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# Genetic Services in Bulgaria

## Country Background: Demography, Geography, History

Bulgaria is a small Balkan country with a population of 8,427,000 and 75.9 people/km$^2$. Of the population, 67.2% is now urban; 18.15% of the population is under 15, 14.85% over 65 and 4.57% over 75. There have been 13 historic centuries of ascent and fall with continuous efforts to preserve national identity and independence. Remarkable economic and cultural progress had been achieved by the 9th and 10th centuries when the Cyrillic alphabet was invented and spread amongst other Slav countries, including Moravia and Russia. In 1878, Bulgaria became once more an independent country after five centuries of Turkish rule. During the following 66 years of relatively democratic development, Bulgaria showed substantial progress in economy, culture and education. In 1944, at the end of World War II, the Communist Party came to power and for 50 years Soviet communism dominated Bulgaria, resulting in isolation from world development. After the dramatic changes in eastern Europe in 1989, Bulgaria is now in a state of transition to a democratic society, trying to give priority to human rights, private initiative and a market economy. However, economic changes are very slow and the country has been in continuous crisis over the last few years, with a high inflation rate (35% in 1995), high unemployment (14.7% in 1995), and a decreasing annual income and worsening demographic situation. The country is ruled by a directly elected President and a one-chamber National Assembly with 240 members. The Socialist (former Communist) Party government as a result of its incompetent economic and political behaviour resigned in February 1997 under the pressure of mass peaceful demonstrations and protests. There is now a clear social orientation and demand towards a policy aiming at new integration into the European political and economic structures.

## Organisation of Health Care

The formerly highly centralised state health care system is being abandoned and replaced with decentralisation of medical care and restoration of private medical practice. However, the major disadvantage of the state health care policy in the last few years has been delay in establishing a health insurance system, although several projects have been proposed. The majority of medical services and professionals are paid from inadequate resources from the central budget and the quality of medical care has decreased. Medical professionals, especially younger ones, lack motivation and patients are losing confidence.

*Primary Care*

Primary care is provided by field medical professionals (doctors, nurses, midwives) working in city polyclinic departments (internal medicine, surgery, obstetrics, paediatrics, ophthalmology, oto-rhino-laryngology) and in village medical services. Primary care in state medical services is free of charge and accessible to all patients, regardless of ethnic or religious group. Many private medical services have appeared recently in cities, and are supposed to provide better-quality medical care and are paid for by the patients. The education of specialists in family medicine started several years ago.

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**Table 1.** Medical genetics staff in Bulgaria

| RGC | CGU | SGCU | Population | Medical | Scientific | Co-Workers |
|---|---|---|---|---|---|---|
| 5 | 20 | 3 | 8,427,000 | 90[a] | 36 | 28 |

[a] 90 is the number of all staff working in the genetic services of the country including specialists in medical genetics, but also doctors in training, nurses and midwives. There are 26 doctors with a recognised specialty of medical genetics.

## History of Medical Genetics

During most of the Communist period there was almost complete ignorance of modern genetic theory and practice. Although the development of medical genetics had been strongly inhibited for several decades, the acceptance by society of new approaches for genetic diagnosis and prevention is surprisingly good.

## Dimension 1: Availability

According to the National Program for Genetic Prevention (1986), approved by the Ministry of Health, specialised genetic services have been organised at several levels. The range of activities and the quality of the genetic services varies considerably depending on the qualification and experience of staff and availability of modern equipment.

*Regional Genetic Centres (RGCS)*

These are based in five university cities – Sofia, Plovdiv, Varna, Pleven and Stara Zagora, with their respective medical faculties. Each covers, on average, a population of 1.7 million. For example, genetic services in Sofia are provided by the Section of Clinical Genetics, Chair of Medical Genetics and Laboratory of Molecular Pathology, involved in pre- and postnatal diagnosis of chromosomal abnormalities, single-gene disorders and other genetic diseases by clinical, cytogenetic and biochemical/molecular methods.

*District Clinical Genetics Units (CGUs)*

Each of the 20 CGUs is located in a large district hospital and includes a physician and a nurse or midwife.

*Specialised Genetic Counselling Units (SGCUs)*

Three SGCUs are found in the Departments of Ophthalmology in Sofia and Stara Zagora and Oto-rhino-laryngology in Sofia.

The basic staff and activities data for the country are given in table 1.

*Number of Genetic Counselling Clinics, Frequency and Patient Numbers per Year (Whole Country)*

There is one in-patient clinic with 16 beds which has 380 admissions per year including postnatal diagnosis and management of patients with dysmorphic syndromes and metabolic disorders. Twenty-nine out-patient clinics deal with the following number of referrals: 20 with up to 100 families per year, 7 with 100–300 families per year and 2 with more than 500 families per year.

*Number of Cytogenetic Laboratories and Number of Samples per Year*

Six regional cytogenetic laboratories do around 2,700 blood tests a year. Three specialised cytogenetic laboratories are attached to the Institute of Endocrinology, the Institute of Oncology and the Central Military Hospital. Three district cytogenetic laboratories exist but they perform less than 100 tests a year and are not considered adequately qualified. There are no officially registered and licensed private genetic laboratories.

The detectability of chromosomal abnormalities (1993) was 53% – 211 affected patients diagnosed out of 400 expected in 80,000 newborns. There is a relatively low efficiency of cytogenetic testing with only 1 positive test out of 13 performed. This is probably associated with insufficient basic knowledge of medical genetics amongst primary health care physicians. Laboratories using more precise clinical indications for postnatal cytogenetic diagnosis have achieved better efficiency, approaching 1:8–1:10. In situ hybridisation is in the process of being introduced into research and services of the cytogenetic laboratory of the Section of Clinical Genetics.

*Number of Molecular Genetics Laboratories and Number of Samples per Year*

The Sofia genetics laboratory performs 60–200 postnatal and 15–20 prenatal tests per year. The same laboratory

is involved in post- and prenatal diagnosis of metabolic disorders, including mass screening for PKU and galactosaemia in 65,000 newborns (80% of all newborns) and selective screening in 700 patients, detecting on average 20 new affected patients a year. Mass newborn screening for congenital hypothyroidism is carried out in a separate laboratory in the Paediatric Endocrinology Department and Paediatric University Hospital. Both screening programs, for metabolic disorders and congenital hypothyroidism, use the same dry-spot samples.

Genetic centres work in close co-operation with each other and exchange diagnostic and scientific information, take part in the meetings of the Society of Human Genetics and the annual meetings of Clinical Genetics. The Genetic Centre in Sofia is the largest and most experienced, and helps the other centres by consulting on complicated cases, providing biochemical and DNA testing, teaching young geneticists, and facilitating the supply of consumables and equipment.

### Dimension 2: Access

Genetic services are financed directly or indirectly by the state. Genetic centres are attached to medical faculties which are funded by the Ministry of Finance. CGUs are funded by the local municipal budget for district hospitals. The cost of some standard procedures (in US$) are:

| | |
|---|---|
| newborn screening for PKU | 0.16 |
| newborn screening for congenital hypothyroidism | 2 |
| selective biochemical screening | 21 |
| sex chromatin | 17 |
| postnatal cytogenetic testing | 105 |
| prenatal cytogenetic testing | 200 |
| prenatal DNA testing | 40–200 |

As a rule, the money from the state is insufficient and most funding for consumables and new equipment comes from other sources, including e.g. international organisations, research projects and private sponsors. Counselling and testing are free of charge to the patient and genetic services are in practice accessible. However, the referral rate does not exceed 50%, comparing the estimated annual needs and registered primary visits. There were about 4,000 primary visits in 1993 although we have calculated the annual requirement for genetic counselling as approximately 8,000 primary visits based on the annual number of births (80,000 in 1993), the proportion of pregnant women over 35 years of age (3.7%) and the incidence of chromosomal abnormalities, neural tube defects, mental retardation in children and other relatively common genetic disorders. All medical professionals are allowed to refer patients to CGUs and genetic centres and about 10% of families are self-referrals. Access for families is limited by the lack of genetic knowledge of non-geneticist doctors. Primary care is not favourable to genetics because of poor undergraduate education and training of medical professionals in medical genetics. This is the main reason for the decision to organise CGUs at the district level, where they can act as mediators between the primary health care services and RGCs. These small units, consisting of a clinical geneticist and a nurse or midwife are intended to collaborate closely with various field specialists, collect and register new families, provide genetic information in simple cases and refer patients and families to the RC or elsewhere. In addition, CGUs take part in the registration of congenital anomalies in newborns and other screening programmes, functioning as a community genetics service. The CGUs have been organised in smaller non-university cities and could play an important role in the field of genetic diagnosis and prevention. Their efficiency generally depends on the qualification of staff and the support of local health care authorities.

The abortion law allows interruption of pregnancy, regardless of the gestation age in any case of proven severe fetal abnormality inconsistent with life e.g. anencephaly and thanatophoric dysplasia. In less severe cases, abortion is not permitted beyond the 26th week of gestation. There are no restrictions of religious or any other kind regarding prenatal diagnosis and selective abortion, which are accepted by almost all religious and ethnic communities.

There are no specific geographic features limiting access except in small villages distantly located in the mountains.

### Dimension 3: Life Sustaining

*Vital Statistics (1994)*

There were 9.4 births per 1,000 with a fertility rate of 1.37 children/woman, 0.63% annual fertility reduction and 13.2 deaths per 1,000. The infant mortality rate reached 13.8% in 1988 but was influenced unfavourably by a severe economic crisis and rose to 16.3% in 1994 due mainly to respiratory disorders, prematurity and congenital anomalies. Life expectancy is 67.2 years for men and 74.8 years for women. The trend over the last few years clearly shows ageing of the Bulgarian population and the most negative annual growth in Europe due to a low birth rate, high infant mortality rate and emigration of young people.

*Genetic Prediction of Disease Susceptibilities*

Because of the limited use of molecular methods, predictive medicine is still in a very early phase of development. From the experience with families with cystic fibrosis, β-thalassaemia, adult polycystic kidney disease and Huntington disease it is clear that most patients prefer to use their 'right to know' the risk of developing a disease or of having affected progeny. The experience is not yet sufficient for definite conclusions concerning the general attitude to presymptomatic diagnosis and lifestyle modification in genetically susceptible individuals. There is no well-developed cancer genetics services network. Two laboratories in Sofia are involved in cancer cytogenetics service and research. In one of them, the chromosome 14 marker and translocation 8;14 in Burkett lymphoma were observed and reported in 1972 and 1979. Cancer family clinics do not exist. Molecular methods have not yet been used for diagnosis and research in cancer.

## Dimension 4: State of the Art

The speciality of Medical Genetics was officially recognised in 1985. Specialist status is reserved for medical doctors who have had 4 years of clinical practice, have attended a 3-month specialised course in the University Department of Medical Genetics in Sofia and have successfully passed the state exam. Laboratory specialists (cytogeneticists, biochemists and molecular geneticists) obtain professional training and experience working in appropriate laboratories in a genetic centre, but there is no officially recognised accreditation/assessment of training for laboratory specialists. The same is true for the training of the genetic nurses and midwives: there are no genetic associates or non-medical counsellors in the genetic services of this country.

Remarkably, genetics was first taught to medical students in 1919 when the Medical Faculty in Sofia was founded. Medical students are now taught genetics in the third year in the Department of Medical Genetics of the medical faculties. The medical genetics course consists of a total of 56 h, 28 h of lectures and 28 h of seminars, devoted to the main problems of medical/clinical genetics. Some information on clinical genetics (8 h) is given to medical students in the fifth year in the paediatrics course.

At the postgraduate level, lectures on clinical genetics are an integral part of the teaching programs of 3-month general and short-term specialised paediatric and obstetric courses. An intensive course of molecular biology for teachers from the medical faculties in Sofia and Plovdiv was organised by the TEMPUS programme in January 1995. The idea was to provide basic molecular genetic information to lecturers from different departments and specialities in order to help them teach their students. The first results were considered to be very good and this experience will possibly be extended further in the same and other medical faculties.

From the beginning of 1996, a 16-hour lecture course was incorporated into the curriculum of the School for Nurses and Midwifes in Sofia on the last year of their education.

## Dimension 5: Non-Harmful

The legal basis of genetic prevention is poorly defined and, for instance, prenatal sex selection is not prohibited by law. Families irrespective of social class may consign handicapped children early in life to special homes without expert information concerning the primary defect and prognosis. Thus, a recent report from the Society for Children's Defence of the Trade Union, 'SUPPORT' showed that only 2,000 out of 30,000 children living in special homes have no identified families. These and other examples suggest that genetic prevention needs appropriate legislation to establish the rights and responsibilities of the affected individuals, individuals' relatives, professionals and the state. The basic concept of the Bulgarian Society of Human Genetics regarding genetic prevention is that it must be recognised as a priority field of the health care system of the country, together with cancer, cardiovascular disease and environmental medicine.

For cytogenetic, enzyme and DNA analyses there is obligatory internal laboratory quality control. All methods used for mass and selective screenings are under international control. For mass screening, the Japanese interlaboratory quality control system is used. For amino acids, organic acids and other metabolites, the European Research Network for evaluation and improvement of screening, diagnosis and treatment of inherited disorders of metabolism (ERNDIM) is involved.

All patients' details of both clinical and laboratory examination are protected in computerised files access to which is limited and strictly controlled.

### Dimension 6: Effectiveness

For the majority of families at increased genetic risk, the most desirable outcome is the birth of a healthy baby or the adoption of a normal child. The attitude to affected fetuses is strongly negative and selective abortion is generally well accepted. The prevention of genetic disorders is achieved by the following main approaches.

Mass ultrasound screening of pregnant women is in use in many maternity hospitals but, as a rule, is not of high quality, with a relatively high percentage of false-positive and false-negative results. The efficiency of the method is much better in genetic centres whose ultrasonographers provide ultrasound expertise in suspected cases of congenital heart disease, skeletal dysplasias, craniofacial, renal and gastrointestinal fetal anomalies.

Non-invasive and invasive prenatal diagnosis are of limited value for population needs. For individual patients and using carefully designed indications and skilful practitioners, invasive prenatal diagnosis (amniocentesis, chorionic villus biopsy or cordocentesis) are considered acceptably safe and reliable. The overall risk for amniocentesis has been estimated at 0.3% with only 2 false positive in 2,311 tests. Unfortunately, only 8–10% of pregnancies at increased risk are currently being tested invasively and the main problem is under-referral. For instance, 600 pregnancies have been tested because of advanced maternal age over the last 12 years. The *annual* number of pregnant women at age above 35 exceeds 2,000. The same situation is observed in neural tube defects where only 550 pregnancies have been tested during the last 12 years although there are 150 new affected conceptuses each year. Prenatal diagnosis has not yet reached substantial demographic efficiency although it is of great importance for the individual family.

There is mass newborn screening for PKU, galactosaemia and congenital hypothyroidism.

Registration of congenital anomalies (RCA) in newborn babies has existed since 1985. From the beginning of 1996, a registry for the region of Sofia has functioned according to the recommendations of EUROCAT. The first results convincingly show this type of RCA is an effective method for early diagnosis and prevention of genetic defects.

### Dimension 7: Consumer Satisfaction

There are no published reports on consumer satisfaction. Several active and influential patient organisations have appeared in recent years. These include the PKU Society, Cystic Fibrosis Society, Bulgarian Association of Mental Retardation and the Autism Society. There is no 'umbrella' organisation.

### Publications Related to Genetic Services


1 Annual Reports of the Genetic Centres, 1993.
2 National Health Care Strategy, Program of the Ministry of Health, 1995.
3 Statistical Handbook, National Institute of Statistics, Sofia, 1995.
4 Health Care System, National Institute of Statistics, Sofia, 1996.
5 Manolov G, Manolova Y: Marker band in one chromosome 14 from Burkett lymphomas. Nature 1972;237.
6 Manolova Y, Manolov G, Kieler J, Levan A, Klein G: Genesis of the 14q+ marker in Burkett's lymphoma. Hereditas 1979;90:5–10.
7 Simeonov E, Hadjiev A, Kincheva V, Liharska K, Brankova M, Nikolov V, Vassileva J: Invasive prenatal diagnosis of genetic defects. Paediatr Sofia 1993;1:27–30.


### Bulgarian Society for Human Genetics


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### Validator

Prof. P. Boyadjiev, MD, PhD
Deputy Minister of Health of Bulgaria:

'The demographic situation as well as organisation of medical care and genetic services are presented objectively. Obviously, a lot is to be done in the future in the field of genetic prevention both from an educational and organisational point of view. Many ideas from the chapter will be taken into consideration in the process of updating the National Program for Genetic Prevention by the present and future Bulgarian Governments. Some financially dependent improvements are impossible at the moment, but the right ideas will be accomplished step by step in the future. The broader application of molecular methods for post- and prenatal diagnosis of genetic defects and genetic predisposition in both rare and common disorders is to be mentioned first amongst them.'