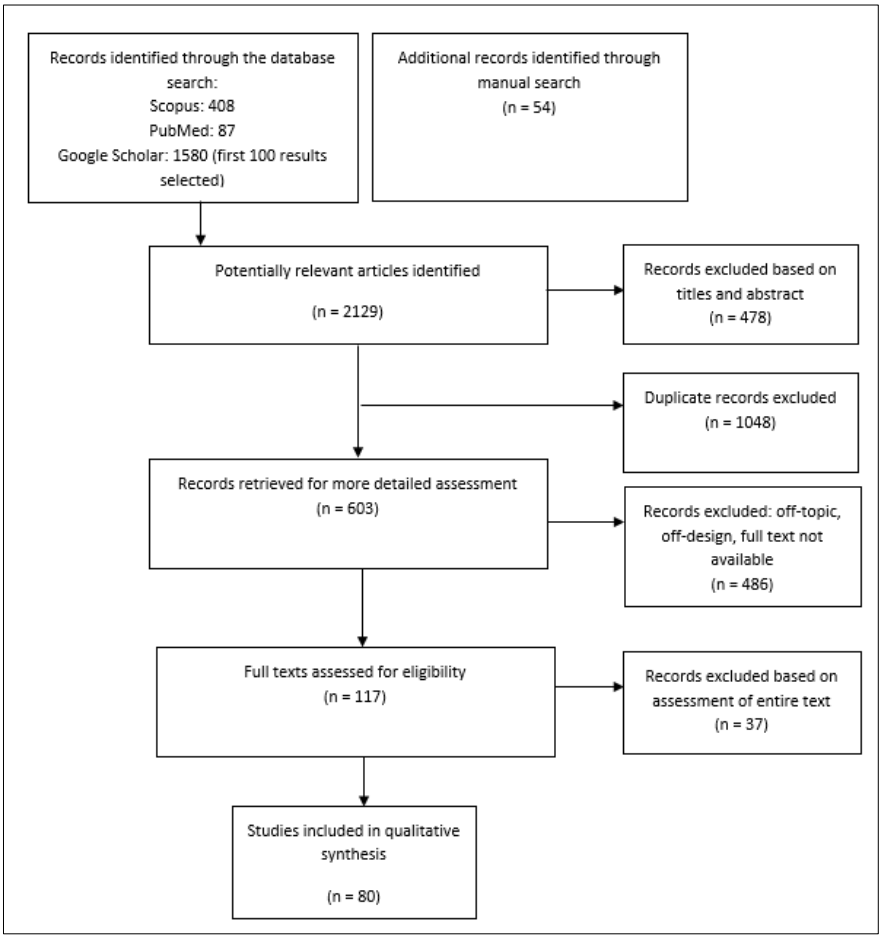

Figure 9. PRISMA flow diagram of the study selection process.

The documents included in the review (Tables 6) addressed a wide range of genetic conditions from pre- and postnatal genetic disorders (chromosomal abnormalities, CF, hearing loss, etc.) to adult onset conditions (e.g. sudden cardiac death, hereditary cancers, diabetes, metabolic disorders, Huntington disease, etc.). The genetic testing or screening programs included preimplantation genetic diagnosis (PGD), prenatal testing (including Non-Invasive Prenatal Testing-NIPT), newborn

screening, diagnostic and predictive testing (e.g. HBOC, Lynch syndrome, FH, cardiomyopathies, etc.).

Table 6. Main characteristics of the documents on policies governing the provision of genetic services in European and extra-European countries

COUNTRY, YEAR	DOCUMENT	ISSUING ORGANIZATION
Europe, 2010	Position statement	ESHG
Canada, 2015	Position statement	CCMG
Canada, 2008	Position statement	Canadian Pediatric Society, CCMG
International, 2006	Position statement	ISONG
International, 2010	Position statement	ISONG
International, 2010	Position statement	ISONG
UK, 2010	Guidelines	EMQGN European Molecular Quality Genetics Network
USA, 2011	Guidelines	NSGC
USA, 2013	Guidelines	NSGC
USA, 2012	Guidelines	NSGC
Australia, 2015	PS	HGSA, RANZCOG
Australia, 2015	Position statement	RANZCOG
Europe, 2006	Recommendations	ESHG; European Society of Human Reproduction and Embryology
Europe, 2015	Position statement	ESHG, European Genetic Alliances Network, Genetic Alliance UK, Medical Research Council, PHG Foundation, Wellcome Trust
Italy, 2010	Recommendations	SIGU
USA, 2014	Guidelines	NSGC
Australia, 2011	Policy recommendations	HGSA, RACP
Australia, 2004	Position statement	HGSA
Belgium, 2014	Guidelines	EuroGentest (European action)
Italy, 2014	Guidelines	SIGU
Italy, 2014	Recommendations	SIGU, SIEOG
Italy, 2013	Guidelines	SIGU
Australia, 2014	Guidelines	HGSA
Europe, 2009	Recommendations	ESHG
UK, 2010	Report	BSHG
Italy, 2013	Recommendations	AIOM, SIGU
Europe, 2013	Guidelines	EuroGentest (European action)
Italy, 2013	General Authorizations for genetic data use	Italian Data Protection Authority
USA, 2015	Position statement	American Society of Clinical Oncology
USA, 2015	Guidelines	ACMG; NSGC
USA, 2015	Policy statement	ACMG
USA, 2003	Guidelines	American Gastroenterological Association
USA, 2009	Guidelines	Heart Failure Society of America
USA, 2014	Guidelines	ACMG

USA, 2008	Report	Washington State Department of Health
Australia, 2013	Position statement	HGSA
UK, 2009	Position statement	Human Genetics Commission
UK, 2003	Report	Human Genetics Commission
UK, 2010	Report	Nuffield Council on Bioethics
Australia, 2007	Position statement	AMA
Belgium, Germany, France, Netherlands, Portugal, Switzerland, and UK, 2012	Policy overview	UK: the Advisory Committee on Genetic Testing and the Human Genetics Commission; Belgium: the National Advisory Committee on Bioethics and the Superior Health Council; France and Portugal: the National Consultative Ethics Committee for Health and Life Sciences and the National Council for Ethics in the Life Sciences; Netherlands: the Health Council and the Council for Public Health and Health Care; Switzerland: the Swiss Society of Medical Genetics; Germany: the German National Academy of Sciences.
Europe, 2012	Policy report	European Academies Science Advisory Council, Federation of European Academies of Medicine
Austria, 2010	Report	Austrian Bioethics Commission
USA, 2015	Position statement	ACMG
USA, 2007	Policy statement	ASHG
Australia, 2012	Position statement	HGSA
Australia, 2012	Position statement	HGSA
Italy, 2008	Report	Ministry of Health
Europe, 2008	Protocol	Council of Europe
UK, 2014	Guidelines	PHG Foundation
USA, 2009	Report	Secretary's Advisory Committee on Genetics, Health, and Society
USA, 2013	Guidelines	ACMG
USA, 2010	Policy statement	American Society of Clinical Oncology
USA, 2015	Position statement	ACMG
USA, 2014	Guidelines	ACMG
USA, 2000	Report	Secretary's Advisory Committee on Genetic Testing-National Institutes of Health
USA, 2012	Position statement	ACMG
USA, 2013	Guidelines	ACMG
USA, 2013	Standards and guidelines	ACMG
Australia, 2003	Report	Australian Law Reform Commission
Australia, 2013	Position statement	HGSA
Australia, 2013	Position statement	Clinical Oncology Society of Australia, HGSA, The Royal College of Pathologist Australia, The Royal Australian College of General Practitioners
Australia, 2015	Position statement	HGSA, RANZCOG
Australia, New Zealand, 2015	Guideline	HGSA
Australia, 2012	Position statement	AMA

USA, 2008	Report	Secretary's Advisory Committee on Genetics, Health, and Society
Australia, 2012	Position statement	National Health and Medical Research Council
Australia, 2008	Guidelines	HGSA
Europe, 2012	Guidelines	Public Health Genomics European Network (PHGEN II)
Australia, 2011	Guidelines	Australasian Society of Cardiac and Thoracic Surgeons, the Cardiac Society of Australia and New Zealand
Australia, 2012	Guidelines	HGSA
Europe, 2013	Recommendations	ESHG
Europe, 2010	Recommendations	EUROPLAN (EURORDIS-Rare Diseases Europe, European Commission)
Italy, 2015	Position statement	AIOM, SIGU, Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica, and Società Italiana di Anatomia Patologica e Citologia Diagnostica
Australia, 2014	Guidelines	HGSA
Europe, 2010	Recommendations	Council of Europe-Committee of Ministers
Netherlands, 2012	Guidelines	Dutch Working Group on hereditary gastric cancer
Europe, 2008	Expert panel recommendations	European Society of Cardiology
USA, 2009	Position statement	American College of Clinical Pharmacology
USA, 2000	Policy statement	ASHG, ACMG

ACMG, American College of Medical Genetics and Genomics; AMA, Australian Medical Association; AIOM, Associazione Italiana Oncologi Medici; ASHG, American Society of Human Genetics; BSHG, British Society for Human Genetics; CCMG, Canadian College of Medical Geneticists; EMQGN, European Molecular Quality Genetics Network; ESHG, European Society of Human Genetics; HGSA, Human Genetics Society of Australasia; ISONG, International Society of Nurses In Genetics; NSGC, National Society of Genetic Counselors; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RACP, Royal Australasian College of Physicians; SIEOG, Italian Society of Obstetric and Gynecologic Ultrasound and Biophysical Methods; SIGU, Italian Society of Human Genetics.

As previously stated, only topics that were not fully addressed in the systematic review on existing genetic delivery models were considered: a) informed consent; b) laboratory quality standards; and c) education, training and role of various HCPs in the provision of genetic services. Where possible, genetic service delivery models were identified.

4.1.2.1 Genetic counselling and informed consent

Policy documents reporting on genetic counselling and informed consent were 67/80 and included genetic services for adult onset conditions, as well as pre- and postnatal genetic screening and testing.

Prenatal and postnatal settings

Several European associations, the US National Society of Genetic Counsellors, and Australian associations reported on issues regarding genetic counselling and informed consent in pre- and postnatal genetic testing services. Some associations focused on specific genetic conditions in prenatal settings and in minors, particularly: i) diagnostic test for spinocerebellar ataxias [Sequeiros et al. 2010]; ii) FMR1 gene mutations [Finucane et al. 2012]; and iii) various chromosomal abnormalities (e.g. Down syndrome, trisomy 13, trisomy 18) [Sheets et al. 2011, Wilson et al. 2013, HGSA-RANZCOG 2015, RANZCOG 2015]. The European associations agreed that all couples at high genetic risk due to structural chromosome abnormalities or monogenic diseases seeking PGD should be seen first by a clinical geneticist or genetic counsellor who will discuss the use of PGD for the genetic disorder, and then by a clinical fertility specialist who will discuss the available options. Prenatal testing should be performed only if couples agree to know the results and accept all the implications of the test. Both pre- and post-test counselling should be provided by an appropriate healthcare professional engaged in prenatal genetic services to enable families to make informed choices [ESHG-ESHRE 2006].

A position statement issued by different European societies highlighted that current public health programs providing newborn screening in Europe use genetic testing without counselling and prescription. Although in many European countries parents receive general information about newborn screening and can give oral consent, an obligation to see a clinical geneticist before newborn screening does not exist in any European country because seeking parental consent could lead to delays in testing, and thus could delay treatment [ESHG, EGAN, Genetic Alliance UK, Medical Research Council, PHG Foundation, Wellcome Trust 2015].

The Italian Society of Human Genetics [SIGU 2011] addressed the issue of informing parents about their child's carrier status following newborn screening. A possible concern is that parents may not pass on the information accurately. On the other hand, there would be logistical problems to ensure that genetic or other professionals pass the information on to a child at an appropriate age. Therefore, minors' carrier status should not be withheld from parents who indicate that they wish to receive it. If carrier status is important to the child's health and its management, then the possible consequences for the child and family should be discussed prior to testing.

Relatively to extra EU-countries, the US societies confirm the importance of genetic counselling by qualified professionals in prenatal settings to facilitate the informed decision-making process. NIPT should be offered to patients at increased risk of chromosome aneuploidy only in the context of informed consent, education, and counselling [Wilson et al. 2013]. In the case of CF, genetic counsellors offering CF carrier screening should ensure that they are providing the most accurate and current information to patients on CF and the CFTR-related spectrum [Langfelder-Schwind et al. 2014].

The Human Genetics Society of Australasia issued a position statement on newborn bloodspot testing and a guideline on sample cards after screening tests are completed. For each newborn, healthcare professionals must be identified as responsible for providing information about the test, offering the test, obtaining appropriate consent, collecting the sample, and completing any requested follow-up. In Australia and New Zealand, a principle of informed refusal or dissent is applied to sample card collection rather than a requirement for informed consent [HGSA and RACP 2004].

Despite a relatively long history of pre- and postnatal testing, healthcare professionals (e.g. obstetricians, midwives) still find counselling in such situations challenging due to low knowledge and skills in genetics; thus, parents may not receive exhaustive information on available testing options. Several associations strongly recommended that evidence-based information leaflets be developed for the families to improve free informed choice. It is also recommended that information should be provided to families in both verbal and written forms, and trained interpreters should be employed for discussion when indicated. The consent form should also include permission to use the samples for research activities, or to eliminate the residual biological sample (blood, DNA, etc.) at the end of the investigation [ESHG-ESHRE 2006, ESHG 2009, SIGU 2011, SIGU 2013, SIGU 2014, SIGU-SIEOG 2014, Skirton et al. 2014, HGSA 2017]. Healthcare professionals are liable in law if they proceed without a consent. They will also be accountable to their regulatory bodies for their practice and need to consider ethical guidance to ensure that they act professionally [BSHG 2010].

Adult onset conditions

The importance of genetic counselling and the involvement of appropriately trained medical geneticists, genetic counsellors, and other specialists in genetic services has been emphasized in policy documents issued in European and extra-European countries. Incidental findings are also discussed being relatively common when next-generation sequencing (NGS) technologies are used in clinical settings. Laboratories should provide information on the chance of unsolicited findings and, where possible, methods that limit results to the clinical question being answered should be preferred. However, if targeted mutation testing is not feasible, the possibility of other findings must be discussed with the patient before the test is performed [AIOM-SIGU 2013, Skirton et al. 2013, Italian Data Protection Authority 2013].

Various American associations also support pre- and post-testing counselling by a qualified healthcare professional when a patient is at risk of a genetic condition. Counselling should include the mode of inheritance, identification of family members at risk, and discussion of the benefits, risks, and limitations of genetic testing and the alternative to testing. Referral to multidisciplinary care centers, when available, is recommended in the post-test stage [Robson et al. 2015, Hampel et al. 2015, ACMG 2015, Winawer et al. 2003, Hershberger et al. 2009, Alford et al. 2014]. In the US, up to 27 states require consent to disclose genetic information, and 17 have laws requiring informed consent for a third party to perform a genetic test or obtain genetic information. Washington State alone treats genetic information the same as other health information under its state health privacy protections [Washington State Department of Health 2008].

Genetic counselling and informed consent are also addressed in the position statement of the Canadian College of Medical Geneticists on genome-wide sequencing (GWS) for monogenic diseases. Precisely, genetic counselling should include: i) formal written informed consent obtained prior to testing; ii) information regarding the limitations of the test methodology used, occurrence of variants of unknown or uncertain significance, and the possibility of incidental findings; iii) discussion of expected outcomes and what will and will not be reported from the test; iv) potential issues related to insurance and discrimination; v) possible (or definite) need for parental samples and additional testing, and information about what will be reported with respect to samples obtained from the parents, or other unaffected family members; vi) explanation on data storage

and additional analysis or re-analysis in the future. Given the complexity of interpretation and counselling, only a clinical geneticist or other physician with good expertise in use of the new technology and clinical interpretation of the results should order clinical GWS [Boycott et al. 2015].

The Human Genetics Society of Australasia (HGSA) emphasizes that predictive genetic information should not be the basis for any social or economic discrimination or disadvantage. Regarding life insurance products, the HGSA believes that the issuance of a life insurance contract should not be contingent on an individual undertaking a genetic test. Close liaison between the insurance industry and the genetics profession is required to accurately interpret predictive test information and its implications for estimating risk [HGSA 2009].

DTC genetic services

DTC genetic services raise many ethical issues as testing is not being conducted in a medical setting which would better support the consumer in understanding and managing the decision to undertake testing and the testing results. Position statements and guidelines of different associations agreed that a DTC genetic test should be carried out only after the person concerned has given free and informed consent. Informed consent can only be provided when a consumer has received relevant information about the genetic test to enable them to understand the risks, benefits, limitations, and implications of the genetic test (including the implications for purchasing insurance). Separate informed consent should be requested by the test provider before biological samples are used for secondary purposes (e.g. research), or before any third party is permitted access to biological samples. Consumers' biological samples and personal genetic data should only be used for research that has been approved by a Research Ethics Committee or other relevant competent authority. Companies offering DTC genetic tests should not provide tests to adults unable to provide informed consent. Genetic tests in respect of children should normally be deferred until the attainment of the capacity to consent, unless other factors indicate that testing during childhood is clinically indicated. If postponement would be detrimental to the child's health, then testing should be organized by a healthcare professional who has responsibility for ensuring that any medical intervention or screening indicated will be arranged, as well as any subsequent care [Human Genetics Commission 2003, Human Genetics Commission 2009, Nuffield Council on Bioethics 2010, AMA 2007].

The policy overview by Borry et. al (2012) reported on DTC genetic testing legislations in some European countries. In France, Germany and in Portugal, genetic testing can only be carried out by request of a medical geneticist, following a genetic counselling consultation and is subject to informed consent of the person in question. In the UK, the Human Genetics Commission Principles cover matters such as information to be provided to prospective consumers, counselling and continuing support, laboratory processes, the provision and interpretation of results, and complaints procedures. Moreover, the UK Human Tissue Act 2004 –legislation primarily concerned with the use of biological samples rather than data– criminalize genetic analysis of human tissue without the consent of the donor. In Belgium, no specific legislation forbids or regulates the provision of DTC genetic tests. However, if a DTC genetic test falls under the practice of medicine, a physician should be involved and the law on patient rights would apply. The Netherlands has no legislation that specifically addresses DTC genetic testing, and companies can offer DTC genetic tests to the public. However, the Dutch Act on population screening seeks to protect individuals against screening programs that may be a threat to health. According to the Act, some forms of DTC genetic tests can only be carried out with a permit issued by the Dutch Minister of Welfare and Sports.

The European Academies Science Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM) listed, in their 2012 report, several recommendations for DTC genetic services that are summarized as follows: i) the scope of DTC genetic services should exclude the provision of diagnostic or presymptomatic genetic information for monogenic diseases, prenatal testing, carrier testing in children and nutrigenomic tests. Further discussion on whether pharmacogenetic testing could be included are needed; ii) tests for high-penetrance genotypes, including monogenic disorders, should generally be provided within the clinical genetic services; iii) transparency in information provision to consumers is fundamental; iv) DTC testing of samples from minors, pregnant women and third parties should not be allowed; v) DTC companies should include proper, additional, consent-seeking when desiring to use data for research. This separate consent should describe the purpose and specify the duration for holding samples and for the genetic information derived. Companies should also describe what would happen to samples and information if the company changes ownership.

Some documents highlighted the dangers related to private commercial companies that are now offering genetic testing not only for genomic prediction of diseases but also for various traits such

as “athletic performance indicators and risk factors for athletes”. The most widely offered test is the so-called “gene for speed”, ACTN3. It is claimed that ACTN3 testing may be used to predict whether an individual is more likely to be suited to sprint/power or endurance sports. However, having the “sprint” genotype does not guarantee that the individual will have any talent as a sprinter or preclude an individual from participating in sports [HGSA 2015a]. Private companies also offer nutrigenomics tests and, following a positive test result, expensive products such as dietary or other types of supplements or cosmetics are offered. Hence, the importance of educating the public that genetic tests should be performed in a clinical setting where qualified healthcare professionals can provide genetic counselling and interpret test results, and higher quality laboratory conditions are provided [HGSA 2015b].

4.1.2.2 Laboratory quality standards

Numerous policy documents issued by European associations discussed criteria for certification and accreditation of medical genetics laboratories that will guarantee high quality standards. The associations agreed that quality standards of laboratory procedures should be defined at European and/or national level, and the analysis of biological samples in genetic testing services should be provided only by competent laboratories. Competence can be established by accreditation to the International Organization for Standardization (ISO) standards 15189 or 17025, or other equivalent recognition. All laboratories offering genetic testing services, including NGS technologies, should implement an internal quality system and participate in External Quality Assessment schemes [ESHG 2010, Sequeiros et al. 2010, ESHG-ESHRE 2006, SIGU 2011, HGSA 2015b, Council of Europe 2008]. The establishment of a national multidisciplinary committee has been recommended to develop standards for laboratories as to when variants of unknown significance and incidental findings should be reported to referring clinicians. This body should also develop advice for clinicians as to whether and how to disclose incidental findings to patients [PHG Foundation 2014]. Furthermore, tests or products used in conjunction with any healthcare service offered should be safe, effective, and fit for purpose, and should meet all the relevant regulations covering In Vitro Diagnostic Devices Directive in the country where the laboratory in question is based. If the samples are obtained within Europe, both the specimen receptacles and any equipment used to obtain the samples must be CE-marked [Nuffield Council on Bioethics 2010].

Concerning DTC testing, commercial companies must be subject to appropriate regulatory oversight, and if they want to sell a self-testing kit, they must convince a regulator that it is safe and meets appropriate standards. Genetic tests used as part of a DTC genetic testing service should be able to identify the genotype of interest both accurately and reliably [Human Genetics Commission 2003, Human Genetics Commission 2009].

In the US, the Centers for Medicare and Medicaid Services (CMS), per the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA), and the Food and Drug Administration (FDA) are the two government agencies with authority to regulate genetic testing. Except for cytogenetics, however, CLIA does not recognize a specialty area for genetic tests, nor does it address the clinical validity of laboratory tests. Therefore, only analytical validity is fully enforced under CLIA, which requires all clinical laboratories, including genetic testing laboratories, to undergo inspections to assess their compliance with established standards. This process includes inspections for personnel qualification and responsibilities, quality control standards, quality assurance, and record keeping. Current regulations do not specify procedures or protocols; they rather require laboratories to ensure that their test results are accurate, reliable, timely, and confidential and do not present the risk of harm to patients. The FDA reviews medical devices for safety and effectiveness; this includes test kits such as those used to collect cheek swab or saliva DNA samples. The CDC collaborates with other public agencies and groups in the private sector to develop laboratory standards and to promote integration of validated genetic tests into clinical and public health practice [Robson et al. 2015, SACGHS 2009]. At the State level, many agencies use CLIA requirements to regulate genetic testing laboratories. The States of New York and Washington, however, independently operate laboratory certification programs, both of which are exempt from CLIA. The New York State Department of Health has one of the most stringent State-level oversight systems, requiring preapproval prior to offering a genetic test in a clinical setting [SACGHS 2009, Rehm et al. 2013, Robson et al. 2010].

The policy documents issued by the US associations agree that clinical genetic testing should be carried out in a fully accredited molecular genetic testing laboratory that has met CLIA standards or that of an equivalent accrediting agency. Clear distinctions should be made between testing for clinical or for research purposes. A laboratory should also have a clear policy on whether it reports incidental findings resulting from genome sequencing. The consumer should be informed of the laboratory's accreditation in conjunction with reporting of the results. Furthermore, a qualified

professional should be involved in the process of ordering a genetic test and laboratory results should be interpreted and delivered by board-certified genetics professionals [Hudson et al. 2007, Hershberger et al. 2009, Finucane et al. 2012, Robson et al. 2015, Rehm et al. 2013, Hedge et al. 2014, ACMG 2015].

In Canada, the Canadian College of Medical Geneticists reported on clinical GWS that should be performed in an appropriately accredited clinical laboratory. Laboratory reports should include specific information describing the clinical GWS methodology used and approach to analysis. The laboratory report should include an interpretation by a clinically trained and certified molecular geneticist [Boycott et al. 2015].

In Australia, the technical competency of medical and forensic testing is ensured by the accreditation scheme operated by the National Association of Testing Authorities (NATA). NATA is an independent, private, not-for-profit company, which operates as an association. Non-accredited genetic testing occurs in Australia in two situations: when a non-accredited laboratory carries out genetic testing or when an accredited laboratory carries out genetic testing that does not comply with genetic testing accreditation criteria. The latter is possible because NATA permits accredited laboratories to conduct testing that does not comply with NATA requirements, provided that the laboratories do not claim to be accredited for the purposes of the test. Overseas laboratories that market genetic testing services via the internet may also fail to be accredited by NATA or an equivalent international accreditation organization [ALRC 2003, HGSA-RACP 2004, HGSA-RACP 2011, COSA, HGSA, RCPA and RACGP 2013, HGSA-RANZCOG 2015, HGSA 2015c, HGSA 2016].
NATA is supported by the Australian Medical Association (AMA), which warns on the quality standards of DTC genetic testing services that cannot be guaranteed. The AMA strongly encourages that genetic testing should only be undertaken with a referral from a medical practitioner [AMA 2012]. Moreover, the Human Genetic Society of Australasia affirms that DTC testing should be performed in a clinical setting because of higher quality laboratory standards and the provision of genetic counselling. DTC testing providers are obliged to educate consumers on genetic testing and to measure how well consumers have understood the information [HGSA 2015a].

In New Zealand, the International Accreditation New Zealand (IANZ) -which is the New Zealand's national authority for the accreditation of laboratories, inspection bodies and radiology practices-

must accredit all laboratories. IANZ recommends that laboratories should participate in external quality assurance activities [HGSA-RANZCOG 2015, HGSA 2015d].

4.1.2.3 Education and training of healthcare professionals

Several documents issued by national and international societies discussed on the importance of education in minimizing the potential harms of genetic testing and in maximizing its potential benefits to diverse communities. Education and training should include ELSI implications of genetic testing, skills in genetic counselling, and innovations in genetic medicine. Inadequate public understanding and physician education are causes of the confusion and risks associated with genetic testing. Relevant associations, colleges, and societies should facilitate professional development [ESHG 2010, Boycott et al. 2015, ISONG 2006, Finucane et al. 2012, ESHG-ESHRE 2006, HGSA-RACP 2014, Skirton et al. 2014, SIGU 2014, BSHG 2010, Council of Europe 2008, NHMRC 2012, EUROPLAN 2010].

The importance of integrating training units dedicated to the scientific, legal, and ethical dimensions of DTC genetic testing into medical and other professional training was underlined in some policy documents [Hudson et al. 2007, HGSA 2015a, HGSA 2015b, ACMG 2016]. Many primary care physicians lack confidence in their ability to perform basic genetic health-related tasks (e.g. interpret and explain risk and benefit based on genetic information); hence, there is need for coordinated effort to improve their education. A sustained effort at genetic education of healthcare professionals is required at various levels: in primary care to inform and refer people appropriately and in specialized care to counsel or refer patients, and to discuss and interpret genetic test results adequately [EASAC-FEAM 2012, EUROPLAN 2010, HGSA 2015e]. The skills required to provide genetic services are not specific to a discipline but rather incorporate elements from oncology, medical genetics, genetic counselling, and more. Associations for medical oncology recommend continued education of oncologists and other healthcare professionals (e.g. nurses) in cancer risk assessment and management of individuals with an inherited predisposition to cancer. Oncology training programs should develop a set of core skills for new trainees and ensure adequate time in training for achieving these skills. Special training should also be offered to genetics professionals dealing with individuals affected by hearing loss to work effectively with sign language interpreters and use a variety of communication aids, including videophones, video relay services, instant

messaging, and visual aids [ISONG 2010, Alford et al. 2014, Robson et al. 2015]. The relevance of informed consent, quality standards of genetic laboratories and healthcare professionals' education and training were also addressed and confirmed in some policy documents [Hudson et al. 2007, AIOM-SIGU 2015, HGSA 2017, Council of Europe 2010]. Contrarily, four documents did not cover the three selected topics but addressed other issues in genetic service provision [ASHG-ACMG 2000, Pelliccia et al. 2008, Ameer and Krivoy 2009, Kluijt et al. 2012].

4.1.2.4 Genetic service delivery models identified in policy documents

The delivery models were identified for adult onset conditions, specifically Model I: Genetic services led by geneticists (for type 2 diabetes, various oncological conditions); Model II: Primary care model (for hemoglobinopathies testing); and Model III: Medical specialist model (for BRCA1/2, Lynch syndrome, and type 2 diabetes testing). The identified pathways were mostly Ia and IIIb, and both pathways involved a geneticist or genetic counsellor in the provision of genetic testing. Model V: DTC genetic testing was associated to Va pathway in which genetic counselling is not provided.

Regarding the geographical distribution of the genetic service delivery models, Model I: Genetic services led by geneticists and Model II: Primary care Model are common in Australia. Model III: Medical specialist Model was individuated mostly in Europe; Model IV: Genetic services integrated into population screening programs was common in Australia; and Model V: DTC genetic testing prevailed in Europe, Australia, and the US.

Three literature records lacking the main topics of the policy review also allowed the identification of delivery models and the related care pathways. The paper by Kluijt et al. (2012) on genetic test for familial gastric cancer enabled the identification of Model I: Genetic services led by geneticists (Ia pathway) and Model III: Medical specialist model (IIIb pathway). Both pathways required the involvement of a medical geneticists or a genetic counsellor. Pelliccia et al. (2008) also identified Model III: Medical specialist model in the document on cardiovascular abnormalities in athletes, while the paper by Ameer and Krivoy (2009) on advertising of genetic testing enabled the identification of Model V: DTC genetic testing.

4.1.3 Structured interviews addressing healthcare professionals

4.1.3.1 Delivery models for the provision of BRCA1/2 genetic testing in Europe

Section A. Expert profile

The results of the interim analysis are based on data from 10 European countries (Czech Republic, Estonia, France, Hungary, Ireland, Poland, Portugal, Sweden, the Netherlands, and the United Kingdom), with a response rate of 35% (18/51 experts). Of the 12 countries included in the research, data were not collected from two countries (Spain, Italy), while Poland was the most represented with three respondents. Responses of two experts from the Netherlands who piloted the survey questionnaires are not included in the present analysis.

Section B1. Access to genetic services

The first case presented to the experts was on access to genetic testing of an individual with an increased risk of breast cancer due to ethnicity (i.e. Ashkenazi Jewish), regardless of his family and personal history or familial mutation status. In most countries, the individual may access genetic services mainly through medical geneticists (16/18 experts), private laboratories (8/18 experts) or all medical specialists, such as gynecologists, oncologists, radiologists, and more (7/18 experts). Major disagreements were observed among experts regarding access mediated by GPs, medical specialists, private laboratories, and DTC services in Poland. In Portugal, direct access is only possible for two genetic services in the country. Patients can also access genetic services directly in France, but genetic testing for BRCA1/2 is not offered considering only the individual's ethnicity. Direct access to private laboratory or DTC testing is not allowed in Ireland.

The second case was on access to family history collection of an individual without cancer but with a family history suggestive of BRCA mutation. The individual's family history could be identified by medical geneticists (12/18 experts), all medical specialists (10/18 experts) or primary care physicians (9/18 experts). Disagreements among experts were mostly on identification by geneticists (Estonia, Hungary, Poland) and primary care physicians (Estonia, France, Ireland, Poland, UK). Two experts, in disagreement with the third responder, reported identification of patients through population

screening programs in Poland. In Estonia, medical specialists refer to medical geneticists according to clinical guidelines. Direct access to geneticists was reported for Portugal and France.

The third case regards access to genetic testing of an individual without cancer but with a known familial BRCA mutation. Access occurs prevalently through geneticists (15/18 experts), primary care physicians (6/18 experts) or all specialists (5/18 experts). Contradictory responses were mostly on access through geneticists (Ireland, Poland), primary care physicians (France, Ireland, Poland), and screening programs (Hungary, Poland). The individual can also be referred through the proband, who is asked to inform relatives about the availability of a test (Ireland, France).

The last case regards access to BRCA1/2 testing of an individual with breast or ovarian cancer. According to responses, genetic testing for BRCA mutation is offered to: i) only individuals with increased risk after performing a risk assessment (13/18 experts), there were disagreements among experts from Czech Republic, Estonia, France, Hungary, and Poland; ii) all individuals with early onset breast cancer or specific tumor hystotype (13/18 experts); and iii) all individuals with ovarian cancer (10/18 experts).

Section B2. Pathways after access to genetic testing

Patients are referred to genetic counselling for BRCA1/2 mostly by all medical specialists (13/17 experts), medical geneticists (10/17 experts), GPs and oncologists (7/17 experts, respectively), or gynecologists (6/17 experts) (Table 7). Specially trained professionals can initiate patient referrals in the UK (i.e. nursing staff from family history clinics) and France. Contradictory responses were mostly on referring gynecologists and oncologists (France, Hungary, and Ireland). The counsellors of pre-test genetic counselling are prevalently geneticists (16/17 experts), specially trained professionals (6/18) and oncologists (4/17 experts). All medical specialists were indicated in Poland, but there is a disagreement among experts. The specially trained professionals are genetic counsellors (France, Ireland, UK, and Sweden).

Referrals to genetic testing (Table 7) are principally made by geneticists (12/17 experts), oncologist and other trained professionals (5/17 experts, respectively). Contradictory responses regarded all

445 medical specialists, medical geneticists, gynecologists (Hungary) and oncologists (Hungary, UK,
446 Ireland). The specially trained professionals are genetic counsellors (Ireland, France, and Sweden).
447
448 The counsellors of post-test genetic counselling (Table 7) are mainly medical geneticists (17/17
449 experts), followed by other trained professionals (5/17 experts) and oncologists (4/17 experts). The
450 trained professionals were genetic counsellors (France, Ireland, Sweden, and UK). The healthcare
451 professionals involved in the post-test management of at-risk individuals (follow-up) are mostly
452 surgeons (16/17 experts), oncologists (13/17 experts), radiologists (11/17 experts) and geneticists
453 (8/17 experts). Other medical specialists (6/17 experts) were breast and plastic surgeons (UK,
454 Portugal, the Netherlands) and gastroenterologists (Czech Republic).
455
456 In case of detected BRCA1/2 mutations, cascade screening is provided for family members of the
457 index case in all participating countries (17/17 experts). Family members are contacted for screening
458 mostly by specially trained professionals in all countries (12/17 experts), except in Hungary, and by
459 genetic counsellors in France, Hungary, Poland, Portugal, and the UK (6/17 experts).
460
461 Genetic laboratories for BRCA1/2 testing are mostly affiliated with universities or academic centers
462 in the participating countries (12/17 experts), except in Ireland. They are also provided at local level
463 (9/17 experts), except in Hungary, Sweden, the Netherlands, and UK. Laboratories are affiliated with
464 regional genetic services in most countries (9/17 experts), except in Estonia, Portugal, Sweden and
465 in the Netherlands.
466
467 *Section C. Genetic service delivery models*
468
469 Healthcare professionals with the most prominent role in the provision of BRCA genetic testing and
470 in patient management in a multidisciplinary team are mostly medical geneticists (8/17 experts)
471 (Table 8). Other professionals (4/17 experts), such as genetic counsellors (France) and oncologists
472 (Portugal) were also indicated. In Ireland, geneticists carry out testing and counselling while
473 surveillance and follow-up are under the supervision of GPs and referring physicians. Pathways
474 associated with BRCA1/2 genetic testing are:
475 i) Patient-General practitioner or Medical specialist-Counsellor-Lab (16/17 experts), it is present in
476 all countries;

ii) Patient-General practitioner or Medical specialist-Lab (6/17 experts), it is not present in Czech Republic, Ireland, Poland, and the UK;

iii) Patient-Counsellor-Lab (6/17 experts), it is present in Czech Republic, France, Ireland, Poland, and Sweden;

iv) Patient-Lab, it was reported only in Portugal.

Overall, the genetic service delivery models for BRCA1/2 genetic testing identified through the present survey are Model I: Genetic services led by geneticists; Model III: Medical Specialist Model; Model IV: Genetic services integrated into population screening programs; and Model V: DTC genetic services.

Table 7. Healthcare professionals involved in patient pathways after access to genetic services for BRCA1/2 testing in Europe

Healthcare professionals	Czech Republic	Estonia	Hungary	Ireland	Poland	Portugal	Sweden	Netherlands	UK	France
B2. Who can refer to genetic counselling for BRCA1/2 testing?										
General practitioner				✓		✓		✓	✓	✓
All medical specialists	✓	✓	✓	✓				✓	✓	✓
Medical geneticist			✓	✓	✓	✓	✓		✓	✓
Radiologist						✓			✓	✓
Oncologist			✓	✓		✓	✓		✓	✓
Surgeon				✓		✓			✓	✓
Gynecologist			✓	✓		✓			✓	✓
Other medical specialists						✓			✓	
Specially-trained professionals									✓	✓
B3. Who are the counsellors of pre-test genetic counselling for BRCA1/2 testing?										
General practitioner										
All medical specialists					✓					
Medical geneticist	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Radiologist										
Oncologist		✓		✓		✓			✓	
Surgeon										
Gynecologist		✓								
Other medical specialists										
Specially-trained professionals				✓						✓
B4. Who can refer directly to genetic tests for BRCA1/2?										
General practitioner						✓				
All medical specialists		✓	✓			✓	✓			
Medical geneticist	✓		✓	✓	✓	✓			✓	✓
Radiologist						✓				
Oncologist			✓			✓	✓	✓	✓	
Surgeon						✓				
Gynecologist			✓			✓	✓	✓		
Other medical specialists				✓		✓	✓			
Specially-trained professionals				✓			✓		✓	✓

Table 7 continues

Healthcare professionals	Czech Republic	Estonia	Hungary	Ireland	Poland	Portugal	Sweden	Netherlands	UK	France
B7. Who are the counsellors of post-test genetic counselling?										
General practitioner										
All medical specialists										
Medical geneticist	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Radiologist										
Oncologist			✓	✓		✓	✓			
Surgeon										
Gynecologist			✓							
Other medical specialists										
Specially-trained professionals										
B11. Which healthcare professionals are involved in the post-test management of at-risk individuals?										
General practitioner		✓		✓				✓	✓	✓
All medical specialists								✓		✓
Medical geneticist	✓	✓	✓		✓		✓	✓	✓	
Radiologist	✓	✓		✓	✓	✓		✓	✓	✓
Oncologist	✓	✓	✓	✓	✓	✓	✓			✓
Surgeon	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gynecologist	✓	✓				✓		✓	✓	
Other medical specialists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 8. Healthcare professionals with the most prominent role in the management of patient with HBOC in Europe

	Czech Republic	Estonia	Hungary	Ireland	Poland	Portugal	Sweden	Netherlands	UK	France
C1. Which of the following healthcare professionals has the most prominent role in genetic test provision and coordinates treatment and surveillance of patients in a multidisciplinary team?										
Medical geneticist	✓	✓			✓		✓	✓	✓	
Other medical specialists	✓			✓						✓
Primary care physicians			✓							
Physicians engaged in population screening programs										
Other		✓		✓		✓				✓
C2. Which of the following patient pathways are associated to the provision of genetic testing for BRCA1/2?										
Patient → General practitioner or Medical specialist → Counsellor → Lab	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient → General practitioner or Medical specialist → Lab		✓	✓			✓	✓	✓		✓
Patient → Counsellor → Lab	✓			✓	✓		✓			✓
Patient → Lab						✓				
Other				✓						

4.1.3.2 Delivery models for the provision of Lynch syndrome genetic testing in Europe

Section A. Expert profile

The results of the interim analysis are based on data from 12 countries included in the research (Czech Republic, Estonia, France, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, United Kingdom), with a response rate of 38% (20/52 experts). The highest number of experts per country is three (Spain, Poland), followed by two experts (Estonia, Italy, Portugal, the Netherlands) and one expert for the remaining countries. Responses of an expert from the Netherlands who piloted the survey questionnaires are not included in the present analysis.

Section B. Management of care pathways

Individuals may access genetic testing for Lynch syndrome mainly through medical geneticists (14/20 experts); other medical specialists such as oncologists, gynecologists, surgeons, gastroenterologists (12/20 experts); and population screening programs (6/20 experts) (Table 9). Currently, only for Lombardia region (Italy), universal testing for microsatellite instability or mismatch repair defects is enforced for patients that underwent resective surgery for colorectal cancer. Disagreements among experts were mostly on access mediated by geneticists (Estonia, Italy, Poland, Portugal, and Spain).

Risk assessment is performed using clinical criteria (Amsterdam criteria, revised Bethesda guidelines, etc.) prevalently by medical geneticists in all countries (12/20 experts) (Table 9). Experts from Italy and the Netherlands disagreed on this point. Risk assessment is performed using computational models (MMRpredict model, MMRpro model, etc.) only by medical geneticists (Portugal and Spain) and oncologists (Spain). Risk assessment is also carried out through tumor testing (MSI, immunohistochemistry testing, etc.) mostly by medical geneticists (12/20 experts).

Pre-test genetic counselling for Lynch syndrome is requested by all medical specialists (10/20 experts) (Table 9). Disagreements were observed among experts on this point (the Netherlands, Spain, Poland, and Italy). Requests are also made by geneticists in most countries (9/20); experts never indicated radiologists as referring specialists. The counsellors of pre-test genetic counselling

are medical geneticists in all countries (18/20 experts) and oncologists (Estonia, Hungary, Poland, Portugal, Spain). Genetic nurses (France, Poland, Sweden, the Netherlands) and genetic counsellors (Ireland, UK, Sweden) were also indicated.

Genetic testing for Lynch syndrome is mostly prescribed by medical geneticists (18/20 experts), oncologists (8/20 experts) and gastroenterologists (6/20 experts) (Table 9). Disagreements among experts were observed on prescriptions made by geneticists (Poland), oncologists (Italy, Portugal, Spain), gynecologist (Estonia, Italy, Portugal), and gastroenterologists (Estonia, Italy, Portugal, Spain).

Post-test counsellors are predominantly medical geneticists (19/20 experts), oncologists (6/20 experts) and gastroenterologists (5/20 experts) (Table 9). Experts from Poland, Ireland, the UK, and Sweden indicated genetic counsellors. Healthcare professionals involved in the post-test management of Lynch syndrome patients are prevalently gastroenterologists (19/20 experts), gynecologists (16/20 experts), geneticists and oncologists (12/20 each). In case of detected Lynch syndrome, cascade screening is provided for family members of the index case in all countries, except in Hungary (17/20 experts). Family members are contacted mostly through index patients (13/20 experts), except in Sweden (medical geneticists). GPs in Portugal also contact relatives. No response was given for Hungary.

Genetic laboratories for Lynch syndrome testing are generally affiliated with universities or academic centers in most countries (12/20 experts), except in France, Ireland, and Spain. The laboratories are also in the private setting (11/20 experts) or affiliated with regional genetic services (10/20 experts).

Section C. Genetic service delivery models

Healthcare professionals with the most prominent role in the provision of Lynch syndrome genetic testing and in patient management in a multidisciplinary team are mostly medical geneticists (13/20 experts) in all countries (Table 10), except in Ireland where other medical specialists were indicated. Medical geneticists and oncologists were also indicated for Italy, Estonia, and Spain. No professional

was reported for France since the diagnostic phase and surveillance are separate. The pathways associated with Lynch syndrome genetic testing are:

i) Patient-General practitioner or Medical specialist-Counsellor-Lab (15/20 experts). It was individuated in all countries, except in Hungary;
ii) Patient-General practitioner or Medical specialist-Lab (4/20 experts). It was individuated in Hungary, Italy, Spain, and Sweden;
iii) Patient-Counsellor-Lab (3/20 experts). It was individuated in France, Sweden, and the Netherlands.

Overall, the genetic service delivery models for Lynch syndrome genetic testing identified through the present survey are Model I: Genetic services led by geneticists; Model III: Medical Specialist Model and Model IV: Genetic services integrated into population screening programs.

607 Table 9. Healthcare professionals involved in pathways of Lynch syndrome patients in Europe

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Healthcare professionals	Czech Republic	Estonia	France	Hungary	Ireland	Italy	the Netherlands	Poland	Portugal	Spain	Sweden	UK
B1. How have citizens access to genetic testing for Lynch syndrome?												
Primary care							✓		✓	✓		
Screening programs							✓	✓		✓		✓
Private laboratory								✓	✓			✓
DTC services							✓	✓				
Medical geneticists	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Medical specialists			✓	✓		✓	✓		✓	✓	✓	
Other												
B13. Who can request pre-test genetic counselling?												
General Practitioner							✓		✓	✓	✓	
All medical specialists	✓	✓	✓			✓	✓	✓		✓	✓	
Medical geneticist				✓	✓	✓	✓	✓	✓	✓	✓	✓
Oncologist			✓		✓				✓	✓		
Gynecologist			✓						✓			
Gastroenterologist			✓	✓	✓				✓			
Surgeon									✓			
Pathologists												
Radiologist												
Genetic nurse												
Other medical specialists									✓			
Other	✓	✓	✓	✓	✓							
B14. Who are the counsellors of pre-test genetic counselling?												
General Practitioner												
All medical specialist												
Medical geneticist	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Oncologist		✓		✓					✓	✓		
Gynecologist									✓			
Gastroenterologist				✓								
Surgeon		✓		✓								
Pathologist												
Radiologist												
Genetic nurse			✓				✓	✓				
Social worker												
Psychologist												
Other medical specialists												
Other												

609 Table 9 continues

Healthcare professionals	Czech Republic	Estonia	France	Hungary	Ireland	Italy	the Netherlands	Poland	Portugal	Spain	Sweden	UK
B15. Who can request germline genetic tests for Lynch syndrome?												
General Practitioner											✓	
All medical specialists								✓			✓	
Medical geneticists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oncologist		✓				✓					✓	
Gynecologist		✓									✓	
Gastroenterology		✓		✓		✓					✓	
Surgeon		✓		✓							✓	
Pathologist												
Radiologist												
Genetic nurse											✓	
Other medical specialist												
B.18 Who are the counsellors of post-test genetic counselling for Lynch syndrome?												
General Practitioner												
All medical specialist												
Geneticist	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oncologist		✓		✓		✓			✓	✓		
Gynecologist							✓		✓			
Gastroenterologist						✓	✓		✓	✓		
Surgeon				✓								
Pathologist												
Radiologist												
Genetic nurse							✓					
Social worker												
Psychologist												
Other medical specialist												
Other					✓			✓			✓	✓
B22. Which healthcare professionals are involved in the post-test management of Lynch syndrome patients?												
General Practitioner												
All medical specialist												
Medical geneticist		✓		✓		✓		✓	✓	✓		✓
Oncologist	✓	✓		✓	✓	✓		✓		✓		✓
Gynecologist	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Gastroenterologist		✓		✓		✓	✓	✓	✓	✓	✓	✓
Surgeon		✓		✓		✓		✓	✓			✓
Pathologist								✓				✓
Radiologist	✓	✓						✓				
Genetic nurse												
Social worker												
Psychologist								✓	✓			
Other specialist												

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Table 10. Healthcare professionals with the most prominent role in the management of Lynch syndrome patients in Europe

	Czech Republic	Estonia	France	Hungary	Ireland	Italy	Netherlands	Poland	Portugal	Spain	Sweden	UK
C1. Which of the following healthcare professionals has the most prominent role in genetic test provision and coordinates treatment and surveillance of patients in a multidisciplinary team?												
Medical geneticists	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓
Other medical specialists					✓				✓			
Primary care physicians												
Physicians engaged in population screening programs												
Other		✓	✓			✓				✓		
C2. Which of the following patient pathways are associated to the provision of genetic testing for Lynch syndrome?												
Patient → General practitioner or Medical specialist → Counsellor → Lab	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Patient → General practitioner or Medical specialist → Lab				✓		✓				✓	✓	
Patient → Counsellor → Lab			✓				✓				✓	
Patient → Lab												
Other												

4.1.3.3 Delivery models for familial hypercholesterolemia genetic testing in Europe

Section A. Expert profile

The results of the interim analysis are based on data from seven European countries (Czech Republic, Estonia, Hungary, Poland, Portugal, the Netherlands, UK), of the 12 countries included in the research, with a response rate of 22% (12/54 experts). Portugal was the most represented country with six experts, whilst other countries had only one expert.

Section B. Management of care pathways

Individuals may access genetic testing for FH in mainly through medical specialists (10/12 experts), screening programs (6/12 experts) and medical geneticists (5/12 experts) (Table 11). The medical specialists are cardiologists, internists, pediatricians, gynecologists, lipidologists or endocrinologists, and more. Access through DTC services was reported only for Estonia. Major disagreements were over access through screening programs, mediated by medical geneticists, medical specialists or private laboratories in Portugal.

Genetic counselling is offered to individuals at risk of FH before and after genetic testing (Hungary, Portugal, the Netherlands, UK), or only after genetic testing (Poland, Portugal); experts from Portugal disagreed on this point. Pediatricians (5/10) or cardiologists (4/10) mostly request genetic counselling; nurse practitioners and midwives were indicated only in the Netherlands (Table 11). The counsellors are medical geneticists (Poland, Portugal, the Netherlands) or other specialists such as lipidologists, metabolic disorders specialists and internists (Hungary, UK, Portugal). Healthcare professionals use various risk stratification tools to determine which individuals are at risk of FH mutations in all countries, except in Estonia. Risk assessment is usually performed by pediatricians and cardiologists (5/10 experts each). Nurse practitioners and midwives were indicated in the Netherlands.

Genetic testing can be requested by all medical specialists in all countries (except in Hungary and in the UK), and by medical geneticists (Table 11). Major disagreements were on all healthcare professionals requiring testing for FH in Portugal. In case of detected FH, cascade screening is

provided for family members of the index case in all countries, except in Estonia (11/12 experts). Family members are contacted by various healthcare professionals, mainly internists, pediatricians, medical geneticists and GPs. Metabolic specialists were indicated in Czech Republic and in Portugal.

Genetic laboratories for FH testing are mostly affiliated with academic centers or operate in the private sector, except in Poland. They are affiliated with regional genetic services in Estonia, Portugal and in the UK. Other research facilities mentioned were national institutes and the Public Investigation Department in Portugal.

Section C. Genetic service delivery models

Healthcare professionals with the most prominent role in the provision of FH genetic testing and in patient management in a multidisciplinary team are medical specialists, mainly metabolic specialists (Czech Republic, Poland, Portugal, and the UK) (Table 12). Multidisciplinary teams for FH are not available in Estonia. The pathways associated with FH genetic testing are:

i) Patient-General practitioner or Medical specialist-Counsellor-Lab (4/12 experts). It was individuated in Czech Republic, Estonia, Portugal and in the UK;
ii) Patient-General practitioner or Medical specialist-Lab (9/12 experts). It was individuated in all countries, except in the Czech Republic and the UK;
iii) Patient- Counsellor-Lab. It was individuated only in Portugal.

Overall, the genetic service delivery models for FH genetic testing identified through the present survey are Model I: Genetic services led by geneticists; Model III: Medical Specialist Model; and Model IV: Genetic services integrated into population screening programs. Access to testing for FH through DTC services was reported for Estonia, but the appropriate pathway was not indicated by the experts.

690 Table 11. Healthcare professionals involved in patient pathways for Familial hypercholesterolemia testing in
691 Europe
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Healthcare professionals	Czech Republic	Estonia	Hungary	Poland	Portugal	Netherlands	UK
B1. How have citizens access to genetic testing for FH?							
Primary care						✓	✓
Screening programs			✓		✓	✓	✓
Private laboratory		✓			✓		
DTC services		✓					
Medical geneticists		✓			✓	✓	✓
Medical specialists	✓		✓	✓	✓	✓	✓
Other							
B4. Who performs risk assessment for FH?							
General practitioner					✓	✓	✓
All medical specialists					✓	✓	
Medical geneticist	✓					✓	
Cardiologist	✓	✓		✓	✓	✓	
Nutritionist	✓						
Pediatrician	✓				✓	✓	✓
Other medical specialists	✓	✓	✓		✓	✓	✓
B6. Who can request genetic counselling for FH testing?							
General practitioner					✓	✓	
All medical specialists				✓	✓		
Medical geneticist			✓			✓	
Cardiologist					✓	✓	✓
Nutritionist							
Pediatrician					✓	✓	✓
Other medical specialists					✓	✓	✓
B7. Who are the counsellors of genetic counselling for FH testing?							
General practitioner							
All medical specialists							
Medical geneticist				✓	✓	✓	
Cardiologist					✓		
Nutritionist							
Pediatrician					✓		
Other medical specialists			✓		✓		✓
B8. Who can request genetic tests for FH?							
General practitioner					✓		
All medical specialists	✓	✓		✓	✓	✓	
Medical geneticist			✓		✓		✓
Cardiologist					✓		✓
Nutritionist							
Pediatrician					✓		✓
Other medical specialists					✓		✓

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Table 12. Healthcare professionals with the most prominent role in the management of patients with familial hypercholesterolemia genetic testing in Europe

	Czech Republic	Estonia	Hungary	Poland	Portugal	Netherlands	UK
C1. Which of the following healthcare professionals has the most prominent role in genetic test provision and coordinates treatment and surveillance of patients in a multidisciplinary team?							
Medical geneticist					✓		
Primary care physicians							
Other medical specialists	✓			✓	✓		
Physicians engaged in population screening programs			✓				
Other					✓	✓	✓
C2. Which of the following patient pathways are associated to the provision of genetic testing for Lynch syndrome?							
Patient → General practitioner or Medical specialist → Counsellor → Lab	✓	✓			✓		✓
Patient → General practitioner or Medical specialist → Lab		✓	✓	✓	✓	✓	
Patient → Counsellor → Lab					✓		
Patient → Lab							
Other							

4.1.3.4 Delivery models for the provision of inherited thrombophilia (FV LEIDEN, FII G20210A) genetic testing in Europe

Section A. Expert profile

The results of the interim analysis are based on data from six European countries (Estonia, France, Italy, Poland, Portugal, and Sweden), of the 12 countries included in the research, with a response rate of 20% (8/40 experts). Italy and Portugal were represented by two respondents and other countries by one expert. Responses of an expert from the Netherlands who piloted the survey questionnaires are not included in the present analysis.

Section B. Management of care pathways

Access to genetic testing in all countries are predominantly mediated by medical specialists (8/8 experts) and medical geneticists (7/8 experts), except in Sweden for the latter (Table 13). Medical specialists were cardiologists, angiologists, hematologists, gynecologists, pediatricians, and more. Primary care (5/7 experts) and private laboratories are frequent point of access to testing (4/7 experts).

Genetic counselling is offered to individuals at risk of IT before and after genetic testing (France, Sweden), or only after genetic testing (Italy, Poland). All medical specialists can request genetic counselling in France, Italy, and Poland. Genetic counsellors are all medical specialists (Italy), hematologists (France, Poland), or specialist in vascular medicine, cardiologists, gynecologists, internists (France) (Table 13). Risk assessment is performed to identify individuals at risk of IT in four countries (France, Italy, Poland, Sweden). Risk is assessed through family history (France, Italy, Poland), personal history of venous thromboembolism in four countries (France, Italy, Poland, Sweden), and through pre-contraception or pre-conceptional laboratory investigations prescribed by gynecologists without any patient selection in Italy.

Genetic testing for IT can be requested by all medical specialists (Estonia, France, Italia, Poland, Portugal) or GPs (Italy, France) (Table 13). In case of detected IT, cascade screening is provided for

family members of the index case in four countries (France, Italy, Poland, and Portugal). Family members are mostly contacted through index patients (Italy, Poland, and Portugal).

Genetic laboratories for IT testing are generally affiliated with universities or academic centers in most countries (except in Sweden) or operate in the private sector (except in Poland and Sweden).

Section C. Genetic service delivery models

Healthcare professionals with the most prominent role in the provision of IT genetic testing and in patient management in a multidisciplinary team are various medical specialists (e.g. hematologists, internists) and primary care physicians (Portugal) (Table 14). The pathways associated with IT genetic testing are:

i) Patient-General practitioner or Medical specialist-Counsellor-Lab (3/6 experts). It was individuated in Estonia and Portugal;

ii) Patient-General practitioner or Medical specialist-Lab (5/6 experts). It was individuated in all countries.

Overall, the genetic service delivery models for IT genetic testing identified through the present survey are Model I: Genetic services led by geneticists and Model III: Medical Specialist Model.

Table 13. Healthcare professionals involved in patient pathways for inherited thrombophilia testing in Europe

Healthcare professionals	Estonia	France	Italy	Poland	Portugal	Sweden
B1. How have citizens access to genetic testing for IT?						
Primary care	✓	✓	✓		✓	✓
Screening programs						
Private laboratory	✓	✓	✓		✓	
DTC services	✓					
Medical geneticist	✓	✓	✓	✓	✓	
Medical specialists	✓	✓	✓	✓	✓	✓
B2. Is risk stratification performed to determine individuals at risk?						
Yes		✓	✓	✓		✓
No	✓				✓	
B5. Who can request genetic counselling for IT testing?						
General practitioner		✓				
All medical specialists		✓	✓	✓		
Medical geneticist						
Cardiologist						
Nutritionist						
Pediatrician						
B6. Who are the counsellors of genetic counselling for IT testing?						
General practitioner						
All medical specialists			✓			
Medical geneticist						
Hematologist		✓		✓		
Vascular surgeon		✓				
Gynecologist		✓				
Other medical specialists		✓				
Specially-trained professionals						
B7. Who can request genetic tests for IT?						
General practitioner		✓	✓			
All medical specialists	✓	✓	✓	✓	✓	✓
Medical geneticist						
Hematologist						
Vascular surgeon						
Gynecologist						
Other medical specialists						
Specially-trained professionals						

Table 14. Healthcare professionals with the most prominent role in the management of patients with inherited thrombophilia genetic testing in Europe

	Estonia	France	Italy	Poland	Portugal	Sweden
C1. Which of the following healthcare professionals has the most prominent role in genetic test provision and coordinates treatment and surveillance of patients in a multidisciplinary team?						
Medical geneticist						
Primary care physicians					✓	
Other medical specialists		✓				
Physicians engaged in population screening programs						
Other	✓	✓	✓	✓	✓	✓
C2. Which of the following patient pathways are associated to the provision of genetic testing for IT?						
Patient → General practitioner or Medical specialist → Counsellor → Lab	✓				✓	
Patient → General practitioner or Medical specialist → Lab	✓	✓	✓	✓	✓	✓
Patient → Counsellor → Lab						
Patient → Lab						
Other						

4.1.3.5 Policy context of genetic testing and related services in Europe

Section A. Experts profile

Of the 44 experts invited to participate in the online survey, 11 completed the questionnaire, with a response rate of 25%. Eight European countries were represented: Spain, Hungary, Czech Republic, France, Italy, Portugal, the UK, and the Netherlands.

Section B. Policy

A dedicated national plan for Public Health Genomics (PHG-NP), concerning the policy on the use of genomics in healthcare, is in place in two countries (France, Italy) and under development in other two (Spain, UK) (Table 15). All countries have instead a national plan aimed at planning and designing health and social services for rare diseases. Accreditation and participation of genetic laboratories in external quality assessment schemes is mandatory in four countries (Czech Republic, France, the UK, and the Netherlands). Legislations governing the practice of non-medical healthcare

professionals involved in medical genetics are in place in six countries (Hungary, Czech Republic, France, Portugal, UK, and the Netherlands) and are mainly focused on technical staff in genetic diagnostic laboratories, on genetic counsellors and nurses.

Section C. Genetic services: access and availability

Laboratories for genetic testing are mostly in the public health sector in five countries (Spain, Hungary, France, Italy, Netherlands). Regarding the UK, there is no agreement between the two experts on this point (Table 16). All countries provide genetic tests of proven efficacy and related services at no charge to patients. New approaches to meet the demand for genetic services of underserved populations are in place in two countries (the UK and the Netherlands) and under development in three (Spain, France, Portugal). Four countries have legislations that specifically address DTC genetic testing (Spain, France, Portugal, and the Netherlands).

Section D. Professional education and training

According to the experts, professional education in public health genomics and its ethical, legal, and social implications is provided in six countries (Czech Republic, France, Italy, Portugal, the UK, and the Netherlands) with both undergraduate and postgraduate courses; an exception is the Czech Republic which provides only postgraduate courses (Table 17). These courses mainly address physicians, genetic counsellors, and lab technicians. The academic backgrounds of genetic counsellors vary across countries: in three countries (Hungary, Czech Republic, Portugal) only medical doctors can provide genetic counselling and in two of them (Hungary, Czech Republic) only those who are specialized in clinical genetics. In other countries genetic counsellors may have different backgrounds such as biology, genetics, nursing, and psychology.

Table 15. Policies governing the provision of genetic services

Questions	Spain	Hungary	Czech Republic	France	Italy	Portugal	UK	Netherlands
B1. Is there any dedicated national plan for public health genomics (PHG-NP), concerning the policy on the use of genomics in healthcare, in your country?	NO UD -	No	No	Yes	Yes	No	UD UD	No
B2. Is there a national plan or strategy aimed at planning and designing health and social services for rare diseases in your country?	Yes Yes -	Yes	Yes	Yes	Yes	Yes	UD Yes	Yes
B5. Is accreditation and participation of genetic laboratories in external quality assessment (EQA) schemes mandatory in your country?	No No -	No	Yes	Yes	No	No	Yes Yes	Yes
B8. In your country, is there any legislation governing the practice of non-medical healthcare professionals?	No No -	Yes; technical staff in genetic laboratories	Yes; technical staff in genetic laboratories	Yes; genetic counsellors and technical staff in genetic laboratories	No	UD for genetic counsellors	Yes; genetic counsellors, genetic nurses, and technical staff in genetic laboratories	Yes; genetic counsellors, genetic nurses, and technical staff in genetic laboratories

UD, under development

Table 16. Genetic services: access and availability

Questions	Spain	Hungary	Czech Republic	France	Italy	Portugal	UK	Netherlands
C1. In your country, are laboratories for genetic testing mostly in the public health sector?	Yes Yes -	Yes	No	Yes	Yes	No	No Yes	Yes
C2. Are there genetic tests of proven efficacy and related services provided at no charge to patients?	Yes Yes -	Yes	Yes	Yes	Yes	Yes	Yes Yes	Yes
C3. Location and distance from genetic services continues to pose a critical access barrier for individuals who live in rural areas. Has your country developed new approaches to meet the demand for genetic services of underserved populations (e.g. telemedicine)?	UD No -	No	No	UD	No	UD	Yes Yes	Yes
C9. Are you aware of a legislation that specifically addresses direct to consumer (DTC) genetic testing in your country?	Yes Yes -	No	No	Yes	No	Yes	No No	Yes

UD, under development

Table 17. Professional education and training

Questions	Spain	Hungary	Czech Republic	France	Italy	Portugal	UK	Netherlands
D1. Is professional education in public health genomics and its ethical, legal, and social implications provided in your country?	No No -	No	Yes	Yes	Yes	Yes	Yes Yes	Yes
D2. Specify which type of courses are available	NA	NA	PG	UG, PG	UG, PG	UG, PG	UG, PG	UG, PG
D3. Which professional categories are the courses in public health genomics addressing?	NA	NA	Physicians	Physicians, genetic counsellors, PharmD	Physicians, nurses, lab technicians	Physicians, lab technicians	Physicians, nurses, lab technicians, genetic counsellors, genetic nurses, bioinformatics	Physicians, lab technicians, genetic counsellors, genetic nurses
D4. Which are the academic backgrounds of genetic counsellors in your country?	Biology, Genetics, Nursing, Psychology Social workers	Only medical genetics	Only medical genetics	Biology, Nursing	Genetics	Medical doctors	Biology, Genetics, Nursing, Psychology	Genetics, Nursing

UD, under development; UG, undergraduate; PG, postgraduate; NA, not appropriate (the question is not appropriate based on the previous answer)

4.1.3.6 Evaluation of genetic service delivery models in Europe

Section A. Experts profile

Of the 39 experts invited to participate in the online survey, five completed the questionnaire, with a response rate of 12%. Five EU countries were represented: Czech Republic, France, Portugal, Hungary and Italy.

Section B. Activity of genetic services

In the respondents countries, the collection of clinical genetic activity data appears to be in place (France, Hungary, Italy) or under development (Czech Republic, Portugal) (Table 18). This process is already electronic in two countries (France and Hungary) while two other countries are working on computerization (Czech Republic, Portugal). In France, a common software for data collection is used at national level. Nevertheless, an information flow directing data from genetic services to regional or national level to support activities such as health planning, control or evaluation seems to be lacking in all countries. The most commonly used measures to evaluate the activity of genetic services are: i) number of genetic tests performed; ii) number of families or individuals seen; iii) number of new and follow-up appointments; iv) number and type of individual genetic diagnoses; and v) sources of referrals.

Section C. Quality of genetic services

According to the experts, the quality of genetic services is evaluated in three countries (France, Portugal, Italy) (Table 19). The most common quality measures are: i) use of protocols of care; ii) quality of record keeping; iii) agreed plans for follow-up of patients; iv) identification of laboratories and units with which the clinical genetic unit can connect; and v) participation of laboratories in quality assurance schemes.

Section D. Health outcomes of genetic services

Morbidity and mortality data related to genetic diseases are routinely collected in two countries (Czech Republic, Hungary). Nevertheless, they are not use as outcome measures of genetic services. It appears that no country routinely collects Patient Reported Outcomes to evaluate genetic services (Section E. Patient Reported Outcomes of Genetic Services).

Section F. Coverage of genetic services

According to the experts, genetic services coverage is assessed only in the Czech Republic, where it can be assessed for any genetic condition. It is under development in France and regards rare diseases. The main barrier to the realization of universal coverage for genetic conditions in the respondent countries is the possibility to guarantee equity in access to health services.

Section G. Electronic records and genetic information

Electronic records are implemented only in Portugal, and genetic information is included. In France and Italy, electronic records are under development. There seems to be no standardized approaches in monitoring complex pathways involving medical genetics in any country.

Table 18. Activity of genetic services

Questions	Czech Republic	France	Portugal	Hungary	Italy
B1. Do clinical genetic services in your country usually collect, store and retrieve data about their activity?	UD	Yes	UD	Yes	Yes
B2. Is the process of collection, storage and retrieval of data electronic (or will it be if you answered under development)?	UD	Yes	UD	Yes	I am not aware/not certain
B3. It is there a common software for data collection (or will there be if you answered under development)?	UD	Yes, a common software is used at national level	No	No	I am not aware/not certain
B4. Is there in your country an information flow directing data from genetic services to regional or national level in order to support activities such as health planning, control or evaluation?	UD	No	No	No	No
B5. Which of the following measures are used to evaluate the activity of genetic services in your country? (select one or more answers)					
Number of genetic tests performed	✓	✓	-	-	-
Percentage of genetic test performed in association with genetic counselling	-	-	-	-	-
Number of families/individuals seen	-	✓	✓	-	-
Districts of residence of patient and family	-	-	-	-	-
Number of new and follow-up appointments	-	✓	✓	-	-
Number and type of individual genetic diagnoses	-	-	-	✓	-
Sources of referrals	-	✓	-	✓	-
Other	-	Type of individual diagnoses is under development through rare diseases national plans	-	-	-

UD, under development

Table 19. Quality of genetic services

Questions	Czech Republic	France	Portugal	Hungary	Italy
C1. In your country, is the quality of genetic services evaluated?	No	Yes	Yes	I am not aware/not certain	Yes
C2. Which of the following measures are used to evaluate the quality of genetic services in your country (or will be used if you answered under development)? (select one or more answers)					
Use of protocols of care	NA	✓	-	NA	✓
Accuracy of diagnosis	NA	-	-	NA	-
Accuracy of pedigree analysis	NA	-	-	NA	-
Accuracy of risk assessment	NA	-	-	NA	-
Quality of record keeping	NA	-	✓	NA	✓
Quality and promptness of explanatory letters to referring clinicians and patients	NA	-	-	NA	✓
Agreed plans for follow-up of patients	NA	✓	-	NA	✓
Arranging of prenatal tests and post termination counselling	NA	-	-	NA	-
Appointments availability	NA	-	-	NA	✓
Identification of laboratories and units with which the clinical genetic unit can connect	NA	✓	-	NA	✓
Participation of laboratories in accepted quality assurance schemes	NA	✓	-	NA	✓
Other	NA	Rare disease expert centers are submitted to evaluation and requested to build protocols of diagnosis and care. Labs are submitted to EU ISO 15189 adhesion	Quantity of first/following and total appointments	NA	-

NA, not appropriate (the question is not appropriate based on the previous answer)

4.1.4 Knowledge and attitudes of European public health professionals regarding PHG

In the pilot study (Annex 13), no respondent could correctly identify all evidence-based applications (according to the definition of genetic testing provided by the National Human Genome Research Institute-National Institutes of Health, USA) [NHGRI-NIH 2017]. The rate of correct answers was higher among professionals involved in PHG (55%.6 correctly identified at least seven applications vs 24.0% among not PHG professionals). Similarly, a higher rate of professionals working in PHG correctly identified all clinical conditions for which there is (or there is not) evidence supporting the implementation of genetic testing compared to those not involved in genomics' activities (55.6% vs 8.0%). In terms of attitudes, more than one third of the 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. The rate of agreement with this statement was lower among professionals involved in PHG activities (55.6% vs 84.0%). Nearly 70% of respondents thought that genetic testing should be introduced in clinical practice only with evidence of efficacy (all professionals working in PHG strongly agreed with this statement), while a lower rate of respondents thought that it should necessarily be grounded on cost-effectiveness, also among professionals working in PHG (55.6% vs 60.0% in not PHG professionals). Finally, attitudes regarding the role of PH professionals in the actual integration of genomics into public health activities were very positive.

An interim analysis was conducted in October 2017 and the results were presented at the 10th European Public Health Conference held in Stockholm (see annex 15). The results showed 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 public health professionals in PHG are generally positive. Positive attitudes were associated with higher level of knowledge in genomics and with a younger age. If these results will be confirmed at the final analysis of the survey, it can be suggested that initiatives to increase knowledge on PHG among EUPHA members may contribute to fostering the incorporation of genomic applications in public health practice.

By the end of November 2017, 493 people accessed the survey and 382 completed it. Respondents came from all EU-28 countries and some non-EU countries, such as Switzerland (n=25), Thailand (n=1), and Turkey (n=7). Data analysis is currently ongoing.

4.2 The Quebec context

Demographic and professional information

The results of the pilot study are based on responses given by healthcare professionals currently practicing in the province of Quebec (Canada) and with good knowledge and/or practical experience in the provision of at least one of the four selected genetic tests (BRCA1/2, Lynch syndrome, FH, and IT), assessment and policy planning of genetic services. Thirty healthcare professionals participated in the study (Table 20) with a response rate of 18.75% (30/160). The respondents were predominantly female (63.3%), aged 18-33 (43.3%), genetic counsellors (53.35%) and had on average 10 (SD 11.42) years of experience in clinical genetics. The areas of clinical practice are mostly oncology and oncogenetics (50.0%). Their target population are mostly adults; only three respondents practice in pediatric genetics centers. The majority of the respondents have professional experience and/or good knowledge about the provision of BRCA1/2 and Lynch syndrome testing (70.0%) in Quebec.

Table 20. Socio-demographic characteristics of the sample

General characteristics of the sample	N(%)
Language	
English	12(40%)
French	18(60%)
Gender	
Female	19(63.3%)
Male	11(36.7%)
Age (years)	
>65	3(10.0%)
18-33	13(43.3%)
34-49	8(26.7%)
50-65	5(16.7%)

Do not wish to specify	1(3.3%)
Current position	
Physician	5(16.7%)
Genetic counsellor	16(53.3%)
Manager	0(0)
Researcher	9(30%)
Genetic counselling student	2(6.7%)

4.2.1 Part 1: Genetic testing

Section A. Access to genetic services

Individuals at increased risk of HBOC or Lynch syndrome are referred to genetic counselling by various healthcare professionals (Table 21), mostly GPs and oncologists (85.7% and 81%, respectively). Other channels of access to genetic counselling services are direct access (self-referrals), mediated by other medical specialists, nurses or midwives. The counsellors of pre-test genetic counselling are mainly medical geneticists (100%) and genetic counsellors (90.5%). They are also the professional category that mostly perform risk assessment during counselling sessions, followed by oncologists. According to responders, risk assessment is never performed by specially trained professionals (e.g. genetic nurses, midwives, physician assistants, etc.). Up to 50% of the sample indicated validated tools (printed format and computer programs) as HBOC risk assessment tools used in genetic services. Major disagreements were observed regarding Lynch syndrome risk assessment tools, in fact 50% of the sample indicated questionnaires based on national or regional guidelines (printed format) and validated tools (printed format and computer based programs) while the remaining 50% reported the opposite. Questionnaires based on international guidelines on Lynch syndrome (printed format) were indicated by 33% of the sample. Once identified, at-risk individuals are encouraged to undergo genetic counselling (100%) or genetic testing for BRCA1/2 or Lynch syndrome (52.4%). Referrals to genetic testing are carried out by medical geneticists (over 80%) and genetic counsellors (76.2%), while specially trained professionals were not indicated.

Individuals at increased risk of FH are referred to genetic counselling by GPs (72.7%) and medical geneticists (54.5%), followed by genetic counsellors and other medical specialists (36.4%, respectively) (Table 21). Pre-test genetic counselling is performed by medical geneticists (63.6%),

genetic counsellors (54.5%) and other medical specialists, especially cardiologists (36.4%). These three professional categories are also responsible of risk assessment during counselling sessions. According to 33% of the sample, questionnaires based on national or regional guidelines (printed format) and validated tools (printed format and computer based programs) are usually used for FH risk assessment. Once identified, at-risk individuals are encouraged to undergo genetic counselling (100%) or genetic testing for FH (45.5%). Individuals at increased risk of FH are referred to genetic testing by GPs (63.6%), genetic counsellors (54.5%), and medical geneticists (45.5%) in most cases. Individuals at increased risk of IT are mostly referred to genetic counselling by GPs (80%), medical geneticists (50%) and genetic counsellors (40%) (Table 21). Pre-test genetic counselling is usually performed by these three professional categories, who are also responsible for risk assessment and genetic testing referrals. The responders indicated questionnaires based on national or regional guidelines (printed format) as the most common tools used for IT risk assessment (37.5%). Once identified, at-risk individuals are encouraged to undergo genetic counselling (100%) or genetic testing for IT (40%).

Table 21. Access to genetic services in Quebec

A1. Who can refer to genetic counselling in your institution?	**BRCA1/2**	**LYNCH**	**FH**	**IT**
Total respondents	N=21	N=21	N=11	N=10
General practitioner	85.7%	85.7%	72.7%	80%
Medical geneticist	76.2%	76.2%	54.5%	50%
Genetic counsellor	71.4%	71.4%	36.4%	40%
Oncologist	81%	81%	9.1%	20%
Gynecologist	71.4%	57.1%	9.1%	30%
Specially-trained professionals	14.3%	14.3%	0	0
A2. Who are the counsellors of pre-test genetic counselling in your institution?				
General practitioner	14.3%	9.5%	9.1%	50%
Medical geneticist	100%	100%	63.6%	60%
Genetic counsellor	90.5%	90.5%	54.5%	50%
Oncologist	19%	19%	9.1%	10%
Gynecologist	9.5%	4.8%	9.1%	10%
Specially-trained professionals	14.3%	0	0	0
A3. Who can refer directly to genetic testing in your institution?				
General practitioner	30%	28.6%	63.6%	70%
Medical geneticist	85.7%	81%	54.5%	50%
Genetic counsellor	76.2%	76.2%	45.5%	40%
Oncologist	38.1%	38.1%	9.1%	10%
Gynecologist	28.6%	9.5%	18.2%	20%
Specially-trained professionals	0	0	0	0
A4. Who can perform risk assessment in your institution?				

General practitioner	4.8%	5%	9.1%	50%
Medical geneticist	100%	95.2%	100%	100%
Genetic counsellor	100%	100%	100%	100%
Oncologist	23.8%	28.6%	9.1%	10%
Gynecologist	4.8%	4.8%	9.1%	50%
Specially-trained professionals	0	0	0	0

Section B. Pathways after access to genetic testing

Genetic counselling after BRCA1/2 or Lynch syndrome genetic testing is mostly performed by genetic counsellors (90.5%), medical geneticists (85.7%), or oncologists (14.3%) (Table 22). Healthcare professionals engaged in the post-test management of individuals having a positive genetic test results are predominantly professionals involved in treatment and surveillance of the specific genetic disorder (80%) and those who prescribed genetic testing (70%). According to 75% of the sample, medical geneticists and genetic counsellor are equally responsible for genetic testing offered to relatives of probands (cascade testing). After obtaining permission from the proband, relatives are mostly contacted directly by the genetic service for genetic results and testing (65%) and in few cases by the genetic counsellor or medical geneticist (10%), or any physician (5%). Regarding Lynch syndrome testing, five responders specified that the proband can inform his/her relatives and refer them to the genetic service. The genetics department also provides the proband with a family letter to give to relatives, which includes test results and contact information for the genetics service. Genetic laboratories for BRCA1/2 and Lynch syndrome genetic testing are mostly affiliated with regional genetic services (60%) and academic centers (55%). They are also affiliated with other research facilities (20%) or operate at local level (15%). Over 90% of the sample declared that the laboratories participate in quality control procedures. According to 80% of responders, referring healthcare professionals are always informed about the genetic testing results of the testees.

Genetic counsellors (81.8%) and medical geneticists (72.7%) mostly carry out genetic counselling after FH genetic testing (Table 22). Other healthcare professionals are also involved (GPs, oncologists, gynecologists, cardiologists, etc.). Healthcare professionals engaged in the post-test management of individuals having a positive genetic test results are those who prescribed genetic testing (80%) or are engaged in treatment and surveillance of FH (70%). Cascade testing is mostly

under the responsibility of medical geneticists (60%), genetic counsellors (40%) and other medical specialists (40%). After obtaining permission from the proband, relatives are contacted directly by the genetic team for genetic results and testing (70%). According to five respondents, the proband can also inform his/her relatives and refer them to the genetic service. Genetic laboratories for FH genetic testing are affiliated with academic centers (45.5%), regional and local genetic services (36.4% each) and other research facilities (9%). Over 80% of the sample declared that the laboratories participate in quality control procedures. Moreover, referring healthcare professionals are always informed about the test result (72.7%).

Post-test genetic counsellors of individuals with or at risk of IT (Table 22) are predominantly genetic counsellors (80%), medical geneticists (70%) are GPs (50%). Healthcare professionals engaged in the post-test management of individuals having a positive genetic test results are those who prescribed genetic testing (88.9%) or are engaged in treatment and surveillance of IT (77.8%). Cascade testing is mostly under the responsibility of GPs and medical geneticist (55.6% each), as well as genetic counsellors (44.4%). After obtaining permission from the proband, relatives are mostly contacted directly by the genetic team for genetic results and testing (66.7%). The proband can also inform his/her relatives and refer them to the genetic service. Genetic laboratories for IT genetic testing are mostly affiliated with academic centers or operate at local level (40% each). The laboratories participate in quality control procedures (87.5%) and referring healthcare professionals are always informed about the test result (70%).

Table 22. Pathways after access to genetic testing services in Quebec

B3. Who are the counsellors of post-test genetic counselling in your institution?	BRCA1/2	LYNCH	FH	IT
Total respondents	N=21	N=21	N=11	N=10
General practitioner	4.8%	4.8%	9.1%	50%
Medical geneticist	85.7%	85.7%	72.7%	70%
Genetic counsellor	90.5%	90.5%	81.8%	80%
Oncologist	14.3%	14.3%	9.1%	10%
Gynecologist	4.8%	4.8%	9.1%	40%
Specially-trained professionals	0	0	0	10%
B6. Which healthcare professionals at your institution are involved in the post-test management of individuals having a positive genetic test result?				
Professionals who have performed risk assessment	40%	40%	40%	33.3%
Professionals who have prescribed genetic counselling	55%	55%	40%	33.3%
Professionals who have prescribed genetic testing	70%	70%	80%	88.9%
Professionals who are involved in treatment and surveillance of the genetic disorder	80%	80%	70%	77.8%
B7. Who is responsible for genetic testing offered to relatives of probands (cascade testing) in your institution?				
General practitioner	5%	5%	10%	55.6%
Medical geneticist	75%	75%	60%	55.6%
Genetic counsellor	75%	75%	40%	44.4%
Oncologist	35%	35%	0%	0
Gynecologist	5%	5%	0	11.1%
Specially-trained professionals	0	0	0	0
B8. How are relatives of probands contacted for genetic results and testing?				
Directly	65%	65%	70%	66.7%
Via a physician	5%	5%	0	0
Genetic counsellor	10%	10%	0	0
Oncologist	0	0	0	0
Gynecologist	0	0	0	0
Specially-trained professionals	0	0	0	0

Section C. Genetic service delivery models

According to the majority of the sample (67%), medical geneticists have the most prominent role in BRCA1/2 and Lynch syndrome genetic test provision and coordinate treatment and surveillance of patients in a multidisciplinary team (Table 23). A respondent reported that the prominent role is decided case by case (e.g. oncologists, cardiologists, etc.), based on the underlying genetic disorder. The pathways associated with BRCA1/2 and Lynch syndrome genetic testing are:

a) Patient-General practitioner or Medical specialist-Counsellor-Lab (77.8%)
b) Patient-General practitioner or Medical specialist-Lab (5.6%)
c) Patient-Counsellor-Lab (11.1%)

The genetic service delivery models for BRCA1/2 and Lynch syndrome genetic testing identified through the present survey are Model I: Genetic services led by geneticists, Model IV: Genetic services integrated into population screening programs, and Model III: Medical Specialist Model that is less common.

Fifty percent of the sample declared that medical geneticists and other medical specialists have the most prominent role in FH genetic test provision and coordinate treatment and surveillance of patients in a multidisciplinary team (Table 23). The pathways associated with FH genetic testing are:

a) Patient-General practitioner or Medical specialist-Counsellor-Lab (80%)
b) Patient-General practitioner or Medical specialist-Lab (30%).
c) Patient-Counsellor-Lab (20%)

The genetic service delivery models for FH genetic testing identified through the present survey are Model I: Genetic services led by geneticists and Model III: Medical Specialist Model.

According to the responders, medical geneticists and primary care physicians have the most prominent role in IT genetic test provision and coordinate treatment and surveillance of patients in a multidisciplinary team (Table 22). The pathways associated with IT genetic testing are:

a) Patient-General practitioner or Medical specialist-Counsellor-Lab (77.8%)
b) Patient-General practitioner or Medical specialist-Lab (44.4%)
c) Patient-Counsellor-Lab (22.2%)

The genetic service delivery models for IT genetic testing identified through the present survey are Model I: Genetic services led by geneticists, Model II: Primary Care Model, and Model III: Medical Specialist Model which is less represented.

Table 23. Genetic service delivery models in Quebec

Questions	BRCA1/2	LYNCH	FH	IT
C1. Which of the following healthcare professionals has the most prominent role in genetic test provision and coordinates treatment and surveillance of patients in a multidisciplinary team?				
Medical geneticist	66.7%	66.7%	50%	44.4%
Primary care physicians	22.2%	22.2%	20%	44.4%
Other medical specialists	22.2%	22.2%	50%	22.2%
Physicians engaged in population screening programs	11.1%	11.1%	0	0
C2. Which of the following patient pathways are associated to the provision of genetic testing?				
Patient → General practitioner or Medical specialist → Counsellor → Lab	77.8%	77.8%	80%	77.8%
Patient → General practitioner or Medical specialist → Lab	5.6%	5.6%	30%	44.4%
Patient → Counsellor → Lab	11.1%	11.1%	20%	22.2%
Patient → Lab	0	0	0	0

4.2.2 Part 2: Evaluation of genetic services

The questionnaire on evaluation of genetic services in the province of Quebec had the least number of responders. In fact, only three participants completed it; therefore, the results are not included in the present analysis.

4.2.3 Part 3: Policies governing the provision of genetic services in Quebec

Section A. Policy

Thirty professionals responded to the policy questionnaire. Those engaged in policy planning and/or research on genetic services were three, of which only one was aware of a plan or strategy aimed at planning and designing health and social services for rare diseases in Quebec. However, the responder did not specify any document. The majority of the sample was not aware of provincial or local guidelines that can help health departments organize genetic services to act not only as services, but also as research and educational resources. However, three responders specified that the guidelines were under development.

Regarding laboratory standards, accreditation and participation of genetic laboratories in external quality assessment schemes are not mandatory in Quebec (54%) and are not even promoted (62%).

Most professionals (62%) are aware of guidelines of local ethics committees engaged in the evaluation of research protocols involving biobanks and biological materials. Some professionals indicated the tri-council policy document as an example.

The responders were aware of legislations governing the practice of non-medical healthcare professionals in Quebec, in particular for genetic nurses and technical staff in genetic diagnostic laboratories (60% each). Registration or accreditation system for non-medical staff trained in genetics is available in Quebec (80.8%) and consists of a certification issued by the American and Canadian boards of genetic counsellors. Different associations are also available for non-medical staff trained in genetics, these are the Canadian, Quebec and American associations of genetic counsellors.

Section B. Genetic services: access and availability

In Quebec, laboratories for genetic testing are mostly in the public health sector (88.5%) and genetic tests of proven efficacy are covered by public health insurances if requested by physicians as reported in clinical guidelines (e.g. BRCA1/2).

According to 96% of responders, the current provision of genetic services does not meet the population needs in Quebec, in terms of access and availability. In particular, access to services in rural areas is not guaranteed. However, different approaches are under development to meet the demand for genetic services of underserved populations (e.g. telemedicine). Other issues related to the provision of genetic services are low genetic literacy among physicians, insufficient staff and genetic centers. The biggest issues healthcare providers are facing with respect to the provision of genetic services in Quebec are lack of integration between genetics and overall healthcare system (80.8%), low public genetic literacy (65.4%), lack of education about genetics for healthcare providers and lack of adequate genetic facilities (61.5% each). Public health professionals could support healthcare providers in the provision of genetic services in Quebec by informing the general population about genetic services (88.5%) and providing training and continuing education for healthcare professionals (73%). Considering commercial companies, a legislation that specifically addresses DTC genetic testing is lacking in Canada and all participants gave a correct answer.

Section C. Professional education and training

Education in public health genomics and ELSI issues is provided mostly to genetic counsellors (100%), physicians (92.3%) and nurses (73%).

4.2.4 Newborn screening programs

The research on policies governing the provision of genetic testing and related services was enhanced through a literature review on policies, ELSI issues of newborn screening programs in European and extra-European countries (including Canada). Although newborn screening is a public health program that has been in effect for 50 years, it is now being considered as a suitable platform for population-based WGS, raising new concerns about the potential benefits and harms of expanding its use for research and practice. The results of the review are published in *OBM Genetics,* vol. 2 (issue 3) (Annex 16).

V. Discussion

Following the completion of the human genome sequence in 2003, several genome discoveries have led to the development of a different approach to disease management, where prevention, diagnosis and treatment may be customized to each individual based on its own genetic susceptibility (personalized medicine). This approach is in contrast with public health practice, which focuses on population-based interventions. Therefore, the incorporation of genomics into public health can be considered a paradox [Khoury 2011]. Notwithstanding, incorporation of genomics into population health sciences is increasing and widely supported by a wide range of stakeholders, both within and outside of the scientific and public health communities. In-dept understanding of the different aspects of genomics medicine and the possible areas of application is crucial for the proper integration of genomic information into healthcare programs. The research on genetic service delivery models, policies and methods to assess genetic services is therefore an attempt to enhance the application of genomics discoveries in public health practice.

The present research enabled the classification of genetic programs into five genetic service delivery models, according to which healthcare professionals play the most prominent role in patient care pathways. Genetic services led by geneticists correspond to the “classic” model of genetic services (e.g. for rare diseases) provided mainly by geneticists; this is still the most common model of delivery. However, genetic applications are increasingly utilized by a wide range of healthcare professionals who are involved to various degrees in patient management (e.g. different medical specialists, nurses, technicians, midwives, social workers, and so on). More recently developed professional roles (i.e. genetic counsellors, genetic associates, genetic nurses) have been identified in several settings where they are vital in supporting clinicians in multidisciplinary teams. This is particularly evident in genetic services led by medical specialists, which is the second most common model of delivery. Genetic services are also progressively integrated into population-based screening programs. The review by Battista et al. (2012) reported on two early examples of this model, namely prenatal and newborn screening programs, while the present study identified more than 40 genetic testing programs integrated into population-based screening activities (i.e. CF and HBOC in Ashkenazi Jews, hemoglobinopathies in Mediterranean and North African populations). Although the integration of genetic testing services and screening programs is still at an early phase

and not yet widely distributed, it underlines current efforts to strengthen the PHG framework, which represents an integrated system where genetic medicine is combined with health promotion and disease prevention activities. Efforts have also been made to integrate genetic knowledge into primary healthcare, but the primary care model is one of the least represented in the review. This could be because the primary care physicians providing the genetic services lack the relevant knowledge and skills. In fact, GPs represent the professional category that was least likely to have a genetic background compared to other healthcare professionals in the review. Battista et al. (2012) considered the primary care model "as the first step favoring the gradual introduction of integrated genetic services" and maintained high expectations for this model. The primary care model could be considered a pioneer of integrated services, but the medical specialist model has certainly overshadowed it in recent years. Regarding DTC services, only five programs were identified in the review and the responders of the European and the Canadian surveys did not indicate it. However, the model should be much more common considering the easy access to genetic testing offered by commercial companies and the increasing tendency to purchase medical products through the internet.

Although some genetic tests with insufficient evidence of clinical utility and validity are offered to the general population, most genetic tests identified in the study have considerable evidence of efficacy and cost-effectiveness and are ready for full implementation in clinical and public health practice. Leading examples of such genetic tests and included in Tier 1, are BRCA1/2 genetic testing, genetic screening for Lynch syndrome, and FH. However, not all programs offering these three tests can be considered equivalent or recommended. Economic evaluations of genetic applications recognize three categories of BRCA1/2 genetic testing programs as cost-effective: i) population-based screening among Ashkenazi Jews; ii) family history-based screening, although methods on how to select high-risk women from the general population and the related cost are not detailed in literature studies; and iii) cancer-based genetic screening, which includes tools for the identification of affected women at higher risk of inherited breast and ovarian cancers [D'Andrea et al. 2016]. In the case of Lynch syndrome and FH, colorectal cancer-based universal screening programs or those targeting individuals <70 years old [Di Marco et al. 2018], and cascade screening of FH offered to relatives of index cases, are cost-effective [Rosso et al. 2017]. As a general approach, genomic applications should be evaluated rigorously prior to their introduction into clinical and public health practice by adapting the Health Technology Assessment framework for the evaluation of new

technologies [Pitini et al. 2018]. Those applications with proven efficacy and cost-effectiveness should be implemented in healthcare systems and made available to all citizens, as part of their right to safe and quality healthcare.

BRCA and Lynch syndrome testing were the most frequently offered genetic tests. The most cost-effective BRCA tests are all delivered predominantly via the geneticist model, followed by the medical specialist and the primary care models. Furthermore, physicians involved in population screening programs provide BRCA testing among Ashkenazi Jews and referrals are carried out by different medical specialists. Lynch syndrome testing, including the cost-effective strategies, is mostly delivered by the geneticist and the medical specialist models and in a few cases by the primary care model. BRCA and Lynch syndrome are typical examples of genetic disorders still managed principally by geneticists, although there is a progressive shift towards the involvement of other medical specialists. However, the clinical conditions mostly require the collaboration of several different specialists in a multidisciplinary team. Among other cost-effective approaches, FH cascade testing of relatives of index cases is delivered mainly through the medical specialist and the primary care models. This indicates that FH is mostly managed by primary care physicians, endocrinologists, or lipid specialists, and not necessarily by geneticists. The newborn screening panel, alongside BRCA screening among Ashkenazi Jews, is another cost-effective genetic testing service delivered via population-based screening programs.

Despite the evidence supporting the use of specific genetic and genomic applications, there is a risk that they will not be implemented or will be implemented haphazardly [Burke et al. 2006]. One of the factors limiting the successful implementation of genomic discoveries into routine clinical and public health practice is the lack of expertise in medical genetics, as pointed out in the surveys and in the literature reviews [Ricker et al. 2006, Byck et al. 2006, Drury et al. 2007, Kirke et al. 2015]. Lack of or limited knowledge, competency, and confidence of healthcare professionals in providing genetic risk assessments, genetic counselling, and referrals to clinical genetic centers can be overcome through proper information dissemination, education, and training activities. Another important barrier to implementation is related to funding for genomic research, which is public in most countries. The amount of funding provided, and the subsequent allocation of funds vary according to the healthcare budget and research priorities in each setting [Pohlhaus et al. 2008]. This leads to differences in the development and availability of genetic technologies across

geographic regions. Collaborations between government health agencies, national organizations, genetic service providers, and universities, nationally as well as internationally, in genomic research are necessary for the identification of priorities in research funding and the sustainability of genomic technologies.

Along with economic issues, national policies governing the use of genomic applications also affect the proper implementation of genetic discoveries in mainstream medicine. In recent years, international organizations, and commissions such as the Organization for Economic Development and Cooperation, the World Health Organization and the European Commission have been working together to develop evidence-based consensus on international standards and best practices of genetic services. Despite the efforts, several countries have not enacted regulations governing the use of genetic applications in clinical practice [WHO 2003]. France and Italy are the only countries, among those considered in the study, with a National Plan for PHG. The Italian national plan recommends intervention strategies and concrete actions to the Italian Regions to develop and/or empower an understanding of predictive genomic applications, and to implement new technologies according to the principles of evidence-based medicine [Conferenza Stato Regioni 2013]. In addition, the Italian national plan for innovation of the health system based on omics sciences, focused on the effectiveness and sustainability of genomic applications, was approved in 2017 [Conferenza Stato Regioni 2017]. All countries have instead a national plan aimed at planning and designing health and social services for rare diseases. In the US, genetic services are regulated at both the federal (by the Food and Drug Administration according to the Clinical Laboratory Improvement Amendments) and state levels [Washington State Department of Health 2008, McGuire et al. 2011] leading to substantial differences across the country. For instance, the use of genetic information in health insurance, embryonic and fetal research, and licensing of genetic counsellors are not regulated in all states [Washington State Department of Health 2008].

Regulations governing clinical laboratory quality are also lacking or insufficient in existing policies, as highlighted in several documents. The provision of quality clinical laboratory genetic services requires that genetic testing should be performed by laboratories accredited by recognized national or international organizations. All laboratories offering genetic testing services should implement an internal quality system and participate in external quality schemes. However, accreditation and participation of genetic laboratories in external quality assessment schemes is mandatory only in

four countries (Czech Republic, France, the UK, and the Netherlands). It is not mandatory nor promoted in the province of Quebec. The development of genetic applications should be accompanied by appropriate and uniform legislative oversight that can set quality standards, evaluate performance, and monitor outcomes of services nationwide.

DTC genetic testing legislation also varies across different settings [Washington State Department of Health 2008, Kaye et al. 2008, Gu et al. 2009, Gu et al. 2011]. Only four countries have legislations that specifically address DTC genetic testing (Spain, France, Portugal, and the Netherlands). The challenge for policy makers is to develop a regulatory approach that will prevent potential risks resulting from unsupervised genetic testing (e.g. misinterpretation of genetic test results, distress, anxiety, major burden of healthcare practitioners and the healthcare system), while respecting individual freedom and the free market. Healthcare providers, the public and the media should be kept well informed about the available genetic applications since appropriate education and information is the key in minimizing harms. The media has an important role in conveying information on the latest scientific findings to the public but it is mostly driven by sensationalism and profit. Genomics findings are delivered through culturally accepted and familiar terms for a major diffusion of the news. In case of complex information, such as in the genomics field, these aspects could lead to exaggerations, inaccuracy, thus misinformation that could be harmful to the public. Given that the media can influence public perception of genomic discoveries, genetic education of the media is crucial and should be tackled worldwide [ESHG 2010, Ostergren et al. 2015].

Other critical findings stem from the study. First, some genetic programs, and the related delivery models that have been developed for the provision of the relevant genetic tests, lack sufficient evidence of clinical utility and validity, and are currently not recommended for use in practice. The provision of these tests, classified as Tiers 2 and 3, could be related to faster genotyping technologies, the reduced cost of testing, commercial interests, and major public demand. It should be noted that these genetic programs comprise project proposals and demonstration projects (e.g. risk stratification models for genetic risk factors of common diseases), pilot studies (e.g. testing for various genetic conditions mainly for risk assessment purposes), and integrated services (e.g. testing for surfactant dysfunction, skin cancer, or prostate cancer). When considering proposals for full-scale projects, research ethics committees should approve only those studies on genetic tests with

sufficient data on their validity and utility. On the other hand, pilot studies are undertaken to provide a preliminary assessment of benefit and to generate sufficient evidence to warrant a larger study. In this light, the results of pilot studies support the process of informed decision making and therefore could be justified for the assessment of genetic tests not yet included in Tier 1. Second, well-known medical journals and publishers have published the related studies on genetic tests with insufficient clinical data. Journals publishing medical genetics should consider adding the criteria that reported practices or interventions carried out in genetic services as full-scale projects should meet current evidence of efficacy and cost-effectiveness. Third, the percentage of studies reporting on informed consent prior to genetic testing was very low. The fact that consent forms were not reported in most studies may be ascribed to authors taking for granted the fact that informed consent is required prior to any medical intervention, since it is an important component of genetic counselling that assists patients in making informed decisions while prioritizing their healthcare needs, preferences, and personal, religious, and moral values. Professional associations reporting on informed consent in genetic services agree that appropriate written informed consent form should be obtained from patients or their legally authorized representative confirming that they understand the risks and benefits of the procedure. Consent should be obtained for all biological materials to be taken, stored, and analysed. Furthermore, the increasing use of NGS or WGS technologies raise particular concerns since whole-genome scans will provide a unique DNA identifier that could potentially be linked with data obtained or stored in other contexts, creating implications for consent and privacy. Thus, the issue of informed consent should be revisited to determine whether the evolving research practice using large databases of genomic information and the growth of personalized medicine challenges consumers' legal rights. Generally, there must be maximum transparency within the consent process regarding how data are used and shared. Professional associations should offer training on the expanding role of genetics and genomics to a wide range of professionals that are involved in various degree in the field of genetic medicine (e.g. educators, legislators, public health officials, insurers, etc.) to better ensure the appropriate use of genetic data and information. However, these findings do not necessarily indicate that informed consent is not routinely obtained in most clinical settings, which would raise serious ethical and legal issues, but further research is warranted to clarify this issue.

Collection of genetic activity data is another critical issue in most countries giving that only France has implemented a common software for data collection at national level. Routine information flow

directing data from genetic services to regional or national level in order to support health planning, control or evaluation activities is lacking in all countries. In synthesis, there is no standardize approach to monitor care pathways of genetics services in any country. The need to develop or implement existing surveillance systems for genetic data as the key response to these issues is beyond doubt. The system should be compatible with common data analytics and presentation tools, adopt modern technologies and common platforms that can support new and emerging approaches, such as WGS. Then, standardization and centralization of the adopted surveillance system should be a priority in all countries.

The limits of the present study are related to restrictions in language and publication date of the systematic reviews, such that potentially relevant studies might have been excluded. However, most genetic tests were developed following the completion of the human genome sequencing in 2003 [Collins et al. 2003], justifying the choice of year 2000 as the lower date limit of the study. A critical point is the upper date limit of the reviews (2015), which coincides with the first year of the PRECeDI project and which has not been updated. However, the literature reviews are part of a multicenter European project that encompasses a multicenter cross-sectional study in the second phase. The literature search was completed in 2015 and was followed by the development of online questionnaires for the European multicenter cross-sectional study, which is currently ongoing and addresses healthcare professionals with good knowledge on the provision of four selected genetic tests (BRCA1/2, Lynch syndrome, FH, inherited thrombophilia), on policies governing the provision of genetic testing and related services, and on the evaluation of genetic services. The literature findings will be updated with the results of the multicenter cross-sectional study, when available, to incorporate new and relevant information.

Regarding the study conducted in Quebec, the response rate was low, despite email reminders, limiting the generalizability of the findings. In addition, only three responders completed the section on evaluation of genetic services, resulting in loss of valuable information.

Another limitation is related to the cross-sectional design of the surveys (e.g. selection bias, self-reporting). However, selection bias due to recruitment of members from professional associations for the Quebec study and the survey on public health professional in Europe was controlled by asking the participants to forward the questionnaires to colleagues or friends who, for various reasons, were not on the mailing list of the associations. For the European survey on genetic service

delivery models, policies and evaluation of genetic services, national referents were individuated for each participating country with the aim to identify the most suitable experts in their countries.

Further limitation of the research concerns the adoption of the CDC evidence-based database of cost-effective genetic applications [CDC 2018] for the classification of the genetic tests identified in the systematic review. The database does not comprise all possible genomic applications that could be classified using the level of evidence. However, it includes genetic tests identified in the review and it is updated on a regular basis. Finally, due to the heterogeneity of the studies, a meta-analysis was not conducted; therefore, the results of the systematic reviews are presented as a narrative synthesis.

VI. Conclusions

The identification and evaluation of existing genetic service delivery models are important steps towards the enhancement and standardization of genetic service provision. Current delivery models, including the “classic” geneticists model, require the integration of genetics into all medical specialties, collaboration among different healthcare professionals, and the redistribution of professional roles. Prior to implementation in clinical and public health practice, genetic applications should be accompanied by appropriate legislative oversight that can ensure quality by setting standards, evaluating performance, and monitoring outcomes of services. It is advisable to evaluate the appropriate model for the provision a genetic service with respect to the healthcare system and the genetic test provided within a specific genetic program, giving equal value to all elements in the program (i.e. genetic test, population target, clinical pathways, and overall organizational and economic aspects). Moreover, genetic tests of proven efficacy and effectiveness should be offered to citizens as a right to benefit from innovative healthcare.

Professional societies of European and extra-European countries have responded to the different challenges of personalized medicine by developing clinical guidelines and policy statements offering recommendations to clinical or public health practitioners and policy makers. However, more work is required to improve existing policy frameworks and assure the full implementation of the guidelines in clinical practice. In this light, an integrated approach involving national and international professional organizations working with government agencies worldwide is required for a uniform quality assurance of genetic testing and related services and for consumers' protection from social issues, such as the use of genetic information by third parties and genetic discrimination. Genetic education and counselling are critical to the appropriate use, interpretation, and understanding of genetic testing results, therefore major efforts to ensure the education of healthcare providers and the public in genetics medicine are pivotal.

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VIII. Annexes

Annex 1. Delivery models research protocol (Frontiers)

Annex 2. Delivery models extraction form

Annex 3. Lynch syndrome screening pathways (Frontiers)

Annex 4. Country websites (EU countries)

Annex 5. Country websites (extra EU-countries)

Annex 6. Questionnaire on BRCA1/2 genetic testing

Annex 7. Questionnaire on Lynch syndrome genetic testing

Annex 8. Questionnaire on FH genetic testing

Annex 9. Questionnaire on thrombophilia genetic testing

Annex 10. Questionnaire on evaluation of genetic services

Annex 11. Questionnaire on policy of genetic services

Annex 12. Questionnaire addressing public health professionals

Annex 13. Pilot study on public health professionals (Biostatistics)

Annex 14. Canadian setting: consent form, questionnaire on genetic testing, evaluation of genetic services, and policy

Annex 15. Results of the interim analysis on public health professionals

Annex 16. Newborn screening programs (OBM Genetics)