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Genetic Services in Russia

Country Background: Demography, Geography and Infrastructure

Russia has a population of around 149,000,000 with 73% of inhabitants living in urban areas and 27% in rural areas. Even after recent changes, there is still a gigantic land mass totalling 170,754,000 km^2 with an average population density of less than 0.8 people/km^2 although the European part has a population density tenfold that of the Asian. Russia is inhabited by more than 150 different nationalities and ethnic groups. Because the population is so heterogeneous there are great problems resulting from the geographical distribution of genetic diseases and the most efficient ways of dealing with them. There are commensurate opportunities for studies of genome diversity, mutation dissemination and allelic polymorphism.

Health Service Setting

The state budget is not yet approved by the Duma (Parliament). Expenditure on health care is estimated as being only 10–20% of what is actually needed and it is not surprising that funds are inadequate to meet all medical care needs. Officially, all basic funding is the responsibility of the Ministry of Health, which in practice covers no more than 50% of medical care in most medical institutes, clinics and central hospitals. However, the management of health care facilities is largely decentralised and the system is about 80% financed by local and regional taxes with significant funding of regional medical care provided by the relevant regional or city health service departments. Other potential funding sources such as the health insurance system and sponsorships are still in their infancy in Russia. Unfortunately, because of the extreme disproportion between population demands in health care service and its actual official financial situation, more and more medical care facilities both for outpatients and even for in-patients are being charged to the patient.

In 1993, there were 666,500 doctors of all specialities, including dentists, with an average of 45.2 doctors and 129.4 beds per 10,000 population. Roughly half of all medical doctors in the country are GPs. However, primary care is provided by physicians (therapists) or paediatricians working in polyclinics serving defined areas in the cities or countryside for providing home service. GPs as family doctors are still uncommon, though the training of such generalists has now begun in Moscow and in St. Petersburg.

History of Medical Genetics

The history of medical genetics in Russia begins in the Institute of Medical Genetics founded in Moscow by Professor S.G. Levit in 1932. The Institute studied the genetics of common disease (e.g. asthma, diabetes mellitus), twins and population genetics and began to study medical genetic consulting services. In 1934, the first medical genetic clinic was established by the outstanding scientist and clinician Professor S.N. Davidenkov in St. Petersburg

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(Leningrad). He organised a clinic for hereditary neurological disorders and, for the first time in the world, introduced genetic counselling with trained nurses for visiting and primary counselling of high-risk families. Unfortunately, the successful start of medical genetics in Russia was blocked in the mid-1930s when all medical genetic investigations were officially proclaimed eugenic and racists. This era directed by T.D. Lysenko had devastating consequences for genetics as a whole, and for its medical branch in particular. A gradual recovery of medical genetic began in 1961 when the first medical genetics laboratory was revived by S.N. Davidenkov in St. Petersburg and the first Institute of Medical Genetics was established in Moscow. Genetic counselling was introduced into the health care system and the number of clinics increased gradually. In 1990, the Institute of Medical Genetics was converted into the Research Centre of Medical Genetics, being subdivided into the Institute of Human Genetics and the Institute of Clinical Genetics. Another Institute of Medical Genetics was founded in Tomsk in 1985 and other institutes have become involved in medical genetic studies. Clinical genetics was recognised in Russia as a separate medical speciality in 1988.

Medical Genetic Service Setting

Medical genetic services are provided by 600 genetically trained physicians, including 300 working as genetic counsellors, 105 biochemists/molecular geneticists and 190 cytogeneticists. According to official figures, the recommended establishment has been achieved as follows: 80% of the number of genetically trained physicians, 94% of biochemists and molecular geneticists, 82% of cytogeneticists and 70% of genetic nurses and technicians. As a branch of general health care, medical genetic services are hierarchical and territorial with several levels. Top policy is co-ordinated by the Advisory Committee (Consulting Board) on Medical Genetics of the Department of Mother and Child Care in the Ministry of Health. The committee, which includes 18 of the most eminent specialists in medical genetics, determines the strategy for medical genetic services, medical genetic education, distribution, policies on prenatal and postnatal screening. Federal medical genetic registers are permanently under the consideration of the Committee. The second level is represented by seven Federal Medical Genetic Centres (FMGCs, five in Moscow, one in St. Petersburg and one in Tomsk). Each FMGC was established in a pre-existing medical genetic clinical/scientific institute. FMGCs concentrate on the molecular diagnosis of monogenic disorders (mutation identification, allelic polymorphism) as well as detailed cytogenetic analysis of complicated chromosomal rearrangements both in prenatal subjects and in high-risk families. Laboratory investigations are linked to specialised clinical practice in medical genetics. The next level of medical genetic services is provided by ten Regional (interregional) Medical Genetic Centres (RMGCs) located mainly in the 'European' part of the country. RMGCs deal with all types of prenatal diagnosis (not including molecular diagnosis), maternal and newborn screening programmes and Regional Genetic Registers. The base of the medical genetic pyramid is made up of the local medical genetic consulting services in almost 70 units distributed throughout the country, located in the relevant paediatric clinics and polyclinics. Primary genetic consulting and ultrasonographic examinations are carried out in these units.

Dimension 1: Availability

All medical genetic services in Russia are mandated by the principal circular n316 issued by the Ministry of Health on December 12, 1993 ('On the Further Development of Medical Genetic Service in the Russian Federation'). Regulations govern diagnosis at each medical genetic level, the interrelationships between different levels, and the types of diagnostic procedures and basic equipment. A revised version of this circular is now being prepared.

A flow of information occurs both upwards and downwards through the medical genetic pyramid. Genetically handicapped children and all families at high risk of inherited disorders are registered at all levels of the medical genetic service and placed on the relevant local computerised registers of the RMGC and in some instances of the FMGCs which are also responsible for DNA databanks of patients and the families with genetic disorders. Since 1987, a National Register of Chromosomal Disorders has been set up at the Institute of Medical Genetics in Moscow. This includes information on all cases of chromosomal aberrations studied in detail throughout the country. There are many congenital malformation registers throughout the country but these are not linked in a national register. There is work in progress to develop a computerised network because the lack of such a net is believed to reduce significantly the effectiveness of medical genetic services in Russia.

Although routine in European Russia, the availability of newborn screening for PKU and hypothyroidism varies in other parts of the country.

The availability of genetically trained physicians and trained genetic laboratory staff is also very uneven. Molecular genetic services are chiefly concentrated in Moscow and St. Petersburg but are spreading to include other medical genetic centres in Tomsk and Novosibirsk. Genetic counselling and ultrasound examination are available in all genetic centres throughout the country. Invasive sampling and cytogenetic analysis of the fetus are routinely carried out in all Regional and Interregional Medical Centres.

Free (self-determined) abortion up to the end of the 12th week of pregnancy is legally permitted while certain social indications are accepted up to the 22nd week. Restrictions on termination for medical indications are covered by circular n32 ('List of Medical Indications for Artificial Termination of Pregnancy') which states that all fetuses with 'inborn pathology, ascertained prenatally, may be subjected to (artificial) termination irrespective of gestation age'. This regulation is regarded as confusing and in fact most terminations of pregnancy for fetal malformation or inborn disorders are carried out before the 26th week of gestation. Prenatal diagnosis is sometimes used in the third trimester of pregnancy to provide information for obstetricians planning labour strategy and for making decisions on surgical operations on inborn defects after the birth.

There are no official guidelines on indications for prenatal diagnosis and in practice physicians conform to international practices as reported in the literature. However, manuals for medical genetic staff are approved by the Advisory Committee on Medical Genetics at the Ministry of Health and include guidelines and technical descriptions for e.g. cytogenetic analysis, fetal karyotyping and cystic fibrosis (CF) testing.

Ultrasound examination is available throughout the country as over 1,000 ultrasound units of high resolution are already required. Ultrasound examinations are carried out at least twice for most pregnancies. Screening for maternal marker serum proteins (AFP, hGC) is available in many centres but is still far from becoming routine.

Invasive fetal sampling is carried out in many RMGCs and in all FMGCs and includes chorionic villus sampling (CVS) (first trimester), placental biopsy (second trimester), amniocentesis and cordocentesis. Fetal karyotyping is carried out either on direct preparations of CVS or on cell cultures (amniocytes, fetal cord blood lymphocytes) and the decision is made by each centre. Thus the FMGCs of St. Petersburg and Moscow use direct chromosome preparations with differentiation Q-banding supplemented with fetal blood sampled lymphocyte cultures of all ambiguous or chromosomally abnormal cases. CVS or amniocyte cultures are routinely used in other Medical Genetic Centres in Russia.

FISH techniques are used only in the FMGCs in Moscow, St. Petersburg and Tomsk. In the St. Petersburg FMGC, this technique is used for chromosome X, Y, 13, 18, 21 interphase counts and for marker chromosome identification.

Molecular diagnosis is limited to three of the seven FMGCs where it is used for the prenatal diagnosis of about 20 monogenic diseases.

Dimension 2: Access

Officially, all health care systems in Russia, including medical genetic services, are free of charge and so far they remain mostly cost free for all families at high risk of genetic or chromosomal disorders. Prenatal diagnosis of inherited diseases and inborn malformations is usually free of charge. The impact of health insurance systems on the funding of medical genetic services is impossible to estimate at present. Some private laboratories for genetic testing have already appeared.

Patients are generally referred to medical genetics not by GPs but by specialists (e.g. cardiologists, pulmonologists, oculists). Initial care for pregnant women is provided by obstetricians in maternal consultation who can refer women to genetic centres for further investigations and counselling.

The most important factors limiting access to genetic services in Russia are as follows:

difficulties in funding efficient biochemical screening of newborns;

difficulties in funding marker serum protein screening in pregnant women;

lack of a federal computerised register of inherited diseases;

inadequate general quality of medical genetic consultations;

low educational level of patients concerning genetics and poor public awareness of genetic services;

poor co-ordination amongst laboratories and amongst clinical geneticists;

poor networking for rare disorders;

poor organisation of referrals by physicians to genetic services due to ignorance of physicians – general practitioners are not educated as they are in some western European countries;

genetic services are good only in some areas.

Dimension 3: Life Sustaining

The birth rate is declining from 1,379,000 in 1993 to about 1,000,000 in 1995. Life expectancy is also falling and is now 59 years for men and 72 for women. The infant mortality rate varies widely in different parts of Russia from 7.5 to 25 per thousand. Mean maternal age is estimated to be 28.5 years with a trend to an increasing proportion in the over 35 and under 17 age groups in 1995.

There is very little testing for cancer susceptibility genes and it is provided commercially. Cancer family counselling by oncologists trained in medical genetics is provided in special oncological centres and dispensaries.

Dimension 4: State of the Art

Genetics is recognised as a medical speciality. The position of genetic counsellor is usually occupied by medical doctors trained in genetics and having a good clinical background as paediatricians, gynaecologists, and less commonly neurologists or internists. University biology graduates might be recruited by Medical Genetic Centres for specific molecular, biochemical or cytogenetic diagnosis.

Basic education in medical genetics is provided for students in all medical schools. This includes courses in cell biology and general genetics with approximately 30 h of lectures in human and clinical genetics during the 1st year. Four chairs of medical genetics have recently been established in Moscow, St. Petersburg and Tomsk with special emphasis on medical genetic input to clinical disciplines.

There are two primary training programmes, one for clinicians and one for scientists. Each lasts 7 months and they have common elements such as basic knowledge in general and medical genetics. Oral and written exams follow and last 2 days. Shorter periods of training are recommended for genetic counsellors every 3rd year. A special Department of Medical Genetics of the Russian Medical Academy for Postgraduate Study (Moscow) is authorised by the Ministry of Health to oversee postgraduate study by genetic counselling unit specialists. There are two additional postgraduate departments of Medical Genetics, one in St. Petersburg and one in Moscow.

Programmes of education for students and physicians are officially approved and co-ordinated. However, evaluation of training in clinical genetics remains unsatisfactory and teaching of genetics to medical students, training in genetics for physicians, training in molecular technology and the availability of up-to-date laboratory equipment are of reasonable standard only in some. Teaching of genetics to nurses is inadequate.

Considerable efforts are made to stimulate interest in genetics and to provide appropriate information. For example, there are seminars for practitioners, TV and radio programmes, close contacts with patient organisations, and lectures for students. Information on developments in medical genetics nationally and internationally is given in regular reports from the Advisory Committee on Medical Genetics in the *Bulletin of the Interregional Society of Medical Genetics.*

There has been a drastic decline in funding. The most conspicuous progress was made in molecular diagnosis of inherited disorders under the aegis of the State Programme for the Russian Human Genome Project. Sadly these resources are also exhausted.

Dimension 5: Non-Harmful

There is currently little legislation regulating genetic testing and gene therapy. However a state law on genetic engineering was approved on June 5, 1996 and laws concerning IVF, investigations of eggs and embryos, preimplantation testing and gene therapy are being prepared.

External quality control for medical genetics does not yet exist. Legislation for certification of diagnostic activity and screening programmes is now being developed by the Advisory Committee on Medical Genetics.

Medical institutes, hospitals and centres have established their own ethical committees. Ethics in medical genetics have been discussed in the Research Centre for Medical Genetics in Moscow (Prof. V.I. Ivanov) and have included ethical questions arising from the new genetics. Reports have been produced on a number of issues including presymptomatic diagnosis of severe monogenic disorders (Huntington disease, Alzheimer's disease), preclinical testing for mental and oncological diseases, prenatal diagnosis, gene therapy and genetic screening.

Although there is no specific legislation, all genetic information on patients is treated as strictly confidential.

Dimension 6: Effectiveness

It is notoriously difficult to measure the effectiveness of medical genetic services which also overlap with the work of other specialists involved in the management of genetic disorders. The simplest measure is the effective-

ness of prenatal diagnosis, although accurate estimates of the impact of prenatal diagnosis are not yet possible. Nevertheless the incidence of children with Down syndrome born to women over 35 has decreased to some extent in the 'European' part of the country, especially in Moscow and St. Petersburg.

Basic Results of Medical Genetic Services

However, the results of surveys of medical genetics services in Russia in 1994–1995 were discussed at the State Workshop in April 1996. Some of the main findings were as follows.

(1) Medical genetic consultations are free of charge at all levels of medical genetic service in the country.

(2) 797,333 families were referred to medical genetic centres – 81.9% by physicians and the remainder was self-referrals. 78,758 families requested repeat consultations.

(3) Cytogenetic diagnosis is routinely available throughout the country and 23,000 karyotype analyses were performed with chromosome abnormalities identified in 9.65%.

(4) Of all newborns in the country, 74.7% were subjected to PKU screening in 1994 and 54.3% were screened for hypothyroidism. Selective screening for other inborn metabolic defects was accomplished in only 21,509 newborns.

(5) In 1995, 288,956 pregnant women requested prenatal diagnosis from a total of about 1,000,000 pregnant women in 60 geographical regions of Russia. Of these, 73% had a detailed ultrasonographic examination, 52.4% were screened for maternal serum marker proteins (usually AFP and hGC), while only 0.55% (1,590) were sampled for fetal karyotyping and molecular diagnosis of monogenic disorders, 440 in the FMGC of St. Petersburg. In 3.6% of all sampled fetuses, serious abnormalities were found, 0.72% chromosomally abnormal and 2.6% malformed.

(6) During the nine years 1987–1996, the prenatal diagnosis service in north-west Russia investigated 46,276 out of 4.5 million pregnancies registered in the region. 31,210 women had ultrasound examinations resulting in 912 fetuses with severe malformations (2.9%). Selective biochemical screening for neural tube defects was carried out in 12,140 women detecting malformations in 77 fetuses (0.6%). Karyotyping of 2,467 fetuses resulted in identification of 55 (2.2%) with aneuploidy, 30 with trisomy 21. Molecular diagnosis of 459 samples detected 148 fetuses with monogenic diseases.

(7) The FMGC in Moscow (Research Institute for Medical Genetics, Prof. Tatyana V. Zolotukhina) performed ultrasound screening in the second trimester of pregnancy in 7,500 cases detecting 217 fetuses with abnormalities, 16% with chromosomal aberrations. A total of 188 high-risk pregnancies were identified by maternal serum screening (double test) of 2,550. Subsequent sampling revealed chromosomal aberrations in 33 fetuses (17.5%). 950 chordocenteses and 538 CVS were performed in 1990–1995, detecting aneuploidy and structural chromosomal aberrations in 81, including 19 fetuses with trisomy 21; 19 fetuses with chromosomal mosaicism were detected.

Although the actual impact of prenatal diagnosis services on malformation and perinatal death is still difficult to estimate accurately in Russia as a whole, the efficiency of medical genetic services is already beyond doubt.

Dimension 7: Consumer Satisfaction

The option to have prenatal diagnosis has undoubtedly encouraged parents in high-risk families to start pregnancies. This appears to be true for CF, Duchenne muscular dystrophy, PKU, haemophilia A and B and others and also for women at high risk of chromosomal disorders.

There are several patient organisations and association of physicians and parents including the Invalids Association which is the most prominent sponsor of medical genetic services in Russia. Others include the CF Association, the Association of Blind People, the Association of Parents of Children with Neuro-Muscular Disorders and others. There are many articles in the lay press, TV and radio programmes and public lectures. The public response is paralleled by an increasing number of prenatal diagnoses.

Publications Related to Genetic Services

1 Bulletin of Inter-Regional Society of Medical Genetics (in Russian), 1995, 1996.
2 Basic Methods and Organisation Principles in the Prevention of Severe Inherited Disorders. Moscow, Federal Workshop, April 24–26, 1996.
3 First All-Russia Conference in Medical Genetics. Abstracts. Moscow, December 14–16, 1994.

Russian Society for Medical Genetics

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'As a director of the Institute of Medical Genetics and as a Member of Advisory Board on Medical Genetics at the Ministry of Health I am pleased indeed to be a validating authority for the chapter 'Genetic Services in Russia' submitted to CAGSE reports. The Report 'Genetic Services in Russia' is composed by the well-known specialists in medical genetics, that is by Professor Vladislav S. Baranov (St. Petersburg) and by corresponding member of Academy for Medical Sciences, Professor Eugene Ginter (Moscow) responsible for medical genetic services in North West Russia and in the Central Russia, respectively. Herein I do confirm the validation of this chapter as CAGSE report.'