



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

The CAPABILITY Report

Model Approaches for Capacity Building for the Translation of Genetic Knowledge into Practice and Prevention

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LIFE SCIENCES, GENOMICS
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Abbreviations

COVs	Community outreach visitors
CUGC	Clinical Utility Gene Cards
EC	European Commission
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
ELSI	Ethical, Legal, and Social Issues
ESHG	European Society of Human Genetics
EU	European Union
EuroGentest	Genetic Testing in Europe – Network for test development, harmonization, validation and standardization of services
GIG	Genetic Interest Group
GraSCOP	Greater Sekhukhune-CAPABILITY Outreach Project
HNA	Health needs assessment
IPTS	Institute for Prospective Technological Studies
LU	Lund University
MGEP	Medical Genetic Education Programme
MHH	Medizinische Hochschule Hannover
MoH	Ministry of Health
MOHP	"Children with Special Needs" Department/Ministry of Health and Population
NHLS	National Health Laboratory Service
NoE	Network of Excellence
SAMIC	Hospital de Pediatria SAMIC
SSA	Specific Support Action
UKGTN	United Kingdom Genetic Testing Network
WHO	World Health Organisation
WITS	University of the Witwatersrand
WWU	Westfälische Wilhems-Universität

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1. Introduction and Overview

(I. Nippert and A. Christianson)

1.1 Background

Human genome research is leading to the rapidly increasing translation of genetic/genomic data into clinical application. Genetic tests¹ have been developed for the vast majority of recognised genetic conditions, including DNA-based tests for more than 1.100 diseases, with more than 1.000 currently available for clinical testing.

The number of DNA-based tests performed annually in Europe is now over 700.000 and is increasing. The economic dimensions of this activity is estimated around 900.000 € – 28.000.000 € / million citizens/year² and is expected to grow rapidly by the next decade. Although the majority of these tests are used for the diagnosis of rare disorders, **a growing number of tests have broader population based applications** including predictive testing for inherited risk for common disorders, carrier identification and pharmacogenetic testing for variations in drug response.

The use of genetic tests for diagnostic, confirmatory and predictive purposes is expanding in all European countries at an estimated growth rate between 100% and 300% per year.

These genetic tests and other anticipated applications of genome technologies for screening and prevention will impact on the future provision of primary care and prevention services.

The European Union (EU) faces the dual challenge of developing adequate standards for genetic testing while bridging the national, socio-economic and socio-cultural and linguistic differences of its Member States. Accordingly in its report "Towards quality assurance and harmonisation of genetic testing services in

¹ Genetic test = the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect disease – related genotypes, mutations, phenotypes or karyotypes for clinical purposes, including: risk predictions and identifying carriers.

² Jean-Jacques Cassiman: "EuroGentest -Genetic Testing in Europe. A network for test development, harmonization, validation and standardization of services". Presented at the 19th Annual Meeting of the German Society of Human Genetics April 8-10, 2008

the EU" the Institute for Prospective Technological Studies (IPTS) states that genetic testing in Europe, while based upon high quality scientific know-how, suffers from disorganisation and fragmentation of services, caused by a lack of structuring and complementarity at the European level and the absence of a common European objective to provide quality services to all its consumers. The European Commission's Expert Group on Genetic Testing, the IPTS and the European Society of Human Genetics (ESHG) have all expressed ***the need for harmonising quality standards within genetic testing and genetic service provision***. To meet this challenge the FP6 funded Network of Excellence (NoE), "*Genetic Testing in Europe – Network for test development, harmonization, validation and standardization of services*" (*EuroGentest*) was launched in 2005 (www.eurogentest.org). *EuroGentest* will end in June 2010. The World Health Organisation's (WHO) Genomic Resource Centre, when reviewing the current situation in the EU, recommended that ***it could be beneficial for other jurisdictions, such as countries from Latin America or developing countries such as South Africa, to participate in these EU harmonisation activities***, as they may benefit more from the EU approach than from one developed for a single country (e.g. the United States) and because these countries face similar challenges regarding adequate genetic service provision and quality assurance. **This comes at a time when the WHO's Executive Board has recommended the prioritisation of genetic services in developing countries for the management and prevention of genetic/congenital disorders to assist them to attain their MDG4³.**

Middle-income developing countries, such as those participating in this CAPABILITY project, are facing an epidemiological transition. As national health care systems improve an increasing proportion of morbidity and mortality is due to congenital and genetic conditions. Health care systems in these nations are starting to respond to the rising needs for genetic services in primary care and public health. Like in Europe, but to a greater extent, there is a scarcity of personnel trained in genetics. Services are predominately tertiary specialist medical genetic services, usually situated in academic centres because service evolution is highly research dependent. Consequently these services have been developed with little contact with primary care or community-based services. As in Europe the extraordinary diversity of the

³ WHO Executive Board, May 14th, 2009

natural history and clinical implications of genetic conditions has favoured the development of disease specific services (e.g. for cystic fibrosis, haemoglobinopathies, metabolic disorders, neurological conditions, etc.), that often have little contact with each other and fail to recognise their commonalities. ***As in Europe, albeit with lower available resources, these countries need to develop the necessary infrastructure, tools, resources, guidelines and procedures leading to the establishment of harmonised quality medical genetic services.***

1.2 The CAPABILITY project

This report (Chapters 3-4, Annexes 1-7) presents in detail the CAPABILITY approach for capacity building and the outcome of the CAPABILITY demonstration project.

CAPABILITY is a 3-year model project, funded from 2007-2009 by the European Commission (EC) FP6. It is a Specific Support Action (SSA) for the NoE *EuroGentest*. The project was developed jointly by the NoE *EuroGentest* unit 3 "Clinical Genetics, Community Genetics and Public Health" represented by U. Kristoffersson, Lund University, Sweden (LU), J. Schmidtke, Medizinische Hochschule Hannover, Germany (MHH) and I. Nippert, Westfälische Wilhelms-Universität Münster, Germany (WWU) - the latter acted as co-ordinator of CAPABILITY - and unit 6 "Education" leader A. Kent, Genetic Interest Group, London, U.K. (GIG). The European partners were joined by leading experts from: Argentina C. Barreiro, Hospital de Pediatría SAMIC, Buenos Aires (SAMIC), Egypt R. Raouf, "Children with Special Needs" Department/Ministry of Health and Population, Cairo (MOHP) and South Africa A. Christianson, University of the Witwatersrand, Johannesburg (WITS), all being currently engaged in major development projects to integrate genetic services in primary care and prevention in their countries.

There is a commonality of interests shared by the CAPABILITY participants to promote an internationally shared set of basic quality standards for evaluating the clinical utility of genetic testing and the provision of adequate genetic services based upon systematic health needs assessment (HNA).

Because the use of genetic tests for diagnostic, confirmatory and predictive purposes is expanding worldwide, the following challenges are common to both EU and middle- and low-income countries:

- i) The need to develop an evidence-based evaluation process for translating genetic tests or other applications of genomic knowledge for health care.
- ii) The need for capacity building to enable health care systems to integrate adequately genetic/genomic applications with proven clinical utility into practice and prevention.
- iii) The need to establish an evidence-based implementation process for genetic/genomic knowledge into routine practice, including the review of testing practices, to ensure quality standards of services and to allow policy makers and governments informed decision making.

CAPABILITY aims at addressing the lack of internationally shared standards for genetic testing/services provision and the lack of evidence-based models for assessing genetic services needs.

To achieve its objectives CAPABILITY has established an international multidisciplinary working group (members see Annex 8) representing expertise in: clinical genetics, genetic epidemiology, health service research, health technology assessment, evidence-based medicine, molecular genetics, public health genetics and ethics. The working group also includes representatives from parent and patient organisations and primary care providers.

The following tasks were performed by the CAPABILITY working group:

- examination of existing national and international genetic test evaluation approaches that could be adopted to evaluate the utility of genetic tests/genetic knowledge for health care in developing countries;
- identification of priorities for HNA in medical genetic services and priorities for capacity building;
- validation of its capacity building approach by means of a joint demonstration project sensitive to specific health care contexts and service patterns in

developing countries, including the magnitude of assessed needs, available resources and capacities, service gaps, as well as ethical, socio-cultural and legal implications;

- development of recommendations for evidence-based capacity building for medical genetic services.

The CAPABILITY demonstration project consists of the following components:

To start the project a systematic HNA for medical genetic services was conducted in Argentina, Egypt and South Africa. Because limited cogent literature on HNA and examples of its application to medical genetic services are available in the literature, CAPABILITY had to develop its own approach to HNA for medical genetic services with particular reference to middle- and low-income nations.

The CAPABILITY project set out to collect information taking into account: socio-demographic and epidemiological data, health care system data, situational analysis of the availability of services, gaps in service provision, Ethical, Legal, and Social Issues (ELSI) implications taking into account national/regional cultural norms and practices and national laws and guidelines to identify health care needs in these countries and to plan the demonstration project.

The outcome of the HNA surveys conducted in Argentina, Egypt and South Africa can be found in Annexes 1-3. The HNA data obtained from these countries were presented at an international experts workshop for discussion and critical assessment. Subsequently small scale projects for capacity building were designed to address needs identified by the national/local HNA. Capacity projects were conducted in the Chaco Region Las Breñas, Argentina, Om-Khenan area in Giza governorate, Egypt and the Greater Sekhukhune district, Limpopo Province, South Africa (see reports, Annexes 4-6).

In the light of the experiences of the conducted HNA and the input from international experts a general methodology for conducting HNA in middle- and low-income countries was developed. The "Health Needs Assessment for Medical Genetic Services in Middle- and Low-Income Countries" is presented in chapter 3.

The project "Public Private Partnership" was conducted in Germany (J. Schmidtke, MHH). The project addresses the problem how to attract private in order to satisfy the public need for genetic services in countries with very limited resources (see report, Annex 7).

1.3 Demonstration project overview

1.3.1 Argentina - Implementing genetic services in the Chaco region of Argentina (Report, see Annex 4)

The aim of the project was to design and implement a model for local delivery of medical genetic services in primary health care by means of an educational programme, taking into account the characteristics of the province. Thereafter, using funds generated from within Argentina, the aim was to maintain and extend the structures achieved in Chaco and encourage the development of complementary projects in other areas of the country using the knowledge, experience and educational programmes gained from the CAPABILITY project.

The province of Chaco was chosen for this project, in agreement with the Provincial and National Ministries of Health. Chaco is one of the 10 provinces in Argentina lacking genetic services, located in the north-west of the country. Chaco has 1.042.881 inhabitants of whom almost 50.000 belong to Toba, Wichi, and Mocoví communities.

The project was co-sponsored by SAMIC by building and staffing a cytogenetic laboratory in Chaco.

To undertake the project a local working group was established in each Sanitary Area of Chaco to liaise with and assist the CAPABILITY team. By means of a questionnaire the health professional resources, patient profile, available means of communication (print, computers, internet availability, and others) and the preference for the type of teaching material wanted in each Sanitary Area was assessed.

Educational material was then developed to meet the needs in the Sanitary Areas. Two syllabi were prepared, one for people working in primary health care (nurses,

physical therapists, clinical psychologists, health care agents, and midwives) and the second for medical practitioners. Based on these syllabi, teaching material in the forms of a book, CD, and PowerPoint presentations was developed. A web page was designed to make this material easily available and as a resource for continuing medical genetic education and on-line consultation for health professionals in Chaco with the Human Genetics Department in the Hospital de Pediatría Juan P. Garrahan, SAMIC, Buenos Aires.



The training took place at 3 levels

- a) *Initial training:* Training in genetics of health care professionals working at health centers in different sanitary areas in Chaco
- b) *Continuous education:* Communication to achieve periodic updates for the health care professionals to improve the quality of care.
- c) *Amplifying effect:* Design of a module for training new teachers (according to the trainer's profile: a group will act as Education Management/and the others will be Trainer Effectors).

Contents according to the profile will be transferred and connections with the specialized referral center will be maintained to update them.

During the initial training health care workers and professionals in the Sanitary Area were taught and trained by means of a series of seminars, workshops and teaching

consultations (hands-on experience to observe physician-patient relationships and use of skills).

A total of 413 health care workers were trained. While this teaching and training was being undertaken, engagement of the community with the project and with children with congenital and genetic disorders was achieved through the media (newspapers, TV, radio, internet), open talks for the community and workshops for parents with children with congenital and genetic disorders.

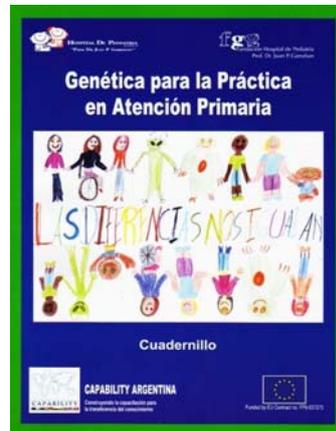


After a pilot project in sanitary zone V, it was decided to incorporate in the remaining sanitary zones community activities in the definition, implementation, development, and continuation of the project in time. From then on, training was not only addressed to health care professionals, but also to health care managers who are leaders in their communities. They served not only as a source of consultation on the community needs, but also as a control mechanism, where adequate solutions related to prevention can be looked for. They facilitate the access of patients to the health care network with key locations for genetic diagnosis and counseling.

The success of the Chaco Outreach Project has become apparent in several ways:

- Referrals of patients with congenital and genetic disorders for medical genetic consultation increased significantly: 3.5 times in those Sanitary Areas comparing before and after the training period, and notably, all patients referred did have a congenital disorder. (The total number of consultations from Chaco was 268 after the training period in 2008-2009 and 77 before the training period in 2006-2007).
- The Ministry of Health in Chaco has decided to extend the project to all 7 Sanitary Areas, and is opening a cytogenetic laboratory because of the anticipated increase in demand.

- Based on the results of the Chaco Outreach Project, the National Ministry of Health has decided to implement and support medical genetic care programmes in 4 provinces in North-East Argentina, including Chaco.
- Because of the demand, the educational material in book and CD format has been distributed widely throughout the country by the Garrahan Hospital Foundation.



1.3.2 Egypt – Knowledge, Attitudes and Practice (KAP) of Medical Genetics in a Rural Egyptian Community (Report, see Annex 5)

This project addressed barriers identified by the Egyptian survey in integrating new medical genetic health services into the existing public health services such as:

- Difficulties in integrating new services into a public health service with many existing vertical programmes.
- Lack of knowledge of health professionals on where and how to access already existing services for the care and prevention of congenital and genetic disorders.
- Long distances from residence to medical genetic facilities, exacerbated by the unavailability of these facilities in some governorates (provinces).
- The financial cost of the services available and lack of insurance coverage or adequate reimbursement.
- Cultural and religious beliefs
- Concerns about privacy and confidentiality.

The project was conducted in the Om-Khenan area in the Hawandia district in the Giza governate.

The following tasks were worked upon: The knowledge, attitudes and practices with respect to congenital and genetic disorders of the villages' 21.525 inhabitants and the medical and para-medical professions responsible for their care were surveyed and analysed.



To achieve the task the first step was the acquisition and evaluation of demographic and other health related data of Om Khenan. Its inhabitants are mostly of low socio-economic status (58%) with low education, 68% having attended primary school education and 30% secondary school. Most males (85%) work as farmers or manually labourers and 68% of women are housewives. Primary health care ensures 98.8% vaccination coverage and 99.7% coverage for neonatal thyroid screening. There are just over 500 births annually with 19% occurring at home. This represents 23.6 births per 1000 population a figure exacerbated by the low use of contraception (32.4%). It can thus be estimated that up to 40 infants are born each year with a congenital or genetic disorder in Om Khenan.

Religion is a strong force in the community, 85% of people being Muslims and 15% Christians. This underpins their beliefs in God and fate, the sanctity of family and their rejection of abortion which is considered a sin. It also motivates their efforts to ensure the health, education and future wellbeing of their children.

With this background a questionnaire for the community knowledge, attitudes and practices with respect to congenital and genetic disorders was developed and piloted.

The questionnaire interrogated community needs with regards congenital and genetic disorders, including available services for care and prevention, and issues related to the need for, how to, and to which group to deliver public education on the topic. It further explored women's knowledge to congenital and genetic disorders; their needs related to these disorders and how to improve the public health services; their needs

for and attitudes to prevention of congenital and genetic disorders; and their practices during pregnancy to prevent these disorders. Specially trained community outreach visitors (COVs) administered the questionnaire to 531 randomly selected families in the village. The informants were mostly wives (80%).

The survey confirmed that public knowledge in the village about congenital and genetic disorders was poor, but 87% of informants considered they needed information on these disorders with 69% preferring to receive it just before marriage and 30% while at school. The latter is 10% more than the percentage of people that attended secondary school. There was a significant relationship between informant knowledge and age, marital status and level of education. Informants (86%) considered the public required access to medical genetic services with 47% considering that this should include mandatory pre-marital consultation and genetic counselling. Interestingly only 8% considered consanguinity should not be allowed, and not surprisingly 69% of informants were against prevention of congenital and genetic disorders by abortion.

Using this and other knowledge gained, an educational programme for nurses and COVs to deliver simplified medical genetic health awareness to the community was developed. To assist them in this task a simple manual was also developed. Work on the project tasks included community education through home visits, group discussions seminars and public education in health care facilities.



The knowledge, attitudes and practice of physicians (general practitioners/ family practitioners, paediatricians and, obstetrician/gynaecologists) in Om Khenan and surrounding health facilities were evaluated by a survey, a focus discussion group and a questionnaire using open ended questions. The results indicated the majority

acknowledge the need for further training in medical genetics including literature, an illustrated book detailing diagnosis, treatment and prevention on common congenital and genetic disorders. Some admitted not having any information on available services and requested information on these and official referral cards to these facilities be made available to them. Regarding public education the majority considered expectant mothers to be the best target and recognised COVs as the most suitable route for community education. The role of the media was noted, with some also proposing the youth population as being a suitable target for education including adding relevant information into the school curriculum. Seminars for physicians working in the community were held to inform them of approaches to common congenital and genetic disorders; current medical genetic services in Egypt; and methods of prevention and early intervention for congenital and genetic disorders.



The Knowledge, Attitudes and Practice Survey on Medical Genetic in a Rural Egyptian Community documented important information for medical genetic services in Egypt and for middle- and low-income nations with similar circumstances. Undoubtedly Egypt has reached a stage of health transition and development that recommend the Egyptian Ministry of Health and Population efforts to develop medical genetic services. They are confronted by the barriers to their task including those documented above and others revealed by the CAPABILITY approach including:

- The lack of health professional knowledge on available services in the country was confirmed. However, this is amplified by the lack of health professional knowledge on congenital and genetic disorders revealed by the project.

- The Knowledge, Attitudes and Practice Survey confirmed that religious and cultural belief will impinge on the implementation of preventive services and interventions- medical genetic screening, prenatal diagnosis and termination of pregnancy, were these to be offered, and attempts to reduce consanguineous marriage.
- The low percentage use of contraceptives and concomitant high birth rate are increasing the birth prevalence of congenital and genetic disorders- chromosomal trisomies and autosomal recessive disorders, in the country. Improving access to and use of contraceptive services would be an effect public health intervention to reduce the burden of these disorders.
- Reducing the frequency of consanguinity is unlikely for a long time. Therefore pre-conception screening and counselling for common recessive disorders (thalassaemia), possibly before marriage which seems acceptable to a large proportion of the Om Khenan population, is a consideration. The early postnatal diagnosis of haemoglobin disorders and inborn errors of metabolism will become a consideration to add to the presently available neonatal screening for congenital hypothyroidism.
- Poor public knowledge and appreciation of congenital and genetic disorders is a barrier to the implementation of medical genetic services in Egypt, but one that is amenable to remediation. In rural situations like Om Khenan public education by COVs and nurses will be important due to the high percentage of people with low levels of education and poverty which would diminish the likelihood that they would benefit from education in school and through the media. However the situation might be different in urban areas were all forms of public education would probably be beneficial. Education should also target males, as over 60% of married women considered their husbands as their preferred adviser. For the same reason all genetic counselling, where possible, should include the husband.

1.3.3 South Africa - Greater Sekhukhune-CAPABILITY Outreach Project (GraSCOP) (Report, see Annex 6)

This project was based on the CAPABILITY HNA survey for this region and on a successful clinical genetic outreach programme to hospitals in Limpopo Province (formerly Northern Province) undertaken in the 1990s. In 2006 the Limpopo Provincial Department of Health and Social Development initiated a task team to plan and implement medical genetic services in the province.

GraSCOP was initiated from that task team to pilot a primary and secondary health care medical genetic service in the Greater Sekhukhune district with the objectives of:

- Testing and developing the principles and practices of primary health care based medical genetic services as outlined in the South African National Department of Health's 'National Guidelines for the Management and Prevention of Birth Defects and Disabilities'.
- Further assessing and developing the Medical Genetic Education Programme (MGEP), a distance learning education programme currently used by the National Department of Health for post graduate nurse training.
- Re-evaluating the epidemiology of congenital disorders in this setting
- Testing the clinical utility of DNA based medical genetic tests and technologies
- Using the knowledge and experience acquired from the project to assist the implementation and development of medical genetic services throughout Limpopo and other provinces in South Africa.

To initiate GasSCOP 38 nurses and 6 primary health care doctors from St Rita's Hospital and its referring primary care hospital underwent training with MGEP. A feature of this teaching was that the inclusion of primary care doctors in the courses was encouraged. Results obtained in the examination rendered were similar to those from previous courses held elsewhere in the country, for those that completed the course. What was different was that 8 candidates did not attend all the contact days and complete the course, and therefore could not write the examination.



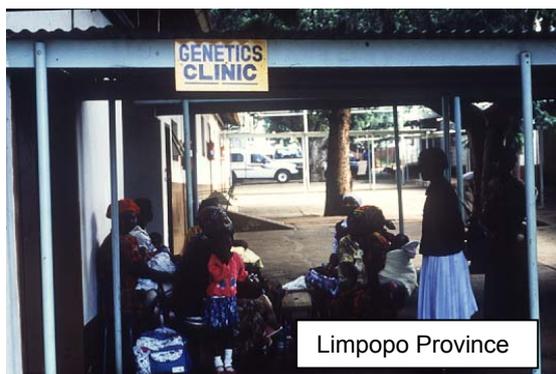
In addition during the GraSCOP programme a trial was undertaken of the MGEP contact day teaching by tele-teaching to hospital based tele-conferencing facilities in Limpopo. This was the first attempt at undertaking the MGEP contact day teaching in this manner and was very successful with 86% of the candidates passing the examination. Further piloting of tele-teaching of the MGEP programme contact days will now be undertaken with hopefully similar results. Doing the contact day teaching for MGEP in this manner ensures the course can be taught to more nurses and doctors at significantly less cost, and travel and inconvenience to both students and lecturers. The second objective of the GraSCOP programme was thus achieved.

The training of the doctors and nursing staff with MGEP was to enable them initially to recognise infants and children with congenital disorders in their hospitals possibly clinically diagnose the more common congenital disorders and initiate relevant investigations and treatment. It was then intended that they refer their patients with their parents, and attend with them, to outreach clinics held at St Rita's Hospital by medical geneticists and medical genetic counsellors of the Division of Human Genetics, NHLS and WITS.

The purpose of nursing staff and doctors attending the outreach clinics with their patients was so that they could receive further 'on the job' teaching and training from the outreach clinic staff. Despite efforts to try and achieve this, it never occurred during the programme. Patients seen at the outreach clinics were only those diagnosed and being treated at St Rita's Hospital.

Reasons for this failure to network the primary care hospitals to St Rita's, the secondary care facility for the district, for the outreach clinics were sought. Two

cogent and interconnected reasons were determined. When the protocol for GraSCOP was developed in 2007 the 2006 figures for vacancies in medical practitioner posts (26.8%) and nursing posts (15%) were available. The 2008 figures record a significant increase in vacancies, to 35.4% for medical practitioners and 43.7% for nursing staff. In 2008, 42.1% of all health professional posts in the public health sector in Limpopo were vacant. This, with the burden of HIV/AIDS and TB in the Province, are placing huge stress on the health services, including available health professionals, in the Province⁴. The care and prevention of congenital and genetic disorders must rate a lower priority in these circumstances, and hospitals quite obviously could not release doctors and nurses from their post to attend the outreach clinics. Additionally, undertaking epidemiological studies in these circumstances was not possible. This is also an explanation for why so many students did not complete the MGEP course.



One positive development resulted from this situation. A cell phone was given to the paediatrician and the neonatal ward at St Rita's Hospital. With a cell phone photographs of infants and children with congenital disorders with dysmorphic feature were taken and MMSed to the Division of Human Genetics. With the photographs and other clinical details obtained by fax or through cell phone conversation, a clinical geneticist in the Division of Human Genetics offered a tentative diagnosis and suggested relevant investigations and treatment to the attending staff at St Rita's Hospital. Although in its early stages this appears to be an acceptable way to offer clinical support to clinicians in rural areas like Greater Sekhukhune.

⁴ Health Systems Trust. South Africa Health Reviews 2006 & 2008. [www.hst.org]

Finally, during GraSCOP, the clinical utility of QF-PCR for the postnatal diagnosis of Down syndrome, using the *EuroGentest* criteria, was evaluated in the circumstances pertaining to South Africa.



Genetic testing for Down syndrome- The S African scenario

Postnatal clinical practice

- 16% DS infants diagnosed in neonatal period
- <50% DS infants diagnosed before 6 months of age

NHLS Laboratory (Jan 2007-May 2008)

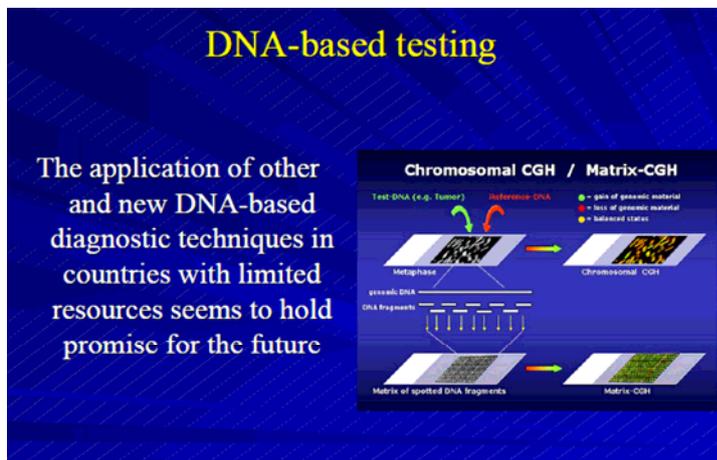
- 653 specimens with DS diagnosis diagnosed with chromosome analysis
- 12% failed culture
- 33% normal chromosomes
- 1% other diagnosis
- 54% DS karyotype
- DS- 95% Trisomy 21
 - 3.6% Translocations
 - 1.4% Mosaics

Cause	Percentage
Prolonged transit time	54%
Culture error	12%
Wrong tube	7%
Insufficient blood	7%
Other	20%

A retrospective audit of chromosomal analyses done in the Division of Human Genetics cytogenetic laboratory from January 2007 to May 2008 documented that 653 specimens were received with a diagnosis of Down syndrome. Of these 12% were unsuccessful due to failed lymphocytes culture growth due to problems occurring before the specimens arrived at the laboratory, mainly prolonged transit time (54%). Normal chromosomes were found in 33% of analyses and 1% had a different diagnosis. A diagnosis of Down syndrome was confirmed in only 54%. Problems of making a clinical diagnosis of Down syndrome in African infants in South Africa has been previously recorded, with only 16% of infants diagnosed in the early neonatal period and less than 50% before 6 months of age.

Initial it was planned to use only specimens from Greater Sekhukhune for the clinical utility evaluation of QF-PCR for the diagnosis of Down syndrome. Then academic paediatricians at the University of Limpopo requested that the postnatal tests for the diagnosis of Down syndrome from the whole province be included in this research. Due to the Division of Human Genetics cytogenetic laboratory losing 50% of its staff in mid 2008 (still not replaced), after consultation with senior academic paediatricians at the Universities of Pretoria and the Witwatersrand in Gauteng Province, the project was extended, as a necessity, to include all postnatal specimens with a clinical diagnosis of Down syndrome received in the laboratory. Lectures were given to paediatricians in the referral area of the Division of Human Genetics on QF-PCR and its use, including counselling information for patients with positive results. A fact

sheet on this was sent to doctors referring patients to the Division of Human Genetics, and accompanies test results for patients confirmed as having Down syndrome. Information from a medical geneticist or genetic counsellor is also available on a designated phone line in the Division of Human Genetics.



Between July 2008 and February 2009, 223 specimens with a clinical diagnosis of Down syndrome were analysed by QF-PCR. A diagnosis of Down syndrome was confirmed in 64% and not confirmed in 36%, results similar to the audit in the cytogenetic laboratory, considering the problem of failed lymphocyte culture was eliminated. QF-PCR cannot differentiate translocation Down syndrome and misses 30% of mosaic Down syndrome in those patients with low mosaicism in the blood. When evaluated against the criteria for clinical utility proposed by *EuroGentest*, it was considered that the use of QF-PCR for the postnatal diagnosis of Down syndrome in the circumstances currently pertaining in South Africa had standing. Although there are disadvantages to using QF-PCR for this purpose these were far outweighed by the advantages including cost-saving and because of staff shortages not being able to offer a confirmatory diagnostic test for Down syndrome.

1.3.4 Lessons learned from the national projects

Object lessons for the development of medical genetic services in middle- and low-income nations are available from the national demonstration projects. These include:

- The involvement, including the political will and commitment, of the health authorities of governments in the initiation and development of services for the care and prevention of people with congenital disorders is essential. This was previously highlighted by the WHO⁵. Evidence of the involvement and commitment of government and health authorities was available from the Chaco outreach project which was sustained and supported during the tenure of two different Ministers of Health and their administrations, in office during the project.
- A functional and stable health care system, with adequate staffing, must be in place for the successful initiation and development of medical genetic services. This is highlighted by contrasting the success of the CHACO Outreach Project with the problems encountered in the South African programme GraSCOP . South Africa is currently experiencing a health care crisis consequent on its HIV/AIDS epidemic and exacerbated by a lack of available health care personnel. The latter was incipient when GraSCOP was muted and deteriorated significantly, and unexpectedly, in Limpopo Province, particularly with respect to nursing staff. Consequently achieving some of the objectives of GraSCOP was not possible in contrast to Chaco where the health care service was functioning and well staffed, allowing the project to advance beyond its original expectations.

Coupled with the need for a functional and stable health care system is the prerequisite of ensuring that previous unmet health needs will not compete for resources and thus limit the development of intended medical genetic services. In the case of South Africa the unmet health needs involved mainly HIV/AIDS and TB, but in other middle- and low-income nations it might involve other infectious diseases.

These points are evidence of the need for middle- and low-income nations to utilise health needs assessment as proposed by CAPABILITY. Undertaken correctly health needs assessment would identify such issues and enable solutions to be sought.

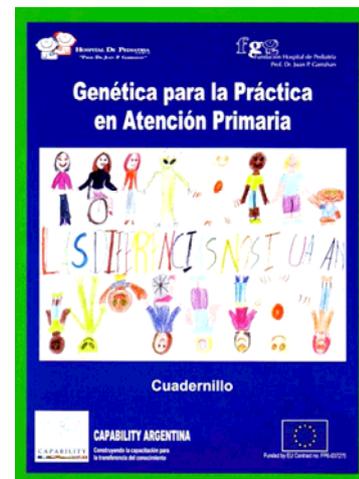
⁵ WHO. Services for the prevention and management of genetic disorders and birth defects in developing countries. WHO, Geneva, Switzerland. 1999. [WHO/HGN//GL/WAOPBD/99.1]

The role of and need for medical genetic education for health care professions and workers was highlighted in all the demonstration projects. This was particularly notable in the Chaco outreach project in which the success of the services developed was reliant on the education of the provinces health care professions and workers. Recent evidence from the development of medical genetic services in Iran recorded that the financial cost of this education is one of the major expenses in initiating and developing medical genetic services⁶ This is an important consideration for the future development of medical genetic services in middle- and low-income nations.

- The Egyptian community education project through its knowledge, attitudes and practices survey demonstrated the lack of medical genetic knowledge of health care practitioners and workers working in the primary health care settings common to all three projects. The development of medical genetic education material and its use for teaching and training health care practitioners and workers is a priority in middle- and low-income nations.

Medical genetic educational material for health care professionals and workers is available word-wide from numerous sources, including the internet. However, it is considered necessary by CAPABILITY for each country to develop its own educational material to meet the specific needs and circumstances of each country, as demonstrated in the Argentinean and Egyptian projects.

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لتوعية المجتمع



⁶ Samavat A. Genetic epidemiology in Iran- a basis for service delivery. PhD thesis. University College, London, UK. 2009.

This had previously been done in South Africa. Apart from addressing the particular circumstances of each country, this raises the profile of the authors in the country and through them adds to the awareness of health professionals and workers of congenital disorders, their care and prevention. The process of developing the educational material for national use can also be used to unify national efforts for the care and prevention of congenital disorders by involving people from throughout the country. This was previously done in South Africa.

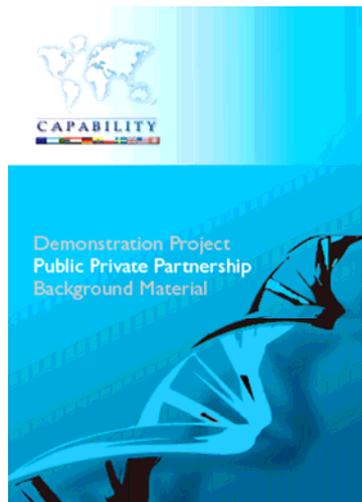
- The Chaco outreach and the Egyptian community education projects illustrated the importance of community involvement in the development of medical genetic services in middle- and low-income nations. The Egyptian project identified the lack of knowledge of such communities regarding congenital disorders, their care and prevention whilst showing their desire to learn about and understand the issues. The Argentinean project illustrated how the communities involvement, including their education is necessary for the development of services for the care and prevention of congenital disorders.

The community knowledge, attitudes and practices assessment of the Egyptian project confirmed that such surveys can be successfully undertaken in middle- and low-income nations and their value to the health needs assessment process.

- The Argentinean project in Chaco clearly illustrated that the success of such a project in developing previously unavailable services in one part of a country frequently stimulates the demand for similar services in other areas. Thus the initiation of such a project needs to be carefully planned to maximise the chances of success, raising the issue of health needs assessment.
- All of the projects confirmed that health needs assessment, as delineated by CAPABILITY, could provide a rational evidence-based method to assist countries identify their health needs for the care and prevention of congenital disorders to enable them to plan appropriate services, sensitive to specific national and local contexts.

1.3.5 Germany – Public Private Partnerships (see Annex 7)

The project "Public Private Partnerships" addressed the problem that health care systems in developing countries, willing to set up the scope of clinical genetic services, in particular genetic testing and screening, all face the problem of very limited resources that can be made available for these novel technologies. In addition health workers' migration and brain drain from developing to developed countries are severely affecting health care in developing countries.



How to attract private funds in order to satisfy the public need for genetic services has so far not been effectively considered in these economies. The project explored such possibilities by collecting background information on Private-Public-Partnership models with the intention to encourage the establishment of genetic services in developing countries built on such principles.

1.3.6 Evaluation approaches for the application of genetic testing in health care services

Chapter 4 presents an overview of national and international frameworks for the evaluation of the clinical validity and utility of genetic testing. Over the last decade questions have been raised specifically in Europe and the United States about appropriate evidentiary standards for the translation of new genetic tests/genetic knowledge into health practice and prevention. In Europe the NoE *EuroGentest* addressed these questions (Unit 3, <http://www.eurogentest.org/unit3/>). In the United

States the ACCE Project piloted an evidence evaluation framework of 44 questions and addressed the components of evaluation: Alytic and Clinical Validity, Clinical Utility and Ethical, Legal and Social Issues. In total the ACCE project examined available evidence for five genetic testing applications. In 2005 the "Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group" was established by the National Office of Public Health Genomics at the Centres for Disease Control and Prevention "to develop a systematic process for evidence-based assessment" for genetic test applications⁷.

In 2007 the PHG Foundation published recommendations for an expanded framework for genetic test evaluation ("Moving beyond ACCE") which was endorsed by the United Kingdom Genetic Testing Network (UKGTN)⁸.

In 2008 the NoE *EuroGentest* published its recommendations for genetic test evaluation⁹.

Chapter 4 provides a comparison of the various national and international frameworks developed so far. The comparison shows that genetic tests evaluation is difficult because a) many genetic disorders are rare and b) number and quality of studies providing evidence are limited. Most studies do not fit very well within the accepted standards for systematic evidence review for clinical utility such as randomised controlled trials or cohort or case-control studies⁷. However, most evaluation approaches have adopted the basic aspects of the ACCE analytic framework and use or recommend the questions developed by ACCE to organise the collection of information (i.e. UKGTN, *EuroGentest* approach) for conditions with relatively high prevalence.

⁷ Teutsch, Steven M. et al.: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. *Genet Med.* 2009 Jan;11(1):3-14.

⁸ Wylie Burke and Ron Zimmern: Moving Beyond ACCE: An Expanded Framework for Genetic Test Evaluation. A paper for the United Kingdom Genetic Testing Network, 2007, (PHG Foundation: www.phgfoundation.org)

⁹ Javaher P, Kääriäinen H, Kristoffersson U, Nippert I, Sequeiros J, Zimmern R, Schmidtke J. EUROAGENTEST: DNA-based testing for inheritable disorders in Europe. *Community Genetics* 2008;11:75.120

For rare conditions a pragmatic decision tree has been developed by *EuroGentest* Unit 3 and published⁹. This decision tree aims at providing a founding that allows decision making in the absence of available data. It follows a constructed line of "evidence" using a series of key questions.

The comparison also shows that evidence collection and assessment - due to the lack of available data – is a time consuming, costly procedure that requires the involvement of multidisciplinary experts representing areas such as: clinical genetics, laboratory expertise, epidemiology, evidence-based medicine, ELSI and economics.

The most important outcome of the comparison is that the way the evidence assessment and the evaluation process are structured and how the outcome is derived from evidence needs to be transparent and accountable. There are ongoing efforts to optimise existing evidence review methods and to maintain a consistent nomenclature such as the *EuroGentest* Clinical Utility Gene Cards (CUGC) for Europe and EGAPP project for the United States.

The comparison reveals that genetic test evaluation is a constant "work in progress" and that the challenge lies in achieving more rapid and less expensive reviews for genetic test applications despite limited available information and without sacrificing the quality of the recommendations.