Capacity Building for the Transfer of Genetic Knowledge into Practice and Prevention

EuroGentest
Genetic Testing in Europe
Network for test development harmonization, validation and standardization of services

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Needs Assessment CAPABILITY Argentina

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Introduction:

The field of genetics in primary care has been a relatively underdeveloped area in health care policies in Argentina. Medical professionals as well as public health care workers did not consider genetic conditions a priority based on the erroneous concepts that medical genetic services are costly and genetic diseases are rare. The idea that genetic diseases are infrequent is wrong because, even if each of these single entities is relatively uncommon, the general impact of the disorders with a partial or total genetic cause is considerable. It has been estimated that 5.1/1,000 live births suffer from a partially or entirely genetic disease, and before the age of 25 years, 3.6/1,000 of them will have a single-gene disorder. Thus, we may expect 2,460 newborns with a Mendelian pathology in our country each year and more than 36,000 persons that suffer from some type of disability partially or entirely due to genetic causes. Genetic disorders account for at least 30% of all hospital admissions in infancy and early childhood and for between 40% and 50% of all deaths in childhood. It is known that at least 15% of clinically controlled pregnancies result in spontaneous abortions before the twelfth week of gestation, 80% of which presents with an embryo with severe structural defects. Of all spontaneous abortions, 50% to 60% are due to chromosomal anomalies. Regarding perinatal mortality (including all stillborn after the 28th week of gestation as well as all newborn that die in the first week of life), studies have shown that 20% to 30% of all perinatal deaths are the result of severe structural alterations. In 80% of these cases, genetic factors are involved. Of all childhood deaths, 20.4% occurring during the first year of life, 9.5% between 1 and 4 years of age, and 5% between 5 and 14 years of age, are caused by major congenital anomalies (Data for Argentina. Source: UNICEF). By 25 years of age, 5% of the population will have a disorder in which genetic factors play a major role in morbidity and mortality.

Additionally, advances and dissemination in the field of genetics to be applied in medical practice create a growing need for improved technology and capacity building in health care workers.

Methodology:

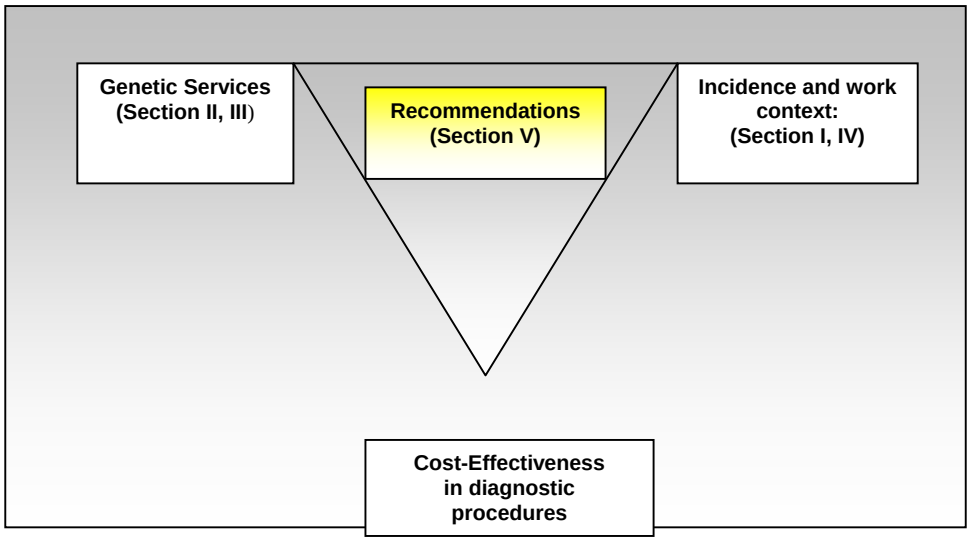
- Data collection and analysis: literature and statistics published to set up a work context (first sections)
- Joint work with the Commission* at the National Ministry of Health to develop an evaluation and categorization of public health care services in genetics in Argentina (last section)

* National Commission of Genetics. Members of the Commission: Alba Liliana, Barbero Pablo, Barreiro Cristina, Chertkoff Lilien, Dain Liliana, Ferreiro Verónica, Francipane

Liliana, Frechtel Gustavo, Gallego Marta Liascovich Rosa, Rozental Sandra

Internal documents of the Commission add information to this preliminary report. All internal documents of CAPABILITY Argentina related to different reports will be presented together at the end of the project.

Contents/Components



SECTION I:

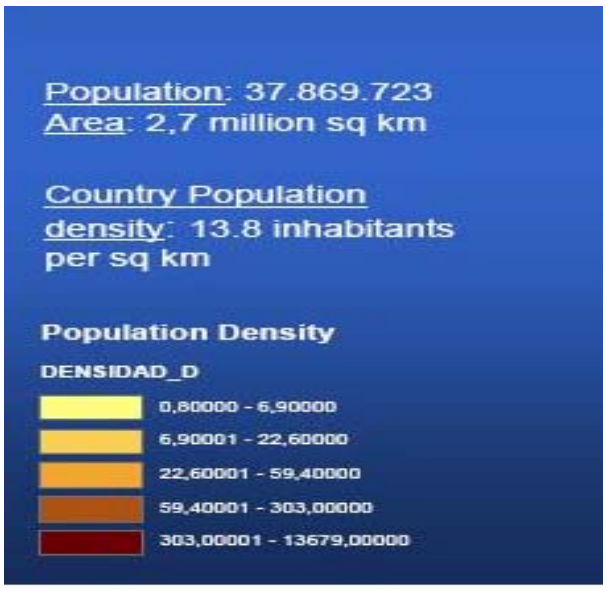
Congenital Defects and Demographic and Sanitary Characteristics in Argentina

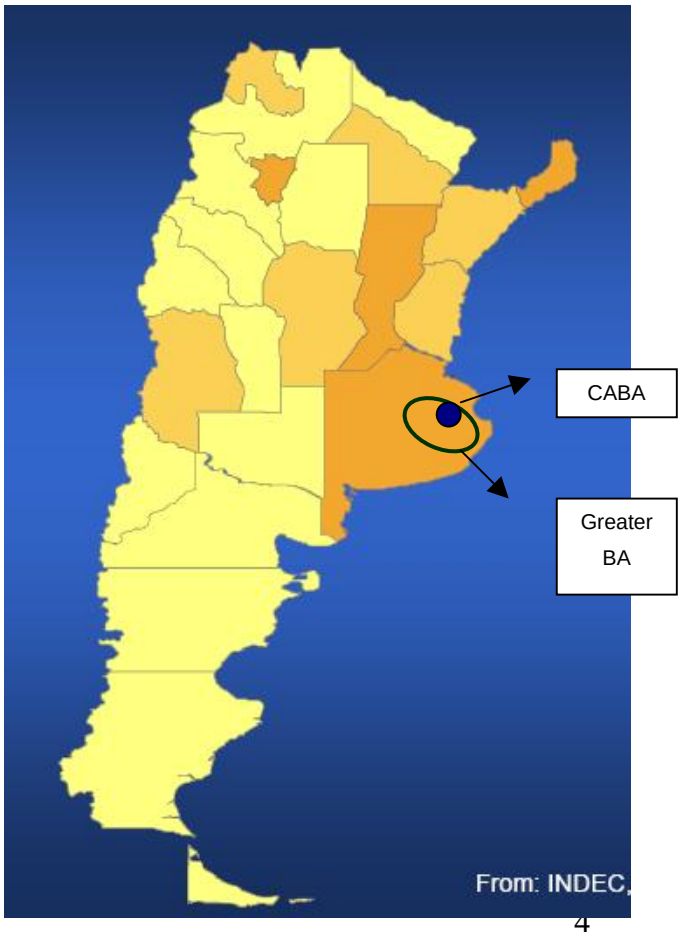
According to data of the INDEC (National Institute of Statistics and Census), in the year 2001 (last national census) the population of Argentina was 37,486,900 with an incidence of 683,495 live births.

In Argentina, there is no national register for the incidence of genetic diseases and/or congenital malformations. Although Argentina participates in the ECLAM (Latin-American Collaborative Study on Congenital Malformations), few maternity clinics are included in the register and only the defects that are detected at birth are recorded in accordance with the aims of the study.

Argentina is a large country and there are two geographical areas that historically hold the highest concentration of population and public health care resources: The City of Buenos Aires (C.A.B.A.); and Greater Buenos Aires (a conglomerate of 19 municipalities in the province of Buenos Aires surrounding the C.A.B.A). The following information was collected from these two areas:

The estimated population of C.A.B.A. is 3,049,900 inhabitants with 42, 375 live births. The estimated population of Greater Buenos Aires is 9,154,800 with 166,141 live births. Many of the inhabitants of Greater Buenos Aires work in the C.A.B.A. and use C.A.B.A health care services. Life expectancy at birth is 71.83 years for Argentina and 72.72 for C.A.B.A

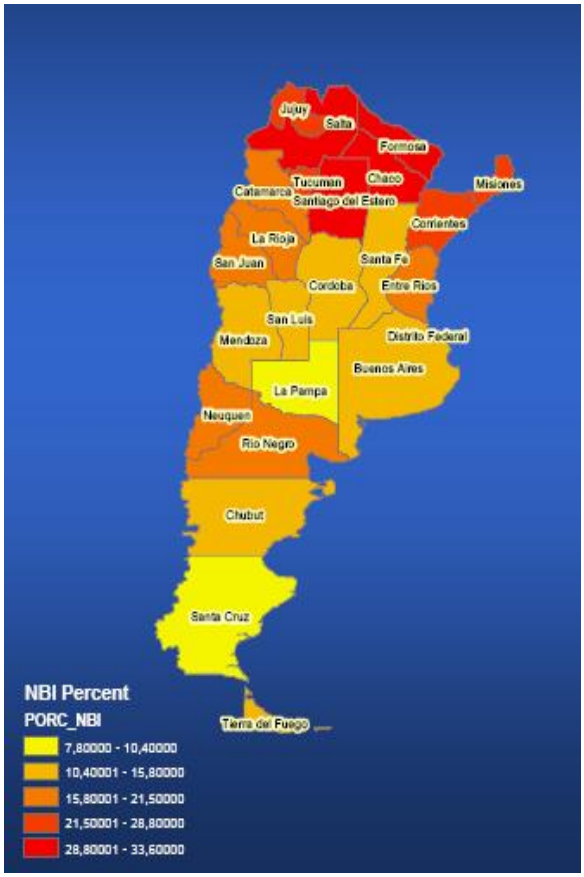




Mortality rate per 1,000 live births is 17.6 for Greater Buenos Aires and 10.7 for C.A.B.A.

Over the last decade, poverty has increased, as shown by indicators such as UBN (unsatisfied basic needs).

The maps show the correlation between childhood mortality and UBN in Argentina.



In 2001, there were 11,516 newborn deaths in Argentina. The causes show that 4,252 (36.9%) of these could have been avoided.

In C.A.B.A, congenital anomalies account for 31% of neonatal deaths and 30% of post neonatal deaths.

The following table shows data of the INDEC, comparing numbers of the whole country with the numbers of the City of Buenos Aires

	Total	Buenos Aires
Annual no. of births (thousands)	698	42
Population under 15 (percentage)	22	18
Infant mortality rate (per thousand live births)	13.3	9.6
Gross birth rate (thousand)	18.2	13.9
Gross mortality rate (thousand)	7.6	11.1
Mean Annual growth rate (1991-2001) (per thousand persons)	10.1	-6.3
Total fertility rate (per woman)	2.30	1.39
Life expectancy at birth in years:	71.93, 68.44 (male) 75.59 (female)	72.72 69.17 (male) 76.45 (female)
Population aged 65+: (percentage),	9.94	17.05

SECTION II:

II-a. Genetic Services.

Genetic services attend to a variety of aspects of diagnosis, prevention, and treatment of diseases with a genetic basis and congenital defects, whatever the cause. The aims are to prevent the occurrence of these disorders, to manage the problems once occurred (early detection and treatment) and to prevent complications and minimize sequelae (medical, psychological, and social rehabilitation). Genetic counseling of affected individuals should be an integrated part of the services**.**

It is important to keep in mind the report of the Advisory Group: Prevention and Control of Genetic Diseases and Congenital Defects, of the PAHO in l984, stating the following:

“Health actions in genetics are not conceptually different from other health actions and comprise various aspects of diagnosis, prevention, and treatment of genetically based diseases and congenital defects. The aims to pursue are: Prevention of the occurrence of these disorders, management of the problems once occurred (early detection and treatment) and prevention of complications and minimization of disability (medical, psychological, and social rehabilitation). Genetic counseling for the affected individuals and their families should be an integrated part of health care services related to congenital defects whatever their cause."

This should be the aim of all genetic health care services. However, in spite of years of efforts, this aim has not been totally accomplished yet. Even though new legislation has been enacted on this subject, no multidisciplinary care is available for handicapped individuals. They are excluded from a society in a country with a 10% unemployment rate where work possibilities are near to zero.

Genetic counseling is restricted to patients who have access to health care institutions with specialists in genetics.

II-b. Current Situation of Genetic Services in Argentina:

Public genetic health care in Argentina is extremely heterogeneous. Several secondary and tertiary care hospitals in Argentina have departments of genetics specially dedicated to the patients and their families.

With the aim of systematizing these centers according to diagnostic possibilities, the National Commission of Genetics defined the following categories:

Category	Description		Operative capacity
A	Consultation with medical geneticists	A1. physicians *ad honorem* A2. Staff physicians	❑ Only clinical diagnosis is made and patients or samples are referred to external laboratories (public or private) for cytogenetic / molecular diagnosis.
B	Laboratories with non-medical professionals (biochemists, biologists or non-medical geneticists)		❑ Receive patients or samples for cytogenetic diagnosis but do not have a medical geneticist for genetic counseling. ❑ Produce lab reports for medical geneticists or other medical specialists from other centers.
C	Services with medical geneticists and cytogeneticists.		❑ Integral patient care both clinical and cytogenetically. ❑ Refer patients / samples for molecular biology / metabolic studies.
D	Centers with medical geneticists and cytogeneticists as well as specialists in molecular biology.		❑ Integral patient care both clinical and cytogenetically. ❑ Molecular diagnosis. *
E	Centers specialized in metabolic disorders and/or molecular diagnosis of specific diseases		❑ Specialized in certain diseases or risk factors (congenital hearing loss, risk genes for hypertension, hematologic disorders, etc.).

There are genetic services in the provinces of Jujuy, Salta, Tucumán, Córdoba, Mendoza, Santa Fe (Rosario), Buenos Aires (La Plata, Mar del Plata), generally working within pediatric hospitals or university centers in the capitals of these provinces. The majorities of these centers are equipped with cytogenetic laboratories or have established an agreement with either a public or private tertiary care center.

These centers have developed individually, with special dedication to clinical genetics, dysmorphology, cytogenetics and/or prenatal diagnosis of chromosomal anomalies. There are only few genetic molecular biology laboratories.

The genetic services in C.A.B.A deserve special consideration: There are 13 general hospitals and 20 specialized hospitals. However, only the pediatric hospitals (Elizalde, Garrahan, and Gutiérrez), the maternity and infant hospital Sarda, and the hospitals Fernández and Santojanni have genetic services. In the City of Buenos

Aires, the Clínicas Hospital depending on the University of Buenos Aires, and the National Center of Medical Genetics (CENAGEM), depending on the ANLIS, also has genetic services. In all these institutions (except the Elizalde hospital) there are cytogenetic laboratories. Only the hospitals Clínicas, Garrahan (SAMIC), and CENAGEM have molecular biology laboratories.

The pediatric hospital Garrahan (SAMIC) is an autonomous entity that receives funding from both the goverment of the C.A.B.A. and the national government. Although geographically situated within the C.A.B.A., in the year 2003 only 16.5% of the children treated at the Garrahan hospital were from the C.A.B.A, while the majority was from Greater Buenos Aires. As the Garrahan is a tertiary reference center, it is easy to imagine that the second most frequent discharge diagnosis is congenital malformation.

Note: the National Commission of Genetics has also made a detailed evaluation of molecular biology testing in services or laboratories in public health care. In Argentina, molecular testing is performed in public institutions for the diagnosis of: Fragile X syndrome, Steinert´s myotonic dystrophy, Prader Willi syndrome, Angelman syndrome, cystic fibrosis, Rett syndrome, Duchenne/ Becker muscular dystrophy, spinal muscular atrophy, familial neurofibromatosis 1, neurofibromatosis 2, adrenal hyperplasia (21-hydroxylase), Huntington's disease, retinoblastoma, achondroplasia, hypochondroplasia, β thalassemia, hemophilia B, hemochromatosis, Y microdeletion, Charcot-Marie-Tooth disease, Kennedy´s disease, congenital hearing loss, porphyria, hereditary breast and colon cancer, Von Hipple- Lindeau disease, and monogenic Mody-type diabetes. When molecular diagnosis for a certain disease is performed, not necessarily others are performed as well, depending on diagnosis protocols and supplies. However, when a center has the necessary equipment and trained personnel, it is possible to incorporate molecular diagnosis for a new disease by only adding the supplies.

II-C. Main Difficulties for the Functioning of Genetic Services:

Due to the scarcity of centers with genetic services throughout the country, many patients have to travel long distances to an urban center to be attended appropriately. On the other hand, the lack of knowledge on the basic principles of

medical genetics and the unawareness of indications for the proper referral of the patient for genetic consultation leads to patients and families that are seen late or not at all.

The genetic services available in the C.A.B.A are public and not paid for by the patients. This has led to an increased demand by Social Security services, either of patients whose families have lost the benefit after the father became unemployed, or of Social Insurance Companies that do not cover expensive studies. Added to the shortage of genetic services in public hospitals, this situation has resulted in a delay in appointment times and studies performed. On the other hand, this large demand also makes it more difficult to see the patients that are referred from other hospitals from the C.A.B.A., Greater Buenos Aires, and the rest of the country that lack geneticists and technology to perform specialized studies. In these centers, the patients are often reevaluated before performing cytogenetic or molecular studies, unnecessarily prolonging time dedicated to the patient. The need to create new genetic services in the provinces and the implementation of a collaborative network is evident.

The increase of the value of the American dollar and the devaluation of the salaries in Argentina have greatly reduced the possibilities to send samples for diagnostic studies abroad and increased the cost of supplies for local studies, making the care for patients with genetic pathologies even more difficult.

SECTION III

III-a. Human Resources for Patient Care in Medical Genetics

Even though medical genetics has a relatively long history in Argentina (since 1968), only in 1991 the Ministry of Health recognized genetics as a specialty in medicine. Specialists are trained (postgraduate training) in the Residency Program of Medical Genetics at the National Center of Medical Genetics or through fellowship programs in hospitals and specialized centers. Similar programs are available for specialists in cytogenetics. Private fellowship programs exist for specialization in molecular biology.

The Argentine Society of Genetics (S.A.G.) has the authority to award specialist degrees in Medical Genetics, Cytogenetics, and Molecular and Biochemical Genetics. Within the Society there is a section of Human Genetics that joins specialists throughout the country.

Geographical, social, political, and economic circumstances in the country make it necessary for genetics in primary care to become part of the training for a medical degree. Additionally, other members of the health care team should be trained to recognize genetic risk factors for families in their work area. Efficient links should be established between local health care workers and specialists in tertiary care centers.

Medical Genetics has not yet become an integrated subject in the medical degree at public national and provincial universities and the teaching of medical genetics continues being incomplete and fragmented.

III-b. Research in Medical Genetics.

In the 70s, a process took place in which research that was fundamentally done at universities was taken over by separate institutions. Currently, the policy of the government is to try to revert this situation and research at universities is again being encouraged. Research in genetics is subject to the same difficulties as research in general.

There are several prestigious research institutions in Argentina, such as the Research Institute of Genetic Engineering and Molecular Biology, Instituto Campomar, governmental institutions such as the CONICET and the Agency of Scientific and Technologic Promotion that depend on the National Secretary of Science and Technology. These institutes have post-graduate training programs in research and provide fellowships and subsidies for research porgrams. The funding for these programs, however, is insufficient. Currently, the National Commission of Genetics is evaluating all research protocols. In 2007, a Workshop for Priorities in Research in Health in Genetics, coordinated by Dr. Victor B. Penchaszadeh, was held within the framework of the Forum for Health Research in Argentina.

SECTION IV

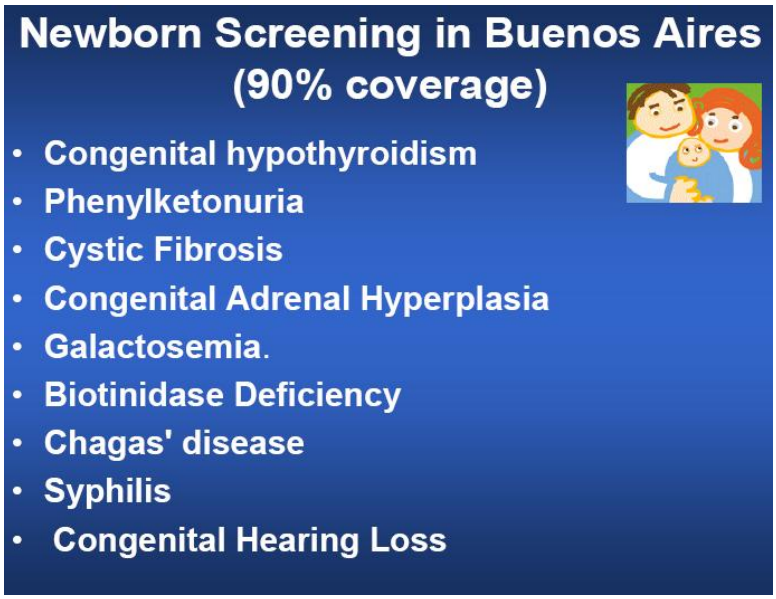
IV-a. Neonatal Screening Program.

The program of neonatal screening was implemented in 1985. The program has covered the areas of the C.A.B.A. and Greater Buenos Aires better than the rest of the country. Progressive incorporation of the different tests that nowadays make up neonatal screening was accompanied by a national legislation on the subject. In spite of this, the coverage of the population was still less than 50%. Over the past years, the National Commission on Neonatal Screening has kept strict statistical records and implemented strategies to improve this situation. The establishment of networks has improved coverage in the provinces.

NATIONAL LAWS

- **Law 23,413** (1986) Neonatal screening of phenylketonuria is mandatory in all maternity wards and hospitals with neonatal care facilities and is considered a routine practice in public institutions, and for social security, social insurances, and health insurances.
- **Law 23,874** (1990) Early testing for congenital hypothyroidism is added.
- **Decree 1316/94 (**1994). Regulates Laws 23,413 and 23,874 defining who is responsible for neonatal screening.
- **Law 24,438** (1994): Testing for cystic fibrosis is added.
- **Resolution 508/96** (1996**)** Establishes guidelines for the procedures of sample taking and analysis.
- **Law 22,360**. Prevention and Fight against Chagas Mazza disease is declared a national priority.

In Buenos Aires, neonatal screening has been extended to a broader range of tests and currently covers 90% of the population.



Since September 5, 2007, public and private hospitals are obliged by Law 26,279 to take a blood sample of all newborns to detect nine diseases. These guidelines do not only warrant early detection, but early treatment as well.

Law 26,279 adds cystic fibrosis, galactosemia, congenital adrenal hyperplasia, biotidinase deficiency, retinopathy of prematurity, Chagas´ disease, and syphilis to the first neonatal screening (phenylketonuria and hypothyroidism). The new guideline states: "Each person with a diagnosis of one of these diseases made before this law has come into effect is automatically included in the population that is treated and followed up because of this law".

Additionally to the detection of these nine diseases in newborns, the law determines that health insurances and other health care institutions are required to "incorporate as routine services" drug treatments, special dietary supplements, formulas, and foods for each pathology, as well as all other necessary therapies, kits, and equipments.

IV-b. Parent Associations

Throughout Argentina, there are associations that join patients and parents of children with congenital malformations and diseases with a genetic etiology, generally organized by parents with special worries and needs.

One of the first of these associations was the spina bifida association which, in addition to supporting the parents in the expensive treatment and rehabilitation of their children, organizes sports events for handicapped children and the association of children with cleft lip and palate.

However, parent associations of children with rare diseases have more difficulties due to the infrequency of these diseases. In 2007, a new project PID 22826/04 was set up called: “Rare diseases in Argentina: A social, medical, legal, and scientific point of view. The project has been approved by the National Agency of Science and Technology, associated with the Ministry of Science, Technology, and Productive Innovation, through the FONCYT (Scientific and Technological Research Fund), resolution Nº354/05. The main aims of the project are:

- Make an estimate diagnosis of the status of patients and families with rare diseases in Argentina, including medical, legal, institutional, social, and scientific aspects.
- Create an initial database of public information on medical, legal, and social aspects of rare diseases.
- Create an office of public information on medical, legal, and social aspects of rare diseases.
- Create an office of public information and orientation and a web site for health care professionals and families to consult.
- Propose policies to resolve critical problems identified in the diagnosis.

SECTION V

V-a. Primary, Secondary, and Tertiary Care in Genetics in Argentina

The need for networking

Primary Health Care is defined as the delivery of health care at the most local level of the health care system with methods that are practical, scientifically sound and socially acceptable. Everyone in the community should have access to it. Primary health care in genetics should be available through active participation of the individual and their families.

Action undertaken to reach these goals in primary care should fundamentally, to prevention (health promotion and protection). And be addressed to the detection of the entirely or partially genetic pathology

Secondary Care and Tertiary Care attention will be adequate to the level of complexity of the health institution providing service. For example: specialized care for complex genetic studies is given by specialists who work in a center that has personnel and facilities for special investigation, generally located in large urban centers and receiving patients who are referred from regional centers.

The aim is to readapt and reorganize human resources and technology, building a NETWORK of medical genetics.

To establish a network of increasing complexity in hospitals. This must have medical services which provide primary care and prevention for congenital diseases in general hospitals and care centers for more complex pathologies and secondary prevention in specialized hospitals, with the existence of one or two services of high complexity as regional reference centers.

The NETWORK is a tool to develop a system of coherent and cost-effective health care. It provides different levels of decision-making, pointing to integrated care (prevention, treatment, rehabilitation, and socialization) for the patient with an entirely or partially genetic pathology, as well as a programmed system for training of personnel and use of resources, exchange of knowledge and information, and patient referral.

V-b. Recommendations for Genetic Care Provision in Argentina

Over the past years, geneticists and health care policy makers have become aware of the need to develop joint strategies to improve genetic health care in Argentina. In 2006, the National Commission of Genetics was established within the Ministry of Health. The initial aims were to set up a national network of genetics to broaden and standardize genetic care throughout the country. This was a first step toward the design of new programs in public health care for health promotion and disease prevention.

The National Commission of Medical Genetics updated the registration of public medical genetic services (2007). Based on the results, the following recommendations were made*:*

1) Create at least 1 genetic service in provinces that have none.

Minimum requirements: (infrastructure in a public hospital)

Areas	**Equipment**	**Human resources**
Consulting room for clinical genetics	Anthropometric instruments, stretcher, computer with internet conection, digital camera	Clinical medical geneticist
Cytogenetic laboratory	SEE NOTE *	• Cytogeneticist (either a biochemist, biologist or non-medical geneticist) • Technician

The number of services per province should multiply in the future according to the demographic and epidemiologic characetristics and needs of the population.

NOTE *: The Cytogenetic Laboratory in Public Hospitals

In Annex II of the report, different work areas are specified (extractions; cultures and technical activities; microscopy); The estimated cost of installing a laboratory for the processing of peripheral blood samples, chorionic villus and amniotic liquid sampling (USD 5600) and monthly maintainance of supplies (USD 100). The surface of the work area should be related to the number of employees and workload. The number of professionals depends on the quantity of studies performed at the laboratory and should be enough for the assurance of reliable results in the shortest time possible. Requirements for the professional team have been specified. The registration system, shipment of samples, and reporting of the results were standardized.

2) Staffing and equipment of the already existing genetic services, at least 1 (one) per province, with a basic infrastructure (consulting room and cytogenetic laboratory), and qualified human resources who meet the minimum requirements pointed out in recommendation 1.

Most existing services are part of hospitals that have basic equipment and physical space. As such, only staffing, minimum specific equipment, and a regular flow of supplies are needed.

3) Medium-term development of a prenatal diagnostic area linked to the local genetic service per province, that will be responsible for the diagnosis and preconception and prenatal counseling for couples and pregnant women at risk.

4) Within the network, regional reference laboratories should be established specialized in molecular and biochemical diagnosis of genetic diseases with a prevalence or diagnostic complexity that exceeds the provincial level. Similarly, all samples of pathologies that are not currently studied in the country should be sending abroad to international laboratories.

5) Development of a quality control program to which all cytogenetic and molecular biology laboratories within the network should adhere to assure homogeneity and quality of the procedures.

6) Diffusion of the "Fetal Health Line", among health care agents and the general population, which provides information on teratogenic agents that, may harm the fetus.

7 Encourage a better integration of medical genetic services within the health care system through management training for health care agents to locally resolve simple problems and adequately and timely refer the population at risk to secondary and tertiary care genetic services.

8) Development of an ongoing education program of medical genetics for geneticists and other health care professionals.

9) Promotion of education of the general public on the prevention of congenital anomalies and genetic diseases.

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