MEDGEN

Technion Tel Aviv University

Tempus

Developing Medical Genetics Education
Through Curriculum Reforms and
Establishment of Postgraduate Training Programs

Policy Brief of Medical Genetic Services in Israel

This genetic health policy brief is an objective analysis of current health care issues in the Medical Genetics field in Israel.

What are genetic/hereditary disorders?

Genetic diseases contribute to a significant proportion of health problems.

About 20% of infant deaths are due to genetically determined disorders (Hoyert et al. 2001). As many as 70% of children admitted to a pediatric intensive care units have genetically determined disorders (FitzPatrick et al. 1991). Patients with genetic disorders have an average of 5.3 admissions as compared to 1.6 for patients with non-genetic conditions (Hall et al. 1978). Among hospitalized children, an underlying disorder with a significant genetic component is present in about 70% (McCandless SE et al. 2004). Adult patients with a single gene or chromosomal disorder account for 1.9% of hospital admissions (Dye et al.2011). Over 7000 genetic diseases are listed in OMIM (Online Mendelian Inheritance in Man), a database that catalogues the known genetic diseases, and links them to relevant genes, if these are known.

Understanding the genetic causes of a disease has important benefits. This knowledge not only allows physicians to inform families about their risks of having children with the specific disease, but it can also influence the treatment of the disease.

Medical genetics is the specialty of medicine that involves the genetic screening, diagnosis, and management of genetic disorders, as well as presymptomatic genetic testing. Clinical (or medical) geneticists and genetic counsellors are health professionals who provide comprehensive diagnostic, management, and genetic counselling services for patients with genetic disorders. They are able to diagnose and manage genetic disorders, perform genetic risk assessment, help families with decision making, explain the causes and natural history of genetic disorders and interact with other health care professionals in the provision of services for patients with genetic disorders. In addition, they may coordinate genetic screening programs. Adverse effects of genetics service provision by non-genetics professionals include genetic testing and screening errors, medical mismanagement and unnecessary use of health care resources (Bensend et al. 2014).

Recently, advances in medical genetics have led to a better understanding of the molecular basis of disease and has resulted in improved clinical diagnosis and in novel approaches for prevention and treatment of genetic diseases. In parallel, the accompanying wide public awareness of these developments has raised expectations for more accurate assessment of genetic risk, treatment and prevention of genetic disease. Unfortunately, public awareness of genetic counselling is still low; there are studies showing that in some countries about 70% of the population have not heard of genetic counselling (Maio et al. 2013). In recent years, expectations of benefits of genetic testing have been raised among the public, resulting in more positive opinions (Henneman L et al. 2013).

What are the clinical features of genetic disorders?

Genetic disorders or disorders with a genetic component have diverse clinical presentations. Clinical signs and/or symptoms may be present at birth or appear later in life. Several categories of hereditary disorders are listed below.

Congenital anomalies. Congenital anomalies (birth defects) are structural anomalies that are present at the time of birth and can cause physical and/or intellectual disability. Their prevalence among newborn is 2-3%. These anomalies occur in the fetus during pregnancy. Examples of congenital anomalies include heart defects, neural tube defects, kidney underdevelopment, limb anomalies, brain anomalies and other anomalies. Birth defects have

a variety of causes including genetic etiology, chromosomal aberrations or environmental factors such as infections during pregnancy, alcohol consumption or use of certain medications. Frequently it is not possible to identify the exact cause leading to birth defects. Some congenital anomalies can be prevented. For example, adequate intake of folic acid can reduce the risk of neural tube defects. Frequently, structural congenital anomalies can be detected prenatally by fetal ultrasound.

Neurodevelopmental disorders.

Intellectual disability. Intellectual disability is characterized by significant limitations both in intellectual functioning and in adaptive behavior. Intellectual disability is present in about 1%-3% of the population and frequently has a genetic cause. Causes of intellectual disability include infections, trauma before or after birth, toxic substances and, most frequently, genetic causes (reviewed in Ropers et al. 2010). More frequent causes of intellectual disability are Down syndrome, fetal alcohol syndrome and fragile X syndrome. Most cases of intellectual disability cannot be detected prenatally. Screening for Down syndrome and fragile X syndrome is available in certain countries, including Israel (Shohat et al. 2003, Berkenstadt et al. 2007).

Autism spectrum disorders. Autism comprises a clinically heterogeneous group of disorders collectively referred to as autism spectrum disorders (ASD). Persons with ASD share common features including impaired social relationships, impaired language and communication and repetitive behaviors. Twin studies have established that the heritability of autism is over 90%. An increase in the prevalence of ASD is being reported worldwide. Known genetic causes of autism include cytogenetically visible chromosomal abnormalities (~5%), copy number variants (10%-20%) and single gene disorders (~5%). Although a significant progress has been made in deciphering genetic basis of autism, the cause in most cases still remains unknown.

Neuromuscular genetic diseases. Neuromuscular diseases are conditions that result in muscle weakness and fatigue, as well as cramping, stiffness and joint deformities. Sometimes these diseases also affect heart function and breathing. Most neuromuscular diseases are progressive in nature. Some disorders are present at birth, while others have childhood or adult onset. Life expectancy and severity varies by the specific disease. As a rule, strengthening exercises do not prevent muscle decline in neuromuscular diseases. Examples of neuromuscular disorders include spinal muscular atrophy, Duchenne and Becker muscular dystrophy, myotonic dystrophy and many other diseases. Most genetic neuromuscular diseases have no cure. Available treatments can increase mobility and prolong life.

Autoinflammatory disorders. Autoinflammatory diseases are diseases related to abnormal functioning of the immune system. Usually these diseases are characterized by flares and disease-free intervals. During the flare, fever, pain, rash or other symptoms might be observed. The symptoms might occur every few weeks or months; they might be triggered by certain factors, such as exposure to cold. One of the most frequent autoinflammatory conditions is the disease Familial Mediterranean Fever (FMF). People with this condition have recurring episodes of fever, abdominal pain, swollen joints, chest pain and skin rash. In Israel, it occurs most commonly in people of North African Jewish descent but can also be present in people from other ethnic origins (Shohat et al. 1995). If untreated, people frequently develop renal problems. The medication colchicine has been used successfully as a treatment.

Inherited metabolic disorders. Metabolic disorders, also called inborn errors of metabolism, refer to inherited conditions most frequently caused by enzymatic defects. Some metabolic disorders can be diagnosed by routine screening tests performed at birth and others are identified only after a child or adult shows symptoms of a disorder such as abnormal growth, vomiting, jaundice, increased size of the liver and the spleen, abnormal intellectual

development, unusual facial features, skin rash and other features. One example is the disease phenylketonuria. Due to a defective enzyme, children with this disease cannot process the amino acid phenylalanine. Without treatment, phenylalanine accumulates in the body and leads to intellectual disability. Many inherited metabolic disorders can be treated by dietary restriction or dietary supplements. Some metabolic disorders, such as Gaucher disease, Pompe disease or mucopolysaccharidoses, can be treated by enzyme replacement therapy. In some metabolic conditions, bone marrow transplantation can stop or reverse the progress of the disease.

Hereditary cancer syndromes. Most people who develop cancer do not have a genetic predisposition to cancer. However, some people are born with a gene mutation that puts them at a higher risk for cancer than other people. Approximately 5-10% of all cancers are hereditary. Individuals who inherit a genetic change in one of the cancer-related genes will have a higher likelihood of developing cancer within their lifetime. The most common type of hereditary cancer is breast and ovarian cancer caused by mutations in the BRCA1 and BRCA2 genes. Another example of familial cancer is hereditary non-polyposis colorectal cancer syndrome (HNPCC or Lynch syndrome). This syndrome is characterized by early onset bowel cancer and uterine cancer, as well as other cancers. Lynch syndrome is caused by mutations in several genes related to the repair of DNA. Reliable screening techniques have been developed in order to diagnose people carrying abnormal cancer-related genes. For persons who have a hereditary cancer syndrome, various options exist for either intensive screening or prophylactic surgery.

Reproductive problems. Reproductive disorders including infertility and recurrent pregnancy loss are diagnosed in 10-15% of couples of reproductive age. The causes or these disorders include anatomical, endocrine, genetic, infectious or psychological factors. Most frequently, fertility problems are not hereditary. However, genetic factors might serve as a contributing factor in some couples who experience infertility or recurrent pregnancy loss. In some instances, genetic testing might identify a genetic factor contributing to infertility. Identifying a genetic cause for infertility can help to choose the most appropriate infertility treatment. Knowing the cause of infertility may increase the chances of a successful pregnancy. Chromosomal abnormalities are relatively common genetic factors in human reproductive disorders, implicated in about half of early pregnancy losses. They may be structural (inherited translocations or inversions) or numerical (XO, XXY). Other genetic causes of infertility include microdeletions on the Y chromosome and cystic fibrosis.

Rare (Orphan) disorders. A disease is defined as rare in Europe when it affects fewer than 1 in 2000 persons and in the US when it affects fewer than 200,000 Americans. Over 6000 rare diseases exist; 80% of rare diseases have a genetic origin. Rare diseases are characterized by a broad diversity of clinical symptoms. The lack of sufficient scientific knowledge and information on rare disorders often results in a delay in diagnosis or initial misdiagnosis. The ongoing implementation of a more comprehensive approach to rare diseases has led to the development of public health policies in many countries. Such a policy is still not available in Israel. In the recent years efforts have been made to encourage companies to develop orphan drugs. In Israel, the Rare Genomics Institute-Israel has been established in order to support local Israeli patients with rare genetic diseases of unknown origin. Israel also has its national representative at Orphanet - the reference portal for information on rare diseases and orphan drugs.

What are the psychosocial impacts?

Having a genetic condition in the family is an emotional burden (McAllister et al. 2007). Several specific points related to the great psychosocial burden of having a genetic condition are listed below:

1. **Living without diagnosis**. Having an undiagnosed genetic condition is quite common. For example, about half of children with cognitive impairment have no definite genetic diagnosis. Frequently individuals with genetic conditions have a number of different problems that do not all fit into one specific recognized condition. Frequently parents feel disappointed and frustrated when the results of genetic testing do not provide any definite answers. Not having a diagnosis may make people feel out of control of the situation.
2. **Self-accusation**. Parents of children with genetic disorders are often worried that the birth of an affected child is their fault and look for explanations related to pregnancy, emotional status, diet or other factors.
3. **Need for psychological support to cope with the disease**. Adjusting to a genetic disease triggers many emotions such as resignation, helplessness, anger and frustration. After the diagnosis is confirmed, the main issue to cope with is the psychological burden of life-long treatment. In addition, psychosocial aspects include social difficulties in forming interpersonal relationships, achieving autonomy and attaining educational goals.

Who provides care for genetic/hereditary disorders and in what setting?

The Medical Genetics service in Israel offers clinical and diagnostic services relevant to the modern practice of medical genetics. Services are provided by medical geneticists and genetic counsellors working closely with other health professionals, molecular and cytogenetic laboratories and diagnostic imaging and departments of pathology. Medical Genetic services include the following:

- **Community Genetics Department at the Ministry of Health.** The department is responsible for operating the national newborn screening, promoting the broadening of the range of genetic services offered in the health basket, legalization of certain aspects in the genetic service, integration of genetics into public health, and collection of updated information on specific mutations and genetic disorders in Israel. Information collected by this department is available at The Israeli National Genetic Database web site http://server.goldenhelix.org/israeli/
- **Clinical genetics services**. Medical Genetics services are provided in genetic institutes in all major hospitals, as well as in ambulatory settings outside hospitals. These services aim at diagnosing genetic conditions and assessing recurrence risk for the genetic condition and providing recommendations for follow-up and treatment. Genetic counselling is given both by medical geneticists and genetic counsellors.
- **Specialized clinics**. Specialized centers for diagnostics and treatment of rare disorders provide multidisciplinary services for patients with specific genetic disorders.
- **Laboratory genetics services**. These diagnostic services are used for molecular and cytogenetic diagnostics of inherited diseases. Samples are referred to the laboratory from clinical genetics services. In Israel, genetic tests are performed in public and private genetic laboratories. Molecular pathology testing is provided in pathology departments in hospitals.
- **Preimplantation genetic testing.** This type of testing is widely available in several public hospitals.
- **Genetic screening services**. These services aim at genetic disease prevention in the general population or in specific populations in Israel. Guidelines for genetic screening are provided by Department of Community Genetics at the Israeli Ministry of Health. The list of diseases recommended for screening is available at the web site

http://www.health.gov.il/Subjects/Genetics/checks/screening-genes/Pages/default.aspx

Counselling regarding recommended genetic screening tests in most settings is provided by a specialized medical staff.

What are standard treatments and therapies?

Most genetic disorders can be treated only symptomatically; specific curative treatments are only rarely available.

Possible treatments for genetic disorders include:

- Surgery for birth defects
- Specific diet, hydration, acid-base management, elimination of toxic metabolites for inborn errors of metabolism
- Organ transplantation
- Bone marrow transplantation
- Enzyme replacement therapy
- Specific treatments for selected disorders
- Gene therapy
- Psychosocial management

What costs are associated with genetic/hereditary disorders?

Costs associated with genetic disorders have been estimated for several genetic conditions and are usually high. For example, it has been calculated that the lifetime cost of care for a cystic fibrosis patient is approximately US $300,000 in the United States (van Gool et al. 2013).

Costs associated with genetic disorders include:

1. Costs of recurrent hospitalizations and other medical as well as paramedical services.
2. Costs of non-genetic testing (muscle biopsy, magnetic resonance imaging, metabolic evaluations and many other standard medical testing procedures).
3. Costs of genetic testing. Recently, costs of molecular testing have decreased due to the development of high-throughput deep sequencing technologies. On the other hand, the demand for genetic testing has increased dramatically.
4. Costs of prenatal and preimplantation diagnosis, including costs of in vitro fertilization.
5. Costs of specific treatments. For some rare diseases specific therapies are available. Some of these therapies, e.g. enzyme replacement therapy, are extremely expensive and can cost hundreds of thousands of Euros per year.

What is the role of genetic services?

Diagnostics and prevention of genetic diseases

A. **Diagnosing genetic disease.** *Diagnostic testing* is used to confirm a diagnosis of a specific genetic disease caused by changes in genes or chromosomes. The results of a diagnostic test can influence a person's choices about health care and the management of the disease.

B. **Determining if a person is a carrier** of a mutation that could lead to disease in their children. *Carrier testing* is used to identify individuals who carry one mutated and one normal copy of a specific gene and 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 severe genetic disorders. If carrier testing is applied to specific population, this type of testing is called *carrier screening*.

C. **Predicting if a disease or trait that is not yet detectable by other medical tests may occur in the future.** *Presymptomatic testing* is offered to people who are healthy at the time of testing but have a family member with a genetic disorder that is not present at birth but develops later in life. This type of testing can determine whether a person will develop a genetic disorder before any signs or symptoms appear. *Predictive testing* is used to identify genetic changes that increase an individual's risk of developing a disorder with a genetic component, such as certain types of cancer, diabetes and other diseases. The results of predictive testing can provide information about a person's risk of developing a specific disorder and help with applying specific prophylaxis or treatment and making decisions regarding lifestyle. The terms presymptomatic and predictive testing can be used interchangeably.

D. **Providing a possibility to prevent the birth of a child with a severe genetic condition.** *Prenatal testing* is used to detect an abnormality in a chromosome or a specific genetic mutation in the fetus during pregnancy. Practically it is conducted using an invasive procedure such as chorionic villi sampling or amniocentesis, which are connected to higher risk (mainly abortion). This type of testing is performed if the parents are carriers of a specific genetic disease or there is a suspicion that the fetus might have a chromosomal abnormality due to an abnormal fetal ultrasound or maternal biochemical screening results. *Preimplantation genetic testing (PGD)* is used to detect genetic mutations in embryos at risk for a specific genetic condition in couples using in vitro fertilization. When one or both genetic parents have a known genetic abnormality, genetic testing can be performed to determine if the embryo(s) carries a genetic abnormality and only those embryos without the abnotmality are re-implanted. PGD provides an alternative to diagnostic procedures during pregnancy such as amniocentesis. It offers a good solution for preventing heritable genetic disease, thereby eliminating the dilemma of pregnancy termination following unfavorable prenatal diagnosis.

Patient Management and Creation of Guidelines

Management guidelines are aimed at specifically addressing genetic and non-genetic evaluation, conditions to consider in a differential diagnosis and diagnostic algorithms. A multidisciplinary approach is important for development of clinical practice guidelines for patient management. Guidelines usually include guidance on aspects of genetic diagnostics, genetic counselling, prenatal diagnosis and screening, functional assessment, nutritional management, therapeutics and coordination of care.

Education

One of the roles of medical genetics professionals is to address the educational needs of health professionals who are not genetic specialists. They also should provide guidance on educated use of genetic tests by non-genetic specialties. Educational activities include development of resources in order to support and spread the knowledge in medical genetics to medical students, health professionals and general public. Raising awareness of specific genetic conditions is important in expediting diagnosis and taking advantage of specific therapies.

Who uses genetic services? Where are the gaps?

Genetic services are an integral part of a multidisciplinary health care system. All genetic services including laboratory and clinical services should be standardized, accredited, and have a system of quality control.

Users of medical genetics services in Israel are:

- Women aged 35 and above, with pregnancies in which there are abnormal results in first trimester biochemical screening (nuchal translucency + PAPPA and free beta HCG) or in the second trimester biochemical screening - triple screening blood test (alpha fetoprotein, beta HCG, UE3), or in pregnancies with abnormal fetal ultrasound findings.
- Spouses or partners with tests (chromosomal or molecular) indicating a high recurrence risk in their offspring and seeking prenatal or preimplantation testing.
- Individuals with a genetic disorder/disorder in family members or in a fetus including birth defects, inborn errors of metabolism, neuromuscular disorders or any other known/suspected genetic disorders (e.g. cystic fibrosis, hereditary spastic paraplegia, polycystic kidney disease, Marfan syndrome, neurofibromatosis, tuberous sclerosis, Huntington disease, spinocerebellar ataxia, genetic skin diseases and any other genetic disease).
- Individuals who have family members with intellectual disability in the family.
- Individuals with a cognitive disability, including mental retardation.
- Individuals with infertility or recurrent pregnancy loss.
- Individuals with sensory impairments (blindness, deafness)
- Individuals with short stature or other skeletal dysplasias
- Individuals with suspected familial cancer syndromes.
- Individuals exposed to potentially harmful physical, chemical or biological factors in pre-, peri- and post-conception periods, including cancer survivors
- Consanguineous marriages/partnerships
- Individuals seeking advice with the interpretation of results of commercial direct-to-consumer genetic testing

Are high quality genetic services available and accessible?

Availability of services

- **Neonatal screening policy**. In Israel, all newborns are screened for nine rare metabolic diseases and two endocrine diseases. All activities related to these tests and quality control is carried out under the supervision of the Ministry of Health. The national newborn screening program covers all expenses for screening.
- **Prenatal screening for detection of fetuses with Down syndrome**. Israel has a state-administered prenatal screening program. Currently it includes integration of first trimester biochemical screening (nuchal translucency + PAPPA and free beta HCG) and the second trimester biochemical screening blood test (alpha fetoprotein, beta HCG, UE3) results. Amniocentesis is publically funded if the calculated Down syndrome risk is higher that 1:386. *Novel technologies for prenatal detection of Down syndrome such as NIPT (non-invasive prenatal testing) are still not governmentally funded.*

- **Genetic diagnostic and counselling services**. Genetic testing and medical genetic counselling of adults and parents of newborns and children. Counselling regarding congenital malformations diagnosed prenatally are available at genetics institutes in all major hospitals in Israel, as well as at ambulatory services outside hospitals. Invasive diagnostic procedures such as chorionic villous sampling or amniocentesis are available in all areas in Israel. *The main drawback of genetic counselling services in Israel is a long waiting list for genetic consultation; as a consequence, patients are forced to use private services instead of public services.*
- **Laboratory services.** Genetic testing is usually ordered by a medical geneticist or genetic counsellor. Available tests include testing for any known mutation prenatally or postnatally, chromosomal tests, chromosomal microarray, linkage analysis and sequencing of any gene. Many diagnostic genetic tests are reimbursed, including specific mutation testing, linkage analysis, or sequencing of a gene in a family, and chromosomal microarray in certain defined cases. Genetic testing abroad is possible and is reimbursed for patients if no laboratory in Israel performs the required testing. While public funding largely covers prenatal screening and diagnostic services, they have limitations on coverage. *The diagnostics of all highly heterogeneous genetic disorders (when mutations in two genes do not explain 90% of the cases of a specific disease) remain at a patient's personal expense. Modern diagnostic tests such as whole exome sequencing and multigene sequencing panels are not governmentally funded. As a consequence it is not possible to establish molecular diagnosis and to offer prenatal or preimplantation testing for a large proportion of individuals with heterogeneous Mendelian diseases.*
- **Genetic screening**. The Israeli Medical Genetics Association has published guidelines for preventive population genetic screening. These screening tests are provided at no direct cost to patients all over the country. Additional genetic screening tests are available but are partially funded by health service organizations and some are not funded at all.
- **Preimplantation genetic diagnostics**. This type of service is widely available in several hospitals and is financially covered by health service organizations according to defined criteria.
- **National centers specializing in diagnosis and treatment of specific disorders**. Several centers in Israel are recognized as providers of expert services in the field of rare genetic diseases. *For most genetic diseases there still are no expert centers.*
- **National disease registries.** Only a few registries are maintained in Israel, including a cystic fibrosis registry and a registry of genetic syndromes causing bone marrow failure. *However, there is no registry of patients with most genetic diseases in Israel.*
- **National mutation database**. This up-to date database for Israel is available at http://server.goldenhelix.org/israeli/
- **Education in Medical Genetics.** Four one-week courses for physicians on current developments in medical genetics take place at the Rabin Medical Center and at Tel Aviv University.

Recommendations

Our recommendations for improvement medical genetics services in Israel include:

- Expansion of a nationwide registry of hereditary disorders to more disorders.

- Creation of educational programs for health professionals on use of the new genomic technologies and to develop bioinformatics skills; development of education and adaptation of the society to meet the needs of patients with hereditary disorders.
- Integration of genomic medicine into mainstream practice by increasing funding for development of ambulatory medical genetics services.
- Development of specialized health care and management facilities for a larger number of hereditary disorders.
- Inclusion of funding for exome sequencing/multiple gene panel sequencing as a first tier diagnostic test for heterogeneous disorders in the health basket
- Recognition of increased time needed for genetic counselling sessions and interpretation of the results of genetic testing.

What genetic service delivery or policy issues do hereditary disorders highlight?

Ethical challenges. Stigmatization of people with genetic disorders and carriers of recessive genetic conditions might cause direct harm in certain population groups and act as barriers to the effective implementation of genetic services. Genetic testing and screening should be supported by genetic counselling. Decisions to participate in all genetic testing and screening programs should be voluntary. Individuals should be provided with clear information regarding specific genetic tests before undertaking the test. *Education is a key tool in reducing discrimination and stigmatization.*

Availability of novel genetic services and duty to recontact. Genetic counselling is a time-consuming and labor-intensive process due to the rarity of many genetic disorders, difficulty in establishing diagnosis in individuals with dysmorphic features and availability of novel high-throughput genomic technologies. As a result of progress in the medical genetics field, new indications for genetic testing and growing public awareness compromises the ability of genetics service providers to meet growing needs for counselling and evaluation is becoming increasingly challenged. Therefore, there is a need for increased funding of genetic counsellors and clinical geneticists. Duty to recontact patients may be considered if a new diagnostic test has been developed, if new information that may alter the prognosis or recurrence-risk estimates is available, or if new treatment is available. T*ime allocated for genetic consultation in most settings is too short in order to be able to update patients and their families on latest advances relevant to their disorder and to recontact former patients.*

Duty to distribute up-to-date knowledge in the field on medical genetics. Education about medical genetics for the public, medical and other health professionals is crucial in order to make the best use of genetic services. Close cooperation with patient and parent organizations can promote awareness on diagnostic and therapeutic advances of genetics. *Governmentally funded educational programs in new developments in the medical genetics field are lacking.*

Legal challenges. Legal protections should be undertaken to prevent genetic discrimination, which would occur if insurance companies or employers were to treat people differently because they have a gene mutation that increases their risk of a disease. Currently, there is a law in Israel regarding genetic information which in line with issues discussed above should prohibit any discrimination based on genetic information. *Sufficient information of aspects of genetic testing covered by this law is still not available to many medical professional as well as to individuals with genetic disorders.*

References

1. Hoyert DL, Freedman MA, Strobino DM, Guyer B. Annual summary of vital statistics: 2000. Pediatrics, 2001;108:1241–1255.
2. FitzPatrick DR, Skeoch CH, Tolmie JL. Genetic aspects of admissions to a paediatric intensive care unit. Arch Dis Child 1991;66:639–64.
3. Hall JG, Powers EK, McIlvaine RT, Ean VH. The frequency and financial burden of genetic disease in a pediatric hospital. Am J Med Genet 1978;1:417-36.
4. McCandless SE, Brunger JW, Cassidy SB. The burden of genetic disease on inpatient care in a children's hospital. Am J Hum Genet. 2004;74:121-7.
5. Dye DE, Brameld KJ, Maxwell S, Goldblatt J, O'Leary P. The impact of single gene and chromosomal disorders on hospital admissions in an adult population. J Community Genet. 2011;2:81-90.
6. Bensend TA, Veach PM, Niendorf KB. What's the harm? Genetic counsellor perceptions of adverse effects of genetics service provision by non-genetics professionals. J Genet Couns. 2014;23:48-63.
7. Maio M, Carrion P, Yaremco E, Austin JC. Awareness of genetic counseling and perceptions of its purpose: a survey of the Canadian public. J Genet Couns. 2013;22:762-70.
8. Henneman L, Vermeulen E, van El CG, Claassen L, Timmermans DR, Cornel MC. Public attitudes towards genetic testing revisited: comparing opinions between 2002 and 2010. Eur J Hum Genet. 2013;21:793-9.
9. Ropers HH. Genetics of early onset cognitive impairment. Annu Rev Genomics Hum Genet. 2010;11:161-87.
10. Shohat M, Frimer H, Shohat-Levy V, Esmailzadeh H, Appelman Z, Ben-Neriah Z, Dar H, Orr-Urtreger A, Amiel A, Gershoni R, Manor E, Barkai G, Shalev S, Gelman-Kohen Z, Reish O, Lev D, Davidov B, Goldman B. Prenatal diagnosis of Down syndrome: ten year experience in the Israeli population. Am J Med Genet A. 2003;122:215-22.
11. Berkenstadt M, Ries-Levavi L, Cuckle H, Peleg L, Barkai G. Preconceptional and prenatal screening for fragile X syndrome: experience with 40,000 tests. Prenat Diagn. 2007: 27:991-4.
12. Daniels M, Shohat T, Brenner-Ullman A, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. Am J Med Genet. 1995;55:311-4.
13. McAllister M, Davies L, Payne K, Nicholls S, Donnai D, MacLeod R. The emotional effects of genetic diseases: implications for clinical genetics. Am J Med Genet A. 2007;143:2651-61.
14. van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. Value Health. 2013;16:345-55.

This project has been funded with support from the European Commission:
Grant Agreement 544331-TEMPUS-1-2013-1-AM-TEMPUS-JPCR
This publication reflects only the author's view and the Agency and the Commission are not responsible for any use that may be made of the information it contains.